

38TH ANNUAL MEETING
OF THE HISTIOCYTE SOCIETY
SEPTEMBER 18-20, 2022

STOCKHOLM

STOCKHOLM, SWEDEN AND ONLINE



WELCOME TO OUR HYBRID ANNUAL MEETING



Dear Colleagues,

It is with great pleasure that the Histiocyte Society welcomes you to Stockholm for its 38th Annual Meeting, from September 18-20, 2022. This year we are finally returning to an in-person meeting format! After pivoting to virtual-only formats in 2020 and 2021, this will be our first in-person meeting since 2019. Of course, as technology now makes it possible, for those who cannot be there in person, we have also offered a virtual attendance option. We look forward to seeing each and every one of you!

This year's program continues to offer the cutting edge of clinical and scientific advances related to the histiocytoses. Our program will feature symposia focused on HLH and LCH. The HLH symposium, titled "Expanding/refining our understanding of harmful immune activation" will examine HLH in contexts beyond familial HLH. The LCH symposium, "New Horizons for LCH", will focus on MAPK inhibition and the questions surrounding upfront and/or longer-term use. Since we last met in Stockholm in 2004, our field has advanced tremendously with new insights into disease pathogenesis and new, effective targeted therapies for all forms of histiocytoses. In 2004, we were honored to have Her Majesty Queen Silvia of Sweden join a portion of our meeting. This year, we are looking forward to another visit from Her Majesty. Fittingly, during the Queen's visit, we will host a special symposium focused on updates in HLH and LCH over the past two decades. Finally, YOU will be key ingredient for an exciting meeting. Not only your cutting-edge science, displayed in short talks and a poster session, but your presence after a long world-wide struggle with an unfortunate pandemic, will make our meeting a vigorous, joyous, and memorable one.

Our meeting will be held at the Grand Hôtel in downtown Stockholm, with pre-meeting sessions on Saturday and Sunday taking place at the Karolinska University Hospital.

We are beyond grateful to the City of Stockholm and Region Stockholm for welcoming us all to this beautiful city during our Welcome Reception taking place on Sunday night at Stockholm City Hall. City Hall is the location of the esteemed Nobel Prize banquets and will make for a wonderful backdrop for an exciting evening as we officially open the meeting.

A highlight of the meeting each year is the Annual Banquet. This year's banquet will be no exception as it will be held at the lovely Opera Terrace, so named for its prior location under Gustav III's opera house. Finally, on Monday night (after the poster session) there will be optional excursions available (pre-registration was required) to either the ABBA Museum or a dinner boat cruise around Stockholm. We hope you take advantage of all of these fun and exciting events!

As you know, a great deal of time, energy and resources go into planning the meeting each year. We are grateful to our long-term partner and sponsor, the Histiocytosis Association and our other sponsors, without whose generous support this meeting would not be possible. Finally, we are all grateful to our local host, Jan-Inge Henter and his team, for their tireless efforts to make this an excellent meeting.

Looking forward to seeing you all in Stockholm!

Sincerely,
Michael Jordan

A handwritten signature in black ink, appearing to read "M. Jordan".

President
Histiocyte Society

THANK YOU, CITY OF STOCKHOLM AND REGION STOCKHOLM

We would like to express our great appreciation to the **City of Stockholm** and **Region Stockholm** for their generous sponsorship of our 2022 Welcome Reception. The Welcome Reception will be taking place on Sunday, September 18, 2022 at the beautiful Stockholm City Hall, the esteemed location of the Nobel Prize Banquets.

Our delegation consists of over 160 in-person attendees from all around the world. Nearly 90% of our attendees stem from an impressive 25 countries outside of Sweden.

The Histiocyte Society is excited to meet again for the first time in nearly 3 years and are equally excited to be meeting in Stockholm. Researchers from Stockholm have made major clinical and scientific progress in the diseases that are the subject for this conference, and thereby saved thousands of lives, so we see Stockholm as a significant and meaningful location to once again come back together to share the latest research and activities in the world of histiocytosis and build connections that will begin with our Welcome Reception.

THANK YOU!



HER MAJESTY QUEEN SILVIA OF SWEDEN



We are honored to have Her Majesty Queen Silvia of Sweden join our meeting on Monday, September 19, 2022.

Photography: The royal family constantly has cameras aimed at them. Photography is allowed, but it should be done from a safe distance, not close by. Self-portraits together with royals with mobile cameras, so-called selfies, and the like are avoided. Visitors are therefore asked to inform the audience, participants or others present in advance to respect this in connection with photography.

Coffee Break: On Monday, September 19, please note that the first 20 minutes of the coffee break will be normal, however the last 10 minutes of the coffee break, everyone must be seated in the meeting room before Her Majesty enters.

Other: Be sure to listen for any additional direction that may be given regarding the visit of Her Majesty Queen Silvia.

THANK YOU TO OUR LOCAL ORGANIZERS

Much hard work and dedication has gone into making this meeting a success. We would like to particularly thank the local organizing team in Stockholm. This meeting would not be possible without their organization and coordination.

Local organizing committee:

Jan-Inge Henter (chair)
Désirée Gavhed (co-chair)
Tatiana von Bahr Greenwood, Magdalini Lourda, Nikolas Herold

Local supporting team:

Anette Langebäck	Nikolaos Tsesmetzis
Ingrid Lilienthal	Egle Kvedaraite
Hala Habash	Indranil Sinha
Frida Holm	Sabina Enlund
Agnes Sorteberg	Alexandra Löfstedt

ABOUT THE HISTIOCYTE SOCIETY

The **Histiocyte Society** is a professional medical association comprised of more than 240 physicians and scientists from around the world. Members of the organization are considered to be the leaders in understanding and treating histiocytic disorders. The Society is committed to advancing knowledge about histiocytic disorders and improving outcomes for patients through the planning, development, sponsorship and oversight of clinical research.

Building Knowledge

The Histiocyte Society hosts an annual scientific meeting in different locations around the world. Attendance is open to members of the Society as well as other professionals working in the field of histiocytic disorders and related studies. Meetings feature presentations of individual and collective research efforts as well as keynote lectures from guest speakers; special-interest groups convene to discuss and develop new and innovative treatment regimes. This interactive forum allows the best and brightest minds in the histiocytosis community to share the most progressive information and to shape the future of research. Beyond the prolific exchanges that occur during the meeting, presenters work collectively to extend their reach by publishing subsequent articles and manuscripts in scientific journals worldwide.

Advancing Treatment

Through extensive research and collaboration, the Histiocyte Society has made numerous, significant strides in the fight against histiocytic disorders. The Society has established scientific standards for histiocytic disorders that are accepted worldwide; they include: 1) A common language of uniform disease classification, 2) Standardized diagnostic criteria, and 3) Guidelines for patient evaluation and follow-up. The Society remains dedicated to facilitating essential and innovative clinical research – developing critical knowledge and increasingly effective treatments in the pursuit of a cure.

ANNUAL MEETING PROGRAM



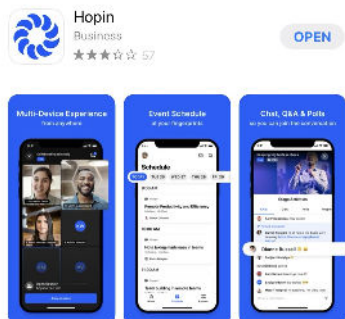
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2022 ANNUAL MEETING MOBILE APP/COMPUTER ACCESS



Downloading the Hopin mobile app will insure that you get the most out of your Annual Meeting experience. To download the app, simply go to your app store (available on iOS and Android), and download the app you see below. Once downloaded, you can log in and have access to everything that will be happening during the meeting. Alternatively, you can also access the online platform by using the following link: <https://hopin.com/events/hs2022mtg>

If you have questions while using the online platform or the mobile app, we will have tech support available. To access, simply navigate to the schedule and look for the Tech Support room. Once you enter, there will be someone there on screen to assist you.

HISTIOCYTOSIS ASSOCIATION AND HISTIOCYTE SOCIETY

Separate Organizations, One Goal



The Road to Partnership

Three-month old Bethany Toughill was diagnosed in 1983. Bethany's dad, Jeff, and her mother, Sally, experienced the same fear that today's parents feel when learning that their child has this disease. Alone and frustrated, Sally and Jeff were led to find other families affected by histiocytosis so that they could emotionally support each other. In 1986 they founded the Histiocytosis Association, a community comprised of patients, parents, family members and friends.

At about the same time that the Association was founded, a group of physicians formed the Histiocyte Society – an international group of clinicians and scientists committed to improving the lives of patients with histiocytic disorders by conducting clinical and laboratory research into the causes and treatment of this disease. Recognizing that these two groups had the same goal, Histiocytosis Association Founder Jeffrey Toughill offered the Association's business resources to help manage the Histiocyte Society. Thus began the partnership that still exists today.

A True Partnership

The Histiocytosis Association and the Histiocyte Society remain separate organizations working toward a common goal, with the Histiocytosis Association serving as the Society's administrative center (Secretariat) and primary source of funding. The Histiocytosis Association serves the administrative needs of the Histiocyte Society by:

- Organizing and managing the Society's annual scientific and Executive Board meetings,
- Managing the overall organizational, administrative and financial operations,
- Aiding in the development of organizational guidelines and operating procedures,
- Building, developing and maintaining the organization and annual meeting websites,
- Facilitating communication between Society members and the Executive Board, and
- Building and managing the Society's membership database.

The Histiocytosis Association Mission

The Histiocytosis Association is dedicated to raising awareness about histiocytic disorders, providing educational and emotional support for patients and families and funding research leading to better treatments and a cure.

The Histiocytosis Association Research Program

At the very heart of the Histiocytosis Association is the steadfast commitment to finding a cure for histiocytic disorders. The Histiocytosis Association is committed and focused on a threefold research plan and philosophy:

- Funding basic science research being conducted worldwide identified through a competitive, peer-review process modeled after that of the National Institutes of Health. The Histiocytosis Association requests research proposals on a yearly basis – usually around May. Once research proposals are received the Histiocyte Society Scientific Committee serves as the first-step review. Scores from this review are then submitted to the Histiocytosis Association's Medical & Scientific Advisory Committee (MSAC) for a second review. The SAC then makes a recommendation to the Histiocytosis Association's Board of Trustees concerning grants to be funded.
- Funding clinical studies that result in identifying the best possible treatments for histiocytic disorders.
- Facilitating research by administratively managing the Histiocyte Society.

Since 1992, nearly 200 individual awards have been made to date, representing more than \$7 million to support critical research around the world. Grant amounts now average \$50,000 per project but have been awarded in amounts up to \$100,000 in the past. The Histiocytosis Association of Canada (HAC) has provided \$265,000 of that funding.

Two Organizations, One Goal

The Histiocytosis Association and the Histiocyte Society have been committed partners for over 35 years. Though separate organizations, they share a common goal that binds their continued partnership - to find better treatments and, ultimately, a cure leading to a world free of histiocytic disorders.

To learn more about the Histiocytosis Association visit www.histio.org.

GUEST SPEAKER HIGHLIGHTS



Dr. Sabrin Albeituni graduated in Biology from Birzeit University, Palestine and earned her PhD in Microbiology and Immunology in 2015 from the University of Louisville, KY. She then pursued her postdoctoral training in the laboratory of Dr. Kim Nichols at St. Jude Children's Research Hospital in Memphis, TN. During her training she studied the mechanisms of JAK1/2 inhibition either alone or in combination with dexamethasone as a novel therapy for the treatment of HLH. She performed preclinical studies in murine models of HLH and found that the JAK1/2 inhibitor, ruxolitinib, ameliorates the clinical manifestations of disease in HLH through IFN-gamma dependent and independent mechanisms. Her work set the ground for a clinical trial that is being sponsored by St. Jude to use ruxolitinib for the treatment of HLH. Currently she is a Scientist in Dr. Nichols' laboratory, and her main research focus is to investigate the cellular and molecular mechanisms governing the pathogenesis of HLH. In addition, she is working on finding novel targets to dampen inflammation in HLH.

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Dr Oussama Abl is a Professor of Pediatrics at the University of Toronto and a pediatric oncologist at the Hospital for Sick Children in Toronto. He is the founder and Co-Director of the Pediatric Histiocytosis Program and a member of the Leukemia/Lymphoma section at the Hospital for Sick Children. His clinical and research interests focus on better understanding of the optimal treatment of Rare Histiocytic Disorders (RHD) especially Rosai-Dorfman disease, pediatric Langerhans cell Histiocytosis, acute promyelocytic leukemia (APL) and rare non-Hodgkin's Lymphomas. He is the Co-Editor of the "Histiocytic Disorders" textbook, the Principal Investigator of the International Rare Histiocytic Disorders Registry (IRHDR) and the Canadian national coordinator of the LCH-IV Trial. He was the Chair of the Histiocyte Society-Rare Histiocytic Disorders Steering Committee for 10 years and currently remains as a member of this committee and served for two terms as a member of the Histiocyte Society-Education Committee. His other interests include promoting educational materials on LCH, RHDs and APL. Dr Abl has co-authored more than 120 publications and book chapters focused on pediatric histiocytoses and leukemia/lymphoma. He is also the founder and Co-Chair of the Asian-Middle Eastern (AME) Histiocytosis Network.

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Carl Allen, Professor of Pediatrics at Baylor College of Medicine, Co-Director of the Lymphoma and Histiocytosis Programs, along with his research group, focuses on clinical and translational research efforts to develop and test improved therapeutic strategies for children with histiocytic disorders, lymphoproliferative disorders and lymphomas. As Director of Research for Global HOPE, he is also working with colleagues to develop and deploy capacity-building initiatives for care of children with cancer and blood disorders in Sub-Saharan Africa. His overall professional goal is to improve outcomes for children with cancer and blood disorders by addressing areas of greatest unmet need through innovative research, collaboration and mentorship.

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Ulf Anderson has served as a pediatrician in Stockholm since 1974, mainly as a pediatric rheumatologist. In parallel he performed basic studies in inflammation and immunology at Stockholm University and the Karolinska Institute. His PhD project, defended in 1982, dealt with ontogeny studies of human lymphocyte functions. He then focused on cytokines, alarmins and interactions between the central nervous system and the immune system. His major scientific contributions: a) inventor of globally used cellular methods enabling quantification of individual cytokine/ chemokine-producing cells by flow cytometry or imaging technology (Immunol Rev 119:65, 1991); b) co-discoverer with Kevin Tracey in New York of the central role of extracellular HMGB1 as the prototypical alarmin molecule (Science 285:248, 1999); spent 25 years on studies of HMGB1 biology aiming to identify means to target HMGB1 in pathological inflammation; identifying HMGB1 as a neurotransmitter released from nociceptors directing inflammation (PNAS 118:e2102034118, 2021); c) explorative studies together with Kevin Tracey during the latest two decades on the the cholinergic anti-inflammatory pathway (Annu Rev Immunol 30:313, 2012). Extracellular HMGB1 promotes inflammation, while acetylcholine prevents HMGB1 release and inhibits inflammation. Vagus nerve stimulation, via invasive or non-invasive methods, thus offers exciting novel clinical opportunities to control challenging inflammatory diseases (J Intensive Med. doi.org/10.1016/j.jointm.2022.02.001, 2022).



GUEST SPEAKER HIGHLIGHTS



Petter Brodin is Professor of pediatric immunology at Imperial College London and at Karolinska Institutet in Stockholm, Sweden. The Brodin lab (<https://brodinlab.com/>) develops and applies novel experimental and computational methods to describe human immune system variation with a particular interest in the immune systems of children, its development early in life, and its role in health and disease during childhood. After completing a MD/PhD program at the Karolinska Institutet, Brodin joined the Mark M Davis's laboratory at HHMI, Stanford University School of Medicine as a postdoctoral fellow, investigating the contribution of heritable and non-heritable sources of variation in immune systems of twins (Brodin et al, Cell, 2015). Following this, Brodin returned to Sweden to establish a national facility for immunomonitoring at the Swedish infrastructure hub, Science for Life Laboratory. He also established his own research program applying systems-immunology methods to the study of immune system development early in life. The Brodin lab established a birth cohort and showed differences in early life adaptation between preterm and term infants (Olin et al, Cell, 2018), the global repertoire of maternal antiviral antibodies (Pou et al, Nat. Med, 2019) as well as the imprinting effect of select colonizing microbes such as bifidobacterial early in life (Henrick et al, Cell, 2021). The Brodin lab has also applied its technologies for systems-level immune system analysis during the COVID-19 pandemic to understand COVID-19 in children (Brodin, P, Immunity 2022), the immunology of MIS-C (Consiglio et al, Cell, 2020), LongCOVID (Brodin et al, Nature Medicine, 2022), and severe COVID-19 (Rodriguez et al, Cell Reports Med, 2020) and are active members of the global COVID-Human Genetic Effort (<https://www.covidhge.com/>).

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Joe Carcillo will be presenting a talk entitled Hyperferritinemic Sepsis and Multiple Organ Dysfunction Syndrome during the HLH Symposium.

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Matthew Collin is Professor of Haematology at Newcastle University and Newcastle Upon Tyne Hospitals. He received a PhD in 1992 and graduated in Medicine in 1995 from Oxford University. His research focuses the role of human monocytes, macrophages and dendritic cells in immunity and disease. He is a Wellcome Trust Senior Investigator and is funded by the MRC, Histiocytosis Association, Bright Red, and Histo UK.

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Dr. Eli Diamond is an Associate Attending Neuro-Oncologist at Memorial Sloan Kettering Cancer Center. He is the Chair of the Rare Histiocytic Disorders Steering Committee of the Histiocyte Society and a member of the Board of Trustees of the Histiocytosis Association and Chair of the Science Committee of this Board. His clinical practice and research focus on the treatment of adults with various histiocytic neoplasms, with additional focus upon neurologic manifestations of disease. He is an NIH-funded principal investigator whose research spans molecular pathogenesis, therapeutics, symptomatology, and caregiver needs.

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Jean Donadieu, MD, PhD, is a pediatrician, Hemato oncologist and epidemiologist. After a fellowship in the pediatric immunology unit of Necker hospital, Paris (Pr Griscelli, Pr Fischer), appointed as pediatrician in the hemato oncologic department of Trousseau Hospital, Paris. Coordinator of the French histiocytosis registry since 1993 and coordinator of the pediatric branch of the French histiocytosis reference center. Authors of 97 papers in the field of histiocytosis till now. Former coordinator of the Euro histio net networks. Presently, member of the board of the European consortium for histiocytosis. In medicine, adept of evidence based medicine. In histiocytosis, hope to contribute to a global vision of the subject and a global management of the patients.

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Dr. Julien Haroche is a professor in internal medicine, at Pitié-Salpêtrière hospital, Paris, France. Since 2003, his main research field is Erdheim-Chester disease (ECD) upon which he has acquired a world-renowned experience. To date, he has seen more than 380 patients followed at his institution. His other research fields are the other histiocytoses, such as Langerhans cell histiocytosis, mixed histiocytoses (LCH & ECD) and Rosai-Dorfman disease. He is also interested in vasculitis, systemic lupus and antiphospholipid syndrome. During the past 15 years, he has described most relevant clinical and radiological aspects and increased the awareness of ECD; he has showed that interferon α was a first line efficient therapy. His team was the first to use targeted therapies in adult patients with histiocytoses in 2012. Since then more than 175 patients have received BRAF and/or MEK inhibitors at his institution.

GUEST SPEAKER HIGHLIGHTS



Jan-Inge Henter earned an MD from Uppsala University 1980 and after internship in Uppsala he completed a fellowship in Pediatrics in Stockholm 1987. In 1990 he defended a PhD-thesis at the Karolinska Institutet with focus on hemophagocytic lymphohistiocytosis (HLH). He is specialized in Pediatric Hematology and Oncology, and Professor at the Karolinska Institute since 2004. He was Principal Investigator of the international HLH-94 and HLH-2004 studies. He also studied underlying biological and genetic defects in HLH. Another main interest is secondary forms of HLH. He has also interests in many other fields in medicine, including Langerhans cell histiocytosis as well as End-of-Life Care. He has received numerous prizes and co-authored more than 250 publications. He was President of the Histiocyte Society 2004-2007, and Founding President of the International Conference for Rare Diseases and Orphan Drugs (ICORD). During 2012 – Sept 2017 he was Director of Research and Education of the Karolinska University Hospital in Stockholm, Sweden. He describes himself as a curious and enthusiastic explorer of the World, and everything in it.

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AnnaCarin Horne MD, PhD is a pediatric rheumatologist with an interest in immune dysregulation, hyperinflammation and neuroinflammation. She earned her MD from Lund University and completed her clinical training at the Karolinska University Hospital, Stockholm, Sweden. Currently she is a senior consultant at the Karolinska. AnnaCarin defended her PhD-thesis at the Karolinska Institute with focus on hemophagocytic lymphohistiocytosis (HLH). Her interest and research activities have remained mainly within this syndrome.

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Caroline Hutter will be speaking during the LCH Education Session on Sunday, September 18.

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Dr. Ashish Kumar is a physician-scientist at Cincinnati Children's Hospital Medical Center, and Professor of Pediatrics at the University of Cincinnati College of Medicine in the division of Bone marrow transplant and Immune Deficiency. At Cincinnati Children's, he is the co-director of the Histiocytosis Center, and director of the fellowship training program in pediatric hematology-oncology.

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Dr. Rebecca Marsh is a Professor of Clinical Pediatrics affiliated with the University of Cincinnati and an Immunologist and Bone Marrow Transplant Physician at Cincinnati Children's Hospital. She is Co-Director of the Diagnostic Immunology Laboratory, Director of the Primary Immune Deficiency Program, and Clinical Director of the HLH Center of Excellence at Cincinnati Children's Hospital. Dr. Marsh's clinical and research interests center around HLH, XIAP deficiency, inborn errors of immunity, and allogeneic hematopoietic cell transplantation for patients with inborn errors of immunity.

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Dr. Kevin McNerney is a pediatric hematologist-oncologist and specializes in blood and marrow transplantation at the Johns Hopkins All Children's Hospital Cancer & Blood Disorders Institute and is an Assistant Professor at Johns Hopkins School of Medicine. Dr. McNerney earned his medical degree from the Geisel School of Medicine at Dartmouth in Hanover, New Hampshire. He completed a categorical pediatric residency from Yale New Haven Hospital in New Haven, Connecticut, followed by a fellowship in pediatric hematology-oncology and an advanced fellowship in pediatric cancer immunotherapy and bone marrow transplant from Children's Hospital of Philadelphia (CHOP). He has a master's degree in Translational Research from the University of Pennsylvania and completed the Cell and Gene Therapy clinical training program at University of Pennsylvania and the CHOP. Dr. McNerney's clinical and research interests include hematopoietic stem cell transplantation for hematologic cancers including B-acute lymphoblastic leukemia, acute myeloid leukemia, refractory lymphomas, and the application of cellular immunotherapies such as chimeric antigen receptor (CAR) T-cells in the treatment of relapsed and refractory childhood malignancies. His recent projects have focused on identifying groups with increased inflammatory toxicities and poor outcomes following CAR T therapy.

GUEST SPEAKER HIGHLIGHTS



Dr. Milen Minkov, M.D., Ph.D. is currently full professor for specialized pediatrics at the Sigmund Freud University, Head of the Clinic of Pediatrics and Adolescent Medicine at Clinic Floridsdorf of the Vienna Healthcare Group, as well as, Consultant for Pediatric Hematology and Chair of the International LCH Study Reference Center at St. Anna Kinderkrebsforschung, Children's Cancer Research Institute in Vienna, Austria. Dr. Minkov graduated with honors from the Russian State Medical University, Moscow, in 1991 and completed his residency and fellowship in pediatrics and pediatric hematology (1991-1995) at the Russian Federal Institute for Pediatric Hematology in Moscow. His medical training at the Faculty of Pediatrics of the State Medical University in Moscow and the residency in general pediatrics in large central hospitals of the Russian Federation gave him an encounter to rare diseases and a pediatric training unique in its breadth and depth. Professor H. Gadner in the internationally renowned St. Anna Children's Hospital in Vienna trained him in pediatric hemato-oncology (1995-2000). This particular field of pediatrics became the focus of his further clinical and scientific career. In his professional career since 1991, Dr. Minkov provided clinical care, supervised trainees, conducted clinical research at the Children's Cancer Research Institute, and was PI of several international trials. He has been actively teaching and mentoring medical students at the Medical University of Vienna since 1997 (Assistant Professor 1997-2007, Assoc. Professor 2007-2012, and Professor of Pediatrics since 2012). Since 2012, he has been a mentor at the Open Medical Institute of the American-Austrian Foundation. In 2017, the Sigmund Freud University in Vienna appointed him a full professor for specialized pediatrics. Dr. Minkov's clinical experience covers the full spectrum of pediatric hematology/oncology. His research has been focused on LCH and other histiocytoses. His scientific treatise encompasses over 100 peer-reviewed papers, six book chapters, contributions to clinical guidelines, and consensus papers. Dr. Minkov was in 1997 the first recipient of the Mark Nesbit Award for Clinical Science of the Histiocyte Society. For his merits, he was awarded the title "honored professor" of the Federal State Research Center of Pediatric Hematology, Oncology, and Immunology in Moscow in 2016. He was president of the Histiocyte Society 2016-2019 and is currently president of the European Consortium for Histiocytosis (ECHO). He is a member of several professional societies and networks and a medical advisor of patient and parent organizations.



Dr. Kim Nichols is a Full Member in the Department of Oncology at St. Jude Children's Research Hospital, where she serves as Director of the Division of Cancer Predisposition and active member of the Histiocytosis and Immune Dysregulation Treatment Team. Dr. Nichols' clinical and research interests focus on better understanding the molecular and cellular mechanisms underlying HLH and related disorders of the immune system and using this information to develop new and more effective therapies. Dr. Nichols has been a longstanding member of the Histiocyte Society, and she currently serves as Chair of the HLH Steering Committee, member of the Executive Board and President Elect of the Society.



Brooks Scull has been the Laboratory Director of the Texas Children's Cancer Center Histiocytosis Program at Texas Children's Hospital and Baylor College of Medicine in Houston, Texas for the past 10 years. His work has included large scale proteomic and biomarker studies of Langerhans cell histiocytosis (LCH), hemophagocytic lymphohistiocytosis (HLH), and pediatric Hodgkin lymphoma. He has also investigated the gene expression profile of HLH and alternative BRAF mutations of LCH. He is currently working to develop mouse models of myeloid and monocyte derived disorders for pre-clinical testing of therapeutic strategies.



David T Teachey, MD is a Professor of Pediatrics at the University of Pennsylvania Perelman School of Medicine and attending physician in the Division of Oncology at the Children's Hospital of Philadelphia. He is a laboratory-based physician scientist with a strong translational research focus in acute lymphoblastic leukemia and disorders of immune dysregulation.



Dr. Astrid van Halteren completed her master degree in Biomedical Sciences at the University of Amsterdam in 1991. After defending her PhD thesis in 1996 (Vrije Universiteit Amsterdam), she moved to the Leiden University Medical Center (LUMC), where she started to work in the hemato-oncology field before being introduced to histiocytosis in 2008. As a certified specialist in immunology, she became intrigued by the inflammatory component of histiocytosis lesions. Her research team has investigated characteristics of lesional T-cells, co-published on newly identified driver mutations, studied intracellular processing of neoantigens encoded by the most prevalent molecular alteration (BRAF^{V600E}) and recently completed a multi-centre study addressing associations between the three most common mutations and clinical presentation of pediatric LCH. Two abstracts presenting the results of these studies have been nominated by the Histiocyte Society for the Nezelof Prize for best Basic Science (2015) and the Nesbit Prize for Best Clinical Science (2019). As of August 2022, she will be affiliated with the Centre for Histiocytic Disorders established at the Erasmus University Medical Center in Rotterdam, which is acknowledged by the ECD Global Alliance and the Dutch Federation of University Medical Centers. In this new position, she will implement molecular monitoring and central biobanking in conjunction to the diagnosis and treatment of adult histiocytosis patients. She will also continue her research on the hematopoietic 'cell-of-origin', which is performed in close collaboration with the Princess Máxima Centre for Pediatric Oncology where she is appointed as co-PI.

GUEST SPEAKER HIGHLIGHTS



Dr. Brigitte Widemann oversees and active basic, translational and clinical research program for children and young adults with hematologic and solid malignancies s chief of NCI's POB. Dr. Widemann joined the NCI in 1992 as a pediatric hematology oncology fellow after having obtained her MD and completed pediatric residency at the University of Cologne in Germany. Her research has been focused on drug development and early clinical trials for children with refractory solid tumors or genetic tumor predisposition syndromes, in particular neurofibromatosis type 1 (NF1). The work of her research team on NF1 resulted in the first U.S. Food and Drug Administration approved medical therapy, the MEK inhibitor selumetinib, for children with NF1 and inoperable, symptomatic plexiform neurofibroma. She received tenure at the NIH in 2009 and became the Chief of the POB in 2016. Dr. Widemann is a member of the Association of American Physicians and recipient of the AACR-Joseph H. Burchenal Award for Outstanding Achievement in Clinical Cancer Research. She has authored more than 200 original scientific papers, reviews, and book chapters, and has conducted many clinical trials.



Matthias Wilk graduated from the University of Duesseldorf School of Medicine (Germany). Throughout his residency and clinical fellowships at the University Hospitals in Duesseldorf (Germany) and Zurich (Switzerland), Matthias was dedicated to experimental research in Hematology in addition to his clinical curriculum. Amongst others, Matthias studied the impact of Clonal Hematopoiesis on Long-Term-Survivors of Allogeneic Hematopoietic Stem Cell Transplantation and approaches to repurpose TPO agonists as chemosensitizers in Hematopoietic Stem Cell Transplantation. He also co-developed a humanized mouse model for Langerhans Cell Histiocytosis (LCH) that allows studying human LCH in a murine model suitable for drug testing. Fascinated by histiocytic disorders, Matthias then joined the laboratory of Miriam Merad at the Icahn School of Medicine at Mount Sinai in New York. In collaboration with the team of Carl E. Allen at the Texas Children's Hospital in Houston, he is studying Neurodegenerative Disorders in LCH. Therefore, he developed different mouse models for histiocytic disorders that recapitulate key features of human neurodegenerative LCH. The models he developed do not only permit studies on the pathogenesis of neurodegenerative LCH but also allow testing therapeutic approaches for this condition.



**SPECIAL SCIENTIFIC SESSION WITH HER MAJESTY QUEEN SILVIA:
PROGRESS AND CHALLENGES IN HISTIOCYTIC DISORDERS**

Carl Allen
Petter Brodin
Jan-Inge Henter

PATHWAYS TO RATIONALE CURE(S) FOR PATIENTS WITH LCH

Carl Allen
Baylor College of Medicine, Texas Children's Cancer and Hematology Centers, Houston, TX USA

The Histiocyte Society was formed in 1985 by 15 inaugural members inspired by their patients to identify rationale cures for children and adults suffering with histiocytic disorders. Over the past century, clinicians and pathologists noted patterns of disease and histologic findings now recognized as Langerhans cell histiocytosis (LCH). Patients develop granulomatous lesions with characteristic CD207+ dendritic cells that can arise as single lesions or life-threatening disseminated disease. Despite the wide range of clinical presentations, LCH lesions are histologically indistinguishable based on severity of disease, leading to historically uncertain classification as an immune versus neoplastic disorder. Heroic efforts by the Histiocyte Society supported international trials that tested front-line chemotherapy agents, intensity and duration of therapy, and clinical risk-stratification that now define global standard of care. Over the past decades, scientific breakthroughs have identified clonality, MAPK activation, ontogeny and senescence as fundamental features of LCH. Ongoing research efforts supported by the Histiocyte Society and its "progeny" organizations strive to identify a rationale cure for every patient, an foundational aspiration that is now an achievable goal.

IMMUNE SYSTEM REGULATION AND DYSREGULATION IN COVID-19 AND RELEVANT TREATMENTS

Petter Brodin
Karolinska Institutet, Stockholm, Sweden

Professor Brodin will discuss the different disease presentations described following SARS cov2 infection in humans, what is currently known about their molecular basis and mechanisms. He will also discuss possible ways of targeting these diseases by immunomodulation.

