34th Annual Meeting of the Histioocyte Society

Meeting Program and Abstracts

Epic Sana Lisboa
Lisbon, Portugal
October 22 - 23, 2018
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# MEETING SPONSORS

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[Image of meeting sponsors]
Dear Colleagues,

The Histiocyte Society cordially welcomes you to the 34th Annual Meeting, which is being held in Lisbon, Portugal on October 22-23, 2018.

Lisbon, one of the oldest European capitals, is Portugal’s economic and cultural center. It has a worldwide reputation for neoclassical architecture, great food, nostalgic music and romantic places. Its geographic location and pleasant climate make it an attractive location for both business and tourism.

Pursuing collaboration with other professional societies is one of the priorities of the Histiocyte Society. Having a back-to-back Meeting with the European Society for Immunodeficiencies Deficiencies (ESID) was another important reason for choosing Lisbon as a venue for our Annual Meeting this year. We would like to strengthen our relationship and promote collaboration in the field of hemophagocytic lymphohistiocytosis. For this reason, we have offered a reduced registration fee to ESID members interested in attending our meeting, will provide a lecture on HLH and primary immune deficiencies followed by a thematic HLH symposium, and will host a working meeting of the leaderships of the two Societies.

Our Program Committee put a lot of work into preparing an attractive agenda for this year’s meeting. On the Pre-Meeting day (October 21st) we invite newcomers and young physicians to educational state-of-the-art lectures on diagnosis and treatment of LCH, HLH and rare histiocytoses. This year’s plenary speaker is Prof. Frederic Geissmann, a renowned expert on macrophage biology, who will share new findings on uncovering the pathobiology of CNS-LCH. The traditional Jon Pritchard Lecture on the Nikolas Symposium is dedicated to epigenetics and myeloid differentiation and their implications in histiocytic disorders. The backbone of the meeting program is built by the scientific sessions, the thematic symposia on LCH and HLH, as well as by the Meet the Expert sessions. I hope for a productive scientific exchange and lively discussions in a friendly atmosphere with familial spirit.

The social highlight of our meetings is, as always, the Annual Banquet. This year it will take place at Kais Restaurant and Skones Club. After the dinner, the dance floor will be yours till 0100.

As you know, a meeting of this format requires a lot of time, energy and resources to be properly organized. I would like to especially appreciate our symbiotic partner and key sponsor, the Histiocytosis Association, without whose generous support, this meeting would not be possible.

I look forward to seeing you in Lisbon!

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.

2018 ANNUAL MEETING MOBILE APP - INVITATION IN YOUR EMAIL

The 2018 Histiocyte Society Annual Meeting has a free mobile event app! The best way to gain access to the app is to click on the invitation that was sent to the email you provided during registration for the Annual Meeting. You can also search for “Histiocyte Society Annual Mtg” in your app store. Only registered attendees have access to the mobile app. See the emailed invitation for detailed instructions for logging into the app.

The Annual Meeting app password is “hsmtg2018”.

The app is available in the App Store and Google Play and in HTML5 for Blackberries, Windows phones, and older devices. There is also a desktop/laptop version which you can access at hsmtg2018.zerista.com.

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 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 2018 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 Medical & Scientific Advisory Committee (MSAC) for a second review. The SAC then makes a recommendation to the Histiocytosis Association’s Board of Trustees concerning grants to be funded.
- Funding clinical studies that result in identifying the best possible treatments for histiocytic disorders.
- Facilitating research by administratively managing the Histiocyte Society.

Since 1992, 189 individual awards have been made to date, representing more than $6.8 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 35 years. Though separate organizations, they share a common goal that binds their continued partnership - to find better treatments and, ultimately, a cure leading to a world free of histiocytic disorders.

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

HISTIOCYTE SOCIETY EXECUTIVE BOARD
President ................................................. Milen Minkov 2016-2019
President-Elect ....................................... Michael Jordan 2017-2019
Treasurer ............................................... Karin Beutel 2016-2018
Secretary ............................................... Kim Nichols 2017-2018
Member-at-Large ................................................... Carl Allen 2017-2020
Member-at-Large .................................................. Scott Baker 2017-2020

HISTIOCYTE SOCIETY EDUCATION COMMITTEE
Kimo Stine, Chairperson 2016-2018
Itziar Astigarraga ........................................ 2016-2018
Gleb Bronin .................................................. 2017-2019
Patrick Campbell ............................................ 2017-2019
Barbara Degr .................................................. 2017-2019
Michael Henry ............................................... 2017-2019
Elena Siani .................................................... 2017-2019

HISTIOCYTE SOCIETY SCIENTIFIC COMMITTEE
Rebecca Marsh, Chairperson 2017-2019
Ed Behrens .................................................... 2016-2018
Stephan Ehl .................................................... 2016-2018
Julien Haroche .............................................. 2017-2019
Jennifer Picarsi .............................................. 2017-2019
Johannes Visser ............................................. 2017-2019

HISTIOCYTE SOCIETY STUDY GROUP CHAIRPERSONS
Adult Histiocytosis ........................................ Michael Girschikofsky
Epidemiology/Late Effects ......... Riccardo Haupt / Vasanta Nanduri
HLH .............................................................. Jan-Ing Jon Henter
LCH-IV .................................................. Milen Minkov/Carlos Rodriguez-Galindo
Rare Histiocytosis Disorders .................................. Oussama Abla

HLH STEERING COMMITTEE
Stephan Ehl, Chairperson .................................. 2016-2020
Itziar Astigarraga ........................................ 2016-2020
Scott Baker .................................................... 2018-2022
Jan-Ing Jon Henter ......................................... 2014-2018
Anna Carin Home ......................................... 2015-2019
Gritta Janka .................................................. 2016-2020
Michael Jordan ............................................. 2017-2021
Kai Lehmborg ................................................ 2017-2021
Kim Nichols .................................................. 2015-2019
Elena Sieni .................................................... 2015-2019
Zhao Wang ................................................... 2015-2019

LCH STEERING COMMITTEE
Carl Allen, Co-Chairperson ................................ 2016-2020
Karim Beutel, Co-Chairperson .......................... 2017-2021
Michael Girschikofsky ................................... 2015-2019
Michelle Hermiston ....................................... 2017-2021
Rima Jubran .................................................. 2017-2021
Stephan Ladisch ............................................ 2015-2019
Milen Minkov ................................................ 2014-2018
Vasanta Nanduri ............................................ 2016-2020
Carlos Rodriguez-Galindo ................................ 2014-2018
Barrett Rollins ............................................... 2017-2021
Kimo Stine .................................................... 2014-2018
Cor van den Bos ............................................ 2015-2019
Johannes Visser ............................................. 2015-2019

RARE HISTIOCYTIC DISORDERS STEERING COMMITTEE
Oussama Abla, Chairperson 2016-2020
Jorge Braier .................................................. 2016-2020
Eli Diamond .................................................. 2015-2019
Jean-Francois Emile ...................................... 2017-2021
Michael Girschikofsky ................................... 2017-2021
Julien Haroche ............................................... 2017-2021
Eric Jacobsen ................................................ 2015-2019
Ron Jaffe ...................................................... 2015-2019
Zdenka Klevenova ........................................... 2015-2019
Akira Morimoto ............................................. 2017-2021
Jennifer Picarsi .............................................. 2015-2019
Sheila Weitzman ............................................ 2016-2020

HISTIOCYTE SOCIETY PAST PRESIDENTS
Carlos Rodriguez-Galindo ................................ 2013-2016
Jim Whitlock .................................................. 2010-2013
Alexandra Filipovich ...................................... 2007-2010
Jan-Ing Jon 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

LISBON 2018
ACKNOWLEDGEMENTS AND RECOGNITIONS

NEZELOF PRIZE IN CLINICAL SCIENCE Awardees

Elena Sieni ................................................................. 2017
Francesca Minola ......................................................... 2016
Alexandra Löfstedt ....................................................... 2015
Vasanta Nanduri .......................................................... 2014
Carl Allen ................................................................. 2013
Stephen Simko ............................................................ 2012
Thomas Lehmbecher .................................................... 2011
Rebecca Marsh ............................................................ 2010
Rebecca Marsh ............................................................ 2009
Jorge Braier ............................................................... 2008
Kenneth McClain ......................................................... 2007
Loretta Lau ................................................................. 2006
Anna Carin Home ........................................................ 2005
Marie Ouachée-Chardin ................................................. 2004
Manuel Steiner ............................................................ 2003
Jorge Braier ............................................................... 2002
Wolfgang Holter ........................................................... 2001
Kazuhito Kogawa .......................................................... 2000

ROBERT J. ARCECI AWARD FOR BEST POSTER

Caroline Hutter ......................................................... 2017
Sandra Ammann ......................................................... 2016

HISTIOCYTE SOCIETY GOLDEN PIN RECIPIENTS

Jorge Braier ............................................................... 2017
Lisa Filipovich ............................................................ 2017
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. Toughtill ..................................................... 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

Hirofumi Shibata .......................................................... 2017
Edward Behrens .......................................................... 2016
Benjamin Durham ........................................................ 2015
Samuel Chiang Cern Cher .............................................. 2014
Gayane Badalan-Very/Kim Nichols .................................... 2013
Edward Behrens .......................................................... 2012
Edward Behrens .......................................................... 2011
Michelle Hermiston ..................................................... 2010
Michael Jordan ............................................................ 2009
Matthew Collin ............................................................ 2008
Kejian Zhang ............................................................... 2007
Alessandra Santoro ....................................................... 2006
Udo zur Stadt .............................................................. 2005
Cristiana Costa/Kimberly Risma ...................................... 2004
Michael B. Jordan ........................................................ 2003
Susan Lee/Joyce Villanueva ............................................. 2002
Maurizio Aricò ............................................................. 2001
Pieter Leenen ............................................................. 2000

TRAVEL SCHOLARSHIP RECIPIENTS

Congratulations to the Histiocyte Society’s 2018 Travel Scholarship recipients:

Yasmine El Chazli for the abstract titled,

SOLUBLE IL-2 RECEPTOR ALPHA IN CEREBROSPINAL FLUID OF CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

This abstract will be presented during the Poster Presentation Session on Monday, October 22, 2018.

Paul Kemps for the abstract titled,

INCIDENCE AND CLINICAL CORRELATIONS OF SOMATIC MAPK PATHWAY MUTATIONS IN PEDIATRIC AND ADULT LANGERHANS CELL HISTIOCYTOSIS

This abstract will be presented during the Poster Presentation Session on Monday, October 22, 2018.

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.
EPIC SANA LISBOA HOTEL 1ST FLOOR MEETING ROOMS

EPIC SANA LISBOA HOTEL FLOOR PLANS
### AT-A-GLANCE PRE-MEETING AGENDA

#### SATURDAY • OCTOBER 20, 2018

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<th>Location</th>
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<td>Executive Board Meeting*</td>
<td>Oliva</td>
</tr>
<tr>
<td>1030–1100</td>
<td>Coffee Break</td>
<td>Oliva</td>
</tr>
<tr>
<td>1430–1600</td>
<td>Website Committee Meeting*</td>
<td>Oliva</td>
</tr>
<tr>
<td>1600–1630</td>
<td>Coffee Break</td>
<td>Foyer</td>
</tr>
<tr>
<td>1600–1700</td>
<td>Rare Histiocytic Disorders Steering Committee Meeting*</td>
<td>Oliva</td>
</tr>
<tr>
<td>1700–1800</td>
<td>LCH Steering Committee Meeting*</td>
<td>Oliva</td>
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#### SUNDAY • OCTOBER 21, 2018

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<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>Foyer</td>
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<tr>
<td>0800–0900</td>
<td>LCH-IV Study Management Group Session*</td>
<td>Closed Session</td>
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<tr>
<td>0900–1130</td>
<td>LCH Disease Discussion Session*</td>
<td>Morus II</td>
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<tr>
<td>0900–1130</td>
<td>HLH Education Session*</td>
<td>Morus IV</td>
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<td>1000–1030</td>
<td>Coffee Break</td>
<td>Morus IV</td>
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<tr>
<td>1200–1430</td>
<td>LCH Education Session*</td>
<td>Morus IV</td>
</tr>
<tr>
<td>1230–1330</td>
<td>Lunch</td>
<td>Flor de Lis Restaurant</td>
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<tr>
<td>1230–1330</td>
<td>Histiocytosis Association MSAC Committee Meeting*</td>
<td>Morus III</td>
</tr>
<tr>
<td>1300–1330</td>
<td>Poster Presentation Setup</td>
<td>Vitis</td>
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<tr>
<td>1330–1430</td>
<td>Rare Histiocytic Disorders Discussion Session*</td>
<td>Morus II</td>
</tr>
<tr>
<td>1400–1600</td>
<td>HLH Steering Committee Meeting*</td>
<td>Morus III</td>
</tr>
<tr>
<td>1430–1800</td>
<td>HLH/MAS Disease Discussion Session*</td>
<td>Morus II</td>
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<tr>
<td>1500–1730</td>
<td>Rare Histiocytoses Education Session*</td>
<td>Morus IV</td>
</tr>
<tr>
<td>1600–1630</td>
<td>Coffee Break</td>
<td>Foyer</td>
</tr>
<tr>
<td>1830–2030</td>
<td>Welcome Reception</td>
<td>EPIC SANA Lisboa Hotel - Scale Bar &amp; Terrace</td>
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### AGENDA

#### MONDAY • OCTOBER 22, 2018

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<td>0800</td>
<td>Meeting Registration and Check-In</td>
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<tr>
<td>0800</td>
<td>Poster Presentation Setup</td>
<td>Vitis</td>
</tr>
<tr>
<td>0800–0900</td>
<td>Education Committee Meeting*</td>
<td>Nux</td>
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<tr>
<td>0800–0900</td>
<td>AME Histio Working Group Meeting</td>
<td>Morus II</td>
</tr>
<tr>
<td>0900</td>
<td>Opening Ceremonies</td>
<td>Morus III &amp; IV</td>
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<tr>
<td>0915</td>
<td>Guest Speaker Presentation</td>
<td>Morus III &amp; IV</td>
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<tr>
<td>1000</td>
<td>Coffee Break</td>
<td>Morus III &amp; IV</td>
</tr>
<tr>
<td>1030–1230</td>
<td>Symposium: Mechanism and Targeted Therapies of CNS Histioytosis</td>
<td>Morus III &amp; IV</td>
</tr>
<tr>
<td>1230–1330</td>
<td>Lunch</td>
<td>Flor de Lis Restaurant</td>
</tr>
<tr>
<td>1230–1330</td>
<td>HLH Meet the Expert Lunch Session*</td>
<td>Castanea</td>
</tr>
<tr>
<td>1230–1330</td>
<td>LCH Meet the Expert Lunch Session*</td>
<td>Laurus</td>
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<tr>
<td>1230–1330</td>
<td>New Investigator’s Luncheon*</td>
<td>Morus II</td>
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<tr>
<td>1330–1515</td>
<td>Scientific Session I: Oral Presentations</td>
<td>Morus III &amp; IV</td>
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<tr>
<td>1515–1545</td>
<td>Coffee Break</td>
<td>Foyer</td>
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<tr>
<td>1545–1715</td>
<td>Scientific Session II: Presidential Symposium</td>
<td>Morus III &amp; IV</td>
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<tr>
<td>1715–1915</td>
<td>Poster Presentation Session</td>
<td>Vitis</td>
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#### TUESDAY • OCTOBER 23, 2018

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<th>Time</th>
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<tr>
<td>0800</td>
<td>Meeting Registration and Check-In</td>
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<tr>
<td>0830–0915</td>
<td>Jon Pritchard Lecture on the Nikolas Symposium</td>
<td>Morus III &amp; IV</td>
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<tr>
<td>0915–1000</td>
<td>Histiocyte Society &amp; ESID Lecture</td>
<td>Morus III &amp; IV</td>
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<td>1000</td>
<td>Coffee Break</td>
<td>Morus III &amp; IV</td>
</tr>
<tr>
<td>1030–1230</td>
<td>Symposium: HLH Therapy - Update and Future Perspectives</td>
<td>Morus III &amp; IV</td>
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<tr>
<td>1230–1330</td>
<td>Lunch</td>
<td>Flor de Lis Restaurant</td>
</tr>
<tr>
<td>1230–1330</td>
<td>Rare Histioctoses Meet the Expert Lunch Session*</td>
<td>Castanea</td>
</tr>
<tr>
<td>1230–1330</td>
<td>Joint HS/ESID Executive Boards Luncheon*</td>
<td>Nux</td>
</tr>
<tr>
<td>1400–1530</td>
<td>Scientific Session III: Oral Presentations</td>
<td>Morus III &amp; IV</td>
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<tr>
<td>1530–1630</td>
<td>Presentation of Late Breaking Abstracts</td>
<td>Morus III &amp; IV</td>
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<tr>
<td>1630–1700</td>
<td>Coffee Break</td>
<td>Morus III &amp; IV</td>
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<tr>
<td>1630–1730</td>
<td>General Assembly Business Meeting*</td>
<td>Foyer</td>
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<tr>
<td>1730–1800</td>
<td>Executive Board Meeting*</td>
<td>Morus III &amp; IV</td>
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<tr>
<td>1730–1800</td>
<td>Education Committee Meeting*</td>
<td>Morus III &amp; IV</td>
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<tr>
<td>1845–1900</td>
<td>Group Transportation to Histiocyte Society Annual Banquet</td>
<td>EPIC SANA Lisboa Hotel Lobby</td>
</tr>
<tr>
<td>1930–0100</td>
<td>Histiocyte Society Annual Banquet, Closing Ceremonies &amp; Awards*</td>
<td>Kais Restaurant &amp; Skones Club</td>
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* Indicates closed session

* Indicates that advance registration was required
Dear Members of the Histiocyte Society and Histiocytosis Community,

It is with deep sorrow that I inform you that our beloved colleague, mentor and friend Dr. Giulio John D'Angio, 96, a renowned radiation oncologist, a pioneer in the treatment of pediatric cancer and a founding member of the Histiocyte Society, died on Friday, September 14, 2018 in Philadelphia, Pennsylvania USA.

"Dan" D'Angio was a fascinating personality. He never failed to welcome newcomers to our Society by involving them in a friendly talk, encouraging them and giving advice and support whenever needed. He was not only one of the founders of the Histiocyte Society and the author of its original bylaws, but also someone who, over decades, consistently cared for the Society. Although he never held a formal officer position, he did not hesitate to remain actively involved and question policies or Board decisions if he was not convinced that they would best serve our common mission.

I had the privilege to be warmly welcomed by Dan when I joined the Society as a young resident in 1992. It was a privilege to discuss my first scientific papers with him and to receive stimulating ideas and critique that encouraged me to challenge established paradigms and think outside the box.

He was definitively one of the anchors of the Society who attracted and welcomed new members and attendees with unmatched warmth and kindness.

His lifetime scientific contributions to pediatric oncology and the histiocytic disorders as well as his humanistic legacy will serve as an inspiring example for generations of scientists and physicians to come.

We all mourn with his family and will strive to honor his legacy through the outstanding work our Society continues to accomplish because of the foundation he helped to build.

