ISSVA
International Society for the Study of Vascular Anomalies

ISSVA WORLD CONGRESS 2022

THE LATEST IN VASCULAR ANOMALIES

INTERNATIONAL SOCIETY FOR THE STUDY OF VASCULAR ANOMALIES

10-13 MAY 2022

PROGRAM & ABSTRACT BOOK

Table of Contents

Presidential Welcome Letter

On behalf of the ISSVA board, I would like to welcome you to the 2022 ISSVA World Congress.

Just over two years ago, the ISSVA board met to discuss the unfolding situation of an emerging infectious disease and its potential impact on our upcoming World Congress. At the time, we debated going ahead with the meeting, deferring it or cancelling altogether. We ultimately decided to reschedule the Vancouver meeting for what then seemed an improbably long time of two years away and pivoted to a first ever virtual World Congress. The virtual meeting was a huge success, and we followed a year later with our first "Debates and Updates" meeting in 2021 which was also highly successful.

Now, at last, Gerald Legiehn, Jugpal Arneja and their colleagues are able to welcome ISSVA members to beautiful Vancouver, Canada. And this will be yet another 'first': a hybrid World Congress, combining online attendance with our long-delayed Vancouver meeting. For those of us lucky enough to attend in person, we look forward to renewing friendships and resuming interrupted discussions on the big and small questions in vascular anomalies. For those attending virtually, we believe that all we have learned in the last two online meetings will allow us to bring you as up to date as possible with the latest developments in the field. Question and answer can be the most informative aspect of any meeting, and we will try to give everyone, at home or in the room, equal opportunity to participate. Please bear with the session chairs and show courtesy as we work to get this balance right, and give everyone, wherever they are, the best possible conference experience.

While so many of us have been isolated at home in the last two years, progress has continued in the understanding of biology and treatment of vascular anomalies. I am confident that there will be a wealth of new information over the week to take away. Dov Goldenberg and the scientific committee reviewed 457 submitted abstracts to invite 97 podium presentations and 243 poster presentations for what promises to be an exciting and informative program.

Traditionally, this meeting has been preceded by a pre-congress educational day where updates have been provided on a range of topics in vascular anomalies. Since we now run an alternate year meeting dedicated to teaching and updates on hot topics, we have an opportunity to refocus this day on activities vital to the future of the specialty. We will still run the 'primer course' on vascular anomalies which will be open to both in person and virtual attendees, but there will now be additional sessions on the ISSVA classification, clinical trials and vascular anomalies networks. These will regrettably only be open to those in person, but depending on demand we hope to be able to open such sessions to everyone in the future. In the meantime we will make any outcomes from these meetings available to all.

So welcome again to the ISSVA World Congress, please enjoy the meeting.

Tony Penington
President, ISSVA

Introduction to ISSVA

The International Society for the Study of Vascular Anomalies (ISSVA) is a multidisciplinary international society of physicians, scientists, and health care providers united by an interest in vascular anomalies. The Society aims to promote the highest standards of care for patients with vascular anomalies by advancing clinical and scientific knowledge concerning causes, diagnosis and treatment, and by education of physicians, health care providers, patients and the community. The Society encourages the free flow of information between its members and interested groups, through meetings and teaching programs, and by the dissemination of a classification scheme and pertinent scientific data.

About the World Congress

(formerly the Workshop)

The International Society for the Study of Vascular Anomalies (ISSVA) is the formalization of prior biennial international workshops, which were started in 1976. Over time, the ISSVA workshops grew to the point of gathering hundreds of international specialists of various medical disciplines involved in the treatment of patients afflicted with vascular anomalies. These biennial workshops, which eventually evolved into the World Congress, have fostered time proven personal contacts, collaboration, and informal exchange of scientific knowledge concerning vascular anomalies.

2020-2022 Board of Directors

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Hybrid Format & Getting Around

General Information, COVID-19 & Travel

The ISSVA World Congress: The Latest in Vascular Anomalies, is ISSVA's biannual Congress, which is attended by a wide array of specialists including intervention radiologists, dermatologists, plastic surgeons, ENT surgeons, pediatricians, pediatric surgeons, oncologists and pathologists, presents the latest developments in this fast moving area. The ISSVA World Congress 2022 will be the first hybrid meeting hosted by ISSVA.

For in-person attendees, detailed information about travel to Vancouver, Canada, up to date COVID-19 protocol and more information is available on the ISSVA Travel Web Page.

COVID-19 Vaccination Requirement

The ISSVA Board of Directors has elected to require all in-person meeting attendees (and their guests if attending social events) to be fully vaccinated against COVID-19 by a vaccine that is approved by their national government in order to create a safe environment for all in-person delegates. While ISSVA accepts any government-approved vaccine to attend the in-person meeting, the country of Canada may have different requirements so please guarantee that the vaccine you have received is also recognized by the country of Canada.

COVID-19 Task Force

In order to create a safe, yet engaging in-person meeting environment, ISSVA has created a COVID-19 Task Force to stay abreast of changes both locally and globally. This Task Force will regularly re-assess the environment and health risks so they can implement or remove proper protocol to create a safe environment so you and all of our guests can focus on the scientific meeting and the incredible city of Vancouver.

Entry into Canada

The Government of Canada requires that all international visitors carry a valid passport to enter Canada. In addition to your passport, you may also require a visa. For current entry requirements, please visit the Canada Border Services Agency site. Advance travel planning and early visa application are important. It is recommended that you apply early for your visa.

At the moment, Canada also requires all foreign passport holders to show proof of full COVID-19 vaccination upon arrival to the country.

Vancouver, BC, Canada

Vancouver, British Columbia, Canada and the surrounding metro region offers visitors unique neighborhoods and big city amenities surrounded by beautiful water and mountain views, which are easily accessible! Learn more about Vancouver on their Tourism Website: www.tourismvancouver.com

Venue
The in-person activities of the ISSVA World Congress 2022 will take place at the Westin Bayshore Hotel in Vancouver, British Columbia, Canada.

Time Zone
Vancouver is in the Pacific Time Zone.

Virtual Website: Platform, Access & Credentials

The virtual meeting will be hosted by the Chime Live platform, which will be accessible by all registered meeting delegates (both in-person and virtual). This platform will offer the live talks, host the recorded talks until 13 June 2022 and will also contain all ePosters, which will be available for viewing and comments both prior to and after the Congress.

All registered meeting delegates will have access to the platform from about 3 May 2022 to 13 June 2022. Individual log in credentials will be distributed early May from the platform's host, Encore.

Continuing Medical Education Credits

Accreditation Statement

In support of improving patient care, this activity has been planned and implemented by Amedco LLC and International Society for the Study of Vascular Anomalies. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physicians (ACCME) Credit Designation

Amedco LLC designates this **live activity/enduring material** for a maximum of **25.5** *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Claim CME Credits

1. Go to http://issva.cmecertificateonline.com/
2. Click on the "World Congress 2022" link.
3. Evaluate the meeting and click the hyperlink provided on the last page to claim your credit certificate.
4. Save/Download/Print all pages of your certificate for your records.

Questions? Email Certificate@AmedcoEmail.com

Key Dates & Enduring Materials Availability

Registered Delegates will receive their Virtual Platform Credentials: 03 May 2022

Posters go Live: 03 May 2022

Live Scientific Sessions: 10 May 2022 (Pre-Congress Day) & 11-13 May 2020 (Congress) from 8:00 - 15:00 **Pacific Time**

Recorded Scientific Sessions: Available until 13 June 2020

Poster Hall: 03 May - 13 June 2022

Program at a Glance

Tuesday, 10 May (Pre-Congress Day)		
Time	**Session Title**	**Room**
Parallel Sessions		
08:00 - 10:00	Primer, Part I: Classification; Vascular Tumors	Salon ABC
08:00 - 10:00	Classification Presentation	Salon F
10:00 - 10:30	Coffee Break	Foyer
10:30 - 12:30	Primer, Part II: Vascular Malformations	Salon ABC
10:30 - 12:30	Clinical Trials in Vascular Anomalies	Salon F
12:30 - 13:30	Lunch Break	Foyer
Pre-Congress Day Joint Sessions		
13:30 - 15:00	Establishing Networks of Vascular Anomaly Teams	Salon ABC
15:00 - 15:30	Coffee Break	Foyer
15:30 - 17:00	Compelling Case Discussion	Salon ABC
Welcome Reception & Opening Remarks		
17:00 - 19:00	Welcome Reception & Opening Remarks	Salon DE

Wednesday, 11 May		
Time	**Session Title**	**Room**
Journal of Vascular Anomalies (JoVA)		
7:30 - 7:55	JoVA: Meet the Editors	Salon F
Oral Abstract Presentations		
08:00 - 10:05	Session 1: Vascular Tumors	Salon ABC
10:05 - 10:30	Coffee Break	Salon DE
10:30 - 11:35	Session 2: Capillary Malformations	Salon ABC
11:35 - 12:10	Keynote Address: Lewis Cantley	Salon ABC
12:10 - 13:15	Lunch Break	Salon DE
13:15 - 15:40	Session 3: Lymphatic Malformations	Salon ABC
15:40 - 16:00	Coffee Break	Salon DE
General Assembly (ISSVA Members Only)		
16:00 - 17:00	General Assembly	Salon ABC

Thursday, 12 May		
Time	**Session Title**	**Room**
Non-CME Symposium		
07:00 - 07:55	Sponsored Symposium: See the Full Program for Details	Salon F
Oral Abstract Presentations		
08:00 - 10:00	Session 4: Venous Malformations	Salon ABC
10:00 - 10:30	Coffee Break	Salon DE
10:30 - 12:00	Session 5: Combined Vascular Malformations I	Salon ABC
12:00 - 13:30	Lunch Break	Salon DE
13:30 - 15:30	Session 6: Arteriovenous Malformations	Salon ABC
15:30 - 16:00	Coffee Break	Salon DE
16:00 - 17:30	Session 7: Multidisciplinary Studies in Vascular Anomalies I	Salon ABC
Congress Dinner (ticket required)		
18:45 - 22:00	Congress Dinner	Hotel Lobby

Friday, 13 May		
Time	**Session Title**	**Room**
Running Club (pre-registration required)		
06:00 - 07:00	ISSVA Running Club	Hotel Lobby
Oral Abstract Presentations		
08:00 - 10:00	Session 8: Difficult Cases in Vascular Anomalies	Salon ABC
10:00 - 10:30	Coffee Break	Salon DE
10:30 - 12:00	Session 9: Combined Vascular Malformations II	Salon ABC
12:00 - 13:30	Lunch Break	Salon DE
13:30 - 15:30	Session 10: Multidisciplinary Studies in Vascular Anomalies II	Salon ABC
Closing Ceremony & Farewell Reception		
15:30 - 16:00	Closing Ceremony	Salon ABC
16:00 - 16:30	Farewell Reception	Foyer

Pre-Congress Day Sessions

All session and presentation times are in the **Pacific Time Zone**. Presenters are subject to change.

Tuesday, 10 May (Pre-Congress Day)

Parallel Sessions

Primer Part I: Introduction to Vascular Anomalies - Classification; Vascular Tumors

Moderators: Douglas Courtemanche, Leo Schultze Kool

8:00 **Welcome** | *Tony Penington (Australia)*
8:10 **The ISSVA Classification** | *Paolo Gasparella (Austria)*
8:35 **Infantile Hemangioma: Diagnosis and Associations** | *Eulalia Baselga (Spain)*
9:00 **Infantile Hemangioma: Management** | *Carine van der Vleuten (Netherlands)*
9:25 **Liver Hemangioma (neonatal/adult) & Other Tumors** | *Steven Fishman (United States)*

Classification Presentation (in-person only)

8:10 **Classification Presentation & Discussion** | *Ilona Frieden (United States) & Tony Penington (Australia)*

Primer Part II: Introduction to Vascular Anomalies - Vascular Malformations

Moderators: Jugpal Arneja, Gerald Legiehn

10:30 **Multidisciplinary Approach** | *Tony Penington (Australia)*
10:50 **Genetics of Vascular Malformations** | *Sarah Sheppard (United States)*
11:10 **Vascular Malformations – IR Options** | *Annouk Bisdorff-Bresson (France)*
11:30 **Vascular Malformations – Surgical Options** | *Dov Goldenberg (Brazil)*
11:50 **Vascular Malformations – Medication Options** | *Adrienne Hammil (United States)*
12:10 **How to Build and Maintain a Vascular Anomalies Team** | *Jugpal Arneja (Canada)*

Clinical Trials in Vascular Anomalies (in-person only)

Moderators: Leo Schultze Kool, Francine Blei

10:30 **Open Studies in Europe** | *Laurence Boon (Belgium)*
11:00 **Open Studies in the United States** | *Denise Adams (United States)*
11:30 **Update OVAMA / PROMIS** | *Merel Stor (Netherlands)*

Combined Sessions

Establishing Networks of Vascular Malformation Centers & Patient Organizations

Moderators: Tony Penington, Steven Fishman

13:30 **Introduction** | *Leo Schultze Kool (Netherlands)*
13:35 **European and Reference Networks** | *Miikka Vikkula (Belgium)*
13:55 **North American Networks** | *Denise Adams (United States)*
14:15 **Patient organizations and patient driven research - CLOVES Syndrome Community and PIK3CA Related Conditions Collaborative Research Network** | *Kristen Davis (United States)*
14:30 **Patient organizations and Networks - The European Perspective** | *Caroline van den Bosch (Netherlands)*

Compelling Case Discussion

Moderators: Francine Blei, Tony Penington, Leo Schultze Kool

15:00 **A male infant with KHE succesfully treated with sirolimus** | *Veroniek Harbers (Netherlands)*
15:14 **Multiple pyogenic granulomas occurring in a segmental distribution on the lower lip** | *Ilona Frieden (United States)*
15:28 **Interstitial Bleomycin for High Flow Vascular Anomaly of the Fourth Finger** | *Jay Shah (United States)*
15:42 **Mutation Testing to Guide Targeted Therapies** | *Elissa Engel (United States)*
15:56 **A Unique Case of Chyluria in a Pediatric Patient** | *Renata Maricevich (United States)*
16:10 **Angiopoietin-2 as a Diagnostic Tool in Complex Vascular Anomalies** | *Elissa Engel (United States)*
16:24 **Orbit Decompression Sclerotherapy** | *Sudhen Desai (United States)*
16:38 **Massive portal vein thrombosis associated with kaposiform lymphangiomatosis-like phenotype in two patients** | *Abhay Srinivasan (United States)*

Congress Program

All session and presentation times are in the **Pacific Time Zone**. Presenting author is underlined; presenters are subject to change. See below for full abstracts.

Wednesday, 11 May

Session 1: Vascular Tumors

Moderators: Shoshana Greenberger, Ilona Frieden & Joyce Bischoff

08:00 **Welcome** | *Tony Penington (Australia)*

08:15 **Infantile Hemangioma Masqueraders** | *Ashley Ng (United States), Eric Monroe, Kara Gill, Catharine Garland, Jason Pinchot, Carol Diamond, Beth Drolet and Lisa Arkin*

08:26 **Analysis of therapeutic decisions for infantile hemangiomas: A prospective study comparing the Hemangioma Severity Scale with the Infantile Hemangioma Referral Score** | *Tong Qiu (P.R. China) and Yi Ji*

08:37 **Infantile hemangioma sensitivity to propranolol treatment relies on unique cellular and extracellular features** | *Sandra Oucherif, Priscilla Kaulanjan-Checkmodine, Sorilla Prey, Muriel Cario-Andé, Christine Léauté-Labreze, Alain Taieb, Hamid Reza Rezvani and Francois Moisan (France)*

08:48 **Non-β-Blocker Enantiomers of Propranolol and Atenolol Inhibit Vasculogenesis in Infantile Hemangioma** | *Caroline Seebauer (Germany), Matthew S. Graus, Lan Huang, Alex McCann, Jill Wylie Sears, Frank Fontaine, Tara Karnezis, David Zurakowski, Steven J. Staffa, John B. Mulliken, Joyce Bischoff and Mathias Francois*

08:59 **Neurocognitive functioning, physical health, and mental health of school-aged children treated with propranolol or atenolol for infantile hemangioma** | *Mireille M. Hermans (Netherlands), André B. Rietman*, Renske Schappin*, Peter C.J. de Laat, Elodie J. Mendels, Johannes M.P.J. Breur, Hester R. Langeveld, Saskia N. de Wildt, Corstiaan C. Breugem, Marlies de Graaf, Martine F. Raphael and Suzanne G.M.A. Pasmans*

09:10 **SEGMENTAL NON-INVOLUTING CONGENITAL VASCULAR ANOMALY WITH ATROPHY, ULCERATION AND SCARRING (SNICVAUS): FURTHER EVOLUTION OF THE SPECTRUM OF "CONGENITAL HEMANGIOMA"** | *Marta Ivars (Spain), Ilona Frieden, Lauren E. Provini, Lisa Weibel, Martin Theiler, Michel Wassef, Agustina María Lanoël, Lara Rodriguez Laguna, Victor Martinez-Glez, Nicole Kittler, Jose Manuel Azaña-Defez, Sarah Chamlin, Beth Drolet, DARIUSZ WYRZYKOWSKI and Jua*

09:21 **Segmental infantile haemangioma involving S1 S2 and scalp is the strongest predictor of neurovascular and structural brain anomalies in PHACE syndrome.** | *Shannon Carter (United States), Nathanael Lucas, Vijeya Ganesan, Neda Alband and Caroline Mahon*

09:32 **Chronic lymphedema in patients with kaposiform hemangioendothelioma: incidence, clinical features, risk factors and management** | *Yi Ji (P.R. China)*

09:43 **Large cervicofacial vascular anomaly, a difficult case: Is this a NICH?** | *Carol MacArthur (United States), Alison Small, Melinda Wu and Gary Nesbit*

Session 2: Capillary Malformations

Moderators: Eulalia Baselga, Maria Garzon & Beth Drolet

10:30 **GNA11-mutated Sturge-Weber Syndrome has distinct neurologic and dermatologic features.** | *Anne Dompmartin (France), Carine van der Vleuten, Valérie Dekeuleneer,, Thierry Duprez, Nicole Revencu, Julie Desir, Leo Schultze Kool, Miikka Vikkula and Laurence Boon*

10:41 **Phosphorylated-S6 Expression in Sturge-Weber Syndrome Brain Tissue** | *Meghan McCann (United States), Andrew Cho, Carlos A. Pardo, Thuy Phung, Adrienne Hammill and Anne M. Comi*

10:52 **Endothelial GNAQ p.R183Q increases angiopoietin-2 and drives formation of enlarged capillary malformation-like blood vessels in mice** | *Lan Huang (United States), Colette Bichsel, Alexis Norris, Jeremy Thorpe, Sanda Alexandrescu, Anna Pinto, David Zurakowski, Mustafa Sahin, Arin K. Greene and Joyce Bischoff*

11:03 **A Core Outcome domain Set for clinical research on CApillary Malformations (the COSCAM project): an e-Delphi process and consensus meeting** | *Ginger Beau Langbroek (Netherlands), Albert Wolkerstorfer, Sophie E.R. Horbach, Phyllis I. Spuls, Kristen M. Kelly, Susan Robertson, M Ingmar van Raath, Firas Al-Niaimi, Taro Kono, Pablo Boixeda, Hans Joachim Laubach, Ashraf M. Badawi, Agneta Troilius Rubin, Merete Hae*

11:14 **Shared DECision-making in patients with capilLARy malformATIONs (the DECLARATION-project): preliminary results of a multinational prospective study** | *Ginger Beau Langbroek (Netherlands), Uzaifa Sheikh, Albert Wolkerstorfer, Sophie E.R. Horbach, Chantal MAM van der Horst and Dirk T. Ubbink*

Keynote Address

Moderators: Francine Blei & Dov Goldenberg

11:35 **Relevance of the phosphoinositide 3-kinase (PI3K) signaling pathway and the development of PI3K pathway inhibitors and metabolic regulation in vascular anomalies.** | *Lewis C. Cantley, PhD (United States)*

Session 3: Lymphatic Malformations

Moderators: Ionela Iacobas, Michael Dellinger & Gresham Richter

13:15 **Novel discovery of ROS1:PPFIBP1 fusion protein in General Lymphatic Anomaly** | *Angela Kadenhe-Chiweshe (United States), Alain Borzuck, Michael Baad, Bradley Pua and Catherine Mcguinn*

13:26 **MDFIC mutations cause autosomal recessive Complicated Lymphatic Anomaly** | *Alicia B. Byrne, Pascal Brouillard, Drew L. Sutton, Jan Kazenwadel, Saba Montazaribarforoushi, Genevieve A. Secker, Anna Oszmiana, Milena Babic, Kelly L. Betterman, Peter Brautigan, Melissa White, Sandra G. Piltz, Paul Q. Thomas, Christopher N. Hahn, Matthias Rath, Ute Felbor, Christoph G. Korenke, Christopher L. Smith, Kathleen H. Wood, Sarah E. Sheppard, Denise M. Adams, Ariana Kariminejad, Raphaël Helaers, Laurence M. Boon, Nicole Revencu, Lynette Moore, Christopher Barnett, Eric Haan, Peer Arts, Miikka Vikkula (Belgium), Hamish S. Scott and Natasha L. Harvey*

13:37 **Detection of PIK3CA mutations in aspirated cyst fluid is comparable to surgically resected tissues: minimally invasive diagnostics for lymphatic malformations** | *Dana M. Jensen, Kaitlyn Zenner, Tori T. Cook, Victoria Dmyterko, Randall Bly, Sheila Ganti, Jonathan Perkins and James T. Bennett (United States)*

13:48 **Novel murine model of Notch4 haploinsufficiency develops HHT-like and LM-like phenotypes** | *Glicella Salazar-De Simone, Joseph McCarron, Ajit Muley, June K. Wu and Carrie Shawber (United States)*

13:59 **KRAS-driven model of Gorham-Stout disease effectively treated with trametinib** | *Anna McCarter, Nassim Homayun Sephr, Raphaël Helaers, Christine Galant, Laurence M. Boon, Pascal Brouillard, Miikka Vikkula and Michael Dellinger (United States)*

14:10 **Lymphatic Endothelial Cell Secretome Negatively Regulates Bone Cell Differentiation and Function** | *Ernesto Solorzano (United States), Takhar Kasumov, Michael Kelly and Fayez Safadi*

14:21 **Dynamic Contrast Enhanced Magnetic Resonance Lymphangiography in Atypical Lymphatic Malformations** | *Raja Shaikh (United States)*

14:32 **Fenestration of the lateral wall of the orbit : An easy and safe access to perform sclerotherapy of post-septal orbital macrocystic lymphatic malformations (PSO-MLM)** | *Antoine FRAISSENON, Francis FORTIN, Loic VIREMOUNEIX, Arnaud GLEIZAL, Julie PICARD, Pierre BRETON and Laurent GUIBAUD (France)*

14:43 **Minimally Invasive Management of Bilateral Head and Neck Lymphatic Malformations** | *Clare Richardson (United States), J. Nathaniel Perkins, Madeleine Drusin, Sheila Ganti, Dana Jensen, Victoria Dymterko, James Bennett, Tara Wenger, John Dahl, Randall Bly, Juliana Bonilla-Velez, Amy Geddis and Jonathan Perkins*

14:54 **Sirolimus for in utero management of a large fetal LM** | *An Van Damme (Belgium), Emmanuel Seront, Jean Marc Biard, Sandra Schmitz, Caroline de Toeuf de Toeuf, Philippe Clapuyt, Miikka Vikkula and Laurence M. Boon*

15:05 **Clinical and functional expression associated with stop-codon mutations in the CELSR1 gene causing primary lymphedema of the lower limbs** | *Sandrine Mestre Godin (France), Aurelie LAY, Salma Adham, Pascal BROUILLARD, David GENEVIEVE, Erick MERCIER, Sophie GUILLEMARD, Monira NOU HOWALDT, Jochen Rössler, Michèle BIGORRE, Hélène VERNHET KOVACSIK, Miikka Vikkula and Isabelle QUERE*

15:16 **The challenges in pediatric primary lymphedema: investigations, genetic findings, clinical features, treatment, and complications.** | *Catherine McCuaig (Canada), Josee Dubois, Julie Powell, Jérôme Coulombe, Niina Kleiber, Louise Caouette-Laberge, Patricia Bortoluzzi, sandra ondrejchak, Chantal Lapointe and Caroline Colmant*

15:27 **Lymphedema and Sports: A Case Series of Athletic Patients** | *Christopher Sudduth (United States) and Arin K. Greene*

Thursday, 12 May

Session 4: Venous Malformations

Moderators: Anne Dompmartin, Francine Blei & Michel Wassef

08:00 **Somatic mutations in GJA4 drive venous malformation in the skin and liver, and reveal a novel pathway for therapeutic intervention** | *Nelson Ugwu, Lihi Atzmony, Katharine T. Ellis, Gauri Panse, Dhanpat Jain, Christine J. Ko, Naiem Nassiri (United States) and Keith A. Choate*

08:11 **Plasma cell-free DNA after embolization: a novel, sensitive method for molecular diagnosis of venous malformations** | *Yi Sun, Deming Wang, Zhenfeng Wang, Lixin Su, Xindong Fan and Ren Cai (P.R. China)*

08:22 **Sensitive phase-specific detection of somatic double TEK mutations in venous malformations using ddPCR** | *Kaitlyn Zenner, Sabrina Wilcox, Dana M. Jensen, Victoria Dmyterko, Randall Bly, Juliana Bonilla-Velez, John Dahl, Sheila Ganti, Jonathan Perkins and James Bennett (United States)*

08:33 **Development and validation of a novel diagnostic nomogram to diagnose venous malformations from vascular malformations** | *Xitao Yang, Mingzhe Wen, Deming Wang, Lixin Su (P.R. China) and Xindong Fan*

08:44 **Treatment of venous malformations: from bench to bedside** | *Lola Zerbib (France), Niina Kleiber, Antoine Fraissenon, Paul Isenring, Clement Hoguin, Sophia Ladraa, Quitterie Venot, Charles Bayard, Marina Firpion, Celia Chapelle, Gabriel Morin, Mitchell Braun, Kristin Ammon Shimano, Whitney Eng, Josée Dubois, Laurent Guibaud*

08:55 **Clinical Utility of Clinical, Radiologic and Histologic Assessment of Verrucous Venous Malformation** | *Alexandria Brown and Thuy Phung (United States)*

09:06 **Percutaneous sclerotherapy of large venous malformations (VM) using sequential combination of Aetoxisclerol and bleomycin foam (SCABF): A series of 80 procedures with clinical and MR volumetric assessment.** | *Antoine FRAISSENON, Francis FORTIN, Vincent*

DUROUS, Loic VIREMOUNEIX, Arnaud GLEIZAL, Julie PICARD, Pierre BRETON and Laurent GUIBAUD (France)

09:17 **SAFETY-EFFICACY OF PERCUTANEOUS INJECTION OF CHITOSAN OR CHITOSAN EMBOLIZING AND SCLEROSING GELS IN A TIE2-ASSOCIATED VM XENOGRAFT MOUSE MODEL** | *Ricardo Holderbaum do Amaral (Switzerland), Ha-Long Nguyen, Sophie Lerouge, Fatemeh Zehtabi, Arthur Haroutounian, Miikka Vikkula and Gilles Soulez*

09:28 **Surgical Resection of Labial Venous Malformations: A Single Center Experience** | *Claire A. Ostertag-Hill (United States), John B. Mulliken, Belinda Dickie and Steven J. Fishman*

09:39 **Photo-targeted nanoparticle drug delivery systems for venous malformations** | *Kathleen Cullion (United States), Michelle Pan, Claire Ostertag-Hill and Daniel Kohane*

09:50 **Use of Alpelisib in Extensive Venous Malformations Refractory to Other Therapies** | *Whitney Eng (United States), Kristin Shimano, Denise Adams, Mitchell Braun, William Hoffman, Tamjeed Sikder, Sophie Dilek and Ilona Frieden*

Session 5: Combined Vascular Malformations I

Moderators: Thuy Phung, Miikka Vikkula, Steven Fishman

10:30 **Expanded Genetic Landscape in Complex Vascular Anomalies** | *Dong Li (United States), Sarah Sheppard, Michael E. March, Christoph Seiler, Lifeng Tian, Mark R. Battig, Leticia S. Matsuoka, Bede N. Nriagu, Nora Robinson, Alexandria Thomas, Erin Pinto, Fengxiang Wang, Cuiping Hou, Renata Pellegrino, Fernanda Thompson, Charlly Kao, Le*

10:41 **NRAS Q61R Mutation in Human Endothelial Cells Causes Vascular Malformations** | *Elisa Boscolo, Patricia Pastura, Sandra Schrenk, Jillian Goines, Devin Pillis, Punam Malik and Timothy Le Cras (United States)*

10:52 **Endothelial MAP2K1 Mutation Causes Abnormal Vascular Development in Inducible Mouse Strain** | *Christopher Sudduth (United States), Patrick Smits, Matthew P. Vivero, Yu Sheng Cheng and Arin K. Greene*

11:03 **Integration of mRNA/miRNA sequencing and proteomics to identify novel molecular targets in vascular anomalies** | *Ravi Sun, Haihong Zhang, Stephanie Byrum, Gresham Richter and Graham Strub (United States)*

11:14 **Using spatial transcriptomics in vivo to elucidate pathway alterations in vascular anomalies harboring GNAQ variants** | *Aman Prasad, Jared Brown, Ashley Ng (United States), Christina Kendziorski, Lisa Arkin and Beth Drolet*

11:25 **GNAQ mutation in the murine endothelium causes aberrant vascular morphogenesis and KMP that are rescued by MEK inhibition** | *Sandra Schrenk, Jillian Goines, Sara Szabo and Elisa Boscolo (United States)*

11:36 **Proteasome inhibitors effectively inhibit venous and lymphatic malformations** | *Noa R. Shapiro-Franklin (United States), Emma Iaconetti, Ajit Muley, Hai Li, Charles Karen, Carrie J. Shawber and June K. Wu*

11:47 **Pharmacokinetics of Bleomycin Sclerotherapy in Patients with Vascular Malformations** | *Joana Mack (United States), Eric Peterson, Shelley Crary, Jeffery Moran, Kathleen Neville and Gresham Richter*

Session 6: Arteriovenous Malformations

Moderators: Dov Goldenberg, Tony Penington, Gerald Legiehn

13:30 **Genotyping and clinical course in 100 patients with arteriovenous malformations.** | *Lara Rodriguez Laguna (Spain), Paloma Triana Junco, Victor Martinez-Glez and Juan Carlos Lopez-Gutierrez*

13:41 **Somatic Mutational Landscape of Extracranial Arteriovenous Malformations and Phenotypic Correlations** | *Franck-Neil El Sissy (France), Michel Wassef, Benoit Faucon, Didier Salvan, Sophie Nadaud, Florence Coulet, Homa Adle-Biassette, Florent Soubrier, Annouk Bisdorff Bresson and Mélanie Eyries*

13:52 **Somatic SOS1 Variants Associated with Extracranial Arteriovenous Malformation** | *Matthew P. Vivero (United States), Yu Sheng Cheng, Salim Afshar, Amir Taghinia, Harry P. W. Kozakewich, Arin K. Greene and Whitney Eng*

14:03 **Activating MAP2K1 Mutation in Zebrafish Endothelial Cells Causes Arteriovenous Shunts** | *Christopher Sudduth (United States), Nicola Blum, Yu Sheng Cheng, Matthew P. Vivero, Patrick Smits, Nathan D. Lawson and Arin K. Greene*

14:14 **Atypical arterio-venous malformations: different disease?** | *Giacomo Colletti (Austria), Mattia Di Bartolomeo, Sara Negrello, Arrigo pellacani, Gregory Levitin, Linda Rozell-Shannon and luigi chiarini*

14:25 **Ethanol embolization combined or not with surgery and close clinical follow-up can effectively control extracranial arterio-venous malformations** | *Ke Chen (Canada), Jean-Nicolas Racicot, Josee Dubois, Patrick Gilbert, Patricia Bortoluzzi, Julie Powell, Alain Danino, Marie-France Giroux and Gilles Soulez*

14:36 **Trans-ophthalmic arterial ethanol embolotherapy for arteriovenous malformations: A single center experience** | *Xitao Yang, Mingzhe Wen, Deming Wang, Lixin Su and Xindong Fan (P.R. China), Ren Cai*

14:47 **Thalidomide Therapy in Severe Arteriovenous Malformations** | *Laurence M. Boon (Belgium), Valérie Dekeuleneer, Julien Coulie, Liliane Marot, Anne-Christine Bataille, Frank Hammer, Philippe Clapuyt, Anne Dompmartin and Miikka Vikkula*

14:58 **Trametinib as a Promising Therapeutic Option in Alleviating Vascular Defects in an Endothelial KRAS-Induced Mouse Model** | *Ha-Long Nguyen, Laurence M. Boon and Miikka Vikkula (Belgium)*

15:09 **Monocentric Pilot Trial evaluating the safety and efficacy of Trametinib in Arterio-Venous Malformations that are refractory to standard care** | *Julien Coulie (Belgium), Emmanuel Seront, Valerie Dekeuleneer, Frank Hammer, Véronique Roelants, Miikka Vikkula and Laurence M. Boon*

15:20 **MEK inhibition for treatment of vascular malformations in patients with RAS-MAPK pathway upregulation** | *Kristen Snyder (United States), Jill Dayneka, Christopher L. Smith, Abhay Srinivasan, Lea F. Surrey, Yoav Dori, Jean B. Belasco, Hakon Hakonarson, Denise Adams and Sarah Sheppard*

Session 7: Multidisciplinary Studies in Vascular Anomalies I

Moderators: Gulraiz Chaudry, Gresham Richter, Julie Prendiville

16:00 **Assessing the Diagnosis of a Vascular Birthmark, Anomaly, and/or Related Syndrome (VBARS) on the Family** | *Linda Rozell-Shannon (United States)*

16:11 **Expansion of Multidisciplinary Vascular Anomalies Center Telehealth Services** | *Lauren Hill, Taizo Nakano (United States), Aparna Annam, Danielle Katz and Ann Kulungowski*

16:22 **Assessing Quality of Life in Patients with Vascular Malformations** | *Andrew Mangan, Kyle P. Davis, Chrystal Lau, Jeffrey Flowers, Deanne King and Gresham Richter (United States)*

16:33 **Clinical characteristics associated with pain in patients with peripheral vascular malformations.** | *Merel Stor (Netherlands), Max M. Lokhorst, Sophie E.R. Horbach, Danny A. Young-Afat, Tijmen M. Kappen, Naomi M. Van Hout, Phyllis I. Spuls and Chantal M.A.M. van der Horst*

16:44 **Responsiveness of the Patient-Reported Outcome measure for Vascular Malformation (PROVAM) Questionnaire in patients with low-flow vascular malformations** | *Natalie Ring (United States), Ryan W. England, Mina Motaghi, Albert Wu and Clifford Weiss*

16:55 **Utility of Germline Genetic Testing for Neurovascular Anomalies in Pediatrics** | *Ionela Iacobas (United States), Hannah L. Helber, Karen Chen, Peter T. Kan, Daniel Davila-Williams, Omar Tanweer, Vernon R. Sutton and Samuel G. McClugage*

17:06 **Multimodal Treatment for Fibroadipose Vascular Anomaly: Single-Institution Experience of 106 Cases** | *Kelly Barry (United States), Marilyn G. Liang and Whitney Eng*

17:17 **How "Academic" is ISSVA? Characterization of the Conversion of Meeting Presentation to Publication from the 2016 and 2018 ISSVA Workshops** | *Norbert Banyi (Canada), Sahdev Baweja, Young Ji Tuen, Marija Bucevska and Jugpal Arneja*

Friday, 13 May

Session 8: Difficult Cases in Vascular Anomalies

Moderators: Dov Goldenberg, Denise Adams, Joseé Dubois

08:00 **A case of malignant transformation of vascular tumor with somatic PTEN variant** | *Sarah Keiko Daley (United States), Huy M. Do, Sara Regina Kreimer, Michael Jeng, Joyce Teng and Serena Y. Tan*

08:11 **Endovascular and conservative treatment of huge kaposiform hemangioendothelioma (KHE) complicated by recurrent hemothorax** | *Iryna Benzar (Ukraine)*

08:22 **Kaposiform lymphagioendothelioma with recurrent idiopathic pericardial effusion successfully treated with anti-IL1 therapy** | *Simona Avčin (Slovenia), Nataša Toplak, Martin Thaler and Janez Jazbec*

08:33 **Hypertrophic Progressive Vascular Anomaly due to somatic GNAQ209 mutation with Recalcitrant Ulceration** | *Lauren Provini, Patricia Cornett, Rachelle Durand, Timothy McCalmont and Ilona Frieden (United States)*

08:44 **Venous malformation with associated segmental overgrowth attributable to mosaic pathogenic deletion in NSD1 gene** | *Janette diMonda, Anne Gill, Michael Briones, Rachel Swerdlin, Jay Shah, Matthew Hawkins and Rossana Sanchez Russo (United States)*

08:55 **Scientific Committee Presentation** | *Dov Goldenberg (Brazil)*

09:06 **A compelling case of extensive VVM that affected breast development** | *SHIH-JEN CHANG, LIZHEN WANG, YAJING QIU and Lin Xiaoxi (P.R. China)*

09:17 **Direct Stick Embolization of a Rectal Venous Malformation via Transanal Minimally Invasive Surgery** | *Anudeep Yekula, Oluwaseun Ayoade, Vikram Reddy, Haddon Pantel and Naiem Nassiri (United States)*

09:28 **A child with a progressive aneurysm syndrome requiring aortoiliac bypass with biallelic variants in LRP1, possible novel arteriopathy gene?** | *Madison Heisler, Victoria Dmyterko, Dana M. Jensen, Zoe Nelson, Catherine Amlie-Lefond, Patrick Healey, Daniel Hallam, Daniel Miller, Jonathan Perkins and James T. Bennett (United States)*

09:39 **Difficult Case Presentation: Targeted Treatment of an Extensive MAP2K1-Mutant AVM of the Suprahyoid Neck and Face in a 12-Year Old Girl** | *Joshua Smith (United States), Neeraja Swaminathan, Rajen Mody, Steven W. Pipe, James Bennett, Jonathan Perkins and David Zopf*

Session 9: Combined Vascular Malformations II

Moderators: Laurence Boon, Juan-Carlos Lopez-Gutierrez, Leo Schultze Kool

10:30 **Lymphatic Differentiation and Microvascular Proliferation in Vascular Anomalies Lesions Following ISSVA Classification System** | *Amalia Mulia Utami (Indonesia), Max M. Lokhorst, Mara Kruijt, Onno J. de Boer, Chantal M.A.M. van der Horst and Allard C. van der Wal*

10:41 **Cell-free DNA obtained during sclerotherapy as a novel method for molecular analysis of venous and lymphatic malformations.** | *Merel Stor (Netherlands), Max M. Lokhorst, Sophie E.R. Horbach, Sanne M. Schreuder, Roy Reinten, Saskia M. Maas, Naomi M. van Hout, Carel J.M. van Noesel and Chantal M.A.M. van der Horst*

10:52 **Benefit of systematic central nervous system screening in capillary malformation-arteriovenous malformation syndrome: an observational study.** | *Olivia Boccara (France), Juliette Mazereeuw, Ludovic Martin, Didier Bessis, Thomas Hubiche, Christine Chiaverini, Anne Dompmartin, stephanie Mallet, Juliette Miquel, Hélène Aubert, Eve Puzenat, Claire Abasq, Laurence Gusdorf, Smail Hadj-Rabia and Annabel Maruani*

11:03 **Parkes Weber Syndrome with Lymphedema Caused by a Somatic KRAS Variant** | *Whitney Eng, Christopher Sudduth, Dennis Konczyk, Patrick Smits (United States), Steven J. Fishman, Ahmad Alomari, Denise Adams and Arin K. Greene*

11:14 **Targeted medical therapy reduces head and neck PIK3CA-related overgrowth** | *Madeleine Drusin, Clare Richardson, J. Nathaniel Perkins (United States), Sheila Ganti, Erika Lutsky, Catherine Bull, James Bennett, Tara Wenger, William Dobyns, Randall Bly, John P. Dahl, Juliana Bonilla-Velez, Ezgi Mercan, Erik Stuhang, Eden Palmer, Seth Friedman, Michael Bindschadler and Jonathan A. Perkins*

11:25 **Preliminary results of the VASE trial evaluating Sirolimus in Vascular Malformations refractory to Standard Care: Beyond the 2-year treatment with sirolimus.** | *Emmanuel Seront (Belgium), An Van Damme, Annouk Bisdorff Bresson, Philippe Orcel, Anne Dompmartin, Marie-Antoinette Sevestre, Philippe Clapuyt, Frank Hammer, Catherine Legrand, Miikka Vikkula and Laurence M. Boon*

11:36 **EPIK-P1: Retrospective Chart Review Study of Patients With PIK3CA-Related Overgrowth Spectrum (PROS) Who Received Alpelisib** | *Guillaume Canaud (France), Juan Carlos López Gutiérrez, Alan Irvine, Nii Ankrah, Athanasia Papadimitriou, Antonia Ridolfi and Denise M. Adams*

11:47 **Is there a place for prophylaxis with DOACs in Klippel-Trenaunay Syndrome and other low-flow vascular malformations with intravascular coagulopathy and thromboembolic events?** | *Carine van der Vleuten (Netherlands), Lilly Zwerink, Edith Klappe, Elke de Jong and Maroeska te Loo*

Session 10: Multidisciplinary Studies in Vascular Anomalies II

Moderators: June Wu, Jugpal Arneja, Sarah Sheppard

13:30 **Management of sirolimus treatment for tumors associated with Kasabach-Merritt phenomenon** | *Agathe Labonnelie, Véronique Soupre, Annabel Maruani, Salavatore Cisternino, smail Hadj-Rabia and Olivia Boccara (France)*

13:41 **Intramuscular Vascular Malformations: classification on the basis of clinical-haemodinamic-imaging and histologic findings. Implication on therapeutic approach** | *Moneghini Laura (Italy), Alfredo Zocca, Marcello Napolitano and Gianni Vercellio*

13:52 **MENTAL HEALTH EVALUATION IN PATIENTS WITH VASCULAR ANOMALIES** | *Joana Mack (United States), Tiffany Howell, John Block and Shelley Crary*

14:03 **Lymphatic phenotype of Noonan Syndrome: Innovative diagnosis and therapies for lymphatic diseases in Noonan Syndrome** | *Lotte Kleimeier (Netherlands), Caroline van Schaik, Erika Leenders, Jos M. Draaisma and Willemijn Klein*

14:14 **Prospective Observational Study of Pain Severity and Pain Interference Outcomes Following Percutaneous MRI-guided Laser Ablation or Cryoablation for Painful Peripheral, Soft Tissue Vascular Anomalies: 12-month Outcomes** | *Scott Thompson (United States), Erica M. Knavel Koepsel, Garret M. Powell, Emily C. Bendel, Haraldur Bjarnason, Stephanie F. Polites, Desirae L. Howe-Clayton, Katelyn Anderson, Megha Tollefson and David A. Woodrum*

14:25 **Differences in response to low dose sirolimus between children and adults with vascular anomalies?** | *Veroniek Harbers (Netherlands), Frédérique Bouwman, Lilly Zwerink, Carine van der Vleuten, Bas Verhoeven, Gerard Rongen, Willemijn Klein, Ingrid van Rijnsoever, Leo Schultze Kool and Maroeska te Loo*

14:36 **No Association of Sirolimus with Wound Complications in Children with Vascular Anomalies** | *Steven Mehl (United States), Richard Whitlock, Rachel Ortega, Ionela Iacobas, Renata Maricevich, Tara Rosenberg and Kristy Rialon*

14:47 **Clinical Response to PI3K Inhibition in a Cohort of Children and Adults with PIK3CA Related Overgrowth Spectrum (PROS) Disorders** | *Alexandra Jane Borst (United States), Prashant Raghavendran, Sharon Albers, Sara Zarnegar-Lumley and James Phillips*

14:58 **Safety of Alpelisib in Patients with PIK3CA-Related Overgrowth Spectrum (PROS): Secondary Analysis from the EPIK-P1 Medical Chart Review** | *Guillaume Canaud (France), Denise M. Adams, Alan Irvine, Nii Ankrah, Anthanasia Papadimitriou, Antonia Ridolfi, Fabian Romen and Juan Carlos López Gutiérrez*

15:09 **Clinical Characteristics and Management Of Cutaneous Toxicities Associated with the MEK Inhibitor Trametinib** | *Tiffany Wu (United States) and Joyce Teng*

Closing Ceremony & Farewell Reception

Oral Abstracts

Session 1: Vascular Tumors

Infantile Hemangioma Masqueraders

Ashley Ng (University of Wisconsin - Madison); Eric Monroe (University of Wisconsin - Madison); Kara Gill (University of Wisconsin - Madison); Catharine Garland (University of Wisconsin - Madison); Jason Pinchot (University of Wisconsin); Carol Diamond (University of Wisconsin - Madison); Beth Drolet (University of Wisconsin - Madison); Lisa Arkin (University of Wisconsin School of Medicine)

Purpose: Vascular anomalies in children encompass a wide spectrum of diseases with overlapping features. Many vascular anomalies are mistaken for infantile hemangiomas, which are characterized by high-flow vascular lesions that appear within weeks of birth, grow rapidly within the first few months of age, and typically begin to involute around the first year of life. The purpose of this presentation is to describe a series of infantile hemangioma "masqueraders" with an educational focus on useful strategies for the highly trained specialist to correctly diagnose vascular anomalies in children.

Methods: Patients were identified by physician members of the multi-interdisciplinary birthmarks and vascular anomalies clinic at the University of Wisconsin-Madison. Cases included those with the presumed diagnosis of infantile hemangiomas where further workup and evaluation established an alternative diagnosis.

Results: We herein describe a series of 6 cases of hemangioma masqueraders, most without response to oral propranolol (Table 1). Clinical and radiographic pearls to differentiate these lesions from infantile hemangiomas will be discussed.

Conclusion: Clinical history, physical exam, radiologic imaging, and interdisciplinary assessment can help with the appropriate diagnosis of hemangioma masqueraders. Clinical history of rapid growth in the first few months of life may still accompany other vascular anomalies, and clinicians should stay attuned to alternative diagnoses with further workup, particularly when beta-blocker treatment produces minimal improvement.

Analysis of therapeutic decisions for infantile hemangiomas: A prospective study comparing the Hemangioma Severity Scale with the Infantile Hemangioma Referral Score

Tong Qiu (University of Sichuan at China); Yi Ji (West China Hospital of Sichuan University)

Purpose: In view of the high incidence of infantile hemangioma (IH) in infants and young children, a comprehensive and reasonable evaluation scale for treatment is urgently needed. This study compared the influence of the Hemangioma Severity Scale (HSS) and the Infantile Hemangioma Referral Score (IHReS) on treatment decisions for infantile hemangioma patients. We aimed to establish a reliable and effective evaluation method for treatment decisions.

Methods: This study conducted a prospective cross-sectional study to determine whether treatment was needed for IH patients after evaluation with HSS and IHReS.

Results: A total of 266 consecutive referred IH patients were evaluated for the risk of IH, and the treatment rate was 80.8%. The area under the curve (AUC) of the subject receiver operating characteristic curve (ROC) of treatment decision-making after assessment by the HSS was 0.703 (95% CI: 0.634-0.772), and that after assessment by the IHReS was 0.892 (95% CI: 0.824-0.960).

Conclusion: For decisions regarding the treatment of IH patients, the IHReS has a higher efficiency and sensitivity than the HSS. However, the specificity of the IHReS is lower than that of the HSS.

Infantile hemangioma sensitivity to propranolol treatment relies on unique cellular and extracellular features

Sandra Oucherif (U1035 BMGIC University of Bordeaux); Priscilla Kaulanjan-Checkmodine (Bordeaux University); Sorilla Prey (Bordeaux University Hospital); Muriel Cario-Andé (Bordeaux University); Christine Léauté-Labreze (Bordeaux University Hospital); Alain Taieb (INSERM 1035 Bordeaux); Hamid Reza Rezvani (Bordeaux University); Francois Moisan (Bordeaux University)

Purpose: Propranolol, a nonselective β-adrenergic receptor blocker, is the first-line treatment for severe infantile hemangiomas (IH). The antitumor effect of propranolol is still largely misunderstood, due to the lack of a validated in vitro model of IH. Aquaporin-1 (AQP1), an aqueous channel modulated in angiogenesis and in tumor cell migration, was decreased in propranolol treated mice and correlated with tumor growth inhibition, whereas overexpression was associated with increased tumor growth. We therefore looked at AQP1 in IH, which made it possible to identify interstitial cell named telocytes (TC). Theses recently described interstitial cells are characterized by long cytoplasmic processes, the telopods, which form a three-dimensional communication network between cells, in multiple organs including the skin, especially around dermal vessels.

Methods: The localization and markers of TC have been studied in a panel of HI, healthy skin and other vascular tumors. Then from fresh IH tissue, three cell types were isolated and cultured for functional study: endothelial cells, pericytes and telocytes. To study the functional role of TC in the pathophysiology of IH and its response to propranolol, we performed capillary like tube formation assays, seeding IH endothelial cells, pericytes and telocytes together as an IH model. We then studied the response to propranolol with AQP1 downregulated by shRNA. Moreover we quantified circulating molecules in IH tissues in order identify other critical factors for propranolol response.

Results: Our immunostaining analysis revealed that expression profile AQP1 is different in IH compared to other vascular tumors. Furthermore, AQP1 expression is exclusively restricted to perivascular TC in IH. Our in vitro IH model was then instrumental into identifying the roles of AQP1 and other critical factors in propranolol response.

Conclusion: Altogether, we show that sensitivity of our IH model to propranolol relies on the crosstalk between vascular and perivascular lesional cells when specific microenvironmental factors are present.

Non-β-Blocker Enantiomers of Propranolol and Atenolol Inhibit Vasculogenesis in Infantile Hemangioma

Caroline Seebauer (University Hospital Regensburg); Matthew S. Graus (University of Sydney); Lan Huang (Boston Children's Hospital); Alex McCann (The University of Queensland); Jill Wylie Sears (Boston Children's Hospital); Frank Fontaine (Gertrude Biomedical Pty Ltd); Tara Karnezis (Gertrude Biomedical Pty Ltd); David Zurakowski (Boston Children's Hospital); Steven J. Staffa (Boston Children's Hospital); John B. Mulliken (Boston Children's Hospital); Joyce Bischoff (Boston Children's Hospital); Mathias Francois (The University of Sydney)

Purpose: Propranolol and atenolol, current therapies for problematic infantile hemangioma (IH), are composed of R(+) and S(-) enantiomers: the R(+) enantiomer is largely devoid of β-blocker activity.

Methods: We show both R(+) propranolol and R(+) atenolol inhibit hemangioma stem cell (HemSC) to endothelial differentiation. Furthermore, both R(+) enantiomers inhibit the formation of IH-like blood vessels from HemSC in a murine xenograft model.

Results: As our previous work implicated the transcription factor SOX18 in propranolol-mediated inhibition of HemSC to endothelial differentiation, we tested a known SOX18 small molecule inhibitor (Sm4) and show that this compound inhibits HemSC vessel formation in vivo in a similar manner as the R(+) enantiomers. To uncover mechanism(s), we examined how R(+) propranolol alters SOX18 transcriptional activity. We show that R(+) propranolol directly interferes with SOX18 target gene trans-activation, disrupts SOX18-chromatin binding dynamics and reduces SOX18 dimer formation.

Conclusion: With these new results, we propose that β-blockers propranolol and atenolol may act independently of β-adrenergic receptors and instead the mechanism of drug action for both propranolol and atenolol when used to treat IH includes R(+) enantiomer targeting of SOX18 transcriptional activity. The use of the R(+) enantiomers could increase safety and efficiency by reducing β1- and β2-related side effects in the treatment of infantile hemangioma and possibly in other types of vascular anomalies in which SOX18 plays a role.

Neurocognitive functioning, physical health, and mental health of school-aged children treated with propranolol or atenolol for infantile hemangioma

Mireille M. Hermans (Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Department of Dermatology - Center of Pediatric Dermatology, the Netherlands; Vascular Anomaly Center Erasmus MC Rotterdam, the Netherlands); André B. Rietman (Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Department of Child and Adolescent Psychology/Psychiatry, the Netherlands); Renske Schappin* (Department of Surgery, Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands; Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Department of Dermatology – Center of Pediatric Dermatology, the Netherlands); Peter C.J. de Laat (Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Department of Pediatric Hemato-oncology, the Netherlands; Vascular Anomaly Center Erasmus MC Rotterdam, the Netherlands); Elodie J. Mendels (Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Department of Dermatology - Center of Pediatric Dermatology, the Netherlands; Vascular Anomaly Center Erasmus MC Rotterdam, the Netherlands); Johannes M.P.J. Breur (Department of Pediatric Cardiology, Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands; UMCU Center for Vascular Anomalies Utrecht, the Netherlands); Hester R. Langeveld (Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Department of Intensive Care and Pediatric Surgery, the Netherlands; Vascular Anomaly Center Erasmus MC Rotterdam, the Netherlands); Saskia N. de Wildt (Department of Pharmacology and Toxicology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands; Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Department of Intensive Care and Pediatric Surgery, the Netherlands); Corstiaan C. Breugem (Department of Plastic, Reconstructive and Hand Surgery, Amsterdam University Medical Center, the Netherlands; Center for Vascular Anomalies Amsterdam, the Netherlands); Marlies de Graaf (Department of Dermatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands; UMCU Center for Vascular Anomalies Utrecht, the Netherlands); Martine F. Raphael (Department of Pediatric Oncology, Emma Children's Hospital, Amsterdam University Medical Center, the Netherlands; Center for Vascular Anomalies Amsterdam, the Netherlands); Suzanne G.M.A. Pasmans (Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Department of Dermatology – Center of Pediatric Dermatology, the Netherlands; Vascular Anomaly Center Erasmus MC Rotterdam, the Netherlands)*

Purpose: Concerns have been raised about the impact of beta-blocker treatment on the development of children with complicated infantile hemangioma (IH). This study evaluated the functioning of school-aged children who had been treated with propranolol or atenolol for IH during infancy. Since atenolol has more hydrophilic and β1-selective features than propranolol, fewer long-term side effects were expected.

Methods: All eligible children (n=158), aged ≥6 years old, were invited to participate in this two-center cross-sectional study. The primary outcome, the Wechsler Intelligence Scale for Children–V Cognitive Proficiency Index (CPI), measured working memory, processing speed, and attention. Secondary outcomes were other neurocognitive functions (e.g. general intelligence, executive functioning), sleep behavior, physical health (e.g. physical measurements, developmental history, clinical examination), and mental health (e.g. emotional and behavioral problems, quality of life). Parents' outcome was parenting stress.

Results: Data of 105 children (36 propranolol, 69 atenolol; 6.0–11.8 years; 19% male) were analyzed. Children treated with propranolol or atenolol did not differ on the CPI or on secondary outcomes. Although overall functioning was in line with norms, we found higher blood pressure, impaired affect recognition, increased attention problems, and lower social quality of life. Parents showed more physical problems, depressive symptoms, and parent-child relationship problems. Post-hoc analyses showed substantially lower CPI scores for males, compared to participating females (10.3 IQ points, medium effect size), and compared to matched norms (12.4 IQ points, medium effect size).

Conclusion: Long-term functioning does not differ between children treated with propranolol or atenolol for IH. Overall functioning appeared satisfactory. However, specific problems were in line with the short-term side effects of beta-blockers and suggest underlying central nervous system problems. These problems require further follow-up. Timely support should be given to parents. These results emphasize that prescribers and parents of patients should weigh the risks and benefits before starting treatment of IH with beta-blockers.

SEGMENTAL NON-INVOLUTING CONGENITAL VASCULAR ANOMALY WITH ATROPHY, ULCERATION AND SCARRING (SNICVAUS): FURTHER EVOLUTION OF THE SPECTRUM OF "CONGENITAL HEMANGIOMA"

Marta Ivars (University Clinic of Navarra); Ilona Frieden (UC San Francisco); Lauren Provini (University of California, San Francisco); Lisa Weibel (Pediatric Dermatology Department, University Children's Hospital Zurich); Martin Theiler (Children's Hospital Zurich); Michel Wassef (Dept of pathology, Lariboisiere hospital); Agustina María Lanoël (Hospital Nacional De Peditatría Garrahan); Lara Rodriguez Laguna (Vascular Malformations Section, Institute of Medical and Molecular Genetics (INGEMM), La Paz Hospital); Victor Martinez-Glez (Vascular Malformations Section, Institute of Medical and Molecular Genetics, INGEMM-CIBERER-IdiPAZ, Hospital Universitario la Paz); Nicole Kittler (UCSF); Jose Manuel Azaña-Defez (Albacete University Hospital); Sarah Chamlin (Ann and Robert H. Lurie Children's Hospital of Chicago); Beth Drolet (MCW); DARIUSZ WYRZYKOWSKI (Dept. of Surgery and Urology for Children and Adolescents; MEDICAL UNIVERSITY OF GDANSK); Juan Carlos Lopez-Gutierrez (Vascular Anomalies Center. La Paz Children´s Hospital)

Purpose: The ISSVA classification of vascular anomalies is a well-established framework that maintains two categories, vascular malformations and vascular tumors.

In recent years, as new clinical phenotypes have been described and NGS has improved our understanding of their molecular and genetic underpinnings, it has become apparent that this binary is

problematic, at least for a minority of vascular anomalies. Herein we describe new and previously-reported cases of a segmentally distributed vascular anomaly overlaps with NICH but has unique clinical features that expand our understanding of the spectrum of NICH, with features of both vascular tumor and malformation.

Methods: Retrospective international multicenter study. A total of 25 patients were identified, including 13 previously published and 12 unpublished cases. Some had been given a diagnosis of port-wine stain, others of unusual congenital hemangioma.

Results: All patients had the following features: Congenital onset, segmental distribution, red to purple skin coloration with well-defined margins, variable degrees of atrophy, ulceration, pain, scarring and persistence. The degree of surface lesional hypertrophy varied from flat stain-like areas to bulky, thick plaques. Histological examination showed areas of increased density of ectatic vessels associated with ill-defined solid lobules and focally decreased dermal elastic fibers. GLUT-1, WT1 and Ki67 immunostains were negative. In some patients the enlarged vessels showed positivity for D2-40. Imaging studies when available were variable with some cases showing low-flow admixed with higher flow areas (36%) while other patients (32%) having low-flow on Doppler ultrasound studies. In cases where genomics was available (11/25) a postzygotic activating missense mutation in GNA11/GNAQ (209) was detected in 9 patients.

Conclusion: We describe an unusual phenotype of type of vascular anomaly and provide a unifying framework for a better clinical understanding. Like NICH, nearly all those with genomic identification had GNAQ/GNA11 exon 209 mutations but their clinical did not support a straight-forward diagnosis of NICH.

Segmental infantile haemangioma involving S1 S2 and scalp is the strongest predictor of neurovascular and structural brain anomalies in PHACE syndrome.

Shannon Carter (CDHB); Nathanael Lucas (CDHB); Vijeya Ganesan (UCL); Neda Alband (Cambridge University Hospitals NHS Foundation Trust,); Caroline Mahon (University of Otago, Canterbury DHB)

Purpose: PHACE (Posterior fossa malformations, Haemangioma (IH), Arterial anomalies, Cardiac defects, Eye anomalies) syndrome evaluation calls for thorough clinical examination, echocardiogram and MRI/MRA of the head, neck vessels, the latter requiring general anaesthetic with gadolinium contrast. We investigated whether IH distribution could predict specific PHACE morbidities and therefore rationalise investigation.

Methods: In this multicentre, retrospective cohort study we assessed clinical and radiologic findings in infants with a segmental plaque IH of the head and/or neck measuring >5cm, who underwent full PHACE evaluation. We calculated the IH surface area using clinical photography and facial mapping. Univariate analysis was completed with Chi squared tests and a p value of <0.05 was considered significant.

Results: A total of 143 infants with IH >5cm of the head and neck were studied. Of these, 100 met criteria for PHACE and 43 did not. Univariate analysis revealed that IH surface area >20% of the face and crossing S1 and S2 segments are independent predictors of major structural brain anomalies (12/31 vs 9/89, p=0.0001, and 18/74 vs 6/63, p=0.023, respectively). In addition, S1/S2 with contiguous scalp involvement is not only a significant predictor of major structural brain malformations, (13/42 vs 11/95, p=0.0006), but also major intracranial arterial anomalies (26/40 vs 42/91, p=0.047), and posterior fossa malformations (10/42 vs 8/95, p=0.014), and approached significance for predicting major cardiac anomalies (15/42 vs 21/101, p= 0.06), compared to those without upper facial or scalp IH.

Conclusion: The presence of a segmental IH crossing S1/S2 facial placodes involving the scalp and IH surface area, are independently predictive of structural intracranial and neurovascular anomalies in PHACE. These findings may allow for the development of a digital predictive IH mapping tool to identify high-risk individuals based on clinical examination alone. Digital mapping may further refine the IH distributions associated with PHACE morbidity in the future.

Chronic lymphedema in patients with kaposiform hemangioendothelioma: incidence, clinical features, risk factors and management

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Purpose: There are no cohort studies of chronic lymphedema in patients with kaposiform hemangioendothelioma (KHE). We sought to characterize the incidence, clinical features, risk factors and management of chronic lymphedema in patients with KHE.

Methods: We conducted a multicenter retrospective analysis of patients who had a minimum of 3 years of follow-up after the onset of KHE and/or Kasabach-Merritt phenomenon (KMP). Clinical features were reviewed to determine the possible cause of chronic lymphedema. The degree of lymphedema, risk factors and management strategies were analyzed.

Results: Among the 118 patients, chronic lymphedema was confirmed by lymphoscintigraphy 1 year after the onset of KHE and/or KMP in 13 patients. In 8 patients with lymphedema, extremity swelling was evident in the presence of KHE and/or KMP. In all patients with lymphedema, a unilateral extremity was affected, along with ipsilateral KHE. Most (84.6%) patients reported moderate lymphedema. Lymphedema was more common in patients with larger (≥10 cm) and mixed lesions involving the extremities ($P<0.01$). A history of KMP and sirolimus treatment were not predictors of lymphedema ($P>0.05$). Overall, 76.9% of patients received sirolimus treatment after referral, including 53.8% who presented extremity swelling before referral. Seven (53.8%) patients received compression therapy. Five (38.5%) patients reported lymphedema-associated decreased range of motion at the last follow-up.

Conclusion: Chronic lymphedema is a common sequela of KHE and can occur independently of KMP and sirolimus treatment. Patients with large and mixed KHE involving extremities should be closely monitored for this disabling complication.

Large cervicofacial vascular anomaly, a difficult case: Is this a NICH?

Carol MacArthur (OHSU); Alison Small (Oregon Health and Science University); Melinda Wu (OHSU); Gary Nesbit (OHSU)

Session 2: Capillary Malformations

GNA11-mutated Sturge-Weber Syndrome has distinct neurologic and dermatologic features.

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Purpose: Sturge-Weber syndrome (SWS) is a neurocutaneous disorder commonly caused by somatic activating mutations in GNAQ. GNA11 somatic mutations have been reported in 5 cases. It is not clear if their phenotypic features differ from GNAQ-SWS.

Methods: Within two VASCERN-VASCA multidisciplinary centers we looked for patients with clinical characteristics in the SWS-spectrum without a GNAQ mutation, but rather a GNA11 mutation. Clinical and radiological data was collected retrospectively and prospectively, including MRI with Susceptibility-Weighted Images (SWI) and 3D postcontrast FLAIR

Results: We identified three patients with SWS associated with a somatic GNA11 mutation. They had disseminated CM and hyper- or hypotrophy of an extremity, which is not common in GNAQ-SWS. At birth, the CMs of the face, trunk and limbs were pink and patchy, and slowly darkened with age evolving to purple color. Two of the patients had glaucoma. All had neurological symptoms and moderate brain atrophy associated with pial angioma. Specific MRI sequences, SWI and 3D postcontrast FLAIR, were necessary to visualize the pial angiomas

Conclusion: We can differentiate two distinct forms of SWS; GNAQ-SWS and GNA11-SWS. GNAQ-SWS is characterized by a more homogeneous dark-red CM at birth commonly associated with soft tissue hypertrophy underlying the CM. The CM in GNA11-SWS is more reticulate and becomes darker in time; the neurological picture is milder and can develop slowly in infancy or even only in adulthood. Neurologic symptoms may consist of headaches, vestibular or ear anomalies and are undiagnosed for years. Leptomeningeal angiomatosis is usually detected during childhood in GNAQ-SWS with conventional post-contrast T1-weighted images, whereas specific MRI sequences are necessary to visualize the pial angioma of GNA11-SWS: SWI and 3D postcontrast FLAIR. Therefore, neurologic, and radiologic follow-up is indicated even in adulthood for GNA11-SWS. Genetic diagnosis of clinical syndromes will provide increasing clarity on diagnosis and prognosis.

Phosphorylated-S6 Expression in Sturge-Weber Syndrome Brain Tissue

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Purpose: Sturge-Weber Syndrome (SWS) is a rare neurovascular disorder associated with port-wine birthmarks, glaucoma, and abnormal leptomeningeal blood vessels. It is most commonly caused by a R183Q somatic mutation in GNAQ predicted to result in impaired deactivation of the protein Gαq, and downstream pathways such as the Ras-Raf-MEK-ERK and mTOR pathways. The GNAQ mutation is reportedly enriched in endothelial cells. We stained human tissue for a marker of mTOR activity to address the hypothesis that mTOR activity is common in SWS abnormal leptomeningeal vessels.

Methods: Using a Phosphorylated-S6 (p-S6) antibody, a marker for mTOR pathway activity, we analyzed p-S6 protein expression in human brain tissue samples from SWS subjects and epilepsy controls. Microphotographs were taken of each sample at standardized settings, and focused on the leptomeningeal endothelial layer, leptomeningeal vessels, non-vascular leptomeningeal tissue, and

cerebral cortex. Two observers independently analyzed each image, blinded to diagnosis, and noted the presence or absence of phospho-S6-ribosomal protein expression

Results: SWS brain tissue was more likely to have leptomeningeal endothelial p-S6 antibody staining, compared to epilepsy controls, while the percentage of samples with p-S6 staining in perivascular cells and cortex were not significantly different.

Conclusion: Our study demonstrates that Sturge-Weber brain samples commonly have Phospho-S6 expression in the endothelial cells of abnormal leptomeningeal vessels. This result, along with prior work indicating Phospho-S6 expression in the endothelial cells lining capillary malformations from port-wine birthmarks of patients with SWS, supports the hypothesis that mTOR activity is involved in the pathogenesis and/or progression of the leptomeningeal vascular malformation. This finding implicates mTOR as a potential treatment target for Sturge-Weber Syndrome.

Endothelial GNAQ p.R183Q increases angiopoietin-2 and drives formation of enlarged capillary malformation-like blood vessels in mice

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Purpose: Capillary malformation (CM) is a common vascular malformation. It occurs sporadically and is associated with Sturge-Weber syndrome (SWS). A somatic mutation in GNAQ (c.548G>A, p.R183Q), encoding the G-protein αq subunit, was found to be enriched in endothelial cells (ECs) in skin CM and SWS brain CM. This study aimed to determine how the Gαq-R183Q alters endothelial signaling and disrupts capillary morphogenesis.

Methods: Lentiviral vectors encoding the wild-type (WT) or p.R183Q GNAQ were introduced into human endothelial colony forming cells (EC-WT and EC-R183Q respectively). The WT- and mutant ECs were applied to bulk RNA-seq. The altered gene expression was confirmed by qRT-PCR, ELISA and Western blot in EC-R183Q and by immuno-staining in human CM tissue sections. Furthermore, EC-R183Q were injected into nude mice to examine their ability to form CM-like vessels.

Results: Constitutively activated phospholipase C β3 (PLCβ3), a downstream effector of Gαq, was detected in EC-R183Q and human CM tissue sections. Bulk RNA-seq analyses indicated constitutive activation of protein kinase C (PKC), NF-κB and calcineurin signaling in EC-R183Q. The increased expression of downstream targets Angiopoietin-2 (ANGPT2) and Down Syndrome Critical Region Protein 1.4 (DSCR1.4) were confirmed in EC-R183Q and human CM tissue sections. The Gαq inhibitor YM-254890 and siRNA targeted to PLCβ3 reduced mRNA levels of these targets in EC-R183Q whereas the pan-PKC inhibitor AEB071 reduced ANGPT2 but not DSCR1.4. When implanted in vivo, EC-R183Q formed

enlarged blood vessels. shRNA knockdown of ANGPT2 in EC-R183Q normalized the enlarged vessels to sizes comparable those formed by EC-WT.

Conclusion: Endothelial Gαq-R183Q causes constitutive activation of PLCβ3, leading to increased ANGPT2 and a pro-angiogenic, pro-inflammatory phenotype. EC-R183Q are sufficient to form enlarged CM-like vessels in vivo, and ANGPT2 inhibition prevents the enlargement. Our study demonstrates that endothelial Gαq-R183Q is causative for CM and identifies ANGPT2 as a contributor to CM phenotype.

A Core Outcome domain Set for clinical research on CApillary Malformations (the COSCAM project): an e-Delphi process and consensus meeting

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Purpose: There is limited evidence on the best available treatment options for capillary malformations (CMs), mainly due to the absence of uniform outcome measures in trials on therapies. A Core Outcome Set (COS) enables standard reporting of trial outcomes, which facilitates comparison of treatment results.The objective of this study was to reach international consensus on a core outcome domain set (CDS), as part of a COS, for clinical research on CMs.

Methods: Sixty-seven potentially relevant outcome subdomains were identified based on the literature, focus group sessions, and input from the COSCAM working group. These outcome subdomains were presented in an online Delphi consensus procedure to CM experts (medical specialists and authors of relevant literature) and (parents of) CM patients (international patient associations). During three study rounds, the participants repeatedly assessed the importance of these outcome subdomains on a 7-point Likert scale. Other relevant outcome subdomains could be proposed only during the first round. Consensus was defined as ≥80% agreement on the importance of an outcome subdomain in both participant groups. The CDS was finalized in an online consensus meeting.

Results: A total of 269 participants from 45 countries participated in the first study round. Of these, 106 were CM experts from 32 countries, encompassing mainly dermatologists (59%). In addition, 163 (parents of) CM patients from 28 countries participated, of which the majority had Sturge-Weber syndrome (58%). Following the consensus process, consensus was reached on 11 outcome subdomains: color/redness, thickness, noticeability, distortion of anatomical structures, glaucoma, overall health-related quality of life, emotional functioning, social functioning, tolerability of treatment, patient satisfaction with treatment results and recurrence.

Conclusion: Our CDS is recommended to be used as a minimum reporting standard in all future CM therapeutic trials. The next step is to select appropriate outcome measurement instruments to measure the core outcome subdomains.

Shared DECision-making in patients with capilLARy malformATIONs (the DECLARATION-project): preliminary results of a multinational prospective study

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Purpose: Shared decision-making (SDM) is considered a vital communicative process in modern healthcare, in which clinicians and patients make a joint decision about the therapeutic strategy that best fits the patient's preference, based on best available evidence and the patients' personal values and preferences.

A capillary malformation (CM) is a preference-sensitive condition for which multiple treatment options are available, and therefore particularly suitable for SDM. The aim of this study was to evaluate preferences regarding decision-making and assess current SDM-behavior in CM care.

Methods: Adults and children with CMs facing a treatment-related decision were recruited from three Dutch, one British, and one Australian university hospital. Consultations were audio-recorded. The participant's preferences regarding decision-making were measured prior to the consultation using the Control Preferences Scale. After the consultation, participants completed the SDM-Q-9 and CollaboRATE questionnaires, while physicians completed the SDM-Q-Doc questionnaire. Two researchers independently and objectively rated SDM-behavior from the audiotapes, using the Observing Patient Involvement (OPTION-5) instrument. Results were presented as percentages of the maximum score (i.e. optimal SDM).

Results: So far, 24 participants (6 CM-patients and 18 parents of CM-patients) have been included. Most participants preferred active participation in treatment decision-making, of whom 36% wanted to share the decision with the physician and 56% preferred to make the final decision after seriously considering the physician's opinion. Objective OPTION-5 scores were low (median 30.0; IQR 15.0-37.5), whereas subjective patient- and physician SDM-Q scores were high (medians of 71.1 (IQR 60.0-80.0) and 75.6 (IQR 68.3-82.2), respectively). The median CollaboRATE score was 85.2 (IQR 77.8-92.6).

Conclusion: Currently, objectively measured SDM behavior is still far from optimal in CM care, although patients and parents express a strong desire to be actively involved in treatment decision-making. SDM in this disorder should be improved by enhancing awareness about the concept and knowledge about the conduct of SDM.

Session 3: Lymphatic Malformations

Novel discovery of ROS1:PPFIBP1 fusion protein in General Lymphatic Anomaly

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MDFIC mutations cause autosomal recessive Complicated Lymphatic Anomaly

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Purpose: Complex lymphatic anomalies (CLAs) are often characterised by the dysfunction of core collecting lymphatic vessels. These include the thoracic duct and cisterna chyli, and present as chylothorax, pleural effusions, chylous ascites and/or lymphoedema. They are severe disorders often resulting in foetal or perinatal demise. While mutations in RAS/MAPK and PI3K/AKT signalling pathway components have been documented in some patients, the genetic aetiology remains uncharacterised in the majority of cases.

Methods: Whole exome or genome sequencing was used to detect pathogenic variants in four cohorts of patients with fetal hydrops, chylous ascites, chylothorax and/or lymphedema. A mouse line with a premature stop codon in MDFIC was generated using CRISPR/Cas9, and analysed in detail. MDFIC function was also studied in cell cultures.

Results: We identified homozygous and compound heterozygous mutations in MDFIC in six families. MDFIC encodes the MyoD family inhibitor domain-containing protein. The generated mouse model of the human MDFIC truncating mutation (Met131fs*) revealed that homozygous mutant mice died perinatally, exhibiting chylothorax, the accumulation of lipid rich chyle in the thoracic cavity catalysed by lymphatic vessel rupture. The lymphatic vasculature of homozygous Mdfic mutant mice was profoundly mis-patterned, particularly in the diaphragm and thoracic wall, and exhibited defects in lymphatic vessel valve development. Mechanistically, we determined that MDFIC interacts with, and regulates the activity of, GATA2; a key transcription factor important for development and function of the lymphatic vasculature.

Conclusion: Our work is the first to reveal a crucial role for MDFIC in CLAs and in the lymphatic vasculature. These discoveries enable more precise differential diagnosis of CLAs. Ultimately, understanding the genetic and mechanistic basis of CLAs will facilitate the development and implementation of novel therapeutic agents able to effectively treat this complex, devastating disease.

Detection of PIK3CA mutations in aspirated cyst fluid is comparable to surgically resected tissues: minimally invasive diagnostics for lymphatic malformations

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Purpose: To determine whether cyst fluid cell free DNA (cfDNA) can be used as a diagnostic material for genetic testing in individuals with isolated lymphatic malformations (LM).

Methods: Cyst fluid was collected from individuals with LM who had undergone surgery and had known tissue-based pathogenic variants in PIK3CA, as well individuals with LM who had never undergone

surgery. cfDNA was extracted from cyst fluid and tested for PIK3CA variants using digital droplet PCR (ddPCR). Singleplex and multiplex ddPCR assays (screening p.Glu542Lys, p.Glu545Lys, p.His1047Arg, and p.His1047Leu) were used. Cyst fluid samples without a PIK3CA hotspot variant by ddPCR screening were sent for deep whole gene sequencing of a panel of vascular anomaly genes.

Results: All individuals with a known tissue-based pathogenic variant had the matching PIK3CA variant detected in cyst fluid cfDNA (100%, N = 7). Pathogenic variants in PIK3CA were also identified in cyst fluid cfDNA in 12/16 (75%) of the individuals who has never undergone surgery. Two independent cystic spaces were sampled in one individual, revealing intralesional variability in the PIK3CA variant allele fraction within a single LM. A pathogenic variant in BRAF (p.Val600Glu) was detected on deep panel-based sequencing of one of the remaining 4 cyst fluid cfDNA samples without a PIK3CA variant.

Conclusion: PIK3CA detection rate from aspirated cyst fluid cfDNA is comparable to surgically resected tissue. We speculate that this is related to the close relationship between cyst fluid and lymphatic endothelial cells. Our findings support increased use of cyst fluid as a diagnostic analyte for individuals with LM, which may guide targeted medical therapies without biopsy or surgery.