PROGRESS AND CHALLENGES IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Jan-Inge Henter^{1,2}
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Hemophagocytic lymphohistiocytosis (HLH) represents a clinical syndrome when the immune system runs amok and causes uncontrolled hyperinflammation that becomes self-damaging and often fatal. Progress on HLH has been fantastic over the last decades, both clinically and biologically. This refers in particular to primary HLH (pHLH), Mendelian inherited affecting mainly children, but increasingly also to the non-Mendelian secondary HLH (sHLH) affecting mainly adults. In the early 1980s, even the most common pHLH, familial HLH (FHL), was almost unknown and with 100% often rapid mortality. Now we know that FHL is one of the most frequent inherited fatal immunodeficiencies, caused by defect cytotoxic lymphocytes (natural killer cells/cytotoxic T cells) with deficient production of perforin or deficient degranulation of perforin-containing vesicles resulting in defect killing of their target cells. Actually, FHL taught the medical community how downregulation of the immune system works! Treatment of FHL includes first an initial therapy aiming to reduce the hyperinflammation followed by stem cell transplantation aiming to replace the immune system. International clinical studies (HLH-94/HLH-2004), including >20 countries each, have both shown around 90% survival after 2 months with the drugs etoposide and dexamethasone. Interestingly, etoposide promotes programmed cell death (apoptosis) rather than proinflammatory lytic cell death (pyroptosis), conceivably ameliorating subsequent systemic inflammation. Another drug with impressive pre-transplant survival is alemtuzumab. While the post-transplant survival in HLH-94/HLH-2004 was 48-56%, there are now reports of ≥90% survival, such as with less toxic conditioning (RIC), suggesting that with early transplant an overall long-term survival ≥80% is possible. Remaining challenges in pHLH include earlier diagnosis, refined treatment (maybe by stratification and combining current and novel therapies), and spreading best-practice world-wide. Secondary HLH is much more common than pHLH and likely caused by a combination of endogenous and exogenous components; most often triggered by severe infections, neoplasms, and systemic rheumatic disorders. The fatality is high if untreated. Unfortunately, diagnosis (and treatment) is often delayed, if at all recognized. Treatment concepts for sHLH in adults have been imported from pediatrics, and then adapted such as using lower and less frequent doses of etoposide, and with shorter treatment duration, or even only steroids in moderate cases. In all, many thousands of sHLH patients have now survived thanks to anti-inflammatory HLH treatments. The knowledge on hyperinflammation and HLH is rapidly expanding. HLH has been reported in numerous conditions as dengue fever, pandemic influenza, and many others. HLH is rare in COVID-19 but the first drug approved for COVID-19, dexamethasone, is since long a cornerstone in the treatment of hyperinflammation/HLH. Remaining challenges include how to diagnose sHLH early and adapt treatment to the various forms of sHLH.

**HLH SYMPOSIUM:
EXPANDING/REFINING OUR UNDERSTANDING OF HARMFUL IMMUNE ACTIVATION**

Ulf Anderson
Joe Carcillo
David Teachey

**THE OUTCOME OF MACROPHAGE ACTIVATION SYNDROME IS DETERMINED BY THE INTERPLAY BETWEEN MODE OF
CELL DEATH, HMGB1, AND ACETYLCHOLINE**

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Macrophage activation syndrome (MAS) constitutes one subtype of HLH with underlying autoimmune/autoinflammatory conditions. The central cause is due to impaired granule-mediated cytotoxicity exerted by natural killer (NK) cells and T lymphocytes, meant for elimination of virus-infected cells, malignant cells and to prevent exaggerated immune responses. The normal outcome after a cytotoxic immune cell attack is apoptosis in the target cell, but if the intervention fails the mode of cell death will be lytic with release of potent proinflammatory mediators named damage-associated molecular pattern molecules (DAMPs). Etoposide is a chemotherapeutic compound that induces apoptosis in activated and transformed cells and is thus used to convert lytic to apoptotic cell death in target cells in both primary and secondary forms of HLH.

Programmed proinflammatory lytic cell death, pyroptosis, caused by activated inflammasomes is central for the creation of the cytokine storm in MAS. Pyroptosis mediates IL-18 release, which robustly stimulates NK and T cells to produce IFN- γ , the key macrophage-activating signal, which initiates a burst of inflammatory cytokines and chemokines. Lytic cell death also mediates a discharge of the prototype DAMP, high mobility group box protein 1 (HMGB1), a nuclear molecule present in all cell types. When HMGB1 is extracellularly released in excess, it occupies a central functional role in the pathogenesis of MAS, to be further outlined in the oral presentation.

All organs are controlled by the central nervous system and the immune system represents no exception. The best so far studied inflammation-inhibiting mechanism is mediated by the cholinergic antiinflammatory pathway regulated by the vagus nerve system via acetylcholine release acting on $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7$ nAChR) expressed on many cell types including activated macrophages. Therapeutic opportunities offered by boosting this endogenous antiinflammatory system will be discussed.

HYPERFERRITINEMIC SEPSIS AND MULTIPLE ORGAN DYSFUNCTION SYNDROME

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The diagnosis of Hemophagocytic Lympho Histiocytosis or Macrophage Activation Syndrome is more common in children or adults who are non-critical in the outpatient or hospital setting with a history of predisposing chronic illness related to these conditions or if previously healthy with a history of persistent fever and progressive hepatosplenomegaly; however, in the emergency department and critical care settings the diagnosis of Hyperferritinemic Sepsis induced Multiple Organ Dysfunction Syndrome becomes prominent. In this session we will discuss human and rodent literature describing this third condition that commonly shares the 8 clinical criteria used to diagnose Hemophagocytic Lympho Histiocytosis and Macrophage Activation Syndrome and at autopsy shows non-malignant Hyperplastic Hemophagocytic Histiocytosis most commonly without any T cell or B-cell infiltration. We will review the adult, pediatric and animal data suggesting that this condition is not necessarily driven by interferon gamma nor T-cell mediated macrophage activation, but instead by free hemoglobin (CD163 mediated activation) related to blood transfusions and hypercomplementemia/endothelial activation mediated disseminated intravascular coagulation; and, by sequential exposure to virus followed by bacterial -antigens that cause aerobic glycolysis driven macrophage activation remediable with 2-deoxyglucose. We will show that children and adults can be diagnosed at the bedside with this condition on the basis of combined hepatobiliary dysfunction, disseminated intravascular coagulation, and hyperferritinemia and review Dr Kernan's provocative reports of *Inherited Errors of Immunity* pathogenic variants related to this clinical diagnosis. We will further discuss published and ongoing clinical trials testing use of plasma exchange, methylprednisone, IVIG, and Interleukin 1 receptor antagonist protein therapies in children and adults with this condition. In conclusion, we will highlight our newly commenced 1,000 patient PRECISE trial directed at pediatric sepsis patients with ferritin levels < 10,000, in which those with immune depression and ferritin levels < 2,000 are randomized to placebo or low dose GM-CSF x 7 days, whereas those without immune depression or with ferritin levels between 2,000 to 10,000 are randomized to placebo or Interleukin 1 receptor antagonist protein for 7 days.

HYPERINFLAMMATION, CYTOKINE RELEASE SYNDROME, AND HLH WITH CAR-T CELL THERAPY

David Teachey

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A number of novel immunotherapies, including chimeric antigen receptor T-cells (CAR-T) have revolutionized the treatment of several malignancies over the past decade. Patients treated with many of these immunotherapies can develop a cytokine storm syndrome termed cytokine release syndrome (CRS). While CRS is often mild, it can be life-threatening. Early reports by our group and others demonstrated that severe CRS clinically and biologically has significant overlap with hemophagocytic lymphohistiocytosis (HLH). Fortunately, most patients with severe CRS respond to treatment with cytokine blockade, using drugs such as the IL6R inhibitor tocilizumab. Tocilizumab has been shown not to impact the efficacy or persistence of CAR-T, leading to recent trials testing preventative strategies. As new CAR-T cell therapies have been developed, it has also been recognized that there are some biologic differences in the pathophysiology of CRS based on the antigen targeted, the disease treated and the patient population. Further, some patients can develop "late" CRS that has a different cytokine profile and is successfully managed in some cases with different targeted therapies, including the IL1R inhibitor anakinra. This seminar will review the biology, clinical presentation and treatment of CRS after CAR-T and other immunotherapies.

JON PRITCHARD LECTURE ON THE NIKOLAS SYMPOSIUM

PRITCHARD LECTURE 2022

Astrid van Halteren

Leiden University Medical Center, Leiden, The Netherlands

From May 12-15, Mr. and Mrs. Kontoyannis and their invited guests celebrated thirty years of the Nikolas Symposium during a highly interactive meeting in Athens, Greece. While the 2022 symposium also included a special session dedicated to clinical research performed by Greek histiocytosis experts, the major theme of the symposium was 'Neurodegeneration in LCH'. The organizers brought together expert clinicians and researchers to discuss the clinical aspects of neurodegeneration, including neuro-cognitive and behavior deficits, and the origin and function of myeloid-lineage derived cells, including microglia cells, that can be found in the brain under steady state or (experimental) pathological conditions. We also discussed several strategies for therapeutic intervention, which either aim at functional enhancement or regeneration of microglia and neurons in the context of Alzheimer's Disease. I will present the highlights of these inspiring talks.

LCH SYMPOSIUM: NEW HORIZONS FOR LCH

**Jean Donadieu
Ashish Kumar
Brigitte Widemann**

DABRAFENIB AND TRAMETINIB ARE EFFECTIVE FIRST LINE THERAPIES FOR PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS AND OTHER HISTIOCYTOSSES

Ashish Kumar

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Standard of care treatment for Langerhans Cell Histiocytosis (LCH) is conventional chemotherapy which unfortunately has high failure rates. Since most LCH cases are driven by activating mutations in the BRAF-MEK-ERK pathway, BRAF- and MEK-inhibitors have been used successfully in a few patients whose disease was refractory or relapsed after treatment. We describe 34 patients (26 LCH, 2 Juvenile Xanthogranuloma, 2 Rosai-Dorfman Disease, 4 presumed single site-CNS histiocytosis) treated at a single center with the BRAF inhibitor dabrafenib and/or the MEK inhibitor trametinib. Mutations directly activating the BRAF-MEK-ERK pathway were found in 26 patients. Sixteen patients aged 1.3-21 years had received chemotherapy before receiving the inhibitor, 9 of whom had multisystem LCH with risk-organ involvement and had progressed on therapy or relapsed. With a median treatment duration of 3.1 years, 15 (94%) have sustained favorable responses {12 No Active Disease (NAD) or NAD with residual diabetes insipidus (DI) and/or sclerosing cholangitis, 1 Active Disease Better (ADB)}. One patient with isolated CNS disease had stabilization. Eighteen patients (ages 0.2-45 years), received the inhibitor as first-line treatment. With a median treatment duration of 2.0 years, all have had sustained favorable responses. Three patients with presumed isolated CNS/pituitary-stalk histiocytosis demonstrated stabilization or improvement of disease. Overall, inhibitors were well tolerated, with rash being the most common adverse effect. Five patients with single system LCH discontinued therapy and remain off therapy without recurrence. Our experience demonstrates that patients with histiocytoses, including infants, can be treated safely, and effectively with dabrafenib or trametinib as first-line therapy.

MEK INHIBITORS IN PEDIATRIC ONCOLOGY AND RARE DISEASES: CURRENT ROLES AND FUTURE POSSIBILITIES

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RAS pathway activation through somatic or germline mutations in RAS pathway genes is present in many adult and pediatric cancers and genetic tumor predisposition syndromes. Substantial efforts to develop effective RAS pathway targeting agents are underway by academia and pharmaceutical industry. The MEK inhibitor selumetinib recently received regulatory approval for children with the RASopathy neurofibromatosis type 1 (NF1) and inoperable symptomatic plexiform neurofibromas. MEK inhibitors also demonstrate activity in other conditions including sporadic and NF1 associated low grade gliomas. The identification of recurrent MAPK pathway mutations in histiocytic disorders raises the prospect for therapies effectively targeting this pathway. I will review the status of the clinical development of MEK inhibitors (clinical trials, toxicities, activity) in pediatric oncology and highlight lessons learned from the clinical development of MEK inhibitors for NF1 related benign and malignant peripheral nerve sheath tumors.

CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES IN PATIENTS WITH HISTIOCYTIC NEOPLASMS HARBORING CLASS 3 MAP2K1 MUTATIONS, INCLUDING NOVEL TREATMENT WITH THE ERK INHIBITOR ULIXERTINIB

Eli L. Diamond¹, Marc Rosenblum¹, Mariko Yabe¹, Kseniya-Petrova-Drus¹, Jasmine H. Francis¹, Raajit K. Rampal¹, Mario E. Lacouture¹, Veronica M. Rotemberg¹, Vaios Hatzoglou¹, Robert Young¹, Gary A. Ulaner^{2,3}, Ryan Reddy¹, Omar Abdel-Wahab¹, and Benjamin H. Durham¹

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PURPOSE: The second most frequently mutated gene driving HN is MAP2K1, with broad responsiveness to MEK inhibition reported. The most common MAP2K1 variant observed is the exon 3 p.E102_I103 in-frame deletion, among the Class 3 MAP2K1 mutants predicted to be resistant to allosteric MEK inhibition. We present clinical and treatment characteristics of HN patients with Class 3 MAP2K1 mutations. **METHODS:** Patients with HN and p.E102_I103del or similar mutations were included. Sites of disease were captured. First- and later-line treatments were categorized as observation, chemotherapy, immune modulation, MEK inhibition (MEKi; trametinib/cobimetinib/binimetinib), or ERK inhibition (ulixertinib). Clinical and radiologic responses were captured as partial response (PR), complete response (CR), stable disease (SD) or progressive disease (PD) by PET/CT. **RESULTS:** 16 patients were identified. 8 (50%) were female, and median age at histiocytosis diagnosis was 31 (range 22-58). 10 patients had Langerhans cell histiocytosis (LCH), 4 had Erdheim-Chester disease (ECD), 2 had mixed histiocytosis. Most frequent sites of HN were bone (16; 100%), lymph node (8; 50%), brain (8; 50%), and skin/subcutaneous (4; 25%). Mutations were MEK1 p.E102_I103del (13; 81%), p.L101_I103delinsF (1; 6%), p.P105_I107delinsL (1; 6%), and p.I103_A106del (1; 6%). Of 11 patients treated with chemotherapy or immune modulation, 9 had CR/PR, 1 SD, 1 PD. 7 of these 9 with CR/PR/SD had subsequent progression. Of 8 patients treated with MEKi, 8/8 (100%) had CR/PR, however 4 (50%) had subsequent progression. 3 of these, plus one treatment-naïve patient, were treated with an oral ERK1/2 inhibitor, ulixertinib, on prospective protocols. 3 of 4 had clinical or radiologic CR/PR. **CONCLUSIONS:** HN with Class 3 MAP2K1 mutations represent a diverse spectrum of disease characterized by frequent bone, nodal and neurologic involvement, and poor responses to chemo/immunomodulatory therapy. This entity demonstrates resistance to MEKi in some patients, a phenomenon previously undocumented, and response to ERK inhibition.

NEURO FILAMENT AS A BIOMARKER OF NEURO DEGENERATION IN LCH : A COHORT BASED STUDY

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PURPOSE: To assess the relevance of Blood (plasma, serum) and Cerebro spinal fluid (CSF) Neurofilament light chain (NfL) as a biomarker to identify and to follow patients with Langerhans Cell Histiocytosis (LCH) and neuro degenerative (ND) features. **METHODS:** Blood and CSF NfL levels were assessed by using Single Molecule Array (Simoa) (Quanterix®) in patients included in the cohort of the French registry. Organ extension was defined according to the literature and previous publications. 9 patients, with ethnic neutropenia and 2 with unexplained central diabetes insipidus composed a control group. **RESULTS:** Interim analysis enrolled 93 patients with documented LCH (median age at diagnosis 2.1 years range 0- 19 years) with the following disease extent: 30 SS, 29 MS+RO- and 33 MS+RO+ 1 Lung+. The proportion of patients with ND features, Neuro tumoral features and Pituitary involvement was 32%, 9% and 35% respectively. B RafV600E variant was detected in 48 patients (72%), absent in 19 (28%). A total of 133 blood and 33 CSF NfL dosages were performed. Sequential blood dosage was performed in 34 patients and sequential CSF dosage in 6. No evident correlation was observed between CSF and blood level. Median (min-max) NfL blood level was 6.53 (0.5 -219) pg/ml in patients and 4.3 (1.4 -7.6) pg/ml in controls. NfL CSF level was 319 (28-2841) pg/ml in patients contrary to 85 pg/ml in the sole control with central idiopathic DI. Preliminary analysis suggests that ND patients compare to patients without, displays a higher blood NfL level (median value 8.9 vs 5.3 pg/ml) and CSF NfL level (377 vs 118 pg/ml) (wilcoxon test < 0.001). **CONCLUSION:** Both blood and CSF NfL level appeared to be a interesting biomarker to identify ND LCH. Additional data and analyses with longitudinal follow-up remain necessary to validate such biomarker in LCH.

MORE THAN JUST LCH: THE DIAGNOSIS AND CLINICAL SIGNIFICANCE OF MIXED HISTIOCYTOSIS

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PURPOSE: Mixed histiocytosis (MH) is defined as the synchronous or metachronous occurrence of lesions with Langerhans cell histiocytosis (LCH) and/or non-LCH morphological and immunohistochemical features in the same patient. We aim to review the literature dealing with MH and propose a clinical classification. **METHODS:** We analyzed 105 patients and divided them into three groups. **RESULTS:** Type-1 MH included previously untreated adult patients with MS presentation, and synchronous or metachronous LCH and NLCH lesions. Erdheim-Chester disease (ECD) was diagnosed in 77% of cases. Osteosclerotic bone lesion, neurodegeneration, and diabetes insipidus were frequently observed and 89% of cases were BRAF-mutated. Two patients had an associated myeloid malignancy. Most patients experienced a PR or an SD. Four patients died of disease-related causes (14%) within a median of 7-months. Type-2 MH is represented by pediatric LCH patients developing juvenile xanthogranuloma (JXG) lesions after systemic chemotherapy. 90% displayed MS involvement. Bone lesions showed LCH histopathology in 76%, whereas most skin lesions showed NLCH infiltrates only (57%). BRAFV600E mutation was found in 80% of cases. In many patients, cutaneous JXG lesions remained stable or increased in number during the follow-up. Type-3 MH grouped patients presenting with single lesions characterized by LCH infiltrates in association with areas of NLCH. The median age at presentation was of 3-years and most patients developed single cutaneous lesions. A Rosai-Dorfman disease component was present in 79% of cases. 1/3 type-3 MH tested patients resulted BRAFV600E-mutated. 42% of patients achieved CR, after surgical excision. The sub-classification we proposed allows us to distinguish patients with different clinical histories, disease burdens therapeutic needs and outcomes. In all the three groups, the molecular data support the concept of a single clonal disorder with heterogeneous manifestations, despite the co-occurrence of two unrelated histiocytic diseases.

NOTCH DEPENDENT CROSS-TALK BETWEEN DC2 AND DC3/ MONOCYTE LINEAGES PROMOTE PATHOGNOMONIC LCH PROGRAM

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Langerhans cell histiocytosis (LCH) is a potentially fatal neoplasm, stemming from the mononuclear phagocyte (MNP) system. Our knowledge of LCH origin and pathogenesis, and thus the development of effective therapies, are hampered by an inability to proficiently discriminate neoplastic cells from normal MNPs at single-cell resolution. Here, we used single-cell RNA-seq and protein analysis to decipher LCH lesions, assessing LCH cell heterogeneity, comparing them to normal MNPs within tumor. We found LCH-discriminatory signatures pointing to senescence and escape from tumor immune surveillance. We also uncovered two major lineages of LCH with DC2- and DC3/Monocyte-like phenotypes, which high-content imaging detected across different pathological tissue sites. Our results present a dual origin model of LCH cell development with an underlying neoplastic "hit" occurring prior to fate commitment to DC2 and DC3/Monocyte lineages. Moreover, using receptor-ligand analyses in LCH lesions in combination with HLA-A2 based lineage tracing in vitro we detect NOTCH dependent cross-talk between DC2 and DC3/monocyte lineages, and its capacity to promote the pathognomonic LCH program. Together these data demonstrate lineage convergence in neoplastic transformation of MNPs and describe lineage cooperation in gaining LCH program.

ABSTRACTS NOMINATED FOR THE NEZELOF AWARD IN BASIC SCIENCE:

IMPACT OF IMMUNOPROTEASOME INHIBITION IN PRECLINICAL STUDIES OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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PURPOSE: Primary hemophagocytic lymphohistiocytosis (pHLH) comprises a group of severe hyperinflammatory disorders associated with germline loss-of-function variants affecting PRF1, UNC13D, STX11 and STXBP2 - genes essential for perforin-dependent cytotoxicity. Consequently, humans and mice with pHLH exhibit reduced or absent lymphocyte killing. This killing function is critical for normal immunoregulation, as is evident in perforin-deficient mice, where failure of CD8 T cells to eliminate activated antigen-presenting cells leads to prolonged and excessive T cell activation and cytokine production. The immunoproteasome plays essential roles in processing and presentation of antigens and associated immune effector cell functions. We thus hypothesized that immunoproteasome inhibition might lessen inflammation in HLH. **METHODS:** To test this hypothesis, we developed an in vitro model of HLH in which splenocytes from P14 mice (which carry a T cell receptor specific for the Lymphocytic Choriomeningitis virus (LCMV) gp33 peptide) were labelled with carboxyfluorescein succinimidyl ester, pulsed or not with the immunoproteasome inhibitor ONX-914, and infected with LCMV. Subsequently, we measured LCMV-specific T cell proliferation and cytokine production. To examine the effects of immunoproteasome inhibition in vivo, LCMV-infected perforin-deficient mice were treated with KZR-616 (zetomipzomib; an immunoproteasome inhibitor optimized for in vivo use) on varying days post-infection. On days 8-9, we examined immune cell subsets, serum cytokine levels, and lymphocytic tissue infiltration. **RESULTS:** Immunoproteasome inhibition significantly reduced in vitro antigen-specific CD8 T cell proliferation and interferon-gamma (IFN γ) production and did so in a dose-dependent manner. Untreated LCMV-infected animals developed organomegaly with increased T cells, neutrophils, and serum IFN γ levels. Each of these parameters was significantly diminished following zetomipzomib treatment. Upon ex vivo antigen stimulation, CD8 T cells from zetomipzomib-treated mice exhibited significantly decreased IFN γ production. **CONCLUSION:** Immunoproteasome inhibition represents a rational and potentially beneficial therapeutic strategy for HLH. Studies are ongoing to optimize the effects and decipher the underlying mechanisms.

MYELOID PROGENITORS DEFINE EXTENT OF DISEASE IN MOUSE MODELS OF HISTIOCYTIC DISORDERS: BRAFV600E EXPRESSION IN MONOCYTE LINEAGE RECAPITULATES ERDHEIN-CHESTER PHENOTYPE

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PURPOSE: Langerhans cell histiocytosis (LCH) is a myeloid neoplastic disorder characterized by activating mutations in BRAFV600E or other MAPK pathway genes, with a wide spectrum of clinical presentations. In order to test the impact of cell of origin on disease phenotype, we developed mouse models in which BRAFV600E is enforced at distinct stages of differentiation with Cre-inducible models that enforce expression of BRAFV600E. ITGAX/CD11c is expressed across a range of myeloid dendritic cell and monocyte lineages where MS4A3 is expressed exclusively in monocytes and monocyte-derived cells. **METHODS:** BRAFV600E expression was enforced through Cre-mediated recombination to create BRAFV600ECD11c and BRAFV600EMS4A3 mice. Mice were analyzed at weeks 5, 10, 25, and 52 for body and organ weights and histology. Tissues were characterized by immunohistochemistry, gene expression, Luminex, CYTOF and RNASeq. **RESULTS:** BRAFV600ECD11c mice exhibited a more aggressive phenotype than BRAFV600EMS4A3 counterparts, though both developed diffuse histiocytic infiltration. Kinetics of organomegaly, histiocytic infiltration, and systemic inflammation was much slower in the BRAFV600EMS4A3 mice. Notably, BRAFV600EMS4A3 demonstrated increased enrichment of CD207-negative macrophages in spleen, liver and bone marrow. BRAFV600EMS4A3 mice readily survived past 52 weeks, while BRAFV600ECD11c had 100% mortality by 16 weeks. Bulk RNASeq and Ingenuity Pathway Analysis identified relative decrease in macrophage functionality in BRAFV600EMS4A3 mice. Additionally, macrophage infiltrate was observed in heart, major blood vessels and kidneys of BRAFV600EMS4A3 where these organs were not affected in BRAFV600ECD11c. **CONCLUSION:** The same mutation that creates a LCH-like phenotype in CD11c-derived cells creates an ECD-like phenotype in monocyte-derived cells. This study demonstrates a critical role for ontogeny in pathogenesis of histiocytic disorders. Further, the BRAFV600EMS4A3 mouse provides an ECD model for pre-clinical testing of therapeutic strategies.

BONE MARROW-DERIVED BRAFV600E-MUTATED CELLS DRIVE NEURODEGENERATION IN A MOUSE MODEL OF LANGERHANS CELL HISTIOCYTOSIS

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PURPOSE: Progressive neurodegeneration (ND) a devastating and ultimately fatal complication in some survivors of multi-system high-risk Langerhans Cell Histiocytosis (MS-RO+ LCH). Patients often develop LCH-ND years after the diagnosis despite successful treatment of systemic disease. BRAFV600E+ cells have been identified in areas of active neurodegeneration. However, it is unclear if the cell of origin is mutated microglia or mutated peripheral blood cells invading into the brain. Embryonic origin versus hematopoietic origin (or both) is a critical question to be able to cells to the brain as well as identify, prevent, and cure LCH-ND. We therefore tested a mouse model of bone marrow (BM)-derived BRAFV600E cells to migrate to the brain. **METHODS:** We used BM chimera to study the transition of BRAFV600E-mutated mechanisms of neurologic alterations therein. Therefore, congenic WT mice were conditioned with head-shielded Total Body Irradiation and transplanted with BM from SCLCre-ER-TxBRAFV600ExRosa26YFP [LCH chimera] or SCLCre-ER-TxBRAFWTxRosa26YFP [control chimera]. Cre-recombination was induced after an engraftment period of 4 weeks. Mice were analyzed 4 months after Tamoxifen induction. **RESULTS:** LCH chimera exhibit a parenchymal infiltration with BM-derived BRAFV600E+ macrophages four months after Cre-recombination while control chimera do not have substantial numbers of YFP reporter-tagged cells in the brain. The localization pattern of BRAFV600E+ macrophages in the brain recapitulates the pattern observed in humans with a focus in brain stem and cerebellum. BM-derived BRAFV600E macrophages accumulate at the interface between the bloodstream and the CNS parenchyma with 10-fold higher frequency than BM-derived BRAFWT+ macrophages and are associated with signs of local inflammation and astrocyte activation. Finally, LCH chimera exhibit signs of neurologic decline that is partially reversed by targeted treatment. **CONCLUSION:** We provide a mouse model that recapitulates MS-RO+ LCH and provide early evidence that BM-derived mutant cells can invade the brain parenchyma and give a murine model of LCH-ND.

PURPOSE: Rare histiocytic disorders (RHDs) include Juvenile xanthogranuloma (JXG) family, Erdheim-Chester disease (ECD), Rosai-Dorfman disease (RDD), Histiocytic malignancies (HM), ALK+ histiocytosis, indeterminate-cell histiocytosis (ICH) and secondary histiocytosis after leukemia/lymphoma. **METHODS:** The IRHDR opened in 2015 to collect data on RHDs worldwide, with central pathology (CP) review. **RESULTS:** Through May 2022, 158 patients were enrolled, median age 19 years (0.11-87), 93 males; 66 survivors, 3 deceased, 89 not reported (NR). Median follow-up 1.5 years. 91 had CP review: 3 excluded (not RHDs), 8 had different RHDs eligible for registry. JXG 52: 23 cutaneous (2 secondary to leukemia-JMML), 16 systemic (2 secondary to leukemia-ALL), 5 adult JXG, 1 Progressive Nodular, 1 reticulohistiocytoma, 1 necrobiotic, 5 NR. RDD 39: 19 nodal, 19 systemic (ocular, skin, CNS, GI), 1 NR. Observation, surgery +/- steroids were effective in cutaneous JXG and most nodal RDD. Most systemic JXG patients responded to LCH-III therapy, while most systemic RDD patients were refractory to steroids/ chemotherapy. Refractory/relapsed (RR) JXG and RDD patients had partial responses with cladribine, clofarabine +/- cytarabine; severe resistant cases responded to MEK-inhibitors (I). ECD 34: variable responses obtained with several multiagent therapies (interferon, MTX/steroids, cytarabine, rituximab, surgery); best/durable responses obtained with BRAF/MEK-I. HM 10: 1 secondary to leukemia (ALL), 3 multisystemic; ALL-like therapy (+/- surgery) was effective in 70%; 30% were refractory to clofarabine/cladribine (1 died). ALK+ histiocytosis 5; prolonged remissions observed with surgery (localized), LCH-III therapy and crizotinib (systemic), 1 died. Mixed Histiocytosis 6: 4 ECD/LCH, 1 ECD/RDD, 1 RDD/LCH; all multisystemic; many were resistant to multiple agents; majority responded to BRAF/MEK-I. ICH 2: skin/bone: responsive to steroids. **CONCLUSIONS:** Expert pathology review is helpful in RHDs. Genome sequencing benefits systemic cases which can be refractory but may respond to targeted (ALK/BRAF/MEK) inhibitors. However, optimal duration and long-term safety of these inhibitors remain unclear.

ABSTRACTS NOMINATED FOR THE NESBIT AWARD IN CLINICAL SCIENCE:

TREATMENT OUTCOMES OF THE RARE HISTIOCYTIC DISORDERS: FIRST DESCRIPTIVE ANALYSIS OF THE IRHDR-REGISTRY

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LATE EFFECTS AFTER HEMATOPOETIC CELL TRANSPLANTATION IN PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A HISTIOCYTE SOCIETY AND PEDIATRIC DISEASE WORKING PARTY OF EBMT STUDY

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PURPOSE: Hematopoietic cell transplant (HCT) is the only curative approach for primary, relapsed or refractory secondary hemophagocytic lymphohistiocytosis (HLH). Survival has improved but little is known about late effects in survivors. The aim of this study was to assess type and frequency of late effects in HLH patients after HCT. **METHODS:** This is a retrospective study of patients <18 yrs, who received an allogeneic HCT between 1/2004 and 12/2016 and who were alive at least two years post-HCT and reported to the EBMT registry. A supplemental late effects questionnaire was sent to EBMT centres. The project was funded by Histo UK. **RESULTS:** Data on 288 patients (124 females, 164 males) was collected. The median age at HLH diagnosis was 5.2 mo. (0-17 yrs). The majority, 276 (96%) were diagnosed as primary HLH. The median age at HCT was 1.2 yrs (0.1-17.3 yrs). Data on remission status was available for 254 patients, 181 (60%) were in complete remission at time of HCT. Status of clinical neurological symptoms prior to the conditioning was available for 251 patients and 73 (29%) were reported to have active CNS disease at the time of HCT. A majority of patients (83%) received busulfan based myeloablative conditioning. After median follow-up of 8.2 years (7.5-8.6 yrs) the probability of survival was 96% (92.8 - 97.7%). Reported late effects affected many organ systems with a striking predominance of neurological (18%) and neurocognitive late effects (21%). Analyses of severity and outcomes associated with pre-HCT status and other treatment factors are underway and will be presented. **CONCLUSION:** This is the largest cohort of survivors after HCT for HLH providing a comprehensive assessment of late effects. Neurological or neurocognitive late effects were present in almost 33% of survivors indicating the importance of CNS disease control and close neurological/neurocognitive follow-up post-HCT.

CAR-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (carHLH) IS ASSOCIATED WITH PRE-INFUSION INFLAMMATION AND HIGH DISEASE BURDEN AND PREDICTS POOR OUTCOMES FOLLOWING TISAGENLEUCEL IN PEDIATRIC B-ALL

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**POSTERS NOMINATED FOR THE
ROBERT J. ARCECI PRIZE FOR BEST POSTER**

BASIC LCH POSTER NOMINEES

Poster #1



**OUTLINING A CELLULAR SCORE BASED ON THE PRESENCE OF
CIRCULATING CD207+ CD1A+ CELLS IN LANGERHANS CELL
HISTIOCYTOSIS**

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PURPOSE: Langerhans cell histiocytosis (LCH) is characterized by an atypical accumulation of CD207+ and CD1a+ cells in almost any tissue with putative myeloid precursors circulating in the blood. Here, we aim to standardize a screening method of CD207+ and CD1a+ circulating cells in a drop of blood of patients with LCH. **METHODS:** Employing flow cytometry, 202 blood samples from patients with LCH and 23 controls were examined. A standardized cellular score was defined by measuring CD207+ and CD1a+ expression in monocytes and dendritic cells, based on CD11b, CD14, CD11c, and CD1c subsets, giving a unique value for each sample. Additionally, three patients (bone, multisystem and skin compromise) were included to test the trajectory of the cellular score associated with biochemical parameters and clinical status. **RESULTS:** A ROC curve was used to validate the scoring system (AUC: 0.849) with a threshold value obtained with Youden's test (Y index: 14), defining the presence of circulating CD207+CD1a+ cells. Remarkably, a fraction of patients with no apparent clinical manifestation at the time of sampling also presented these circulating cells (29.6%). A positive correlation between the cellular score and sCD40L, sIL-2Ra, and CXCL12 molecules in plasma was also found. During the follow-up, circulating CD207+CD1a+ cells were evidenced just before the clinical manifestation in bone compromise. The patient with multisystem involvement showed circulating cells just before bone reactivation and during the clinical manifestation. The patient with skin involvement, have also circulating cells before and/or during at least one of the clinical reactivations. **CONCLUSION:** Analyzing circulating CD207/CD1a cells, we have set a cellular score that could help with prognostic accuracy, early reactivation, and follow-up with minimal invasiveness.