Milen Minkov
President of the Histiocyte Society
Matthew Collin is Professor of Haematology and Director of the Northern Centre for Bone Marrow Transplantation at Newcastle University and Newcastle-upon-Tyne Hospitals NHS Foundation Trust. He did a Ph.D. with Siamon Gordon and post-doctoral stints with Derek Hart and Miriam Merad. He received a Leukaemia Research Fund UK Bennett Senior Fellow in Experimental Haematology and set up the Human DC Lab in Newcastle in 2008 (http://www.hudendritic.org). Research in the Human DC Lab focuses on the haemopoietic origin of dendritic cells and macrophages and their role in human pathology including immunodeficiency, histiocytosis and graft versus host disease.

Marco Colonna is the Robert Rock Belliveau MD Professor, Pathology & Immunology, at the Washington University School of Medicine in St. Louis, MO USA. His laboratory is broadly interested in innate immunity, focused in three main areas: 1) Innate lymphoid cells (ILCs) in mucosal immunity, 2) Plasmacytoid dendritic cells and IFNα/beta in host defense and autoimmunity, and 3) Innate immune mechanisms in Alzheimer’s disease and neurodegeneration.

Eli L. Diamond is an Assistant Attending Neurologist at Memorial Sloan Kettering Cancer Center (MSK) where he treats a large cohort of adults with Erdheim Chester Disease, Langerhans cell histiocytosis, Rosai-Dorfman disease, and other histiocytic disorders. He leads the multidisciplinary effort at MSK in the treatment for histiocytosis and led the histiocytosis cohort of the Vemurafenib basket trial that resulted in regulatory approval of this drug for Erdheim-Chester Disease. He has several active research protocols including the ongoing clinical trial of Cobimetinib for BRAF-wildtype histiocytosis. He has particular interest in neurologic involvement and symptomatology related to the histiocytic neoplasms and is conducting a longitudinal study of neuroimaging and neurocognitive function in adults with histiocytosis, funded by the Histiocytosis Association and the Erdheim-Chester Disease Global Alliance. He is the Principal Investigator of the Global ECD Patient Registry which is housed at MSK. He has served on the Education Committee of the Histiocytosis Association, the Rare Histiocytic Disorders Steering Committee, and the Medical and Scientific Advisory Board of the Histiocytosis Association. Dr. Diamond holds a Career Development Award from the American Society of Clinical Oncology.

Stephan Ehl graduated in medicine after attending Universities of Aachen, Erlangen and Munich in 1991. Following his internship at the University Children’s Hospital Ulm, he completed a post-doc with Prof. Zinkernagel in Zürich, Switzerland. Since 1998, Stephan Ehl is a pediatrician at the University Medical Center in Freiburg where he became a senior consultant in 2002 and Medical Director of the Centre of Chronic Immunodeficiency in 2008. His research focuses on immunodeficiencies predisposing to immune dysregulation. This includes autoimmune-lymphoproliferative immunodeficiencies, profound combined immunodeficiencies and hemophagocytic lymphohistiocytosis. Research extends from basic immunological studies in animal models to human genetic and immunological studies to diagnostic studies and clinical trials. Stephan Ehl has served as a member of the ESID board and currently heads the HLH working group of the Histiocyte Society.

Frederic Geissmann is the William E. Snee Chair of Immunology at Memorial Sloan Kettering Cancer Institute. He received his MD at the University of Paris, Paris VI Pierre et Marie Curie and Ph.D. at the University of Paris, Paris V Rene-Descartes. His research is focused on cellular and molecular mechanisms that control the differentiation, maintenance, and physiological functions of macrophages and monocytes and their roles in tissue homeostasis and disease processes. Over the past ten years, The Frederic Geissmann Lab has investigated the developmental origin and homeostasis of macrophages and the related cell types monocytes and dendritic cells. These cells play a major role in diverse types of cancer and can either restrain or promote cancer progression and metastasis. The Geissmann Lab is now building on previous work to investigate mechanisms by which tissue macrophages may control tissue growth and metabolism and whether these same mechanisms play a role in cancer initiation and development.

From 1988 to 1996, Tayfun Güngör was in pediatric training at the University Frankfurt/Main, Germany (board certification in Pediatrics 1996). His post-doc position was at the University of Ulm, Germany, from 1996 to 1997. Since 1997, he has been the Senior Physician of Pediatric Hematology, Oncology and Immunology at the University Children’s Hospital in Zürich, Switzerland. He received diplomas in Pediatric Rheumatology at the Hôpital Necker Enfants Malades in Paris and Cellular Therapy at the Université de Haut-Alsace/Mulhouse (1998 and 2000). He was the head of the Stem Cell Laboratory in 2000 and the Head of the Division Stem Cell Transplantation (2008). He also was Assistant Professor (2008) and Associate Professor of Pediatrics and Stem Cell Transplantation at the University of Zürich, Switzerland (2015). He has N=75 authored or co-authored full papers in peer-reviewed journals. He has special interest in chronic granulomatous disease and hemophagocytic lymphohistiocytosis and their treatment by hematopoietic stem cell transplantation and cellular therapies using reduced-intensity conditioning regimens with matched and unmatched donors.
**GUEST SPEAKER HIGHLIGHTS**

**Michael Jordan** graduated from the University of Texas Southwestern Medical School in 1993. After completing a pediatrics residency at the Children’s Hospital of Dallas, he began a Pediatric Hematology/Oncology fellowship at The Children’s Hospital, Denver, Colorado. After completing clinical training, Dr. Jordan joined the laboratory of Drs. Philippa Marrack and John Kappler in 1997, where he studied T cell biology. In 2002, Dr. Jordan joined the faculty there first as an Instructor of Pediatrics and then as an Assistant Professor at the University of Colorado Medical School. In 2004 he moved to Cincinnati Children’s Hospital/University of Cincinnati, where he is currently a Professor of Pediatrics in the divisions of Immunobiology, and Bone Marrow Transplantation and Immune Deficiency. The Jordan lab studies the pathophysiology and treatment of primary immune regulatory disorders, including hemophagocytic lymphohistiocytosis. His contributions include pioneering work to model and understand the pathophysiology of HLH and the investigation of new modalities of therapy for this disease.

**Kim Nichols** is a pediatric oncologist whose research focuses on understanding the molecular and cellular mechanisms that predispose to hemophagocytic lymphohistiocytosis (HLH), particularly when it occurs in the context of Epstein Barr Virus (EBV) infection. Dr. Nichols was among the first to identify the gene defective in X-linked lymphoproliferative disease (XLP), a rare primary immunodeficiency associated with increased risk for EBV-induced HLH, B cell lymphomas and progressive hypogammaglobulinemia. For the last 18 years, Dr. Nichols and her research group have worked to dissect how the XLP gene product SAP regulates immune cell development and function and coordinates host immunity to EBV. Through these efforts, she and her collaborators have identified key roles for SAP during regulation of Th2-type cytokine production, natural killer (NK) and invariant NKT (iNKT) cell cytotoxicity, iNKT cell development and T cell restimulation-induced cell death. Dr. Nichols has also explored the use of B-cell directed therapies such as rituximab, as well as other targeted approaches to develop a multi-institution clinical trial for HLH that incorporates the use of this medication. Dr. Nichols is a past member of the Scientific and Education Committees and a current member of the HLH Steering Committee of the Histiocyte Society (HS), where she also participates in several of the HLH working groups and serves as a Member-at-Large on the HS Executive Board.

**James A. Whitlock** is the Division Head and Women’s Auxiliary Millennium Chair in Haematology/Oncology and Director of the Garron Family Cancer Centre at The Hospital for Sick Children, Senior Associate Scientist in the Child Health Evaluative Sciences Program at the SickKids Research Institute, and Professor of Paediatrics at the University of Toronto. Dr. Whitlock’s research interests include the biology and treatment of childhood acute leukemias, the development of new drugs for the treatment of childhood cancers, and the biology and treatment of histiocytic disorders. He was the inaugural Vice-Chair for New Agents and Relapse studies for the Acute Lymphoblastic Leukemia Committee of the Children’s Oncology Group, and is current or past Chair or Vice-Chair of several COG clinical trials. He is the lead investigator for an international phase I trial of nelarabine combination therapy for relapsed T-cell ALL (T2008-002: NECTAR) through the Therapeutic Advances in Childhood Leukemia (TACL) consortium, and served two terms as the first chair of TACL’s Steering & Prioritization Committee. He is a past President of the Histiocyte Society, an international scientific organization which supports research in, and conducts clinical trials for, histiocytic disorders. He is the current Chair of C17, the national organization for Canadian childhood cancer and blood disorder centres.
Oussama Abla joined the faculty of the Department of Paediatrics at The Hospital for Sick Children (SickKids) in 2000. Abla is an Academic Clinician in the Division of Haematology/Oncology and a member of the Division’s Leukemia/Lymphoma and In-Patient Services Sections. Abla is an associate professor in the Department of Paediatrics at the University of Toronto. He received his MD degree from the University of Genoa, Italy in 1989. His post-graduate training included a paediatric residency at the Gaslini Children’s Hospital in Genoa and a paediatric haematology/oncology fellowship at SickKids in Toronto. Abla’s clinical interests include paediatric leukemia/lymphomas with a special interest in Acute promyelocytic leukemia (APL), paediatric primary CNS lymphoma, rare paediatric lymphomas, as well as Langerhan’s cell Histiocytosis (LCH) and rare histiocytosis.

Gritta Janka studied medicine in Germany and Switzerland. She received her training as a pediatrician and later as a pediatric hematologist and oncologist in Munich, Germany, and spent a year at the Dana Farber Cancer Center in Boston which then was called “The Jimmy Fund”, working as a fellow with Emil Frei, III. From 1993 until her retirement she was associate professor and vice director of the Department of Hematology and Oncology, University Hospital of Hamburg. Throughout her medical career, main fields of interest have been acute lymphoblastic leukemias where she chaired the multicenter CoALL Study Group for many years; hematology, where she still gives bi-annual training courses for pediatric hematologists, and especially histiocytic diseases. A family with three babies with HLH of whom she took care in the seventies aroused her interest in this disease, prompting her to write the first review on familial HLH in 1983. Ever since she has remained deeply involved in this disease. Her group in Hamburg described two of the four genetic defects for familial HLH and published many articles on HLH. Dr. Janka was a founding member of the HLH Study Group, which developed the two international studies for HLH. She was chairperson for these studies for Central Europe. She later chaired the project “CureHLH” from the European Union where eight partners from five countries cooperated. Dr. Janka is a member of the HLH Steering Committee of the Histiocyte Society that she chaired from 2013-2017.

Kimo Stine is a Professor of Pediatrics at the University of Arkansas for Medical Sciences and is located at Arkansas Children’s Hospital in Little Rock, Arkansas. He has been on faculty there for 26 years. He received his Medical Degree from the University of Kansas as well as completing his Pediatric Residency there. Kimo completed his Pediatric Hematology Oncology Fellowship at Duke University Medical Center. His involvement in the Histiocyte Society began over 15 years ago when he was invited to attend a meeting. He is the site PI for LCH-IV, LCH-CLO, a coordinating PI for the salvage stratum for high risk LCH in LCH-IV. Kimo was elected to the Education Committee of the Histiocyte Society in 2009 and 2014 and is also on the Board of the Histiocytosis Association. Besides an active clinical program in Pediatric Sarcomas, Histiocytosis, and rare tumors, he is the Medical Director for the Hemophilia Treatment Center and the Program Director for the Pediatric Hematology Oncology Fellowship program at his center.
**Carl Allen** is currently Co-Chair of the Lymphoma and Histiocytosis Programs at the Texas Children’s Cancer and Hematology Centers (TXCH), where he directs translational research efforts. His research focus is on understanding mechanisms of aberrant immune function in human disease, including histiocytic disorders, lymphoproliferative disorders and lymphomas. His team has a history of productive collaborations (Miriam Merad (Mount Sinai), Matthew Collin (Newcastle), Florent Ginhoux (Singapore) and Markus Manz (Zurich)) to use complementary experimental models and approaches to understand pathogenesis of Langerhans cell histiocytosis. Their work to date has contributed to re-defining the cell of origin as an immature myeloid precursor (Allen et al., JI 2010), determined that state of differentiation of cell of origin determines clinical manifestations of disease (Berres et al., JEM 2014), created the first mouse models of LCH (Berres et al., JEM 2014), and identified functionally active recurrent mutations in MAP2K1 and BRAF in LCH (Chakraborty et al., 2014; Chakraborty et al., 2016). Together with Carlos Rodriguez-Galindo, they were awarded a grant to establish the North American Consortium for Histiocytosis Research, now including more than 30 institutions, which has launched 2 clinical trials and a LCH correlative biology study.

**Julien Haroche** is a professor in internal medicine, at Pitié-Salpêtrière hospital, Paris, France. Since 2003, his main research field is Erdheim-Chester disease (ECD) upon which he has acquired a word-renowned experience. To date, he has seen more than 150 patients followed at his institution. His other research fields are the other histiocytoses, such as Langerhans cell histiocytosis, mixed histiocytoses (LCH & ECD) and Rosai-Dorfman disease. He is also interested in vasculitis, lupus and antiphospholipid syndrome. During the past decade, he has described most relevant clinical and radiological aspects and increased the awareness of the disease, and showed that interferon α was a first line efficient therapy. Recently BRAFV600E mutations was shown in 50 to 75% of ECD cases lending support to the sustained and reproducible efficacy of BRAF inhibitors in severe cases of BRAFV600E mutated ECD. His team was the first to use BRAF inhibitors in BRAF mutated histiocytoses. He is also involved in the description of other recurrent somatic mutations of the MAP kinase and AKT pathways, including mutations of NRAS, and PIK3CA. Following the characterization of recurrent mutations of the MAK kinase pathway in ECD, the disease is now considered as an inflammatory myeloid neoplasia.

**Caroline Hutter** is attending physician in pediatric hematology/oncology at the St. Anna Children’s Hospital in Vienna, Austria. She earned her M.D. from the Medical University of Vienna and Ph.D. from UCL/Cancer Research UK. In addition to her role in the treatment of children and adolescents with cancer, her research focuses on the pathogenesis of Langerhans cell histiocytosis.

**Michael Jordan** graduated from the University of Texas Southwestern Medical School in 1993. After completing a pediatrics residency at the Children’s Hospital of Dallas, he began a Pediatric Hematology/Oncology fellowship at The Children’s Hospital, Denver, Colorado. After completing clinical training, Dr Jordan joined the laboratory of Drs. Philippa Marrack and John Kappler in 1997, where he studied T cell biology. In 2002, Dr Jordan joined the faculty there first as an Instructor of Pediatrics and then as an Assistant Professor at the University of Colorado Medical School. In 2004 he moved to Cincinnati Children’s Hospital/University of Cincinnati, where he is currently a Professor of Pediatrics in the divisions of Immunobiology, and Bone Marrow Transplantation and Immune Deficiency. The Jordan lab studies the pathophysiology and treatment of primary immune regulatory disorders, including hemophagocytic lymphohistiocytosis. His contributions include pioneering work to model and understand the pathophysiology of HLH and the investigation of new modalities of therapy for this disease.

**Kai Lehmberg** did his undergraduate medical training in Kiel, Essen (Germany), and London (UK). He is a pediatrician at the Department of Paediatric Haematology and Oncology and the Division of Paediatric Stem Cell Transplantation and Immunology at the University Medical Centre Hamburg Eppendorf (Germany). He has dedicated his scientific interest to clinical research in immune deficiencies and immune dysregulation with focus on haemophagocytic lymphohistiocytosis (HLH). His particular interests are acquired forms of HLH with infectious, rheumatological, and malignant triggers, and stem cell transplantation for hereditary HLH. Dr. Lehmberg heads the German national reference center for HLH in Hamburg (genetics, clinical counseling, cytology) and co-ordinates the data management of the international HLH registry, run by the Histiocyte Society and the European Society for Immune Deficiencies. He managed the European CureHLH project and coordinated the treatment studies HLH-2004 and EURO-HIT-HLH studies in Germany. He chairs the HS study group on HLH subtypes.
**REBECCA MARSH** is currently an Associate Professor in the Division of Bone Marrow Transplantation and Immune Deficiency at Cincinnati Children’s Hospital. She has several responsibilities within the Division, including being the Clinical Director of the Immunodeficiency Program, the Director of the Primary Immune Deficiency Fellowship, and Co-Director of the Diagnostic Immunology Laboratory. Her clinical practice centers exclusively around the diagnosis, treatment and transplantation of patients with primary immune deficiencies, and focuses on HLH and XIAP deficiency. Her clinical research centers around developing better diagnostic testing for patients with HLH, improving salvage treatment regimens, and improving transplant outcomes for patients with HLH. My translational and basic research focuses on understanding why XIAP Deficiency leads to HLH and finding new treatment approaches. She has several publications of note and has been awarded the Nesbit Award for Clinical Research by the Histiocyte Society twice.

**KEN MCCAIN** has dedicated his clinical and research efforts on the histiocytic diseases for 39 years beginning with his oncology fellowship at the University of Minnesota. Since 1986 he has been at the Texas Children’s Cancer Center in Houston where he is a Professor of Pediatrics. In 2002 he organized a Histiocytosis Center and was joined by Dr. Carl Allen in 2006. Together they have developed a robust clinical program which has attracted many patients from around the world. Because of the large number of specimens collected from patients enrolled on research studies they have developed successful translational research studies with collaborators from several other institutions. LCH patients with neurologic dysfunction have been a special research interest leading to innovative therapies and new biologic understanding of this problem. Dr. McClain has cared for adult patients with histiocytic diseases for nearly 30 years. He is a past president of the Histiocyte Society and been a member of the education and scientific committees as well as worked with the Adult, HLH, LCH, and Rare Disease committees.