Novel murine model of Notch4 haploinsufficiency develops HHT-like and LM-like phenotypes

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Purpose: Notch1 and Notch4 have overlapping and dynamic expression in the developing and homeostatic vasculature. In mice, loss of endothelial Notch1, or ectopic expression of constitutively active Notch1 or Notch4 leads to vascular malformations. In humans increased and reduced NOTCH4 expression has been described in vascular malformations. We hypothesized that Notch4 is necessary for proper vascular development and that reduced Notch4 signaling would lead to vascular malformation development.

Methods: We developed a novel conditional Notch4 mouse in which lox-P sites are flanking exon 1. Mice with heterozygous deletion of Notch4Ex1 (N4Ex1/+) were bred, and the resulting 5 litters of mice assessed for blood and lymphatic defects. Wholemounts and sections were stained for the lymphatic marker, LYVE1, and assessed by microscopy.

Results: Analysis of 2-week old pups generated from N4Ex1/+ and N4Ex1/+ matings revealed a significant loss of homozygous N4Ex1/Ex1 mice (n=1/30, Chi-Squared; TTEST $p<0.0136$). At 2 weeks, 57% of N4Ex1/+ male and female mice had redder skin than control littermates. At 6-week mice, some N4Ex1/+ mice developed telangiectasias on the tongue, feet, mouth and intestinal walls, and mild limb edema. Blood and lymphatic vessels in N4Ex1/+ lungs and liver were dilated. N4Ex1/+ lungs also has arteriovenous shunts and blood-filled lymphatics associated with alveolar thickening and immune cell infiltration. In N4Ex1/+ livers, venous enlargement, lymphatic vessel dilation with increased density surrounding the portal triads, and a reduction of LYVE1+ sinusoidal vessels were observed. Congestion in the sinusoidal vessels was associated with fibrin clots in the portal and central veins, that was also seen in the lungs.

Conclusion: Notch4 is necessary for development of the blood and lymphatic vasculature and that decreased Notch4 signaling contributes to the development of vascular malformations in mice similar to HHT and LMs. Taken together the data suggest that vascular Notch4 functions are dose-dependent.

KRAS-driven model of Gorham-Stout disease effectively treated with trametinib

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Purpose: Gorham-Stout disease (GSD) is a sporadically occurring lymphatic disorder. Patients with GSD develop ectopic lymphatics in bone, gradually lose bone, and can have life-threatening complications such as chylothorax. The etiology of GSD is poorly understood and current treatments for this disease are inadequate for most patients. The objective of this project was to identify and characterize a genetic mutation for GSD.

Results: To explore the pathogenesis of GSD, we performed targeted high-throughput sequencing with samples from a GSD patient and identified an activating somatic mutation in KRAS (p.G12V). To characterize the effect of hyperactive KRAS signaling on lymphatic development, we expressed an active form of KRAS (p.G12D) in murine lymphatics (iLECKras mice). We found that iLECKras mice developed lymphatics in bone, which is a hallmark of GSD. We also found that lymphatic valve development and maintenance was altered in iLECKras mice. Because most iLECKras mice developed chylothorax and died before they had significant bone disease, we analyzed the effect of trametinib (an FDA-approved MEK1/2 inhibitor) on lymphatic valve regression in iLECKras mice. Notably, we found that trametinib suppressed this phenotype in iLECKras mice.

Conclusion: Together, our results demonstrate that somatic activating mutations in KRAS can be associated with GSD and reveal that hyperactive KRAS signaling stimulates the formation of lymphatics in bone and impairs the development of lymphatic valves. These findings provide insight into the pathogenesis of GSD and suggest that trametinib could be an effective treatment for GSD.

Lymphatic Endothelial Cell Secretome Negatively Regulates Bone Cell Differentiation and Function

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Purpose: Complex Lymphatic Anomalies (CLA) are rare conditions characterized by malformed lymphatics in soft tissue and ectopic lymphatics in bone. Gorham-Stout Disease (GSD) is an aggressive type of CLA characterized by regional bone involvement resulting in cortical bone loss. Lymphatic endothelial cells (LECs) and their secretome are crucial to induce LECs migration to bone and resultant cortical destruction seen in GSD. To better define factors resulting in the GSD bone phenotype, we assessed the effect of LEC-conditioned medium (L-CM) on osteoblast and osteoclast differentiation and function in vitro and in vivo.

Methods: Osteoblast (MC3T3 cells) differentiation was assessed at days 7, 14, and 21 in the absence or presence for varying concentrations of LECs conditioned media (L-CM) through staining of alkaline phosphatase, collagen, and mineralization. Murine hematopoietic stem cells harvested from C57BL/6 mice were differentiated into mature osteoclasts while treated without/with L-CM over a 10-day period. Osteoclasts were assessed for differentiation and activity through tartrate-resistant acid phosphatase

staining. In vivo, mice calvarae were assessed for bone formation or bone resorption in the absence/presence of L-CM through μ-CT analysis. Finally, L-CM was subjected to mass spec analysis to identify factors in the LEC secretome possibly related to bone destruction.

Results: L-CM treatment was found to inhibit osteoblast viability, proliferation, and differentiation while stimulating osteoclast differentiation and function in vitro and in vivo. Mass spec analysis identified the presence of osteoclast stimulating factor-1, macrophage colony stimulating factor, and receptor activator for nuclear factor κ-B ligand.

Conclusion: Our study revealed that lymphatic secretome leads to a decrease osteoblast differentiation and function, while accelerating osteoclast maturation and function. Here we provide evidence that direct interaction between lymphatics and bone leads to bone loss in vitro and in vivo. Additionally, we identified proteins secreted by LECs might be responsible, at least in part, for lymphatics-induced bone loss.

Dynamic Contrast Enhanced Magnetic Resonance Lymphangiography in Atypical Lymphatic Malformations

Raja Shaikh (Boston Children's Hospital)

Purpose: Recent advances in magnetic resonance imaging of the lymphatic circulation (Magnetic Resonance Lymphangiography-MRL) with the ability to obtain high quality 3D reconstruction has transformed the display of the lymph vessels and substantially enhanced the ability to better understand such lymphatic disorders. The purpose of this presentation is to discuss the MRL imaging findings in atypical lymphatic malformations.

Methods: 25 pediatric patients underwent MRL procedures to evaluate central lymphatic drainage abnormalities for various indications such a protein losing enteropathy, lymphatic edema, chylous ascites, chylous pleural/pericardial effusion and respiratory issues. Contrast enhanced dynamic MRL was performed by accessing inguinal lymph nodes and injecting gadolinium contrast with serial magnetic resonance imaging. The commonly performed MRI sequences during MRL include: 1) T2-weighted imaging; 2) pre and post contrast T1-weighted dynamic MR imaging; 3) Occasionally pre and post contrast steady state free precession (SSFP) balanced EKG triggered sequence with fat-suppression (3D FIESTA), which provides good visualization of the vessels relationship to the lymphatic channels (Fig P.C). For dynamic contrast enhanced MRI, gadobutrol (macrocyclic non-ionic gadolinium) at 0.1mmol/kg of body weight was used. The images were post processed and used for interpretation.

Results: MRL imaging findings in various atypical lymphatic malformations such as 1. Congenital chylothorax 2. Congenital chylous ascites 3.Primary lymphedema 3. Central conducting lymphatic anomaly 4. Kaposiform lymphagiomatosis 5.Protein losing enteropathy 6.Generalized lymphatic anomaly 7. Gorham Stout’s disease will be presented and discussed.

Conclusion: Contrast enhance dynamic MRL of the lymphatic system has created a substantial change in the evaluation and management of lymphatic diseases. Understanding the lymphatic anatomy, their disease patterns, optimized use of MRL and post-processing imaging techniques, can help in accurate diagnosis and management of the poorly understood lymphatic disorders.

Fenestration of the lateral wall of the orbit : An easy and safe access to perform sclerotherapy of post-septal orbital macrocystic lymphatic malformations (PSO-MLM)

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Purpose: Treatment of PSO-MLM is a real challenge and a watch-and-wait strategy is most often proposed for asymptomatic patients. Surgery may be indicated to relieve optic nerve compression and acute proptosis due to intralesional hemorrhage. However, complete excision is difficult, often unsuccessful, and has high complication rates (orbital hemorrhage, optic nerve injury). Sclerotherapy is also challenging because of both limited percutaneous access and risks of increased orbital pressure related to postprocedural swelling. In keeping with this therapeutic challenge, we offered to selected patients fenestration of the lateral wall of the orbit to both reduce orbital pressure and create a safe access to perform sclerotherapy.

Methods: Fenestration of the lateral wall of the orbit was performed in three patients (7YO, 21YO, 21YO). Symptoms included acute proptosis related to intracystic hemorrhage (n=2) and chronic pain (n=2). Post-procedure clnical and MR data was assessed.

Results: Partial decrease in orbital pressure was obtained in the three patients. In two patients, persistent of chronic/acute orbital pain led to additionally perform sclerotherapy. Percutaneous procedures were performed under general anesthesia though the fenestrated lateral orbital wall using orbital sonographic guidance allowing optic nerve identification. After cyst aspiration and opacification to exclude venous drainage, sclerotherapy was performed using bleomycin injection under fluoroscopy. Patients were discharged in the 24 hours following the procedure. Clinical and radiological follow-up at 3 months demonstrated complete resolution of symptoms and nearly complete resorption of the PSO-MLM.

Conclusion: In patients with symptomatic PSO-MLM, fenestration of the lateral wall of the orbit offers decompression of the orbit and a safe access to perform sclerotherapy. Fenestration could potentially also be discussed in asymptomatic patients with large intra-conal MLM, considering the high risk of intralesional bleeding.

Minimally Invasive Management of Bilateral Head and Neck Lymphatic Malformations

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Purpose: Patients with severe (De Serres stage V) bilateral head and neck lymphatic malformations (BHNLM) historically require aggressive invasive management, often with surgical resection and

tracheostomy. With the advent of targeted medical therapy, treatment paradigms are shifting. We hypothesized that targeted therapy in conjunction with selective minimally invasive procedures, such as aspiration, reduce morbidity in patients with BHNLM.

Methods: Retrospective case review was performed of patients with stage V BHNLM treated exclusively at a single institution from 2000-2021. Patients were divided into two cohorts: those primarily managed with targeted therapy (pTT) and those who were not (non-pTT). Data regarding interventions, clinical outcomes, morbidity, and mortality were compared.

Results: Twelve BHNLM were identified and 8 met inclusion criteria. Of these, 2 (25%) were in the pTT cohort and 6 (75%) were non-pTT. Seven patients (including both pTT patients) underwent ex-utero intrapartum treatment (EXIT) procedure and intubated at delivery. Genotype most commonly was a PIK3CA p.E545K variant (n=6/7, 86%). For the non-pTT cohort, primary treatment included surgical resection (n=4, 67%), sclerotherapy (n=2, 33%), and needle aspiration (n=1, 17%). Four non-pTT patients (4/6 67%) required tracheostomy, and all had multiple hospitalizations for BHNLM treatment in the first year of life. Two patients (2/6 33%) expired prior to discharge. For the pTT cohort, targeted monotherapy with sirolimus (n=2) was initiated within 30 days of birth. After age 2 alpelisib (n=1) was also initiated. Both pTT patients were treated with selective cyst aspiration and were extubated within one month. Repeat intubations and tracheostomy were unnecessary, discharge home was within 3 months of delivery, and no readmissions occurred.

Conclusion: Targeted therapy combined with malformation cyst aspiration may be superior treatment for BHNLM compared to traditional management. In this study, pTT patients were extubated early without tracheostomy or prolonged or multiple hospitalizations. More work is needed to further investigate these trends.

Sirolimus for in utero management of a large fetal LM

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Purpose: Prenatal diagnosis of lymphatic malformation (LM) can be done as early as the first trimester is possible and represents a challenge for clinicians. Although sirolimus has demonstrated efficacy in the treatment of LM in neonates as well as in adult patients, its efficacy in utero and absence of long-term side effects for the management of fetal LM remains unexplored.

Methods: The parents had obtained agreement for medical pregnancy interruption. They consulted us for discussion of potential in utero therapies. We explained the high risk of premature delivery or potential lethality of in-utero sclerotherapy or surgery. We alternatively discussed the possibility of trying maternal sirolimus treatment, as we had an actively recruiting clinical trial on sirolimus in vascular malformations, and since sirolimus crosses the placental barrier. We obtained agreement from our institution's ethical committee, and informed consent from both parents.

Results: We report the successful management of a large fetal LM that was treated with sirolimus (taken orally by mother) from 22 weeks of gestation to one week before delivery. Sirolimus resulted in a rapid decrease of LM volume and allowed uncomplicated delivery. The girl is now 5 years old and has a normal psychomotor development.

Conclusion: We report the first fetus affected with an extensive life-threatening cervicofacial LM that was effectively treated in utero using sirolimus and with a sufficiently long-term follow-up to confirm its safety. This patient highlights the safety of this medication during pregnancy: the mother had classical benign short-term side effects, but more importantly none of the mother or the child exhibited long-term adverse side effects. We highlight the importance of a close monitoring of maternal and fetal serum sirolimus levels for optimal adaptation of sirolimus dosing.

Clinical and functional expression associated with stop-codon mutations in the CELSR1 gene causing primary lymphedema of the lower limbs

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Purpose: Germinal loss of function variants in the CELSR1 gene causes primary lymphedema (PLE). The frequency of lymphedema varies amongst carriers and seems more frequent in women. Whether this reflects a more severe lymphatic anomaly in women or an ability to develop alternative lymphatic pathways in men is unknown.

Methods: This is a descriptive single-center cohort study approved by the local ethics committee.

Results: We studied exomes within our PLE cohort (n=339) and identified 14 CELSR1 stop-codon mutation carriers (9 women and 5 men) within 5 families. Nine carriers had lymphedema (8 women and 1 man), three carriers did not have PLE (1 woman and 2 men) and two carriers who refuse to be clinically examined. Twelve subjects agreed additional clinical examination, lower-limb lymphoscintigraphy, lympho-MRI and renal ultrasound. In carriers with bilateral lymphedema (n=4), lymphoscintigraphy showed delayed lymphatic drainage or no drainage (n=2), and deep ganglion recruitment (2 women). In unilateral cases (n=5), only one had a contralateral sub-normal lymphoscintigraphy, two had deep node relay (one man/ one woman). In mutation-carriers without PLE, lymphoscintigraphy showed functional deficiencies or anatomical variants for one or both lower limbs, and deep lymph node recruitment in one man and woman. Lympho-MRI showed rich pelvic lymphatic tissue in five carriers with PLE and two carriers without PLE. Thoracic duct was described atretic in one and mildly dilated in two others (all men). Renal anomalies were found in four carriers with PLE, one

carrier without PLE and two carriers with no clinical information either 50%. This justifies a systematic exploration for asymptomatic carriers.

Conclusion: All clinically unaffected lower-limbs extremities were abnormal in lymphoscintigraphy. The clinical penetrance of lymphedema is thus 64% (9/14) but 100% have impaired lymphoscintigraphy (n=10/10). The discrepancy suggests residual and/or compensating lymphatic mechanisms but lymphoscintigraphy does not explain the difference in symptomatology between men and women.

The challenges in pediatric primary lymphedema: investigations, genetic findings, clinical features, treatment, and complications.

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Purpose: Pediatric lymphedema is usually primary, due to a hypoplastic and dysfunctional lymphatic malformation. It is critical to report diagnostic investigations, genetic findings, clinical features, treatment, and complications to increase knowledge of this orphan disease. Our review brings new insights into this chronic condition that requires burdensome lifelong compression, and may be complicated by cellulitis and physical and psychological pain.

Methods: Medical records of patients under 18 years of age referred between 1996 and 2021 to our specialized lymphedema clinic were reviewed. Data regarding demographics, sex, age at presentation, location of the lymphedema, internal involvement, genetics, symptoms and signs, complications, investigations, and treatment were collected.

Results: Of 180 referred patients, lymphedema was confirmed in 151, in whom 136 had primary lymphedema. Median age of apparition was 7.0 years and was significantly lower in boys than in girls. Congenital onset was more frequent in boys (24/48 (50.0%) vs 24/88 (27.3%) in girls, p=0.007); onset during adolescence was more frequent in girls (47/88 (53.4%%) versus 12/48 (25.0%) boys p=0.001). Lower limbs were the most impacted (88.2%), and 11 patients had lymphedema of the genitals. Lymphoscintigraphy confirmed dysfunction in 65/80 (81.3%) tested. Sixty-two patients had genetic testing, and 38 (63.3%) of them were discovered to have a pertinent genetic mutation. The most common mutated gene was the FLT4 gene (in 9 patients). Seven patients (5.1%) had associated extensive/central lymphatic malformation and 24 (17.6%) had a polymalformative genetic syndrome. Treatment consists of compression and physiotherapy.

Conclusion: Pediatric primary lymphedema is more frequent in girls, affects mostly the lower limbs, and is most often sporadic; genetic testing positivity was higher than previously reported. It is important that these patients be referred to a tertiary vascular anomalies center, given a significant proportion have an associated genetic syndrome and/or are associated with a more complex lymphatic malformation.

Lymphedema and Sports: A Case Series of Athletic Patients

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Purpose: Lymphedema is a chronic, progressive condition without a cure. Although the disease can cause significant morbidity, it is not a contraindication to participating in sports. The purpose of this

study was to illustrate patients who are able to perform vigorous athletic activities in order to encourage individuals newly diagnosed with lymphedema.

Methods: Our Lymphedema Program database was reviewed for patients who performed significant sports, outside of routine exercise and fitness. Inclusion criteria were: a confirmed diagnosis of lymphedema, age>16, and body mass index (BMI) < 30. Age, sex, type of lymphedema (i.e., primary or secondary), location of disease, BMI, and athletic activities were recorded.

Results: Fourteen patients met inclusion criteria: 7 males and 7 females. Average age was 34 years (range 17-77) and lymphedema was primary (n=11) or secondary (n=3). All subjects had lower extremity disease: right leg (n=6), left leg (n=5), bilateral (n=3). The average BMI was 23 (range 18-27). Sports performed by the cohort included: marathon running (n=3), soccer team (n=2), skiing (n=2), basketball team, rugby, swimming team, college lacrosse team, hockey team, college tennis team, surfing.

Conclusion: Patients with lower extremity lymphedema are able to engage in competitive sports and a wide range of athletic activities. Individuals typically have a normal BMI and active lifestyle. Patients with lymphedema should be encouraged to participate in athletic pursuits that they enjoy and to maintain a normal BMI.

Session 4: Venous Malformations

Somatic mutations in GJA4 drive venous malformation in the skin and liver, and reveal a novel pathway for therapeutic intervention

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Purpose: The term “cavernous hemangioma” has been used to describe vascular anomalies with histology featuring dilated vascular spaces, vessel walls consisting mainly of fibrous stromal bands lined by a layer of flattened endothelial cells, and an irregular outer rim of interrupted smooth muscle cells. Hepatic hemangiomas (HH) and cutaneous venous malformations (cVM) share this histologic pattern, and we examined lesions in both tissues to identify genetic drivers.

Methods: We undertook paired whole exome sequencing (WES) of lesional tissue and normal liver from HH subjects. Paired targeted sequencing of cVMs and normal epidermis was subsequently performed to detect genetic mutations in shared pathways as those identified in HHs.

Results: WES of lesional tissue and normal liver from HH subjects revealed a recurrent GJA4 c.121G>T, p.Gly41Cys somatic mutation in 4 of 5 unrelated cases, and targeted sequencing in paired tissue from 9 additional HH subjects identified the same mutation in 8. Paired targeted sequencing of 5 cVMs and normal epidermis, found the same GJA4 c.121G>T, p.Gly41Cys somatic mutation in 3. GJA4 encodes gap junction protein alpha 4, also called connexin 37 (Cx37), and the p.Gly41Cys mutation falls at a residue highly conserved among vertebrates. We investigated the impact of the Cx37 mutant via lentiviral transduction of primary human endothelial cells. We found that the mutant induced changes in cell morphology and activated SGK1, a serine/threonine kinase known to regulate cell proliferation and apoptosis, via non-canonical activation. Treatment with spironolactone, an inhibitor of angiogenesis, suppressed SGK1 activation and reversed changes in cell morphology.

Conclusion: These findings identify a recurrent somatic GJA4 c.121G>T, p.Gly41Cys mutation as a driver of hepatic and cutaneous venous malformations, revealing a new pathway for vascular anomalies, with spironolactone a potential pathogenesis-based therapy.

Plasma cell-free DNA after embolization: a novel, sensitive method for molecular diagnosis of venous malformations

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Purpose: Venous Malformations(VMs) mainly harbor somatic mutations in TEK and PIK3CA genes. Cell-free DNA has been reported as a molecular diagnostic tool for VMs. As a sclerosant for the embolization of VMs, absolute ethanol can rapidly denudate venous endothelial cells. We hypothesized that peripheral plasma cfDNA after absolute ethanol embolization may become a more sensitive and reliable approach to achieve a molecular diagnosis.

Methods: We collected peripheral blood samples, cfDNA samples isolated from peripheral plasma before and 1hour after ethanol embolization in 24 patients with VM in the main study group, and paired plasma cfDNA samples from the lesion site in 7 of those patients. Next-generation sequencing (NGS) with a targeted panel was conducted to detect somatic mutations. To confirm our findings, we further analyzed peripheral plasma cfDNA of post-embolization from 88 patients in an independent validation

Results: Variants were detected in cfDNA samples but none in peripheral blood. The detection rates in peripheral plasma cfDNA of pre-embolization and post-embolization were 12.5% (3/24) and 87.5% (21/24). As for the 7 patients who underwent lesion plasma cfDNA analysis, the detection rates in lesion plasma cfDNA, peripheral plasma cfDNA of pre- embolization, and post-embolization were 71.4% (5/7), 0% (0/7), and 85.7% (6/7). The area under the ROC curve were 0.8571 (P=0.0253), 0.5625 (P=0.4579), and 0.9375 (P<0.0001), respectively. For the variants allele frequency(VAF) of CfDNA, five out of seven patients recorded higher VAFs in post-embolization cfDNA rather than that in lesion plasma cfDNA. In an independent validation group with post-embolization cfDNA analysis in 88 patients, 111 variants in TEK, PIK3CA, GLMN, AKT, and PTEN were identified in 90.9% (80/88) patients.

Conclusion: Peripheral plasma cfDNA of post-embolization realize the combination of molecular diagnosis and treatment for venous malformations and could be a safe, sensitive, and reliable method for molecular diagnosis.

Sensitive phase-specific detection of somatic double TEK mutations in venous malformations using ddPCR

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Purpose: Activating mutations in TEK account for 50% of sporadic venous malformations (VeM) with a subset having two somatic TEK mutations, usually on the same allele ("cis"). Better understanding of the timing and distribution of these double TEK mutations is needed, but this requires sensitive methods that can detect the mutations and determine their allele-specific orientation ("phase"). Our objective was to develop assays to characterize somatic double TEK mutations in tissue and correlate findings with clinical features.

Methods: Lesion and adjacent non-lesion samples from individuals with VeM undergoing surgery were collected. Patients with somatic TEK mutations identified by deep gene sequencing were included for further study. Multiplex droplet digital PCR (ddPCR) assays were designed to detect single and double mutations and to determine their phase.

Results: TEK mutations were identified in 22 individuals. 14 (63%) had a single p.Leu914Phe mutation. Double TEK mutations at p.Tyr897 and either p.Arg915 or p.Arg918 were found in 8 individuals (36%). Multiplex ddPCR assays were developed to screen lesion (N = 15) and non-lesion samples (N = 14) from these 8 individuals. The expected mutation(s) were identified in all lesion samples: 7 double mutation in cis, 3 p.R915/918 mutation alone, and 5 with both double cis and single p.Arg915/918 mutations. Mutations were detected in 50% of non-lesion samples (N= 7/14), which were primarily single p.Arg915/918 mutations (N =5). The p.Tyr897 mutation was never identified alone. All individuals with a p.Leu914Phe mutation had unifocal VeM while 38% (3/8) of double TEK mutant individuals had multifocal malformations.

Conclusion: Double mutations were found in cis at p.Tyr897 and either p.Arg915 or p.Arg918. The presence of the p.Arg915/918 mutation in non-lesion samples and the absence of samples possessing the p.Tyr897 mutation alone suggests that the p.Arg915/918 mutation occurs prior to the p.Tyr897 mutation. Multifocal disease is associated with detection of double TEK mutations.

Development and validation of a novel diagnostic nomogram to diagnose venous malformations from vascular malformations

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Purpose: Accurate diagnosis of venous malformations(VMs) remains difficult. Misdiagnosis carries potential grave implications. We aimed to develop and validate a novel diagnostic nomogram for VMs.

Methods: In total, 572 eligible patients were recruited from 3 centers. Among them, 344 consecutive patients were used in the derivation cohort for the establishment of a diagnostic equation and nomogram; laboratory results, and imaging results were used to derive the diagnostic model and nomogram. 228 consecutive patients were included for two external validation cohorts.

Results: Eight parameters were identified as valuable parameters used for establishing diagnostic equations. The regression model was built based on these variables: lymphocyte level, age, prothrombin

time, activated partial thromboplastin time, thrombin time, fibrinogen level, D-dimer level, and MRI diagnosis of calcification. Accordingly, the nomogram of the above model was developed for clinical practical use. This model displayed good calibration and good discrimination with a C-index of 0.954. A high C-index of 0.945 was reached in the interval validation. The multi-center external validation cohort still gave good discrimination C-indexes of 0.870 and 0.906, respectively.

Conclusion: The derivation and validation cohorts identified and validated one highly accurate and practical diagnostic nomogram for VMs. This diagnostic nomogram can be conveniently used to identify some difficult VMs cases, allowing for decision-making in a clinical setting.

Treatment of venous malformations: from bench to bedside

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Purpose: Venous malformations are a very disabling condition characterized by dilated blood vessels with disrupted vascular wall leading to hemorrhage, infections, and intravascular coagulation. Currently, treatments mainly consist in sclerotherapy, surgery, and symptomatic medication but these options are still insufficient with transient benefit. Specific targeted therapies remain uncharted. The vast majority of patients affected by venous malformations presents either PIK3CA or TEK activating mutation.

Methods: With this knowledge, we generated and characterized the first PIK3CA-mutated inducible mouse model of generalized low-flow vascular malformations that greatly recapitulates patients' phenotype.

Results: We assessed the survival, blood features, histology, and cell pathway activation of these mice with various standard treatments. One of the tested drugs showed outstanding results leading to a pilot to treat human patients with remarkable reduction of vascular malformations and D-dimer levels.

Conclusion: Based on these findings, we demonstrate that this repositioned treatment may be a new promising therapeutic strategy in patients affected by venous malformations.

Clinical Utility of Clinical, Radiologic and Histologic Assessment of Verrucous Venous Malformation
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Purpose: Verrucous venous malformation (VVM) is a rare congenital vascular anomaly that can be difficult to diagnose because it shares similar characteristics with other vascular malformations. Clinical examination, diagnostic imaging and tissue biopsies are important in the assessment of VVM. Our study aims to evaluate the extent of diagnostic concordance between initial clinical assessment and diagnostic imaging with tissue analysis for VVM

Methods: We retrospectively reviewed 26 cases from 2011-2019 at our pediatric hospital with a histopathologic diagnosis of VVM. Patients without clinical evaluation, diagnostic imaging or tissue studies were excluded. Overall, 9 patients (7 males and 2 females) aged 6 months to 17 years were included in the study cohort. Each patient's initial clinical evaluation, imaging and histopathologic studies were assessed for diagnostic concordance.

Results: 78% (7/9) of patients had final clinical diagnosis of VVM that differed from the initial diagnosis after appropriate diagnostic studies were performed. The initial clinical diagnoses included lymphatic malformation, hemangioma and glomuvenous malformation. For 7 cases with ultrasound imaging, 43% (3/7) were correctly diagnosed as VVM by ultrasonography. Furthermore, 67% (6/9) of all patients received a correct diagnosis only after surgical resection and histologic assessment of the lesion.

Conclusion: The study demonstrates diagnostic challenges clinicians face with patients presented with VVM. Our data suggest clinical evaluation alone is not sufficient to diagnose VVM, since the extent of tissue involvement by the lesion may not be fully assessed clinically. Early implementation of tissue biopsy and ultrasound studies may significantly expedite and improve diagnostic accuracy of VVM.

Percutaneous sclerotherapy of large venous malformations (VM) using sequential combination of Aetoxisclerol and bleomycin foam (SCABF): A series of 80 procedures with clinical and MR volumetric assessment.
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Purpose: Evaluation of a sclerosing protocol using SCABF, to both increase effectiveness of sclerotherapy for large/extensive VM and reduce adverse events of bleomycin by decreasing flow within the lesion.

Methods: Forty-five patients were included (mean age 14.5Y, range 1-65). The mean VM volume was calculated on fat-sat T2-weighted MR images. Number of procedures per patient, amount of foam per procedure as well as adverse events were noted. Outcome was evaluated on both post-procedure MR volumetry, as well as on the clinical response. Outcome was considered as good or excellent for volume reduction between 50-70% or above 70% respectively. Comparison between patients with (WPT) or with no previous therapy (NPT) was also assessed.

Results: The mean VM volume was 95.9 +/-206.2 mL on pretherapeutic MR imaging. Eighty sclerotherapies were performed, with a mean of 1.8 procedures per patient. An average of 13.2 +/- 5.3 ml of Aetoxisclerol foam and 6.67 +/- 3.6 mg of bleomycin foam were sequentially injected per procedure. Post-procedure MR volumetry demonstrated good and excellent results after the last sclerosis in 17 (29.8%) and 17 (29.8 %) patients respectively. The number of excellent procedures after the last sclerosis was higher in the NPT (40%) compared to the WPT group (24.3%). Interestingly, despite a volumetric response below 50% in 20 patients, 65% of these patients do not ask for an additional procedure due to almost complete relief of the symptoms, suggesting that part of T2-weighted hyperintensity on post-procedure MR volumetry corresponds, at least partially, to post-sclerotic tissue. Adverse events included flu-like symptoms (26%), focal hyperpigmentation (8.8%), and nausea and vomiting (22%) in the early post-operative course.

Conclusion: In our experience, sclerotherapy using SCABF represents an effective therapy for large or refractory with good or excellent in approximately 60% of our patients after a mean number of 1.8 procedures with minimal side effects.

SAFETY-EFFICACY OF PERCUTANEOUS INJECTION OF CHITOSAN OR CHITOSAN EMBOLIZING AND SCLEROSING GELS IN A TIE2-ASSOCIATED VM XENOGRAFT MOUSE MODEL

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Purpose: To compare the effects of embolization with chitosan hydrogel (CH) with or without a sclerosant (sodium tetradecyl sulphate, STS) versus STS-foam, placebo (saline) and an untreated control group in a murine xenograft model for venous malformation (VM).

Methods: Subcutaneous VMs were generated by injecting HUVEC_TIE2-L914F cells + matrigel into the backs of athymic mice (Day, D0). Once established at D10, solutions were injected through direct VM puncture. 64 lesions were randomly assigned to one of five treatment groups (untreated, n= 8; saline, n=9; 3%STS-foam, n=15; CH, n=15; 1%STS-CH, n=17). To prepare chitosan thermogels, a chitosan-Visipaque320 solution was mixed with a β-glycerophosphate-containing gelling agent; for 1%STS-CH, an appropriate volume of 3%STS (Sotradecol) was added to the gelling agent. To make 3%STS-foam, the Tessari technique was performed. VMs were regularly evaluated for 20 days after intervention. At D30, matrigel plugs were culled and assessed by histological analyses for Ulex europaeus I (UEA1) expression and vessel size measurement.

Results: All lesions were successfully punctured and injected. Skin ulceration occurred on 26 plugs (1 untreated, 10 3%STS-foam, 3 CH and 12 1%STS-CH), leading to the loss of three 3%STS-foam and one 1%STS-CH plug. Both chitosan formulations effectively controlled growth of lesions compared to untreated or 3%STS-foam groups at D30 ($p<0.05$). Vessel sizes were smaller with both CH formulations compared to untreated and saline groups ($p<0.05$). Additionally, there was a trend towards smaller vessels within the 1%STS-CH group vs. the CH group compared to 3%STS-foam ($p<0.05$ and $p=0.0592$, respectively).

Conclusion: CH formulations can be safely injected into lesions developed within matrigel plugs of a VM xenograft mouse model. The ability of CH to control lesion growth suggests a promising therapeutic effect, performing better than the gold standard (STS-foam) on several variables. A long-term follow-up study is needed to evaluate if 1%STS-CH prevents recurrence better than CH alone.

Surgical Resection of Labial Venous Malformations: A Single Center Experience

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Purpose: Venous malformations (VMs) involving the vulva are rare but often very debilitating due to pain and cosmetic concerns. Treatment with sclerotherapy, surgical resection or a combination thereof may be considered. However, the optimal approach to treatment remains unclear with a scarcity of literature on this condition. We report our experience performing surgical resection of labial VMs.

Methods: A retrospective review of patients who underwent partial or complete surgical resection of a labial VM between 1998 and 2021 was performed. Demographics, peri-operative factors, and clinical outcomes were assessed.

Results: Twenty-seven patients underwent 37 surgical resections (partial and complete) over a 23-year period. Three patients had associated syndromes (1 CLOVES, 1 KTS, 1 BRBNS). Considering anatomic distribution, 5 patients had focal labial VMs, 2 patients multifocal labial VMs, and 20 patients extensive VMs. Indications for intervention included pain (n=30), impairment of urinary and/or sexual function (n=4), bleeding (n=5), and cosmesis (n=5). Seventeen patients underwent a single surgical resection, 4 patients underwent multiple partial resections, and 6 patients underwent a combination of sclerotherapy and surgical resection(s), with a median age of 14 years (range 1-33) at first surgical intervention. All patients requiring multiple surgeries had extensive VMs. Median operative time was 126 minutes with a median estimated blood loss of 150mL. Post-operative complications included wound infection/dehiscence (n=3), hematoma managed conservatively (n=1), and UTI (n=1). Of the 19 procedures with postoperative admission, median postoperative length of stay was 1 day. The median follow-up after the most recent intervention was 8 months with 3 patients lost to follow-up. At follow-up, 2 patients were experiencing recurrent discomfort.

Conclusion: Surgical resection offers a safe and effective approach to treating labial VMs. Focal VMs may be resected with a single operation, whereas extensive labial VMs may require multiple interventions to achieve safety and good cosmetic outcomes.

Photo-targeted nanoparticle drug delivery systems for venous malformations

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Purpose: Pharmacotherapy of venous malformations has limited efficacy and potentially limiting toxicity. Drug-loaded, stimulus targeted nanoparticle drug delivery systems have the potential to

accumulate specifically within tissues where vasculature is abnormal, leading to increased drug accumulation in target tissues with less drug accumulation in off-target sites. This approach has the potential to result in increased drug efficacy and decreased toxicity compared to other systemic treatments. Here, we developed nanoparticles that accumulate by photo-triggered targeting. Nanoparticles are decorated with a cell penetrating peptide, which is inactivated by a caging molecule, and will travel throughout the bloodstream in the inactivated state. Upon irradiation with light, the caging group is removed which facilitates nanoparticle accumulation in irradiated tissues. We hypothesize that nanoparticles will accumulate in target tissue by virtue of enhanced permeation and retention and through active photo-triggered nanoparticle targeting.

Methods: We used a mouse model of venous malformations, in which human umbilical vein endothelial cells expressing the most frequent venous malformation causing TIE2 mutation (TIE2-L914F), were injected into immune-deficient mice. 19 nm micellar photo-targeted nanoparticles were synthesized and fluorescently labeled to allow for in vivo tracking. Nanoparticles were characterized, injected systemically, and analyzed for nanoparticle accumulation within venous malformations by in vivo imaging systems.

Results: We demonstrated that intravenously injected, photo-targeted nanoparticles have greater than 10-fold more accumulation within murine venous malformations compared to injection of either nanoparticles without photo-targeting or free fluorophore.

Conclusion: Nanoparticulate drug delivery approaches have the potential to markedly improve drug delivery to target tissues, including venous malformations.

Use of Alpelisib in Extensive Venous Malformations Refractory to Other Therapies

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Purpose: Severe and extensive venous malformations (VM) can lead to significant morbidity including localized intravascular coagulopathy (LIC), bleeding and pain. Symptoms are often progressive and limited treatments exist. We report 5 patients with extensive VMs with notable clinical response after treatment with the oral PIK3CA inhibitor alpelisib.

Methods: A retrospective chart review of 5 patients with extensive VMs with characteristic clinical and imaging findings was performed. Genetic testing was performed in three patients and demonstrated somatic TEK mutations (TEK p.R918C; p.L914F); the other two patients could not have a biopsy performed due to bleeding risk. Patients ranged in age from 6 to 48 years. All patients received multi-modal treatment prior to starting alpelisib, including repeated sclerotherapy, debulking surgeries, and medical therapies including sirolimus without sufficient improvement. Doses of alpelisib varied from 50 to 250 mg daily.

Results: All 5 patients had clinical improvement within 3 months of starting alpelisib. Three patients who required regular red blood cell transfusions became transfusion-independent. LIC improved in all 5 patients, including improvement in fibrinogen and D-dimer levels as well as decrease or discontinuation of anticoagulation. Patients with pain had notable improvement in their symptoms and all patients reported improved quality-of-life. VM lesion size decreased (assessed via clinical measurement or MRI) and lesions became softer and more compressible. Alpelisib was well-tolerated with no grade 3 or 4

adverse events (AEs). AEs included headache (n=2), nausea (n=1), and glucose intolerance (1). None of the patients discontinued the medication due to AEs.

Conclusion: In five patients with extensive VMs, alpelisib resulted in marked clinical response within 3 months of treatment. Alpelisib is a promising systemic treatment for severe VMs, in both TEK-positive cases and in patients unable to have genetic testing performed due to biopsy risk.

Session 5: Combined Vascular Malformations I

Expanded Genetic Landscape in Complex Vascular Anomalies

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Purpose: Comprehensive genomic analyses were performed to aid in molecular diagnosis of patients with complex vascular anomalies.

Methods: 249 individuals were evaluated from our institution's Complex Lymphatic and Comprehensive Vascular Anomaly Centers. Routine exome (~80x), high coverage exome (~500x), amplicon-based ultra-deep coverage targeted sequencing (>50,000x, panel of 35 genes), UMI-based ultra-deep coverage targeted sequencing (~100,000x, panel of 49 genes), blocker displacement qPCR/Sanger assay, and ddPCR were applied to various DNA types isolated from blood, saliva, lesional tissue, lymph node, FFPE, endothelial cells isolated from lymphatic effusions, and cfDNA from plasma and lymphatic fluid.

Results: Germline and somatic pathogenic variants were identified in 34 individuals (34/102, 33.3%) with complex lymphatic anomaly or primary lymphedema. For other diagnoses (e.g., CM, AVM, VM, LM, CLOVES, hemangioma, FAVA, angiokeratoma), the molecular diagnostic yield exceeded 75% when lesional tissues were available (60/79). Interestingly, the variant allele frequency (VAF) of pathogenic somatic variants ranged from 0.2% to 44%. VAF >2% can be detected by deep exome (n = 51), by which we can also identify pathogenic germline variants (e.g. RIT1, GLMN, and FLT4) missed by panel sequencing. Analysis of ultra-deep panels (n = 70) resolved seven difficult cases with VAF ranging from 0.41% to 1.98% (i.e., 4 CCLA, 2 KLA, and 1 FAVA). All germline variants were confirmed by sanger sequencing, and all somatic variants were confirmed using a blocker method or ddPCR.

Conclusion: Our strategy to collect multiple tissues and perform a tiered testing has increased our capability to identify pathogenic somatic mutations and inform clinical diagnosis. When a biopsy of affected tissue was not recommended, endothelial cells enriched from effusions, as part of clinical care, and cfDNA provide promising and less invasive alternatives to resolve the genetic etiology. Our

comprehensive genomic platform with extremely deep sequencing has increased our capacity to discover somatic variants of low VAF (<1%).

NRAS Q61R Mutation in Human Endothelial Cells Causes Vascular Malformations

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Purpose: Somatic mutations in NRAS are known to drive the pathogenesis of melanoma and other cancers but their role in vascular anomalies and specifically human endothelial cells is unclear. The goals of this study were to determine whether the somatic activating NRAS Q61R mutation in human endothelial cells induces abnormal angiogenesis and to develop in vitro and in vivo models.

Methods: Lentiviral constructs were generated with doxycycline regulated NRAS Q61R or NRAS wild type (NRAS WT). Each construct was introduced into human endothelial cells. NRAS Q61R and NRAS WT expressing human endothelial cells were characterized in vitro and in vivo. Changes in endothelial cell morphology, proliferation, migration, and downstream signaling pathways were assessed. Vascular morphogenesis was compared in a 3D in vitro angiogenesis model. A xenograft model was generated by taking NRAS Q61R and NRAS WT human endothelial cells enrobed in Matrigel® and injecting the endothelial cells under the skin of nude mice on a doxycycline-containing diet.

Results: Doxcycline-induced expression of NRAS Q61R in human endothelial cells caused a shift to an abnormal spindle-shaped morphology, increased proliferation, and migration. NRAS Q61R endothelial cells had increased phosphorylation of ERK and S6 compared to NRAS WT cells indicating hyperactivation of MAP kinase and PI3 Kinase/mTOR pathways. NRAS Q61R mutant human endothelial cells generated abnormal enlarged vascular channels in a 3D fibrin gel model and in xenografts in nude mice.

Conclusion: NRAS Q61R can drive abnormal angiogenesis in human endothelial cells. Our in vitro and in vivo models may be used to determine mechanisms and test new therapeutic targets since current medical therapies are limited to use of Sirolimus that is only partially effective.

Endothelial MAP2K1 Mutation Causes Abnormal Vascular Development in Inducible Mouse Strain

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Purpose: Arteriovenous malformation (AVM) is defined by abnormal connections between arteries and veins instead of a normal capillary bed. Extracranial AVM is caused by an activating MAP2K1 mutation in endothelial cells. The downstream events and underlying mechanism that result in AVM are not known. The purpose of this study was to describe how the MAP2K1 mutation alters endothelial cell function.

Methods: ROSA-GT-Map2k1-K57N+/- mice were crossed with Tg(Cdh5-CreER+/-; ROSA-GT-mTmG+/+) mice to produce offspring that would express mutant Map2k1 mRNA in endothelial cells after administration of tamoxifen. 9-day-old mouse brains were dissected and examined for phenotypic changes. Cerebral endothelial cells were isolated using anti-CD31 magnetic Dynabeads (Invitrogen). ddPCR was performed to calculate recombination frequency of the mutant allele. Bulk RNA sequencing was performed, and gene expression was compared using DESeq2. Genes with an adjusted p-value <

0.05 and absolute log2 fold change > 1 were called as differentially expressed genes. Significantly differentially expressed genes were clustered by their gene ontology.

Results: Mutant mouse brains had abnormal vascular development with diffuse punctate vascular lesions. Confocal imaging identified vascular sacculations. The control mouse brain had normal vascular development and lacked these lesions. Mutant allele recombination frequency was 27% in the mutants and 0.1% in the control. Map2k1 expression was higher in mutant endothelial cells (log2FoldChange 2.18). 581 genes were significantly differentially expressed. The gene ontology pathways impacted most were (1) positive regulation of cell migration (GO:0030335) and (2) cell adhesion (GO:0007155).

Conclusion: Expression of mutant Map2k1 in mouse endothelial cells results in abnormal cerebral vascular development. The transcriptome of these mutant cells shows significant changes in pathways affecting cell migration and cell adhesion. This inducible mouse strain is a promising animal model to study how the endothelial MAP2K1 mutation causes AVM and to test pharmacotherapy (MEK inhibitors) to treat AVM.

Integration of mRNA/miRNA sequencing and proteomics to identify novel molecular targets in vascular anomalies

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Purpose: Lymphatic malformation (LMs) are vascular anomalies (VAs) containing endothelial cells (LM-ECs) that harbor somatic DNA mutations, however these mutations are only present in a small fraction of cells. Epigenetic dysregulation of gene expression is a key mediator of multiple cancer pathogeneses, but whether this occurs in LMs is unknown. Here we demonstrate a powerful multi-omics-based approach to profile the expression of all miRNAs and mRNAs in LM-ECs and integrate this data with a simultaneously generated mass spectrometry-based proteomic analysis of all peptides. Comparison to an identically generated profile from normal lymphatic endothelial cells (HDLECs) yields a functional list of potentially altered miRNA-mRNA-peptide triads which may be dysregulated in LMs and may serve as promising molecular targets.

Methods: LM tissue/fluid was collected from patients undergoing surgical treatment. LM-ECs were isolated with magnetic bead capture and cultured and HDLECs served as normal controls. miRNA-seq, mRNA-seq, and phosphoproteomics were performed, and multi-omics data integration analysis was used to generate a network of miRNA-mRNA-protein expression.

Results: Ten patients underwent resection of LM lesions/fluid, and HDLECs were obtained from 3 patients for comparison. Multi-omics analysis detected 2,632 miRNAs, 45,368 mRNAs, and 6,221 proteins. Comparison between LM-ECs and HDLECs yielded 127 differentially expressed miRNAs, 3,468 mRNAs, and 550 proteins. 307 differentially expressed matched mRNA-protein pairs were detected. Functional analysis of the 50 most significantly up or downregulated mRNA-protein pairs demonstrated pathways involved in regulation of lymphangiogenesis, cytoskeleton dynamics, growth/differentiation, migration, proliferation, apoptosis, fatty acid metabolism, and cell-cell adhesion as differentially regulated in LM-ECs.

Conclusion: Employing a multi-omics approach to pathway discovery is a powerful tool in the identification of epigenetic regulation of genes in vascular anomaly endothelial cells, potentially uncovering novel therapeutic targets.

Using spatial transcriptomics in vivo to elucidate pathway alterations in vascular anomalies harboring GNAQ variants

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Purpose: Somatic mosaic mutations in several genes including in the GPCR coupled G-protein subunit GNAQ are associated with vascular anomalies. The downstream molecular changes at the mRNA and protein level resulting from these mutations remain uncertain, resulting in a lack of treatments. Understanding these alterations is imperative for creating targeted interventions for vascular anomalies.

Methods: We utilized a first-of-its-kind, multimodal approach to elucidate pathway alterations. First, we performed high-resolution targeted whole exome sequencing to determine the genotype of affected skin in four pediatric patients. We then coupled genotyping to novel deep clinical phenotyping, including clinical images, colorimetric analysis, optical coherence tomography, and 3D photography. Finally, we optimized an experimental and computational pipeline for 10x Visium spatial transcriptomics to analyze differential gene expression in affected skin compared to anatomically matched normal skin.

Results: High-resolution sequencing primed for low variant allele frequency detection confirmed the most common somatic mosaic variant (GNAQ R183Q) without co-occurring mutations at mean VAF of 4%. Deep clinical phenotyping, including novel OCT imaging, revealed a statistically significant increase in vessel diameter and density in affected skin but not in anatomically matched normal skin. Unbiased spatial transcriptomics was performed with high quality data obtained establishing the utility of this method: the proportion of reads confidently mapped to the genome was ≥ 90% for all samples, total per-sample reads was ~400 to ~625 million, and on average 17,602 genes were detected per sample (out of ~25,000 expected in the human genome) with at least 5 mRNAs. Our results reveal novel and important findings with respect to pathway alterations including in the MAP kinase pathway.

Conclusion: We present comprehensive genotyping, deep clinical phenotyping, and molecular analysis using novel modalities in GNAQ variant vascular anomalies.

GNAQ mutation in the murine endothelium causes aberrant vascular morphogenesis and KMP that are rescued by MEK inhibition

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Proteasome inhibitors effectively inhibit venous and lymphatic malformations

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Purpose: Venous and lymphatic malformations (VMs and LMs) carry postzygotic somatic mutations in malformation endothelial cells (VMECs, LMECs) leading to PI3K/AKT/mTOR hyperactivation. Off-label use of the mTOR inhibitor sirolimus and PI3K inhibitor alpelisib has confirmed the validity of a pharmacological approach. However, treatment response is neither complete nor curative. We hypothesized that a high-throughput screen (HTPS) against VMECs and LMECs carrying PIK3CA mutations would identify novel candidate drugs for the treatment of VMs and LMs.

Methods: VMECs (n=2) and LMECs (n=4) carrying PIK3CA mutations were screened by HTPS using a library of 1,344 drugs at 1uM. Relative viability to controls were determined at 48 hours. Effective inhibitors were compared to sirolimus and alpelisib in a dose response viability assay. VMECs (n=2) and LMECs (n=2) were then subcutaneously implanted into nude mice. Malformations were left to develop before beginning randomized treatment with vehicle or oprozomib, a proteasome inhibitor. Implants were harvested and analyzed. Statistical analysis was performed with one-way ANOVA with posthoc Tukey's HSD and student's t-test.

Results: HTPS identified three proteasome inhibitors (PIs) that significantly suppressed VMEC and LMEC viability when compared to sirolimus and alpelisib: carfilzomib, delanzomib, and ixazomib ($p<0.0001$, ANOVA). At clinically relevant doses, all 6 available PIs significantly inhibited VMEC and LMEC viability in dose response viability assays ($p<0.005$, student's t-test). Oprozomib effectively inhibited VM and LM development in vivo. When compared to controls, oprozomib-treated cohorts resulted in significantly decreased LM lymphatic channel size ($p<0.02$) and decreased VM vascular areas ($p<0.007$).

Conclusion: We identified a novel class of drugs, PIs, that significantly inhibited VMEC and LMEC viability with superior efficacy than sirolimus and alpelisib, in vitro and in vivo. These data demonstrate that PIs may be efficacious in VM and LM treatment. Additional studies are needed to further understand mechanisms of PI efficacy.

Pharmacokinetics of Bleomycin Sclerotherapy in Patients with Vascular Malformations

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Purpose: Bleomycin, a chemotherapy agent that inhibits synthesis of DNA, has been increasingly utilized in sclerotherapy for both adults and children with vascular malformations. A serious long-term risk of intravenous bleomycin is dose-dependent interstitial pneumonitis following systemic administration. However, little is known about absorption and circulating levels of bleomycin when used in sclerotherapy for patients with vascular malformations.

Methods: IRB-approved prospective study on patients receiving bleomycin sclerotherapy in the management of vascular malformations. Depending on the type of vascular malformation, bleomycin was administered either in the lumen or interstitial space of the involved lesion. A bleomycin assay measured serum bleomcyin plasma concentrations vs. time at 7 intervals following treatment. Pharmacokinetic parameters were obtained for each participant and included peak plasma concentration after administration (Cmax), time to reach peak plasma concentration (Tmax), volume of distribution (Vd), elimination half-life (t1/2), the volume of plasma cleared of the drug per unit time (CL), and total systemic exposure (AUC).

Results: Fifteen patients were enrolled (5 lymphatic, 4 venous, and 6 arteriovenous malformations). Bleomycin was administered interstitially (IS) in 11 patients and intraluminal (IL) in 4. Median age of 13 years (range 2-67). Pharmacokinetic analysis revealed terminal elimination half-life ($t1/2\lambda z$) of 88.51 (± 23.09) and 111.61 (± 37.75) min for the IS and IL groups, respectively. The volume of distribution (Vd) was 4.86 (± 6.74) and 1.55 (± 0.54) L for the IS and IL groups, respectively. The area under the curve (AUC) was 53.9 (± 23.45) and 129.17 (± 93.57) mg*min/L for the IS and IL groups, respectively. There

were no statistically significant differences in t1/2λz, Vd, or AUC parameters between the IL and IS groups. However, the total volume of distribution (Vd,) for our study was 3.44L.

Conclusion: Bleomycin is absorbed systemically when used as a scleroscant for vascular malformations when injected either interstitially or intraluminal.

Session 6: Arteriovenous Malformations

Genotyping and clinical course in 100 patients with arteriovenous malformations.

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Purpose: Arteriovenous malformations (AVMs) are congenital high flow vascular anomalies that can arise sporadically or as a part of hereditary syndromes. They are caused by germline or somatic alterations in different genes, most of them discovered in recent years. Herein we provide new genetic findings and genotype-clinical course correlation in AVMs.

Methods: We have retrospectively reviewed the phenotype, clinical course, and treatment in a cohort of 100 patients with AVMs. Genetic study was performed on the affected tissue sample from all the patients tested by high throughput sequencing (custom designs panel and whole exome sequencing).

Results: Patients were classified according to phenotype into isolated AVMs (69%), including intramuscular fast-flow vascular anomalies and sporadic lesions, and syndromic forms (31%) including CM-AVM (type 1 and 2), PTEN-hamartoma tumor syndrome (PHTS) and Parkes Weber syndrome (PWS). Pathogenic variants were detected in 67% (67/100) patients in genes described in AVMs: MAP2K1 (22%), KRAS (17%), HRAS (1%), RASA1 (9%), EPHB4 (2%), BRAF (4%), PTEN (3%); and in not previously associated genes: PIK3CA (9%), FGFR3 (2%), GJC2 (1%), GNAQ (3%), GNA14 (1%). In 7 out of 9 cases with a pathogenic variant in PIK3CA, a concomitant pathogenic variant in MAP2K1, KRAS, PTEN, or RASA1 genes was also detected, suggesting a digenic mechanism. Somatic pathogenic variants in KRAS, BRAF and MAP2K1 showed a more aggressive progression of lesions, requiring multiple surgeries and/or amputation, whereas AVMs with germline pathogenic variants in RASA1, showed a milder course without requiring surgical intervention.

Conclusion: We have detected a correlation between the gene affected and the aggressiveness of the lesions. We have also detected pathogenic variants in genes not previously described in AVMs. The presence of concomitant pathogenic variants in two different genes could be showing a mechanism of cumulative defects, which has implications for the genetic diagnosis and for targeted drug treatments.

Somatic Mutational Landscape of Extracranial Arteriovenous Malformations and Phenotypic Correlations

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Purpose: Somatic genetic variants may be the cause of extracranial arteriovenous malformations, but few studies have explored these genetic anomalies, and no genotype–phenotype correlations have been identified.

Methods: This study included twenty-three patients with extracranial arteriovenous malformations that were confirmed clinically and treated by surgical resection, and for whom frozen tissue samples were available. Targeted next-generation sequencing analysis was performed using a gene panel that included vascular disease–related genes and tumor-related genes.

Results: Twenty-three patients (15 males and 8 females) were included in this study. The mean age was 35 years old (min: 9 years old; max: 65 years old). We identified a pathogenic variant in 17 out of 23 samples (73.9%). Pathogenic variants were mainly located in MAP2K1 (n=7) and KRAS (n=6), and more rarely in BRAF (n=2) and RASA1 (n=2). KRAS variants were significantly ($p<0.005$) associated with severe extended facial arteriovenous malformations, for which relapse after surgical resection is frequently observed, while MAP2K1 variants were significantly ($p<0.005$) associated with less severe, limited arteriovenous malformations located on the lips.

Conclusion: Our study highlights a high prevalence of pathogenic somatic variants, predominantly in MAP2K1 and KRAS, in extracranial arteriovenous malformations. In addition, our study identifies for the first time a correlation between the genotype, clinical severity and angiographic characteristics of extracranial arteriovenous malformations. The RAS/MAPK variants identified in this study are known to be associated with malignant tumors for which targeted therapies have already been developed. Thus, identification of these somatic variants could lead to new therapeutic options to improve the management of patients with extracranial arteriovenous malformations.

Somatic SOS1 Variants Associated with Extracranial Arteriovenous Malformation

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Purpose: Arteriovenous malformation (AVM) is a fast-flow vascular anomaly characterized by abnormal arterial to venous circulatory shunts resulting in tissue ischemia, ulceration, and bleeding. Most extracranial AVMs harbor a somatic mutation in MAP2K1, but some AVMs do not have an identifiable variant. Here we report additional somatic perturbations in the SOS1 gene in two patients with complex, extracranial AVMs.

Methods: Two patients with extracranial AVMs had affected tissue collected during a clinically-indicated procedure. Genomic DNA was extracted and targeted next-generation sequencing (NGS) was performed. The coding regions of 447 genes implicates in cancer were captured and sequenced. A candidate somatic mosaic mutation was confirmed with molecular cloning and Sanger sequencing following re-extraction of DNA from additional banked tissue.

Results: Patient 1 is a 21 year-old male with an extensive AVM involving the right pelvis, gluteal region, and lower extremity associated with penile and scrotal lymphedema. Patient 2 is a 15 year-old male with an AVM of his right cheek and jaw. Neither patient had clinical features of Noonan syndrome (ie. short stature, congenital heart defects, cryptorchidism, or craniofacial abnormalities). Sequencing coverage averaged 179x and 312x for patient's 1 and 2 respectively. Two in-frame insertion–deletion mutations in exon 10 of SOS1 were identified: c.1465_1466ins39, p.R489delinsLKEKFLRKVLKKKS for patient 1 with a variant allele frequency (VAF) of 10.0%; and c.1306delins46, p.N436delins16 for patient 2 with a VAF of

5.6%. The SOS1 mutation for patient 1 was confirmed after re-extracting fresh genomic DNA with molecular cloning and Sanger sequencing.

Conclusion: SOS1 encodes a guanine nucleotide exchange factor for RAS proteins and promotes RAS activation. SOS1 mutations are implicated in a variety of disorders including RASopathies such as Noonan syndrome. We report somatic mosaic variants in SOS1 associated with extracranial AVM. Our report expands the genotypic landscape of AVM and may have important implications for treatment of this disorder.

Activating MAP2K1 Mutation in Zebrafish Endothelial Cells Causes Arteriovenous Shunts

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Purpose: Arteriovenous malformation (AVM) is a sporadic vascular malformation defined by a nidus of irregular blood vessels connecting arteries to veins instead of a normal capillary bed. Somatic activating mutations in MAP2K1 cause extracranial AVM. The purpose of this study was to create an AVM animal model using zebrafish.

Methods: Single-cell stage casper;Tg(gata1:dsred) zebrafish embryos were injected with 1 nL of transgenesis mixture: 100 ng/µL of either (1) Control (pTol2-Fli:GFP) or (2) Mutant (pTol2-Fli:GFP-kdrl:MAP2K1K57N) plasmid DNA + 40 ng/µL Tol2 transposase mRNA. Erythrocytes in these fish express the fluorescent protein dsRed. Embryos were anesthetized with 0.4 mg/mL Tricaine, embedded in 1% low-melt agarose (Biotech) and then imaged using a Zeiss LSM 800 Confocal Microscope or a Nikon SMZ18 Fluorescence Microscope. Confocal images were obtained using Zen Blue version 2.5. Embryos were imaged 72 hours post-fertilization. Blood flow was visualized using dsRed fluorescence.

Results: Injection of MAP2K1K57N plasmid resulted in abnormal arteriovenous shunts (58/96 transgenic embryos, 60%). The phenotype consisted of either (1) a proximal shunt with blood flowing through a direct connection between proximal aortic vessels to the common cardinal vein and immediately back into the heart (39/58 embryos, 67%) or (2) a mid-trunk shunt between the dorsal artery and posterior cardinal vein (19/58 embryos, 33%). Shunts were not present in control zebrafish (n=65). Endothelial cells at the site of the shunt expressed high levels of the marker transgene confirming shunts contained mutant endothelial cells.

Conclusion: Zebrafish endothelial cells expressing mutant MAP2K1 form abnormal arteriovenous shunts. The phenotype recapitulates extracranial human AVM. Mutant MAP2K1 zebrafish are a promising animal model for testing pharmacotherapy to treat AVM.

Atypical arterio-venous malformations: different disease?

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Purpose: AVMs clinically present with skin discoloration, thrill, bruit and bleeding. On Ultrasound they appear as an agglomeration of tortuous vessels, with multidirectional blood flow. On MRI the classical feature is multiple and tangling flow voids.

Rarely though, they may show a relative paucity of vessels and a detectable mass effect which makes diagnosis much less straightforward. We called these "atypical" AVMs.

Methods: We retrospectively analyzed all the cases of Extracranial Head and Neck AVMs that we treated at our institution between 2008 and 2021. Demographic, clinical pictures, imaging (US and MRI) and histologic data were retrospectively collected. Type of treatment and relapse rates were also assessed.

Results: Among 120 Extracranial Head and Neck AVMs treated between 2008 and 2021, 10 cases of atypical AVMs were found. All AVMs were contained within muscular fasciae. Clinically, these AVMs appeared as stiff, mildly compressible, pulsating swelling. On US they presented as hyperechogenic masses with distinct margins and interspersed high flow - low resistance vessels. On MRI all AVMs showed a mass effect with Isointense signal on T1w and Hyperintense signal on T2w sequences. Tortuous vessels were visible as tangling flow voids. However, as compared to "regular" AVMs, "Atypical" ones had a relative paucity and size of the vessels. Histologically, groups of disorganized arteries and veins were present. However, their size was smaller as compared to "typical" AVMs. The lesions were all intramuscular. The muscle fibers immediately surrounding the vessels were smaller and inhomogeneous in their architecture. Conversely, the muscle fibers located far from the lesion appeared normal. All atypical AVMs were surgically removed and no relapses were detected at follow up (average FU: 43 months).

Conclusion: Diagnosing an AVM is usually straightforward. However, the here reported "atypical" AVMs can be trickier to identify. After surgery, their prognosis seems to be more favorable.

Ethanol embolization combined or not with surgery and close clinical follow-up can effectively control extracranial arterio-venous malformations

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Purpose: Arteriovenous malformations (AVM) are congenital high flow lesions that have a wide range of clinical manifestations, varying from asymptomatic to high-output heart failure. We looked at the long-term outcome of patients with extra-cranial AVMs following different types of treatment.

Methods: We performed a retrospective study, collecting data on all cases of proven extracranial AVMs at two university hospitals from 1985 to 2021. We documented whether the patient received conservative, endovascular, surgical, or combined treatments. The clinical response of treatments was assessed using the Schobinger's classification. Our primary endpoint was to evaluate the evolution of Schobinger stage. Our secondary endpoints included complication and clinical recurrence rates after intervention.

Results: 190 proven cases of extracranial AVMs were included in the study. Mean follow up time was 7.0 years [0.0-28.0 years]. The mean Schobinger stage was 2.11 at baseline and 1.32 at final follow-up ($p<0.001$). For the cohort, 52 patients were treated conservatively, 104 patients received endovascular treatment alone, 3 patients received surgical treatment alone, and 31 patients received combined therapy. Overall, 71 patients (37%) achieved complete remission, 34 patients (18%) achieved improvement of symptoms, 81 patients (42%) remained stable, and 4 patients (2%) worsened. No clinical worsening was observed in the 52 patients (Schobinger stage 1-2) that did not receive any

endovascular or surgical treatment. Major complications were observed in 7 patients (4%), leading to death in 2 cases- one from procedural complications and one from post-procedure nosocomial infection.

Conclusion: Ethanol embolization with or without surgery is safe and efficient for long-term control of extracranial AVMs. We observed that not all patients evolve from Schobinger stage 1-2 to a further stage, and clinical observation without treatment can be suitable and appropriate for asymptomatic patients.

Trans-ophthalmic arterial ethanol embolotherapy for arteriovenous malformations: A single center experience

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Purpose: Arteriovenous malformations (AVMs) which are mainly derived from ophthalmic artery (OphA) branches are not common, however, their clinical management is very challenging. We aimed at evaluating the safety and efficacy of Trans OphA ethanol embolotherapy for these lesions.

Methods: We retrospectively reviewed 26 patients with AVMs fed by OphA, who underwent transOphA embolization using ethanol from February 2015 to December 2019. Sixty-six transOphA embolotherapy procedures (range, 1-4 procedures; mean, 2.5 procedures) were performed. Degree of devascularization, visual field, visual acuity, and quality-of-life outcomes was compared and analyzed at follow-ups (mean, 32.6 months; range month 10-60). Complications were recorded.

Results: Twenty of the 26 patients (77%) reported complete or >90% AVM devascularization while six patients (23%) showed >70% devascularization. Eleven patients (42%) presented with visual acuity impairments with 3 being completely relieved, 6 showing some improvements. Eight patients (42%) presented visual field defects with 4 being completely relieved, 3 showed some improvements while there was no change in one patient. Ten patients (38.4%) presented with diplopia and exophthalmos with 2 being completely relieved, 6 showed major improvements while 2 showed minor improvements. Twelve patients experienced bleeding, which was controlled in all cases (100%). The pain was resolved in 6 patients (23%) while one patient (4%) was significantly improved. All patients (100%) exhibited cosmetic deformities with 17 being completely relieved. Moreover, all patients (100%) exhibited impaired daily life, which was resolved in 21 patients with 5 patients reporting major improvements. Three had a transitory blurry vision which resolved completely 24 hours after embolization. No vision loss, death, or permanent disability in all patients.

Conclusion: TransOphA ethanol embolotherapy was found to be efficacious, safe and it achieved symptomatic resolution or improvement of AVMs fed by OphA with acceptable complications without the risk of visual impairment.

Thalidomide Therapy in Severe Arteriovenous Malformations

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Purpose: Arteriovenous malformations (AVMs) are destructive fast-flow lesions and the most difficult to treat vascular anomalies. Embolization followed by surgical resection is commonly used; however, complete resection is rarely possible and partial resection often leads to dramatic worsening. Accumulating data implicate abnormal angiogenic activity and hyperactivation of the RAS-MAPK signaling pathway in AVMs development. Thalidomide, an inhibitor of vascular proliferation, was tested in management of AVMs.

Methods: We conducted a prospective experimental observational study in 18 patients with a severely symptomatic AVM refractory to conventional therapies. Thalidomide was given 50 to 200 mg/day for 2 to 52 months.

Results: All patients experienced rapid reduction of pain (VAS from 6-10 to 0-5) (18/18), cessation of bleeding (11/11), and healing of ulcers (6/6). Cardiac failure resolved in all three affected patients. Reduced vascularity on arteriography was observed in two patients. One AVM appeared cured after 19 months of thalidomide and an 8-year follow-up. Eight AVMs were stable after a mean thalidomide cessation of 58 months, and four lesions recurred after 11.5 months. Combined treatment with embolization permitted dose reduction (50 mg/day) in 5 patients with clinical improvement. Five patients continued low dose thalidomide. Grade 3 side-effects were dose-dependent including asthenia (n=2), and erythroderma (n=2).

Conclusion: Thalidomide is efficacious in the management of chronic pain, bleeding, and ulceration of extensive AVMs recalcitrant to conventional therapy.

Trametinib as a Promising Therapeutic Option in Alleviating Vascular Defects in an Endothelial KRAS-Induced Mouse Model

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Purpose: Somatic activating KRAS mutations have been reported in patients with arteriovenous malformations. We aimed to generate a murine model of KRAS-induced vascular lesions for preclinical therapeutic trials.

Methods: We activated KRAS within vascular endothelial cells (ECs) by breeding LSL-Kras(G12D);Cdh5(PAC)-CreERT2 [iEC-Kras(G12D)] mice. Neonatal mice were induced(*) via daily intragastric injections of tamoxifen during postnatal days (PN) 1-3. For drug treatment, lactating dames were given 1 daily dose of 2 mg/kg trametinib or vehicle via oral gavage for 5 days, beginning from pups aged PN8. Pups were euthanized at PN14 or 16 and the brain, heart, liver, and intestines were removed for immunohistology. Images were acquired using a Mirax Midi slide scanner or a Zeiss confocal microscope and analyzed with ImageJ. JMP Pro was used for statistical analyses: a student t-test for Comparison between two groups, a one-way ANOVA for >2 groups, and a Kruskal-Wallis Test when a nonparametric comparison was needed. A $p<0.05$ was considered significant.

Results: Mortality and phenotypes varied amongst the pups, with only 31.5% surviving at PN14. Phenotypes (focal lesions, vessel dilations) developed in a consistent manner, although with unpredictable severity within multiple soft tissues (ex. brain, liver, heart). Overall, the pups developed significantly larger vessel sizes, compared to control littermates. We subsequently tested whether the MEK inhibitor trametinib could alleviate lesion progression. Survival of the pups improved to 76.9% at PN14, and the average vessel sizes were closer to controls than in un- and vehicle-treated mutants at PN16.

Conclusion: Trametinib had variable efficacy in treating lesions in our iEC-Kras(G12D*) model. Significant improvement was seen in cerebral vessels; however, no significant differences were seen within the liver amongst treatment groups. Even if the vascular defects were not completely resolved, the enhanced life span demonstrates a positive effect for trametinib and its possible role in the therapy for KRAS-induced VMs in patients.

Monocentric Pilot Trial evaluating the safety and efficacy of Trametinib in Arterio-Venous Malformations that are refractory to standard care

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Purpose: The Mitogen Activated Protein Kinase (MAPK) pathway plays a key role in cell growth, proliferation and survival. Excessive activation of this pathway is observed in a significant proportion of patients with Arteriovenous malformations (AVMs). Trametinib is an oral MEK inhibitor, which targets

the MAPK pathway. The aim of this trial was to evaluate safety and efficacy of trametinib in adult AVM patients affected with extensive stage III AVM refractory to conventional treatment.

Methods: Ten adult patients received trametinib daily for a planned treatment duration of 1 year (EudraCT: 2019-003573-26). They were followed clinically every month for the first three months and then every three months. Biological analysis and radiological imaging were done every six months.

Results: The ten AVM patients had facial (8), auricular (1) or foot AVM (1). They all experienced deformation with either severe pain (n=7), bleeding (n=2) and/or ulceration (n=1). Trametinib was first given at 2mg daily in 2 patients but resulted in grade 3 cutaneous rash after 15 days despite daily minocycline prevention and resulted in trametinib interruption despite a clinical benefit. For the 8 following patients, a starting dose of trametinib at 0.5 mg was used and progressively increased, in association with minocycline +/- isotretinoic acid. Six of the eight presented a grade 2 (n=5) and 3 (n=1) cutaneous toxicity. With a median follow-up of 9 months (6-12 months), 90% of patients (n=9/10) had a clinical/radiological benefit on trametinib: decrease in pain intensity (n=6/7), resolution of ulceration (n=1/1), cessation of bleeding (n=1/2). In six patients the AVM volume decreased clinically. Clinical response was observed within the two first months of treatment.

Conclusion: Inhibition of MAPK pathway seems promising for AVM management. Cutaneous toxicity is a major complication that is problematic and can be difficult to manage, even with tretinoic acid.

MEK inhibition for treatment of vascular malformations in patients with RAS-MAPK pathway upregulation

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Purpose: Vascular malformations (VM) cause severe morbidity and mortality. Previously, our group used continuous cycle trametinib, a MEK1/2 inhibitor, to successfully treat the significant symptomology associated with complex lymphatic anomalies (CLA) in individuals with activating RAS pathway mutations (Li et al 2018, Foster et al 2020, Dori et al 2020), but no clinical trials have been performed. Therefore, we reviewed our clinical experience to evaluate the safety and efficacy of MEK inhibition for VMs.

Methods: We performed a retrospective cohort study of patients with VMs treated with MEK inhibition including an update of our previously reported patients. Responses were identified as significant response (SR; normalization of presenting primary signs or symptoms), partial response (PR), stable disease (SD), and progressive disease (PD).

Results: Four male and six female patients, 9 months to 30 years of age were dosed with trametinib from 0.006 to 0.03 mg/kg/day (maximum 2 mg). Eight patients had germline or mosaic rasopathies, one patient had EPHB4-related lymphatic disorder. Six patients with central conducting lymphatic anomaly (CCLA), two with primary phenotype of kaposiform lymphangiomatosis (KLA), and two patients with arteriovenous malformations (AVMs). Six patients were previously treated with sirolimus and all treated with a variety of procedures. Both patients with KLA had SR. One patient with AVM had SR and one had PR. Of the six patients with CCLA, one had SR, three had PR, one each had SD and PD. Adverse effects included pneumatosis, panniculitis, paronychia, and elevated creatinine phosphokinase. No

patients had cardiac or ophthalmologic toxicity. One patient, with pneumatosis, discontinued treatment.

Conclusion: Patients with KLA and patients with CCLA had mixed responses. Limitations include the small study size, retrospective study, and confounding effect of prior surgical/interventional procedures. These results encourage future clinical trials to systematically evaluate MEK inhibition for VMs.

Session 7: Multidisciplinary Studies in Vascular Anomalies I

Assessing the Diagnosis of a Vascular Birthmark, Anomaly, and/or Related Syndrome (VBARS) on the Family

Linda Rozell-Shannon (Vascular Birthmarks Foundation)

Purpose: The Vascular Birthmarks Foundation (VBF) conducted a study in 2019 to assess how the diagnosis of a family member with a VBARS affected the family.

Methods: Survey Monkey was used with a self-reporting mixed-methods qualitative/quantitative instrument.

Results: Of the 112 participants who completed the study, 79% noted that the diagnosis had a negative impact, 7% stated that it had no effect; another 7% stated that it made the family "stronger" and the remaining 7% said it encouraged them to raise awareness. Some of the negative impact responses noted when asked to elaborate, included the following direct comments: I won't be able to go back to work. I have to take care of my son's SWS. My newborn baby was diagnosed a month ago. It has taken away the joy of having a newborn. I cried after seeing my baby with a birthmark. I worry every day about her being bullied. It was devastating, at first, but we are closer because of it. A lot of doctors' appointments and sleepless nights due to medication. Financially, it has ruined us. It has made us more aware of differences in other. I was devastated. 18 years later, I'm still angry my child has this. The misinformation was more stressful than the diagnosis. Constant fear of the birthmark returning. My husband and I fight over this all the time. He doesn't want treatment for our son's PWS. I don't think we will last.

Conclusion: VBF recommends that VBARS physicians suggest that the families contact established support groups so that they can experience a sense of community. We also recommend that VA multidisciplinary centers, as well as treatment specialists, include a recommendation for a related support network and/or a mental health provider to help the affected families to navigate these difficult times.

Expansion of Multidisciplinary Vascular Anomalies Center Telehealth Services

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Purpose: Due to increased programmatic growth and an enlarging multi-state catchment area, the Vascular Anomalies Center aimed to offload clinic volumes and streamline long-distance patient care. We hypothesized that expanded access outside of clinic hours with telehealth services would increase quantity and quality of patient communication and prevent delays in care.

Methods: The Division of Pediatric Surgery sponsored licensure for the Vascular Anomalies Center (VAC) Advanced Practice Registered Nurse (APRN) in the five states adjacent to Colorado. VAC clinic and

telehealth volumes were followed from 2016 to 2021 using the electronic medical record search tool Epic Slicer Dicer. Visit data was organized by location, year, and type of visit (new patient, follow up visit, or acute complaint).

Results: Patient encounters per year increased by almost 200% from 357 encounters in 2016 to a projected year end volume of 1040 encounters in 2021 (Figure 1). Telehealth encounters per year increase from 3 encounters in 2019 to 118 encounters in 2021 (Figure 2). Within the 2021 telehealth encounters, 33% (39 of 118 patients) were new patients, 58% (69 of 118) were follow up visits, and 8% (10 of 118) were acute complaints (Table 1).

Conclusion: Expansion of telehealth encounters has been critical to manage the rapid growth demonstrated in our VAC clinic. Telehealth encounters have been increasingly utilized for intake and triage of new patients, routine follow-up including medication monitoring and review of imaging results, and evaluation and triage of acute complaints. Multidisciplinary management has been preserved through weekly team patient-review meetings. Without expanded use of telehealth, we predict wait times for in-person visits would have increased from weeks to months depending on the distance from our center. Parent and patient feedback has been unanimously positive in support of telehealth to help quality of communication and expedite implementation of care plans

Assessing Quality of Life in Patients with Vascular Malformations

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Purpose: Evaluate self-reported quality-of-life metrics in patients with vascular malformations (VMs).

Methods: The PedsQLTM Measurement Model was utilized to measure health-related quality of life (HRQOL) in patients diagnosed with VMs between January 2020 and September 2021. Questionnaires are designed to evaluate physical, emotional, social, and school functioning and were scored on a scale from 0 to 100, with higher scores indicting better HRQOL. Differences in quality-of-life outcomes based on age, type of malformation, sex, and location of malformation were evaluated.