BASIC LCH POSTER NOMINEES

Poster #2



**MAPK INHIBITORS IN CHILDREN WITH REFRACTORY HISTIOCYTOSIS:
AN INTERNATIONAL STUDY OF 199 CASES**

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Poster #3



SCREENING FOR NEURODEGENERATION IN LCH WITH NEUROFILAMENT LIGHT IN PLASMA

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PURPOSE: CNS involvement in Langerhans cell histiocytosis (CNS-LCH) can cause slowly progressive neurodegeneration (ND-CNS-LCH), frequently unresponsive to conventional LCH-directed therapy. A population-based study reported that at least 24% of all children with LCH develop signs of ND-CNS-LCH on long-term follow-up with magnetic resonance imaging. Therefore, a strategy for early detection, treatment, and monitoring of ND-CNS-LCH is imperative. In most LCH patients, somatic activating genetic alterations in the mitogen-activated protein kinase (MAPK) pathway can be detected. We recently showed that neurofilament light protein (NFL) in cerebrospinal fluid (CSF-NFL), a sensitive and well-established biomarker of neuroaxonal damage, appeared to be a relevant surrogate biomarker even in ND-CNS-LCH. Furthermore, targeted MAPK inhibition, which has shown pronounced clinical efficacy in systemic refractory LCH, effectively reduced CSF-NFL suggesting even inhibition of neurodegeneration in CNS-LCH. The purpose of the current study was to investigate the correlation between NFL in plasma (p-NFL) and CSF-NFL, and to evaluate if p-NFL could be used to screen for elevated CSF-NFL (to identify ND-CNS-LCH) and for therapeutic monitoring. METHODS: We compared paired samples of p-NFL and CSF-NFL in 10 LCH patients (19 samples) with or without known neurodegeneration. RESULTS: Although no linear correlation was found between p-NFL and CSF-NFL in this small cohort, nine samples had abnormal CSF-NFL (defined as ≥ 380 ng/L) with corresponding p-NFL ≥ 2 ng/L and ten samples had CSF-NFL < 380 ng/L, whereof eight (80%) with p-NFL < 2 ng/L ($p < 0.001$; Fisher's exact test). Hence, the sensitivity of p-NFL ≥ 2 ng/L to identify abnormal CSF-NFL (≥ 380 ng/L) was 100%, and the specificity 80%. CONCLUSIONS: It appears as if p-NFL may be used to screen for elevated CSF-NFL, and hence for ND-CNS-LCH, but confirmation in a larger study population is recommended. For consecutive monitoring in individual patients we still recommend CSF-NFL. Further studies on CSF-NFL and p-NFL in CNS-LCH are encouraged.

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PURPOSE: To present the outcome of 199 children with histiocytosis treated by off-label MAP kinase inhibitors (MAPKIs) in 21 different countries. METHODS: Patients, including 187 LCH, 5 RDD, 1 ECD, 5 JXG and 1 malignant histiocytosis (MH), were treated according to the causative mutation. Vemurafenib (n=139), Dabrafenib (n=35), Encorafenib (n=1), Cobimetinib (n=24), Trametinib (n=29) were prescribed. The indications in LCH was refractory RO+ disease (n=102), refractory RO- disease (n=38), neurodegeneration (n=24), sclerosing cholangitis (SC) (n=7), pulmonary involvement (n=11), and refractory disease in non-LCH histiocytosis. RESULTS: Median follow up after therapy begin was 2.8 years (range, 0.1-7.6) for a total of 503 person-years. In RO+ patients, the clinical response developed very fast, usually within 2 weeks. One death was observed (0.9%) within few days of treatment. As previously observed, therapy withdrawal in this group results in disease reactivation and no more than 7/102 patients were off-therapy for >1 year. Different drugs were used to maintain response (vinblastine, mercaptopurine, cladribine, cladribine/cytarabine, clofarabine, HSCT), but did not appear durably sufficient to allow a definitive therapeutic withdrawal. Noteworthy, 3 deaths and 1 secondary MDS were observed among patients who received several combination chemotherapies, while no fatality was seen in patients who have received only targeted therapies. In RO- LCH, in Lung LCH and in non-LCH histiocytosis, therapeutic response appears to be delayed (usually three or more months). The sole patient with MH did not respond. In SC, MAPKI fail to improve the anatomic lesion. Side effects were mainly transient and confined to the skin. No secondary skin cancer was observed. Effect in neurodegeneration remains difficult to evaluate, as MAPKIs were commenced at various times after clinical manifestation. CONCLUSION: MAPkinase inhibitors commonly prescribed off-label, offer useful therapeutic resources in refractory histiocytosis.

Poster #4



FACTORS ASSOCIATED WITH SHORT-TERM OUTCOME IN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS - A RETROSPECTIVE ANALYSIS OF THE DAL-HX, LCH I-III STUDY COHORTS

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PURPOSE: Langerhans cell histiocytosis (LCH) is a disease with wide range of clinical presentations and outcome. This retrospective analysis explores risk factors for early progression or death in multisystem LCH (MS-LCH). **METHODS:** 1,125 MS-LCH patients (611 males and 514 females), from the DAL-HX and the LCH I-III studies were analyzed. The median age at diagnosis/follow-up was 1.5 years/5.2 years. The endpoints of this analysis were death or event (death or progression) within 12 weeks. **RESULTS:** A total of 152 deaths and 605 events with 5-year OS and EFS of 85%±1 and 42%±2 was observed. The 12-week OS was 96% ±1 (40 early deaths) and the 12-week EFS was 88% ±1 (132 early events). Notably, the 92 patients alive with progression at week 12 had a poor overall survival with a 5-year OS rate of 58% (±5), while the 520 patients without event at week 12 had a 5-year OS of 92% (±1). In the univariate analysis, age, involvement of the liver (LI), lung (pulmonary involvement, PI), hematopoietic system, spleen, skin and gastrointestinal involvement (GI) at diagnosis had a significant impact on 12-week OS and EFS. In multivariate analysis, the cumulative hazard ratio (cHR) for 12-week EFS remained significant for LI (cHR=2.6, p=0.001), PI (cHR=1.7, p=0.007) and GI (cHR=1.8, p=0.007). When LI occurs in combination with GI or PI, 51/160 patients (38%) had a progression or died within 12 weeks. The 27 of these 51 patients that were alive at week 12 had a poor 5-year OS of 43% (±10). For PI without involvement of LI and GI (n=141) the 12-week EFS/OS was 94%±2/94%±2 with a 5-year OS 94%±2. **CONCLUSION:** The risk factors LI and -GI known to predict overall survival predict also early progression and death. LI is the strongest predictor of early disease progression, early and long-term death.

BASIC LCH POSTER NOMINEES

Poster #5



IS MULTI SYSTEM INFLAMMATORY SYNDROME SECONDARY TO COVID (MIS-C) SAME AS SEPSIS ASSOCIATED SECONDARY SHLH?

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PURPOSE: COVID 19 infection in children is generally mild, however some of them develop an unique immunological phenomenon called MIS-C (multi-system inflammatory syndrome, which is a hyperimmune state resulting in vasculitis, myocarditis and end organ damage. We compared immune status of MIS-C with another viral infection triggered hyperinflammatory state; sepsis hemophagocytic lymphohistiocytosis (SHLH) to understand the pathogenesis of this novel clinical syndrome. **METHODS:** We included patients with MIS-C, SHLH and viral sepsis (S). Blood samples were collected after written informed consent, utilizing protocols approved by our institution. We evaluated differential leukocyte counts, soluble markers of T cell and macrophage activation (sIL-2R, sCD163 and Ferritin) in plasma and did immunophenotyping of T cells and monocytes on cryopreserved peripheral blood mononuclear cells. **RESULTS:** Total of 62 children (MIS-C 27, Sepsis 27 & SHLH 8) were included with age ranging from 1 to 16 years. Total leukocyte counts did not differ across the groups. MIS-C had higher neutrophil counts as compared to SHLH and sepsis. (Median cu/mm : MIS-C -10062, SHLH-4434, S- 3138). Monocyte (M) and lymphocyte (L) numbers were comparable with SHLH but lesser than sepsis (Median M/L cumm MIS-C -390/1488, SHLH-252/1565, S-795/2841). Plasma levels of sIL-2R in MIS-C and SHLH were similarly elevated as opposed to sepsis (Median pg/ml MIS-C- 17824, SHLH- 25702, S - 3653). sCD163 levels was elevated highest in SHLH, followed by MIS-C and Sepsis (Median ng/ml SHLH- 2.18, MIS-C 0-96, S- 0.25). Similar trend was seen in proportions of activated T cells (HLADR+CD38+) across the groups (Median % SHLH 32.5, MIS-C- 4.31, S 1.14). Median CD4:CD8 in MIS-C (2.5) is comparable to sepsis (1.2) but significantly higher than SHLH (0.75). There was no difference in monocyte activation. **CONCLUSION:** MIS-C is a hyperimmune state but the immune profile has features overlapping with SHLH and sepsis. It is a different hyperimmune syndrome as compared to SHLH and needs more mechanistic studies.

Poster #6



ETOPOSIDE FOR PRIMARY HLH - BETTER THAN ITS REPUTATION

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PURPOSE: Primary hemophagocytic lymphohistiocytosis (pHLH) is a life-threatening hyperinflammatory syndrome that develops in patients with a genetic predisposition (FHL2-5, CHS, GSII, SAP, XIAP). In previous HLH-94 and HLH-2004 studies, etoposide-based treatment followed by hematopoietic stem cell transplantation (HSCT) led to 51% and 59% overall survival in pHLH patients. Contemporary data are lacking, but are essential to put novel treatment approaches (emapalumab, alemtuzumab, ruxolitinib) into perspective. **METHODS:** We evaluated all primary HLH patients registered in the international Histiocyte Society/ESID HLH registry 2016 - 2021 with one-year follow-up. **RESULTS:** Among 88 patients, 63 had FHL2-5, 13 had GS2/CHS, 9 had XLP1/2 and 3 had undefined pHLH. 13 patients were diagnosed without symptoms, 11 of them were transplanted and all 13 were alive and well. Among 75 symptomatic patients, 95% fulfilled HLH-2004 criteria, while 3 presented with CNS-HLH and 1 had less than 5 HLH criteria. 9 patients (3 FHL) only received IVIG/steroids/ cyclosporine A, while 68 received major HLH-directed drugs (first-line etoposide in 85%). 31% of patients received at least one additional major drug (mostly alemtuzumab). 74 patients underwent HSCT, 8 died before HSCT. 1-year follow-up, overall 72/88 (82%) patients were alive. 74% of patients receiving first-line etoposide were alive after 1 year. **CONCLUSIONS:** Contemporary prognosis of pHLH patients receiving first-line etoposide-based therapy is better than anticipated, suggesting important advances in early diagnosis, supportive therapies and HSCT

procedures. However, salvage therapies were used in 1/3. Importantly, early HSCT of asymptomatic siblings resulted in 100% survival, emphasizing the potential benefit of newborn screening.

Poster #7



MAP KINASE ACTIVATING DEATH DOMAIN (MADD) DEFICIENCY IS A NOVEL CAUSE OF IMPAIRED LYMPHOCYTE CYTOTOXICITY

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BACKGROUND: Most hereditary forms of hemophagocytic lymphohistiocytosis (HLH) are caused by defects of cytotoxicity, including Griscelli syndrome 2 (GS2, RAB27A deficiency). Deficiency of the mitogen activated protein (MAP) kinase activating death domain protein (MADD) results in a protean syndrome with neurological and endocrinological involvement. MADD acts as a guanine-nucleotide exchange factor for small GTPases, including RAB27A. **METHODS:** A female infant with syndromal features, secretory diarrhea, and features of HLH underwent routine exome sequencing. Degranulation and cytotoxicity of cytotoxic cells and platelet secretion were analyzed. To prove the relationship between the detected MADD defect and the detected functional impairment, we performed the assays in an NK-92mi cell line, in which we had introduced a CRISPR/Cas9 based MADD knock-out. A second MADD deficient patient was analyzed for confirmation. **RESULTS:** A homozygous splice site mutation in MADD was identified. Aberrant splicing caused by this mutation leads to an in-frame deletion of 30 bp and favors other aberrant variants. Patient NK cells and cytotoxic T cells showed a severe degranulation defect leading to absent perforin-mediated cytotoxicity. Platelets displayed defective ATP secretion, comparable to GS2. MADD deficient NK-92mi cells showed a degranulation defect and impaired cytotoxicity similar to that of the patient. The defect of cytotoxicity was confirmed in the second MADD deficient patient. **CONCLUSION:** In conclusion, RAB27A-interacting MADD is involved in vesicle release by cytotoxic cells and platelets. MADD deficiency causes a degranulation defect, most likely due to impaired RAB27a activation, and represents a novel disease predisposing to an HLH phenotype.

Poster #8



SCD25 AND FERRITIN LEVELS BEST DISTINGUISH CHILDREN WITH HEMOPHAGOCYTTIC LYMPHOHISTIOCYTOSIS FROM RELEVANT CONTROLS

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a disorder of immune dysregulation that presents with relatively nonspecific features of severe inflammation. Current diagnostic criteria are based on enrollment criteria established for the HLH-2004 clinical trial despite their unknown sensitivity or specificity. We aim to optimize the discriminatory power of the HLH-2004 parameters using a large cohort of curated controls. **METHODS:** We gathered a cohort of control patients with HLH features for comparison to patients with confirmed HLH. Controls included patients younger than 21 years in whom a CBC, ferritin, and one additional HLH-related parameter were obtained within a narrow time frame. Patients presenting with fever were defined as HLH-relevant controls, and patients who also had soluble CD25 (sCD25) measured as high pretest probability controls. Peak values obtained within 14 days of presentation were compared to peak pre-treatment values in patients with HLH. Receiver-operating curves were used to identify useful diagnostic parameters. Cutoff points were derived from the highest Youden-index point. **RESULTS:** We identified 18,204 potential controls, 912 HLH-relevant controls, and 321 high pretest probability controls in our hospital database during 2010-2020. Each laboratory diagnostic parameter showed significant discriminatory ability (area under the curve (AUC)≥0.7) between the HLH and control groups. The individual parameters with the greatest discriminatory power were sCD25 (AUC 0.89) and ferritin (AUC 0.95 compared to HLH-relevant controls, AUC 0.94 compared to high pretest probability controls). Discriminatory ability improved with a combined elevation of sCD25 and ferritin (AUC 0.96). Optimized thresholds of sCD25 and ferritin were higher than HLH-2004 cutoffs in each analysis. When comparing controls to genetically diagnosed patients, sCD25 had the highest discriminatory power with an AUC of 0.96, and with ferritin, a combined AUC of 0.98. **CONCLUSION:** Of the HLH-2004 criteria, sCD25 and ferritin had the highest discriminatory power, that increased further when combining the two parameters.

Poster #9



HYPERINFLAMMATION IN CRITICALLY ILL PATIENTS IN INTENSIVE CARE

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is characterized by excessive inflammation and high mortality. The biology in secondary HLH (sHLH) is multifactorial and remains unclear. Improved survival in intensive care (ICU) requires identifying patients with inappropriate hyperinflammation that may benefit from HLH-directed therapy. To better distinguish ICU patients with hyperinflammation, we aimed to describe and compare critically ill with and without sHLH in relation to risk factors and mortality. **METHODS:** ICU patients with hyperferritinemia and/or inappropriate thrombocytopenia were prospectively studied for clinical and laboratory features, including HLH-parameters and lymphocyte 2 function assays, for descriptive analysis and comparison of HLH and non-HLH patients. **RESULTS:** Fifty patients (38 males, median 62 years) were included, with 28-day mortality 46%. Sepsis/septic shock and respiratory failure were main reasons for ICU admission. Eighteen patients (36%) were assessed to have developed sHLH (median HScore=207) and 32 not ("non-HLH", median HScore=138). HLH patients had higher maximum ferritin compared to non-HLH (41,564µg/L and 10,924µg/L, p=0.016), also observed in non-survivors compared to survivors. Ferritin correlated positively with HScore (p<0.001). HLH patients and non-survivors showed a faster rate of increase of ferritin, which was associated with an increased risk of death (p<0.01). Compared to HLH patients, non-HLH non-survivors had more severe organ failure with marked liver injury and hyperferritinemia, but HLH patients displayed a higher ferritin/alanine transaminase ratio. We observed an overall lymphopenia (p=0.036). Furthermore, natural killer(NK)-cell and cytotoxic T-cell numbers were lower

in HLH patients (p=0.016 and p=0.030). **CONCLUSION:** Our study indicates a high level of hyperinflammation/sHLH in the more critically ill patients at ICU. Extreme and rapidly rising hyperferritinemia is associated with increased mortality and should prompt evaluation for HLH. We recommend ferritin/ALT ratio as a complementary parameter in sHLH evaluation. A low frequency of NK-cells and CTLs may contribute to the development of sHLH in some critically ill patients.

Poster #10



CLINICAL SIGNIFICANCE OF PLASMA SOLUBLE MICB IN CHILDREN WITH EBV-ASSOCIATED HEMOPHAGOCYTOIC LYMPHOHISTIOCYTOSIS

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BACKGROUND: HLH is a potentially fatal systemic inflammation disease in children. The most common cause is EBV infection. MHC class I polypeptide-related sequence B (MICB) is a membrane protein inducibly expressed upon cellular stress, viral infection, or malignant transformation, thus marking these cells for clearance through NKG2D positive lymphocytes. MICB can be released into plasma through several mechanisms, reducing NK cell cytotoxicity. **METHODS:** We conducted clinical research on HLH patients and cell research in vitro. In the retrospective clinical part, 112 HLH patients were enrolled in this study. Real-time quantitative PCR, standard ELISA methods, and LDH release tests were used respectively to examine the expression of MICB mRNA, the levels of soluble MICB (sMICB), and the activity of NK cells in those patients. **RESULTS:** In clinical studies, compared with the non-EBV-HLH group, the EBV-HLH group had lower NK cell activity (P < 0.05). The level of sMICB in the EBV-HLH group was significantly higher than in non-EBV-HLH, IM, and CAEBV patients (P < 0.05). A high level of sMICB was associated with poor treatment response and poor prognosis (P < 0.05). Cellular studies showed that an increased level of membrane MICB (mMICB) could positively correlate with the killing activity of NK92 cells (P < 0.05), and a high level of sMICB (1250-5000pg/ml) could reduce the killing effect of NK92 cells (P < 0.05). **CONCLUSION:** The expression level of sMICB in EBV-HLH patients increased, and a high level of sMICB at the initial onset indicated a poor treatment response. The killing activity of NK cells in EBV-HLH patients decreased more significantly. The high level of sMICB (1250-5000pg/ml) inhibits the killing activity of NK92 cells.

Poster #11



PLASMA PROTEIN PROFILES CORRELATE HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) SIGNATURE WITH MORE SEVERE PEDIATRIC COVID-19

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PURPOSE: In general, children have less severe disease with SARS-CoV2 infection than adults. However, some children do experience life-threatening sequelae from infection. In order to analyze inflammatory responses to SARS-CoV2 and clinical outcomes, this study evaluates the plasma protein profiles of pediatric COVID19 patients compared to HLH, severe sepsis, Kawasaki disease, febrile viral illness, and healthy controls. METHODS: The Luminex platform measured 150 analytes in 108 patients with pediatric COVID19, 32 of which developed MIS-C, 16 with HLH, 14 with severe sepsis, 25 with Kawasaki disease, 21 with febrile viral illness, and 20 health controls. The results were tested for significant proteins with a p<0.05 and those that passed with an FDR cut off of 0.1 and 80% confidence. Semi-supervised learning using protein analyte profiles of inflammatory disease were used to predict COVID19 similarities and clinical outcomes were compared. RESULTS: Analyte comparison COVID19 patients revealed increase in CXCL9 in patients with MIS-C. Semi-supervised predictions revealed HLH as the most common predictor and showed that an HLH plasma signature in pediatric patients with COVID19 was associated with higher instances of MIS-C, longer hospital stay, and higher instances of respiratory failure. CONCLUSION: This evaluation of plasma proteins demonstrated that pediatric patients with SARS-Cov2 infection with inflammatory plasma profile similar to an HLH signature experienced more severe disease. These results reflect complex range of immune responses in children with COVID19, and they support potential for prospective risk stratification using plasma biomarkers.

Poster #12



THE PROTECTIVE ROLE OF TRANSCRIPTION FACTOR NRF2 IN MURINE HYPERINFLAMMATION

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PURPOSE: Hyperinflammatory syndromes like hemophagocytic lymphohistocytosis (HLH) and macrophage activation syndrome (MAS) are characterized by organomegaly, multi-lineage cytopenias, and elevated serum cytokines. The transcription factor Nrf2 and its binding partners are an important sensor for inflammatory and redox stress. Downstream of Nrf2 are antioxidant response elements responsible for restoration of redox homeostasis within the cell. Here we investigate the protective role of Nrf2 in a mouse model of hyperinflammation. METHODS: Murine hyperinflammation was induced in vivo using repeated TLR-9 agonism with intraperitoneal injection of CpG. In vitro nitrogen radical production and signaling was done using bone marrow derived macrophages. RESULTS: Nrf2 knockout mice develop significantly worse organomegaly, higher serum interferon gamma (IFNg) levels, and evidence of bone marrow stress compared to wildtype controls. Both peritoneal and bone marrow derived macrophages from Nrf2 knockout mice demonstrate elevated cytokine production and nitrogen radical formation in response to IFNg and TLR9 stimulation. Nrf2 activation using the small molecule monomethyl fumarate (MMF) can reduce nitrogen radical formation and is protective in this mouse model of hyperinflammation. CONCLUSION: Together these findings suggest a protective role of Nrf2 in hyperinflammatory states and represents a promising target for clinical application.

NOTES

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Poster #13



INDIVIDUALIZED ALEMTUZUMAB DOSING FOR INDUCTION OF DISEASE REMISSION PRIOR TO HSCT IN CHILDREN WITH HLH

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BACKGROUND: Allogeneic hematopoietic stem cell transplantation (HSCT) can cure primary hemophagocytic lymphohistiocytosis (pHLH), but an efficient bridging therapy to control hyperinflammation prior to HSCT is pivotal to improve clinical outcome. Alemtuzumab was shown to successfully inhibit hyperinflammation with minimal toxicity, but highly variable alemtuzumab pharmacokinetics (PK) may influence response to treatment. We aim to explore if individualized alemtuzumab dosing based on PK monitoring may improve treatment efficacy and prevent over-dosing. **METHODS:** Six children with molecularly confirmed pHLH from birth to 14 months old were treated with an individualized alemtuzumab dosing regimen at the Leiden University Medical Center, The Netherlands, between 2018 and 2021. Reasons for this approach were insufficient response to first-line treatment, prevention of chemotherapy-related toxicity in a newborn with mild disease, or critical organ failure which precluded the administration of conventional treatment. Initial dosing ranged from 1-2.5mg/kg (mean dose=2mg/kg) depending on clinical disease activity. According to the individual response to treatment, further alemtuzumab (mean cumulative dose = 4.1 mg/kg) was given until optimal clinical disease control was reached. In parallel, alemtuzumab levels were determined in patient serum. HSCT was scheduled when plasma alemtuzumab levels were estimated to be around the drug lympholytic level of 0.1mcg/ml. **RESULTS:** All children tolerated alemtuzumab well and experienced optimal overall survival and event free survival with high quality of life at a median follow-up time post-transplant of 12 months (range 5-39). Main transplant complication was acute graft-versus-host disease (aGvHD) which occurred in all but one patient (83%). However, only one child developed severe (grade III) aGvHD. All patients responded to immunosuppressive therapy, allowing progressive tapering of immunosuppressants. There were no severe virus complications post-transplant. **CONCLUSION:** Our experience shows excellent clinical outcome of individualized alemtuzumab dosing in these critically ill children. This approach may further improve clinical outcome including control of aGvHD.

Poster #14



1-YEAR SURVIVAL IN A NATIONWIDE COHORT OF PATIENTS WITH HLH IN ENGLAND: 2003-2018

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PURPOSE: Haemophagocytic lymphohistiocytosis (HLH) is rare, results in high mortality and is increasingly being diagnosed. Little is known about how survival varies by underlying aetiology in different age groups. **METHODS:** Cases of HLH diagnosed in England between 1/1/2003 and 31/12/2018 were identified using a validated approach using national linked electronic health data from hospital admissions and death certification. We calculated 1-year survival using Kaplan-Meier estimates by calendar year, age group, sex and any associated comorbidity (malignancy, inflammatory rheumatological or bowel diseases (IBD)) associated with the diagnosis of HLH. We modelled 1-year survival and interactions between age and associated comorbidity using Cox regression. **RESULTS:** There were 1628 people with HLH included. Overall, 1-year survival was 50% (95% Confidence interval 48-53%) which varied substantially with a U-shaped survival with age ($p < 0.01$), sex (males, 46%, worse than females, 55% $p < 0.01$) associated comorbidity (rheumatological/IBD, 69%, survival was better than haematological malignancy, 28%, other malignancy, 37% $p < 0.01$) and calendar year (getting worse over time 2003-2008 56%, 2014-2018 47% $p < 0.01$). Those aged 0-14 and 15-54 years had a 3-fold increased risk of death at 1-year among HLH associated with haematological or non-haematological malignancy compared to rheumatological disease/IBD. Predicted 1-year survival decreased markedly with age in those with rheumatological disease/IBD (age 0-14, 84%; 15-54, 73%; >55, 27%) such that among those aged >55 years survival was poor regardless of underlying disease process. For all sub-groups, the vast majority of deaths occurred within three months of HLH diagnosis. **CONCLUSION:** The 1-year survival following diagnosis of HLH varies considerably by age, sex, associated comorbidity and calendar year. Survival was substantially better in those with inflammatory rheumatological diseases or IBD among young and middle age groups compared to those with underlying malignancy, whereas in older age groups survival was uniformly poor regardless of the underlying disease.

Poster #15



THE TREATMENT BASED ON RUXOLITINIB AND AMPHOTERICIN B IS EFFECTIVE FOR RELAPSED LEISHMANIASIS-RELATED HEMOPHAGOCYTTIC LYMPHOHISTIOCYTOSIS: A CASE REPORT AND LITERATURE REVIEW

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BACKGROUND: Hemophagocytic lymphohistiocytosis (HLH) is known as a life-threatening syndrome, and Leishmania is the most common protozoan triggering infection-related HLH. It is thus important to find the root cause and treat it effectively. **Case report:** We report a 44-year-old man with a history of antisynthetase antibody syndrome. The patient progressed rapidly to meet the HLH-2004 diagnostic criteria, despite the unknown etiology. Although the patient was promptly treated with the HLH-1994 protocol to achieve remission, he still relapsed after glucocorticoid reduction. When the cause was looked for, it was found out that HLH was secondary to Leishmania infection. The symptoms of HLH were rapidly alleviated by the treatment based on Ruxolitinib and Amphotericin B. **CONCLUSION:** Etiological screening plays a crucial role in leishmaniasis-related HLH. An experienced pathologist and real-time PCR for Leishmania would be substantially beneficial. The treatment based on Ruxolitinib and Amphotericin B proved effective in alleviating relapse of visceral leishmaniasis-related HLH.

Poster #16



LABORATORY MARKERS OF CENTRAL NERVOUS SYSTEM INVOLVEMENT IN CHILDREN WITH HEMOPHAGOCYTTIC LYMPHOHISTIOCYTOSIS: A PILOT STUDY

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PURPOSE: Central nervous system (CNS) disease among patients with hemophagocytic lymphohistiocytosis (HLH) has not been standardized, which complicates the study of CNS-HLH and its management. The aim was to investigate cerebrospinal fluid (CSF) ferritin, triglycerides (TG), and lactate dehydrogenase (LDH) as simple and readily available laboratory markers of CNS-HLH. **METHODS:** A retrospective study including children treated for HLH at Alexandria University Children's Hospital with available frozen pre-treatment CSF sample. CNS disease was positive if abnormal neurologic symptom/sign, abnormal CSF analysis (pleocytosis and/or elevated protein), or abnormal neuroimaging. TG, ferritin and LDH were measured in the CSF samples.

RESULTS: 33 children with HLH met the inclusion criteria. Their age ranged from 1.1 to 196 months at diagnosis with a median of 13.5 months. The majority were females (69.7%). Seven patients were negative for CNS-HLH (19.4%) and 29 patients (80.6%) were positive according to the classical CNS-HLH criteria. At the end of the follow-up, 45% of patients have died. Significant correlations were found between CSF TG and CSF protein and leukocytes ($P= 0.036$ for both), and between CSF TG and serum ferritin ($P= 0.037$). Only ferritin showed a significant correlation between its serum and CSF levels ($P< 0.0001$). CSF Ferritin and LDH were higher in non-survivors. **CONCLUSIONS:** CSF TG may have a diagnostic value as a marker of CNS-HLH, while CSF Ferritin and LDH may have a prognostic value. Further studies are needed to verify these preliminary findings.

Poster #17



VARIATION OF CONSULTING PRACTICES, DIAGNOSTIC APPROACHES AND MANAGEMENT OF HEMOPHAGOCYTTIC LYMPHOHISTIOCYTOSIS AMONG NORTH AMERICAN AND LATIN AMERICAN PHYSICIANS

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BACKGROUND: Hemophagocytic Lymphohistiocytosis (HLH) and Macrophage Activation Syndrome (MAS) are life-threatening hyperinflammatory conditions of pathologic immune activation. While disparities in the management and outcomes in low- to middle vs high-income countries have been demonstrated for multiple diseases, little data exists related to disparities related to rare diseases such as HLH. **OBJECTIVE:** To describe the differences in the management of HLH among pediatric Hematology/Oncology (HO) physicians in United States (US) and Latin America (LA). **METHODS:** An online survey querying referral and management preferences for HLH was sent to pediatric HO physicians in the US and LA. The survey included a description of two cases: a classic EBV related HLH and a classic autoimmune-related MAS. **RESULTS:** Seventy physicians responded: 52.86% US vs 52.8% LA. All physicians prioritized consulting HO physicians for EBV-induced HLH. For autoimmune-related MAS, US physicians prioritized rheumatology consultation, while LA physicians preferred HO and rheumatology equally. Preferred first-line treatment were steroids. For second-line treatment, US respondents preferred targeted biologic therapies while LA physicians chose IVIG. One third of LA physicians reported being unable to obtain medications that they would consider using as first line therapy. **CONCLUSION:** Practice differences for HLH exist among US and LA HO physicians, many of which are related to the lack of availability of certain tests and medications in LA.

Poster #18



HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: CLINICAL REVIEW AT THE PHILIPPINE CHILDREN'S MEDICAL CENTER

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PURPOSE: This study aims to describe the clinical characteristics, treatment received and outcome of patients diagnosed with HLH at the Philippine Children's Medical Center from 2004 to 2017. **METHODS:** A retrospective analysis of records of children 0 -18 years of age diagnosed with HLH from January 2004 to December 2017 was done. **RESULTS:** A total of 39 patients were included in the study which gave an incidence of 1.22 per 3000 patients admitted under 18 years of age. There were 29 males (74.4%) and 10 females (25.6%) with a male to female ratio of 2.9:1 Mean age was 6.12 ± 3.89 years. The average time from initial presentation to diagnosis was 6 weeks and 2 days. The most commonly seen clinical and laboratory features observed in these patients were fever (100%), splenomegaly (71.8%), anemia (87.17%), thrombocytopenia (79.48%) and hypertriglyceridemia (69.23%). Only 5 patients were confirmed familial HLH with 3 having XLP gene mutation, and one each having syntaxin and perforin gene mutations. Majority of patients received a combination of treatment based on the HLH 2004 regimen while almost one third only received antibiotics. Only 23% of patients survived during the study period and all but one of these patients received drug combinations based on the HLH 2004 protocol. **CONCLUSION:** HLH is a rare but important condition that must be recognized early and treated appropriately in order to optimize survival. The mortality rate in 39 patients seen in this institution is high. There is a need to better utilize the diagnostic criteria of the disease and to employ a more uniform treatment strategy. Increasing awareness among health care personnel can also improve case finding, characterization and treatment.

Poster #19



SARS-CoV-2 INFECTION DID NOT TRIGGER HLH RELAPSE IN A PATIENT WITH CTLA-4 INSUFFICIENCY WHO PREVIOUSLY PRESENTED WITH LEISHMANIA AND EBV INFECTION-INDUCED HLH

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PURPOSE: Cytotoxic T-lymphocyte antigen-4 (CTLA-4) checkpoint pathway may related to hemophagocytic lymphohistiocytosis (HLH); the association between COVID-19 and HLH is still debated. Our aim is to describe a CTLA-4 deficient patient presenting with leishmania and EBV triggered-HLH, and the clinical and immune responses to SARS-CoV-2 generated during her follow-up. **METHODS:** NK-cytotoxic function assessed by 51Cr-K562 lytic assay;

lymphocyte subsets, perforin expression, NK-cell degranulation and coexpression of CD25 and CD134 on memory T-cells by flow cytometry. Whole exome sequencing with Sanger confirmation. **RESULTS:** A 16-year-old female was first admitted in March 2020 with severe thrombopenia and readmitted 3 months later to study polyadenopathy. In October 2020, she suffered a mild COVID-19 (ageusia, anosmia) showing positive IgG anti-SARS-CoV-2-Spike (694.0 UA/mL) 6 months after the infection. In March 2021 -during her third hospital admission- she fulfilled HLH criteria along with leishmaniasis infection and EBV reactivation. Later on we have found granulomatous-lymphocytic interstitial lung disease (GLILD). Normal serum immunoglobulins, weakly positive ASMA and anti-thyroglobulin autoantibodies were detected. Circulating lymphocytes and HLH-oriented studies were all normal. A new, "de novo" heterozygous missense mutation c.425G>A (p.Gly142Asp) in CTLA-4 was identified, affecting a conserved domain of the protein and probably pathogenic according to our in silico results (PolyPhen). Following both the second (June 2021) and third SARS-CoV-2 BNT162b2 vaccine immunization, specific IgG>40.000 UA/mL and positive anti-SARS-CoV-2-Spike memory CD4+ T-cell responses were detected. **CONCLUSION:** We report a young patient with a new heterozygous germline mutation in CTLA-4 associating HLH induced by common triggers (leishmania, EBV) but not by SARS-CoV-2 infection. This case does not support a relevant role of SARS-Cov-2 as potential etiological trigger of HLH. Our patient has been able to generate robust specific responses against SARS-CoV-2, while other reported insufficient CTLA-4 patients show suboptimal antibody responses to SARS-CoV-2, probably due to their stronger immunosuppressor therapies.