**MILEN MINKOV**, M.D., Ph.D. is currently full professor for specialized pediatrics at the Sigmund Freud Private University, Head of the Clinic for Neonatology, Pediatrics and Adolescent Medicine at the Rudolfsstiftung Hospital, as well as, Consultant for Pediatric Hematology and Chair of the International LCH Study Reference Center at St. Anna Children’s Hospital, Vienna, Austria. Dr Minkov graduated from the Russian State Medical University, Moscow in 1991 and completed his residency and fellowship in pediatrics and pediatric hematology/oncology at the Russian Federal Institute for Pediatric Hematology in Moscow and in St. Anna Children’s Hospital in Vienna. Between 1996 and 2012, he worked in St. Anna Children’s Hospital, where he provided clinical care, supervised trainees, administered the Department of Outpatient Hematology/Oncology, and conducted clinical research at the Children’s Cancer Research Institute. He has been actively involved in teaching and supervision of medical students at the Medical University of Vienna since 1997 (Assistant Professor 1997-2007, Assoc. Professor 2007-2012, and Professor of Pediatrics since 2012). Since 2012, he is mentor at the Open Medical Institute of the American-Austrian Foundation, and since 2016 Honored Professor of the Federal State Research Center of Pediatric Hematology, Oncology and Immunology in Moscow. Dr. Minkov’s clinical experience covers the full spectrum of pediatric hematology/oncology, with a particular expertise in non-malignant hematology. His research has mainly been focused on LCH. He has over 100 published papers in peer-reviewed medical journals, contributed to a number of book chapters, guidelines and consensus papers. Dr. Minkov was in 1997 the first awardee of the Mark Nesbit Award for Clinical Science of the Histiocyte Society and is currently president of the Histiocyte Society. He is member of several professional societies and networks and medical advisor of patients and parent organizations.
MEETING AGENDA: SATURDAY • OCTOBER 20, 2018

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* ................................................................. Oliva
1030 – 1100  Coffee Break .................................................................................. Oliva
1430 – 1600  Website Committee Meeting* ........................................................... Oliva
1600 – 1630  Coffee Break ................................................................................. Foyer
1600 – 1700  Rare Histiocytic Disorders Steering Committee Meeting* ................ Oliva
1700 – 1800  LCH Steering Committee Meeting* ................................................... Oliva

MEETING AGENDA: SUNDAY, OCTOBER 21, 2018

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 ..................................................... Foyer
0800 – 0900  LCH-IV Study Management Group Session* ........................................ Closed Session
Session Moderator: Milen Minkov
0900 – 1130  LCH Disease Discussion Session* ....................................................... Morus II
Session Moderators: Carl Allen, Karin Beutel
0900 – 1130  HLH Education Session* ................................................................. Morus IV

BIOLOGY AND DIFFERENTIAL DIAGNOSIS
Michael Jordan
Cincinnati Children’s Hospital Medical Center, Cincinnati, OH USA

DIAGNOSIS AND FIRST-LINE TREATMENT OF GENETIC HLH
Kai Lehmberg
University Medical Centre Hamburg Eppendorf, Hamburg, Germany

HSCT AND SALVAGE OPTIONS FOR GENETIC HLH
Rebecca Marsh
Cincinnati Children’s Hospital Medical Center, Cincinnati, OH USA

1000 – 1030  Coffee Break .................................................................................. Foyer
1200 – 1430  LCH Education Session* ................................................................. Morus IV

BIOLOGY OF LCH
Caroline Hutter
St. Anna Children’s Hospital, Vienna, Austria

MANAGEMENT OF ADULT-ONSET LCH
Milen Minkov
St. Anna Children’s Hospital, Vienna, Austria

MANAGEMENT OF PEDIATRIC LCH
Ken McClain
Texas Children’s Hospital, Houston, TX USA

1230 – 1330  Lunch ............................................................................................. Flor de Lis Restaurant
1230 – 1330  Histiocytosis Association MSAC Committee Meeting* ...................... Morus III

* Indicates closed session
* Indicates that advance registration was required
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<td>1300 – 1830</td>
<td>Poster Presentation Setup</td>
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<td>1330 – 1430</td>
<td>Rare Histiocytic Disorders Discussion Session*</td>
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<td>Session Moderator: Oussama Abla</td>
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<td>1400 – 1600</td>
<td>HLH Steering Committee Meeting*</td>
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<td>1430 – 1800</td>
<td>HLH/MAS Discussion Session*</td>
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<td>Session Modorators: Stephan Ehl</td>
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<td>1500 – 1730</td>
<td>Rare Histiocytoses Education Session*</td>
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<td>Carl Allen</td>
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<td>Julien Haroche</td>
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<td>Pitié-Salpêtrière Hospital, Paris, France</td>
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<td>1600 – 1630</td>
<td>Coffee Break</td>
<td>Foyer</td>
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<td>1830 – 2030</td>
<td>Welcome Reception</td>
<td>EPIC SANA Lisboa Hotel - Scale Bar &amp; Terrace</td>
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<td>0800 – 1700</td>
<td>Meeting Registration and Check-In</td>
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<td>0800 – 1200</td>
<td>Poster Presentation Setup</td>
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<td>0800 – 0900</td>
<td>Education Committee Meeting*</td>
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<td>0800 – 0900</td>
<td>AME Histio Working Group Meeting</td>
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<td>0900 – 0915</td>
<td>Opening Ceremonies</td>
<td>Morus III &amp; IV</td>
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<td>Milen Minkov, Histiocyte Society President</td>
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<tr>
<td>0915 – 1000</td>
<td>Guest Speaker Presentation</td>
<td>Morus III &amp; IV</td>
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<td>Session Moderator: Milen Minkov</td>
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<td>1000 – 1030</td>
<td>Coffee Break</td>
<td>Foyer</td>
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<tr>
<td>1030 – 1230</td>
<td>Symposium: Mechanism and Targeted Therapies of CNS Histiocytosis</td>
<td>Morus III &amp; IV</td>
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<td>Session Moderator: Johannes Visser</td>
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<td>1230 – 1330</td>
<td>Lunch</td>
<td>Flor de Lis Restaurant</td>
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<td>1230 – 1330</td>
<td>HLH Meet the Expert Lunch Session*</td>
<td>Castanea</td>
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<td>Lunch will be provided in the foyer outside of the Castanea for Meet The Expert attendees only.</td>
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<tr>
<td>Gritta Janka</td>
<td>University Hospital of Hamburg, Hamburg, Germany</td>
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<td>1230 – 1330</td>
<td>LCH Meet the Expert Lunch Session*</td>
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<tr>
<td>Kimo Stine</td>
<td>Arkansas Children’s Hospital, Little Rock, AR USA</td>
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<td>New Investigator’s Luncheon*</td>
<td>Morus II</td>
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<td>Lunch will be provided in the foyer outside of Morus II for New Investigator Luncheon attendees only.</td>
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<td>Lunch will be provided in the foyer outside of the Flor de Lis Restaurant for lunch.</td>
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<td>1330 – 1515</td>
<td>Scientific Session I: Oral Presentations</td>
<td>Morus III &amp; IV</td>
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<td>Session Moderators: Barbara Degar and Kimo Stine</td>
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<td>Clonal Hematopoiesis in Erdheim-Chester Disease: A Monocentric Study on 101 Patients</td>
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<td>Incidence and Risk Factors for Clinical Neodegenerative Langerhans Cell Histiocytosis</td>
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<td>Sebastien Hertier, Jean-Francois Emile, Mohamed-Aziz Barkaoui, Jean Miron, Zofia Helias-Rodzewicz, Khe Hoang-Xuan, Ahmed Idbaih, Jean Donadieu</td>
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* Indicates closed session
+ Indicates that advance registration was required
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**DABRAFENIB INDUCES RAPID, DURABLE REMISSION IN PATIENTS WITH RISK-ORGAN LCH, INCLUDING SECONDARY HLH**  
Ashish R. Kumar, Lynn Lee, Mary Krupski, Jason P. Clark, Matthew Burwinkel

**CNS LANGERHANS CELL HISTIOCYTOSIS: COMMON HEMATOPOIETIC ORIGIN FOR LCH-ASSOCIATED NEURODEGENERATION AND MASS LESIONS**  

**BRAFV600E MUTATION-BEARING PROGENITOR CELLS AS A POTENTIAL CELL OF ORIGIN OF MYELOID CELLS PRESENT IN LCH LESIONS**  
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**CLINICAL OUTCOMES WITH MAPK INHIBITION FOR PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS**  

**GENOMIC ANALYSIS OF C-GROUP JUVENILE XANTHOGRANULOMA FAMILY LESIONS IDENTIFIES NOVEL KINASE ALTERATIONS AND DISTINCTIVE MORPHOLOGIC PATTERNS**  
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SIGNIFICANCE OF TH1/TH2 CYTOKINES IN OUTCOME PREDICTION OF HLH
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CLINICAL LCH POSTER NOMINEES

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**RETROSPECTIVE ANALYSIS OF EFFICACY AND SIDE-EFFECTS OF DABRAFENIB IN TREATMENT OF 21 BRAF-V600E MUTATION POSITIVE LCH CHILDREN**
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Poster Location #75
**LANGERHANS CELL HISTIOCYTOSIS OF THE GASTROINTESTINAL TRACT: RISK ORGAN STATUS**
Hoi Soo Yoon, Jae Hee Lee, Jennifer Michlitsch, Michael Jeng

**BASIC RARE HISTIOCYTIC DISORDERS POSTER PRESENTATIONS**

Poster Location #76
**ROSAI-DORFMAN DISEASE WITH EGFR MUTATION ON METACHRONOUS LESIONS**
Arturo Bonometti, Alessandra Rappa, Alberto Croci Giorgio, Mariarosa Arra, Roberta Riboni, Francesca Magnoli, Mattia Novario, Elena Dallera, Paolo Catarsi, Patrizia Morbin, Marco Paulli
Poster Location #77
RETICULOHISTIOCYTOSES, GENERALIZED ERUPTIVE HISTIOCYTOSIS AND MYELOID NEOPLASM: A SYSTEMATIC REVIEW
Arturo Bonometti, Jessica Gliozzo, Chiara Moltrasio, Filippo Bagnoli, Emanuela DeJuli, Emanuela Passoni, Emilio Berti

Poster Location #78
LANGERHANS CELL HISTIOCYTOSIS THERAPY FOR THE TREATMENT OF LIFE-THREATENING ROSAI DORFMAN DISEASE
Nadia Chaudhry-Waterman, Paul Kent

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CORONARY ARTERY CALCIFICATION IS COMMON AND SEVERE IN ERDHEIM-CHESTER DISEASE BUT UNRELATED TO BRAF MUTATION STATUS
Marcus Y. Chen, Diana Melo, Jeannie H. Yu, Sujata M. Shanbhag, W. Patricia Bandettini, Sara Haroutunian, William A. Gahl, Juvenee I. Estrada-Veras, Kevin J O'Brien

Poster Location #80
SPONTANEOUS RESOLUTION WITHOUT THERAPY OF SYSTEMIC JUVENILE XANTHOGANGLIOPLASMA IN AN INFANT: CASE REPORT
Rina Dvir

Poster Location #81
UPDATE ON THE EFFICACY OF JANUS KINASE 1-2 INHIBITION WITH BARICITINIB IN REFRACTORY NONLANGERHANS CELL HISTIOCYTOSIS
Daniel El Fassi, Kristian Kofoed, Holger Jon Møller, Claus Henrik Nielsen, Signe Ledou Nielsen, Lone Skov

Poster Location #82
VARIANT ALLELIC FREQUENCY IN ADULTS WITH BRAF MUTATED HISTIOCYTOSES AND RESPONSE TO BRAF INHIBITORS
Jean François Emile, Sarah Melloul, Zofia Helias-Rodzewicz, Fleur Cohen-Aubart, Frederic Charlotte, Sylvie Fraitag, Nathalie Terrones, Quentin Riller, Thibaud Chazal, Anne Moreau, Marianne Kambouchner, Marie Christine Copin, Jean Donadieu, Valerie Taly, Zahir Amoura, Julien Haroche

Poster Location #83
OBSTRUCTIVE UROPATHY AND NEPHROPATHY IN ERDHEIM-CHESTER DISEASE
Juvenee Estrada-Veras, Kevin J. O'Brien, Sara Haroutunian, Kavya Mathur, Louisa Boyd, Elaine Jaffe, Mark Raffeld, Arlene Sirajuddin, William Gahl, Ashkan Malayeri

Poster Location #84
PROGRESSIVE NODULAR HISTIOCYTOSIS. REPORT OF A PEDIATRIC CASE
M. Laura Galluzzo, Nilda González Robbón, Guido Felizzia, Cristian Sánchez La Rosa, María Marta Buján, Jorge Braier, Benjamin H. Durham, Omar Abdel-Wahab, Eli L. Diamond

Poster Location #85
ROSAL DORFMAN WITH POSITIVE PHOSPHO ERK STAINING WITHOUT MAPKINASE MUTATIONS SUCCESSFULLY TREATED BY DABRAFENIB / TRAMETINIB ASSOCIATION IN A 11 YEARS OLD TEENAGER.
Jean Donadieu, Marie France, Ray Lunven, David Lussato, Sebastien Herrlier, Zofia Helias-Rodzewicz, Michel Peuchmair, Jean François Emile

Poster Location #86
INTERSTITIAL LUNG DISEASE IN ERDHEIM-CHESTER DISEASE
Bernadette Gochuico, Sara Haratounian, Juvenee Estrada-Veras, Jianhua Yao, Louisa Boyd, Kavya Mathur, William Gahl, Mojdeh Mirmomen, Ashkan Malayeri, David Kleiner, Elaine Jaffe, Kevin O'Brien

Poster Location #87
DISSEMINATED MALIGNANT HISTIOCYTOSIS IN AN INFANT - CASE REPORT
Ana Paula Kuczynski, Carlos Rodriguez-Galindo, Isabela Werneck da Cunha

Poster Location #88
LOCALIZED ALK POSITIVE HISTIOCYTOSIS WITH AN KIF5B (KINESIN FAMILY MEMBER 5B) - ALK (ANAPLASTIC LYMPHOMA KINASE) FUSION IN THE SUBGLOTTIS OF A 3 YEAR OLD BOY
Bo-Yee Nang, Nikolaus Wolter, Evan Propst, Brendan Dickson, James Whitlock
MEETING AGENDA: MONDAY, OCTOBER 22, 2018

Poster Location #89
NOVEL BRAF FUSIONS IDENTIFIED IN TWO PEDIATRIC HISTIOCYTIC NEOPLASMS: HIGHLIGHTING THE NEED FOR HISTOLOGIC, MOLECULAR, AND CLINICAL CORRELATION FOR BEST DIAGNOSIS
Lea Surrey, Pierre Russo, Michael Hogarty, Richard Womer, Ronald Jaffe, Marilyn M. Li, Jennifer Picarsic

Poster Location #90
GAIN OF FUNCTION MUTATIONS OF PIK3CD AS A CAUSE OF CHRONIC ACTIVE EPSTEIN-BARR VIRUS INFECTION
Qing Zhang, Lei Cui, Yun-Ze Zhao, Dong Wang, Hong-Hao Ma, Li Zhang, Hong-Yun Lian, Tian-You Wang, Rui Zhang, Zhi-Gang Li

POSTER LOCATION MAP: VITIS

*Poster locations are approximate and subject to change upon arrival. Each poster will have a designated sign attached to the display board that will signify final location assignments.

IMPORTANT: Authors MUST use ONLY the mounting materials provided.
Posters MUST be REMOVED by 2030 on Monday, October 22, 2018. Any remaining posters will be discarded.
MEETING AGENDA: TUESDAY, OCTOBER 23, 2018

0800 – 1300  Meeting Registration and Check-in ........................................................................................................... Foyer

0830 – 0915  Jon Pritchard Lecture on the Nikolas Symposium ......................................................................................... Morus III & IV
Session Moderator: Carl Allen

MYELOID CELL PROGRAMMING AND DIFFERENTIATION
Matthew Collin
Newcastle University, Newcastle upon Tyne, United Kingdom

0915 – 1000  Histiocyte Society/ESID Lecture ................................................................................................................. Morus III & IV

HLH IN PRIMARY IMMUNE DEFICIENCIES PHENOTYPE
Stephan Ehl
Centre of Chronic Immunodeficiency University Medical Center - Freiburg, Freiburg, Germany

1000 – 1030  Coffee Break ......................................................................................................................................................... Foyer

1030 – 1230  Symposium: HLH Therapy - Update and Future Perspectives ................................................................. Morus III & IV
Session Moderator: Rebecca Marsh

INHIBITING CYTOKINES AND CYTOKINE RECEPTOR SIGNALING
Kim Nichols
St. Jude Children’s Research Hospital, Memphis, TN USA

IFN GAMMA
Michael Jordan
Cincinnati Children’s Hospital, Cincinnati, OH USA

HSCT
Tayfun Gündör
University of Zurich, Zurich, Switzerland

1230 – 1330  Lunch .................................................................................................................................................... Flor de Lis Restaurant

1230 – 1330  Rare Histiocytoses Meet the Expert Lunch Session* .................................................................................. Castanea
Lunch will be provided in the Foyer outside of the Castanea for Meet The Expert attendees only.

Oussama Abla
The Hospital for Sick Children, Toronto, ON, Canada

1230 – 1330  Joint HS/ESID Executive Boards Luncheon* ......................................................................................... Laurus
Closed Meeting. Lunch will be provided in the foyer outside of the Laurus for attendees of this luncheon.

1400 – 1530  Scientific Session III: Oral Presentations ....................................................................................................... Morus III & IV
Session Moderator: Patrick Campbell

GENETIC AND MECHANISTIC DIVERSITY IN PEDIATRIC HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Emily M. Mace, Tiphanie P. Vogel, Harshal A. Abhyankar, Maria I. Diaz, Helen E. Heslop, Robert A. Krance,
Caridad A. Martinez, Trung C. Nguyen, Dalia A. Bashir, Jordana R. Goldman, Asbjørg Stray-Pedersen, Luis A. Pedroza,
M. Cecilia Poli, Juan C. Aldave Becerra, Sean A. McGhee, Waleed Al-Herz, Aghiad Chamdin, Zeynep H. Coban-Akdemir,
Shalini N. Jhangiani, Donna M. Muzny, Tram N. Cao, Diana N. Hong, Richard A. Gibbs, James R. Lupski, Jordan S. Orange,
Kenneth L. McClain, Carl E. Allen

ARE PROTEINS OF THE DEGRANULATION MACHINERY REQUIRED FOR RUBELLA VIRUS CONTROL IN THE SKIN?
Stephan Ehl, Miriam Heizmann, Sarah Lena Maier, Carsten Speckmann, Bianca Tesi, Claudia Khurana,
Nora Naumann-Bartsch, Abbas Agaimy, Daniela Huzly, Yenan T. Bryceson, Annette Schmitt-Graeff, Kai Lehmberg

CELL-SPECIFIC GENE EXPRESSION IN LANGERHANS CELL HISTIOCYTOSIS REVEALS DISTINCT PROFILES IN LESION CD207+ CELLS BASED ON BRAFV600E MUTATION
Howard Lin, Karen Phaik Har Lim, Harshal Abhyankar, Rikhia Chakraborty, Brooks Scull, Olive Eckstein, Daniel Zinn,
Walter Olea, Thomas Burke, M. John Hicks, Miriam Merad, Tsz-Kwong Man, Kenneth L McClain, Carl E. Allen

IMPACT OF A MULTIDISCIPLINARY TASKFORCE AND ELECTRONIC TRIGGER IN THE IDENTIFICATION AND

* Indicates closed session
* Indicates that advance registration was required
TREATMENT OF PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Andrew Martin, Archana Dhar, Teresa Jones, Marilyn Punaro, Julie Fuller, Katie Stewart, Leandra Woolnough, Lorien Nassi, Tracey Wright, Maite De La Morena, Keiji Akamine, Mailan Nguyen, Cindy Darnell, Josh Koch, Samuel Davila, David Zwick, Hung Luu, Amal Aqul, Christina Stylianou, Norberto Rodriguez-Baez, Paul Sue, Michael Sebert, Chris Wysocki, Victor Aquino, Ruth Anne Herring, Do Vy

HISTOLOGY OF ROSAI-DORFMAN DISEASE IN A SUBSET OF PATIENTS WITH ERDHEIM-CHESTER DISEASE: A DISTINCT ENTITY MAINLY DRIVEN BY MAP2K1.