Results: Fifty-five patients completed developmentally appropriate PedsQLTM questionnaires during the study period. Mean age was 18.1 years (range: 6 to 47 years) and a majority were female (60%). The most common type of VM was venous malformation (32.7%), followed by arteriovenous malformation (20.0%) and Klippel-Trenaunay Syndrome (16.4%). Primary location of VMs included 28 (50.9%) lower extremity, 11 (20.0%) upper extremity, 7 (12.7%) head/neck, 7 (12.7%) chest/back, and 2 (3.6%) abdomen/retroperitoneum. Overall, physical functioning had the lowest score (72.9), followed by school functioning (73.3), emotional functioning (76.5), and social functioning (85.4). There was a statistically significant difference in mean physical functioning scores between age groups with young children (5-7 years) scoring the highest at 93.8 and adults (26+) scoring the lowest at 53.4 (p=0.009). Males scored lowest in school functioning (74.4), while females scored lowest in physical functioning (70.5). There was no significant difference between groups based on sex, type of VM, or primary VM location.

Conclusion: Patients with VMs appear to by most impacted by physical and school functioning and less impacted by social functioning. Differences in physical functioning scores were observed between age groups. Further studies should focus on quality of life based on type of treatment.

Clinical characteristics associated with pain in patients with peripheral vascular malformations.

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Purpose: The aim of this study was to investigate risk factors associated with pain in patients with peripheral vascular malformations (VMs) and to assess how pain affects quality of life.

Methods: Between June and December 2020, all adults and children (n=523) from our local database with peripheral VMs were invited to complete the Outcome Measures for VAscular MAlformations (OVAMA) questionnaire to evaluate the presence, frequency, and intensity of pain. Additionally, patients completed several Patient-Reported Outcome Measurement Information System (PROMIS) scales to evaluate their quality of life. Risk factors associated with pain were identified in bivariate analysis and multivariable logistic regression. Quality of life domains were compared between patients who experienced pain and patients who did not.

Results: 164 patients (31%) completed the questionnaires, half of the patients (52%) reported pain in the past four weeks and 57% of these patients reported pain daily or several times a week. Female gender ($p=0.009$), lesions located in the upper extremity ($p<0.001$) or lower extremity ($p<0.001$), and intramuscular/intraosseous lesions ($p=0.004$) were independently associated with pain. The following quality of life domains were diminished in patients who experienced pain in comparison to patients who did not: pain interference($p<0.001$), physical functioning($p<0.001$), and social participation($p<0.001$) in adults, and pain interference($p=0.001$), mobility($p=0.001$), and anxiety($p=0.024$) in children.

Conclusion: Pain is a frequently reported complaint in patients with VMs and is present in approximately half of the patients. Patients with lesions located in the upper or lower extremity, intramuscular/intraosseous lesions, and female patients are more likely to experience pain. The presence of pain negatively impacted patients' quality of life. Although VMs are a benign condition and expectative management is frequently applied, our study shows that pain is a serious concern and needs to be actively assessed. Pain is a sign of various etiologies, which should be examined in order to properly treat the pain.

Responsiveness of the Patient-Reported Outcome measure for Vascular Malformation (PROVAM) Questionnaire in patients with low-flow vascular malformations

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Purpose: To assess the responsiveness of the Patient-Reported Outcome Measure for Vascular Malformation (PROVAM) questionnaire to changes in health-related quality of life of patients with low-flow vascular malformations.

Methods: We previously developed and validated PROVAM, a 30-item instrument which assesses pain (50 points), impact on emotional/social wellbeing (25 points), and impact on function (25 points), for a total possible score of 100, with higher scores indicating higher severity. From July 2019 to November 2021, 42 patients with low-flow vascular malformations completed at least two PROVAM questionnaires at different timepoints. Of these, 34 underwent treatment between questionnaires. The primary outcome was instrument responsiveness, assessed by analyzing the differences between pre- and post-procedure PROVAM scores for the 34 patients who underwent treatment using Wilcoxon-signed rank test. Instrument responsiveness was further evaluated using clinic notes for all 42 patients, with symptom change translated into a 7-point score, ranging from “markedly worsened” to “markedly improved.” The correlation between change in total PROVAM score and change in symptom score was determined.

Results: There was a statistically significant, strong positive correlation between change in total PROVAM score and change in patient symptoms as determined from clinical visits, $r_s = 0.74$, $p < 0.001$. Of the 34 patients who underwent treatment with sclerotherapy, 30 (88%) experienced a post-treatment decrease in total PROVAM score, while 4 (12%) experienced an increase. Total PROVAM score decreased significantly from before to after treatment (median -13.5 points; $p < 0.001$). Sub-scale analysis also showed a significant decrease in the scores for pain (median -9.0; $p < 0.001$), impact on social/emotional wellbeing (median -2.5; $p=0.009$), and impact on function (median -2.5; $p=0.004$).

Conclusion: The PROVAM questionnaire is responsive to clinical improvement and may be useful to assess health-related quality of life in patients treated for vascular malformations.

Utility of Germline Genetic Testing for Neurovascular Anomalies in Pediatrics

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Purpose: Pediatric neurovascular anomalies are usually diagnosed after an acute event, often with devastating consequences. When appropriate genetic testing reveals an alteration for the patient, family members benefit from screening potentially preventing acute neurological events. We evaluated the positive yield of our genetic germline testing for pediatric patients presenting with cerebral arteriovenous malformations (AVM), cerebral cavernous malformations (CCM), or macrocephaly.

Methods: Pediatric patients with neurovascular anomalies were discussed in the multidisciplinary neurovascular clinic and offered germline genetic testing. If a pathogenic mutation is identified, family members are offered testing as well. Between Jan 2019 and Nov 2021 seventy-nine samples were submitted. Patients presenting with cerebral AVM are tested for Hereditary Hemorrhagic Telangiectasia (HHT) or Rasa1-EPHB4; cerebral cavernomas, for Cerebral Cavernous Malformation panel (CCM); and macrocephalic patients, PTEN.

Results: From a total of 79 samples, 56 (71%) were for new patients and 23 (29%) were familial testing after an index case returned positive. From the de novo cases, 26 (46%) were submitted for HHT panel, 19 (34%) for CCM panel, 4 (7%) for PTEN, 7 (13%) for Rasa1-EPHB4. Fifteen patients were identified to

have pathogenic genetic alterations and six to have variants of unknown significance (VUS) that in the clinical context were deemed to be pathogenic. In total twenty-one samples (26.5%) identified actionable mutations leading to screening interventions. None of the patients or family members had been tested or undergone preventative surveillance previously. One VUS was found in ENG, 3 in GDF2 (2 from the same family), and 2 in SMAD4 (both from the same family).

Conclusion: Genetic testing resulted in a high number of positive results. A structured multidisciplinary center with coordinated approach for all patients presenting with neurovascular anomalies helps identify and provide early screening and treatment in a high number of patients.

Multimodal Treatment for Fibroadipose Vascular Anomaly: Single-Institution Experience of 106 Cases

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Purpose: Fibroadipose vascular anomaly (FAVA) is a rare, complex vascular malformation characterized clinically by pain, contracture, swelling, and functional limitation of the affected limb. Treatments for FAVA include sclerotherapy, cryoablation, surgical resection, and medical therapy, but limited data exists on the relative use of these therapies and patient response. Outcomes data for FAVA are limited by the rarity of the diagnosis and paucity of large, high-quality studies. The purpose of this study is to describe the clinical characteristics, treatment approach, and clinical response of patients with FAVA.

Methods: A single-institution, IRB-approved retrospective chart review of patients diagnosed with FAVA was performed. All cases had histopathologic confirmation of FAVA. Demographics, presenting features, treatment modalities, and clinical response were evaluated.

Results: A total of 106 patients were evaluated. Female to male ratio was 3:1; median age at symptom onset was 10 years; median time from symptom onset to FAVA diagnosis was 4 years. Presenting symptoms included pain (94%), functional limitation (25%), swelling (13%), and joint contracture (9%). Most FAVA (92%) involved the lower extremities: calf (37%), thigh (31%), ankle (9%), foot (7%), knee (6%), and buttock (3%). Upper extremity involvement included the arm (14%) and hand/wrist (5%). Partial or full surgical resection (88%), sclerotherapy (56%), and cryotherapy (29%) were the most frequent treatment modalities. Twelve patients received medical therapy with an mTOR inhibitor; nine had a partial response. Sixty percent of patients received multimodal treatment; 41% of patients had persistent pain after multimodal therapy. Neural invasion (p=0.0029), contracture at presentation (p=0.014), and multifocal disease (p=0.0013) were associated with persistence of pain after treatment.

Conclusion: A combination of surgical, interventional, and medical therapies are used to treat FAVA. Despite multimodal treatment, many FAVA patients have persistence of pain. Further investigation into the mechanism of disease and exploration of therapeutic targets are needed.

How "Academic" is ISSVA? Characterization of the Conversion of Meeting Presentation to Publication from the 2016 and 2018 ISSVA Workshops

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Purpose: Presentations at scientific conferences and subsequent publications play a critical role in a specialty's advancement. Previous estimates suggest that about half of the content presented at

conferences is not published. The objective of this study is to characterize the conversion from meeting presentations to publications from the 2016 and 2018 International Society for the Study of Vascular Anomalies (ISSVA) Workshops.

Methods: The PubMed interface (MEDLINE) and Google Scholar were used to search for abstracts that were presented at the 2016 and 2018 ISSVA Workshops. Excluded presentations included keynotes, research letters, and education-related theses. Parameters reviewed included conversion rate, time to publication, senior author subspecialty, study design and level of evidence, journal name and 5-year impact factor. Data collection occurred between September 8 and October 30, 2021.

Results: 40.43% (226/559) of searched conference abstracts were published in peer-reviewed journals (42.61% (98/230) for 2016 and 38.91% (128/329) for 2018). The median publication time from presentation was 16 months (range -28.9 to 41.1). The most frequent specialties of 224 senior authors were: plastic surgery (21.4%), dermatology (20.0%), and radiology (10.7%). Authors published in 123 separate journals, where the majority of publications appeared in Journal of the American Academy of Dermatology and Pediatric Dermatology, each 5.3% (12/226) of the total. A majority of publications (51.3%) had a case-series study design and were level 4 evidence. The median 5-year impact factor was 3.49 (range: 1.15 to 54.64).

Conclusion: From the 2016 and 2018 ISSVA meetings reviewed, less than half of the shared content was converted to peer-reviewed publications. Studies were published in a wide range of journals, in alignment with specialty. ISSVA authors are not converting a majority of presentations to published work. There is an opportunity for the Journal of Vascular Anomalies to capture a tremendous amount of high-quality content.

Session 8: Difficult Cases in Vascular Anomalies

A case of malignant transformation of vascular tumor with somatic PTEN variant

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Purpose: PTEN hamartoma of soft tissue (PHOST) comprises predominantly fat, fibrous tissue and abnormal vessels. Although PHOST can be locally infiltrative, malignant transformation is exceedingly rare. Here we present a case of PHOST that eventually underwent malignant transformation to angiosarcoma in a young adult.

Results: An 18-year-old female presented with rapid enlargement of a submandibular “bump” that was stable for over 10 years. Over the next two years, she underwent multiple biopsies and resections. Selected specimens were reviewed by different consultants, initially with a wide spectrum of diagnoses including “myofibroma”, “low grade sarcoma”, “malignant hemangioendothelioma variant, likely arising from a hemangioma/vascular malformation”. Consensus from repeated debulking procedures was of an atypical vascular neoplasm “without evidence of malignancy” arising in a “venous malformation with associated papillary endothelial hyperplasia”. Molecular testing performed on a resection specimen revealed a pathogenic PTEN R130Q variant. PTEN germline testing was negative. The patient was in apparent remission for six months before imaging showed relapse accompanied by persistent pain, swelling and recurrent abscesses, treated with sclerotherapy and percutaneous aspiration. Over the next three months, bleeding and growth persisted despite initiating mTOR inhibition, prompting radical re-resection. Pathology revealed a highly infiltrative vascular proliferation with marked cytologic atypia

and architectural complexity consistent with angiosarcoma. Malformed vessels were also seen, suggesting an arteriovenous malformation.

Conclusion: This case highlights multiple challenging aspects of diagnosing and managing vascular lesions. Malignant vascular lesions are exceedingly difficult to distinguish from reactive hyperplasia at early stages as cytology does not reliably reflect biological potential. Malignant transformation of a vascular malformation is even more challenging to recognize given its rarity and overlapping features with complex vascular anomalies including recurrences and presence of somatic variants. Vigilance is required to assess the risk of malignant transformation especially in rapidly progressing complex vascular anomalies that carry genetic variants with oncogenic potential.

Endovascular and conservative treatment of huge kaposiform hemangioendothelioma (KHE) complicated by recurrent hemothorax

Iryna Benzar (pediatric surgeon)

Kaposiform lymphagioendothelioma with recurrent idiopathic pericardial effusion successfully treated with anti-IL1 therapy

Simona Avčin (University children's hospital Ljubljana); Nataša Toplak (University children's hospital Ljubljana); Martin Thaler (University children's hospital Ljubljana); Janez Jazbec (University children's hospital Ljubljana)

Hypertrophic Progressive Vascular Anomaly due to somatic GNAQ209 mutation with Recalcitrant Ulceration

Lauren Provini (University of California, San Francisco); Patricia Cornett (University of California, San Francisco); Rachelle Durand (University of California, San Francisco); Timothy McCalmont (University of California, San Francisco); Ilona Frieden (UC San Francisco)

Venous malformation with associated segmental overgrowth attributable to mosaic pathogenic deletion in NSD1 gene

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Purpose: To describe a case of a somatic pathogenic NSD1 variant in a patient with a venous malformation and segmental overgrowth of left lower extremity.

Methods: Medical records were reviewed, including imaging, labs, medications and procedures. Molecular testing from DNA obtained from cultured fibroblasts from affected area in left lower extremity was performed per commercial laboratory protocol.

Results: A 17-year-old female with an extensive left lower extremity venous malformation and corresponding segmental overgrowth who underwent tissue biopsy of the affected area for genetic testing. An NGS panel at a commercial genetic testing laboratory identified a mosaic pathogenic deletion of at least exons 2-23 of NSD1. The NSD1 genes has been associated with Sotos syndrome. Our patient does not have the typical gestalt or learning disability typically seen with this disorder. Her height and/or HC are not above 2 SD from the mean for sex and age. It has been previously reported through expression studies on fibroblasts of patients with Sotos syndrome that there may be deregulation in the

MAPK/ERK signaling pathway. Notably, this is a pathway that has been implicated in the etiology of vascular anomalies. This gene is not commonly included in vascular panels.

Conclusion: We hypothesize her mosaic deletion in NSD1 is causing overgrowth and vascular anomaly of her affected tissue. - We will attempt to pursue further studies including a microarray to determine breakpoint and also further molecular studies to rule out common genes that may be implicated in vascular anomalies with overgrowth (such as PIK3CA) in which low level mosaicism may not be reliably detected by the current test our patient has had. - Through this difficult case we seek input from experts in the field regarding the possible relationship of the variant with the phenotype and input from similar cases and discuss next steps.

A compelling case of extensive VVM that affected breast development

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Direct Stick Embolization of a Rectal Venous Malformation via Transanal Minimally Invasive Surgery

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Purpose: Rectal venous malformations (VM) are rare clinical entities with variable presentation and require a unique tailored strategy based on the symptom severity, location, and extent of the lesion.

Methods: A 49-year-old male patient with an incidentally discovered asymptomatic 6.5 cm rectal mass on non-contrast computerized tomography (CT) urogram was performed for the evaluation of microscopic hematuria. Colonoscopy revealed a bluish bulge in the recto-sigmoid region with a >50% luminal narrowing. Contrast-enhanced Magnetic Resonance Imaging (MRI) demonstrated a voluminous, lobulated cluster of venous malformation with marked rectal luminal impingement and ample phleboliths. Selective visceral angiography confirmed no evidence of pathologic high flow arterialization of mass. A complete hematologic evaluation revealed elevated D-Dimer levels consistent with a diagnosis of venous malformation-associated localized intravascular coagulopathy (LIC) and a prophylactic regimen of rivaroxaban was initiated. Multidisciplinary surgical management was planned to perform direct stick embolization (DSE) using Transanal minimally invasive surgery (TAMIS).

Results: TAMIS was performed, and the GelPoint Mini system was set up to provide direct visualization of the rectal VM. A 21-gauge spinal needle was inserted into the GelPoint Mini and was used to puncture the malformation. After confirmation of blood return, trans needle venography was performed to delineate the contour of the VM. DSE was performed by injecting 3% sodium tetradecyl sulfate under direct fluoroscopic visualization. The needle track was plugged with Surgiflo matrix with excellent hemostasis. There was no untoward inflammation, blanching, hyperemia, or ulceration on the mucosa.

Post-operative recovery was uneventful with only a self-limiting and expected case of post-embolization syndrome managed by oral antipyretics and NSAIDs.

Conclusion: TAMIS allowed visualization, access, and a stable maneuverable platform for DSE as opposed to flexible or rigid endoscopy. This procedure potentially avoids morbidity and function changes associated with resection. The requirement of a multidiscipline team and hybrid OR may be limited for widespread adoption.

A child with a progressive aneurysm syndrome requiring aortoiliac bypass with biallelic variants in LRP1, possible novel arteriopathy gene?

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Purpose: We present a 6-year-old female with multiple, bilateral fusiform aneurysms, extending from head to pelvis. Extensive genetic testing has not revealed any known cause, but biallelic variants in the candidate gene LRP1 (Low-density lipoprotein receptor Related Protein 1) have been identified. The purpose of this presentation is to determine if other ISSVA members have seen similar presentations, to examine them for LRP1 variation.

Methods: She presented with a pulsatile arm mass at 4 years. Imaging showed aneurysms of internal carotids, maxillary, brachial, infrarenal abdominal, and internal iliac arteries. She had poor dentition and mildly translucent skin, but the rest of her physical exam was normal. There was no craniosynostosis or cleft palate.

Results: After initial management of her internal carotid aneurysms with flow diverting coils, she underwent aortoiliac bypass graft with left nephrectomy due to an expanding eccentric abdominal aortic aneurysm. Her post-operative course was complicated by bilateral middle cerebral artery strokes leaving her with right sided weakness. Pathology of her resected abdominal aorta revealed aneurysmal dilation secondary to non-inflammatory collagen vascular disease, with diffuse-type degeneration of the aortic media. Despite similarities with Loeys-Dietz syndrome, no mutations were identified in the known genes associated with this or any other arteriopathy. Exome sequencing identified a paternally inherited missense variant in LRP1 (NM_002332.2:c.12527G>A: p.Arg4176Glu). Targeted long-read sequencing identified a maternally inherited intronic variant predicted to create a new splice acceptor (c.6187-83G>A) upstream of exon 39.

Conclusion: The significance of these LRP1 variants remains uncertain. Previous studies have demonstrated a TGF-beta dependent role for LRP1 regulating vascular wall architecture, and common variants in LRP1 have been associated with increased risk for common, adult-onset abdominal aortic aneurysms. While we are aware of two other (unpublished) children with aortic aneurysms who have rare LRP1 variants, more patients are needed to establish the pathogenicity of LRP1 in this patient.

Difficult Case Presentation: Targeted Treatment of an Extensive MAP2K1-Mutant AVM of the Suprahyoid Neck and Face in a 12-Year Old Girl

Joshua Smith (University of Michigan); Neeraja Swaminathan (University of Michigan Pediatric Hematology & Oncology); Rajen Mody (University of Michigan Pediatric Hematology & Oncology); Steven W. Pipe (University of Michigan Pediatric Hematology & Oncology); James Bennett (University of

Washington, Seattle Childrens Research Institute); Jonathan Perkins (Division of Pediatric Otolaryngology – Head & Neck Surgery, Seattle Children's Hospital/University of Washington); David Zopf (University of Michigan Pediatric Otolaryngology)

Purpose: Arteriovenous malformations (AVMs) of the head and neck in children pose unique challenges for prevention and treatment of their associated symptoms and functional and cosmetic sequelae. Herein, we present a difficult case of a now 12-year-old female with an extensive AVM of the suprahyoid neck and face in whom DNA sequencing identified a pathogenic MAP2K1 mutation. We pose clinical issues related to targeted MAP2K1 inhibition with trametinib as our patient enters adolescence.

Methods: This is a case report of a female child who initially presented to our institution at the age of four with AVM of the right suprahyoid neck and face. We summarize her clinical presentation and course, imaging features, and numerous AVM-directed treatments. Finally, we discuss her genetic sequencing profile and implications for targeted therapy.

Results: At initial presentation, MRI showed AVM involving right facial soft tissue, auricle, nasal cavity, nasopharynx, oropharynx, and bilateral larynx. At two separate institutions, she had previous trial of oral propranolol, multiple IR-guided AVM embolization procedures, and yttrium aluminum garnet (YAG)-laser treatments. Her case was presented to our Multidisciplinary Vascular Anomalies team and consensus was reached for close clinical observation given relative quiescent nature of disease and mostly self-limited symptoms (e.g., epistaxis). Over the ensuing eight years, she was followed very closely and treated for intermittent epistaxis and oral cavity bleeding. At age 12, given anticipated puberty and concern for unpredictable AVM growth, she had lesion biopsy with DNA sequencing. This revealed a pathogenic deletion in the MAP2K1 gene (c.303_308del6; p.Glu102_Ile103del). She was subsequently referred to our pediatric hematology team for consideration of treatment with MEK inhibitor trametinib.

Conclusion: We present a unique case of a now 12-year-old female with extensive AVM of the suprahyoid neck and face and pose clinical questions related to targeted medical therapy with the MEK inhibitor trametinib.

Session 9: Combined Vascular Malformations II

Lymphatic Differentiation and Microvascular Proliferation in Vascular Anomalies Lesions Following ISSVA Classification System

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Purpose: Previous studies have shown discrepancies between histological and clinical diagnosis in a series of vascular malformations due to a lack of immunohistochemistry (IHC) staining. Accurate diagnosis is important for clinical practice and trials on therapeutic effectiveness. Therefore, this study investigated the involvement of the lymphatic vessels and microvascular proliferation (MVP) in lesions with the use of IHC markers in a large series of vascular anomalies (VA) and examined the effectiveness of International Society for the Study of Vascular Anomalies (ISSVA) classification in diagnosing VA clinically and histologically.

Methods: A series of biopsies and excisions of 138 patients with VA were reviewed histologically on hematoxylin stains, and IHC multiplex staining for D2-40 (lymph vessels marker), vWf (blood vessels

endothelial cells marker) and Ki67 (proliferation marker) antibodies were added. Revised diagnosis was made following ISSVA classification system.

Results: Of 28 cases which showed substantial numbers of D2-40+ lymph vessels, 42.9% (n=12) were not diagnosed as lymphatic lesion in initial report of clinical and histological diagnosis. Lesions with MVP were found in 37.7% (n=52). The highest rates were found in 4 subtypes of VA: 5.8%(n=8) in infantile hemangioma, 5.8%(n=8) in arteriovenous malformations, and 5.1% (n=7) in lymphatic venous malformations. After IHC staining was added, 94.2% (n=130/138) of cases could be diagnosed following ISSVA classification and in 29% (n=40 /138) clinical diagnosis was supported by histological diagnosis.

Conclusion: Lymphatic differentiation occurs more often than expected, hence it is recommended to apply lymphatic vessel markers (D2-40) when diagnosing VA. MVP should also be considered as an important histopathological feature for future prognosis of symptomatic vascular malformations. The ISSVA classification system is proven effective for diagnosing VA when IHC staining re-applied appropriately.

Cell-free DNA obtained during sclerotherapy as a novel method for molecular analysis of venous and lymphatic malformations.

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Purpose: Vascular malformations (VM) are caused by somatic pathogenic mutations in various genes and a tissue biopsy needs to be performed to detect the somatic mutation. In oncologic management, cell-free DNA (cfDNA) from plasma is emerging as a minimal-invasive alternative approach to standard tumor biopsies. Sclerotherapy provides a convenient way to collect blood or lymph fluid from the VM, as it is standardized aspirated to prevent dilution of the sclerosing agent. This study aimed to investigate if cfDNA obtained during sclerotherapy is an adequate method for molecular analysis of VMs.

Methods: Aspirated blood/lymph fluid during sclerotherapy were collected of children and adults with VeMs (n=8), LMs (n=4) or combined malformations (n=1). cfDNA was isolated from plasma or lymph fluid and analyzed for pathogenic mutations in 23 VM-associated genes using Next-Generation Sequencing. In case a mutation could not be detected in patients with LMs, the cfDNA was analyzed using a cfDNA-assay with molecular barcodes (including PIK3CA), which led to a lower detection limit (0.1%).

Results: Aspirated fluids during sclerotherapy provided a convenient method to collect plasma, also in deeper positioned and intramuscular VMs. Somatic mutations were detected in cfDNA of patients with

VeMs (4/8; 1 TEK, 3 PIK3CA) and LMs (3/4; 3 PIK3CA). In 2 patients with a LM the somatic mutation was only detected using the cfDNA-assay. No mutation was found in a patient with a combined LM/VeM.

Conclusion: Our study shows that somatic mutations could be detected in cfDNA obtained during sclerotherapy in patients with VeM and LM and thus is an excellent alternative for tissue biopsies. Particularly for deep positioned VM or other unenforceable tissue biopsies, cfDNA provides a solution. Two PIK3CA-mutations could only be detected using the cfDNA-assay due to the higher sensitivity. Ideally, a cfDNA-assay for the TEK-gene and other VM-associated genes will be developed to increase the detection rate.

Benefit of systematic central nervous system screening in capillary malformation-arteriovenous malformation syndrome: an observational study.

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Purpose: Capillary malformation-arteriovenous malformation (CM-AVM) syndrome has an increased risk of central nervous system (CNS) arteriovenous malformation (AVM), evaluated at about 10 to 15% of patients, leading many physicians to perform systematic screening in asymptomatic patients especially in children. We studied the detection rate of CNS AVM by magnetic resonance imaging (MRI) in patients presenting with dermatological clinical features of CM-AVM but without neurological symptoms.

Methods: Retrospective multicentric study in French reference centers for vascular anomalies. Patients presenting with CM-AVM syndrome without neurological symptoms and for whom CNS screening by at least a brain MRI, were included. Rate of detection of CNS anomalies, their type, the treatment that was conducted since, and the clinical neurological outcome after screening were studied. We retrieved molecular diagnosis when it was performed, and studied the associated phenotype.

Results: 57 children (0-18 y) mean 6.5 years, and 11 adults; 42 female, 26 male. Nine patients had asymptomatic brain anomalies at initial screening, including 1 AVM, 2 hamartomas, 3 arterial aneurysms, and 3 venous anomalies. Two patients presented neurological symptoms during subsequent follow-up leading to brain AVM diagnosis. Spine MRI was performed in 30 patients, always normal. Pathogenic variants of RASA1 and EPHB4 were identified in 23 and 14 patients, respectively. Lip telangiectasia were noted in 5 patients with EPHB4 variants and 4 patients with RASA1 variants.

Conclusion: This study shows that the detection rate of CNS AVM, especially spine AVM, in asymptomatic patients seems low. However, other types of brain anomalies may be associated with CM-AVM, and brain AVMs might occur during follow-up, especially during puberty in children. Thus, screening modalities need to be discussed with patients and parents. Identifying an accurate “at risk” period of CNS AVM onset would help define the best time for screening.

Parkes Weber Syndrome with Lymphedema Caused by a Somatic KRAS Variant

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Purpose: Parkes Weber syndrome is a vascular malformation overgrowth condition typically involving the legs. Its main features are diffuse arteriovenous fistulas and enlargement of the limb. The condition has been associated with pathogenic germline variants in RASA1 and EPHB4. The purpose of this study was to identify the cause of Parkes Weber associated with lymphedema.

Methods: Two unrelated male patients referred to our Vascular Anomalies Center were diagnosed with Parkes Weber syndrome by physical examination, MRI, and angiography. Imaging demonstrated diffuse arteriovenous fistulas throughout the leg, subcutaneous microcystic lymphatic anomalies, and lymphedema. Both individuals were negative for germline RASA1 variants and had overgrown skin and subcutaneous tissue excised to reduce the size of their limb. The resected specimens underwent targeted exome sequencing.

Results: Both patient specimens contained a mosaic KRAS variant (NM_004985.5:c.35G>A; p.Gly12Asp). Variant allele fractions were 13% (Patient 1) and 9% (Patient 2). Droplet digital PCR confirmed the variant in the resected tissue of Patient 1 (Patient 2 was not tested), and did not identify the variant in the whole blood DNA of either subject.

Conclusion: KRAS variants, which cause somatic intracranial and extracranial arteriovenous malformations, also result in Parkes Weber syndrome with lymphatic malformations. Individuals with suspected Parkes Weber syndrome without RASA1 or EPHB4 germline variants should be tested for somatic KRAS variants, especially if they exhibit lymphatic malformations.

Targeted medical therapy reduces head and neck PIK3CA-related overgrowth

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Purpose: Targeted medical therapy to suppress PIK3CA activation is being trialed in patients with head and neck PIK3CA-related overgrowth spectrum (PROS). Measures of treatment effectiveness could be malformation volume reduction quantification and malformation composition change. Two imaging modalities were selected for this purpose, three dimensional photos (3DP) and magnetic resonance imaging (MRI). 3DP can be used to determine facial volume and MRI can be used to determine malformation size and composition. Our study aims to assess changes in malformation volume and composition in head and neck PROS patients on alpelisib using 3DP and MRI.

Methods: PROS patients with overgrowth (four, stage 2-5 lymphatic malformations and one facial infiltrating lipomatosis)on alpelisib therapy (50mg/day per Novartis extended use protocol) participated in a prospective IRB-approved cohort study. Subjects had head and neck 3DP every three months and head and neck MRI every 6 months. Data from these images were registered in 3D Slicer and segmentation masks were created. Facial volumes were determined from 3DP surface landmark measures from these masks. MRI masks were further processed in MATLAB to quantitate malformation volume and composition. Volume measures were normalized to normal childhood growth. The component volumes were compared for each time point.

Results: Median participant age at treatment initiation was 3 years (Range 2-12 years) and average drug therapy duration, with compliance, was 10 months (range 4-22 months). All patients had facial volume reduction as measured with 3DP (median 5%, range 1-25%) and malformation volume on MRI (median 6, range 3-17%). Volume changes were proportional for 3DP and MRI when compared at the same time points. Malformation composition change was seen with reduction of fluid and fat content.

Conclusion: Targeted medical therapy to suppress PIK3CA activation in head and neck PROS reduces facial volume and changes malformation composition, as measured with serial 3DP and MRI.

Preliminary results of the VASE trial evaluating Sirolimus in Vascular Malformations refractory to Standard Care: Beyond the 2-year treatment with sirolimus.

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Purpose: The preliminary results of the prospective ongoing VASE trial demonstrated an efficacy of sirolimus in 82% of patients with symptomatic slow-flow vascular malformations. In the trial, sirolimus is stopped after 2 years of treatment, but can be reintroduced in case of symptoms resurgence.

Methods: This study is registered as the VASE trial in EudraCT: 2015-001703-32. Here we studied the efficacy of sirolimus in patients treated for at least 6 months. We also evaluated the outcome of patients that completed their 2-year treatment duration, and stopped sirolimus treatment.

Results: On November 2021, 185 patients were enrolled in the trial, including 155 patients with a follow-up of at least 6 months. Twenty-two patients stopped sirolimus due to lack of efficacy, resulting in an efficacy rate of 86%. Fifty-nine patients completed the 2-year treatment. Sirolimus treatment allowed surgery in 16 patients and sclerotherapy in 3 patients. Twenty-one presented a resurgence of symptoms that required sirolimus reintroduction: 13 venous malformations (VM), 2 Klippel-Trenaunay syndrome (KTS), 1 capillaro-venous malformation (CVM), 1 lymphatic malformation (LM), 1 glomuvenous malformation (GVM), 1 Generalized Lymphatic Anomaly (GLA), 1 capillary malformation with dilated veins (CMDV), and 1 CLOVES. Of these patients, genetic analysis detected 5 PIK3CA, 5 TIE2, 1 PTEN and 1 GNAQ mutations. The median time to sirolimus restart was 6 months (15 days-18 months). All patients presented benefit from sirolimus reintroduction but in 3 patients, the amplitude of this benefit was less important than initially, requiring additional treatment.

Conclusion: In conclusion, sirolimus continues to demonstrate strong efficacy in patients with slow-flow vascular malformations and allows revolutionary treatment in a significant portion of patients. Limited duration of treatment appears as a promising strategy as only 36% of patients required reintroduction of sirolimus after arrest. Further analysis are ongoing in order to better characterize optimal duration of sirolimus treatment.

EPIK-P1: Retrospective Chart Review Study of Patients With PIK3CA-Related Overgrowth Spectrum (PROS) Who Received Alpelisib

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Purpose: PROS is a group of rare disorders driven by mutations in PIK3CA, with no medical treatment approved. Alpelisib, a PI3Kα inhibitor, showed promising results in patients (n=19) with PROS (Venot, Nature 2018). Here, we evaluate alpelisib in a larger population to confirm its clinical benefit in PROS.

Methods: EPIK-P1 was a retrospective non-interventional medical chart review of patients (≥2 years) with PROS treated with alpelisib. Patients had severe/life-threatening conditions, confirmed PIK3CA mutation, and received ≥1 dose of alpelisib (adults, 250 mg/day; pediatric, 50 mg/day) ≥24 weeks before data cutoff. The primary objective assessed efficacy by proportion of responders (≥20% reduction in the sum of target lesion[s] volume) at week 24 via independent central review. Secondary objectives assessed safety and clinical benefit.

Results: Data were abstracted from 57 patients (full-study population: 18 adults, 39 pediatrics) at 7 sites in 5 countries. Median length of exposure was 18.1 months (range, 3.4-49.9). In the primary endpoint analysis, 37.5% (12/32; 95% CI, 21.1-56.3%) of patients with complete cases (patients without missing response) responded. 23 out of 31 patients (74.2%) reported any reduction in sum of target lesion volume at 24 weeks (mean reduction, 13.7%). No patient with a complete case experienced disease progression. At week 24, the proportion of patients with improvement in the most frequent (full-study population) PROS-related symptoms/signs was pain 90.9% (20/22), fatigue 76.2% (32/42), vascular malformation 78.9% (30/38), limb asymmetry 69.0% (20/29), and disseminated intravascular coagulation 55.2% (16/29). In the first 24 weeks, there were no surgeries due to disease progression.

Adverse events (AEs) and treatment-related AEs were experienced by 82.5% (47/57) and 38.6% (22/57) of patients, respectively; no deaths were reported. The most common treatment-related AEs were hyperglycemia (7/57, 12.3%), aphthous ulcer (6/57, 10.5%), and stomatitis (3/57, 5.3%).

Conclusion: Real-world data demonstrate alpelisib is clinically effective and well tolerated in patients with PROS.

Is there a place for prophylaxis with DOACs in Klippel-Trenaunay Syndrome and other low-flow vascular malformations with intravascular coagulopathy and thromboembolic events?

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Purpose: Low-flow vascular malformations (VM) and in particular Klippel-Trenaunay syndrome (KTS) have a high prevalence (>30%) of thrombo-embolic events (TEE) at a young age, resulting in severe chronic pain or more serious sequelae. No standard (prophylactic) protocols exist for anticoagulant treatment.

Methods: Literature on TEE in KTS and VM was elaborately studied and data of our cohort of 173 KTS-patients were retrospectively analyzed for TEE and the use of anticoagulant treatment.

Results: TEE have a high prevalence in VM and occur at a young age. Patients in our cohort had a median (IQR) age in years of 26.0 (13.0-44.0); 56 patients (32.4%) have experienced a TEE (SVT, DVT and PE). Ten (5,8%) patients had had PE. None of the patients had a (history of) clearly provoked TEE. The mean age for the first TEE (including SVT) was 28.13 (SD = 16.44; range 0-70) years and for the first severe event (DVT or PE) was 33.75 (SD = 16.93; range 0-71) years. DOAC-treatment may lead to substantial reduction in symptoms with reduced pain from chronic phlebitides in part of the patients with improved quality of life, as reported by patients themselves.

Conclusion: Based on the literature-study and analyses of our own cohort of 173 patients with KTS, we hypothesize that prophylactic treatment with DOACs in this specific patient-group might have a clinically significant effect. Future research has to focus on which patients will benefit from prophylactic treatment with DOACs to prevent serious TEE and/or reduce pain and also what the possible risk factors could be, previous coagulation-problems and/or abnormal venous anatomy? As long as the aforementioned questions have not been answered, the approach of anticoagulant treatment, either or not with a DOAC can be chosen on an individual basis with a choice based on shared decision making.

Session 10: Multidisciplinary Studies in Vascular Anomalies II

Management of sirolimus treatment for tumors associated with Kasabach-Merritt phenomenon

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Purpose: Sirolimus is effective for Kasabach-Merritt phenomenon (KMP), a rare and severe consumptive coagulopathy associated with kaposiform hemangioendothelioma and tufted angioma. Guidelines are lacking for the ideal duration of treatment and the discontinuation strategy or whether a prophylactic treatment can be proposed. To evaluate the long-term management of sirolimus treatment for KMP-associated tumors.

Methods: This was a retrospective study of children receiving sirolimus for KMP-associated tumors from January 2014 to October 2020. The children were divided into those with sirolimus discontinuation and those with prolonged treatment. Clinical, biological and treatment factors were studied in both groups.

Results: Twelve patients were included. Overall normalization of platelet counts and D-dimer levels was reached at a mean of 1.2 and 8.8 months, respectively. With sirolimus discontinuation (n=6), the mean sirolimus treatment period was 14.8 months, and the relapse rate after discontinuation was 66% (n=4). The therapeutic efficacy was preserved when sirolimus was re-started. We found no factor associated with relapse. With prolonged sirolimus treatment, the mean current dose of 0.026 mg/kg/d, corresponding to a mean residual level of 2.44 ng/ml, was associated with maintained clinical and biological remission; the mean treatment period was 3.4 years. Seven patients had side effects. Aspirin maintained remission in 3 patients after sirolimus discontinuation.

Conclusion: Sirolimus remains highly effective even with lower doses than recommended for treating KMP-associated tumors. Maintenance treatment with a minimal efficient dosage allows for durable remission. Aspirin can be discussed as an alternative.

Intramuscular Vascular Malformations: classification on the basis of clinical-haemodinamic-imaging and histologic findings. Implication on therapeutic approach

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Purpose: Intramuscular Vascular Malformations (IVM) are rather common. Their clinical impact often starts in young adults. Their imaging and histological presentation could be different and their treatment is still controversial. On the basis of the experience of a single surgeon during a 10 year period is possible to propose a classification related to clinical-hemodynamic-imaging and histologic findings and its impact on therapeutic strategy.

Methods: This re-evaluation consisted of 49 patients (26 male, 23 female) aged from 4 to 56 submitted to surgery, often after other types of unsuccessful treatments. Surgical treatment was limited to muscle mass involved in vascular malformation. Lower limb was involved in 35 patients (71,4%); upper limb in 10 patients (20,4%) and other side of the body in 4 patients (8,1%). We excluded cases of head and neck vascular malformations because of the peculiar musculature in this side.

Results: Ultrasound Doppler, magnetic nuclear resonance imaging and histological evaluation permitted us to recognize 5 different types of IVM: venous “cavernous” (IMV-C)(16,3%); venous diffuse/dispersed (IMV-D)(44,8%); venous with micro-artero-venous shunts (IMV-MS)(6,1%); artero-venous with macro-shunts (IMV-AVM)(12,2%) and venous with fibro-lipomatous component (FAVA)(12,2%). After surgical resection we observed complete recovery in all the patients, except mild residual symptoms in 2 patients and 2 early redo-surgery (one case for hemorrhage and the other for tendons retraction).

Conclusion: IVM are common vascular malformation. Their clinical impact can be heavily disabling due to calcifications, nerve compression, pain, disfigurement and functional impairment. IVM could be

classified in different types on the bases of hemodynamic and imaging, confirmed by histologic evaluation. On the bases of our experience, "economic" surgical resection of single muscle could be the first line treatment in all the cases, supported by preoperative embolization in AVMs type. But less invasive treatments (embolization, sclerosis, intralesional laser, medical therapy) must be considered in cases of extensive multiple muscular involvement.

MENTAL HEALTH EVALUATION IN PATIENTS WITH VASCULAR ANOMALIES

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Purpose: Patients with vascular anomalies can have significant disfigurement, poor quality of life and chronic pain, all of which can affect their mental well-being. Although most of the multidisciplinary care is focused on the medical and surgical treatment of the vascular anomaly, it is critical to also assess and address the mental health concerns of this population.

Methods: IRB approved retrospective study of patients with a vascular anomaly attending a single center multidisciplinary clinic between July 2020 to November 2021. All patients who were assessed at least once by the team psychologist were included.

Results: Twenty-six patients were included. Median age was 14 years (range: 3-29). Nineteen female, 7 male. Diagnoses included the following: vascular tumor (1), capillary (2), venous (6), lymphatic (3), arteriovenous (3), combined (5), KTS (6). Thirty-one percent (8 of 26) of patients reported a previous mental health diagnosis. Seven of the 8 were diagnosed with anxiety and/or depression. Only 50% of patients with a mental health diagnosis received mental health treatment. Eleven percent of patients confirmed bullying at school. 96% of patients did not have a family history of mental health issues. Eleven percent of patients reported a history of suicidal ideation. Only 3 of the 26 patients disclosed substance abuse. Forty-two percent of patients complained of chronic pain.

Conclusion: Patients with vascular anomalies may be more susceptible to mental health issues for a variety of reasons. Including a psychologist as an integral part of their multidisciplinary care is, therefore, extremely beneficial to aid patients and families in obtaining mental health therapy.

Lymphatic phenotype of Noonan Syndrome: Innovative diagnosis and therapies for lymphatic diseases in Noonan Syndrome

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Purpose: Dysregulation of the Ras/MAPK signalling pathway is suggested to play a pivotal role in the development of the lymphatic system in patients with Noonan Syndrome (NS). Pathogenic gene variants in the Ras/MAPK pathway can therefore lead to lymphatic diseases such as chylothorax, protein losing enteropathy, and lymphedema. Diagnosis of the lymphatic phenotype in patients with NS remains difficult due to its variable nature. Therefore, we aim to give an overview of the clinical presentation of lymphatic disease in relation to central conducting lymphatic anomalies (CCLA) in Noonan syndrome, including innovative diagnostic methods and therapeutic options.

Methods: We included seven NS patients with symptoms of lymphatic flow disorders. The central conducting lymphatic system was imaged using intranodal contrast in dynamic MR lymphangiography (DMRL). Images were compared to the clinical presentation of lymphatic disease. Based on the images, treatment plans were adjusted.

Results: All 7 NS patients had abnormalities of the thoracic duct, ranging from aplasia to abnormal size, often accompanied by central flow disorders. In addition, the severity of clinical symptoms varied between patients, and during life.

Conclusion: We will review the (protocollary and experimental) diagnostic and therapeutic options in NS patients who have symptoms of central conducting lymphatic anomalies.

Prospective Observational Study of Pain Severity and Pain Interference Outcomes Following Percutaneous MRI-guided Laser Ablation or Cryoablation for Painful Peripheral, Soft Tissue Vascular Anomalies: 12-month Outcomes

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Differences in response to low dose sirolimus between children and adults with vascular anomalies?

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Purpose: Sirolimus is effective in a subset of patients with vascular anomalies, however, it is unknown at what age sirolimus should be started. We hypothesized that sirolimus is more effective if treatment starts during childhood. This open label phase III clinical study investigated the differences in treatment outcome between children and adults.

Methods: Patients with untreatable vascular anomalies received sirolimus (target levels: 4-10 ng/ml) during a 6-month period (Challenge), followed by withdrawal. If complaints returned, sirolimus was reintroduced. Pain and other symptoms, QoL, size (MRI) and toxicity were measured before and after each treatment period. Response to treatment was defined as decrease in pain, other symptoms, size, or improvement in QoL.

Results: In total 33 children and 35 adults (1-60 years) were included and analyzed. At baseline adults had significantly more pain (estimated marginal mean (EMM) pain scores of EMM 6.2 (95%CI 5.21-7.20) versus 4.5 (95%CI 3.23-5.68) in children p=0.03). Additionally, adult patients had an impaired QoL compared to the normal population. This difference was higher compared to children.

Sirolimus was effective in 76.5% of the patients, with a low incidence of (severe) toxicities, after Challenge. Children had a higher response rate of 90.6 % (n=29/32) versus 65.7% (n=23/35) in adults, (p=0.014). In addition, children responded earlier during sirolimus treatment; with a hazard ratio of 0.53 (95% CI 0.303-0.928, p=0.025). No differences were observed in safety, and reoccurrence of symptoms. Nevertheless, more of children needed to restart with therapy (n=24 versus n=11; P=0.001).

Conclusion: This study reveals that children frequently more and earlier responded to sirolimus therapy compared to adults, without a difference in safety. Moreover, adults experienced high pain scores and impaired QoL at baseline. These results indicate benefits of starting sirolimus during childhood. However, the point of concern is lack of knowledge of long term consequences.

No Association of Sirolimus with Wound Complications in Children with Vascular Anomalies

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Purpose: Sirolimus has demonstrated efficacy as a treatment option for several types of vascular anomalies; however, it has a potential side effect of delayed surgical wound healing. The purpose of this study was to evaluate the association of sirolimus with postoperative complications in the pediatric vascular anomaly population.

Methods: A retrospective cohort study was performed for children with a vascular anomaly who underwent excisional or debulking procedures from 2015–2020. Patient demographics, vascular anomaly characteristics, operative variables, sirolimus dosing information, and perioperative outcomes were collected. Univiariate analysis was performed to compare outcomes based on administration of sirolimus.

Results: Fourty-seven patients with vascular anomalies underwent a total of 57 surgical procedures (21 with and 36 without perioperative sirolimus). The most common anomalies were lymphatic (32, 68%) and venolymphatic (10, 21%) malformations. The most common anatomical locations were cervicofacial (30, 64%) and isolated extremity (7, 15%). Of the patients who received perioperative sirolimus, the median preoperative and postoperative drug levels were comparable (preoperative 6.9 ng/mL (IQR 4.9–10.1); postoperative 6.5 ng/mL (IQR 4.7–9.4)). The rate of postoperative complications (sirolimus 19%, without sirolimus 14%; p=0.44) and wound complications (sirolimus 14%, without sirolimus 6%; p=0.26) were statistically comparable between the cohorts.

Conclusion: Our results suggest sirolimus may not significantly increase perioperative complication rates in pediatric patients undergoing resection of their vascular anomaly.

Clinical Response to PI3K Inhibition in a Cohort of Children and Adults with PIK3CA Related Overgrowth Spectrum (PROS) Disorders

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Purpose: We describe, through a series of five cases, the clinical response and safety of alpelisib (BYL719) use in children and adults with PIK3CA-related overgrowth spectrum (PROS) disorders at our center.

Methods: We reviewed clinical records of five patients followed by the pediatric hematology and multidisciplinary vascular anomalies teams at Vanderbilt University Medical Center from October 2019 through September 2021. All patients carried a clinical and/or genetic diagnosis of PROS and were treated with alpelisib provided by a Novartis managed access program.

Results: We highlight improvement in symptoms and objective overgrowth measurements in all patients (Table 1). We note dose-dependent hyperglycemia in one patient and gastrointestinal side effects in two

of five patients. No patients experienced any serious side effects. All patients elected to continue alpellisib as of their last visit due to self-reported improvement in quality of life and symptoms on therapy.

Conclusion: This case series reports on the real-world use of a PI3K inhibitor in the management of children and adults with PROS. Ongoing clinical trials will provide efficacy and safety data as these drugs become more widely used in patients with vascular anomalies and syndromes secondary to somatic PIK3CA mutations.

Safety of Alpelisib in Patients with PIK3CA-Related Overgrowth Spectrum (PROS): Secondary Analysis from the EPIK-P1 Medical Chart Review

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Purpose: PROS comprises rare disorders driven by mutations in PIK3CA. Alpelisib, a PI3Kα inhibitor, targets the underlying cause of PROS. Efficacy of alpelisib in PROS was demonstrated in EPIK-P1; 37.5% of complete cases showed ≥20% reduction in target lesion volume after 24 weeks. Here, we report safety outcomes from EPIK-P1.

Methods: EPIK-P1 was a retrospective non-interventional chart review of patients ≥2 years with PROS with severe/life-threatening conditions and PIK3CA mutation, treated with ≥1 alpelisib dose (adults: 250 mg/day, pediatrics: 50 mg/day) ≥24 weeks before cutoff. Safety was a secondary objective.

Results: At cutoff, 91.2% of patients (52/57) were receiving treatment. In adults (n=18), any-grade AEs were experienced by 88.9% (16/18); 50.0% (n=9) and 5.6% (n=1) experienced grade ≥3 AEs and treatment-related grade ≥3 AEs, respectively. Among adults, 3 (16.7%) experienced treatment-related serious AEs (SAEs): cellulitis (grade ≥3), hyperglycemia (grade 2), and venous thrombosis of the limb (grade 1) were reported in 1 patient (5.6%) each. In pediatrics (n=39), any-grade AEs were experienced by 79.5% (31/39) overall, including 81.8% (9/11), 75.0% (9/12), and 81.3% (13/16) of patients in age subgroups, 2-5 years, 6-11 years, and 12-17 years, respectively. Grade ≥3 AEs were experienced by 4 (N=39; 10.3%) pediatric patients (1 aged 2-5 years, 3 aged 12-17 years). Grade ≥3 SAEs occurred in 3 pediatric patients (7.7%); none experienced a treatment-related grade ≥3 AE or SAE. Following alpelisib initiation, pediatric patients grew normally. AEs led to dose adjustment and/or interruption in 27.8% (5/18) of adults and interruption in 5.1% (2/39) of pediatric patients. No AE led to discontinuation or death. The most frequent all-grade treatment-related AEs were hyperglycemia (27.8%, 5/18) in adults, aphthous ulcer and stomatitis (7.7%, 3/39 each) in pediatric patients.

Conclusion: Across all ages, alpelisib was well tolerated in patients with PROS. EPIK-P1 demonstrates the tolerability and promising clinical benefit in patients with PROS.

Clinical Characteristics and Management Of Cutaneous Toxicities Associated with the MEK Inhibitor Trametinib

Tiffany Wu (Stanford University); Joyce Teng (Stanford University)

Purpose: Complex vascular anomalies, including arteriovenous malformations and generalized lymphatic anomalies, are often associated with mutations in the RAS/MAPK pathway. Patients with vascular anomalies are at risk for bleeding, pain, infection, and functional impairment. Targeted therapy, such as use of the small molecule protein kinase inhibitor trametinib, has been FDA-approved for

treatment of metastatic melanoma. Trametinib has also been repurposed for the management of morbidities in patients with vascular anomalies. Laboratory surveillance, as well as cardiac, pulmonary, and ocular evaluation, are needed while on targeted therapy. Aside from fatigue and diarrhea, dermatologic toxicity - especially acneiform eruptions - is the most common adverse event experienced by patients. It is estimated that therapeutic interruption occurs in over 30% of oncology patients receiving trametinib, likely due to these cutaneous adverse effects.

Methods: Retrospective chart review of twelve patients (6 teenagers, 6 adults) with vascular anomalies and treated with trametinib from our institution was conducted.

Results: Frequency of cutaneous toxicity was greater than 80% at current recommended dosages (0.025 mg/kg/daily in teenagers, 2 mg daily in adults). Adults appeared to have more severe cutaneous reaction (grade 3) compared to teenagers (grade 2). The cutaneous eruptions observed typically started on the face 2-3 weeks after initiation of therapy, then rapidly extended to involve the chest, back, and shoulders. The eruption appeared to peak 2-3 months into treatment before subsiding gradually. All patients who experienced cutaneous side effects required topical treatments. Two patients received oral antibiotics, and one discontinued therapy.

Conclusion: Overall, our study indicates high prevalence of cutaneous toxicity associated with the use of trametinib in vascular anomaly patients. It is important for clinicians to be knowledgeable about these cutaneous adverse effects to provide proper counseling to patients and to avoid therapeutic interruption. Future larger scale study is needed to identify risk factors and develop optimized management.

Poster Abstracts

Arteriovenous Malformations

P014

Treatment of a large arterio-portal-venous malformation of liver including an aneurysm of the Ductus venosus in a newborn with Trisomy 21

Moritz Wildgruber, Sinan Deniz, Jens Ricke and Michael Köhler

P017

High Prevalence of mutation in Cell-free DNA of Extracranial Arteriovenous Malformation: a new method to detect the genotype

Ren Cai, Yi Sun, Zhenfeng Wang, Deming Wang, Lixin Su and Xindong Fan

Purpose: Extracranial Arteriovenous Malformations(AVMs) were primarily caused by somatic mutations in KRAS and MAP2K1 genes. Targeted chemotherapies are emerging but require a molecular diagnosis. Since the AVMs were high flow and high pressure. It is hard to acquire the AVM lesion tissue where the mutant variants were only detected in. Few were detected in Cell-free DNA(CfDNA). Since absolute ethanol embolism is one of the effective methods for treating AVM. We hypothesized that CfDNA of post-embolism could provide the genotype of patients with AVMs.

Methods: Peripheral Blood, lesion tissue specimens under the guidance of digital subtraction angiography(DSA), CfDNAs isolated from plasma of 40 patients underwent interventional embolism(before and after as T1(1h, setting first injecting ethanol moment as T0)). 4 patients 's CfDNAs were collaborated in 8h(T8), 16h(T16), 24h(T24), 48h(T48), and 72h(T72) after T0. All the specimen were sequenced by a targeted NGS panel of vascular anomalies

Results: Variants were detected in tissue and CfDNA but none in peripheral blood. The prevalence for tissue, CfDNA of pre-embolism and post-embolism(1h) were 73%(27/37), 27.5%(11/40), and 90%(36/40), respectively. KRAS(p.Gln61, p.Gly12) and MAP2K1(p.Gln56, p.Lys57) were the mutant hot spots. Novel mutations in BRAF, RASA1, KRAS, and MAP2K1 were also detected in tissue and cfDNA. As for specificity, area under the ROC curve were 0.8125($P<0.0001$), 0.6375($P=0.0343$), and 0.9500($P<0.0001$). For the variants allele frequency(VAF) of CfDNA, the VAF reached a surge at T1, then a second surge at T24.

Conclusion: AVMs were caused by mutations in RAS/MAPK pathway where cfDNA of post-embolism(T1) of absolute ethanol interventional therapy could provide the accurate genotype of the patients in sensitivity and specificity. VAF detected in T24 could provide information related to the natural metabolism such as the prognosis of indications or targeted chemotherapy. Overall, CfDNA of post-embolism provides us a new method for approaching the precise medicine of AVM.

P021

Difficult Case of High-Flow Digital Arteriovenous Malformation with Overgrowth

Jay Shah and C. Matthew Hawkins

P025

Dominant outflow vein embolization techniques in treatment for high-flow arteriovenous malformations with absolute ethanol

Lixin Su, Zhenfeng Wang, Deming Wang, Ren Cai, Yi Sun, Xitao Yang, Mingzhe Wen, Lianzhou Zheng and Xindong Fan

Purpose: The aim of this study was to assess the management and outcomes of arteriovenous malformations (AVMs) with dominant outflow vein (DOV) treated with coils and absolute ethanol.

Methods: A retrospective review was performed from November 2016 to May 2018 on all patients with a high-flow AVM and associated DOV who underwent absolute ethanol embolization. Indications, techniques, complications, and outcomes were reviewed.

Results: Sixteen patients underwent transvenous embolization of high-flow AVMs with a DOV. The median age was 26.6 years (13.7-43.2 years). The AVM was located on an extremity in 10 patients (62.5%) and in the face in 6 patients (37.5%). DOV embolization through direct percutaneous puncture with coils was performed in all patients. Absolute ethanol was used to obliterate the fistula. Technical angiographic success was seen in all patients. 8 patients (50%) experienced a complete response to treatment, whereas 8 (50%) experienced a partial response. 8 patients (50%) required further procedures for residual symptoms.

Conclusion: AVMs with a DOV can be successfully treated by coils and absolute ethanol embolization. Percutaneous puncture embolization of the DOV may assist in reducing flow. Furtherly, improve the therapeutic efficiency of absolute ethanol treatment and reduce complications

P026

Dominant outflow vein embolization is the key point of treatment for arteriovenous malformation in the mandible

Lixin Su, Zhenfeng Wang, Ren Cai, Yi Sun, Xitao Yang, Deming Wang, Mingzhe Wen, Lianzhou Zheng and Xindong Fan

Purpose: To evaluate the safety, efficacy, and medium-term outcome of treatment for arteriovenous malformation in the mandible with coils and ethanol.

Methods: From January 2014 to July 2015, 9 consecutive patients (mean age 18.9 years [range 11-32 years]) with symptomatic AVMs of the mandible were enrolled. The data from panorama and computed tomography (CT) scans were available before embolization. Diagnosis of AVM in the maxilla was made based on findings from the clinical examination and Imaging features. A microcatheter was induced into the dominant outflow vein via a direct percutaneous puncture needle. Electrolytically detachable coils and 0.018 mm coils were super-selectively placed to decrease the flow and volume of the arteriovenous fistulas via a microcatheter. Absolute ethanol was injected to obliterate the fistulas. Clinical follow-up was performed in all patients. Therapeutic outcomes were determined by evaluating the degree of devascularization at follow-up angiography and symptoms and signs.

Results: The mandible-AVM features presented on contrast-enhanced CT include enhancement in the cancellous bone that is mostly centered on the root of the first molar. In essence, it is an enlarged dominant outflow vein (DOV). Transvenous release of coils combined with absolute ethanol embolization for DOV was used in all cases. The amount of ethanol used ranged from 3 to 30 mL (mean 16.7 mL) in a single session. 8 of 9 patients were cured, and 1 had partial remission. Follow-up times ranged from 18 to 42 months (medium25.6 months), and there was no recurrence of the lesions. Minor complications occurred in 2 of the 9 patients. There were no major complications.

Conclusion: DOV is the pathological basis for the treatment of mandibular arteriovenous malformation. Embolization of DOV in the mandible is a feasible, safe, and highly effective method for the management of mandibular AVMs.

P030

Mosaic GNA11 mutations and the second hit in KRAS in Phakomatosis pigmentovascularis are associated with intraosseous arteriovenous malformations in the jaw

Yi Sun, Deming Wang, Lixin Su, Zhenfeng Wang, Xindong Fan and Ren Cai

P034

Transcatheter renal arterial ethanol embolization for congenital renal arteriovenous malformations

Jingbing Wang, Jianxiong You, Chunyu Jiang, Ren Cai and Xindong Fan

Purpose: To evaluate the efficacy and safety of renal artery embolization (RAE) with ethanol for congenital renal arteriovenous malformations (AVMs) .

Methods: Clinical data of l5 patients (7women and 8men; mean age, 55 years; age range,28–72 years) with congenital renal arteriovenous malformations manifested mainly as gross hematuria were retrospectively analyzed. Among them, 12 cases were initial treatment and 3 cases underwent unsuccessful embolization with coils and polyvinyl alcohol particles in other hospitals. Selective renal angiography was performed in all 15 patients. super-selective catheterization of the culprit arteries was carried out and transmicrocatheter arterial embolization with ethanol in 12 cases or Glubran/Lipiodol mixture in 3cases. Technical success was defined as complete occlusion of feeding arteries with no residual nidus observed on post-embolization angiography. Clinical failure was defined as recurrence of haematuria, presence of AVM on follow-up enhanced computed tomography scan.

Results: 13 patients (86.7%) underwent a single session of RAE, while 2 patients (13.3%) had two sessions of RAE. The ethanol dose used in one procedure Was 5—25m1.Successful embolization of the congenital renal arteriovenous malformations was obtained in all patients. The gross hematuria disappeared within 24— 48 hours after the treatment. Lumbago at treated side, low fever, abdominal distension, nausea, vomiting, etc. occurred within one week and no other serious complications developed. During the 6—108 months follow-up, the clinical success rate after initial RAE was 86.7% (13/15). Overall clinical success rate, including multisession RAE, was 100% (15/15). The technical success rate of 16 procedures was75% (12/16). Among 4 technical failures in 4 patients, 4 achieved clinical success without additional RAE.

Conclusion: Transcatheter arterial ethanol embolization is a safe and effective treatment for congenital renal arteriovenous malformations.

P035

Trametinib effective treatment in a large KRAS-mutated Arteriovenous Malformation

Ren Cai, Yi Su, Zhenfeng Wang, Deming Wang, Lixin Su and Xindong Fan

P040

A complicated KRAS-mutated Arteriovenous Malformation treated by MDT Treatment

Ren Cai, Yi Sun, Zhenfeng Wang, Xia Gong, Deming Wang, Lixin Su and Xindong Fan

P042

Trametinib, the MEK inhibitor, preliminary use in severe extracranial Arteriovenous Malformations

Ren Cai, Yi Sun, Zhenfeng Wang, Deming Wang, Lixin Su and Xindong Fan

Purpose: Extracranial Arteriovenous Malformations(AVMs) were caused by somatic KRAS and MAP2K1 mutations, where upregulate the phosphorylation of the RAS/MAPK pathway. Trametinib, the MEK1/2 inhibitor, was reported effective in treating BRAF mutated melanoma and KRAS mutated non-small cell lung cancer. However, few cases were reported in AVM. In this study, we reported our preliminary clinical report in treating severe AVM by oral trametinib.

Methods: We enrolled 4 Yakes VI type volunteers of AVM patients, who had poor prognoses by formal treatment such as interventional therapy and surgical excision. After obtaining consent from the patients, we performed the genetic sequencing by targeted NGS panel of RAS/MAPK genes for matching the genotype. All patients took the oral trametinib 2mg as a daily dosage following the instructions. The effect was estimated by monthly MRI(enhanced) and standard photo taking. Side effects were also recorded.

Results: 4 patients were 2 KRAS(p.Gln61His), 1 KRAS(p.Gly12Cys), 1 MAP2K1(p.Gln56Glu) somatic mutations. 3 were craniofacial, 1 was abdominal. Patients with MAP2K1(p.Gln56Glu) mutant ended up with intolerable acne, low fever, and edema. All KRAS mutant patients received a good response, especially in KRAS(p.Gln61His) ones, whose lesion and complications such as ulcer and hemorrhage were much more improved than KRAS(p.Gly12Cys). While KRAS(p.Gly12Cys) patient's acne was much severer than the KRAS(p.Gln61His)s'.

Conclusion: This is the first preliminary clinical study of oral trametinib treating severe extracranial AVM. We concluded that in this study, the trametinib was effective in treating the AVM with KRAS mutations. It was still unknown whether or not that trametinib could treat AVM with MAP2K1 mutants. In the meanwhile, we found that KRAS(p.Gln61His) responded better with trametinib than KRAS(p.Gly12Cys). Side effects of trametinib in treating AVM were low fewer, acne, seborrheic dermatitis, and diarrhea, etc. Well-controlled clinical trials are still urgently required to determine the dosing, duration, long-term safety, efficacy, etc.

P063

Preoperative Percutaneous SurgiFlo Injection for Complicated Facial Arteriovenous Malformations

Johanna T. Fifi MD, Maximilian J. Bazil, Alice Lee, Teresa O MD, Milton Waner MD, Tomoyoshi Shigematsu MD PhD and Alejandro Berenstein

Purpose: Facial arteriovenous malformations (AVMs) are high-flow, vascular lesions with shunting through a nidus that often presents with mass effect or bleeding. Surgical resection of large lesions can lead to significant intraoperative blood loss and incomplete AVM resection may result in rapid AVM expansion. Selective preoperative embolization may reduce intraoperative blood loss and help delineate the extent of the nidus. We have developed a percutaneous technique injecting SURGIFLO® hemostatic matrix into the nidus to achieve maximal devascularization. We describe our experience with Surgiflo as an adjunct to traditional preoperative embolization.

Methods: We performed a retrospective chart review of patients treated with percutaneous Surgiflo for facial AVMs over a ten-year period. Patients undergoing preoperative Surgiflo embolization 1-3 days prior to surgical excision were included. The technique involves multiple direct punctures of the facial AVM with 22 and/or 24-gauge angiocaths, geographical confirmation by blood return or employing contrast/ultrasound, and injecting Surgiflo repeatedly in a circumferential fashion around the lesion.

Results: There were 109 patients treated with direct puncture Surgiflo. Thirty-seven of 109 patients had combined therapy. The average age at time of treatment was 27.2 years (SD 14.9 years, range 2-66 years). Patients received between 1-14 separate resections, however, not every procedure was selected for preoperative SurgiFlo. Twenty-one cases were performed with Surgiflo as an alternative to a liquid embolic and 15 were performed with Surgiflo as an adjunct to NBCA, PVA/Embogold Particles, or Onyx18/34. Concerning blood loss, 27 cases (73.0%) achieved less than 20mL, 9 cases (24.3%) between 20-500mL, and 1 case (2.7%) reported over 500mL. There were no perioperative complications with the Surgiflo prior to surgical excision.

Conclusion: Preoperative, percutaneous, intravascular Surgiflo for embolization for facial AVM resection is safe and appears to ameliorate risk of blood loss during surgery.

P064

STAGED MULTIMODAL TREATMENT OF A PREVIOUSLY LIGATED PELVIC ARTERIOVENOUS MALFORMATION WITH A 10-CM ANEURYSMAL DRAINING VEIN

Shin Mei Chan, Julia F. Chen and Naiem Nassiri

Purpose: Herein, we describe a case of a 70-year-old man with a pelvic Yakes IIB AVM erroneously treated years prior via proximal surgical ligation of the feeding right internal iliac artery without obliteration of the nidus or draining vein. At presentation, he harbored a persistent AVM with massive aneurysmal degeneration of the draining vein to 10 cm. Given inaccessibility of the main feeding artery, a staged, multimodal embolotherapeutic approach was devised and executed for obliteration of this life-threatening AVM.

Methods: A multi-stage approach was utilized: 1) Superselective, transarterial embolization of feeding lumbar arterial collaterals via n-BCA and packing coils, 2) retrograde, transvenous coiling of the aneurysmal nidus outflow tract using the complete Penumbra Ruby coil portfolio in a staged systemic manner for complete, large volume sac obliteration, 3) prophylactic covered endovascular reconstruction of the aortic bifurcation – CERAB – to further obliterate feeding collateral recruitment.

Results: Following all operation stages, the patient had uncomplicated recoveries and was discharged on post-operation days 0, 2, and 1, respectively. At one month follow-up after the last procedure, he was clinically stable and had no complaints. His abdominal pulsatile mass was no longer appreciable. He returned to all daily activities. Follow-up US imaging is scheduled in three months.

Conclusion: Nidal obliteration of AVMs remains the cornerstone of successful therapy. Proximal ligation does not work and can lead to life-threatening persistence of the AVM. Proper delineation and classification of AVM angioarchitecture has therapeutic benefits and is routinely recommended. For Yakes IIB AVMs – as demonstrated herein – the aneurysmal venous outflow tract must be addressed. Superselective delivery of high-density packing coils can be used in lieu of liquid embolic agents for large volume elimination. A staged, scaffolding and packing approach is ideal. CERAB is an effective but underutilized prophylactic technique for reducing further collateral recruitment in giant pelvic AVMs.

P069

Clinical characteristics and interventional embolization of pelvic arteriovenous malformations

Xindong Fan, Zhenfeng Wang, Deming Wang, Xitao Yang, Mingzhe Wen, Lianzhou Zheng, Xiao Li, Yi Sun, Ren Cai and Lixin Su

Purpose: To retrospectively assess the technical and clinical safety and effectiveness of interventional embolotherapy for pelvic arteriovenous malformations using absolute ethanol with coils.

Methods: Between March 2013 and October 2016, 10 consecutive patients had pelvic AVMs underwent ethanol embolization combined with detachable and pushable coil-assisted DOV occlusion. All patients completed the course of clinical follow-up and imaging follow-up results from the final treatment session were available for eight patients. The therapeutic effects, degree of devascularization and complications at the time of the follow-up arteriography were evaluated as the clinical outcomes.

Results: Seven (70.0%) of the ten patients exhibited complete responses, and three (30.0%) patients exhibited partial responses. Minor complications, including blistering and focal swelling, occurred in all 10 patients (100%) but showed spontaneous and complete recovery. No major complications occurred.

Conclusion: Ethanol embolization has the potential to control pelvic AVMs using coil-assisted DOV occlusion with an acceptable risk of minor and major complications.

P072

Embolotherapy for high-flow arteriovenous malformations in the hands using absolute ethanol with coil-assisted dominant outflow vein occlusion

Xindong Fan, Deming Wang, Zhenfeng Wang, Ren Cai, Xiao Li and Lixin Su

Purpose: To evaluate the management, outcomes, and technical and clinical safety of coil-assisted dominant outflow vein (DOV) occlusion for the ethanol embolization of high-flow arteriovenous malformations (AVMs) in the hands.

Methods: Between March 2013 and October 2016, 12 consecutive patients who had AVMs with DOV underwent ethanol embolization combined with detachable and pushable coil-assisted DOV occlusion. All patients completed the course of clinical follow-up (range, 14-57 months; mean, 36.7 months), and imaging follow-up results (range, 8-25 months; mean, 16.6 months) from the final treatment session were available for eight patients. The therapeutic effects, degree of devascularization, and complications at the time of the follow-up arteriography were evaluated as the clinical outcomes.

Results: The patients underwent 23 ethanol embolization procedures (range, 1-3; mean, 1.9) with 24 detachable coils and 223 pushable coils. The average stretched the length of the total coils per patient was 320.17 cm. Seven (58.3%) of the twelve patients exhibited complete responses, and five (41.7%) patients exhibited partial responses. Minor complications, including blistering and focal swelling, occurred in all 12 patients (100%) but showed spontaneous and complete recovery. No major complications occurred.

Conclusion: Ethanol embolization has the potential to control high-flow hand AVMs using coil-assisted DOV occlusion with an acceptable risk of minor and major complications.

P073

Comprehensive analysis of dysregulated exosomal long non-coding RNA networks associated with arteriovenous malformations

Xiao Li, Ren Cai, Deming Wang, Lixin Su, Yi Sun and Xindong Fan

Purpose: Arteriovenous malformations (AVMs) are congenital vascular lesions with a high tendency for aggravation and recurrence after treatment, and their genesis remains enigmatic. In this study, we investigated exosomal long non-coding RNA (lncRNA) and mRNA expression and constructed a competitive endogenous RNA regulatory network in AVMs.

Methods: Ethics approval was provided and informed written consent was given prior to the inclusion of all participants. Blood samples were obtained from patients with AVMs and healthy controls at

[hospital] from May to November 2018, and total exosomes were isolated and validated. Differentially expressed exosomal lncRNAs and mRNAs were detected by RNA-seq, analyzed by bioinformatic methods, and validated by qRT-PCR. A competitive endogenous RNA regulatory network was constructed. The characteristics of the captured extracellular vesicles confirmed to the features of exosomes.

Results: A total of 117 dysregulated exosomal lncRNAs and 1,159 dysregulated exosomal mRNAs were identified in AVMs. qRT-PCR demonstrated that the exosomal lncRNAs MIR4435-1HG, LINC00657, LOC101927854, and SEPT5-GP1BB were upregulated in AVM exosomes. The Gene Ontology (GO) terms hemopoiesis and negative regulation of neuron projection development were significantly enriched in relation to dysregulated exosomal cis lncRNAs. A total of 199 GO terms and 80 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were enriched for the dysregulated exosomal mRNAs. In the exosomal lncRNA-miRNA-mRNA-related ceRNA regulatory network, the top 3 significant modules involved 31 dysregulated exosomal lncRNAs and 114 dysregulated exosomal mRNAs, which were enriched in the Rap 1, Ras, MAPK signaling pathways and platelet activation KEGG pathway.

Conclusion: This study comprehensively identified dysregulated exosomal lncRNAs and mRNAs in AVMs, demonstrated the involvement of dysregulated lncRNA and mRNA patterns in AVMs and constructed an exosomal competitive endogenous RNA regulatory network.

P076

Clinical and imaging features of intraosseous arteriovenous malformations in jaws: a 15-year experience of a single center

Xindong Fan, Deming Wang, Zhenfeng Wang, Ren Cai, Xitao Yang, Mingzhe Wen, Lianzhou Zheng and Lixin Su

Purpose: Intraosseous arteriovenous malformations in jaws (j-AVMs) are rare congenital high-flow vascular anomalies with a high tendency of life-threatening hemorrhage and are regarded as one of the most dangerous hemorrhagic diseases in the maxillofacial region. Pre-treatment clinical and imaging evaluations serve as the most important diagnostic modalities.

Methods: A retrospective study involving 211 patients with j-AVMs from November 2003 to November 2017 was performed. The male-to-female ratio of j-AVMs was approximately 4:3. The mean age of the patients with j-AVMs is 21.86.

Results: Bleeding was the main complaint associated with j-AVMs. J-AVMs occurred in the mandible more often than in the maxilla (64.93% and 32.23%, respectively). Most j-AVMs (95.26%) occurred in the posterior teeth region. Classical imaging features of j-AVMs included: an unclear maxillary sinus with a mild ground-glass appearance (maxillary j-AVMs) and a clear oval or irregular lucency that is mostly centered on the root of the first molar (mandibular j-AVMs) on OPGs, enhancement in the cancellous bone on contrast-enhanced CTs. Other atypical features of j-AVMs were also concluded.

Conclusion: A comprehensive diagnose system based on clinical and imaging features of j-AVMs could provide valuable reference data for clinical management of j-AVMs and help avoid improper iatrogenic trauma or delayed treatment.

P078

Potential anti-arteriovenous malformations effect of sirolimus on angiogenesis induced by venous hypertension in the maxillofacial region

Xiao Li, Deming Wang, Zhenfeng Wang, Ren Cai, Yi Sun, Lixin Su and Xindong Fan

Purpose: This study aimed to explore the possible role and mechanism of venous hypertension (VH) in the occurrence and development of arteriovenous malformations (AVMs) and to study the therapeutic effect of VH regulation on AVMs to provide insight into AVM pathogenesis and explore new treatments.

Methods: Maxillofacial VH models were established by cervical vascular anastomosis. Osteogenesis and angiogenesis in the model rats were analyzed by imaging and histology, and the inhibitory effects of intraperitoneal (IP) sirolimus injection on angiogenesis were detected. The effect of sirolimus on the biological behavior of human umbilical vein endothelial cells (HUVECs) cultured in vitro and the mechanism of sirolimus were detected by cytology.

Results: The local microvessel density increased, the vessels showed tortuous dilation, and mRNA and protein levels of angiogenesis-related genes were increased in the venous hypertension environment. These phenomena were alleviated or eliminated by IP injection of a sirolimus solution. Sirolimus inhibited proliferation, tubule formation, migration, invasion, angiogenesis-related gene transcription and translation, and phosphorylation of mammalian target of rapamycin (mTOR) and its downstream substrate proteins S6K1 and 4EBP1.

Conclusion: Abnormal angiogenesis caused by VH is related to abnormal activation of the mTOR pathway, which is important in regulating local angiogenesis; sirolimus inhibited hypertension-induced excessive angiogenesis in vivo and in vitro through the mTOR signaling pathway. This study provides a basis for further mechanistic study of AVM formation and insight into sirolimus as a possible target drug for AVM management.

P080

Mandible Arteriovenous Malformations: Classification and Treatment

Deming Wang, Zhenfeng Wang, Lianzhou Zheng, Mingzhe Wen, Xitao Yang, Lixin Su, Yuchen Shen and Xindong Fan

Purpose: The purpose of this study was to evaluate the outcome of management of mandible arteriovenous malformations(AVMs) based on a modified classification.

Methods: From April 2016 to June 2021, fifty-three patients mandible AVMs that had undergone coils and absolute ethanol embolization treatment were retrospectively evaluated. The mean age was 17.0 years (age range, 6–41 years). All of these cases were treated with detachable coils and/or fibered coils obliteration of the nidus combined with ethanol in fifty-three patients. Clinical follow-up was performed in all patients. Therapeutic outcomes were determined by evaluating the postprocedural image and clinical outcome of symptoms and signs.

Results: Digital subtraction angiography revealed that mandible AVMs originated from the branch of the external carotid artery in all patients. A direct percutaneous puncture approach was used and a microcatheter was inserted into the sac through a direct percutaneous puncture needle in all patients. Coils embolizations for vein sac were performed via direct percutaneous puncture. Follow-up times ranged from 3–43 months(mean, 24.0 months). All patients remained symptom-free and there was no angiographic recurrence of the lesions. Minor complications occurred in seven of the fifty-three patients. There were no major complications.

Conclusion: Embolization of mandible AVMs based on the modified classification facilitated the procedure, and it help to assess the outcome of mandible AVMs management.