Poster #20



HARNESSING THE ELECTRONIC MEDICAL RECORD TO FACILITATE EVALUATION OF SUSPECTED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) may manifest as overwhelming inflammation and clinically appears very similar to sepsis. Due to the heterogeneity of the presentation, it has been helpful to create a screening HLH order set in the electronic medical record (EMR). **METHODS:** This is a retrospective review of the creation, execution and revision of a screening order set in the electronic medical record at a freestanding academic pediatric hospital in Kansas City, MO, USA. **RESULTS:** Communication between pediatric hematologist/oncologist and pediatric intensive care physicians identified a need for an order set to expedite evaluation of patients with possible HLH. This plan was created in February 2016 and has been used 45 times through March 31, 2022. In July 2021 the PowerPlan was revised to reflect preference in laboratory testing and updates in clinically relevant diagnostic criteria. Given the rarity of this diagnosis, it is difficult to determine if this PowerPlan hastened a diagnosis of HLH, but has assisted with consistent evaluation of patients with suspected HLH. **CONCLUSION:** HLH requires prompt evaluation and treatment to avoid risk of mortality. An electronic order set in the EMR at this pediatric academic hospital has led to consideration of this diagnosis.

Poster #21



ETOPOSIDE-CONTAINING REGIMEN IS AN IMPORTANT APPROACH FOR ADULTS WITH HISTIOCYTIC NECROTIZING LYMPHADENITIS-ASSOCIATED HEMOPHAGOCYTTIC LYMPHOHISTIOCYTOSIS

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PURPOSE: Histiocytic necrotizing lymphadenitis (HNL) is a benign, self-limiting disease with good prognosis. However, a small number of patients may progress to hemophagocytic lymphohistiocytosis (HLH), and few clinical reports have been published at present. **METHODS:** This study analyzed the clinical characteristics and prognosis of adult patients with histiocytic necrotizing lymphadenitis-associated hemophagocytic lymphohistiocytosis (HNL-HLH). Between September 2014 and January 2022, twenty-one adult patients with HNL-HLH were retrospectively assessed. **RESULTS:** Eighteen of twenty-one patients were treated with etoposide-containing regimens. The results showed that sixteen patients achieved complete response, four achieved partial response, and the overall response rate reached 95.2%. Among them, five patients were treated with ruxolitinib, and all achieved remission. The median overall survival (OS) was not reached. The 1-year OS was 95.2%, and the 5-year OS was 88.9%. Patients younger than 40 years had better OS ($P = 0.046$). **CONCLUSION:** A chemotherapy regimen containing etoposide is an important treatment for adult patients with HNL-HLH that can significantly improve efficacy. Ruxolitinib shows good therapeutic potential in the short term and age may be a prognostic factor affecting survival.

Poster #22



A CLINICAL STUDY OF SECOND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN TREATMENT OF HEMOPHAGOCYTTIC SYNDROME WITH ENGRAFTMENT FAILURE

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OBJECTIVE: The purpose of this study was to evaluate the efficacy of second allogeneic hematopoietic stem cell transplantation (allo-HSCT) in treatment of hemophagocytic syndrome with engraftment failure. **METHODS:** We collected ten patients with hemophagocytic syndrome after failure of the first allo-HSCT in our hospital from June 2015 to July 2021, and analyzed the treatment process and prognosis retrospectively. Concurrently, we analyzed effects of remission status, donor selection and preconditioning regimen of patients before second allo-HSCT on transplant-related complications, transplant-related mortality and transplantation efficacy. **RESULTS:** All ten patients achieved complete donor implantation. The median implantation time of neutrophils and platelets was 12 days (10-19 days) and 24 days (11-97 days). Two patients died of transplant-related thrombotic microangiopathy (TMA). Three cases developed Grade I acute graft versus host disease (aGVHD), one developed Grade II aGVHD, two cases developed Grade III aGVHD, and three cases had limited chronic GVHD. Seven patients were concomitant with viral infection. The overall survival rate was 80%. The transplant-related mortality and the incidence of GVHD after

transplantation were 20% and 60%. **CONCLUSIONS:** Second allo-HSCT is an effective treatment for hemophagocytic syndrome with engraftment failure. **Key words:** Second allo-HSCT, Engraftment failure, Hemophagocytic syndrome

Poster #23



A CASE REPORT OF HEMOPHAGOCYTTIC LYMPHOHISTIOCYTOSIS (HLH) ASSOCIATED WITH ANTI-PD-1 IMMUNE CHECKPOINT INHIBITOR (ICI) THERAPY WITH CEMIPIMAB AND CHRONIC LYMPHOCTIC LEUKEMIA (CLL) : ATTEMPTING DRUG REMOVAL WITH PLASMA EXCHANGE (PLEX) IS NOT SUFFICIENT

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HLH is a rare immune related adverse event (irAE) following ICI therapy. PLEX offers the dual possibilities of removing cytokines and chemokines that are implicated in HLH pathogenesis and removing cemiplimab, a large IgG4 construct favorable for apheresis due to its volume of distribution (5.3L) and half life (20 days). Cemiplimab was administered at 350 mg/m²/cycle for the treatment of locally advanced mucosal squamous cell cancer in a 67 yo woman with severe hypogammaglobulinemia and mild splenomegaly associated with untreated, good prognosis CLL. On day 2, cycle 2 cemiplimab, persistent daily high fever began. After an extensive and comprehensive work up for mimics, HLH was diagnosed 21 days later based on hyperferritinemia (48,988 ng/ml), new severe pancytopenia, nucleated hemophagocytosis (marrow), hypofibrinogenemia, hypertriglyceridemia, soluble IL-2 receptor elevation (30,672 pg/ml, normal < 858 pg/ml), and massive hepatosplenomegaly. Childhood and family history were negative. Sequencing detected a pathogenic mutation in RNASEH2 and a variant of unknown significance in UNC13D. Anakinra 100 mg twice daily and dexamethasone 10 mg/m² daily were initiated. By HLH day 3, HLH had not remitted, prompting PLEX of one plasma volume/day x 3 days (100% plasma, Day 1; 50% plasma, 50% albumin on Days 2, 3) followed by immune globulin (IVIG) 400 mg/kg replacement. Dexamethasone and anakinra were tapered over a week as fever remitted, fibrinogen normalized, and ferritin declined by 1.5 log. Prednisone 20 mg daily was initiated with taper. On HLH day 26, on prednisone 7.5 mg po daily, HLH relapsed. Anakinra 100 mg twice daily and IVIG 2 g/kg were administered with remission. On HLH day 43, treatment was prednisone 10 mg daily and anakinra 100 mg daily, followed by canakinumab 300 mg substitution on HLH day 59. Prednisone was tapered slowly and discontinued on HLH day 127. HLH has not relapsed at 9 months.

Poster #24



CLONALLY RELATED T-CELL MALIGNANCIES AND HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A PEDIATRIC PATIENT

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PURPOSE: To present the case of a patient with a history of T-cell acute lymphoblastic leukemia (T-ALL) who developed a clonally-related mature T-cell lymphoma and concomitant hemophagocytic lymphohistiocytosis (HLH). **METHODS:** Case report. **RESULTS:** An 8-year-old female with a history of T-ALL in remission for three years presented with fatigue and abdominal pain and was subsequently found to have clinical and laboratory evidence of HLH, meeting six of eight HLH-2004 diagnostic criteria. Genetic studies revealed variants of uncertain significance in AP3D1, PRF1, SLC7A7, and UNC13D, all of which had Combined Annotation Dependent Depletion (CADD) scores greater than the Mutation Significance Cutoff (MSC), suggesting high phenotypic impact. Viral studies were negative and a bone marrow aspirate showed no evidence of T-ALL relapse. An abdominal CT demonstrated splenomegaly with hypodense masses throughout the spleen, a mass contiguous with the small bowel, and retroperitoneal lymphadenopathy. Biopsy of a supraclavicular lymph node revealed a clonal T-cell population that was found to harbor the same T-cell receptor (TCR) rearrangement as the prior T-ALL clone, though with a mature atypical T-cell immunophenotype most consistent with a monomorphic epitheliotropic intestinal T-cell lymphoma. Targeted next generation sequencing of this tumor specimen revealed pathogenic variants in ATM, JAK3, KRAS, NOTCH1, NOTCH2, SH2B3, and TET2, as well as single copy loss of CDKN2A, a finding also present at the initial T-ALL diagnosis. Given these findings, the patient received both HLH- and lymphoma-directed therapy, but experienced disease progression and died of severe acute respiratory distress syndrome and multiple organ dysfunction. Autopsy revealed extensive and aggressive lymphoma involving multiple organ systems as well as hemophagocytosis in the spleen and bone marrow. **CONCLUSION:** This case highlights the importance of maintaining a high index of suspicion for malignancy as a trigger for HLH and demonstrates the potential for development of a second clonally-related T-cell malignancy.

Poster #25



DOCK2 MUTATION AND RECURRENT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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PURPOSE: To describe a pediatric patient with recurrent hemophagocytic lymphohistiocytosis (HLH) and a missense DOCK2 mutation contributing to impaired natural killer (NK) cell function in vitro. **METHODS:** Patient data was abstracted via the electronic medical record. Patient mutant (commercial sequencing) and wild-type (WT) DOCK2 cDNA were transduced into the NK-92 human NK-cell line by FOAMY virus. Transduced NK-92 cells were mixed independently with K562 erythroleukemia target cells triggering degranulation

and cytotoxicity. Degranulation (CD107a expression) and cytotoxicity were measured by flow cytometry with monoclonal antibody and Live/Dead near-IR dye, respectively. **RESULTS:** An 11-year-old male with a history of prematurity complicated by necrotizing enterocolitis requiring significant bowel resection and parenteral nutrition via an implanted central line was hospitalized 17 times in the past 5 years for central line infections, including *Staphylococcus aureus*, *Candida albicans*, and *Klebsiella pneumoniae*. The infections resulted in high fevers, pancytopenia, and hepatosplenomegaly, with increases in serum ferritin >1,000 ng/mL (maximum 52,650 ng/mL), sCD25, and liver transaminases (meeting HLH-2004 criteria). He frequently required intensive care with vasoactive medications and invasive respiratory support to combat distributive and cardiogenic shock. These episodes resolved with antibiotics, increased anakinra (rhIL-1Ra) frequency, and glucocorticoids. At baseline, his disease is controlled with anakinra 100 mg twice daily, but his peripheral blood NK-cell function remains markedly diminished. A genetic immunodeficiency panel revealed a rare (0.1%) missense variant in DOCK2 c.1334A>G (p.Asn445Ser). Over-expression of the DOCK2 mutant in NK-92 cells stimulated with K562 target cells in vitro diminished degranulation (65% of WT, n=3, p=0.001) and target cytotoxicity (86% of WT, n=3, P=0.043). **CONCLUSION:** This secondary HLH patient's DOCK2 mutation diminishes NK-cell function in vitro and likely contributes to recurrent HLH triggered by infection via a threshold disease model. This study adds to existing evidence of DOCK2's importance in NK-cell cytotoxicity and demonstrates DOCK2's potential influence on HLH.

Poster #26



REDUCED INCIDENCE OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN JAPAN DURING THE COVID-19 PANDEMIC

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PURPOSE: Various infectious diseases have dramatically decreased during the COVID-19 pandemic. In Japan, the most frequent cause of HLH in children and adolescents and young adults was infection. In this study, we assessed the incidence of six hematological diseases including HLH, before and during the COVID-19 pandemic. **METHODS:** We analyzed the public dataset from the Blood Disease Registration maintained by the Japanese Society of Hematology. From 2016 to 2019, the mean number of patients registered was 42,406 ± 5,046. In 2020, this figure was 46,471. To analyze changes in annual incidence, we calculated the mean and standard deviation for the 2016-2019 data, and compared this to the annual incidence of each disease in 2020. **RESULTS:** The total incidence of HLH decreased to 73.7%, compared with the 2016-2019 mean incidence of HLH (152.0 vs. 206.3±10.2). Furthermore, HLH incidence in 2020 decreased by 77.5% in those less than 20 years old, and 77.9% in those

over 20 years old. Similarly, the incidence of IM and aITP decreased by 91.5% and 78.4% in 2020, compared to the respective mean incidences of IM and aITP from 2016 to 2019. The decrease in the number of IM and aITP patients was larger among those less than 20 years of age, compared to those 20 years of age or older (IM: 84.8% vs. 96.6%, and aITP: 52.6% vs. 106.5%). On the other hand, the incidences of LCH, ALL, and B-NHL did not decrease in 2020 (LCH, 109.9%; ALL, 102.9%; and B-NHL, 111.9%). CONCLUSIONS: The incidence of HLH decreased during the COVID-19 pandemic. Lifestyle changes may be implemented during the COVID-19 pandemic, specifically social distancing, wearing of face-masks, alcohol disinfection, and school closure, effectively reduced contact and droplet transmission.

Poster #27



CLINICAL STUDY OF HAPLOIDENTICAL STEM CELL TRANSPLANTATION FOR PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN CHILDREN

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PURPOSE: To investigate the efficacy of haploidentical Stem Cell Transplantation (haplo-HSCT) for children with primary hemophagocytic Lymphohistiocytosis (PHLH). METHODS: A retrospective analysis was performed on 29 pediatric patients with PHLH undergoing haplo-HSCT between January 2016 and June 2021. RESULTS: Of the 29 patients, 17 were male and 12 were female, median age was 4.8(0.3-15) years. 7 were FHL-2 (PRF1), 11 were FHL-3 (UNC13D), 3 were FHL-5 (STXBP2), 1 was XLP1 (SH2D1A) and 5 were XLP2 (XIAP). Five cases were CNS-HLH. The median time to diagnose HLH to accept Haplo-HSCT was 9.2 (4 - 48) months. All patients received induce chemotherapy with HLH-94, HLH-2004 or DEP regimen before transplantation, 8 patients achieved complete remission (CR) and 21 achieved partial remission (PR). All donors received HLH-related gene sequencing, cytotoxic function testing and plasma EBV-DNA testing. 16 donors were derived from the father and 13 donors were from the mother. The Conditioning regimen was VP-16 / Bu / Flud / ATG ± CTX. The GVHD prophylaxis was either CSA or FK-506+MMF+Basiliximab. 27 patients achieved Stable hematopoietic reconstruction and two showed primary graft failure, which was obtained hematopoietic reconstruction after a secondary Haplo-HSCT. The median time of neutrophil engraftment was 13 (10 - 18) days, and that of platelet engraftment was 22 days (9 - 56) days. The incidence of II-IV acute GVHD was 55.2% (16 / 29), and that of chronic GVHD was 37.9% (11 / 29).With a median follow-up of 26.8 (6 - 72) months, the expected 5-year overall survival (OS) after transplant was 76.5% and the transplant-related mortality rate was 20.7% (6 / 29).The expected 5-year OS rate of patients with CR and PR before transplantation was 85.7% and 72.6%, respectively. CONCLUSION: Haplo-HSCT is an effective alternative treatment for PHLH in children < especially when appropriate unrelated donors are not available.

Poster #28



IMPACT OF PRESENTING SIGNS AND SYMPTOMS AND TREATMENT ON OUTCOMES OF PEDIATRIC PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN VIETNAM

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a rare hyper-inflammatory disorder characterized by a cytokine release syndrome that we see frequently at Children's Hospital No.1 in Ho Chi Minh, Vietnam. The goal of this research is to evaluate the association between clinical manifestations, laboratory features at diagnosis, and treatment with risk of recurrence and 3-year overall survival (OS). METHODS: A retrospective cohort study of children aged < 16 years with HLH diagnosed at Children's Hospital #1 in Ho Chi Minh City, Vietnam from 2014 to 2018. Information on diagnosis, clinical, laboratory, and treatment details were extracted from the medical record, entered into RedCap, and analyzed with STATA version 14. Descriptive data were expressed as mean ± standard deviation unless noted. RESULTS: A total 190 patients met diagnostic criteria based on the HLH -2004 protocol inclusion criteria. Median age at diagnosis was 2.6 years, male to female ratio was 1.0. The most common triggers were EBV infection (64.4%), CMV infection (23%) and sepsis (12.6%). Malignancy was not identified as a trigger in this cohort. The 3-year overall survival (OS) of all patients was 73.5% (CL 95%, 66.6% - 79.3%). Using a multivariate Cox regression model, age below 12 months, hyponatremia, and neurologic involvement at diagnosis, were associated with poor 3-year OS. Rapid improvement of ferritin concentration by at least 1000 ug/L after 1 week of treatment was associated with favorable 3-year OS. CONCLUSIONS: HLH is a rare disease with high mortality. EBV infection is the most common trigger in Vietnamese children. HLH should be treated early in infants, and children with neurologic symptoms. Serial analysis of the ferritin concentration is a good marker to follow treatment response and to guide rapid taper of therapy in children with HLH, especially in low-income countries where secondary infection risk in immunocompromised patients is high.

Poster #29



CLINICAL FEATURES OF PATIENTS WITH INFECTION INDUCED HLH: SET ETOPOSIDE ASIDE

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a severe overwhelming hyperinflammatory syndrome. Diagnostic criteria do not help to distinguish between primary or secondary HLH upfront. In addition, HLH awareness and treatment has grown dramatically in recent years, leading to an increase in treatment with etoposide. Unfortunately, treatment of HLH secondary to infection with steroids and etoposide can worsen the infection, thus leading to increased morbidity and mortality. The purpose of

this study was to retrospectively analyze clinical features of secondary HLH. METHODS: This is an IRB-approved retrospective, single center study from January 2017 to May 2022. Patients with a diagnosis of HLH secondary to infection with either cytomegalovirus (CMV), Epstein-Barr virus (EBV), or Ehrlichia chaffeensis were included. Patients with primary HLH, HLH secondary to malignancy, or received etoposide were excluded. RESULTS: Thirty-eight patients were identified with a diagnosis of HLH. Five patients (4 females, 1 male, median age of 6 years, age range 3-19 years) had secondary HLH to EBV (2) and Ehrlichia Chaffeensis (3). Four patients were started on doxycycline for presumed tick-borne illness, of which two were started on steroids. Ferritin level decreased by a minimum of 50% and platelets improved by a minimum of 45% within 48 hours of meeting HLH criteria for three patients treated with doxycycline alone and one patient who was treated with doxycycline and steroids. One of the patients on doxycycline and steroids had worsening clinical status and required Anakinra for definitive treatment. CONCLUSION: Patients treated for the underlying infection with antibiotics +/- steroids had a dramatic improvement from a clinical and laboratory standpoint. We examined the features of a very small cohort with HLH secondary to EBV/CMV/Ehrlichia. Future studies could include development of a clinical decision support tool using machine learning algorithms that include demographics, laboratory, and clinical features to distinguish primary and secondary HLH during initial presentation.

Poster #30



ARTIFICIAL INTELLIGENCE PROVIDES DEEPER GENETIC INSIGHT: PROFILE OF PRIMARY AND SECONDARY HLH USING LARGE SCALE ELECTRONIC HEALTH RECORDS

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a heterogeneous group of immune dysregulation disorders in children and adults. Most recently, HLH-like hyperinflammatory symptoms have been associated with severe hematological complications for patients undergoing immune checkpoint inhibitor therapies, such as anti-PD1 and anti-CTLA4. We retrospectively reviewed patients with suspected clinical diagnosis of HLH in a large NYC-based health system and a reference laboratory in the United States. METHODS: We developed a hybrid rule and deep learning-based clinical natural language processing(NLP) system to extract various clinical data elements from the electronic health records and executed analyses of HLH patients' de-identified clinical data through the Sema4 Centrellis Health Insight system, which include gold standard assessment of the accuracy of NLP-extracted clinical data. RESULTS: We found 440 patients with a clinical suspected diagnosis of HLH. For the 109 NYC patient cohort, 93 genetic variants were found in 38 patients; however, most of these genetic defects were associated with T and B cell development and function, lymphoproliferation, inflammation, and oncogenesis, and only a few were associated with primary HLH. In contrast, from the reference lab group, we found 33 of 331 patients with variants in HLH associated genes. CONCLUSION: We reports a large cohort of subjects with clinical suspected HLH, only small portion of patients with defects in lymphocyte

cytotoxicity or regulation of the inflammasome that characterize primary HLH. Many of these patients had B or T cells lymphatic malignancies, autoimmune disorders and/or recurrent infections. Although the exact disease mechanisms remain unknown, HLH like symptoms presented in these patients may be associated with the biologic treatments of the primary illnesses whose short- and long-term effects need further investigation. Overall, the Sema4 Centrellis health insight system empowered us for a longitudinal review of the clinical and genetic profiles in a large cohort of HLH patients.

Poster #31



INSIGHT INTO THE NATURAL HISTORY AND TREATMENT OUTCOMES OF HEMOPHAGOCYtic LYMPHOHISTIOCYTOSIS (HLH): THE INTO-HLH REGISTRY STUDY DESIGN

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PURPOSE: Hemophagocytic Lymphohistiocytosis (HLH) is a complex, hyperinflammatory syndrome resulting from the interplay of genetic predisposition and various environmental factors. In the last 25 years, scientific insights and treatments have evolved substantially with novel targeted therapies. However, approximately 30% of patients do not respond to therapy despite available treatment options. Thus, there is an unmet need for a deeper understanding of the natural history, clinical/ etiologic diversity, complications, and treatment outcomes of HLH patients, specifically from North America. The proposed study aims to establish a robust registry to better understand the natural history of HLH. METHODS: To address these knowledge gaps, we established a non-interventional, observational study with a dual-enrollment method for maximum engagement. Patients will be consented and enrolled in the study via the traditional Physician Driven Arm (PDA) and a Patient-Powered Arm (PPA), in which patients will be directly recruited through the Registry's website (www.hlhregistry.org). The Registry will include > 200 patients with clinically suspected or confirmed HLH, including familial and other subtypes of HLH. Medical records will be acquired by CCHMC and abstracted by the INTO-HLH Registry Team (IHRT) into pre-specified case report forms (CRF). Patients will be followed for at least five years, and physicians at the PDA sites will perform minimal data abstraction reflecting their subjective narrative regarding patients' treatments and responses. In addition, the patients will be offered to answer optional patient-reported outcomes questionnaires and correlative biology studies. RESULTS: The primary objective of the research is to describe the natural history of patients with HLH, and the secondary objective is to describe treatment patterns, responses, and outcomes. Health-related quality of life, disease-related health burden, and the relationship between biologic variability and clinical

outcomes will be assessed as exploratory objectives. CONCLUSION: The INTO-HLH Registry aims to advance clinical understanding to improve treatment outcomes in HLH.

Poster #32



MOLECULAR AND CLINICOPATHOLOGIC CHARACTERIZATION OF PEDIATRIC HISTIOCYTOSES

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PURPOSE: From children with histiocytosis, define the spectrum of somatic mutation and genotype phenotype correlation for each histiocytosis subtype. METHODS: Based on the French national network, 381 biopsies were review in our national expert histiocytosis reference center. RESULTS: A total of 334 LCH, 1 ECD, 19 RDD, 22 XGJ and 5 malignant histiocytosis (MH) were analyzed. BRAFV600E was the most common mutation found for LCH, highlighted in 50.2% (n=168). Among LCH WT for BRAFV600E, 97 were studied by DNA targeted-NGS and the following mutations were found: MAP2K1 exon 2 or 3 mutations (40%), BRAF exon 12 deletions (26%), BRAF exon 12 duplication (8%). Four patients had V600 codon mutation other than V600E. Four other patients harbored mutations in others genes (CSF1RQ965*, EZH2R684H, NF1R1250W, TET2Q810*). Finally, 18% remained WT. BRAFV600E was the only genetic event significantly correlated with LCH phenotype: 84 % of multisystem organ-risk positive (OR+) LCH and 100 % of neurodegenerative-LCH disease were positive for BRAFV600E. Other mutants were exceptionally associated with severe presentation (OR+ or severe lung involvement). Conversely, BRAFV600E mutation was only observed in 1/46 patient with non L-group histiocytosis (RDD, n=1) and among them, 41 were studied by DNA targeted-NGS. For RDD, 22.2% (4/18) had MAP2K1 mutations, one had KRASG13D, one had DNMT3AR749C mutation and 61.1% (11/18) were WT. For JXG, two had KRAS mutations (KRASG12R, KRASQ70_Y71ins), one had MAP2K1 mutation, one had CSF1RQ970* mutation, one had DNMT3AM548I mutation and 15/20 (75%) remained WT. Finally, among four NGS-studied MH, two had KRAS mutation (KRASQ61H, KRASA146P), one had ETV6M389I mutation and one had BRAFG469R associated with NF1E1266* mutation. CONCLUSION: In this study, we were able to decipher the mutational spectrum of childhood LCH and clinical correlation. More throughout study are necessary to investigated molecular mechanism responsible for JXG and RDD disease.

Poster #33



INDOMETHACIN REDUCE HOMING AND MIGRATION GENE EXPRESSION IN INFLAMMATORY LANGERHANS LIKE DENDRITIC CELLS

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PURPOSE: Indomethacin, a non-selective COX inhibitor, has proven to be an effective treatment for patients with skeletal manifestations of Langerhans cell Histiocytosis (LCH). Nevertheless, the specific mechanism leading to the clinical improvement of this drug in LCH has not yet been established. We hypothesize that indomethacin can affect the homing to the bone in Langerhans cells (LC) and their precursors. METHODS: In the current work, we evaluated the expression of homing and migration molecules in sorted circulating mononuclear myeloid cells of patients with LCH and healthy controls by qPCR and flow cytometry. To dissect the effect of indomethacin on the expression of homing related genes, we standardized an in-vitro inflammatory Langerhans like dendritic cells "LC-like" model (IL-4 plus GM-CSF plus TGFb plus TNFa plus dexamethasone) from control CD14 monocytes in contrast to conventional dendritic cells (GM-CSF plus IL-4) in the absence and presence of indomethacin (30 to 100 uM). RESULTS: We have found that AXL, a tyrosine kinase receptor involved in cancer cell migration, is significantly increased in patients with LCH (N=13, P=0.01) and particularly higher in bone compromise (N=6, P=0.0001). Furthermore, sorted myeloid cells of patients with bone LCH have increased expression of CCR6 (N=6), a chemokine receptor which higher expression is associated with homing to the bone. In addition, in-vitro inflammatory LC-like cells were characterized by high levels of AXL, CXCR4 and CCR6, compared to conventional dendritic cells. We have found that in vitro indomethacin treatment of this inflammatory "LC-like" significantly reduced AXL receptor expression (N=6, P=0.03), and decreased the inflammatory cytokine TNFa, and the chemokine receptor CCR6. CONCLUSION: Our results suggest that indomethacin could be affecting the homing of LCH precursors to the bone and consequently reducing tissue damage.

Poster #34



METABOLITES WITH POTENTIAL DIAGNOSTIC VALUE IN PLASMA OF LANGERHANS CELL HISTIOCYTOSIS CHILDREN WITH POSTERIOR PITUITARY INVOLVEMENT

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PURPOSE: To figure out early diagnostic markers for posterior pituitary involvement in children with LCH. In our hospital, 70 percent of Langerhans cell histiocytosis (LCH) with posterior pituitary involvement developed the sequel of diabetes insipidus (DI). Therefore, early diagnosis and treatment of posterior pituitary involvements are very important. **METHODS:** In total, 72 plasma samples collected from children with LCH and 30 plasma samples collected from healthy children were enrolled in this study. The children with LCH were divided into 3 groups: patients with posterior pituitary involvements (Group PI), patients with CNS-risk lesions but without posterior pituitary involvements (Group CNS-risk), and patients without posterior pituitary involvements or CNS-risk lesions (Group NPC). Through non-targeted metabolomics sequencing, we analyzed the Metabolites with potential diagnostic value for posterior pituitary involvement. **RESULTS:** Metabolomics sequencing showed that the Bilirubin and L-Cystine were significantly upregulated in the peripheral blood of LCH children with pituitary involvement (PI). Prostaglandin D2 was obviously down-regulated in the peripheral blood of LCH children with PI. Roc Curve analysis showed that significant up regulations of Bilirubin and L-Cystine or down regulations of Prostaglandin D2 may be used to predict the PI development of LCH children when compared with children of CNS-risk involvement and NPC involvement group. **CONCLUSIONS:** The bile secretion, arachidonic acid metabolism, cysteine metabolism and methionine metabolism may play critical roles in the progression of pituitary involvement of LCH children. Study of LCH metabolomics will promote the development of early diagnosis and treatment of LCH.

Poster #35



COMPARISON OF BASIC CYTOPHYSIOLOGICAL FEATURES OF THREE CELL LINES DERIVED FROM PROGRESSIVE LANGERHANS CELL HISTIOCYTOSIS OF BONE AND SKIN

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Pre-clinical in vitro models for LCH studying are limited due to problems with establishing cell lines characterized by increased proliferation and clonogenic potential in long-term cultures. This study has compared the cytophysiological features of three cell lines derived from LCH patients with lesions affecting the skin (RAB-1; HAN-1) and bone (CHR-1). The bromodeoxyuridine (BrdU) incorporation assay was performed to determine the number of actively dividing LCs, which were also identified by cell cycle analysis. A colony formation assay was performed to assess the ability of LCs to survive and reproduce colonies.

The cell growth was also established based on evaluating metabolically active cells using MTS assay and Alamar blue. The ultrastructure of LCs was monitored with a confocal microscope and scanning electron microscope. Molecular markers associated with histiocytosis progression and invasion were determined at mRNA (RT-qPCR) and protein (Western blot). Additionally, RT-qPCR was used to detect long non-coding RNAs (lncRNAs) and small non-coding RNAs (miRNAs) regulating oncogenesis. The established primary cell cultures were adherent and heterogenic in size and morphology, with a predominant fibroblast-like morphotype. The cells were characterized by a centrally located, round nucleus well-developed actin cytoskeleton and improved mitochondrial metabolism, evidenced by increased membrane potential. The RAB-1 cell line showed the highest intracellular accumulation of CD207, vimentin (VIM), metalloproteinase 9 (MMP-9), CTLA4, CEACAM6, HLADR+DP+DQ, and intercellular adhesion molecule 1 (ICAM-1). At the same time, RAB-1 showed the highest proliferation activity, associated with increased DNA synthesis and replication, evidenced by increased BrdU incorporation and frequency of S-phase cells. The mean population doubling time of LCH primary cell lines was 61+12 hours. All cell lines showed increased levels of miR-145-5p and lncRNA MEG3, indicating the potential role of those molecules as cell-specific biomarkers. The obtained models can be used for studies to develop targeted and personalized therapies for LCH.

Poster #36



CLINICAL IMPLICATIONS OF CIRCULATING BRAFV600E PRECURSORS IN LANGERHANS CELL HISTIOCYTOSIS

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PURPOSE: Langerhans Cell Histiocytosis (LCH) is a myeloproliferative neoplasia driven by somatic mutations in the mitogen-activated protein kinases pathway (MAPK) with clinical manifestations ranging from single indolent lesions to severe and potentially lethal multifocal disease. LCH is clinically staged as "high risk" (e.g. liver, spleen and/or bone marrow involvement) or "low risk" (e.g. no risk organ involvement) due to risk of death. However, defining clinical risk status may be variable between sites due to differences in imaging techniques (e.g. PET-CT vs x-ray/ultrasound) or inconsistent histologic protocols (e.g. morphology only vs VE-1 antibody). We previously identified peripheral blood mononuclear cells (PBMC) with BRAFV600E in all patients with HR LCH and less frequently in LR LCH. In order to more definitively determine the clinical significance of BRAFV600E+ PBMC at diagnosis, we analyzed an extended cohort with longitudinal clinical evaluations. **METHODS:** In this study, genomic DNA was isolated from the PBMCs of patients with active LCH before initial therapy and the percentage of circulating cells with the BRAFV600E allele in patients was estimated by quantitative polymerase chain reaction. Clinical results were analyzed from medical records. **RESULTS:** Pre-therapy peripheral blood samples were collected from 314 patients with clinically detectable active disease, and PMBC with BRAFV600E were identified in 40 of the patients. The presence of BRAFV600E+ PBMC in

LCH patients was found to be significantly associated with high risk disease, relapse, and development of neurodegeneration. CONCLUSION: Mutually exclusive somatic mutations in MAPK pathway genes are identified in almost all cases of LCH. However, mechanisms underlying clinical heterogeneity in this "single mutation" disease are incompletely defined. Results from this study support potential for pre-therapy BRAFV600E to predict clinical risks and inform pathogenic mechanisms in LCH.

is limited in Spain and clinical information about only 13 patients was available after a national survey and the review of LCH-IV cases. Refractory MS-LCH showed rapid tumor regression, but relapse after stopping therapy appeared in most cases. The efficacy in LCH-ND is still controversial. The development of new international trials with targeted therapies might contribute to reduce burden by chemotherapy in LCH patients and improve the knowledge about its effectiveness and safety in children.