RUXOLITINIB FOR REFRACTORY/RELAPSED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Jingshi Wang, Yini Wang, Lin Wu, Wenyuan Lai, Zhao Wang

DIFFERENT TH1/TH2 CYTOKINE PATTERNS BETWEEN PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) AND EBV RELATED HLH
Xiaojun Xu, Ze-bin Luo, Yongmin Tang, Hua Song, Weiqun Xu, Ning Zhao

1530 – 1630
Presentation of Late Breaking Abstracts ................................................................. Morus III & IV
Session Moderator: Rebecca Marsh

1630 – 1700
Coffee Break ......................................................................................................... Foyer

1630 – 1730
General Assembly Business Meeting* ......................................................... Morus III & IV

1730 – 1800
Executive Board Meeting* ............................................................................. Morus III & IV
Education Committee Meeting* ....................................................................... Morus III & IV
Scientific Committee Meeting* ........................................................................ Morus III & IV

1845 – 1900
Meet for Group Transportation to Histiocyte Society Annual Banquet ...............EPIC SANA Lisboa Hotel Lobby
Group will meet in hotel lobby for bus transportation to the Annual Banquet

1930 – 0100
Histiocyte Society Annual Banquet, Closing Ceremonies & Awards* ............... Kais Restaurant & Skones Club
Awarding of Nesbit Prize for Excellence in Clinical Science
Awarding of Nezelof Prize for Excellence in Basic Science
Awarding of Robert J. Arceci Prize for Best Poster

*Looping buses will return to EPIC SANA Lisboa every half hour starting at 2200.
The pathophysiology of neurodegenerative diseases is poorly understood and there are few therapeutic options. Neurodegenerative diseases are characterized by progressive neuronal dysfunction and loss, and chronic glial activation. Whether microglial activation, which is generally viewed as a secondary process, is harmful or protective in neurodegeneration remains unclear. Late-onset neurodegenerative disease observed in patients with histiocytoses, which are clonal myeloid diseases associated with somatic mutations in the RAS-MEK-ERK pathway such as BRAF(V600E), suggests a possible role of somatic mutations in myeloid cells in neurodegeneration. Yet the expression of BRAF(V600E) in the haematopoietic stem cell lineage causes leukaemic and tumoural diseases but not neurodegenerative disease. Microglia belong to a lineage of adult tissue-resident myeloid cells that develop during organogenesis from yolk-sac erythro-myeloid progenitors (EMPs) distinct from haematopoietic stem cells. We therefore hypothesized that a somatic BRAF(V600E) mutation in the EMP lineage may cause neurodegeneration. Here we show that mosaic expression of BRAF(V600E) in mouse EMPs results in clonal expansion of tissue-resident macrophages and a severe late-onset neurodegenerative disorder. This is associated with accumulation of ERK-activated amoeboid microglia in mice, and is also observed in human patients with histiocytoses. In the mouse model, neurobehavioural signs, astrogliosis, deposition of amyloid precursor protein, synaptic loss and neuronal death were driven by ERK-activated microglia and were preventable by BRAF inhibition. These results identify the fetal precursors of tissue-resident macrophages as a potential cell-of-origin for histiocytoses and demonstrate that a somatic mutation in the EMP lineage in mice can drive late-onset neurodegeneration. Moreover, these data identify activation of the MAP kinase pathway in microglia as a cause of neurodegeneration and this offers opportunities for therapeutic intervention aimed at the prevention of neuronal death in neurodegenerative diseases. (Mass E et al Nature. 2017 Sep 21;549(7672):389-393. doi: 10.1038/nature23672. Epub 2017 Aug 30.)

The neurodegenerative form of LCH (ND-LCH) is an uncommon complication of LCH. ND-LCH is clinically characterized by the progressive onset of ataxia, dysarthria, other cerebellar signs, paresis and less commonly cognitive impairment. Radiologic features of ND-LCH include hyperintense lesions best visualized on T2 MRI predominantly in the pons, cerebellum, and basal ganglia, in patients with clinical disease and in asymptomatic patients years before clinical symptoms emerge.

Risk factors for ND-LCH include diabetes insipidus and LCH involving craniofacial bones, suggesting that loco-regional spread of LCH cells to the central nervous system is an important factor in the development of ND-LCH.

The pathophysiology of ND-LCH has been unclear, due to its rarity and to the challenges associated with obtaining pre-morbid biopsies. Neuropathologic examinations in a small number of cases have demonstrated “a T-cell-dominated inflammatory process...characterized by neuronal and axonal destruction with secondary demyelination.” (Grois, Brain, 2005). Current therapeutic options for ND-LCH are limited.

The identification of BRAF alterations in the majority of LCH cases has led to the development of new targeted therapeutic strategies for LCH, including ND-LCH. Early data indicate that BRAF inhibitors can have significant activity in patients with ND-LCH. Evidence supporting a central role for aberrant MAPK signaling in the pathogenesis of ND-LCH and a potential role for BRAF and MEK inhibitors in the treatment of patients with ND-LCH will be discussed.
The subject of myeloid cell differentiation impacts widely on human pathology. In recent years, investigators have continued to refine the differences between resident and recruited cells and between cells occupying distinct anatomical sites. It is now clear that dendritic cells are continually renewed from precursors arising in the bone marrow. Macrophages, on the other hand have a much wider range of half-lives ranging from inert populations that were seeded during embryogenesis to populations that are almost as transient as blood monocytes. The origin of histiocytosis is still debated. Although it is possible to relate everything from isolated lesions to multi-system disease to stages of haematopoietic development, it is difficult to refute a potential contribution from embryonic remnant macrophages that are present in most tissues, or even haematopoietic progenitors that circulate in the periphery.

Hemophagocytic lymphohistiocytosis (HLH) comprises a heterogeneous spectrum of disorders associated with the uncontrolled activation of T cells and macrophages that copiously secrete numerous pro-inflammatory cytokines. The resulting cytokine storm can lead to severe and often life-threatening immunopathology. A similar cytokine storm has been described in patients receiving T-cell based cancer immunotherapies, such as chimeric antigen receptor transduced T cells and bi-specific T cell engaging antibodies. Recent human and murine studies have provided tremendous insights into the cytokines and signaling pathways that are active in these syndromes, including interferon-gamma, Tumor Necrosis Factor-alpha, and interleukins (IL)-1, IL-6, and IL-18. These cytokines are central to HLH pathogenesis and responsible for many of the associated signs and symptoms of disease. Given the wealth of emerging data, novel therapies targeting these cytokines, their receptors or the downstream signaling pathways are being tested in the treatment of HLH. In this presentation, several of these cytokine-directed therapies will be discussed, including any pre-clinical and available clinical information.
CLONAL HEMATOPOIESIS IN ERDHEIM-CHESTER DISEASE: A MONOCENTRIC STUDY ON 101 PATIENTS

Julien Haroche1; F. Cohen-Aubart1; S. Poulain2; A. Marceau-Renaud2; N. Duployez2; JF. Emile2; C. Settegrana2; F. Nguyen-Khac3; D. Roos-Weil4; F. Charlotte5; J. Donadieu5; Z. Amoura1

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2 Biology and Pathology Center, Laboratory of Hematology, Centre Hospitalier Universitaire (CHU) Lille, Lille, France; Cancer Research Institute, INSERM Unite Mixte de Recherche (UMR), Lille, France
3 Versailles University, Paris-Saclay University, Boulogne, France; Pathology Service, Hôpital Universitaire Ambroise Pare, AP-HP, Boulogne, France
4 Department of Biological Hematology, University Hospital La Pitie-Salpêtrière, AP-HP, Paris, France
5 Department of Pathology AP-HP, Pitie-Salpêtrière Hospital, Paris, France
6 Department of Haematology, AP-HP, Trousseau Hospital, Paris, France

Introduction: Erdheim-Chester disease (ECD) is a rare histiocytosis characterized by the accumulation of CD68+ CD1a- foamy histiocytes in various tissues and organs. In 2016, ECD was reclassified as an inflammatory myeloid neoplasm, following the discovery of recurrent somatic genetic alterations of the RAS-RAF-MEK-ERK in histiocytes. The frequent association with a LCH and with other hemopathies raised the question of a clonal hematopoiesis in ECD. Patients and methods We studied by high-throughput sequencing (Ampliseq System, conformally to the recommendations from the manufacturer) the molecular alterations presented in the bone marrow aspiration of 101 ECD patients, among 36 genes frequently mutated in myeloid hematopathies. The raw sequencing data were then analyzed with Torrent Browser (Therofisher) and SeqNext (JSI Medical System). The presence of a BRAFV600E mutation was sought in the bone marrow aspiration and within histiocytic cells. Results: Of the 101 patients with ECD, 10 (10%) had associated myeloid hemopathy and 44 (43.5%) had at least another mutation than BRAFV600E in one of the 36 genes studied. A total of 85 mutations were found (1-6 genes per patient), on a small number of genes. The most frequently mutated genes were TET2, ASXL1, DNMT3A, NRAS, CBL, KRAS, JAK2 and SRSF2. The presence and number of mutations were related. Some patients presented several mutations within the same gene, in particular TET2, ASXL1 and NRAS. A BRAFV600E mutation was present in 23 patients, and some of the 101 patients received BRAF inhibitors. The presence of a TET2 mutation in the medullogram was correlated with the BRAFV600E status (in histiocytes) (p= 0.04). Conclusion: ECD is associated with a high prevalence of myeloid hemopathies but also with a high proportion of age related clonal hematopoiesis. The long-term impact of these abnormalities should be clarified, especially in histiocytic patients treated with anti-BRAF and/or anti-MEK targeted therapies.

INCIDENCE AND RISK FACTORS FOR CLINICAL NEURODEGENERATIVE LANGERHANS CELL HISTIOCYTOSIS

Sebastien Herlitz1,2; Jean-François Emile3,4; Mohamed-Aziz Barkaoui1; Jean Miron5; Zofia Heilas-Rodzewicz2,6; Khe Hoang-Xuan6; Ahmed Idibah7; Jean Donadieu1,2

1 French Reference Center for Langerhans Cell Histiocytosis, Trousseau Hospital, Paris, France
2 EA4340, UVSQ, Universite Paris-Saclay, Boulogne-Billancourt, France
3 Pathology Department, Ambroise Pare Hospital, Assistance Publique:Hôpitaux de Paris, Boulogne-Billancourt, France
4 Department of Neurology, Pitie -Salpêtrière Hospital, Assistance Publique:Hôpitaux de Paris, Paris, France

Purpose: Neurodegenerative Langerhans cell histiocytosis (ND LCH) is a delayed and disabling complication of LCH for which incidence and risk factors are not well defined. Methods: Based on a national prospective registry of 1897 pediatric LCH patients, we determined the incidence rate of clinical ND LCH (cND-LCH) and analyzed risk factors, taking into account disease extent and molecular characteristics. Results: Among 1,897 LCH patients, 36 (1.9%) were diagnosed with a cND-LCH. The median delay of cND-LCH occurrence after LCH diagnosis was 6.5 years, and the 10-year cumulative incidence of cND-LCH was 4.1%. cND-LCH typically affected patients previously treated for a multisystem, risk organ:negative LCH, represented in 69.4% of cND-LCH cases. Pituitary gland, skin, and base skull/orbit bone lesions were more frequent (P<0.001) in cND-LCH patients compared to those without cND-LCH (respectively 86.1% vs. 12.2%, 75.0% vs. 34.2%, and 63.9% vs. 28.4%). Of note, we observed no cND-LCH among patients with LCH onset after age 10 years. For the group of cND susceptible patients' (n=671) who comprised children who had experienced LCH disease with pituitary or skull base or orbit bone involvement, this group had a 10-year cND risk of 7.8% vs. 0% for patients who did not meet these criteria. Finally, BRAFV600E status added important information among these cND susceptible patients, with the 10-year cND risk at 33.1% if a BRAFV600E mutation was present compared to 2.9% if it was absent (P=0.002). Conclusion: We identified significant clinical and molecular risk features for cND-LCH. Further studies should focus on a cND risk-based screening to evaluate specific interventions.

DABRAFENIB INDUCES RAPID, DURABLE REMISSION IN PATIENTS WITH RISK-ORGAN LCH, INCLUDING SECONDARY HLH

Ashish Kumar; Lynn Lee; Mary Knupski; Jason P. Clark; Matthew Burwinkel

Cincinnati Children’s Hospital Medical Center, Cincinnati, OH USA

Purpose: Determine therapeutic efficacy of single-agent Dabrafenib in BRAF-V600E positive LCH. Methods: Infants with BRAF-V600E positive multisystem risk-organ LCH were treated with Dabrafenib. When available, affected bone marrow cells were transplanted into immune deficient mice. Results: Five consecutive infants, all with multi-system risk organ LCH affecting the bone marrow, liver, spleen, or thymus were treated at our institution. Three of the patients had been previously treated with a variety of LCH therapies and remained refractory. Four patients met criteria for the diagnosis of HLH as per HLH-2004. BRAF-V600E was detected in all patients by immunohistochemistry and molecular assays. Oral Dabrafenib resulted in rapid clinical resolution of disease in all patients. With a median follow up of 18 months (range 3-24 months), all patients remain in complete clinical...
remission, with no evident adverse effects. For the first two patients, both previously treated with a variety of chemotherapy regimens, BRAF-V600E positive cells remain detectable in the bone marrow after 24 months of treatment. On the other hand, patient 3 who was treated with Dabrafenib upon progression after just one cycle of induction chemotherapy, is negative after 12 months of therapy. Bone marrow cells obtained from patients prior to initiating therapy engrafted and induced disease in immune deficient mice. Serial transplantation into secondary recipient mice induced disease with shorter latency. Tissue analysis revealed infiltration of spleen and liver by human cells that were BRAF-V600E positive. Conclusions: Oral Dabrafenib results in rapid, sustained clinical remission in patients with multisystem risk organ LCH, including those with secondary HLH. Early initiation of treatment may result in molecular remission. Patient derived xenograft models of LCH are feasible and could be useful for testing novel therapeutic approaches.

CNS LANGERHANS CELL HISTIOCYTOSIS: COMMON HEMATOPOIETIC ORIGIN FOR LCH-ASSOCIATED NEURODEGENERATION AND MASS LESIONS

Kenneth McClain1; Jennifer Picarsic2; Rikika Chakraborty1; Daniel Zinn1; Howard Lin1; Harshal Abhyankar1; Brooks Scull1; Albert Shih1; Karen Phaik Har Lim1,2; Olive Eckstein1; Joseph Lubega1; Tricia Peters1,4; Walter Olea1; Thomas Burke1; Nabil Ahmed1; John Hicks1,4; Brandon Tran2; Jeremy Jones6; Robert Dauser6; Michael Jeng2; Robert Baciocchi6; Deborah Schiff6; Stanton Goldman1,10; Kenneth M. Heym11; Harry Wilson12; Benjamin Carcamo13; Ashish Kumar14; Carlos Rodriguez-Galindo15; Nicholas Whipple15; Patrick Campbell15; Geoffrey Murdoch15; Julia Kofler16; Simon Heales17; Marian Malone18; Randy Wolfg19; Joseph Quinn19; Paul Orchard20; Michael Kruever21; Ronald Jaffe22; Markus Manz23; Sergio Lira24; William Parsons1,25; Miriam Merad26; Ts-z Kwong Man1; Carl Allen1

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7 Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA
8 Department of Internal Medicine, The Ohio State University, Columbus, OH, USA
9 Department of Pediatrics, University of California-San Diego, La Jolla, CA, USA
10 Medical City Children's Hospital, Dallas TX and Texas Oncology, PA, USA
11 Department of Pediatrics, Cook Children's Medical Center, Fort Worth, TX, USA
12 Department of Pathology, Texas Tech University Health Sciences Center El Paso, TX, USA
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16 Department of Pathology, Division of Neuropathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
17 Chemical Pathology, Great Ormond Street Hospital for Children, London, United Kingdom
18 Laboratory Medicine, Great Ormond Street Hospital for Children, London, United Kingdom
19 Layton Aging and Alzheimer's Disease Center, Oregon Health and Science University, Portland, OR, USA
20 Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA
21 Barrow Neurological Institute, Phoenix Children's Hospital; Child Health, Neurology & Genetics, University of Arizona College of Medicine, Phoenix, AZ, USA
22 Department of Pathology, Magee-Women's Hospital of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
23 Division of Hematology, University of Zurich, University Hospital Zurich, Zurich, Switzerland
24 Immunology Institute, Icahn School of Medicine, New York, NY, USA
25 Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA
26 Department of Oncological Sciences, Tisch Cancer Institute, Icahn School of Medicine, New York, NY, USA

Purpose: Langerhans cell histiocytosis brain involvement (CNS LCH) may include mass lesions and/or a neurodegenerative syndrome (LCH-ND) of unknown etiology. This study aimed to define mechanisms of pathogenesis that drive CNS LCH. Methods: Cerebral spinal fluid (CSF) biomarkers including CSF proteins and extracellular BRAFV600E DNA were analyzed in CSF from patients with CNS LCH lesions compared to CSF from patients with brain tumors and other neurodegenerative conditions. Additionally, the presence of BRAFV600E was tested in peripheral mononuclear blood cell (PBMC) populations as well as brain biopsies from LCH-ND patients, and response to BRAFV600E inhibitor was evaluated in 4 patients with progressive disease. Results: Osteopontin was the only consistently elevated CSF protein in patients with CNS LCH compared to patients with other brain pathologies. BRAFV600E DNA was detected in CSF of only 2/20 (10%) cases, both with LCH-ND and active lesions outside the CNS. However, BRAFV600E+ PBMC were detected with significantly higher frequency at all stages of therapy in patients who developed LCH-ND. Brain biopsies of patients with LCH-ND demonstrated diffuse perivascular infiltration by BRAFV600E+ cells with monocyte phenotype (CD14+CD33+CD163+P2RY12-) and associated osteopontin expression. Three of four patients with LCH-ND treated with BRAFV600E inhibitor experienced significant clinical and radiologic improvement. Conclusions: BRAFV600E+ cells in PBMC and infiltrating monocytes in the brain of LCH-ND patients is consistent with LCH lesion CD207+ cells and LCH-ND inflammatory monocytes arising from a common hematopoietic precursor. Therapy directed against monocytes with activated MAPK signaling may be effective for LCH-ND.
BRAFV600E MUTATION-BEARING PROGENITOR CELLS AS A POTENTIAL CELL OF ORIGIN OF MYELOID CELLS PRESENT IN LCH LESIONS

Astrid van Halteren¹; Yanling Xiao²; Eline Steenwijk¹; Xin Lei²; Arnoud Schmitz³; Joanna Grabowska²; Cor van den Bos⁴;⁵; Jannie Borst²

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Purpose: We have recently identified in human bone marrow and peripheral blood a myeloid progenitor population, which is oligopotent for granulocyte (Gr), macrophage (MΦ), osteoclast (OC) and dendritic cell (DC) development. We predicted that this so called GMODP could also give rise to Langerhans cells (LC), the myeloid cell type commonly found, together with MΦ and OC, in Langerhans Cell Histiocytosis (LCH) lesions. We hypothesized that in case the BRAFV600E mutation is acquired by GMODP cells, the mutation should be detected in its in vitro generated offspring cells. Methods: To examine a putative role of blood-borne GMODP in LCH, their frequencies were assessed in healthy controls (HC) and therapy-naïve LCH patients. GMODP sorted from HC or from patients displaying BRAFV600E mutation in LCH-affected tissue(s) were cultured under LC or DC differentiation-promoting conditions. Presence of BRAFV600E mutation in GMODP-derived progeny was analysed by Taqman PCR or digital droplet PCR. Results: GMODP frequency in blood is significantly higher in LCH patients than in HC (p=0.002). GMODP was also detected in LCH lesions. Total cell counts of LC cultures generated from LCH patients was higher when compared to yields generated from the same number of HC-derived GMODP. LC output was identified by the presence of HLA-DR+ CD11c+ CD14+ CD207+ CD1a+ cells. The percentage of CD1a+ CD207+ cells was increased in LCH patient-derived LC cultures. The BRAFV600E mutation was detected in both LC and DC offspring of LCH patient-derived GMODP. Conclusion: Human GMODP can differentiate into LC-like cells in addition to their already reported Gr, MΦ-, OC- and DC-differentiation potential. LCH patient-derived GMODP display proliferative and differentiation advantage when exposed to LC differentiation-promoting stimuli. Our result suggests that somatically mutated GMODP may be the cell of origin in LCH lesions, but further studies are needed to assess their role in the various presentation forms.
Hemophagocytic Syndrome (HLH) and Primary Immunodeficiencies (PIDs): Report from the HLH Italian Registry

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Purpose: Aim of this study is to explore the role of PID-associated genes in patients with HLH. Methods: Since 2017, patients referred to the Italian Registry for HLH, with normal Perforin and CD107a expression and wild type SAP and XIAP (males), underwent Target Resequencing for all known familial HLH (FHL)-related genes and a panel of PID-associated genes. Results: Thirtyseven patients with HLH were enrolled, median age 6.5 years (quartiles: 1.5, 6.5, 12.2). HLH-2004 diagnostic criteria were complete in 11/37 (30%) patients and partial (central nervous system only, n=2) in 26/37 (70%). Eleven of the 37 (30%) patients had a known underlying disease: acute lymphoblastic leukemia (n=3), anaplastic large cell lymphoma (n=1), systemic juvenile idiopathic arthritis (n=2), Kawasaki disease (n=1), Shwachman-Diamond disease (n=1), malaria (n=1), leishmaniasis (n=1), cystic fibrosis (n=1). None of the patients was found to be affected by FHL. Thirty of the 37 (81%) patients harbored variants in one or more genes. Monoallelic variants in only FHL-related genes were found in 4/37 (11%) patients: STXB2 (n=2), PRF1 and Rab27a (n=1), PRF1 and LYST (n=1). Variants in only PID-associated genes were found in 17/37 (46%). Six of the 17 (35%) patients were diagnosed with PID because of biallelic variants respectively in: TET2 (n=1), IL10RA (n=1), CBL (n=1) and monoallelic variants in FAS (n=2); 11/17 (23%) patients had a uncertain significance in one or more of the following genes: DOCK2, TMEM173, CTH, PLCG2, STIM1, CARD11, CASP8, CXCR4, NLRC4, IL10RA, STAT5B, WAS, ORAI1. Multiple monoallelic variants in both FHL and PID-associated genes were found in the remaining 8/37 (22%) patients. Conclusions: The 81% of patients previously classified as secondary HLH harbored variants in one or more FHL/PID-associated genes, leading to redefine the diagnosis in PID in 16% of cases and possibly increasing the susceptibility to develop HLH in various clinical contexts.