P081

Upper Lip Arteriovenous Malformations Cosmetic Outcome: Surgical Consideration after Ethanol Embolization

Deming Wang, Zhenfeng Wang, Lianzhou Zheng, Lixin Su, Yuchen Shen and Xindong Fan

Purpose: Upper lip arteriovenous malformations(AVMs) are rare and cause functional and cosmetic problems This study was to evaluate the surgical outcome of upper lip AVMs after ethanol embolization.

Methods: 8 consecutive patients with symptomatic AVMs of the upper lip from January 2016 to July 2021 were enrolled. The mean age was 20.9 years (age range, 10–35 years). Microcatheter via an artery and direct puncture needle approach was used for ethanol embolization of lip AVMs. Absolute ethanol was injected to obliterate the nidus. After that, cosmetic surgery was performed to revise the upper lip disfigurement and the outcomes of surgical management were assessed.

Results: Absolute ethanol embolization through intraarterial and direct puncture needle approach was used in all cases. The amount of ethanol that was used ranged from 5 to 25 mL (mean, 12.7 mL) in a single session. All of 8 patients with upper lip AVMs were embolized using absolute ethanol getting to devascularized of the nidus, and surgical revision for the upper lip disfigurement. Follow-up times ranged from 6 to 32 months (mean, 18.7 months), and there was no angiographic recurrence of the lesions. Minor complications occurred in two of the eight patients. There were no major complications.

Conclusion: Surgical methods will bring more satisfactory cosmetic outcomes for the upper lip AVMs after ethanol embolization.

P082

How is Quality-of-Life Captured in the Hereditary Hemorrhagic Telangiectasia Population?: A Scoping Review of Quality-of-Life Instruments

Anna J. Gong, Adham Khalil, Prateek Gowda, Tushar Garg and Clifford R. Weiss

Purpose: Hereditary Haemorrhagic Telangiectasia (HHT) is a hereditary disease characterized by arteriovenous malformations found throughout the body's mucosal membranes, skin, and visceral organs. Studies evaluating health related quality of life (HRQOL) in patients with HHT are rapidly expanding but it is unclear what gaps in the literature remain. In this scoping review, we discuss the existing HRQOL outcome measures used in the HHT population, study designs used, and future works required.

Methods: A scoping review was conducted using the Arksey and O'Malley methodological framework. PubMed and Scopus, two bibliographic databases, were queried for studies using keywords relevant to quality of life, patient reported outcomes, and hereditary hemorrhagic telangiectasia. Two independent reviewers completed abstract and full-text screening to identify studies evaluating quality of life metrics in HHT patients, study type, and were collected.

Results: The search yielded 188 unique articles. 68 were selected for full-text screening. 63 met eligibility criteria and included 5 randomised trials (RT) or secondary analysis of a RT (7.9%), 11 cross-sectional studies or secondary analysis of cross-sectional (17.5%), 24 prospective studies (38.0%), 20 retrospective studies (31.7%), 2 qualitative studies (3.2%) and 1 case-control study (1.6%). Among eligible articles, 34 distinct QOL instruments were used across all studies. 19 studies characterized

baseline HRQOL. 47 studies evaluated pre- and post- treatment quality of life. Of these, 36 evaluated HRQOL before and after therapies targeting epistaxis and nasal symptoms; four targeted therapies for liver AVMs and high output heart failure. Three studies evaluated therapies for both epistaxis and GI bleeding. One evaluated treatment targeting GI bleeding alone.

Conclusion: The ability to compare results across studies remains challenging given the heterogeneity in outcomes measures. Further development of standardized, validated HHT-specific PRO instruments is needed. Instruments that capture the multi-system illness experience specific to the HHT patient are particularly critical.

P086

Curative Coils Embolization of Congenital Arteriovenous Fistulae in the Parotid Region

Deming Wang, Zhenfeng Wang, Lianzhou Zheng, Mingzhe Wen, Xitao Yang, Lixin Su, Yuchen Shen and Xindong Fan

Purpose: To evaluate the clinical effect of embolization of congenital parotid arteriovenous fistula (AVF) using coils and absolute ethanol.

Methods: From January 2015 to December 2019, 8 patients with congenital AVF in the parotid region were admitted to the Department of Interventional Radiology XXXXX. AVF was confirmed by angiography of the common carotid artery and vertebral artery through femoral artery puncture with the Seldinger technique. Using coaxial microcatheter to reach the fistula via an artery or using direct percutaneous puncture to reach the dilated vein and introduced microcatheter to the fistula via puncture needle. Combined detachable coils with fiber coils, and used absolute ethanol to occlude the fistula. Then the outcome was evaluated.

Results: There were 7 males and 1 female involved in this study. The average age was 28.5 years (3-58 years). All of the 8 patients were confirmed AVF in the parotid region by angiography, five on the right and three on the left. The feeder artery was the external carotid artery, and the outflow vein was the external jugular vein. Among them, 6 patients used a coaxial microcatheter to reach the fistula via an artery, 2 patients used a direct percutaneous puncture after failure via transarterial approach. All 8 patients were treated with absolute ethanol, the total amount of which was 17.4 ml on average. After embolization, the external carotid angiography demonstrated that the fistula was completely occluded, the branches of the external carotid artery at the distal end of the fistula were normal, and there was no obvious reflux vein. One patient had temporary facial paralysis on the same side of the operation area. The 8 patients were followed up for 6-12 months without recurrence.

Conclusion: Embolization with coils combined with absolute ethanol is a safe and effective treatment for congenital parotid AVF.

P093

Somatic second hit mutations in RAS/RAF/MEK pathway in capillary malformation-arteriovenous malformation: Moving beyond RASA1

Yi Sun, Zhenfeng Wang, Yunjie Zhang, Deming Wang, Lixin Su, Yunjie Zhang, Xindong Fan and Ren Cai

Purpose: The hypothesis of a somatic second hit in RASA1 mutation has been proposed to explain the multifocality of capillary malformation-arteriovenous malformation syndrome (CM-AVM). Due to the rarity and limited availability of tissue samples of CM-AVM, it is challenging to prove this hypothesis. We aimed to identify the potential somatic second hit mutations in both CM-AVM1and CM-AVM2 patients.

Methods: Tissue samples from minimal biopsies were collected from 63 CM-AVM patients with typical phenotypes of AVM/AVF. Several atypical cases were further evaluated with peripheral blood samples. Next-generation sequencing (NGS) with a targeted gene panel of vascular anomalies was performed to identify molecular changes.

Results: Among 63 patients with CM-AVM, second hit mutations in RASA1 (25.4%, 16/63) and EPHB4 (7.9%, 5/63) were the mutant hot spots. Novel second hit mutations in KRAS, MAP2K1, BRAF, ACVRL1, and PIK3CA were also detected. 40 (63.5%, 40/63) patients had germline or mosaic RASA1 mutations, and were diagnosed as CM-AVM 1. 23 (36.5%, 23/63) patients harbored germline or mosaic EPHB4 mutations, and were diagnosed as CM-AVM 2. Among 40 CM-AVM1 patients, somatic second hits in RASA1 were detected in 14 of 40 (35%) patients, following by MAP2K1(5%,2/40), PIK3CA(5%,2/40), KRAS(2.5%,1/40)and BRAF(2.5%,1/40). Among 23 CM-AVM2 patients, somatic second hits in EPHB4 were detected in 5 of 23 (21.7%) patients, following by RASA1 (8.7%,2/23), KRAS(8.7%,2/23), MAP2K1(4.3%,1/23)and ACVRL1(4.3%,1/23). Among 12 patients with mosaic RASA1/EPHB4 mutations, 3 distinct somatic second hit variants in RASA1 were detected in 3 individuals with mosaic RASA1 mutations.

Conclusion: Our data suggested that about half of CM-AVM type 1 and 2 patients have somatic second hit mutations in RAS/RAF/MEK pathway. In addition to the RASA1 and EPHB4 second hit, the identification of variants in KRAS and MAP2K1 genes, which have been proved as pathogenic genes in AVMs, further emphasized the influence of gene alterations in the RAS pathway on CM-AVM.

P094

Complications after embolization of extracranial arteriovenous malformation

Sang Yub Lee, Jongmin Lee, Ho Yun Chung, Seok-Jong Lee, Seung Huh, Ji Yoon Kim and Kyung Rae Kim

Purpose: Arteriovenous malformation (AVM) is difficult to treat and has a high complication rate. Understanding the mechanism and possible complications of sclerosing agents are essential to reduce the complications. This retrospective study reviewed complications after AVM embolization in a single center multidisciplinary team.

Methods: Retrospective data collection performed who received AVM embolization in a single multidisciplinary team last 15 years. Demographics, angiographic classification, embolic agents, and complications were reviewed. Factors that may cause complications were also analyzed.

Results: Eighty-seven patients (mean age 32 ± 28 years and 37 males) received a total 210 procedures during the study period. Location of AVM was as follows: Head and neck (n=27), trunk (n=12), extremity (n=33), and internal organ (n=14). According to Cho-Do's angiographic patterns, AVMs were classified as follows: Type I (n=5), type II (n=14), type IIIa (n=19), type IIIb (n=31), and type IIIa+b (n=14). Ethanol, coil, n-butyl cyanoacrylate (NBCA), bleomycin or those combinations were used for embolization. Total 50 complications (23.8%) were reported during 210 procedures. Nineteen were minor and 31 were major complications. Among 50 complications, trans-arterial access was most common (n=42) and remains were trans-arterial + direct puncture (n=4) and direct puncture (n=4). 46 of 50 (92%) complicated cases were developed by using ethanol or NBCA with trans-arterial injection. After adoption of angiographic classification-based treatment strategy, complication rates were markedly decreased (36% to 11%).

Conclusion: This study showed a 23.8% complication rate in AVM embolization. 31 of 50 complications were major complications requiring additional treatment and prolonged hospitalization. Trans-arterial injection of ethanol or NBCA showed a higher complication rate. And by adopting angiographic classification-based treatment, complication rate was markedly decreased.

P097

Ethanol embolization of lingual arteriovenous malformations: Experience in 52 patients during 11 years

Lianzhou Zheng, Lixin Su, Deming Wang, Zhenfeng Wang, Mingzhe Wen, Xitao Yang, Xiao Li, Yi Sun, Ren Cai and Xindong Fan

Purpose: Lingual arteriovenous malformations (AVMs) are extremely rare in clinical practice, which has limited comprehensive research to find standard treatment protocols. This study summarizes the clinical features of lingual AVMs and assesses the safety and efficacy of ethanol embolotherapy in the management of these lesions.

Methods: Our study group was composed of 52 patients with lingual AVMs treated by ethanol embolization, all of whom received general anesthesia. The optimal access to the nidus of the AVM was by direct puncture, transarterial catheterization, transvenous catheterization, and a combination of these routes. Pure ethanol was manually injected into the nidus of the AVMs. The observed major or minor complications related to ethanol embolization were analyzed, and periodic follow-up of the patients was performed. The devascularization of the lingual AVMs between baseline and final angiography and the clinical outcomes of symptoms and signs after ethanol embolization were evaluated.

Results: There were 171 embolization procedures (mean, 3.3; range, 1-20) including 166 ethanol embolizations performed; the average volume of ethanol injected in a single ethanol embolization session was 29.8 mL (range, 1-65 mL). Therapeutic outcomes were complete response in 17 patients (33%), partial response in 33 patients (63%), and no response in 2 patients (4%). The effective therapeutic outcomes were gained in 96% of the patients with lingual AVMs treated with ethanol embolization; 25 (48%) of the patients had 83 complications, which were necrosis, infection, hemorrhage of the puncture point, transient hemoglobinuria, postoperative irritability, airway constriction, and coil migration, occurring in 78 procedures (46%). Regular follow-up of all the patients was performed, with an average follow-up period of 37.9 months (range, 1-125 months) after the last treatment.

Conclusion: Ethanol embolization of lingual AVMs is safe and efficacious and is recommended to be the potential preferred method in the treatment of these complicated lesions.

P100

Ethanol Embolization of Auricular Arteriovenous Malformations: Preliminary Results of 17 Cases

Lianzhou Zheng, Ren Cai, Yi Sun, Lixin Su and Xindong Fan

Purpose: Because of the relatively rare and extremely varied clinical presentations, arteriovenous malformations (AVMs) involving the auriculae are technically challenging clinical entities to diagnose and, ultimately, manage. The purpose of our study was to present our initial experience of ethanol embolization in a series of 17 patients with auricular AVMs and assess the interim therapeutic outcomes of this method.

Methods: Our study group consisted of 17 patients. Transcatheter arterial embolization and/or direct percutaneous puncture embolization were performed. Pure or diluted ethanol was manually injected. Follow-up evaluation was obtained on the basis of physical examination and angiography at 3- to 4-month intervals and telephone questionnaire at 1-month intervals in all patients.

Results: During the 29 ethanol embolization procedures, the amount of ethanol used ranged from 4 to 65 mL. The obliteration of ulceration, hemorrhage, pain, infection, pulsation and bruit in most of the patients was obtained. The reduction of redness, swelling, and warmth was achieved in all of the patients, and 15 of the patients achieved a downstaging of the Schobinger status. According to the angiographic findings, AVMs were devascularized 100% in 3 patients, 76% to 99% in 5 patients, 50% to 75% in 6 patients, and less than 50% in 3 patients. The most common complications were reversible necrosis and blister.

Conclusion: Ethanol embolization has proved efficacious and safe in the treatment of auricular AVMs and has the potential to be accepted as the primary mode of therapy in the management of these lesions.

P102

Trametinib as a Promising Therapeutic Option in Alleviating Vascular Defects in an Endothelial KRAS-Induced Mouse Model

Ha-Long Nguyen, Laurence M. Boon and Miikka Vikkula

Purpose: Somatic activating KRAS mutations have been reported in patients with arteriovenous malformations. We aimed to generate a murine model of KRAS-induced vascular lesions for preclinical therapeutic trials.

Methods: We activated KRAS within vascular endothelial cells (ECs) by breeding LSL-Kras(G12D);Cdh5(PAC)-CreERT2 [iEC-Kras(G12D)] mice. Neonatal mice were induced(*) via daily intragastric injections of tamoxifen during postnatal days (PN) 1-3. For drug treatment, lactating dames were given 1 daily dose of 2 mg/kg trametinib or vehicle via oral gavage for 5 days, beginning from pups aged PN8. Pups were euthanized at PN14 or 16 and the brain, heart, liver, and intestines were removed for immunohistology. Images were acquired using a Mirax Midi slide scanner or a Zeiss confocal microscope and analyzed with ImageJ. JMP Pro was used for statistical analyses: a student t-test for Comparison between two groups, a one-way ANOVA for >2 groups, and a Kruskal-Wallis Test when a nonparametric comparison was needed. A $p<0.05$ was considered significant.

Results: Mortality and phenotypes varied amongst the pups, with only 31.5% surviving at PN14. Phenotypes (focal lesions, vessel dilations) developed in a consistent manner, although with unpredictable severity within multiple soft tissues (ex. brain, liver, heart). Overall, the pups developed significantly larger vessel sizes, compared to control littermates. We subsequently tested whether the MEK inhibitor trametinib could alleviate lesion progression. Survival of the pups improved to 76.9% at PN14, and the average vessel sizes were closer to controls than in un- and vehicle-treated mutants at PN16.

Conclusion: Trametinib had variable efficacy in treating lesions in our iEC-Kras(G12D*) model. Significant improvement was seen in cerebral vessels; however, no significant differences were seen within the liver amongst treatment groups. Even if the vascular defects were not completely resolved, the enhanced life span demonstrates a positive effect for trametinib and its possible role in the therapy for KRAS-induced VMs in patients.

P103

Absolute ethanol embolization of lip arteriovenous malformations: Observational results from 10 years of experience

Xitao Yang, Mingzhe Wen, Deming Wang, Lixin Su and Xindong Fan

Purpose: This study aimed to evaluate the safety and efficacy of ethanol embolization of lip arteriovenous malformations (AVMs).

Methods: Seventy-six patients with lip AVMs were treated with 173 ethanol embolization procedures. Lip AVMs were treated by direct puncture alone in 21 patients (35 procedures, 21%), transarterial embolization alone in 13 patients (18 procedures, 10.4 %), and a combination of both in 60 patients (120 procedures, 69.3%). Adjunctive surgical resection was performed after embolization for cosmetic purposes based on the patient's request including patient preference, functional impairment, and skin necrosis. The mean duration of follow-up was 30.9 (+/- 27.6) months. Follow-up included clinic visits and telephone follow-up to evaluate for clinical signs and symptoms of the AVMs as well as the quality of life measures.

Results: Fifty-one of 76 patients showed 100% devascularization of AVMs on arteriography, followed by 23 with 76%-99% devascularization, and 2 with 50%-75% devascularization. Of the 76 patients, 40 achieved complete symptom relief, and 25 achieved major improvements in cosmetic deformity after embolization. Additionally, 54 patients achieved satisfactory function and aesthetic improvement with ethanol embolotherapy, while 22 achieved similar outcomes with a combination of ethanol embolotherapy and surgical intervention. Thirty-three complications (including one major complication) occurred in a total of 173 embolization procedures.

Conclusion: Ethanol embolization of lip AVMs is efficacious as a mainstay in managing these lesions, with acceptable complications. Surgical resection after embolization may improve function and cosmesis in a subset of patients.

P109

Treatment of Craniofacial Arteriovenous Malformation with Balloon-assisted Embolization technique: A Single Center Experience.

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Purpose: To report our experience performing dual lumen balloon-assisted embolization in craniofacial arteriovenous malformation (AVM) treatment.

Methods: We performed a retrospective clinical chart review collecting Schobinger staging, angiographic characteristics, type and amount of embolic agents, post procedure complications and long-term follow-up in craniofacial AVMs.

Results: Between 2013-2021, 19 patients were treated (58% Females; mean age 31.6y; range 12-50). Initial Schobinger stage was II in n= 13 and III in n=6. Angiographically, 8 patients presented compact nidus and all, except one, large AV shunt. A total of 22 embolization sessions (mean 1.15/patient) were performed with two types of DMSO compatible balloons (19 Scepter® and 3 Eclipse-duo®). Seventeen procedures (77,2%) had good angiographic outcome (>75% AVM occlusion). Mean FUP time was 22.6months (range 1 – 46). In n=11 (57,8%) we considered total remission (final Schobinger stage I); In n=4 (21%), partial remission (final stage II), among these n=3 with persisting clinical symptoms; In n=2 had no clinical modification (remaining stage III) and n=2 were lost to FUP. In three (15%) complementary treatment with surgical resection was required (mean 161d after embolization). The

main embolic agent used was ethanol 98% (mean 4.5ml) and glue (mean 2.3ml), in n=12 each, followed by ethylene vinyl alcohol (mean 6.3ml) and PHIL (mean 4.6ml) in n=5 each. Among the 22 procedures, 5 complications occurred: 4 minor (2 transient skin discoloration, solved before ending the procedure and 2 embolic material dissemination without clinical repercussion) and one major (vessel rupture during balloon inflation promptly treated with glue injection with no clinical repercussion).

Conclusion: Dual lumen balloon-assisted embolization for craniofacial AVM, as Scepter® and Eclipse-duo®, is a feasible endovascular technique, allowing an accurate AVM nidus embolization without a rapid washout of the embolic material, with an acceptable risk of minor and major complications

P114

SURGICAL TREATMENT OF ARTERIOVENOUS MALFORMATIONS OF THE BUTTOCK

Claude Laurian, Claudine Massoni, Pierre Cerceau, Nikos Paraskevas and Annouk Bisdorff Bresson

Purpose: In buttock AVM's, embolization techniques and surgical resection are treatment options in symptomatic patients. Our aim was to evaluate long-term results after surgical resection.

Methods: Between 1998-2019, 16 patients with AVM of the buttock were retrospectively observed in our vascular anomalies center: 12 had surgical resection. Investigations included Ultrasound (US) and CT scan with vascular reconstruction. The main end points of the study were additional surgery, residual AVM, and quality of life.

Results: Over an 18- year period, 12 patients underwent surgical resection (6 female , 6 men, mean age 27 years (15-42)). Seven had previous procedures: 6 arterial embolization's, 3 surgical biopsies, 1 ligature of internal iliac artery. All were symptomatic: 12 with intermittent pain and a pulsatile mass (6 false port-wine stains) and 7 had trophic lesions (4 with recurrent hemorrhage). CT scans showed most AVMs located in the cellular spaces of the buttock area. Twelve patients had surgical resection of cellular tissue involved with preservation of gluteal muscle.

The mean follow-up was 80 (20- 216) months. In 4 patients, complementary surgery was required: 3 for residual AVM, 2 for extravasation of embolic material extrusion and 3 for surgical reconstruction. On the last follow-up CT scan, 8 patients (67%) had no residual AVM, 2 had persisting hypervascularised tissue, and 2 had residual AVM.

Conclusion: In buttock AVM's, the nidus is located in the cellular tissue without any muscle involvement, which is surprising. Surgery remains a reliable treatment approach with few post-operative complications, but often requires a staged approach to cure the AVM. Pre-operative embolization, particularly with non resorbable embolic material, makes AVM resection and imaging follow-up more difficult (artifact) and should be avoided.

P125

Transcatheter arterial ethanol embolization for congenital renal arteriovenous malformations

Jianxiong You, Chunyu Jiang, Xindong Fan and Jingbing Wang

Purpose: To discuss the effect and safty of trans-microcatheter arterial embolization with ethanol for the treatment of congenital renal arteriovenous malformations.

Methods: Clinical data of 13 patients with congenital renal arteriovenous malformations manifested mainly as gross hematuria were retrospectively analyzed. Selective renal angiography was performed in all 13 patients. After the diagnosis was confirmed. Super-selective catheterization of the diseased arteries was carried out and trans-microcatheter arterial embolization with ethanol was conducted.

Results: A total of 15 procedures were completed in 13 patients. The ethanol dose used in one procedure was 5-25 ml. Successful embolization of the congenital renal arteriovenous malformations was obtained in all patients. The gross hematuria disappeared within 24-48 hours after the treatment. Lumbago at the treated side, low fever, abdominal distension,nausea, vomiting, etc. occurred within one week and no other serious complications developed. During the follow-up period lasting for 4-96 months, no recurrence of hematuria was observed and the renal function remained normal.

Conclusion: Transcatheter arterial ethanol embolization is an economic, safe, and effective treatment for congenital renal arteriovenous malformations.

P132

Treatment of pathologic radial fracture associated with arteriovenous malformations using ethanol injection combined with bone cement implantation: a case report

Chunyu Jiang, Jianxiong You, Ren Cai, Yi Sun, Jingbing Wang and Xindong Fan

Purpose: Arteriovenous malformations (AVMs) are rare congenital vascular lesions associated with early quiescence, late expansion, and, ultimately, infiltration and destruction of local soft tissue and bone. The extremities are a common location of peripheral AVMs. Furthermore, the management of peripheral AVMs using ethanol have been well documented. However, the management of pathologic fracture associated with AVM is still critical challenges for clinicians. Here, we present a case of pathologic radial fracture associated with AVMs that was treated by ethanol injection combined with bone cement implantation.

Methods: A 26-year-old woman, firstly diagnosed as right radial fracture associated with AVMs, which was treated by plaster external fixation instead of internal fixation due to the high risk of massive blood loss. CT revealed that the midshaft radius fractured but with no displacement. However, the second radial fracture occurred 3 months after the first clinical visit. So, she received first-time treatment with ethanol injection. To correct midshaft radius fracture, she received another two interventional operations using ethanol injection combined with bone cement implantation. At last, the acute pain induced by radial fracture disappeared. Furthermore, the function of the right upper extremity recovered.

Conclusion: We present the first report of pathologic fracture associated with AVMs that achieved bony union using ethanol injection combined with bone cement implantation.

P134

METHOD OF ORGAN-PRESERVING REMOVAL OF ARTERIOVENOUS MALFORMATION OF THE JAWS IN CHILDREN

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Purpose: To develop a method for preserving jaws and teeth in case of arteriovenous malformations (AVM) of the jaws in children.

Methods: 10 children aged from 7 to 17 with AVM of the jaws were treated. 2 patients had malformation of the upper jaw and zygomatic bone, 7 patients - of the lower jaw, 1 patient - unilateral malformation of upper and lower jaws. Required examination methods: MSCT of the skull with intravenous bolus contrast enhancement and selective carotid angiography. These diagnostic methods helped to reveal the presence of arteriovenous shunts in the body of jaw with a turbulent blood flow

leading to jaw destruction. All children underwent the operation on AVM removal. Surgery technique: the removal of jaw cortical lamina on the side of malformation from the vestibular side, staged exposure of pathological tissues, represented by destructively altered bone with many pathological vessels. During the operation, the hemostasis was carried out using medical wax; when removal of pathological tissues in the lower jaw, the lower alveolar nerve had to be preserved. To ensure additional hemostasis during an exposure of pathological tissues in the upper jaw, a special catheter with an inflatable holding balloon was inserted into the maxillary sinus cavity. Teeth on the malformation side were preserved and immobilized by means of wire-composite splint. The surgical wound was sutured in layers and drained.

Results: Good clinical result was achieved in 10 children. All pathological tissues were totally removed while jaws and teeth preserved. Maximum follow up period lasted 9 years. In all patients, the pathological cavity was replaced by a full-fledged bone tissue that was confirmed by MSCT. Teeth on the lesion side were immobile and intact.

Conclusion: The described surgery tactic allows to preserve facial bones, teeth and avoiding impaired chewing function and deformation of teeth range and jaws during postoperative period.

P145

Intramuscular capillary hemangioma presenting as pseudo-AVM

Antoine FRAISSENON, Francis FORTIN, Loic VIREMOUNEIX, Juliette MIQUEL, Michel WASSEF and Laurent GUIBAUD

Purpose: Since the entity “intramuscular capillary hemangioma (IMCH)” was reported at the 2012 Workshop in Malmö, few articles have described this condition, which remains a provisionally unclassified vascular anomaly in the latest 2018 ISSVA classification. Herein, our goal is to emphasize a specific and confusing presentation of this entity as clearly mimicking an AVM.

Methods: The clinical, imaging, pathological, and follow-up data of five patients referred to our Vascular Anomaly Center for AVM are reviewed.

Results: Patients (3 males and 2 females) were initially referred at 2, 5, 8, 11 and 29 years for a soft tissue lesion involving exclusively muscular tissue (hand n=1, forearm n=1, thigh n=2, neck n=1). All lesions were high flow lesions with increased arterial flow reaching 2750 mL/min in one case. CT angiography as well as arterial phase of angiography mimicked in all cases an intramuscular AVM with enlarged arterial supply and venous drainage. However, MR images showed in all cases a well circumscribed muscular lesion on both T2- and post-gadolinium T1-weighted images, which was atypical for AVM despite large flow voids within the lesion. In 3 cases, more than one muscle was involved by the lesion. After review by an international expert, pathological examination (available in 3 patients) demonstrated IMCH (called AVM on the initial pathological report in 2 cases). After initial embolization, surgery was performed in 3 cases, whereas two cases underwent exclusively embolizations. After a follow up ranging from 10 to 30 years, the lesions remain stable or do not recur.

Conclusion: Imaging and pathological patterns of IMCH must be recognized in order to avoid misdiagnosis as AVM, since therapeutic management and outcome differ widely between these entities.

P150

Management of lip arteriovenous malformations with percutaneous polidocanol sclerotherapy: A retrospective study of 20 patients

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Purpose: Arteriovenous malformation (AVM) progresses over time and has a high recurrence rate after treatment. This study aimed to evaluate the efficacy of polidocanol sclerotherapy for the treatment of lip AVM.

Methods: A retrospective review of consecutive patients who underwent percutaneous sclerotherapy using 3% polidocanol foam for lip AVM between 2008 and 2019 was performed. Demographics, treatment procedures, and clinical follow-up were analyzed using medical records. Photographs were used to evaluate improvements in appearance at later follow-up as follows: excellent (symmetrical appearance), good (definitive reduction), fair (slight reduction), and poor (unchanged or worse).

Results: A total of 20 patients were identified: 9 men and 11 women. Median age at initial sclerotherapy was 33.9 years. Schobinger stage was II in 14 patients and III in 6 patients. Thirteen patients had received previous treatment. AVM involved the upper lip in 10 patients and the lower lip in 10 patients. The median number of sclerotherapy sessions was 3 times. Blood vessel cramps were used to apply compression on lips in nine patients for flow control, and near-infrared fluorescence imaging was used in seven patients to visualize the blood flow during sclerotherapy. Following sclerotherapy sessions, resection was conducted in 13 patients. The median follow-up period after the initial sclerotherapy was 35 months. The clinical outcome was excellent in 7 patients, good in 11 patients, and fair in 2 patients. Patients with fair results had large lesion extending to the cheek.

Conclusion: This case series demonstrates polidocanol sclerotherapy is an effective treatment for lip AVM with mostly less than four sessions. To enhance efficacy and safety of polidocanol sclerotherapy, use of blood vessel cramps or near-infrared fluorescence imaging were effective. Polidocanol sclerotherapy may have potential effect to inhibit recurrence after following resection.

P172

Treatment of extremity Arteriovenous Malformations using Retrograde Transvenous Ethanol Embolization with tailored outflow-control technique

CHEN HUA, XI YANG, HECHEN JIA, YUANBO LI, YUNBO JIN and Lin Xiaoxi

Purpose: To assess the treatment results of patients with extremity AVMs treated by ethanol embolization using tailored outflow-control technique.

Methods: Medical records of 13 patients (7male, 6 female; age range, 6-58 years) with extremity AVMs between 2016 and 2020 were reviewed. Direct percutaneous puncture of the outflow vein was performed with a tourniquet placed proximal to the puncture site. The outflow was controlled before embolization with an optimal tightness of tourniquet which was confirmed only when opacification of the nidus and the draining veins, but not the feeding arteries, was evident under test injection of contrast medium. The nidus was eradicated by bolus injection of ethanol. Adjustment of the tourniquet was performed after each injection depending on the real-time changes in the hemodynamics and angioarchitecture of the lesion to maintain an optimal outflow-control, exactly the same as (pre-) embolization.

Results: A total of 42 embolization sessions were performed in 13 patients (mean, 3.2±1.8 sessions). The dosage of ethanol used per single session was 19.0±9.2 mL (range, 3.5 to 34 mL). All patients received

post-treatment follow-ups (mean, 40.7±25.8 months). Ethanol embolotherapy was effective in all patients. Cure was achieved in 7 patients (53.8%), and improvement was achieved in 18 patients(46.2%). A total of 4 minor complications occurred in 4 patients during the 42 treatment sessions (4/42, 9.5%). All the complications resolved spontaneously

Conclusion: The results of present study demonstrate that retrograde transvenous ethanol embolization with tailored outflow-control technique is a highly effective therapy for extremity AVMs with a mild risk of minor complications.

P174

Comorbid Congenital hemifacial overgrowth and brain arteriovenous malformation

HECHEN JIA, CHEN HUA, YUNBO JIN and Lin Xiaoxi

P175

Long-term Efficacy and Recurrence of Interstitial Bleomycin Injection for Early-stage Extracranial Arteriovenous Malformation

HECHEN JIA, YUNBO JIN, CHEN HUA, XI YANG and Lin Xiaoxi

Purpose: Early intervention of extracranial arteriovenous malformations (AVMs) plays important role in preventing progression and incidence of associated dysfunction. This study is aim to investigate the long-term efficacy of Interstitial bleomycin injection for early-stage extracranial AVMs.

Methods: Patient with early-stage extracranial AVMs underwent interstitial bleomycin injection from September, 2014 to November, 2017 were reviewed. Clinical outcome, including redness, swelling, warms, and palpitated pulse, and aesthetic outcome were recorded.

Results: Forty-five patients with extracranial AVMs underwent interstitial bleomycin injection(IBI). The median followed up duration was 77(ranging 48-85) months. Of 33 patients achieved significant improvement by IBI, 29 (87.9%) patients remained stable, 4 (12.1%) patients recurred after improvement of AVMs. Nine patients remained stable after additional treatment including surgical resection, embolization or more sessions of IBI, and one patient continue worsening without additional intervention. Long-term complication include hyperpigmentation, unevenness or atrophy of soft-tissue. No major complication was founded.

Conclusion: Interstitial bleomycin injection is a effective therapy for early-stage extracranial with low long-term recurrence and can be an alternative treatment for risky lesions or clinicians do not have enough experience of ethanol embolization.

P182

Potential of Callispheres microspheres in the treatment of vascular malformation: in vivo evaluation in the rabbit central auricular artery embolization model

LAN LUO, XI YANG, YUNBO JIN and Lin Xiaoxi

Purpose: To evaluate the in vivo efficacy of bleomycin-loaded CSM (BCSM) in the rabbit central auricular artery model, so as to lay a theoretical foundation for future clinical practice.

Methods: Ten New Zealand rabbits were applied in this study with left ears assigned to CSM group (N = 10) and right ears assigned to bleomycin-eluting CSM group (N = 10) by a self-control method. Partial rabbit central auricular artery embolization was performed using 0.5mL CSM or 0.5mL BCSM (0.5mL

CSM containing 2mg bleomycin).Macroscopic and histopathological examination were performed after operation.

Results: All rabbits in the CSM group and the BCSM group were successfully embolized by the central auricular artery. The overall operation assessment results of the two groups were similar. Both CSM group and BCSM group can accurately, effectively embolize the target artery, which can lead to similar degree of tissue congestion and inflammation in, while BCSM causes more severe necrosis and vessel damage. Compared to CSM group, BCSM group had less microvascular number over time.

Conclusion: Both CSM and BCSM can effectively embolize the central auricular artery of rabbit ear, while BCSM has a stronger effect on vessel damage and occlusion, which may be an innovative and excellent choice in the clinical practice of intractable vascular malformation related diseases.

P189

Angiogenic Effects of Oscillatory Shear Stress on Endothelial and Vascular Smooth Muscle Cells of Arteriovenous Malformations

Ho Yun Chung, Tae Hyun Park, Jeong Yeop Ryu, Joon Seok Lee, Jennifer H. Shin, Sang Yub Lee, Jong Min Lee, Ji Yoon Kim, Seung Huh, Seok Jong Lee, Suin Kwak, Hyun Mi Kim and Eun Jung Oh

Purpose: The mechanisms that cause arteriovenous malformations(AVMs) have not been elucidated yet. Mechanical stimulation and force by blood flow can be one of pathophysiologic factors of AVM. This study was conducted to test the hypothesis that angiogenesis could be promoted in response to mechanical stress via regulation of pro-angiogenic factors in AVM cells.

Methods: The tissue samples of six patients with AVMs and six tissue samples of normal arteries were used. Endothelial cells(ECs), vascular smooth muscle cells(VSMCs) were isolated and cultured. Shear force for 24 hours with 7 dynes/cm2 was applied. In each group, real-time PCR were performed for Angiopoietin II, Aquaporin1 and transforming growth factor-β receptor-1(TGF-βR1) from ECs and VSMCs. Immunofluorescences was also performed to evaluate the level of protein expressions.

Results: In both normal and AVMs tissues, Angiopoietin II and TGF-βR1 under shear stress showed higher expressions in ECs and VSMCs than under the non-sheared groups. Aquaporin1 of normal tissues ECs with shear stress was not significant difference than without shear stress, and Aquaporin1 of normal tissues VSMCs with shear stress was expressed 1.9 times higher than without shear stress. Aquaporin1 of AVMs showed more decreased expression in ECs and increased expression in VSMCs when shearing stress was applied. In addition, expressions of Angiopoietin II and TGF-βR1 in AVMs were higher in both ECs and VSMCs than in normal tissues with or without shear stress. However, expressions of Aquaporin1 in AVMs were increased only in VSMCs without shearing and in all other cases expressions were decreased than normal tissues. Immunofluorescence also showed similar results.

Conclusion: Although Aquaporin1 was not as expected, Angiopoietin II and TGF-βR1 were associated with angiogenesis of AVMs. Based on this study, AVMs were closely related to shear stress and highly sensitive to it. It is suggested that shear stress can be one of factors of AVMs pathophysiologic mechanism.

P195

Systemic Hemodynamic Changes in Low-Dose Ethanol Embolotherapy for Soft-Tissue Arteriovenous Malformations

XI YANG, CHEN HUA, HECHEN JIA, YUANBO LI, HAO GU, YUNBO JIN and Lin Xiaoxi

Purpose: Ethanol embolotherapy is considered an optimal choice for the treatment of arteriovenous malformations (AVMs); however, there are some complications associated with this treatment. This study aimed to prospectively investigate systemic hemodynamic changes in high-flow AVMs using ethanol embolotherapy.

Methods: From September 2012 to September 2014, 34 male patients and 26 female patients with AVMs who underwent embolotherapy (100 sessions in total) with absolute ethanol were included in this study. Invasive systemic blood pressure (SBP) and heart rate (HR) were recorded before and after each injection and throughout the procedure. Differences between the initial and highest SBP (ΔmaxSP) and HR values (ΔmaxHR), as well as the initial and final SBP (ΔSP) and HR (ΔHR) values, were analyzed. We aimed to explore the potential association between these values and the amount of ethanol that was used.

Results: The total ethanol used was variable (0.01–0.40 mL/kg; mean: 0.20 mL/kg). SBP and HR increased after ethanol injection in most sessions (91 in 100 sessions). SBP decreased in 9 sessions (9 in 100 sessions), while HR, oxygen saturation, and end-tidal CO2 decreased in one of the 9 sessions. ΔmaxSP and ΔmaxHR averaged 38.4 mmHg and 27.8 bpm, respectively (both $P<0.05$), while ΔSP and ΔHR averaged 3.4 mmHg and 4.0 bpm, respectively (both $P<0.05$). ΔmaxSP and ΔmaxHR were positively correlated with the total dose of ethanol injected.

Conclusion: Elevations in SBP and HR during ethanol embolotherapy are common, temporary, and most likely pain-mediated; these increases tend to be positively correlated with ethanol dose. Hypotension may be regarded as an acute complication of ethanol embolotherapy. Hypotension combined with bradycardia, oxygen desaturation, and decreased end-tidal CO2 may be a potential predictor of cardiovascular collapse.

P211

Efficacy and safety of embolo-sclerotherapy of arteriovenous malformation based on the experience from a single specialist centre

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Purpose: To evaluate the efficacy and safety of EST, particularly foamed sodium tetradecyl sulfate (STS) 3% in the treatment of arteriovenous malformations (AVMs) in a single specialist centre.

Methods: All patients with AVMs who underwent EST from 01 January 2015 – 31 December 2019 were retrospectively reviewed. Types of AVM were grouped into Schobinger's classification. All ESTs were performed either with foam sclerosants (STS 3% and polidocanol), ethanol, coils and/or other substances including Onyx and Gelfoam. Outcome measures included treatment effects and

complications. Continuous variables were compared using analysis of variance (ANOVA) F test. Other discrete variables were compared across the categories using Chi-squared tests. P <0.05 were considered significant.

Results: A total of 65 patients with AVMs, with a mean age of 36 years (range 1-74 years) were included. The age of patients with Type IV AVM were significantly (p=0.014) higher than others, while no significant gender difference. The use of EST with foam STS was significantly lower for type IV AVM (0.0%) than the others (p=0.003). Complications were significantly higher in type III AVM (21.1%)) compared to others (p=0.009). A total of 6 (9.2%) patients experienced complications for example, upper lip necrosis and partial facial weakness. The number of days in follow-up was not significantly different across all types of AVM. However, compared to type III AVM, type II showed a significantly lower number of days in follow-up (p=0.038). In the first procedure, the doses of either STS 3% and alcohol were not significantly different across the types of AVM.

Conclusion: EST, in particular foam sclerotherapy with STS 3%, was clinically effective and safe to treat patients with AVM. This study showed that foam sclerotherapy with STS 3% may be used as an alternative to ethanol in the treatment of AVMs although further studies would be needed to confirm this.

P233

Image-guided interstitial bleomycin injections for treatment of high flow arteriovenous malformations in children and adolescents

Anne Gill, Jay Shah, Rachel Swerdlin and C. Matthew Hawkins

Purpose: High-flow arteriovenous malformations (AVM) remain one of the most challenging vascular malformations to treat. Standard treatment options include surgical resection and embolization; based on the location of the AVM, these treatment options may be technically challenging or high risk. Image-guided percutaneous injection of bleomycin (IPIB) into the interstitial perivascular space of AVMs has been proposed as a novel, safe, and efficacious treatment option for AVMs. The purpose of this study is to evaluate the safety and efficacy of interstitial bleomycin injections for the treatment of high-flow AVMs in children and adolescents.

Methods: IRB approved retrospective review identified 15 patients (mean age 11.7 yrs, 12 male, 3 female) from 10/2018- 8/2021 who presented to a multi-disciplinary, tertiary-care vascular anomalies clinic with an AVM. All AVMs were classified according to Schobinger criteria; class I: 1, class II: 5, class III: 9. 10 patients underwent both ethanol embolization with concomitant IPIB; 5 patients had IPIB alone. All patients required multiple IPIB procedures (mean = 3.5; range: 1-10). Location of AVMs: Head/neck = 8; Extremity/hand/foot = 6; chest wall = 1.

Results: 4/15 patients had complete resolution of symptoms; 9/15 patients were clinically improved; 2 patients' symptoms were unchanged (both patients yet to complete the treatment plan). Average clinical follow up = 13.8 months (range 2-25 months). No patients were lost to follow-up. In 5 patients, angiography was performed to validate clinical improvement, and all lesions showed decreased vascularity. Major complications = 0. 2/10 patients had skin injury secondary to EtOH infusion. 3/15 patients had minor, transient skin discoloration at an IPIB site.

Conclusion: IPIB for high flow AVM shows promising improvement in clinical symptoms and vascularity on post-treatment angiography. The findings are not limited to low-severity lesions or specific anatomical locations. The durability of IPIB will need to be critically evaluated.

P248

TREATMENT WITH TRAMETINIB OF A KRAS POSITIVE FAST FLOW ARTERIOVENOUS MALFORMATION IN A SIX YEARS OLD GIRL. CASE REPORT.

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Purpose: Fast flow arteriovenous malformations (AVM) in children are a rare and challenging pathology where genetic testing results can provide guidance in the management. We aim to present the case of a six years old girl with a fast flow AVM treated successfully with trametinib, in order to advocate for the efficacy of this medical therapy in selected cases.

Methods: We describe the case of a six years old girl with a AVM and capillary malformation in upper left limb, who had failed several previous interventions that we treated with trametinib in light of genetic results, obtaining clinical stabilization. We describe genetic findings as well as imaging test results and complications during the follow up.

Results: A six years old girl with no previous clinical history but a AVM and capillary malformation in upper left limb underwent therapeutic embolization, partial resection of the malformation and ligation of an arteriovenous fistula twice due to clinical progression. Depite of our suspicion of a capillary malformation-arteriovenous malformation (CM-AVM), RASA1 was negative and KRAS mutation was found. In the light of this finding and due to the lack of clinical improvement, the patient was treated with trametinib.Trametinib was effective in stabilizing the development of the malformation, achieving so far good control over sintomathology of the patient. To date, she has tolerated the treatment with no side effects. Accidental occlusion of the left brachial artery occurred after embolization due to migration of coils and glue.

Conclusion: Fast flow AVM are a complex and unpredictable pathologies where genetic testing results can provide guidance for targeted medical therapies. Given its relatively high safety profile, trametinib could be a promising option in the treatment of these patients. We advocate for a proper multidisciplinary approach and highlight the value of using genetic testing in the approach of these abnomalies.

P255

Clinical Characteristics And Management Of Cutaneous Toxicities Due To MEK Inhibitor

Joyce Teng and Tiffany Wu

P303

Osteolysis in patients with KRAS-related arteriovenous malformations

Victor Martinez-Glez, Paloma Triana Junco, Carolina García Torrijos, Vanesa Viana-Huete, Pablo Lapunzina, Juan Carlos Lopez-Gutierrez and Lara Rodriguez Laguna

Purpose: Somatic, activating variants of the KRAS gene have been identified in a large proportion of intracranial and extracranial arteriovenous malformations (AVMs). Pathogenic somatic variants in KRAS have also been found in patients with segmental overgrowth and vascular malformations, in patients with melorheostosis and lymphatic malformations, and patients with osteolysis associated with lymphatic malformations within the Gorham-Stout disease. We reviewed a series of patients associating KRAS-related AVMs and osteolysis.

Methods: KRAS-positive cases or those with osteolysis were reviewed in a cohort of 60 patients with AVMs in whom deep NGS custom panel had previously detected a pathogenic variant.

Results: In a total of 17 of the 60 patients with AVMs, somatic activating KRAS variants were detected. All cases showed known pathogenic variants in codons 12, 13, or 61. Nine of the 17 cases had osteolysis. There were six females and three males ranging from 5 to 56 years of age. The AVMs were present in upper limbs (3/9), lower limb (1/9), sacrum (1/9), and the facial (3/9) and cervical (1/9) regions. All of them had osteolysis adjacent to the AVM detected by diagnostic imaging techniques. No osteolysis was detected in any patient showing variants in another known gene causing AVMs.

Conclusion: We show that osteolysis is associated with AVMs caused by somatic pathogenic variants in KRAS. These variants, frequently found in AVMs, are known to stimulate uncontrolled growth of vascular and lymphatic endothelial cells and could also be stimulating the osteolysis —as in Gorham-Stout disease— through the release of osteolytic factors or by osteoblastic inhibition, irrespective of the type of predominant vascular malformation. These results also show that MEK inhibition may represent a promising treatment for osteolysis, a marker of aggressiveness in these patients.

P314

Preliminary study of Genetic Landscape of 1 kilo-genotype of AVM in China

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Purpose: Arteriovenous Malformations are abnormal bypass connections between arteries and veins. Previous research reported that AVMs were mutated by KRAS and MAP2K1. The RAS/MEK signaling pathway plays a crucial role in both oncogenesis and cell proliferation. Trametinib, an inhibitor of MEK, has been used in anaplastic neurofibroma type 1 and melanoma. Formal tissue specimen of extracranial AVM was hard to get and the prevalence was low (60%), which blocked the process of targeted chemotherapy. Therefore, we launch our project of collecting the genetic landscape of 1000-genotype of AVM in China, which will contribute to the genetic study as well as future targeted chemotherapy.

Methods: Up to Nov.2021, 193 extracranial participants were enrolled in this study. Participants were clinically diagnosed with Extracranial AVM without a family history. Peripheral blood(n=193), tissue specimen(n=37), cfDNAm (n=193) were collected, and all specimens were sent to sequenced by targeted Next-Generation Sequence genes panel. Phenotypes and genotypes were recorded by later group matching.

Results: All peripheral blood was negative. The prevalence of tissue specimens was 73%(27/37) while CfDNA was 91%(175/193). The total prevalence was 93%(179/193). In 179 gene mutations, KRAS(n=63), MAP2K1(n=76) were majorities, followed by RASA1(n=9) and BRAF(n=6). In KRAS mutations(n=63), there were 34 KRAS(p.G12) , 13 KRAS(p.E61), and 16 novel mutations. In MAP2K1 mutations(n=76), there were 20 MAP2K1(p.Q56), 34 MAP2K1(p.K57), and 22 novel mutations. For genotype-phenotype matching, all mutations were prone to the craniofacial(28/34 in KRAS(p.G12)). For phenotype-genotype matching, in head and neck KRAS: MAP2K1:BRAF was 48:52:4, and in extremities, KRAS: MAP2K1:BRAF was 12:21:2.

Conclusion: This is the preliminary result of our project of 1000 genotypes of AVM in China. AVM was caused by mutations in RAS/MAPK pathways. The Head and neck were prone to KRAS and MAP2K1 mutations while extremities were prone to MAP2K1 mutations. KRAS(p.G12), KRAS(p.E61), MAP2K1(p.Q56), and MAP2K1(p.K57) were mutation hot spots of AVM.

P333

Investigation of the genetic mechanism of telangiectasia and arteriovenous malformation formation in Hereditary Hemorrhagic Telangiectasia (HHT)

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Purpose: Telangiectasias and arteriovenous malformations (AVMs) are the characteristic lesions of Hereditary Hemorrhagic Telangiectasia (HHT). A recent report demonstrated that somatic loss of function variations in the HHT causative genes, ENG and ACVRL1, are associated with skin telangiectasias (Snellings et al, 2019). Our goal was to investigate if the same somatic second hit genetic mechanism that drives the formation of skin telangiectasias in HHT was responsible for the formation of nasal telangiectasia and solid organ AVMs in patients with HHT.

Methods: DNA was extracted from 15 fresh/frozen nasal telangiectasia, 4 dermal telangiectasia, and 10 control tissue biopsies that had been resected from nine unrelated individuals genetically diagnosed with HHT. DNA was also extracted from formalin fixed paraffin embedded (FFPE) brain, lung, and liver AVM samples. Extracted DNA was evaluated using a ~750 vascular malformation and cancer next-generation sequencing (NGS) gene panel down to 1% somatic mosaicism.

Results: Heterozygous germline mutations were identified in all tissue specimens. Telangiectasia tissues from 5/9 unrelated cases had a pathogenic somatic mutation in the same gene that had the germline mutation. Four of fifteen (26.7%) nasal telangiectasia and one of four (25%) dermal telangiectasia had a detectable somatic second hit. Somatic mosaicism ranged from 1.03-1.96% with an average of 1.44% across the five positive tissues. All other telangiectasia samples and control biopsies tested negative for a detectable somatic mutation. Analysis of the AVM tissues is currently underway.

Conclusion: This is the first report that nasal telangiectasia in HHT are caused by very low level somatic second hit mutations. Our data is consistent with the Snellings et al, 2019 report, and suggest that bi-allelic loss of ENG and ACVRL1 is required for the development of vascular malformation lesions observed in HHT.

P334

Multicenter Assessment of Image-guided Embolization of Arteriovenous Malformations of the Hand using EVOH

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Purpose: To evaluate safety and outcome of image-guided embolization for treating arteriovenous malformations (AVMs) of the hand using ethylene-vinyl alcohol copolymer (EVOH).

Methods: A retrospective, multicenter cohort of 15 patients with AVMs of the hand, treated with 35 image-guided embolotherapies using EVOH was investigated. Clinical history, symptomatology and imaging findings were assessed to evaluate clinical outcome (symptomfree, partial relief of pain, no improvement of pain, and clinical progression despite embolization), lesion devascularization (total, 100%; near-total, 90-99%; substantial, 70-90%; partial, 30-70%; and failure, 0-30%), and peri- and postprocedural complication rates (major complications classified according to CIRSE guidelines). Substratification analysis was performed with respect to the involvement of different anatomical compartments and the injected volume of the embolic agent.

Results: Patients were treated for pain (93.3%), skin ulceration (46.7%), and local bleeding (33.3%). The mean number of embolotherapies was 2.3 (± 1.1), in 3 patients a planned surgical resection was

conducted after embolization. Clinical outcome after a median follow-up of 18 months revealed an overall response of 11/15 patients (73.3%). Imaging at last follow-up revealed 70-99% reduced vascularization in 12/15 patients (80%) including 2 patients (13.3%) with a near-total devascularization of 90-99%. Peri- and postprocedural complications occurred in 8.5% and 31.5%, respectively, including 17.1 % major complications, in one case requiring a previously unplanned resection. Involvement of the finger was associated with increased rates of persistent symptoms compared to other groups (p=0.049). No significant difference between the embolic agent volume injected and complication rates was found (p=0.372).

Conclusion: Image-guided embolization using EVOH-based liquid embolic agents is effective for treating AVMs of the hand in the mid-term. Additional surgical treatments including amputations maybe be required and emphasize the need for an interdisciplinary approach. Overall, AVMs including the fingers were associated with higher rates of persistent symptoms following embolization compared to the involvement of more proximal hand compartments.

P353

Title: Combined embolization and percutaneous cryoablation for local therapy of MAP2K positive high flow vascular lesions. Report of two pediatric cases.

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Purpose: To report two children with MAP2K high flow vascular lesions treated successfully with a combination of embolization and cryoablation.

Methods: Case 1 A 24-year-old female with a history of capillary malformation right back since birth, first presented with a mass at the same site in 2015. In 2018 further enlargement of the mass was associated with intermittent sharp and throbbing pain, significant disfigurement and impairment of quality of life. MR imaging revealed an enhancing high-flow infiltrative mass with feeders from the subclavian, intercostal, and lateral thoracic arteries. Case 2 10yr old boy with a lump left forehead since age 3yr presenting with first onset of headaches. Clinically the lesion was consistent with an AVM, confirmed by MR imaging to be predominantly arising from the left ophthalmic artery and smaller contributions from both superficial temporal arteries (STA). Initial local surgical resection resulted in early recurrence at 3 months.

Results: In case 1 core biopsy indicated an “intra-muscular hemangioma”. The lesion was recalcitrant to sirolimus over the course of 12 months. Mutational analysis revealed a MAP2K mutation and trametinib therapy was initiated, ceased due to shortness of breath, severe acne, scalp and hand rash associated with paresthesia and thrombocytopenia. She then underwent endovascular embolization followed by cryoablation. Follow-up physical exams, most recent 10/2021, have shown continued reduction in the size after a single session of cryoablation. The patient is asymptomatic and reports a significant improvement in QOL. In case 2 angiography demonstrated similar findings to MR imaging. The patient underwent bilateral STA embolization and local left forehead cryoablation. Resected surgical tissue revealed a MAP2K1 mutation after which Trametinib was initiated. Most recent follow up 10/2021 revealed stable resolution of left forehead lesion.

Conclusion: These two cases highlight the innovative use of endovascular embolization and local nidal cryoablation in two MAP2K high flow lesions in children.

P375

Diagnosis and Management of Thoracic and Shoulder Arteriovenous Malformations (AVM)

Wayne Yakes

Purpose: To determine the efficacy of Endovascular Repair of Thoracic and Shoulder Arteriovenous Malformations (AVMs). Previous reports have documented the utter futility of Onyx, Coils, and nBCA of endovascular treatment and authors plainly state these lesions are untreatable.

Methods: 16 patients (11 female, 5 male) presented for repair of shoulder and thoracic AVMs. 3 patients had extension of AVM to the supraclavicular and axillary areas. 3 patients had multiple AVMs. 7 patients had previous failed therapies (embo: PVA/coils/gelfoam; Onyx, nBCA; surgeries: excisions/arterial bypass Left subclavian Axillary, Brachial, and Radial). All patients underwent ethanol endovascular AVM repair; 4 patients had additional coil embolizations (132 treatments). Patient age range 18-76 years; mean age 36.

Results: 15 patients are cured at long-term arteriographic follow-up (follow-up 22 – 192 months; mean follow-up: 42 months). 1 patient with bilateral shoulder AVM and multiple other AVMs therapy is on-going. Complications include 2 patients with minor superficial blisters, 1 patient with transient left radial nerve injury with complete recovery and 1 patient with clot embolus to hand, Rx with urokinase w/distal 3rd phalanx removed. Thus, major complications were 2/132 procedures, 1 being transient. 1 patient at 27-year arteriographic follow-up remains cured.

Conclusion: A JVIR report of shoulder AVM endovascular repair documented total failure of the current approaches even when coupled with shoulder quadrant amputation whereby recurrence was universal. These authors stated that shoulder AVMs were not possible to treat. This report documents that cure of these difficult lesions is possible with ethanol endovascular approaches and direct puncture approaches. No other publications in the world literature documents cure of AVMs in this anatomy consistently.

Long-term cures are noted with the use of ethanol, and ethanol and coils to successfully treat these complex, problematic lesions. A low major complication rate is noted. This patient series finally documents a curative procedure for this lesion.

P377

Ear Arteriovenous Malformation Management

Wayne Yakes

Purpose: To determine the efficacy of Ethanol Endovascular Repair of Ear Arteriovenous Malformation (AVMs).

Methods: 14 patients (9 female, 5 males; age range 6-39 years; mean age: 22 years) with ear AVMs presented for therapy. 2 patients had failed prior embolizations (PVA/coils/nBCA/steroids) and 2 patients had other therapies (laser/excisions/grafting). All patients presented with a grossly enlarged painful ear, and 5 patients had intermittent bleeding. All patients underwent transcatheter and direct puncture ethanol treatments. (86 procedures).

Results: All 14 patients were cured of their AVM at long-term follow-up (mean follow-up: 52 months). 1 patient had transient partial VII nerve palsy. 2 patients had minor blisters and ear injuries that healed on the outer tragus. The longest follow-up demonstrating cure is 12 years.

Conclusion: Ethanol endovascular repair of ear AVMs can achieve cures in this vexing lesion that previously was treated with resection of the ear and with high recurrence rates. This series documents long-term cures of AVMs of the ear and scalp that were not treatable by endovascular approaches as

previously documented in the world's literature. Permanent treatment of the auricular AVMs is documented and no recurrence occurred in any patient. Only one article is published (group from Shanghai, China) emulating this technique with curative results.

P378

Ethanol and Coil Embolization of Complex Dural Arteriovenous Fistula (AVF)

Wayne Yakes

Purpose: To evaluate the efficacy of ethanol, ethanol and coils, nBCA, and Onyx management of complex dural AVF.

Methods: 13 patients (mean age 39 years; 8 females, 5 males). All patients presented with dural AVF involving the transverse sinus, sigmoid sinus and cavernous sinus. 1 patient suffered from high output cardiac state due to the massive size of her combined dural fistula and scalp AVM. All patients underwent MR and cerebral arteriogram evaluations. Patients underwent ethanol embolization, coil embolization, ethanol and coil embolization, nBCA embolization and Onyx embolization to treat these acquired dural AVF.

Results: 12 of 13 patients were endovascularly cured of their disease at a mean follow-up of 5 months. 1 patient's therapy is on going. In those patients who had thrombosed sigmoid sinuses and partially thrombosed transverse sinuses with venous drainage being cortical because of the occluded sinuses, novel approaches were utilized to reach the point of fistualization and treat with coils and ethanol. Sacrifice of the diseased transverse and sigmoid sinus was also utilized to treat the large dural AVF involving these segments. In the cavernous sinus coil embolization and nBCA embolization was utilized via surgical cut-down to access the Superior Ophthalmic Vein to navigate to the Cavernous Sinus when the Inferior Petrosal Sinus was incomplete. In those patients presenting with pulsatile tinnitus it was absent at follow-up. Headaches also resolved. Except for one patient with a transient homonymous hemianopsia, no other complications occurred.

Conclusion: Complex acquired dural AVF can be treated and cured by endovascular means. With meticulous technique complications can be avoided. Many embolic agents are successful in ablating dural AVF in all dural sinuses; ethanol, coils, Onyx.

P379

Ethanol Embolotherapy Management of Pelvic Arteriovenous Malformations (AVM)

Wayne Yakes

Purpose: To determine the curative role of ethanol endovascular and/or ethanol coils in the treatment of large pelvic arteriovenous malformations (AVMs).

Methods: 48 patients (25 females; 23 males; age range: 4 - 86 years; mean age: 37 years) underwent 315 endovascular procedures (6.5 procedure/patient) to treat their pelvic AVMs. 2 patients had bilateral pelvic AVMs (1 male; 1 female). 2 patients had traumatic lesions (2 males). Patients underwent transarterial, retro-grade transvenous, and direct puncture embolization procedures. Embolic agents included absolute ethanol and coils, at times in combination.

Results: 41 patients cured of their pelvic AVM (mean follow-up: 43 months) and 7 patients' treatments are on-going. Pelvic AVMs were cured by using ethanol, coils, or in combination. The addition of coils was particularly useful in those AVMs with aneurysmal venous outflows and in those AVMs with giant venous aneurysms. 3 patients suffered transient sciatic nerve injuries. 1 patient suffered an ipsilateral

perineal numbness that also completely resolved. 4 instances of perineal blistering and tissue injury with one injection, was treated uneventfully. 1 patient had a rectal wall injury requiring bowel diversion, and after healing, underwent re-anastamosis. 1 elderly patient died within 30 days of a 4th procedure from pulmonary embolus (PE). 1 patients coils eroded thru bladder wall and endoscopically removed. 1 patient had a small bleed that was self-limited not requiring transfusion.

Conclusion: Endovascular approaches to manage pelvic AVM have proven to be curative at long-term follow-up. In our cases, surgery adjunctively to remove the AVM has not been required. Despite previous embolizations with coils, glue, Onyx, and surgical ligations prior to being referred to our institution, endovascular and direct puncture approaches using ethanol, ethanol and coils, has proven to curatively manage pelvic AVMs involving soft tissue and bone with low complication rates and no recurrences. Longest arteriographic follow-up documenting cure is 24 years.

P381

Mandibular Arteriovenous Malformation (AVM) Diagnosis and Curative Treatment

Wayne Yakes

Purpose: Determine optimal management strategies for the treatment of intraosseous mandibular AVM.

Methods: 12 patients (9 females, 3 males), age 9 -14; mean age 10, underwent endovascular therapy to treat mandibular AVMs. 9 patients had distinct intraosseous AVMs. 3 had additional multiple facial and intra-maxillary AVMs requiring treatment. Outside institutions recommended massive hemi-facial resections in these patients. 4 patients had prior PVA and gel foam embolization, 1 patient had lip graft, 1 had prior mandible surgery, all that had failed.

Results: All 12 patients have demonstrated MR and angiographic cure of AVMs. 1 patient's therapy is not completed and is on-going. The patients mandibular AVMs cured, a third AVM in this patient in the infratemporal fossa is still undergoing treatment. The follow-up range is 11 months – 41 months, with a mean follow-up of 29 months. No complications were noted in treatment of mandibular AVMS. 1 patient required a minor gingival surgery after treatment of an additional intramaxillary AVM with inferior extension.

Conclusion: Endovascular approaches to manage mandibular AVM can be curative. The mandibular intraosseous variety is largely a fistula between artery and vein within the bone and the bulk are Yakes Type IIIa/IIIb AVMs. All respond and can be cured by endovascular ethanol therapy alone. Surgery was not required in any patient. Surprisingly no complications were encountered in this patient series. Long-term cures are noted in this patient series with endovascular approaches alone. No massive surgical resections in any patient, even in patients with multiple AVMs of the soft tissues, mandible and maxilla, was required to effect cure. In patients who suffered hemorrhages from floating teeth, bone formed and stabilized the teeth and no further hemorrhages occurred. Ethanol sclerotherapy proved curative in mandibular intraosseous AVMs in patients who had additional facial soft-tissue and intramaxillary AVMs that were cured as well at long-term follow-up.

P382

The Retrograde Vein Approach as a Curative Treatment Strategy for Yakes Type I, IIb AVMs, IIIa AVMs, and IIIb AVMs

Wayne Yakes

Purpose: To evaluate the role of Retrograde Vein and Direct Puncture Retrograde Vein Endovascular Repair of Large Peripheral AVMs.

Methods: 87 patients (45 males, 42 females; age: 14 - 72, mean age: 27 years) presented for repair of AVMs involving head and neck, shoulder, chest wall, intra-thoracic, abdominal, renal, pelvic, buttock, and extremities. Ethanol and ethanol/coils were the embolic agents used. Retrograde transvenous catheterizations and vein direct puncture retrograde vein approaches were used in all patients.

Results: 85 of 87 patients are cured at long-term follow-up (f/up: 14 months to 138 months; mean: 42 months) and 2 patients' therapy is on-going. Complications include 1 pelvic AVM post-Rx small bleed not requiring transfusion; 1 pelvic AVM coils eroded into bladder wall removed uneventfully via trans-urethra endoscopy; 2 infections treated with antibiotics; 2 patients' coils superficially eroded and uneventfully removed; and 1 patient subcutaneous hematoma removed (7/87 patients; 8% minor complications).

Conclusion: Retrograde vein and direct puncture vein access and embolization of AVMs in many anatomic locations have proven curative at long-term f/up of AVMs in multiple anatomic locations with a low complication rate. Reproducible and consistent results of this technique have been reported only in 4 publications in the world's literature: by Yakes (1990), Gomes (1994), Jackson (1996) and Cho (2008). In the Yakes AVM Classification System, these approaches can routinely effect AVM cures in Yakes Types I, IIa, IIIa, and IIIb.

P388

Hybrid therapeutic intervention with synchronous collaboration of interventional radiologists and surgeons to care AVMs

Fumio Nagai, Shunsuke Yuzuriha and Masahiro Kurozumi

Purpose: The hybrid therapeutic intervention is composed of synchronous collaboration of interventional radiologists and surgeons in one room, and flow control and sclerotherapy or excision at the same time. We will present our hybrid interventions of AVMs in this presentation.

Methods: Radiologists and surgeons gathered in a hybrid operating room. Angiographic morphology of the target lesion was classified using the modified angiographic classification system (Cho, 2006) according the findings of selective angiography. Considering its flow pattern and the classification, the most efficient and effective flow control way such as temporal surgical clamping with vessel clip/loop, hand compression, balloon blocking, embolizing with gelatin/coil, or combination of these were discussed and decided in the team. Immediately after confirming well flow control by angiography, sclerotherapy or surgical excision of the shunting lesions of the AVM was performed. After the therapeutic session, temporal clamps were released and post-therapeutic flow around the lesion was checked by angiography or CT. All procedures were completed in one room.

Four cases with 3 different types of AVMs were treated with the hybrid therapy.

Results: Various clinical symptoms such as pain, bleeding or disfigurement were relieved although complete cure had not been attained in three cases of them. All AVMs were well controlled.

Conclusion: This hybrid therapeutic intervention composed of multi-disciplinal teams in one room enable to treat problematic AVMS more safely, efficiently and effectively than the ordinal therapies.

P409

Variant Allele Frequency of Mutation in AVM: fistula, nidus cyst, and draining vein

Ren Cai, Yi Sun, Zhenfeng Wang, Deming Wang, Lixin Su and Xindong Fan

Purpose: Arteriovenous Malformations(AVMs) were rare but severe vascular anomalies, which were 4.7% of all Vascular Anomalies but will lead to hemorrhage, ulcer, deformities, and even heart failure, etc. Targeted chemotherapy such as trametinib, the MEK inhibitor was preliminary put into practice in a few severe patients and receive a response. Herein, we report a single case of the mutation variant allele frequency(VAF) of the fistula, nidus cyst, and draining vein of a Yakes II AVM patient. We are about to figure out the targeted therapeutic site and the progressive factor of AVM.

Methods: During our surgical excision of a scalp AVM patient. After the excision, the specimens of fistula, nidus cyst, and the draining vein(proximal and distal) were collected and sent for targeted Next-generation Sequencing. Peripheral blood was also collected and went through NGS as normal control.

Results: As result, peripheral blood and distal draining vein were negative. The rest tissue specimens were somatic KRAS(p.Gln61His) mutants. The VAF of fistula, nidus cyst, and proximal draining vein were 10.32%, 8.27%, and 2.6%, prospectively.

Conclusion: Somatic KRAS(p.Gln61His) could cause extracranial AVM. The Variant Allele Frequency of Mutant was highest in the fistula, then the nidus cyst, which reveals the fact that the mutation attack leading to the fistula was the primary factor of forming AVM. The hemodynamic therapy of the fast flow and high pressure of the draining vein was the secondary factor of forming and aggravating the AVM, which caused the nidus cyst's blowing up. The MEK inhibitor, Trametinib's target were the fistulas. The specimen of biopsy in the fistula was the meaningful method for confirming the genotype before the targeted therapy. More advanced biopsy methods were needed for genotype conforming because of the hardness and danger of the fistula biopsy.

P411

Clinical characteristics, diagnosis and follow-up of Capillary Malformation-Arteriovenous Malformation syndrome (CM-AVM): a systematic review

Adèle Essemilaire, Serge Bracard, Laetitita Goffinet, Jean-Luc Schmutz and Anne-Claire Bursztejn

Purpose: Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM) belongs to RASopathies' family and was first described in 2003. There are two main clinical forms, CM-AVM1 and CM-AVM2, due respectively to mutations of the RASA1 gene or EPHB4 gene.

We aimed to identify the clinical characteristics of CM-AVM syndrome and establishing recommendations for radiological and genetic screening, and follow-up.

Methods: We performed a systematic literature review according to the Preferred Reporting Items For Systematic Review and Meta-Analyses (PRISMA) Guidelines in the MEDLINE database. We included original case reports, research articles, cohort studies, descriptive cross-sectional studies and literature review up to December 31, 2019 that met these following keywords: Capillary malformation - Arteriovenous malformation syndrome OR CM-AVM syndrome.

Results: 45 articles were included with a total of 680 patients with CM-AVM syndrome (81% CM-AVM1, 19% CM-AVM2). Capillary malformations (CMs) were observed in 93.8% of cases and were surrounded

by a white halo suggesting vascular steal in half of CM-AVM1 patients and in a quarter of CM-AVM2 patients. Perioral telangiectasia and Bier's spots were present specifically in CM-AVM2 syndrome. 180 patients (26.5%) presented a fast-flow vascular lesion, with 151 who had at least one arteriovenous malformation (AVM) (83.9%) and 29 who had an arteriovenous fistula (AVF) (16.1%). The prevalence of these fast-flow lesions was 29.8% in CM-AVM1 and 12.3% in CM-AVM2. AVMs/AVFs were diagnosed at the complication stage in 21.7% of cases (diplegia, tetraparesis, epilepsy, loss of abilities, etc.). PKWS was present in 6.5% of patients.

Conclusion: CM-AVM syndrome should be suspected in case of atypical multifocal CMs. AVMs/AVFs must be systematically searched by brain and spine magnetic resonance imaging (MRI) at initial diagnosis. No clinical or genetic features were significantly associated with an increased risk of AVM/AVF. Clinical follow-up is required, with rapid use of imaging in case of new symptoms. A genetic counselling is recommended.

P441

The Distribution of Head and Neck Arteriovenous Malformations

Milton Waner, Whitney Pafford, Tali Shnitzer and Teresa O

Purpose: Clinical observation has noted that head and neck AVMs are not random and occur in distinct anatomic sites. Our objective was to test this and analyze these focal and diffuse sites.

Methods: A retrospective chart review of AVMs of the head and neck presenting to a tertiary care vascular anomalies center was performed over a 17 year period. The head and neck was divided into anatomic zones and the photos of each patient with an AVM were analyzed and charted. Only patients with adequate photo documentation were included. Where available, childhood photos were reviewed as well. The age the lesion became evident was also noted.

Results: There were a total of 187 head and neck AVMs over a 17 year period with an age range of 5 months to 73 years. The similarities within each anatomical site were striking. This leads us to believe that the distribution of focal AVMs of the head and neck is not random and appears to follow a pattern. The most common sites were the cheek (25%) followed by the lower lip (8.6%) and pinna (6.4%). A review of the embryological development of the head and neck suggests that the distribution of AVMs within the head and neck is related and appears to be present at an early stage in embryological development.

Conclusion: The distribution of AVMs within the head and neck is not random and is related to the embryological development of the head and neck and occur most commonly in the cheek.

Capillary Malformations

P051

Genetic landscape in capillary malformation-arteriovenous malformation in East Asia: a large cohort with 85 patients

Yi Sun, Zhenfeng Wang, Yunjie Zhang, Deming Wang, Lixin Su, Xindong Fan and Ren Cai

Purpose: Capillary malformation-arteriovenous malformation syndrome (CM-AVM), a rare autosomal dominant disorder mainly manifested with capillary malformations and risk of high-flow vascular lesions, is caused by germline RASA1 or EPHB4 mutations. Cutaneous mosaicism in RASA1 mutations has also

been identified in CM-AVMs. We aimed to investigate the potential repertoire of genetic alterations in CM-AVM in east Asia.

Methods: Peripheral blood specimens or tissue samples were collected from 85 patients with a clinical diagnosis of CM-AVM. Next-generation sequencing (NGS) with a targeted gene panel of vascular anomalies were performed to identify molecular changes. Several atypical cases were further evaluated by NGS of tissue samples or blood samples from the proband's parents.

Results: Germline RASA1 variants were detected in 36 patients (42.4%; 36/85). Thirty individuals (35.5%; 30/85) had germline EPHB4 mutations. Twelve distinct mosaic mutations in RASA1, and two in EPHB4 (p.Arg739*; p.Leu192fs), with an allele frequency ranging from 5% to 33% were identified in fourteen index patients (16.5%; 14/85). Three individuals (3.5%; 3/85) had both germline mutations in RASA1 and EPHB4, and molecular analysis of the probands' parents showed that these two mutations were inherited from the father and/or mother. Beyond RASA1 and EPHB4 mutations, we identified two upstream variants of the RAS/RAF/MEK pathway in PDGFRB (p.Ile569Val) and EGFR (p.Arg680Trp) genes in two index patients, respectively.

Conclusion: Our data show that most CM-AVMs are caused by germline mutations in RASA1 and/or EPHB4, followed by mosaic RASA1/ EPHB4 mutations. Few atypical cases are caused by upstream gene mutations of the RAS/RAF/MEK pathway. We hypothesize that CM-AVMs can be summarized as complex vascular malformations caused by different gene alterations in the RAS/RAF/MEK pathway. The findings of this study expand the knowledge of genotypes in CM-AVM syndrome, potentially facilitating a more accurate and comprehensive classification of CM-AVM.

P120

Genetic Mutations in Patients with Atypical Sturge-Weber Syndrome

SangEun Yeom, Bernard Cohen, Clifford Weiss, Nara Sobreira, Adrienne Hammill and Anne Comi

Purpose: This study aimed to assess genetic variation which can underlie the vascular malformations in patients presenting for evaluation of Sturge-Weber syndrome (SWS), and to broaden our understanding of related genes and variations.

Methods: Five patients presented with a clinical diagnosis of SWS; all with atypical features leading us to obtain genetic testing. Neuroimaging, and clinical information were gathered, including demographics, neurologic symptoms, characteristics and extent of the birthmarks, family history, and eye involvement. The study was done with patient/parent consent and IRB approval.

Results: Patients were referred for facial capillary malformations and vascular brain involvement suggestive of SWS spectrum; three also had glaucoma. All presented with neurologic symptoms associated with SWS (developmental delays, headaches, and/or stroke), but only 3 had epilepsy. Atypical features included extensive capillary malformation body involvement, reticular capillary malformation, significant limb hypertrophy, vascular family history, lack of seizures, or extensive dilated deep draining vessels on neuroimaging rather than leptomeningeal vascular malformation. Somatic genetic testing in three patients noted a PIK3CA-p.Met1043Ile pathogenic variant in the first, a GNA11-p.R183C pathogenic variant in the second, and a potentially pathogenic 9p23 deletion including PTPRD and PTPRD-AS2 genes in the third patient. Germline testing in two patients demonstrated a RASA1 frameshift pathogenic variant in one, and a germline ~580 kb deletion disruption the COL3A1, COL5A2 and SLC40A1 genes in the other.

Conclusion: While most patients with typical SWS have the GNAQ-p.R183C somatic variant, pathogenic variants in other genes may be identified in atypical patients which have implications for prognosis, drug

trial eligibility, and medical care. Here we propose a workflow for genetic testing indicated for patients presenting for a SWS evaluation based on our experience using germline and/or somatic targeted gene sequencing, gene panels, whole exome sequencing and/or SNP array for molecular evaluation of these patients.

P160

Learning difficulties among children with regional and diffuse capillary malformations

Katariina Mattila, Päivi Salminen and Kristiina Kyrklund

Purpose: To characterize the clinical features of regional and diffuse capillary malformations (CMs) of the limbs in children, and to assess for the occurrence of coexistent learning disabilities (LDs) based on our clinical observation that they may be more common among these patients.

Methods: After institutional approval, the records of all children with CMs treated in our tertiary institution between 2002-2019 were retrospectively reviewed. Regional or diffuse CMs of the limbs were included, as were CMs associated with venous or lymphatic anomalies. CMs involving one limb including the adjacent area were considered regional, whereas CMs spanning >2 anatomical locations were considered diffuse. On control visits, patients >7 years of age were enquired about progress at school, and those who mentioned difficulties were offered neuropsychological evaluation.

Results: We identified 121 patients (68 male; 56%) with regional (n=65; 54%) or diffuse (n=56; 43%) CMs. Sixty-eight (56%) patients had overgrowth or undergrowth of the affected limb. Concomitant venous and or lymphatic anomalies were found on MRI in 19 patients, with an additional 7 patients having prominent veins. Of 60 patients >7 years of age, 23 (38 %) reported LDs which were confirmed by neuropsychological examination. Fifteen of these 23 patients had very similar findings on assessment with poor working memory, dyslexia and auditory-linguistic deficits. No statistically significant correlation between LDs and overgrowth was found (r(60)= .082, p= .534) or between LDs and regional vs diffuse CMs (r(60)= -.188, p=.151).

