Dear Colleagues,

It is with great pleasure that the Histiocyte Society welcomes you to Singapore for its 33rd Annual Meeting on October 3-4, 2017. We are back in Asia and that is not by chance. In accordance with the Society’s vision to evolve into a world leader in the field of histiocytoses and its mission to improve patient outcomes everywhere, we are dedicated to bringing science and clinical know-how closer to the patients. The population of Asia accounts for more than half of the world population. We chose Singapore for its perfect location and infrastructure. Since its independence was proclaimed in 1965, this unique city-state has evolved into a modern, international hub and tourist attraction. It offers a great opportunity to combine the intensive scientific exchange with relaxing sightseeing in a marvelous environment. Our meeting venue, the Marina Mandarin Singapore, is located in the heart of Singapore’s Central Business District and is within walking distance of popular tourist attractions such as Gardens by the Bay and the Singapore Flyer.

This year the Board and the Program Committee have slightly changed the meeting format to meet the common wish for a two-day main meeting. Nevertheless, you will still experience the scientific sessions, the invited lectures and the thematic symposia. This year we will also be hosting educational sessions on the management of LCH, HLH and rare histiocytoses, which will parallel the working group meetings on the pre-meeting day. For the main meeting we were able to win renowned biology experts and clinicians as speakers, who will keep you abreast with the recent advances in the basic and clinical science, will stimulate opinion exchange and discussions, and may hopefully initiate new projects.

The social highlight of the meeting each year is the Annual Banquet. This year’s banquet will be held at Gardens by the Bay, Asia’s foremost garden destination. Gardens by the Bay has earned numerous awards and accolades including the World Building of the Year in 2012 at the World Architecture Festival, the President’s Design Award (Singapore) in 2013, the Outstanding Achievement Award by the Themed Entertainment Association in 2014, the Largest Glass Greenhouse (Flower Dome) in the Guinness Book of World Records for 2015, and the TripAdvisor Certificate of Excellence in 2016. We hope to have together an unforgettable evening at this unique location.

As you know, a great deal of time, energy and resources go into planning the meeting each year. We are grateful to our annual key sponsor, the Histiocytosis Association, without whose generous support this meeting would not be possible.

I hope you take time to enjoy the multicultural spirit and the touristic highlights of Singapore during your stay.

I look forward to collaborating with you throughout this exciting annual meeting.

Milen Minkov
President
Histiocyte Society
ABOUT THE HISTIOCYTE SOCIETY

The Histiocyte Society is a professional medical association comprised of more than 200 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.

NEW 2017 ANNUAL MEETING MOBILE APP - “ATTENDEE HUB”

The 2017 Histiocyte Society Annual Meeting has a free mobile event app! Search for “AttendeeHub” in your app store. Then, search for Histiocyte Society. Only registered attendees have access to the mobile app. See the emailed invitation for detailed instructions for logging into the app.

The app is available in the App Store and Google Play and in HTML5 for Blackberries, Windows phones, older devices and laptops.

All of the information in the program book is in the app, plus much more! Create your own custom agenda, read all of the abstracts, connect with colleagues, access maps of Singapore and the poster presentation locations, post pictures, and get the latest news and information right at your fingertips!

For directions on how to download and access the app, look for an invitation in your email or go to www.histiocytesociety.org/app on your mobile device. App accounts are linked to the email used to register for the annual meeting.

*Standard data and text messaging rates may apply depending on your service provider.

ANNUAL MEETING PROGRAM

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Photography Consent

Registration for, attendance at, and participation in the 2017 Histiocyte Society Annual Meeting and other activities constitutes an agreement by the participant to allow the Histiocyte Society to use and distribute (both now and in the future) the registrant’s or attendee’s image and/or voice in photographs, video, electronic reproductions and audio of such events and activities.
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 President 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 Scientific Advisory Committee (SAC) 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, 166 individual awards have been made to date, representing more than $6.5 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 nearly 30 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.
ACKNOWLEDGEMENTS AND RECOGNITIONS

HISTIOCYTE SOCIETY EXECUTIVE BOARD

President .............................................................. Milen Minkov 2016-2019
Past-President ..................................... Carlos Rodriguez-Galindo 2016-2017
Treasurer .............................................................. Karin Beutel 2016-2018
Secretary .............................................................. Michael Jordan 2016-2018
Member-at-Large ........................................ AnnaCarin Horne 2014-2017
Member-at-Large ........................................ Kim Nichols 2014-2017

HISTIOCYTE SOCIETY EDUCATION COMMITTEE

Kimo Stine, Chairperson ................................................. 2016-2018
Itziar Astigarraga .......................................................... 2016-2018
Anne-Sophie Carret ..................................................... 2015-2017
Barbara Degar ............................................................. 2015-2017
Eli Diamond ................................................................. 2015-2017
David Dix ................................................................. 2015-2017
Kai Lehmborg .............................................................. 2015-2017

HISTIOCYTE SOCIETY SCIENTIFIC COMMITTEE

Yenan Bryceson, Chairperson ............................................ 2015-2017
Ed Behrens ................................................................. 2016-2018
Stephan Ehl ............................................................... 2016-2018
Julien Haroche ............................................................ 2015-2017
Caroline Hutter ........................................................... 2015-2017
Rebecca Marsh .......................................................... 2015-2017
Johannes Visser .......................................................... 2015-2017
Kejian Zhang .............................................................. 2015-2017

HISTIOCYTE SOCIETY STUDY GROUP CHAIRPERSONS

Adult Histiocytosis .................................................... Michael Girschikofsky 2014-2018
Epidemiology/Late Effects ............................................. Riccardo Haupt /Vasanta Nanduri 2017-2019
HLH ................................................................. Jan-Inge Henter 2016-2020
LCH-IV .............................................................. Milen Minkov/Carlos Rodriguez-Galindo 2016-2019
Rare Histiocytic Disorders ................................................. Oussama Abla 2016-2020

HLH STEERING COMMITTEE

Stephan Ehl, Chairperson ............................................... 2016-2020
Itziar Astigarraga ...................................................... 2016-2020
Jan-Inge Henter ....................................................... 2014-2018
AnnaCarin Horne ..................................................... 2015-2019
Eiichi Ishii .............................................................. 2014-2017
Gritta Janka .............................................................. 2016-2020
Michael Jordan ......................................................... 2013-2017
Kim Nichols .............................................................. 2015-2019
Elena Sieni .............................................................. 2015-2019
Zhao Wang .............................................................. 2015-2019

LCH STEERING COMMITTEE

Cor van den Bos, Chairperson ........................................ 2015-2019
Carl Allen ................................................................. 2016-2020
Karin Beutel ............................................................. 2013-2017
Jean Donadieu .......................................................... 2015-2017
Michael Girschikofsky .................................................. 2015-2019
Michelle Hermiston .................................................... 2017-2021
Rima Jubran .............................................................. 2013-2017
Milen Minkov ............................................................ 2014-2018
Vasanta Nanduri ....................................................... 2016-2020
Carlos Rodriguez-Galindo ............................................ 2014-2018
Barrett Rollins .......................................................... 2017-2021
Kimo Stine ............................................................... 2014-2018
Johannes Visser ........................................................ 2015-2019
Sheila Weitzman ........................................................ 2016-2020

RARE HISTIOCYTIC DISORDERS STEERING COMMITTEE

Oussama Abla, Chairperson ........................................... 2016-2020
Jorge Braier .............................................................. 2016-2020
Eli Diamond ............................................................. 2015-2019
Eric Jacobsen ............................................................ 2016-2019
Ron Jaffe ................................................................. 2015-2019
Zdenka Krenova .......................................................... 2015-2019
Jennifer Picarsic ......................................................... 2015-2019

HISTIOCYTE SOCIETY PAST PRESIDENTS

Carlos Rodriguez-Galindo ............................................... 2013-2016
Jim Whitlock ............................................................. 2010-2013
Alexandra Filipovich ..................................................... 2007-2010
Jan-Inge Henter ........................................................ 2004-2007
R. Maarten Egeler ....................................................... 2001-2004
Kenneth McClain ......................................................... 1998-2001
Göran Elinder ........................................................... 1996-1998
Helmut Gadner .......................................................... 1992-1996
Stephan Ladisch ......................................................... 1989-1992
Blaise Favara ............................................................ 1987-1989
Christian Nezelof ........................................................ 1985-1987

SINGAPORE 2017
ACKNOWLEDGEMENTS AND RECOGNITIONS

NESBIT PRIZE IN CLINICAL SCIENCE Awardees
Francesca Minoia .......................... 2016
Alexandra Löfstedt ......................... 2015
Vasanta Nanduri ........................... 2014
Carl Allen ................................... 2013
Stephen Simko .............................. 2012
Thomas Lehrbecher ......................... 2011
Rebecca Marsh .............................. 2010
Rebecca Marsh .............................. 2009
Jorge Braier ................................ 2008
Kenneth McClain ............................ 2007
Loretta Lau ................................... 2006
AnnaCarin Horne ................................ 2005
Marie Ouachée-Chardin ...................... 2004
Manuel Steiner ................................ 2003
Jorge Braier ................................ 2002
Wolfgang Holter .............................. 2001
Kazuhiro Kogawa ............................ 2000

ROBERT J. ARCECI AWARD FOR BEST POSTER
Sandra Ammann ................................ 2016

HISTIOCYTE SOCIETY GOLDEN PIN RECIPIENTS
Gritta Janka .................................. 2016
Stephan Ladisch ................................ 2016
R. Maarten Egeler ............................. 2015
Sheila Weitzman .............................. 2014
Shinsaku Imashuku ........................... 2010
Helmut Gadner ............................... 2008
Jon Pritchard ................................. 2006
Giulio D’Angio ............................... 2002
Sally Kivilis .................................. 2001
Elizabeth Kontoyannis ....................... 2000
Paul Kontoyannis ............................. 2000
Jeffrey M. Toughill ........................... 1998

HISTIOCYTE SOCIETY HONORED MEMBERS
Helmut Gadner ................................ 2008
Shinsaku Imashuku ........................... 2007
Gritta Janka .................................. 2007
Valerie Broadbent ............................ 2000
Blaise Favara ................................. 1998
Mark Nesbit ................................... 1998
Christian Nezelof ............................ 1998

NEZELOF PRIZE IN BASIC SCIENCE Awardees
Edward Behrens ................................ 2016
Benjamin Durham .............................. 2015
Samuel Chiang Cern Cher ................. 2014
Gayane Badalian-Very/Kim Nichols ....... 2013
Edward Behrens ................................ 2012
Edward Behrens ................................ 2011
Michelle Hermiston ........................... 2010
Michael Jordan .............................. 2009
Matthew Collin ................................ 2008
Keijan Zhang ................................ 2007
Alessandra Santoro ............................ 2006
Udo zur Stadt ................................ 2005
Cristiana Costa/Kimberly Risma ........... 2004
Michael B. Jordan ............................ 2003
Susan Lee/Joyce Villanueva .................... 2002
Maurizio Arico ................................ 2001
Pieter Leenen ................................ 2000

TRAVEL SCHOLARSHIP RECIPIENTS
Congratulations to the Histiocyte Society’s 2017 Travel Scholarship recipients:

Farhan Fazal
for the abstract titled,
“SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN PATIENTS WITH SEPSIS”
This abstract will be presented during the Poster Presentation Session on Tuesday, October 3, 2017.

Nwe Khaing
for the abstract titled,
“CLINICAL PRESENTATION AND OUTCOMES OF LANGERHANS CELL HISTIOCYTOSIS (LCH) IN YANGON CHILDREN HOSPITAL”
This abstract will be presented during the Poster Presentation Session on Tuesday, October 3, 2017.

Xiao Shuai
for the abstract titled,
“REAL-WORLD OUTCOMES OF TREATMENT FOR ADULT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: RETROSPECTIVE STUDY OF 148 PATIENTS OVER 8 YEARS IN A TERTIARY HOSPITAL IN CHINA”
This abstract will be presented during the Poster Presentation Session on Tuesday, October 3, 2017.

Each year the Histiocyte Society awards at least one scholarship based on the applicant’s demonstration of need for financial assistance in order to attend the Annual Meeting. Scholarships are awarded in the amount of $1,000 US and are based on the availability of funds.
AT-A-GLANCE PRE-MEETING AGENDA

**SUNDAY • OCTOBER 1, 2017**

0800 – 1330  Executive Board Meeting* ................................................................. Level 6 - Boardroom
1030 – 1100  Coffee Break .................................................................................. Level 6 - Boardroom
1400 – 1600  HLH Steering Committee Meeting* ........................................... Level 6 - Boardroom
1600 – 1630  Coffee Break .................................................................................. Level 6 - Boardroom
1600 – 1700  Rare Histiocytic Disorders Steering Committee Meeting* .......... Level 6 - Boardroom
1700 – 1800  LCH Steering Committee Meeting* ................................................ Level 6 - Boardroom

**MONDAY • OCTOBER 2, 2017**

0800 – 1700  Meeting Registration and Check-In .................................................. Level 1 - Foyer
0800 – 0900  LCH-IV Study Management Group Session* .................................. Closed Session
0900 – 1130  LCH Disease Discussion Session* .................................................. Level 1 - Taurus
0900 – 1130  HLH Educational Session* .............................................................. Level 1 - Capricorn
1000 – 1030  Coffee Break .................................................................................. Level 1 - Capricorn
1130 – 1230  LCH Adult Disease Discussion Session* ......................................... Level 1 - Taurus
1200 – 1430  LCH Educational Session* .............................................................. Level 1 - Capricorn
1230 – 1330  Lunch ............................................................................................... Level 1 - Foyer
1230 – 1330  Histiocytosis Association MSAC Committee Meeting* ............... Level 6 - Vanda 3
1330 – 1430  Rare Histiocytic Disorders Discussion Session* .......................... Level 1 - Taurus
1330 – 1430  Histiocytosis Collaborative Summit* ............................................. Level 6 - Vanda 3
1430 – 1600  Follow-up HLH Steering Committee Meeting* .............................. Level 1 - Taurus
1600 – 1800  HLH Disease Discussion Session* .................................................. Level 1 - Taurus
1500 – 1730  Rare Histiocytoses Educational Session* ....................................... Level 1 - Capricorn
1600 – 1630  Coffee Break .................................................................................. Level 1 - Foyer
1830 – 2030  Welcome Reception ....................................................................... Level 5 - Vanda Ballroom

* Indicates closed session
* Indicates advance registration was required
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>0800</td>
<td>Meeting Registration and Check-In</td>
<td>Level 1 - Foyer</td>
</tr>
<tr>
<td>0800</td>
<td>Poster Presentation Setup</td>
<td>Level 1 - Libra &amp; Gemini</td>
</tr>
<tr>
<td>0800</td>
<td>Education Committee Meeting*</td>
<td>Level 6 - Vanda 4</td>
</tr>
<tr>
<td>0800</td>
<td>Scientific Committee Meeting*</td>
<td>Level 6 - Vanda 5</td>
</tr>
<tr>
<td>0900</td>
<td>Opening Ceremonies</td>
<td>Level 1 - Taurus &amp; Leo</td>
</tr>
<tr>
<td>0915</td>
<td>Guest Speaker Presentation</td>
<td>Level 1 - Taurus &amp; Leo</td>
</tr>
<tr>
<td>1000</td>
<td>Coffee Break</td>
<td>Level 1 - Foyer</td>
</tr>
<tr>
<td>1030</td>
<td>Symposium: EBV Associated HLH</td>
<td>Level 1 - Taurus &amp; Leo</td>
</tr>
<tr>
<td>1230</td>
<td>Lunch</td>
<td>Level 1 - Capricorn</td>
</tr>
<tr>
<td>1230</td>
<td>HLH Meet the Expert Lunch Session*</td>
<td>Level 1 - Aquarius</td>
</tr>
<tr>
<td>1230</td>
<td>Rare Meet the Expert Lunch Session*</td>
<td>Level 1 - Pisces</td>
</tr>
<tr>
<td>1330</td>
<td>Scientific Session I: Oral Presentations</td>
<td>Level 1 - Taurus &amp; Leo</td>
</tr>
<tr>
<td>1500</td>
<td>Coffee Break</td>
<td>Level 1 - Foyer</td>
</tr>
<tr>
<td>1530</td>
<td>Scientific Session II: Presidential Symposium</td>
<td>Level 1 - Taurus &amp; Leo</td>
</tr>
<tr>
<td>1700</td>
<td>Poster Presentation Session</td>
<td>Level 1 - Libra &amp; Gemini</td>
</tr>
<tr>
<td>0800</td>
<td>Meeting Registration and Check-In</td>
<td>Level 1 - Foyer</td>
</tr>
<tr>
<td>0830</td>
<td>Presentation of Late Breaking Abstracts</td>
<td>Level 1 - Taurus &amp; Leo</td>
</tr>
<tr>
<td>0900</td>
<td>Jon Pritchard Lecture on the Nikolas Symposium</td>
<td>Level 1 - Taurus &amp; Leo</td>
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<tr>
<td>0945</td>
<td>Coffee Break</td>
<td>Level 1 - Foyer</td>
</tr>
<tr>
<td>1015</td>
<td>Symposium: Pursuing A Rational Cure For LCH</td>
<td>Level 1 - Taurus &amp; Leo</td>
</tr>
<tr>
<td>1200</td>
<td>Lunch</td>
<td>Level 1 - Capricorn</td>
</tr>
<tr>
<td>1200</td>
<td>AME Histio Working Group Meeting</td>
<td>Level 1 - Aquarius</td>
</tr>
<tr>
<td>1300</td>
<td>LCH Meet the Expert Lunch Session*</td>
<td>Level 1 - Pisces</td>
</tr>
<tr>
<td>1300</td>
<td>Scientific Session III: Oral Presentations</td>
<td>Level 1 - Taurus &amp; Leo</td>
</tr>
<tr>
<td>1430</td>
<td>Coffee Break</td>
<td>Level 1 - Foyer</td>
</tr>
<tr>
<td>1500</td>
<td>General Assembly Business Meeting*</td>
<td>Level 1 - Taurus &amp; Leo</td>
</tr>
<tr>
<td>1630</td>
<td>Executive Board Meeting*</td>
<td>Level 1 - Taurus</td>
</tr>
<tr>
<td>1630</td>
<td>Education Committee Meeting*</td>
<td>Level 1 - Taurus</td>
</tr>
<tr>
<td>1630</td>
<td>Scientific Committee Meeting*</td>
<td>Level 1 - Taurus</td>
</tr>
<tr>
<td>1815</td>
<td>Group Transportation to Histiocyte Society Annual Banquet</td>
<td>Marina Mandarin Singapore Lobby</td>
</tr>
<tr>
<td>1900</td>
<td>Histiocyte Society Annual Banquet, Closing Ceremonies &amp; Awards*</td>
<td>Gardens by the Bay</td>
</tr>
</tbody>
</table>

* Indicates closed session
* Indicates that advance registration was required
Benjamin H. Durham is a hematopathologist and molecular genetic pathologist who currently serves as a genomic pathology research fellow in molecular oncology in the Department of Pathology at Memorial Sloan Kettering Cancer Center. Dr. Durham studies the molecular hematopathology and functional genomics of poorly characterized hematopoietic malignancies such as the histiocytoses and hairy cell leukemia in the laboratories of Omar Abdel-Wahab, M.D., a hematologist and cancer biologist, and Christopher Y. Park, M.D., Ph.D., a hematopathologist and stem cell biologist, in the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center. Dr. Durham’s most recent work under the mentorship of Omar Abdel-Wahab has focused on the genomic landscape and functional genomics of the systemic histiocytic neoplasms that led to the first description of kinase fusions in the histiocytic neoplasms, the discovery of the first activating MAP2K1 and ARAF mutations in the non-Langerhans cell histiocytic neoplasms, and the first published use of MEK inhibition and sorafenib in patients with refractory, life-threatening, systemic histiocytoses, which led to dramatic clinical responses. This work was co-first authored by Eli L. Diamond, Benjamin H. Durham, and Julien Haroche and published in Cancer Discovery late in 2015. Dr. Durham also performs the functional genomics correlative studies for a phase II investigator-initiated clinical trial of single agent cobimetinib in systemic histiocytosis patients being conducted by Eli L. Diamond, M.D. at Memorial Sloan Kettering Cancer Center. Dr. Durham is also actively investigating the cell of origin of the non-Langerhans cell histiocytoses and the development of murine models of histiocytic neoplasms. Dr. Durham received his Bachelor of Science degree in biochemistry and molecular biology from the University of Alabama at Birmingham, Birmingham, AL. He received his M.D. from the University of Alabama School of Medicine. He completed his anatomic and clinical pathology residency at St. Louis University School of Medicine, St. Louis, MO. He then completed his hematopathology fellowship at the University of California, Davis, School of Medicine, Sacramento, CA, and his molecular genetic pathology fellowship at Columbia University College of Physicians and Surgeons, New York, NY. Benjamin Durham has been the recipient of several honors during the course of this work on the histiocytoses that include a 2015-2016 Senior Investigator Training Award for Fellows from the American Society of Hematology; a 2015 Stowell-Orbison Award Certificate of Merit from the United States and Canadian Academy of Pathology; the 2015 Pathologist-in-Training Award from the Society for Hematopathology; the 2015 Nezefol Prize in Basic Science from the Histiocyte Society; his selection as one of the Dr. Jon Pr Stowell Orbison Award Certificate of Merit from the United States and Canadian Academy of Pathology; and his selection as one of the Dr. Jon Pritchard Fellows of the 2016 Nikolas Symposium.

Florent Gihoux graduated in Biochemistry from the University Pierre et Marie CURIE, Paris VI and obtained a Masters degree in Advanced Studies in Immunology from the Pasteur Institute, Paris. He then started his PhD in the Immunology Team of GENETHON, Evry and obtained his PhD in 2004 from the University Pierre et Marie CURIE, Paris VI. As a postdoctoral fellow, Florent Gihoux joined the Laboratory of Miriam Merad in the Mount Sinai School of Medicine (MSSM), New York where he studied the ontogeny and the homeostasis of cutaneous dendritic cell populations, with a strong focus on Langerhans cells. In 2008, he became an Assistant Professor in the Department of Gene and Cell Medicine, MSSM and member of the Immunology Institute of MSSM. He joined the Singapore Immunology Network (SIgN), A*STAR in May 2009 as a Principal Investigator. He joined the EMBO Young Investigator (YP) program in 2013 and is a Web of Science Highly Cited Researcher since 2016. His laboratory is now focusing on the ontogeny and differentiation of macrophages and dendritic cells (DCs).

Tom Gross received a combined MD-PhD degree from the University of Nebraska Medical Center. He is board certified in pediatric hematology-oncology. Dr. Gross has been a faculty member at University of Nebraska Medical Center in the Departments of Pediatrics and Pathology (1993-98), Director of the Pediatric Blood and Marrow Transplant Program at Cincinnati Children’s Hospital Medical Center (1998-2002), the Division Chief and Gordon Teter Chair of Pediatric Cancer Research at Nationwide Children’s Hospital and the Ohio State University (2002-2013), the Deputy Director of Science at the Center for Global Health (CGH) at the National Cancer Institute (2013-present). Dr. Gross is an international expert in pediatric lymphoma and blood and marrow transplantation and has published over 100 peer-reviewed articles and co-authored 38 textbook chapters. He has chaired national and international clinical trials, including co-chair of the recently completed international, randomized study for advanced mature B-cell lymphoma. He has extensive ethics and regulatory experience in clinical trials, including 10 years on the Ohio State Cancer Center IRB, numerous DSMB, including chair of LCH-IV DSMC and Children’s Oncology Group (COG) DSMB. He has been a consultant for both FDA and EMA. He has held leadership positions in COG including Chair of NHL Disease Committee, Scientific Chairs Committee, and served on Executive Committee, Scientific Council and currently serves on the NCI Pediatric Leukemia and Lymphoma Steering Committee. He serves as a commissioner for the Lancet Oncology Commission of Pediatric Cancer. He is Deputy Editor of Pediatric Blood and Cancer. As Deputy Director for Science of CGH, he is assists in enhancing international research at NCI and advising countries and professional societies in training, education and developing infrastructure to conduct cancer clinical research and clinical trials.

Evan Newell completed his B.Sc. in Immunology at McGill University and Ph.D. in Physiology at the University of Toronto. He then moved to California for a post-doctoral fellowship at Stanford University with Mark Davis, where he worked on biophysical aspects of T cell antigen recognition and initiated the use of mass cytometry for the study of antigen-specific cells using heavy-metal labelled peptide-MHC tetramers. Now as a principal investigator at the Singapore Immunology Network (SIgN), his lab continues to apply and develop novel approaches for identifying and thoroughly characterizing antigen-specific T cells. This includes the development of combinatorial peptide-MHC tetramer staining, which allows for multiplexed assessment of a large number (>>100) T cell antigen specificities in a single sample. The lab also uses mass cytometry (CyTOF) to deeply probe the phenotypic and functional characteristics of T cells as well as other immune cell types. A major goal of lab is to identify useful biomarkers of clinical outcomes that take advantage of these modern approaches. In particular, the lab is focusing on the study of T cell responses to chronic infection and cancer.
GUEST SPEAKER HIGHLIGHTS

Yongmin Tang is the Professor of Pediatrics and Doctor in Chief, PhD/MD doctorate mentor in the Children’s Hospital of Zhejiang University School of Medicine. He was graduated from the Department of Medicine at Zhejiang Medical University (now Zhejiang University School of Medicine) in 1982, and obtained his Bachelor Degree of Medicine and Master Degree of Pediatric Hematology in 1989. In 1993-1998, he was trained at Children's Hospital Los Angeles, the University of Southern California in the United States of America and obtained his standard ECFMG certificate. Dr. Tang is currently holding the position as the Chief of Hematology-oncology department and the director of Hematology-oncology laboratory at the Children’s Hospital of Zhejiang University School of Medicine. His main research areas are the clinical diagnosis and treatment and lab research on childhood hematology-oncology diseases focusing on immunophenotyping of hematological malignancies, MRD detection by using multi-parameter flow cytometry, clinical relevance of cytokine patterns (for early diagnosis and monitoring of hemophagocytic lymphohistiocytosis and systemic inflammatory reaction syndrome related to septic shock as well as differential diagnosis of G+ vs. G-bacteremia in particular) and therapeutic antibody engineering and immunotherapy including targeting therapy and CAR-T therapy. Dr. Tang currently holds the membership of SIOP and ASH (American Society of Hematology) and serves as the Vice Chairman (in charge of Histiocyte Diseases) of Pediatric Hematology-Oncology Society, Pediatric Branch of Chinese Medical Association; The Chairman Designate of Pediatric Oncology Society, China Anti-Cancer Association; Board Members of many journals both at home and abroad such as <Pediatric Blood & Cancer>, <World Journal of Pediatrics>, <Chinese Journal of Pediatrics> etc. Dr. Tang has obtained 16 grants so far from either US Martell Research Fund for Childhood Leukemia and Cancer or National Natural Science Fundation of China, Provincial Fund of Key Projects etc. He has published more than 190 papers with 55 papers published in English SCI cited journals and participated in writing 7 book/chapters in either Chinese or English and was awarded the second grade of awards from Zhejiang Peoples’ Government and Health Bureau, and received 4 Chinese patents.

Stuart Tangye is the Head of the Immunology Division at the Garvan Institute of Medical Research, Professor in the Faculty Medicine, University of NSW Australia, and an NHMRC Principal Research Fellow. He completed his PhD on B-cell leukemia at UTS in 1995 and undertook postdoctoral training at the DNAX Research Institute for Molecular and Cellular Biology (Palo Alto California, USA; 1996-1999). He returned to Australia in 2000 as a University of Sydney Research Fellow to work with Dr Phil Hodgkin at the Centenary Institute of Cancer Medicine and Cell Biology (University of Sydney). He established an independent research lab in 2002, and was recruited to the Garvan Institute in 2006. His research interests focus on human immunobiology in health and disease. This is achieved by studying lymphocyte development, signalling, differentiation and effector function in patients with diseases resulting from monogenic loss- or gain-of-function mutations in key regulators of immune responses, as well as in corresponding animal models of these human conditions. In the past few years, his lab has made significant contributions to elucidating how these mutations result in some of the clinical features associated with human primary immunodeficiencies. He has been funded by fellowships and project and program grants awarded by the NHMRC, Cancer Council NSW, Jeffrey Modell Foundation, XLP Research Trust and Association for International Cancer Research. Since 1995, he has published ~150 peer-reviewed articles, invited reviews and book chapters, and in 2011 he received the Gottschalk Medal from the Australian Academy of Sciences, which recognises “outstanding research in the medical sciences by scientists no more than 40 years of age”. More recently he was awarded the Faculty of Science Alumni Excellence Award from the University of Technology Sydney (2013), and a Senior Scholarship from the US-Australian Fulbright Commission to undertake sabbatical study at Rockefeller University in New York (2015). He is on the senior editorial boards of J Exp Med, J Immunol and J Clin Immunol. When he is not at work, he enjoys surfing, cycling, swimming and most of all being a Dad to his three beautiful children!

David Teachey, MD is an Associate Professor of Pediatrics and laboratory based physician scientist in the Division of Oncology at the Children’s Hospital of Philadelphia and the University of Pennsylvania School of Medicine. His clinical and research interests are focused on investigating novel therapeutics in a number of rare diseases, including acute lymphoblastic leukemia (ALL), hemophagocytic lymphohistiocytosis (HLH), and autoimmune lymphoproliferative syndrome (ALPS). He is currently the study chair or vice chair for a number of investigator initiated and cooperative group clinical trials. He is the Vice Chair of ALL Biology for the Children’s Oncology Group and is the leader of the HLH team at CHOP. The HLH team at CHOP is a multidisciplinary team with members from over 10 different medical specialties who are involved in the diagnosis and treatment of patients with hemophagocytic syndromes. He made the initial observation that the cytokine release syndrome seen in patients treated with cellular therapies including chimeric antigen receptor T cells and bi-specific antibodies clinically and biologically resembles HLH.
MEETING AGENDA: SUNDAY, OCTOBER 1, 2017

Attendance at the Steering Committee Meetings is limited to members of that Steering Committee. A detailed agenda will be provided by the Steering Committee Chairperson.

0800 – 1330 Executive Board Meeting* ............................................................................................................................................. Level 6 - Boardroom
1030 – 1100 Coffee Break.................................................................................................................................................................... Level 6 - Boardroom
1400 – 1600 HLH Steering Committee Meeting* ........................................................................................................................................ Level 6 - Boardroom
1600 – 1630 Coffee Break.................................................................................................................................................................... Level 6 - Boardroom
1600 – 1700 Rare Histiocytic Disorders Steering Committee Meeting* ................................................................................................ Level 6 - Boardroom
1700 – 1800 LCH Steering Committee Meeting* ........................................................................................................................................ Level 6 - Boardroom

MEETING AGENDA: MONDAY, OCTOBER 2, 2017

Attendance at pre-meeting sessions is limited to members of the Histiocyte Society who have registered in advance to participate. A detailed agenda will be provided to those registered for this day at the meeting. Educational Sessions required advanced registration.