Clinical Outcomes with MAPK Inhibition for Pediatric Langerhans Cell Histiocytosis

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Purpose: Langerhans Cell Histiocytosis (LCH) is an inflammatory myeloid neoplasia with activating mutations in MAPK pathway genes identified in almost all cases (BRAF-V600E in approximately 60%). Targeted inhibition of MAPK pathway may be an effective therapeutic strategy for children with LCH. The purpose of this study was to report the efficacy and toxicity of a retrospective cohort of patients with LCH treated with MAPK pathway inhibitors. Methods: Medical records were retrospectively reviewed from 18 patients with LCH treated with a MAPK pathway inhibitor at eight institutions. All patients had a proven MAPK pathway mutation and had failed at least one prior systemic treatment. Results: All patients in this series were less than 21 years old (median age at start of therapy 7.05 years; range: 0.4-20.7 years). Ten patients had LCH-neurodegenerative disease (LCH-ND) diagnosed clinically and/or by imaging, while the remaining 8 patients had systemic disease with no LCH-ND. Two patients (11%) achieved a CR, 6 patients achieved a PR (33%), 3 patients only achieved stable disease (17%), and 7 patients experienced progression (38%). Of patients with LCH-ND, all 10 achieved at least PR (40%) or SD (60%), but 4 of these patients eventually progressed. Overall survival was 94% with a median follow-up of 20 months (range 1-42 months). Median PFS was 11.8 months (range 2-36 months), while median time to disease progression or recurrence was 4.6 months (range 1-46 months). Four of the 18 patients (22%) had a Grade 3-4 toxicity: 2 patients (11%) required dose reduction. Conclusions: MAPK pathway inhibitors may be a relatively safe salvage therapy for refractory systemic LCH and LCH-ND but the efficacy and durability of response is undefined. Future prospective trials of MAPK pathway inhibitors for patients with refractory LCH are needed to compare efficacy and toxicity relative to other current salvage strategies.
GENOMIC ANALYSIS OF C-GROUP JUVENILE XANTHOGANULOMA FAMILY LESIONS IDENTIFIES NOVEL KINASE ALTERATIONS AND DISTINCTIVE MORPHOLOGIC PATTERNS

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Purpose: Juvenile xanthogranuloma family lesions (JXG) are classified both within the "L" group (Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease, including extracutaneous/disseminated JXG with activating mutations) and "C" group (non-LCH lesions of the skin and mucosa). While "L" group JXG lesions harbor activating mutations in the mitogen-activated protein kinase (MAPK) pathway, genomic alterations characteristic of "C" group lesions are poorly defined. Therefore, we performed comprehensive sequencing analyses across pediatric JXG C-group lesions with clinicopathologic correlation. Methods: Thirty-eight solitary pediatric JXG family lesions were retrieved with standard pathologic evaluation and immunohistochemistry evaluation. Targeted DNA and RNA sequencing of archived, formalin-fixed, paraffin-embedded (FFPE) tissue was performed on specimens with available material. Results: Cases included cutaneous (n=25) and superficial soft tissue based (n=1) solitary C-group lesions; median age: 2.3 years (0.2-17.8y), male predominance 1.6:1. Kinase alterations were highly prevalent (n=18, 69%), including mutations in MAP2K1/KIT (n=1), KIT (n=3), KRAS (n=1), CSF1R (n=3), CSF3R (n=1), MET (n=1), JAK3 (n=1), ALK (n=1), and kinase fusions in NTRK1 (n=5) and ALK (n=1), without systemic manifestations. Distinctive histologic groups that correlated with mutations include the NTRK1 fusions, which were present exclusively in boys with dense granulomatous lesions containing pathological CD207+ dendritic cells (DCs). Conclusions: Indolent, often self-limiting juvenile xanthogranuloma family lesions include the NTRK1 fusions, which were present exclusively in boys with dense granulomatous lesions containing pathological CD207+ dendritic cells (DCs). These kinase alterations are correlated with distinctive histologic patterns, which may inform the morphological diversity in JXG family lesions. Further functional studies should investigate if these mutations are related to timing of cell differentiation, akin to the LCH model.

PRESENTATIONS NOMINATED FOR THE NEZELOF PRIZE IN BASIC SCIENCE

MAPPING RENDERS DENDRITIC CELLS IN LANGERHANS CELL HISTIOCYTOSIS LESIONS TRAPPED AND RESISTANT TO CELL DEATH

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Purpose: LCH is an inflammatory myeloid neoplasia characterized by granulomatous lesions containing pathological CD207+ dendritic cells (DCs). A unique feature of these DCs is universal MAPK activation resulting from mutually exclusive somatic activating mutations in MAPK pathway genes including BRAFV600E (50-65%), MAP2K1 (10-20%), and other less common alterations. However, mechanisms through which ERK activation in myeloid DC precursors mediates LCH pathogenesis are not known. There remained a clear need for improving our understanding of the mechanisms of LCH pathogenesis to develop therapeutic strategies with improved efficacy and minimal toxicity. Methods: Impact of the somatic BRAFV600E mutation on the key biological functions of DCs including proliferation, differentiation/activation, migration, cytokine production, and apoptosis were determined using mouse experimental models of LCH as well as LCH patient tissue samples. Results: Sustained extracellular signal-related kinase activity induced by BRAFV600E inhibited C-C motif chemokine receptor 7 (CCR7):mediated DC migration, trapping DCs in tissue lesions. Additionally, BRAFV600E increased expression of BCL2-like protein 1 (BCL2L1) in DCs, resulting in resistance to apoptosis. Pharmacological MAPK inhibition restored migration and apoptosis potential in a mouse model of LCH, as well as in primary human LCH cells. Our results also showed that MEK inhibitor-loaded nanoparticles could enhance accessibility of MAPK pathway inhibitors in LCH where development of these promising agents has been challenged by a concerning toxicity profile for a largely pediatric population. Collectively, our results indicate that MAPK tightly suppresses DC migration and augments DC survival, rendering DCs in LCH lesions trapped and resistant to cell death.

JAK INHIBITION IN MURINE HLH: CAREFUL REEXAMINATION REVEALS SIGNIFICANT TOXICITY

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Purpose: The study of hemophagocytic lymphohistiocytosis (HLH) in mice has defined disease pathophysiology and suggested strategies for the targeted therapy of human HLH. Multiple groups have reported that blockade of interferon gamma (IFN-g) or downstream JAK/STAT signaling is effective therapy for murine HLH. JAK inhibitors are associated with toxicities affecting the marrow and liver in clinical use, but significant toxicity has not been reported in murine models of HLH. Therefore, we sought to understand whether toxicity would be a major concern in clinical HLH by carefully re-examining multiple JAK-inhibiting drugs in murine HLH. Methods: Utilizing the
model system which we first reported as a robustly recreating human HLH (LCMV-WE infection of perforin deficient mice), we assessed outcomes after treatment with various JAK inhibitors including ruxolitinib, baricitinib, filgotinib and AZD-4025. We also examined combination therapies incorporating these agents and assessed the effects of disease kinetics on treatment outcomes. Results: We observed that JAK inhibitors have significant toxicities which have not been reported to date in murine HLH. If applied after the full onset of HLH disease, they generally hasten death of experimental animals, instead of prolonging it. Even when applied pre-emptively, before onset of most features of HLH, we found that they allow for poorer survival than has been reported with milder murine models of HLH. We observed that some JAK1-specific agents were less likely to cause premature death, but were still inferior to IFN-g blockade. Baricitinib, a longer-acting JAK inhibitor, appeared to have superior efficacy to ruxolitinib, suggesting that transient blockade of JAK signaling is insufficient to halt HLH pathophysiology. Finally, antibody-mediated blockade of cytokines generally resulted in superior survival compared to monotherapy or combination therapy with JAK inhibitors. Conclusion: JAK inhibitors have significant toxicities which may limit their clinical use in HLH and clinical trials should proceed cautiously.

RUXOLITINIB OVERCOMES CYTOKINE-INDUCED DEXAMETHASONE RESISTANCE IN ACTIVATED CYTOTOXIC T-LYMPHOCYTES: IMPLICATIONS FOR THE USE OF RUXOLITINIB IN REFRACTORY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Purpose: Twenty percent of patients with hemophagocytic lymphohistiocytosis (HLH) are refractory to front-line therapy consisting of the glucocorticoid (GC) dexamethasone and etoposide. Recent case reports have demonstrated the efficacy of ruxolitinib, a JAK1/2 inhibitor, as a component of salvage therapy in refractory HLH. Hypercytokinemia is a hallmark of HLH and many cytokines activate the JAK/STAT pathway, which has been implicated in GC resistance. We recently reported that JAK/STAT signaling confers dexamethasone resistance in T-cell acute lymphoblastic leukemia, and that ruxolitinib overcomes resistance. We therefore hypothesized that cytokine-mediated JAK/STAT signaling might similarly contribute to dexamethasone resistance in HLH and that the efficacy of ruxolitinib in refractory HLH may be due in part to restoring dexamethasone sensitivity. Methods: Murine cytotoxic T-lymphocytes (CTLs) were isolated from healthy mice and activated using beads coupled to anti-CD3 and -CD28 antibodies. Drug sensitivity and protein expression assays were performed using flow cytometry. GC receptor activity was assessed by Western blotting and RT-qPCR. Results: CTLs were exposed to dexamethasone in the presence or absence of one of a panel of cytokines that are upregulated in HLH. In this screen, interleukin-2 (IL2) potently induced dexamethasone resistance. IL2 did not prevent dexamethasone-induced nuclear translocation of the GC receptor or activation of GC transcriptional targets. However, IL2, both alone and in combination with dexamethasone, resulted in increased expression of the pro-survival protein BCL2. Ruxolitinib was sufficient to completely overcome IL2-induced dexamethasone resistance with a concomitant reduction in BCL2 expression. Consistent with these findings, the addition of the BCL2 inhibitor ABT-199 partially restored GC sensitivity. Conclusion: Hypercytokinemia, and specifically IL2, may contribute to dexamethasone resistance in HLH. Through inhibition of JAK/STAT signaling, ruxolitinib effectively overcomes IL2-induced dexamethasone resistance. These findings suggest that the addition of ruxolitinib to standard front-line therapy may have therapeutic benefit for patients with refractory HLH.
GENE EXPRESSION PROFILES DISTINGUISH HEMOPHAGOCYTIC LYMPHOCYTOSIS FROM SEPSIS IN CYTOTOXIC T-CELLS AND HIGHLIGHTS INTERFERON GAMMA PATHWAYS AS MECHANISMS FOR FURTHER EVALUATION

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Purpose: Hemophagocytic Lymphohistiocytosis (HLH) is a life-threatening disorder characterized by uncontrolled activation of lymphocytes and macrophages, in which prompt diagnosis and treatment are essential for survival. HLH shares many overlapping clinical features with other hyper-inflammatory disease including sepsis. This study was designed to evaluate the gene expression profiles of cytotoxic T-cells (CTLs) and monocytes/macrophages (Mono/Mac) in HLH compared to sepsis. Methods: CD3+8+ CTLs and CD3-68+ Mono/Mac were isolated from peripheral blood collected from 12 pediatric patients with HLH (4-familial and 8-secondary), 10 with severe sepsis, and 10 healthy controls. cDNA was prepared and gene expression data was generated using Affymetrix GeneChip® Human Transcriptome Array 2.0. Differentially expressed genes (DEGs) were identified using univariate two-sample t-test correcting for false discoveries with multivariate permutation test with confidence level of false discovery rate assessment at 80 percent and the maximum allowed proportion of false-positive genes at 0.2. Enrichment of previously published Interferon gamma (IFN-γ) gene signatures were determined using Gene Set Enrichment Analysis (GSEA). Results: Significant DEGs in Mono/Mac were only found in HLH vs control totaling 51. The number of DEGs in CTLs totaled: HLH vs control - 957, sepsis vs control - 772, and HLH vs sepsis - 536. In both CTLs and Mono/Mac, the IFN-γ GSEA was enriched in HLH compared to sepsis and control. IFN-γ GSEA was not significant in sepsis vs control. Examination of the leading edge subset revealed enrichment for clinically associated HLH genes in CTLs and more for response elements in Mono/Mac. Conclusions: GSEA suggest that IFN-γ signaling is more significant in CTLs and Mono/Mac isolated from patients with HLH compared to sepsis. The core enrichment genes within the IFN-γ GSEA suggest a potentially biologically important gene set within CTLs that may also be clinically useful to differentiate patients with HLH from those with sepsis.

SIGNIFICANCE OF TH1/TH2 CYTOKINES IN OUTCOME PREDICTION OF HLH

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Purpose. Goal of this research is to further investigate prognostic values of TH1/TH2 cytokines during HLH treatment, and in expectation to distinguish Epstein-Barr virus-associated HLH (EBV-HLH) by cytokine profile. Methods. HLH patients from Nov. 2014 to Oct. 2017 were enrolled. Clinical manifestations before and during treatment were collected. TH1/TH2 cytokines: IL-2, IL-4, IL-6, IL-10, IFNγ and TNFα were tested using Cytometric Bead Array (CBA) method, and results were collected at following time points: before treatment, 2 weeks and 4 weeks after the initiation of treatment. Results. Totally 114 HLH patients (from 1 to 14 years old) were included. Receiver operating characteristic (ROC) curve analysis showed that increasing levels of IFNγ and IL-10 at diagnose (>30.68pg/mL, >35.135pg/mL), 2 weeks (>3.105pg/mL, >6.995pg/mL) and 4 weeks (>2.995pg/mL, >9.075pg/mL) after the initiation of treatment could predict adverse outcome (20/114), including refractory HLH, relapse of HLH, death. Higher IL-6 levels at week 2 (>67.26pg/mL) after the initiation of treatment were also associated with adverse outcome. 67% (6 out of 9) to 89% (8 out of 9) of deaths were covered by high cytokine level groups, identified by these cut-off values. When analyzing these factors together with other clinical manifestations using Cox proportional hazard regression mode, independent factors of unfavorable outcome were IFNγ level at week 2 (>3.105pg/mL), IL-10 level at week 4 (>9.075pg/mL) of treatment and cytopenias affecting≥2 lines at diagnose (P=0.001, 0.004, 0.002 respectively). 42 patients had EBV-HLH, and mean value of their IL-4 levels at diagnose (0.76pg/mL) was lower than that of patients with other etiologies (1.44pg/mL, P=0.028). Conclusion. This study suggested that higher serum levels of IFNγ and IL-10 could predict adverse outcome of HLH patients not only at diagnose, but also during treatment. Although cytokine levels couldn’t distinguish EBV-HLH effectively, further interests may be paid on the relationship between IL-4 and EBV-HLH.

DIFFERENTIAL EXPRESSION OF MICRONAS IN PLASMA OF LANGERHANS CELL HISTIOCYTOSIS (LCH) PATIENTS AND CORRELATION WITH T CELL EXHAUSTION

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Purpose: LCH lesions are mainly comprised of pathologic CD207+ DCs and infiltrating immune cells, the majority of which are T lymphocytes. The mechanisms responsible for recruiting activated and exhausted T cells to LCH...
lesions and contributions of these T cells to pathogenesis are not known. In the past decade, non-coding microRNAs (miRNAs) have been identified as crucial regulators of immune modulation for tumor immune escape. Therefore, we investigated role of miRNAs in T cell function modulation in LCH. Method: Circulating microRNA profiling was performed on plasma samples from LCH and healthy controls (n=10 each) using NanoString platform. Results: Twenty-one miRNAs were differentially expressed in LCH samples. Putative messenger RNA (mRNA) targets of these miRNAs were predicted in situ. hsa-miR-93-5p, which targets PDCD1LG2 and CD69, was downregulated in LCH patients. PDCD1LG2 encodes programmed cell death 1 ligand 2, the ligand for PD-1 receptor, whose expression is high in both progenitor and terminal progeny sub-types of exhausted CD8+ effector T cells. This indicates miR-93-5p downregulation as a possible contributor to T cell exhaustion in LCH. Another factor that is overexpressed in the terminal progeny exhausted CD8+ T effector cells is EOMES (encoding eomesodermin). Two of the 21 differentially expressed miRNAs in LCH, hsa-miR-182-5p and hsa-miR-25-3p, were predicted to target EOMES. Although hsa-miR-182-5p was not downregulated in LCH patient samples, hsa-miR-25-3p is significantly downregulated indicating pleiotropic effect of miRNAs in rendering T cell exhaustion in LCH patients. Conclusion: These data indicate a potential role for miRNAs in regulating the exhausted and dysfunctional status of lesional T cells. miRNA may represent a novel class of diagnostic and therapeutic targets for patients with LCH.