Conclusion: The prevalence of LDs in our study cohort (38 %) was higher than in the general population (approximately 10 %). LDs were not associated with hypertrophy or the extent of the CMs. We recommend offering neuropsychological assessment for patients with regional or diffuse CMs at the age of 5 years in order to identify those patients who require provision of further learning support at school.

P185

Photodynamic treatment can improve the nonuniform erythema blanching after pulsed dye laser in port-wine stains patients

LAN LUO, GANG MA, YUYAN ZHANG, WENXIN YU, XIAOLIN ZHANG, HANRU YING and Lin Xiaoxi

Purpose: To evaluate the erythema uniformity and the effect of PDT treatment for post-PDL PWSs patients with nonuniform blanching erythema.

Methods: A total of 24 PWSs patients underwent HMME-PDT treatments after receiving multiple 595-nm wavelength PDL treatments. Photographs were taken 12 weeks after each treatment. Efficacy outcomes were evaluated by visual and ImageJ evaluation. The design of study was analytical, observational, open, and retrospective.

Results: The uniformity index was improved by 63.95% (SD = 23.79%). ImageJ assessment of the erythema uniformity had a significant consistency with visual assessment ($R2 = 0.9604$, $p < 0.0001$). No patient developed scarring or permanent pigmentation change.

Conclusion: RGB color mode of photographs helps to evaluate the uniformity of PWSs patients' erythema. Photodynamic therapy can improve the nonuniform erythema blanching caused by PDL for the treatment of PWSs patients.

P191

Histological Characteristics of Port-Wine Stains with Complete Regression after Photodynamic Therapy Treatment: A 7-Year Follow-Up

YUE HAN, WENXIN YU, LIZHEN WANG, QINGQING CEN, LAN LUO, JIAFANG ZHU, XIAOLIN ZHANG, GANG MA and Lin Xiaoxi

Purpose: To investigate the morphological features of PWSs treated by PDT and define the histopathological characteristics of PWS that achieve clinical cure.

Methods: Thirteen patients with facial PWSs, who presented with complete regressive PWS lesions after a mean of 4.38 (SD=4.907) sessions of PDT. Post-treatment biopsy samples were obtained from each patient. The number of blood vessels, vascular diameter, and depth were measured and compared in all samples of PDT-regressive sites, PDT-resistant sites, and normal skin.

Results: Within the 7-year follow-up after PDT, there was no recurrence in the regression area of PDT. In the PDT-regressive sites, within 800 µm of the dermal-epidermal junction, the dilated vessels were occluded and remained fissure-like after PDT.

Conclusion: When the vascular lesions within 800 µm of the dermal-epidermal junction were closed after PDT, a stable clinical cure (no recurrence) was achieved.

P222

The originalclinical sub-typesclassificationofthickeningport-wine stains

CHENWEI ZHAO, GANG MA, JIAFANG ZHU and Lin Xiaoxi

Purpose: Hypertrophy is an important feature in the development of PWS. Based on the summary and analysis of our previous cases, we put forward the refined clinical sub-type classification of thickened port-wine stains.

Methods: We collecting 50 previous typical cases , analyzing their imaging data and clinical characteristics, classified and proposed three clinical sub-types: diffusing thickened type, nodular thickened type, and restricted thickened type. Among them, 32 cases were diffusing thickened type, 7 cases were nodular thickened type, and 11 cases were restricted thickened type.

Results: Diffusing thickened type can appear at early age with obvious feature of full-thickness hypertrophy especially thickening of soft tissue. The color of diffusing thickened type is red to purple, lesions involving the V1 area are more likely accompanied by glaucoma， involving the oral mucosa and perioral area are often accompanied by thickened lips. The lesions of nodular thickened type are often purple, and nodular hypertrophy varying in size and severity. According to the pathological results, it can be further divided in: type I, with exocrine glands increasing and hair follicle hypertrophy; type II, with massively expanded blood vessels, honeycomb-like, fewer interstitial tissues and no exocrine glands increasing or hair follicle hypertrophy observed; type III, highly neoplastic nodules with white texture on the cut surface manifested by mild dilation of blood vessels, diffusing collagen issues, interstitial porosity, lymphocyte focal infiltration, and lymphedema-like changes. The restricted thickened type have the mildest hypertrophy of the three types with ultrasound showing increased subcutaneous

vascular shadows, and often observed with mild thickening of the protruding surface of the lesion, without soft tissue hypertrophy and nodule formation.

Conclusion: Based on the analysis of previous cases, we proposed three sub-types of thickened port-wine stains: diffusing thickened type, nodular thickened type, and restricted thickened type.

P224

Reconstruction of Macrocheilia Secondary to Port-wine Stain (PWS) on the Lower Lip

WENXIN YU, JIAFANG ZHU, YUE HAN, XIANGLEI WU, YING LIU, YING SHANG, XI YANG, GANG MA and Lin Xiaoxi

Purpose: We proposed an innovative method for the treatment of macrocheilia secondary to PWS on the lower lip, which was successfully excised and reconstructed.

Methods: A total of 15 patients underwent multidirectional vector bilateral excision of vascular lip anomalies based on the standard of the normal lower lip. Their preoperative and postoperative standard photographs were taken, and postoperative satisfaction and complications were evaluated.

Results: A follow-up conducted over 6 months indicated that the physicians and patients were highly satisfied with the improvement in lip appearance and symmetry. The reconstruction method of macrocheilia enable patients obtain the aesthetic appearance after surgery. The CRL, a' and b' was normalized to 4.59 ($P = 0.016$), 1.05 ($P < 0.001$), and 1.26 posttreatment ($P < 0.01$). Moreover, the procedure is conducive to the formation of mental and labial groove, and scar is concealed. The sublabial sulcus and the vermillion and cutaneous definition were preserved in all cases.

Conclusion: This surgical method can normalize the lower lip appearance, as well reconstruct a natural mental and labial groove with secret scar. The surgical is friendly to beginner and should considered an alternative method.

P232

A complete lower lip and chin unit resurfacing with expanded cheek flaps: an innovative approach for laser resistant scarring or Port-wine stains

Lin Xiaoxi, YAJING QIU, WEI GAO, HUI CHEN, GANG MA and YUNBO JIN

Purpose: Innovative reconstruction of chin and lower lip as a whole facial aesthetic unit by using an expanded cheek flap.

Methods: Six female patients with scars or laser-resistant vascular anomalies on their lower lips and chins underwent reconstruction with this technique. During the first-stage operation, 100-or 200-ml rectangular expanders were implanted underneath the overlying skin on one or both sides of the patients' cheeks. Then, the superficial defects of the lower lip and chin were resected and expanded to the border of the complete lower lip and chin unit. The expander was removed. The expanded cheek skin flap was dissected and rotated to the lower lip and chin (Supplemental figure). The flap had a random blood supply.The donor site was subsequently closed using the remaining expanded cheek skin tissue. The incisions were made within the nasolabial fold, vermilion border and mandibular border. Transverse or oblique linear scars on the cheek were created for "dog-ear" revisions in some cases when needed. Drainage was performed for two days after surgery.

Results: All the expanded cheek skin flaps survived, and no major complications were observed. All the patients were satisfied with the result.

Conclusion: Many techniques are available for lower lip and chin reconstruction. Expanded cheek flaps are one choice for reconstructing large, superficial defects of the chin and lower lip after surgical resection of scarring or laser resistant Port-wine stains.

P293

Therapeutic Strategies for Untreated Capillary Malformations of the Head and Neck Region: A Systematic Review and Meta-Analyses

Gonca Cinkara, Ginger Beau Langbroek, Chantal MAM van der Horst, Albert Wolkerstorfer, Sophie E.R. Horbach and Dirk T. Ubbink

Purpose: Capillary malformations(CMs) of the head and neck region often cause psychological burden. As the effectiveness of modern laser and light therapies is suboptimal, patients often seek different treatments. Other recognized, but not routinely proposed therapies include cosmetic camouflage, surgery, and medical tattooing. Information on therapeutic outcomes is currently lacking for patients to adequately participate in treatment decision-making.

The objective of this study was to review the effectiveness and safety of recognized therapies for untreated CMs of the head and neck: laser and light therapies, photodynamic therapy, cosmetic camouflage, medical tattooing, and surgery.

Methods: PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched up to 16 December, 2020 for observational and experimental studies examining recognized therapies for untreated CMs of the head and neck. Two reviewers independently evaluated the risk of bias of included studies. Predefined treatment and safety outcomes of pooled data were scored using GRADE.

Results: We included 48 observational and three randomized studies (3068 patients), evaluating nine different therapies. No studies on surgery or cosmetic camouflage could be included. The pooled proportion of patients reaching ≥75% clearance was 43% (95%CI 24–64%;I2 =55%) for the pulsed dye laser (PDL) after three to eight treatment sessions (GRADE-score:very low). Other therapies were less effective. Hyperpigmentation was most frequently described after PDL(incidences up to 40%).Pain was most common after photodynamic therapy. Substantial heterogeneity among studies as to patient characteristics and outcomes limited pooling.

Conclusion: PDL seems preferable for treatment-naive CMs of the head and neck region, but demonstrates greater hyperpigmentation rates compared with other therapies. The results are, however, based on lowquality evidence. Future studies using uniform outcome measures and validated metrics are warranted for study comparability. Based on this systematic review, clinicians and patients should be aware of the limited evidence about the available options when making treatment decisions for CMs.

P309

Two-stage treatment of facial hypertrophic port-wine stains with 1064-nm long-pulsed neodymium: yttrium-aluminum-garnet laser and 595-nm pulsed dye laser

Gang Ma, Qingqing Cen, Lan Luo, Yue H, Pinru Wu and Xiaoxi Lin

Purpose: Pulsed dye lasers (PDL) are most widely used for flat port wine stains (PWSs). However hypertrophic PWSs are less responsive to PDL, because many vessels extend deeper than the maximum penetration depth of PDL. To evaluate the efficacy and safety of a two-stage treatment for hypertrophic PWSs with 1064-nm long-pulsed neodymium: yttrium-aluminum-garnet (LP Nd:YAG) laser to firstly destroy the thicken lesions followed by 595-nm PDL to eliminate the residual thin lesions.

Methods: Sixteen patients with hypertrophic PWSs were treated with 3-5 sessions of LP Nd:YAG laser. After the lesions become thin, 5-8 sessions of 595-nm PDL were subsequently used to damage the residual lesions. Clinical improvements were evaluated. Skin biopsies were performed in selected patients.

Results: Of 16 hypertrophic PWSs, 13 (81.25%) showed excellent improvement, 3 (18.75%) showed good improvement. Superficial scar occurred in two patients. All the patients were satisfied with cosmetic outcomes. Mean depth of the deepest vessel damage for LP Nd:YAG laser and PDL was 4.13 mm and 2.27 mm respectively.

Conclusion: Two-stage treatment with LP Nd:YAG laser followed by PDL can be useful for treating hypertrophic PWSs in adults.

P328

Using Optical Coherence Tomography to Elucidate Age- and Genotype-Phenotype Correlations and Response to Pulse Dye Laser in Patients with Port Wine Birthmarks

Ashley Ng, Erica Baugh, John Moon, Jennifer Tran, Ellen Bruhn, Beth Drolet, Kristen Kelly and Lisa Arkin

Purpose: Port wine birthmarks (PWBs) affect 0.3-0.5% of newborns and impact quality of life due to soft tissue overgrowth, nodularity, and life-altering disfigurement. Laser is the current standard of care which works via selective photo-thermolysis to target aberrant blood vessels, though up to 50% of patients remain refractory to laser. Optical coherence tomography (OCT) is a non-invasive device that uses flow-based imaging to quantify vessel size, density, and depth of blood vessels of the skin. The aims of this study are to understand how age and genotype influence vessel characteristics in PWBs and to investigate vascular features associated with response to laser using OCT.

Methods: Patients with PWBs were recruited to participate in a multi-institutional prospective study. Demographic data, medical history, and clinical photographs were obtained from all patients. OCT measurements were taken of areas with the PWB and of anatomically matched control areas. Response to laser treatment was graded using a visual analog scale comparing pre- and post-treatment photographs. Statistical analyses were conducted using SPSS software.

Results: 58 subjects were included in this analysis, mostly females (33, 57%) with ages ranging from 3 months to 68 years. Linear regression of vessel diameter, density, and depth as a function of age did not reveal significant correlations. 13/58 subjects have been genotyped, and genetic analysis is ongoing. A subset of patients with pre- and post-treatment photographs were assessed for laser responsiveness. In comparison to the excellent responders, poor responders had significantly larger vessel diameter ($p=.011$) and were associated with a greater number of prior laser treatments ($p=.01$).

Conclusion: Inherent differences in the vasculature comprising PWB may underlie responsiveness to laser. We did not find significant correlations between vessel depth, diameter, density and increasing age. This may reflect referral bias in a population extensively treated with laser or limitations of the OCT technology itself.

P402

Facial Portwine Stain Overgrowth Patterns

Milton Waner, Teresa O, Itay Chen, Linda Shannon, Hoyun Chung and Martin Mihm

Purpose: Cobblestone formation and tissue hypertrophy are recognized overgrowth patterns seen in patients with facial portwine stains(PWS). Cobblestones develop in 44% of patients and their average

age of onset is 22 years. 60% of patients develop tissue hypertrophy which starts earlier at around 9 years and affects all of the layers of the dermatome including bone. A third pattern, previously unrecognized appears to affect a smaller percentage of patients but has devastating aesthetic consequences. The purpose of this study is to describe the gross and microscopic features of this PWS overgrowth pattern and compare them to known overgrowth patterns.

Methods: Representative patients of each group were studied. The growth patterns were studied using progression photos from childhood as well as tissue samples from patients undergoing surgical correction. Histopathologic staining included hematoxylin and eosin, SOX10 for neural tissue, and smooth muscle actin(SMA) to delineate perivascular musculature.

Results: Early cobblestones are vascular whereas mature cobblestones are fibrotic. Tissue hypertrophy affects all tissue layers with enlargement of all components. The third pattern is made up of what could be mistaken for massive cobblestones but do not start out as cobblestones. The surface of the affected area is expanded into tissue masses throughout the stain. These masses are comprised of a fibrotic stroma with no neural activity in the superficial layers of tissue. The increased vascularity typical of PWS was only present in the skin overlying these masses.

Conclusion: We describe a third rare, previously undescribed clinical and histologic overgrowth pattern made up of massive collagenous overgrowth and devoid of neural tissue.

Combined Vascular Malformations

P006

Endovenous radiofrequency ablation and combined sclerotherapy treatment of marginal veins in paediatric Klippel-Trenaunay syndrome patients

Lynette LW Wee, Mark Jean Aan Koh, Emily Gan, Valerie Ho, Yi Shan Ang, Sharon Wong, Mei Yoke Chan and Luke Toh

Purpose: Klippel-Trenaunay Syndrome (KTS) is an uncommon congenital disorder caused by somatic PIK3CA mutations presenting with a clinical triad of marginal embryonic veins, vascular malformations, and unilateral hypertrophy. Radiofrequency ablation (RFA) is an emerging treatment for KTS. We describe our experience with endovenous RFA, in combination with sclerotherapy for two children with KTS.

Methods: Patient 1 A 3-year-old girl with KTS affecting her right gluteal region and lower limb. Magnetic resonance imaging (MRI) and venogram showed dilated venous system in the distal posterior right calf associated with a dilated lateral marginal vein draining superiorly into the dilated right inferior gluteal and internal iliac veins. She underwent RFA, injection sclerotherapy, glue embolization and laser therapy. Patient 2. A 6-year-old boy with KTS affecting his pre-sacral, gluteal and rectal veins, as well as the entire right lower limb venous network, presented with recurrent per rectal bleeding since 10 months of age. He required repeated blood transfusions for symptomatic anemia. The child underwent coil embolisation of the gluteal veins, RFA and injection sclerotherapy to the right lower limb embryonic vein (thigh and leg), sclerotherapy to perineal venous malformation. He was also started on oral rapamycin.

Results: There was marked clinical and radiological improvement in both patients 6 months post-procedure, with repeat MRI showing reduction in venous vascularity.

Conclusion: We present our clinical experience with RFA of the marginal vein combined with sclerotherapy and mTOR inhibitors showing good intermediate term success for paediatric patients with KTS.

P011

Sclerotherapy Impact on Quality of Life in Patients with Low-Flow Vascular Malformations

Rachel Swerdlin, Anne Gill, Michael Briones, Sean Evans, Jonathan Meisel, Steven Goudy and C. Matthew Hawkins

Purpose: Little is published regarding the quality of life (QoL) in patients with low-flow vascular malformations (LFVMs) and sclerotherapy's impact. We aim to describe the QoL in patients with LFVMs treated with sclerotherapy.

Methods: IRB approved retrospective review of 266 patients ages 2-21 with LFVMs and prospectively completed PedsQL™ QoL survey(s) between 2016-2019. Age 2-7 surveys answered by parents. Age 8-21 surveys answered by child and parent.

Results: QoL based on total number of sclerotherapy procedures: Parent survey median scores showed significantly lower social functioning score (SFS) for patients attending 8+ sclerotherapy sessions compared with attending 1 (p=0.024), 2 (p=0.004), 3 (p=0.017) or 4-7 (p=0.049) sessions. Child scores showed no significant difference in this domain. Parent and child scores showed no difference in physical functioning score(s) (PHFS) based on number of sclerotherapy sessions. QoL based on sclerosing agent: Parent surveys showed significantly higher scores in the emotional functioning domain in patients receiving doxycycline compared to Bleomycin (p=0.008). There was no significant difference in the PHFS, SFS, psychological functioning (PSYFS), school functioning, or total scores (TS) based on sclerosant type per parents. Child scores showed that in PHFS and PSYFS, doxycycline was associated with a significantly higher scores than 3% sodium tetradecyl sulfate (STS) (PHFS p=0.004, PSYFS p=0.027) and Bleomycin (PHFS p=0.039, PSYFS p=0.021). In the SFS and TS, doxycycline was associated with significantly higher scores than 3% STS (SFS p=0.009, TS p=0.008), Bleomycin (SFS p=0.015, TS p=0.023), and multiple sclerosants (SFS p=0.008, TS p=0.047)

Conclusion: Number of sclerotherapy procedures has minimal impact on QoL in patients with LFVMs. Use of doxycycline was associated with the highest QoL scores by parents and children. As doxycycline was used almost exclusively for macrocystic lymphatic malformations in this cohort, this suggests that patients with this type of LFVM have the highest quality of life throughout treatment with sclerotherapy.

P027

Bleomycin Electrosclerotherapy (BEST): initial results in 100 patients with Vascular Malformations

Lutz Meyer, Özlem Cangir and Susanne Hengst

Purpose: To present initial clinical results with a new method of Bleomycin Electrosclerotherapy (BEST) in Lymphatic Malformations (LM), Venous Malformations (VM) and Arterio-Venous Malformations (AVM).

Methods: Institutional review board authorization was obtained for this study, and the study adhered to the Declaration of Helsinki protocols. Retrospective chart review of 100 consecutive patients treated using the BEST technique between September 2020 and November 2021 in a single hospital center. Primary outcome measures were percent reduction in area and volume of malformation, and percentage reduction in coloration of the cutaneous portion of the malformation. Secondary outcome measures were volume of bleomycin used, and number of treatments required.

Results: One hundred patient records were reviewed. No cases were excluded from this review. Mean age at presentation was 13 years (range 0 to 66 years). 44 patients were female, 56 were male. Seventy cases involved Venous Malformation (VM), 24 Lymphatic Malformation (LM), 1 Arterio-Venous Maformation (AVM), 1 CM, 1 CVM, 1 LVM, 1 CLVM, 1 CAVM. Since follow up time is yet to short no final data can be presented. The first clinical results support the impression of a greater reduction of malformation volume using lower Bleomycin doses and fewer treatments.

Conclusion: Based on the current series of 100 patients, Bleomycin Electrosclerotherapy (BEST) appears to improve outcomes in the treatment of Venous Malformations (VM), Lymphatic Malformations (LM), and other vascular anomalies. Less bleomycin and fewer treatments were required to achieve the improved outcomes. It changed decision making in our center when choosing the appropriate treatment method.

P028

DNA from plasma as a promising alternative for detection of gene mutations in patients with Maffucci syndrome

Yi Sun, Lixin Su, Deming Wang, Zhenfeng Wang, Xindong Fan and Ren Cai

P031

Complex vascular anomalies and tissue overgrowth of limbs associated with increased skin temperature and peripheral venous dilatation: Parks Weber Syndrome or PROS?

Yi Sun, Lixin Su, Deming Wang, Zhenfeng Wang, Xindong Fan and Ren Cai

P041

MONITORING OF THE BLEOMYCIN EFFECT ON THE BODY IN SCLEROTHERAPY OF VASCULAR MALFORMATIONS

Lyudmila Yakovenko, Natalia Kiselyova and Alina Kuzmenko

Purpose: Although bleomycin efficacy and a low complication profile of when used in small doses, safety and general and local condition monitoring are necessary for its use. The aim of the work was to explore the reaction of tissues and changes in blood counts in children after bleomycin sclerotherapy.

Methods: Bleomycin sclerotherapy was given to 8 children with LM a cumulative dose of 27 ±8,05 U and 10 children with VM - 37 ±7,37 U at the age of 6 mon. - 18 years. Local tissue status and blood counts before and after sclerotherapy were assessed.

Results: Short-term side effects were observed in the first 2-3 days after sclerotherapy: edema - at LM - 2,625±0,37 scores, at VM - 3,2±0,32 scores; local pain for NRS - LM 3,2±0,32 scores, VM - 3±0,42 scores. Body temperature was 37.0 - 37.4C - 11% of children. The leukocytes level increased in VM by 21% (5.6 - 6.8; p=0.239), in LM by 46% (6.5 - 9.5; p=0.01); the lymphocytes level increased in VM by 16% (38.0–43.1; p=0.1), in LM by 18% (37.4 – 44.7; p=0.575). Changes in direct bilirubin were observed in both groups: by 27% (2.2 - 2.8; p=0.388) in VM, by 30% (2.3 - 3.0; p=0.184) in LM. ALT levels fell by 20% (20.5 - 18.4; p=0.224) in VM and rose by 15% (20.0–23.5; p=0.469) in LM; glucose in LM rose by 12% (4.84-5.44; p<0.01). D-dimer, which was elevated in 30% of VM children from the beginning, decreased by 20% (375.8 - 304.2; p=0.715), fibrinogen increased by 19% (2.6 - 3.0; p=0.222). Changes in all blood counts ranged from the age norm and only the difference mean values of leukocytes and glucose in LM was statistically significant.

Conclusion: Bleomycin sclerotherapy in small doses is safe for venous and lymphatic malformations primary treatment.

P043

Treatment of Vascular Malformations of the Tongue – a single center experience

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Purpose: Vascular malformations of the tongue may lead to macroglossia, dysphagia, pain and bleeding. The aim of this study was to reveal our interventional treatment options and follow-up results in patients with vascular malformations of the tongue.

Methods: This retrospective single-center IRB-approved study based on a local registry documenting all patients treated at [xxx]. We assessed the following endpoints: type of treatment, symptoms, number of interventions, and volume reduction of malformation, assessed clinically and by MR imaging. Indication for interventional therapy was: (1) bleeding, (2) dysphagia, (3) macroglossia with inability to close mouth, (4) speech disorder or (5) progression of the malformation. If these requirements were not fulfilled, only clinical follow-up was performed.

Results: Fourteen patients (10 females) with a mean age of 12.5 (1-56) years with vascular malformations of the tongue between 07/2017 and 07/2021 were included. Interventional treatment was performed in 12 patients due to symptom burden. In 3 patients with arteriovenous malformations embolization was performed; in case of slow-flow malformations (lymphatic, venous or combined) conventional sclerotherapy was performed in 3 patients, and Bleomycin-electrosclerotherapy (BEST) was performed in 6 patients. Two patients had no symptoms and received regular clinical follow-up. Mean number of interventions was 2,4 (1-7), mean follow-up after last intervention was 2,04 (0,3-3,6) years. All patients were symptomfree after the last interventional treatment. The most significant reduction of the volume of the vascular malformation was observed after BEST.

Conclusion: Treatment of vascular malformations of the tongue is contingent on patient's symptoms burden or progression of the disease. BEST leads to the most significant volume reduction of the vascular malformation.

P056

Novel discovery of GNA11 mutation causing intestinal mesenteric lymphatic malformation and reticulated capillary malformation with subtle overgrowth

A. Yasmine Kirkorian, Bhupender Yadav, Gina Krakovsky, Philip Guzzetta, Christina Feng, Yaser Diab, Natasha Shur and Denise Adams

P061

Non-Hotspot PIK3CA Mutations are More Frequent in CLOVES Syndrome than in Lymphatic Malformations

Pascal Brouillard, Matthieu Schlögel, Nassim Homayun-Sepehr, Raphaël Helaers, Angela Queisser, Elodie Fastré, Anne Dompmartin, Laurence M. Boon and Miikka Vikkula

Purpose: Theragnostic management, treatment according to precise pathological molecular targets, requests to unravel patients' genotypes.

Methods: We used targeted next-generation sequencing to screen for somatic PIK3CA mutations on DNA from resected lesional tissue or lymphatic endothelial cells isolated from lesions. Our cohort (n=148) was composed of unrelated patients suffering from a lymphatic malformation (LM), lymphatico-venous malformation (LVM), capillaro-lymphatic malformation (CLM), capillaro-lymphatico-venous malformation (CLVM), CLVM with hypertrophy (Klippel-Trenaunay-Weber syndrome, KTS) congenital lipomatous overgrowth-vascular malformations-epidermal nevi -syndrome (CLOVES), or unspecified PROS (PIK3CA related overgrowth syndrome).

Results: We identified a somatic PIK3CA mutation in 110 / 148 patients (73%). The frequency of the mutant allele ranged from 1% to 25% in tissues, and up to 48% in isolated endothelial cells. We detected a statistically significant difference in the distribution of mutations between patients with CLOVES syndrome compared to LM.

Conclusion: Most patients (73%) with a LM with or without overgrowth harbour a somatic PIK3CA mutation. However, in about 30% of patients, no such mutation was detected. We detected a hotspot mutation statistically more frequently in isolated LMs compared to syndromic cases. Diagnostic genotyping should thus not be limited to PIK3CA hotspots mutations. Moreover, the higher mutant allele frequency of non-hotspot mutations suggests a wider distribution in patients' tissues facilitating detection. Clinical trials have demonstrated efficacy of Sirolimus and Alpelisib in treating patients with isolated LMs and PROS. Genotyping might lead to an increase in efficacy, as treatments could be more targeted, and PIK3CA-mutant and non-mutant cohorts might have differences in response.

P062

A NEW METHOD FOR TREATMENT OF VENOUS AND ARTERIOVENOUS MALFORMATIONS OF THE HEAD AND NECK IN CHILDREN

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Purpose: To increase the efficacy of treatment in children with venous (VM) and arteriovenous (AVM) malformations in hard-to-reach anatomical areas of the head and neck using a new laser method.

Methods: 7 children aged from 2 to 13 with VM (3 patients) and with AVM (4 patients) of head and neck were treated. In 1 child malformation affected the nasal region with overlapping of the right nasal lumen, in 6 children, malformation affected all tissues from the skin to the mucous membrane of the oral cavity, pharynx, larynx. The affection of mucous membrane was a potential source of life-threatening bleeding. All children underwent a surgery of removal of pathological tissues of the mucous membrane using a laser (semiconductor laser, wavelength of 0,97µm, laser power 5-10 W, continuous wave laser regime, noninvasive). The wavelength of 0,97µm is effective in blood vessel malformations due to high absorption of radiation by hemoglobin. All children underwent operational intervention under general anesthesia: inhalation anesthesia with tracheal intubation.

Results: Positive clinical result was achieved in 7 children. There were no postoperative complications detected. Maximum follow-up period lasted for 1 year. During observation period, there were no pathological tissues detected in the area of mucous membrane surgery. The risk of life-threatening bleeding from oral cavity and nose was excluded.

Conclusion: The advantages of the method described are a short duration of surgery, absence of pain in the postoperative period, minimal intraoperative blood loss. Regardless of the lesion depth, a good clinical result is achieved in all patients. The innovation of this method is in the firstly applied laser with a wavelength of 0.97 µm on venous and arteriovenous malformations with the achievement of a stable

good clinical result: preservation of organ functions, normalization of facial aesthetics, elimination of the risk of bleeding from oral cavity and nose, pharynx, larynx.

P075

Effects of sirolimus for localized intravascular coagulopathy of slow-flow vascular malformations

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Purpose: Slow-flow vascular malformations (SFVMs) include lymphatic malformations (LMs), venous malformations (VMs), complex vascular malformations and Klippel-Trenaunay syndrome (KTS). They can lead to localized intravascular coagulopathy (LIC), measured by elevated D-dimer levels, low fibrinogen, and/or thrombocytopenia. It can cause localized thrombosis and/or bleeding, resulting in pain, swelling, and functional limitations. Several studies have demonstrated a beneficial effect of sirolimus for Kasabach-Merritt phenomenon associated with vascular tumors, but there is no evidence of sirolimus effects for LIC.

Methods: We retrospectively assessed the response to sirolimus, objective radiographic response rate, pain, bleeding and data of coagulopathy, in the SFVM patients treated with sirolimus at pre-treatment and 6 months after administration. The study was approved by the Institutional Review Board of the our institutions.

Results: Ninety-two patients with SFVMs (68 lymphatic malformation, 11 VM, 5 KTS, and 8 mixed vascular malformation) were registered. Symptomatic improvement of pain and bleeding was observed in treated patients. Forty-one SFVMs patients had elevated D-dimer levels prior to treatment and there was a statistically significant decrease in D-dimer levels following treatment with sirolimus (p=0.0026). The abnormality of levels of fibrinogen and platelet counts also improved (p=0.0313, 0.002).

Conclusion: Evidence of coagulopathy and LIC symptoms suggest that sirolimus can improves coagulopathy in slow-flow vascular malformations.

P083

Vascular Malformations of the Perineum

M. Christopher Pastor, Jo Cooke-Barber, Tamador Al-Shamaileh, Manish Patel, Adrienne Hammill, Kiersten Ricci and roshni dasgupta

Purpose: Vascular malformations involving the perineum and genitalia are very rare lesions in the pediatric population however are a significant source morbidity and affect quality of life. Early intervention is preferable to watchful waiting.

Methods: A retrospective chart review of all patients presenting to a tertiary care clinic between 01/01/2009 and 01/17/2020 with perineal vascular malformations was performed, demographics, treatments and follow up were analyzed.

Results: 34 patients were identified with complete data, 19 male and 15 female. 4 were diagnosed prenatally, 15 at birth, and 3 prior to 1 year of age. MRI was the imaging modality of choice. The type of malformation and intervention(s) pursued (Table 1). Treatment modalities included compression (94 %), sirolimus (93 % of patients with LM), sclerotherapy (21 %), and surgical excision (44 %). Laser therapy was used for symptomatic blebs and not definitive treatment. A patient with labial venous malformation underwent six sclerotherapy treatments before definitive surgical resection, which was ultimately curative. A young male patient underwent early surgical resection of a scrotal malformation

and has had a favorable outcome only requiring topical sirolimus. All microcystic lymphatic malformations were treated with surgical excision. The CLOVES and CLVM patients were treated selectively with debulking surgery to improve function. Most of the perineal specific surgeries were performed prior the age of 5 (62 %). The youngest patient to have surgical resection was 4 months of age. Watchful waiting has the potential to develop painful blebs, bleeding, and poor body image.

Conclusion: Perineal vascular malformations are both medically and surgically complex and require a sophisticated, coordinated, multi-disciplinary approach. This is the largest series of these complex patients and noted that the type of vascular malformation has significant clinical implications. Treatment modalities should include both medical and surgical treatments, with early surgical intervention if warranted, for the best cosmetic, social, and developmental outcomes.

P090

Serum Differentially Expressed Angiogenic Cytokines in Head and Neck Vascular Malformations

Liming Zhang, Deming Wang, Lixin Su, Zhenfeng Wang and Xindong Fan

Purpose: Head and neck vascular malformations (HNVMs) are congenital condition that is highly complex and difficult to diagnose, monitor and treat. Therefore, it is critical to explore potential serum cytokines related to the pathology and prognosis of HNVMs.

Methods: The relative expression of 31 angiogenic cytokines in 11 healthy subjects and 11 patients with HNVM was detected by antibody-based microarray. ELISA was used to verify the results. We performed GO and KEGG pathway analyses with the differentially expressed cytokines (DECs). We explored the changes in DECs after treatment of patients with HNVMs.

Results: The expression of IL-10, MMP-9 and VEGF-R2 in patients with HNVMs was significantly higher, while the levels of IL-12p40 and angiostatin were significantly lower in the HNVM group than that in the healthy control group ($P<0.05$). The results were confirmed by ELISA. Functional enrichment analysis showed that DECs mainly participated in the processes of the RAS signalling pathway.

Conclusion: Our study not only indicated that IL-10, MMP-9, VEGF-R2 and IL-12p40 may participate in the development of HNVM but also provided a theoretical basis for the discovery of new targeted molecules in the treatment of HNVM.

P110

BRAF and RASA1 variants in a patient with primary lymphedema and capillary malformation

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Purpose: Description of lymphedema and capillary malformation (CM) phenotype with two variants of the RAF/MEK/ERK pathway.

Methods: Clinical and molecular study.

Results: A 20yo male was referred aged 5yo for congenital lymphedema of the left inferior limb and CM of all limbs and trunk. At 13yo the leg with lymphoedema showed rapid overgrowth requiring distal femur epiphysiodesis. He also developed anemic telangiectasia and recurrent capillary pyoderma of the chest. At 18yo he developed genital lymphedema and scrotal chylorrhea. Lymphoscintigraphy showed important stasis phenomenon, major dermal activity of the left inferior limb, poor left lymph nodes impregnation in number and intensity. MRI identified sinuous thoracic duct and dilation of Pecquet's cistern with dense dilated lymphatic system in the left inguinal and retroperitoneal regions, honeycomb

pattern in the left inferior limb subcutaneous tissues and superficial veins dilation. Vascular Doppler-ultrasound did not find arteriovenous fistula or chronic venous insufficiency. RASA1 direct sequencing identified a germline VUS (c.2021G>A, p.Arg647His) in the patient and his asymptomatic father. CM biopsy identified a known oncogenic BRAF somatic activating mutation (c.1781A>G, p. Asp594Gly, 6.52% allelic frequency).

Conclusion: To the best of our knowledge this is the first case of primary lymphedema, CM and capillary pyoderma ever reported where the lymphatic anomaly is the predominant clinical feature associated with two variants on the RAF/MEK/ERK pathway. The activating somatic BRAF mutation likely induces activation of the RAS-MAPK pathway, explaining the CM-AVM-like phenotype, cutaneous CM and rapid bone overgrowth. As some CM-AVM patients have primary lymphedema, this mutation might alone explain the phenotypic combination. However, the RASA1 VUS might also play a role and further functional studies are needed. In this patient with invalidating lymphorrhea, targeted immunosuppressive treatment should be adapted to the pathogenic variants to offer the best results. Here, RAS-MAPK inhibition with a MEK-inhibitor (e.g. trametinib) might be the best option.

P117

Multi-step Approach to Manage a Large, Open Wound in PIK3CA Variant Klippel-Trenaunay Syndrome

Angela T. Drelles, Taizo Nakano, Lauren Hill and Steven L. Moulton

Purpose: A 7-year-old female with pathogenic PIK3CA variant (pH1047L) Klippel-Trenaunay Syndrome (KTS) of the right lower extremity presented with painful lesional bleeding, resulting in symptomatic iron deficiency anemia and decreased quality of life (A). She underwent partial excision of her veno-lymphatic malformation. This was complicated by poor wound healing, abscess formation and Staph Epidermidis Bacteremia. Subsequent standard-of-care therapeutic attempts failed to achieve wound closure (B). Pharmacotherapy with sirolimus had no impact on pain, bleeding, or wound status.

Methods: The vascular anomalies center collaborated with Burn Surgery to develop a novel therapeutic regimen that would promote wound closure.

Results: The treatment course started with an excisional procedure (C); wound VAC therapy followed by a full-thickness skin graft—which initially failed (STSG). A second STSG was preformed using a wound spray Autologous Epidermal Regeneration (ReCell) to fill in the residual open areas of the graft. Intermittent bleeding episodes were managed by oversewing bleeding sites with 3-0 PDS suture, then covering the open areas with MicroLyte, a bioreabsorbable antibacterial synthetic wound matrix. The wound stabilized but wound healing stalled. EpiBurn, a bioactive tissue matrix composed of human amnion/chorion membrane, was applied to the residual open areas, resulting in cessation of bleeding and near complete closure of the wound (D).

Conclusion: Cutaneous veno-lymphatic plaques in KTS may be complicated by pain, bleeding, infection, and poor wound healing. The underlying PIK3CA activating mutation may impact tissue perfusion and inflammation, which impair wound healing. Our patient was refractory to standard-of-care wound care management and targeted mTOR inhibition with sirolimus. A multi-step approach, including the use of MicroLyte with oversewing of bleeding sites, followed by topical application of EpiBurn promoted wound closure. The family has consented to a trial of targeted PIK3CA inhibition with alpelisib, due to residual pain and risk for infection.

P149

Efficacy of Image-Guided Sclerotherapy for Genital Low-Flow Vascular Malformations in Children and Adolescents

Jay Shah, Krista Childress, Abigail Smith, Rachel Swerdlin, Darshan Variyam, C. Matthew Hawkins and Anne Gill

Purpose: Congenital, low flow vascular malformations rarely effect the genitals in children, have been previously managed by supportive therapy or surgical excision, and are historically difficult to treat. Although percutaneous sclerotherapy has become the standard of care in most anatomical locations, the efficacy of sclerotherapy for genital vascular malformations has not been critically analyzed.

Methods: A retrospective review of patient-level data of an academic multidisciplinary vascular anomaly clinic based in a major urban center in the United States of America was utilized to analyze percutaneous sclerotherapy procedures done for congenital low flow vascular anomalies of the genitals in pediatric patients.

Results: 14 patients (age 1.5 to 16 years old) with low flow genital vascular malformations were treated by sclerotherapy, 5 male and 9 female. 4 lesions were macrocystic or mixed lymphatic malformations, while 10 patients had venous malformations. 9 patients had lesions on vulva/labia, 4 patients with lesions on perineum/scrotum, 1 lesion on the glans penis. On average, to reach end of treatment (functional or cosmetic endpoint) patients required 2.6 sclerotherapy treatments (venous- 2.6 treatments; lymphatic- 2.5 treatments). For venous malformations, patients required treatment with 3% sodium tetradecyl sulfate (3 patients), bleomycin (4 patients) or both (3 patients). For lymphatic malformations doxycycline (2 patients) or bleomycin (2 patients) was used. No major complications were noted. 2 patients had local skin necrosis, which healed completely without surgical intervention.

Conclusion: Percutaneous sclerotherapy is a safe and efficacious treatment for low-flow vascular malformations of the genitals in pediatric and adolescent patients.

P153

Real World Experience Using Alpelisib In The Management Of Children And Adults With PROS.

Joyce Teng, Linsey Jacobs, Karen Griggs and Jinwoo Lee

P181

Use of MEK inhibitor in Parkes Weber syndrome with RASA1 mutation

Joana Mack and Shelley Crary

Purpose: Capillary malformation-arteriovenous malformation (CM-AVM), commonly known as Parkes Weber syndrome is a vascular malformation with an autosomal dominant germline inactivating mutation of the RASA1 gene. The phenotypic appearance can vary significantly but can be extensive and debilitating involving limb overgrowth and vascular malformations. Targeted therapy has come to the forefront of treatment for this syndrome. We describe a patient with CM-AVM and RASA1 (c.2604.2A>C heterozygous) mutation who failed treatment with an mTOR inhibitor(sirolimus) and subsequently, a MEK inhibitor(trametinib).

Methods: Chart review.

Results: Patient is a 4 year old female with extensive capillary malformations, micro-arteriovenous fistulas, overgrowth of the right lower extremity along with significant spinal arteriovenous fistulas(AVF). Leg asymmetry was noted in utero. Family history includes RASA1 mutation in mother and brother (who

are both grossly asymptomatic), 2 maternal half-aunts–one with a brain aneurysm and the other with capillary malformations. Surgeries include embolization of the her spinal AVF which developed into a new shunt/AVF. Patient has had significant lower extremity pain. After the use of compression stockings, she bled profusely from her affected right leg which is chronically diffusely warm and 2.5 times larger than the left. Patient was treated with therapeutic levels of an mTOR inhibitor(sirolimus) starting at 2 years old for about a year with no improvement. She was then treated with a MEK inhibitor(trametinib) at 4 years old due to worsening pain and mobility. She was treated for 6 months and had several side effects, including significant hair loss and osteomyelitis which interrupted trametinib for 6 weeks. Assessment at the end of 6 months showed no clinical or radiological improvement, therefore, medication was stopped.

Conclusion: Although oncologic diseases with RASA1 mutation have shown some success with MEK inhibitor treatment, the benefits are unclear in patients with vascular malformations. Targeted therapeutic clinical trials within this population are greatly needed.

P210

The genotype of slow-flow vascular malformation correlates with the efficacy of sirolimus: a pilot study of 24 patients

Hongyuan Liu, Xi Yang, Li Hu, Zian Xu, Hui Chen and Lin Xiaoxi

Purpose: Sirolimus is increasingly used in managing complicated vascular anomalies, while the heterogeneity of the efficacy is still unclear. This study is trying to assess the efficacy of different genotype of slow-flow vascular malformations.

Methods: We retrospectively assessed the medical history, clinical features, imaging features and the genetic test of 24 slow-flow vascular malformation patients who were treated with sirolimus standardly at least 3 months.

Results: There are 37.5% patients with PIK3CA somatic mutation, 41.67% with TEK somatic mutation, 25% without PIK3CA or TEK mutation and 1 patient with both PIK3CA and TEK mutations. Among all the patients, 75% showed improvement of syndromes and 37.5% showed decreased volume of lesion. As for patients with mutation, the efficacy rate is 83.3% and 50% patients with decreased lesion volume. The efficacy rate of patients without mutation is 50% and none of them showed decreased lesion volume.

Conclusion: This pilot study of small simple size indicates the relationship of genotype and the efficacy of sirolimus and prompt the subsequent study to delineate the indications of sirolimus.

P235

Case of Mosaic RASopathy due to KRAS variant G12D with segmental overgrowth and associated peripheral vascular malformations

Vanessa Schmidt, Ilse Wieland, Walter A. Wohlgemuth, Jens Ricke, Moritz Wildgruber and Martin Zenker

P251

The prospective observational study of patients with intractable venous malformation or Klippel-Trenaunay Syndrome to guide designing a proof-of-concept clinical trial for novel therapeutic intervention

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Purpose: The natural history of intractable venous malformation (VM) and Klippel-Trenaunay Syndrome (KTS) has not been quantitatively studied. To obtain benchmark characteristics to guide designing a clinical proof of concept study of our novel drug candidate, the clinical course of the patients was followed for 6 months.

Methods: Forty-four patients were enrolled from 2019 through 2021 and characterized for the demographics and clinical features. The natural course of each patient was evaluated based on lesion volumes, performance status (PS), pain visual analogue scale (VAS), quality of life (QoL), history of infections, and coagulation and fibrinolysis markers at baseline and Day 180. Lesion volumes were measured centrally with MRI using three-dimension volumetric segmentation.

Results: Thirty-four patients (VM=17, KTS=17) whose lesion volume was evaluable by MRI were analyzed (median age 15.9; range 1-53). The mean percent change in lesion volume was 6% (SD 28%) and there was no statistically significant difference between the baseline and Day 180 values. Baseline characteristics did not meaningfully affect changes in lesion volume over 6 months. However, individual data indicated that infection induced transient increase in lesion volumes by MRI. Pain VAS in VM patients and fibrinogen in KTS patients were improved by 9 mm (p=0.043) and by 1.2-fold (p=0.007), respectively, although there were no clinical observations that are evident for the improvement. The lesion volume and pain VAS did not exhibit any correlation at baseline or their changes over 6 months. QoL score was negatively associated with diagnosis (KTS), presence of concomitant therapy, analgesic use, history of resection surgery and infection, lesion volumes, PS, and pain VAS.

Conclusion: This study has demonstrated that no clinically meaningful improvement or deterioration of disease status occurs over 6 months in patients with VM or KTS. Based on the results, a phase 2 clinical trial of a new drug candidate was designed and initiated.

P262

The Rationale for MRI-guided Percutaneous Sclerotherapy of Deep and Eloquent Venous and Lymphatic Malformations

Amanda Baker, Travis Caton, Eric Smith, Matthew Amans, Steven Hetts, Randall Higashida, Andrew Nicholson, Christopher Dowd and Daniel Cooke

Purpose: MRI provides superior evaluation of venous- and lymphatic malformations (VM, LM) for diagnosis and staging. However, ultrasound (US) guidance remains the dominant imaging modality for guiding percutaneous sclerotherapy. Multiple small studies have previously described the technique and success of the MR-guided approach to percutaneous sclerotherapy of low-flow vascular malformations. The purpose of this study is to report a large single-institutional experience with MRI-guidance for percutaneous sclerotherapy of venous- and lymphatic malformations deemed less favorable for ultrasound (US) guided approach.

Methods: Imaging and clinical records between 2016 and 2021 were reviewed. Salient clinical characteristics were extracted from the medical record, including rationale and indication for MR

guidance. Technical aspects including sclerosing agent, lesion location, complications, and outcomes were documented. MR imaging parameters, procedural technique, and potentials are also presented.

Results: In the five-year study period, 25 patients underwent a total of 33 MR-guided sclerotherapy procedures. Three patients were excluded for resolution of the lesion on pre-procedural imaging. Mean patient age was 22.1 (range 2 months to 76 years). The most frequent location was retro-/peri-orbital (n = 6 patients for 13 treatments), followed by rotator cuff musculature (n = 4), deep foot/ankle (n = 4), gluteal musculature (n = 3) and deep compartments of the thigh, arm, and neck (n= 2, each) and face (n = 1). Each case resulted in technically successful deposition of sclerosant agent, confirmed by intraprocedural fat-saturated sequence after gadolinium contrast injection. Two post-procedural complications were encountered. Five patients underwent percutaneous sclerotherapy with US-guidance prior to the initiation of MR-guidance at our institution.

Conclusion: The use of MR-guidance for percutaneous sclerotherapy procedures expands the range of VM and LM amenable to treatment which are inaccessible or less safe as compared to conventional US-guidance.

P264

Targeted therapy improves function in head and neck PIK3CA-related overgrowth

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Purpose: Management of head and neck PIK3CA-related overgrowth spectrum (PROS) conditions is challenging as multiple invasive procedures often leave persistent malformation and impaired function. Targeted medical therapy using the PI3K inhibitor, apelisib, has not been previously reported for treatment of head and neck PROS conditions, including PIK3CA-induced head and neck lymphatic malformations. This study reports the effects of apelisib on function in pediatric patients with head and neck PROS conditions.

Methods: Prospective IRB-approved cohort study of five patients with PROS conditions, placed on alpelisib (50mg/day per Novartis extended use protocol). Demographics, adverse events, serial photos, functional outcomes, and endoscopic data were collected throughout.

Results: Median participant age at treatment initiation was 4 years (Range 2-13) and average drug therapy duration was 10 months (range 4-22 months). Participant lymphatic malformation stages 2-5 (n=4) were represented, and one had facial infiltrating lipomatosis. All participants were compliant with therapy and monthly laboratory assessments. No adverse events occurred and participants had normal growth. Serial photos demonstrated changes in facial morphology. Via monthly standardized functional outcomes questionnaire administration, all participants reported: decreased oral bleeding, tongue swelling, drooling, improved chewing, swallowing, vocalization, breathing, better sleep quality, less sadness or anger, and less avoidance of public activities. Common invasive therapy was avoided (i.e., tracheotomy) in all participants. Serial nasopharyngoscopy performed in participants with oral/pharyngeal bleeding, dysphagia and/or snoring demonstrated reduction of pharyngeal inflammation and supraglottic laryngeal edema.

Conclusion: Apelisib was well tolerated in patients with head and neck PROS conditions. Improved function, quality of life, increased upper airway size and invasive procedure reduction was observed in all participants.

P275

Diagnostic Utility & Lessons Learned from Deep Sequencing Over 300 Vascular Malformations

Candace T. Myers, Catherine R. Paschal, Madelyn Gillentine, Darci Sternen, Bo Yuan, Zoe Nelson, Dana M. Jensen, Victoria Dmyterko, Kaitlyn Zenner, Jonathan A. Perkins and James T. Bennett

Purpose: Vascular malformations are primarily caused by tissue-restricted somatic mutations. Mutation identification increasingly drives targeted medical therapies but requires specialized diagnostic approaches. Here we report results on over 300 individuals using VANSeq, a clinical sequencing assay for vascular malformations validated for blood, saliva, fresh-frozen tissue, and formalin-fixed paraffin-embedded (FFPE) tissue.

Methods: We developed a high-sensitivity next-generation sequencing assay with high coverage (>1,000x read depth) across 44 genes.

Results: Over two years, we performed 317 clinical tests on 304 individuals. The most common clinical indication was isolated vascular malformation (lymphatic or venous), followed by vascular malformation with overgrowth. Of the 317 samples tested, 54% had pathogenic or likely pathogenic findings, 2% had variants of uncertain significance, 36% were negative (no variants reported), 4% had results pending, and 4% of testing could not be completed due to insufficient or poor-quality DNA. DNA was extracted from FFPE tissue (41%), fresh-frozen tissue (33%), peripheral blood (22%), or saliva (4%). Diagnostic yield was highest when affected tissue was tested. The variant allele frequency (VAF) was less than 5% in nearly half of samples with a mosaic pathogenic variant identified (43%, n=143). Across the cohort, variants were reported in 25 of the 44 genes tested; PIK3CA accounted for the majority of positives (n=85), followed by TEK (n=17), GNAQ (n=10), MAP2K1 and RASA1 (n=8, each). Half of patients with TEK pathogenic variants had co-occurrence of a second somatic TEK variant (n=8/17). Four individuals had coexisting somatic activating mutations in two separate genes.

Conclusion: Patients with vascular malformations benefit from precise molecular diagnosis, a requirement for participation in clinical trials examining efficacy of targeted inhibitors. Concomitant mutations frequently coexist with driver mutations in cancer, but this has not been well-documented for vascular malformations. Our experience highlights several considerations unique to clinical testing of vascular malformations.

P276

Missense Mutations in PIK3CA in Angiomatosis of Soft Tissue and Cellular Crosstalk

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Purpose: Angiomatosis of soft tissue (AST) is a benign intramuscular vascular anomaly affecting venous vasculature. The symptoms often include pain and functional impairment. Histologically AST consists of vessels of different origin and size, of which most prominent are wide venous channels and artery-like vessels. Muscle-infiltrating fat is also abundant. AST can be misdiagnosed as intramuscular, common venous malformation (VM). Differential diagnosis of these two entities is important, as sclerotherapy is suitable for most VMs but is inefficient in AST.

Methods: We characterized somatic mutations in 31 non-skin associated venous lesions by ddPCR, of which 20 were AST and 11 VM. Patient-derived cells were used to understand the crosstalk of endothelial cells and intervascular stromal cells in venous lesions. Additionally, matrigel plug mouse model was used to study the role of fibroblasts in formation of venous lesion.

Results: In AST, 16 out of 20 patients carried a missense mutation in PIK3CA gene. Pathogenic PIK3CA variants were accordingly found in AST-derived endothelial cell lines. AST-derived intervascular stromal cells were shown to secrete growth factors, and to induce a pro-angiogenic phenotype of genotypically normal endothelial cells. Fibroblasts were demonstrated to induce formation of venous lesion in vivo.

Conclusion: AST patients having extensive or infiltrating lesions with a missense mutation in PIK3CA gene could benefit from treatment with PI3K/AKT/mTOR inhibitors. Intervascular stromal cells may affect to angiogenic processes in venous lesion.

P279

Minimally invasive molecular diagnostics using cfDNA identifies known tissue based mutations in ~30% of individuals with venous or arteriovenous malformations

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Purpose: Most venous and arteriovenous malformations (VeM and AVM) are caused by mosaic mutations in oncogenes. Molecular diagnosis currently requires surgically excised tissues, but there is increasing demand for non-invasive molecular diagnostics due to the development of targeted medical therapies. We have previously demonstrated feasibility of cell-free DNA (cfDNA) as a diagnostic analyte in a small cohort of individuals with VeM and AVMs. Here we report the diagnostic yield of cfDNA in a larger cohort of 25 individuals with matched tissue and plasma samples.

Methods: DNA was extracted from the cellular fraction (blood-cell derived DNA) and plasma fraction (cfDNA) from individuals with AVM and VeM who had known, tissue-based mutations (TEK, PIK3CA, MAP2K1, BRAF, or KRAS). Samples were screened for known mutations using digital droplet PCR or next generation sequencing.

Results: 14 individuals with VeM and 11 with AVM were included. Tissue-based mutations were detected in in 5/14 individuals with VeM and 3/11 individuals with AVM. The average variant allele fraction (VAF) among positive cfDNA samples was 1.2% (N = 8) in VeMs and 1.7% (N = 4) in AVMs. Twenty-four samples were available from a single individual with double TEK mutations (Y897C/R918H). In this individual the average VAF among positive blood-cell derived samples was 0.3% (N = 3), versus 0.97% (N = 5) among positive cfDNA samples. In one individual a TEK L914F mutation was present within intralesional plasma sample but not in peripherally collected plasma sample obtained at the same time.

Conclusion: Tissue-based mutations were detected in blood in ~30% of individuals with VeM and AVMs. cfDNA derived VAF was higher than blood-cell derived VAF in one individual, and intralesional blood had a higher VAF than peripheral blood in another. These data demonstrate that cfDNA can be a useful diagnostic analyte for molecular diagnosis of AVM and VeM.

P283

Sturge Weber Syndrome with additional features: a possible new entity

Sofia Guelfand Warnken, Ximena Fajre Wipe and Gabriel Neely Erdos

P289

SCLEROSANT THERAPY FOR TREATMENT OF LIMITED CONJUNCTIVAL VASCULAR MALFORMATIONS

Juhi Daga, Aditi Mehta and Usha Singh

Purpose: Slow flow venous vascular malformations of orbit and conjunctiva are uncommon. They may-be limited and localized and cosmetically disfiguring. However, they may engulf vital orbital structures, making complete surgical excision a challenge. An incomplete removal is associated with high recurrence rates. Sclerosant injections offer a valuable mode of therapy that can be delivered directly under visualization for superficial lesions or via fluoroscopic guidance for deeper lesions. We describe three patients where bleomycin was used to reduce/shrink the red-blue mass involving the conjunctiva.

Methods: Three patients presenting with limited mulberry like red conjunctival lesions (conjunctival malformation) were offered sclerosant therapy. Orbital imaging was done to delineate the orbital extension of the lesions. Bleomycin sclerotherapy was administered under direct visualization for the conjunctival component of the slow flow venous malformations. This was done under topical anesthesia. The injections were repeated at 3 weekly intervals till there was resolution of the conjunctival lesion. Final follow was done at 6 months after the last injection

Results: Three patients who had distensible slow flow venous malformations extending into the conjunctiva and anterior orbit were recruited. All three were males and the average age was 23.7 years. The mean duration of symptoms was 11.3 years. The average number of injections was 3.3 (A-5, B-3, C-2) and the average dose was 1.3 units per injection. One patient (A) developed a pseudo-pterygium leading to significant astigmatism after the last injection and underwent surgical excision. On clinical review at 6 months, all had optimum cosmetic outcome with near total resolution of the conjunctival component.

Conclusion: Intralesional injection of bleomycin in small doses for localized anterior conjunctival slow flow malformations is a safe and efficacious treatment modality, and may achieve satisfactory cosmetic outcome.

P317

Treatment of a patient with a Complex Vascular malformation and a Novel PI3K mutation

Geetha Puthenveetil, Eric Won, Jill Stites, Kim Hai, Daniel Jaffurs and Tammam Beydoun

Purpose: The alpha-isoform of phosphatidylinositol-3-kinase (PI3K) encoded by the PI3KCA gene, is responsible for growth and cellular development. Mutations in PIK3CA can occur in the embryonic period, causing mosaic areas of cellular proliferation. While there are known mutations in the gene that cause certain types of cancers, others can result in patterns of overgrowth and vascular malformations - a spectrum of disorders called PIK3CA Related Overgrowth Syndromes (PROS). We present a complex case of a pediatric patient with a newly described variant in the PIK3CA gene causing PROS.

Methods: Targeted next-generation sequencing performed on tissue sample from right upper extremity – obtained during a sclerotherapy procedure.

Results: Thirteen year old male diagnosed with a venous malformation in the right upper extremity during infancy; underwent three debulking procedures to improve function. Referred to our institution at 9 years of age for sclerotherapy and developed a deep venous thrombosis and pulmonary embolism after procedure. Referred to hematology for treatment of thromboses. Treated initially with Enoxaparin, transitioned to Rivaroxaban at prophylactic dosing over the last year. Due to persistent pain and swelling, he was started on Sirolimus with trough levels maintained between 6-10 ng/ml. He continued to have pain and swelling, requiring further sclerotherapy procedures. Genetic testing from tissue was

sent in March 2021 which showed a new variant in the PIK3CA gene – NP_006209.2:p.v344G – which has not been reported previously in PROS phenotypes. Treatment was switched to Alpelisib (a PIK3CA) inhibitor, with improvement in swelling and pain noted over the past 3 months. No adverse effects to medication observed. Patient remains on Xarelto for thrombo-prophylaxis.

Conclusion: We report a novel variant in the PIK3CA gene in a pediatric patient with treatment-refractory PROS. This finding has allowed us to treat the patient with a specific PIK3CA inhibitor and clinical improvement has been observed.

P319

Phenotypic variability in CV-AVM1 syndrome due to a novel RASA1 mutation

Birute Tumiene, Simonas Gatelis and Birute Vaisnyte

Purpose: Capillary malformations (CM) affect 0.5% of population and in most cases are isolated. However, multifocal CM seen in combination with arteriovenous malformations (AVM) and/or arteriovenous fistulas (AVF) and overgrowth may refer to capillary malformation-arteriovenous malformation (CM-AVM) syndrome and warrant further vascular and genetic investigation.

Methods: We report a family (1,5 years old affected son, sister and two affected parents) with combined capillary malformation. While both parents and sister had multifocal CM only, the son presented at birth with multifocal CM and overgrowth of the right leg. Upon vascular investigation by ultrasound, junctions between arterial and venous pool were found in the lower extremity, while dce-MRI and direct angiography disclosed fast-flow right lower extremity AVM. Due to vascular malformation difference in length and size of legs was seen. Because of the diffuse nature of the pathology, no medical interventions were performed and conservative treatments were applied. An additional AVM in the mouth has progressed throughout the years, resulting in recurring bleeding from the patient's gums. Further investigation by clinical genetic was made.

Results: Genetic analysis of the triad (gene panel of 41 genes associated with various vascular anomalies) confirmed the diagnosis of CV-AVM syndrome 1 through the identification of novel undescribed RASA1 potentially pathogenic variant NM_002890.3:c.[2658_2659insTT];[2658_2659=], NP_002881.1:p.[(Thr887LeufsTer6)];[(Thr887=)] in both affected son and father, but was not identified in affected mother or daughter.

Conclusion: Multifocal capillary malformations may be associated with rare hereditary multisystem vascular anomalies and warrant further vascular and genetic investigations. Additional research must be made to better understand factors, that affect expression of different variants of vascular malformations that arise from same pathological gene.

P344

CLOVES Syndrome with an extensive mediastinal lymphatic malformation and scoliosis leading to progressive restrictive pulmonary disease: A therapeutic challenge

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Purpose: To discuss treatment options for a difficult case of CLOVES syndrome complicated by progressive restrictive pulmonary disease secondary to an extensive mediastinal lymphatic malformation (LM) and scoliosis.

Methods: A 32-year-old male with CLOVES, manifesting as a large mediastinal LM, an extensive LM involving the trunk and bilateral upper extremities, and progressive cervicothoracic scoliosis, presented to re-establish care due to disease progression. His course is complicated by progressive restrictive pulmonary disease leading to supplemental oxygen dependence and the development of episodic atrial fibrillation. Previous interventions include multiple debulking procedures of the LM of his trunk and left upper extremity, sclerotherapy of his hand venous anomaly, and posterior spinal fusion (T1-T8).

Results: At last visit five years ago, we recommended treatment with sirolimus for minor pulmonary insufficiency; however, therapy was not given because of concerns regarding possible side effects. In the interim, his orthopnea and hypoxia progressed. He now requires 2L/min of oxygen at rest and 3L/min with activity. On physical exam, he has minimal chest expansion with inspiration. CT chest shows progression of the large mediastinal mass causing tracheal displacement. His progressive pulmonary symptoms and new onset atrial fibrillation can be largely attributed to this mass, further exacerbated by disease involvement of his chest wall and scoliosis. Possible treatment options discussed include: sirolimus, alpelisib, and surgical debulking of the mediastinal LM.

Conclusion: A safe and effective treatment plan is a challenge. Surgical debulking carries a high risk of phrenic nerve injury which could be particularly devastating given this patient's reliance on diaphragmatic breathing. We again recommend medical therapy, but should his symptoms not improve, the potential benefits and risks of surgical intervention have to be thoroughly reconsidered.

P357

Clinical and Imaging Manifestations of Mosaic and Heterozygous PTEN Mutations

Joseph Nguyen, Dhara Kinariwala, William Petersen, Barrett J. Zlotoff, Klaus Hagspiel and Auh Whan Park

Purpose: Phosphatase and tensin homolog (PTEN) tumor suppressor gene downregulates the MAPK pathway, regulating cell cycle progression and metabolism. Germline pathogenic PTEN mutations have been associated with a spectrum of conditions, including PTEN hamartoma tumor syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and SOLAMEN syndrome, that present with diverse clinical manifestations, including arteriovenous malformations (AVMs), macrocephaly, skin lesions, and malignancies. We present clinical features and imaging findings in two patients with PTEN mutations.

Methods: Patient 1 is a 15-year-old female with somatic PTEN mosaicism present in lesional tissue but not detected in peripheral blood lymphocytes. Patient 2 is a 21-year-old female with a heterozygous germline pathogenic PTEN variant that has been observed in PTEN hamartoma tumor syndrome. We followed both patients for over ten years.

Results: Patient 1 presented at age 2 with left lower extremity hemihypertrophy. MRI/MRA showed a predominantly venous malformation involving her left calf and thigh. Follow-up studies showed development of a small AVM in her calf. The venous component subsequently progressed to involve her entire left leg, buttocks, and labia, and the AVM the entire calf, prompting management with sirolimus, transarterial embolization, and sclerotherapy. At age 12, she underwent an emergent left above-the-knee amputation due to uncontrollable hemorrhage from the AVM. Patient 2 presented at age 9 with prominent superficial veins in her right arm and erythema, swelling, and discoloration of the right hand. MRI/MRA showed a complex AVM with a significantly abnormal venous component including venous dilatation, aneurysms, and lakes involving the right hand and distal forearm. She was subsequently managed with ethanol sclerotherapy, coil and alcohol embolization, and sirolimus beginning at age 21. She has retained full function of her right upper extremity.

Conclusion: Somatic PTEN mosaicism and germline heterozygosity can present with similar clinical and vascular manifestations and serious complications necessitating lifelong surveillance and therapy.

P374

Head and Neck Endovascular Repair of Vascular Malformations

Wayne Yakes

Purpose: To determine the efficacy of ethanol embolotherapy of extracranial head and neck vascular malformations of all types, particularly after failure of other endovascular and surgical treatments.

Methods: One hundred and sixty-six patients (64 males, 102 females; mean age: 38 yrs) presented with extracranial arteriovenous malformations (AVMs) of the head and neck area. Over half of the patients had undergone previous failed therapies (Glue, Onyx, PVA, Coils). All patients underwent ethanol embolotherapy under general anesthesia. Forty-five patients had AVMs and 121 patients had venous malformations (VM).

Results: Of 45 AVM patients, 26 patients are cured (mean follow-up 2 ½ years); of 121 venous malformation patients, 65 are at end-therapy (mean follow-up 4 ½ years). The remaining patients are not at end-therapy and are being treated for their residual malformations. In AVM follow-up, arteriography is the main imaging modality to determine cure or residual AVM as MR is less sensitive in the evaluation of residual AVM. In VM follow-up, MR is the main imaging tool, particularly with T- 2 fat suppression and/or STIR imaging. All patients demonstrated improvement post-therapy. Complications were 4.5%, to include bleeding (self-limited), partial 7th nerve palsy (with recovery), skin injury (not requiring skin grafts), infection, and pain.

Conclusion: Ethanol has proven its consistent curative potential at long-term follow-up for high-flow AVMs and low-flow VM lesions at long-term follow-up as lesions in the periphery. Complication rates remain low. The procedures are tolerated well by the patients and done on an out-patient basis. Prior surgery and embolization procedures can cause difficulty in lesion access, but does not obviate further ethanol endovascular treatment.

P380

Management of Tongue Venous and Lymphatic Malformations

Wayne Yakes

Purpose: To determine the efficacy of ethanol embolization in management of tongue venous and lymphatic malformations.

Methods: 48 patients (29 females, 19 males; mean age: 38 years) presented with tongue low-flow malformations. 47 patients had undergone 61 failed previous procedures (embo, laser, surgery, steroid injection, alpha-interpheron, radiation). All patients had baseline arteriograms and MRs. All patients underwent direct puncture ethanol endovascular therapy.

Results: Of 48 patients with venous and lymphatic malformations, 37 patients had dramatic reduction and 11 patients' therapy is on-going with concurrent reductions (mean f/up: 60 months). 1 patient with AVM required additional surgery and 1 patient with mixed veno-lymphatic malformation required surgical debulking of excess tissues. Minor complications such as tongue blisters (9 instances) healed spontaneously; 3 tongue focal areas of necrosis healed spontaneously; 3 infections responded to antibiotic treatment; 1 focal tongue hemi numbness resolved. 1 patient with dense VMs had a portion of the tongue slough and the tongue healed and remolded with no treatment required.

Conclusion: Ethanol embolotherapy is a primary and consistent form of therapy to eradicate low-flow vascular malformations of the tongue permanently at long-term follow-up. Rarely is concurrent surgery required. Ethanol sclerotherapy is a curative treatment in which recurrences do not occur and permanent ablations are the rule. Complications are minor and rare.

P385

Change of Coagulation Profile in veno-lymphatic malformations Following Sclerotherapy.

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Purpose: To evaluate long-term coagulation profile change in veno-lymphatic malformations patients following Sclerotherapy. Little is published about changes of coagulation profile months/ years after sclerotherapy treatment.

Methods: Retrospective study of 1100 in the vascular anomalies program. We recorded age, sex, affected area, the volume of disease, diagnosis, and change in coagulation profile pre and post procedures (platelet count, prothrombin time (PT), partial thromboplastin time (PTT), the international normalized ratio (INR), d-dimer, and Fibrinogen).

Results: We excluded 200 patients with insufficient data. 42.5% of 900 had venous malformation (VM). 12.4% had lymphatic malformation (LM). D-Dimer range remained normal in 53.7% of VM patients, and 9.3% showed normalization from high values. 37.0 % of patients were in the high range, of whom 60% improved (mean of initial D-Dimer reduced from 20.96 times normal range down to 9.10 times the normal range). The remaining 40% had mild D-Dimer increase (from 2.30 times normal range up to 6.0). 98.2% of VM patients had stable normal fibrinogen. 1.8% improved from high to normal. 69% of VM patients had normal PT value, 4.9% improved from high to normal, 16.0% remained in high range and 38.5% slanted towards decreasing values. 94.2% of VM patients had normal platelets. 95.% of patients had normal PTT, 1.25% showed PTT improvement, with 3.75% remaining within the slightly elevated PTT range. 87.5 % of patients retained normal INR range, with an 8.75% decrease of high value to average values. Most lymphatic malformations did not show coagulation profile abnormalities at baseline and follow-up.

Conclusion: Following repeated sclerotherapy, D-dimer either improved or remained normal in most VM patients. Other coagulopathy was rare. Most LM patients did not show coagulopathy.

P404

Sirolimus for Treatment of Pelvic Angiomatosis – First Case Report in the Literature

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Purpose: Angiomatosis is a very rare, slowly progressing vascular lesion. It is histologically characterized by benign variable-sized vascular proliferates associated with a prominent adipocytic component and marked atrophy of the involved musculature. Although associated with a 90% recurrence rate, surgical resection has been the leading and primary treatment option so far.

Methods: We report the case of a pelvic angiomatosis successfully treated with sirolimus.

Results: A girl born in 2006 after an uneventful pregnancy and uneventful early childhood stopped gaining weight at the age of 5 and slowly developed progressive walking problems due to increasing contracture of the right hip interfering severely with school attendance and everyday activities. At 8, a vascularized infiltrative pelvic mass on the right side was diagnosed by MRI. Laboratory testing excluded

bacillary angiomatosis and other infectious or autoimmune diseases. At the age of 9, a biopsy was taken. Histopathologic diagnosis of angiomatosis was confirmed at an international reference center. Diffuse involvement of pelvic and abdominal wall musculature made surgical intervention impossible. At the age of 9.3 years, we decided to start sirolimus treatment based on compassionate use after the informed consent of the parents. The rest is a success story. Monika gained weight, her posture normalized, the walking difficulties disappeared. Sirolimus trough level ranged between 6-8ng/ml for a period of 2-years. The only side-effect was one episode of mucositis. Sirolimus was tapered throughout 2-years, and treatment was stopped in October 2019 at the age of 13. A 2-year follow-up MRI shows minimal signs of increased vascular activity in the lesion without any clinical symptoms.

Conclusion: To the best of our knowledge, this is the first case in the literature showing that sirolimus could be a causal treatment for soft tissue angiomatosis. The time will show if the treatment will need to be reinitiated.

P425

VenaSeal™ closure of superficial embryonic veins in children with Klippel Trenaunay Syndrome

Joao Amaral, Evan Kitamura, Alessandro Gasparetto, Dalia Bozic and Julie Zettel

Purpose: Describe the use of VenaSeal™ medical adhesive to close superficial embryonic veins in two patients with Klippel Trenaunay Syndrome (KTS) with long-term imaging follow-up.

Methods: Informed consent obtained from parents and patients for this report (Research Ethics Board approval exempt). MRI pre procedure demonstrated large superficial veins in the affected lower limbs and presence of deep venous system. After obtaining consent for the procedure under the hospital's Innovation Policy, two male patients (16 and 9 years-old) were treated with VenaSeal™ under General Anesthesia and sterile technique. Venogram pre-closure confirmed presence of deep venous system in both patients. Largest superficial vein accessed in distal leg and 7 French introducer sheath advanced into its proximal aspect. One patient required coil embolization of two large communicating veins. 5 French catheter inserted, system pulled back 5 cm from connection with deep venous system and medical adhesive delivered at 0.1 ml aliquots of n-butyl 2 cyanoacrylate (VenaSeal™; Medtronic, Minneapolis, Minneapolis) every 3 cm to a total of 3.8 mLs and 2.5 mLs, respectively. No pain, discomfort, or swelling post procedure. No compression stocking required.

Results: Both procedures were successful with complete and immediate occlusion of the superficial veins treated. Patients had no bruising as no tumescent anesthesia was required. 11 months post procedure, follow-up MRI and ultrasound shows no flow in the occluded superficial veins. Persistence of collapsed fibrotic vein.

Conclusion: Long-term imaging follow-up demonstrates sustained occlusion of the superficial veins treated with the VenaSeal™ closure system in 2 pediatric patients with KTS. The advantages of this method included a faster procedure (no need of tumescent anesthesia), no risk of thermal injury, faster recovery (no pain or bruising) and no need of post procedure high pressure (30-40 mmHg) compression stockings which is a significant advantage in children.

P444

Everolimus is an effective and safe salvage treatment in patients with vascular anomalies unresponsive to Sirolimus

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Purpose: Treatment with sirolimus is well-established in the field of vascular anomalies, however, not all patients respond efficiently and side effects are not uncommon. Everolimus is an alternative mTOR inhibitor, but data on its use in the field is scarce.

Methods: Here, we describe a chart review of a case-series of 10 patients with a broad variety of entities of vascular anomalies that were treated with everolimus after failing to respond to sirolimus between 2017 to 2020 in VA centers in Europe (Germany and Switzerland) and in the US (Boston). The entities included complex lymphatic anomalies (GLA (4/10), CCLA and KLA (1/10 each)), segmental venous malformation, FAVA, PHTS, pseudomyogenic hemangioendothelioma (1/10 each). Genetic testing was performed in 8/10 and yielded a relevant mutation in 6/8 patients.

Results: A descriptive analysis of the efficacy and safety of everolimus showed amelioration of symptoms with an overall response rate of 70% (7/10 of patients) within 4 weeks of treatment. Intriguingly, one patient responsive to everolimus showed a mutation in ARAF. Evaluation of the patient's mutation using a zebrafish model and transfected lymphatic endothelial cells in a translational approach is ongoing. This may further assess whether everolimus, as opposed to sirolimus, has an effect on the RAS/RAF/MEK/ERK pathway in addition to its mTOR inhibition further potentiating its efficacy and thereby explaining its advantage in treatment response.

Conclusion: So far, this retrospective study demonstrates the efficacy and safety of everolimus as a salvage therapy in patients with various complex vascular anomalies unresponsive to sirolimus, especially when suffering from complex lymphatic anomalies that are otherwise difficult to treat. In a translational approach, functional analysis may provide insights into the molecular mechanisms of the therapeutic effects of everolimus and its advantages compared to sirolimus.

Infantile Hemangiomas

P007

Blockage of glycolysis by targeting PFKFB3 suppresses haemangioma-derived endothelial cell proliferation and induces apoptosis via PI3K-Akt pathway

Kaiying Yang, Tong Qiu, Jiangyuan Zhou, Xue Gong, Yuru Ran, Xuepeng Zhang and Yi Ji

Purpose: Infantile haemangioma (IH) is the most common tumour of infancy with a prevalence of 5%-10%. The exact pathogenesis of IH is not fully known. 6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) is overexpressed in a variety of human cancers and plays important roles in promoting angiogenesis. Here, we explored the role of PFKFB3 in hemangioma-derived endothelial cell (HemEC).

Methods: Glycolytic inhibition by genetic and pharmacologic approaches PFK15 was used to demonstrate the critical role of PFKFB3 in HemEC. Glycolytic flux was measured with the glucose uptake kit, ATP production kit and lactate release kit. Besides, cell proliferation was assessed by Cell Counting Kit-8 (CCK-8) and cell migration ability was determined by transwell migration assay. Apoptotic cells were identified by an Annexin V/PI staining assay. HemECs, hemangioma-derived pericytes and human

umbilical vein endothelial cells (HUVHEMHEMECs) were mixed and injected subcutaneously into 20 flank of BALB/c-nu mice, which were randomly divided into 4 groups based on different treatment methods. Then subcutaneous implants were harvested and evaluated the tumor tissues with microvessel density (MVD) assay and immunohistochemistry.

Results: Inhibition of PFKFB3 with PFK15 and or genetic downregulation of PFKFB3 dramatically suppressed HemEC proliferation and induce HemEC apoptosis. Moreover, PFKFB3 inhibition resulted in reduced glucose uptake, ATP production, and lactate release. Besides, we found that combination of PFK15 and propranolol exerted strong synergistic antitumor activity and in HemEC. We also found that the combination of PFK15 and propranolol induced apoptosis-mediated cell death through inhibition of the PI3K-Akt signaling pathway. More importantly, PFK15 treatment, either as monotherapy or in combination with propranolol led to a marked reduction in tumor growth in mouse xenograft models.

Conclusion: Glycolytic activator PFKFB3 can regulate HemEC proliferation and migration. PFKFB3 inhibition alone or in combination with propranolol may be used as a novel therapeutic strategy for improved therapeutic efficacy and outcomes of IH patients.

P016

Long-term outcomes in PHACE Syndrome, ages 10 and up.

Mitchell Braun, Dawn H. Siegel, Erin Mathes, Julie Powell, Denise Metry, Beth Drolet, Elena Pope, Sarah Chamlin and Ilona Frieden

Purpose: Significant efforts have been made to establish PHACE diagnostic criteria, but little is known about the long-term prognosis or management of this condition. To fill this gap in our knowledge, this study aims to characterize the natural history and overall long-term burden of definite PHACE in patients ages 10 years and older.