0800 – 1700 Meeting Registration and Check-In ........................................................................................................................................ Level 1 - Foyer
0800 – 0900 LCH-IV Study Management Group Session* ................................................................................................................................ level 1 - Foyer
Session Moderator: Milen Minkov, Carlos Rodriguez-Galindo
0900 – 1130 LCH Disease Discussion Session* ........................................................................................................................................ Level 1 - Taurus
Session Moderator: Cor van den Bos
0900 – 1130 HLH Educational Session* ............................................................................................................................................... Level 1 - Capricorn

DIAGNOSIS AND FIRST-LINE TREATMENT OF GENETIC HLH
Jan-Inge Henter
Karolinska Institutet, Stockholm, Sweden

BIOLOGY AND DIFFERENTIAL DIAGNOSIS
Gritta Janka
Children’s University Hospital, Hamburg, Germany

SECOND LINE TREATMENT
Kim Nichols
St. Jude Children’s Research Hospital, Memphis, TN USA

1000 – 1030 Coffee Break.................................................................................................................................................................... Level 1 - Foyer
1130 – 1230 LCH Adult Disease Discussion Session* ........................................................................................................................................ Level 1 - Taurus
Session Moderator: Michael Girschikofsky
1200 – 1430 LCH Educational Session* ............................................................................................................................................... Level 1 - Capricorn

BIOLOGY OF LCH
Rikhia Chakraborty
Texas Children’s Hospital, Houston, TX USA

MANAGEMENT OF PEDIATRIC LCH
Kimo Stine
Arkansas Children’s Hospital, Little Rock, AR USA

MANAGEMENT OF ADULT-ONSET LCH
Michael Girschikofsky Abdellatif Tazi
Elisabethinen Hospital, Linz, Austria Hopital Saint Louis Service de Pneumologie, Paris, France

1230 – 1330 Lunch.................................................................................................................................................................................. Level 1 - Foyer
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<thead>
<tr>
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<tbody>
<tr>
<td>1230</td>
<td>Histiocytosis Association MSAC Committee Meeting*</td>
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<tr>
<td>1330</td>
<td>Rare Histiocytic Disorders Discussion Session*</td>
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<td>Session Moderator: Oussama Abla</td>
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<tr>
<td>1330</td>
<td>Histiocytosis Collaborative Summit*</td>
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<td>Session Moderators: Carlos Rodriguez-Galindo</td>
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<tr>
<td>1430</td>
<td>Follow-up HLH Steering Committee Meeting*</td>
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<tr>
<td>1600</td>
<td>HLH Disease Discussion Session*</td>
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<tr>
<td></td>
<td>Session Moderators: Stephan Ehl</td>
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<tr>
<td>1500</td>
<td>Rare Histiocytoses Educational Session*</td>
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<td>JXG AND RDD</td>
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<td>Oussama Abla</td>
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<td>The Hospital for Sick Children, Toronto, ON Canada</td>
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<tr>
<td>1600</td>
<td>Coffee Break</td>
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<tr>
<td>1830</td>
<td>Welcome Reception</td>
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</tbody>
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* Indicates Closed Session
+ Indicates that advance registration was required
### MEETING AGENDA: TUESDAY, OCTOBER 3, 2017

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>0800 – 1700</td>
<td>Meeting Registration and Check-In</td>
<td>Level 1 - Foyer</td>
</tr>
<tr>
<td>0800 – 1600</td>
<td>Poster Presentation Setup</td>
<td>Level 1 - Libra &amp; Gemini</td>
</tr>
<tr>
<td>0800 – 0900</td>
<td>Education Committee Meeting*</td>
<td>Level 6 - Vanda 4</td>
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<tr>
<td>0800 – 0900</td>
<td>Scientific Committee Meeting*</td>
<td>Level 6 - Vanda 5</td>
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<tr>
<td>0900 – 0915</td>
<td>Opening Ceremonies</td>
<td>Level 1 - Taurus &amp; Leo</td>
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<tr>
<td>0900 – 1000</td>
<td>Guest Speaker Presentation</td>
<td>Level 1 - Taurus &amp; Leo</td>
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**HUMAN DENDRITIC CELLS: FROM DEVELOPMENT TO FUNCTIONS**
Florent Ginhoux
Singapore Immunology Network (SIgN), Singapore

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<th>Time</th>
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<tr>
<td>1000 – 1030</td>
<td>Coffee Break</td>
<td>Level 1 - Foyer</td>
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<tr>
<td>1030 – 1230</td>
<td>Symposium: EBV Associated HLH</td>
<td>Level 1 - Taurus &amp; Leo</td>
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<tr>
<td>1230 – 1330</td>
<td>Lunch</td>
<td>Level 1 - Capricorn</td>
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<tr>
<td>1230 – 1330</td>
<td>HLH Meet the Expert Lunch Session*</td>
<td>Level 1 - Aquarius</td>
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*Lunch will be provided in the Capricorn. Attendees are encouraged to bring lunch with them to this session.*

Michael Jordan
Cincinnati Children’s Health and Medical Center, Cincinnati, OH USA

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<th>Time</th>
<th>Event</th>
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<tr>
<td>1230 – 1330</td>
<td>Rare Meet the Expert Lunch Session*</td>
<td>Level 1 - Pisces</td>
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*Lunch will be provided in the Capricorn. Attendees are encouraged to bring lunch with them to this session.*

Oussama Abla and Sheila Weitzman
The Hospital for Sick Children, Toronto, ON Canada

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<th>Time</th>
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<tbody>
<tr>
<td>1330 – 1500</td>
<td>Scientific Session I: Oral Presentations</td>
<td>Level 1 - Taurus &amp; Leo</td>
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**BONE MARROW IS THE KEY SITE OF EXCESSIVE IFN GAMMA PRODUCTION IN PRIMARY HEMOPHAGOCYTIC LYMPHOMIHCYTOTISOS**
Ruth Gather, Tamara Koegl, Inga Schulte, Nadja Goos, Paul Fisch, Elvira Myschkin, Robert Zeiser, Casey Weaver, Hanspeter Pircher, Peter Aichele, Stephan Ehl

**A RE-EXAMINATION OF MURINE HLH: KINETICS, COMPARATIVE THERAPY, AND NOVEL COMBINATIONS**
Michael Jordan, Vandana Chaturvedi, Nora Lakes, Rohan Srivastava, Amber Hensley

**MAPK MUTATIONS NEGATIVELY AFFECT LESIONAL CD8+ T-CELL - LCH-CELL RATIOS**
Paul G. Kemps, Timo C.E. Zondag, Eline C. Steenwijk, Ronald van Eijk, Veronica Lang, Jan A.M. van Laar, Oussama Abla, Cor van den Bos, Astrid van Halteren

*Indicates closed session
+Indicates that advance registration was required
HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH REFRACTORY LANGERHANS CELL HISTIOCYTOSIS
Kazuko Kudo, Miho Maeda, Nobuhiro Suzuki, Hirokazu Kanegane, Shouichi Ohga, Eiichi Ishii, Yoko Shioda, Toshihiko Imamura, Shin-akau Imashuku, Yukiko Tsumenatsut, Mikiya Endo, Akira Shimada, Yuhki Koga, Yoshiko Hashii, Jiro Inagaki, Masami Inoue, Ken Tabuchi, Akira Morimoto, On the behalf of the Histiocytosis study group of the Japanese Society of Pediatric Hematology/Oncology

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION PROVIDES CURE FOR ADULT PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH): A RETROSPECTIVE STUDY OF THE CHRONIC MALIGNANCIES AND INBORN ERRORS WORKING PARTIES (CMWP AND IEWP) OF THE EBMT

1500 – 1530
Coffee Break..................................................Level 1 - Foyer

1530 – 1700
Scientific Session II: Presidential Symposium..........................................................Level 1 - Taurus & Leo
Session Moderator: Milen Minkov

PRESENTATIONS NOMINATED FOR THE NESBIT PRIZE IN CLINICAL SCIENCE (see page 66 for more information)

PHASE 2 TRIAL OF SINGLE-AGENT COBIMETINIB FOR ADULTS WITH HISTIOCYTIC DISORDERS: INTERIM RESULTS
Eli L. Diamond, Benjamin H. Durham, Ahmet Dogan, David M. Hyman, Raajit Rampal, Gary Ulaner, Lynn Brody, Omar Abdal-Wahab

A PHASE II TRIAL OF LENALIDOMIDE IN ADULTS WITH HISTIOCYTODES
Eric Jacobsen, Robert Redd, Alyssa Nicota, Victoria Patterson, Barbara Virchick

MONOALLELIC MUTATIONS IN GENES RELATED TO FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (FHL): REPORT FROM THE ITALIAN REGISTRY
Elena Sieni, Maria Luisa Coniglio, Laura Vinas, Concetta Micalizzi, Alessandra Todesco, Fabio Timeus, Carmelo Rizzari, Paolo Pierani, Carmen De Fusco, Rosa Maria Mura, Ilaria Fotzi, Maurizio Arico, Claudio Favre for the Italian Histiocytosis working group

PRESENTATIONS NOMINATED FOR THE NEZELOF PRIZE IN BASIC SCIENCE (see page 66 for more information)

HIF1A IS A CRITICAL MEDIATOR FOR PRIMARY AND SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Gang Huang, Rui Huang Yoshihiro Hayashi, Xiaoai Yan, Jiachen Bu, Jiyue Wang, Yue Zhang, Yile Zhou, Yuting Tang, Lingyun Wu, Zefeng Xu, Xin liu, Qianfei Wang, Jianfeng Zhou, Zhiqian Xiao, James P. Bridges, Rebecca A. Marsh, Kejian Zhang, Michael B. Jordan, Yuhua Li

TRANSCRIPTIONAL PROFILES, LINEAGE TRACING WITH BRAF-V600E AND HLA-DQB2 EXPRESSION SUPPORT A MODEL OF BLOOD CD1c+ CELLS AS PRECURSORS TO LCH LESION CD207+ CELLS
Karen Phaik Har Lim, Paul Milne, Michael Poidinger, Kaibo Duan, Howard Lin, Harshal Abhyankar, Daniel Zinn, Olive Eckstein, Rikia Chaakraborty, Evan Newell, Miriam Merad, Kenneth McClain, Chris Tsz-Kwong Man, Florent Ginhoux, Matthew Collin, Carl Allen

A NOVEL CTL-BASED FUNCTIONAL ASSAY REVEALS A STRONG CORRELATION BETWEEN THE PATHOGENICITY OF AN UNC13D VARIANT AND THE INSTABILITY OF ITS TRANSLATED MUNC13-4 PROTEIN; MUNC13-4 PROTEIN EXPRESSION ASSAY IS A RELIABLE METHOD FOR IDENTIFICATION OF PATIENTS WITH FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS TYPE 3
Hirofumi Shibata, Takahiro Yasumi, Saeko Shimodera, Eitaro Hiejima, Kazushi Izawa, Tomoki Kawai, Ryutaroh Shirakawa, Taizo Wada, Ryuta Nishikomori, Hisanori Horiiuchi, Osamu Ohara, Toshio Heike

1700 – 1900
Poster Presentation Session..........................................................Level 1 - Libra & Gemini
POSTERS NOMINATED FOR THE ROBERT J. ARCECI PRIZE FOR BEST POSTER (see page 67 for more information)

CLINICAL HLH POSTER NOMINEES

Poster Location #1
PROFOUND HYPERFERRITINAEMIA IS NOT SO SPECIFIC FOR THE DIAGNOSIS OF HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN ASIAN CHILDREN - A SINGLE CENTRE STUDY FROM SINGAPORE
Ragavendra Kalyanasundaram, Cher Wen Qi, Chan Mei Yoke, Prasad Iyer, Rajat Bhattacharyya

Poster Location #2
PREDICTION MODELS IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: DO WE NEED MORE?
Nita Radhakrishnan

Poster Location #3
THE SUCCESSFUL USE OF RUXOLITINIB FOR REFRACTORY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)
Julie Talano, Larisa Broglie, Lauren Pommert, Monica Thakar, Sid Rao, Rachel Phelan, David Margolis

BASIC LCH POSTER NOMINEES

Poster Location #4
NOTCH SIGNALING INDUCES A LANGERHANS CELL HISTIOCYTOSIS GENE EXPRESSION SIGNATURE IN HUMAN MONOCYTES
Caroline Hutter, Raphaела Schwentner, Gunhild Jug, Maximilian O. Kauer, Wolfgang Holter

CLINICAL LCH POSTER NOMINEES

Poster Location #5
SINGLE-CENTER EXPERIENCE IN TARGETED THERAPY OF BOTH BRAF V600E POSITIVE AND BRAF WT MULTISYSTEM REFRACTORY LANGERHANS-CELL HISTIOCYTOSIS (LCH) WITH RISK ORGANS INVOLVEMENT IN CHILDREN: A REPORT OF 11 CASES
Dmitry Evseev, Irina Kalinina, Anna Mitrofanova, Dmitry Abramov, Elena Raykina, Galina Novichkova, Alexey Maschan, Michael Maschan

Poster Location #6
LANGERHANS CELL HISTIOCYTOSIS IN THE EMMA Children's HOSPITAL: EFFICACY OF TREATMENT, LONG-TERM SURVIVAL, AND PERMANENT CONSEQUENCES IN PATIENTS TREATED DURING THE VINCRIStIN-CyTARaBIn-PReDNIson PROToCOL ERA
Hannah Groenen, Suzan Verduijn, Merian van Overveld, Cor van den Bos

Poster Location #7
A GENOME-WIDE ASSOCIATION STUDY IDENTIFIES CANDIDATE VARIANTS ASSOCIATED WITH INCREASED RISK OF LCH RELAPSE
Erin Peckham-Gregory, Rikhia Chakraborty, Michael Scheurer, Harshal Abhyankar, Kenneth McClain, Carl Allen, Philip Lupo

Poster Location #8
THE USE OF WHOLE BODY MAGNETIC RESONANCE IMAGING FOR SKELETAL STAGING OF CHILDHOOD LANGERHANS HISTIOCYTOSIS: RESULTS OF A RETROSPECTIVE COHORT STUDY
Sebastiaan F Somers, Eline E Deurloo, Anne M.J.B. Smets, Cor van den Bos

Poster Location #9
DIAGNOSTIC AND MANAGEMENT GUIDELINE FOR PATIENTS (<19Y) WITH A THICKENED PITUITARY STALK AND/OR CENTRAL DIABETES INSIPIDUS

CLINICAL RARE POSTER NOMINEES

Poster Location #10
ADRENAL INSUFFICIENCY AND OTHER ENDOCRINOPATHIES IN ERDHEIM-CHESTER DISEASE
Juvianee I. Estrada-Veras, Fady Hannah-Shmouni, Louisa Boyd, Georgios Papadakis, Amit Tirosh, Kevin O'Brien, Brent S. Abel, Monica C. Skarulis, William A Gahl
CLINICAL HLH POSTER PRESENTATIONS

Poster Location #11
EARLY ONSET OF HLH AND INHERITED UNC13D AND JAK3 MUTATIONS IN A PATIENT. A DIFFICULT DIAGNOSTIC AND THERAPEUTIC CHALLENGE
Itziar Astigarraga, Susana Garcia-Obregon, Juana Gil-Herrera, Aizpea Echecarria, Rosa Adan, Miguel Garcia-Ariz, Ricardo Lopez-Almaraz, Yolanda Lopez-Fernandez, Lorena Mosteiro, Belen Compains, Jelve Nejati-Zendegani, Bianca Tesi, Samuel Chiang, Jan-Inge Henter, Yenan Brycesson

Poster Location #12
THE ROLE OF SOLUBLE INTERLEUKIN-2 RECEPTOR (SIL-2R) IN DIAGNOSIS OF ADULT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH): A SINGLE CENTER RETROSPECTIVE STUDY
Luke Chen, Molly Lin, Anna Hayden, Sujin Park, Andre Mattman, Morris Pudek

Poster Location #13
SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN PATIENTS WITH SEPSIS

Poster Location #14
SEPSIS AS A MIMICKER OF HLH IN A PEDIATRIC INTENSIVE CARE UNIT
Allyson Hays, Nicole Gigliotti, Marcia Chan, Erica Molitor-Kirsch

Poster Location #15
CHALLENGES OF HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS CASES IN YANGON CHILDREN HOSPITAL
Tint Myo Hnin, Aye Aye Khaing, Ei Ei Shwe, Myint Myint Than, Htay Htay Tin

Poster Location #16
EVALUATE THE OUTCOME OF HLH TREATMENT IN INITIAL THERAPY (8 WEEKS) AT NATIONAL CHILDREN’S HOSPITAL
La Thi Bich Hong, Nguyen Thi Mai Huong, Le Thanh Hai

Poster Location #17
CLINICAL STUDY OF E-CHOP REGIMEN AS A SALVAGE THERAPY FOR CHILDREN REFRACTORY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Fan Jiang, Yuan Sun, Juan Xiao, Zhouyang Liu, Shifen Fan, Xiaomei Liu, Zhixin Jiang, Yuxia Wang, Ran Zheng, Chongfen Gao, Huanhuan Guan

Poster Location #18
SEVERE DENGUE (SD) COMPLICATED BY REACTIVE HAEMOPHAGOCYTIC SYNDROME (HS) “FIVE YEARS” EXPERIENCE IN A TERTIARY INTENSIVE CARE UNIT (ICU) IN MALAYSIA
Foong Kee Kan, Cheng Cheng Tan, Khairil Erwan Khalid, Prema Supramaniam, Lian Huat Tan

Poster Location #19
PHENOTYPING OF LEUKOCYTE SUBSETS IN PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS ASSOCIATED WITH HEMATOLOGICAL MALIGNANCIES
Monika Klimkowska, Christina Arlinde, Maciej Machaczka

Poster Location #20
CLINICAL CHARACTERISTICS AND PROGNOSTIC FACTORS OF EPSTEIN-BARR VIRUS-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN CHILDREN
Honghao Ma, Wang Tianyou, Zhang Li, Lian Hongyun, Wang Dong, Zhao Yunze, Zhao Xiaoxi, Zhang Rui

Poster Location #21
HLH DIAGNOSTIC CRITERIA EVALUATED ON 83 PATIENTS FROM THE POLISH HLH IN ADULTS PALG REGISTRY
H1N1 VIRUS KILLS BY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) AND IMMUNOSUPPRESSIVE THERAPY (IST) MAY PROTECT AGAINST IT IN NONE-HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS
Said Yousuf Mohamed, Haitham Al-Muhayan, Marwan Shaheen, Ghada El-Gohary, Naeem Chaudry, Amr Hanbaly, Riad Fakih, Randa Nounou, Majed Halim, Fahad Almohareb

MONOCYTOPENIA IS PRESENT IN THE VAST MAJORITY OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) IN ADULTS AND SHOULD BE USED AS A SENSITIVE ADDITIONAL DIAGNOSTIC CRITERION AND ITS RESPONSE TO TREATMENT CARRIES POOR PROGNOSIS

FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A SINGLE-CENTER EXPERIENCE
Maria Moschovi, Archontis Zampogiannis

UNMANIPULATED HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION USING REDUCED-INTENSITY CONDITIONING FOR PAEDIATRIC PATIENTS WITH FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A SINGLE CENTER STUDY
Maoquan Qin, Chenguang Jia, Bin Wang, Guanghua Zhu, Xuan Zhou, Kai Wang, Jun Yang, Yan Yan, Yanhui Luo, Sidan Li

CHARACTERIZATION OF A LARGE UNC13D GENE DUPLICATION IN A PATIENT WITH FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS TYPE 3
Hirofumi Shibata, Eitaro Hiejima, Takahiro Yasumi, Saeko Shimodera, Masayuki Hori, Kazushi Izawa, Masaki Matsuoka, Yasuko Kojima, Akira Ohara, Ryuuta Nishikomori, Osamu Ohara, Toshio Heike

REAL-WORLD OUTCOMES OF TREATMENT FOR ADULT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: RETROSPECTIVE STUDY OF 148 PATIENTS OVER 8 YEARS IN A TERTIARY HOSPITAL IN CHINA
Xiao Shuai, Juan Xu, Xushu Zhong, Yan Li, Wenjiao Tang, Ting Liu, Huanling Zhu, Ting Niu, Yu Wu, Yongqian Jia, Ling Pan, Hong Chang, Xu Cui, Yeping Gong, Bing Xiang, Jie Huang, Jianjun Li, Chuan He, Xinchuan Chen, Liping Xie, Jie Ji, Hongbing Ma, Yang Dai, Zhigang Liu, Xiaoru Huang, Yun Tang, Li Hou, Pu Kuang

SALVAGE HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ADVANCED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Yuan Sun, Juan Xiao, Zhouyang Liu, Fan Jiang, Shifen Fan, Xiaomei Liu, Zhixin Jiang

SUCCESSFUL SECONDARY HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PRIMARY GRAFT FAILURE IN TWO PEDIATRIC CASES WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Yuan Sun, Juan Xiao, Shifeng Fan, Zhouyang Liu, Feng Jiang, Xiaomei Liu, Zhixin Jiang

CLINICAL AND LABORATORY SIGNS OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN PANDEMIC INFLUENZA A (H1N1) INFECTION PATIENTS NEEDING EXTRACORPORAL MEMBRANE OXYGENATION
Tatiana von Bahr Greenwood, Bernhard Holzgreewe, Samuel Chiang, Yini Wang, Bianca Tesi, Yenan Bryceson, Jan-Inge Henter

CENTRAL NERVOUS SYSTEM INVOLVEMENT IN ADULT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: OUR EXPERIENCE IN DIAGNOSIS AND TREATMENT
Zhao Wang, Yue Song, Ruijun Pei, Yini Wang, Jingshi Wang, Wenyuan Lai

CLINICAL FEATURES OF 52 PATIENTS WITH HLH ACCOMPANIED WITH GASTROINTESTINAL BLEEDING
Zhao Wang, Zhili Jin, Yini Wang

CLINICAL FEATURES OF PERINATAL STAGE RELATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Zhao Wang, Yue Song, Yini Wang, Jingshi Wang, Wenyuan Lai
Poster Location #34
MULTIVARIATE ANALYSIS OF PROGNOSIS FOR PATIENTS WITH NATURAL KILLER/T CELL LYMPHOMA-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Zhao Wang, Zhili Jin, Yini Wang, Jingshi Wang, Lin Wu, Ruijun Pei, Wenyuan Lai

Poster Location #35
OUTCOME OF CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS WITH HLH-2004 PROTOCOL IN JAPAN
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Poster Location #36
COMPREHENSIVE STRATEGY TO ESTABLISH THE CLINICAL DIAGNOSIS FOR PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Kejian Zhang, Jinfeng Han, James Denton, Shannon Nortman, Lisa Dyer, C. Alexander Valencia, Michael Jeng, Alexei Grom, Kim Nicholls, Randy Cron, Rebecca Marsh, Michael Jordan

Poster Location #37
SALVAGE TREATMENT OF PEDIATRIC REFRACTORY EPSTEIN-BARR VIRUS-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS WITH L-DEP PROTOCOL
Rui Zhang, Yun-ze Zhao, Li Zhang, Hong-yun Lian, Hong-hao Ma, Dong Wang, Tian-you Wang

Poster Location #38
HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A DECADE OF EXPERIENCE IN A PAEDIATRIC CENTRE IN SOUTH-EAST ASIA
Youjia Zhong, Manlio Villegas, Frances Yeap, Peiling Ooi, Elizabeth Ang, Poh Lin Tan

BASIC LCH POSTER PRESENTATIONS

Poster Location #39
ANALYSIS OF SOMATIC MUTATIONS IN JAPANESE PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS
Tomomi Hayase, Shiori Saito, Yoko Shioda, Toshihiko Imamura, Kenichiro Watanabe, Kentaro Okhi, Yukiko Oh, Yuta Kawahara, Akira Morimoto

Poster Location #40
WHEN LANGERHANS MET CROHN: A CLINICAL CASE REPORT AND A FIRST THREE-DIMENTIONAL RECONSTRUCTION OF HUMAN GUT
Egle Kvendaraitė, David Unnersjö Jess, Désirée Gavhed, Mattias Svensson, Magda Lourda, Jan-Inge Henter

Poster Location #41
HIGH PREVALENCE OF LYMPHOPENIA IN LANGERHANS CELL HISTIOCYTOSIS: CORRELATION WITH EARLY ONSET AND MORE SEVERE DISEASE
Magdalini Lourda, Selma Otsson-Åkfeldt, Sofie Gavhed, Egle Kvendaraitė, Désirée Gavhed, Mattias Svensson, Jan-Inge Henter

Poster Location #42
THE ROLE OF REGULATORY T CELLS IN THE IMMUNE REGULATION OF LANGERHANS CELL HISTIOCYTOSIS
Jenee Mitchell, Daniel Pellicci, Stuart Berzins, George Kannourakis

Poster Location #43
CLINICAL PRESENTATION AND OUTCOMES OF LANGERHANS CELL HISTIOCYTOSIS (LCH) IN YANGON CHILDREN HOSPITAL
Khaing Nwe, Aye Khaing, Tint Hnin, Myint Than

Poster Location #44
PCR-BASED DETECTION OF LANGERHANS CELL HISTIOCYTOSIS (LCH) MOLECULAR SIGNAL IN CELL-FREE DNA FROM PATIENT CEREBROSPINAL FLUIDS (CSF)
Sam Shang, John McIntyre, Ronald Anderson, Aru Narendran, Steven Greenway

CLINICAL LCH POSTER PRESENTATIONS

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TREATMENT OF LCH OF BONE USING INDOMETHACIN
Ron Anderson, George Michael, Jorge Braier, Guido Felizzia, Sophie Willne, Johann Visser, Greg Guilcher
Poster Location #46
VACCINE ASSOCIATED SOFT TISSUE INFILTRATE CAN PREDISPOSE MULTI-SYSTEM LANGERHANS CELL HISTIOCYTOSIS
Gleb Bronin, Alexey Kislyakov, Konstantin Kondratchik

Poster Location #47
LANGERHANS CELL HISTIOCYTOSIS AND NK/T LYMPHOMA AFTER T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA
Jing Cao, Xiaodong Shi

Poster Location #48
LENALIDOMIDE-DEXAMETHASONE: A PROMISING THERAPY FOR LANGERHANS CELL HISTIOCYTOSIS WITHOUT RISK ORGAN INVOLVEMENT
Narendra Chaudhary, Magdalena R, Leenu L Joseph, Rikki R John, Leni G Mathew

Poster Location #49
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Poster Location #50
CLINICAL RESEARCH ON EFFICACY COMPARISON BETWEEN CHFU-LCH 2006 PROTOCOL AND 2012 PROTOCOL FOR CHILDHOOD LANGERHANS CELL HISTIOCYTOSIS
Yang Fu, Hongsheng Wang, Xiaowen Zhai, Xiaowen Qian, Hui Miao, Xiaohua Zhu, Yi Yu, Fengjuan Lu

Poster Location #51
OUTCOME OF CHILDREN WITH LANGERHANS CELL HISTIOCYTOSIS AND SINGLE-SYSTEM INVOLVEMENT: A RETROSPECTIVE STUDY AT A SINGLE CENTER
Yi-Jin Gao, Meng Su, Pan Ci, Chen Jing, Tang Jing-Yan

Poster Location #52
CLINICAL FEATURES AND THERAPEUTIC RESULTS IN A 35-YEAR COHORT OF CHILDREN AND ADULTS WITH LANGERHANS CELL HISTIOCYTOSIS MANAGED AT SINGLE INSTITUTION
Fiorina Giona, Giovanna Palumbo, Luisa Cardarelli, Robin Foa

Poster Location #53
REFRACTORY MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS WITH MARKED AND DURABLE RESPONSE TO DABRAFENIB
Michael M. Henry, James A. Williams

Poster Location #54
TARGETED THERAPY OF JUVENILE XANTOGRANULOMA WITH BRAF V600E MUTATION: A REPORT OF TWO CASES
Irina Kalinina, Dmitry Evseev, Maira Sharashkina, Uliana Petrova, Tatyana Salimova, Natalia Kotskaya, Ksenia Romanova, Julia Dobrynina, Elena Raykina, Anna Mitrofanova, Alexey Maschan, Michael Maschan

Poster Location #55
LANGERHANS' CELL HISTIOCYTOSIS PRESENTING WITH PROPTOSIS IN A CHILD
Fauzia Shafi Khan, Alia Ahmad

Poster Location #56
A 15-MONTHS OLD CHILD PRESENTING WITH HIGHLY AGGRESSIVE BRAF(+) MULTISYSTEM LCH WITH CNS INVOLVEMENT: ARGUMENTS FOR USE OF DABRAFENIB P. O.+ LOW DOSE CYTARABIN I. V. AS THE TREATMENT OF CHOICE
Zdenka Krenova, Jaroslav Sterba, Lenka Mala, Jan Fric, Kamila Bendikova

Poster Location #57
DETECTION OF SOMATIC MUTATIONS BY PCR-BASED NEXT-GENERATION SEQUENCING FROM FIXED CLINICAL SPECIMENS IN CHILDHOOD LCH
Ko Kudo, Rika Kanezaki, Akie Kobayashi, Tomohiko Sato, Takuya Kamio, Shinya Sasaki, Kininori Terui, Atsushi Sato, Masahiro Irie, Yoji Sasahara, Masaru Imamura, Chihaya Imai, Tsutomu Toki, and Etsuro Ito

Poster Location #58
SCLEROSING CHOLANGITIS IN IDENTICAL TWINS WITH LANGERHANS CELL HISTIOCYTOSIS
Chi Kong Li, Tin Wai Chow, Alex Wing Kwan Leung, Frankie Wai Tsoi Cheng, Grace Kee See Lam, Winnie Chiu Wing Chu, Vincent Lee, Matthew Ming Kong Shing
Poster Location #59
DRAMATIC EFFICACY OF DABRAFENIB IN LANGERHANS CELL HISTIOCYTOSIS HARBORING THE BRAF V600E MUTATION: TWO CASES REPORT
Danqing Luo, Xiaodong Shi

Poster Location #60
VEMURAFENIB IN A CHILD WITH LIFE-THERATENING MULTISYSTEM LANGERHANS CELL-HISTIOCYTOSIS
Milan Minkov, Stefan Schoening, Jan Soerensen, Dirk Schwabe, Hans-Michael Kvasnicka, Caroline Hutter, Jean-Claude Alvarez, Thomas Klingebiel, Thomas Lehrnbecher

Poster Location #61
DIABETES INSIPIDUS WITH DECREASING PITUITARY STACK WIDENING BUT METACHRONOUS SKULL LCH LESIONS
Vassilios Papadakis, Elpis Vlachopapadopoulou, Loizos Petrikkos, Anastasia Garoufi, Georgia Papaioannou, George Stakianos, Kalliopi Stefanaki, Stefanos Michalacos, Sophia Polychronopoulou

Poster Location #62
EVALUATION OF MATERNAL AND PERINATAL CHARACTERISTICS AND RISK OF LANGERHANS CELL HISTIOCYTOSIS IN TEXAS, 1995-2011
Erin Peckham-Gregory, Kenneth McClain, Carl Allen, Michael Scheurer, Philip Lupo

Poster Location #63
EFFECTIVE SECOND LINE TREATMENT WITH CYTARABINE IN A PATIENT WITH REFRACTORY MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS (LCH) COMPLICATED WITH MACROPHAGE ACTIVATION SYNDROME (HLH-MAS)
Loizos Petrikkos, Vassilios Papadakis, Ioannis Nikas, Kostantinos Tsitsikas, Kalliopi Stefanaki, Manthoula Valari, Sophia Polychronopoulou

Poster Location #64
AUTOIMMUNOLOGICAL DISORDERS, NEOPLASMS, AND MYCOBACTERIAL INFECTIONS IN PATIENTS WITH PLCH
Eliżbieta Rzadzikowska, Eliżbieta Wiatr, Katarzyna Błasińska-Przerwa, Renata Langfort, Iwona Bestry, Kazimierz Roszkowski-Śliż

Poster Location #65
RISK FACTORS FOR DIABETES INSIPIDUS IN PEDIATRIC PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS TREATED WITH CYTARABINE-BASED CHEMOTHERAPY; THE RESULTS OF JLSG-96/02 STUDY
Kenichi Sakamoto, Akira Morimoto, Yoko Shioda, Toshihiko Imamura, Shinsaku Imashuku

Poster Location #66
CLINICAL FEATURES AND PROGNOSTIC SIGNIFICANCE OF LIVER INVOLVEMENT IN PATIENTS OF LANGERHANS CELL HISTIOCYTOSIS
Xiaodong Shi, Danqing Luo

Poster Location #67
PATTERN OF BONE RECURRENT IN PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS
Yoko Shioda, Osamu Miyazaki, Tomoo Osumi, Keita Terashima, Motohiro Kato, Daisuke Tomizawa, Chikako Kiyotani, Kimikazu Matsumoto

Poster Location #68
GIRL WITH DIABETES INSIPIDUS, GROWTH HORMONE DEFICIENCY AND SLOWLY PROGRESSIVE PITUITARY STACK THICKENING: USE OF ORAL PREDNISOLONE TREATMENT AS TOOL FOR HISTIOCYTOSIS DIAGNOSIS
Elpis Vlachopapadopoulou, Vassilios Papadakis, Vassilios Petrou, Eirini Dikaiakou, Stefanos Michalacos, Sophia Polychronopoulou

Poster Location #69
CLINICAL RESEARCH OF PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS WITH CRANIOFACIAL BONE INVOLVEMENT
Dong Wang, Rui Zhang, Li Zhang, Hong-hao Ma, Yun-ze Zhao, Tian-you Wang, Hong-yun Lian

Poster Location #70
CLASSIFICATION OF ORAL (BONE AND/OR MUCOSAE) LESIONS IN PEDIATRIC PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS
Guido Felizzi, Carolina Benchuya, Veronica Pavan, Melisa Ienco, Diego Rosso, Jorge Braier, Virginia Fernandez de Preliasco, Betina Orman
MEETING AGENDA: WEDNESDAY, OCTOBER 4, 2017