Poster #37



RESULTS OF A NATIONAL SURVEY ABOUT THE USE OF MAPK PATHWAY INHIBITORS IN PEDIATRIC HISTIOCYTOSIS IN SPAIN

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PURPOSE: Access to clinical trials with MAPK-pathway inhibitors in patients diagnosed with histiocytosis is very limited worldwide. The aim of the study is to review the off-label use of these drugs in pediatric patients in Spain and the analysis of the real-world effectiveness and safety. **METHOD:** We developed a survey to know the use of inhibitors among SEHOP members and also we reviewed LCH-IV patients treated with inhibitors. We used the database prepared by the French group about type, indications, response and adverse effects. **RESULTS:** The survey was sent in February 2022 to 300 SEHOP members and colleagues from 11 Spanish hospitals showed interest to participate but data were collected about 7 patients (3- refractory MS-LCH, 2-ND-LCH, 1 mixed histiocytosis and 1-Erdheim-Chester disease). Since LCH-IV study open in Spain in 2017 until April/2022, 127 patients were enrolled and inhibitors were used in 6 patients (3-ND-LCH,2-refractory MS-HR-LCH and 1-high-risk relapse). The main indications for inhibitors were Langerhans cell histiocytosis (LCH) in 11 and rare histiocytosis in 2 patients. BRAF inhibitors were administered in 12 (6-vemurafenib, 6-dabrafenib) and MEK in 2 patients (trametinib). No up-front inhibitors use was reported. Oral tolerance was good, without severe adverse effects. Therapy duration ranged from six months to five years and most of the patients are still on-therapy. **CONCLUSIONS:** Off-label use of MAPK pathway inhibitors in pediatric patients diagnosed with histiocytosis

Poster #38



THE PATHOLOGIC FEATURES OF RELAPSED BRAF-V600E LANGERHANS CELL HISTIOCYTOSIS WITH A CD163 PHENOTYPE

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PURPOSE: In Langerhans cell histiocytosis (LCH), the BRAF-V600E mutation is associated with increased risk of relapse; however, the pathology in such relapses is poorly characterized. We describe the pathology in two pediatric relapses. **METHODS:** A 14-month female with biopsy proven LCH (CD1a/Langerin) arising in the ear/mastoid bone (including MS-LCH: skin, thymus, palate involvement) was treated according to LCH IV protocol. Three months after the cessation of therapy, a cutaneous yellow nodule erupted on right upper back, which was biopsied (A). A 4-year-old male with eye swelling and multiple lytic skull lesions was treated for LCH based on clinical/imaging features. A 6-week MRI assessment showed initial favorable response. At the end of therapy, skeletal survey showed additional lytic lesions and PET scan demonstrated new avid lesions of scapula and soft thigh, the latter which was biopsied (B). **RESULTS:** The cutaneous relapse (A) showed reticulohistiocytoma (RH)-like cells with rare emperipolesis and smaller inconspicuous cells with reniform nuclei. The RH-like cells expressed CD163/CD14/fascin/Factor XIIIa together with light CD1a expression; Langerin negative. The smaller cells were diffusely positive for CD1a/S100/fascin but lacked strong Langerin expression. The soft tissue relapse (B) showed predominantly xanthomatous histiocytes with Touton-like cells, some with focal emperipolesis, and focally clustered smaller cells with reniform nuclei. The xanthomatous cells were diffusely CD163/CD68 positive with focal S100 staining and rare CD1a/Langerin staining. The CD1a/Langerin stains also highlighted the few smaller cells with reniform nuclei. In both cases (A-B), the BRAF VE1 mutant specific immunostain was expressed in all histiocytic components. **CONCLUSION:** These cases provide new insight into the pathology of pediatric relapse/persistent disease in BRAF-V600E mutant histiocytosis, including a CD163+ xanthogranuloma-like phenotype,

admixed with variable CD1a/Langerin expression. Further investigation is needed to understand what contribution this mutant CD163+ phenotype has on relapse/treatment resistance in BRAF-V600E mutant histiocytosis.

Poster #39



COBIMETINIB FOR TREATMENT OF PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS

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BACKGROUND: There are increasing data of targeted therapy efficacy of different types of Langerhans cell histiocytosis (LCH) with inhibitors of BRAF-specific serin-threonine kinase (BRAF-inhibitors) in cases with BRAFV600e mutation published last years. At the same time there are much less published data of use of inhibitors of MAPK/ERK pathway (MEK-inhibitors) in pediatric patients with BRAF-negative forms of LCH. Aim of the study is to evaluate efficacy and safety of MEK-inhibitor cobimetinib in eight pediatric BRAFV600e-negative refractory LCH patients. **MATERIALS AND METHODS:** The study included 10 children with various forms of LCH: 3 - with multisystem (MS) LCH, 5 - with bone involvement of single system (SS) LCH and 2 cases with neurodegeneration. All patients received therapy according to the LCH IV protocol and were diagnosed with progression of LCH during or after termination of the treatment. The response to the therapy in SS-LCH cases was assessed in accordance with the international scale Response Evaluation Criteria in Solid Tumors (RECIST v.1.1). The assessment of the toxicity was performed in accordance with the international scale of Common Terminology Criteria for Adverse Events (CTCAE v.5.0). **RESULTS:** Complete response was not achieved in any patient. Partial response was established in 62,5% cases. One patient was diagnosed with disease progression in three months after termination of the therapy. The incidence of adverse events was high (75%). The most common side effects were diarrhea (75%), rash (50%) and electrolyte disturbances (37,5%). **CONCLUSION:** Cobimetinib therapy is effective in BRAF V600e negative refractory pediatric LCH patients. The response to the treatment can be delayed. All cases of the toxicity were dose depended and successfully resolved after dose correction. Further research is needed to define duration of treatment and optimal pediatric dosage.

Poster #40



NEONATAL LANGERHANS CELL HISTIOCYTOSIS: EXPERIENCE FROM HONG KONG

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BACKGROUND: Langerhans cell histiocytosis (LCH) is a rare disease with diverse clinical course. Neonatal LCH is known but uncommon while information from literature on this group of patients is limited. **PURPOSE:** To provide information on the clinical course and molecular characteristics of patients with neonatal/ congenital LCH. **METHODS:** We performed a retrospective review of medical records of patients diagnosed of LCH at neonatal period in all 6 paediatric oncology centres in Hong Kong from 1997-2021. Tissue samples were retrieved for analysis of BRAF V600E and MAP2K1 mutation by sanger sequencing. **Results:** Six patients with neonatal LCH were identified out of 95 LCH patients diagnosed in the study period. Five had symptoms onset at birth. All except one patient were born full term. The only premature baby had rash at 1 week of life which resolved spontaneously. All patients had single-system involvement of skin rash at disease onset. Three patients (50%) later progress to multi-system disease with risk organ involvement, all of whom required intensive care unit admissions with no mortality. Four out of 6 patients (67%) received chemotherapy. Reactivation was noted in 4 patients, 3 of whom received chemotherapy at initial diagnosis. None of the reactivations involved risk organs. Three (50%) patients developed permanent consequences of diabetic insipidus. One of them had eye involvement resulting in blindness. BRAFV600E mutation was noted in this patient. MAP2K1 mutations were present in 2 patients. **CONCLUSION:** Neonatal/ congenital LCH is characterized by skin involvement at diagnosis. Significant proportion progressed to severe multisystem involvement. Reactivation and permanent consequences are common.

Poster #41



DEVELOPMENT OF ACUTE MYELOID LEUKEMIA WITH MINIMAL DIFFERENTIATION IN A PATIENT ON LONG-TERM VEMURAFENIB FOR HIGH RISK BRAF V600E+ MULTISYSTEM LANGERHANS CELLS HISTIOCYTOSIS WHO RECEIVED SEVERAL LINES OF CHEMOTHERAPIES

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PURPOSE: The use of target therapies in refractory Langerhans cells histiocytosis (LCH) becomes a mortal to a chronic disease. Their use has not been standardized, and long-term risks are under investigation. **METHOD:** Case report of a child on long-term vemurafenib therapy for refractory BRAFV600E LCH who developed an acute myeloid leukemia (AML) with minimal differentiation after several lines of treatment.

RESULT: Three-year old boy, one-month old at diagnosis of LCH MS RO+ with severe compromise of liver, spleen, hematologic and skin with risk organs(RO) dysfunction(severe anemia, thrombocytopenia and hypoalbuminemia). He received 1st line treatment with prednisone(PDN)-vinblastine with transient response. The patient had progressive disease in the liver, spleen and skin. After a second line of treatment with PDN-Vincristine-AraC the patient had bone and skin progression. Cladribine 5mg/m2/day-Cytarabine 100mg/m2/day x5 days was initiated with liver, spleen, hematological involvement, nodes and skin progressive disease. Fourth line treatment with clofarabine 25mg/m2/day x5 days was ineffective with severe transfusional requirements and severe hypoalbuminemia. At 14 months-old, BRAFV600E mutation was detected in a bone marrow biopsy. Target therapy with vemurafenib 40 mg/kg/day was initiated. Transfusional requirements diminished and albumin levels returned to normal. His disease showed NAD of non-risk organs, but AD better in RO (severe hepatosplenomegaly, moderated pancytopenia persisted). After 33 months he began with transfusional requirement and peripheral blast cells. A bone marrow biopsy shows severe myelodysplasia with monosomy 7. Bone marrow's flow cytometry confirmed 23% of CD13+,CD117+,HLA-DR+,CD11a+ aMPO+/- blast cells. Due to an ominous prognosis, palliative care was decided. The patient is in an ambulatory setting with transfusion support, and he is still on target therapy. CONCLUSION: More evidence, longer follow-up and guidelines are necessary regarding targeted therapy. The importance of LCH bone marrow involvement (myelodysplasia) or the therapy in the pathogenesis of secondary AML deserves to be evaluated in these patients.

Poster #42



SOFT TISSUES LANGERHANS CELLS HISTIOCYTOSIS SECONDARY TO VACCINES. TWO CASE REPORTS

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PURPOSE: Langerhans Cells Histiocytosis (LCH) have been defined as a myeloid inflammatory neoplasia with activation of MAPK/ERK signaling pathway. Sometimes it could be triggered by external factors. We describe two cases of soft tissue LCH secondary to vaccines. RESULTS: Case 1. Four-month-old male with isolated cutaneous LCH confirmed by biopsy. The lesion variably responded to local corticosteroid therapy. Eight months later, a reddish painful nodule appeared in the middle of his right thigh in the site of MMR (Measles-Mumps-Rubella) vaccine. The ultrasonography (US) showed a 54x25x17mm mass in relation with the external vastus muscle. As the boy was asymptomatic, parents initially refused to perform the biopsy. Four months later, a new image (MRI) showed the lesion increased in size (95mm) and a new mass of 30mm appeared in the left thigh. The masses were completely excised. Pathology findings were consistent with LCH (CD1a+/CD207+). He was treated with

prednisone and vinblastine for 6 months with complete response. Case 2. An asymptomatic 11-month-old boy that received the Bacillus Calmette-Guerin (BCG) vaccine at birth developed two months later a progressive tumor in the deltoid region. It was assumed as a vaccine complication, but the immunological evaluation did not show positive findings. At 2 and 4 months-old the patient received the DPT-HB-Hib (Diphtheria-Pertussis-Tetanus-Hepatitis B-Haemophilus influenzae type b) vaccine in their thighs without complication. At 6 months of age the patient received the same vaccine in their left thigh and a new tumor appeared. The US showed a hypoechoic vascularized mass that compromised subcutaneous tissue and muscle. An excisional biopsy of the thigh's tumor was performed. The pathology showed LCH (CD1a+/CD207+) with BRAF V600E+ by RT-PCR. A complete baseline evaluation was performed, only a mild eczema of the scalp was found. CONCLUSION: Soft tissue LCH secondary to vaccines appears to be a rare and non-aggressive cutaneous presentation.

Poster #43



VARIATION OF DIAGNOSTIC APPROACHES AND TREATMENT PRACTICES FOR HLH/MAS AMONG PEDIATRIC SUBSPECIALISTS

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PURPOSE: Hemophagocytic Lymphohistiocytosis (HLH) and Macrophage Activation Syndrome (MAS) are hyperinflammatory syndromes of pathologic immune activation with variable, and often, non-specific presentations. Given its complexity, patients with HLH/MAS are cared for by a variety of subspecialists. We compared diagnostic and treatment practices among a variety of subspecialists at pediatric institutions in the United States (US). METHODS: Using a web-based survey, we assessed the consultation, diagnostic and treatment preferences of providers from the different pediatric specialties who care for pediatric HLH/MAS patients. Domains included demographics, provider training level and specialty, experience and comfort level with the diagnosis and treatment of HLH/MAS and institutional approaches toward the diagnosis and management of HLH/MAS. Participants were also given two case scenarios; one describing Epstein-Barr virus (EBV)-associated HLH and another describing an underlying chronic autoinflammatory disorder and MAS. Participants indicated preferred consultants, work up and treatment for each case. RESULTS: Of 263 respondents, 23%, 29%, 39%, 7% identified as hematology/oncology (HO), rheumatology, general pediatrics/critical care/hospitalist, and immunology, respectively. For EBV-HLH, HO was the preferred first consultant by the majority of respondents other than rheumatologists, of whom only 47% agreed. For MAS, 92% of respondents from all specialties favored rheumatology consultation. Preferred diagnostic tests varied by subspecialty with HO more likely than rheumatology to order an infectious workup, NK cell function, soluble IL2 receptor, bone marrow biopsy and genetic testing. First-line therapy also varied, with HO preferring dexamethasone and etoposide and rheumatology more often preferring methylprednisone and anakinra. Half of respondents were unaware of established institutional algorithms for diagnosis and treatment of HLH/MAS. Most (85.6%) favored the development of treatment

algorithms for HLH/MAS and 90% supported a multidisciplinary approach. CONCLUSION: Current consulting patterns, diagnostic workup and treatment approaches of HLH/MAS vary by specialty, highlighting the need for standardized management algorithms and institutional multidisciplinary HLH/MAS teams.

Poster #44



UNUSUAL PATIENT WITH LANGERHANS CELL HISTIOCYTOSIS WITH SEVERE ATYPICAL SKIN, BONE INVOLVEMENT AND ALBINISM

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PURPOSE: To present an unusual patient with a rare association of Albinism and Langerhans cell histiocytosis with severe atypical ulcerative skin involvement, extensive bone lesions and adjacent soft tissue involvement. Case report. A 3 year old boy, with albinism, had a history of severe ulcerative lesions in the right retroauricular region, left parietal and right superior eyelid. The lesions were exudative ulcers, encompassing the entire epidermis and dermis. The largest one in the parietal region measured 3 centimeters. The retroauricular ulcer measured 2 centimeters. Scaling white to red macules in scalp. The right upper eyelid injury prevent the eye from opening. Previously received multiple antibiotic and antifungal treatments. Cerebral MRI reported 3 masses in soft tissues. One on the right orbit with extension to the frontal bone, the second one involved occipital and temporal bones and the third one was localized in the occipital bone. Bone series showed multiple osteolytic lesions in the skull. The frontal bone was almost completely destroyed. The patient had anemia (Hb 8.5g/dL) with no other organ involvement. Pathology reported Langerhans cell Histiocytosis (CD1a, Langerin, S100 protein were positive). Started treatment according to LCH III guidelines (Prednisone, vinblastine, 6-mercaptopurine). After 7 weeks we performed an evaluation, there was marked improvement in the appearance of skin ulcers as well as bone lesions. We are waiting for the genetic study in hair and the centralized review of pathology. **CONCLUSIONS:** A wide spectrum of cutaneous manifestations that can simulate other common dermatoses has been described in Histiocytosis. However, to our knowledge, there have been no previous descriptions in literature of association between albinism and histiocytosis. Further studies may be conducted to established correlation between this entities like has been describe in other like Chediak Higashi syndrome.

Poster #45



AGGRESSIVE UNIFOCAL BONE LANGERHANS CELL HISTIOCYTOSIS WITH SOFT TISSUE EXTENSION BOTH RESPONSIVE TO RADIOTHERAPY: A CASE REPORT

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Langerhans cell histiocytosis (LCH) is a rare haematological neoplasm characterized by the accumulation of CD1a+, CD207/Langerin+ histiocytes within inflammatory lesions. LCH can involve any organ, but osteolytic bone lesions are most often encountered. The vast majority of unifocal bone lesions spontaneously regress after a thick needle biopsy has been taken. We describe the initial presentation of BRAFV600E mutated unifocal bone LCH in the left proximal humerus of a 46-year-old previously healthy woman. Despite multiple surgical interventions, she unexpectedly experienced progressive disease manifestation with significant soft tissue extension to the surrounding musculature, subcutis and epidermis. Because the disease manifestation remained loco-regional, radiotherapy (RT) (total dose of 20 Gy in 10 fractions) was initiated. This approach resulted in swift clinical improvement with a notable reduction of pain already after 7 days. MRI and PET-CT imaging performed 2.5 months after the last RT dose showed a substantial decrease of both tumoral mass and FDG-uptake, indicating a significant radiological response. Follow-up MRI's and PET-CT's demonstrated complete radiological remission at 27 months after RT, without any new lesions. Complete cutaneous and soft tissue healing was observed at 9 months after RT. The patient achieved a complete remission without any side effects. This case highlights that RT is a rational and relative mild local treatment option for patients with aggressive LCH affecting the bone and surrounding soft tissue.

Poster #46



DABRAFENIB FOR RESISTANT BRAF MUTATED MULTI-SYSTEM LANGERHANS CELL HISTIOCYTOSIS

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PURPOSE: Treatment of multisystem Langerhans cell histiocytosis (LCH) with risk organ involvement is challenging given hematologic and infectious toxicity, risk of disease progression and death. This case report describes the use of an oral BRAF inhibitor, dabrafenib, in a pediatric patient with multi-system risk organ positive LCH that was refractory to multi-agent intensive frontline chemotherapy. **METHODS:** This is a retrospective case report of a single patient treated at a freestanding academic pediatric hospital in Kansas City, MO, USA. **RESULTS:** This child was 10 months of age when she developed extensive petechial skin rash in her inguinal and axillary regions and scalp rash similar to seborrhea. She had hepatosplenomegaly with liver dysfunction evidenced by hypoalbuminemia and bone marrow aspirate demonstrated involvement of LCH cells. Radiographic imaging with positron emission testing (PET) was diffusely

positive in liver, spleen and skeleton. BRAF testing was performed on skin biopsy and positive for BRAFV600E mutation. She was treated with vinblastine and prednisone with partial response at six weeks of therapy. She was then transitioned to more intensive chemotherapy with cladribine and cytarabine again with incomplete response. She underwent a splenectomy due to persistent thrombocytopenia and growth delay; histologic exam showed viable LCH cells harboring the BRAFV600E mutation. Since she had exhausted multiple therapeutic options, treatment with oral dabrafenib was initiated after thorough discussion on potential risks and benefits. After 8 months of therapy, she has demonstrated resolution of PET positive lesions and clinical improvement. CONCLUSION: Oral dabrafenib has been successful in suppressing the multi-system risk organ positive LCH manifestations in this patient and improving her quality of life.

Poster #47



LONG TERM TREATMENT OF LCH-RELATED NEURODEGENERATION WITH IVIG AND MEK/BRAF INHIBITION

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PURPOSE: To describe the long-term treatment with intravenous immune globulin (IVIG), MEK (cobimetinib), and B-RAF (dabrafenib) inhibition for a patient with neurodegeneration associated with Langerhans Cell Histiocytosis (LCH). METHODS: The patient is now a 19-year-old male diagnosed with B-RAF-positive, refractory, multifocal bone LCH in 2008. He received two 12-month treatment courses of prednisone and vinblastine, followed by vincristine and cytarabine starting in 2015. A brain MRI revealed neurodegeneration, and he was started on monthly IVIG treatments. Serial brain MRIs remained stable, and in February 2019, he had progressive speech and balance abnormalities, consistent with worsening neurodegeneration. The IVIG was discontinued, and he started treatment with cobimetinib. While on this treatment, his Scale for Assessment and Rating of Ataxia (SARA) scores decreased from 8.5 to 2.5. In October 2020, the cobimetinib was discontinued due to the development of an acneiform rash. He then experienced a progressive decline in neurocognitive functioning and an increase in his SARA score to 8. In July 2021, cobimetinib was restarted with a 25% dose reduction due to rash. One month later, his treatment was switched from cobimetinib to dabrafenib due to painful worsening of the rash. His SARA score at that time was 5.5. As of March 2022, he continued on dabrafenib, and his SARA score had decreased to 3. His most recent brain MRI in December 2021 showed stable neurodegeneration. RESULTS: After a progression of his symptoms on IVIG, the patient had a measurable improvement in his SARA scores while being treated with a MEK or B-RAF inhibitor. CONCLUSION: This patient demonstrates by proof-of-principle that MEK or B-RAF inhibition has a sustainable, objective, therapeutic effect on symptoms of neurodegeneration associated with LCH. Additional studies are required to determine the optimal duration of treatment.

Poster #48



MANAGEMENT OF SEVERE LUNG INVOLVEMENT IN CHILDHOOD LCH: AN EXCEPTIONAL SINGLE-CASE REPORT WITH LUNG TRANSPLANTATION

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PURPOSE: Severe lung involvement in childhood LCH is rare and management is highly challenging. METHODS: We report a 2-year-old boy with very severe diffuse cystic lung lesions followed over 30 months since diagnosis. RESULTS: A 26-month-old boy presented with a respiratory distress, cervical tumor syndrome and skin lesions of the scalp. The thoracic CT-scan revealed diffuse cystic lesions involving the entire lung parenchyma, as well as nodular opacities. The skin biopsy confirmed the diagnosis of LCH with BRAF c.1457_1471 deletion. After 4 weeks of induction with vinblastine-corticosteroid therapy, the patient had a partial response regarding skin lesions and tumor syndrome, but cystic lesions assessed by CT scan worsened (cysts score at 19 versus 14 at diagnosis). Subsequently, second-line therapy with cobimetinib 1mg/Kg/day on days 1-21 in each 28-day cycle was started, leading to rapid complete remission of extrapulmonary lesions. However, the patient presented persistent respiratory insufficiency and experienced 9 hospitalizations in intensive care unit over 18 months (life-threatening pneumothorax, n=6, with heart failure, n=2). Regarding the increase in frequency of pneumothorax, nasal high flow oxygen needs and no improvement of the pulmonary parenchyma imaging with time (cysts score at the maximum value of 24, stable for 12 months), the patient was registered on waiting list for lung transplantation. Two months after, at the age of 3.6 years (weight 11.3 kg, height 92 cm), a bilateral lung transplantation was performed. The immediate postoperative course was straightforward, with rejection prophylaxis with MMF and tacrolimus combination. Cobimetinib therapy was pursued without interruption between cycles to avoid interaction variations. At 11 months post-transplant, the child is at home, eupneic but remains under close medical supervision. CONCLUSION: In childhood LCH, lung transplantation may be considered at last resort under cover of targeted therapy in the presence of severe persistent cystic lung lesions.

Poster #49



CO-OCCURRENCE OF HODGKIN LYMPHOMA IN A PATIENT WITH LANGERHANS CELL HISTIOCYTOSIS: A CASE REPORT

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Langerhans cell Histiocytosis (LCH) is a rare disease characterized by monoclonal proliferation and diffuse infiltration of CD1a+ immature dendritic cells. Bone involvement is a key feature, although it can compromise any organ with exception of heart and kidneys. In this report we present the case of a 30-year-old male patient with a one-month history of iliac crest pain, regional adenomegaly and fever. Bone biopsy showed CD1a+, S100+ histiocytes infiltration. Magnetic resonance imaging (MRI), scintigraphy and ultrasonography showed no signs of systemic compromise. Single system LCH was diagnosed and daily treatment with Indomethacin 150 mg orally was started. Although there were no changes in lymph node size, improvement of pain was reported. A year later, the patient developed lower back pain with asthenia. New MRI revealed involvement of multiple abdominal and retroperitoneal lymph nodes. Inguinal node histology was compatible with nodular sclerosis Hodgkin Lymphoma with no evidence of Langerhans cell Histiocytosis. Treatment for both pathologies is currently being provided with good tolerance. LCH can be associated with other neoplasms, but this scenario is rare. In this report we discuss the co-occurrence of these diseases.

Poster #50



18F-FDG PET/MRI AND DIFFUSION-WEIGHTED MRI FOR STAGING AND TREATMENT MONITORING OF LANGERHANS CELL HISTIOCYTOSIS IN CHILDREN

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PURPOSE: Whole body (WB)18F-FDG PET is commonly incorporated into the clinical care of patients with Langerhans cell histiocytosis (LCH) and causes radiation exposure. We compared the diagnostic accuracy of WB 18F-FDG PET with DW-MRI, which has no radiation involved, for staging and treating LCH in children. MATERIALS AND METHODS: Twenty-three children with LCH underwent 18F-FDG PET and DW-MRI at baseline (n=23) and after chemotherapy (n=16). Two reviewers independently assessed the presence or absence of tumors in 8 anatomical areas. Changes in tumor standardized uptake

values (SUV) and apparent diffusion coefficients (ADC) before and after chemotherapy were compared with a Mann-Whitney U test. The correlation between SUV and ADC was assessed with the Spearman correlation coefficient. Tumor therapy response according to Lugano and PERCIST criteria was compared with a Cohen's kappa test. RESULTS: Sensitivity and specificity were 100% and 100%, respectively for 18F-FDG PET, and 18F-FDG PET/DW-MRI; 95.5% and 100% for DW-MRI. Responders had a significantly different pre-to-post treatment change in SUVratio and ADCmean compared to no-responders (p=0.0006, and p=0.003 for SUVratio and ADCmean, respectively). Pre-to-post treatments changes in SUVratio and ADCmean were inversely correlated for all lesions (r:-0.27, p=0.06). 18F-FDG PET had a higher agreement with Lugano criteria than PERCIST (k: 0.84 vs 0.69), while DW- MRI had a similar agreement with both criteria (k: 0.67 and 0.71). CONCLUSIONS: 18F-FDG PET/MRI and DW-MRI are equally effective for staging and treatment monitoring of LCH. This opens opportunities for personalized radiation-free imaging protocols, where DW-MRI could be considered as an alternative approach without radiation exposure.

Poster #51



CLINICAL RESPONSES IN PATIENTS RECEIVING COMBINATION CHEMOTHERAPY AND MAPK PATHWAY INHIBITION FOR REFRACTORY LANGERHANS CELL HISTIOCYTOSIS

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PURPOSE: Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia driven by activating MAPK pathway mutations. MAPK pathway inhibition (MAPKi) is associated with high response rates in patients. However, MAPKi monotherapy may not be curative, and some patients have progressive disease despite MAPKi. We hypothesize that the combination of chemotherapy and MAPK inhibition may render LCH cells more sensitive to cytotoxicity. In this study, we assess the safety and efficacy of combination therapy in 8 patients with refractory systemic disease (4), neurodegenerative LCH (LCH-ND) (3), and/or CNS juvenile xanthogranuloma (CNS-JXG) (1). METHODS: Records of patients treated with chemotherapy and MAPK inhibitor combination at Texas Children's Hospital from October 2018 to November 2020 were reviewed for peripheral blood/tissue BRAFV600E mutation status, ataxia rating scores, and toxicity. RESULTS: This cohort was heavily pretreated, with a median of 6 (range 1-14) prior therapies. "Combination therapy" included chemotherapy (cytarabine and/or clofarabine) with MAPKi (dabrafenib, vemurafenib, trametinib and/or cobimetinib), with a median treatment time of 6 months (range 2-12 months). Overall best imaging responses were partial response (4/8), stable disease (3/8), and not evaluable (1/8). 5/8 patients had detectable BRAFV600E+ peripheral blood mononuclear cells (PBMCs): 3/5 had a reduced/stable and 2/5 had an increased percentage of BRAFV600E+ PBMCs by the end of combination therapy. Ataxia rating score was improved or stable in all four (3 LCH-ND, 1 CNS-JXG) patients with neurodegeneration, and 2/2 patients with radiologic neurodegeneration without clinical deficits. Common toxicities during

treatment included fever (grade 1), skin rash (grade 1), arthralgia (grade 1), and cytopenia (grade 1-3). CONCLUSION: The combination of chemotherapy with MAPK inhibitors was associated with clinical improvement in some patients with highly refractory systemic LCH, LCH-ND, and CNS-JXG. Prospective multi-center trials are required to further understand the potential benefits and risks of combining chemotherapy with MAPK inhibition.

Poster #52



CLINICALLY SILENT LATE RELAPSE OF LANGERHANS CELL HISTIOCYTOSIS (LCH) IN CNS: VALUE OF REGULAR MONITORING OF RADIOLOGICAL NEURODEGENERATIVE DISEASE RELATED TO LCH AND THE ROLE OF DETECTION OF ELEVATED NFL PROTEIN IN CEREBROSPINAL FLUID

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CASE PRESENTATION: A 4-year old boy presented initially with multisystemic LCH (multifocal bone disease with maximum involvement in right orbit with enourmous exophthalmus, and cervical and axillar lymphadenopathy). While on treatment according to LCH-IV, Stratum I, group 1, he progressed in orbita, while all the other lesions were healed. Treatment was augmented with 6-mercaptopurine and indomethacin. After 2.5 years of therapy he was asymptomatic and had a negative PET/CT whole body scan. On follow-up, MRI of CNS was done yearly to identify possible ND-CNS-LCH. Three years later, radiological ND-CNS-LCH was reveled with bilateral symmetric parenchymal lesions of the cerebellum in the dentate nuclei and the basal ganglia. Furthermore, another three years later, we found on PET/MRI of CNS new metabolic active lesions in plexi choridei, highly suspicious of active LCH. Two independent radiology experts unfortunately confirmed an isolated CNS-LCH relapse, 8 years from the date of initial diagnosis. Our patient received 2 cycles of cladribine according to LCH-IV, Stratum V (for isolated CNS lesions). Treatment response was no better than stable disease. Since tissue from original biopsy was no longer available we could not identify the driving LCH mutation. We highly appreciated the recently published data regarding evidence of reduction of neurofilament light-chain protein (NFL) in active ND-LCH-CNS on treatment with mitogen-activated protein kinase (MAPK) inhibitors. Although clinically without any identified symptoms of neurodegenerative disease, our patient's CSF-NFL level was significantly elevated (1190 ng/l, reference <380 ng/l). This justified us, to the best of our knowledge, to start therapy with a mitogen-activated protein kinase inhibitor (trametinib). The treatment response is awaited as the abstract is written. Our patient is completely asymptomatic until now, and tolerates therapy well with only minor skin problem . The dosis of trametinib is 0.028 mg/kg.

Poster #53



INDOMETHACIN TREATMENT OF BONE LANGERHANS CELL HISTIOCYTOSIS

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PURPOSE: We aim to evaluate the response and outcome of bone LCH patients treated with indomethacin at diagnosis or after reactivation. Its use has not only shown improvement in regards to clinical manifestations but also in accessibility and adherence to the treatment. METHODS: We retrospectively (2018-2022), evaluate the outcome of patients with bone LCH and under indomethacin treatment analyzing bone healing, clinical improvement, toxicity, biochemical parameters and the presence of circulating CD1a + /CD207 + cells in the bloodstream by flow cytometry. RESULTS: 31 patients with bone compromise received indomethacin at a dose of 2 mg/kg/day. Since diagnosis, 21 patients received only indomethacin, and 6 combined with another treatment. Additionally, 4 patients with bone reactivation were included, receiving indomethacin alone (n=2) or combined with another drug (n=2). Clinical and imaging improvements were observed in all groups. Patients receiving indomethacin alone did not show toxicity. The biochemical parameters, including platelets number, eritrosedimentation rate, were restored to normal values after treatment. Curiously, the clinical improvement of bone LCH under indomethacin treatment still showed presence of circulating CD1a + / CD207 + cells, which suggests that the treatment could be restraining the bone arriving of these cells. CONCLUSION: Indomethacin has proven to be a useful drug in the treatment of LCH patients who had bone affection, including patients with reactivation in bone from another primary compromise, reaching a significant clinical improvement.