Methods: This is a multicenter retrospective cohort study with cross sectional patient interviews utilizing standard expert-derived intake forms and validated quality-of-life surveys. Investigators at the 20 participating sites across the United States, Canada, and Spain are contacting their own patients to enroll individuals ≥10 years old with a diagnosis of definite PHACE. Word of mouth and advertisements through the PHACE Syndrome Community will identify additional participants.

Results: It is estimated that 60-100 patients will participate. Data from chart review, participant interviews, and quality of life forms will be discussed. Results will be primarily descriptive and will focus on hemangioma residua, late growth, and hemangioma-related patient reported outcomes; presence and progression of arterial anomalies; learning differences, speech/motor issues, headaches and their impact; cardiac anomalies and surgeries; vision complications; endocrine abnormalities; hearing issues; autonomic dysfunction; dental issues; and social/emotional issues including depression, anxiety, and other mental health diagnoses. Results from quality-of-life forms will estimate disease burden and will be compared to scores in other more common conditions.

Conclusion: This is the largest study investigating long term outcomes in PHACE syndrome. The results will inform future guidelines on long term management and will aid clinicians in counseling patients and their families. Possible associations between patient characteristics or original PHACE diagnosis and outcomes including persistent growth or ulceration of hemangiomas, progressive arteriopathy, stroke, and severe migraine headaches will allow for patient-specific PHACE care and management.

P018

Effect of Atenolol on central nervous system function in pediatric patients with infantile hemangioma

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Purpose: Atenolol for the treatment of Infantile Hemangioma (IH) has the same efficacy as conventional propranolol, but with a better safety profile. Due to its hydrophilic properties, atenolol crosses the blood brain barrier to a lesser degree than the lipophilic beta-blocker propranolol, although beta-blockers may cause brain effects through additional mechanisms. The effect of atenolol treatment on child development has not been studied yet. Therefore, we aimed to examine whether prolonged treatment with atenolol in infancy has late effects on cognitive or behavioral functions.

Methods: Forty-four children aged 3-5 years old with a diagnosis of IH, were compared with 43 similar-aged untreated children with IH. Inclusion criteria included children aged 3-5 years' that were treated with atenolol for at least 6 months; exclusion criteria included risk factors for developmental disorder such as preterm infants, low birth weight, or major birth defects, and prior use of propranolol via dermal or oral administration. The children's parents were asked to answer two questionnaires - Adaptive behavior assessment system II (ABAS II) and Child behavior checklist (CBCL), which evaluated different cognitive and behavioral variables.

Results: The demographic characteristics (i.e gender, academic education) did not differ between the two groups ($P > 0.05$). No differences in each of the key outcomes examined by the two questionnaires, were observed between the groups ($P > 0.05$). On examination of the CBCL results stratified by gender, atenolol treatment had a beneficial effect on the overall score and certain variables related to anxiety and depression among girls ($P = 0.03$).

Conclusion: This study is the first to show that atenolol treatment, at a critical age for CNS development, has no negative childhood developmental consequences. An interesting finding seen among girls by the CBCL questionnaire, showed a beneficial effect of atenolol treatment on anxiety and depression few years after completion of treatment

P044

Lessons learned through 25 years of experience with PHACE: Review and perspectives on management

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Purpose: It has been 25 years since the diagnosis of PHACE was established. Over the past two and a half decades, the medical, scientific, and patient communities have made strides in understanding this condition. The purpose of this project is to review the key features of PHACE syndrome, highlighting its evaluation, diagnosis, and management as well as emphasize current gaps in knowledge to establish next steps in research and patient-centered care.

Methods: Literature review with synthesis of expert opinion.

Results: PHACE syndrome is a disease requiring multidisciplinary long-term care. The authors have proposed recommendations for healthcare maintenance in patients with possible or definite PHACE. These checklists emphasize both the age of the child (i.e. newborns/infants, toddlers, school-aged, adolescents and adults) and potential areas requiring special attention (e.g. skin IH residua, screening for managing migraine headaches, etc.). Topics for future research include long-term outcomes and natural history of PHACE, better understanding of pathogenesis, management of IH residua and late

growth, and standardization of imaging protocols to better visualize relevant affected areas, among others. The importance of patient advocacy groups and support networks will also be emphasized.

Conclusion: Understanding PHACE syndrome requires multicenter and multidisciplinary efforts. Our recommended checklists can be used for both education and practical purposes in patient care settings. Presenting recent expert opinion and highlighting future research projects will inspire future collaborative efforts.

P096

Long-term esthetic outcome of treatment with propranolol or atenolol for infantile hemangioma

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Purpose: Life- or function-threatening infantile hemangiomas (IH) are effectively treated during infancy with beta-blockers, like propranolol and atenolol. We evaluated the long-term esthetic outcome of IH treated with propranolol or atenolol. Furthermore, we predicted the long-term esthetic outcome, using features of the IH, characteristics of the beta-blocker treatment, and demographic parameters.

Methods: School-aged children, who had been treated with propranolol or atenolol for IH during infancy, participated in this two-center cross-sectional study. As a primary outcome, physicians scored the change in appearance of the IH on a visual analogue scale (VAS). This score was based on photographs taken prior to the beta-blocker treatment (collected from medical records), and photographs taken at follow-up. As secondary outcomes, physicians, parents and children evaluated the residual lesion at follow-up. Measures included the Patient Observer Scar Assessment Scale (physician- and parent-rated) and a VAS (child-rated). The physician also recorded sequelae, such as telangiectasia, fibrofatty tissue, and atrophic scar.

Results: 103 IH (35 propranolol, 68 atenolol) were analyzed. No differences between beta-blocker groups on physician-rated VAS (p=.10) or secondary outcomes were found. Physicians, parents, and children were positive about the residual lesion. Minor sequelae were common (86%). Poor physician- and parent-rated esthetic outcomes were predicted by the same characteristics, including a superficial component, ulceration, increased age at treatment initiation, increased cumulative dose, and shorter follow-up time. Child-rated esthetic outcome was only predicted by location; head and neck IH had better esthetic outcome than IH located elsewhere.

Conclusion: Long-term esthetic outcome does not differ between propranolol and atenolol treatment. Although minor sequelae are common, physicians, parents, and children are positive about the residual lesion. The identified risk factors for poor esthetic outcome should be used to optimize parent counseling during beta-blocker treatment, and to guide further treatment strategies (e.g. laser treatment or surgical excision) in the long term.

P124

Infantile Hemangioma with Minimal or Arrested Growth: different clinical presentations in a retrospective case series

Jinia El-Feghaly, Molly Marous, Heidi Bai and Maria Cordisco

Purpose: Infantile Hemangioma with Minimal or Arrested Growth (IHMAG) is misdiagnosed as capillary malformation, arteriovenous malformation or congenital hemangioma. Consequently, it is crucial to be

aware of this entity and its characteristics, to avoid unnecessary evaluation and to provide patients with the appropriate management plan.

Methods: A retrospective chart review approved by the [xxx] Institutional Review Board was done with the search terms: “infantile hemangioma with arrested or minimal growth” and “IHMAG”. 27 cases were retrieved and reviewed for demographic and clinical characteristics as well as outcomes.

Results: Female to male ratio was 2.3:1. Average gestational age was 40 weeks while 7/27 cases were premature. 22/27 lesions were present at birth and 5/27 presented in the neonatal period. Average age at presentation was 3.4 months. 15/27 IHMAG were focal, 11/27 were segmental and 1 was indeterminate. IHMAG was seen on various body sites; with 19/27 located on the lower body half and 8 on the upper half. Size ranged from 1x1cm to 9.5x9cm. In most patients, IHMAG presented as a fine telangiectatic patch with focal areas of bright red papules; ulceration was noted in 5 patients. Semicircular lipoatrophy was seen in 1 patient with segmental IHMAG of the leg. PHACES syndrome was noted in the 2/2 patients with facial segmental IHMAGs. LUMBAR syndrome was ruled out in 2/2 extensive IHMAG on the buttock and lower limbs. Ultrasound was the most used diagnostic imaging modality. 15/27 infants were treated with topical timolol, 5/27 with oral propranolol and 2/27 with a combination of both with an average time to resolution of 8, 13 and 6.5 months, respectively.

Conclusion: Trends of our data are in concordance with prior reports including epidemiologic, clinical, and prognostic factors and possible associated syndromes. Additional studies are warranted to better elucidate the pathogenesis and clinical course of IHMAG.

P137

Propranolol for the treatment of ulcerated infantile hemangiomas: a prospective study

Yi Ji

Purpose: Ulceration is one of the most common complications of infantile hemangiomas (IHs). Several small studies have reported successful treatment of ulcerated IHs with oral propranolol. We undertook a prospective trial to evaluate the efficacy and safety of oral propranolol in patients with proliferating ulcerated IHs.

Methods: Eligible patients were aged 5-24 weeks and had ulcerated IHs. The primary endpoint was the clinical response measured at week 24 after treatment.

Results: Eighty-five patients were included. At week 24, propranolol treatment resulted in excellent and good responses in 38.8% and 54.1% of patients, respectively. Logistic regression analyses revealed that young age (95% confidence interval [CI], 0.368-0.940; P=0.027) and small hemangioma size (95% CI, 0.566-0.931; P=0.012) were independent factors predictive of excellent response. Hemangioma size ($P = 0.001$) and ulceration size ($P < 0.001$) significantly influenced the complete healing time of the ulceration (CHTU). The total time of ulceration correlated significantly and positively with the prior duration of ulceration but not the CHTU. Early study withdrawal owing to adverse events occurred in only 1 patient.

Conclusion: Propranolol is an effective and safe treatment for proliferating ulcerated IHs and should be given early whenever possible.

P154

Risk Factors for Infantile Hemangioma: a Case-Control Study of a Large Sample Size

Xue Gong, Tong Qiu, Kaiying Yang, Jiangyuan Zhou and Yi Ji

Purpose: Infantile hemangioma (IH) is the most common benign vascular tumor in infancy, of which the pathogenesis remains controversial. Risk factors are different among studies due to the limited sample sizes and collected information. The identification of risk factors for IH depends on studies with large sample sizes and as detailed information as possible.

Methods: We conducted a case-control study between 2017 and 2020. Patients were diagnosed with IH during outpatient visits through clinical manifestations, physical examination and other necessary examinations according to the definition and classification system of the International Society for the Study of Vascular Anomalies (ISSVA). Every patient was matched with one control. A standardize questionnaire was designed by trained investigators to gather detailed information from the children's guardians.

Results: After excluding 15 patients due to incomplete information, 912 patients and 912 controls were included in our study. We found that anemia in pregnancy (OR=4.274; $P < 0.001$), miscarriage history (OR=4.125; $P < 0.001$), preterm premature rupture of membranes (PPROM) (OR=2.815; $P < 0.05$), placenta previa (OR=2.497; $P < 0.05$) and threatened miscarriage (OR=2.064; $P <0.05$) were independent risk factors for IH. Different from previous study, our results showed that gestational diabetes mellitus (GDM) (OR=0.785; $P <0.05$) and hypothyroidism (OR=0.627; $P <0.05$) were protective factors for IH. Besides, preterm ($P =0.486$) and low birth weight (LBW) ($P =0.383$) were not risk factors for IH.

Conclusion: Our study revealed some risk and protective factors related to the occurrence of IH. Besides, we found preterm and LBW were not risk factors for IH. We sincerely hope our study can provide novel and reliable insights into further understanding of the pathogenesis of IH, so as to improve the prognosis of IH patients.

P166

Infantile hemangioma derived CD146+ cells form adipose tissue and promote human GLUT1+ angiogenesis in immunodeficient mice.

ZONGAN CHEN, JIALIN CHEN, LEI CHANG, YAJING QIU, YUANBO LI, SHIH-JEN CHANG, QIANYI CHEN, ZHANG YU and Lin Xiaoxi

Purpose: Infantile hemangioma (IH) is the most common infantile vascular neoplasm charactering by a rapid proliferation and following by a slow spontaneous involution lasting for years. Our previous study indicated that CD146+ Hemangioma derived mural-like cells (HemMCs) were the most dynamic cell subset during the transition from the proliferation to involution phases.

Methods: In this study, we identified that CD146-selected cells showed characteristics of mesenchymal stem cells and have distinct angiogenic phenotype and function. And CD146+ HemMCs alone spontaneously differentiated into adipocytes 2 weeks after implantation in immunodeficient mice which increased significantly after 4 weeks. Different from CD133+ hemangioma stem cells (HemSCs), HemMCs did not have the ability to differentiate into endothelial cells. However, HemMCs in combination with HUVEC formed Glut1+ blood vascular in vivo 2 weeks after implantation, which involuted into adipose tissue 4 weeks after implantation. And mCherry-label HemMCs were shown to surround GLUT1+ endothelium at 2 weeks and involved into adipocytes after 4 weeks.

Results: in this study, we identified a specific cell subset which not only was consistent with the evolution of hemangioma but also recapitulated the unique course of hemangioma.

Conclusion: we considered that HemMCs may be a potential target in the construction of hemangioma animal model and the study of the pathogenesis.

P170

Clinical features of segmental infantile hemangioma: a prospective study

Tong Qiu, Kaiying Yang and Yi Ji

Purpose: Infantile hemangioma (IH) is the most common benign tumor in children. However, few studies have reported the clinical features of segmental IH. We aimed to determine the clinical characteristics of segmental IH and to identify features that may aid clinicians in managing segmental IH.

Methods: In the cross-sectional prospective study approved by the Ethics Committee of the hospital, children diagnosed with IH were recruited, and information including patient demographics, IH morphology and anatomical location, complications and treatments were recorded and analyzed.

Results: In total, 153 patients with segmental IH and 1375 patients with nonsegmental IH were enrolled in this study. The average age on the day of the first visit in patients with segmental IH was 3.63±3.23 months. In sixty-nine patients (45.10%), segmental IH was diagnosed at birth. Most segmental IHs (49.67%) occurred in the limbs, while only 22.04% of nonsegmental IHs occurred in the extremities ($P<0.001$). Thirteen patients (8.50%) with segmental IH also had ulceration. Compared with patients with nonsegmental IHs, patients with segmental IHs were more likely to be treated with oral drugs ($P<0.001$).

Conclusion: Segmental IHs mainly occur in the extremities and are frequently diagnosed at birth. Segmental IHs are usually accompanied by ulceration and are mostly located in the head, neck, and perineal area. Oral propranolol is prescribed more often in patients with segmental IH than in those with nonsegmental IH.

P184

Clinical features in PELVIS syndrome : arguments for shared pathogenesis with PHACE syndrome.

Fabian Blanc, Michèle Bigorre and Didier Bessis

Purpose: The association of large segmental hemangioma (IH) on the upper body regions with underlying developmental anomalies is well recognized as PHACE(S) syndrome.

In a similar manner, segmental IH of the lower body regions may be associated with regional developmental defects. PELVIS (perineal, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tags), LUMBAR or SACRAL syndromes are acronymes used to denote the clinical presentation of large perineal IH associated with regional visceral malformations, also including bony deformities and arterial anomalies.

Methods: We report here 9 cases of PELVIS syndromes, and the first case of infraumbilical raphe in PELVIS syndrome.

Results: The infraumbilical raphe was associated with a large segmental IH of the perineum. Ulceration occurred at 9 months of life leading to oral propranolol treatment. Her other regional anomalies included anterior displaced anus and vulva, bifid clitoris, labia majora that were smaller than normal for age, and an increased distance between the labia majora. The 8 other cases presented lower-body clinical features, similar to those described in the PHACE(S) syndrome.

Conclusion: We reported here a new clinical feature associated in PELVIS syndrome : infraumbilical raphe. Only one case of an infraumbilical raphe was previously published. It was associated with a

supraumbilical raphe and a pectus excavatum. These ventral defects, occurring between 6 and 8 weeks of gestational age, are thus frequently associated. These findings support that PELVIS and PHACE(S) syndromes should be considered as similar entities affecting the upper or the lower half of the body respectively, and may share a common pathogenesis.

P187

Hybrid Lung Lesions in Children with Segmental Infantile Hemangiomas: A New Association?

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Purpose: Segmental infantile hemangiomas can occur in the setting of congenital anomalies that are commonly associated with anomalies of the developing vasculature. However, the association with pulmonary anomalies has not been well established. We present two cases of children with large segmental infantile hemangiomas (IH) who were also found to have concurrent congenital pulmonary airway malformations (CPAM).

Methods: Retrospective review of clinical cases and histopathology of two cases seen at a single institution.

Results: Two female patients were identified with both segmental pattern infantile hemangiomas and congenital pulmonary airway malformations (CPAM) with bronchopulmonary sequestration (BPS), also known as “hybrid lesions”.

Conclusion: Congenital thoracic malformations are a spectrum of anomalies that arise during fetal lung development. These cystic lung lesions include CPAM and BPS. These anomalies are believed to develop from a gestational insult occurring between 6-16 weeks. This corresponds with the timing of developmental anomalies known to be associated with segmental infantile hemangiomas. Although the precise mechanisms causing cystic lung lesions are not known, it is proposed that a “malformation sequence” leads to the spectrum of observed thoracic malformations, which is largely guided by the timing and location of a developmental insult. Similarly, the pathogenesis of IHs is thought to be multifactorial, with data suggesting a placental disruption and tissue hypoxia during gestational development as a trigger for the abnormal vasculogenesis leading to IHs. This could therefore be indicative that the concurrence of infantile hemangiomas and pulmonary anomalies in our patients are not coincidental, but rather occur as a result of a shared inciting gestational event. The precise timing of the developmental insult responsible for hybrid lung lesions may trigger the downstream mechanisms that also cause segmental IH formation in the patients presented in this study. This association adds to literature that suggests segmental hemangiomas serve as a marker of underlying congenital anomalies.

P213

Single cell RNA sequencing of infantile hemangioma reveals cellular heterogeneity

ZHANG YU, XUANFENG CHEN, REN CAI, QIANYI CHEN, LEI CHANG, YAJING QIU, ZONGAN CHEN, HANRU YING and Lin Xiaoxi

Purpose: Infantile hemangioma (IH) is a benign neoplasm of infancy with specific natural course from rapid proliferation to spontaneous regression. Despite whole tissue biopsy studies that have advanced the mechanistic understanding of IH, complete understanding of the spectrum of heterogeneity in IH and corresponding changes in the different stages remains elusive.

Methods: We validate a method for generating a droplet-based single-cell atlas of gene expression in IHs. Enzymatic dissociation of 8 IHs in different stages was followed by single-cell sequencing of >30 000 cells.

Results: Clustering analysis of gene expression from hemangioma cells identified 15 populations of cells representing each of the main non-immune cell types: endothelial cells, fibroblast like cells, mural like cells, Schwann cells, and immune cells, including myeloid cells, NK and T cells, and B cells. Among them fibroblast like cell population has not been recognized. Further detailed molecular analyses revealed the heterogeneity of endothelial cells, fibroblast like cells and mural like cells, and the most significant cellular heterogeneity was seen in the distinct endothelial cell populations. Our analyses also revealed the variation tendency of the proportion of major cell types in non-immune cells during the different stages and identified mural like cells as the majority dividing cells in the proliferation stage. In addition, our study revealed extensive networks of intercellular communication and provided a strategy to isolate major cell populations in non-immune cells.

Conclusion: Together, our study presents a comprehensive view of IH in the different stages at single-cell resolution that outlines the characteristics of resident cells in IH. By integrating expression from >1500 genes per cell, we are better able to characterize cellular heterogeneity compared with conventional approaches and provide deeper insights into IH biology that will be helpful in advancing IH diagnosis and therapy.

P220

Intralesional Diprospan Injection for Protruding Lip Infantile Hemangiomas: a Prospective, Comparative, Parallel-Group Study to test for non-inferiority

SHIH-JEN CHANG, LEI CHANG, HSIAO-FEN CHANG, YING SHANG, YAJING QIU and Lin Xiaoxi

Purpose: To investigate intralesional Diprospan injection (IDI) as an alternative treatment for protruding Lip IHs.

Methods: We designed a prospective, non-inferiority, non-randomized, parallel-group, comparative study between OPT and IDI. Primary outcome measurement was treatment response rate. Secondary outcome measurements were changes in lesion measurement and surgical rate. Complications and treatment durations were compared.

Results: IDI was not inferior to OPT with respect to treatment response rate (95.7% vs 76.0%, a difference of 19.7%; 95% CI, −4.4% to 41.6%). The average surgical rate in IDI group was significantly lower than that of OPT group (8.7% vs 40%, p=0.012), and the average duration of treatment for IDI was shorter than OPT (2.1 months vs 6.3 months, p<0.001). Both groups had case(s) of ulceration. There were no cases of drug adverse events.

Conclusion: Intralesional Diprospan is no less effective than oral propranolol in treating protruding localized lip IHs. It provides a shorter treatment period and a lower surgical rate, although care must be taken for risk of ulceration.

P231

Distribution and Clinical Characteristics of Periorbital Infantile Hemangiomas

Teresa O, Emily Ceisler, Caroline Broude, Lauren Pacicco, Kimberly Chan, Aaron Fay and Milton Waner

Purpose: Periorbital infantile hemangiomas(POIH) account for less than 10% of all head and neck IHs but have the highest complication rate(63%) and pose significant risk to a child's developing vision. Our objective is to evaluate the anatomic distribution of POIHs and clinical effects on vision.

Methods: A retrospective chart review of infants with POIH presenting to a vascular anomalies center over a 25-year period were reviewed.

Age at POIH presentation, gender, age at presentation to our center, visual acuity, eyelid position, and astigmatism were recorded. Data included detailed birth history, invasive prenatal testing, number of fetuses during this pregnancy, and postnatal care. Prior medical, laser, or surgical treatments were noted. Seven total sites, and focal and segmental distribution were analyzed.

Results: A total of 528 charts were reviewed - 338(64.0%) involved the upper eyelid, 161(30.5%) lower, and 29(5.5%)upper and lower. Approximately one-third of lesions presented at birth, 1/3 within 1-2 weeks and 1/3 after 2 weeks.

Ninety-one percent of patients had focal lesions and the upper medial eyelid (23%) was the most common site. Nine percent had segmental lesions(V1 or V2) and the upper eyelid was the most common site. Four percent had orbital involvement.

The majority of patients(63%) presented with unilateral astigmatism and the upper medial eyelid was the most common site for astigmatism with an average measurement of 3.81 diopters as well as anisometropia. Ten percent of patients presented with amblyopia. The most common location was the upper medial eyelid which was also most commonly associated with astigmatism and amblyopia.

Conclusion: The medial upper eyelid is the most common site for POIH and is commonly associated with astigmatism, anisometropia and amblyopia. An alarming 10% of children had amblyopia at presentation. We present the largest series of periorbital infantile hemangiomas noted in the English language literature to date.

P241

Apelin receptor can act as a specific marker and therapeutic target for infantile hemangioma.

QIANYI CHEN, HANRU YING, ZHANG YU, LEI CHANG, YAJING QIU and Lin Xiaoxi

Purpose: In this study, we aimed to explore whether apelin receptor (APJ) can become a therapeutic target.

Methods: The expression pattern of APJ in IH and other vascular anomalies was demonstrated using immunohistochemistry-immunofluorescence. Then, the impact of applying APJ antagonist on hemangioma endothelial cells (HemEC) and normal endothelial cells was examined by serials of experiments on cell proliferation and functions.

Results: We have found that Apelin receptor (APJ), expressed only in infantile hemangioma endothelial cells (HemECs) but not in other vascular anomalies, can be defined as a target through which the cellular viability and functions of HemECs would be regulated. Besides, APJ was also detected in propranolol-resistant IH. This inhibitory action could be duplicated in murine hemangioma model formed with an elevated HemECs component.

Conclusion: These results verified the distinctive expression pattern of APJ in IH and specific inhibition of HemECs activity caused by ML221. In consequence, we propose that APJ can act as a promising marker and therapeutic target for IH.

P247

Direct Surgical Excision of Pediatric Hemangioma: Comparative Analysis of Operating Room & In-Office Surgical Outcomes

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Purpose: Hemangiomas are the most common pediatric tumor. They present at birth, can arise anywhere on the body, and may be painful or disfiguring. Hemangiomas can be treated with both medical and surgical therapies. Surgical excision is typically performed either in the operating room under general anesthesia, or in the office using local anesthesia. The literature comparing surgical excision performed in the OR versus in-office is lacking.

Methods: A retrospective chart review was conducted to assess the outcomes of 59 patients who underwent surgical excision of hemangioma by one pediatric plastic surgeon. Procedure location, complications, completeness of resection, and time to procedure were recorded.

Results: 59 patients underwent excision between 2017-2021. 20 patients (range:6 months-12 years of age, mean:38 months) received 23 procedures in the OR and 39 patients (range:1 month-15 years, mean:31 months) received 40 procedures in-office. Average hemangioma size was 2.1 cm for the office group, and 4.1 cm for the OR group. In the OR group, 13/20 patients (65%) had facial hemangiomas, similar to the 23/39 facial hemangiomas (59%) in the office group. Median time from initial consultation to procedure was 72 days for the OR group, and 22 days for the office group. The office group had 25 patients with complete symptom resolution (64%) and 14 with partial resolution (36%); the OR group had 11 patients with complete resolution (55%) and 9 with partial resolution (45%). Neither group experienced any cases of significant (>10cc) blood loss, infection, dehiscence or hematoma requiring evacuation. One patient in each group developed scar hyperpigmentation; both were managed successfully with YAG laser therapy.

Conclusion: In-office surgical excision of hemangioma in pediatric patients may be equally efficacious as in the OR, while maintaining low complication rates and lower time to procedure.

P259

Comparison of the efficacy between topical timolol and pulsed dye laser in the treatment of ulcerated infantile haemangiomas: a randomised controlled study

QIANYI CHEN, LEI CHANG, YAJING QIU, GANG MA and Lin Xiaoxi

Purpose: To compare the efficacy of topical timolol and PDL in promoting ulcer healing in IHs.

Methods: This randomised controlled study recruited infants diagnosed with IHs complicated with recently formed ulcers, without previous treatment. Patients with severe IHs who needed oral propranolol were excluded. The participants were randomly allocated to the topical timolol or PDL group, and then they were required to finish the therapy and participate in follow-up until the ulcers healed. The healing time of each group was recorded and compared between the two groups using the Student t test.

Results: The study included 20 participants, but one participant was lost to follow-up. The clinical data of 19 patients, 10 in the timolol group and 9 in the PDL group, were analysed. There was no significant difference in the existence time, distribution, and size of the ulceration. The mean healing times of the topical timolol and PDL groups were 18.70 and 19.22 days, respectively, with no statistical difference between them. Medical expenses were lower in the timolol group than in the PDL group

Conclusion: Both topical timolol and PDL treatment are effective for treating localised ulcerated IHs, and they can facilitate healing of lesions for similar lengths of time. Keeping the surface of the lesion clean and dry is also required. Considering the much lower costs of timolol, the topical application of timolol is recommended.

P266

Clinical Features, Treatments, and Complications of Anogenital Infantile Hemangiomas

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Purpose: Infantile hemangiomas (IHs) are the most common tumor of infancy; however, IH of the anogenital region remain poorly characterized. We sought to better assess the distribution, ulceration rate, and associated congenital anomalies of anogenital IHs.

Methods: We performed a multi-center retrospective chart review of patients presenting between 2008 and 2018 to 8 tertiary care facilities in North America. Patients less than one year old with a clinical diagnosis of an IH of the anogenital region (vulva, penis, scrotum, perineum, perianal, buttocks, or sacrum) who had clinical photographs of the IH were included in this study.

Results: A total of 435 patients with an IH of the anogenital region were enrolled (319 female [73%]). IHs of the genitalia were most commonly focal (n=297 [68%]), followed by segmental (n=93 [21%]) and indeterminant (n=45 [10%]) patterns. Anogenital IHs were mostly commonly superficial (n= 314 [72%]) and mixed (n=102 [23%]) types, and less frequently reticular/abortive (n=11 [2.5%]) or deep (n=6 [1.4%]) types, Ulceration occurred in over half the cohort (n=232 [53%]) and was associated with mixed type (odds ratio [OR] 3.05; 95% confidence interval [CI] 1.57 to 5.92; P<.001), and buttock (OR 2.78; 95% CI 1.21 to 6.37; P=.016) or perianal involvement (OR 2.48; 95% CI 1.03 to 5.97; P=0.044), as well as treatment with topical timolol (OR 5.18; 95% CI 1.41 to 6.04; P<.001). Congenital anomalies were present in approximately 1 in every 10 subjects with an anogenital IH (n=45 [10%]), and were associated with sacral (OR 4.30; 95% CI 1.64 to 11.2; P=.003) or penile (OR 5.27; 95% CI 1.35 to 20.6; P=.017) location.

Conclusion: Anogenital IHs involving the buttocks or perianal region are at an increased risk for ulceration. Clinicians should consider screening for congenital anomalies in patients with IHs involving the sacrum or penis.

P273

Clinical Characteristics of Infantile Hemangiomas with Aggressive Ulceration

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Purpose: Ulceration in infantile hemangiomas (IH) is a common complication. In a recent large retrospective study of patients with IH ulceration the average heal time was 6 weeks, but more persistent and severe ulceration was noted in ~ 10% of cases. The aim of this study is to further characterize clinical features of IH with more severe, aggressive ulceration.

Methods: Retrospective multi-center cohort study. The previously reported study identified a cohort of 35/363 patients who met at least 2 of the following criteria for aggressive ulceration: (a) significant soft-tissue destruction, (b) worsening of ulceration despite multimodal therapy, and (c) healing time beyond

12 weeks (Fernández et. al, 2021). Clinical features of the IH and ulceration were further analyzed within this cohort.

Results: IH with aggressive ulceration were located on the head and neck in 26% (n=9), trunk in 26% (n=9), diaper area in 26% (n=9) and upper extremities in 22 % (n=8). IH in the diaper area were found to be segmental (100%), superficial (89%), with a thin superficial component (100%) and greater than 10 cm2 (67%). IH on upper extremities were segmental (71%) and greater than 10 cm2 (62.5%). IH on the head/neck were localized (67%), mixed (62.5%), with thick superficial component (78%) and deep ulcerations (78%). IH on the trunk had deep ulcerations (89%) but did not display a significant trend in other clinical features.

Conclusion: This study identified a distinctive phenotype of IH in the diaper/perineal area – segmental, superficial thin IH – with a marked tendency toward aggressive ulceration. In addition, both the head & neck and upper extremity show a strong trend to more localized, thick IH with deep ulcerations. The role of these findings in IH management should be considered in future studies.

P294

Role of Interferon treatment in a neonate with extensive life threatening hemangiomas

Lydia Pathman, Susan Robertson and Roderic J. Phillips

Purpose: To report on the use of interferon-alpha-2a in a neonate with extensive life threatening internal head, neck and thoracic hemangiomas.

Methods: We report a female infant, born at extreme prematurity, 24 weeks gestation. She required ventilation for 5 weeks and airway support for a further 5 weeks. Intermittent oral steroids were used for respiratory support for a total of 8 weeks. She also required thyroxine for hypothyroidism. An extensive superficial segmental head and neck hemangioma developed slowly over the first 16 weeks of life. She had a scheduled MRI performed at term corrected gestational age. This revealed previously unsuspected extensive hemangiomas: intracranially with brainstem and medullary compression, and bilaterally in the neck and upper chest, encasing the oesophagus and trachea with evidence of airway compromise. She was transferred to a tertiary intensive care unit and within two days had deteriorated rapidly, requiring ventilation and major inotropic support. She was commenced on oral propranolol. After one day she worsened further and showed extreme lability of cardiac function and blood pressure, so propranolol was ceased for 36 hours. Given her parlous condition, and after discussion with her parents, interferon-alpha-2a was commenced, along with restarting propranolol at increasing doses.

Results: Her cardiac instability and ventilation problems improved over the subsequent two weeks. Repeat MRI after 16 days of treatment showed a great response, with a 70% reduction in the mass of the largest intracranial tumour. Interferon was ceased after five weeks. Subsequent scans have shown continued shrinking and resolution of tumour masses. Propranolol was ceased after 14 months. At 15 months corrected age, her development is progressing steadily, a few months behind a normal infant, as expected given her prolonged 6 month stay in hospital.

Conclusion: Interferon may have contributed to a rapid shrinking and clearing of hemangioma. It remains a useful option for hemangioma treatment.

P326

Diagnosis and Management of Periorbital Infantile Hemangiomas. Single center experience of last five year period (2017 to 2021)

Josef Malis, Adela Misove, Simona Zimova, Kveta Blahova, Veronika Stara, Martin Kyncl, Jana Cadova, Pavel Pochop and Lucie Sramkova

Purpose: Infantile hemangiomas (IH) are the most common tumors of infancy. Approximately 10% are clinically important with the need of treatment. Hemangiomas near the eye may compromise infant's vision by closing the eyelid or by putting pressure on the eye. We have evaluated 67 children with periorbital IH, The aim of the study was to determine the need for imaging methods, differential diagnostics, duration of conservative therapy and treatment outcomes.

Methods: Within yrs 2017 - 2021 we treated 522 pts with IH by propranolol, dose 3mg/kg/day. Among them 67 infants (13%) had IH localised close to eye (51 girls, 16 boys). Median age 3,5 months (3wks; 20mths), 25/67 had deep IH involving eyelids with various involvement of the orbit. 16/67 were mixed IH. All deep and mixed IH compromised visual function or might during further growth. All these children were investigated by MRI for detection of initial extend of IH. Remaining 26/67 children had superficial IH of various size, but even small lesion on the eyelid margin needed the treatment for its conjunctival irritation. Only 5/67 children had other IH lesions on the skin. Further 6 pts more were referred to our center as periorbital IH, but 3 had lymphatic malformation, 1 rhabdomyosarcoma, 1 neuroblastoma met, 1 soft part sarcoma.

Results: Superficial IH were treated for 6-7 months with 90% complete resolution, deep and mixed needed at least 9mths duration, the longest - one year. All children with deep and mixed IH were investigated by MRI till the complete resolution of IH, 2 children had regrowth of deep IH, one - three months after treatment completion, the second one very soon - bad parents compliance.

Conclusion: Majority of IH are diagnosed clinically, but periorbital localisation needs MRI for disease extension and differential diagnosis. Deep and mixed IH need longer treatment, very often about a year long.

P417

Paradigm Shift in the Management of Infantile Hemangiomas

Esteban Fernandez Faith, Sonal Shah, Mitchell Braun, Elena Pope, Irene Lara-Corrales, Patricia M. Witman, Katya Harfmann, Flora Bradley, Kenneth Jackson, Alexandra Hallagan and Ilona Frieden

Purpose: Beta-blockers have revolutionized the management of infantile hemangiomas (IH), representing an effective treatment for IH proliferation. Prior to the use of beta blockers, active treatment for IH was pursued in a minority of patients. Despite advances in the management of IH, observation continues to be recommended for most patients with IH. The purpose of the study is to characterize management practices of IH at tertiary referral centers in the beta-blocker era.

Methods: Multicenter retrospective study at 3 tertiary referral centers from 2012 to 2016. Data on demographics, clinical characteristics, and management decision were analyzed.

Results: A total of 1,722 patients were enrolled. The median age at presentation was 16.6 weeks (IQR 10.6, 26.4). Some form of active intervention was recommended in 68% of subjects. The most common indications for intervention were risk of disfigurement (74.6%), risk of functional impairment (26.7%) and ulceration (16.8%). Among those with risk of functional impairment, risk for visual compromise was considered in 68.3%, feeding difficulties in 17.9%, and respiratory compromise in 4.8%.

Timolol was used in 70.8% of subjects and systemic beta-blockers in 36% (some received both therapies though most often sequentially not simultaneously). Active treatment was not pursued in 32% of patients. Reasons for observation alone included low risk for complications (82.8%), late presentation (29.5%), and parental refusal (10.5%).

Conclusion: A shift in the management of IH has occurred after the emergence of beta blocker therapy. In a referral (pediatric dermatology) setting, a majority of patients with IH receive active therapy, most commonly due to risk of disfigurement. Efforts to ensure prompt referral and evaluation should be undertaken to optimize outcomes and prevent complications.

P419

Abortive hemangiomas : a literature review

Margaux Sergeant, Laetitia Goffinet, Jean-Luc Schmutz and Anne-Claire Bursztejn

Purpose: Infantile hemangioma with minimal or arrested growth (IH-MAG) is a subtype of infantile hemangioma (IH) that doesn't have a proliferative component or only a minimal one equaling less than 25% of its total surface area. The aim of this study is to describe the clinical characteristics of IH-MAGs and their difference with classic IH.

Methods: A systematic literature review with analysis of individual data was performed by searching the MEDLINE database for scientific articles using the combination of keywords: (hemangioma) AND ((abortive) OR (reticular) OR ((minimal growth)) OR ((arrested growth)) OR (telangiectatic) OR (MAG)).

Results: Seventy-five patients with 80 IH-MAGs were described. Fifty patients (67%) were female and only 11% of patients were born preterm. Unlike IH which are predominant in the cephalic region, most IH-MAG were located on the lower body (45%). Most common clinical features were erythematous macule (95%) and telangiectasias (83%). Ulceration was the most frequent complication, happening in 23 (29%) IH-MAGS. GLUT-1 immunostaining was positive in 21 of the 22 biopsies realized. Progressive fading of the lesion was observed in most cases but telangiectasias and dilated veins persisted over time. Oral propranolol was the most used treatment for IH-MAG and its main indication was ulceration.

Conclusion: This is the first literature review on IH-MAGS. This review demonstrates that IH-MAG is a subtype of IH with its own specificities: preference for the lower body, high risk of ulceration for segmental IH-MAG of the extremities. Better understanding of this lesion is important to improve its diagnosis and management.

P421

Do hemangiomas with minimal or arrested growth really differs from others infantile hemangiomas? A rétrospective, descriptive, comparative study.

Margaux Sergeant, Hélène Rousseau and Anne-Claire Bursztejn

Purpose: Minimal or arrested growth infantile hemangioma (IH-MAG) is a subtype of infantile hemangioma (IH) with a proliferative component that does not exceed 25% of its total surface. The proportion of this subtype of lesion among other type of IH has not been studied yet. We decided to conduct this comparative monocentric retrospective study in the objectives to give an estimate of the proportion of IH-MAG among other type of IH and to compare epidemiologic and clinical characteristics between IH-MAG and other IH. Finally, we wished to study the evolution of IH-MAG.

Methods: We retrospectively searched our photographic database for pictures of IH and IH-MAG between January 2014 and December 2020. Data regarding patient's characteristics, number and type of lesion and lesions' characteristics were then retrieved from patients' files for analysis.

Results: We studied 224 patients with 317 lesions (277 "classic" IH and 40 IH-MAG). The proportion of IH-MAG among other IH was 12.6%. There were no statically significant differences between groups ("classic" IH, IH-MAG and both type of lesion) regarding the female predominance and the rate of premature and low birthweight babies. Most IH-MAG were located on the lower body (52.5%). Ulceration happened in 15% of IH-MAG. Most ulcerated IH-MAG (83.3%) were located on the perineum. volution data were available for 16 patients (with 20 IH-MAG) with a mean follow-up time of 4.3 years. While proliferation papules, erythematous component, and vasoconstriction zones and halos had regressed "a lot" or "completely" in more than 50% of the patients, the dilated veins had only regressed "moderately" at best. The telangiectasias had disappeared "completely" in 8.3% of cases and "moderately" to "a lot" in 50% of cases.

Conclusion: This is the first study comparing IH-MAG to other type of IH. This study shows that IH-MAG are not rare and should be known of pediatricians and dermatologists.

P422

The Natural History of Congenital Hepatic Hemangiomas: Lessons from an International Hepatic Hemangioma Registry

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Purpose: Congenital hepatic hemangiomas are benign vascular tumors. However, their clinical behavior can vary widely from asymptomatic to life-threatening. We reviewed our international hepatic hemangioma registry to characterize the natural history of these lesions.

Methods: Records of patients born between 2004 and 2021 with a congenital hepatic hemangioma were reviewed. Clinical characteristics, imaging studies, and outcomes were evaluated. Sequential hemangioma volumes were calculated using the formula for an ellipsoid.

Results: We identified 93 patients with congenital hepatic hemangiomas of which 49% (n=46) occurred in females. The prenatal detection rate was 34% (n=32). Of affected patients, 33% (n=22) were premature, 11% (n=7) had cutaneous hemangiomas, 1% (n=1) had transient hypothyroidism, 48% (n=23) had transient anemia, and 57% (n=30) had transient thrombocytopenia. A subset experienced cardiomegaly (32%, 29 patients), congestive heart failure (24%, 22 patients), and shunting physiology (26%, 24 patients). Medical therapy was used in 48% of patients including 32% received propranolol (n=25), 36% steroids (n=27), 4% vincristine (n=3), 3% sirolimus (n=2). Procedural interventions were needed in 13% (n=2 liver transplant, n=4 resection, n=6 embolization). The mortality rate was 4%. By 12 months of age, 74% (n=26) had experienced >75% reduction of initial hemangioma volume, and by 24 months, 80% (n=20) had undergone >90% volume reduction. Pharmacotherapy did not affect involution rate; 73% of patients with (n=8/11) and without (n=16/22) pharmacotherapy achieved >75% reduction by 12 months. A very small subset required over three years to complete involution with 80% (n=4/5) undergoing biopsy or MRI for diagnostic confirmation.

Conclusion: Congenital hepatic hemangiomas are associated with prematurity, transient coagulopathy, normal thyroid function, and a subset with negative effects on cardiac physiology. Most patients reach

>75% involution by 12 months of age and >90% involution by 24 months of age. Patients who do not follow this course warrant additional imaging and/or biopsy to confirm an accurate diagnosis.

P447

Using Sirolimus to Treat Intestinal Infantile Hemangioma with Features of PHACES: Case Report and Systematic Review

Elana Kleinman, Tali Stauber, Francine Blei, Denise Adams and shoshana Greenberger

Purpose: We report a case of a 3-month-old female with right aortic arch and aberrant left subclavian artery, who presented with pallor, hemoglobin of 7.1 g/dL, and failure to thrive. Infantile hemangioma (IH) of the small bowel was confirmed on abdominal ultrasound, computed tomography, and biopsy. Brain MRI, ophthalmological and skin examination were normal. Her symptoms persisted with propranolol but addition of sirolimus led to regression of the intestinal hemangioma. Cessation of sirolimus treatment led to regrowth of the hemangioma.

Methods: A systematic review was conducted using PubMed, EMBASE, and Ovid MEDLINE search terms related to intestinal hemangiomas and PHACES between 1982 and 2021. Articles were limited to intestinal IH (age <5). Two reviewers independently screened titles and abstracts to assess for inclusion and settled disputes. Data extracted pertained to sex, age of presentation, symptoms, hemangioma location(s), treatment, outcome, and presence of features and/or diagnosis of PHACES syndrome (posterior fossa malformations, segmental cutaneous hemangiomas, arterial abnormalities, cardiac abnormalities, eye abnormalities, and sternal cleft defects).

Results: A total of 4933 articles were identified by database search; 1613 duplicates and 367 non-English articles were excluded. Thirty articles met inclusion criteria with 48 cases of symptomatic intestinal IH. Of those, 8 had a diagnosis of PHACES. Fifteen cases had facial hemangiomas with major (n=2) and minor (n=2) criteria for PHACES. One case had a minor criterion of PHACES without cutaneous hemangiomas. The most common treatments were corticosteroids (n=28), resection (n=19), and propranolol (n=10). Available outcomes were bleeding arrest (n=22), continued bleeding (n=2), and death (n=3).

Conclusion: This is the first reported case in which sirolimus showed regression of intestinal IH. Our patient lacked cutaneous hemangiomas but had major and minor cardiovascular criterion of PHACES. The potential correlation between intestinal IH and PHACES features deserves more study in consideration of intestinal IH as a minor criterion of PHACES.

P448

Effects of COVID-19 pandemic on infantile hemangiomas' monitoring and treatment

Raluca Tatar and Dan Mircea Enescu

Purpose: The ongoing COVID-19 pandemic has produced many changes in the medical practice all over the world. Since the success of the treatment for infantile hemangiomas (IHs) depends a lot on early diagnostic and start of proper treatment protocol, we wanted to assess how this new reality influenced addressability and therapeutic options in our pediatric plastic surgery department.

Methods: We retrospectively reviewed all our patient records, from January 2019 till November 2021, in order to identify cases with a diagnostic of IHs. We started the search with admitted patients that underwent a surgical procedure, and extended it to consultation records for out-patient visits for the same diagnostic. For cases not indicated for surgery, the monitoring protocol follows, with regulat

check-ups, after the initial visit at which we establish the adepted course of treatment, including local medication, systemic medication or active observation alone.

Results: In the absence of an already established telemedicine routine and insurance covering, we had to keep examining patients in the traditional way. Considering 2019 a regular year, we registered a 68,3% decrease of single patient first visits in 2020, and a 37,8% decrease in 2021. Regarding the surgical excisions for IHs, this was conditioned also by national legal regulations and hospital bed availability (ward capacity reduced by half). We recorded a 77,92% decrease in 2020 (3 cases vs. 13 in 2019), and a 61,53% decrease in 2021 (5 cases).

Conclusion: The COVID-19 pandemic significantly decreased the surgical procedures performed for IHs, together with the initial visits of new patients and follow-up monitoring check-ups. The full impact of this trend will be seen in the future, but we estimate an increase of need for surgical correction of involuting/involuted IHs on different locations.

P452

Hemangioma Education for the General Pediatrician through Project ECHO, a new model

Autumn Atkinson, Kelly Turner, Matthew Greives, Neethu Menon and Adelaide Hebert

Purpose: Hemangiomas are the most common benign tumor of infancy and childhood, affecting 4-5% of all infants. While the lesion is considered “benign”, the tumor undergoes a rapid proliferation phase in the first 6-12 months of life that can be destructive and can cause life threatening complications if not treated early. While the AAP has published Clinical Practice Guideline on the management of hemangiomas in 2019, there is still a barrier between the current scientific/clinical evidence of management by hemangioma experts and the practice and management by primary care providers, who are the first line clinicians to see and diagnosis hemangiomas. This program was developed to close this gap through demonopolizing knowledge through the Project ECHO model.

Methods: Project ECHO (Extension for Community Healthcare Outcomes) is a medical education model that increases workforce capacity to provide best-practice specialty care and reduce disparities. It uses knowledge-sharing networks, led by expert teams using multi-point videoconferencing to conduct virtual sessions and education with community providers. Currently out of the 578 ECHO programs in the United States, only three focus on dermatology and no single program that focuses on pediatric dermatology or vascular anomalies. We propose to outline a new program using the ECHO model for the education of primary care providers on the identification and management of hemangiomas and other vascular anomalies.

Results: The presentation will highlight the need for the ECHO model as described above, our curriculum (6 one-hour sessions over a 3-4 month period), and our expert panel (pediatrics, plastic surgery, dermatology, hematology), and the current progress of our pilot program.

Conclusion: By modeling our program, we hope to gain feedback to implement in our program, spark interest in applying the ECHO model to other vascular anomalies, and showcase a need for the demonopolization of knowledge in vascular anomalies for the primary care provider.

P457

Pulmonary Infantile Hemangioma: Clinical, Radiological, and Pathological Review of Nine Cases

Alexindra Wheeler, Kumar Shashi, Harry Kozakewich and Whitney Eng

Purpose: Infantile hemangioma (IH) is a benign vascular tumor that most commonly involves skin. Pulmonary IH is rare with few reports of clinical presentations and outcomes. We describe the clinical, radiological, and pathological findings of nine patients with pulmonary IH.

Methods: An IRB-approved, retrospective review of pediatric patients with a diagnosis of pulmonary IH was conducted. Cases from patients presenting between 1918 to 2021 were identified in the Department of Pathology database. Histopathologic analysis confirmed pulmonary IH in nine infants, with positive endothelial glucose transporter-1 (GLUT1) immunostaining in eight cases.

Results: All patients presented with respiratory distress, including tachypnea, cyanosis, and hypoxia. The median age at initial presentation was two months (range, birth to 12 months). Five patients had a single pulmonary hemangioma ranging in size from 0.2 to 8.0 cm; four had multiple lesions. Five of nine infants had concurrent multifocal hepatic IH and seven had concurrent skin IH. Chest radiography demonstrated nonhomogeneous, mass-like consolidative opacities or rounded nodules. The median age at pathologic diagnosis was 6.5 months (range, 5 weeks to 16 months). Treatment was primarily supportive. Four patients received medical therapy with one or more of the following: propranolol (n=2), interferon (n=2), and corticosteroids (n=5). Five patients underwent surgical resection of pulmonary masses and two underwent hepatic embolization. Wedge resection was performed in three patients and lobectomy was performed in one patient. Four patients died; causes of death were sepsis, abdominal hemorrhage, pneumonia, and liver failure. All patients who had lung surgery performed or received medical therapy survived.

Conclusion: Although rare, pulmonary IH should be considered in the differential diagnosis of infants with pulmonary masses, especially when accompanied by hepatic IH. Early recognition is critical for patients to receive prompt administration of life-saving treatment.

Lymphatic Malformations

P019

Trametinib associated rhabdomyolysis during treatment of a KRAS variant lymphatic anomaly

Taizo Nakano, Sarah Sheppard, Lauren Hill, Kathryn Chatfield, Aparna Annam and Ann Kulungowski

Purpose: 15-year-old male presented with severe scrotal and dermal chylorrhea, lower extremity lymphedema, and central conducting lymphatic anomaly diagnosed by MR lymphangiogram. Scrotal biopsy demonstrated D2-40+, CD31+, dilated lymphatic channels. Genetics from this tissue sample identified a pathogenic mosaic KRAS variant c.436G>T (NM_033360.4) at 3.3-3.4% allele frequency. A lympho-venous shunt and glue embolization provided moderate clinical improvement but with persistent functional impact, MEK1/2 inhibition with trametinib was initiated.

Methods: He was consented and monitored under an institutional IRB protocol for off-label use of trametinib for patients with pathogenic RAS/MAPK pathway disorders. Trametinib, obtained through commercial insurance, was initiated at 0.5mg (0.005 mg/kg) PO daily. Baseline evaluation included laboratory evaluation (CBC, CMP, PT/aPTT, Creatinine Kinase (CK), Lipase, Amylase, Thyroid panel), physical exam, MRI imaging, echocardiogram/ECG, ophthalmology exam.

Results: Patient reported improvement in leg swelling/edema at the 1 month follow up visit. History and physical exam were normal, however monitoring labs demonstrated a CK of 12,285 U/L (baseline CK of 100 U/L) and a serum creatinine of 0.74 mg/dL (up from 0.5 mg/dL baseline). He was admitted for aggressive intravenous hydration and laboratory monitoring for clinical rhabdomyolysis. He was discharged after 5 days with a normalized serum creatinine, a normalizing CK, and has remained off study therapy.

Conclusion: Isolated cases of drug-induced rhabdomyolysis have been reported in phase III trials of trametinib combined with dabrafenib (BRAF inhibitor) for metastatic melanoma. Our patient presented without weakness and the complication was identified solely on scheduled screening labs. He reported aggressive weightlifting at school in the week prior to presentation, which may have contributed. The case emphasizes the importance of standardized laboratory screening while on trametinib therapy. Increased use of targeted MEK1/2 inhibition for symptomatic vascular anomalies with RAS/MAPK pathway disorders will require prospective trials focusing on safety and accurately defining its side effect profile.

P038

Percutaneous sclerotherapy of head and neck cystic malformations: ten years experience.

Ilaria Paladini and Roberto Menozzi

Purpose: The aim of the study is to evaluate the outcome of mini-invasive treatment of head and neck cystic malformations (lymphangiomas, salivary epithelial duct cysts, salivary mucoceles and branchial cysts) by percutaneous injection of sclerosant agents as Picibanil, Bleomicin or alcool and their recurrence depending on the histological nature and the site of the lesion.

Methods: Between January 2007 and December 2017 , 54 cystic malformations (26 lymphangiomas, 11 salivary epithelial duct cysts, 12 salivary mucoceles, 5 branchial cysts) were treated percutaneously by injection of sclerosant agents. Lymphangiomas were treated with Picibanil (85%),Bleomicin (15%), Picibanil and Bleomicin sequentially (11%), Picibanil and alcool sequentially (4%). All other malformation were treated with Picibanil exclusively in 100% of the cases.

Results: The authors observed a satisfactory reduction in 100% of lymphangiomas ; the number of reintervention was directly proportional to the number of lesions ($p<0.01$), and influenced by histological nature with a better response in macrocystic lymphangiomas, followed by microcystic and micromacrocystic. At the follow up aesthetic improvement was 5 ANA scale points , with 5.87 VAS points and 3.33 QoL points improvement. Salivary epithelial ductal cysts showed 100% of satisfactory reduction with a follow up aesthetic improvement of 5.75 points , with 5.0 VAS points and 4.13 QoL points improvement. On the contrary mucoceles and branchial cysts showed worse response. Only 25% of mucoceles had satisfactory reduction with 5.4 ANA points and 4 QoL points improvement and 100% of branchial cyst had just a temporary clinical response with recurrence at the follow up.

Conclusion: Percutaneous sclerosant treatment of head and neck cysts should be considered the gold standard for all histological types of lymphangiomas and salivary epithelial duct cysts. On the contrary mucoceles and brachial cysts should be treated surgically as first choice and percutaneous option should be considered only in selected cases.

P047

Identitiy Crisis: cystic teratoma of the neck masquerading as lymphatic malformation and lymphatic malformation of the abdomen masquerading as cystic teratoma with managment, outcome and rad-path correlation.

Christopher J. Francis, Megan Hemmrich, Michael Markovitz and Sally Mitchell

Purpose: To understand the overlapping imaging features and clinical presentation of the two entities.

Methods: Cystic teratoma and lymphatic malformation (LM) are two generally benign differential considerations for congenital masses which demonstrate overlapping clinical and imaging findings. It is important to distinguish between these etiologies as cystic teratomas may require surgical excision whereas lymphatic malformations may be treated with minimally invasive sclerotherapy. We present two contrasting cases: a cervical neck teratoma mimicking a LM and an abdominal LM resembling a cystic teratoma.

Results: Case 1: A 9-month-old female presented with a right neck mass discovered on prenatal screening. MRI confirmed a predominantly cystic, mixed soft tissue and cystic right anterolateral neck mass, most consistent with mixed type lymphatic malformation. Despite two rounds of percutaneous sclerotherapy with doxycycline, the lesion continued to enlarge on repeat MRI, crossing the midline and causing mass effect on the trachea. Respiratory distress was exacerbated by COVID-19 infection requiring intubation and eventual tracheostomy. She was started on sirolimus and underwent a third sclerotherapy treatment with doxycycline and STS without improvement. Surgical debulking was performed with pathology returning as mature multicystic teratoma composed of endodermal, neuroglial and mesodermal elements with minimal fat. Case 2: A 13-year-old male with no significant past medical history presented with three weeks of right-sided abdominal pain and constipation. CT showed a cystic lesion. MRI confirmed a multicystic abdominal mass with calcification with mass effect on the small bowel and right ureter causing partial small bowel obstruction and hydronephrosis, most consistent with a large cystic teratoma. However, following surgical excision pathology demonstrated a multicystic mass containing vascular structures with lymphocytic aggregates and nodules consistent with LM.

Conclusion: It is important for radiologists and their interdisciplinary colleagues to be cognizant of the overlapping features of these conditions to avoid errors in diagnosis and management as their treatments differ.

P052

scrotal lymphangioma, surgical management

cesar eduardo jimenez and cesar eduardo jimenez

P053

Anatomical background of abdominal and retroperitoneal lymphatic malformations treatment strategies in children

Iryna Benzar

Purpose: The aim of the study was to set the definitive tactics of abdominal and retroperitoneal lymphatic malformations (LMs) treatment according to their anatomical localization with optimal use of conservative and surgical treatment options.

Methods: Among pediatric patients, who underwent treatment in single hospital since January 2011 till July 2019 we identified 225 patients diagnosed LMs, 28 males to 15 females. Abdominal and retroperitoneal LMs were diagnosed in 40 (17.7%) children. Median patients' age was 4 years old (range 1 month ÷ 17 years old). Sonography, MRI or CT were routinely used as diagnostic options. The median follow-up period was 49.6 ± 5,62 months (9÷119 months).

Results: Out of 40 children enrolled into study, 37 (86.0%) had isolated lesions of bowel or omentum, 3 (7.0%) combined with mediastinal LMs. According to visualizing methods findings, all LMs were divided into following groups: omentum LMs - 7, intestinal and bowel LMs - 24, retroperitoneal - 9, retroperitoneal LMs with cisterna chyli connection – 2. Treatment options used were following: surgical resections of abdominal and retroperitoneal LMs were performed in 32 patients, including 10 laparotomies, 16 pure laparoscopic LM removals, and 6 videoassisted transumbilical bowel resections, affected by LM – for all isolated LMs. Sclerotherapy was chosen as optimal method in 4 children with retroperitoneal LMs. In 2 patients with LM with retroperitoneal connection with thoracic duct we used sclerotherapy under laparoscopic guidance was used. 2 patients received systemic immunosuppression for LMs affecting mesentery root. Abdominal LMs treatment showed excellent results in 35 (81.4%), good in 5 (11.6%), satisfactory in 2 (4.7%), and unsatisfactory in 1 (2.3%) case. In those with radical resections of isolated LMs no recurrences were observed.

Conclusion: Anatomical localization is to be the main factor considered when choosing the treatment strategy of abdominal and retroperitoneal LMs.

P141

NRAS Q61R Mutation Identified in Kaposiform Lymphangiomatosis Induces Angiopoietin-2 Expression by Human Endothelial Cells in Culture

Patricia Pastura, Denise M. Adams, Devin M. Pillis, Punam Malik, Elisa Boscolo and Timothy Le Cras

Purpose: Kaposiform lymphangiomatosis (KLA) is a devastating vascular anomaly with poor survival and highly abnormal lymphatics that can affect several organs. The histopathology of KLA is characterized by clusters of spindle-shaped endothelial cells (EC) accompanying the malformed lymphatic channels. Potential insights into the pathogenesis of KLA have come from the identification of a somatic activating NRAS mutation p.Q61R in lesion tissue and highly elevated levels of the angiogenic factor, Angiopoietin-2 (ANG-2) in the blood of KLA patients. The purpose of this study was to determine whether NRAS Q61R regulates ANG-2 and the signaling pathways involved.

Methods: Lentiviral constructs were generated with doxycycline (Dox) regulated NRAS Q61R or NRAS wild type (NRAS WT). Each construct was introduced into human EC. Changes in EC morphology was assessed 24 and 48 hours after Dox-induced expression of NRAS Q61R or NRAS WT in EC cultures. ANG-2 expression was measured by western blot analysis of EC lysates and ELISA for ANG-2 in the EC culture medium. EC were also treated with inhibitors U0126 and rapamycin to block MAP kinase kinases (MEK1 and MEK2) and mTOR signaling, respectively.

Results: NRAS Q61R expressing human EC developed a spindle-shaped morphology and increased levels of ANG-2 at 24 and 48 hours compared to NRAS WT EC. U0126 treatment blocked the spindle-shaped morphology and increases in ANG-2 expression by NRAS mutant EC whereas rapamycin did not.

Conclusion: The NRAS Q61R mutation induces ANG-2 overexpression and spindled-morphology in human endothelial cells in culture through a mechanism involving MAP kinase signaling. This study suggests that the somatic activating NRAS Q61R mutation in KLA patients drives elevated levels of ANG-2 and spindled EC which may contribute to the disease process.

P165

Management of Localized Axillary Lymphatic Malformations in Childhood

Emir Q. Haxhija, Besiana P. Beqo, Paolo Gasparella, Christina Flucher and Stephan Spendel

Purpose: Treatment of children with axillary lymphatic malformations (LMs) is mainly based on an individualized multidisciplinary approach. Our study aimed to evaluate the management and outcome of children with localized axillary LMs.

Methods: We retrospectively reviewed all data of patients diagnosed with localized axillary LMs at our Institution between 2006 and 2021. We analyzed the age at first presentation, the LMs size, the diagnostic approach, the treatment technique, complications, and recurrence until the last follow-up. Descriptive data analysis was performed.

Results: Twenty patients (10m;10f) with a median age of 2.2 years (range:0–17years) were included. Each patient was evaluated by ultrasound (US). Five (5/20) patients with a median age of 3 (range: 1–6years) did not receive further imaging. Their median LM-volume calculated by US was 8ml (range: 3–11ml). Four of these patients underwent surgical resection, and the remaining one did not undergo any type of treatment. Fifteen (15/20) patients were additionally evaluated by MRI. Their median age was 2 years (range: 0.5-17years). The MRI-calculated median LM-volume was 77ml (range: 10–1035ml). All these 15 patients underwent surgery. Six patients presented with large LMs extending into the cervical (n=2, Figure) and upper arm region (n=4). One patient was unsuccessfully treated with OK-432-sclerotherapy before successful surgical resection. A second suction drain was needed postoperatively in one child. The median follow-up time was 8 years (range 1–14years). In 2 cases, local recurrences were reported at 6 and 9 years postoperatively, with corresponding LM-volumes of 2ml and 3ml, respectively. No further intervention was needed as patients did not present complaints. Despite extensive dissection, not one neurovascular injury was reported.

Conclusion: Meticulous surgical resection after appropriate diagnostic imaging is an excellent option for treating localized axillary LMs. We define vascular malformations as localized when we estimate that complete resection is possible without postoperative functional deficits.

P167

Characteristics and long-term outcomes of common (cystic) simple lymphatic malformations in 164 children: a tertiary center experience

Hanna Hyvönen, Päivi Salminen and Kristiina Kyrklund

P168

Cervicofacial lymphatic malformations with tongue involvement treated with sirolimus: lessons learned from a 10-year follow-up.

Emir Q. Haxhija, Sebastian Tschauner, Paolo Gasparella, Besiana P. Beqo, Stephan Spendel, Wolfgang Zemann, Holger Till and Michael E. Hoellwarth

Purpose: Cervicofacial lymphatic malformations (LMs) with tongue involvement are very difficult to treat and require a multidisciplinary approach.

Methods: We describe a series of 5 female patients with cervicofacial LMs who were started on sirolimus in 2010-2011. Sirolimus was orally administered, targeting trough levels of 5–15ng/ml. A detailed 10-year clinical course is documented.

Results: The mean age at initiation of sirolimus therapy was 23±9months (range 7-33). Two patients underwent surgical interventions before sirolimus initiation. The mean duration of initial treatment was 22±19months (range 3-46). All patients experienced a significant size reduction of their cervicofacial LMs, clearly noticeable at 4-weeks post-treatment onset. Additionally, the tongues cleared from proliferative areas and bleeding. However, after stopping sirolimus treatment, slow reactivation of LMs was noted even in cases that showed a complete response to the therapy. Four patients are on and off sirolimus depending on parents' compliance and patients' need. So far, every re-start of sirolimus treatment was followed by an excellent response. Trough levels of 5ng/ml are targeted for the long-term treatment. Apart from mucositis and leukopenia no side effects were noted. To prevent further jaw deformation from the increased size of the tongue muscle, the modified keyhole technique for tongue resection was performed in 3 patients. Two of these patients needed two surgical procedures for satisfactory tongue reduction which were performed without complications during sirolimus treatment. One of the latter patients needed an extensive upper and lower jaw reconstruction at the age of 12.

Conclusion: We support the immediate postnatal treatment start and the long-term therapy with sirolimus for children with debilitating cervicofacial LMs. We do not stop sirolimus treatment even if surgical intervention is needed. Sirolimus therapy alone has shown not to be enough for complete normalization of the tongue size. Thus, we support early surgical reduction of the tongue to prevent significant jaw deformation.

P197

Programmed cell death 4 (PDCD4) is downregulated by overexpression of the oncogenic microRNA-21 in lymphatic malformation endothelial cells

Ravi Sun, Haihong Zhang, June Wu, Carrie Shawber, Jonathan Perkins, Stephanie Byrum, Gresham Richter and Graham Strub

Purpose: MicroRNAs (miRNAs) are produced by all eukaryotic cells and function by attenuating protein synthesis by targeting messenger RNAs (mRNAs). Lymphatic malformations (LMs) contain endothelial cells (LMECs) harboring mutations in PIK3CA, however the function of miRNAs in LMs and LMECs is unknown. Here we demonstrate that miR-21, a known oncogenic miRNA, is expressed at high levels in LM tissue when compared to surrounding normal tissue. LMECs express miR-21, which targets the tumor suppressor PDCD4 (programmed cell death 4). PDCD4 binds to the translation initiation factor eIF4A and inhibits the transcription factor AP-1, leading to increased proliferation and migration and resistance to apoptosis. We propose that inhibition of miR-21 in LMs with anti-miR-21 may be a novel molecular therapeutic modality in the treatment of LMs.

Methods: LM tissue/fluid and adjacent normal tissue was collected from 20 patients undergoing surgical treatment for LMs. LMECs were isolated from LM tissue using magnetic beads and cultured. RT-PCR analysis of 6 miRNAs known to function in lymphangiogenesis and migration/proliferation was performed and compared between LM tissue/normal tissue and LMECs/normal lymphatic endothelial cells (HDLECs). LMECs were transfected with antagomir or miR-mimic and expression was determined with RT-PCR, and the expression of the miR-21 target PDCD4 was determined with proteomics and western blot. LMEC proliferation and migration assays in the presence or absence of antagomir/mimic were performed to determine the effect of miRNA manipulation.

Results: miR-21 was upregulated in LM tissue when compared to surrounding normal tissue. LMECs are culturable and express miR-21, which is inhibited by transfection with anti-miR-21. LMECs proliferate and migrate at higher rates than HDLECs, and proliferation of LMECs appears attenuated in the presence of anti-miR-21. The tumor suppressor PDCD4 is downregulated in LMECs and is a direct target of miR-21.

Conclusion: miR-21-mediated PDCD4 inhibition may be a novel therapeutic target in the treatment of lymphatic malformations.

P215

Primary surgical resection of intra-abdominal lymphatic malformations in children – outcomes from a single tertiary center

Hanna Hyvönen, Päivi Salminen and Kristiina Kyrklund

P228

Video-based education of the lymphatic system and lymphatic malformations

Ann Kulungowski, Lauren Hill, Aparna Annam, Nathaniel Billington and Taizo Nakano

Purpose: Lymphatic malformations occur in 1:4,000 live births, however, patients and parents identified the normal and malformed lymphatic circulatory system as a poorly understood subject with few adequate educational resources. In addition to a lack of standardized resources, the field lacks appropriate tools to validate the efficacy of materials developed for patient education.

Methods: After comprehensive literature review and in collaboration with a medical illustrator, two digitally animated videos were produced covering the normal lymphatic system and lymphatic malformations. Subjects were recruited from a single center multidisciplinary vascular anomalies center. The Patient Education Materials Assessment Tool – Audio/Visual (PEMAT-A/V), a health literacy tool used to assess comprehension, was utilized to evaluate efficacy. The PEMAT has demonstrated strong internal consistency, interrater reliability, and construct validity.

Results: Twenty-four subjects participated by watching the educational videos in clinic and completing a PEMAT-A/V survey. Table 1 contains demographic information for respondees. 80% of survey respondees were parents. Nine (37.5%) patients were newly diagnosed patients; 15 patients were established with diagnosis. Half (12) received prior verbal education on the lymphatic system. All subjects reported that the video series increased understanding of the lymphatic system. Table 2 summarizes PEMAT-AV question and responses. The only question that scored less than 90% “Agree” response was about charts, graphs, and tables, which were not included in the video series.

Conclusion: The video-based education series is an understandable and actionable way to transmit complex medical information to patients and their families. Improved comprehension of a patients underlying medical problem allows for better shared decision making and patient confidence in medical team and therapy. Our next aim is to translate the videos into Spanish and to compare the video-based education versus standard-of-care oral education from a medical provider.

P263

EXTREMELY SEVERE COMPLICATIONS DURING SURGICAL TREATMENT OF INTRAABDOMINAL LYMPHATIC MALFORMATIONS

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Purpose: Vascular anomalies treatment should not be worse than the original disease. However, the attempt of complete surgical resection of the lesion can sometimes lead to extremely severe sequelae due to vascular injury during surgery. The aim of this paper is to present a series of cases of severe complications in patients with intraabdominal lymphatic malformations (IALM).

Methods: We describe a retrospective series of 3 cases referred to our Vascular Anomalies Center between 2003 and 2020 from other institutions after surgical complications during IALM resection.

Results: A total of 3 patients were included (2 males and 1 female). In the first 2 cases severe vascular injury of superior mesenteric artery and celiac trunk took place during elective surgery in which IALM radical resection was attempted (mesenteric IALM in one case and retroperitoneal in the other). Both patients developed ischemic bowell and hepatic involvement requiring multivisceral transplantation at 4 and 3 years of age respectively. The first patient remains asymptomatic more than 10 years later, but the second patient died 4 months after transplantation due to acute cellular rejection and graft-versus-host disease. The third case suffered superior mesenteric artery injury during an emergency surgery for suspected appendicitis at 5 years of age where a venous-lymphatic vascular malformation was found in the distal ileum, cecum and ascending colon. Consequently, he developed intestinal ischemia that required 2 isolated intestinal transplants with chronic rejection and 2 subsequent multivisceral transplants. He died at 17 years of age due to multiorgan failure secondary to fulminant septic shock.

Conclusion: Management of IALM must be conservative, only considering surgery when refractory to other treatments and never attempting a radical resection. Patients, families and physicians need to be aware of the severe potential complications of surgical resection in IALM. A multidisciplinary approach is mandatory in these complex patients.

P277

Somatic activating BRAF variants cause isolated lymphatic malformations

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Purpose: Previous work has shown that approximately 80% of isolated lymphatic malformations (LM) have somatic pathogenic variants in PIK3CA. Our objective was to identify additional genetic causes of isolated LM other than PIK3CA.

Methods: Individuals with isolated LM in which tissue was available were screened for hotspot PIK3CA pathogenic variants (p.Glu542Lys, p.Glu545Lys, and p.His1047Arg). DNA from individuals without a PIK3CA mutation ("PIK3CA-negative individuals") was sent for high-depth targeted sequencing using a panel of 44 vascular anomaly associated genes ("VANSeq"). Variants were confirmed using digital droplet PCR (ddPCR) on additional tissue samples from the same lesion, when available. A BRAF p.Val600Glu specific monoclonal antibody was used to confirm the mutation and localize mutant cells.

Results: PIK3CA mutations were detected in 84 of 106 individuals (79%) with isolated LM. Of the 22 PIK3CA-negative individuals, 15 had sufficient DNA for VANSeq high depth gene panel sequencing. Three of these fifteen (20%) had the same pathogenic p.Val600Glu substitution in BRAF. The variant allele fraction (VAF) of these BRAF variants was very low (0.3-2%), but confirmed by ddPCR. A mutation specific BRAF antibody-stained lymphatic endothelial cells in BRAF mutant LMs but not in PIK3CA mutant LMs.

Conclusion: Somatic activating BRAF mutations, already known to drive numerous cancers, melanocytic nevi, and arteriovenous malformations, are now known to contribute to isolated lymphatic malformations too. BRAF mutations are present within lymphatic endothelial cells, and are found in ~3% (3/106) of individuals with isolated LM. Although this is a relatively small fraction compared with PIK3CA (~80%), it is a clinically significant as patients with BRAF mutant LMs may not respond to PIK3CA targeted therapies, and vice versa. Our results add to the genetic heterogeneity of vascular

malformations and emphasize the importance of precise molecular diagnostics in management of these conditions.

P297

Multicystic and diffuse lymphatic malformation of the mesentery in a child

iqbal dogar and Mohammad Bilal Mirza

P298

Identification of ANGPT2 Mutations as a Novel Cause of Primary Lymphedema

Pascal Brouillard, Marie F. Smeland, Veli-Matti Leppänen, Trine Prescott, Oystein Holla, Kari Alitalo, Laurence M. Boon and Miikka Vikkula

Purpose: Primary lymphedema (PLE) and hydrops fetalis are associated with mutations in >40 genes. They explain <40% of cases. To clarify pathogenesis, improve molecular diagnostics and strengthen stratification of patients, we looked for additional genes that can cause PLE.

Methods: We used whole exome sequencing to screen individuals within our PLE cohort of >900 index patients for novel mutations using our Highlander software to filter variants.

Results: A heterozygous angiopoietin 2 (ANGPT2) gene deletion was observed in 1 family, and 4 heterozygous variants of interest in 4 other families. In a consanguineous family with recurrent pregnancy loss due to severe non-immune hydrops fetalis, a homozygous ANGPT2 variant was identified. The latter substitution introduced a cryptic splice site predicted to result in loss of ten nucleotides with shift in reading-frame, leading to a premature stop codon. RNA analysis demonstrated loss of mutant allele, indicative of loss of function via nonsense-mediated mRNA decay. Parents had reduced serum ANGPT2 levels. The homozygous fetuses likely had no ANGPT2 expression. Functional analyses of the 4 dominant heterozygous substitutions unraveled that 3 led to decreased ANGPT2 secretion and even inhibited wild-type ANGPT2 secretion (dominant-negative effect). The fourth dominant mutant showed reduced integrin-□5 binding and its expression in mouse skin promoted hyperplasia and dilation of lymphatic vessels.

Conclusion: We identified six mutations in the TIE2-ligand ANGPT2 as a novel cause of PLE and hydrops fetalis. These mutations alter ANGPT2 structure and function. The data underscore ANGPT2 loss, dominant negative and gain-of-function as mechanisms leading to PLE, with a more severe lethal phenotype in homozygous fetuses. The ANGPT2 gene should be included in diagnostic PLE screens. These results give new insights into the ANGPT-TIE signaling mechanisms and underscores functional validation of variants to understand etiopathogenic mechanisms.

P337

Successful treatment of Kaposiform Lymphangiomatosis with selumetinib

Nadine SantaCruz, Denise Adams, Melisa Ruiz-Gutierrez and Meghan O'Hare

Purpose: Kaposiform lymphangiomatosis (KLA) is a rare lymphatic anomaly with a high morbidity and mortality. Recent data suggest a role for inhibitors of the RAS/RAF pathway. Here we present a case of a clinical response to selumetinib in a KLA patient.

Methods: The patient presented as a 21 yo male with hemoptysis. Chest x-ray showed bilateral pulmonary infiltrates and an enlarged cardiac silhouette. Echocardiogram confirmed cardiac tamponade. He underwent pericardiocentesis and was subsequently transferred to a regional referral

center for lymphangiogram and was diagnosed with KLA. Initial treatment included prednisone and sirolimus. His pericardial drain was successfully removed, and he was discharged home on a steroid taper.

Results: The patient did not tolerate his steroid taper and remained on low dose prednisone. He continued therapy with sirolimus however developed multiple episodes of grade 3 oral ulcers. Unfortunately, he demonstrated disease progression with progressive pulmonary infiltrates on and worsening exertional dyspnea so was changed to trametinib. On trametinib he developed marked peripheral edema thought to be secondary to trametinib. Therapy was changed again to everolimus. Over the following months he continued to deteriorate developing lower extremity edema, progressive dyspnea and nighttime hypoxia. He was then started on selumetinib. Within weeks his lower extremity edema had resolved and he showed laboratory evidence of treatment response.

Conclusion: Despite aggressive therapy, KLA has an estimated overall survival of 34% (Croteau et al, 2014) and additional treatments are needed. Several recent studies suggest KLA is driven by mutations in the PI3K-AKT-mTOR pathway (Barclay et al 2019; Ozeki et al, 2019 Foster et al, 2020). Here we present the successful treatment of KLA with selumetinib. This case suggests an alternative therapy for KLA though additional studies are needed to confirm the efficacy of selumetinib in KLA.

P338

Bleomycin Injections for Orbital Lymphatic and Lymphatic-Venous Malformations

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Purpose: Lymphatic orbital malformations (LM) are associated with ocular morbidity and facial disfigurement. Surgery is challenging and may not be effective. We describe the outcome of bleomycin injections for venous LM and lymphatic-venous malformation (LVM) malformations of the orbit in 5 tertiary referral centers between 01/2010 and 12/2018.

Methods: Multicenter retrospective case series, five oculoplastic referral centers: Sheba and Rabin Medical Centers, Israel; Mulago Hospital, Uganda; Sri Sankaradeva Nethralaya, India; and Clinique Ophtalmologique de Tunis, Tunisia. All patients diagnosed with orbital LM/LVM were assigned to successive (range 1-6) intralesional 5 international units (IU) bleomycin injections. They all underwent complete ophthalmic and orbital evaluations, orbital imaging, and ancillary testing as needed. Clinical photographs were assessed pre- and post-treatment along with objective assessments of clinical improvement. Additional injections were provided in cases of incomplete response.