RARE HISTIOCYTIC DISORDERS POSTER PRESENTATIONS

Poster Location #71
JUVENILE XANTHOGRANULOMA, NEUROFIBROMATOSIS TYPE 1, MESENCHYMAL HAMARTOMA OF THE LIVER AND UNDIFFERENTIATED EMBRYONAL SARCOMA IN A YOUNG CHILDREN. CASE REPORT
Guido Felizzia, Maria Laura Galluzzo, Veronica Solernou, Maria Marta Bujan, Jorge Braier, Alvarez Mariana

Poster Location #72
ROSAI DORFMAN DISEASE IN CHILDREN- A RARE DISEASE WITH DIVERSE CLINICAL COURSE
Heidi Barola, Apurba Ghosh, Irene Marim, Khawn D Tawng, Rajat Bhattacharyya

Poster Location #73
ADULT PATIENTS WITH MIXED HISTIOCYTOSES
Juvenile Estrada-Veras, Kavya Mathur, Louisa Boyd, Kevin O'Brien, Pamela J Gardner, Mark Raffeld, Elaine Jaffe, William Gahl

Poster Location #74
HIGHER METABOLIC ACTIVITY SEEN ON 18F-FDG PET/CT, IN THE ADRENAL GLANDS OF PATIENTS WITH ERDHEIM-CHESTER DISEASE HARBORING THE BRAF V600E MUTATION
Juvenile Ibrahim Estrada-Veras, Georgios Z. Papadakis, Georgios C. Manikis, Fady Hannah-Shmouni, Kevin J. O'Brien, William A. Gahl

Poster Location #75
OBSTRUCTIVE UROPATHY AND NEPHROPATHY IN ERDHEIM-CHESTER DISEASE

Poster Location #76
A CASE OF SEVERE CNS INVOLVEMENT IN MACROPHAGE ACTIVATING SYNDROME
Kwang Nam Kim, Chuhl Joo Lyu

Poster Location #77
OCULAR JUVENILE XANTHOGRANULOMA: A REPORT OF THREE INFANT CASES INVOLVING IRIS
Yui Kimura, Yoko Shiota, Shugyoku Ra, Sachiko Nishina, Tomoyo Yoshida, Tadashi Yokoi, Tomoo Osumi, Chikako Kiyotani, Motohiro Kato, Daisuke Tomizawa, Keita Terashima, Takako Yoshioka, Noryuki Azuma, Kimikazu Matsumoto

0800 – 1300
Meeting Registration and Check-In

0830 – 0900
Presentation of Late Breaking Abstracts
Session Moderator: Barbara Degar

0900 – 0945
Jon Pritchard Lecture on the Nikolas Symposium
Session Moderator: Cor van den Bos

0945 – 1015
Coffee Break

1015 – 1200
Symposium: Pursuing A Rational Cure For LCH
Session Moderator: Carlos Rodriguez-Galindo

TRANSITIONAL ADVANCES IN THE MOLECULAR PATHOGENESIS OF THE HISTIOCYTIC NEOPLASMS
Benjamin Durham
Memorial Sloan Kettering Cancer Center, New York, NY USA

THE CHALLENGES OF DESIGNING CLINICAL TRIALS WITH TARGETED DRUGS IN RARE DISEASES
Tom Gross
National Institutes of Health Center for Global Health, Rockville, MD USA

OPPORTUNITIES FOR DEVELOPING BIOMARKERS FOR DISEASE RESPONSE AND OUTCOME
Evan Newell
Singapore Immunology Network (SIgN), Singapore

1200 – 1300
Lunch

* Indicates closed session
* Indicates that advance registration was required
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
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<tr>
<td>1200 – 1300</td>
<td><strong>AME Histio Working Group Meeting</strong> ...........................................</td>
<td>Level 1 - Aquarius, Lunch will be provided in the Capricorn. Attendees are encouraged to bring lunch with them to this session. Session Moderators: Oussama Abla and Roula Farah</td>
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<tr>
<td>1200 – 1300</td>
<td><strong>LCH Meet the Expert Lunch Session</strong> ...........................................</td>
<td>Level 1 - Pisces, Lunch will be provided in the Capricorn. Attendees are encouraged to bring lunch with them to this session. Carlos Rodriguez-Galindo St. Jude Children’s Research Hospital, Memphis, TN USA</td>
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<tr>
<td>1300 – 1430</td>
<td><strong>Scientific Session III: Oral Presentations</strong> ..................................</td>
<td>Level 1 - Taurus &amp; Leo, Session Moderator: El Diamond and Patrick Campbell</td>
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<tr>
<td>1300 – 1500</td>
<td><strong>ABDOMINAL FINDINGS IN ERDHEIM-CHESTER DISEASE (ECD): MRI AND CT ASSESSMENT ON A COHORT OF 61 PATIENTS</strong></td>
<td>Juvianee I. Estrada-Veras, Moozhon Nikpanah, Lauren Kim, S. Mojdeh Mirmomen, Rolf Symons, Kevin O’Brien, William A. Gahl, Ashkan A. Malayeri</td>
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<tr>
<td>1300 – 1500</td>
<td><strong>COMPUTED TOMOGRAPHY (CT) FINDINGS OF PULMONARY AND MEDIASTINAL INVOLVEMENT IN ERDHEIM CHESTER DISEASE (ECD)</strong></td>
<td>Juvianee I. Estrada-Veras, S. Mojdeh Mirmomen, Arine Sirajuddin, Moozhon Nikpanah, Rolf Symons, Kevin O’Brien, William A. Gahl, Ashkan A. Malayeri</td>
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<tr>
<td>1300 – 1500</td>
<td><strong>NEEDS ASSESSMENT OF HISTIOCYTOSIS PHYSICIANS IN ASIA AND THE MIDDLE EAST: RESULTS OF AN “AME-HISTIO NETWORK” QUESTIONNAIRE</strong></td>
<td>Roula Farah, Ahmed Naqvi, Zhao Wang, Wenyuan Lai, Rsumi Dalu, Jia Zhang, Muhammad Ashraf, Iris Kventisil, Jing Cao, Yunze Zhao, Dong Urang, Shaheen Shamji, Akira Morimoto, Faisal Al Anzi, Michael Weintraub, Xiaodong Shi, Arinobu Tojo, Masayuki Kobayashi, Eiichi Ishi, Joanne Yacobovich, Michael Golan, Yuan Sun, Junhua Li, Yoko Shiota, Ichivo Morakani, Pm Zhao, Rui Zhang, Danqing Luo, Jong Jin Seo, Qhamezha Bahoush, Talal Al-Harbi, Alia Ahmad, Rafie Raza, Zehra Fadoy, Yi-Jin Gao, Shui Yen Soh, Carlos Rodriguez-Galindo, Stephan Laidisch, Gritta Janka, Oussama Abla on behalf of the Asian and Middle Eastern (AME) Histiocytosis Network</td>
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<tr>
<td>1300 – 1500</td>
<td><strong>BRAF V600E MUTATION IS ASSOCIATED WITH A CARDIAC AND NEUROLOGICAL PHENOTYPE BUT NOT MORTALITY IN ERDHEIM-CHESTER DISEASE: RESULTS FROM A SINGLE-CENTER 165-PATIENT COHORT</strong></td>
<td>Julien Haroche, Jean-François Emile, Fabrice Carrat, Zofia Helias-Rodzewicz, Valérie Taly, Frédéric Charlotte, Philippe Cluzel, Jean Donadieu, Ahmed Idbaih, Stéphane Barette, Zahir Amoura</td>
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<tr>
<td>1300 – 1500</td>
<td><strong>LANGERHANS CELL HISTIOCYTOSIS IN ADULTS IS ASSOCIATED WITH ADDITIONAL SOLID AND HEMATOLOGIC MALIGNANCIES</strong></td>
<td>Jennifer Ma, James Laird, Karen Chau, Monica Chelius, Andrew C. Bell, Junting Zheng, Zhigang Zhang, Benjamin H. Lok, Joachim Yahalom</td>
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<tr>
<td>1300 – 1500</td>
<td><strong>C-REACTIVE PROTEIN AND BONE PAIN AT DIAGNOSIS PREDICT THE OUTCOME OF PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS WITH SINGLE-SYSTEM MULTIFOCAL LESIONS: RESULT OF THE JAPAN LANGERHANS CELL HISTIOCYTOSIS STUDY GROUP-02 PROTOCOL STUDY</strong></td>
<td>Akira Morimoto, Yoko Shiota, Toshihiko Imamura, Kazuko Kudo, Toshiyuki Kitoh, Hiroshi Kawaguchi, Hiroaki Goto, Yoshiyuki Kosaka, Yukiko Tsunematsu, Shinsaku Imashuku, on behalf of the Japan LCH Study Group</td>
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<tr>
<td>1430 – 1500</td>
<td><strong>Coffee Break</strong> ..................................................................................</td>
<td>Level 1 - Foyer</td>
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<tr>
<td>1500 – 1630</td>
<td><strong>General Assembly Business Meeting</strong> .............................................</td>
<td>Level 1 - Taurus &amp; Leo</td>
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<td>1630 – 1715</td>
<td><strong>Executive Board Meeting</strong> .................................................................</td>
<td>Level 1 - Taurus</td>
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<tr>
<td>1815 – 1840</td>
<td><strong>Meet for Group Transportation to Histiocyte Society Annual Banquet</strong> ...........................................</td>
<td>Marina Mandarin Singapore Lobby Group will meet in hotel lobby for bus transportation to the Annual Banquet Wristbands will be distributed and are required for entrance into Gardens by the Bay.</td>
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<tr>
<td>1900 – 2400</td>
<td><strong>Histiocyte Society Annual Banquet, Closing Ceremonies &amp; Awards</strong> ...........................................</td>
<td>Gardens by the Bay, Awarding of Nesbit Prize for Excellence in Clinical Science 18 Marina Gardens Drive Singapore 018953 Phone: +65 6420 6848 Website: <a href="http://www.gardensbythebay.com.sg">www.gardensbythebay.com.sg</a></td>
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Dendritic cells (DCs) are professional antigen-presenting cells that mediate immune responses. Important questions on the origins and differentiation paths of human DC populations remain unanswered. First, we combined two high-dimension techniques, single-cell mRNA sequencing and Cytometry by Time of Flight mass spectrometry to define and characterize human DC precursors (pre-DC) present in adult bone marrow and blood and revealed that pre-DC comprises distinct lineage-committed sub-populations. We also characterized the human fetal DC lineage and show that similar DC subpopulations can be identified in fetal tissues and are related to adult populations. However, fetal DC strongly promoted regulatory T-cell induction and inhibiting T-cell tumour-necrosis factor-α production through arginase-2 activity, indicating that they mediate homeostatic immune-suppressive responses during gestation. Altogether, we show that the DC lineage shares common development pathways from early fetal development to adulthood. However, DC functions differ drastically depending on the environment in which they are immersed.

Epstein-barr virus (EBV) infection is rare in western countries, however, it is very common in oriental nations especially in China. The natural EBV infection morbidity rates in Chinese population are more than 90% confirmed by anti-EBV antibody determination. Fortunately, the majority of those infections are latent and mild in terms of clinical presentations, however, some severe cases do exist from severe infectious mononucleosis (IM) or severe hemophagocytic lymphohistiocytosis (HLH) which is usually fatal if prompt intervention is not administered. Some 10-15% of IM patients may experience high fever, lymphadenopathy and splenomegaly with severe liver function damage, however, only very rare patients may develop HLH with 30~50% of death. Some patients may gradually develop into chronic phase after a short period of acute onset or directly into chronic phase without any sign of acute infection. The chronic active EBV infection (CAEBV) is a serious problem and usually can not be treated effectively with high rate of mortality. Another presentation of EBV infection may manifest as lymphoproliferative disease or malignancy. From this complicated scenario of the disease, diagnosis, especially early recognition and diagnosis are extremely difficult with conventional approaches. Th1/Th2 cytokines including IL-2, IL-4, IL-6, IL-10, TNF-α and IFN-γ are secreted by a variety of cells including T cells, monocytes or macrophages. Specific Th1/Th2 cytokine patterns for the diagnoses of HLH (significantly elevated serum IFN-γ and IL-10 with slightly elevated IL-6) and/or HLH complicated with bacterial infection (significantly elevated serum IFN-γ, IL-10 and IL-6) or bacterial infection only (significantly elevated IL-6 (G+ bacterial infection), IL-6 and IL-10 (G- bacterial infection), have been identified in our group. These cytokine patterns can be used to monitor the disease status of the EBV infection severity in terms of latent infections, regular type of infectious mononucleosis without HLH or with HLH onset in various degrees of severity, status of CAEBV infection and CAEBV infection to HLH onset, so that the clinical decisions can be easily made based on the cytokine patterns presented in a given patient over the process of disease. In summary, Th1/Th2 cytokine patterns identified can be used as useful diagnostic tools to monitor various types of EBV infections and help for clinical decision making.
GUEST SPEAKER PRESENTATIONS

TUESDAY, OCTOBER 3, 2017 • 1030
LEVEL 1 - TAURUS & LEO

CYTOKINE STORM AND CAR-T CELLS

David Teachey
Children’s Hospital of Philadelphia, Philadelphia, PA USA

Chimeric antigen receptor (CAR)-modified T cells with anti-CD19 specificity are a highly effective novel immune therapy for relapsed/refractory hematologic malignancies. Dramatic responses have been reported in patients with relapsed/refractory acute lymphoblastic leukemia and other B-cell malignancies. Cytokine release syndrome (CRS) is a significant and life-threatening toxicity seen after CAR T cell therapy. CRS is characterized by abnormal activation of macrophages and T-cells, leading to a clinical and biologic picture mirroring hemophagocytic lymphohistiocytosis. Patients with severe CRS develop marked hyperferritinemia, splenomegaly, and hypofibrinogenemia. Extensive cytokine profiling demonstrates marked elevation in a number of cytokines, chemokines and soluble receptor in patients with severe CRS, including interferon gamma, IL6, and IL10. CRS can be successfully treated with IL6R blockade with tocilizumab with the majority of patients demonstrating rapid improvement in symptoms. The clinical and biologic description of CRS after CAR T cells will be described with focus on how improved understanding of CRS has led to novel insights into the biology of hemophagocytic syndromes.

GUEST SPEAKER PRESENTATIONS

WEDNESDAY, OCTOBER 4, 2017 • 1015
LEVEL 1 - TAURUS & LEO

PURSING A RATIONAL CURE FOR LCH SYMPOSIUM

Benjamin Durham, Memorial Sloan Kettering Cancer Center, New York, NY United States
Tom Gross, Center for Global Health, National Cancer Institute, Rockville, MD United States
Evan Newell, Singapore Immunology Network (SIgN), Singapore

TRANSITIONAL ADVANCES IN THE MOLECULAR PATHOGENESIS OF THE HISTIOCYTIC NEOPLASMS

Benjamin H. Durham1,2, Eli L. Diamond3, Omar Abdel-Wahab2
1. Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, United States
2. Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, United States
3. Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, United States

The systemic histiocytoses encompass a clinically heterogeneous group of disorders leading to tissue damage secondary to the accumulation and infiltration of pathological cells thought to be derived from the dendritic or monocyteic lineages with accompanying inflammation. For decades, whether or not the histiocytoses were inflammatory or neoplastic disorders was unclear, and their cellular origins have long been obscure and heavily debated. However, the rise of the molecular era led to the discovery of recurrent BRAFV600E mutations in approximately 50% of patients with Langerhans cell (LCH) and non-Langerhans cell histiocytoses (non-LCH), which provided the first convincing evidence that these are indeed neoplasms. This also supplied a molecular biomarker to map the cell(s)-of-origin of these neoplasms. Since the discovery of BRAFV600E mutations in LCH and Erdheim-Chester Disease (ECD), diverse kinase alterations have been uncovered in BRAFV600E, wild type histiocytic neoplasms. These advances have led to great progress in our understanding of the pathogenesis and treatment of these disorders.

Activating kinase alterations discovered in BRAFV600E-wild type LCH and non-LCH result in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway. These include recurrent activating mutations in ARAF, MAP2K1, NRAS, and KRAS in LCH and non-LCH; PIK3CA/D and MAPK1 (ERK2) mutations in non-LCH; recurrent BRAF and ETV3-NCOA2 fusions recently reported in LCH and non-LCH; and ALK and NTRK1 fusions in non-LCH. Activating, in-frame BRAF deletions have also been described in LCH. Finally, mutations in MAP2K2, MAP3K1, and HRAS have been described in ECD, LCH, and histiocytic sarcoma (HS), respectively.

These discoveries have refined the understanding of the histiocytoses as clonal, myeloid neoplasms driven by constitutive MAPK signaling and identified molecular therapeutic targets with promising clinical responses to RAF and MEK inhibition. The wider use of RAF inhibitors has led to the recent FDA breakthrough consideration of vemurafenib for BRAFV600E-mutant ECD and implementation of MEK inhibitor clinical trials for patients with histiocytic disorders. Current challenges include understanding the optimal targeted therapeutics for patients lacking the BRAFV600E mutation. In addition, uncovering other targetable alterations in less systematically studied histiocytic neoplasms such as juvenile xanthogranuloma (JXG), Rosai-Dorfman disease (RDD), and histiocytic sarcoma (HS) will be important.

The purpose of this presentation will be to review recent, published molecular advancements from the past 7 years, as well as to provide updated analyses from our ongoing unpublished efforts at cataloging mutations in the histiocytoses through whole exome and targeted sequencing efforts. Furthermore, we will discuss the impact these insights have had on our understanding of the molecular pathophysiology and cellular origins of these rare, enigmatic diseases.
Clinical trials have played a significant role in improving the outcome of children with cancer and histiocytosis. International collaboration is often necessary to enroll sufficient number of patients on answer important clinical questions in rare diseases, such as pediatric cancer and histiocytosis. Dr. Gross will discuss some of the essential elements required to successfully perform international clinical trials and discuss emerging challenges, in particular human subject and regulatory regulations. As there is no model or approach that will guarantee success for all clinical trials, Dr. Gross will discuss 4 potential models for international clinical trials - centralized, distributive, mixed and parallel- and the advantages and challenges of each. Time will be provided to for audience questions and discussion.
Purpose: IFNγ is a critical cytokine in the pathophysiology of primary hemophagocytic lymphohistiocytosis (HLH), but its cellular sources, the tissues driving the response and the kinetics of IFNγ production remain incompletely understood. This is relevant for understanding factors determining success and failure of anti-IFNγ therapy.

Methods: We used IFNγ Thy1.1KI reporter mice, adoptive transfer of luciferase transgenic T cells and TCR spectratyping in different tissues to characterize the localization, diversity and IFNγ production of pathogenic T and NK cells in HLH. Disease was induced in perforin deficient (PKO) mice by lymphocytic choriomeningitis virus (LCMV) and by a novel protocol with murine cytomegalovirus (MCMV).

Results: In response to the infectious triggers, T cells accumulated in lymph nodes and spleen in PKO and wt mice, but then rapidly spread to peripheral tissues in PKO mice. Excessive IFNγ production was observed in PKO CTL, less in CD4 T cells in both infection models. NK cells showed excessive IFNγ production after MCMV, but not after LCMV infection. The overall T cell response was less diverse in PKO mice and while the same oligoclonal pattern was observed in spleen, liver and bone marrow, organ-specific changes in the clonal hierarchies were noted. This was particularly pronounced in the bone marrow, where by far the most excessive IFNγ production could be demonstrated, independent of the viral load.

Conclusion: In primary HLH, oligoclonal T cell responses evolve in lymphoid tissues and then distribute to peripheral organs, where they are further edited. The key site of CTL dependent excessive IFNγ production is the bone marrow, which is a major site of HLH pathology. Control of bone marrow driven cytokine production appears to be a key target of anti-inflammatory therapy.

A RE-EXAMINATION OF MURINE HLH: KINETICS, COMPARATIVE THERAPY, AND NOVEL COMBINATIONS

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Purpose: The study of hemophagocytic lymphohistiocytosis (HLH) in mice has provided unique insights into immune regulation, defined disease pathophysiology, and suggested several strategies for the targeted therapy of human HLH. Multiple groups have studied the therapeutic potential of blocking interferon gamma (IFN-g), JAK/STAT signaling, and other conventional or novel approaches in mice. However, it is not clear how well therapy in these models reflects clinical realities in patients, or how these therapies may compare with, or complement each other. Methods: We performed a stringent kinetic analysis of multiple markers of HLH or immune activation in LCMV-infected normal or perforin deficient mice, assessing soluble CD25, serum granzyme B, IFN-g, CXCL9, ALT, LDH, ferritin, CBC indices, spleen size/inflammatory infiltrates, and a detailed clinical scoring system. We also examined select indices and survival after various therapeutic interventions. Results: This kinetic analysis revealed that murine HLH may be divided into 3 phases: normal immune activation, pre-symptomatic immune hyper-activation, and the fully developed HLH clinical syndrome. Consequently, all therapeutic interventions may be categorized as pre-emptive, pre-symptomatic, or post-HLH, based on their timing. We observed that while many interventions were effective pre-emptively, therapy was much more challenging after HLH developed. Toxicities of etoposide and JAK inhibitors were substantial in this context and IFN-g blockade had incomplete efficacy. Gene expression and cell signaling studies revealed unique targets in these mice. Results of studies examining comparative, combination, and novel therapies will be presented. Conclusion: A careful definition of the kinetics of HLH development is essential for interpreting the results of therapeutic studies in murine models. The context for specific therapies has a significant impact on both efficacy and toxicity, which may be relevant for clinical contexts. This approach is revealing innovative and potentially optimal combinations for targeted therapy of human HLH.

BONE MARROW IS THE KEY SITE OF EXCESSIVE IFN GAMMA PRODUCTION IN PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Purpose: The study of hemophagocytic lymphohistiocytosis (HLH) in mice has provided unique insights into immune regulation, defined disease pathophysiology, and suggested several strategies for the targeted therapy of human HLH. Multiple groups have studied the therapeutic potential of blocking interferon gamma (IFN-g), JAK/STAT signaling, and other conventional or novel approaches in mice. However, it is not clear how well therapy in these models reflects clinical realities in patients, or how these therapies may compare with, or complement each other. Methods: We performed a stringent kinetic analysis of multiple markers of HLH or immune activation in LCMV-infected normal or perforin deficient mice, assessing soluble CD25, serum granzyme B, IFN-g, CXCL9, ALT, LDH, ferritin, CBC indices, spleen size/inflammatory infiltrates, and a detailed clinical scoring system. We also examined select indices and survival after various therapeutic interventions. Results: This kinetic analysis revealed that murine HLH may be divided into 3 phases: normal immune activation, pre-symptomatic immune hyper-activation, and the fully developed HLH clinical syndrome. Consequently, all therapeutic interventions may be categorized as pre-emptive, pre-symptomatic, or post-HLH, based on their timing. We observed that while many interventions were effective pre-emptively, therapy was much more challenging after HLH developed. Toxicities of etoposide and JAK inhibitors were substantial in this context and IFN-g blockade had incomplete efficacy. Gene expression and cell signaling studies revealed unique targets in these mice. Results of studies examining comparative, combination, and novel therapies will be presented. Conclusion: A careful definition of the kinetics of HLH development is essential for interpreting the results of therapeutic studies in murine models. The context for specific therapies has a significant impact on both efficacy and toxicity, which may be relevant for clinical contexts. This approach is revealing innovative and potentially optimal combinations for targeted therapy of human HLH.

MAPK MUTATIONS NEGATIVELY AFFECT LESIONAL CD8+ T-CELL - LCH-CELL RATIOS

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Purpose: Neoplastic Langerhans Cell Histiocytosis (LCH)-cells express constitutively active MAPK proteins. It is, however, unclear whether (neo)-peptides, derived therefrom, can trigger immune cells. We collected data on mutational status, Human Leukocyte Antigen (HLA) genotype and lesional immune signature to assess how each factor affects LCH presentation and outcome. Methods: A Dutch-Canadian cohort, containing both pediatric and adult LCH patients, was established for this study. Blinded tissue biopsies from first disease onset were analyzed for BRAFV600E expression, by microdissection and PCR, and in some cases also for other LCH-related mutations. T-cell numbers and phenotype were assessed in the same biopsies by triple immunofluorescent staining and ImageJ software. Results: Clinical data on 163 LCH patients, with a median follow-up time between date of biopsy and last hospital visit of 7.84 years, were collected. Among these patients, 152 biopsies were analyzed for T-cell numbers, and 137 for BRAF mutational status. HLA genotype was determined for 102 patients. Most patients presented with SS-LCH (n=116). Remaining patients were diagnosed with MS-RO- (n=34) or MS-RO+ (n=13) disease. The incidence of BRAFV600E mutation in this cohort is 50.7%. Remarkably low CD8+ T-cell numbers were found in first onset LCH biopsies, with a median of 0.02 CD8+ T-cells per LCH-cell (range 0.00-4.96). Striatification revealed that BRAFV600E lesions displayed a significantly lower number of CD8+ T-cells per LCH-cell (p<0.0001), with a median of 0.02 CD8+ T-cells per 1 LCH-cells (range 0.00-1.25). The same holds true for MAP2K1 mutation-bearing lesions (p=0.045). BRAF mutation status, but not CD8+ T-cell: LCH-cell ratio, had a negative impact on event-free survival. Conclusion: These data show that LCH lesion-infiltrating CD8+ T-cells do not have major impact on disease outcome. Our observation that CD8+ T-cells are clearly outnumbered by LCH-cells suggests that the constitutively active MAPK pathway somehow drives immune evasion.

RAEEXAMINATION OF MURINE HLH: KINETICS, COMPARATIVE THERAPY, AND NOVEL COMBINATIONS

Michael Jordan, Vandana Chaturvedi, Nora Lakes, Rohan Srivastava, Amber Hensley

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Purpose: The study of hemophagocytic lymphohistiocytosis (HLH) in mice has provided unique insights into immune regulation, defined disease pathophysiology, and suggested several strategies for the targeted therapy of human HLH. Multiple groups have studied the therapeutic potential of blocking interferon gamma (IFN-g), JAK/STAT signaling, and other conventional or novel approaches in mice. However, it is not clear how well therapy in these models reflects clinical realities in patients, or how these therapies may compare with, or complement each other. Methods: We performed a stringent kinetic analysis of multiple markers of HLH or immune activation in LCMV-infected normal or perforin deficient mice, assessing soluble CD25, serum granzyme B, IFN-g, CXCL9, ALT, LDH, ferritin, CBC indices, spleen size/inflammatory infiltrates, and a detailed clinical scoring system. We also examined select indices and survival after various therapeutic interventions. Results: This kinetic analysis revealed that murine HLH may be divided into 3 phases: normal immune activation, pre-symptomatic immune hyper-activation, and the fully developed HLH clinical syndrome. Consequently, all therapeutic interventions may be categorized as pre-emptive, pre-symptomatic, or post-HLH, based on their timing. We observed that while many interventions were effective pre-emptively, therapy was much more challenging after HLH developed. Toxicities of etoposide and JAK inhibitors were substantial in this context and IFN-g blockade had incomplete efficacy. Gene expression and cell signaling studies revealed unique targets in these mice. Results of studies examining comparative, combination, and novel therapies will be presented. Conclusion: A careful definition of the kinetics of HLH development is essential for interpreting the results of therapeutic studies in murine models. The context for specific therapies has a significant impact on both efficacy and toxicity, which may be relevant for clinical contexts. This approach is revealing innovative and potentially optimal combinations for targeted therapy of human HLH.

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HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH REFRACTORY LANGERHANS CELL HISTIOCYTOSIS

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Purpose: Effect and indication of hematopoietic stem cell transplantation (HSCT) has been still undetermined for children with refractory Langerhans cell histiocytosis (LCH). We retrospectively analyzed 30 children with refractory LCH undergoing HSCT in Japan. Methods: Total 30 children with refractory LCH who underwent an allogeneic HSCT were registered in the HLH study group of the EBMT in Japan. Results: The male/female ratio was 18/12. At diagnosis of LCH, the median age was 10 months (range, 3-60 months), and the median interval between the diagnosis and HSCT was 349 days (range, 51-3,773 days). Eleven patients underwent HSCT using myeloablative conditioning (MAC) regimen, whereas 19 patients received reduced intensity conditioning (RIC) regimen. Donor sources were related donor in 9 patients and unrelated in 21 patients (cord blood 19 and bone marrow 2). Neutrophil recovery was observed in 24 patients and the median time to engraftment was 21 days. Acute GVHD of grade II - IV, chronic GVHD were observed in 6 and 4 patients, respectively. With median follow-up of 18 months after HSCT, 13 patients died and 8 of them within 3 months after HSCT. The overall survival (OS) was not different between RIC and MAC. In regard to disease status at HSCT, recipients with no active disease/partial response (n=6) had better outcome than those with active disease/stable/ progressive (n=19) (5-year OS 100% vs. 52.1%, p=0.035) (5 data missing). Conclusions: Of 30 HSCT recipients for refractory LCH, 17/30 (57%) are alive while post-transplant death occurred in 13/30 (43%). Novel measures are required to stabilize the disease activity before HSCT.

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION PROVIDES CURE FOR ADULT PATIENTS WITH HEMOPHAGOCYTIC LYMPHOCIYTOSIS (HLH): A RETROSPECTIVE STUDY OF THE CHRONIC MALIGNANCIES AND INBORN ERRORS WORKING PARTIES (CMWP AND IEWP) OF THE EBMT


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Purpose: Allogeneic stem cell transplantation (alloSCT) is indicated in familial, recurrent or progressive hemophagocytic lymphohistiocytosis (HLH); hemophagocytic syndrome). While data for alloSCT outcomes are available for the pediatric setting, information for adults is very limited. The aim of this study was to retrospectively analyze the information from the EBMT databases about adult HLH patients who underwent allogeneic stem cell transplantation. Methods: We obtained data of 70 adult (≥18 years of age) patients transplanted due to HLH. Additionally, 33 responses from the clinical centers were received for an HLH-oriented questionnaire. Results: Median
age at transplantation was 28 (range: 18-65). There was a slight male predominance 45/70 (64%). Reduced intensity conditioning was used in 22/67 (33%) of patients. The median survival time was 9.4 months. The three year OS was 41% (95% CI 29-54%). For patients who survived until 3 months, this proportion was more favorable with an OS of 61% (95% CI 46-77%) at 3 years after transplantation. After 12 months no relapses of HLH were recorded; the cumulative incidence reached 15% (95% CI: 5-24%). The non-relapse mortality reached 35% (95% CI: 22-47%) after 15 months. Unlike the pediatric population, where reduced intensity conditioning (RIC) was associated with higher survival, in adult patients there was no difference between the conditioning types. Data from 33 questionnaires have confirmed clinical picture typical for HLH at the diagnosis: fever in 31/32 (97%), splenomegaly in 28/30 (93%), hemophagocytosis 26/30 (87%) and hyperferritinemia with median concentration of 6,102 ng/ml (range: 63-260,160). Gene with the most frequently found mutations was STXBP2 (6/15). Conclusion: To our knowledge, this is the largest analyzed group of adult patients with HLH who underwent allogeneic stem cell transplantation. Relatively low relapse incidence confirms that alloSCT can effectively cure HLH. Patients who survive the first period after this procedure can expect a long disease-free survival.
Background: The identification of recurrent BRAFV600E mutations in Erdheim-Chester disease (ECD) and Langerhans cell histiocytosis (LCH) led to a breakthrough in treatment of severe forms of disease with BRAF inhibition. The finding that nearly all BRAF-wildtype ECD/LCH lesions harbor mitogen activated protein kinase (MAPK) pathway alterations raised the possibility of treatment of BRAF-wildtype ECD with MEK inhibition. Methods: This is a phase 2 trial of Cobimetinib 60mg daily for patients with (1) BRAF-wildtype histiocytosis or (2) BRAFV600-mutated histiocytosis intolerant or without access to BRAF inhibitor therapy. The primary outcome is metabolic response by 18F-FDG PET scan. Results: 11 patients have enrolled: 8 ECD, 1 Rosai-Dorfman disease (RDD), 1 mixed ECD/RDD, and 1 LCH. Three patients have BRAFV600E mutated disease. Ten patients (4 ECD, 1 RDD, 1 RDD/ECD, 1 LCH) have had response assessments. One patient died (Grade 5 respiratory failure, related to infection) before the first response assessment and one patient was removed from study due to toxicity (Grade 3 retinal vein occlusion) related to drug. Two patients withdrew consent from the study to pursue off-trial therapy. Grade 3/4 toxicities have been hyponatremia (27%), lymphopenia (27%), hyperlipidemia (18%), and hyperglycemia (18%). The most common Grade 1-2 toxicities have been hypoalbuminemia (91%), fatigue (73%), increased alkaline phosphatase (73%) and anemia (63%). Five patients have required dose reduction to 40mg. All patients but one have had a metabolic response in target lesions; 30% (3 patients) a complete metabolic response, 40% (4 patients) a partial metabolic response, 10% (one patient) has stable metabolic disease. All patients have had symptomatic benefit as measured by symptom and QOL scales. Conclusions: Interim results from this trial demonstrate robust efficacy of single-agent Cobimetinib in histiocytic disorders, regardless of BRAF mutational status. Toxicities have been manageable and similar to those observed in previous trials of Cobimetinib.