Poster #54



RETROSPECTIVE ANALYSIS OF CLOFARABINE SALVAGE THERAPY IN REFRACTORY MULTIFOCAL LANGERHANS CELL HISTIOCYTOSIS

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PURPOSE: LCH is a neoplastic inflammatory disorder driven by recurrent somatic mutations in the MAPK pathway in myeloid precursors. Over 50% of patients with systemic LCH are not cured with front-line therapies and data to guide salvage options are limited. In this study, we describe 32 patients with relapsed/refractory LCH who were treated with clofarabine. METHODS: Data were extracted from clinical records of patients treated

with clofarabine for LCH by Texas Children's Hospital physicians or collaborators between May 2011 and 2022. RESULTS: Patients were treated with a median of two chemotherapeutic regimens prior to receiving clofarabine; median age was 4 (5 months to 37 years). The typical treatment course was 25mg/m² daily for 5 consecutive days per month; 28%(9/32) received treatment for less than 6 months; 25%(8/32) for 6-9 months; and 44%(14/32) for 9-19 months. OS in this cohort was 97%(31/32) and PFS was 66% with median 2-year follow-up (range: 2 months to 6 years); 72%(23/32) experienced complete responses, 6%(2/32) partial responses, 9%(3/32) maintained stable disease, and 13%(4/32) developed progressive disease during the study period. Patients treated for LCH-associated neurodegeneration had relatively worse outcomes (29%(2/7) PR, 29%(2/7) PD, 42%(3/7) SD, and one patient relapsed after treatment) than patients with systemic disease without LCH-ND (92%(23/25) CR, 8%(2/25) PD, 6 patients relapsed after treatment). Toxicities included cytopenias, severe vomiting, and bacterial infections, but the majority tolerated chemotherapy in the outpatient setting. The one patient who died had severe multisystem-LCH with associated HLH that did not respond to chemotherapy/MAPK inhibition. CONCLUSION: Clofarabine monotherapy has activity against LCH in heavily pretreated patients, the majority of whom achieved durable remission. Prospective multi-center trials are warranted to determine long-term efficacy, optimal dosing, and late toxicities of clofarabine and relative cost and patient reported outcomes compared to alternatives (e.g. MAPK inhibitors) in patients with relapsed/refractory LCH.

Poster #55



THE CASE OF ACQUIRED VEMURAFENIB RESISTANCE IN BRAF V600E POSITIVE MULTISYSTEM PEDIATRIC LCH

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PURPOSE: To present a clinical case of acquired vemurafenib resistance in BRAF V600E positive multisystem Langerhans-cell histiocytosis (LCH). METHODS: The 2-year-old boy was diagnosed with LCH with skin and risk organs (liver, spleen, bone marrow) lesions. BRAF V600E mutation was confirmed by PCR of the skin biopsy and ddPCR of cfDNA and sorted myeloid precursor population (CD34+CD117+). The patient was treated with the combination of vemurafenib (240 mg/day) and cytarabine plus cladribine (100 mg/m²/day and 6 mg/m²/day respectively, days 1-5), and vemurafenib cessation was attempted, which was followed by the relapse (tri-lineage cytopenia). Vemurafenib was reintroduced successfully with complete recovery of peripheral blood counts. One year after the restart of vemurafenib therapy, the child experienced several episodes of fever, mild hepatosplenomegaly, and progressive tri-lineage cytopenia, which resolved only after prednisone treatment. In addition, inflammatory markers (such as IL-6 and CRP) were elevated. All other causes were ruled out (infection, vemurafenib intolerance, drug forgery). Considering all of the above, we suspected a subclonal event and added MEK inhibitor trametinib (0.5 mg/day) to the backbone of vemurafenib therapy. RESULTS: The combination of BRAFi and MEKi therapy was successful, and the condition improved rapidly with full recovery after one week of treatment. During the follow-up after 2 months, no signs of disease were observed. Molecular dissection of the case is currently ongoing. CONCLUSION: This case represents the possibility of acquiring the secondary mutations in BRAF-positive patients on targeted therapy, which was not reported previously.

That questions the safety of long-term inhibitory therapy in high-risk pediatric LCH patients.

Poster #56



EFFICACY OF ALPELISIB IN PI3K-DRIVEN LANGERHANS CELL HISTIOCYTOSIS

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PURPOSE: Langerhans cell histiocytosis (LCH) is a histiocytic neoplasm characterized by the accumulation of clonal dendritic cells frequently harboring MAPK activating mutations. The purpose of this study is to report a case of PI3K-driven LCH successfully treated with an isoform specific PIK3CA inhibitor. METHODS: We review the case of a 46 year-old female who presented with headaches, polydipsia and polyuria. Following a pathological water deprivation test, a diagnosis of central diabetes insipidus was established and desmopressin treatment was initiated. Nearly three years following her presentation, night sweats, episodes of fever and worsening dry cough emerged. Imaging studies including PET/CT disclosed radiological features suggestive of pulmonary LCH. A lung biopsy confirmed the diagnosis of LCH and molecular studies identified the M1043V PIK3CA mutation. Thereafter, new disease foci developed: cervical lymphadenopathy and a lytic vertebral lesion involving D11. The patient received palliative radiotherapy directed at D11 followed by systemic therapy with Alpelisib, via the Managed Access Program at Novartis. Response to treatment was assessed clinically and using PET/CT. At the molecular level, the effect of Alpelisib was assessed by measuring PTEN expression levels and cell-cycle regulating noncoding RNA molecules via quantitative RT-PCR. RESULTS: Alpelisib treatment resulted in rapid amelioration of night sweats within 6 days, decrease in back pain within 3 weeks and normalization of all abnormal PET foci within 3 months of treatment. The complete metabolic response observed currently persists more than a year following treatment initiation. Treatment with Alpelisib is well tolerated except for a mild increase in HbA1C. Moreover, PTEN, the main regulator of the PI3K pathway was upregulated following 3 and 9 months of treatment, in parallel to downregulation of small noncoding RNAs molecules that regulates its expression. CONCLUSION: This is the first study demonstrating that the alpha-catalytic subunit of PI3K is a targetable noncanonical driver of LCH.

Poster #57



LONGITUDINAL PLASMA CELL FREE DNA BRAFV600E LEVELS AS A BIOMARKER OF DISEASE STATUS IN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS (LCH)

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BACKGROUND: Langerhans cell histiocytosis (LCH) is a myeloid neoplasm that can present with single organ (LCH-SS) or disseminated multiorgan disease (LCH-MS). The BRAFV600E mutation is reported in about 60% of patients with LCH and is associated with more severe presentations. In other tumors, the BRAFV600E allele is detected in circulating cell-free DNA (cfDNA) and has been used to mirror response to treatment. Currently, LCH therapy decisions are based on nonspecific laboratory markers. We sought to determine whether changes in cfDNA levels of BRAFV600E can predict treatment response or relapse in LCH. **METHODS:** cfDNA by Digital Droplet PCR performed at ARUP laboratories was measured at various time points in a cohort of LCH patients. Time points were determined based on the following disease statuses: newly diagnosed, disease recurrence and surveillance. Results were reported as BRAFV600E mutant allele frequency and number of BRAF V600E mutant copies per mL. The limit of detection ranged from <0.01%-0.5% mutant allele frequency. **RESULTS:** Seventeen patients were enrolled; the majority were males (71%) and Hispanic (53%). Thirty-five percent had LCH-SS and 35% had LCH-MS. Two had cfDNA at the level of detection at the time of study enrollment. They subsequently had decreased mutant allele frequency and number of BRAF V600E mutant copies, one achieving nondetectable status during their maintenance course and the other with stable disease and decreased cfDNA. Another participant had detectable disease, after having nondetectable disease and being one year off therapy. Imaging correlated with disease recurrence, showing pituitary disease involvement. **CONCLUSIONS:** Though limited by our sample size and study duration, our data shows that BRAFV600E in cfDNA may be a useful biomarker to monitor therapy response. Through serial monitoring for the presence of BRAFV600E in cfDNA, we may have the ability to detect relapse sooner.

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PURPOSE: In Japan, we have achieved low mortality rates with cytarabine, vincristine (VCR) and prednisolone-based chemotherapy (JLSG-96/-02 trials) in children with multifocal bone (MFB) and multisystem (MS) Langerhans cell histiocytosis (LCH). However, relapse rates were still high and, as a result, event-free survival (EFS) rates were unsatisfactory. The Japan Children's Cancer Group have conducted the nationwide clinical trial, LCH-12, to verify whether relapse rates are reduced by intensifying early maintenance phase with increasing doses of VCR. **METHODS:** Newly diagnosed patients with MFB or MS LCH, younger than 20 years at diagnosis, were enrolled between Jun 2012 and November 2017. Patients with MFB and MS LCH were treated for 30 and 54 weeks, respectively. The primary end point of the study was 3-year EFS rate. The events included poor treatment response, exacerbation during the treatment, failure to achieve no active disease at the end of the treatment, relapse, or any death. **RESULTS:** Total 150 patients (43 with MFB and 107 with MS LCH) were eligible. Data were current as of November 2020, with a median follow-up of 5.1 years (range, 2.5-8.3 years) and 5.4 years (range, 2.4-8.4 years) for living patients with MFB and MS disease, respectively. One patient with MS LCH died of sepsis in the induction phase. EFS rates at 3 years were 66.7% [95% confidential interval (CI), 56.5-77.0] for MFB and 59.8% [95% CI, 49.9-68.4] for MS LCH. These lower limit of 95% CI in both MFB and MS LCH were inferior to the null hypothesis of the trial (65.0 % and 60.0 %, respectively). These EFS rates were almost the same as that of JLSG-02 trial. **CONCLUSION:** Intensification of treatment with VCR did not improve outcomes in pediatric patients with MFB and MS LCH. Other strategy is required to improve the outcomes.

Poster #58



INTENSIFICATION OF TREATMENT WITH VINCA ALKALOID DOES NOT IMPROVE OUTCOMES IN PEDIATRIC PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS* RESULTS FROM THE JPLSG LCH-12 STUDY

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Poster #59



MODIFIED TREATMENT FOR PEDIATRIC MULTISYSTEMIC HISTIOCYTOSIS DURING SARS-COV2 LOCKDOWN. SERIES OF CASES

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PURPOSE: Backbone treatment of multisystemic histiocytosis (MS-LCH) is steroids in combination with chemotherapy (vinblastine/vincristine and/or cytarabine). This approach requires a central venous access (CVA) placement because of the possibility of citostatic extravasation and length of treatment. SARS-CoV2 lockdown forced us to adapt standard treatment in order to skip CVA placement, use of available cytostatics, reduce toxicity and hospital visits. We report here our experience using a modified treatment (MT). **METHODS:** Series of 4 pediatric patients (pt) of MS-LCH treated during 2020 with a MT. Induction: Oral Methylprednisone 40 mg/m² daily for 4 weeks, tapering for 2 weeks, and subcutaneous/intravenous cytarabine 100 mg/m²/day for 4 days, day 1-14. Evaluation at 6th week. If NAD or ADB, continuation treatment: Methylprednisone 40 mg/m²/day for 5 days every 15 days and subcutaneous/intravenous cytarabine 100 mg/m²/day for 4 days every 3 weeks. Clinical and hematologic evaluation every 3 weeks. We studied the presence of circulating CD207+/CD1a+ cells (cc) by flow cytometry. **RESULTS:** Female 3pt. Identical twins (pt#1,2). Age at diagnosis: 7, 7, 11 and 29 months. Involvement: skin, lymph nodes and hematopoietic (pt#1,2,3,4), ear (pt#2,3,4), bone (pt#3), hepatosplenomegaly (pt#4). All pt achieved ADB after 6 weeks of treatment. Reactivation: 1pt because of non-adherence to treatment. No grade 3/4 toxicity. COVID infection with mild symptoms (pt#1,2). Status: all alive with NAD at 2 years (pt#1,2) and 1 year (pt#3,4) of treatment. All pt started with a low score for cc and increased them with the treatment in negative trend to their clinical status. **CONCLUSION:** This MT was feasible to treat pt with MS-LCH during the SAR-Cov2 lockdown, even those with risk organ involvement. We were able to skip CVA and reduce toxicity. Treatment could be restraining cc migration to the lesions.

Poster #60



LANGERHANS CELL HISTIOCYTOSIS (LCH): UKRAINIAN PROSPECTIVE STUDY IN A REAL-LIFE COHORT, UPDATED RESULT

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PURPOSE: The main idea is the use of type of LCH and molecular alterations (MAPK/ERK pathways) to evaluated factors predicting overall (OS) and event free survival (EFS). **METHOD:** 19 patients with LCH (range 1-58, median age 29.5) were treated in NCI (Kyiv, Ukraine). 6, 11 and 2 pts have SS-LCH and MS-LCH and Pulmonary type of histiocytosis stratification, respectively. Detection of 23 mutations in BRAF (V600E) and NRAS (12, 13, 61 codons) genes were performed by real time PCR analysis using TaqMan Probe-Based Assays (Applied Biosystems, USA). **RESULTS:** The overall response rate was 42.1% and 31.6% patients achieved stable disease during the follow-up period (median duration - 44.5 months). Unfortunately, 26.3% primary patients had refractory disease. 66% vs 81% cases of relapse were diagnosed in SS-LCH vs MS-LCH groups, respectively (P<0.05). There were no significant differences in EFS between stratification types of LCH (25% in SS vs 20% in MS type, respectively P=0.7). A 3-year EFS rate for patients with early relapse was 14% compared with 33% for patients with late relapse (P=0.009). We did not find any significant in OS between types of LCH. A BRAF mutation was detected in 43.75% cases: 4 patients had an early relapse and 1 patient - late relapse. We did not notice significant independent effect of BRAF mutation on LCH clinical outcome, except NRAS. Multivariate analysis showed that the presence of NRAS Q61R mutation

is associated with poor EFS in LCH patients with HR of 6.1 [95% (CI) 0.2-12.6, p=0.008]. **CONCLUSION:** Our study showed patients with NRAS mutation associated with poor clinical outcome. BRAF mutation status had no impact on disease progression and clinical outcome. Perhaps with an increase in the number of patients, we will be able to determine the role of type of LCH and BRAF mutation in the clinical outcome.

Poster #61



CONFIRMED EFFICACY OF CYTARABINE MONOTHERAPY AND CYTARABINE COMBINED WITH CLADRIBINE IN PEDIATRIC REFRACTORY/RELAPSED LANGERHANS CELL HISTIOCYTOSIS TREATMENT

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OBJECTIVE: To analyze the efficacy and safety of Cytarabine (Ara-C) monotherapy and Ara-C combined with Cladribine(2-CDA) in paediatric refractory/relapse (R/R) Langerhans cell histiocytosis (LCH) treatment. **METHODS:** We retrospectively analyze children with R/R LCH, who accepted Ara-c monotherapy and Ara-C plus2-CDA treatment in the same period at Beijing Children's Hospital, from January 2014 to December 2019. **RESULTS:** A total of 190 children were enrolled, including 96 of Ara-C monotherapy and 94 of Ara-C plus2-CDA treatment. At diagnosis, circulating cell-free BRAFV600E was positive in 61 of 127 patients (48.03%). Gene mutations in biopsy tissue was detected positive in 84 of 109 patients (77.06%). The overall response rate (ORR) for monotherapy was lower than that of combination therapy(78.8% vs. 85.1%, P=0.273). The 3-year event free survival rate (EFS) for combination treatment was higher than that of monotherapy(76.7%±3.4% vs. 63.9%±5.0%, P=0.024). The 3-year EFS of combination treatment in the MS-RO+ group was higher than that of monotherapy, but there was no significant difference in 3-year EFS between the SS-RO- and the MS-RO-group (57.1%±8.7% vs. 32.1% ±8.8%, P=0.047; 93.8%±6.1% vs. 80.7%±7.8, P=0.280; 79.4%±6.2% vs. 75.6%±6.7%, P=0.280). The incidence of myelosuppression and gastrointestinal reactions during monotherapy was lower than that during combination treatment (P<0.001 and P<0.001). Compare to monotherapy, the symptoms and imaging abnormalities of children with diabetes insipidus improved after combination treatment (0.00% vs. 44.4%, P=0.066; 0.00% vs. 20.0%, P=0.526). The cure rate in children with pulmonary involvement after combination treatment was higher (39.3% vs. 75.7%, P=0.003). **CONCLUSION:** Compared to Ara-C monotherapy, the 3-year EFS is higher in Ara-C plus2-CDA treatment, especially in the MS-RO+ group. All the side effects are mild to tolerate, but the incidence of myelosuppression and gastrointestinal reactions in monotherapy is lower. Combination therapy is

more effective in children with lung or pituitary involvement, especially in children with diabetes insipidus.

Poster #62



NEURODEGENERATIVE CENTRAL NERVOUS SYSTEM LANGERHANS CELL HISTIOCYTOSIS IN A PEDIATRIC POPULATION

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To describe clinical and imaging findings in patients with neurodegenerative central nervous system Langerhans cell histiocytosis (ND-CNS-LCH). Descriptive study of a pediatric population in one institution with ND-CNS-LCH, in the last 10 years in a neurologic institution in Buenos Aires, Argentina. A total of 38 patients with LCH, 3 showed neurodegenerative images, 2 boys were symptomatic and 1 girl had no clinical disorder. All patients had LCH during first infancy, compromising head bones, 2 of them also had skin and pituitary compromise. They had 6, 11 and 5 years from LCH diagnosis to neurodegenerative presentation. 1 patient was rapidly diagnosed, the other was symptomatic for more than 2 years and the last patient, who was asymptomatic, was diagnosed by control MRI. One patient showed only cognitive and visual impairments, while the other presented with progressive ataxia, tremors, visual and cognitive impairments, with tendency to drug abuse and psychosis, requiring to be hospitalized several times. Hyperintensity in dentate nuclei was present in all cases. Symptomatic patients showed white matter hyperintensity in T2 weighted images in pontine and cerebellum areas, with mild cerebellar atrophy, no hyperintensity of basal nuclei in T1 weighted images was observed. To date, the girl has never developed symptoms after 5-year follow-up. Both boys were treated with gammaglobuline and methylprednisolone with partial response. All 3 patients are alive and well with a Karnofsky/Lansky of 90 in all cases, with mild ataxia remaining in one of them. No BRAFV600E mutation study was able to be performed either in blood or CSF samples. DG-CNS-LCH could be a severe disabling disorder, going from asymptomatic to mild moderate and severe. Cognitive impairments can be misdiagnosed for several years. Therefore, the importance of a high level of awareness and a radiology team with experience in CNS disorders is mandatory in these cases.

Poster #63



REACTIVATION OF PEDIATRIC LANGERHANS CELLS HISTIOCYTOSIS IN PAKISTAN - A TEN YEAR STUDY

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PURPOSE: Between 2 to 9 children per million per year are affected by Langerhans Cell Histiocytosis (LCH) globally. Reactivation rates for multisystem LCH remain above 30%, presenting more commonly in those with risk organ (RO) involvement and BRAF positivity. Considering the rarity of LCH and dearth of reported data in Pakistan, this study was conducted to assess clinical

outcomes of pediatric LCH patients with reactivation of disease. METHODS: A retrospective study was conducted by the Pediatric Hematology and Oncology Department at Indus Hospital and Health Network in Pakistan. Children 0 to 16 years with LCH reactivation between 2009 and 2019 were enrolled. Modified Salvage protocol (2-CdA 5mg/m²/day for five days) was used in cases of single-system relapse whereas multisystem reactivation was treated with Salvage protocol (2-CdA 9mg/m²/day for five days). RESULTS: Of 46 patients registered with LCH during this time period, 12 (26%) presented with reactivation. Mean age was 3.01 -3.62 years and 58% were female. Six children had single system LCH, 2 had multisystem LCH (MS-LCH) without RO involvement and 4 had MS-LCH with RO involvement. Eight patients with reactivation were treated with Modified Salvage protocol, 2 of whom expired. Three patients were treated with Salvage protocol, all expired. One child who presented with reactivation while on observation was treated with LCH-III protocol and survived. CONCLUSION: Outcomes of pediatric LCH are suboptimal in low -middle income countries such as Pakistan due to unique challenges, namely malnutrition and treatment related mortality. Moreover, specialized molecular testing facilities and targeted therapies such as BRAF inhibitors must be made available in resource-strained settings to broaden treatment options and improve clinical outcomes of children with LCH.

Poster #64



CLINICAL RESISTANCE ASSOCIATED WITH A RARE MAP2K1 MUTATION IN AN ADULT PATIENT WITH MULTI-SYSTEM LANGERHANSCELL-HISTIOCYTOSIS (MS-LCH)

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PURPOSE: We report a case of MS-LCH, refractory to cytotoxic and targeted therapy (MEK-inhibitor). We identified a rare MAP2K1 Mutation (MAP2K1 exon3 p.E102_I103del), which is possibly associated with a poorer response to targeted therapy. CASE REPORT - The 35 y/o male patient was diagnosed in 2019 with MS-LCH (pulmonary, nodal, bone), with no further comorbidities, besides a history of smoking (20 pack years). Molecular diagnostics at that time showed no BRAF or MAP2K1 Mutations. Smoking cessation, treatment with cytarabine and bisphosphonate were initiated. After 6 cycles, PET-CT scan showed partial response of some lesions (nodal, pulmonary) but progression of bone lesions (C1 vertebrae, Os Ilium). Given the patient's good clinical condition and unfavorable localization of the bone lesion of the cervical spine, systemic therapy was stopped and radiation (10x 2 Gy) of Vertebra C1 was performed. 4 months later, PET-CT scan showed worsening of the pulmonary lesions (confirmed by biopsy). Next generation sequencing (NGS) did not show pathogenic somatic mutations. As the patient had restarted smoking, smoking cessation was again achieved. 3 months later, PET-CT scan showed complete remission of the pulmonary manifestations. 6 months later, the patient presented with worsening dyspnea. Lung function showed a severe degree of respiratory impairment. PET-CT scan showed progression of

pulmonary manifestations. Treatment with the MEK-Inhibitor Cobimetinib was initiated. After 6 month, lung function got worse, with further progression in PET-CT scan. Retrospective analysis of sequencing data revealed a MAP2K1 p.E102_I103del Mutation, already present at time of diagnosis. Treatment regime change is being evaluated, including evaluation for lung transplantation. CONCLUSION: MEK-Inhibition in LCH is an effective treatment but certain mutations seem to be associated with poorer clinical response. This example demonstrates that a better understanding of targeted therapy with respect to the different genetic alterations of LCH is highly needed in adult patients with MS-LCH.

Poster #65



IDENTIFYING BRAFV600E GENE MUTATION AMONG IRANIAN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS (LCH)

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PURPOSE: Langerhans cell histiocytosis (LCH) is an inflammatory neoplasm of myeloid origin with variable degrees of skeletal, cutaneous, pulmonary, and pituitary involvement. The pathologic CD1a+/CD207+ cells have activating mutations in the mitogen-activated protein kinase (MAPK) pathway (particularly in BRAFV600E). METHODS: Patients with the diagnosis of LCH between 2009 to 2020 from three Iranian referral centers were enrolled. Categorized based on the detection of BRAFV600E mutations by real-time polymerase chain reaction assay, patients were compared in respect of demographic and clinical features, response to treatment, and outcome. RESULTS: Fifty LCH patients, 17 (34%) female and 33 (66%) male, were enrolled in the study. 30 (60%) patients had somatic mutations in the BRAFV600E gene and 20 (40%) patients had wild-type genotype. The frequency of mutations in patients less than 8 years old (particularly < 2 years) was significantly higher (p= 0.024). The most common organ involvement was observed in bone (n=43, 86%), followed by lymph nodes (n=14, 28%), skin (n=12, 24%), and central nervous system (n=2, 4%). In half of patients (n=25, 50%), bone was the only organ affected. Multi-organ involvement was observed in 21 (42%) patients, not significantly different between BRAFV600E Positive (14 of 21, 66.7%) and BRAFV600E negative (7 of 21, 33.3%) groups (p=0.380). Most (7 out of 8) patients with risk organ involvement and all four patients with central nervous system involvement had BRAFV600E mutations. BRAFV600E positive group demonstrated an overall lower response to treatment compared to BRAFV600E negative group (53% vs. 85%, p=0.056). Moreover, patients negative for BRAFV600E mutations were considerably more resilient than the BRAFV600E positive group in response to first-line agents (p=0.001). BRAFV600E mutation was found in 6 of 7 deceased patients. CONCLUSION: BRAFV600E mutation may be related to the onset age, type and

severity of clinical manifestations, response to treatment, and outcome in LCH patients.

Poster #66



MONITORING OF BRAF CF-DNA LOAD IN PERIPHERAL BLOOD USING BIOCARTIS IDYLLA SYSTEM IN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS

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PURPOSE: Activation mutation of BRAF oncogene (BRAF V600E) is the most common genetic alteration in Langerhans cell histiocytosis (LCH). The mutation can be found in peripheral blood (PB) of some patients with LCH. We present data of longitudinal monitoring of BRAF V600E cell-free DNA (cfDNA) level in peripheral blood of several patients enrolled to LCH-IV treatment study. METHODS: Semi-automatic Biocartis Idylla System was used; the detection limit of mutated allele is around 0.01% of mutated BRAF V600E cfDNA in PB. RESULTS: Seven patients was followed, 2 had multi-system LCH with risk organs positivity (RO+MS-LCH), 2 had multi-system LCH (RO-MS-LCH), 1 multifocal bone disease, 1 CNS-risk single bone lesion, all had systemic LCH treatment; 1 skin involvement only treated with topical steroids. Median age at diagnosis was 22.1 months (5.2-74.3), median follow-up 18.6 months (3.8-70.4). In 4 patients treated with chemotherapy, the BRAF V600E cfDNA in PB negativity was reached in median of 5.7 months (0.8-13). One with no systemic treatment (skin LCH), the BRAF V600E cfDNA was detected only at diagnosis, in the subsequent samplings, first was done 2.9 months later, BRAF V600E cfDNA was negative. In 2 patients, BRAF V600E cfDNA negativity in PB was not reached, 1 patient with RO-MS-LCH is still treated with chemotherapy (follow-up 6.1 months), in 1 patient with RO+MS-LCH treated with chemotherapy, BRAF V600E and MAP2K1/2 inhibitor and allogeneic bone marrow transplantation, BRAF V600E is continuously detected in PB for more than 5.8 years. CONCLUSION: Semi-automatic Biocartis Idylla System can be used for detection and monitoring of BRAF V600E cfDNA in PB of patients with LCH.

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Poster #67



CLADRIBINE COMBINED WITH CYTARABINE REGIMEN AS A SALVAGE THERAPY FOR PAEDIATRIC REFRACTORY/RELAPSED LANGERHANS CELL HISTIOCYTOSIS: A SINGLE-ARMED, SINGLE-CENTER STUDY

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OBJECTIVE: We performed a single-armed, single-centre study (ChiCTR2000030457) to investigate the efficacy and safety of Cladribine (2-CDA) combined with Cytarabine (Ara-C) as a salvage therapy for paediatric refractory/reactivation Langerhans cell histiocytosis (LCH). **METHODS:** A retrospective analysis was performed in children with R/R LCH, who accepted 2-CDA plus Ara-C treatment at Beijing Children's Hospital, from January 2014 to December 2019. **RESULTS:** A total of 94 patients were enrolled in this study, including 64 boys and 30 girls, with a median age of 5.38 (0.45-13.61) years at diagnosis. There were 78, 16, 32 patients with multisystem, single system (multiple bone destruction), and risk-organ involvement respectively. At diagnosis, circulating cell-free BRAFV600E (cfBRAFV600E) was positive in 30 of 61 patients (49.18%). Gene mutations in biopsy tissue was detected positive in 37 of 47 patients (78.72%). The overall response rate was 85.1%. The median follow-up time was 4.60 (1.71-7.08) years. The 3-year event free survival rate was 76.7%±3.4% and the 2-year cumulative rate of progression or reactivation was 20.2%. Multivariate Logistic regression analysis showed that risk organ involvement was independently correlated with reactivation or disease progression after second-line treatment (P=0.027, OR=3.138, 95% CI=1.141-8.633). In 30 patients with pituitary involvement, 90% of the pituitary MRI abnormal signals recovered, 44.4% of the diabetes insipidus symptoms improved after second-line treatment. All the 94 patients had myelosuppression and gastrointestinal reactions during chemotherapy, which were mild to moderate. **CONCLUSIONS:** 2-CDA plus Ara-C treatment can be used as a salvage therapy with high efficiency and low reactivation rate in paediatric R/R LCH, and had a certain effect on pituitary involvement. The main side effects were mild to moderate myelosuppression and gastrointestinal reactions. The long-term reactivation rate still needs to be studied.

Poster #68



MULTISYSTEM INVOLVEMENT RISK AND TREATMENT PATTERNS IN PEDIATRIC PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS: A POPULATION - BASED STUDY

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BACKGROUND: Langerhans cell histiocytosis (LCH) is a rare monoclonal histiocytic neoplasm. Little is known about clinical factors associated with LCH single- vs. multi-system involvement at the time of diagnosis. **METHODS:** Data on 1549 LCH patients diagnosed between 2010-2018 were extracted from the Surveillance, Epidemiology and End Results (SEER) Program database using SEER*Stat (8.3.9.2) software by applying ICD-O-3 9751/3 code, and the patient demographic and clinical characteristics were analyzed. Patterns of single- vs. multisystem involvement were examined using multivariable logistic regression analysis. Odd ratio (OR) and 95% confidence interval (CI) were reported. **RESULTS:** Data on 968 pediatric patients (0-19 years; mean age = 4 years) were available for analysis. Of them, 62.2% were males; 16.7% were non-white. Bone (65.9%), skin (13.4%), bone marrow (BM) (7.0%), and lymph nodes (LN) (3.6%) were the four most common primary sites; 36.1% pediatric patients underwent primary lesion surgery, 1.2% underwent radiotherapy, and 47.7% underwent chemotherapy. Disseminated/multi-system involvement was reported for 30.9% patients. LCH in BM (OR=3.776, 95% CI=1.939-7.351, P<0.001) and LN (OR=3.274, 95% CI=1.443-7.427, P=0.005) were most commonly associated with multi-system LCH involvement at diagnosis; similar results were also observed in adult patients (OR=17.780, 95% CI=6.469-48.867, P<0.001 for BM LCH; OR=5.156, 95% CI=2.131-12.471, P<0.001 for LN LCH). Among pediatric patients, craniofacial osseous LCH was more likely to be treated with surgery (OR=2.822, 95% CI=1.199-6.639, P=0.018) compared to skeletal lesions in other sites, whereas vertebral body LCH was less likely to be treated with surgery (OR=0.175, 95% CI= 0.058-0.527, P=0.002). The non-white patients were less likely to receive surgery compared to white patients (OR=0.470, 95% CI= 0.272-0.812, P=0.007). **CONCLUSIONS:** LCH in BM and LN are associated with the highest risks of multi-system involvement, which may require active surveillance. Active attempts are needed to mitigate the racial disparity in surgery utilization in pediatric skeletal LCH patients.

Poster #69



HETEROGENITY OF HISTIOCYTOSIS WITH MAP2K1 MUTATIONS

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PURPOSE: BRAFV600E is the most frequent mutation detected in Langerhans cell histiocytosis (LCH) and Erdheim Chester disease (ECD). MAP2K1 gain of function mutation have also been described in

histiocytoses, including in Rosai Dorfman disease (RDD). METHODS - MAP2K1 mutations were investigated within DNA extracted from biopsies with histiocytosis confirmed by histology review. RESULTS - MAP2K1 mutations were detected in 173 samples of 166 patients, and occurring in 23.7% of the BRAF/NRAS/KRAS/MAP2K1 mutations that we detected in histiocytosis samples during the last 4 years. Samples contained 79 deletion or deletion-insertion (DELINS), and 91 single base substitution (SBS). DELINS and SBS of MAP2K1 corresponded to 24 and 25 different mutations respectively, localized within the exon 2 coding for a negative regulatory domain or the exon 3 coding for a catalytic domain of the MEK1 protein. The type of MAP2K1 mutation was correlated with the age of patient at the time of biopsy. Indeed, DELINS accounted for 78.7% (37/47), 43.4% (33/76) and 14.3% (6/42) in patients of [less than 18 years], [18 to 60 years] and [more than 60 years], respectively. This age-dependent type of mutation was due to the main types of histiocytosis: DELINS accounted for 89% (58/65) of LCH, 7% (3/46) of RDD and 25% (11/43) of ECD mutations, which median age of biopsies were 15.5, 42.8 and 64.1 years respectively. Few patients with typical clinic and imaging of ECD can have RDD histology; they are mainly males and have MAP2K1 mutation in most cases. In the present series, 13/43 (30%) of ECD patients had a mixed histiocytosis with RDD, which is more than expected. These 13 patients had similar age as those with pure ECD (median 59.4 versus 66.0 years). CONCLUSION - MAP2K1 mutations are frequent in histiocytoses, and mutation type is dependent on the type of histiocytosis.

Poster #70



EXPRESSION OF CSF1R IN HISTIOCYTOSIS

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PURPOSE: CSF1R activation is essential in macrophage homeostasis and for differentiation of Langerhans cells. Activating mutations of CSF1R have been reported in some histiocytoses, one of which had a complete response to targeted therapy with pexidartinib. We investigated the expression of CSF1R in histiocytosis. METHODS: Immunohistochemistry was performed on formalin fixed biopsies using anti-CSF1R (Mouse clone FER216, Millipore) and anti-MCSF (Rabbit clone EP1179Y, Abcam). RESULTS: We analyzed CSF1R expression in 80 cases, including 39 cases of L group: Langerhans cell histiocytosis (n=18), Erdheim-Chester disease (n=9), mixed histiocytosis (n=6), indeterminate cell histiocytosis (n=5), ALK+ histiocytosis (n=1). The series also included 19 cases with Rosai-Dorfman disease, 6 cases of C group, and 14 with malignant histiocytosis. Age ranged from 0.1 to 72 years. Histiocytosis biopsies were from various tissues, including skin (n=19), lymph nodes (n=15), bone (n=11), central nervous system (n=7), soft parts (n=6), and retroperitoneum (n=5). CSF1R was expressed by histiocytes infiltrating the tissues in 72/77

(93.5%) cases and negative in 5, while 3 cases were not interpretable. In most cases, the intensity of staining was similar or higher than in control tenosynovial giant cell tumors (TSGCT), while in 9 cases, the intensity of staining was low. All the 18 LCH as well as the 3 MH of LC subtype had a strong expression of CSF1R. Neither negativity nor low intensity of staining were restricted to one type of histiocytosis nor with mutational status. Twenty-four of these cases were also stained with MCSF, of whom 22 (92%) were positive. CONCLUSION: CSF1R was detected on histiocytes in more than 90% of cases, with a strong expression in most of them. Our results suggest that, as successfully done for TSGCT, treatment targeting CSF1R should be investigated in histiocytoses resistant to other therapies.