CLINICAL LCH POSTER NOMINEES

Poster Location #4

THE VALUE OF CELL-FREE BARFV600E DETECTION IN CHILDREN WITH LANGERHANS CELL HISTIOCYTOSIS

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Purpose: BARFV600E mutations have been identified in approximately 50% of Langerhans cell histiocytosis (LCH) cases. The aim of this study was to investigate the clinical value of BARFV600E mutation detection in cell-free (cf) DNA in a paediatric LCH cohort. Methods: A droplet-digital PCR assay was applied for quantitative detection of the cfBARFV600E in plasma of 57 children with tissue BARFV600E-mutated LCH. Results: cfBARFV600E was detected positive (≥0.1%) in 44 (77.2%) of 57 tissue BARFV600E-mutated LCH patients at diagnosis, cfBARFV600E was positive in 24/25 (96.0%) of patients with risk-organ positive multisystem (RO + MS) LCH, 9/11 (81.8%) of RO- MS and 11/21 (52.4%) of single-system (SS) LCH (P=0.001). Positive cfBARFV600E load was also higher for the 24 RO + children (median, 2.1%; range, 0.1%-24.0%) than for the 9 RO- children (median, 0.3%; range, 0.1%-1.6%) or 11 SS patients (median, 0.4%; range, 0.1%-8.9%) (P=0.001). Of the 44 patients with positive cfBARFV600E, 54.5% had a RO + MS LCH, which was compared to 7.7% of patients with negative detection (P=0.001). The ages of patients with positive cfBARFV600E were significantly lower than those of negative detection. The median age was 1.5 years and 4 years, respectively (P=0.033). liver and spleen involvements were also associated with positivity detection (liver: 52.3% vs.7.7%, P=0.004; spleen 34.1% vs.7.7%, P = 0.084). Moreover, the early treatment responses at six weeks after vinblastine-steroid induction therapy of positive patients were significant worse than those negative patients (P = 0.018). Conclusion: These results indicated that cfBARFV600E was associated with the clinical characteristics and early treatment responses of patients with LCH, and could be served as a promising biomarker in childhood LCH.

CHARACTERIZING ORBITAL INVOLVEMENT IN PEDIATRIC-ONSET LANGERHANS CELL HISTIOCYTOSIS BASED ON MRI FINDINGS

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Purpose: Langerhans cell histiocytosis (LCH) is a rare myeloid neoplasia driven by mutations in the MAPK pathway. Involvement of the orbit structures is a characteristic, although rare disease location. Methods: A retrospective review of LCH patients from the GPOH cohort with orbital involvement and available MRI scans, who have been either enrolled into one of the consequent trials DAL-HX 83 : LCH-III, or registered, for a second opinion between 1983 and 2017. The central imaging review was performed independently by two experienced radiologists. Results: Thirty-four patients, median age at diagnosis 3.4 years, have been included in the present analysis. Orbital involvement was seen in the setting of a multisystem LCH (MS-LCH) in 14, as a part of multifocal bone disease in 6, and was the only disease manifestation in 14 patients. Involvement of the orbit was present at LCH diagnosis in the majority of the patients. The orbit-forming bones were affected with the following frequency: zygomatic (50%), frontal (41%), temporal (26%), sphenoid (21%), lacrimal (15%), ethmoid (6%), and maxilla (3%). Orbital involvement was unilateral in most cases (n=31). Proptosis was present in 6 patients. We have not observed involvement of the eye globe, or optic nerve infiltration. The orbital lesions were always extracanal. Associated extraorbital imaging findings were: a dural tail sign (56%); neurodegeneration (24%), or hypophysal-pituitary mass (12%). In 28 cases with at least two MRI scans orbital lesions had resolved in 39% and 50% after 1 and 2 years of follow-up, respectively. Conclusion: Predominantly unilateral orbital involvement can be seen both in the setting of a more disseminated disease, but also as the only disease manifestation. Orbital lesions in LCH are exclusively extracanal and the zygomatic and frontal bones are most commonly affected. The eye bulb and the optic nerve were not affected in our patient cohort.
Sclerosing cholangitis in childhood Langerhans cell histiocytosis: natural history and associated factors

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Purpose: Sclerosing cholangitis (SC) in Langerhans cell histiocytosis (LCH) is a severe, life-threatening complication which is rarely reported. Methods: Based on a national prospective registry of 1897 pediatric LCH patients, we studied the natural history of SC in our cohort, determined its incidence rate, and analyzed associated factors. Results: Among 1,897 LCH patients, 28 patients (1.5%) were diagnosed with SC. The median delay of SC occurrence after LCH diagnosis was 0 year (range, 0 : 12.2 years), as 21/28 patients presented within days on both occasions. Conclusion: The optimal duration of MAPK inhibitor therapy is unknown and concerns about reactivation results in an increasing number of children on long-term MAPK inhibitor therapy. Further studies are needed to explore rational therapeutic strategies.
POSTER PRESENTATIONS - PRIZE NOMINEES
MONDAY, OCTOBER 22, 2018 • 1715

Poster Location #9

CUTANEOUS ADVERSE EVENTS IN CHILDREN TREATED WITH BRAF-INHIBITOR VEMURAFENIB FOR REFRACTORY BRAF (V600E) MUTATED LANGERHANS CELL HISTIOCYTOSIS: A EUROPEAN COHORT STUDY

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Poster Location #8

EARLY COMPREHENSIVE ASSESSMENT AND TREATMENT WITH MAPK INHIBITORS FOR NEURODEGENERATIVE LANGERHANS CELL HISTIOCYTOSIS (ND-LCH)

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Purpose: ND-LCH is a potentially progressive invalidating late form of LCH due to MAPK pathway activation of the microglia. We set off a prospective evaluation of all ND-LCH cases looking for early diagnosis and treatment with the aim of changing the natural history of the disease. Methods: Comprehensive neurocognitive and neurophysiological evaluation (SEPs, BAERs), craniospinal MRI, CSF markers (osteopontin, S100β) and BRAFV600E analysis (CSF, peripheral blood, BM) were performed to all patients at risk for ND-LCH from January 2017 to April 2018. Patients with radiological changes and neurological/neuropsychological abnormalities or neurocognitive dysfunction were treated with MAPK inhibitors (Dabrafenib or Trametinib).

Results. ND-LCH MRI changes were present in 4/128 (3%) patients. Median age at LCH diagnosis was 3.7 years (0.5-10.3) with skin involvement in all cases (3/4 MS-LCH). All patients had 2 relapses before ND-LCH was detected. Two cases (50%) had BRAFV600E. Radiological changes appeared years after LCH diagnosis (median 4.7years) and central diabetes insipidus was uniformly present concomitantly or before them. Neurological/neuropsychological anomalies or neurocognitive dysfunction were detected after MRI diagnosis. Abnormal SEPs and BAERs were found in one patient. Upon ND-LCH diagnosis, one patient had MS-LCH active disease and other had BM detection of BRAFV600E. After 6 months of treatment, 3/4 patients showed radiological improvement and 2/4 neurocognitive amelioration. The patient with the longest history of ND-LCH (8.5 years) did not show any evidence of clinico-radiological response. Osteopontin levels before treatment were high (mean value 799 g/L) in all cases, with osteopontin/S100B mean ratio of 453 (284-559). After treatment, osteopontin levels became normal and mean ratios decreased (71.55). Conclusion. Combining neurophysiological and neurocognitive evaluations with radiological imaging help for early detection of ND-LCH. CSF Osteopontine is a potential diagnosis marker and treatment response surrogate. Early detection and treatment with imAPK could change the natural history of neurological deterioration in ND-LCH patients.
Purpose: The somatic BRAF (V600E) mutation occurs in 38 to 64% of children with Langerhans Cell Histiocytosis (LCH). It is associated with high-risk features and poor response to chemotherapy. In several EU centers, children with refractory BRAF (V600E) mutated LCH are treated with BRAF-inhibitor Vemurafenib (VMF). In adults, VMF is known to induce frequent paradoxical cutaneous tumors and multiple other cutaneous adverse events (CAE), but little is known in pediatric populations. The aims of this study were i) to evaluate the frequency of CAEs in children treated with VMF for LCH, ii) to evaluate their severity iii) to evaluate their impact on continuation of VMF and iv) to describe pediatric specificities. Methods: Multicentric retrospective observational study on the European cohort of children treated with VMF alone for refractory BRAF (V600E) mutated LCH between October 2013 and January 2018. Results: Among 53 patients treated, data was available for 38 patients, median age 2.2 years [0.2-20.4], 60.5% female. Median treatment duration was 183.5 days [20-759]. Thirty (78.9%) had at least one CAE: rash (39.5%), photosensitivity (28.9%), xerosis (26.3%), keratosis pilaris (23.7%), neutrophilic panniculitis (15.8%). The majority of CAEs were grade 1 (65.8%) or 2 (26.8%). Grade 3 was observed in 3.7% of cases, no grade 4 or 5 was observed. Only one CAE led to permanent VMF discontinuation (severe photosensitivity with recurrent angioedema for which reintroduction was not contraindicated, but refused by the patient). Dose reduction was necessary in 10.9% of cases; temporary treatment discontinuation in 6%, always leading to CAE resolution. Unlike in adult populations, no cutaneous tumor, palmoplantar hyperkeratosis, erythrodysesthesia or severe cutaneous drug rash were observed. Conclusion: CAEs are frequent but only rarely severe, and have little impact on VMF continuation. A monthly dermatological exam during therapy remains mandatory to manage CAEs and screen thoroughly for possible paradoxical cutaneous tumors.

**CLINICAL RARE POSTER NOMINEES**

Poster Location #10

**BRAF-V600E MUTATION IN CENTRAL NERVOUS SYSTEM JUVENILE XANTHOGRANULOMA LESIONS (CNS-JXG): A VARIABLE PATHOLOGIC AND CLINICAL SPECTRUM**

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Purpose: Juvenile xanthogranuloma (JXG) with ERK activating mutations now falls under the histiocytic “L” (Langerhans) group designation (including Langerhans cell histiocytosis, Erdheim-Chester disease (ECD), and extracutaneous JXG), but its distinction from ECD requires correlating clinical and radiographic imaging. We investigate the pathologic and clinical spectrum of central nervous system (CNS) JXG type lesions with and without BRAF-V600E mutation. Methods: Eighteen CNS-JXG lesions were retrieved with pathologic evaluation. A subset underwent mutational testing for BRAF-V600E (PCR and/or immunohistochemistry (VE1-IHC)). Results: The median age was 14 years (0.5-67 y) (n=18). Involved sites included: cerebral/cerebellar/ventricles/dural/leptomeninges/hypothalamic/pituitary axis (HPA)/Meckel’s cave, with a subset having a multifocal CNS distribution (n=7). Eight (44%) CNS-JXG lesions cases had a reportable BRAF status: The BRAF-V600E positive cohort (n=4) had a median age of 6.5 years (3-12 y) versus 44.5 years (14-53 y) in the BRAF wild type cohort (n=4). Among the BRAF-V600E positive lesions: one was a manifestation of pediatric ECD with associated long-bone sclerosing lesions. The other three had no findings of ECD. One showed mild cytologic atypia with skin dissemination, and was started on Clofarabine/dexamethasone. Two involved the HPA with associated diabetes insipidus (DI), of which one had multifocal intracranial lesions with initial response on dabrafenib. The other was a unifocal xanthomatous pituitary lesion, biopsied after 12 weeks on standard LCH therapy for presumptive stalk involvement. This patient continued on LCH based therapy for 12 months, with a stable course 2.5 years after treatment. Conclusion: CNS-JXG lesions present with a varied clinicopathologic spectrum and require correlation of morphology/immunophenotype, molecular, and radiographic imaging in order to best direct clinical management. More follow-up is needed to draw definite conclusions about possible clinicopathologic correlations between BRAF-V600E and wild-type cases, but these lesions may occur in a younger subset, for which ECD should still be ruled out with appropriate imaging.

**NOTES**
STXBP3: NOVEL GENE ASSOCIATED WITH VERY EARLY ONSET OF IBD, HEARING LOSS AND IMMUNODEFICIENCY

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Purpose - Very early-onset inflammatory bowel disease (VEO-IBD), defined by the onset of IBD before 6 years of age, is often associated with more severe and extensive disease than IBD in older patients. Some VEO-IBD cases have been linked to mutations in primary immunodeficiency genes, which regulate immunity and hyperinflammatory pathways; however, the underlying pathophysiological mechanisms are still poorly understood. Here we aim to identify novel gene mutations associated with VEO-IBD and immune disorders and how they contribute to disease. b. Methods - We utilized Whole Exome Sequencing and bioinformatics to recognize novel gene variants and applied cell biological and biochemistry approaches to determine their biological relevance. c. Results - Here we describe eight patients from four unrelated families manifesting with VEO-IBD, immunodeficiency and severe bilateral sensorineural hearing loss - each carrying either heterozygous or compound heterozygous deleterious mutations in Syntaxin-Binding Protein 3 gene (STXBP3). These mutations interfere with either intron splicing or protein stability, lead to reduced STXBP3 protein expression, which in turn, affect cytotoxic T-Lymphocyte (CTL) and epithelial cell function. STXBP3 knock-down in control CTLs significantly reduces cytotoxic activity, mimicking the patients’ CTL defects. Strikingly, forced expression of STXBP3 rescues patient CTL function. Live-cell microscopy analyses show that STXBP3 is required for recycling of RAB11A-containing endosomes to the plasma membrane. Defects in this process prevent the delivery of key effector proteins that are required for granule secretion and epithelial cell polarity d. Conclusion - Our results identify STXBP3 as a causal gene for the development of VEO-IBD with associated immunodeficiency and hearing loss.
Purpose: HLH and septic patients share many clinical features. Our aim was to evaluate sCD25 and sCD163 utility as sepsis markers in pediatric and adults patients and to compare their serum levels to those in HLH patients. Methods: sCD25 and sCD163 serum concentrations were determined by ELISA in a cohort of septic, HLH and healthy donors. sCD25 serum concentration was reported in 23 HLH cases of HLH-2004 protocol in Spain. Results: Sixty-three adult septic patients (42males/21females; median age: 61.9 years-old) and 60 healthy adults (37males/23 females; median age:51 years-old) were included. Thirty-seven pediatric septic patients (17males/20females; median age: 3.65 years-old) and ten healthy children (4males/6females; median age: 6.7 years-old) were enrolled. Seven cases of HLH (2males/5females; median age: 2.92 years-old) and data from twenty-three HLH patients (13males/10females; median age: 1.23 years-old) were included from HLH-2004 study data. In adults, median concentrations of the two markers were higher in septic patients than in healthy donors (sCD25: 4,072.68pg/ml vs 844.42pg/ml; sCD163: 1,651.95ng/ml vs 634.87ng/ml). In pediatric patients, both markers were also higher in septic patients when compared to healthy donors (sCD25: 8,905.15pg/ml vs 1905.90pg/ml; sCD163: 1,194.13ng/ml vs 870.48ng/ml). In our cohort of HLH patients, sCD25median concentration was 7,207.59ng/ml and for sCD163 was 1,154.46ng/ml. However, patients included in HLH-2004 protocol, exhibited higher sCD25 median concentration (14,550pg/ml). In 12 HLH patients sCD25 values were expressed in U/ml and sCD25>2,400U/ml in 7. Results expressed in U/ml or pg/ml cannot be compared. Conclusion: Our results show that sCD25 and sCD163 revealed significantly increased levels in sepsis and HLH. For HLH diagnostic criteria sCD25 measurement units and cutoff levels should be carefully considered. Lack of a formula to convert concentration values among ELISA tests could misinterpret the results and comparison is difficult among studies. More specific diagnostic criteria are needed for differential diagnosis between sepsis and HLH.

Objective: to analyze the prognosis different age and etiology and explore the potential risk factors for hemophagocytic lymphohistocytosis. Methods: we continuously reviewed patients who were admitted for hemophagocytic lymphohistocytosis from January 2015 to April 2016 in our institution. All patients were followed up for 18 months. Survival time was from initial treatment to outcome (or end of follow-up). Clinical data and laboratory examination data were collected from electronic medical record. The analysis was executed using COX regression analysis. Results: a total of 37 patients with AOSD-HLH were observed after following up, including 28 female and 9 male patients. The middle age was 26 years old. The manifestations, including fever(100%), rash (86.4%) and splenomegaly (83.7%), were identified. The laboratory finding, including increasing serum ferritin(97.3%), hemophagocytic phenomenon (83.3%) and increasing CRP were confirmed. IL-18 was increased at acute period but decreased at recovery period in all patients. After 12 years follow-up, 6 dead were confirmed (83.7%). Conclusion: increasing IL-18 is risk factor for HLH.
Purpose: Central nervous system (CNS) affection can occur in association with systemic manifestations, or as isolated CNS Hemophagocytic Lymphohistiocytosis (HLH). We aimed to study the value of cerebrospinal fluid (CSF) soluble interleukin-2 receptor alpha subunit (sIL2Rα) assay as a marker of CNS affection in children with HLH. Methods: In a retrospective study, we analyzed the data of patients diagnosed as HLH at Alexandria University Children's Hospital over 3 years. Patients were considered as "CNS-HLH positive" when they had either neurological manifestations, abnormal findings on MRI or routine CSF analysis and as "CNS-HLH negative" when they did not show any of these findings. Results: We analyzed the data of 22 HLH patients; with an equal number of males and females. Their age ranged from 1 month to 11 years with a median of 5 months. Seven (31.8%) patients had a confirmed genetic disease predisposing to HLH (Grey hair syndromes), while the remaining 15 (68.2%) patients were diagnosed according to the HLH-2004 diagnostic criteria. In the seven (31.8%) patients who were CNS-HLH positive, the median CSF sIL2Rα was 1310 pg/ml (range 100 to 17329) which was higher than that of CNS-HLH negative patients (270 pg/ml, range 80 to 3700). Moreover, the median CSF sIL2Rα level was comparable in patients with a positive routine CSF analysis compared to those with a negative one (290 vs 285 pg/ml). Conclusion: CSF sIL2Rα assay could detect CNS-HLH in children with a greater sensitivity. The absence of statistically significant correlation between serum and CSF levels of sIL2Rα indicates that it is locally produced in the CSF and could be a valuable biological marker of disease activity. Larger prospective studies are warranted to determine the diagnostic and prognostic value of CSF sIL2Rα levels in HLH patients.

Poster Location #18

ISOLATED CENTRAL NERVOUS SYSTEM HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A CASE SERIES

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Purpose: Isolated central nervous system hemophagocytic lymphohistiocytosis (CNS HLH) without systemic signs or symptoms is rare and can present a diagnostic dilemma. This series reviews the presentation, physical exam, laboratory, and radiological findings of patients who either presented with primary isolated CNS HLH or relapsed, isolated CNS HLH. Methods: A systematic chart review revealed three pediatric patients diagnosed with either primary or relapsed isolated CNS HLH at the Phoenix Children's Hospital from 2015-2017. Results: All three patients presented with focal CNS symptoms ranging from paresthesias to weakness and/or seizures. Two patients had no personal or family history of HLH, while one patient had been previously treated for systemic HLH with chemotherapy and a matched sibling donor BMT. At the time of CNS HLH presentation, systemic HLH findings were absent in all three patients. Two of the patients were found to have elevated soluble interleukin-2 (IL2) as well as decreasing or absent natural killer (NK) cell function at presentation. Neuroradiology findings included both focal and diffuse CNS involvement. Brain biopsies revealed lymphohistiocytic infiltrates. Genetic analysis for common HLH mutations revealed combinations of known and likely pathogenic mutations. All three patients are currently alive and disease free. Two of the three patients have undergone BMT, while the other continues to be closely observed without intervention. Conclusion: Patients with CNS HLH can present with stroke-like symptoms and neuroimaging findings can be non-diagnostic. CNS HLH is rarely in the differential diagnosis as patients may not have a personal history of HLH, a family history of children affected with HLH, or meet HLH systemic diagnostic criteria. This can result in delays in treatment. The diagnosis of primary isolated CNS HLH requires a high index of suspicion, thoughtful evaluation, prompt genetic evaluation, and treatment despite the lack of systemic criteria.