A PHASE II TRIAL OF LENALIDOMIDE IN ADULTS WITH HISTIOCYTIC DISORDERS

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Purpose: Evaluate the efficacy and safety of lenalidomide in adult patients with Langerhans cell histiocytosis (LCH), histiocytic sarcoma (HS) and Erdheim-Chester disease (ECD). Methods: Patients 18 or older with LCH, ECD or HS in need of systemic therapy are eligible. Initial lenalidomide dose is 10 mg daily on days 1-21 of a 28-day cycle. If no grade 3 or greater toxicity occurs during cycle 1 the dose is escalated to 25 mg. The primary endpoint is overall response rate (ORR) using MRI and PET/CT per International Working Group criteria. All patients were required to take aspirin 81 mg daily if not on systemic anticoagulation at baseline. Results: Eleven of a planned 12 patients have been enrolled. Histologies were ECD (n = 3), HS (n = 2), and LCH (n = 6). BRAF mutations were identified in 2 of 11 patients. Seven patients received prior treatment. The number of treatments received was 1 (n = 1/7), 2 (n = 3/7), 3 (n = 2/7), and 7 (n = 1/7). Four of 11 patients have responded; all with LCH (2 CR and 2 PR). One LCH patient subsequently progressed after achieving CR. 2 additional LCH patients have had SD but improvement in symptoms. All 3 ECD patients had SD and both HS patients had PD as best response. Median duration of response has not been reached. One patient with HS died, all others remain alive. The most common toxicities were fatigue (n = 6), neutropenia (n = 5), nausea (n = 4), anemia (n = 3), thrombocytopenia (n = 3), and rash (n = 3). The only grade 3 toxicities were neutropenia and thrombosis (n=1 each). No grade 4 or grade 5 toxicities occurred. Conclusion: Lenalidomide has excellent activity in LCH though lesser activity in ECD and HS.
the 27 remaining, 25 were missense (14 predicted as probably damaging), 1 STOP, 1 frameshift. Two patients had mutations in 2 different genes. Conclusions: 9% of patients reported to the Italian HLH Registry carries monoallelic variants in at least one FHL-related gene, including 52% being probably damaging. Altogether these patients are characterized by later onset, partial/milder disease, and partial functional defect. Thus, monoallelic mutation in one FHL-related gene defines a predisposing factor for HLH.

**PRESENTATIONS NOMINATED FOR THE NEZELOF PRIZE IN BASIC SCIENCE**

**HIF1A IS A CRITICAL MEDIATOR FOR PRIMARY AND SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS**

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Purpose: Although a steroid/etoposide-based regimen, as first-line therapy, is effective to treat hemophagocytic lymphohistiocytosis (HLH), it still has substantial morbidity. Thus, novel, less toxic therapies for HLH are needed. Methods: We took bio-informatic approaches and reanalyzed published microarray data of patients with familial hemophagocytic lymphohistiocytosis (FHL) and patients with systemic juvenile idiopathic arthritis (sJIA), which is tightly associated with secondary HLH. To validate the human HLH data, HIF1A levels were measured in two established HLH mouse models by flow cytometry. Furthermore, to determine the role of HIF1A in HLH, a transgenic mouse line with inducible expression of HIF1A/ARNT proteins in hematopoietic cells was generated and analyzed. Results: Our transcription factor-target enrichment analysis predicted HIF1A as one of the common key transcription factors in both FHL and sJIA datasets; gene set enrichment analysis (GSEA) showed that the HIF1A signature is also significantly enriched in both datasets. Gene ontology analysis revealed that the common leading edge genes of the HIF1A signature are related to chemotaxis, glycolysis, and immune response. Consistent with human HLH data, elevated HIF1A protein levels were confirmed in both the Lymphocytic choriomeningitis virus infected Prf1-/- HLH model and the CpG-treated model. Moreover, hematopoietic specific expression of HIF1A/ARNT proteins in the C57BL/6 background caused lethal HLH-like phenotypes: severe anemia, thrombocytopenia, multi-organ failure, splenomegaly, and femininity. Mechanistically, these mice showed type-1 polarized macrophages, reduced NK cells, and slightly changed dendritic cells, but unaffected T/B cell populations. Furthermore, the HLH-like phenotypes in this mouse model are independent on their adaptive immunity or IFN-γ signaling, since induction of the HIF1A/ARNT allele resulted in similar phenotypes in the Rag1-/- and Ifngr-/- background. Conclusion: Our data revealed that the HIF1A signaling pathway is a critical mediator for both primary and secondary HLH and could potentially be a therapeutic target for a broad spectrum of HLH.

**TRANSCRIPTIONAL PROFILES, LINEAGE TRACING WITH BRAF-V600E AND HLA-DQB2 EXPRESSION SUPPORT A MODEL OF BLOOD CD1c+ CELLS AS PRECURSORS TO LCH LESION CD207+ CELLS**

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Purpose: Langerhans Cell Histiocytosis (LCH) is characterized by granulomatous lesions that include pathologic CD1a+CD207+ dendritic cells (DC). Activating somatic MAPK pathway gene mutations have been identified in hematopoietic stem cell and lesion DCs in patients with high-risk LCH, though the differentiation pathway remains uncertain. The purpose of this study was to define the origin of LCH lesion CD1a+/CD207+ cells. Methods: We compared transcriptional characteristics of LCH lesion CD1a+/CD207+ cells to established gene signatures from human peripheral blood and tissue myeloid populations including CD14+ monocytes, CD16+ monocytes, CD14+ DCs, macrophages, epidermal Langerhans cells, CD1c+ myeloid dendritic cells (mDCs) and CD141+ mDCs. Additionally, quantitative PCR of BRAF-V600E and HLA-DQB2 surface expression were used to identify clonal lesion and peripheral blood monocyte and dendritic cell populations. Results: When comparing lesion CD1a+/CD207+ cells to blood and tissue DC/monocyte populations, the CD1c+ mDC gene signature was most similar to gene expression profile of lesion CD1a+/CD207+ cells. In order to further test the hypothesis that LCH CD1a+/CD207+ cells arise from CD1c+ mDCs, we investigated subpopulations within the LCH lesions for the BRAF-V600E allele and found that, in addition to CD1a+ and CD1a+CD207+ DCs, BRAF-V600E was also identified in LCH lesional CD1c+ mDCs. Furthermore, HLA-DQB2, highly expressed in LCH CD1a+CD207+ cells, was also expressed in LCH lesion CD1c+ cells, but not in any other lesion myeloid subpopulations. Furthermore, HLA-DQB2 was expressed only in peripheral blood of patients with active high-risk LCH, and HLA-DQB2+ CD1c+ blood monocytes were highly enriched for the BRAF-V600E allele. Conclusion: These data support a model where blood CD1c+ mDCs with hyperactive ERK migrate to lesion sites and differentiate into LCH CD1a+CD207+ cells. If differentiation from CD1c+ DCs to CD1a+CD207+ cells is critical to LCH pathogenesis, blocking this process may represent a novel therapeutic opportunity.
A NOVEL CTL-BASED FUNCTIONAL ASSAY REVEALS A STRONG CORRELATION BETWEEN THE PATHOGENICITY OF AN UNC13D VARIANT AND THE INSTABILITY OF ITS TRANSLATED MUNC13-4 PROTEIN; MUNC13-4 PROTEIN EXPRESSION ASSAY IS A RELIABLE METHOD FOR IDENTIFICATION OF PATIENTS WITH FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Purpose: Familial hemophagocytic lymphohistiocytosis (FHL) is a fatal syndrome of immune dysregulation and hyper-inflammation. Biallelic loss-of-function mutations in UNC13D gene encoding Munc13-4 protein cause FHL type 3 (FHL3). All the reported FHL3 cases evaluated for protein expression levels are shown to have significant reduction of Munc13-4 protein expression levels regardless of types of UNC13D mutations. We have previously reported that FHL3 can be rapidly screened by detecting intraplatelet Munc13-4 expression, but its reliability has not been evaluated. The purpose of this study is to elucidate the pathogenicity of a given UNC13D mutant and to evaluate the reliability of Munc13-4 expression assay as a FHL3 screening method. Methods: We first determined the effectiveness of intraplatelet Munc13-4 expression assay by summarizing the result of FHL screening performed at our laboratory from 2011 to 2016. Next, we picked up 13 reported pathogenic missense UNC13D mutations and evaluated their influence on Munc13-4 protein expression, as well as on degranulation and cytotoxic function by transiently expressing cDNA constructs in human FHL3 model cell lines. Results: Munc13-4 protein expression levels of the 14 FHL3 patients diagnosed at our laboratory were all significantly reduced regardless of their types of mutation, and flow cytometric detection of intraplatelet Munc13-4 protein identified these patients with high sensitivity and specificity. Eleven out of 13 reported UNC13D missense mutations caused significant reduction of Munc13-4 protein expression and functional defects in the transfected cell lines. The remaining two reportedly pathogenic UNC13D mutants did not cause reduction of Munc13-4 protein expression. Moreover, the degranulation and cytotoxic function of model cell lines transfected with these mutants were normal. Conclusion: The pathogenicity of an UNC13D variant strongly correlates with the instability of its translated Munc13-4 protein, and FHL3 patients are likely amenable to rapid detection by Munc13-4 expression assay.
Purpose: Profound hyperferritinaemia of >10,000 mcg/L has been shown to be highly specific for the diagnosis of haemophagocytic lymphohistiocytosis (HLH) in western literature but similar studies are lacking in Asian children. Methods: We did a retrospective study over 6 years (2010-2015) and reviewed the records of all paediatric (up to 17 yrs of age) inpatient admissions with a ferritin value of >500 mcg/L and identified children diagnosed with HLH as per the HLH 2004 criteria in this period. Children on regular transfusion, with incomplete work-up or with samples taken outpatient were excluded. Sensitivity and specificity of hyperferritinaemia were calculated at ferritin levels of > 500 mcg/L, >2,000 mcg/L and >10,000 mcg/L. Results: Sixty children were identified with high ferritin of >500 mcg/L and only 9 were confirmed to have HLH. All children diagnosed with HLH had ferritin of >10,000 mcg/L. Sensitivity of hyperferritinaemia in the diagnosis of HLH was consistently high at all ferritin levels of >500 mcg/L, >2,000 mcg/L and 10,000 mcg/L (100% with Confidence Interval of 66.37-100%). However, specificity was found to be much lower, at 35.29% (95% CI of 22.43%-49.33%) for 2,000 mcg/L and 76.47% (95% CI of 62.51%-87.21%) for 10,000 mcg/L. Twenty-one children had ferritin of >10,000 mcg/L of which 12 did not have HLH and had an alternative diagnosis mostly infection. Conclusion: Profound hyperferritinaemia, although a useful screening test is not very specific for the diagnosis of HLH in Asian children. Macrophages in Asian populations are likely to be genetically more hyper-responsive and secrete more ferritin secondary to infectious stimuli and may not have associated HLH. As HLH specific investigations like NK cell function, CD25 assay and genetic testing are not readily available in Asia, reliance on hyperferritinaemia in diagnosis of HLH should be used with great caution to avoid over-diagnosis and unnecessary treatment.

Poster Location #2

PREDICTION MODELS IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: DO WE NEED MORE?

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Purpose: Hemophagocytic Lymphohistiocytosis (HLH) comprises a spectrum of conditions characterised by hyper-inflammation triggered by infection, malignancies or autoimmuneity. HLH is still diagnosed based on criteria that were suggested more than a decade ago. There are hardly any markers that would help the clinician differentiate primary HLH which would need immunosuppression and hematopoietic stem cell transplant from "secondary" HLH triggered by easily treatable infections. Various prognostic scores have been evaluated in HLH addressing various aspects of the disease and its management. We evaluated all the prognostic scores studied in HLH as part of the present study. Methods: A systematic search of PubMed/Pubmed-
Langerhans cell histiocytosis (LCH) is a histiocytic disorder characterized by the accumulation of CD1a+ langerin+ cells of unknown origin in different tissues. We have previously shown that Notch signaling is active in LCH lesions and that stimulation of the Notch pathway can induce CD1a and langerin expression in human CD14+ monocytes. Here we provide evidence that Notch signaling induces primary human CD14+ monocytes to acquire an LCH gene signature in vitro. In contrast, langerin+ cells derived in vitro from CD1c+ DCs or IL4-stimulated CD14+ monocytes differ in their gene expression signature from primary LCH cells. Inhibition of Notch signaling using a gamma secretase inhibitor abrogated the capacity of CD14+ monocytes to differentiate into langerin+ cells, whereas CD1c+ DCs were not affected. Additionally, JAG2 enhances the promoter activity of a RBPJ luciferase gene reporter construct thereby demonstrating Notch pathway activation in CD14+ monocytes. Chromatin immunoprecipitation using antibodies against RBPJ and histon marks for chromatin activation (H3K4me3) and repression (H3K27me) revealed that promoter regions of bone fide Notch target genes were bound by RBPJ and showed enriched binding of H3K4me3 upon differentiation of CD14+ monocytes towards CD1a+ langerin+ cells, while at the same time binding of H3K27me decreases. These data lead us to propose a model in which CD14+ monocytes are the precursors of the LCH cells and in which JAG2 mediated activation of the Notch pathway initiates a differentiation of monocytes towards LCH cells in selected niches and thus contributes to LCH pathogenesis.

CLINICAL LCH POSTER NOMINEES

Poster Location #5

SINGLE-CENTER EXPERIENCE IN TARGETED THERAPY OF BOTH BRAF V600E POSITIVE AND BRAF WT MULTISYSTEM REFRACTORY LANGERHANS-CELL HISTIOCYTOSIS (LCH) WITH RISK ORGANS INVOLVEMENT IN CHILDREN: A REPORT OF 11 CASES

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Purpose: To evaluate retrospectively the efficacy and tolerability of the targeted therapy in a cohort of children with multi-system LCH, refractory to or intolerant to standard chemotherapy. Methods: Among 11 cases of multi-system LCH with risk organ involvement 9 were BRAF V600E positive and 2 were BRAF wild type. Median age of manifestation was 3.4 months (1-12 months), median age at diagnosis was 12 months (3-22 months). Preceding chemotherapy was according to the LCH-IV protocol. All patients received initial therapy with VBL + PRED, 7 received Ara-C + 2-CdA as second line therapy. At the start of vemurafenib therapy all patients had active disease with median DAS 13.4 points (4 : 22). Nine patients were were treated with vemurafenib (median dose was 44.6 mg/kg/day (37-50)), median time of follow-up was 201 day (76-407) and 2 patients were treated cobimetinib (median dose 20 mg/day; median time of evaluation - 120 days ) with or without concomitant chemotherapy (1 received mono vemur, 1 received mono cobimet, 1 received cobimetinib + 2-CdA, 5 received vemur + VBL + PRED + MTX + 6-MP, 3 received vemur + low-dose Ara-C + 2-CdA). Results All 11 patients had partial or complete response to therapy. At day 28 median DAS was 5.4 points (2 : 11). Main toxicities were skin toxicity (91%) and QTs elongation (45%). 1 patient couldn't tolerate vemurafenib due to severe vomit and weight loss and died later due to disease progression. 1 patient died during vemurafenib intake due to severe liver lesion of unknown origin. Conclusion: Targeted therapy with either BRAF or MEK inhibitors induces marked clinical and laboratory responses in patients with multi-system LCH, refractory to standard chemotherapy. The optimal schedule, potential toxicities, rational therapeutic combinations and treatment regimens should be studied prospectively.

BASIC LCH POSTER NOMINEES

Poster Location #4

NOTCH SIGNALING INDUCES A LANGERHANS CELL HISTIOCYTOSIS GENE EXPRESSION SIGNATURE IN HUMAN MONOCYTES

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Purpose: Langerhans Cell Histiocytosis (LCH) is a neoplastic disease that varies widely in clinical presentation. In the Emma Children’s Hospital/Academic Medical Center, Amsterdam, Netherlands, protocols were introduced. Methods: A cohort of patients treated between 1962 and 2008 was identified from our patient-database. Clinical staging, treatment and response to treatment, reactions and permanent consequences were evaluated. Results: Of the 97 patients identified, 14 (14.4%) patients had multisystem LCH (MS-LCH) with risk-organ (RO) involvement, 17 (17.5%) MS-LCH without RO involvement, 27 (27.8%) multifocal bone/special site LCH and 39 (40.2%) unifocal LCH. Overall 11 patients (11.3%) died, 87 patients (95.6%) attained no active disease (NAD). Fifty- eight percent of the MS-LCH patients on the VCP-regimen attained NAD (80% of the MS -RO+ patients). Of the 10 MS-RO+ patients 8 reached NAD, 3 after treatment intensification. Two other poor-responders died. Two experienced reactivation. All MS-RO- patients reached NAD, 4 after treatment intensification. Five out of 10 had a reactivation, 1 of the 5 died. Twenty-eight (28.9%) patients suffered from permanent consequences (PC), the most common Diabetes Insipidus (DI) in 9.3%. Of the multisystem patients 4 (12.9%) patients and of the single system patients 5 (7.6%) patients were found with DI. Conclusion: Overall survival for MS-RO+ patients on the VCP-regimen is comparable to that of LCH-III, as is the incidence of DI in the whole cohort. Although the total number of patients on the regimen is limited, treatment results are comparable to those obtained in the JLSG-studies.

POSTER PRESENTATIONS - PRIZE NOMINEES

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radiography and 45 lesions were detected on WB MRI. Sensitivity of WB MRI was 90%. Conclusions: WB MRI seems promising as a whole-body technique during staging of pediatric LCH patients with sensitivity of 90% in our cohort. In our study, WB MRI detected additional lesions, but the clinical relevance of these lesions is under debate. Future research should therefore focus on the value of WB MRI and plain radiography in a prospective setting.

**Poster Location #8**

THE USE OF WHOLE BODY MAGNETIC RESONANCE IMAGING FOR SKELETAL STAGING OF CHILDHOOD LANGERHANS HISTIOCYTOSIS: RESULTS OF A RETROSPECTIVE COHORT STUDY

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**Purpose:** Whole-body magnetic resonance imaging (WB MRI) can be used for staging of several paediatric malignancies. In the past, two small studies have been performed using WB MRI for staging of LCH. The aim of this study was to assess the role of WB MRI during staging at diagnosis and to compare WB MRI to plain radiography in the cohort of the Emma's Children Hospital. Methods: A retrospective cross-sectional cohort study was performed. Patients diagnosed with LCH were eligible. For this study, patients were included if they had total body MRI at baseline and if targeted comparative imaging of MRI-positive lesions was available. All imaging (both WB MRI and plain radiography) was reassessed by two pediatric radiologists independently and scored for presence of lesions. For this study, plain radiography was regarded as the reference standard. Results: Twelve patients were included for this study. A total of 55 lesions were detected and for 48 lesions comparative imaging was available. Thirty lesions were detected by plain
Purpose: Erdheim-Chester disease (ECD) is a non-Langerhans cell histiocytic neoplasm resulting in chronic inflammation and fibrosis. The majority of patients harbor the BRAF V600E mutation in affected tissue. ECD involves multiple organ-systems and causes endocrinopathies. Abnormalities of the Hypothalamic Pituitary Adrenal (HPA) axis and other endocrine pathways have not been extensively investigated in ECD. Methods: Sixty consecutive patients with ECD participated in a National Institutes of Health (NIH) approved study. Results: Forty-seven percent of patients had diabetes insipidus treated with vasopressin. Adrenal gland and pituitary stalk infiltration was present in 21/60 (35%) and 14/55 (25.45%). Both were observed in 5/55 (9.09%). Twenty-five patients (25/55, 45.45%) had no infiltration in the HPA axis. Twenty patients (20/60) had a prior diagnosis of AI. No patient presented with adrenal crisis as the initial manifestation of ECD. All patients with AI reported lack of education toward sick day rules. Glucocorticoid replacement therapy was not required in 11/21 patients with adrenal gland infiltration or in 4/14 with pituitary/stalk infiltration. Mineralocorticoid replacement therapy was not required in all patients. Thirty patients (30/56, 53.5%) harbored the BRAF V600E mutation, and were more likely to have adrenal gland infiltration with comparable rates for pituitary/stalk infiltration. High-sensitivity C-reactive protein was significantly higher in patients with adrenal gland infiltration and positive BRAF V600E mutation. Other endocrine abnormalities included hypogonadism in 60%. Insulin-like growth factor levels were abnormal in one-third of cases, 22% had hypothyroidism. Occasional abnormalities in parathyroid, and prolactin hormones were seen. Conclusions: Infiltrative processes of the HPA axis in patients with ECD tend to favor the adrenal glands in BRAF-positive patients, without influencing the rates of AI, although there is a poor biochemical-radiological concordance in ECD. Patients with ECD should be educated on the risk for and the management of endocrine abnormalities and followed closely by an endocrinologist.
EARLY ONSET OF HLH AND INHERITED UNC13D AND JAK3 MUTATIONS IN A PATIENT: A DIFFICULT DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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Purpose: Several HLH-associated genes are required for cytotoxic lymphocyte exocytosis. HLH is the first manifestation of other primary immunodeficiencies, including severe-combined-immunodeficiency (SCID). The type and combination of mutations correlate with age at onset, clinical presentation and severity of cytotoxic impairment. We present a case diagnosed with early-onset HLH and monoallelic UNC13D and JAK3 mutations. Methods: We reviewed clinical, laboratory, immunological and pathological data. Familial genetic study was performed by whole-exome sequencing (WES) and confirmed by Sanger sequencing. Results: A girl was diagnosed with CMV infection, severe HLH and bowel involvement at 2 months and responded well to HLH-2004 therapy. Initial genetic studies detected a heterozygous UNC13D c.1021C>G p.Gln341Glu mutation inherited from the father, but immunological functional assays didn’t impaired lymphocyte exocytosis. The following years the patient had failure to thrive and mild respiratory infections, but SCID was ruled out. Later she had intermittent episodes of fever, maligias and cytopenia with complete resolution, followed by progression to persistent hematopoesinomegaly, abdominal adenopathies and hepatitis. WES revealed two rare JAK3 variants c.1142+3G>T and c.878G>A p.Cys293Tyr, which were confirmed by Sanger sequencing in patient and the mother. In subsequent immunological studies, NK cell and cytotoxic T cell functional assays were not impaired drastically. At the age of 5, after mild pneumonia and rhinovirus infection, she developed severe HLH with autoimmune hepatitis. She responded partially to HLH-therapy, but died (sepsis and fungal infection). Autopsy confirmed HLH-immunopathology. Conclusion: Genetic screening by high-throughput sequencing, immunological phenotyping and functional assays are important in order to establish correct diagnosis in HLH patients. Monoallelic and polygenic inherited defects in the genes UNC13D (from father) and JAK3 (from mother) may have colluded for development of fatal HLH. It is not clear how HLH and SCID-associated gene mutations might combine for a digenic inheritance, but combined mutations represent a diagnostic and therapeutic challenge.

THE ROLE OF SOLUBLE INTERLEUKIN-2 RECEPTOR (sIL-2R) IN DIAGNOSIS OF ADULT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH): A SINGLE CENTER RETROSPECTIVE STUDY

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Purpose: Serum soluble interleukin-2 receptor (sIL-2r) is considered an important disease marker in hemophagocytic lymphohistiocytosis (HLH). The HLH-2004 diagnostic criteria report sensitivity of 93% and specificity of 100% for sIL-2r >2,400U/ml for pediatric HLH. No studies have reported the performance characteristics of this test in adult HLH patients. We conducted a retrospective study to evaluate the clinical utility of sIL-2r in adult HLH patients, including sensitivity, specificity, and prognostic significance. Methods: Retrospective data was collected on adult patients with at least one sIL-2r level at Vancouver General Hospital in Vancouver, Canada between March 2012 and April 2017. Patients were subdivided into HLH and non-HLH groups. Sensitivity, specificity, prognosis associated with sIL-2r >10,000U/ml, utility as a marker of disease activity and mean sIL-2r between subgroups of HLH were evaluated. Results: 79 patients were included, 41 with HLH and 38 with an alternate diagnosis (non-HLH). The sensitivity of sIL-2r >2,400 U/ml was 93% (95% CI 0.79 : 0.98) and specificity 66% (95% CI 0.49 : 0.79). Specificity improved to 92% (95% CI 0.76 : 0.98) with a threshold of sIL-2r >10,000U/ml. Similar to ferritin, sIL-2r levels correlated with disease activity. Within the HLH group, sIL-2r >10,000U/ml was not associated with worse prognosis. Higher sIL-2r levels were seen in malignancy associated HLH (MAHS) as compared to infection associated HLH (IAHS) and macrophage activation syndrome (MAS). Conclusion: sIL-2r >2,400U/ml is a sensitive test for diagnosis of adult HPS/HLH and is useful in monitoring disease activity. At higher levels (sIL-2r >10,000U/ml), this biomarker loses sensitivity but gains specificity in diagnosing HPS/HLH. Higher sIL-2r levels may indicate MAHS when the underlying etiology is unclear. Further prospective studies are needed to further confirm the utility of sIL-2r in diagnosing adult HLH.

SECONDARY HEMOPHAGOCYTIC LYMPHOMHOSTIOCYTOSIS IN PATIENTS WITH SEPSIS

Farhan Fazal: naveet Wig: Naval Kishore Vikram; Manish Soneja; Gita Satpathy; Pravas Chandra Mishra; R.M.Pandey; D.K.Mitra; S.K.Panda; P.K.Chaturvedi

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition characterized by uncontrolled inflammation and has common clinical and laboratory features with sepsis. The study is conducted to know the clinical and laboratory features of Secondary HLH in patients with sepsis. Method: This is a prospective observational study where patients presenting with Sepsis and Bicytopenia are included. The patients underwent relevant investigations for diagnosis of HLH according to HLH 2004 diagnostic criteria. Patients fulfilling the criteria were further analysed regarding the clinical features, laboratory parameters and microbiology investigations for etiology of secondary HLH. The treatment received and the final outcome of the patient was also studied. Results: There were 16 patients who were screened, out of which 9 fulfilled the diagnostic criteria. There were 4 men and 5 women with secondary HLH. The etiology were Dengue (1), Pulmonary Aspergillosis (2), HIV (1), Typhoid (1), MDR Tuberculosis (1), Visceral Leishmania (1), Staph aureus (1), Unknown(1). Fever, organomegaly, hyperferritemia and bicytopenia was seen in all patients. Lymphadenopathy was seen in 2 patients, Neuropsychiatric symptoms in 2 patients. Bone marrow was done in 6 patients as the others did not give consent. Hemophagocytes were seen in 50% of them. Highest ferritin levels was 21,723 seen in the patient with Staph aureus associated Sepsis. Steroids with etoposide according to HLH 1994 treatment protocol was given to 3 patients but unfortunately 2 of them died. 5 patients received only Dexamethasone in tapering doses for 8 weeks with supportive care and all of them survived . 1 patient could not receive any treatment for HLH as she died before the results of investigations were available. Conclusion: HLH should be suspected in sepsis patients with bicytopenia. Infection associated HLH is treated with steroids. Infection associated HLH in not uncommon and and early recognition and treatment can improve outcome.
**POSTER PRESENTATIONS - CLINICAL HLH**

**Poster Location #14**

**SEPSIS AS A CIMICKER OF HLH IN A PEDIATRIC INTENSIVE CARE UNIT**

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a disease of overwhelming inflammation with a high mortality rate. Early recognition and initiation of treatment may improve survival. This study examined five pediatric control patients without HLH in the pediatric intensive care unit (PICU) at Children’s Mercy Hospital with clinical diagnosis of sepsis and one pediatric patient with HLH in the PICU for the diagnostic criteria and known and exploratory cytokine levels. Methods: This prospective study was approved by the IRB at Children’s Mercy Hospital Kansas City Missouri, USA. Chart review for clinical diagnostic criteria and additional blood sent for laboratory criteria of HLH. Cytokine levels on day 1 and 3 of PICU admission performed when samples available. Plasma cytokines were evaluated using magnetic bead immunoassay. Results: Total of six patients enrolled on study; five that did not meet diagnostic criteria for HLH and one patient that did satisfy diagnostic criteria for HLH. The child with HLH had the most elevated serum ferritin of greater than 10,000 ng/ml compared with mean ferritin of 1574 ng/ml for non HLH patients. The patient with HLH also had the most elevated soluble interleukin 2 level of 8,039 U/ml compared to median value of 1551 U/ml for non-HLH patients. Conclusion: The use of serum cytokine levels may identify children with HLH and lead to earlier initiation of therapy.

**Poster Location #15**

**CHALLENGES OF HAEMOPHAGICOTIC LYMPHOHISTIOCYTOSIS CASES IN YANGON CHILDREN HOSPITAL**

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Purpose: To evaluate the management and outcome of HLH cases in our center. Methods: A retrospective study in a five year period (from 2012 January - 2016 December). Diagnosis is mainly based on the clinical criteria and haemophagocytosis in bone marrow morphology proposed by HLH2004 because of limited facilities to detect genetic defects of familiar HLH and modern technique to find the association with Epstein-Barr virus, serum markers of sCD25 and circulating sCD163. Treatment is according to HLH2004 for primary HLH and for those who can diagnose a secondary cause, treated according to the disease (without bone marrow transplant). Results: Total 11 cases of HLH were diagnosed during five years. Majority of patients were girls (1:2.7), all cases presented with fever and hepatosplenomegaly however only 36%(4/11) presented with lymphadenopathy. Patients presented with skin eruptions, CNS abnormalities and DIC are 18%(2/11), 18%(2/11), 36%(4/11) respectively. Four cases have strong family history and treated as possible Familiar HLH. Among the secondary HLH, the causes were tuberculosis(1/7), langerhan cell histiocytosis(1/7), Non Hodgkin Lymphoma (1/7), EBV infection (1/7) and unknown(3/7). Three cases 27% abandoned treatment, five cases 46% expired and three cases 27% were still on treatment. Two children relapsed 6 months and 4 months after offtreatment. Conclusion: HLH, a severe rapidly overwhelming inflammation with a high mortality rate. Early recognition and initiation of treatment may improve survival. This study examined five pediatric control patients without HLH in the pediatric intensive care unit (PICU) at Children’s Mercy Hospital with clinical diagnosis of sepsis and one pediatric patient with HLH in the PICU for the diagnostic criteria and known and exploratory cytokine levels. Methods: This prospective study was approved by the IRB at Children’s Mercy Hospital Kansas City Missouri, USA. Chart review for clinical diagnostic criteria and additional blood sent for laboratory criteria of HLH. Cytokine levels on day 1 and 3 of PICU admission performed when samples available. Plasma cytokines were evaluated using magnetic bead immunoassay. Results: Total of six patients enrolled on study; five that did not meet diagnostic criteria for HLH and one patient that did satisfy diagnostic criteria for HLH. The child with HLH had the most elevated serum ferritin of greater than 10,000 ng/ml compared with mean ferritin of 1574 ng/ml for non HLH patients. The patient with HLH also had the most elevated soluble interleukin 2 level of 8,039 U/ml compared to median value of 1551 U/ml for non-HLH patients. Conclusion: The use of serum cytokine levels may identify children with HLH and lead to earlier initiation of therapy.