Poster #71



ELF4 EXPRESSION IN NK CELLS REGULATES MATURATION AND PROLIFERATION

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PURPOSE: ELF4 is a transcription factor that drives cell-cycle progression, negatively regulates naïve CD8+ T cell proliferation, and is essential for NK cell development and function. Abrogated ELF4 expression is associated with autoinflammatory disease in humans, and a hypomorphic variant causing an NK cell deficiency in a young patient also associated with lymphoproliferative disease, including AITL and other lymphoid malignancies in an older patient. Aged *Elf4*^{-/-} mice have been reported to spontaneously develop lymphocytic infiltrates. Here, we explore mechanisms of NK maturation associated with ELF4 expression. METHODS: We characterized the maturation of NK cells in a previously established knockout mouse. Using human NK cells, we analyzed correlation of ELF4 expression with NK maturational stages and proliferation. RESULTS: We found that *Elf4*^{-/-} mice had significantly increased CD27+CD11b⁻ immature and decreased CD27-CD11b⁺ mature NK cells. In humans we validated a trend of increased expression of ELF4 as the cells matured and identified a significant increase between stages 4a and 4b NK cells and significant increase in tonsils from stage 4b and 5 NK cells. Further in NK cell precursors, ELF4 expression correlated with proliferation as measured by Ki67 staining. CONCLUSION: We show that ELF4 is necessary for NK cell maturation in mice. The significant increase in ELF4 expression between CD56bright and CD56dim NK cells complements other data that suggests the ELF4 drives linear maturation from stage 4 to 5. Furthermore, the distinct ELF4 expression profile in stage 4a and 4b in human NK cells provides insight into the possible role of ELF4 in the maintenance of the immunoregulatory stage4 CD56bright NK cells and driving the maturation of this subset cells into cytotoxic stage5 CD56dim NK cells. Therefore, aberrant expression or function of ELF4 may play a role in hyperinflammatory/lymphoproliferative conditions resulting from dysfunctional NK cell regulation.

Poster #72



PU.1 IMMUNOHISTOCHEMICAL MARKER FOR THE DIAGNOSIS OF HISTIOCYTOSIS

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PURPOSE: Histologic diagnosis of histiocytosis may be difficult. Among more than 2500 cases referred for review some final diagnoses were non specific inflammation, dermatopathic lymphadenitis, prurigo, scabies, mycobacterial infection, sarcoidosis, follicular dendritic cell sarcoma, tenosynovial giant cell tumor, B or T cell lymphoma, Hodgkin's disease, mastocytosis and histiocyte-rich tumor of unknown origin. It can be very difficult to identify tumor cells, when the density of reactive histiocytes is high within the tumor stroma. Our purpose was to investigate the interest of the nuclear marker PU.1 for the diagnosis of histiocytosis. PU.1 is expressed by macrophages, neutrophils and B lymphocytes, but it is not used for diagnosis in most pathology laboratories, except in a few expert centers. **METHODS:** Diagnosis of histiocytosis was confirmed by review of all slides. Immunohistochemistry was performed with the PU.1 antibody (EPR3158Y, Abcam), and compared with the B cell nuclear marker PAX5 when required. **RESULTS:** PU.1 was positive in all the cases of histiocytosis that we tested: Langerhans-cell histiocytosis (n=10), Erdheim-Chester disease (n=9), mixed histiocytosis (n=2), Rosai-Dorfman Disease (n=12), C group (n= 17), ALK+ histiocytosis (n=5) and malignant histiocytosis (MH) (n=14). Histiocytes showed a nuclear high or moderate expression. Among 30 consecutive cases referred as malignant histiocytosis (MH), only 14 were confirmed while 16 were histiocyte-rich malignant tumors. All these latter cases were negative for PU.1, except one diffuse large B cell lymphoma. **CONCLUSION:** PU.1 is widely expressed by all types of histiocytosis. In tumors with nuclear atypia, PU.1 is very useful to differentiate histiocytosis from histiocyte-rich malignant tumors.

Poster #73



OCT2 EXPRESSION IN ROSAI-DORFMAN DISEASE AND OTHER HISTIOCYTOSIS

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PURPOSE: Expression of OCT2 has been reported to be characteristic of Rosai-Dorfman disease (RDD) in a series of 33 cases (Ravindran et al. Am J Surg Pathol. 2021). Our purpose was to investigate its specificity in a larger cohort of samples of various types of histiocytoses. OCT2 is known as a B lymphocyte marker, and is currently used in many pathology laboratories for the diagnosis of non-Hodgkin or Hodgkin lymphomas. We first sought to confirm that OCT2 is expressed by RDD and then we addressed its specificity by analysing other types of histiocytoses. **METHODS:** Biopsies were referred from many different laboratories and tissues were fixed and embedded in unknown conditions. Diagnosis of histiocytosis was confirmed by review of all slides. Immunohistochemistry was performed with the OCT2 antibody (EPR12482-106, Abcam). **RESULTS:** RDD biopsies originated from lymph node (n=14), skin (n=16), bone (n=4), meninges (n=4) and various others sites. All RDD samples (n=48) were positive for OCT2. The two samples from patients with H syndrome were positive, one of which being a non specific histiocyte infiltration. OCT2 was positive in all tested mixed histiocytoses [Erdheim-Chester disease (ECD)+ RDD] (n=6), but negative in all ECD (n=11). 8/15 cases of C group histiocytosis showed a positivity, some of which with low intensity (3/15). A few cases were positive in Langerhans-cell histiocytosis (3/11) and ALK+ histiocytosis (2/3). **CONCLUSION:** OCT.2 was expressed in all RDD or mixed histiocytoses with RDD component. It may also be positive in some histiocytoses of other type.

Poster #74



OUR AIM IS TRUE AND ON TARGET - THE INITIAL DANISH EXPERIENCE ON TARGETED THERAPY IN ERDHEIM-CHESTER DISEASE

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PURPOSE: To describe the response to targeted therapies in Erdheim-Chester disease (ECD), and to evaluate the induced whole-blood response

to immunostimulation by the TruCulture method. METHODS: Case reports RESULTS: Patient one had been treated for an unspecified inflammatory rheumatological disorder with high-dose glucocorticoids and anti-interleukin-6, moreover he had a pituitary macroadenoma. FDG-PET/CT showed "hairy-kidney sign" and characteristic bone lesions. The ECD diagnosis was confirmed histologically and by the presence of the BRAF-V600E mutation. The patient's symptoms improved markedly immediately after starting vemurafenib. All other therapy was discontinued. Response FDG-PET/CT showed metabolic remission, his pituitary function is improving, his hematological abnormalities have normalized. Patient two with treatment-refractory hypertension was found to have major infiltrative changes surrounding the kidneys when evaluated for secondary hypertension. A biopsy was consistent with ECD and revealed a MAP2K mutation. The patient did not have bone or pituitary lesions but had marked perinephritic changes and arterial sheathing on FDG-PET/CT. He proved intolerant to pegylated-interferon-alfa. We initiated cobimetinib (20 mg once daily due to tolerability issues). Three months into the treatment his blood pressure, plasma-renin levels and findings on FDG-PET/CT are improving. Using the TruCulture method, we evaluated the induced whole-blood responses to in vitro stimulation with CD3/CD28 antibodies (T-cell receptor stimulation), lipopolysaccharide, Resiquimod R848, and Poly I:C stimulating Toll-like receptor (TLR)4,TLR7/8 and TLR3, respectively. Both patients exhibited reduced cytokine responses to the TLR stimuli, mimicking bacterial and viral infections. Interestingly, the most consistent feature being reduced Interferon-gamma release. The patients exhibited low to normal responsivity to T-cell receptor stimulation, contrasting our initial experience in untreated Rosai-Dorfman disease. Paired post-treatment evaluations are awaited. CONCLUSION: Targeted therapy in ECD was clinically efficient in these patients. This is the first report on the use of dynamic evaluation of the induced whole-blood response using the TruCulture method in a histiocytic disease.

Poster #75



PEDIATRIC AND ADULT INDETERMINED CELL HISTIOCYTOSIS ARE CLINICALLY AND PROGNOSTICALLY DIFFERENT DISEASES

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Indeterminate cell histiocytosis (iCH) is a L-group histiocytosis, with unknown incidence, often presenting during adulthood, with single or multiple erythematous papules and nodules. Pediatric cases are very uncommon. iCH is histologically similar to Langerhans cell histiocytosis (LCH) and expresses S100p and CD1a, but it is negative for CD207/langerin. Its clinical course seems to be indolent, frequently with self-remissions. However, literature reports also numerous cases of association of iCH with hematological malignancies that pursue a more aggressive behavior. In our practice, we encounter 4 cases of iCH, including a pediatric case pursuing a self-limited course and 3 fatal cases in adults, with associated hematological neoplasms (AHN). We, therefore, wondered whether these two specific clinical subgroups of iCH would show any clinical or prognostic differences compared to all other cases. For this reason, we systematically reviewed the literature, outlined the features of all described iCH cases, and tried to compare pediatric and adult patients. We gather 93 papers and included in the study 76 papers, describing 106 patients. The mean age at diagnosis of our cohort was 44 years, (M:F=1.4:1). Around 75% of cases

were adults, while the remaining were children, with a mean age of 5 years. Most patients display a cutaneous single-system disease, and less than a tenth had a multisystem involvement. AHN was observed in a quarter of patients, mostly adults (p=0.007) with a multisystem presentation (p=0.007). The median follow-up was of 24.5 months with 26% of deaths. The number of deaths correlated with age, multisystem involvement, and presence of AHN (p<0.02). Our work suggests that iCH may be a clinically and prognostically heterogeneous condition including pediatric patients with a single-system and self-limiting disorder and adult patients that may develop AHN with multisystem involvement in up to a third of cases and display a reduced survival.

Poster #76



USE OF EMAPALUMAB (ANTI-INTERFERON-GAMMA MONOCLONAL ANTIBODY) FOR ACTIVE DISEASE CONTROL FOLLOWED BY HEMATOPOETIC CELL TRANSPLANTATION IN A PATIENT WITH REFRACTORY SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS WITH ASSOCIATED LUNG DISEASE

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PURPOSE: Macrophage activation syndrome (MAS), a secondary form of HLH, is a serious life-threatening complication associated with systemic juvenile idiopathic arthritis (sJIA). MAS is characterized by fever, hepatosplenomegaly, liver dysfunction, cytopenias, coagulation abnormalities and hyperferritinemia, potentially progressing to multiple organ failure and death. Overproduction of interferon gamma (IFN γ) is considered a major driver of hyperinflammation in MAS and HLH murine models. A subset of patients with sJIA treated with cytokine targeted biologics could develop progressive interstitial lung disease (ILD) which is often difficult to manage. Allogenic hematopoietic cell transplantation (allo-HCT) could potentially be a curative immunomodulatory strategy for patients with refractory sJIA/MAS. METHOD: Herein we report a patient with refractory sJIA/MAS complicated with lung disease that was managed with IFN γ neutralizing antibody using emapalumab followed by an allo-HCT that resulted in permanent correction of the underlying immune dysregulation with improvement of lung disease. RESULT: We present a 4yo girl with sJIA complicated by recurrent MAS and progressive ILD. She developed worsening disease that was refractory to glucocorticoids, anakinra, methotrexate, tocilizumab and canakinumab. She had chronic elevation of serum inflammatory markers, notably soluble interleukin-18 and CXCL9. Emapalumab, initiated at 6mg/kg (1 dose) and continued at 3mg/kg twice weekly for a total of 4 weeks, resulted in achieving disease remission and normalization of inflammatory markers prior to allo-HCT. She received a reduced intensity conditioning regimen with fludarabine/alemtuzumab/melphalan/thiotepa followed by a matched sibling donor bone marrow transplantation. Tacrolimus and mycophenolate mofetil were used for GVHD prophylaxis. At 6 month post-transplant, she achieved full donor engraftment with complete donor-derived immune reconstitution. She had complete resolution of sJIA symptoms including marked improvement in lung disease along with normalization of serum IL-18 and

CXCL9 levels. CONCLUSION: Use of emapalumab followed by allogeneic HCT could help achieve CR in refractory sJIA/MAS who have failed standard of care.

Poster #77



DEATH ANALYSIS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN TREATMENT OF PEDIATRIC CHRONIC ACTIVE EPSTEIN-BARR VIRUS INFECTION: A REPORT OF 17 CASES FROM A SINGLE CENTER

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OBJECTIVE: To explore the factors affecting survival and causes of death in patients with CAEBV infection who underwent HSCT, we present our single institutional experience. METHODS: A total of 71 patients with CAEBV infection were retrospectively reviewed from July 2015 to March 2022. All patients underwent HSCT, and 17 patients died. We mainly analyzed the clinical data of the 17 dead patients. RESULTS: There were 8 males and 9 females. The median age at HSCT was 9.2 (4.1~17.3) years old. 7/17 patients (41.2%) were complicated with hemophagocytic lymphohistiocytosis (HLH) before HSCT. 7/17 patients (41.2%) were complicated with infection when HSCT. 6/17 patients (35.3%) underwent salvage transplantation at the state of disease progression, 11/17 patients (64.7%) achieved partial remission. The median time of death was 1.6 (0.1~11) months after transfusion, and 12 patients (70.6%) died within 100 days. Neutrophil successfully implanted in 12 patients (70.6%). 5 patients (29.4%) died of thrombotic microangiopathy (TMA), 3 patients (17.6%) died of HLH, 3 patients (17.6%) died of pulmonary hemorrhage, 2 patients died of graft-versus-host disease, 2 patients died of septic shock and the remaining 2 patients died of multiple organ failure and cardiac arrest separately. The death rate was higher in patients undergoing HSCT before 2018 (36.8%, 7/19) than that in patients undergoing HSCT after 2018 (19.2%, 10/52). The death rate was lower in cocktail conditioning regimen 1 group (14.3%, 7/49) than in cocktail conditioning regimen 2 group (30%, 3/10) and reduced-intensity conditioning regimen group (58.3%, 7/12). The death rate was similar in patients undergoing haploid HSCT (27.3%, 12/44) and matched sibling donor HSCT (23.1%, 3/13), but higher than that in unrelated HSCT (14.3%, 2/14). CONCLUSION: This study found most deaths occurred early after transplantation in pediatric CAEBV infection. And the most common causes of death were TMA, HLH and pulmonary hemorrhage.

Poster #78



THE GERMAN RARE HISTIOCYTOSIS REGISTRY AND CONSULTATION - EXPERIENCES IN ROSAI DORFMAN DISEASE CASES

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PURPOSE: Rare histiocytoses (non-LCH) include very different diseases. In children, besides juvenile xanthogranulomatosis, Rosai-Dorfman disease (RDD), is most frequent. Here, a large German case series is analysed. METHODS: In

2012, the German registry/consultation service for non-LCH - part of International IRHDR - was initiated, including 97 patients so far. RESULTS: 20 RDD patients were reported, all but one survivors (3 months to 5 years follow-up); 9/10 female/male; 0 infants, 2 1 y old, 5 2-4 y old, 12 5-18 y old, 1 >18y. 7 had cervical lymph node involvement only (all <5 y); 4 had CNS involvement only (all 5-8y), 9 had special or multiple organ involvement (most bone, but also kidneys, skin, glands, and other organs, age from 1 to >18y). In two, a mixed/overlap histiocytosis was found (RDD/Erdheim-Chester disease, RDD/LCH), one patient had H-syndrome (germline), one patient first had systemic RDD, then Acute Lymphoblastic Leukemia, and died from it. Genetic analysis was performed in 6; showing 1 ALK, 1 KRAS, and 1 MAP2K1 mutation, and the H syndrome in 1 case, two were negative. 7 patients who had cervical lymph node disease only, received resection followed by observation in 5 cases, and steroids in 2. 4 patients having CNS involvement were treated by observation after resection in 1, steroids in 2, and targeted therapy in 1 case. The systemic cases received steroids in 2 cases, polychemotherapy in 3 cases, and targeted therapy in 1; the others combined therapies or unknown. CONCLUSION: RDD is heterogeneous: In localized lymph node cases, typically age 1-5y, observation or steroids are appropriate. CNS disease is typical for children in school age. Individual courses like systemic or with mixed/overlap histology or malignant transformation, may require individual therapies. Molecular analyses are crucial to enable targeted therapies. Appropriate consultation depends on international registration, which should be propagated.

Poster #79



DEFINING GENETIC DRIVER MUTATIONS, CLINICAL CHARACTERISTICS, AND OUTCOMES IN CHILDREN AND YOUNG ADULTS WITH RARE HISTIOCYTIC DISORDERS

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BACKGROUND: Langerhans Cell Histiocytosis (LCH), the most common myeloid neoplastic histiocytic disorder, is characterized by MAPK pathway driver mutations in hematopoietic precursors that give rise to granulomatous lesions with CD207+ cells. Non-Langerhans Cell Histiocytosis (non-LCH) represents a group of rare histiocytic disorders that may cause cutaneous or disseminated disease. Although similar features exist between LCH and non-LCH, there are limited data to predict risks or guide therapy. This study aimed to determine significant features of non-LCH at presentation, mutational status, and treatment responses to support diagnostic and treatment decisions for these patients. METHODS: Records of patients with non-LCH treated at Texas Children's Hospital from 2012-2021 were reviewed. Available clinical and molecular data were analyzed. RESULTS: 88 patients (33 Male, 55 Females; Mean age 16.4years) were included in this study. 46.6% of patients had RDD, 42% had JXG, 3.4% had combined LCH/JXG, and 9.1% had a variation of RDD, JXG, or non-LCH with mixed features. Of the 41 patients with some genetic testing,

33% were found to have BRAFV600E by qPCR; alternative MAPK pathway mutations were identified in 39%; and 2 were known to have germline NF1 mutations. The most commonly affected sites of disease were skin (38.6%), bone (22.7%), lymph nodes (22.7%), soft tissue (20.4%), and CNS (19.3%). Initial therapies included surgery (16%), observation (18%), steroids (15%), and clofarabine (12.5%). 83% of patients experienced disease progression or relapse. 67% of the patients needed multiple therapies to achieve disease control (median=2). Relapsed therapies included clofarabine, observation-only, surgical resection, other chemotherapy, and MAPK inhibitors. Despite treatment challenges, overall survival was high (97.7%). CONCLUSION: This study characterizes non-LCH as relatively refractory to therapy compared to LCH. Molecular characterization identified frequent recurrent MAPK pathway mutations, supporting routine molecular analyses and favoring further trials to evaluate the early use of targeted inhibitors for patients with non-LCH.

Poster #80



CLINICAL AND PATHOLOGIC SPECTRUM OF PEDIATRIC ALK POSITIVE HISTIOCYTOSIS HARBOURING ALK GENE TRANSLOCATION: A REPORT FROM A SINGLE INSTITUTION

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PURPOSE: To highlight the clinical and pathological spectrum of pediatric cases of ALK positive-histiocytosis from our institution. **METHODS:** All non-Langerhans cell histiocytosis diagnosed during the last three years were reviewed. Four cases of ALK positive-histiocytosis were identified. Further analyses for ALK gene fusion using the Tru-sight pan-cancer RNA Seq Panel were performed. **RESULTS:** There were one female and three males, ages ranged from 2 to 12 years old. All had localized disease without neurologic involvement. One patient had a single lung lesion, another had a small subglottic mass and two patients had solitary scalp lesions. The histopathology varied from xanthogranuloma features with lipidized histiocytes with some Touton giant cells (one scalp lesion), dense cellularity with ovoid to spindle cells with fascicular and/or storiform growth patterns admixed with lymphocytic infiltrate (lung lesion and second scalp lesion), to sheets of epithelioid histiocyte-like cells (subglottic lesion). Nuclear features varied from ovoid vesicular nuclei with regular nuclear contour, to ovoid nuclei with mild fold or indentation of their contours. Necrosis was absent. The histiocytes were CD163+ and CD68+, and ALK+ (focal to patchy, weak to moderate), and CD1a-ve, Langerin-ve, S100-ve and Braf (V600)-ve. Three cases showed KIF5B-ALK fusion, and the fourth case showed EML4-ALK. Two cases were well defined and were completely excised, and the others had an infiltrative-type border with neoplastic cells extending to the resection margins. All cases were treated by surgical resection. Three cases were recently diagnosed, and one case showed no recurrence after 4 years. **CONCLUSION:** ALK positive-histiocytosis with ALK gene translocation is a distinct entity with a variable clinicopathologic spectrum. It may present as single or multi-system disease. An integrated histological, immunohistochemical and molecular approach to evaluate the ALK gene is recommended, particularly in cases of non-LCH, as this will contribute to disease classification and therapeutic decision making.

Poster #81



CONGENITAL RARE MULTISYSTEM HISTIOCYTOSIS - CASE REPORT

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A 5-weeks old girl was referred to our hospital after two hospitalizations in regional centers for failure to gain weight, intensive regurgitation and bloody stools. At birth a few skin lesions with morphology of violaceous macules were observed. At 3 weeks of age due to lack of weight gain, bloody stools and fever she was admitted to local hospital. Laboratory tests revealed elevated inflammatory markers. Empirical antibiotic therapy was implemented without improvement. She was transferred to another hospital, where inflammatory markers were increasing, hypoalbuminemia and anemia were present. Infectious etiology (including EBV, CMV) and food allergy were excluded. She was then referred to our center. At admission she was pale, cachectic, scattered reddish macules were present. During hospitalization cervical lymphadenopathy, hepatosplenomegaly and spread of skin lesions were observed. A biopsy of the skin lesion was performed and histiocytic disorder diagnosed, however there were no markers of Langerhans cells; BRAF mutation (+). An endoscopic examination of the gastrointestinal tract revealed extensive inflammatory lesions and erosions in the stomach, duodenum, and rectum. Histopathological examination of the material taken from the intestine was consistent with histiocytosis. The pathology specimens were reviewed by independent pathologist. Indeterminate cell histiocytosis with skin, lymph nodes, digestive system and bone marrow involvement was diagnosed. Chemotherapy with vinblastine and prednisone was implemented, initially with very good response, however, after 4 months of treatment, the disease progressed (bloody stools, fever, new skin lesions). Chemotherapy with cladribine and cytarabine was introduced resulting in CR. During chemotherapy reduction as in protocol second relapse was observed, leading to treatment intensification (cladribine and cytarabine) again with good response. BRAF inhibitors are considered. **CONCLUSION:** Involvement of the gastrointestinal tract in histiocytic disorders is rare and could be overlooked as in our patient, it usually occurs in children with systemic disease and carries a poor prognosis.

Poster #82



DERMATOSCOPIC-HISTOPATHOLOGICAL CORRELATION OF JUVENILE XANTHOGRANULOMA: A CASE SERIES OF 6 PATIENTS

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Conflicts of Interest - none

PURPOSE: Juvenile Xanthogranuloma (JXG) is a non-Langerhans cell histiocytic disorder with benign course often self-limiting without any sequelae. Dermatoscopic features of JXG include characteristic orange-yellow background coloration with clouds of paler yellow deposits, erythematous border, subtle pigment network and white linear streak. This case series aims to evaluate dermatoscopic features of JXG in patients with skin of colour, the population in which it is not clearly defined and to correlate these dermatoscopic features with histopathological findings. **METHODOLOGY:** Retrospective evaluation of archived dermatoscopic were done in cohort of six patients of JXG by two of the authors. Histopathological analysis was done by a dermatopathologist and dermatoscopic-histopathological correlation attempted. **RESULTS:** A total of 25 lesions were subjected to dermatoscopic examination with findings of yellow-white or yellow-brown structureless area, yellow orange background with surrounding erythema and telangiectasia, surface scaling, linear telangiectatic vessels, white fibrotic areas/streaks, hemorrhagic spots, ulceration and different pigmentation pattern. Histopathological findings included basal layer pigmentation in epidermis in early-stage lesions also. Other findings included lympho-histiocytic infiltrate and positive IHC. **CONCLUSIONS:** The small sample size limits the dermatoscopic and histopathological correlation. Though JXG is self-limiting in most of the cases, in minority of cases it can involve internal organs. Hence biopsy is often done to confirm the diagnosis so that regular follow up can be done. Though JXG is self-limiting in most of the cases, in minority of cases it can involve internal organs. Hence biopsy is often done to confirm the diagnosis so that regular follow up can be done. More studies can be done in future for the same as dermatoscopy can replace the need for subjecting children to invasive procedures for establishing diagnosis of JXG. The most commonly described "setting-sun" appearance may not be seen as frequently in skin of colour.

Poster #83



COBIMETINIB USE IN ERDHEIM-CHESTER DISEASE: A CASE REPORT WITH NEUROLOGIC INVOLVEMENT

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Erdheim-Chester Disease (ECD) is a rare non-Langerhans cell Histiocytosis characterized by CD68+ CD1a- histiocytes systemic infiltration with main

involvement of bone tissue. Approximately 30 - 50% of patients will have some degree of central nervous system (CNS) involvement. At the time of this report, there have been less than 1000 cases described throughout history. We present the case of a 40 year old male with a one-year history of ataxia, dysmetria and vomiting. Magnetic resonance imaging (MRI) showed a left cerebellum solid tumor that was removed by neurosurgery. Histology evidenced CD68+ CD1a- BRAF V600E- xantomized histiocytes infiltration and positron emission tomography (PET-TC) evidenced additional involvement in C1 vertebrae, zygomatic bone and tensor fasciae latae muscle. An ECD diagnosis was made. Four months later the patient developed facial paresthesia with hypoesthesia, lingual dysarthria, whereas the ataxia worsened (ECOG performance status grade 3). MRI revealed a new right ponto-cerebellar tumor, considered by neurosurgery as non surgical. The patient began daily treatment with Cobimetinib 60 mg orally. Six months later, major clinical and imaging improvements were achieved. Paresthesia, hypoesthesia and dysarthria disappeared, while ataxia returned to initial grade (ECOG performance status grade 2). New MRI showed significant reduction of tumor size, whereas PET-TC evidenced decreased metabolic activity. Treatment was well tolerated. In this report we describe the effectiveness of Cobimetinib in an ECD patient with CNS involvement, BRAF V600E wild type.

Poster #84



SUCCESSFUL TREATMENT OF ROSAI-DORFMAN DISEASE IN A CHILD WITH VINBLASTINE AND PREDNISONE: A CASE REPORT

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PURPOSE: Describe a case of Rosai-Dorfman disease in a child who had a good response to vinblastine and prednisone. **METHODS:** Rosai-Dorfman disease (RDD) is a rare proliferative histiocytic disorder, significantly more common among Caucasian and blacks. The disease typically presents with extensive cervical lymphadenomegaly, most often bilateral and painless. Extranodal tissue involvement may affect some patients, especially the skin, soft tissues, upper airway, bones, urogenital system, lower airway and oral cavity. They usually have complete disease regression without treatment. We present the case of a 4 year old Caucasian boy who developed a right cervical enlargement without pain, 2.5 kg weight loss and sweating in one month, associated with high fever in the last three days. Physical examination revealed a well appearing child with lymph node enlargement about 7 cm in diameter, in the right cervical region. Cardiologic, respiratory and abdominal examinations were normal. Initial laboratory tests showed Hb 10,8 g/dL, WBCs 18.7 x 10³/μL Platelets 437x10³/μL, ESR 107 mm, C reactive protein 246 mg/L. Cervical ct scan revealed right lymphadenomegaly measuring 42x43 mm while abdominal and chest ct scan were normal. Lymph node biopsy showed pathologic features consistent with the diagnosis of Rosai Dorfman disease. **RESULTS:** The patient started treatment with steroids, prednisone 2mg/kg/day. As there was no improvement 30 days after the start of treatment, it was decided to associate vinblastine with prednisone according to HCL III protocol. After 6 weeks the lymphadenomegaly had a significant decrease and in the next 3 months it resolved completely. The patient completed 52

weeks of treatment without complications and persists in remission 7 years after the end of treatment. CONCLUSION: Prednisone and vinblastine may be effective to treat RDD in children.

Poster #85



BRAF V600E-MUTATED ROSAI-DORFMAN-DESTOMBES DISEASE PRESENTING AS A DISSEMINATED MIXED HISTIOCYTOSIS

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PURPOSE: Although BRAF-V600E is detected in over 50% of Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD), it is limited to rare case reports in Rosai-Dorfman Destombes disease (RDD). We report a BRAF-V600E positive RDD presenting as a disseminated mixed histiocytosis. **METHODS:** A 61-year-old woman with bilateral groin masses presented with intense head pain and unintentional weight loss. A head MRI revealed moderate narrowing of the left internal carotid artery. CT/PET imaging revealed hypermetabolic bilateral groin masses, cervical lymphadenopathy, azygoesophageal/paraspinal soft tissue and right shoulder subcutaneous tissue along with multiple sclerotic and lytic lesions involving rib, vertebrae (C1, T11, T12), right iliac bone, and right proximal femur. Needle core biopsy of a left inguinal mass was performed with subsequent excision, immunostaining and molecular testing. **RESULTS:** The resected inguinal mass (8x7 cm) demonstrated an enlarged lymph node with massive sinus histiocytosis that spilled into the paracortex, forming nodular aggregates and disrupting the architecture with fibrosis. The large RDD were positive for S100/OCT-2/CD163 and strongly positive for mutant specific BRAF-VE1 immunostain. There was no high-grade atypia. Also admixed with the predominant RDD component within sinuses were smaller collections of cells with reniform nuclei and a LCH immunophenotype (S100+/CD1a>Langerin staining). Collections of histiocytes with foamy cytoplasm and rare Touton giant cells were also found along the periphery. Next generation sequencing confirmed the BRAF-V600E mutation. A limited bone marrow biopsy did not reveal diagnostic abnormalities. The patient will be further evaluated upon completion of an 8-week prednisone taper. **CONCLUSIONS:** This is a rare case of a disseminated BRAF-V600E mutant histiocytosis with a predominant RDD component and minor LCH component with low langerin expression. Clinical/radiographic exclusion of ECD and evaluation of circulating cells with BRAF-V600E should be considered in such cases. If disease persists or recurs, BRAF/MEK inhibitor therapy might be a therapeutic option.

Poster #86



CHRONIC ACTIVE EPSTEIN-BARR VIRUS INFECTION WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT IN CHILDREN: A CLINICAL STUDY OF 22 CASES

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OBJECTIVE: To analyze the clinical features, treatments, and prognosis for chronic active Epstein-Barr virus infection (CAEBV) with central nervous system (CNS) involvement in children. **METHODS:** Patients with CAEBV admitted to Beijing Children's Hospital, Capital Medical University from January 2017 to December 2020 were enrolled in this study. They were divided into a CNS group and a non-CNS group based on the level of CNS involvement. **RESULTS:** Twenty-two patients developed CNS diseases, accounting for 23.9% (22/92) of CAEBV patients in the same period. In the CNS group, only 2 patients presented with neurological symptoms. Cerebrospinal fluid (CSF) examination demonstrated normal protein concentration and cell number in the CNS group. Only seven patients were positive for CSF EBV-DNA. Four patients regularly monitored CSF EBV-DNA loads, including 3 were negative after transplantation. Twenty-one patients had neuroimaging abnormalities. In the CNS group, 7 (31.8%) patients died. The 3-year overall survival was lower in the CNS group than in the non-CNS group (63.6%±11.9% vs. 86.9%±4.1%, P=0.027). Compared to the non-CNS group, blood EBV-DNA loads and CD4+/CD8+ ratio of T lymphocytes in the CNS group were higher (P<0.001 and=0.002), while fibrinogen levels and natural killer (NK)-cell activity were lower (P=0.047 and 0.048). Children with CAEBV were more likely to develop CNS diseases with low NK-cell activity (NK-cell activity<14.00%, P=0.023) or high alanine aminotransferase (ALT) levels (ALT levels>40U/L, P=0.032). **CONCLUSION:** CAEBV with CNS involvement has non-specific clinical manifestations, laboratory data, neuroimaging, and worse prognosis. Blood fibrinogen levels and NK-cell activity in CAEBV children with CNS involvement are lower than those without CNS involvement, while blood EBV-DNA loads and CD4+/CD8+ ratio of T lymphocytes are higher. Children with CAEBV who presented with HLH, NK-cell activity<14.00%, serum ALT>40U/L, and high blood EBV-DNA loads are prone to develop CNS diseases.