Poster Location #19

PROCALCITONIN IS NONSPECIFICALLY ELEVATED IN ADULT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Purpose: Procalcitonin (PCT) has gained popularity to de-escalate antibiotics, particularly regarding sepsis associated with lower respiratory tract infections. Secondary Hemophagocytic Lymphohistiocytosis in adults is often mistaken for bacterial sepsis due to its nature as a cytokine storm. We sought to investigate PCT in HLH. Methods: Fifty-nine adult HLH patients at Stanford Health Care were identified from January 2012 to May 2017. We analyzed the first hospitalization for HLH and the first day of high suspicion for HLH was identified, defined as meeting sepsis criteria with fever and either bacteraemia or splenomegaly. We reviewed the PCT value ordered within 1 day from the day of high suspicion for HLH and the total days of antibiotics. Expert review was done to confirm whether or not a primary infection was present at the
time of ordering PCT. Results: Seventeen patients had PCT ordered at the
time of high suspicion for HLH. With the exception of one patient, all PCT
values were over 0.5 ng/ml, with median of 3.7 ng/ml (range 0.2-20); median
concurrent creatinine was 1.5 mg/dL (0.54-8.4). Two patients had a primary
infection, with a median PCT of 3.8 ng/ml (range 3.7-3.9) and median
creatinine of 2.08 mg/dL (1.9-2.1). Fifteen patients had no primary infection,
with a median PCT of 2.8 ng/ml (range 0.2-20) and median creatinine of 1.2
mg/dL (0.54-8.4). There was no association between whether or not PCT was
ordered and days of antibiotics administered (p=0.73). Conclusion: HLH in
adults appears to elevate PCT at the time of high suspicion for HLH even in
the absence of a primary infection. Therefore, procalcitonin is not a reliable
marker to assess for presence or absence of infection in these patients.
Ordering PCT was not associated with a statistically significant reduction in
antibiotic days compared to those without PCT.

Poster Location #20

CLINICAL CHARACTERISTICS AND TREATMENT OF EBV-BARR
VIRUS-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN
CHILDREN

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Objective To explore the clinical characteristics and treatment of EBV-HLH in
children.Methods Retrospective analysis was used to summarize the clinical
characteristics, laboratory findings and treatment of pediatric patients with
EBV-HLH admitted in Beijing Children’s Hospital from September 2015 to
December 2017. Results A total of 157 EBV-HLH patients were enrolled,
accounting for 59.02% (266) of admitted HLH cases in the same period. The
male to female ratio was 0.76:1. The median onset age was 42 (3-189)
months. With a median follow-up duration of 237 (21-835) days, the estimated
overall survival rates for patients at 1, 3, 6, and 12 months were 95.2%,
89.4%, 85.4% and 83.5%. The clinical features of EBV-HLH were similar to
other HLH, which were accompanied by multiple organ dysfunction. Only the
differences of ANC, ALT and FIB were statistically significant between 9 cases
of primary HLH and cases without abnormal genetic changes
(P=0.027, 0.049, 0.033). Of 157 patients, 13 cases were primary EBV
infection, 144 cases were reactivation of previous infection, survival time was
statistically significant between two groups (P=0.047). Conclusion EBV-HLH is
the most common type of HLH, with various clinical manifestations, poor
prognosis and high mortality. If the children continue to have high fever, the
blood cell progressive reduction and liver function damage should be highly
alert to the possibility of HLH, even if the bone marrow puncture has no
hemophagocytic phenomenon. The clinical characteristics and routine
laboratory examinations are of little significance in differentiating whether EBV
-HLH has potential genetic abnormalities. Reactivation of previous EBV
infection were more likely to cause HLH, and the survival rate was lower than
that of primary EBV infection. Early diagnosis, early treatment and active use
of multiple means to control cytokine storm are important for improving
prognosis. Hematopoietic stem cell transplantation should be used as soon as
possible in order to improve transplantation tolerance and prognosis in
relapsed and refractory HLH.
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**POSTER PRESENTATIONS - CLINICAL HLH**

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**Purpose:** HLH is a syndrome of uncontrolled hyperinflammation with a high mortality. Most deaths occur in the first weeks since diagnosis. The search for the predictive factors is usually impaired by low number of patients. Aim of this study was to perform analysis in search of prognostic factors in HLH and to suggest other potentially clinically relevant parameters based on an alternative approach. Methods Data of a large cohort of 90 adult patients with HLH from the HLH in Adults Database affiliated with PALG (Polish Adult Leukemia Group) were analyzed. Risk factor analysis was made by the Cox regression in an univariate and then reassessed in multivariable analysis. Additionally, an alternative method using dichotomization of continuous variables based on the optimal cutoff point was applied. This approach has a high risk of false-positive results therefore it can help in excluding non-promising variables. Its advantage is also that it not only suggest that a continuous variable may have a significance as a prognostic factor, but also which threshold may be clinically relevant. Results In the univariable analysis: autoimmune disease as a triggering factor (MAS : macrophage activation syndrome), hepatomegaly, hypertriglyceridemia (>265mg/dl), RBC (red blood cell count) and (in a lower number of patients) antithrombin-III were found as prognostic factors. In a multivariate model MAS (HR 0.16; 95%CI: 0.04-0.69) and hepatomegaly (HR 0.52; 0.29-0.94) retained this status. After a dichotomization of the continuous variables also other potentially promising parameters (with thresholds) were found. Conversely, the variables associated with diagnosis (number of HLH-2004 criteria, HScore) and ferritin concentration (as well as fibrinogen and D-dimers, albumin and time from diagnosis) did not reveal predictive value. Conclusion MAS syndrome and hepatomegaly may be associated with relatively better prognosis in newly-diagnosed adult HLH patients. Variables associated with the diagnosis may not be simultaneously good prognostic factors.

**Poster Location #22**

**CLINICAL CHARACTERISTICS OF CHILDHOOD HEMOPHAGOCYTIC SYNDROME AND ANALYSIS OF UNDERLYING GENETIC DEFICIENCY**

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**Objective:** To investigate the clinical manifestations, the laboratory findings, treatments protocol, overall survival rate of children with hemophagocytic lymphohistiocytosis (HLH). Methods: In order to analysis retrospectively of clinical data in pediatric patients who were hospitalized in Shenzhen Children's Hospital meeting with the "HLH-2004" diagnostic criteria from January 2010 to June 2017, we summarized the clinical manifestations and laboratory data, treatment and outcomes of these patients. We developed a custom panel to capture the exons of 9 genes associated with HLH to detect single nucleotide variants (SNVs) by next generation sequencing (NGS). Results: The data of 144 HLH cases were analyzed, pHLH accounted for 14.3% (6/42), sHLH accounted for 87.5% and reasons of unknown resources accounted for 8.3% (12/144) respectively. sHLH divided into infection-associated HLH, autoimmune-associated HLH and malignancy-associated HLH. They were accounted for 79.9% (115/144), 3.5% (5/144) and 4.2% (6/144), respectively. EBV-associated HLH was prominent in infection-associated HLH, accounting for 45.1% (65/144). The mortality was 18.1% (26/144) and overall survival was 81.9% (118/144). Univariate analysis showed that prolonged APTT, jaundice and elevated BUN were indicated unfavorable prognosis. Multivariate analysis indicated that jaundice and elevated BUN increased the risk for poor prognosis by 6.83 and 6.30 times. Forty-two cases were analyses by genetic method. Six cases had suspected and known mutations, while 15 cases were genes carrier. Genetic evaluation revealed two novel mutations in the LYST gene: c.715G>T and c.4695delA in a five-year-old Chediak-Higashi Syndrome (CHS) boy. We performed sibling HLA-matched hematopoietic stem cell transplantation (HSCT) in the remission of HLH. He had full-donor chimerism with complete reconstitution at 13 months of follow-up after transplantation. Conclusion: EBV was the main cause for HLH, Jaundice and elevated BUN were indicated unfavorable prognosis. Overall survival is 81.9%. It was a good opportunity to perform HSCT in the stable phase of CHS patient.

**Poster Location #23**

**ACQUIRED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: VIRUS-TRIGGERED DISEASE WITHOUT TENDENCY TO RECUR**

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**Purpose:** Patients with inflammatory bowel disease (IBD) are at risk of developing the life-threatening inflammatory syndrome of acquired hemophagocytic lymphohistiocytosis (HLH) due to chronic systemic inflammation as well as exposure to immunosuppressive therapy (IST). Methods: Patients with IBD and acquired HLH (exclusion of hereditary HLH, e.g. XIAP) in the German HLH cohort were evaluated regarding underlying disease, prior IST, management, and outcome. Results: Median age of the 17 patients was 16 years (3.5-29). The majority suffered from Crohn's disease (65%) while 35% were affected by ulcerative colitis. Median duration of IST prior to HLH was 26 months (2-60) and consisted of azathioprine (94%), steroids (6%) and 6-MP (6%). In 88% of patients, a viral trigger was identified,
of which EBV (60%) and CMV (27%) were the most common. At the time of diagnosis of HLH, IBD-directed IST was terminated in all patients. In addition, most patients (88%) received HLH-directed IST, while 12% achieved remission by mere termination of immunosuppression. 73% of patients with HLH specific therapy received only steroids (84% of them received IVIG), while 27% additionally received etoposide. Antiviral therapy (rituximab or val ganciclovir) was administered in 53% of patients. Overall mortality was 12%. Interestingly, no HLH recurrence was reported, with a median follow-up of 2 years (range 0.2-9). Conclusions: IST is a double-edged sword. It can favor development of HLH by facilitating viral infections. However, even more intensive IST may be needed to control the hyperinflammation. Termination of IBD-directed IST and, if required, initiation of HLH-directed IST is curative in most cases. The risk of HLH recurrence appears to be low.

Poster Location #24
STAGE IV EPSTEIN-BARR VIRUS (EBV) CLASSIC HODGKIN LYMPHOMA (CHL) WITH HEPATIC INVOLVEMENT MEETING CRITERIA FOR HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) AT STANFORD: CLOSE MIMIC VERSUS TRUE HLH
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Purpose: Assess the impact of Stage IV CHL, an IL-2 receptor shedding (sIL2-R) malignancy associated with fever and EBV, on the accuracy and timing of the diagnosis of adult HLH. Methods: Retrospective chart review. Results: Of 62 consecutive adults with suspected HLH from 2014 to May, 2018, four cases (six per cent) met strict pathologic criteria for CHL, all EBV associated. All presented with unremitting fevers and critical illness including two with liver failure. Their ages were 18, 55, 57, and 72 years at the time of diagnosis. Two of the patients had a strong family history of HL. None had identifiable mutations for primary HLH by Cincinnati Childrens Hospital NGS panel. Two of the four had florid hemophagocytosis. All patients had abnormal liver function, hepatosplenomegaly, two with abnormal FDG uptake and/or FDG avid liver nodules, one with FDG-avid spleen nodules. There was no significant difference between sIL2-R levels, ferritin, time to diagnosis, and EBV viral loads of the cohort compared to the other 58 patients with non-HL associated adult HLH (data to be shown). Two of the four patients would not have met HLH criteria if ferritin and sIL2-R had been normal (data to be shown). All received dexamethasone and etoposide containing regimens emergently followed by standard CHL regimens. Hepatic insufficiency affected therapy choice in three of four (data to be shown). Lengths of hospital stay exceed 3 months in three of four patients. Three of four are alive (range 4 months-3 years). Conclusion: CHL can present with hyperferritinemia and/or a cholestatic pattern of hepatic injury. CHL did not clearly delay diagnosis. Strict pathologic criteria for EBV associated CHL and CHL-like lymphoproliferations must be evaluated in the clinical context of hyperinflammation to optimize immediate and long term therapy. Complexity of care and resource utilization is high.

Poster Location #25
A DATA DRIVEN APPROACH TO IDENTIFY "SIMPLER"DIAGNOSTIC TOOLS FOR HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a hematologic disorder that is caused by a genetic defect (familial HLH) or is secondary to systemic disease, infection or cancer (secondary HLH). It is caused by an overstimulation of the immune system that provokes phagocytosis of hematopoietic lineages. For the diagnosis of HLH, five out of currently eight criteria are required, which can be time consuming to obtain. This may stall definitive treatment, while early initiation of treatment is imperative for a better outcome. Hence, we used a data driven approach to identify a minimal parameter-set to facilitate early decision-making for HLH. Methods: We retrospectively included 264 patient records from five Dutch tertiary hospitals, for whom functional HLH diagnostics (e.g. NK-lysis, CD107, perforin) were performed in a central lab (UMC Utrecht). The HLH-2004 criteria were used to evaluate HLH occurrence and subsequent data was recorded. We used principal component analysis (PCA) to identify HLH distinctive symptoms. Results: We identified 17 familial HLH (age 7.5 years (0:23.3)) and 70 secondary HLH patients (age 20.5 years (0:44)). These patients presented with either splenomegaly, elevated ferritin or cytopenia (100% sensitivity (96:100), 48% specificity (39:58)). The variance in the PCA was caused by splenomegaly and tissue phagocytosis combined with either cytopenia or combined elevation of ferritin and sIL2. Hence, we named them major and minor criteria respectively. The presence 2/4 of these criteria predict the presence of HLH with 75% (63:86) sensitivity and 92% (79:88) specificity. Conclusion: We identified a simplified diagnostic tool to identify patients suspected for HLH: 1) the lack of either splenomegaly, elevated ferritin or cytopenia excludes HLH; 2) HLH is highly suspected when a patient presents with a combination of 2/4 criteria. These new insights may enable early treatment initiation for HLH.

Poster Location #26
A CASE OF SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN AN ADULT PATIENT
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BACKGROUND. Previously fit and well 77 year old gentlemen presented to his local hospital following a fall. On subsequent investigations he was found to have a history of recent fevers, thrombocytopenia, ferritin > 40,000 ug/L, D-Dimer > 6000 ug/L, raised triglycerides (3.7 mmol/L) and raised LDH (>5000 U/L). His virology tests came back positive for EBV (viral load 5,49 copies/mL). Based on results he was suspected to have developed secondary Haemophagocytic Lymphohistiocytosis (HLH). Soluble CD25 was requested and came back at > 20,000. Bone marrow aspirate&biopsy showed possible evidence of haemophagocytosis and features in keeping with diffuse large B-cell lymphoma (DLBCL) non germinal centre phenotype. PET scan demonstrated widespread uptake in bones, liver and spleen. Patient started treatment with RCHOP chemotherapy with Etoposide. DISCUSSION. HLH is a rare clinical syndrome characterised by fever, hepatosplenomegaly, cytopenias and progressive multiple-organ failure. HLH in adults is often secondary to autoimmune diseases, cancer, or infections in contrast to familial HLH. The patient in our case fulfilled five of the eight diagnostic criteria (fever, splenomegaly, cytopenia, hypertriglyceridaemia/hypofibrinogenemia, haemophagocytosis in biopsy, low/absent natural killer (NK) cell activity, hyperferritinaemia, and elevated soluble CD25 receptor). Of interest, our patient had both, an underlying malignancy (DLBCL) and an infection (positive EBV). The treatment was based on HLH-2004 protocol developed for paediatric patients as no trials have been performed in adults. CONCLUSION. Secondary HLH is a rare condition seen in adult population largely driven by underlying autoimmune disorders, malignancy or infection. It should be considered in patients presenting with a history of fever, haematosplenomegaly and laboratory abnormalities including cytopenias, very high ferritin, clotting abnormalities and evidence of haemophagocytosis. Investigations to find out underlying pathology should be undertaken and soluble CD25 is a useful test in diagnosis of secondary HLH in adults.
Introducción: Aunque la sepsis y la hemofagocitosis secundaria (SHPS) presentan similitudes clínicas y bioquímicas, los pacientes con SHPS requieren un enfoque clínico diferente. El propósito de este estudio fue explorar las características bioquímicas y las concentraciones de citocinas en pacientes con SHPS y sepsis para identificar marcadores diferenciales.

El estudio incluyó 102 pacientes: 55 con SHPS (edad media de 62 años, rango 2-76 años) y 47 con sepsis (edad media de 62 años, rango 5-80 años). Los niveles de ferritina total y de ferritina glucosilada fueron 0.85 y 0.76, respectivamente. Según el análisis ROC, los valores (mmol/l) para SHPS y sepsis se encontraron en 3.1 (Q1-3.75, Q3-16.5) y 1.5 (Q1-0.8, Q3-2.7), respectivamente. El siguiente análisis estadístico fue efectivo (p<0.01) para uso clínico. El método de ROC es más efectivo en la detección de diferencias entre SHPS y sepsis.

Conclusion: Según nuestros datos, los niveles de triglicéridos, ferritina y porcentaje de ferritina glucosilada fueron 0.85, 0.76 y 0.8, respectivamente. Según el análisis ROC, los valores (mmol/l) para SHPS y sepsis se encontraron en 3.1 (Q1-3.75, Q3-16.5) y 1.5 (Q1-0.8, Q3-2.7), respectivamente. El método de ROC es más efectivo en la detección de diferencias entre SHPS y sepsis.
Purpose: In this study, the correlation between clinical features and genetic subtypes in Korean familial HLH (FHL) was investigated. Methods: FHL data from 10 hospitals were retrospectively collected. Patients diagnosed with FHL according to the HLH-2004 diagnostic criteria, and with causative gene mutation identified were included. Results: A total of 48 FHL patients were reported. There were 7 (14.6%), 37 (77.1%), 1 (2.1%), 2 (4.2%), and 1 (2.1%) patients with PRF1, UNC13D, STX11, STXBP2, and SH2D1A gene mutations. Median age at diagnosis 3.2 months (range, 7 days-13 years), and 77.0% of the patients were diagnosed under the age of 1 year. There was no statistical difference in the clinical presentations and laboratory findings at diagnosis between genotype groups. Most of the patients received HLH chemotherapy, and 30 patients (62.5%) reached complete remission at the end of induction. Eighteen showed reactivation, and there was no difference in reactivation rates by genotype. Eight patients died before hematopoietic stem cell transplantation (HSCT). The 5-yr overall survival (OS) rate of 36 transplanted patients was 75.0%, whereas that of 12 who could not receive HSCT was 25.2% (P<0.001). Four patients are alive in complete remission without HSCT for a median duration of 10 months (range 5.7-20.1 months). There was no difference in OS by genotype. Among the 26 FHL3 patients, 5 (19.2%) died before HSCT. The 5-yr OS rate of 16 transplanted patients was 62.5%, whereas that of 9 who could not receive HSCT was 22.2% (P=0.008). Conclusion: Our study showed that the unique reactivation pattern and poor prognosis were related to the PRF1 gene mutation. The OS rate was increased by HSCT in the FHL3 patients. Therefore, early diagnosis and prompt HSCT are necessary for this genotype group.