**Poster Location #16**

**EVALUATE THE OUTCOME OF HLH TREATMENT IN INITIAL THERAPY (8 WEEKS) AT NATIONAL CHILDREN'S HOSPITAL**

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Background: Hemophagocytic lymphohistiocytosis (HLH) is characterized by multisystem inflammation. HLH includes the great majority of patients with macrophage-related disorders. The predominant clinical findings of HLH are fevers, hepatosplenomegaly and cytopenia. Other common findings include hypertriglyceridemia, coagulopathy with hypofibrinogenemia, hepatitis, elevated levels of ferritin and serum transaminases, and neurological symptoms. Survival as reported in the three largest reports on HLH from 5% (1- year) of Janka 1983 to 22% (5-year) of Anco 1996 and 55% (5-year) of HLH- 94 in 2002. The aim of this study was to evaluate the outcome after 8 weeks of initial therapy follow HLH-2004 protocol at National Children’s Hospital, Vietnam. Method: Retrospective study 53 patients with HLH characteristics were treated by initial therapy (6 weeks) of HLH-2004 protocol from Aug 2010 to Jul 2011. The patients were confirmed diagnosis HLH base on Henter 2004 of the Histocyte Society. Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria): Fever, splenomegaly, cytopenias. Triglyceride ≥3.0 µmol/l and/or fibrinogen ≤ 1.5 g/L. Hemophagocytosis is in bone marrow but no evidence of malignancy. Ferritin ≤ 500 µg/l, low or absent NK- cell activity, soluble CD 25 ≤ 2400 U/ml. HLH should be suspected in a patient when they have following signs and symptoms: hepatomegaly, lymphadenopathy, hypotension, hepatosis. Statistical analysis was performed with the SPSS program. Results: The patients < 2 years old had 84.9% ( < 1 year: 47.2%). The male to female ratio was 1:1. There were 40/53 patients (75.5%) had EBV positive and 16/53 (30.2%) had CMV positive. 32% of patients had neurological signs such as convulsion 82.4%, cerebral nerve failure 23.5%. Respiratory failure had 37.7% and cardiac insufficiency was 45.1%. After 8 weeks of initial therapy, 22 patients (41.5%) achieved complete remission and continued therapy. In the first 2 months, mortality rate was 58.5% include 24 patients (54.5%) died from week 1-4 and 7 patients (13.2%) died from weeks 4-8. The cause of deaths: multi-organs failure (68.8%), coagulopathy disorder (16.1%), sepsis (16.1%). Conclusion: Children with HLH finished initial therapy of HLH-2004 protocol were 41.5%. Our survival rate still lower than the other centers because delay treatment.

**Poster Location #17**

**CLINICAL STUDY OF E-CHOP REGIMEN AS A SALVAGE THERAPY FOR CHILDREN REFRACTORY HEMOPHAGICOTIC LYMPHOHISTIOCYTOSIS**

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Purpose: To investigate the efficacy with E-CHOP regimen as a salvage therapy for children refractory hemophagocytic lymphohistiocytosis(HLH).

Methods: Total 18 patients with refractory HLH were enrolled in this study. The efficacy of treatment with E-CHOP regimen after 2 and 4 weeks were evaluated according to the United States Midwest Cooperative HLH Group. Results: Of 18 refractory HLH patients, 8 were males and 10 females. The median age was 4.5(1-11) years old. The overall response rate (ORR) was 83.3% (15/18), including 6 patients (33.3%) achieved complete remission (CR) and 9 patients (50%) achieved partial remission (PR). The underlying disease of HLH were identified in 17 patients, including 4 case of primary HLH (CR 3 cases, PR 1 case), 2 cases (PR) of tumor associated HLH and 11 cases (CR 2 cases, PR 6 cases) of EBV associated HLH. There were still one cases with unknown underlying disease. The 3 patients who had no response to E-CHOP died...
within 2 to 4 weeks after salvage therapy. Fifteen patients who achieved PR or CR survived to undergo allogenic hematopoietic stem cell transplantation (allo-HSCT) or splenectomy. Conclusion: The study suggested that E-CHOP regimen appeared to be an effective salvage protocol for children patients with refractory HLH.

Poster Location #18
SEVERE DENGUE (SD) COMPLICATED BY REACTIVE
HAEMOPHAGOCYTIC SYNDROME (HS) “FIVE YEARS” EXPERIENCE IN
A TERTIARY INTENSIVE CARE UNIT (ICU) IN MALAYSIA
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Purpose: Malaysia recorded 215 dengue deaths from 108,698 cases in 2014. Johor state had second highest mortality, with 25 deaths from 6,323 cases reported. We observed rising incidence of HS with possible higher mortality. This study aimed to determine incidence and significance of HS, clinical features, associating factors and mortality rate in SD. Methods: A retrospective cohort study of confirmed dengue cases in our 29-bedded adult (> 12 years old) ICU from 2010 to 2014. SD was defined using WHO 2009 classifications. HS was diagnosed clinically and scored using HLH-2004 diagnostic criteria (without molecular and immunological studies), proposed HLH diagnostic criteria 2009 (HLH 2009) and HScore. Univariable and multivariable logistic analyses were performed to identify associating factors. Results: Among 8802 ICU admissions, we had 198 (20.97%) dengue. After excluding 9 patients with missing medical records, we had 198 (70.97%) SD, 20.2% died. Severe leak, severe bleed, lethargy, hepatomegaly, APACHE, SAPS II and SOFA score, HS probability >= 0.7 were clinically consistent with HS (28 cases, mortality rate 39.3%). Only maximum ferritin (p-value<0.05) were significant by multivariable logistic analysis. HS probability >= 0.7 were clinically consistent with HS (28 cases, mortality rate 39.3%). Median age was 33.5 years (IQR:16). 64.3% female. Fourteen had bone marrow biopsy, 12 (86%) demonstrating haemophagocytic activities. Median duration of ICU stay was 3 days (IQR:5). Median duration from onset of dengue symptoms to death was 9 days (IQR:8). Eight out of 11 (72.2%) patients with maximum ferritin > 100,000 microgram/L died. Severe organ involvement, lethargy, diaphoresis, hepatomegaly, SOFA score, HLH 2009, continuous veno-venous haemofiltration, intubation, maximum AST, ALT, LDH and lactate were significant associating factors for SD mortality (p-value<0.05). None were significant by multivariable logistic analysis. Conclusion: HS was commonly associated with SD and had higher mortality.

Poster Location #19
PHENOTYPING OF LEUKOCYTE SUBSETS IN PATIENTS WITH
HEMOPHAGOCYTIC LYMPHOHISTOCYTOSIS ASSOCIATED WITH
HEMATOLOGICAL MALIGNANCIES
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Purpose: Hemophagocytic lymphohistiocytosis (HLH) involves uncontrolled activation of monocyte/macrophage system, with resulting hyperinflammatory syndrome, which in adults is often triggered by malignancy. The study was aimed to evaluate leucocyte immune profiles of patients with hematological malignancies and secondary HLH. Methods: Tissue samples from 42 adult patients (15 women, 27 men; aged 26-85 years) with malignancy-associated HLH (22 lymphoid, 20 myeloid tumors) were investigated by flow cytometry. The patients were evaluated and treated at the Hematology Center between 2009-2016, and their samples analyzed routinely at the Department of Clinical Pathology and Cytology, both at Karolinska University Hospital. Samples were obtained prior to (31 patients) or after established HLH-diagnosis (24 patients), with paired BM samples in 13 subjects. Neoplastic clones were excluded from analysis. Results were compared to a cohort of 35 adult patients without malignancy and HLH. Results: Non-neoplastic monocytes were increased in 40% patients with myeloid (M) and 31% subjects with lymphoid (L) tumors but a subset of patients had monocytopenia (10% M, 15% L). Aberrant lymphocyte marker expression could be found on non-malignant myeloid cells in all M-tumors. Lymphocyte subsets showed both quantitative and qualitative aberrations, with NK-cytopenia equally common before and after HLH diagnosis. Prior to HLH diagnosis, decrease in T-cells was found more often in M- than in L-tumors (60% vs. 25%), whereas the reverse was observed in established HLH. M-tumors were associated with increased CD4/CD8 ratio as compared to L-tumors, where the loss of T-cell markers was uniform. B-cell lymphopenia was prominent in the entire cohort, and progressed after HLH diagnosis (67% vs. 74%). Conclusion: Shifts in leucocyte subsets and phenotypical changes occurred in both M- and L-malignancies, however with different patterns and to different extents. It remains to be clarified if those reflect impact of the underlying malignancy on BM microenvironment or the HLH-associated phenomena.

Poster Location #20
CLINICAL CHARACTERISTICS AND PROGNOSTIC FACTORS OF
EPSTEIN-BARR VIRUS-ASSOCIATED HEMOPHAGOCYTIC
LYMPHOHISTIOCYTOSIS IN CHILDREN
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Objective: To investigate the clinical features and prognostic factors of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) in children. Methods: The clinical and laboratory data of children with EBV-HLH were retrospectively analyzed at a single institute in China from September 2015 to January 2017. Statistical analysis was performed using SPSS 20.0. Results: A total of 76 cases of EBV-HLH were identified, accounting for 55.07% of HLH (138 cases), of which 4 cases were diagnosed as primary HLH. There were 31 boys and 45 girls in total and the median age of onset was 42 months. The clinical features of EBV-HLH were similar to other HLH, which were accompanied by multiple organ dysfunction. Only the differences of alanine aminotransferase and fibrinogen were statistically significant between 4 cases of primary HLH and cases without abnormal genetic changes (P=0.048, 0.043). Compared with the state of remission, the median levels of serum ferritin (SF), serum EBV-DNA, soluble interleukin-2 receptor (sCD25), IFN-γ and IL-10 during disease activity status and outbreaks were significantly increased (P<0.001). With median overall survival of 172 days, the overall survival rates in 1, 3, 6 and 12 months were 96.5%, 88.5%, 80.7% and 76.6%. Multivariate analysis showed the independent risk factors of poor prognosis included absolute neutrophil count (ANC)<0.5x10⁹/L (HR=0.200, 95% CI:0.031-0.789, P=0.028), SF>2,000 ug/L (HR = 6.723, 95% CI:1.444-31.297, P=0.015), serum EBV-DNA>1x10⁵/ml (HR=10.582, 95% CI:1.424-74.745, P=0.011) and blood routine failed to recover in 2 weeks (HR=9.681, 95% CI:0.031-0.745, P=0.015). Serum EBV-DNA and cytokine are
sensitive indicators for monitoring HLH activity. Children with ANC<0.5x10⁹/L, SF>2,000 ug/L, serum EBV-DNA>1x10⁵/ml and blood routine failed to recover in 2 weeks are easier to continually uncontrolled or outbreak, and reactivate after complete remission or even cause death.

Poster Location #21

**HLH DIAGNOSTIC CRITERIA EVALUATED ON 83 PATIENTS FROM THE POLISH HLH IN ADULTS PALG REGISTRY**


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Purpose: The most widely used HLH-2004 criteria are frequently used for adults, but they were not validated in this group. Additionally, 2 out of these 8 criteria are rarely available (i.e. sCD25 concentration and NK-cell activity), which forces modification and inclusion of patients with 4 (instead of 5) criteria fulfilled when only 6 are tested and ferritin concentration exceeds 2,000 ng/ml. Recently a new alternative named HScore was proposed for adults. Diagnosis made above 169 out of 337 points and it does not require any specialized tests. Methods: Data of patients from the Polish Registry of HLH in Adults (under the auspices of Polish Acute Leukemia Group) were analyzed. The median age of 83 patients was 38 years (range 18-82), with a 60% male predominance. Patients were diagnosed based on HLH-2004 criteria (including the abovementioned modification) and a direct comparison of both diagnostic systems was made. Results: All patients presented with hyperferritinemia (median 11,400 ng/ml) and some degree of cytopenia (with 75% fulfilling the duocytopenia criterion). Patients were almost uniformly febrile (99%; 82/83) and had splenomegaly and/or hepatomegaly (93%; 77/83). In this group diagnosed with modified HLH-2004 criteria median HScore was 258. All patients were above threshold of 169 (range:169-337). It peaked in virus-associated HLH 286 (p<0.01; compared to the other triggering factors). Unexpectedly, hypertriglyceridemia (not hyperferritinemia) was responsible for the highest number of HScore points (50.2 vs 41.9; p=0.0001). Conclusion: HLH should always be included in the differential diagnosis of febrile patients with organomegaly and cytopenia, especially when hyperferritinemia occurs. The use of HScore may allow diagnosis of more patients in an earlier stage than HLH-2004 criteria, but should be used with caution because it may also give more false positive results. Previous results of the patient should be analyzed to avoid including normal results among the HScore criteria.

Poster Location #22

**H1N1 VIRUS KILLS BY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) AND IMMUNOSUPPRESSIVE THERAPY (IST) MAY PROTECT AGAINST IT IN NONE-HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS**

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Purpose: to study contribution of HLH to death after H1N1 infection in adults during an outbreak at a single institution and the impact of concurrent immunosuppressive therapy (IST) used in transplantation and other disorders on HLH. Methodology: Retrospective data of adults with H1N1 presented to ER/OPC/ICU of KFSHRC in Riyadh, SA during an outbreak between August 20, 2015 and February 23, 2016. IST group were on one of the following drugs: CSA, FK506, Mycophenolate or prednisone > 10mg/d or any combination. None-IST group was on no IST. H1N1 was tested via PCR of the nasopharyngeal swab or nasal or tracheal tube aspirates of the ventilated patients. Those with hematological manifestations were also followed prospectively. HLH was diagnosed based on HLH 2004 criteria. Results: 136 patients (15-92y; median 37y) tested positive for H1N1 and presented mainly with cough/fever/pneumonia. 25 patients were on IST: 10 allogeneic HSCT, 8 Solid organ transplants, and 7 had immune or allergic diseases (2
Poster Location #23

**MONOCYTOPEINIA IS PRESENT IN THE VAST MAJORITY OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) IN ADULTS AND SHOULD BE USED AS A SENSITIVE ADDITIONAL DIAGNOSTIC CRITERION AND ITS RESPONSE TO TREATMENT CARRIES POOR PROGNOSIS.**

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**Background:** HLH can cause life threatening cytopenia (s) and organ failure with very high mortality. Early diagnosis and management are essential for survival. The current HLH 2004 criteria are not optimal. Monocytopenia is not included in the diagnostic criteria although HLH is associated with activation, mobilization of and shift of monocytes to tissues where phagocytosis occurs. Hypothesis and Goal: Monocytopenia could be a sign of "shift" and active tissue hemophagocytosis and treatment of HLH should induce reversal of monocytopenia. Methodology: A retrospective analysis adults diagnosed by the hematologist consult service at our institution and presented with fever and cytopenia(s) between August 1st , 2015 and June 30th, 2016 and were diagnosed with HLH based on at least 5 of 8 HLH2004- criteria. Monocytopenia was defined as the lowest absolute Monocytic count <0.2/ul within 2 weeks of diagnosis. Results: A total of 29 patients (9 females) (16-82 Y) with diverse diagnoses. 27 (93%) were monocytopenic. 12 (41%) patients had active cytopenia. Discussion: Monocytopenia should be used as an additional diagnostic criterion and its response to treatment carries poor prognosis.

Poster Location #25

**UNMANIPULATED HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION USING REDUCED-INTENSITY CONDITIONING FOR PAEDIATRIC PATIENTS WITH FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A SINGLE CENTER STUDY**

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**Purpose:** Primary hemophagocytic lymphohistiocytosis (HLH), also known as familial HLH (FHLH), is a very rare autosomal recessive immune disorder, characterized by hypercytokinemia and excessive T-cell and macrophage activation. Although it can develop at any age, the onset of the disease typically occurs within the first months or years of life. Methods: We present three cases of FHLH diagnosed and treated in our center in the last twenty years. Results: The first two patients were siblings with their parents coming from the same small Greek island. The first case was a 2.5-year-old girl that presented with anemia, thrombocytopenia, hepatosplenomegaly and fever. The bone marrow aspiration revealed high hypocellularity. The disease progressed rapidly and the child died within a few days after the diagnosis, before receiving chemotherapy. The second case was a 2.5-month-old boy that presented with pancytopenia, hepatosplenomegaly and sepsis. He was treated according to the HLH-94 protocol and four months after achieving remission, he underwent bone marrow transplantation (BMT) with an HLA-matched unrelated donor. Eventually, one month after the BMT, the disease relapsed and the child died. The third case was a 5-month-old girl from Syria with her parents being second cousins. She presented with fever, lymphadenopathy, pancytopenia and hepatosplenomegaly. She received treatment according to the HLH-94 protocol, she achieved remission but unfortunately, a compatible donor could not be found. The disease relapsed during the continuation therapy and the child died. Conclusion: FHLH is a rare but potentially fatal disease, even after the BMT. It is characterized by a very rapid progression and thus more intensified treatment protocols are needed. Current treatment protocols achieve remission but recurrence can occur even during the continuation therapy. BMT prolongs event-free survival but does not increase the survival rate.

Poster Location #24

**FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A SINGLE-CENTER EXPERIENCE**

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**Purpose:** Reduced-intensity conditioning (RIC) based unmanipulated haploidentical (HID) hematopoietic stem cell transplantation (HSCT) in the treatment of paediatric familial hemophagocytic lymphohistiocytosis (FHLH) is rarely reported. We conducted a retrospective study of five patients including three of PRF1, two of XIAP. Four of five donors have heterozygous mutation. Conditioning regimen was fludarabine/ cyclophosphamide/ antithymocyte globulin with or without low-dose irradiation. Mobilised marrow and blood stem cells were used as the grafts. All five patients achieved engraftment. All patients have been alive and achieved complete remission (CR) without any serious regimen-related toxicity with a median of 12 months follow-up time (range, 6-18 months) after HSCT. Four of five patients have mixed chimerism ranging from 17% to 97% but remain free of disease. One patient Loss of donor chimerism to 1% and relapsed, and no improvement in donor chimerism was seen following DLI. He underwent stem cell boost, the donor chimerism increased to 99% and achieved CR2. Three patients developed acute graft-versus-host disease (GVHD) I – II°. One patients developed IV° GVHD after DLI. The HID HSCT with RIC regimen is an effective treatment for patients with FHLH. The safety of this regimen requires long-term follow-up and more prospective studies.
Purpose: Familial hemophagocytic lymphohistiocytosis (FHL) type 3 accounts for 30 to 40% of all FHL cases. More than 100 mutations in UNC13D gene throughout the 32 exons have been described to date and those affecting mRNA splicing are the most common molecular defect. The purpose of this study is to present the first case of FHL3 carrying intragenic duplication of UNC13D gene. Methods: A one-month old boy with positive family history of hemophagocytic lymphohistiocytosis had a defect in NK cell degranulation and absent Munc13-4 protein expression. Conventional sequencing of genomic DNA demonstrated a heterozygous deep intron mutation: c.118-308C>T derived from his father, while no mutation in UNC13D gene was identified in maternal allele. We therefore analyzed complementary DNA (cDNA) to identify an additional aberration in UNC13D gene. Results: PCR detected an insertion, approximately 500 base pairs in length, between exon 6 and 17 of UNC13D gene transcript. PCR amplification using a forward primer in exon 11 and a reverse primer in exon 9 produced an abnormal product in the mother and the patient. Sequencing of the product revealed that exon 12 was followed by exon 7. We amplified patient's genomic DNA using a forward primer in exon 11 and a reverse primer in exon 9 and obtained a 2.5kb long product. Direct sequencing of the product revealed that 5'-end of intron 12 was fused with 3'-end of exon 7 sharing 23bp homologous sequences within an AluSx element in intron 6 and an AluSz element in intron 12. Conclusion: The first FHL3 case with intragenic duplication of the UNC13D gene was reported. We propose that a screening for FHL3 with NK cell degranulation 4 protein expression assays are useful not to overlook these patients.

REAL-WORLD OUTCOMES OF TREATMENT FOR ADULT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: RETROSPECTIVE STUDY OF 148 PATIENTS OVER 8 YEARS IN A TERTIARY HOSPITAL IN CHINA

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is an increasingly recognized hyperinflammatory disorder in adults, with high morbidity and mortality. There is currently no standard treatment for adult HLH patients. HLH-94 and HLH-2004 protocols, which have been developed for pediatric HLH, are widely used in practice for adult HLH. However, the efficacy and toxicities of these protocols have not been strictly evaluated and the relevant reports are lacking. Our study aims to investigate the effects of different protocols on the clinical outcomes of adult HLH patients in a real-world setting. Methods: We performed a retrospective study in the largest tertiary hospital in Southwestern China over an 8-year period. We identified 148 adult patients fulfilling the HLH-04 diagnostic criteria, and analyzed etiology, clinical features, treatment regimens, and clinical outcomes. Results: The average age was 35 years (16-83 years) and 89 patients were male. Underlying diseases included malignancy (66.2%), infection (18.2%), autoimmune disease (1.4%), iatrogenic disease (0.7%), and etiopathic HLH (13.5%). Patients were treated with HLH-94 based regimen (25.7%), HLH-2004 based regimen (24.3%), and other therapies (physician choice, 50.0%) respectively. The HLH-94 regimen achieved better response rate (68.4%, P=0.001), as compared with HLH-2004 (33.3%) and other therapies (34.7%), and showed less toxicity. The median overall survival was 55.11 days. The HLH-94 treated group had better short-term survival profile, i.e. on day 30 (P=0.201) and day60 (P=0.008), compared with other two groups, but there was no benefit in long-term survival (P=0.201). In multivariate analyses, the Hodgkin lymphoma subtype of malignancies and the use of chemotherapy were associated with better outcomes. Conclusion: For adult HLH patients, the HLH-94 regimen might be associated with better treatment response, less toxicity, and higher short-term survival rate when compared with HLH-2004 and other therapies, but there is no long-term survival benefit. Continuing research effort remains necessary for optimizing treatment for adult HLH.
Purpose: Graft failure (GF) is a fetal and life-threatening complication in HLH with allo-HSCT, the standard treatment has not been established. Methods: we summarize two challenging case of HLH who experienced GF following first HSCT and successfully engrafted following salvage secondary HSCT. Results: One case is a 6-year-old boy diagnosed with EBV-HLH, treated with the haploidentical HSCT following the conditioning regimen consisted of VP-16/Bu/Flud/ATG. The patient presented the clinical manifestation resembling those of immune encephalitis on the day 3 after the first HSCT. The methylprednisolone pulse therapy was administered immediately and the clinical symptoms improved. But Primary GF occurred and was diagnosed on day 24. The EBV-DNA load increased, subsequently the patient developed HLH. Fortunately, the patient underwent the secondary unrelated allo-HSCT following the conditioning regimen consisting of VP-16/Ara-C/Bu/CTX/ATG, GVHD prophylaxis consisting of FK506 and MMF. Consequently, the patient achieved neutrophil engraftment on day 14 and 100% donor chimerism after the second HSCT. During the clinical course of the second HSCT, the main complication was poor platelet graft function, and platelet engraftment on day 84. Until now, the patient was disease-free for 26 months. The other case is a 3-year-old boy diagnosed with primary HLH, treated with unrelated allo-HSCT following the conditioning regimen consisted of VP-16/Bu/Flud/ATG. The patient presented the clinical manifestation resembling those of acute liver failure on the day 12 after the first HSCT. The methylprednisolone pulse therapy and plasma exchange were administered immediately, and the clinical symptoms improved. But Primary GF occurred and was diagnosed on day 21. Therefore, the patient underwent the secondary unrelated allo-HSCT following the conditioning regimen consisting of VP-16/Mel/Flud/ATG, GVHD prophylaxis consisting of FK506 and MMF. Consequently, the patient achieved neutrophil engraftment on day 12, platelet engraftment on day 10 and 100% donor chimerism after the second HSCT. During the clinical course of the second HSCT...
poor prognosis. CNS-HLH had a poor prognosis and the intrathecal injection is an effective way to treat it.

**Poster Location #32**

**CLINICAL FEATURES OF 52 PATIENTS WITH HLH ACCOMPANIED WITH GASTROINTESTINAL BLEEDING**

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Objective: To explore the clinical features of patients with hemophagocytic lymphohistiocytosis accompanied with gastrointestinal bleeding. Methods: The clinical data of 52 patients diagnosed HLH accompanied with gastrointestinal bleeding in our hospital from January 2015 to March 2017 were analyzed retrospectively. Results: For the 52 HLH patients with digestive tract hemorrhage, 1-month survival rate was 74.7%, 3-month survival rate was 53.6%, 6-month survival rate was 32.9%, and 12-month survival rate was 23.3%. Thrombocytopenia (P=0.036), other sites of bleeding (P=0.030) and Ealleogenic hematopoietic stem cell transplantation (P=0.026) had significant impacts on patients. Conclusion: HLH accompanied with gastrointestinal bleeding was considered a threaten of life, which indicate poor prognosis of patients. Thrombocytopenia and "other sites of bleeding" shorten the survive time of patients, "allogeneic" hematopoietic stem cell transplantation improve the survive time of patients.

**Poster Location #33**

**CLINICAL FEATURES OF PERINATAL STAGE RELATED-HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS**

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a rare and severe clinical syndrome characterized by a dysregulated hyperinflammatory immune response. Hemophagocytic lymphohistiocytosis manifesting during pregnancy/postpartum continues to be a rare entity. From the clinical observation of case in our center, we found out that many the cases of the pregnancy/postpartum related HLH was in the perinatal stage. This study was to analyze the clinical features of perinatal stage related-HLH. Methods: A analysis of 11 patients with HLH who were in the perinatal stage during January 2011 and October 2016 was conducted. Obstetric materials, clinical features, associated disease/factors and therapeutic outcomes were analyzed. Perinatal stage is the period between 28th week of pregnancy to one week after delivery. Results: Among the 11 patients, nine of them were primipara. As for the onset time of HLH, five were during pregnancy and six were during postpartum. Six of these patients was complicated with other associated disease/factors, and infection was the commonest (5/11), while the other five had an unclear etiology. Four patients who were in pregnancy were treated with HLH/94/04 protocols after the cessation of pregnancy, while the six who were in postpartum were also treated with HLH/94/04. The overall response rate was 63.6% (9/11). Two patients in postpartum died of HLH. Conclusions: Perinatal stage HLH is commonly observed in the pregnancy/postpartum HLH. As for the possibility of immune disorders when maternal is in perinatal stage, the pregnancy/postpartum itself can lead to the onset of HLH. Infection is still the commonest associated factors, which may be related to the imbalance of Th1/Th2. HLH/94/04 protocols after the cessation of pregnancy may be effective, but the cessation of pregnancy itself may not be enough for the perinatal stage related-HLH. The perinatal stage related-HLH still has a better outcome than the other subtype of secondary-HLH.

**Poster Location #34**

**MULTIVARIATE ANALYSIS OF PROGNOSIS FOR PATIENTS WITH NATURAL KILLER/T CELL LYMPHOMA-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS**

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Objective: A major cause of Hemophagocytic lymphohistiocytosis (HLH) is malignant neoplasms of the blood system, among which NK/T cell lymphoma is one of the most common risk factor. Patients with NK/T cell lymphoma hemophagocytic lymphohistiocytosis (NK/T-LAHs) have a worse prognosis and higher mortality. We aimed to explore the factors that affect the prognosis of NK/T-LAHs. Methods: Clinical data of 42 patients with NK/T-LAHs diagnosed by Beijing Friendship Hospital from June 2008 to June 2016 were analyzed retrospectively. Results: The survival time was counted until August 1, 2016. For the 42 NK/T-LAHs patients, 1-month survival rate was 48.9%, 2-month survival rate was 36.7%, 3-month survival rate was 26.8%, 6-month survival rate was 23.0%, and 12-month survival rate was 15.4%. NK/T-LAHs patients who underwent allogeneic hematopoietic stem cell transplantation (Allo-HSCT) (P = 0.000), exhibited peripheral blood Epstein-Barr virus (EBV)-positivity (P = 0.004), and achieved overall response (OR) remission after initial induction therapy (P = 0.007) had statistical significance. Conclusion: NK/T-LAHs is a disease of poor prognosis and high mortality. NK/T-LAHs patients who achieved OR remission after the initial induction therapy had better prognosis than non-remission patients and Allo-HSCT was an effective way to prolong the survival of NK/T-LAHs patients. However, EBV positivity in peripheral blood was a poor prognostic factor in NK/T-LAHs patients.

**Poster Location #35**

**OUTCOME OF CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS WITH HLH-2004 PROTOCOL IN JAPAN**

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Purpose: Prognosis of hemophagocytic lymphohistiocytosis (HLH) in children has varied from spontaneous regression to fatal. Protocols with intensive chemotherapeutic and immune-therapy, such as HLH-94 or HLH-2004, have improved the outcome of HLH, with heterogeneity among different subtypes. In western countries, most children with HLH have the primary form (mainly familial HLH,
FHL), whereas in Eastern Asia including Japan, the secondary form (mainly EBV-associated HLH) is more prevalent. Therefore, it may be useful to establish the next strategy by the evaluation of outcomes among different HLH subtypes in Japan. Methods: Ninety patients with HLH of less than 18 years old were registered to the HLH-2004 protocol in Japan from February 2007 to November 2011. Out of 82 eligible patients, nine patients were excluded from the efficacy analyses: three long-term outlook, one withdrawal before the trial treatment, and five protocol violation. Forty-one (56.2%), 9 (12.3%), and 23 (31.5%) patients had EBV-HLH, FHL, and HLH of unknown etiology, respectively. Patients with resistant or relapsed disease after the treatment with HLH-2004 and those with FHL received hematopoietic stem cell transplantation (HSCT). Results: The 5-year overall survival (OS) rate was 73.9% (95% CI, 62.2%-85.5%). Induction rate after initial therapy was 58.9%. OS rates significantly differed among HLH subtypes: 85.3%, 66.7%, and 56.2% for EBV-HLH, FHL, and unknown etiology, respectively. Other clinical features including central nervous system involvement and laboratory findings at onset were not associated with the outcome. Of 17 patients undergoing HSCT, the 5-year OS of patients with (n =6) and without remission before HSCT (n=11) were 83.3% and 54.5%, respectively (p = 0.273). Conclusion: Outcome of children with HLH, who were treated with the same protocol, differs among different subtypes. Therefore, the strategy for different subtypes including FHL or EBV-HLH should be established as a new study.

Poster Location #36

COMPREHENSIVE STRATEGY TO ESTABLISH THE CLINICAL DIAGNOSIS FOR PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a heterogeneous disorder. Defects in at least 14 genes (AP3B1, BLOC1S6, CD27, ITK, LYST, MAGT1, PRF1, RAB27A, SH2D1A, SLC7A7, STX11, STXBP2, UNC13D (MUNC13-4), XIAP (BIRC4)) have been associated with familial HLH and associated conditions. A timely and cost effective diagnostic strategy is needed to support a more personalized treatment plan to achieve a better outcome. b. Methods: We developed a comprehensive testing strategy including a 14 gene Next Generation Sequencing (NGS) testing panel and reflex to long PCR and exon centric copy number variation (CNV) analysis, and complemented with epigenetic and protein expression analysis to evaluate a comprehensive testing algorithm for the diagnosis of HLH and associated disorders. c. Results: By reviewing the testing results in the first 1460 clinically suspected HLH patients, we found 125 patients to have single or bi-allelic mutations in HLH related genes, 204 have variants with unknown clinical significance, 69 patients carried variants in more than two genes. In addition, gross deletions and duplications have been identified in 10 patients in seven (SH2D1A, XIAP, MAGT1, RAB27A, STXBP2, LYST, SLC7A7) HLH genes. Interestingly, one female patient with one nonsense mutation in BIRC4, also affected by X inactivation abnormalities. For the non-genetic studies, perforin expression analyses detect 78% of patients and carriers with PRF1 variants. XIAP and SAP protein analyses by flow cytometry found 87% and 95% of patients with likely pathogenic variants in SH2D1A and BIRC4 genes respectively. d. Conclusion: To achieve a definitive diagnosis in patients with HLH, a comprehensive approach is desired which includes sequencing, CNV and epigenetic studies as well as immunological work up. This comprehensive testing strategy provide cost effective testing platforms with reasonable clinical sensitivity for patients with HLH.