Poster #87



CRIZOTINIB IN TREATMENT OF ATYPICAL ALK-REARRANGED HISTIOCYTE-RICH TUMOR. CASE REPORT

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PURPOSE: Atypical ALK-rearranged histiocyte-rich tumor is a rare variant of malignant histiocytosis without established treatment. **METHODS:** Clinical and laboratory details of a patient with disseminated atypical ALK-rearranged histiocyte-rich tumor. **RESULTS:** A 53 year old female presented with a painful abdominal tumor which was managed by surgery involving partial dissection of small bowel, colon and the urinary bladder. After 5 months the abdominal discomfort resumed. CT-scan revealed a tumor measuring 110x113 mm and multiple lesions in the liver. The ECOG was 2/3 with haemoglobin level of 8.5 gr/dl, elevation of alkaline phosphatase x 2 upper limit normal (ULN) and gamma-glutamyltransferase (GGT) 2.5 x ULN, serum glutamic pyruvic transaminase x 2 ULN and serum glutamic oxaloacetic transaminase x 3 ULN. After reviewing the initial histological specimens a diagnosis of Atypical ALK-rearranged histiocyte-rich tumor with SQSTM1-ALK mutation was made. Treatment with ALK-inhibitor, crizotinib 250 mg bid, was started. After three days the patient felt improvement with reduction of pain and fatigue. After the first week GGT elevated to 10xULN. During the next 4 weeks anemia resolved and liver function tests normalized. After 8 months partial remission was achieved. The treatment continued. During the 14 months of observation no severe adverse reactions were reported. **CONCLUSION:** Crizotinib led to a stable response with acceptable tolerability in a patient with atypical ALK-rearranged histiocyte-rich tumor.

Poster #88



MUTATIONAL PROFILING OF ROSAI-DORFMAN DISEASE: A MULTI-INSTITUTIONAL STUDY

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BACKGROUND: Mutations in the mitogen-activated protein kinase (MAPK) pathway have been reported in Rosai-Dorfman disease (RDD). However, the mutational profiling of RDD remains limited to small case series. We report the mutational profiling data by next-generation sequencing (NGS) of 46 patients with RDD. **METHODS:** This study was approved by the institutional board review. Patients with RDD who were seen at Mayo Clinic and University of Alabama at Birmingham and underwent multi-gene testing with NGS were included in this study. **RESULTS:** Of the 46 patients with RDD who met the inclusion criteria, the median age at diagnosis was 56 years (range 17-79) with 35 patients (76%) being female. In 9 patients (20%), NGS failed due to an inadequate amount of histiocytic tissue in the biopsy samples. Of the 37 patients who had a successful NGS, 20 (54%) had a known pathogenic mutation, which included missense KRAS mutations (9) and missense MAP2K1 mutations (3). The majority of KRAS mutations affected exon 3 (7) and specifically were p.K117N (4) or p.A146T (3). Other mutations occurred in ARAF, ASXL1, CDK11B, CDKN2A, CREBBP, FOS, IDH2, KLF4, MLL1, NF1, PIK3CA, PTEN, PTPRD, SGK1, SMARCA, and TP53. In the 17 patients (46%) without pathogenic mutations identified, 9 had at least one variant of undetermined significance detected. **CONCLUSION:** Slightly over half of the RDD patients in our cohort were found to have a known pathogenic mutation, with KRAS missense mutations being the most frequent followed by MAP2K1 missense mutations. Unlike other histiocytic subtypes, fusion genes were not detected in any case. One in five patients had NGS test failure due to inadequate histiocytic tissue in the biopsy samples. Further studies are necessary to define the nature and driver of RDD patients without pathogenic mutation and develop novel tests to sequence biopsy samples with low histiocytic burden.

Poster #89



PERSONALIZED MEDICINE IN ERDHEIM-CHESTER DISEASE WITHOUT MAPK PATHWAY ALTERATIONS

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PURPOSE: Because activating MAPK pathway alterations (RAS/RAF/MEK) are predominant in ECD, BRAF or MEK inhibitors are effective and commonly used treatments. However, optimal treatment strategies for patients without MAPK alterations are unclear. **METHODS:** We describe three ECD patients found to have novel non-MAPK pathway alterations. The patients were treated with off-label drugs targeted to the specific alteration, then monitored with clinical and radiographic response evaluations. **RESULTS:** Patient #1 is a 27-year-old female with rapidly progressive disease involving the central nervous system, both brain and spinal cord, which was refractory to cobimetinib and cytarabine. A CSF1R in-frame deletion (p.S560_P566del) was identified and in-silico modeling indicated a gain-of-function mutation. She was treated with pexidartinib, which led to a complete clinical response within two months. At her last

follow up after three months of treatment, her MRI showed a complete response. Patient #2 is a 55-year-old female with skin and bone involvement. We identified a KIF5B-FGFR1 fusion and she was treated with pemigatinib. She experienced a near complete clinical response in three months. At her last follow up after six months of treatment, she continued to see clinical improvements in her skin. Patient #3 is a 40-year-old male with bone marrow, gastrointestinal-tract, and subcutaneous tissue involvement. His disease was refractory to cladribine, hydroxyurea, methotrexate, tocilizumab, and cobimetinib. Tumor NGS revealed a FLT3-MEF2C fusion, which was targeted with sorafenib. He achieved a complete clinical and partial radiographic response within three months. At his most recent follow up after 10 months, he continued to be in a partial radiographic response. CONCLUSION: We report sustained clinical and/or radiographic responses in three ECD patients with novel mutations successfully treated with off-label use of three different kinase inhibitors, pexidartinib, pemigatinib, and sorafenib. Two of these cases were refractory to MEK-inhibitor therapy, thereby suggesting alternate pathogenic mechanisms for ECD.

Poster #90



MODIFIED MYELOABLATIVE CONDITION REGIMEN FOR ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH CHRONIC ACTIVE EB VIRUS INFECTION: A RETROSPECTIVE ANALYSIS OF A SINGLE-CENTER

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OBJECTIVE: To evaluate the feasibility and clinical effect of the modified myeloablative condition (MAC) regimen for allogeneic hematopoietic stem cell transplantation (allo-HSCT) in children with chronic active EB virus infection (CAEBV). METHODS: Children with CAEBV who underwent allo-HSCT with a modified MAC regimen in Beijing Children's Hospital, Capital Medical University, from October 2016 to June 2021 were retrospectively analyzed. Data relating to the clinical manifestations, engraftment, and prognosis of the children were extracted from medical records. RESULTS: Forty-one patients, including 24 males and 17 females, with an onset age of 73.0 (44.5, 94.5) months and a transplantation age of 92.6 (60.4, 120.7) months, were enrolled in this study. The mean time from diagnosis to transplantation was 8.5 (5.0, 16.3) months. The mean observation time was 28.2 (15.3, 40.2) months. All patients received the modified MAC regimen. After transplantation, 23 patients (56.1%) developed aGVHD, 14 patients had cGVHD, 9 patients had TMA and 17 patients had CMV infection. The 3-year overall survival (OS) rate was estimated to be 88.8% ±5.4%, and the 3-year EFS rate was estimated to be 85.0%±5.7%. Multivariate analysis showed that the degree of aGVHD > degree II was an independent risk factor for death (OR=22.634, 95%CI 1.303 -393.150, P=0.032). CONCLUSION: Modified MAC regimen is safe and effective for allo-HSCT in the treatment of pediatric CAEBV. The degree of aGVHD > degree II was an independent risk factor for death.

Poster #91



LONG-TERM OUTCOMES FOR THE TREATMENT OF ERDHEIM-CHESTER DISEASE WITH CLADRIBINE OR INTERFERON-ALPHA

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PURPOSE: Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis. While treatment with targeted agents (BRAF or MEK inhibitors) have high response rates, long term treatment is generally required. While systemic treatment like cladribine and interferon-alpha have lower response rates, the responders may have long-term of remission without requiring maintenance therapy. It also may be a more cost-effective strategy. Here we describe the efficacy of cladribine and interferon-alpha in the treatment of ECD and report on the long-term outcomes. METHODS: We retrospectively reviewed medical records from January 1, 1998 to December 31, 2020 at Mayo Clinic. RESULTS: A total of 118 adult patients with ECD were identified. 27 patients received cladribine and 15 patients received interferon alpha treatment. The overall clinical response rate to cladribine was 48% (11 of 23) (4% [1 of 23] complete response and 43% [10 of 23] partial response), with median duration of response (DOR) 50.2 months (5-133). The overall radiological response rate to cladribine was 38% (8 of 21) (5% complete response [1 of 21] and 33% partial response [7 of 21]) with median DOR unreached (15-249). The overall clinical response to interferon-alpha was 58% (7 out of 12) (33% [4 of 12] complete response and 25 [3 of 12] partial response), with median DOR unreached (27-181). The radiological response to interferon-alpha was 56% (5 of 9, all partial response), with median DOR unreached (19-180). CONCLUSION: Cladribine and interferon-alpha have moderate efficacy in ECD treatment and responders may have durable responses.

Poster #92



CENTRAL NERVOUS SYSTEM ERDHEIM CHESTER DISEASE, EXPERIENCE FROM ONE CENTER

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PURPOSE: Erdheim Chester Disease (ECD) is a non-Langerhans cell histiocytosis with multiple organ involvement. Central nervous system (CNS) involvement is a poor prognostic factor. Diagnosis might be challenging when presenting as the first clinical manifestation. We present a case series from one center, including six patients with ECD and CNS lesions. METHODS: Retrospective review of clinical records of patients with histiocytosis assessed at a tertiary neurological center in Buenos

Aires, Argentina between 1/2012 and 4/2022 was done. Patients with confirmed diagnosis of ECD with CNS involvement were selected. Clinical characteristics, Magnetic Resonance Imaging (MRI), pathology and treatment response were evaluated. RESULTS: Eight patients with ECD diagnosis were evaluated, six had CNS involvement. Median age 48 (range 20-60). Brain MRI showed sellar/supra-sellar lesions in 2 patients and tumorous parenchymal findings in 4 patients. Median delay from neurological symptoms to diagnosis was 7 months (0-48). Four patients had exclusive CNS involvement. Affected sites in those with multi-organ disease were lungs (2) and bone (1). One patient had a synchronous diagnosis of a pineal primary CNS Lymphoma (pCNSL). Treatment was varied; 1 used methotrexate. The patient with concomitant pCNSL was treated with surgery for the sellar/suprasellar ECD and RVMP protocol for the pCNSL. Three patients received targeted therapy (1 dabrafenib, 2 trametinib). The other with sellar/suprasellar ECD only surgery. One patient died 4 months after diagnosis due to a respiratory infection. Median overall survival was 53 months. Responses were seen in those with medical treatment. CONCLUSION: We describe a small sample of patients with CNS ECD. Diagnosis in patients with parenchymal involvement of the CNS is frequently challenging and delays treatment. It comprises a numerous list of differential diagnoses which delay diagnosis and treatment. High awareness of disease among physicians, and specially neurologists and neuro oncologists, might improve time to diagnosis and outcome.

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REAL-WORLD DEMOGRAPHICS, CLINICAL CHARACTERISTICS, AND TREATMENT PATTERNS OF PATIENTS TREATED WITH EMAPALUMAB FOR HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) AND NON-HLH CONDITIONS IN THE UNITED STATES: THE REAL-HLH STUDY

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening, hyperinflammatory syndrome caused by overproduction of proinflammatory cytokines, particularly interferon gamma (IFN γ). Real-world evidence is lacking on emapalumab, an anti-IFN γ monoclonal antibody approved for patients with primary HLH (pHLH) by FDA in November, 2018. **METHODS:** A retrospective medical chart review conducted across 33 US hospitals identified patients treated with ≥ 1 dose of emapalumab between November 20, 2018, and October 31, 2021. Data were extracted from time of emapalumab initiation to end of data availability, death, or study end (December 31, 2021). **RESULTS:** Study patients (N=105; mean age [\pm SD], 9.2 [8.5] years) were mostly male (56.2%) and non-white (63.8%). Mean age (\pm SD) at HLH diagnosis for patients with pHLH (n=41) and presumed secondary HLH (sHLH, n=57) was 4.7 (7.9) and 9.3 (7.5) years, respectively. In pHLH and sHLH (n=98), the most common reasons for initiating emapalumab were treatment of refractory (39.8%), progressive (23.5%), and recurrent (22.4%) disease. In the non-HLH group (n=7), 5 (71.4%) patients received emapalumab before (n=1) or following (n=4) hematopoietic stem-cell transplantation (HSCT) to prevent graft rejection or failure. Median (range) time to emapalumab initiation from HLH diagnosis was 30 (2-759) and 16.5 (1-2278) days among patients with pHLH and sHLH, respectively. Median (range) emapalumab starting and cumulative treatment doses were 1.4 (0.8-9.8) and 66.8 (1.0-512.2) mg/kg in pHLH; 1.1 (0.7-5.9) and 21.3 (1-336.5) mg/kg in sHLH; and 8.7 (0.7-10.3) and 10.3 (3.9-40.0) mg/kg in non-HLH. Median (range) maximum administered emapalumab dose was 3.8 (0.8-11.2) mg/kg in pHLH; 2.3 (0.7-12.5) mg/kg in sHLH; and 8.7 (0.7-10.3) mg/kg in non-HLH. Emapalumab was most commonly discontinued due to HLH resolution/ remission and patients proceeding to HSCT (pHLH [65.9%]; sHLH [31.6%]). **CONCLUSION:** This is the first study describing real-world treatment patterns with emapalumab across a diverse patient population with HLH and non-HLH conditions.

DISTINGUISHING SEPSIS AND SEPSIS ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS BY PLASMA CYTOKINE PROFILE AND T- CELL PHENOTYPING

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PURPOSE: Sepsis associated hemophagocytic lymphohistiocytosis (SHLH), is a fatal complication of sepsis where there is dysregulated immune hyperactivation. SHLH is clinically similar to sepsis, however distinguishing them is critical, as urgent, aggressive immunosuppressive treatment is needed in SHLH which is detrimental in sepsis. Current diagnosis of SHLH is based on HLH-2004 criteria which is non specific. We propose to study the plasma cytokines and peripheral blood T cell phenotype to identify these two clinical syndromes. **METHODS:** We included patients with sepsis (n=27), SHLH (n=11), primary HLH (n=5) and healthy controls (n=14). Blood samples were collected after written informed consent, utilizing protocols approved by our institution. Plasma Cytokine levels were measured using 30 -plex luminex and T cell immunophenotyping was done on cryopreserved peripheral blood mononuclear cells. **RESULTS:** Total leucocyte and absolute neutrophil counts were lower in SHLH as compared to sepsis. Median % of activated CD 4 T cells (CD 38 +, HLADR+) was significantly higher in SHLH (11.36 vs 1.04). However, CD 8 activated T cells had a similar trend but did not reach significance (Median % SHLH vs sepsis = 19.9 & 2.01). There was a significant difference in CD 4: CD8 between the groups (Median SHLH vs Sepsis = 0.75 & 2.28). We also observed that plasma IL-2r levels in SHLH is higher (Median SHLH vs Sepsis is 25702pg/ml & 4168pg/ml) reflecting increased T cell activation which is in keeping with phenotyping data. Soluble CD 163 and ferritin which are markers of macrophage activation were higher in SHLH (Median 2.2 ng/ml vs 0.6 ng/ml and 1078 ng/ml vs 554 ng/ml). In SHLH there were elevated IFN-G (Interferon Gamma) and its regulatory proteins (IP 10& MIG), IL-1RA & IL-6. **CONCLUSION:** T cell activation profile, CD4: CD8 ratios & plasma cytokines have the potential to distinguish SHLH from sepsis.

A MULTINATIONAL SERIES OF 26 PATIENTS WITH MIXED HISTIOCYTIC NEOPLASMS HIGHLIGHTING A DIVERSE MUTATIONAL LANDSCAPE AND SUPERIOR EFFICACY OF TARGETED THERAPIES

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PURPOSE: Patients with mixed histiocytosis comprise a small minority of patients with histiocytosis, and limited observations exist regarding the

spectrum of this entity. METHODS: Retrospective series of patients with pathologically-confirmed mixed Erdheim-Chester disease (ECD)/Langerhans cell histiocytosis (LCH), ECD/Rosai-Dorfman-Destombes disease (RDD), RDD/LCH, and ECD/RDD/LCH. Clinical variables collected included demographics, sites of disease, and tumor sequencing. Treatments were dichotomized to conventional (corticosteroid/immunosuppressive/chemotherapeutic) versus targeted therapy (BRAF/MEK inhibitor) modalities. Modalities were compared with respect to (1) frequency of complete or partial response (CR, PR) and stable disease (SD) by PET/CT or CT/MRI and (2) proportion of those with CR/PR/SD experiencing subsequent disease progression despite therapy, considering all instances of each modality. RESULTS: 26 patients were studied. 19 (73%) were male. The median age was 53.6 with a range of 18.0 to 74.1 years. Mixed subtypes were ECD/LCH in 19 (73%), ECD/RDD in 5 (19%), RDD/LCH in 1 (4%), and ECD/RDD/LCH in 1 (4%). 17 (65%) patients were diagnosed with histiocytosis subtypes asynchronously, 14 (82%) with LCH or RDD first. Somatic mutations were identified in 25/26 patients: BRAFV600E in 15 (58%), MAP2K1 in 4 (15%), and one each of MAP2K2, MAPK3, KRAS, non-V600 BRAF, RAF1, and BRAF fusion. 37 instances of conventional therapy led to CR in 5 (14%), PR in 8 (22%), SD in 6 (16%). However, 18 of these 19 (95%) had subsequent progression. 29 instances of targeted therapy led to CR in 10 (34%), PR in 15 (52%), SD in 2 (7%). 4 of these 27 (15%) had subsequent progression ($p < 0.0001$ versus conventional therapy). CONCLUSIONS: Mixed histiocytosis represents a diverse spectrum of mutational entities with nearly invariable progression following conventional therapies. Patients with histiocytic neoplasms should be evaluated with meticulous attention to the possibility of mixed disease to improve outcomes with early implementation of targeted therapies.

OCULAR FINDINGS IN PATIENTS WITH HISTIOCYTOSIS

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Memorial Sloan Kettering Cancer Center

PURPOSE: Histiocytoses are clinically heterogeneous and can manifest as localized or diffuse multi-system disease, with the most severe cases causing neurologic disability or other end-organ compromise. This present study characterizes the frequency and nature of ocular findings in patients with histiocytic neoplasms including abnormalities by ophthalmoscopy and multimodal imaging. We also investigated whether clinical disease features were associated with ocular abnormalities. METHODS: This retrospective review included patients with histiocytosis who completed comprehensive ophthalmic assessment and multimodal imaging at Memorial Sloan Kettering Cancer Center from June 2014 through March 2022. Descriptive statistical measures were used to characterize the cohort. Association between ophthalmic findings and variables of interest was analyzed using the Chi-squared test or Fisher's test as appropriate. RESULTS: One-hundred-eighty-two eyes of 91 patients (46 males, 45 females) with histiocytic neoplasms (Erdheim-Chester Disease (ECD) 34, Rosai-Dorfman (RDD) 21, Xanthogranuloma (XG) 7, Mixed histiocytosis 14, Langerhans cell histiocytosis (LCH) 15) were examined. 43% of patients had ocular disease findings including anterior segment 9%, posterior segment 22%, orbital 12%, neuroophthalmic 12% and eyelid 9%. Compared to LCH, non-LCH subtypes (ECD, RDD, XG) were statistically more likely to exhibit ocular findings, particularly in the posterior segment ($p = 0.04$). Findings were not different by BRAFV600E mutational status ($p > 0.11$). Patients with neurological sites of histiocytic disease were statistically more likely to exhibit ocular findings ($p = 0.006$). CONCLUSIONS: Approximately 40% patients with histiocytosis have measurable ocular abnormalities manifesting in various layers of the eye. Ocular

disease is statistically more frequent in patients with non-LCH subtypes compared with LCH, associated with neurological sites of histiocytic disease; but not BRAFV600E mutational status. Given the high propensity for ocular manifestations in histiocytic disease, inclusion of an ophthalmology or ophthalmic oncology specialist may be a valuable part of comprehensive histiocytosis care.

DEEP PROTEOMIC ANALYSIS OF FAMILIAL HLH PATIENT'S SERUM INDICATE THAT IFN-g AND IL-6 JAK-STAT3 SIGNALING DRIVE THE DISEASE PATHOLOGY

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PURPOSE: Experimental models of Hemophagocytic lymphohistiocytosis (HLH) revealed a disorder characterized by cytotoxic T cell activation and driven by IFN-g. Recently a wider protein array of 135 proteins in human plasma demonstrated that IFN-g signaling in HLH is uniquely elevated compared to sepsis. However, to date, broader proteomic methods have not been utilized to study familial HLH (FHL). METHODS: We conducted a SomaLogic proteomic study of 7,596 proteins in the serum of seven FHL patients treated at Schneider Children's Medical Center of Israel and seven age-matched controls (ages five weeks- 58 months). Genetic lesions were identified in 5 of these patients (1 PRF1, 3 UNC13D, and 1 RAB27A), while two had no known genetic defects. For unsupervised clustering of patient results, primary component analysis, T-SNE, and K-M cluster analysis were performed. Later, volcano and heatmaps were performed to identify differential proteins. Finally, gene set enrichment analysis (GSEA) with hallmark pathways was performed to identify the significant pathways. RESULTS: FHL samples clustered separately from aged-matched pediatric controls. C-X-C motif chemokine 9 (CXCL9, $p = 0.02$, $q = 0.148$), C-X-C motif chemokine 10 (CXCL10, $p = 0.0055$, $q = 0.08$), Interleukin-18 binding protein (IL18BP, $p < 0.0001$, $q = 0.0004$), and heme oxygenase-1 (HO-1, $p < 0.0001$, $q = 0.01$) were among the highest differential proteins. High expression of HO-1 suggests a direct mechanism for chronic HLH-like pathology reported in rare HO-1 deficient patients. GSEA pathway analysis revealed that IFN-g response and IL6/ JAK-STAT signaling were most significantly enriched, while IL2-STAT5 and MTOR signaling were also enriched. CONCLUSION: We report the first deep proteomic analysis of FHL compared to healthy pediatric controls. These findings support prior findings from experimental preclinical models and prior, more limited cytokine studies. More extensive proteomic characterization may identify novel pathways for therapeutic targeting in HLH.

THE OPTIMIZED HLH INFLAMMATORY (OHI) INDEX IDENTIFIES LYMPHOMA PATIENTS WITH UNEXPECTEDLY HIGH MORTALITY NOT RELATED TO DISEASE PROGRESSION

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening inflammatory syndrome that may complicate hematologic malignancies (HM). We recently developed a simplified diagnostic and prognostic index termed the 'optimized HLH inflammatory' (OHI) index comprising the combined elevation of sCD25 (>3,900 U/mL) and ferritin (>1,000 ng/mL) . In this study, we examined whether mortality in OHI-positive patients is directly related to progressive malignancy vs. HLH-associated causes. METHODS: We performed a multicenter, retrospective study of patients with newly diagnosed lymphoma for whom sCD25 and ferritin levels were measured either as routine surveillance or during HLH investigation and classified patients by their OHI status. The individual disease-relevant international prognostic index was used to estimate the predicted prognosis at the initial malignancy diagnosis. Predicted five-year overall survival was calculated based on the relevant prognostic index and was compared between OHI+ and OHI- patients. The actual survival at five years/last follow-up was recorded, as was the cause of death. The odds ratios (ORs) for observed vs. predicted mortality was calculated using the Chi-square test. RESULTS:100 lymphoma patients were studied: 37 were OHI+, and 63 were OHI-. The disease-relevant international prognostic index-predicted 5 - year survival did not differ between OHI + and OHI- patients. However, the observed 5-year survival in OHI+ patients was lower than predicted (12%), reflecting a mortality incidence that was four times higher than predicted by standard prognostic scoring (OR 3.9; CI 1.3-12.1). By contrast, OHI- patients had better survival (79%) than predicted by their prognostic scores (OR 0.15; CI 0.07-0.34). In addition, more than half of the OHI+ patients died from non-malignant causes, while most deaths among OHI- patients (92%) were from progressive malignancy. CONCLUSION: Death in OHI+ patients was largely due to causes other than progressive malignancy, suggesting that the OHI identifies a harmful inflammatory state and deserves further prospective study.

NOTES

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NESBIT PRIZE IN CLINICAL SCIENCE



The Histiocytosis Association, in conjunction with the Histiocyte Society, is offering an annual prize for the best clinical article at their Annual Meeting. It will be given in honor of Dr. Mark Nesbit, renowned pediatric oncologist, teacher, and supporter of the many families dealing with histiocytic disorders. The prize will be awarded to a physician or scientist who is carrying out clinical research to the therapy, biology or pathogenesis of one of the histiocytic disorders. The goal of the Award is

to stimulate and promote the activities of clinical scientists from all around the world to study specific aspects of these puzzling diseases.

Dr. Mark Nesbit completed his medical training at George Washington Medical School in 1959. The remainder of his medical training was at the University of Minnesota where he specialized in pediatric hematology and oncology. In 1967 he joined the faculty at the University of Minnesota, achieving the rank of Professor of Pediatrics in 1973. Dr. Nesbit assumed the position of Director of the Division of Pediatric Hematology and Oncology at the University of Minnesota where he built one of the most productive and nationally recognized programs during his 14 year tenure. Professor Nesbit has been a leader in the development of clinical research for the treatment of leukemia and has a special interest in histiocytosis, bone tumors and the late complications of cancer survivors. In addition, Dr. Nesbit has helped countless young investigators with their careers in the field of pediatric hematology and oncology.

Of the contributions made by Professor Nesbit towards better understanding of the histiocytic disorders, we highlight the following three:

- Histiocytic disorders had been a continual interest from the onset of Professor Nesbit's career. His first publication was entitled: "Histiocytosis X".
- Dr. Nesbit played an important role in the organization of the Histiocyte Society. Besides his active input in the Epidemiology Study Group of the Histiocyte Society, he served on the Education Committee. His interest and initiative for increasing the activity and visibility of the Histiocyte Society has been an important part of the Society's evolution.
- Dr. Nesbit was a member and participant as a Board of Trustees member of the Histiocytosis Association. His activities in the Association made him a national source of information on the diagnosis and treatment of histiocytosis. In 1990, Professor Nesbit received the Outstanding Investigator Award from the Histiocytosis Association.

In conclusion, Dr. Nesbit has made substantial contributions to research in the field of histiocytosis. His dedication to the organization of interested investigators has resulted in a strong research agenda to better understand the etiology, diagnosis, treatment and long-term outcome of children with Langerhans cell histiocytosis. His compassion for patients and their families has always been evident, by his willingness to consult with both physicians and family members.

The Histiocytosis Association and the Histiocyte Society thought it entirely compatible with the support and the work of Dr. Nesbit within the world of the histiocytoses to offer this prize in his name. The candidates for the Nesbit Award need not be physicians, but the focus of the work should be on some aspect of the histiocytic disorders, be it in clinical medicine, allied pursuits such as nursing, psychology, social work, occupational therapy, etc.

Judgment will be based on a written abstract describing work done by the candidate him/herself. It is understood that the winning abstract may have co-authors, but that the first author must be the major contributor who is awarded the Nesbit Award. The Program Committee will provide time during the Annual Meeting for presentation of the winning paper. The decision by a special committee of the Histiocyte Society will be based on originality, completeness, scientific accuracy, and contribution to science. The prize will consist of \$500 US and a certificate.

NEZELOF PRIZE IN BASIC SCIENCE



In order to stimulate the activities of scientists and clinicians from around the world studying the histiocytic disorders, the Histiocyte Society is sponsoring an annual prize for the best scientific article at the Annual Meeting. The Award will be given in honor of Dr. Christian Nezelof, renowned pathologist, investigator, teacher, founding member and first President of the Society, to a physician or scientist who is carrying out basic research on the therapy, biology or pathogenesis of one of the histiocytic disorders.

Dr. Christian Nezelof studied medicine in Paris, France during and after the Second World War. In 1948 he specialized in Pediatrics at the Hospital des Enfants Malades. In the early fifties, as a young pediatrician, he published the first clinical report on cystic fibrosis in France. In 1956 he worked in the Department of Pathology at the Sick Children Hospital in London under the direction of Professor Bodian, a famous British pathologist who first described cystic fibrosis in children. On returning to France he completed training in Pediatric Pathology. During the period of 1960-1968 Dr. Nezelof served as a full-time pathologist at Necker-Enfants Malades, where he became Chairman of the Department of Pathology in 1968. In parallel, from 1970, for 15 years he was Head of INSERM Research Unit and created the Groups of Pediatric Pathology located at the Necker-Enfants Malades Hospital.

The many contributions by Dr. Nezelof include:

- Dr. Nezelof contributed significantly to the development of Pediatric Pathology as a subspecialty by creating a network of various specialties and also trained many clinicians and foreign pathologists. He has served as a consultant for the world of histiocytosis, always giving a friendly and illuminating answer to anyone's questions.
- In 1960, Dr. Nezelof played a key role in describing a clinical condition of immunodeficiency in childhood, in which the existence of a "split" in the human lymphoid system toward T and B-cells was recognized. An immune-deficient child was described as afflicted by a thymic hypoplasia, but with normal level of immunoglobulins ("Lympho-cytophtisie avec normogamma-globulinemie"). In the pediatric literature this condition became known as Nezelof's syndrome.
- In the field of histiocytosis, his seminal contribution was that Letterer-Siwe, Hand-Schuller-Christian and eosinophilic granuloma are linked to the same cell, having a common ultrastructural marker designated as the Langerhans body (Birbeck granule). In his paper "Histiocytosis X: Histogenetic arguments for Langerhans cell origin", he noted the dendritic lineage of this disease. Not long afterwards the term Langerhans cell histiocytosis was introduced.

Histiocytic disorders continue to be one of his major fields of interest. In 1982 Dr. Nezelof described the successful growth in nude mice of a tumor after injection of cells from the pleural effusion of a child with malignant histiocytosis. After this manuscript entitled: "Tumor cell line characterization of a malignant histiocytosis transplanted into nude mice" his team has described successful establishment in vitro of the Malignant Histiocytosis DEL cell line.

The Society thought it entirely consistent with Dr. Nezelof's great interest in new developments of basic pathophysiology, bridged with his key-role in supporting others that this prize be given in his honor. The awardee need not be a physician, but the focus of the work should be on some aspect of the pathophysiology of the histiocytic disorders.

Judgment will be based on a written abstract describing work done by the candidate him/herself. It is understood that the winning abstract may have co-authors, but that the first author must be the leader of the project and the one who is awarded the Nezelof Award. The Program Committee will provide time during the Annual Meeting for presentation of the winning paper. The decision by a special committee of the Histiocyte Society will be based on originality, completeness, scientific accuracy, and contribution to science. The prize will consist of \$500 US and a certificate.

ROBERT J. ARCECI PRIZE FOR BEST POSTER



The Histiocyte Society offers an annual prize for the best poster presented at the Annual Meeting. It is given in honor of Dr. Robert J. Arceci, world renowned pediatric oncologist, scientist and teacher with invaluable contributions to the field of histiocytoses.

Dr. Arceci completed his undergraduate studies at Trinity College, received his Ph.D. and M.D. from the University of Rochester, and then completed his Residency in Pediatrics and Fellowship in Pediatric Hematology/Oncology at Boston Children's Hospital and Harvard Medical School. Following faculty appointments at Harvard Medical School, Dana-Farber Cancer Institute and Boston Children's Hospital, he became Director of Pediatric Hematology/Oncology at Cincinnati Children's Hospital Medical Center. In 2000, Dr. Arceci became Director and King Fahd Professor of Pediatric Oncology and Professor of Oncology and Pediatrics at the Johns Hopkins University School of Medicine where he worked until 2012.

In late 2012, Dr. Arceci joined Phoenix Children's Hospital as Co-Director of the Ronald A. Matricaria Institute of Molecular Medicine and held the dual role of Division Chief for the Center for Cancer and Blood Disorders at Phoenix Children's Hospital. He also served as a professor of Pediatrics on the faculty at the University of Arizona College of Medicine-Phoenix, Department of Child Health.

Dr. Arceci was a member of numerous scientific and medical societies, advisory committees and review boards, and has been the recipient of several prestigious honors and awards. He has served on a variety of committees in the Pediatric Oncology Group, the Children's Cancer Group and the Children's Oncology Group, including Chairperson for the Myeloid Leukemia Committee and Vice-Chair of the Biology and Therapeutics Translational Committee. Dr. Arceci was Editor-in-Chief of Pediatric Blood and Cancer and previously served as Editor-in-Chief of the Journal of Pediatric Hematology/Oncology and Associate editor of the Journal of Pediatrics. In addition to these leadership roles, Dr. Arceci was an excellent clinician, known both nationally and internationally. He was considered one of the world's experts on histiocytic disorders and pediatric acute myelocytic leukemia (AML).

Dr. Arceci was an active member of the Histiocyte Society for many years and a beloved colleague, friend and mentor. In addition, he played an integral role as the Chairman of the Nikolas Symposium to promote translational research in Langerhans cell histiocytosis.

The prize will be awarded to (1) poster presenter whose poster demonstrates an exceptional level of science and relevance to the histiocytic disorders and is presented in a clear, original and organized manner.

The abstracts selected for poster presentations which receive one of the top ten scores will be recognized as finalists for consideration for this award. Final selection of the award winner will be made through a separate round of grading to occur during the Poster Presentation Session at the Annual Meeting. Only those poster presenters in attendance of this session will be considered eligible for the award.

It is understood that the winning poster may have co-authors, but that the first author must be the leader of the project and the one who is awarded the Robert J. Arceci Award for Best Poster. The decision by a special committee of the Histiocyte Society will be based on scientific content, originality, relevance and organization of presentation. The prize will consist of \$250 US Dollars and a certificate. This award will be presented during the Closing Ceremonies of the Annual Meeting.