Results: A total of 21 patients (17 females, mean ± standard deviation age 18 ? 13 years, range 2-48 years) underwent bleomycin injections. The mean injection dose was 12 ? 10 IU in 1-3 injections. There was a dramatic improvement in lesion size, appearance, proptosis, and ocular motility in 20/21 patients (95%) after a mean follow-up of 18 months. Visual acuity slightly improved after treatment (20/50 to 20/30, P = 0.076). No side effects were noted after bleomycin injections.

Conclusion: Bleomycin injections for LM/LVM of the orbit are effective; local or systemic side effects were not seen in this series. To the best of our knowledge, this is the largest reported series of this treatment.

P362

EPHB4 Mutation Causes Adult and Adolescent-Onset Primary Lymphedema

Arin K. Greene, Pascal Brouillard, Christopher Sudduth, Patrick Smits, Dennis J. Konczyk and Miikka Vikkula

Purpose: Primary lymphedema results from the anomalous development of the lymphatic system that typically presents during infancy, childhood, or adolescence. Adult-onset primary lymphedema occurs when symptoms present after 21 years of age and occurs in 10% of patients. Mutations associated with adult-onset lymphedema have not been identified. The purpose of this investigation was to search for variants that cause adult-onset primary lymphedema.

Methods: A 47 year-old-father and his 14 year-old-son both presented with unilateral lower extremity swelling and underwent lymphoscintigraphy. Genomic DNA was extracted from whole blood and affected tissue in the father and from whole blood in the son. Whole exome sequencing (WES) was performed using 1 µg of genomic DNA. Variants were called and annotated using the Highlander software. RNA was isolated from resected lymphedema tissue in the father.

Results: Lymphoscintigram confirmed lymphatic dysfunction in both the father and son. In the father's whole blood DNA, WES identified a heterozygous 2 bp insertion at chr7:100,410,488T>TGC (c.1998_1999insGC; p.Ile667Alafs*25) in exon 12 of the EPHB4 gene (NM_004444.4). The same mutation was present in the son's whole blood DNA and in resected tissue from the father's affected extremity. RNA sequencing showed that the allele carrying the premature stop codon resulting from the frameshift did not undergo complete nonsense-mediated mRNA decay, but was rather stable, accounting for 30% of the reads.

Conclusion: A germline mutation in EPHB4, likely resulting in expression of a truncated protein, can cause adult and adolescent-onset primary lymphedema. Variants in EPHB4 may be responsible for causing primary lymphedema in patients without an identifiable mutation in other known lymphedema-associated genes. As the spectrum of mutations responsible for specific lymphedema phenotypes continues to be elucidated, genetic testing will play an increasing role in the diagnosis and management of patients with primary lymphedema.

P363

Primary Upper Extremity Lymphedema Caused by a CELSR1 Variant

Christopher Sudduth, Patrick Smits, Yu Sheng Cheng, Klaus Schmitz-Abe, Pankaj Agrawal and Arin K. Greene

Purpose: Primary lymphedema of the upper extremity is rare and often is associated with syndromic or generalized lymphedema. No genetic variants have been associated with non-syndromic, non-generalized upper extremity disease. The purpose of the study was to identify novel causes for primary lymphedema of the arm.

Methods: A 17-year-old healthy male with right upper extremity swelling since infancy was confirmed to have lymphedema by lymphoscintigraphy. He subsequently developed right leg disease in adolescence and his mother had lower extremity lymphedema as well. Genomic DNA was extracted from the blood of the patient and mother using DNeasy Blood and Tissue Kit (Qiagen, Hilden, Germany). Whole exome sequencing (WES) was performed on the patient's DNA (Psomagen, Rockville, MD). Sanger sequencing was used to confirm variants identified by WES.

Results: WES of genomic DNA from the subject identified a frameshift deletion resulting in a premature stop codon in exon 3 of the CELSR1 gene hg19: chr22:46,835,160_46,835,166del (c.4326_4332del; p.T1443Gfs*14). The variant was confirmed in the patient and his mother by Sanger sequencing.

Conclusion: A novel variant in CELSR1 causes non-syndromic upper extremity lymphedema; other variants in this gene previously have been associated with lower extremity disease. CELSR1 should be included in variant screening for patients with non-syndromic primary upper limb lymphedema.

P366

Utilization of Healthcare Resources in Lymphatic Anomalies Patients: An Assessment of Healthcare Burden

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Purpose: Patients with lymphatic anomalies (LAs) often require life-long inter-disciplinary care. Due to the paucity of data on the healthcare utilization of these patients, the burden on the healthcare system is unquantified. We hypothesize that complex LAs will utilize significantly higher healthcare resources compared to simple LAs.

Methods: A retrospective, longitudinal study was performed on LA patients seen at one hospital system between 1/1/2019-12/31/2020. Data was collected on healthcare utilization from each patient's first presentation/initial diagnosis including: office visits, number of hospitalizations, hospital days, average lengths of stay (LOS), imaging studies, procedures, and specialists involved. All variables were normalized to per year utilization. Using publicly available national averages, approximate costs incurred for each patient were calculated and normalized to per year utilization. Involvement of airway and/or >1 anatomic area was defined as "complex" LAs. Additionally, patients with Klippel-Trenaunay Syndrome (KTS) were assessed as part of the "complex" group and as their own sub-group. Statistical analysis was performed with Welch's t-test.

Results: Preliminary analysis of 26 patients (16 female, 10 male; median age 6 years) included 11 simple, 11 complex, and 4 KTS cases. When compared to simple LAs, the combined complex LA and KTS group had significantly higher numbers in all measured metrics ($p<0.05$). When KTS was removed, the complex LAs were still significantly higher in all metrics except office visits ($p=0.069$). Complex cases incurred significantly higher costs/year (12X higher than simple LAs, $p<0.002$).

Conclusion: Our preliminary study demonstrates that LM care is chronic and costly, especially for complex LAs. The overall average cost/year of our cohort (minus procedure costs) is greater than $23,000/year. Understanding healthcare needs and utilization for LA patients will improve our ability to consolidate and optimize care with potential for decreasing cost and burden on healthcare system.

P384

Retrospective Analysis of a Randomized and Open Label Study to Evaluate the Safety and Efficacy of OK-432 in Patients with Lymphatic Malformations

Richard J. Smith, Diane Burke, Nancy Bauman, Jacqueline Zummo, Khushboo Belani, Ilolochika Emuh, McKenna Metcalf and Jenny Han

Purpose: Lymphatic malformations (LM) are rare and serious anomalies that most commonly arise in the head and neck in children. OK-432 is an immunotherapeutic derived from Streptococcus pyogenes [Group A, Type 3] Su strain used in the treatment of LM. The purpose of the Phase 2, randomized study (1998-2005) and open-label study (2005-2017) was to assess the efficacy and safety of OK-432 in LM.

Methods: In the randomized study, subjects were randomized 2:1 to receive treatment immediately (immediate treatment group [ITG]) or delayed by 6 months (delayed treatment group [DTG]). In the open-label study, subjects were enrolled for compassionate use access to OK-432. Subjects received 4 doses of OK-432 approximately 6 weeks apart. Efficacy was assessed 2 weeks post-treatment (randomized) and 1 to 6 months post-treatment (open-label). Data were analyzed as observed.

Results: The retrospective analysis of source verified data included 246 randomized subjects and 275 open-label subjects, with the majority of subjects 6 months to 18 years of age. In the randomized study, the primary efficacy endpoint was clinical success (defined as complete [90%-100%] or substantial [60%-89%] reduction in LM volume measured radiographically) in the ITG versus the spontaneous resolution of the LM in the DTG. In randomized subjects with data available for primary endpoint evaluation (N=150), 69.1% of subjects demonstrated clinical success in the ITG and 7.5% of subjects showed spontaneous resolution in the DTG ($p<0.0001$). In the open-label subjects with data available for primary efficacy endpoint evaluation (N=78), 73.1% of subjects achieved clinical success. Local/systemic reactions peaked in the first few days and resolved within 2 weeks. Subjects were followed for up to 3 years post treatment with no safety concerns.

Conclusion: In these studies, OK-432 was efficacious and favorably safe in treating macrocystic and mixed-cystic LM. Results are consistent with approximately 30 years of OK-432 experience in published studies.

P424

Paradoxical reactivation of Hepatitis C infection with Sirolimus therapy for Lymphatic malformation – the need for pre-treatment screening protocol for viral markers.

Malathi Munisamy, Geethanjali Sahadevan, Pazhanivel Mohan and Senthamizh Selvan

Purpose: Sirolimus a serine/threonine kinase which regulates the signalling pathway PI3K/AKT/mTOR has been reported to decrease the size of Lymphatic malformations and alleviate associated symptoms owing go its antiangiogenic and antiproliferative properties. Though sirolimus is an immunosuppressant, it has the potential to suppress viral replication of hepatitis C virus thereby being used in patients undergoing liver transplantation for HCV-related liver disease. We herein report a case of paradoxical reactivation of hepatitis C virus infection induced by sirolimus during treatment of microcystic lymphatic malformation in a 11 year old girl.

Results: A 11 year old girl presented with rapidly enlarging swelling and pain in the left thigh and leg. She had undergone excision and grafting 8 years prior. In view of recurrence and rapid progression, she was initiated on Sirolimus therapy following standard protocol. Two weeks post therapy, she was found to have elevated liver enzymes which on further evaluation revealed Anti Hep C antibody positivity with high viral RNA copies. Considering hepatitis C viral reactivation, sirolimus was withheld and she treated with Velpatasvir 100 MG and sofosbuvir 400 mg for three months. At the end of 3 months, viral copies were undetectable and she was restarted on sirolimus with no further complications.

Conclusion: This case is being reported to create awareness regarding Hepatitis C reactivation with sirolimus therapy which warrants screening for viral hepatitis markers prior to initiation of sirolimus.

P428

The Role of GPNMB on Lymphangiogenesis

Trinity Samson, Joshua Castor, Ernesto Solorzano, Hope Ball, Michael Kelly and Fayez Safadi

Purpose: Complex lymphatic anomalies (CLAs) include a group of overlapping rare diseases characterized by lymphatic dysfunction. Having intersecting presentations and varying multiorgan locations makes them difficult to diagnosis and treat. Each CLA has a component of bony involvement with osteolysis resulting in bone weakening and loss. Sirolimus, an inhibitor of mammalian target of rapamycin (mTOR), is a potential efficacious treatment for CLAs. Due to its similar pharmacologic activity, we investigated the effects of Glycoprotein nonmetastatic melanoma protein B (GPNMB), a transmembrane glycoprotein, on lymphatic cell proliferation, viability, migration, tube formation and autophagy. GPNMB is known to suppress mTOR and play a role in bone homeostasis. Our results are first to demonstrate GPNMB's effect on the lymphatic system.

Methods: C57BL/6 Primary Mouse Lymphatic Endothelial Cells (mLECs) were treated with recombinant osteoactivin (rOA), an orthologue of GPNMB, at 10-100ng/mL. Cell viability was measured with the MTS assay and proliferation via the MTT assay. mLEC migration was assessed using mechanical linear scratch, followed by treatment of 10ng/mL and 50ng/mL rOA. Growth into the scratched area was analyzed. Tube formation was evaluated visually following 10ng/mL and 50ng/mL rOA treatment. Gene expression for autophagy markers following 10ng/mL and 50ng/mL rOA treatment was assessed via qPCR.

Results: No significant differences in cell proliferation or viability were noted following rOA treatment at various doses. Migration assays showed a significant increase in mLEC migration distance following 10ng/mL rOA but not 50ng/mL treatment (Figure 1). Preliminary tube formation results suggested increased tube formation with 50ng/mL treatment and no difference in 10ng/mL treatment group. qPCR analysis of mLECs treated with 50ng/mL showed a significant increase in autophagy markers ATG-7, ATG-12 and Beclin-1 compared to untreated cells.

Conclusion: Our data suggest GPNMB can modulate lymphatic migration and tube formation, potentially through increased autophagy. These data are first to show GPNMB's effect on the lymphatic system.

Other Tumors

P049

A rare case of atypical cardiac tumor on left ventricle combined with bleeding facial vascular malformation and meningocele.

alejandro vivero, Melina Mana, Aldo Hugo Tabares, Jorge Andres Galindez and Maria Jose Cabrera Ferreyra

P068

Myopericytoma in Neonate with Jejunal Atresia

Habiba Hashimi and Shannon Castle

Purpose: Myopericytoma is a benign, pericytic tumor characterized by concentrically distributed perivascular proliferation of myoid spindled cells that has been described to occur most commonly in skin and soft tissues of the extremities. Cases of gastrointestinal involvement have been reported in immunocompromised patients and associated Epstein-Barr viral infection. Herein, we report myopericytoma-associated jejunal atresia.

Methods: The patient is a 37w5d boy born via spontaneous vaginal delivery to an 18-year-old woman with good prenatal care and a pregnancy complicated by polyhydramnios. Breast feeding was attempted but our patient had recurrent bilious emesis and he was transferred to the neonatal intensive care unit.

Abdominal roentgenogram demonstrated central dilated bowel. The patient had no reported episodes of hemodynamic instability.

A decompressive oral-gastric tube was inserted and there was clinical improvement in abdominal distension; subsequent upper gastrointestinal contrast study demonstrated dilated proximal small bowel with no contrast passing beyond the ligament of Treitz concerning for obstruction versus volvulus. Comprehensive metabolic panel and complete blood count within normal limits. He was taken emergently for exploratory laparotomy.

Results: On exploration, four segments of obliterated bowel were noted starting approximately 20 centimeters distal to the ligament of Treitz and were resected. His postoperative course was uncomplicated.

Histologically, a vascular process that is highly unusual and had interfered with normal development of various layers of bowel was seen. Pathologic features typically characterizing intestinal atresia, such as luminal obliteration, destruction of formed tissue, fibrosis, and calcification, were lacking. In sum, these lesions were noted to have morphologic features consistent with myopericytoma.

Conclusion: In summary, we report a rare case of myopericytoma of the small bowel in a neonate. Myopericytoma is an important diagnosis to be considered in the differential for intra-abdominal neoplasm as it has an increased likelihood for malignant development in deeper compartments; fortunately, post-excision recurrence is rare.

P022

Four cases of DFSP with clinical and pathological diagnosis referred as vascular malformation based on imaging diagnosis

NARIAKI TAKAMURA, MUNETOMO NAGAO, CHIEKO MIURA, SAKIKO FUKUSHI, KIKUKO WATANABE and YOSHIMICHI IMAI

Purpose: Dermatofibrosarcoma protuberans (DFSP) is a rare raised intermediate-grade malignant tumor of the subcutaneous tissue that occurs predominantly in adults in their 20s to 50s.

DFSPs are generally dark red in color and have an elastic firmness, but are often misdiagnosed because they are slow growing and often appear as if they are benign tumors.

Methods: We present four clinically suggestive cases in which patients were referred to our hospital as vascular malformations after MRI imaging, and as a result, resected specimens were found to be DFSP.

Results: There were four cases: a 19-year-old man, a 28-year-old man, a 47-year-old woman, and a 51-year-old woman. MRI images showed low signal on T1-weighted images and high signal on fat-suppressed T2-weighted images in all cases, and contrast-enhanced MRI was performed in two cases, all of which showed contrast effects. Based on these imaging findings, the patients were referred to our hospital based on the report of vascular malformation. From the clinical symptoms, it seemed atypical for a vascular malformation. Excisional biopsies were performed in all four cases, and the pathological diagnosis was DFSP.

Conclusion: Because these imaging findings are typical of both vascular malformations and DFSP, it is difficult to completely exclude DFSP from suspicion of vascular malformations based on MRI imaging findings alone. Therefore, it is necessary to make a comprehensive diagnosis based on visual and palpation findings, echographic findings, and the course of treatment.

Sclerotherapy is considered for the treatment of vascular malformations, but if the malignancy is malignant, sticking to sclerotherapy will delay the diagnosis, so it is important to perform a biopsy as soon as possible if there is no improvement.

P074

Local suture ligation-assisted percutaneous sclerotherapy for kasabach-merritt phenomenon-associated kaposiform haemangioendothelioma

Xindong Fan, Ren Cai, Yi Sun, Deming Wang, Zhenfeng Wang and Lixin Su

Purpose: Kaposiform haemangioendotheliomas (KHEs) complicated by the Kasabach-Merritt phenomenon (KMP) are rare and severe neoplastic lesions often associated with locally aggressive disease, consumption coagulopathy, and high mortality rates. Current regimens have yet to achieve a satisfactory therapeutic effect. Thus, an effective and minimally invasive approach for treating complex KHE/KMP cases is necessary for clinical management. The present case series describes patients with KHE/KMP who underwent local suture ligation-assisted percutaneous sclerotherapy to minimize surgical trauma and ensure effective treatment.

Methods: Between September 2015 and September 2017, 3 consecutive patients with KHE/KMP underwent staged local suture ligation-assisted percutaneous sclerotherapy. Of these patients, 2 presented with medical histories of corticosteroid treatment with unsatisfactory outcomes. The patients underwent a stepwise synthetic serial therapy program consisting of percutaneous sclerotherapy and adjunctive pharmacotherapy accompanied by a suture ligation procedure. Clinical, radiological, pathological, and laboratory data were analyzed to evaluate the outcomes of the therapy.

Results: All patients were successfully managed with the proposed procedure. Significant relief of clinical symptoms and improvements in haematological indicators were achieved. No recurrence or complications were observed during regular follow-up (4, 19 and 28 months).

Conclusion: Local suture ligation-assisted percutaneous sclerotherapy was demonstrated to be a safe and effective treatment for KHE/KMP, being minimally invasive, involving simple manipulation and providing a clear treatment benefit in certain cases. Further studies involving larger sample sizes are required to thoroughly evaluate the procedure, which can potentially be used as a novel therapeutic option for KHE/KMP treatment.

P084

Congenital Hemangiomas: A Retrospective Single-Center Study of 99 Cases

giung Ha, Eun Hye Lee, Jung Young Kim, Kyung Duck Park, Yong Hyun Jang, Weon Ju Lee and Seok-Jong Lee

Purpose: Congenital hemangiomas (CHs) are fully developed at birth and are classified into subtypes based on subsequent involution pattern: rapidly involuting CH (RICH), partially involuting CH (PICH) and non-involuting CH (NICH). This study aimed to investigate the clinical features and understand disease entity of CH to distinguish it from other hemangiomas.

Methods: A retrospective study of the medical records of CH patients in our vascular anomalies clinic from 2008 to 2018.

Results: Of the 99 CH patients (33 RICH; 28 PICH; and 38 NICH), the ratio of female to male was 1.1:1. All of them presented a single lesion with a mean diameter 4.17cm (range, 1-16cm). The most frequently involved areas were trunk (35.4%), followed by lower extremities (30.3%) and head and neck (17.2%).

Red-stippled faint blue plaque (35.4%) was the most presented feature, followed by bluish gray patch (33.3%). Telangiectasia and peripheral halo were observed in 57 (57.6%) and 43 (43.4%) cases, respectively. Ten patients (10.1%) suffered from pain and/or tenderness. The microscopy of 49 cases showed quite variable degree of lobulation of capillaries surrounded by fibrosis, interlobular thick-walled large vessels and/or centrilobular irregular and often stellate vessels. The diagnosis of CH was confirmed by negative GLUT-1 staining in all 49 cases.

Conclusion: It provides useful information about the characteristics of CH, which should be differentiated from infantile hemangioma.

P106

Complex Pancreatic and Hepatic Kaposiform Hemangioendothelioma: A Case Report and Literature Review

Chengbo Ai, Tong qiu, Jiangyuan Zhou, Chuan Wang and Shuguang Jin

Purpose: Kaposiform hemangioendothelioma (KHE) is a rare vascular tumour that causes progressive angiogenesis and lymphangiogenesis and often associated with the life-threatening Kasabach-Merritt phenomenon (KMP). Complex pancreatic and hepatic KHE is exceedingly rare as KHE often occurs in the skin or soft tissue, only eight cases of pancreatic KHE with sufficient information have been published, reviewing of this case may improve our understanding of the diagnosis and treatment of the visceral KHE.

Methods: A 5-year-old girl was admitted to our hospital with a 3-year history of thrombocytopenia, and right hepatic atrophy and pancreatic lesion for 15 months. Imaging manifestations shows right hepatic atrophy, stenosis of the right branch of the portal vein and lesion of pancreatic head (an approximately 2.3 × 1.3 cm hypo-intense signal), bone marrow puncture showed normal platelet production and the liver and pancreas biopsy did not reveal a definitive diagnosis and aggravate KMP and compression symptoms such as obstructive jaundice and pancreatitis. Corticosteroid's therapy is effective but cannot be reduced or stopped and finally tolerated. KHE was clinically suspected due to elevated D-dimer and fibrin degradation products, however, sirolimus treatment for 7 months was ineffective.

Results: We performed the right hepatic artery embolization and a Whipple operation after discussion of multi-disciplinary team, histological and immunohistochemical examination suggested KHE. Three months postoperatively, the patient's liver function, pancreatic enzymes and blood clotting function returned to normal.

Conclusion: Visceral KHE patients may only have symptoms of KMP, it is difficult to make a definitive diagnosis through necessary biopsy as a sufficient sample may not be obtained, and it may aggravate KMP and compression symptoms. Non-invasive or minimally invasive treatments should be prioritised, however, if they are ineffective or the tumour compression symptoms are obvious, the patient's condition should be evaluated, and timely surgery should be performed to confirm the diagnosis and treat.

P112

Management of sirolimus treatment for tumors associated with Kasabach-Merritt phenomenon

agathe Labonnelie, Véronique Soupre, Annabel Maruani, Salavatore Cisternino, smail Hadj-Rabia and olivia boccara

Purpose: Sirolimus is effective for Kasabach-Merritt phenomenon (KMP), a rare and severe consumptive coagulopathy associated with kaposiform hemangioendothelioma and tufted angioma. Guidelines are

lacking for the ideal duration of treatment and the discontinuation strategy or whether a prophylactic treatment can be proposed. To evaluate the long-term management of sirolimus treatment for KMP-associated tumors.

Methods: This was a retrospective study of children receiving sirolimus for KMP-associated tumors from January 2014 to October 2020. The children were divided into those with sirolimus discontinuation and those with prolonged treatment. Clinical, biological and treatment factors were studied in both groups.

Results: Twelve patients were included. Overall normalization of platelet counts and D-dimer levels was reached at a mean of 1.2 and 8.8 months, respectively. With sirolimus discontinuation (n=6), the mean sirolimus treatment period was 14.8 months, and the relapse rate after discontinuation was 66% (n=4). The therapeutic efficacy was preserved when sirolimus was re-started. We found no factor associated with relapse. With prolonged sirolimus treatment, the mean current dose of 0.026 mg/kg/d, corresponding to a mean residual level of 2.44 ng/ml, was associated with maintained clinical and biological remission; the mean treatment period was 3.4 years. Seven patients had side effects. Aspirin maintained remission in 3 patients after sirolimus discontinuation.

Conclusion: Sirolimus remains highly effective even with lower doses than recommended for treating KMP-associated tumors. Maintenance treatment with a minimal efficient dosage allows for durable remission. Aspirin can be discussed as an alternative.

P139

Sirolimus plus prednisolone vs sirolimus monotherapy for kaposiform hemangioendothelioma: a randomized clinical trial

Yi Ji

Purpose: Kasabach-Merritt phenomenon (KMP) in kaposiform hemangioendothelioma (KHE) is characterized by life-threatening thrombocytopenia and consumptive coagulopathy. This study compared the efficacy and safety of sirolimus plus prednisolone versus sirolimus monotherapy as first-line treatment strategies for KHE patients with KMP in the largest cohort to date.

Methods: Participants were randomized to receive either sirolimus in combination with a short course of prednisolone or sirolimus monotherapy for at least 12 months. The primary outcome was defined as durable platelet response (platelet count >100×109/L) achievement at week 4. Participants completed efficacy assessments at 2 years after the initial treatment.

Results: At week 4, a durable platelet response was achieved by 35 of 37 patients given sirolimus and prednisolone versus 24 of 36 patients given sirolimus monotherapy (difference 27.9%; 95% CI, 10.0% to 44.7%). Compared with the sirolimus monotherapy group, the combination treatment group showed an improvement in measures of a durable platelet response at any point during the initial 3-week treatment period, median platelet counts during weeks 1 to 4, the proportion of patients achieving fibrinogen stabilization at week 4, and objective lesion response at month 12. Patients receiving combination therapy had fewer blood transfusions and a lower total incidence of disease sequelae than patients receiving sirolimus alone. The frequencies of total adverse events and grade 3–4 adverse events during treatment were similar in both groups.

Conclusion: The responses seen in patients with KHE with KMP were profound and encouraging, suggesting that sirolimus plus prednisolone should be considered as a first-line treatment for KHE patients with KMP.

P169

Multifocal plaque–like congenital hemangiomas: a variant of CHs or an intrinsically different hemangiomatous entity

CHEN HUA, WEI GAO, LIZHEN WANG, XIA GONG, HECHEN JIA, YUANBO LI, YUNBO JIN and Lin Xiaoxi

Purpose: We report a series of unusual congenital hemangiomas which differ from common CHs in their appearance, postnatal behavior and histopathology.

Methods: A total of 7 patients with unusual plaque–like angiomatous lesion were reviewed and analyzed for history, physical findings, imaging and histopathologic characteristics.

Results: All lesions were extensive angiomatous plaque and visible at birth, covering a large cutaneous area. A predominant female preponderance was observed (female n=5; male n=2); and these lesions were located on the limb(n=3), forehead(n=2), neck(n=1) and chest(n=1). All cases appeared to be sporadic. The majority of lesions were multifocal (n=5), large, atrophic, red to violaceous, multilobulated plaque. Radiographic studies exhibited heterogeneity and fast-flow in all lesions which were limited to the skin and subcutaneous tissue and poorly circumscribed. Typically, these lesions demonstrated neither proliferation nor involuting course after birth. Development of central white discoloration was present in majority of the lesions (5/7). Five lesions underwent incisional biopsy. Overlapping histologic features with RICH in the late stage of involution were revealed. However, large malformed veins, scar tissue, loose fibrous tissue were absent, unlike typical involuted RICH. Immunohistochemical staining was negative for Glut-1 in all specimens.

Conclusion: In summary, we have described a distinct clinicopathological entity that differs from previously reported CHs in both clinical and histological features. The present series might extend the spectrum of ISSVA classification system. However, whether these lesions are a variation of CHs or an intrinsically different hemangiomatous entity remains to be determined.

P173

Kaposiform Hemangioendothelioma with Spinal Involvement: Case Report and Literature Review

Tong Qiu and Yi Ji

Purpose: Kaposiform hemangioendothelioma (KHE) is a rare, locally invasive vascular tumor that mostly appears in infants and adolescents. KHE with spinal involvement is extremely rare. The aim of this study was to review the imaging features, clinical manifestations and treatment of KHE patients with spinal involvement.

Methods: We reviewed patients with KHE who were admitted to Pediatric Surgery of our hospital from April 2014 to August 2020, and the cases were compared.

Results: Seven patients with spinal involvement were enrolled in the study, including four (57.1%) males and three (42.9%) females. The age at onset ranged from 1.0 day to 4.0 years, with an average of 1.6 years. Five (71.4%) had pain due to bone destruction, three patients (42.9%) had decreased range of motion (ROM), four (57.1%) patients had scoliosis, two (28.6%) patients developed claudication, and three patients (42.9%) presented with a soft tissue mass in the neck of the back. Five patients (71.4%) had the Kasabach-Merritt phenomenon (KMP), with a minimum platelet value of 8×109/L. All patients were treated with sirolimus, and showed regression of the lesion and/or normalization of the hematologic parameters.

Conclusion: KHE with spinal involvement is difficult to diagnose due to its rarity and variable symptoms, which need to be recognized to start early treatment. The management of KHE with spinal involvement

should be performed by a multidisciplinary team. Sirolimus can improve outcomes in patients with KHE with spinal involvement.

P198

Superficial Kaposiform Hemangioendothelioma or Tufted Angiomas Successfully Treated with Topical Rapamycin

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Purpose: To evaluate the long-term benefit and tolerance of topical 0.5% sirolimus in superficial kaposiform hemangioendothelioma or tufted angiomas.

Methods: In this prospective single-center study, 0.5% sirolimus gel vs placebo gel was applied triple per day to superficial kaposiform hemangioendothelioma (KHE) or tufted angiomas (TA). All the patients were randomized to receive sirolimus gel or placebo. After 3-month application, each patient underwent assessment every 12 weeks during treatment and at 4 weeks after discontinuation of the treatment.

Results: Twenty-five patients were enrolled. X patinets (%) remained stable at 3 months and 9 (56%) improved after 3 to 6 months of treatment. Of these patients, 6 relapsed within 7 months after the withdrawl of the drug, and 1 were still responding at 1 year. The rest XX patients showed no response to the treatment after 3-month application. Treatment was well tolerated with no serious adverse events.

Conclusion: Topical 0.5% sirolimus applied triple per day produced positive responses in treatment of superficial KHEs and TAs.

P209

Characteristic appearance of spindle cell hemangiomatosis, often misdiagnosed as venous malformation

Hongyuan Liu, Yamin Rao, Gu Hao, Xi Yang, Li Hu, Hui Chen and Lin Xiaoxi

Purpose: Spindle cell hemangiomatosis (SCH) is a benign multifocal vascular proliferation that mostly occurs in the distal extremities. It is a relatively rare disease and causes difficulties in clinical diagnosis and differential diagnosis of venous malformation. This study aims to figure out the characteristic appearance of SCH.

Methods: We retrospectively assessed the medical history, and clinical features, imaging features, pathological features, genetic results and follow up of 11 patients diagnosed pathologically with spindle cell hemangiomatosis after surgery.

Results: There are two types of clinical appearances in spindle cell hemangiomatosis in the distal extremities: bleb-like nodules and varix-like nodules. Bleb-like nodules are mostly superficially located in the palm or interphalangeal joints with obvious hemorrhage in lesions and mainly composed of cavernous spaces rather than spindle cells. Varix-like nodules are located in the back of the hands or arms with normal skin color and mainly composed of solid areas of accumulated spindle cells. Surgery is the standard therapy for spindle cell hemangiomatosis, while sclerotherapy is invalid. Despite the tendency to develop new lesions, there are no residual lesions at the surgical site during follow up.

Conclusion: Bleb-like nodules in the palm and interphalangeal joints are a typical clinical appearance in spindle cell hemangiomatosis which can help make clinical and a differential diagnosis of venous malformation. Surgery is the standard therapy for spindle cell hemangiomatosis with no residual lesions remaining at the surgical sites.

P218

Surgery management of the Kasabach-Merritt phenomenon patients unresponsive to conservative therapy

HONGZHAO LEI, BIN SUN, CHANGXIAN DONG, MIAOMIAO LI, HONGYU ZHANG and YUANFANG ZHANG

Purpose: The current study retrospectively analyzed the clinical data and management outcomes of these Kasabach-Merritt phenomenon (KMP) patients unresponsive to conservative treatments.

Methods: A retrospective analysis was conducted on the clinical characteristics and follow-up data of eighty-six KMP patients who were treated with surgical resection. The average age of the patients, including forty-six male and forty female, was 2.7 months (range, 2 days-1 year and 11 months). All patients had received more than one type of conservative managements before surgery, but the treatments were unresponsive. Surgical excisions were performed in all patients, including thirty-nine patients with completely resection and forty-seven patients with subtotal excisions. Therapeutic results were evaluated by platelet count and lesion size.

Results: All surgical specimens of eighty-six patients were pathologically examined. The pathological examination showed two pathology types including sixty-nine kaposiform hemangioendothelioma (KHE) and seventeen tufted angioma (TA). None of cases simultaneously met with the criterion of KHE and TA.

Curative treatment of KMP is defined as restoration of normal hemostasis and elimination of tumor. Eighty-four (97.7%) patients achieved curative treatment and two (2.3%) died from post-operation multiple organ failures. Thrombocyte count rapidly restored to normal levels within 1–3 days post complete resection operation, hemoglobin and blood coagulation function gradually returned to normal range within 1-2 weeks. The platelet count in patients treated with incomplete excision fluctuated over time but often remained above 60 × 10 9/L, a significantly higher level than the preoperational level. The residual lesions slowly disappeared within 3–18 months after continuous medication.

Conclusion: Surgical excision is an effective and reliable management for KMP following adequate preoperative care. The optimal timing of surgery is critical for KMP patients. The results show that benefit risk ratio is higher in the early-surgery patients than the late-surgery patients.

P260

Multifocal Kaposiform Hemangioendothelioma in a Newborn

Olivia Cohen, Stephanie Florez-Pollack, Mary Larijani, Melinda Jen, James Treat, Denise Adams and Michael Acord

Purpose: We report the a case of multifocal cutaneous kaposiform hemangioendothelioma (KHE) and associated Kasabach-Merritt Phenomenon (KMP) in a newborn successfully managed with medical intervention.

Methods: A full-term male infant was born at in the special delivery unit due to the presence of a large anterior cervical mass (5.9 x 8.0 x 7.3 cm) found on fetal ultrasound. At delivery the infant had normal vital signs, hypoglycemia of 38 mg/dL, thrombocytopenia of 16 103/µL, hypofibrinogenemia of 43 mg/dL, and elevated AFP 28,349 ng/mL, prompting transfer to the neonatal intensive care unit for management. Physical exam revealed a 5 cm firm violaceous warm tumor on the left anterolateral neck; scattered mauve non-blanching patches on the trunk, thighs, scalp; and a single perianal blue 0.5 cm nodule. MRI and ultrasound-guided biopsy of the cervical mass and skin lesions were performed. Methylprednisolone 2 mg/kg/day was initiated on day of life (DOL) 1 along with platelet and cryoprecipitate transfusions. Oral sirolimus 0.08 mg twice daily was initiated on DOL 4.

Results: Histopathology demonstrated cellular nodules with spindled cells forming slit-like vascular spaces, platelet microthrombi, and myofibroblastic changes in both specimens. CD31 positivity of endothelial cells, SMA positivity diffusely in pericytes, and D2-40 positivity of spindled cells confirmed the diagnosis of KHE. Fibrinogen and platelet levels normalized on DOL 8. Over subsequent weeks the skin lesions completely faded and the neck mass showed a decrease in volume, increased softness, and color lightening.

Conclusion: This is the first case reported of a newborn with multifocal cutaneous KHE associated with KMP, confirmed on histopathology, and showing a rapid response to IV steroids and sirolimus therapy. Multiple cutaneous lesions present on the trunk and limbs may be indicative of multiple satellite lesions but the possibility of metastatic lesions from the neck mass that occurred during development can't be ruled out.

P305

MORTALITY PREDICTIVE FACTORS IN CONGENITAL HEPATIC HEMANGIOMA

CARLOS DELGADO-MIGUEL, Paloma Triana, Antonio Muñoz-Serrano, Miriam Miguel-Ferrero, Lara Rodríguez-Laguna, Francisco Hernández, Manuel López-Santamaría and Juan Carlos López-Gutiérrez

Purpose: Background: Congenital Hepatic Hemangiomas (CHHs) are classified as benign vascular tumors according to the ISSVA classification. Clinical, histological and genetic correlation has recently been described in patients with long term survival, although only few cases with fatal outcome have been reported. In most cases, death was secondary to cardiac failure and coagulpathy. However, no mortality risk factors have been identified to date. The aim of this study is to identify potential predictors of mortality in patients with CHH.

Methods: Methods: A retrospective review of CHH patients diagnosed in our institution from January 1991 to October 2021 was performed, who were classified into two groups according to their survival. Demographic, gestational, imaging and laboratory data at diagnosis were collected and compared between both groups.

Results: Results: A total of 28 patients were included (11 males; 17 females) of whom 4 died as a result of CHH evolution, due to cardiac failure and coagulopathy, with a median age of 11 days. No differences in demographic or gestational data were reported. There were neither differences when comparing imaging tests, nor in the location, the number of affected liver segments or the CHH estimated volume. Upon analysis of laboratory data at diagnosis, deceased patients had a significant elevation of median liver enzymes GOT (359u/L vs. 45 u/L; p=0.009) and GPT (313 u/L vs. 20 u/L; p=0. 005), as well as a decrease in the median platelet count (85250/µL vs. 337000/µL; p=0.004), prothrombin activity (54% v.s 93%; p<0.001) and fibrinogen (131mg/dL vs. 284mg/dL; p=0.003), with no differences in blood count or biochemistry data.

Conclusion: Conclusions: CHH clinical behavior can be innocuous or life-threatening. Coagulation disorders and increased liver enzymes at diagnosis seem to be the main predictors of mortality. However, multicenter studies are needed to confirm these results.

P336

Large neurofibromas misdiagnosed as vascular anomalies

Manisha Notay, Lauren Provini, Mark Mamlouk and Ilona Frieden

Purpose: Plexiform neurofibromas (PNF) are benign tumors which arise from the peripheral nerve sheath and are often associated with neurofibromatosis type 1 (NF1). Their clinical and radiological

appearance can mimic vascular anomalies. We review seven cases of neurofibromas initially misdiagnosed as vascular anomalies.

Methods: Retrospective study conducted via investigator recall of patients with prior diagnosis of a vascular anomaly who were later found to have a confirmed diagnosis of neurofibroma. Those with records of at least one imaging modality (CT, MRI or ultrasound) were included. Further case information including pathology, photographs and clinical history were collected.

Results: All seven cases had been previously diagnosed as a vascular anomaly (table 1). They include 4 cases of PNF, one diffuse neurofibroma and one neurofibroma not otherwise classified were diagnosed with biopsy and clinical-radiologic correlations. One patient is awaiting biopsy but diagnosed based on clinical radiologic correlation and diagnostic features of NF1. The most common diagnosis prior to that of a plexiform neurofibroma was a venous malformation (4 patients), followed by infantile hemangioma (2 patients). In terms of location, 5/7 involved the head and neck, one on the extremity and one in the genital region. Four had pain in the affected area. 4/7 met diagnostic criteria for NF1. We also found two small case series reporting similar findings(1,2)

Conclusion: Collectively ours and previous reports emphasize that large neurofibromas can erroneously be diagnosed as vascular anomalies. Neurofibromas share many radiological features with vascular anomalies, including prominent vascularity, cystic and fluid-fluid levels. The target appearance (hyperintense signal with central hypointense signal) on T2 weighted MRI can mimic the appearance of phleboliths in venous malformations. These shared radiological features can often lead to misdiagnosis.

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P415

Clinical and Histopathological Characteristic of Non-Involuting Congenital Hemangioma in Young and Old Age Group

Amalia Mulia Utami, Gonca Cinkara, Max M. Lokhorst, Onno J. de Boer, Chantal M.A.M van der Horst and Allard C. van der Wal

Purpose: Non-Involuting Congenital Hemangioma (NICH) is a vascular tumor, can cause significant complications such as bleeding, ulceration, high-output cardiac failure, or thrombocytopenia. Despite the fact that NICH is developed at birth, keep proliferating, and never regress, the postnatal growth and cell death activities in NICH has not been well described. The nature of apoptosis in different ages group is unclear. Understanding the different characteristic of NICH is essential for further research into treatment. Therefore, this study was aimed to investigate the difference in clinicopathological characteristic of NICH between young and old age group.

Methods: Immunohistochemistry (IHC) staining was applied on surgical specimens of clinically and histopathologically diagnosed cutaneous NICH in young age of patients (n=4) and old age (n=5) with several cell-cycle dependent antibodies (Caspase-3 for apoptosis, CitH3 for etosis, P62 for autophagy, and Ki67 for proliferation). Then, double staining was also performed to evaluate the cell-specific immunolocalization on smooth muscle cell using SMA-1 and endothelial cell using vWf. The expressions were compared between the two groups and was scored semi-quantitatively. The samples were also stained with D2-40 for the involvement of lymphatic vessels

Results: There was significant difference in autophagy process between young and old age group (U= 2,50, p<0,05). Most young age group showed a positive expression of P62 (n=3), while the old age group

did not. On the other hand, there was no significant difference in proliferation, apoptosis, etosis, and mast cells activities, also involvement of lymphatic vessels, between those two groups.

Conclusion: The young age NICH presented more autophagy activities than the old age group, which could have a role in promoting cell death. There is an unchanged apoptosis and proliferation activities between two groups. However, further research is required with greater sample sizes for better understanding of the role of these cell cycle process in NICH.

P427

The notorious clinical masquerader: A report of six cases of cutaneous angiosarcoma

Malathi Munisamy, Aravind Sivakumar, Prasanth Ganesan, Srinivas BH and Chaitanya PVK

Purpose: Cutaneous angiosarcoma of elderly is a very rare disease accounting for about 2% of all soft tissue sarcomas. It has a very aggressive course with a poor prognosis. It is a notorious clinical masquerader, with many clinical presentations including bruise-like lesions, violaceous nodules and plaques, and flat infiltrating hemorrhagic areas mimicking benign vascular tumors, inflammatory lesions, edema, and infection. The varied clinical presentation demands a histopathological evaluation for diagnosis. Herein we report six cases of primary cutaneous angiosarcoma with rare clinical presentations especially in people with skin of color.

Methods:

Results: The mean age of our study population was 65 years with male preponderance (2:1). The mean duration of lesions was 3 months. Five patients presented with lesions involving scalp and face while one had involovement of face and neck. All of these has with varied presentations (a) noduloulcerative lesion mimicking squamous cell carcinoma with a preop biopsy suggestive of pseudoepitheliomatous hyperplasia for which he underwent wide local excision and postop biopsy demonstrated angiosarcoma (b) hematoma like presentation suggestive of a hobnail hemangionma (c) diffuse infiltrated plaques mimicking carcinoma erysipeloides (d) diffuse infiltrated plaques mimicking scleromyxedema (e) crusted plaque with a preop biospsy suggestive of seborrreheic keratosis which later was diagnosed as angiosarcoma on repeat biopsy due to rapid progression (f) oozy ulcerated plaque mimicking erosive pustular dermatosis of scalp. Three patients underwent paclitaxel chemotherapy and three underwent radiotherapy. Three of them succumbed while two patients are responding to chemotherapy and one had recurrence on default.

Conclusion: Cutaneous angiosarcoma especially of head and neck region of the elderly can be a great mimicker as it can present with different morphologies and since it has a very aggressive course and poor prognosis, a high index of suspicion should be considered for the prompt diagnosis and early intervention.

Other Vascular Anomalies

P005

Imaging of vascular malformations with a high-intensity focused ultrasound probe for treatment planning

James Danahey, Veronica Lee, Nima Nassiri, Alan Dardik, Ralf Seip and Naiem Nassiri

Purpose: We aimed to investigate whether a current commercially available high-intensity focused ultrasound (HIFU) probe can adequately image targeted vascular malformations (VMs) in anticipation of HIFU treatment planning and delivery.

Methods: Ten consecutive patients scheduled to undergo treatment of symptomatic peripheral VMs confirmed by routine preoperative contrast-enhanced magnetic resonance imaging and soft tissue duplex ultrasound were enrolled. Lesions were situated less than 6 cm from the skin. After induction of general anesthesia and before surgical intervention, the Sonablate HIFU probe (SonaCare Medical, LLC, Charlotte, NC) was used to obtain multiple B-mode images of the targeted VM. Imaging quality and process feasibility was assessed using a questionnaire. Patients subsequently underwent surgical intervention and clinical follow-up for their VM per the standard protocol.

Results: Study included 10 participants aged 21 to 67 years (mean ± standard deviation, 36.5 ± 16.5 years). Six (60%) identified as female. VMs consisted of eight venous (80%), one lymphatic (10%), and one combined lymphovenous (10%) malformation. Lesions were in the extremities only (50%), trunk only (20%), trunk and extremities (20%), or neck and extremities (10%). In all 10 patients, the boundary and location of the VM could be visualized via the HIFU probe despite the diminished B-mode imaging resolution, and the absence of Doppler functionality did not prevent the identification of VMs. Difficulty in preparing the study device for imaging was 1.1 ± 0.3 and difficulty in use was 1.1 ± 0.1, (1 = easy, 5 = difficult). Stability of the acoustic coupling was 1.3 ± 0.2, (1 = very stable, 5 = unstable).

Conclusion: We were able to ultrasonically identify and outline all targeted peripheral VMs using a commercially available HIFU probe in anticipation of treatment planning and delivery. Baseline magnetic resonance imaging and soft tissue duplex ultrasound remain essential tools for guiding probe placement and HIFU imaging.

P010

SIROLIMUS: UNRAVELING SOME UNANSWERED QUESTIONS

Paloma Triana Junco and Juan Carlos Lopez-Gutierrez

Purpose: Sirolimus has become the third leg in the treatment of vascular anomalies, along with interventional and surgical treatment. Despite years of experience, there are questions that remain unanswered: which patients should we treat?, for how long?, what dosage and blood levels are optimal?

Methods: A retrospective review of patients with vascular anomalies treated with sirolimus during a 9-year period was performed. The variables analyzed included subtype of the vascular anomaly, sirolimus dosage and levels, symptoms and response among others.

Results: 129 patients were included: tumor (7), lymphatic malformation (60), venous malformation (16), combined malformation and PROS (26), others (22). Overall response was positive in 90.8%. Median duration of treatment was 5.5 months (0-110).

Initial analysis revealed no correlation between dosage and levels. Response was not influenced by dosage and levels, neither by subtype of vascular anomaly, location, extension or symptoms. However the lower the age of starting sirolimus, the better the response, mainly under 5 years of age (p=0.004).

Regarding time until a positive response, at 6 months of treatment 67% of patients had responded while at 12 months over 84% did. By age, patients under 5 years showed positive response at a median time of 2 months, patients over 15 years at 5 months and patients between 5-15 years at 7 months. Time until a positive response was not influenced by severity neither by subtype of vascular anomaly.

Conclusion: Overall response to sirolimus was good. Risk factors for a negative response were not found, most patients responded irrespective of their severity in location, extension or symptoms.

Many patients can respond between 6-12 months of treatment, so we should maintain sirolimus for at least one year before confirming success or failure. Besides, patients under 5 years old respond better and faster making our goal to attempt for an early treatment.

P020

Multiple congenital vascular lesions in a newborn; a diagnostic challenge

Inés Gracia-Darder, Maria Tejedor, Rafael F Ramos Asensio, Aniza Giacaman, Pere R Balliu Badia and Ana Martin Santiago

Purpose: Differential diagnosis of multiple vascular lesions in neonates is challenging and the terminology used in the literature is confusing.

Methods: We present a newborn with multiple congenital cutaneous and visceral vascular lesions with signs of brain death due to cerebral hemorrhage.

Results: A full-term newborn by urgent cesarean due to pathological cardiotocographic record was performed requiring resuscitation with artificial ventilation and cardiac massage. Severe neurological involvement, bulging fontanel, and multiple vascular papules and skin nodules were evidenced. A CT scan revealed signs of severe hypoxemic encephalopathy and extensive cerebral bleeding that were compatible with brain death together with physical examination and electroencephalogram. She has also a large right thoracic mass. Although the therapeutic effort, she died on the 5th day. In the necropsy study, the skin lesions consisted of a proliferation of capillary-like vessels, with a lobulated pattern, with prominent endothelium, without atypia, anastomosed with each other in some areas. Immunohistochemistry showed positivity for CD31 and negativity for ERG, D2-40, and GLUT-1. Similar lesions with hemorrhages were seen in the lung, pleura, retroperitoneum, kidney, and brain. These findings were compatible with the diagnosis of multifocal congenital haemangioma with visceral involvement or disseminated congenital pyogenic granuloma. A genetic study was performed in tissue and blood that was negative for a panel of genes associated with vascular abnormalities including GNA11,GNAQ,GNA14,PIK3CA,BRAF,KRAS,NRAS,HRAS.

Conclusion: Literature describes GLUT1-vascular tumors that are clinically and histologically similar to those of our patient using different terms such as diffuse neonatal hemangiomatosis, congenital hemangiomatosis, multifocal congenital haemangioma with visceral involvement, and disseminated congenital pyogenic granuloma (GPCD). The risk of severe brain bleeding and the postnatal appearance of new lesions has been highlighted as a feature of GPCD. In our case, the intracranial hemorrhage led to a situation of brain death that would not permit to treat or follow the evolution of the tumors.

P058

Factors Affecting Pathways to Care for Patients with Vascular Anomalies: Parental Perspectives

Bryan Sisk, Katherine Abell and Anna Kerr

Purpose: Vascular anomalies (VA) are rare disorders that often require complex, multidisciplinary care. Many families affected by VAs experience challenges when seeking care for their child because clinicians are unfamiliar with the condition. Without expert care, children with VAs can receive inaccurate diagnoses, inappropriate treatments, and insufficient management of symptoms and morbidities. However, no prior studies have characterized the factors that influence these families' pathways to care. Without this critical information, we cannot provide guidance to clinicians, patients, parents, and advocacy groups on how to best support families to overcome care challenges. In this study, we aimed to characterize these factors from the perspectives of parents of children with VAs.

Methods: Semi-structured interviews with 24 parents (21 women; 3 men; Mean age = 41.4 years) of children with VAs living in the US, recruited through patient advocacy groups (K-T Support Group and CLOVES Syndrome Community). We performed thematic analysis to assess parental perspectives on barriers and facilitators to accessing expert care.

Results: In preliminary analysis of 10 transcripts, we identified 6 overarching levels of factors that influence pathways to care for VAs: Individual (parental characteristics; clinician characteristics), Clinical (disease characteristics; timing and accuracy of diagnosis), Scientific (availability of information; scientific progress; proven treatment options), Healthcare System (availability of experts; complexity of care coordination; availability of local resources; insurance and financial issues), Community (social support networks), and Luck (chance encounters; opportunities and privilege). These factors influence both the initial access to care and the ongoing maintenance of care. Further thematic analysis will allow us to develop a model for pathways to care.

Conclusion: Parents of children with VAs report multiple factors that facilitate or impede their ability to provide their child with optimal care. These factors represents possible targets for future interventions to improve care delivery for families affected by VAs.

P099

Psychiatric comorbidity in vascular malformations and congenital overgrowth syndromes: pain as a major cause.

Lilly Zwerink, Meeder Elise, Joost Janzing, Maroeska te Loo and Carine van der Vleuten

Purpose: Klippel-Trenaunay syndrome (KTS) is caused by a somatic PIK3CA-mutation and therefore belongs to the group of PIK3CA-related overgrowth spectrum (PROS) group. It affects one or more limb(s) with a capillary malformation, venous and lymphatic malformations, combined with soft tissue or bony hypertrophy. Psychiatric morbidity seems more common in KTS.

The objective of the study was to investigate the prevalence rate of psychiatric comorbidity, and clinical features possibly associated with psychiatric diseases in patients suffering from KTS

Methods: A retrospective cohort study with data collected from medical dossiers of KTS patients (n=174), such as the presence of psychiatric disease, use of psychotropic drugs and complementary clinical information (e.g. pain or presence of thromboembolic events).

Results: Twenty-eight of 174 (16.1%) patients were diagnosed with a psychiatric disease. The most common psychiatric diseases were depression (n=11, 6.3%) and mental retardation (n=9, 5.2%). Patients

(both adults and children) who experienced pain more than half the time are prone to psychiatric disease, with an OR of respectively 3.35 (95%CI 1.19-9.42, p = .02) and 10.5 (95%CI 2.10-52.47, p= .004)

Conclusion: The prevalence of psychiatric disease in KTS is comparable to the general population. Pain, if present during more than half of the days, is associated with psychiatric diseases in both adults and children with KTS. This finding is valuable; focus on pain management with analgesics, anticoagulants or possibly targeted therapy with sirolimus or other (PIK3CA) inhibitors is of great importance for mental health in this group that already has a significant burden due to the condition.

P108

MRI characteristics of peripheral soft tissue vascular anomalies following MRI-guided laser ablation or cryoablation

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Purpose: To evaluate MRI characteristics of peripheral soft tissue vascular anomalies (VA) after MRI-guided laser ablation or cryoablation.

Methods: A retrospective review was performed of pre- and post-ablation MRI of 11 patients enrolled in a prospective observational study who underwent MRI-guided laser ablation or cryoablation of symptomatic peripheral soft tissue VA. MRI were independently reviewed for VA signal characteristics, T2-hyperintense maximal dimension, and semi-quantitatively the percent enhancement at baseline and percent decrease in T2 signal and enhancement of the treated portion at follow-up. Change in VA size was compared using Wilcoxon signed rank test.

Results: 11 patients underwent MRI-guided laser ablation or cryoablation for treatment of symptomatic slow flow (venous, n=10) or high flow (arteriovenous, n=1) VA in the extremities (lower n=9, upper n=2). Post-ablation MRI was performed in all patients, with 10 of 11 performed with gadolinium contrast at a mean follow-up of 25.9±10.6 months (range 9.7 to 46.8 months). Pre- and post-treatment, VA were predominantly T1-isointense 8 (73%) and T2-hyperintense 11 (100%). Pre-ablation MRI mean T2-hyperintense maximal dimension was 8.7±6.1 cm (range, 0.8 to 32.4 cm) with a statistically significant reduction in size post-ablation: 7.3±5.7 cm (-1.4±2.1 cm; p=0.037). Percent decrease in total VA T2 signal by area was 1-25%—5 (46%), 51-75%—2 (18%), and 76-99%—4 (36%). Pre-ablation MRI percent of total VA enhancement was: 0-25%—1 (9%), 26-50%—2 (18%); 51-75%—3 (27%); and 76-100%—5 (46%). Post-ablation MRI percent decrease of total VA enhancement was: 0%—1 (10.0%), 1-25%—4 (40%); 26-50%—0 (0%); 51-75%—2 (20%); 76-99%—3 (30.0%); and 100%—0 (0%).

Conclusion: Peripheral soft tissue VA demonstrate small changes in size and variable reduction in T2 signal and enhancement following MRI-guided laser ablation or cryoablation. Therefore, post-ablation MRI should be interpreted carefully in conjunction with patient's clinical symptoms.

P121

USE OF LEVONORGESTREL INTRAUTERINE SYSTEM IN PATIENTS WITH VASCULAR MALFORMATIONS

Laura Hollenbach, Shelley Crary and Joana Mack

Purpose: To describe the experiences of treating the reproductive needs of patients with vascular malformations with the levonorgestrel intrauterine system (LNG-IUS), known as an intrauterine device (IUD).

Methods: A chart review was performed of all patients who received gynecologic care within a single center's multidisciplinary vascular anomalies clinic from 2018 – present. Data was then gathered on patients who were treated with the LNG-IUS including: indication for use, change in menstrual pattern, continuation rate, complications of the device.

Results: Adolescents and young women seen by Gynecology were offered treatment of their reproductive needs with options, including LNG-IUS when appropriate. Median age was 19 years (Range 12-30). Twelve patients underwent placement of the LNG-IUS. Diagnoses included: venous(5), lymphatic(1), arteriovenous(2), combined including Klippel-Trenaunay(4). Indications for placement included abnormal uterine bleeding, contraception and menstrual associated pain. Three were placed under general anesthesia. There were no unsuccessful insertions. The only complication was one expulsion which occurred during an episode of heavy menstrual bleeding while the patient was fully anticoagulated. This patient subsequently underwent replacement of the LNG-IUS. All patients reported a reduction in menstrual flow and 9 achieved amenorrhea, defined as no menstruation for 6 months. All patients have continued the device and none have requested removal.

Conclusion: Vascular malformations and their treatment can pose special reproductive concerns. It is important to assess the contraceptive needs of these patients as some may have an increased risk of thrombosis and thus will be limited to progestin only options. Others may require birth control while receiving treatment with teratogenic medications or a pregnancy may worsen their malformation. Furthermore, some treatments such as anticoagulation may increase menstrual flow. The LNG-IUS appears to be a promising treatment option with minimal systemic absorption of progesterone.

P151

Prevalence of vascular malformations

Tony Penington, Rod J. Phillips, Nerida Sleebs and Jane Halliday

Purpose: Epidemiological data on the prevalence of vascular anomalies are important for resource allocation and research. Birth registries fail to collect the high proportion of cases which present later in life. Our vascular anomalies team has been the only major service for children and adults in a stable, relatively geographically isolated state of 6.8 million people for the last 20 years and so is uniquely placed to estimate prevalence.

Methods: Dates of birth and of presentation for patients attending the service between 1999 and 2020 have been reviewed and related to published birth figures for the study period. Estimates of delay to presentation have been used to allow for cases born with a malformation but yet to be seen.

Results: Excluding capillary malformations which could not be quantified, 1319 low flow malformations were seen over 21 years, including 557 VM; 437 LM; 61 VLM; 102 intramuscular malformations; 44 Klippel-Trenaunay; 60 GVM; & 26 VVM. A total of 151 AVMs were seen in the same period. Median age of presentation to the service was higher than expected: LM 4.4y; VM 10.7y; Intramuscular malformations 14.4y; & AVM 25.8y. Assuming that the majority of cases in the state were seen, and allowing for delayed presentation, the overall prevalence of low-flow malformations (excluding capillary malformations) is estimated to be between 0.6 to 1 cases per 1,000 live births. AVM prevalence is estimated at less than one per 10,000 births.

Conclusion: This study provides a more accurate estimate than previously available of prevalence of vascular malformations and new data on age of onset. Exact figures are difficult to produce because of delayed onset of symptoms and delayed presentation, particularly AVMs where delays between onset of

symptoms and review in a specialist unit are substantial. Further data on body location and other factors will be presented.

P214

Portal vein thrombosis associated with kaposiform lymphangiomatosis-like phenotype in two patients

Michael Acord, Fernando Escobar, Denise Adams, Tricia Bhatti, Anne Marie Cahill, Jennifer Pogoriler, Sarah Sheppard, Kristen Snyder, Char Witmer and Abhay Srinivasan

Purpose: To report acute portal vein thrombosis (PVT) in two patients with similar imaging features of a complex vascular malformation with phenotype like kaposiform lymphangiomatosis (KLA).

Methods: Patient 1 was a 12-year-old male with a mediastinal slow-flow vascular malformation since infancy with progressive dyspnea and skin lesions. Imaging showed mesenteric and mediastinal lymphatic malformation (LM) and pulmonary cysts with interstitial LM, splenic cysts, and portal vein ectasia. He presented with acute PVT in the setting of fever and abdominal pain. Fibrinogen and platelets were normal. He underwent transjugular intrahepatic portosystemic shunt (TIPS) creation and thrombectomy.

Patient 2 was a 20-year-old healthy male who presented with abdominal pain and dyspnea on exertion. Work-up revealed an extensive mesenteric vascular mass involving the posterior mediastinum, associated with pulmonary nodules, a pulmonary cyst, splenic cysts, bone lesions, and large burden PVT. Fibrinogen was normal. He underwent TIPS creation, thrombectomy, and percutaneous biopsy of the mesenteric mass.

Results: In patient 1, pathology of the resected mediastinal lesion from infancy revealed D2-40 and CD31-positive LM with occasional reactive spindle cells. At one-year follow-up, his TIPS remains patent, but his vascular malformation has progressed. He remains on rivaroxaban and has initiated sirolimus.

In patient 2, pathology revealed scattered dilated venous and lymphatic channels with occasional reactive spindled to round cells. The spindle cell component did not stain for D2-40 or PROX1. Angiopoetin-2 was marginally elevated. TIPS creation was well tolerated although biopsy was complicated by intra-abdominal hemorrhage. He was discharged on sirolimus and enoxaparin.

Conclusion: KLA-like phenotype was observed in both patients, but with absence of spindle cells, effusions, and hypofibrinogenemia. PVT in this setting may be due to an unknown coagulopathy, abnormal venous architecture, or inflammation in the adjacent malformation. TIPS creation should be considered for PVT to prevent gut ischemia and chronic portal hypertension.

P229

COVID-19 Infection among Patients with Vascular Anomalies/SECURE-VA registry

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Purpose: The SECURE-VA registry was designed to capture pertinent information about COVID-19 infection occurring in individuals living with vascular anomalies (VA) around the world. We describe the outcomes and complications of COVID-19 among pediatric and adult patients living with VA.

Methods: This study is a cross-sectional analysis of 47 patients aged eight (8) months to 39 years with VA who were infected with COVID-19 and diagnosed with PCR-based or antibody COVID-19 test. Patient history, physical findings, and clinical outcomes were entered into the SECURE-VA registry between May 2020 and November 2021 by the physicians caring for these patients. The distribution, outcomes, and complications of COVID-19 among this subset of patients were recorded and reported.

Results: As of November 2021, forty-seven (47) cases have been entered into the SECURE-VA registry. Demographic characteristics are reported below (see table 1). Rapamycin (61.7%), Sulfamethoxazole/Trimethoprim (25.5%), and Rivaroxaban (12.8%) are the most common VA medications. Three (6.4%) patients were hospitalized due to COVID-19, and two of the three hospitalized patients developed worsening d-dimer. There were no reported deaths. The top three diagnoses were Microcystic/Macrocytic lymphatic malformation (9 patients; 19.1%), Klippel-Trenaunay syndrome (6 patients; 12.8%), and Generalized Lymphatic Anomaly (4 patients; 8.5%). Of the 47 reported patients, 13 (27.7%) patients had worsened VA disease during their COVID-19 infection, and thirteen (27.7%) had their VA medications withheld during their COVID-19 infection. The most commonly reported symptoms developed during COVID-19 infection were worsening pain (13 patients; 27.7%), growth of VA (4 patients; 8.5%), worsening D-dimer (3 patients; 6.4%), and thrombosis (1 patient; 2.1%).

Conclusion: We continue to collect and report the distribution and clinical outcomes of COVID-19 among patients with VA. Further studies and a larger sample size are needed to better characterize the effects of COVID-19 among patients living with VA.

P238

Cost-effectiveness of treatment of congenital vascular anomalies with sirolimus

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Purpose: In previous research we have shown that sirolimus is effective with positive response rates of 77%. Because sirolimus can be considered an expensive drug a trade off against its benefits in terms of quality of life (QoL) and reduction of interventive procedures need to be made. The purpose of the study was to evaluate the cost-effectiveness of low dose sirolimus in patients with vascular anomalies.

Methods: In a study of 74 patients with vascular anomalies, the cost-effectiveness of sirolimus was evaluated. Patients received sirolimus during a 6-month-period (Challenge). The utility and costs were determined before and after Challenge using QoL, medical and productivity costs surveys. Utility was calculated based on the SF6D system for adults and PedsQoL scores were used to express effectiveness in children. Costs were determined from a medical and societal perspective. Net monetary benefit was assessed to determine the chances of money saving and when sirolimus was cost-effective compared to usual care.

Results: Due to missing or incomplete data, a total of 33 patients were evaluable for calculation of cost-effectiveness. After Challenge, the mean improvement in PedsQoL was 14.33 points (7.81-20.25) and mean improvement in utility was 0.06 QALYs (0.02–0.11). In children an insignificant increase of costs of €137.05 per patient was observed (95%CI −€2,035.58 - €2,312.89). In adults, there was an insignificant decrease in medical costs of −€1,751.57 (95%CI −€4,128.27 - €571.70). With a Willingness To Pay (WTP) of €20k per gained QALY, it was 96% certain that sirolimus was more cost-effective (P=0.039), compared to usual care in adults. Even a with a WTP of €0,- it is possible that in the 81.5% of the cases a treatment with sirolimus will result in cost-savings.

Conclusion: Based on the first pharmaco-economic analysis performed it seems that treatment with low dose sirolimus will result in cost-savings in the adult population.

P249

Effect of gene testing on a vascular anomalies service

Maria Shilova, Paromita Das Gupta and Roy Kimble

Purpose: Introduction:

Genetic testing has changed the diagnostic approach to vascular anomalies from purely a clinicohistological to a multimodal approach encompassing genetic data. This paradigm shift has allowed clinicians to become more accurate in their diagnostic process and has allowed patients to access appropriate multidisciplinary treatment. Identifying specific genetic variants has also allowed patients to access gene-blocking medications in countries where such drugs are licenced; this is the first targeted treatment for vascular anomalies. Our centre has been fortunate to have access to genetic panel testing without direct cost to patients, allowing for such testing for many complex patients.

Purpose:

To evaluate how genetic panel testing has altered patient diagnoses and treatment options.

Methods: This is a retrospective chart review of patients who attend the vascular anomalies multidisciplinary clinic at our hospital, who have undergone genetic testing of their vascular anomaly with a specialised 27-gene vascular anomalies panel. Patient charts were reviewed to evaluate if their diagnosis or management changed as a result of the genetic test result.

Results: Sixty genetic tests were completed for patients with vascular anomalies, of which 42 detected a genetic mutation. As a direct result of genetic testing, 25 patients received a confirmation of their diagnosis, and 18 patients had a change made to their diagnosis. The genetic test result changed management in 11 patients and identified 30 patients potentially suitable for genetic blocking drugs in the future.

Conclusion: Our centre's experience demonstrates that genetic testing is worthwhile in children with vascular anomalies and should be made easily accessible to patients worldwide.

P252

Health Disparities in Vascular Anomalies for Patients with Skin of Color

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Purpose: Vascular anomalies, a disparate group of ailments occurring in up to 8% of the general population can have a myriad of cutaneous manifestations. While organizations such as International Society for the Study of Vascular Anomalies (ISSVA) have been formed to advance the diagnosis, management and investigation of these disorders, little focus has been given to the demographics and phenotypes of these lesions across the spectrum of skin complexion. The aim of this study was to evaluate time to primary referrals to a Vascular Anomalies Center (VAC) by ethnicity/race in patients with concern for vascular anomaly.

Methods: We analyzed all patient-level data of an academic multidisciplinary VAC based in a major urban center in the United States from 2016 to present. We examined the age at presentation to VAC for definitive diagnosis or treatment of suspected vascular anomaly. Comparisons between self-reported ethnicity/race groups were performed.

Results: Retrospective analysis included 2262 patients referred for evaluation of suspected vascular anomaly. The majority of patients were white (59.4%). Asian patients(4.5%) presented to the VAC nearly one year later than white patients (5.3 v. 4.5 years), with Black patients (19.0%) presenting nearly 2

years later (6.3 years). There was no difference in the age at presentation for Hispanic patients (17.1%; 4.5 years) These findings in variations between groups was statistically significant after single factor ANOVA analysis (p<.001).

Conclusion: There is a significant delay in initial presentation to a VAC for Black and Asian patients by nearly 1-2 years. Although the causes for this may be multi-variate, it highlights the need for expansion of studies and resources in patients with skin of color. To provide timely and equitable delivery of care, interventions which target barriers to access may be necessary.

P258

Novel mouse models for studying G protein alpha subunits in vascular anomalies

Jingjing Zhou, Lisa Arkin, Aman Prasad, Ashley Ng, Beth A. Drolet and Hao Chang

Purpose: Over the past 20 years, genetic investigations have identified mutations in multiple genes in patients with vascular anomalies. However, very few of these mutations have been proven causative. Furthermore, how patients with identical mutations manifest distinct clinical phenotypes is poorly understood. We try to address these unanswered questions by elucidating the role and mechanisms of GNAQ and GNA11, two members of G protein subunit alpha, in vascular anomalies.

Methods: We have generated three novel mouse genetic models carrying GNAQ R183G, GNAQ R183Q, and GNA11 R183C under the control of the tet-responsive elements. Mutant GNA protein expression can be induced in mouse tissues when combined with the Cre-inducible rtTA allele.

Results: We crossed the tet-GNA R183G transgenic mice with Krt14-Cre, which enables the conditional expression of mutant GNA proteins in the ectoderm and its derivatives. We induced the transgene expression at embryonic days (E) 14.5 and harvested embryos at E18.5. We found that mutant skin was covered by white granules and had increased vascularity with pink discoloration. Eyes were open and external ears were poorly developed. All these morphological features indicate abnormal differentiation of epithelial cells with disrupted hair follicle formation. This data suggests that the GNAQ R183G can be turned on in a tissue-specific (by Cre) and time-specific manner (by doxycycline) in the tet-GNAQ R183G mice that we generated. We are using several endothelial cell-specific and inducible Cre lines to determine whether the expression of mutant GNAQ/11 in endothelial cells causes vascular defects and whether vascular phenotypes will be affected by the tissue environment.

Conclusion: Our mouse models will not only provide a definite answer to whether the expression of mutant GNA proteins can cause vascular anomalies, but also provide useful tools for dissecting the mechanisms for disease pathogenesis, which will facilitate the development of novel targeted therapies.

P265

Genetic Counseling for Vascular Anomalies: One Institution's Experience Expanding Access and Accelerating Molecular Diagnosis

Zoe Nelson, Tara Wenger, Carrie Capri, James T. Bennett and Jonathan Perkins

Purpose: The recognition that even isolated vascular malformations have identifiable genetic causes, with the potential for targeted treatments, is increasing demand for genetics within vascular anomalies clinics. Vascular anomalies providers may not have the expertise to manage complex genetic testing. Genetic counselors are trained to guide genetic testing and interpret test results. There is great variability in the utilization of genetic counselors, even amongst large vascular anomaly centers. We report our center's experience.

Methods: Genetic counseling occurred within our vascular anomalies center from February 2020. Genetic counseling visits were established for certain patients who traditionally were referred to a medical geneticist or who previously did not receive genetic care. Genetic counselor and medical geneticists established triage criteria; information from the department's weekly patient care conference was used for assessment. Each case underwent review with a clinical geneticist or vascular anomalies specialist. Common referral indications were isolated vascular malformations and rule-out HHT and CM-AVM syndrome.

Results: We conducted 123 genetic counseling visits. In the four months since full time genetic counseling became available, 64 genetic counseling visits occurred; ten visits occurred with a geneticist. Wait time to visit was ten to twelve months for a geneticist visit and one to two weeks for genetic counseling. Genetic counselors ordered 33 genetic tests leading to molecular diagnosis in 23 patients. Further workup was necessary in seven patients, who were triaged to a geneticist as urgent.

Conclusion: Genetic counselors are positioned to partner with vascular anomalies programs to provide access to genetic testing. Vascular anomalies departments seeking access to genetic services for their patients may consider recruiting a genetic counselor. Utilizing this service for simplex disease and anomalies improves availability of medical geneticists to evaluate and diagnose complex patients, leading to more rapid diagnosis for patients of all indications.

P271

Mapping vascular malformation intralesional genetic heterogeneity using ddPCR and cell-type specific markers

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Purpose: Most vascular malformations (VM) are due to somatic mutations in oncogenes. Mutation identification plays an increasing role in management of these conditions due to the presence of targeted medical therapies. However, mutation detection is challenging because most cells within the malformation possess no mutation. Our objective was to correlate mutation levels and expression of cell-type specific markers onto preoperative cross-sectional imaging to "map" intralesional genetic heterogeneity in three-dimensional space.

Methods: Patients with lymphatic and venous malformations (LM and VeM) undergoing surgical resection were included. Multiple lesion and non-lesion samples were collected from each individual. When possible, samples were mapped to preoperative MRI. Mutations were detected by deep sequencing and/or droplet digital PCR (ddPCR). Only patients with pathogenic mutations were included in downstream analysis. Expression levels for PROX1 and TEK, markers for lymphatic and vascular endothelial cells, respectively, were measured and normalized to GAPDH expression using ddPCR.

Results: 164 samples (116 lesion and 48-non-lesion) from 17 mutation-positive individuals (13 LM and 4 VeM) were included. Variants were present in 112/116 (97%) lesion samples. Variant allele fraction (VAF) ranged from 0.2-11.4% with 21% of lesion samples having a VAF <1%. Variants were present in 21/48 (44%) non-lesion samples including fat (7/11), muscle (7/12), and skin (2/10). No association was identified between VAF and sample location on MRI. A 1% increase in PROX1 expression was associated with a 0.85% increase in VAF in LM samples (log-transformed linear mixed model: $p < 0.001$, 95% CI: 0.57-1.12).

Conclusion:

P274

Headaches as a Morbidity of Head and Neck Vascular Malformations

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Purpose: Headaches are known to be a symptom of certain vascular anomalies including intracranial AVMs, PHACE, and Sturge-Weber Syndrome, but chronic headaches as a prominent symptom of extra-cranial vascular malformations (VascM) without intracranial involvement has not been well described. We aim to characterize these clinical features including outcomes following treatments for VascM and migraine medications.

Methods: This is a retrospective case series of 12 patients. Exclusion criteria included lack of chronic headache, intracranial location of VascM, PHACE or Sturge-Weber Syndrome. Demographic data, vascular anomaly and headache characteristics, interventions and outcomes were analyzed.

Results: Of 12 patients, 9 had venous malformations, 1 AVM, 1 infantile hemangioma and 1 capillary malformation. All were in a cervicofacial location; 6/12 had peri-orbital involvement. Age at presentation to clinic ranged from 1.5 to 64 years, with age of headaches onset from 6 months to 34 years. Headache quality included poking, throbbing, and pulsating. Headache duration ranged from 15 minutes to 2 days. Frequency included daily to monthly episodes. Of 8 patients who reported a specific location of the headache, 7/8 had headaches on the same side as their vascular anomaly. Of 5 patients evaluated by neurology diagnosed with migraine, 1 reported reduction in headache frequency following migraine medications, while others experienced minimal response. 6/12 patients underwent sclerotherapy and 3/6 reported improvement in headache severity following the procedure.

Conclusion: Headaches are an under-recognized symptom of cervicofacial vascular anomalies, with increased risk for upper face and periorbital locations. In patients with migraines they may serve as a trigger. In this small case series, headaches did not respond well to standard migraine medications, while adequate treatment of the VascM did reduce headache severity in some patients. The association and treatment of headaches in VascM should be explored in larger cohorts in future studies.

P282

Sustained PI3K signalling activation in endothelial cells lead to extracellular changes in vascular malformations

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Purpose: Low flow vascular malformations are caused by the aberrant activation of PI3K signalling driven by somatic mutations in the TEK and PIK3CA genes. Mutations in TEK only appear in pure venous malformations whereas PIK3CA mutations are present in venous, venolymphatic and most lymphatic vascular malformations. We aimed to understand the molecular programmes and biological processes underlying the sustained expression of these activating mutations in endothelial cells.

Methods: We have set up the isolation and culture of primary endothelial cells derived from patients' vascular malformations. We have analysed the transcriptome of these cells by RNA sequencing and performed pathway enrichment analysis. Finally, we have validated our results in vitro and in vivo using mouse postnatal retinas and vascular malformations' biopsies from patients.

Results: We have defined the transcriptomic programmes driven by sustained expression of TEK and PIK3CA mutations in primary endothelial cells derived from patients' vascular malformations. Both genotypes lead to changes in molecular programmes governing cell adhesion and extracellular matrix dynamics. Specifically, the integrin alpha-9 (ITGA9) is overexpressed upon PI3K signalling activation in

endothelial cells. In line with this, EDA-containing cellular fibronectin (EDA-FN), a specific extracellular binding partner of ITGA9, is aberrantly deposited in vascular malformations in a mouse model of the disease. Also, pericytes covering these malformations show aberrant features.

Conclusion: Cell-intrinsic sustained PI3K signalling activation in endothelial cells lead to molecular changes modifying the extracellular compartment of the vascular malformations. These changes are relevant for designing therapeutic strategies and understand the pathological development of the disease.

P284

The appearance of peripheral vascular malformations and its impact on the quality of life.

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Purpose: Peripheral vascular malformations often occur in visible areas and can therefore impair aesthetic appearance. Yet, data on appearance in this population is limited. This study aimed to examine appearance problems and their impact on health-related quality of life (HR-QoL) in patients with vascular malformations.

Methods: All patients with peripheral vascular malformations (384 adults and 194 children) from our local database were invited to complete the Outcome Measures for VAscular MAlformations (OVAMA) questionnaire to evaluate potential appearance problems on a five-point Likert-scale, higher scores indicate more appearance problems (patient-reported size, swelling, color-difference, texture-difference, facial distortion, bodily distortion, being stared at, reduced self-esteem, and dissatisfaction with appearance). Additionally, multiple Patient-Reported Outcome Measurement Information System (PROMIS) scales were used to evaluate HR-QoL. Subgroups of patients reporting more appearance problems were identified using univariate analysis. Associations between appearance problems and various HR-QoL domains were assessed.

Results: A total of 184 patients completed the questionnaires, 121 patients (66%) reported that one or more appearance outcome was severely affected, scoring it 4 or 5 out of 5. The following factors were associated with more appearance problems: facial localization, capillary/combined origin, subcutaneous tissue involvement, larger size, overgrowth, and the lesion being part of a syndrome. In adults, the appearance outcomes dissatisfaction with appearance and reduced self-esteem correlated with HR-QoL domains more anxiety and more depression. Additionally, reduced self-esteem correlated with less participation. In children, bodily distortion and being stared at correlated with HR-QoL domain less peer relationships.