Poster Location #37

SALVAGE TREATMENT OF PEDIATRIC REFRACTORY EPSTEIN-BARR VIRUS-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS WITH L-DEP PROTOCOL

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Background: Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) is more prevalent in Asian population. Previous studies have shown that more than 30 % patients with EBV-HLH do not respond to standard therapy. In this study, efficacy and safety of L-DEP (PEG-asparagase-doxorubicin-etoposide-methylprednisolone) protocol as a salvage therapy for pediatric refractory EBV-HLH was evaluated. Methods: From January to December of 2016, 18 patients with refractory EBV-HLH were treated with L-DEP protocol at Beijing Children’s Hospital. Treatment efficacy and adverse events were evaluated at 2 and 4 weeks post L-DEP treatment. Results: Over all response rate (ORR) was 72.2% (13/18), among which there were 38.9%(7/18) complete response (CR) rate and 33.3% (6/18) partial response (PR) rate. Two patients had familial HLH (FHL) triggered by EBV. The patient with FHL-2 achieved CR and the other one with FHL-3 had no treatment response and died. The All 6 patients with chronic active EBV infection-associated HLH had treatment response with 3 CR. Five patients without treatment response died 10 to 20 days post L-DEP protocol. Ten of 13 patients with treatment response underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT), among which 6 were alive. Compared with the level of serum EBV-DNA before salvage treatment (median 2.7x104 copies/mL), that levels at 2 weeks (median 1.46x103 copies/mL) and 4 weeks (median 7.27 x102 copies/mL) after receiving the L-DEP regimen were significantly lower (P = 0.028 all). All patients had lII degree bone marrow suppression and one patient had reversible pancreatitis due to PEG-asparagase. Conclusions: This study suggests that L-DEP is a safe and effective salvage therapy prior to allo-HSCT for refractory pediatric EBV-HLH. Keywords: PEG-asparagase, liposomal doxorubicin, Epstein-Barr virus, Hemophagocytic lymphohistiocytosis, Pediatric

Poster Location #38

HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A DECADE OF EXPERIENCE IN A PAEDIATRIC CENTRE IN SOUTH-EAST ASIA

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Purpose: Haemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of hyperinflammation. If recognized early, it can be effectively controlled to allow definitive diagnosis and therapy according to underlying aetiology. We aim to share a decade of clinical experience in a paediatric center in South-East Asia (SEA). Methods: We retrospectively reviewed patients who met the diagnostic
criteria of HLH-2004 from Jun 2005 to Dec 2016. Results: Eighteen patients with a diagnosis of HLH were screened. Of these, 9 fulfilled HLH-2004 diagnostic criteria. Mean age at diagnosis was 39 (4 to 117) months. Fever, splenomegaly and hyperferritinaemia were consistently found in all 9 patients. Majority presented with cytopenia (7 of 9) and haemophagocytosis (8 of 9). Hypertriglyceridaemia and/or hypofibrinogenemia were seen in a third of the patients. The underlying etiologies of HLH included suspected/confirmed primary HLH (n=7) and cancers (n=2). Majority (7 of 9 patients) were tested positive for EBV infections. Of 7 patients with suspected primary HLH and had research tests done in Karolinska Institute, Sweden; only 2 patients were found to have an associated mutations (UNC13D and XIAP). Majority (8 of 9) of patients responded to HLH 1994/2004 based therapy. Haematopoietic stem cell transplants were performed in 4 with confirmed/ suspected primary HLH. At a median follow-up of 3.3 (range, 0.2 to 11.8) years; 7 of 9 patients are alive and cured/well. Of the 2 patients who died, 1 died progressive malignant disease and another of transplant complication. Conclusion: Majority of patients in our small series survived HLH. The high survival rate is likely related in part to early treatment. A significant number of patients with clinically suspected primary HLH lack a genetic diagnosis when screened for associated mutations. There is a possibility that novel mutations specific to South-East Asians remains to be discovered.
Background: Mutually exclusive somatic mutations in mitogen-activated protein kinase (MAPK) pathway genes have been identified in about 75% of patients with Langerhans cell histiocytosis (LCH). In western countries, BRAF V600E mutation accounts for about 50%, followed by MAP2K1 mutations for about 25%. Previous reports from Japan, using relatively low sensitivity methods, showed the frequencies of BRAF V600E mutation was varied (21-59%).

Methods: Forty four Japanese patients with LCH were tested for BRAF V600E mutation in biopsied lesional tissues by using allele-specific real-time polymerase chain reaction-based assay kit (Entrogen, Woodkand Hills, CA). The detection limit of this assay kit is 1%. Seven of BRAF V600E negative patients were tested for MAPK pathway genes by next-generation sequencing (NGS). Results: Of 44 patients, 40 were children and 4 were adults. The median age at diagnosis was 3 years-old (range: 4 months - 66 years). Eighteen patients had single-system disease and twenty-six patients had multisystem disease. Seventeen cases (38.6%) harbored BRAF V600E mutation and all of these were children. Among 7 of BRAF V600E mutation negative patients, NGS revealed that 5 (71.4%) were positive for MAP2K1 mutation and one of these was also positive for ERBB3 mutation. Conclusions: Though the number of cases are small, in Japanese LCH patients, the frequency of BRAF V600E mutation might be low compared to Western countries, while that of MAP2K1 mutations might be high.

Purpose: Langerhans cell histiocytosis (LCH) is characterized by accumulation of immune cells in granulomas resulting in tissue destruction. The disease may be mild affecting a single system (most commonly bone or skin) or severe disseminated affecting at least two systems (multi-system), and it has been associated with genetic and immunological abnormalities. Since we often observed low lymphocyte counts in our LCH patients we decided to evaluate this in a systematic way and to investigate potential links to the disease pathogenesis. Methods: Lymphocyte and monocyte counts at LCH diagnosis, at periods with and without treatment and correlation of the findings to disease category, age and organ involvement. Values in healthy children and adults served as controls. Results: Immunophenotyping of blood cells in 19 patients showed lymphocyte counts below the lowest age-specific reference limit for 8/19 patients and close to the lowest limit for the rest. Decreased B-cell and NK-cell counts, as well as monocyte counts, were mainly observed in patients on treatment, but T-cell counts were significantly lower compared to controls regardless of treatment. Particularly affected of these abnormalities were patients with multi-system disease. To increase our study cohort, we reviewed the medical records of the LCH patients admitted in Astrid Lindgren Children's Hospital over a 15-year period. 7/40 treatment-naive patients at diagnosis were found to be lymphopenic and 4/7 had multi-system disease. 15/40 patients were lymphopenic at least once during periods without treatment and, most importantly, almost all patients had frequently lymphocyte counts close to the lowest age-specific reference limit even at periods without treatment.

Conclusion: We observed high prevalence of lymphopenia in LCH patients, associated with earlier disease onset and more severe disease course. This finding is likely related to LCH pathogenesis and may be a piece in the puzzle that may help improve understanding this intriguing disease.
POSTER PRESENTATIONS - BASIC LCH

Poster Location #42
THE ROLE OF REGULATORY T CELLS IN THE IMMUNE REGULATION OF LANGERHANS CELL HISTIOCYTOSIS

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Purpose: Langerhans cell histiocytosis (LCH) is characterised by lesions containing CD1a+ and/or CD207+ dendritic cells as well as an inflammatory infiltrate including T cells. New treatment options are required for patients who remain unresponsive to current standards. FOXP3+ regulatory T cells (Tregs) are present in high numbers in LCH lesions (suggestive of an immune-suppressive environment), but the frequency and importance of other T cells with regulatory functions, such as gamma delta T cells, mucosal associated invariant T cells and type I natural killer T cells is for the most part not established. This project represents the most comprehensive analysis of unconventional T cells in patients with LCH. b. Methods: We have analysed LCH tissue samples from blood and lesions stored in the Fiona Elsey Cancer Research Institute’s Tissue Bank. Cells were characterized using 13-colour flow cytometry, and in vitro assays of T cell function. Results: We report that the frequency and function of unconventional T cells are altered in patients with LCH compared to healthy donors. Conclusion: These findings suggest that immune regulation is defective in LCH and that changes in these T cell subsets may be important factors in LCH onset and progression. Targeting these factors could therefore be a promising avenue of investigation in the development of new immune based therapies.

Poster Location #43
CLINICAL PRESENTATION AND OUTCOMES OF LANGERHANS CELL HISTIOCYTOSIS (LCH) IN YANGON CHILDREN HOSPITAL

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Purpose: Langerhans cell histiocytosis (LCH) is a rare disease, usually occurs in early age with varying clinical presentations. The aim of this study is to analyse the nature of the disease and outcomes of the treatment in our setting. Methods: This was a retrospective study from 2012 to 2016 based on the medical records and imaging records of patients at the Hemato-Oncology Unit of Yangon Children Hospital. Results: Twenty-nine patients were enrolled. There were 2 cases in 2012, 3 cases in 2013, 9 cases in 2014, 4 cases in 2015 and 11 cases in 2016. Male to female ratio was 1.2. Almost all were treated with LCH III treatment. According to their presentations, 4 (13.7%) had single system involvement, 9 (31%) had multi-system involvement and 16 (55.1%) had disease to the liver, spleen and haematopoietic system. Skin involvement, lytic lesions of the skull and hepatosplenomegaly occurred in almost all cases. Only 3 cases involved lymphadenopathy. 7 (24.1%) patients defaulted, 1 (3.4%) abandoned treatment, 11 (37.9%) were still on treatment, 7 (24.1%) were on follow up and 4 (13.7%), expired: 1 was due to drug toxicity, others - due to disease progression. There was only one case of LCH associated with diabetes insipidus (DI): the child had full recovery and was on regular follow up. In 7 follow up cases, 1 case relapse and treated with relapse regimen. Patients on treatment received PO prednisolone, PO 6-mercaptopurine, and IV vinblastine. Conclusions: Although LCH is a rare disease, we admitted 29 patients in 5 years. They presented with various symptoms. Almost all cases involved the bone, skin and extramedullary haemopoietic system. Even though there were defaults due to transportation issues, achieving remission is possible.

Poster Location #44
PCR-BASED DETECTION OF LANGERHANS CELL HISTIOCYTOSIS (LCH) MOLECULAR SIGNAL IN CELL-FREE DNA FROM PATIENT CEREBROSPINAL FLUIDS (CSF)

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Purpose: Langerhans cell histiocytosis (LCH) is an orphan disease that predominantly affects children. LCH is difficult to diagnose due to non-specific presenting symptoms. However, early diagnosis is critical for effective treatment, particularly if disease involves the central nervous system (CNS). The CSF was centrifuged and pelleted cells were used for whole exome sequencing (WES) and cfDNA was isolated from the supernatant (2 mL) using a modified protocol and the QIAmp Circulating Nucleic Acid kit (Qiagen). Exon 15 of BRAF containing the c.1799T>A mutational was amplified using isolated cfDNA and a modified PCR protocol. Purified cfDNA products were Sanger sequenced. Results: cfDNA was successfully isolated from human CSF (0.15 and 0.16 ng/μL for samples 1 and 2, respectively). Our modified PCR protocol successfully identified the c.1799T>A mutation in both samples. WES did not detect the mutation in the pelleted cells despite coverage depth >1100 reads. Conclusion: Pure cfDNA can be successfully isolated from small volumes of CSF obtained from children with LCH. A modified PCR protocol successfully detected the c.1799T>A mutation in both CSF cfDNA samples while standard WES of the cellular material did not. Our protocol represents a potential liquid biopsy for the diagnosis of LCH affecting the CNS.

NOTES
Histiocytosis (LCH) cells which has led to investigation of indomethacin therapy can be effective treatment in patients with localized disease. 

**VACCINE ASSOCIATED SOFT TISSUE INFILTRATE CAN PREDISPOSE MULTI-SYSTEM LANGERHANS CELL HISTIOCYTOSIS**

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Ethiology and ways of dissemination of Langerhans cell histiocytosis (LCH) still remains obscure. Some cases demonstrate both immunologic and neoplastic theory. Purpose: The study of multy-system LCH (MS-LCH) developed after unsuccessful treatment of purified vaccine associated infiltrate. Methods: 2 cases were evaluated. Repeat imaging including magnet resonance tomography and computer tomography was performed. Biopsy with immunohistochemistry tests and direct DNA sequencing with real time PCR were used. Results: We observed 2 cases of MS-LCH treated in our clinic initially as vaccine associated soft tissue infiltrates. Both kids were male of their second year of age. Both had several months long history of surgical treatment of soft tissue infiltrate with purification in hip, which occurred in place of vaccination. Performed biopsy revealed LCH. BRAF mutations were found in both cases. Extensive search for another lesions more typical for LCH was performed but nothing was found. Infiltrates were removed and after course of antibiotics healed up completely. No steroids or chemotherapy treatment was performed. After 6 months of follow up we observed multy-focal bone disease in 1 case. Solitary pituitary stalk thickening with central diabetes insipidus occurred after 9 months of follow up. Both kids were examined. No active lesion in the place of primary infiltrate was found. Systemic chemotherapy with vinblastine and prednisone was successful in both cases. Conclusions: These cases demonstrate the possibility of development BRAF positive MS-LCH after long time treatment of solitary soft tissue lesion associated primary with vaccination.

**LENALIDOMIDE-DEXAMETHASONE: A PROMising THERAPy FOR LANGERHANS CELL HISTIOCYTOSIS WITHOUT RISK ORGAN INVOLVEMENT**

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Background: Treatment of refractory/ relapse Langerhans Cell Histiocytosis (LCH) is still unsatisfactory. Currently recommended cladribine-cytarabine protocol is quite toxic. Hence lenalidomide-dexmethasone combination, if effective, may be a cheap and well tolerable option for the treatment. Case History: Two and half years-old girl presented with scaly papular skin lesions over scalp, polyuria/polydipsia for 3 months. Investigations revealed diagnosis of multisystem LCH (skin and multifocal bone) with no-risk organ involvement with diabetes insipidus. LCH-3 protocol was administered to her. At 6 weeks assessment skin lesions resolved. At the end of treatment, bone scan was normal. She had mal-occlusion of teeth. She was kept on follow up. Two years later, malocclusion of teeth was still persistent. PET CT revealed metabolically active (SUV 4.18) lytic lesion in the left mandibular ramus with soft tissue involvement.

**LANGERHANS CELL HISTIOCYTOSIS AND NK/T LYMPHOMA AFTER T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA**

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To report the disease evolution and treatment of an 5-year-old boy achieved complete remission of T-cell ALL for 18 months and skin rashes pathology ascertained LCH and T-cell lymphoma. An 5-year-old man due to fever, hepatomegaly and splenomegaly was diagnosed with T-cell acute lymphoblastic leukemia (T-ALL). He was treated with induction chemotherapy using the China CCLG group protocol and achieved complete remission. Eighteen months after the diagnosis of T-ALL, he developed a severe multorgan histiocytosis that is clinically suggestive of LCH. We prescribed the secondline treatment for LCH (cytarabine and 2-chlorodeoxyadenosine), he achieved partial remission. The rashes disappeared for 2 weeks and recurred. T lymphoma was found by review of skin pathology, and NK / T cells were done by bone marrow of flow cytometry.2 courses of chemotherapy of CHOP-E were used, but the disease was progressively exacerbated with more rashes, hepatomegaly, splenomegaly and pancytopenia. LCH with T lymphoma was considered by third skin biopsy and immunohistochemistry. Rashes, peripheral blood, bone marrow and cerebrospinal fluid flow cytometry were all provided evidence for NK-T lymphoma. The secondline treatment for LCH (cytarabine and 2-chlorodeoxyadenosine) was applied again, the condition was transitional improved for 2months with rashes disappeared, liver and spleen shrinked, and normal blood. Hepatomegaly, splenomegaly and pancytopenia were recurred and hematopoietic stem cell transplantation was put on the agenda. Only few literatures of T-ALL with LCH were reported, and so was LCH with lymphoma. Maybe the case of T-ALL with LCH and NK / T lymphoma was firstly reported. The disease evolution and effect of conventional chemotherapy application were described, and bone marrow hematopoietic stem cell transplantation had been conducted. The further follow-up for final prognosis would be done.
component resulting in floating teeth. The right maxillary sinus was expanded by the soft tissue, resulting in thinning and erosions of the sinus walls. The high parietal lytic lesion was not taking uptake. She received 12 cycles of lenalidomide (2.5 mg for <15 kg and 5 mg for >15 kg; for 3 weeks every 4 weeks cycles) and dexamethasone (0.8 mg/kg every weekly). After completion of 6 cycles, PET-CT scan revealed reduction in soft tissue and SUV (3.05). After 12 cycles, PET-CT showed reduction in size of metabolically active soft tissue in the right maxillary sinus region with increase in sclerosis in the right maxilla. Ill-defined lytic area in body of mandible on left side appeared less prominent. In view of unknown long term safety of lenalidomide in children, we decided to continue with pulse prednisolone 40 mg/m² x 5 days every 3 weeks till complete remission. Conclusion: Dexamethasone lenalidomide combination is a cheap, well-tolerated and effective regimen at least for non-risk organ disease.

**Poster Location #49**

**HEMOPHAGOCYTIC LYMPHOPHILOSIOTIC ASSOCIATED WITH VISCERAL LEISHMANIASIS AND EPSTEIN BARR VIRUS-REACTIVATION IN A SCANDINAVIAN MALE WITHOUT RECENT TRAVEL HISTORY: A POTENTIAL ADVERSE EVENT TO ANTI-TUMOR NECROSIS FACTOR-ALPHA THERAPY**

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**Purpose:** To describe the occurrence of hemophagocytic lymphophistiocytosis (HLH) associated with visceral leishmaniasis (VL) in a Scandinavian patient with no recent travel history, following treatment with the Tumor Necrosis Factor-alpha inhibitor Infliximab. And to review data on the occurrence of VL in a non-endemic country. Methods: Case report and review of existing data. Results: A 68 year-old Danish male suffering from sarcoidosis received infliximab due to disease aggravation. At the time of treatment he had near-normal hematological parameters. Twenty-six days after infliximab initiation he was hospitalized due to fever. On admission he was pancytopenic and had elevated triglyceride and ferritin levels (137,000 μg/l). HLH was suspected and treatment with dexamethasone, immunoglobulin, and antibiotics was initiated. The patient improved on treatment, however, 4 days later he suffered a retroperitoneal bleed and eventually succumbed to this complication. A bone marrow examination verified ongoing hemophagocytosis. Furthermore, parasites resembling Leishmania amastigotes were visualized. VL was confirmed by PCR (Leishmania donovani complex). Leishmania serology by immunofluorescence antibody testing was borderline positive. Additionally, the patient had active Epstein Barr viremia (initially 7,000 and max 127,000 copies/ml), but was found IgM negative with serology. The patient had never presented symptoms of VL and VL is not endemic in Scandinavia. He had no travel history from highly VL endemic regions but had visited Italy, Spain, and Greece, 6, 10, and 14 years prior to admission. Conclusion: HLH may be induced iatrogenically by immunomodulatory drugs. In the presented case, Infliximab is believed to have activated a dormant subclinical VL infection in a patient with no recent travel history. As VL-associated HLH often responds favourably to Ambisome treatment, screening for VL, preferably by PCR, should be carefully considered in all HLH patients. Testing for VL may be relevant in spite of identification of alternative HLH-triggers as Epstein Barr Virus infection.

**Poster Location #50**

**CLINICAL RESEARCH ON EFICACY COMPARISON BETWEEN CHFU-LCH 2006 PROTOCOL AND 2012 PROTOCOL FOR CHILDHOOD LANGERHANS CELL HISTIOCYTOSIS**

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**Purpose:** To compare the efficacy and adverse reaction of CHFU-LCH 2006 protocol (based on LCH-III protocol) and its updated version CHFU-LCH 2012 protocol. Methods: Children diagnosed between January, 2006 and November, 2012 were managed under 2006 protocol. Children diagnosed later between December, 2012 and December, 2015, received 2012 protocol (removal of melphotrexate and treatment for SS-LCH extended to 12 months). Results: There were 96 patients enrolled in 2006 protocol and 86 patients enrolled in 2012 protocol. Among patients in the MS-LCH subgroup, there were 4 and 5 cases respectively in 2006 and 2012 group quitted the protocol and was transferred to other rescue protocols. There were 5 and 4 cases dead, respectively. There were totally 93 children categorized as MS-LCH in our study. The rate of EFS and OS among children with risk organ (RO) involvement children were also significantly lower than those without RO. The EFS rate was significantly lower in children who did not respond to the initial 6-week therapy than those who responded. The 5-year EFS for SS-LCH subgroup was (84.8±5.3)% and (86.7±6.1)% for the 2006 and 2012 group, the 5-year projected OS was 100% in both groups. The 5-year EFS for MS-LCH subgroup was (50.0±7.1)% and (53.2±10.0)% for the 2006 and 2012 group, the 5-year OS was (90.0±4.1)% and (90.6±4.5)% for the 2006 and 2012 group. The Grade 3/4 chemotherapy related adverse reactions occurred in 50.0% of patients with MS-LCH in the 2006 group, which was significantly higher than that in the 2012 group. Conclusion: The 2012 protocol non-inferior to 2006 protocol with less adverse reaction to chemotherapy. However, the EFS of MS-LCH is still not satisfactory in both groups, the treatment strategy may be further modified to improve prognosis. Risk organs involvement and response to 6 weeks initial chemotherapy are the most important prognostic factors for MS-LCH.

**Poster Location #51**

**OUTCOME OF CHILDREN WITH LANGERHANS CELL HISTIOCYTOSIS AND SINGLE-SYSTEM INVOLVEMENT: A RETROSPECTIVE STUDY AT A SINGLE CENTER**

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**Purpose** To improve our understanding of patients with single-system LCH (SS-LCH), we did a descriptive review of the clinical patterns and outcome of children with SS-LCH treated at Shanghai Children's Medical Center. Methods: From 2010 to 2014, 60 evaluable newly diagnosed patients with histopathology-confirmed SS-LCH were enrolled. Systemic chemotherapy was given to all patients. Two protocols were used in our institution during the period of this study: DAL HX-83 study based protocol or LCH-II study based protocol. Treatment decision was according to the physician's own experience. Results Of the 60 patients (37 boys and 23 girls), the median age was 3.9 years (range, 0.3 to 15.3 years). Bone was the most frequently affected organ (56/60, 93.3%). Of the 56 patients suffered from SS-LCH, 46 (82.1%) responded to initial treatment. The 3-year event free survival (EFS) and 3-year overall survival (OS) for all cases were 100% and (79.1±5.4)%, respectively. The 3-year EFS of SS-LCH patients with unifocal disease at diagnosis was significantly higher than that of those with multifocal disease (54.7±3.6% vs. 51.3±11.1%, p=0.000). When stratified by initial number of sites involved (unifocal or multifocal), the differences in 3-year EFS
were not statistically significant between the DAL HX-83 cohort and the LCH-II cohort (SS-LCH, unifocal group: 100% vs. 92.6±5.0%, respectively, P=0.362; SS-LCH, multifocal group: 42.2±12.7% vs. 80±17.9%, respectively, P=0.144). Seven patients experienced 1 or 2 reactivations with first activation occurring 9 months after the diagnosis. All these 7 patients with disease reactivation were initially bone involvement. Only the number of initial sites was associated with an increased risk of reactivation. Conclusions To better care patients with SS-LCH, our next step is to optimize disease stratification and treatment modalities based on the current published evidence.

Poster Location #52
CLINICAL FEATURES AND THERAPEUTIC RESULTS IN A 35-YEAR COHORT OF CHILDREN AND ADULTS WITH LANGERHANS CELL HISTIOCYTOSIS MANAGED AT SINGLE INSTITUTION

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Purpose: The aim of this study was to analyze clinical features and therapeutic results in children and adults with Langerhans cell histiocytosis (LCH) according to different disease classifications. Methods: One-hundred-twenty-two patients (median age: 26.4 years) with LCH were considered. Fifty-one patients (19 children and 32 adults) were treated according to the same protocols (AIEOP 83, AIEOP-IX 89, LCH-I, LCH-II) from 1981 to 2000; 54 adults and 17 children were treated according to the GIMEMA LCH 2001 guidelines and to the LCH-III and LCH IV studies, respectively, from 2001 to 2015. Patients were divided according to: a) the Histiocyte Society criteria (two groups: single system, SS-LCH, and multi-sistem,MS-LCH); b) a disease score utilized in the GIMEMA LCH 2001 guidelines: Group 1 (unifocal SS), Group 2 (multifocal MS), Group 3 (MS without bone involvement), Group 4 (MS with bone involvement); c) Group 5 (honey combing pulmonary involvement). Results: A single-site involvement was recorded in the majority of children (58%), while a multi-system involvement was more frequent in adults (54%). Children with SS-LCH had a significantly better response than those with MS-LCH (95% vs 67%, P=0.023), while there was no difference between subgroups when the GIMEMA LCH 2001 guidelines score was utilized. Group 1 and Group 4 adults of have a significantly higher response rate than those of other groups (72% vs 38%, P=0.001), but no difference was observed between patients with SS-LCH and those with MS-LCH. The overall progression-free survival (PFS) at 200 months was significantly better in SS-LCH patients compared to those with MS-LCH (48% vs 31%, P=0.02). No difference in PFS was observed in adults, while children with SS-LCH showed a significantly better PFR compared to those with MS-LCH (83.5% vs 37.5%, P=0.002). Conclusion: Our experience suggests that the HS criteria developed for children could be not appropriate for LCH adults.

Poster Location #53
REFRACTORY MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS WITH MARKED AND DURABLE RESPONSE TO DABRAFENIB

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Purpose: To evaluate the efficacy of the single agent oral B-RAF kinase inhibitor dabrafenib in a patient with refractory multisystem B-RAF V600E mutation positive Langerhans Cell Histiocytosis (LCH). Methods: IRB approval was obtained for compassionate-use dabrafenib for a 2 year old with multisystem B-RAF V600E mutation-positive LCH, with gastrointestinal, skin, bone, lymph node and hepatosplenic involvement who was previously treated with multiple cycles of cytarabine, cladribine, cytarabine/cladribine combination therapy, and alentuzumab, but with refractory disease after each agent. Biopsies of the gastrointestinal tract showed diffuse LCH involvement from the gastric mucosa to the rectum. She presented with knee & hip pain, abdominal pain, diarrhea, and massive hepatosplenomegaly extending to the pelvis. Dabrafenib mesylate was administered orally as a 10 mg/ml liquid formulation reconstituted from powder (5.25 mg/kg/day divided twice daily). Results: This patient had a marked response to treatment with dabrafenib within 1-2 months with resolution of abdominal distension, diarrhea, lymphadenopathy, and hepatosplenomegaly. Dabrafenib was extremely well tolerated with adverse effects of only transient hypokalemia and intermittent skin rash. This remission has been maintained for 12 months to date. Conclusion: This marked, prolonged response to an oral B-RAF inhibitor that was extremely well tolerated, shows proof-of-principle that the B-RAF mutation identified in LCH can drive proliferation, and that its inhibition has great therapeutic promise. Further studies are needed to see if dermatologic toxicities/skin malignancies are also seen in children, and if there are additional unanticipated toxicities unique to children, as well as to define the optimum duration of therapy.

Poster Location #54
TARGETED THERAPY OF JUVENILE XANTGRANULOMA WITH BRAF V600E MUTATION: A REPORT OF TWO CASES

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Purpose: To evaluate the efficacy of the BRAF inhibitor vemurafenib efficacy in the treatment of refractory BRAF V600E-positive juvenile xantogranuloma in children. Methods and Results: Patient 1 (1.1 y.o. at the moment of diagnosis) was diagnosed with JXG with lesions of chest bones, shoulder girdle bones, femur, sacrum, multiple skull lesions with soft-tissue retrobulbar component, liver and spleen enlargement. Patient was treated with salvage regimen of LCH-IV (cytarabine + cladribine), but experienced severe infectious complications. Computed tomography showed no improvement in any of the lesions. BRAF V600E was detected with Sanger sequencing in biopsied lesion. Considering this, vemurafenib was administered at 480 mg/day as monotherapy. After 6 months all skeletal lesions fully resolved except for skull lesions that resolved partially. Soft-tissue component resolved completely. Patient 2 (4.5 y.o. at the moment of diagnosis) was diagnosed with JXG of suprasellar and supraorbital region (soft-tissue component) and diabetes insipidus. IC-1 as first-line therapy was performed (vinblasticine + prednisone), without effect. Cladribine was administered as a second-line therapy, but the tumor volume increased progressively (+27% of tumor size). Considering that and BRAF V600E mutation in tumor, vemurafenib was administered (480 mg/ day). After 3 months of therapy a 1/3 reduction of tumor was registered with MRI scan. Conclusion: vemurafenib may induce significant responses in BRAF V600E-positive non-LCH histiocytic disorders in children.

Poster Location #55
LANGERHAN'S CELL HISTIOCYTOSIS PRESENTING WITH PROPTOSIS IN A CHILD

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Background: Langerhan's cell histiocytosis (LCH) is a rare disease accounting for less then 2% of new cases enrolled each year in the Children's Hospital Lahore, it is the most common type of childhood histiocytic disorder in
children under 15 years of age. Purpose: to report an unusual presentation of LCH in a child. Methods: We report the case of a 3 year old female who presented to our hospital with fever & exophthalmos of left eye, on complete blood count only mild anemia was present, skeletal survey revealed no bony lesion, vertebral bodies & intervertebral spaces were normal and so were joint spaces. Bone marrow examination & abdominal ultrasound also were normal, however CT scan revealed lytic lesion involving left temporal bone, floor of left orbit & left zygomatic arch with associated soft tissue component extending into Left pterygo palatine fossa & nasopharynx, minimal soft tissue component also seen in Left retro-orbital extracanal space with mild proptosis of Left eyeball. MRI revealed large heterogenously enhancing mass with necrotic component within seen along Left infratemporal, Left parapharyngeal space, basi-sphenoid & along Left globe suggestive of sarcomatous mass. Histological examination of the soft tissue mass biopsy revealed neoplasm composed of sheets of Langerhan's cells along with eosinophils, foam cells & lymphocytes. Immunohistochemistry revealed S100 & CD1a positivity in tumor cells, confirming LCH diagnosis. Induction vinblastine weekly 6mg/m2 for 6 weeks & prednisone. Repeat MRI after 3 months revealed significant interval change 7x6.6 cm mass had shrunk to 3 x 2.3 cm. Discussion: LCH has varied clinical manifestations depending on organs involved, bone involvement being commonest followed by lung,liver, lymph node & skin etc. Definite diagnosis depends on histopathology of tissue biopsy with immunohistochemistry. This is the only case of LCH presenting with proptosis & normal skeletal survey over a period of six years.

Poster Location #56

A 15- MONTHS OLD CHILD PRESENTING WITH HIGHLY AGGRESSIVE BRAF(+) MULTISYSTEM LCH WITH CNS INVOLVEMENT: ARGUMENTS FOR USE OF DABRAFENIB P. O.+ LOW DOSE CYTARABIN I. V. AS THE TREATMENT OF CHOICE

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Purpose: our patient had a history of an unrecognized skin and bone Langerhans cell histiocytosis (LCH) for almost 4 months in a community hospital. On admission he looked critically ill, he had multisystem involvement with risk organs (bone marrow infiltration of 60-70%), involvement of the liver and rapidly progressing neurologic symptomatology due to massive involvement of the splanchnocranium with direct involvement of the middle cranial fossa. Cytospin of the likor did not show individual malignant cells, but has revealed positivity of BRAF 600/602 StripAssay (on the 1% sensitivity level). Patient was rapidly worsening. Progression of neurologic symptoms and massive infiltration of bone marrow with LCH is known to be associated with inferior outcome with the use of standard regimens so upfront targeting the known driving mutation was considered here. Methods: Dabrafenib was chosen here because of more favorable data from juvenile animal studies. Considering the massive CNS involvement the ARA-C 100mg/m2/day as i.v. infusion was added together with dabrafenib. Results: the treatment response after two weeks (time the abstract is written): bone marrow cleared to maximally 30% not viable looking CD1a+, Langerin + cells, CSF positivity dropped to the level of 0.1% for BRAF 600/602 StripAssay only. Clinically we have observed marked clinical improvement with the possibility for out patient based care starting from the day 8. Child is able to walk, play, neurologic status has completely returned to normal. Next to activated the RAS-RAF-MEK-ERK pathway distinct plasma protein profiles exists in LCH suggesting that probably pathologic myeloid cells contribute to the inflammation of the disease (Daniel Zinn, USA, Texas). Proteomic analyses of the pretreatment plasma and CSF of our patient are pending. Conclusion: we present rapid response of the neurologic status in a child with BRAFV600E mutated LCH to out patient treatment with dabrafenib and standard dose i.v. ARA-C.

Poster Location #57

DETECTION OF SOMATIC MUTATIONS BY PCR-BASED NEXT-GENERATION SEQUENCING FROM FIXED CLINICAL SPECIMENS IN CHILDHOOD LCH

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Purpose: Langerhans cell histiocytosis (LCH) is characterized by inflammatory histiocytic neoplasms that exhibit oncogenic constitutive activation of the RAS/MAPK pathway. Somatic mutations of BRAF and MAP2K1 have been identified in 70-80% of LCH cases. Recent studies have reported the clinical potential of targeted therapies using BRAF or MEK inhibitors. Sensitive molecular assays for detecting oncogenic mutations in LCH will enable the prediction of patient response to targeted agents. The aim of this study is to establish a method for detecting low frequency mutations from fixed LCH specimens by polymerase chain reaction (PCR) based on deep sequencing. Methods: We extracted genomic DNA from formalin-fixed, paraffin-embedded clinical specimens from 20 patients with childhood LCH. Two samples were excluded because of low quality PCR amplification. We studied 18 cases using a PCR-based targeted next generation sequencing platform with custom designed primers that contained overhang adapter sequences. The amplicon libraries generated for MiSeq were analyzed for detecting mutations in Exon12, 15 of BRAF gene and Exon2, 3 in MAP2K1 gene. Results: We detected somatic mutations in 17 of 18 samples (94%) at various allele frequency (3.3-30%, median 8.6%). BRAF was mutated in 15 of 18 samples (83%) and MAP2K1 was mutated in 5 of 18 samples (28%). BRAFV600E, the most frequent mutation in LCH, was identified in 9 of 18 samples (50%). In-frame deletions in exon 12 of the BRAF gene was found in 4 of 18 samples (22%). Conclusion: We identified genetic alterations of BRAF or MAP2K1 in over 90% of childhood LCH cases at even low allele frequency. High resolution analysis using formalin-fixed, paraffin-embedded clinical specimens could be a reliable implement as companion diagnostics for clinical use.

Poster Location #58

SCLEROSING CHOLANGITIS IN IDENTICAL TWINS WITH LANGERHANS CELL HISTIOCYTOSIS

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Introduction: Survival of children with Langerhans cell histiocytosis (LCH) has improved in the past decades. Disease involvement of liver carries a worse prognosis. Sclerosing cholangitis is an uncommon complication of LCH with high mortality. Little is known to its aetiology, disease course or the best
treatment. We report a pair of twin brothers who presented with sclerosing cholangitis. The clinical course after treatment with chemotherapy was studied. Methods: The clinical courses, radiological and histological features were studied. Twin 1 presented at 26 months of age with jaundice, rash and ear discharge, with marked hepatosplenomegaly. Blood test revealed hyperbilirubinemia and markedly elevated ductal enzymes. Magnetic resonance cholangiogram showed features of sclerosing cholangitis. LCH was diagnosed by liver biopsy and skin biopsy. Twin 2 was asymptomatic other than mild rash. He had no jaundice and liver was only mildly enlarged. Screening blood tests showed markedly elevated alkaline phosphatase but normal bilirubin. Imaging revealed similar findings as Twin I but with less severity. Skin biopsy confirmed LCH. Results: Twin I received chemotherapy according to LCH-III protocol, with vinblastine and prednisone, followed by maintenance of 6-mercaptopurine for total of 3 years. Liver function improved but radiological features remained static, and the patient developed portal hypertension. Chemotherapy has been stopped for 2 years and the condition remained static. Twin II was also treated with LCH-III chemotherapy. He showed good response with normalisation of liver function. Radiologically there was mild decrease in periportal inflammation. Discussion: The prognosis of sclerosing cholangitis in LCH is usually poor. Our patients demonstrated the effect of chemotherapy in controlling the disease. Twin II actually had normalisation of liver function. This suggests early diagnosis and timely treatment may lead to better outcome. The occurrence of LCH with SC in monozygotic twin also raised the role of genetic factor in the disease pathogenesis.

Poster Location #59

DRAMATIC EFFICACY OF DABRAFENIB IN LANGHERANS CELL HISTIOCYTOSIS HARBORING THE BRAF V600E MUTATION: TWO CASES REPORT

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Objective: To explore the effect of BRAF inhibitor Dabrafenib in Langerhans cell histiocytosis harboring the BRAF-V600E mutation. Methods: After informed consent, In first patient, we executed the reduced intensity chemotherapy (Vindesine 3mg/m2, every two weeks for one times; oral Prednisone for 1 weeks, and 1 weeks off ) combined BRAF inhibitor Dabrafenib oral treatment (50mg/d, twice). Serial 18-FDG PET-CT Scan was used to assess the efficacy and tolerability of the therapeutic regimen before and after treatment. In the second patient, we used single-agent Dabrafenib (50mg/d, twice) since the effect of chemotherapy was not obvious, and many complications such as bone marrow suppression, infection and gastrointestinal adverse reactions occurred in the treatment duration. Results: In first case, Serial 18-FDG PET-CT scans after 5 months of treatment revealed marked improvement of the lymph nodes compared with the former, and the curative effect was significant. The detection of BRAF-V600E gene in this patient showed a markedly decrease in the abundance of mutation. In the second case, There has been largely improved on rash, vulvar ulcer, lymph nodes, liver and spleen after 3 months treatment. The liver function and appetite of children were significantly higher than before. Conclusion: The BRAF inhibitor Dabrafenib may become a potent approach either combined with reduced intensity of chemotherapy, or used as single-agent in refractory high-risk patient that harboring the BRAF V600E mutation. It may reduce the toxicity of chemotherapy and lower the risk of relapse.

Poster Location #60

VEMURAFENIB IN A CHILD WITH LIFE-THERATENING MULTISYSTEM LANGHERANS CELL-HISTIOCYTOSIS

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Background: Most children with Langerhans cell histiocytosis (LCH) can be cured with conventional chemotherapy, but children with risk-organ dysfunction not responding to first-line treatment still have a poor prognosis. The BRAF inhibitor vemurafenib might be a salvage option in these patients, but clinical experience of this drug is limited, in particular in children. Case report: A febrile 2 year-old girl presented in poor clinical condition. Examination revealed cervical lymphadenopathy and hepatosplenomegaly. Laboratory assessment revealed pancytopenia (hemoglobin 7.1 g/dL, leukocytes 3.23 G/L, platelets 68 G/L) and low total protein (5.3 g/dL). The clinical condition rapidly deteriorated, and the girl needed regular transfusions of red blood cells and platelets. LCH was diagnosed in a biopsy of a cervical lymph node. Induction therapy with prednisone and vinblastine was started, but did not improve the clinical condition, as neither did the addition of etoposide. After the BRAF mutation V600E was detected, therapy with vemurafenib was started (20 mg/kg/day), which resulted in a rapid clinical improvement and hematologic recovery. Despite relatively high vemurafenib plasma levels, therapy was well tolerated with mild alopecia and photosensitivity of the skin as only side effects. After 16 weeks of treatment with vemurafenib, the girl is in good clinical condition. However, BRAF V600E alleles are still detected in the blood. Perspectives: To date, the experience with vemurafenib in the treatment of children with LCH is scarce. Most of the reported patients showed a rapid response to vemurafenib, but optimal treatment duration is unclear. Potential side effects of vemurafenib include the development of skin cancer, but on the other hand, cessation of therapy is associated with a high risk of relapse. Therefore, we plan in our patient an overlapping chemotherapy with prednisone, vincristine, and cytarabine. Whether the assessment of BRAF allows valid monitoring of the disease needs to be established.

Poster Location #61

DIABETES INSIPIDUS WITH DECREASING PITUITARY STACK WIDENING BUT METACHRONOUS SKULL LCH LESIONS

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Purpose: Diabetes insipidus (DI) can be the sole presenting sing of Langerhans cell histiocytosis (LCH), associated with hypothalamic/pituitary dysfunction not responding to first-line treatment still have a poor prognosis. The BRAF inhibitor vemurafenib might be a salvage option in these patients, but clinical experience of this drug is limited, in particular in children. Case report: A febrile 2 year-old girl presented in poor clinical condition. Examination revealed cervical lymphadenopathy and hepatosplenomegaly. Laboratory assessment revealed pancytopenia (hemoglobin 7.1 g/dL, leukocytes 3.23 G/L, platelets 68 G/L) and low total protein (5.3 g/dL). The clinical condition rapidly deteriorated, and the girl needed regular transfusions of red blood cells and platelets. LCH was diagnosed in a biopsy of a cervical lymph node. Induction therapy with prednisone and vinblastine was started, but did not improve the clinical condition, as neither did the addition of etoposide. After the BRAF mutation V600E was detected, therapy with vemurafenib was started (20 mg/kg/day), which resulted in a rapid clinical improvement and hematologic recovery. Despite relatively high vemurafenib plasma levels, therapy was well tolerated with mild alopecia and photosensitivity of the skin as only side effects. After 16 weeks of treatment with vemurafenib, the girl is in good clinical condition. However, BRAF V600E alleles are still detected in the blood. Perspectives: To date, the experience with vemurafenib in the treatment of children with LCH is scarce. Most of the reported patients showed a rapid response to vemurafenib, but optimal treatment duration is unclear. Potential side effects of vemurafenib include the development of skin cancer, but on the other hand, cessation of therapy is associated with a high risk of relapse. Therefore, we plan in our patient an overlapping chemotherapy with prednisone, vincristine, and cytarabine. Whether the assessment of BRAF allows valid monitoring of the disease needs to be established.

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lesions that increase size wise, even with isolated/localized disease. We present a patient with DI and regressing pituitary lesion, whilst new LCH bone-disease evolved. Presentation: A 2.5 year-old boy presented with polyuria/polydipsia of acute onset. DI diagnosis was established after a fluid deprivation and desmopressin substitution commenced. Thyroid function, cortisol, prolactin and IGF-I levels were normal. MRI demonstrated increased size of the pituitary (height of 6.5 mm), with superior protuberance. Additionally focal thickening of the pituitary stalk was noticed (3.4mm). The bright spot of the neurohypophysis was absent. Detailed evaluation for LCH and germ-cell tumor, including skeletal survey and serum/cerebrospinal fluid a-FP and hCG was negative. A suspicious radiolucent right femoral lesion was biopsied and proved negative. Follow-up: A 3-month follow-up MRI demonstrated normalization of the pituitary size (height of 2.4 mm), with homogeneous contrast uptake. In parallel, the desmopressin dose was decreased. Spinal MRI was normal. Three months later though, a soft, jellatinous, painless 2.5x2.5 cm lesion of the medial occipital area appeared, presenting features of an osteolytic lesion with mild contrast uptake on MRI. The lesion was curettaged with intralesional steroid infusion. Pathology was compatible with LCH (S100/CD1a/Langerin positive), no BRAF-V600E mutation was detected. Full disease reevaluation including a PET-CT scan proved negative, with further decreasing, normal appearing pituitary stalk (2 mm). With two system, low-risk disease the patient started treatment on LCH-IV Protocol (Stratum-I), with appropriate initial response. Conclusion: Spontaneous regression of the pituitary lesion was seen in parallel with metachronous skull bone lesion evolution in a young BRAF-V600E negative LCH patient. End organ LCH lesions can have different timing and pacing of regression/evolution. Careful monitoring and evaluation of the patients guides appropriate management and eventually cure.

Poster Location #62

EVALUATION OF MATERNAL AND PERINATAL CHARACTERISTICS AND RISK OF LANGERHANS CELL HISTIOCYTOSIS IN TEXAS, 1995-2011

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Purpose: Langerhans cell histiocytosis (LCH) is a myeloid neoplasia with a median diagnosis age of 30 months. In studies of pediatric malignancies, maternal and perinatal characteristics have been successfully evaluated to determine the impact of inborn variation on disease risk. We have reviewed registry data to determine if maternal and perinatal characteristics influence LCH development. Methods: Information on Texas-born LCH cases (n = 164) for the period 1995-2011 was obtained from the United States (U.S.) Texas Cancer Registry. Birth certificate controls were randomly selected at a ratio of 10:1 for the same period matched on birth year. Unconditional logistic regression was used to generate adjusted odds ratios (aOR) with 95% confidence intervals (CI). Results: Our findings indicate specific characteristics influence LCH risk. Non-Hispanic Black mothers were suggested as less likely to give birth to offspring who developed LCH compared to non-Hispanic White (NHW) mothers (aOR: 0.50; 95% CI: 0.24-1.03). Hispanic mothers were at increased risk of giving birth to offspring who developed LCH compared to NHW mothers (aOR: 1.58; 95% CI: 1.07-2.35). Children born from two Hispanic parents experienced an increase in LCH risk compared to children born from two NHW parents (aOR: 1.83; 95% CI: 1.15-2.90). Mothers born in Mexico versus the U.S. were suggested as less likely to give birth to offspring who developed LCH (aOR: 0.66; 95% CI: 0.41-1.07). Mothers who resided along the U.S.-Mexico border at time of infant birth were less likely to give birth to offspring who developed LCH (aOR: 0.54; 95% CI: 0.29-0.98). Conclusion: Maternal and parental race/ethnicity were strongly associated with LCH risk. Further, mothers who resided along the U.S.-Mexico border at time of infant birth, and Mexico-born mothers, were less likely to give birth to offspring who developed LCH. These findings highlight novel risk factors that warrant assessment in future studies.

Effective Second Line Treatment with Cytarabine in a Patient with Refractory Multisystem Langerhans Cell Histiocytosis (LCH) Complicated with Macrophage Activation Syndrome (HLH-MAS)

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Purpose: To present the use of intermediate dose Cytarabine-only as a second-line treatment in a child with refractory multisystem LCH. Methods: Single case presentation. Results: A 12-month-old male toddler was admitted to our hospital due to prolonged febrile episodes, polytenia and hepatosplenomegaly with significant abdominal distention. Scalp, retroauricular and abdominal skin rash was noticed. Biopsies of the scalp and abdominal skin were performed and established the diagnosis of LCH, positive for BRAF-V600E by PCR. Further clinical, laboratory and imaging studies did not reveal lymphadenopathy, definitive bone disease, lung infiltration, brain/ pituitary infiltration or diabetes insipidus. Bone marrow (BM) biopsy revealed decrease cellularity, homogeneous hemagocytosis and rare CD1a/ Langerin+ cells, negative for BRAF-V600E by PCR. The IC-1 course (Vindablastine/Prednisone) of LCH-IV protocol (Histiocyte Society) was started. Skin cleared; there was very mild improvement of the hepatosplenomegaly, while the pancytenia and febrile courses remained. Due to the persisted hemagocytosis in BM and the clinical suggestion of HLH-MAS he was started on HLH-2004 protocol with dexamethasone/etoposide/cyclosporine for 4 weeks, with no significant improvement. Due to refractoriness of LCH, he was started on second line treatment with Cytarabine monotherapy at 500mg/m2 q12 hours for 10 doses every 4 weeks. The patient showed clinical improvement after the first course, with gradual recovery of the pancytenia and the hemagocytosis and attained clinical remission (CR) after the 2nd course. Clinical, laboratory and imaging reevaluation after 3rd and 5th course (including PET-CT) confirmed remission. The patient received a total of 5 well-tolerated courses of Cytarabine monotherapy, and afterwards he was started on continuation treatment (Part2) with Vindablastine/Prednisone/6-Mercaptopurine/ Methotrexate according to LCH-IV protocol. He is in CR and good clinical status on 4 months of Part2 treatment. Conclusion: Intensive Cytarabine monotherapy could be a successful and well-tolerated second line treatment for patients with refractory multisystem LCH and concurrent HLH-MAS.
Purpose: Pulmonary Langerhans cell histiocytosis (PLCH) is a disease, which can potentially lead to the development of cancer, autoimmunological diseases, and opportunistic infections. The aim of this study is to present the frequency of these conditions. Material and Methods: Over a period from 2000 to 2015, 90 patients with PLCH were admitted to our Department. The mean age of patients was 35.78 ± 13.24 years, and 97% of them were cigarette smokers. The mean observation time was 62.9 ± 48.61 months. Results: Three patients (3%) developed neoplastic diseases. One, 58-year-old man with regression of pulmonary lesions was diagnosed with cholangiocarcinoma after 5 years of observation, a 52-years-old woman developed chronic myelogenous leukemia after 5 courses of cladribine treatment, and one woman 28-years-old had ovarian hamartoma, 4 years after chemotherapy. Systemic lupus erythematous was noticed in a 36-year-old man 2 years after chemotherapy, a 48-year-old woman was diagnosed at the same time with PLCH and biliary cirrhosis, and two men with psoriasis. Three (3.3%) patients had pulmonary mycobacteriosis, one patient Pneumocystis jiroveci pneumonia, and 9(10%) patients had frequent severe pulmonary infections. All patients, who experienced frequent respiratory infections were treated with corticosteroids. Conclusions: Despite that, patients with PLCH were smokers, the non-smoking related malignancies were observed. Autoimmunological disorders were more frequently noticed than in general population. Severe pulmonary infections were mainly observed in patients who were under immunosuppressive treatment.

Poster Location #65
RISK FACTORS FOR DIABETES INSIPIDUS IN PEDIATRIC PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS TREATED WITH CYTARABINE-BASED CHEMOTHERAPY; THE RESULTS OF JLSG-96/02 STUDY

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Objective: To analyze the clinical manifestations, treatment and prognosis of LCH patients with liver involvement. Methods: We conducted a retrospective study to evaluate the clinical datas of 110 LCH patients. From April 2011 to April 2015, newly diagnosed patients with histopathologically confirmed LCH were enrolled in this study. The patients were classified into two groups according to whether existed liver involvement. The clinical manifestations and efficacy of treatment were compared between two groups. The patients were followed up for 1-5 years, and the overall survival and disease-free survival were analyzed by log-rank test. Results: The median age at diagnosis was 5 years (range 2-204 months). Among them, there were 68 cases of male and 42 cases of female patients. The symptoms of 43 cases of hepatic LCH included with liver biochemistry abnormalities (16), hepatomegaly (22), liver biochemistry abnormalities (5), 16 cases were diagnosed as sclerosing cholangitis by abdominal CT scan or liver biopsy. Standard chemotherapy protocol was used in all the patients, however, salvage therapy were used in 20 cases who were poor response to the standard treatment. The total effective rate of treatment was 77.3%, and the effective rate was about 51.2% in hepatic LCH patients. Liver transplantation was performed in 4 patients and 5 patients died during the follow-up. Conclusion: There is a higher incidence of liver involvement in children LCH, and clinical prognosis of LCH with liver involvement is poor. The effect of regular conventional chemotherapy on hepatic LCH is not obviously and the salvage therapy should be considered seriously with the treatment related toxicity and side effects. Once LCH with sclerosing cholangitis was diagnosed, we can only improve the survival of patients through liver transplantation at the early timing.

Poster Location #67
PATTERN OF BONE RECURRENCE IN PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS

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Introduction: Bone is the most frequent recurrent site in patients with Langerhans cell histiocytosis (LCH). To describe characteristic patterns of bone recurrence, clinical course of the relapsed cases were analyzed. Patients and Methods: A retrospective review was conducted for the 70 children with LCH treated at our institution between 2002 and 2017. Among
these cases, ten (5 males and 5 females) with bone involvement both at diagnosis and relapse and with full imaging studies were analyzed. Results: Median age at diagnosis was 2.0 years (0.8-10.8) and median follow-up time was 7.5 years (5.2-12.8). Five cases initially presented with multi-focal bone involvement, and 5 with multisystem disease including one with risk organ involvement. Seven cases experienced multiple recurrences ranging 3 to 6 times. Median period from initial diagnosis to the last relapse was 4.3 years (0.8-6.4), and median follow-up time from the last relapse was 4.0 years (0.4-8.5). Number of bone relapse had reached to 28 in total; twelve solitary and sixteen multifocal, for which the sites were variable. Four cases relapsed at the same bone; one at the same mastoid bone 10 months after the therapy completion. Another three relapsed after 3 to 7 year interval in the same bone (vertebrae, femur and scapula), however all of the recurrent sites changed their position subtly from its original sites. Discussion and Conclusion: Recurrence of LCH occurs in various places and quite unpredictably, even after a long interval. As presented in our cases, relapses may occur at the same bone, but often with site changes. Such features may derive from the fact that LCH is a neoplasm of myeloid origin that could change its lesions anywhere. Thus, therapy and follow-up aiming a localized control does not fit for the patients with multifocal LCH, rather a systemic approach is mandatory.

Poster Location #68

**GIRL WITH DIABETES INSIPIDUS, GROWTH HORMONE DEFICIENCY AND SLOWLY PROGRESSIVE PITUITARY STACK THICKENING: USE OF ORAL PREDNISOLONE TREATMENT AS TOOL FOR HISTIOCYTOSIS DIAGNOSIS**

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Purpose: To present the use of oral prednisolone treatment for therapy and probable diagnosis of isolated Langerhans Cell Histiocytosis (LCH) pituitary lesion. Clinical presentation: A prepubertal 5 11/12 year-old girl presented with polyuria, polydipsia and decreased growth velocity. Height was on 10th-25th %ile, weight on 50th-75th %ile. Laboratory evaluation revealed central hypothyroidism (TSH:2.7µU/mL, FT4: 0.84ng/dl), low basal FSH and LH, normal cortisol, ACTH and prolactin levels (baseline and stimulated). Serum and CSF a-fetoprotein and ßhCG were negative. Skeletal survey was normal. MRI disclosed a slight hyperintense signal of the posterior pituitary gland and round thickening of the middle pituitary stalk d:4mm with avid contrast enhancement. The pituitary gland was of normal size 4.5x13x8.5mm Repeat MRI 10 months later showed augmentation of the pituitary stalk thickening (6mm) which further increased to 6.9 mm six months later. The bright signal of the posterior pituitary was absent. Growth hormone deficiency was diagnosed. She received PDN 40 mg/m²/daily for 2 months with pituitary stalk decrease to 4.6mm. She then received 5-day pulses q2 weeks x7 and q3 weeks for a total of 12 months treatment. At 12 months, the pituitary stalk measured <3 mm and remains so, with normal appearance 21 months off-treatment. Patient is 26 months off-treatment on follow up. Results: There was appropriate response to PDN-treatment with normalization of the pituitary stalk, highly suggesting the diagnosis of histiocytosis. The patient continues to be on replacement therapy (desmopressin/ßthryoxine), and she was started on growth hormone therapy six months ago, resulting in growth acceleration. MRI remains unchanged. Conclusion: Biopsy driven, pathology can lead to definitive diagnosis. Alternatively, a less invasive approach, is careful PDN LCH-type treatment. Prompt response, evident by decreasing thickening of pituitary stalk as observed in our patient, is highly suggestive but not confirmatory for LCH diagnosis. Careful follow-up is warranted.

Poster Location #69

**CLINICAL RESEARCH OF PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS WITH CRANIOFACIAL BONE INVOLVEMENT**

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Purpose: The objective of this article was to elucidate the clinical characteristics and prognosis of pediatric Langerhans cell histiocytosis (LCH) with craniofacial bone involvement. Methods: A retrospective analysis was performed in LCH patients registered between January 2007 and July 2013 at a single institute. They were stratified and treated according to Histocyte society LCH-III protocol. Results: A total of 145 patients with craniofacial bone involvement were analyzed out of 232 LCH patients (62.5%). Among the 145 patients, there was 104 cases with CNS-risk bone involvement (CNS-risk group) and 41 cases without CNS-risk bone involvement (non-CNS-risk group). The age of patients in CNS-risk group (median age 25.5 months) was significantly lower than the non-CNS-risk group (median age 58.0 months), P<0.01. The rate of patients classified as LCH-III Group 1 in CNS-risk group (70.2%) was higher than the non-CNS-risk group (34.1%), P<0.01. The relapse rate in CNS-risk group (44.2%) was higher than the non-CNS-risk group (14.6%), P<0.01. The 3-year event-free survival rate (EFS) in non-CNS-risk group was higher than that in CNS-risk group, (P<0.01). The incidence of diabetes insipidus in CNS-risk group (21.2%) was higher than the non-CNS-risk group (12.2%), while without statistical significance. In addition, this research didn't find significant differences in gender, additional bone (other than craniofacial bone) involvement between the two groups. Conclusions: The incidence of craniofacial bone involvement in LCH patients was high. Moreover, the children with CNS-risk bone involvement were mainly infants and young children, with a more serious clinical manifestation, a lower EFS and a higher relapse rate.

Poster Location #70

**CLASSIFICATION OF ORAL (BONE AND/OR MUCOSAE) LESIONS IN PEDIATRIC PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS**

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Purpose: Langerhans cell histiocytosis (LCH) could affect different organs and tissues. Oral cavity could be implicated and also could even be the first lesion of the disease and in many cases the only clinical involvement. In our knowledge there are not information related to the classification of oral lesions (OL) of LCH. Therefore, we conducted a study to classify the oral lesions of pediatric patients with LCH. Methods: Sixty two patients were recruited for oral evaluation. The patients with OL were classified according the affected tissues involved in: bone, mucosae, and bone/mucosae (tooth, bone and periodontal involvement). Results: Of a total of 62 patients, 40% showed OL and 48.4% were associated to multisystem disease and 51.6 % were associated to single system disease (unifocal lesion 56.3% and 43.7% multifocal lesion). Forty seven and four percent had oral bone lesions, 10.5% had mucosae lesions and 42.1% had bone/mucosae lesions. Oral lesion observed in the unifocal
single system involvement were exclusively osseous, in multifocal single system patients the involvement was bone and oral mucosae, meanwhile in a multisystem patients the lesions were osseous, mucosae, or osseous and mucosae lesions. The principal clinical features were: pain, swelling and osteolytic lesions founded in x-ray and CT scan of maxillary bones lesions. The principal features of bone/mucosae lesions were: gingival and mucosal enlargements with extensive bone loss, severe tooth mobility, localized bone loss, mobility of permanent teeth, early eruption of teeth and, insolated mucosae involvement were: palate reddish dots lesions, pericoronaritis in the first permanent molars, and erosive lesion in the labial mucosae. Conclusions: Multidisciplinary team is a necessary approach to achieve an early diagnosis and adequate treatment of oral cavity by pediatric dentistry to improve the quality of life of patients with LCH.
JUVENILE XANTHOGRANULOMA, NEUROFIBROMATOSIS TYPE 1, MESENCHYMAL HAMARTOMA OF THE LIVER AND UNDIFFERENTIATED EMBRYONAL SARCOMA IN A YOUNG CHILDREN. CASE REPORT

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Purpose: Juvenile Xanthogranuloma (JXG) is a histiocytic disorder, that affects the skin and rarely others organs. Its association with Neurofibromatosis type 1 (NF1) has been established. We present a patient with this association and moreover with a mesenchymal hamartoma of the liver (MHL) with a foci of undifferentiated embryonal sarcoma (USL). Methods: Case report. Chart and literature review. Results: 26 months old male, without NF1 family history, began at 3 months of age with “cafe au lait” macules of different diameters in trunk and extremities associated with axillary/groin freckling. At about 18 months of age, he developed a localized followed by disseminated JXG confirmed by skin biopsy. A CT scan was performed and an abdominal mass was found in the right flank. The mass (6.9 cm x 4.5 cm x 5.4 cm) was unique, polylobated and mainly cystic shaped with peripheral enhancement of the contrast. It was located at segment IV of the liver. Alpha fetoprotein dosage was normal. The mass was completely resected without complications and the pathology findings were: mesenchymal liver hamartoma with small foci (0.8 x 0.4 cm) of undifferentiated embryonal sarcoma of liver. The surgical margins were negative. The staging workup was performed and no evidence of extrahepatic disease was found. At 5 months of follow-up the patient is alive without evidence of recurrence. After the literature review, we do not found the association of NF1 and JXG with MHL or USL. Conclusion: Due to the low frequency, these diseases may deserve to be included in the international registry of rare histiocytic diseases of the Histioocyte Society, in order to increase the knowledge about these disorders. More data is needed to understand the pathogenesis of the association between NF1, XGJ, MHL and USL.

ADULT PATIENTS WITH MIXED HISTIOCYTOSES

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Purpose: The histiocytoses are a heterogeneous group of rare, potentially fatal neoplasms characterized by inflammation and infiltration of dendritic cells or macrophages. Histiocytic infiltration can affect multiple organ systems such as bones, central nervous system and retroperitoneum, resulting in tissue damage and organ failure. Histiocytoses are classified as Langerhans cell histiocytosis (LCH) or non-LCHs based on clinical, immunohistochemical and radiographic features. The presence of two histiocytic diseases in a single individual is termed “mixed histiocytosis”. Here we illustrate the distinctive clinical and molecular features of patients with mixed LCH and Erdheim-Chester disease (ECD) evaluated at the National Institutes of Health (NIH). Methods: Biopsy samples from seventy-five patients enrolled in an approved NIH protocol were reviewed to confirm the presence of a histiocytic disorder, and to test for the BRAF V600E mutation. Results: Four cases (5.3%) of mixed LCH and ECD were found. Of the mixed cases, three tested positive for the BRAF V600E mutation. All patients had bone disease, two patients were diagnosed with diabetes insipidus, commonly seen in LCH and ECD. One patient showed LCH and ECD infiltrates in the lung. One patient presented with mixed infiltration in the skin, colon and mandible, showing the multi-system involvement of these diseases. Conclusion: Our findings illustrate the unique clinical and molecular presentations of four mixed LCH and ECD cases, which adds to other reports, suggesting that such cases may not be rare. The discovery of the BRAF V600E mutation in >50% of LCH and ECD patients highlights the overlap of mitogen-activated protein kinase (MAPK) pathway mutations in the pathogenesis of histiocytoses, and in fact, three of our cases had BRAF V600E mutation in LCH and ECD affected tissue. The increasing number of reported mixed histiocytoses expands our understanding of the diversity of these conditions and mutation testing offers improved treatments.
A higher metabolic activity seen on 18F-FDG PET/CT, in the adrenal glands of patients with Erdheim-Chester disease harboring the BRAF V600E mutation

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Purpose: ECD is known to affect several organs, including the adrenal glands. Aim of the current study was to investigate potential association between adrenal metabolic activity and the BRAF V600E mutation status. Methods: Fifteen ECD patients (mean age at first ECD-manifestations: 53.9±6.3 years) were evaluated with whole-body 18F-FDG-PET/CT studies. Eleven patients harbored the BRAF V600E mutation, 4 were BRAF-negative, while in one patient the mutation status was not tested. PET-acquisition commenced 60 minutes after intravenous administration of 10-11mCi of 18F-FDG, while a non-contrast, low dose CT scan was performed for attenuation correction and co-registration. Metabolism in the adrenals was assessed by quantifying 18F-FDG uptake, using the MIM Vista workstation (version 6.5.9). A VOI encompassing both adrenal glands was drawn, and an automated SUVmax threshold-based approach was applied in order to include all 18F-FDG-avid regions of the adrenals, while excluding low-level background activity. The software allows automatic generation of separate VOIs encircling all areas above the SUVmax threshold set by the user (SUVmax threshold was set at 2). Afterwards, the following parameters were automatically obtained: SUVmax, SUVmean (average SUV), total 18F-FDG-avid adrenal volume (TV) and total glycolytic activity (TGA) of the adrenals, determined as the summation of the activity of each individual 18F-FDG-avid adrenal region, which is the product of each region’s volume multiplied by its’ SUVmean respectively. Finally, statistical analysis was performed using R software (version 3.3.3). Results: Mann Whitney test revealed statistical differences (p<0.05) in TV and TGA values between BRAF-positive and BRAF-negative ECD patients, with mutation carriers showing significantly higher mean TV (11.33 vs 3.2) and TGA values (29.3 vs 7.58). Conclusion: ECD patients who harbor the BRAF V600E mutation have hypermetabolic adrenals when compared to mutation-negative counterparts, implying increased susceptibility of BRAF-positive ECD-patients to adrenal involvement and potentially adrenal insufficiency.

Poster Location #75

Obstructive Uropathy and Nephropathy in Erdheim-Chester Disease

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Purpose: Erdheim-Chester Disease (ECD) is a rare, life-threatening neoplasm associated with retroperitoneal fibrosis (RPF), which can cause an obstructive uro-nephropathy and irreversible renal dysfunction. Treatment for these complications includes systemic therapy for ECD, ureteral stenting, and rarely, nephroscopy tubes, ureterolysis, or renal transplantation. This study highlights the prevalence and management of obstructive uro-nephropathy (and the association with BRAF mutation status) in a cohort of ECD patients. Methods: Sixty-one ECD patients gave informed consent for an approved protocol at the National Institutes of Health (NIH). ECD and BRAFV600E status was confirmed by histopathological and molecular analysis of biopsy samples. Radiographic imaging studies were evaluated at NIH. Results: Twenty-one (34%) patients with RPF had either bilateral or unilateral hydronephrosis/ureter (18 men and 3 women; mean age 59 years), and one had concomitant cystomegaly. This includes two (10%) with symptomatic renal artery stenosis (RAS). Of the twenty-one patients, analysis of renal function showed: mean glomerular filtration rate = 66 mL/min, mean creatinine = 1.3 mg/dL, mean Cystatin-C = 1.38 mg/dL, and mean 24-hr urine protein = 421 mg/dL. Seven of the twenty-one patients (33%) with hydronephrosis/ureter had either bilateral or unilateral ureteral stents, and one of the seven required a nephrostomy tube after stenting. Two patients (10%) had renal artery stents for stenosis. One patient (5%) underwent ureterolysis for severe bilateral obstruction, but was eventually transplanted. Correlation between BRAFV600E status and presence of obstructive uro-nephropathy in the cohort was statistically significant using Fisher exact test (value=0.007; p-value < 0.05) The stented patients had all been treated for ECD with various agents, but hydronephrosis persisted and all required long-term ureteral and/or renal artery stenting to prevent further renal damage. Conclusion: ECD-associated RPF can cause an obstructive uro-nephropathy, leading to irreversible renal dysfunction. Despite therapy, some patients require stenting to maintain renal function.