Conclusion: Severe appearance complaints are present in two-thirds of patients with peripheral vascular malformations, and they can lead to impaired mental health. Therefore, aesthetic appearance problems should not be underestimated. Clinicians should acknowledge appearance-related aspects, monitor psychosocial well-being and offer intervention aimed at improving satisfaction with appearance.

P315

The European Reference Network (ERN) for Rare Vascular Diseases (VASCERN): VASCA-Working Group - towards Better Management of Vascular Anomaly Patients

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Purpose: Vascular Anomalies, like other rare diseases, need multidisciplinary expert centers for quality management. This is essential for diagnosis, evaluation of prognosis and treatment, and for research. The European Commission established European Reference Networks for Rare Diseases in 2017. VASCERN is one of them (https://vascern.eu/), and includes the Vascular Anomaly working group (VASCERN-VASCA).

Methods: The VASCA includes 7 nationally endorsed multidisciplinary Vascular Anomaly Centers, 1 Affiliated center and 2 Collaborating Centers. Work is done by monthly virtual meetings and two annual face-to-face meetings. During the past five years, the group has worked on: 1) Diagnostic and Management Pathways, 2) FAIR-based Registry, 3) gene validation for diagnostic genetic testing, 4) National networks, 5) Educational materials “Pills of Knowledge”, 6) VASCA seminars and 7) Discussions on Difficult Cases using CPMS.

Results: 1) Diagnostic and Management Pathways on Severe/Rare IH, CM, VM and LM have been finalized (manuscripts being drafted) and two original studies were published; 2) A FAIR-based federated registry is being set up; 3) the genetic subworking group has generated a gene validation matrix; 4) National networks are being established; 5) several YouTube Videos were published; 6) VASCA webinars were initiated; and 7) the Clinical Patient Management System (CPMS) was used to discuss difficult cases. All the finalized documents are available on the VASCERN web-site (http://vascern.eu/). We also use Facebook, YouTube and Twitter to disseminate our work. Visits within the centers of the network will soon start with funding from the EU, and for specific projects EJP-RD funding may be applied for.

Conclusion: The networking of Expert Centers via ERN has tangible results for VA patients. While further development of the aforementioned projects is continued, VASCA-WG has also initiated new activity groups. Five new expert centers are to join VASCA in January 2022.

P322

Evaluating patient reported outcomes in paediatric cutaneous vascular anomalies.

Dujanah Siddique Bhatti and Jennifer Greenhowe

Purpose: Paediatric cutaneous vascular anomalies can have a detrimental effect on the quality of life. To quantify the impact of vascular anomalies and their treatment, Patient Reported Outcome Measures (PROMs) give a ‘voice’ to the children and their families to express their views. In children with vascular anomalies, we aim to routinely evaluate quality of life at each visit to the vascular anomalies multidisciplinary team (MDT) clinic, primarily with the use of paediatric Quality of Life Inventory (PedsQL) and the Children's Dermatology Life Quality Index (CDLQI).

Methods: A prospective observational departmental study at Hospital has commenced to explore PROMs at all stages of management in the MDT clinic. We routinely use the paediatric Quality of Life Inventory (PedsQL) and the Children's Dermatology Life Quality Index (CDLQI) as our primary indicators for new and return patients. We also have specific PedsQL Pain questionnaires to use when pain is identified as a significant symptom. The purpose of this paper is to describe the implementation of PROMs as a routine component of the vascular anomalies MDT service.

Results: All of the paediatric patients and families managed through our vascular anomalies MDT are offered routine PROMs questionnaires to complete at each clinic visit. We have established a clinical database to follow PROMs outcomes for each individual patient and identify areas which may need further attention from the clinical group, including opportunities to offer clinical psychology input where required. As the database progresses we may apply for permission to analyse the outcomes for different groups of patients, such as those receiving different management strategies.

Conclusion: We are routinely using PROMs to help manage individual patients and identify factors important to their care. We hope to see a significant impact on PROMs post treatment in paediatric vascular anomalies in the future.

P330

Integration of Digital PCR in the molecular diagnosis of vascular anomalies

Eulalia Baselga

Purpose: Purpose: An integrated diagnostic approach based on morphologic and molecular features is essential for precise diagnosis of vascular anomalies (VA), and identification of patients that can benefit from targeted therapy. Accordingly, we implemented next generation sequencing (NGS) and digital PCR (dPCR) to daily clinical practice.

Methods: Methods: 110 frozen (n=83) and formalin-fixed paraffin-embedded (FFPE) (n=27) punch biopsies from 101 patients with VA (2 FAVA; 11 lymphatic (LM); 30 capillary (CM); 50 venous (VM), 2 arteriovenous (AVM) malformations; 4 vascular tumors; 2 Lymphedema) diagnosed and treated at our institution were analyzed. All patients were younger than18 years of age at diagnosis. For dPCR, we employed commercial and custom designed assays for detection of hotspot mutations affecting PIK3CA, TEK, GNA11 and GNAQ genes. dPCR-negative samples were analyzed using a custom NGS panel covering the complete coding sequence of genes recurrently mutated in VA (62 genes).

Results: Results: dPCR enabled detection of hotspot mutations in 33 out of 110 (30%) DNA samples, including small biopsies (fresh/frozen and FFPE). 26 mutations (79%) were present at variant allele frequency <10% (VAF range 0.5-9.8%). PIK3CA hotspot mutations (E542K; E545K; H1047R) were identified in 26% of cases, including 80% LMs and 18% VMs. TEK L914F mutation was present in 6% of VMs. GNAQ (R183Q; G209R) and GNA11 (R183C) in 20% and 6% of CMs, respectively.

NGS was performed in 26 (24%) samples. Mutations linked to VA were identified in 14 samples (PIK3CA (43%), TEK (14%) and RASA1 (7%)), affecting mainly PI3K/AKT/mTOR and MAPK/ERK signaling pathways.

Conclusion: Conclusions: Our comprehensive molecular analysis enabled precise and reproducible detection of pathogenic mutations in 43% of patients with VA. dPCR was found to be a clinically applicable approach for accurate, rapid and cost effective detection of specific DNA variants, especially for common LM, whereas NGS permitted screening of VM with higher variant variability.

P341

Assessing Quality of Life in Patients with Vascular Malformations

Andrew Mangan, Kyle P. Davis, Chrystal Lau, Jeffrey Flowers, Deanne King and Gresham Richter

Purpose: Evaluate self-reported quality-of-life metrics in patients with vascular malformations (VMs).

Methods: The PedsQLTM Measurement Model was utilized to measure health-related quality of life (HRQOL) in patients diagnosed with VMs between January 2020 and September 2021. Questionnaires are designed to evaluate physical, emotional, social, and school functioning and were scored on a scale

from 0 to 100, with higher scores indicting better HRQOL. Differences in quality-of-life outcomes based on age, type of malformation, sex, and location of malformation were evaluated.

Results: Fifty-five patients completed developmentally appropriate PedsQLTM questionnaires during the study period. Mean age was 18.1 years (range: 6 to 47 years) and a majority were female (60%). The most common type of VM was venous malformation (32.7%), followed by arteriovenous malformation (20.0%) and Klippel-Trenaunay Syndrome (16.4%). Primary location of VMs included 28 (50.9%) lower extremity, 11 (20.0%) upper extremity, 7 (12.7%) head/neck, 7 (12.7%) chest/back, and 2 (3.6%) abdomen/retroperitoneum. Overall, physical functioning had the lowest score (72.9), followed by school functioning (73.3), emotional functioning (76.5), and social functioning (85.4). There was a statistically significant difference in mean physical functioning scores between age groups with young children (5-7 years) scoring the highest at 93.8 and adults (26+) scoring the lowest at 53.4 (p=0.009). Males scored lowest in school functioning (74.4), while females scored lowest in physical functioning (70.5). There was no significant difference between groups based on sex, type of VM, or primary VM location.

Conclusion: Patients with VMs appear to by most impacted by physical and school functioning and less impacted by social functioning. Differences in physical functioning scores were observed between age groups. Further studies should focus on quality of life based on type of treatment.

P342

Psychosocial concerns in youth with vascular anomalies: Results from a brief clinic screening measure

Nicole M. Schneider, Dara M. Steinberg, Darla Espinoza, Tara L. Rosenberg and Ionela Iacobas

Purpose: Children with chronic illnesses, particularly those that impact their physical appearance and mobility, are at risk to experience a multitude of psychosocial difficulties. Despite ample literature highlighting this finding, very limited research has been conducted to understand the psychological impact of pediatric vascular anomalies. Our study aimed to examine the prevalence and impact of mood, behavior and adherence, social, and pain-related concerns among a sample of children with vascular anomalies.

Methods: Brief parent and child/adolescent psychological screening measures were created by a pediatric psychologist and member of a multidisciplinary Vascular Anomalies team at a large, tertiary-care hospital in the United States. Measures were distributed to all patients over the course of several months prior to the COVID-19 pandemic, with families completing forms during clinic visits.

Results: Forty-seven children/adolescents ages 8 and older completed screening measures, with the majority (N=30) being over 12 years of age. Thirty-four parents of children ages 5 and older completed parent proxy measures. Responses were provided via a 5-point Likert scale, with higher numbers indicating more concern. The most concerning issue for pre-adolescents ages 8-12 was pain (M=2.7, SD=1.6), with less distress about physical appearance (M=1.5, SD=0.9). Self-reported concerns in the older cohort showed nearly equal concern about pain (M=2.1, SD= 1.3) and physical appearance (M=2.2, SD=1.5). Parental concerns showed the same trend. Adherence concerns were reported more frequently by adolescents and parents of adolescents. Psychotherapy involvement was also assessed; parents indicated that one-third of children and 11% of adolescents currently received therapy to address psychosocial concerns.

Conclusion: Our results preliminarily highlight that youth with vascular anomalies experience psychosocial difficulties. Findings demonstrate the need for multidisciplinary clinics to provide holistic support for patients and families, most notably related to coping with physical appearance concerns and pain management secondary to illness and treatment.

P392

Investigation of Vascular Anomalies Transition of Care Practices

Neha Kinariwalla, Margaret Scollan, Eulalia Baselga, Esteban Fernandez Faith, Christine Lauren, Margaret Lee, Laura E. Levin, Kimberly D. Morel, Julie Powell, Megha Tollefson and Maria Garzon

Purpose: Pediatric to adult transition of care (TOC) is a critical component of healthcare for adolescents and young adults with chronic or special health care needs. There is consensus among health care professionals and patients regarding the importance of supporting and facilitating a well-executed transition to adult care. There are many potential barriers to a successful transition and a paucity of information regarding transition of care models for patients with vascular anomalies. This study asesses the transition of care practices and protocols that are currently utilized by vascular anomalies specialists at vascular anomalies centers in the United States and Canada. This project examines current clinical practices, identifies gaps in understanding of TOC, and highlights areas where further investigation is needed.

Methods: In this observational study, a questionnaire will be administered to specialists in the US and Canada who care for pediatric patients at vascular anomalies programs. Participants have been identified from vascular anomalies scientific/medical organizations, research consortiums, publications in the literature, and from input from other specialists in the vascular anomalies community. The study is approved by the [xxx]. The survey will be conducted using Qualtrics, a HIPAA-compliant survey research tool. We will aggregate data on understanding of TOC practices and protocols, common barriers and support systems for TOC, as well as formal transition of care program structures. This will allow for a better understanding of how resources for transition of care vary based on geographic region, type of institution, and size of the program.

Results: Data collection begins in December 2021. Data analysis will be completed prior to the meeting.

Conclusion: Analysis will be limited to characterizing similarities and differences in transition of care practices and identifying areas with wide variation to better understand practice trends, their possible implications, and opportunities for practice improvement.

P410

Molecular Characterization of Vascular Anomalies Tissues Guides Clinical Diagnosis

Scott Henslee, Whitney Wooderchak-Donahue, J. Fred Grimmer, Philippe Szankasi, Ashini Bolia, Josue A. Flores Daboub, Alice Frigerio, David A. Stevenson and Pinar Bayrak-Toydemir

Purpose: Our goal was to identify the pathogenic variants in affected tissue taken from a cohort of unrelated patients with various clinically diagnosed vascular anomalies.

Methods: DNA was extracted from fifty-eight fresh/frozen affected tissue samples and evaluated using a custom 736 vascular anomaly/cancer gene NGS panel down to 1% somatic mosaicism.

Results: Pathogenic variants were identified in 51% (30/58) of vascular anomaly tissue biopsies, including 65% (17/26) of lymphatic malformation (LM), 24% (5/16) of hemangioma (congenital and infantile), and 73% (8/11) of other various vascular anomalies. Three novel PIK3CA variants (c.3205_3206insTTTT, c.263G>A, c.1035T>A), and one novel PIK3R1 variant: (c.1384_1395del) were identified in LM tissue. In addition, we report the first pathogenic GNA14 c.512C>T variant identified in a GLUT 1 positive infantile hemangioma lesion. Variant allele frequency ranged from 1-11% with an average of 4% for all positive cases. The majority (60%) of the negative results were in infantile hemangioma tissue.

Conclusion: The 736 NGS vascular anomaly/cancer gene panel is an effective way to detect low levels of mosaicism in these lesions. Given the challenge that many vascular anomalies present to diagnose, genetic testing is an invaluable tool for clinicians to utilize in the process of diagnosis and determining treatment.

P440

Vascular Malformations Are Not Part of the Clinical Spectrum of Turner Syndrome

Bede N. Nriagu, Lydia S. Williams, Allison Britt, David Low, Abhay Srinivasan, Theodore G. Drivas, Elaine H. Zackai, Kristen Snyder, James R. Treat and Sarah Sheppard

Purpose: Some studies have described vascular malformations (VMs) as part of the clinical spectrum of Turner syndrome. To determine if vascular malformations are due to somatic pathogenic variants in genes associated with vascular malformations or part of Turner syndrome, we tested lesional tissue in two patients with co-occurrence of Turner syndrome and VMs.

Methods: Patient 1 is an 11-year-old female with a lymphatic malformation of the right foot, lymphedema, and Turner syndrome. She was noted to have lymphedema of the hands and feet, and extra nuchal skin at birth. Patient 2 is a 3-year-old female diagnosed with Turner syndrome on chorionic villus sampling due to the presence of a cystic hygroma. Physical exam at 15 months of age was notable for VMs on her left foot with overlying patchy port-wine stains. Penn Somatic Overgrowth and Vascular Malformations Panel for genetic testing was performed on the VM lesional tissue for both patients.

Results: Penn Somatic Overgrowth and Vascular Malformations Panel identified somatic pathogenic variants in PIK3CA (c.3140A>G; p. His1047Arg) from genomic DNA isolated from vascular malformation tissue.

Conclusion: In these two patients with Turner syndrome, the vascular malformations are due to somatic pathogenic variants in PIK3CA. Our results suggest that vascular malformations are not a rare clinical feature of Turner syndrome, but rather the co-occurrence of Turner syndrome and somatic pathogenic variants.

P442

Ferumoxytol-enhanced whole body MRI for characterization of genetic, syndromic and diffuse vascular anomalies

Anna Lillis, Sahana Rajesh, Sara N. Smith, Ramkumar Krishnamurthy, Leah E. Braswell, Raimie Lewis, Bhuvana Setty, Ibrahim Khansa, Gregory Pearson, Esteban FernandezFaith, Patricia Witman, Katya Harfmann, Richard Kirschner, Amanda Jacobson-Kelly, Amanda Wh

Purpose: To evaluate feasibility of an abbreviated large field-of-view 3T MR imaging protocol following administration of Ferumoxytol blood-pool contrast agent to characterize diffuse vascular anomalies.

Methods: Following IRB approval, clinical, imaging and management information from 27 patients (15 M, 12 F), with mean age of 11.9 (0.2-52.4) years, and mean weight of 56 (7-156) kg, who underwent MR imaging using the diffuse vascular anomalies protocol was reviewed. Imaging was performed on a Siemens 3T scanner after administration of Ferumoxytol (average of 2.4 mg/kg), acquiring composite 3D RAVE/VIBE, axial SSFSE T2 without fat saturation and 3D T2-SPACE (3DT2). Technical image quality for each sequence and clinical grading of reporting elements were graded in 15 patients by 2 experienced pediatric vascular imagers using a standardized scale (1:non-diagnostic to 5:excellent). Descriptive statistics were utilized.

Results: Indications for imaging included prior diagnosis of a specific syndromic or genetic lesion (60%), or leg length discrepancy/superficial varicosities/edema/capillary stain. The full protocol, including composite image creation, was successful in 62.3% with a learning curve demonstrated. Mean scan time was 62.1 min (26-123 min). Overall technical image quality was an average of 4.5/5 for RAVE, 4.3 for VIBE, 4.8 for SSFSE T2, and 3.6 for 3DT2. All studies were considered diagnostic, with RAVE/VIBE and SSFSE T2 mandatory for adequate assessment. Mean clinical grade of selected reporting elements were: arteries (4.4/5), deep veins (4.6/5), anomalous veins (4.7/5), deep/intramuscular VM (4.8/5), macrocystic lymphatic malformations (LM) (4.7/5), microcystic LM (4.6/5), overgrowth (4.6/5), fatty hypertrophy (4.6/5), edema (4/5), and spine (4.2/5) and bone involvement (4.7/5). Even with prior vascular anomaly specialist assessment in 74% of cases, final diagnosis and management plan was changed in 66% of cases, with a specific diagnosis of PIK3CA/CLOVES in 47%.

Conclusion: We demonstrate feasibility of a 60 minute, large FOV MR imaging protocol using Ferumoxytol targeted for diffuse vascular anomalies.

P443

Complications and deaths related to systemic sirolimus treatment of vascular anomalies in pediatric patients: a single institution experience

Liliana Montoya, Michael Joseph Lavery, Judith O'Haver, Alok Kothari and Harper Price

Purpose: Sirolimus is being increasingly utilized for vascular anomalies (VA) in the pediatric population; however, there is a paucity of data in the published literature regarding the short- and long-term morbidity and mortality associated with this treatment. Our purpose is to describe the morbidity and mortality in our patient population at our institution.

Methods: Retrospective chart review of a single center's experience with systemic sirolimus use for VA in a convenience sample of pediatric patients from 12/1/15 to 5/31/20.

Results: Twenty-eight patients, ages 0-20 years, were treated with systemic sirolimus for VA. The most common diagnoses were lymphovenous or lymphatic malformations (LM) with extensive and untreatable disease, significant functional impairment, or visceral involvement. Eight patients required cessation of sirolimus therapy, some just temporarily, most often due to infection and mucositis. Two patients required discontinuation of sirolimus due to the development of diabetic ketoacidosis and hyperlipidemia. Hospitalizations were seen in eleven patients during their sirolimus course, four of whom required ICU admission. Reasons for admission included mucositis, pain, infections and related complications, and apnea/respiratory distress. We report a solitary death in an infant with a LM of the lower face and neck who was gastrostomy tube and tracheostomy dependent. Shortly after one year of age, while on sirolimus therapy for 13 months, our patient was admitted to an outside hospital for sepsis. Following discharge, the patient passed away in hospice care. Past treatments for the LM also included sclerotherapy and brief courses of prednisolone. This patient had two hospital admissions for infection after initial hospitalization at birth and three ICU admissions.

Conclusion: Pediatric deaths (n=1) or severe complications related to sirolimus treatment were uncommon at our institution. There may be risk factors that contribute to poor outcomes which are difficult to ascertain secondary to heterogeneity and limitations of the available evidence.

P445

Refining genetic variant detection strategies for vascular anomalies

Natasha Brown, Timothy E. Green, Michelle G. de Silva, Denisse Garza, Mark F. Bennett, Duncan MacGregor, Susan J. Robertson, Phillip S. Bekhor, Roderic J. Phillips, Jodie Simpson, Tony Penington and Michael S. Hildebrand

Purpose: Cost remains a significant barrier to genetic diagnosis of vascular anomalies (VA). Targeted gene panels and Exome Sequencing (ES) are expensive if performed to an adequate read depth to detect somatic pathogenic variants at low variant allele fractions (VAF). We address this challenge by utilizing alternative techniques.

Methods: We applied a range of inexpensive diagnostic strategies prior to further genomic sequencing including: 1) reanalysis of existing clinical exome data utilizing the latest bioinformatic algorithms for identifying somatic variants; 2) droplet digital PCR (ddPCR) for recurrent variants and 3) Sanger sequencing of known hotspot regions.

Results: We screened 19 patients with VA, identifying pathogenic somatic variants in 9/19 (47%). Cases included 18 low-flow (lymphatic, venous, lymphatic/venous or capillary) lesions, and one high-flow (arterio-venous) lesion In two patients with previous non-diagnostic tissue-based ES, reanalysis of ES data identified the causative variant (TEK p.L914F; KRAS p.G12A), both subsequently confirmed using ddPCR (VAFs: TEK 9-20% in two different samples; KRAS 6.84%) ddPCR alone identified the causative variant in 2/6 (33%), while ddPCR plus hotspot Sanger sequencing identified the causative variant in 5/11 (45%). Variant allele fractions (VAFs) ranged between 1.00-33% in affected tissue. Variant spectrum included recurrent (eg. PIK3CA: E545K; H1047R) and non-recurrent variants (eg. GNAQ: p.Q209R; PIK3CA: p.Q546K).

Conclusion: Typical clinical sequencing strategies, including standard depth ES and gene panels, are insufficient to detect pathogenic variants with low VAFs in VA. ddPCR is a highly sensitive and low-cost method to improve diagnostic yield for recurrent variants. Furthermore, identification of recurrent variants at low VAF in existing tissue derived ES data is feasible, and could be incorporated into clinical diagnostic pathways. In further work we aim to refine the optimum range of ddPCR assays. Molecularly diagnosed patients with disease intractable to standard care may be eligible for our new clinical trial of mTOR or MEK pathway inhibitors.

P449

The Spectrum of Congenital Vascular Anomalies of the Liver: A Multimodality Imaging Review

Brian Han, Mark Ferguson and Marguerite Parisi

Purpose: Congenital vascular anomalies of the liver are rare entities that take on different physical forms and clinical presentations, with imaging being important in the diagnosis and follow-up of these entities. The purpose of this educational presentation is to provide a multimodality imaging review of several different congenital vascular anomalies of the liver that have been observed at a single pediatric tertiary care center. These include infantile hepatic hemangiomas, congenital portosystemic shunts, and congenital intrahepatic arterioportal shunt. The clinical course and management/treatment for each of these entities, to also include the role of imaging in follow-up, will also be briefly discussed.

Methods: Radiologic imaging findings seen with different congenital vascular anomalies of the liver will be reviewed with case examples. Imaging modalities include ultrasound, CT/CTA, MR/MRA, and catheter-based angiography. The clinical course and treatment of these entities will also be reviewed.

Results: Imaging findings seen in congenital vascular anomalies of the liver vary and can be nuanced, with each imaging modality serving as a piece of the puzzle in the work-up of these entities. Infantile hepatic hemangiomas are subdivided into three types: focal, multifocal, and diffuse. Congenital portosystemic shunts are subdivided into type I (end-to-end shunt) and type II (side-to-side shunt). Type I congenital portosystemic shunts are further subclassified as type Ia or type Ib. The clinical course and treatment of these entities vary and can include any or a combination of the following: observation, medical, endovascular, and surgical. Imaging is not only important in diagnosis, but also aids in clinical management and decision-making at both initial presentation and follow-up.

Conclusion: After reviewing this educational presentation, the reader will be able to recognize imaging features for the spectrum of congenital vascular anomalies of the liver, as well as been informed of management/treatment options and understand the role of imaging in follow-up of these entities.

P451

Anatomical mapping of vascular anomalies of the lips

Rafael Zatz, Vnia Kharmandayan, Esther Mihwa Choi, Rolf Gemperli and Dov Charles Goldenberg

Purpose: The lip is the body region more often affected by vascular anomalies (VAs). Identifying the appropriate etiology of the lesion is significantly important when determining the treatment of choice for the patient. This study aimed to determine the association between the anatomical positioning and the characteristics of the lesions and the etiological diagnosis of VAs of the lips to identify the appropriate tool to be used in clinical practice.

Methods: A retrospective analysis was performed in 150 patients with VA of the lips evaluated between 1999 and 2017. The etiological diagnosis was based on the International Society for the Study of Vascular Anomalies 2014 classification. Clinical and photographic analysis was performed to assess the anatomical pattern of involvement and map the lesions.

Results: An infantile hemangioma was observed to a lesser extent in only one lip and was situated more centrally, with rare involvement of the labial commissure. Venous and venous-lymphatic malformations and arteriovenous malformations (AVMs) involving the upper lip were predominantly located more laterally and caused significant deformity. However, AVMs more often extended beyond the limits of the vermilion. Capillary malformations were observed in the entire lower lip in some patients. Simple lymphatic malformations were observed in the entire upper lip with significant distortion in some patients.

Conclusion: The initial presentation of VAs often comprises minimal changes; hence, establishing an assertive diagnosis is considered difficult. Specific patterns of involvement were observed for each etiological diagnosis studied. Anatomical mapping can be used as an auxiliary diagnostic tool and can possibly identify an appropriate clinical intervention in patients with VAs of the lip.

Venous Malformations

P029

Percutaneous sclerotherapy of head and neck venous malformations with different sclerosant agents: follow-up and comparison of 27 cases

Ilaria Paladini and Roberto Menozzi

Purpose: To assess the objective and subjective effectiveness of percutaneous sclerotherapy of head and neck venous malformations, comparing different sclerosant agents outcomes.

Methods: Between November 2017 and April 2019 , 27 patients (age 1-63) underwent percutaneous sclerotherapy for head and neck venous malformations .

Lesions were evaluated by a multidisciplinary team composed by intervetional radiologist and maxilla-facial surgeon, and characterized using MRI.

Under conscious or deep sedation, percutaneous 21 G needle flebography of the lesions was performed to study entity and distribution of its venous drainage . Sclerosant agents inyected were Bleomycin (11 cases), alcool (9 patients), Bleomycin and alcool in consecutive sessions (7 patients).

Clinical follow-up was at 4 months after interventions

Results: Average volumetric reduction was of 68% (median 70%, DS 24.07), with an average of 1.7 interventions for each patient. 23 out of 27 patients have been subjected to aesthetic evaluation using ANA scale, with an average improvement of 4.26 points (median 4, DS 2.6), and to Quality of Life Index assessment with an average improvement of 3 points (median 3, DS 1.6).

Patients treated only with Bleomycin showed a best improvement in lower sessions compared to the others (median reduction of 70% vs 50%; average sessions 1.4 vs 1.7).

Conclusion: Percutaneous sclerotherapy is safe and effective in treatment of venous head and neck malformations. In our experience Bleomycin shows the best response.

P046

The effect of compression stockings on the morphology of venous malformations? Results of a prospective randomized trial

Werner Lang, Antje Mükke, Tobias Hepp and Rafael Heiß

Purpose: Compression therapy is one component of treatment of venous malformations. However, there is no evidence about effect of volume reduction with respect to class of compression. Also, patients' compliance and comfort of stockings is mandatory for continuous treatment.

This study was designed to proof the effect of compression therapy of venous malformations in upper and lower extremity.

Methods: Patients with venous malformations in upper and lower extremities (N=20) were eligible for the study. Patients and physicians were blinded to the compression class. All patients got class I and II for 4 weeks each in a random order. Quality of life was measured by the SF-12 score. The volume of the extremity was obtained by perometry measurements (PM), the absolute volume of the lesion itself was measured by magnetic resonance imaging.

Results: In comparison with the baseline measurements taken at the beginning of the study, both compression classes showed significant differences in the MRI scan ($p<0.001$). Moreover, the mean difference between both compression classes deviates significantly from zero ($p=0.0385$). This effect

further remains significant after adjusting for baseline measurements (p=0.01). In contrast, measurements taken with the perometer, did not reveal a significant difference in comparison to the baseline values (p=0.26 and p=0.055). Comparison between compression classes, however, showed significant differences in means (p=0.024). Adjustment for baseline measurements again led to the same conclusion (p=0.029). The SF-12 did not show any significant difference between both classes of compression.

Conclusion: There is no difference in the overall volume of the extremity between class I or II. However, absolute volume of the malformation is significantly reduced by class II stockings. As patients' comfort, measured by SF-12 quality assessment, showed no difference class II compression stockings will be highly recommended for conservative treatment of patients with venous malformations with sequelae of swelling and local pain.

P048

Somatic Mutation progression in the development of the Cerebral Cavernous Malformation

Douglas Marchuk, Daniel Snellings, Jacob Lowy and Issam Awad

Purpose: To determine the relevance of somatic mutations to Cerebral Cavernous Malformation (CCM) pathogenesis in familial and sporadic cases and in the associated Developmental Venous Anomaly (DVA).

Methods: We performed deep (2000X) genomic sequencing on 71 surgically-resected CCM lesions from familial and sporadic cases. For three of these we performed single-nucleus DNA sequencing to determine the cellular phase of multiple somatic mutations in the same lesion. For three sporadic CCMs that were adjacent to a DVA, we sequenced cells from the DVA and the adjacent CCM and validated these using ddPCR.

Results: Sporadic CCMs exhibit either a Gain-of-Function mutation in MAP3K3 or bi-allelic Loss-of Functions mutations in one of the three CCM genes. CCMs from familial cases, already harboring a Loss-of-Function mutation in one of the three CCM genes, only exhibit a second Loss-of-Function mutation in the wild-type allele of the inherited mutant gene. Many sporadic and familial CCMs acquire an additional somatic mutation in PIK3CA. These PIK3CA mutations are identical to the Gain-of-Function PIK3CA mutations found in cancer. Single-nucleus DNA sequencing shows that these multiple mutations occur in the same nucleus/cell. Finally, DVAs adjacent to a sporadic CCMs exhibit a somatic Gain-of-Function mutation in PIK3CA. The exact same mutation in PIK3CA is then found in the adjacent CCM, but the CCM also shows a Gain of Function mutation in MAP3K3.

Conclusion: We propose a model where a CCM develops when either two, bi-allelic Loss-of-Function mutations occur in one of the CCM genes, or a single Gain-of-Function mutation occurs in MAP3K3, but never both sequences. Sporadic and familial CCMs harbor Gain-of-Function PIK3CA mutations, and up to 3 somatic mutations have been found in the same cells, showing that CCM follows a cancer-like disease progression. Finally, the DVA harbors a Gain-of-Function mutation in PIK3CA, and forms an anatomic and genetic primer for sporadic CCM development.

P065

intramuscular venous malformations: sclerosis treatment and/or surgical excision

Dirk Loose

Purpose: : In general, sclerotherapy is the gold standard for extratruncular intramuscular venous malformations. A vein of the malformed venous conglomerate in question should be punctured under

the control of an image converter so that the sclerosant can be safely administered intravascularly. Unfortunately, we have increasingly been assigned patients who are significant after several sclerotherapy sessions with exhibited pain .

Methods: After a corresponding detailed angiological and imaging diagnosis, the sclerosed regions in the extremities were surgically resected. In all cases, thrombosed vein areas were found, but mostly increased muscle necrosis as an expression of extravasal injections of sclerosing agents. If the lower leg area was affected, equinus foot positions in addition were often found. In order to reduce or even avoid a later recurrence, a subsequent one is recommended as total excision of the malformation as possible, namely the thrombosed part and also the remaining non-sclerosed part. The over-and-over running suture (according to Loose) has proven itself to achieve reliable hemostasis and a reduction in recurrence.

Results: : We report on 56 patients in whom the upper extremity was affected 13 times and the lower extremity 43 times. Chronic lower leg pain resulted in the development of an equinus foot in 12 patients, and an Achilles tendon plasty had to be performed at the same time. In a follow-up of 24 years, we recorded 8 recurrences of the malformation, which were treated by renewed excision successfully.

Conclusion: : A more precise sclerotherapy could give much better results than we currently do had to watch. Against this background, it must be considered in each individual case whether a primary vascular surgical excision performed by an experienced vascular surgeon would not cause fewer problems than an inadequately performed sclerotherapy.

P088

Joint contracture after sclerotherapy of limbs venous malformation

Zhenfeng Wang, Deming Wang, Ren Cai, Yi Sun, Lixin Sun and Xindong Fan

Purpose: Venous malformation is a relatively common disease among all vascular malformations. Its manifestations are diverse, ranging from venous lakes to part of complex syndromes involving the whole body. Among them, venous malformations involving the limbs, especially the joint area, may cause severe contractures after treatment. We collect and report such cases to remind colleagues of the dangers of this situation.

Methods: Since 2016, we have collected 33 venous malformations patients with joint contractures and recorded their conditions.

Results: Seven of them suffered from huge venous malformations involving the entire limb or even multiple limbs, and had joint contractures before they came to see the doctor. Three of them had fractured before and developed joint contractures after the fracture healed. One patient chose to undergo above-knee amputation of a severely contracted lower limb because he was unable to take care of himself. The remaining 26 patients did not have obvious joint contractures before treatment, and gradually experienced varying degrees of mobility restriction after treatment. The joints involved included finger joints, metacarpophalangeal joints, wrist joints, elbow joints, shoulder joints, knee joints and ankle joint.

Conclusion: For patients with severe VM, the abnormally proliferated blood vessels cause the compressive destruction of bones and joints, resulting in damage or loss of joint function, and the damaged tissue is prone to fractures, further aggravating the damage. Most patients have not reached this level during treatment. We believe that their joint contractures after treatment are due to joint adhesions caused by fibrosis after treatment. Some patients underwent an orthopedic examination after the occurrence of joint contractures and found severe bone adhesions. In order to prevent this, care

must be taken when treating venous malformations in the joint area. The remaining part is reserved to prevent severe joint contractures, and sometimes it will not reduce the quality of life.

P089

Sclerotherapy of male perineal venous malformation

Zhenfeng Wang, Deming Wang, Ren Cai, Yi Sun, Lixin Su and Xindong Fan

Purpose: Venous malformation is a relatively common disease among all vascular malformations. Its manifestations are diverse, ranging from venous lakes to part of complex syndromes involving the whole body. Among them, male perineal venous malformations are rare. In order to prevent serious complications during treatment, we often give more conservative treatment.

Methods: Since 2016, we have collected 12 male patients with perineal venous malformations and recorded their conditions.

Results: 11 patients had malformed blood vessels involving the penis and scrotum, and 1 patient had malformed blood vessels only in the penis. These patients all received at least 1 and at most 4 sclerotherapy. In the treatment process, we mainly use polydocanol foam. Two patients had large lesions in the cavernous region, and we were given sclerotherapy with absolute ethanol. After treatment, the lesions of all patients have shrunk to varying degrees. We have not received reports of sexual dysfunction such as erectile dysfunction.

Conclusion: Therefore, we believe that polidocanol foam sclerotherapy for perineal venous malformations is safe and effective. If absolute ethanol can be used safely to prevent complications such as necrosis, patients with large cavernous venous malformations can also consider using absolute ethanol for sclerotherapy. However, due to the limited number of patients, the reliability of this conclusion needs further verification.

P091

MiR-18a-5p acts as a novel serum biomarker for venous malformation and promotes angiogenesis by regulating the thrombospondin-1/P53 signaling axis

Liming Zhang, Zhenfeng Wang, Deming Wang, Lixin Su and Xindong Fan

Purpose: Venous malformation (VM) is a kind of congenital vascular anomaly with high recurrence, screening for VM lacks an efficient, inexpensive, and noninvasive approach now. Serum miRNAs with stable structures are expected to become new postoperative and post ablative monitoring biomarkers.

Methods: We identified a prognostic serum miR-18a-5p and validated its function in VM.

Results: A higher expression level of miR-18a-5p was detected in VM patients than in healthy individuals. We found miR-18a-5p plays a promotive role in human umbilical vein endothelial cells in vitro. In addition, immunohistochemistry (IHC) results showed a distinct increase of vessels in the miR-18a-5p mimics group and a decrease of vessels in the inhibitors group compared to the control group in a murine VM model. Furthermore, thrombospondin-1 (TSP1), a potential miR-18a-5p-binding protein, was identified via RNA-seq, luciferase reporter, and RNA immunoprecipitation (RIP) assays. Moreover, miR-18a-5p regulated the activation of P53 signaling pathway constituents and consequently led to the regulation of proliferation, migration, invasion, and angiogenesis.

Conclusion: These results provide a strong theoretical basis for further investigations into the pathological mechanism of VM and may provide novel, non-invasive biomarkers for VM diagnosis and monitoring.

P113

Morphological characteristics of truncular venous malformations in overgrowth syndromes: a preliminary study

olivia boccara, Véronique Soupre, Sophie Kaltenbach and Claudine Massoni

Purpose: Limb truncular venous malformations are frequently encountered in overgrowth syndromes. CLOVES and KTS are related to PIK3CA somatic mosaic pathogenic variants and are associated to geographic capillary malformation (CM). Phakomatosis pigmentovascularis (PPV) is related to GNAQ (purple well delineated segmental CM) or GNA11 (pale pink, ill-defined reticulated PWS) variants. We aim to describe the peculiar features of truncular venous malformations in both syndromes.

Methods: Retrospective study of truncular venous anomalies explored by US doppler in patients presenting either geographic CM or PPV CM of the limb.

Results: : 23 patients. Geographic CM group: 3 female, 9 male aged from 4 to 37 years (median 11.3 y). PIK3CA pathogenic variant confirmed (n=3/3). Inferior limb: n=12. Superficial veins are abnormal (hypoplasia, agenesia, valvular incontinence) in 11 patients; persistent marginal veins: n=10/12. Deep veins abnormalities (n=9/12) consisted of narrowed and enlarged veins, with irregular caliber of some segments (n=2). PPV group: 7 female, 4 male age from 5 to 20 years, (median: 14.5 y). Inferior limb n=7, neck and superior limb n=2 whole body n=2. GNA11 pathogenic variant confirmed n=2/2. 6/11 patients present with abnormal deep veins, always consisting of hypoplasia and/or agenesia, involving the vena cava in 2 patients. No ectatic or incontinent deep veins were observed. Persistent marginal veins: n=3; superficial veins are ectatic in all patients but one who presents with hypoplasia and agenesia of superficial veins. The 2 patients with extensive CM present with anomalies of limb arteries.

Conclusion: In both syndromes all patients have abnormal superficial veins. Deep veins ectatic or incontinent features seem to be specifically related to the PIK3CA spectrum. Persistent marginal veins are usually present in PIK3CA spectrum with also agenesis of superficial veins, which seems rarer in PPV, in which anomalies of limb arteries were encountered.

P116

SURGICAL RESECTION OF VENOUS MALFORMATIONS OF THE FOREARM

Claude Laurian, Claudine Massoni, Francesca Toni, Pierre Cerceau, Nikos Paraskevas, Michel Wassef, olivia boccara and Annouk Bisdorff Bresson

Purpose: To investigate the outcomes of surgical resection of venous malformations (VM) developed in the anterior compartment of the forearm.

Methods: Over a nine year time period (2010-2019) , 130 patients with forearm VMs were observed.

We retrospectively reviewed 31 patients treated by surgery in our institution. Investigations included Doppler ultrasound (DE) and MRI in T2 fat sat. The main outcome end points were functional results, residual VM, and quality of life.

Results: 26 females, 5 males, mean age 31 years(range12-51). Fifteen of the 31 had previously undergone procedures: 9 partial resections, 6 sclerotherapy treatments (1 to 4 sessions). Patients were symptomatic presenting with: 22 intermittent pain, 9 permanent pain, 21 loss of grip strength (5 of them had complete impotence of the hand) and 2 paresthesia in median nerve territory. The median time to surgery after the initial symptom was 13 years (range 2-20). Three of 31 patients required

additional surgery, 2 for residual symptomatic VM, 1 for lengthening of deep flexor tendon. MRI follow-up examens were performed between 6 and 24 months after surgery

At the last follow-up visit, 25 of 31 patients reported no residual pain, 5 had some residual paresthesia. Three patients were lost of follow-up between 6 and 12 months. We also noted that educational and professional activities did not change.

Conclusion: Long term outcomes suggest that VM of forearm can be developed in cellular space of the anterior compartment, surgical resection is a valuable treatment option based on retrospective single center analysis. However, it is an invasive approach and needs to be used selectively due to the difficulty of surgical resection, the need to preserve troncular nerve and to correct consequences of muscle contracture.

P127

Preoperative LMWH anticoagulant therapy for venous malformations with severe localized intravascular coagulopathy

Mingzhe Wen, Xitao Yang, Lixin Su, Ren Cai, Yi Sun and Xindong Fan

Purpose: To evaluate the safety and feasibility of preoperative low molecular weight heparin（LMWH）anticoagulant therapy for venous malformations with severe localized intravascular coagulopathy(LIC).

Methods: Data for patients with the diagnosis of VMs coupled with severe LIC who underwent preoperative LMWH anticoagulant therapy between July 2016 and August 2021 were retrospectively reviewed and analyzed. Low-molecular-weight heparin (LMWH) was used to control consumptive coagulopathy. The coagulation function, a measure of therapeutic effect, was evaluated.

Results: The patients underwent a total of 25 preoperative LMWH therapy, with an average of 2.5 sessions per person. Coagulation abnormality was gradually improved, that is, D-dimer was gradually decreased and fibrinogen was gradually increased. Fibrinogen at 0.5-1.0g/L, LMWH anticoagulation treatment can generally improve fibrinogen to more than 1.0g/ L in 3-5 days; Fibrinogen is less than 0.5g/L, LMWH anticoagulation treatment can generally improve fibrinogen to more than 1.0g/L in 5-7 days. No complications occurred, including bleeding, heparin-associated thrombocytopenia, and allergic reactions.

Conclusion: Preoperative LMWH anticoagulant therapy can temporarily improve the coagulation function of patients, so as to avoid bleeding and thrombosis complications after surgery or sclerotherapy.

P147

Outcome after Surgical Treatment of Venous Malformations of the Hand in Childhood.

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Purpose: Surgical approach for treatment of Venous Malformations (VMs) of the hand is challenging. The hand`s small functional units, dense innervation, and terminal vasculature can be easily compromised during a surgical intervention, leading to an increased risk of functional impairment, cosmetic consequences, and negative psychological effects.

Methods: To evaluate the results of surgery for treating VMs of the hands in children, we have conducted a retrospective review of all surgically treated patients diagnosed with VMs of the hand between 2000 to 2019. Descriptive data analysis was performed.

Results: Twenty-nine patients (females=15) with a median age of 9.9 years (range 0.6–18) were included. Eleven patients presented with VMs involving at least one of the fingers. In 16 patients, the palm and/or dorsum of the hand was affected. Two children presented with multifocal lesions. All patients presented with swelling. Diagnosis of VMs was achieved by clinical evaluation (n=3), ultrasound (n=8), MRI (n=9), and both, ultrasound and MRI (n=9). Indications for surgery were given because of pain and restriction of function (n=17), and when lesions were evaluated as completely resectable (n=12). The VMs could be excised entirely in 18 patients (Figure), while in 11 children the nerve sheath infiltration made complete surgical resection impossible. At the median follow-up of 111 months (range 1-216 months) recurrence occurred in 11(37.9%) patients after a median time of 22 months (range 2–36 months). Eight patients (27.6%) were reoperated because of pain, while 3 patients were treated conservatively. The rate of recurrence did not significantly differ between patients presenting with(n=4) or without(n=7) local nerve infiltration. All surgically treated patients who were diagnosed without preoperative imaging developed a relapse.

Conclusion: Surgical removal of isolated and well-defined VMs of the hand is a good option with reasonable recurrence rates if preceded by accurate diagnostic imaging and meticulous surgical planning.

P178

Complicated Infantile Lower Lip Venous Malformations: Successful managed by Long-pluse 1064nm Nd:YAG Laser

HUI CHEN, LI HU, XI YANG, HONGYUAN LIU, YIFEI ZHAO, ZIAN XU, YAJING QIU, GANG MA, YUNBO JIN and Lin Xiaoxi

Purpose: To evaluate the efficacy and safety of long-pulse Nd:YAG lasertherapy for complicated infantile lower lip VMs（CILL-VM）.

Methods: Eight cases with CILL-VM were included in this study between may 2018 to Apr 2021. The average age is 7.8 months (4~12 months). 3 cases got entire low lips and 5 cases partial involved with obvious low lips thicken and ectropion. 4 cases had extensive facial, intraoral and airway lesions. The long-pulse Nd:YAG laser device was Lumenis One or M22 (Lumenis, USA) with parameter of 6mm spot diameter (crystal with skin contact cooling), 125~130 J/cm2 fluence, 8~12ms pulse width (double pluses) and 70ms pulse interval. The treatment was under no anaesthesia, and treatment endpoint in each session was that the lesion in laser beam shrank quickly, the mucosa was not so pale and the whole lesion volume decreased notably immediately. The interval of each treatment was 2~3 months.

Results: All cases had dramatically improvement evaluated by pre- and post- photographs after 1~3 sessions. The treatment time was 3~5 minutes in each session. The subsidence of lip swelling was in 2~3 weeks. Only 3 case had limited and self-healing mucosal necrosis. No other serious complicated happened.

Conclusion: LP- Nd:YAG laser had high clearance rate of CILL-VM with limited sessions, and simple treatment process, short recovery period and low risk are also its superiorities, which can avoid too early and relative high-risk sclerotherapy.

P196

Retrospective Clinical Study for Surgical Management of Intramuscular Venous Malformations in KNUH VA Center

Yun Hyun Kim, Hyun Ki Hong, Seok Jong Lee, Jong Min Lee, Sang Yub Lee, Seung Huh, Ji Yoon Kim, Suin Kwak, Hyun Mi Kim, Eun Jung Oh and Ho Yun Chung

Purpose: Venous malformation (VM) is the most common type among vascular malformations. Intramuscular venous malformations (IMVMs) are lesions involving the muscles and causing clinical symptoms such as pain, swelling, limitation of motion, etc. We only referred to VM limited to muscles as intramuscular venous malformation (IMVM), except for intramuscular hemangioma. The purpose of this study is to compare clinical outcomes in IMVM between sclerotherapy and surgical treatment.

Methods: Among 492 VM patients treated in our vascular anomalies center between July 2011 and August 2020, 63 IMVM patients were studied by conducting a retrospective review. Pain, limitation of motion, swelling and quality of life (QoL) were evaluated based on patients' subjective statements, while radiologic outcomes were assessed by qualified radiologists in our center. The complications were also evaluated. In addition, we analyzed which group was further improved in the sclerotherapy and surgical treatment group by using radiologic and clinical findings.

Results: Although there were no significant differences in pain (p=0.4705), swelling (p=0.3222) and complication (p=0.2062) between two groups, surgical treatment group gained statistically significantly better outcomes in limitation of motion (p=0.0101), QoL (p=0.0132) and radiologic outcome (p=0.0171), than sclerotherapy group. Both doppler ultrasonography and MRI findings showed that IMVM was better improved in surgical treatment group.

Conclusion: Although there have been some studies on therapies for IMVM, a definite guideline for it has not been yet known so far. Based on this study, surgical intervention is recommended to be actively used in treating IMVM.

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P200

Radio-pathologic Features of Hepatic and Intramuscular Venous Malformations

Mason LaMarche, Jonathan Davick and Mohammad Amarneh

Purpose: To establish pathologic and radiographic characteristics of intramuscular and hepatic venous malformations. Historically, these malformations have been inappropriately labeled as hemangiomas which limits physician's awareness of these diagnoses including their responsiveness to pharmacologic and minimally invasive interventions. The study provides supports the International Society for the Study of Vascular Anomalies (ISSVA) classification of both hepatic and intramuscular "hemangiomas" as venous malformations.

Methods: A retrospective review was conducted for patients with possible venous malformations affecting the liver or musculature at a single institution from January 2000 to July 2021. Search terms to identify possible cases included: hemangioma, arteriovenous malformation, and venous malformation. Each case was reviewed by a board-certified pediatric pathologist and board-certified pediatric diagnostic and interventional radiologist.

Results: We identified 10 intramuscular venous malformations and 28 hepatic venous malformations. Intramuscular venous malformations are often symptomatic with a common concern being pain (9/10;

90%). Histopathologic features of intramuscular and hepatic venous malformations overlap including the presence of venous structures, papillary endothelial hyperplasia, and phleboliths. Intramuscular and hepatic venous malformations have differing magnetic resonance imaging (MRI) findings. Intramuscular venous malformations are T1 isointense (7/8; 87.5%) with uniform enhancement with administration of contrast (6/8; 75%). Hepatic venous malformations are T1 hypointense (23/24; 95.8%) with peripheral nodular discontinuous enhancement that progressed centripetally (20/24; 83.3%).

Conclusion: Histopathology demonstrates a significant overlap between intramuscular and hepatic venous malformations. Intramuscular venous malformations have tubular, small spaces which, combined with the location of the lesion along extremities, causes patients to experience symptoms from sequelae of slow-flow malformations. Conversely, hepatic venous malformations are spherical and demonstrate radiographic findings of a large venous. Notably, neither demonstrated any radiologic or pathologic features of high cellular turnover implied with the historic name hemangioma. Despite subtle differences in MRI findings, both entities demonstrate characteristics of slow-flow lesions consistent with their current ISSVA classification.

P201

The Diverse Clinical Courses and Features of Verrucous Venous Malformation

SHIH-JEN CHANG, QIANYI CHEN, XI YANG, YAJING QIU and Lin Xiaoxi

Purpose: To understand the clinical course of VVM and gain insight to its clinical pattern.

Methods: Forty clinically and pathologically diagnosed VVM patients were enrolled. Patients' data and VVM characteristics were documented. Elaborative reviews of patient history were conducted to understand the progression of each patient's lesion, timing of keratinization, incidences of complications, and how their lesions impacted their lives.

Results: Twenty-eight patients (70.0%) had localized lesions and 12 (30.0%) had diffuse lesions. All lesions involved the upper or lower limbs. Thirteen of 37 (35.1%) patients had a somatic MAP3K3 mutation (c.1323C>G). Twenty-six (65%) patients' lesion initially presented as a red patch; 9 (22.5%) were a purplish color; and 5 patients (12.5%) were a subcutaneous lump. Progression of the lesion is common and most patients acquired hyperkeratosis at early childhood. Strong indicators for hyperkeratosis include VVMs that initially presented as red skin patches, purple patches, and diffuse lesions.

Conclusion: There exists different initial presentations of VVMs. Its diverse clinical course and characteristics need to be explored in more depth.

P208

Verrucous Venous Malformation on the face

SHIH-JEN CHANG, XI YANG, LIZHEN WANG, GANG MA, YAJING QIU and Lin Xiaoxi

P212

Dabigatran etexilate is efficacious in consumptive coagulopathy and pain associated with venous malformations.

Hongyuan Liu, Li Hu, Xi Yang, Zian Xu, Hui Chen and Lin Xiaoxi

Purpose: The consumptive coagulopathy treatment and pain management are crucial in venous malformations (VM). Dabigatran etexilate, as a non-vitamin K antagonist oral anticoagulant (NOAC) has

known advantages over LMWH and VKAs, which have been reported to be used in several localized intravascular coagulation (LIC) cases associated with VM.This study aimed to confirm the efficacy and safety of dabigatran etexilate in consumptive coagulopathy treatment and pain management in VM.

Methods: This was a retrospective observational cohort study conducted in the Hemangioma and Vascular Anomalies Center of Shanghai Ninth People's Hospital. 19 outpatients diagnosed with LIC associated with VM were treated with dabigatran etexilate from September 2019 to June 2021. The patients gave their oral consent and then underwent biological testing of blood routine examination and coagulation functions before and after treatment. The dosage of dabigatran etexilate was 110mg bid for adults and 55mg bid for children.

Results: All patients benefited from dabigatran etexilate treatment. Pain improved in all evaluable 16 patients. Fibrinogen and D-dimer levels improved in 18/19 patients. FDP level improved in 10/14 patients. There are no significant differences of D-dimer, fibrinogen, and FDP between the short-term medication (<10days) and long-term medication (≥10 days). Dabigatran etexilate is well tolerated in all patients. No bleeding event happened during the follow-up.

Conclusion: Our study confirmed the efficacy and safety of dabigatran etexilate in treating pain and LIC in venous malformation patients. Dabigatran etexilate is a suitable choice for preoperative patients to modify coagulation and patients with pain.

P237

Endoscopic sclerotherapy combined with diode laser for pharyngeal venous malformations

LI HU, YIYUAN SUN, XI YANG, HAO GU, ZIAN XU, HONGYUAN LIU, HUI CHEN, YUNBO JIN and Lin Xiaoxi

Purpose: Venous malformations located in the head and neck region involving pharynx often present snoring, dysphagia and dyspenea, which makes it a complex and challenging condition to tackle. This study aimed to investigate the safety and efficacy of endoscopic sclerotherapy combined with diode laser in the pharyngel venous malformations.

Methods: We retrospectively collected clinical and radiological data of 19 patients who received endoscopic sclerotherapy with or without diode laser in our vascular anomaly center between July 2020 and November 2021. Among them, 13 patients underwent tracheotomy before endoscopic sclerotherapy in case of life-threatening airway obstruction. All patients were treated with 3% polidocanol-bleomycin foam sclerotherapy under suspension laryngoscope. 16 patients received combined diode laser therapy. The wave length of diode laser was 980nm and the diameter of optical fiber was 600 μm. The output power was 15W. Outcome was classified as worse, no change, minor improvement (<50% decrease in size), marked improvement (≥50% decrease), or cure. Complications were recorded.

Results: The 19 patients (11 females, 8 males) received a total of 44 sclerotherapy sessions. Complete resolution of the lesion was observed in 4 (21.1%) patients and 8 (42.1%) patients showed considerable reduction of the swelling, while one presented worse on the laryngoscope findings. Complications (uncontrolled intraoperative bleeding) occurred in one (5.3%) patient. Nasal packing hemostasis was applied and was removed 3 days later. No respiratory troubles or other severe complications occurred.

Conclusion: Endoscopic sclerotherapy combined with diode laser is a safe and effective therapeutic strategy for pharyngeal venous malformations.

P250

PIK3CA Positive FAVA in a Patient with Defective Mismatch Repair

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Purpose: We present a 16-year-old female with fibroadipose vascular anomaly (FAVA) in her right thigh, multiple vascular plaques, and bifrontal intracalvarial lymphatic malformations, who possessed defective mismatch repair due to MSH6 gene mutation as well as mosaic PIK3CA mutations.

Methods: Diagnostic testing included MR imaging of her lower extremities and brain, saliva-based exome sequencing, histopathologic examination of normal and abnormal skin tissue, and deep mosaic sequencing of PIK3CA and other genes involved in vascular anomalies.

Results: Exome sequencing identified biallelic variants in the DNA mismatch repair gene MSH6, suggesting a diagnosis of Lynch syndrome or Constitutional Mismatch Repair Deficiency (CMMRD), both of which are cancer predisposition syndromes. The possibility that her multifocal vascular malformations were directly due to MSH6 mutations was considered, but molecular testing from biopsy of vascular lesion was pursued and revealed a pathogenic variant in PIK3CA (p.H1047R). In addition, immunohistochemical staining clarified that only one of the MSH6 variants (p.Asp1028Glyfs*5) was disease causing

Conclusion: We conclude that our patient has dual diagnoses of Lynch syndrome and PIK3CA-related overgrowth spectrum (PROS). By not resting with the exome-based diagnosis of Lynch syndrome this patient is now eligible for medical therapy (Alpelisib) for treatment of her FAVA associated pain. In addition, we speculate that the defective mismatch repair proteins may have indirectly led to the vascular malformations by increasing the chances of post-zygotic mutation. This case exemplifies that negative testing for PIK3CA on a germline specimen does not rule out a somatic PIK3CA variant, even when vascular lesions are widespread.

P288

Correlative radiologic and immunopathologic study of a large series of "giant hepatic hemangiomas" reveals a consistent phenotype: intrahepatic portal venous malformation.

David Gullotti, Ryan W. England, Paula E. North and Clifford R. Weiss

Purpose: When > 5 cm in size, adult hepatic vascular anomalies are often termed “giant cavernous liver hemangiomas”. Integrative clinicoradiopathologic study of these lesions is rarely reported, however, hampering proper classification and treatment decisions for symptomatic patients. We sought to clarify the histologic nature and nosologic classification of these radiologically distinctive lesions.

Methods: Retrospective, IRB-approved study of patients with “giant cavernous liver hemangiomas” resected from 2008-2019 at a major tertiary care hospital was performed. Clinical demographics/presentation and imaging features were reviewed; tissue immunopathologic analysis was performed (including H&E, h-caldesmon, SMA, CD31, and D240 staining).

Results: Twenty-five patients were included (average age 48 [range 31-67] years; 80% female). Of 23 patients with imaging available for review, initial diagnosis was made by MRI in 65% (N=15); CT in 35% (N=8). Lesional size by imaging averaged 13.2 (range 5.4-25) cm in largest cross-section and 1025 (45-4356) cc in volume. In 14/23 patients, imaging revealed additional smaller hepatic “hemangiomas”; 3 also had extra-hepatic lesions. 96% (N=22) of lesions abutted the main, right, or left portal veins; 83% (N=19) abutted the middle, right, or left hepatic veins. Portal venous thrombosis was not observed.

Histological analysis of resected lesions (25/25) universally revealed mass-like portal tract expansion by dilated, back-to-back, thin-walled portal venous tributaries separated by paucicellular, hepatocyte-free, fibrous tissue. Lesional venous walls were rimmed by extremely scant smooth muscle (variably highlighted by SMA and h-caldesmon staining) lined by CD31-positive/D240-negative endothelial cells. Intervening fibrous tissue contained SMA-positive h-caldesmon-negative myofibroblasts and scattered small, D240-positive lymphatics. Peripherally displaced bile ducts and small arteries were commonly seen. Organizing thrombi were rarely present. Margins sharply abutted normal hepatocellular parenchyma with sometimes mildly dilated, but otherwise unremarkable, central veins.

Conclusion: In a study of 25 so-called “giant cavernous liver hemangiomas”, all displayed consistent features of intrahepatic portal venous malformation.

P295

Pharmacokinetics and pharmacodynamics of alpelisib in TEK/TIE2 mutated venous malformations

Amandine Remy, Josee Dubois, Thai Tran, Yves Théorêt, Paul Gavra, Rochelle Winikoff, Chantal Lapointe, Sandrine Essouri and Niina Kleiber

Purpose: Despite the high morbidity associated to extensive venous malformations (VM), some patients fail all existing treatments (sclerotherapy, surgery, heparin, sirolimus). About 60% of VM are due to a TEK mutation encoding TIE2 receptor on venous endothelial cells. This leads to a dysregulated expression of angiogenic factors and altered vascular development. In vitro data suggests that PIK3CA inhibition may be effective in reversing TIE2 overactivation. We hypothesized that alpelisib could improve the condition of patients with refractory VM.

Methods: Alpelisib was obtained via Novartis Managed Access Program: •Patient 1: 16-years-old with a sirolimus-resistant extensive leg VM suffering chronic pain and ambulating difficulties. Her baseline localized intravascular coagulation (LIC) led to a life-threatening bleeding after a minor external surgery.

Based on a favorable clinical response, two additional patients were treated: •Patient 2: 12-year-old displaying an extensive VM of both legs and right upper arm and severe LIC. After a profound thrombosis, chronic heparin was started and later switched to sirolimus. On sirolimus, he showed a recurrence of the previously operated equinus foot, only partially corrected the LIC and developed a proteinuria. •Patient 3: 18-year-old with an extensive leg VM with chronic pain and functional impairment. A baseline nephropathy contra-indicated sirolimus. Daily oral doses were 50mg for patient 2, 100mg patient 1 and 3. After 6 months of treatment, we performed: •MRI •Area under the curve (AUC sampling times: 0,0.5,1,1.5,2,3,6 and 8h post-dose).

Results: Patients experienced: •After 1-2 month: very marked decrease in pain •Improved functionality •Dramatic improvement of LIC (platelets and fibrinogen normalization) •No significant improvement in equinus foot •On MRI: decreased size of the venous lakes Three minor adverse events were noted (1 headache, 1 superficial thrombosis, 1 self-resolved foot pain). AUC0-24h patient 1=22968 ng*h/ml; AUC0-24h patient 2=5774 ng*h/ml

Conclusion: Alpelisib is a very promising treatment of VM displaying a TEK mutation.

P301

The abnormal reduction of vascular wall resident stem cells causes the deficiency of vascular cells in venous malformations

Wenqiang Lai, Houfu Xia and Gang Chen

Purpose: Vascular wall resident stem cells (VW-SCs) play a key role in vascular homeostasis, but its role in venous malformations (VMs) remains unclear. The present study aims to explore the distribution of VW-SCs in VMs and evaluate the correlation between the abnormality of VW-SCs and the development of VMs.

Methods: By immunohistochemistry, immunofluorescence and real-time qPCR, the expression of VW-SC-related markers were investigated in tissue samples from VM patients (n = 22) and healthy volunteers (n = 17). Spearman rank correlation test was adopted to analyze the relevance between the number of VW-SCs and the stability of vascular cells.

Results: VMs were characterized by discontinuous endothelium and sparse perivascular cell coverage. Both the protein and mRNA expression levels of CD34, vWF, VEGFR2, CD44, CD90, CD105 were significantly downregulated in VMs compared with that in normal skin tissues. Based on immunohistochemistry and immunofluorescence, progenitor and stem cells were sporadically distributed or even absent within and outside the endothelium of VMs, while they exhibited organized signal in normal venules. More importantly, the expression levels of above mentioned VW-SC markers were positively correlated with the density and the integrity of both endothelial cells and perivascular cells.

Conclusion: VM-SCs might play an important role in maintaining vascular homeostasis by remedying instability of endothelial cells. The abnormal reduction of VW-SCs possibly results in the deficiency of vascular cells in VMs.

P310

Rab27a induces vascular dysfunction by promoting EV-MMP14 secretion in venous malformations

Gaohong Chen, Jiegang Yang and Gang Chen

Purpose: It has been revealed that extracellular vesicle (EV) secretion is abnormally elevated in venous malformations (VMs). The present study aims to investigate the role of increased EV secretion in the progress of VMs.

Methods: Cells over-expressing TIE2-L914F and TIE2-WT were constructed with Human Umbilical Vein Endothelial Cells (HUVECs) to simulate VM-ECs and normal mature ECs (as control), respectively. EVs were isolated from the conditioned media of VM-ECs or the lesion fluids (LFs) of VM patients, followed by characterization with transmission electron microscopy (TEM) and quantification with nanoparticle tracking analysis (NTA). The degradation capacity of EVs from VM-ECs were evaluated with matrix degradation assay and western-blotting. Correlation analysis was then performed both in vitro and in vivo to explore the regulator responsible for the secretion of EV-MMP14. Genetic depletion of Rab27a in VM-ECs was further conducted to verify the role of abnormal EV secretion in regulating MMP14-mediated extracellular matrix (ECM) degradation of VMs.

Results: The concentration of EVs were drastically enhanced in both conditioned medium from TIE2-L914F-HUVECs and VM-LFs, compared with that in control group. Increased level of MMP14, together with promoted ECM degradation ability were identified in VM-EVs both in vitro and in vivo. Using immunofluorescence staining, MMP14 was proved to co-localize with Rab27a, the protein regulating EV secretion. Moreover, the expression level of Rab27a and MMP14 were positively correlated in the

endothelium of VM tissues. Knockdown of Rab27a in VM-ECs reduced the secretion of EV-MMP14, thus impaired the ECM degradation correspondently.

Conclusion: Rab27a possibly regulates the development of VMs by promoting the EV-MMP14-mediated ECM degradation.

P347

Treatment of dilated superficial veins in patients with venous malformations: Initial experience using the Clarivein device.

Paul Lewis, Kevin Wong, Gresham Richter and Shelley Crary

Purpose: In time, dilated superficial veins can become a cause of significant morbidity in patients with venous malformations due to venous hypertension, thrombophlebitis and thromboembolic events. Current trends are to prophylactically treat these veins, however methods widely vary and include surgical resection, radiofrequency ablation and sclerotherapy. We present our experience embolizing these veins with the Clarivein device, a pharmacomechanical embolization system designed to treat varicose veins.

Methods: Retrospective review of eight patients from two children's hospitals undergoing treatment of dilated superficial veins (including but not limited to the lateral marginal vein). Demographics at time of treatment, initial results and followup including complications, symptoms and available imaging were reviewed.

Results: Eight patients were reviewed. Six patients had imaging followup and results include two complete occlusions, one progressing venous fibrosis, two mixed results with both occluded and patent segments, and one persistently patent vein. One patient does not yet have post treatment imaging and one patient was lost to followup. Of the seven patients with clinical followup, there was one suspected pulmonary embolism, one thrombophlebitis. No complications such as skin or nerve injury. Post procedural pain was minimal in all patients.

Conclusion: Pharmacomechanical embolization of superficial veins in venous malformation patients with the Clarivein device may be a cost-effective option with minimal complications or postprocedural morbidity.

P364

The effect of nanoparticle size on accumulation in venous malformations

Claire Ostertag-Hill, Kathleen Cullion, Michelle Pan and Daniel S. Kohane

Purpose: Despite being the most common vascular malformation, venous malformations (VMs) frequently present a therapeutic challenge with current treatment options including medications with systemic toxicity and procedural interventions of high technical difficulty and risk of hemorrhage. Utilizing a nanoparticle (NP) delivery system may allow for enhanced drug delivery to VMs and thereby decreased systemic toxicity. NPs can preferentially accumulate in tissues with abnormal vasculature, a concept known as the enhanced permeation and retention (EPR) effect. EPR has been documented in tumors and in bioengineered vessels. While EPR has not been previously studied in VMs specifically, we hypothesize that NPs will preferentially accumulate in VMs due to EPR. Supporting this hypothesis, we have observed EPR-like effects in patients with VMs. Here we aim to study whether EPR occurs in VMs and will examine the effect of NP size on accumulation within VMs in vivo.

Methods: In this study, we used a murine model of VMs. In this model, human umbilical vein endothelial cells (HUVECs) expressing the most frequent VM-causing TIE2 mutation, TIE2-L914F (HUVEC-TIE2-L914F), are injected subcutaneously into immune-deficient mice. Within 10 days, these mice develop vascular lesions similar to those described in human VMs. We injected fluorescently labeled hollow silica NPs (HSNPs) of a range of sizes systemically and studied NP accumulation.

Results: All NPs were spherical by transmission electron microscopy. The fluorophore tagged HSNPs had hydrodynamic diameters of 35.2nm, 82.3nm, and 207nm. Following systemic NP administration, the biodistribution of NPs was assessed using confocal microscopy and an in vivo imaging system, comparing accumulation in VMs to accumulation in other murine organs.

Conclusion: This study helps determine the optimal NP size for EPR and NP accumulation within VMs and lays the foundation for engineering NPs for the treatment of VMs, balancing therapeutic drug loading and passive selective accumulation based on the EPR effect.

P371

Bockenheimer Disease is Associated With a TEK Variant

Christopher Sudduth, Dennis J. Konczyk, Patrick Smits, Whitney Eng, Alyaa Al-Ibraheemi, Joseph Upton and Arin K. Greene

Purpose: Bockenheimer disease is a venous malformation involving all tissues of an extremity. Patients have significant morbidity and treatment is palliative. The purpose of this study was to identify the cause of Bockenheimer disease to develop pharmacotherapy for the condition.

Methods: Paraffin-embedded tissue from 9 individuals with Bockenheimer disease obtained during a clinically-indicated operation underwent DNA extraction. Droplet digital PCR (ddPCR) was used to screen for variants most commonly associated with sporadic venous malformations [TEK (NM_000459.5:c.2740C>T; p.Leu914Phe), PIK3CA (NM_006218.4:c.1624G>A; p.Glu542Lys and NM_006218.4:c.3140A>G; p.His1047Arg)].

Results: ddPCR detected a TEK L914F variant in all 9 patients (variant allele fraction 2%-13%). PIK3CA E542K and H1047R variants were not identified in the specimens. Sanger sequencing and restriction enzyme digestion confirmed variants identified by ddPCR.

Conclusion: A pathogenic variant in the endothelial cell tyrosine kinase receptor TEK is associated with Bockenheimer disease. Pharmacotherapy targeting the TEK signaling pathway might benefit patients with the condition.

P389

Case-report: A young man with a symptomatic venous malformations and hypertension, treated with ACE-inhibitor.

Sigurd Berger, Therese Halvorsen Bjark, Eric Dorenberg and Rune Andersen

Purpose: In this case report, we present a young male with a symptomatic venous malformation that was diagnosed with hypertension. Treatment with an ACE-inhibitor was initiated, which led to an interesting observation.

Methods: We present a 39 year old male who since childhood experienced weakness of the left forearm and hand, as well as activity related pain. In August 2018, due to increasing pain and swelling, he was referred to the National vascular anomaly center. MRI and ultrasound showed an extensive

intramuscular venous malformation of the forearm and hand. Different invasive treatment approaches were discussed.

Results: In December 2018, however, before treatment of the venous malformation was initiated, he was diagnosed with hypertension and was given antihypertensive treatment with Renitec, an ACE-inhibitor. The dose given was 10 mg x 1/ day. Soon after initiation of treatment, the patient reported considerable symptomatic improvement with less pain and swelling. On MRI images, calculated volume of the malformation was reduced from 254,9 cm^3 to 132,5 cm^3, a reduction of 48.0%. Due to symptomatic improvement, no invasive treatment was performed. At follow-up in September 2021, he was still on antihypertensive medication with Renitec. He reported mild symptoms, probably due to thrombophlebitis episodes, and treatment with platelet inhibitor was initiated.

Conclusion: Venous malformations have traditionally been treated with surgery or sclerotherapy. Unfortunately, the treatment effect is often unsatisfying, especially in complex and extensive malformations. Recent publications (Siljee 2016, Tan 2019) have shown that components of the Renin-Angiotensin-System (RAS) are expressed in embryonic stem-cell like populations of venous malformations, and it has been hypothesized that such primitive cells may be a potential therapeutic target by manipulation of the RAS. In this context, our observation warrants further research on the link between RAS and venous malformations, and whether ACE-inhibitors may have a role in pharmacomedical treatment of symptomatic lesions.

P438

Somatic Genetic Testing Provides Diagnosis of Verrucous Venous Malformation in a Patient with Discrepant Radiology, Pathology, and Clinical Findings.

Allison Britt, James Treat, David Low, Anne Marie Cahill, Maria Queenan, Amber Bolli and Sarah Sheppard

Purpose: Verrucous Venous Malformation (VVM) is frequently misdiagnosed clinically. This case demonstrates the value of genetic testing to inform correct diagnosis.

Methods: Patient provided consent for retrospective case report.

Results: Patient is the product of a pregnancy complicated by maternal bleeding and bedrest due to past miscarriages. At birth, a red flat patch with overgrowth of his right hand, arm, and shoulder was noted. The overgrowth and red color persisted and began to cause pain, which prompted his initial evaluation at age 10. He was given a diagnosis of capillary vascular malformation and overgrowth. Routine MRI of the right arm showed no definitive vascular anomaly and no fatty infiltration of the muscle with some overgrowth. At 12 yo, there was a telangiectatic vascular patch on the right arm with verrucous papules over the top and hyperkeratotsis. Based on history, physical exam and imaging, the differential diagnosis included capillary malformations due to PIK3CA, GNAQ, or GNA11; HRAS associated hyperkeratotic lesions; VVM associated with MAP3K3; or hyperkeratotic cutaneous capillary venous malformation associated with KRIT1, CCM2, and PDCD10. Pathology from skin biopsy was most consistent with a capillary malformation and showed mildly acanthotic epidermis with hyperkeratosis overlying dilated, thin-walled vascular channels, some containing erythrocytes, within the papillary dermis. Vascular spaces are lined by bland endothelial cells. Abnormal vessels are confined to the superficial dermis. A somatic genetic testing panel including 34 genes was performed on two affected specimens collected via skin biopsy. Results showed a likely pathogenic variant in the MAP3K3 gene c.674C>T, p.Ser225Phe at variant frequencies of 4.2-4.6% from sample one and 7.3-8.0% from sample two, confirming the diagnosis of Verrucous Venous Malformation.

Conclusion: Somatic genetic testing provided this patient with the diagnosis of VVM when radiology, pathology, and clinical findings were discrepant. His new genetic diagnosis influences treatment and prognosis.

Social Programs (in-person only)

Welcome Reception

We invite all in-person attendees to the Welcome Reception, which will occur in the Westin Bayshore Foyer on Tuesday, 10 May from 17:00 - 19:00. There will be light appetizers and drinks available, as well as the opportunity to network with colleagues and visit the Exhibition Hall. We will also have a welcome from the ISSVA President, Prof Tony Penington, plus introductions from our local hosts and Enjolras Award winners. This reception is included with the registration of all in-person delegates.

Tuesday, 10 May • 17:00 - 19:00
Location: Westin Bayshore Foyer

Congress Dinner

Join colleagues for an evening of celebrating the ISSVA World Congress 2022 and the city of Vancouver. Appetizers, carving stations, and drinks will allow you to mingle with colleagues while seeing the exhibits of the Vancouver Aquarium and exploring the aquatic life of British Columbia and the oceans of the world. The aquarium is a short walk from the meeting venue so dress casually and wear comfortable shoes. Alternately, bus transportation will be available.

The Congress Dinner requires an additional ticket to attend; extra tickets will be available at the Registration Desk onsite.

Thursday, 12 May • 19:00 - 22:00
Location: The Vancouver Aquarium
Busses (from Westin Bayshore Lobby): 18:45 - 22:00

Running Club

The ISSVA Running Club will be meeting the morning of Friday, 13 May for a casual run through Stanley Park. To join this group, we request a donation of $50 USD to the ISSVA Education Fund.

Friday, 13 May • 06:00 - 07:00
Meet at: Westin Bayshore Lobby

Farewell Reception

At the conclusion of the scientific sessions on Friday, 13 May, there will be a brief Farewell Reception consisting of drinks. This reception is included with the registration of all in-person delegates.

Friday, 13 May • 16:00 - 16:30
Location: Westin Bayshore Foyer

Non-CME Symposia & Affiliate Meetings

Non-CME Symposia

Pierre Fabre (in-person & virtual)
We are proud to announce a non-CME symposium supported by Pierre Fabre:

"Beta-Blocker Treatments for Infants with Infantile Hemangiona: Update on Long-Term Developmental Outcomes" | *Chair: Julie Powell, MD (Montreal, Canada)*

Segmental facial hemangioma and propranolol treatment: developmental issues | *Olivia Boccara, MD (Paris, France)*
Long-term follow-up of children treated with propranolol or atenolol for infantile hemangioma: the results of Project Beta | *Suzanne G.M.A. Pasmans, MD (Rotterdam, Netherlands) & Mireille M. Hermans, MSc. (Rotterdam, Netherlands)*

Thursday, 12 May • 07:00 - 07:55
Location: Westin Bayshore • Salon F

Journal of Vascular Anomalies (*JoVA*) Meet & Greet

***Journal of Vascular Anomalies* (*JoVA*) Editorial Board Meet & Greet (in-person only)**
The Editorial Board of the Journal of Vascular Anomalies (JoVA) invites you to a meet and greet with them on Wednesday, 11 May 2022 from 7:30 - 7:55 Pacific Time in Salon F. This meeting will only be available to in-person attendees.

Affiliate Meetings

Vascular Anomalies Canada (in-person only)
Vascular Anomalies Canada is a patient advocacy group located in Canada and they will be hosting a meeting for their growing membership on Tuesday, 10 May 2022 from 13:00 - 13:30 Pacific Time in Salon F. This meeting will only be available to in-person attendees. For further information, please contact Dr. Philip John at philipjohn@eastlink.ca.

International Patient Advocacy Group Meeting (in-person only)
HEVAS and CLOVES Syndrome Community are offering a meeting for patient advocacy groups that are interested in the opportunity to meet and coordinate efforts. This meeting will occur Tuesday, 10 May 2022 from 19:00 - 20:30 Pacific Time in Salon F. This meeting will only be available to in-person attendees. For further information, please contact Caroline van den Bosch at C.vd.Bosch@hevas.eu or Noreen Fairley at noreen@clovessyndrome.org.

Vascular Anomalies Coordinator Meeting (in-person only)

Texas Children's Hospital will be hosting a meeting for vascular anomaly coordinators on Wednesday, 11 May 2022 from 16:00 - 18:00 Pacific Time in Salon F. This meeting will only be available to in-person attendees. For further information, please contact Darla Espinoza at djespino@texaschildrens.org.

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