A Case of Severe CNS Involvement in Macrophage Activating Syndrome

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Introduction: Macrophage Activating Syndrome (MAS) is a rare but potentially fatal disease. MAS is currently classified among the secondary forms of hemophagocytic lymphohistiocytosis (sHLH). The reasons is that MAS shares clinical and laboratory features with primary genetic HLH (pHLH). The diagnosis of MAS is usually delayed due to the presence of non-specific
symptoms at presentation and managed as in sepsis. All unfortunately progressed to multiple organs dysfunction and died. The underlying causes for MAS were considered to be juvenile rheumatoid arthritis. MAS is treated with NSAIDs, corticosteroids, DMARDs and biologic therapy. Case and Review: A 12.3-year-old girl presented prolonged fever for more than 2 months. And confused mental status was developed 1 week ago. Her skin rash appeared on face and trunk for 1 year (wax and wane). She was admitted to tertiary hospital for full work-up of FUO. All cultures results were negative. Finally she was transferred to the university hospital due to the mental dysfunction. WBC 19,320/mm3, Hb 10.7g/dL, platelet 208,000/mm3, ESR 66mm/hr, CRP 18.8mg/dL, AST/ALT 1,373/374 IU/L, TBilirubin 2.2, BUN/Cr 53.7/2.53mg/dL, PT/aPTT 18.1/64.4sec, Fibrinogen 8,093ng/dL, CSF WBC 16/mm3, protein 68.3mg/dL, EEG : background suppression with no epileptic discharge. Brain MRI : focal high signal intensity in the right parietal deep white matter. r/o ADEM. Bone marrow biopsy : hemophagocytic histiocytes are seen and immunohistochemical stain for CD 68 was increased histiocytes. She received MPD pulse for 3days. After the prolonged fever was disappeared. Results: Her CNS condition and cytokine storm were improved after MPD pulse. After receiving MPD pulse for 3days, she took medicine of cyclosporine A and Etanercept. Conclusion: We should consider the possibility of CNS involvement in MAS who developed febrile seizure with FUO. We report a successful use of MPD pulse and cyclosporine A therapy of MAS in CNS involvement.

Introduction: Juvenile xanthogranuloma (JXG) is an uncommon non-Langerhans cell histocytic inflammatory disorder that generally presents in children as self-limiting skin lesions. Extracutaneous organ involvement is sometimes life-threatening and requires systemic therapy. Case reports: Case 1. A 4-month-old boy presented with hyphema and glaucoma, and yellowish-white nodule was recognized on his left iris. Three months after a 6-week topical and systemic corticosteroids, local relapse occurred. Although successfully re-treated, his corrected visual acuity was 0.02 at the age of five. Case 2. A 3-month-old boy presented with right corneal opacity and glaucoma due to severe anterior synchia of the iris. He was successfully treated with 6-week topical and systemic corticosteroids followed by 3-month low-dose maintenance, but his right eye had no light perception. Case 3. A 19-day-old boy presented with right conjunctival injection and corneal opacity. Abnormal iris associated with white membranous tissue was noticed in. He is currently under low-dose maintenance following 6-week topical and systemic corticosteroids. In all cases, monomorphic histiocytic infiltration in the patient's iris was pathologically observed. The diagnosis of JXG was based on immunohistochemical staining of positive CD68 and CD163, and negative CD1a. There was no evidence of skin and other lesions. Topical and systemic steroid therapy was effective for all the cases, although an early recurrence occurred in Case 1. Discussion and Conclusions: Ocular JXG is rare. It mainly occurs in the iris of young children. Topical, periocular, and systemic corticosteroids is effective, however, the prognosis of visual function remains poor. Our experience of an early relapsed case might indicate the necessity of a prolonged systemic therapy. Moreover, JXG should be included in a possible differential diagnosis when a patient present with conjunctival injection and/or glaucoma. Early diagnosis and intervention, together with close cooperation with ophthalmologists, may be critical for a better prognosis of visual function.
ABDOMINAL FINDINGS IN ERDHEIM-CHESTER DISEASE (ECD): MRI AND CT ASSESSMENT ON A COHORT OF 61 PATIENTS

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Purpose: To define variability of abdominal involvements in ECD as seen on Magnetic Resonance Imaging (MRI) and Computed Tomography (CT), and to investigate the correlation between BRAFV600E mutation and frequency of findings. Methods: This single center prospective study was performed on 61 biopsy-proved ECD patients (46 men), who signed written informed consent. The MRI or CT images (45 MRI, 16 CT) were reviewed by two experienced radiologists in consensus. 58 patients had tissue samples available for BRAFV600E testing. The correlation between the mutations and frequency of involvements was analyzed using Fischer exact test; p-value ≤ 0.05 was considered significant. Results: 52 patients had abdominal involvement, and 9 showed normal imaging findings. Perinephric fat involvement was the most common finding, seen in 41 (67%) patients. In 34 (56%) cases, perirenal involvement extended to renal sinuses. 37 (61%) patients had sheathing or stenosis of proximal ureters. Isolated calyceal ectasia and hydronephrosis were observed in 8 and 23 patients, respectively. 29 (48%) patients, had stenosis of proximal ureters (p<0.001), adrenals gland involvement (freq 60%), described as sheathing or stenosis of renal artery (30 patients), periaortic infiltration (26 patients) and infiltration of other aortic branches (15 patients). Among patients with positive BRAFV600E results [54% (31/57)], significant positive correlation was found between the mutation and frequency of perinephric fat infiltration (p: 0.002), renal sinuses involvement (p<0.001), sheathing or stenosis of proximal ureters (p<0.001), hydronephrosis (p<0.001), adrenal gland involvement (p<0.001), periaortic infiltration (p: 0.02), sheathing or stenosis of renal artery (p<0.001) and sheathing of other aortic branches (0.04). Conclusion: Due to the high incidence and poor prognosis of retroperitoneal and abdominal peri-vascular involvements in ECD, abdominal MRI or CT imaging should be performed at the time of diagnosis and during disease monitoring. BRAFV600E mutation status could be helpful in evaluating frequency of involvements.

COMPUTED TOMOGRAPHY (CT) FINDINGS OF PULMONARY AND MEDIASTINAL INVOLVEMENT IN ERDHEIM-CHESTER DISEASE (ECD)

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Purpose: To prospectively evaluate pulmonary and mediastinal findings on computed tomography (CT) and demonstrate their correlation with BRAFV600E mutation in Erdheim Chester Disease (ECD). Methods: We designed a prospective study of 61 ECD patients (46 males) who gave written informed consent. All patients underwent chest CT and the images were reviewed in consensus by two experienced radiologists. Correlation with BRAFV600E mutation was performed on 58 cases by using Fischer exact test. P-value <0.05 was considered significant. Results: 16 patients had respiratory manifestations (11 had shortness of breath, 3 had chronic dry cough and 2 had recurrent sinusitis) and 45 patients were symptom free. Pulmonary involvement was seen in 55 patients (90%); among which interstitial lung disease was the most common (44 patients), including interlobular septal thickening in 42 and bronchial wall thickening in 8 patients. Nodular opacities were classified by the pattern of distribution: in 22 cases, nodules were located in subpleural regions, including lung fissures; in 8 of them nodules were diffusely distributed and in 8 cases, nodules were not found in subpleural regions. 9 patients (15%) had pleural involvement and 38 (62%) had mediastinal involvement on CT imaging. Right coronary artery was the most frequent vessel sheathed with histiocytic infiltration (21 patients) followed by thoracic aorta (18 patients). 31 patients tested positive for BRAFV600E mutation; BRAFV600E mutation positive is significantly associated with higher frequency of both non-subpleural nodules (P-value: 0.04) and sheathing of the coronary arteries (P-value: 0.01). Conclusion: Even though pulmonary and cardiovascular involvements are common in ECD, patients are usually asymptomatic. This study presents pulmonary and mediastinal involvement of ECD in detail, and evaluates the correlation between BRAFV600E mutation and distribution of findings. Poor prognosis of ECD is increased with presence of cardiovascular involvement; therefore, special attention should be paid to understanding of these findings.

NEEDS ASSESSMENT OF HISTIOCYTOSIS PHYSICIANS IN ASIA AND THE MIDDLE EAST: RESULTS OF AN “AME-HISTIO NETWORK” QUESTIONNAIRE

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Background: Histiocytic disorders can present with a wide range of clinical manifestations and severity. Data on the needs of physicians looking after such patients in Asia and the Middle East (AME) is lacking. A group of experts from these regions convened during the 2016 Histocyte Society meeting, and created the “AME Histio Network”. Objectives: To assess the challenges that physicians from AME encounter when treating patients with histiocytic disorders, with regards to diagnosis and treatment, availability of molecular/genetic testing, and to assess the existence of national consensus guidelines. Methods: A 15-item questionnaire was distributed. Questions included: the presence of national registries and patient support groups, availability of specialized diagnostic testing, and existence of treatment guidelines. Results: Thirty-five participants from ten countries responded. Most did not have a national histiocytosis association, a parent support group, or a histiocytosis registry. Specialized imaging studies were available in almost all centers, while sophisticated genetic/molecular testing such as BRAF-V600E and HLH genetic testing were lacking in many institutions. Most centers have adopted the International LCH and HLH treatment protocols, and most did not have difficulty finding the most common histiocytosis chemotherapy drugs. Novel drugs such as cladribine, clofarabine and BRAF-inhibitors were not readily available in many centers. There was a great interest in participating in national registries, clinical trials, genetic/molecular studies and in exchanging information and resources. Due to the heterogeneity of participating countries, priorities and expectations varied depending on the country and its available resources. Conclusions: The lack of national histiocytosis associations, parent organizations, and treatment guidelines were noted by most participants. The diagnostic and treatment challenges varied among different countries due to economic, rather than geographic, reasons. Establishing international training scholarships to support physicians from countries with limited resources, and partnerships between centers could be the first steps in facing these challenges.

BRAF V600E MUTATION IS ASSOCIATED WITH A CARDIAC AND NEUROLOGICAL PHENOTYPE BUT NOT MORTALITY IN ERDHEIM-CHESTER DISEASE: RESULTS FROM A SINGLE-CENTER 165-PATIENT COHORT

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Erdheim-Chester disease (ECD) is an inflammatory myeloid neoplasm characterized by a heterogeneous phenotype. Between 60 and 75% of ECD patients carry the BRAFV600E mutation. We lack genetic-phenotype association studies. The BRAFV600E mutation was investigated in a large French ECD cohort. The association between the presence of this mutation and the clinical phenotype, as well as the overall mortality, was analyzed with uni- and multivariate analyses. A total of 165 patients (119 men, mean age at diagnosis 56.4 years) were included, and the BRAF status could be obtained for 133. The presence of the BRAFV600E mutation was significantly associated with cardiac (73 versus 27%, p < 0.0001) and cerebellar (23 versus 4%, p=0.007) involvement, diabetes insipidus (35 versus 16%, p=0.03) and retro-orbital infiltration (31 versus 11%, p=0.02). Regarding heart involvement, cardiac right atrial pseudotumor was the cardiac localization that was most closely linked to BRAF status (univariate odds ratio (OR) 14.81, 95% confidence interval (95% CI) 4.87-44.97, p<0.0001). Survival was not different among the BRAFV600E and wild-type patients. As shown by the uni- and multivariate analyses, overall mortality was associated with age at diagnosis, retroperitoneal involvement (HR 3.85, confidence interval 1.68-8.83) and lung involvement (HR 2.74, confidence interval 1.38-5.43). The central nervous system was also confirmed to be an independent predictor of death. Interferon-alfa and targeted therapies were associated with better survival. The presence of the BRAFV600E mutation in ECD is associated with cardiac and neurological involvements but not mortality. Retroperitoneal and lung involvements are associated with worse survival.

LANGERHANS CELL HISTIOCYTOSIS IN ADULTS IS ASSOCIATED WITH ADDITIONAL SOLID AND HEMATOLOGIC MALIGNANCIES

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Purpose: The increased rate of additional malignancies in Langerhans cell histiocytosis (LCH) patients is a notable concern that has been previously observed. Reports in the literature have included mixed case reports of adults and children, or small case series focused on the pediatric LCH population. However, to our knowledge there has not been a large, single-institution study in consecutive adult LCH patients, nor a large recent study in the modern era after the widespread use of tumorigenic agents such as etoposide. Here we report our 25-year single institution experience of adult LCH patients with additional malignancies. Methods: We identified 155 consecutive patients ≥18 years with histologically confirmed LCH (S100+, CD1a+) at our center between 1990-2015. Demographics and detailed oncologic history were recorded to identify patients with additional malignancies, excluding non-melanoma skin cancers. The Kaplan-Meier method was used to estimate overall survival. Results: Of 155 adult LCH patients, 46 (30%) patients had an additional malignancy. Median age was 54 years (range 28-89) with a median follow-up of 3.7 years (0.1-22.2). Overall survival (OS) was 11.2 years, with 32 (70%) alive at last follow-up. There were a total of 61 non-LCH malignancies among the 46 patients, with 30 (49%) preceding LCH diagnosis, 10 concurrently (≤3 months; 22%), and 21 (46%) after. Ten patients presented with 2 malignancies in addition to their LCH diagnosis, and 2 patients presented with 2 malignancies. There were 45 solid tumors (74%), 9 lymphomas (15%), and 7 other hematologic malignancies (11%). Conclusion: The cohort of adult LCH patients demonstrates an exceptionally high number of additional malignancies, consistent with existing literature. However, our study includes predominantly malignancies diagnosed preceding or concurrent with LCH, suggesting a cause of malignancy independent of LCH treatment. Further exploration of the biology of this rare disease may elucidate the mechanism of increased additional malignancies.
C-REACTIVE PROTEIN AND BONE PAIN AT DIAGNOSIS PREDICT THE OUTCOME OF PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS WITH SINGLE-SYSTEM MULTIFOCAL LESIONS: RESULT OF THE JAPAN LANGERHANS CELL HISTIOCYTOSIS STUDY GROUP-02 PROTOCOL STUDY

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10Department of Laboratory Medicine, Uji-Tokushukai Medical Center, Uji, Japan

Background: Langerhans cell histiocytosis (LCH) with single-system (SS) multifocal bone (MFB) lesions is rarely fatal, but the patients may experience relapses and develop sequelae. The factors that associate with the post-treatment outcome of SS-MFB disease are not known. Patients and Methods: We assessed the outcomes of all consecutive newly diagnosed pediatric patients with LCH with SS-MFB lesions who were treated with the Japan Langerhans Cell Histiocytosis Study Group (JLSG)-02 protocol in 2002–2009. The protocol consists of 6 weeks induction with cytarabine, vincristine, and prednisolone followed by maintenance therapy for 48 weeks. Events were defined as poor response to the induction therapy, relapse and any death. Results: In total, 82 patients with a median follow-up duration of 8.0 years were eligible for analysis. At 6 weeks, 92.7% responded to the induction. However, 27.6% of the responders experienced relapses and 2.4% developed central diabetes insipidus. None of the patients died. The 5-year event-free survival (EFS) rate was 66.7%. Patients who had higher serum C-reactive protein (CRP) levels and bone pain at diagnosis had significantly lower EFS. Of 81 excluding one patient whose data was missing, 27 had normal CRP levels (<0.3 mg/dL) and no bone pain at diagnosis (Group 1). Another 27 were either CRP-positive or had bone pain at diagnosis (Group 2). The remaining 27 were both CRP-positive and had bone pain (Group 3). Group 1 and Group 2 had similar average EFS (81.5% vs. 77.3%, p=0.810). By contrast, Group 3 had a much lower average EFS (44.4%) than Group 1 and Group 2 (p=0.006 and p=0.008, respectively). Conclusions: High serum CRP and bone pain at diagnosis were independent poor prognostic factors in pediatric patients with SS-MFB type LCH, who were treated with the JLSG-02 protocol.
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 have 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.

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.

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.
The Histiocyte Society is offering an annual prize for the best poster presented at the Annual Meeting. It will be 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.
The Society shall be governed and guided by the principles set forth in these By-Laws.

ARTICLE I
OFFICES, REGISTERED OFFICE, AND REGISTERED AGENT

Section 1. Offices. The principal office of Histiocyte Society, Inc. (the "Corporation") shall be located within or without the State of New Jersey, at such place as the Board (as defined below), in its sole discretion, shall from time to time designate. The Corporation may also maintain additional offices at such other places as the Board may from time to time designate.

Section 2. Registered Office and Registered Agent. The Corporation shall have and continuously maintain a registered office and a registered agent in the State of New Jersey, as required by the New Jersey Nonprofit Corporation Act (the "Act"). The registered agent shall be either an individual resident of the State of New Jersey or a corporation authorized to transact business in the State of New Jersey, in accordance with the Act.

ARTICLE II
PURPOSES AND MISSION

Section 1. Purposes. The purposes for which the Corporation is formed are as set forth in the Corporation's Certificate of Incorporation (the "Certificate of Incorporation").

Section 2. Mission. The mission of the Corporation is to: (i) improve the state of knowledge of the histiocytic disorders and improve the welfare of patients with these disorders; (ii) promote, facilitate, and carry out research in histiocytic disorders; (iii) facilitate and provide a forum for health care professionals for effective communication concerning these aims; (iv) promote education and to educate physicians, scientists, and others in matters related to the histiocytic disorders; (v) advise lay organizations in educational and other matters concerning the histiocytic disorders; and (vi) collaborate with organizations that have common goals.

ARTICLE III
MEMBERSHIP

Section 1. Classes. The Corporation shall have three (3) classes of members: (i) ordinary members (the "Ordinary Members"); (ii) honored members (the "Honored Members"); and (iii) emeritus members (the "Emeritus Members").

A. Ordinary Members. Ordinary Members shall be health care professionals who are active in patient care, education or research in the histiocytic disorders. Ordinary Members pay dues, may participate in all activities of the Corporation, and hold office.

B. Honored Members. Honored Members are distinguished individuals, who, in the view of the Board, have made extraordinary contributions to the Corporation. Honored Members enjoy all the rights and privileges of Ordinary Members, but do not pay dues and may not hold office.

C. Emeritus Members. Emeritus Members are Ordinary Members who have retired from active involvement in the field. Emeritus Members enjoy all rights and privileges of Ordinary Members, but do not pay dues and may not hold office.

Section 2. Qualifications. The Board shall determine, in its sole discretion, the qualifications, dues, terms, and other conditions of each class of member.

Section 3. Voting Rights. All members shall have the right to vote on the following matters: (i) election of the Board and officers; (ii) election of members of the Education and Scientific Committees and other committees as deemed appropriate by the Board; (iii) approval of the annual budget proposed by the Board; (iv) approval of any amendments to these Amended and Restated Bylaws (these "Bylaws"); and (v) other issues as the Board may choose to bring before the members. Voting on all other matters is expressly reserved for the Board.

Section 4. Member Meetings. There shall be an annual meeting of the members upon such date, time, and place as the Board shall determine. Special meetings of the members may be called by the President or upon the request of a majority of the voting members.

Section 5. Notice. Members shall receive not less than thirty (30) nor more than sixty (60) calendar days prior written notice of all member meetings. Notice shall be given in the manner specified in Article VIII of these Bylaws. The purpose for which a special meeting is called shall be stated in the notice. Any member may waive notice of any meeting by a written (including electronic) statement, either before or after the meeting. Notwithstanding the foregoing, attendance and participation at a meeting without objection to notice shall constitute a waiver of notice.

Section 6. Quorum and Voting. Each voting member shall have one vote on each voting matter. A quorum shall consist of at least ten percent (10%) of the total voting members. A majority of the votes cast on each voting matter at which a quorum exists shall constitute a valid action of the members.

Section 7. Removal. Any member may be removed from membership by a majority vote of the Board only: (i) for cause, which is defined as failure to pay dues for three (3) consecutive years; or (ii) other causes as determined by the Board in its sole discretion. The Board shall be the sole judge of moral, ethical, and professional qualifications required for election to or termination of membership.

Section 8. Action by Written Consent. Except as otherwise expressly prohibited by the Act, applicable law, the Certificate of Incorporation or these Bylaws, any action required or permitted to be taken at a meeting of the members (other than the biennial election of Board members), may be taken without a meeting upon the written consent of members who would have been entitled to cast the minimum number of votes which would be necessary to authorize the action at a meeting at which all members entitled to vote thereon were present and voting; provided, that: (i) the Corporation provides to all other members advance notification setting forth the proposed action consented to; (ii) the proposed action is not consummated before the expiration of ten (10) days from the giving of the notice (and twenty (20) days from the giving of the notice in the case of any action taken pursuant to Chapter 10 of the Act); and (iii) the notice sets forth the existence of such ten (10) day period; provided further, that the writings are filed with the minutes of the members.

ARTICLE IV
BOARD OF TRUSTEES

Section 1. Powers. There shall be a Board of Trustees of the Corporation (the "Board"), which shall supervise and control the business, property, and affairs of the Corporation, except as otherwise expressly provided by the Act, applicable law, the Certificate of Incorporation, or these Bylaws. All members of the Board shall serve without financial compensation.

Section 2. Number and Qualifications. The Board of the Corporation shall be composed of no less than five (5) and no more than nine (9) individuals. The number of Board members may be decreased (but in no event to fewer than three (3) members), however, no decrease shall have the effect of shortening the term of any incumbent member of the Board.

Section 3. Composition. The Board shall consist of those individuals then serving as the President, the President-Elect, the Past President, the Secretary, the Treasurer, and two Members-at-Large.
HISTIOCYTE SOCIETY GOVERNING BY-LAWS

Section 4. Election and Term of Office. The members of the Board shall be elected by the voting members as set forth in Article V, and shall serve until their successors are elected and qualified, or their earlier removal, resignation or death.

Section 5. Resignation and Removal. Any Board member may resign at any time by giving written notice to the President. Such resignation shall take effect at the time specified therein, or, if no time is specified, at the time of acceptance thereof as determined by the President. A Board member may be removed with cause by vote of a two-thirds majority of the Board at a duly held meeting with a quorum present. The remaining Board members of the Corporation shall be the sole judge of moral, ethical, and professional qualifications required for removal from the Board.

Section 6. Vacancies. Vacancies on the Board, whether caused by resignation, removal, death, an increase in the authorized number of Board members or otherwise, may be filled by the affirmative vote of a majority of the remaining Board members, although less than a quorum, or by a sole remaining Board member. A Board member elected to fill a vacancy shall serve for the unexpired portion of such term.

Section 7. Meetings. A regular annual meeting of the Board of the Corporation shall be held each year, at such time, day, and place as shall be designated by the Board. Special meetings of the Board may be called at the direction of the President or by a majority of the Board members then in office, to be held at such time, day, and place as shall be designated in the notice of the meeting.

Section 8. Telephone Meetings. Any one or more Board members may participate in a meeting of the Board by means of a conference telephone or similar telecommunications device that allows all persons participating in the meeting to hear each other. Participation by telephone or other telecommunications devices shall be equivalent to presence in person at the meeting for purposes of determining if a quorum is present.

Section 9. Notice. Notice of the time, day, and place of any meeting of the Board shall be given not less than twenty-four (24) hours prior to such meeting, in the manner set forth in Article VIII. The purpose for which a special meeting is called shall be stated in the notice. Any Board member may waive notice of any meeting by a written (including electronic) statement, either before or after the meeting. Notwithstanding the foregoing, attendance and participation at a meeting without objection to notice shall constitute a waiver of notice.

Section 10. Quorum. A majority of the Board members then in office shall constitute a quorum for the transaction of business at any meeting of the Board.

Section 11. Manner of Acting. Except as otherwise expressly required by the Act, applicable law, the Certificate of Incorporation or these Bylaws, the affirmative vote of a majority of the Board members present at any meeting at which a quorum exists shall be the act of the Board. Each Board member shall have one vote.

Section 12. Action by Written Consent. Except as otherwise expressly prohibited by the Act, applicable law, the Certificate of Incorporation or these Bylaws, any action required or permitted to be taken at any meeting of the Board, or any committee thereof, may be taken without a meeting if all the members of the Board or of such committee consent thereto in writing (including by electronic transmission), and the writings are filed with the minutes of the Board or committee.
HISTIOCYTE SOCIETY GOVERNING BY-LAWS

accordance with the applicable term structures set forth in Section 1 of this Article V.

Section 3. Term of Office. Each officer of the Corporation shall be installed at the annual meeting of members at which they are elected, and shall hold office for terms as set forth in Section 1 of this Article V, or until their respective successors shall have been duly elected and qualified, or their earlier removal, resignation or death.

Section 4. Resignation and Removal. Any officer may resign at any time by giving written notice to the President. Such resignation shall take effect at the time specified therein, or, if no time is specified, at the time of acceptance thereof as determined by the President. An officer may be removed with cause by vote of a two-thirds majority of the Board at a duly held meeting with a quorum present.

Section 5. Vacancies. Vacancies shall be filled by a majority vote of the Board.

ARTICLE VI
COMMITTEES

Section 1. Standing Committees. Standing Committees include the: (i) nominating committee (the "Nominating Committee"); (ii) program committee (the "Program Committee"); (iii) scientific committee (the "Scientific Committee"); (iv) education committee (the "Education Committee"); and (v) disease steering committee (the "Disease Steering Committee"). The Board in its sole discretion may create other committees on an ad-hoc basis.

A. Nominating Committee. The Nominating Committee shall be composed of the President, President-Elect, Past-President, Secretary, and Treasurer, and shall be responsible for providing the Board with candidates for office, membership, and standing committees, as requested by the Board from time to time.

B. Program Committee. The Program Committee shall be composed of the President, Secretary, Chairperson of the Education Committee, Chairperson of the Scientific Committee, the Secretariat, and additional members chosen from among the members of the Corporation (as determined by the Board, in its sole discretion). The President shall act as Chairperson of the Program Committee. The Program Committee shall be responsible for planning, organizing, and executing the annual meeting of members and for presenting the program materials to the Board prior thereto for Board approval. The Program Committee may, in its sole discretion, solicit assistance from others, who may or may not be members of the Corporation.

C. Scientific Committee. The Scientific Committee shall be composed of no less than five (5) and no more than nine (9) Ordinary Members. The Scientific Committee shall review proposals for research and related activities according to guidelines developed by the Board, make recommendations to the Board, and present the Board with annual reports and plans concerning the Corporation’s research activities. Members of the Scientific Committee will be elected by voting members of the Corporation at the time of the annual meeting of the member.

D. Education Committee. The Education Committee shall be composed of no less than five (5) and no more than nine (9) Ordinary Members. The Education Committee will oversee the educational activities of the Corporation, and review and score the abstracts to be presented at the annual meeting of members. The Education Committee will also present the Board with annual reports and plans concerning the Corporation’s educational activities. Members of the Education Committee will be elected by voting members of the Corporation at the time of the annual meeting of the member.

Members will serve two (2) year terms and may serve up to six (6) consecutive years if re-elected. The Education Committee will select its own chairperson within ten (10) days of the close of the annual meeting.

E. Disease Steering Committees. The Disease Steering Committees shall oversee the scientific agenda for their respective diseases and will present the Board with annual reports and plans concerning the research and educational activities for those diseases. Members of the Disease Steering Committees will be appointed by the Board, per standard operating procedures as defined by the Board.

Section 2. Committees and Task Forces. The Board may create and appoint members to such other committees and task forces, as it shall deem appropriate in its sole discretion. Such committees and task forces shall have the power and duties designated by the Board, and shall give advice and make recommendations to the Board.

Section 3. Vacancies. Temporary vacancies in the membership of committees may be filled by the Board until the time of an annual meeting and election as specified above.

Section 4. Rules. Each committee and task force may adopt rules for its meetings not inconsistent with the Act, applicable law, the Certificate of Incorporation, these Bylaws or any rules adopted by the Board.

ARTICLE VII
AGENTS

Section 1. Agents. The Board may appoint agents, such as a secretariat (the "Secretariat"), with such powers and to perform such acts and duties on behalf of the Corporation, as the Board may determine from time to time, in its sole discretion.

ARTICLE VIII
MISCELLANEOUS PROVISIONS

Section 1. Fiscal Year. The fiscal year of the Corporation shall be the calendar year.

Section 2. Notice Procedures. Whenever under the provisions of these Bylaws notice is required to be given to a Board member, officer, committee member or member, such notice shall be given in writing by first-class mail or overnight delivery service with postage prepaid to such individual at such individual's address as it appears on the records of the Corporation. Such notice shall be deemed to have been given when deposited in the mail or the delivery service. Alternatively, notice may also be given by facsimile, electronic mail, or hand delivery, and will be deemed given when received.

ARTICLE IX
INDEMNIFICATION

Section 1. Indemnification Generally. Unless otherwise prohibited by the Act or applicable law, the Corporation may indemnify any current or former Board member or officer, and may by resolution of the Board indemnify any agent, against any and all expenses and liabilities incurred by such individual in connection with any claim, action, suit or proceeding to which such individual is made a party by reason of being a Board member, officer or agent. However, there shall be no indemnification in relation to matters as to which such individual shall be adjudged to be guilty of a criminal offense or liable to the Corporation for damages arising out of such individual’s own gross negligence in the performance of a duty to the Corporation. Amounts paid in indemnification of expenses and liabilities may include, but shall not be limited to, counsel fees and other fees, costs and disbursements, and judgments, fines, and penalties against, and amounts paid in settlement by, such Board member, officer or agent. The Corporation may advance
expenses or, where appropriate, may itself undertake the defense of any officer or agent. However, such officer or agent shall repay such expenses if it should be ultimately determined that such individual is not entitled to indemnification under this Article IX.

Section 2. Insurance. The Board may also authorize the purchase of insurance on behalf of any Board member, officer or other agent, against any liability incurred by such individual which arises out of such individual’s status as a Board member, officer or agent, whether or not the Corporation would have the power to indemnify the person against that liability under the law.

ARTICLE X
DISTRIBUTION OF ASSETS UPON DISSOLUTION

Section 1. Distribution of Assets Upon Liquidation. In the event of the liquidation or dissolution of the Corporation, after payment of all debts, all remaining assets shall be distributed only as permitted by the Act, applicable law, and the Certificate of Incorporation.

ARTICLE XI
AMENDMENTS TO BYLAWS

Section 1. Amendments to Bylaws. These Bylaws may be amended (or new bylaws adopted) upon the affirmative vote of a majority of the voting members; provided, that the proposed changes have been approved by the Board, and circulated to the voting members not less than thirty (30) nor more than sixty (60) calendar days prior to such vote to approve same.

HISTIOCYTE SOCIETY CONSTITUTION

Article I: Name
The name of the society shall be the “Histiocyte Society”. This is a non-profit organization duly registered in the United States of America.

Article II: Aims
1. To improve the state of knowledge of the histiocytic disorders and the welfare of patients with these disorders and their families.
2. To promote, facilitate and carry out research in histiocytic disorders.
3. To facilitate and provide a forum for health professionals for effective communication concerning these aims.
4. To promote education and to educate physicians, nurses, other health professionals, scientists, legislators, and other lay persons in matters related to the histiocytic disorders.
5. To advise lay organizations in educational and other matters concerning histiocytic disorders.
6. To collaborate with other organizations with common aims.

Article III: Amendments and Revisions
1. Changes may be made by an affirmative vote of two-thirds (2/3) of a quorum at a general meeting of the Society, provided proposed changes have been submitted to and approved by the Board and circulated among the members at least one (1) month prior to the general meeting.
2. Proposed changes may originate with any ordinary member of the Society. They should be submitted to the Secretary at least two (2) months prior to the general meeting.
3. Changes properly proposed to the Board will be presented at the next general meeting with the recommendation of the Board.

Article IV: Dissolution
1. Dissolution shall be proposed, processed, and voted on as for amendments and revisions, Article III.
2. In a case of dissolution of the Society, any funds remaining after payment of all outstanding debts will be donated to one or more organizations, with aims and objectives consonant with those of the Society, to be selected by the Board.
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