Background: Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal disease characterized by impaired natural killer and cytotoxic T-cell function. The standard approach to treatment involves the administration of broadly immunosuppressive and cytotoxic agents, such as high-dose steroids and etoposide. Despite significant progress in the treatment of HLH, however there is still some pediatric patients with HLH experience treatment failure. Additionally, as compared to EBV-induced infectious mononucleosis patients, CD5- CTL (CD3+CD8+) expansion is evident in 4 of the 5 EBV-HLH tested. Panel gene for familial HLH was negative in 8 out of 8 patients tested. Management included dexamethasone, etoposide and cyclosporine in 10, 6 and 3 patients respectively. Seven patients received biologicals (rituximab, alemtuzumab and anakinra in 7, 3 and one patients, respectively). Hematopoietic stem cell transplantation (HSCT) was considered for 5 patients, 3 of them died prior to HSCT and one died post-HSCT. Conclusion: We report a T/NK cell-mediated EBV-HLH in non-Asians, mainly Hispanic, patients. Prompt diagnosis and HSCT are needed for severe disease, as prognosis is poor. CD5- CTL expansion may serve as a diagnostic clue.

Background: Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal illness characterized by impaired natural killer and cytotoxic T-cell function. The standard approach to treatment involves the administration of broadly immunosuppressive and cytotoxic agents, such as high-dose steroids and etoposide. Despite significant progress in the treatment of HLH, however there is still some pediatric patients with HLH experience treatment failure. However, survival of this group of patients still remains poor. Therefore, there is an urgent need to identify novel targeted therapies that enhance the survival of HLH. Methods: A 2-year-old boy was presented with fever, rash and cough. At that time, the patient was considered as the bacterial infection, however, the antibiotic treatment was not effective. After admission to our hospital, the relevant examinations of the patient were completed and he met the HLH diagnostic criteria. Subsequently, HLH-94 regimen was administered, and the children developed pneumonia, neurological complications. Plasma exchange was carried out and the children are not suitable for the use of cytotoxic drugs for chemotherapy, considering the obvious pancytopenia in this case. After communication with the parents, it is recommended to orally take Ruxolitinib monotherapy. Results: After 3 days of oral Ruxolitinib, the pancytopenia began to recover, and returned to normal after 1 week. Meanwhile, the manifestation and the level of cytokine was improved largely. Currently, all indicators recover and the children lives with good quality of life. Conclusion: For children with relapsed and refractory HLH, the general situation is poor to tolerate chemotherapy. The targeted therapy of Ruxolitinib could be considered as a feasible second line therapy.
Purpose: Early initiation of therapy is crucial for survival in hemophagocytic lymphohistiocytosis (HLH). We analyzed the biomarkers of HLH if it could predict the extent of treatment needed and mortality. Methods: Children diagnosed with HLH at our center between Jan 2010 and Jan 2018 were included in the analysis. It was a prospective observational study. Results: 89 patients fulfilled the inclusion criteria. Median age at diagnosis was 5 years (13 days to 18 years). 8 patients had primary HLH. In secondary HLH, 7 patients had no identifiable trigger. The rest had infections (n=50), malignancies (n=10) and rheumatological illnesses identified (n=14). Clinical features included fever (99%), cytopenia (83%), hepatosplenomegaly (77%), transaminits (SOGT:SGPT>200U/L, 70%), hypertriglyceridemia (80%), hypofibrinogenemia (52%), hyponatremia (42%) and bone marrow hemophagocytosis (88%). Median ferritin was 4,776 ng/ml (range 44,9000). On comparing biomarkers in 69 patients to the extent of treatment needed, transaminits was predictive for intensive HLH therapy (80%) or at least steroids (20%), while 31% of those without transaminits could be managed with treatment of trigger alone (p=0.01). Clubbing 8 factors (fever, hepatosplenomegaly, cytopenia, ferritin ≥3000, hypertriglyceridemia, hypofibrinogenemia, hyponatremia and SGPT≥200), all patients with ≥5 factors and 36.4% with ≤3 factors (p=0.03), while mortality was 71.4%, 34.6% and 9.1% respectively (p=0.02). Mortality was higher with hyponatremia (77.8% vs. 34.2%, p=0.026), SGPT≥200 U/L (50% vs. 21.1%, p=0.04), hypofibrinogenemia (55% vs. 26.3%, p=0.03) and sIL2Rα≥3,200 U/ml (85.7% vs. 20.0%, p=0.003). On multivariate analysis, hypofibrinogenemia was the only independent prognostic factor for mortality (adjusted OR 7.4 [1.1:49.2]). Conclusions: Analysis of biomarkers can upfront predict strength of treatment needed.

Poster Location #33
THE USAGE OF ETOPOSIDE IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS DURING PREGNANCY/POSTPARTUM
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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a rare and severe clinical syndrome characterized by a dysregulated hyperinflammatory immune response. HLH manifesting during pregnancy/postpartum continues to be a rare entity. However, there is no established treatment guideline for it to date. The treatment in previous literature including steroids, intravenous immunoglobulin (IV Ig), steroids combined with IV Ig and chemotherapy, but the effects turn out to be unclear. From a clinical observation of cases from four centers, we found out that the usage of etoposide (VP-16) may be important. Methods: A analysis of HLH during pregnancy/postpartum from four centers between January 2011 and March 2018 was conducted. Clinical features were collected. The treatment strategy and the effect of them was analyzed. Results: There were 15 patients included. Before the usage of VP-16, 7 of them were treated with steroids, 3 were steroids combined with IV Ig, 4 were not treated and 1 was with fludarabine and methylprednisolone. In the 11 treated patients, 7 had an decrease in temperature but the laboratory findings were not improved, and the other 4 patients just kept getting worse. Median time of the interfere of VP-16 was 44.5 (9-176) days after the onset of disease. After the VP-16, most of cases got a normal temperature within 48 hours. In general, 9 got complete remission (CR), 4 achieved partial remission (PR), the other 3 didn't response and finally died of HLH. 3 patients suffered relapse and 2 of them were found of underlying cause (lymphoma and leishmania). All of the 13 CR/PR patients keep surviving for long term. Conclusions: As for the HLH during pregnancy/postpartum, VP-16 can suppress the inflammatory process more quickly and effectively, which may be related to the special immune features during pregnancy. Still, the treatment towards the underlying cause is important for long-time remission.

Poster Location #34
ANALYSIS THE PROGNOSIS OF TRANSPLANTATION FOR EBV RELATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) USING RELATED DONORS WHO WERE EBV CARRIERS
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Objective: To observe the prognosis of transplantation for EBV related HLH using related donors who were the EBV carriers. Methods: Donors: From December 2015 to May 2018, 44 cases diagnosed with EBV viral related HLH (EBV-HLH) using related donors of which 41 cases receiving haploidentical transplantation and 3 cases receiving matched sibling transplantation. The 13 healthy donors were EBV carriers before transplantation with EBV whole blood test positive and EBV plasma test negative and other 31 donors' EBV test were negative in both plasma and whole blood. Patients: Median age was 4.5 years and median follow-up time was 14 months. Before transplantation, there were 12 cases in complete remission (CR), 24 cases in partial remission (PR), and 7 cases in active disease (AD). Patients received unmanipulated combined marrow and peripheral blood stem. Results: 1-year and 3-year overall survival (OS) rates for the 41 patients were both 73.6%. 13 cases died within 1 year after transplantation. 1-year OS of transplants for patients with EBV positive and negative were 61.5% and 77.4% respectively (p = 0.35). Of 44 cases, 22 cases were reactivated with EBV after transplantation. The 22 cases with EBV reactivated included 10 cases (76.9%) which using donors with EBV positive and 12 cases (38.7%) which using donors with EBV negative. The ratio of EBV reactivated in the cases using the donors with EBV positive was higher than donors with EBV negative (p = 0.046). Only 3 cases with donors' EBV positive did not detect the plasma EBV including 2 cases death early and 1 case EBV negative consistently. Conclusions: In China, most people carried EBV. Before transplantation the donors need EBV routine test. The patients' overall survival using the donors with EBV positive had no significant differences from the donors with EBV negative after transplantation. However, the ratio of EBV reactivated in the cases using the donors with EBV positive was higher than donors with negative. It should be avoided the donors with EBV positive to decrease costs and risks. But if it can't be avoided, the EBV carrying donor is still an alternative choice.
**Poster Location #35**

**CLINICAL SUMMARIZATION OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR X-LINKED LYMPHOPROLIFERATIVE SYNDROME TYPE 2**

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Purpose: To analyze the clinical characteristics of children patients with X-linked lymphoproliferative syndrome type 2 (XLP-2) receiving hematopoietic stem cell transplantation (HSCT). Methods: We retrospectively 8 children patients with XLP-2 from June 2015 to January 2018, the clinical features and outcome were analyzed. 7 cases received haploidentical donor HSCT (Haplo-HSCT), 1 case received unrelated donor HSCT (URD-HSCT). Before transplantation, 6 cases were in partial remission (PR), 2 cases were in no remission (NR). The conditioning regimen was busulfan (BU), fludarabine (fla), etoposide (VP-16), and arabinosyl cytosine (ara-C) or not. 2 cases engraftment failure were replace BU to MEL. Graft versus host disease (GVHD) prophylaxis based on donor sources. The median MNC count was 9.07 (8.45-9.98) × 10^6/kg. The median follow-up time was 18.5 (2-23) months. Results: The 8 cases met the diagnostic criteria of XLP-2, the median age was 2.3 (1.2-5.3) years. All patients were well tolerated, median time to neutrophil engraftment was 10 (8-13) days, median time to platelet engraftment was 17 (13-23) days. 2 patients presented gran failure, and the secondary HSCT was survival to the present. Mix chimerism after transplantation developed in 2 patients, 4 patients developed grade II to III acute GVHD. Among 3 patients with EB virus (EBV) reactivation, 4 patients with cytomegalovirus viremia, 3 patients developed thrombotic microangiopathy (TMA). At the last follow up, 6 patients survived with no complications, one patient developed chronic GVHD, 2 patients died; one patient died from TMA, one patient died from bronchiolitis obliterans (BO). Conclusion: XLP-2 were susceptible to the EBV strains. Hematopoietic stem cell transplantation is the only treatment. However, the effects of BU or FLU on pretreatment toxicity and long-term prognosis need further study.

**Poster Location #36**

**HIGH SERUM CYTOKINES LEVEL REDUCE RED BLOOD CELL SURVIVAL IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS PATIENTS**

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Purpose: To assess red blood cell survival in hematophagocytic lymphohistiocytosis (HLH) patients and analyze the latent factors affect the red blood cell life span in HLH patients. Methods: We collected alveolar air of 30 HLH patients including 15 onset cases and 15 response cases after chemotherapy, and retrieved their clinical characteristics data. We also collected 30 healthy subjects’ alveolar air as blank control. We used the SEEKYA device to measure alveolar carbon monoxide concentration (endogenous PCO) and further calculate the life span of red blood cells. Results: The median RBC survival of 30 HLH patients was 45 days, about 67% shorter than 30 healthy subjects (138 days, P<0.001). In 30 HLH patients, the endogenous PCO of 15 onset cases increased by 63% (P<0.05) compared to 15 response cases. The IL-18, IFN-γ and TNF-α level in onset HLH patients was significantly higher than response HLH patients after chemotherapy. Splenic volume, bone marrow hematophagocytosis and high IL-2, IL-4, IL-18, IFN-γ and TNF-α level showed negative correlation with the RBC life span (P<0.05), while haemoglobin concentration, high IL-10 and IP-10 level showed positive correlation with the RBC life span (P<0.05). Conclusion: Uncontrolled serum cytokines release such as IL-18, IFN-γ and TNF-α could result in RBC destruction and reduce the red blood cell survival in HLH Patients.

**Poster Location #37**

**HEMATOPOIETIC STEM CELL TRANSPLANTATION COULD BE A POSITIVE WAY TO IMPROVE THE OUTCOME OF SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS**

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is not only a hereditary disease, but also a common endpoint for many clinical conditions. Hematopoietic Stem Cell Transplantation (HSCT) is now recommended for primary HLH, while the positive role in secondary HLH is still an open question. Methods: The HLH patients received HSCT were analyzed for clinical features and outcomes in order to discuss the application prospect of HSCT in secondary HLH therapy. Results: 109 of 958 HLH cases received HSCT, with the median age of them was 23-year-old. In this cohort, 71 cases were EBV-HLH, 27 cases were lymphoma associated HLH (LAHS), and others were primary HLH. Transplant of allogeneic HSCT (allo-HSCT) was from matched related donors in 28 cases, from unrelated donors in 4 cases, and from haplo-identified donors in 77 cases. Other 10 cases were underwent autologous HSCT (auto-HSCT). The overall survival (OS) was 63.3%, and the 1-year OS was 77.8%, 65.6% and 58.8% in primary HLH, EBV-HLH and LAHS, respectively. Most of death occurred in the first year after HSCT. Recurrent disease is the major death cause in EBV-HLH group and LAHS group. The underlying disease of HLH showed no significant influence on the long-term prognosis when the patients received HSCT. In addition, the OS were also less correlated with gender, condition regimen, and stem cell donor. However, the age (P=0.02) and the remission status of HLH before HSCT (P<0.0001) were independent risk factors for prognosis. LAHS patients received auto-HSCT achieved the similar outcome compared with non-HLH patients who also underwent auto-HSCT. And allo-HSCT might be a life-saving straw for aggressive lymphoma. Allo-HSCT could improve the outcome of elderly and refractory EBV-HLH patients by increasing the long-term survival by 35 percentage points (P<0.0001). Conclusion: HSCT played a positive role in secondary HLH and indications of HSCT deserved further clinical research.

**Poster Location #38**

**LYMPHOCYTE SUBTYPES SELECTIVELY INFECTED BY EBSTEIN-BARR VIRUS MIGHT BE CORRELATED TO THE HETEROGENEITY IN PROGRESSION OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS**

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Purpose: Epstein-Barr virus (EBV) is the most common trigger to induce hematophagocytic lymphohistiocytosis (HLH) with marked heterogeneity in progression. The response of uniform treatment and prognosis might be different in HLH patients complicated with EBV infection. Methods: Flow cytometry sorting and magnetic cell sorting were used to isolate the major sub-population of lymphocytes, such as CD3+CD4+ T cells, CD3+CD8+ T cells,
Purpose: The aim of this study was (1) to compare the levels of soluble ST2 (sST2), sCD163, IL-10, IFN-γ, TNF-α and IL-18 in patients with primary haemophagocytic lymphohistiocytosis (pHLH) and macrophage activation syndrome (MAS) and (2) to investigate whether they can help differentiate the two diseases. Methods: A total of 54 participants were recruited in this study, including 12 pHLH patients, 22 MAS patients and 20 healthy subjects. We measured the levels of sST2 and sCD163 in serum by using ELISA. The serum levels of IL-10, IFN-γ, TNF-α and IL-18 were analyzed using a Luminex 200 instrument. The levels of those cytokines in pHLH, MAS and healthy controls were compared and we further evaluated their roles as potential markers to differentiate those diseases. Results: The serum levels of sST2 and sCD163 in MAS patients were markedly higher than that in pHLH patients (395.79±320.62ng/ml vs 80.75±87.04ng/ml, P=0.0015; 3418.12±2692.00 ng/ml vs 1731.96±1262.07ng/ml, P = 0.04). There was no significant difference in the expression of IL-10 (3.975, 0-357.88 pg/ml vs 20.40±30.49pg/ml), IFN-γ (446.13±384.86pg/ml vs 306.89±281.60 pg/ml), TNF-α (78.24±63.94 pg/ml vs 61.48±64.69 pg/ml) and IL-18 (1052.56±1214.21 pg/ml vs 463.33±597.04 pg/ml) between MAS and pHLH, whereas the expression of those cytokines elevated significantly in both pHLH and MAS compared to the healthy group. Conclusion: Patients with pHLH and MAS show some differences in cytokine profiles. The elevated levels of IL-10, IFN-γ, TNF-α and IL-18 can contribute to the diagnosis of HLH, but may not discriminate pHLH from MAS. Levels of sST2 and sCD163 in MAS were significantly higher than that in pHLH, and sST2 and sCD163 may serve as markers to distinguish pHLH from MAS.

Poster Location #39

SOLUBLE ST2 AND CD163 AS POTENTIAL BIOMARKER TO DIFFERENTIATE PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS FROM MACROPHAGE ACTIVATION SYNDROME

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Background: The clinical feature of EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH) vary significantly. For refractory and recurrent EBV-HLH, the hematopoietic stem cell transplantation (HSCT) is inevitable and only one curative measure. Purpose: We summarized that 38 cases of EBV-HLH received reduced-intensity conditioning hematopoietic stem cell transplantation (RIC-HSCT) in children. Patients and methods: 38 consecutive refractory EBV-HLH from June 2015 to Dec 2017 in our center were analyzed. The median age of patients was 4.2 (0.9-12) years old. The median time from diagnosis to transplantation was 6.84 (2 to 20) months. 24 Patients with haploidentical transplantation received unmanipulated combined marrow and peripheral blood stem cells for transplant and 14 patients with unrelated donor transplantation received peripheral blood stem cells. We used the conditioning with etoposide, busulfan and fludarabine plus anti-thymocyte globulin (ATG) added cyclophosphamide or not. Chemotherapy before transplantation included 94 or 04, IE-CHOP or IL-DEP etc. Plasma EBV copies turned negative in 22 cases, persistent positive in 16 cases before the HSCT. 2 cases experienced GF following first HSCT and successfully engrafted following salvage secondary HSCT. Results: A median follow-up of 21(6 ~ 30) months showed that 31/38 patients are alive and well with a survival rate of 81.5±7.6%. The incidence of acute GVHD was 31. 6%(10/31) and that of...
chronic GVHD was 29.4% (9/31). The incidence of Epstein-Barr virusemia was 40% and 70% in cytomegalovirus. The main causes of death were 2 cases of transplantation associated thrombotic microangiopathy, 2 cases of severe infection, 1 case of bronchiolitis obliterans and 2 case of posttransplant relapse. Conclusions: The good outcome could be acquired in EBV-HLH using appropriate RIC-HSCT in children, even after graft failure.

**Poster Location #42**

**GENETIC CHARACTERIZATION OF PEDIATRIC PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN CHINA: A SINGLE CENTER STUDY**

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a rare and fatal disease, which can be categorized as primary HLH (pHLH) and secondary HLH. Methods: SPSS was used in all statistical analysis of the data. Results: This retrospective study enrolled 46 pHLH patients, including 28 familial HLH (FHL) patients. In pHLH patients, the median age at diagnosis was 2.3 years (range. 0.2:13.7 years) and 58.7% patients were diagnosed within 3 years old. The probable overall survival (OS) at 12 and 24 months were 84.1% and 77.1%, respectively. Genetic analysis showed that the most common mutations were in UNC13D (n=15. 12.5%) and LYST (n=12. 10.0%); the frequency of PRF1 mutations was moderate (n=9. 7.5%). Notably, a total of 59 mutations sites in the HLH-related genes were detected, of which 39 mutations were novel and predicted to be probable pathogenic by SIFT, which were detected in their parents’ samples. The mutations in CUBN, TYK2 and NCF2 were the most frequent genetic abnormalities in HLH patients, thereinto, CUBN c.9229G>A was detected in 2 pHLH patients. The patients with disruptive mutations (such as indels, deletions, nonsense mutations, and splice errors) were significantly younger than those with other types of mutations at diagnosis (4.6 years versus 1.0 year. P=0.015). Moreover, in FHL patients, the incidence of severe CNS symptoms such as seizure was higher and NCF2 mutations may be associated with poor prognosis. The assays of CD107a degranulation and NK activity showed no statistical difference in one or two genes heterozygous mutations and gene-affected mutations. Thus, there may be a digenic mode of inheritance or dominant-negative monoallelic mutations mode in pHLH patients. Conclusion: There were many mutations in HLH-causing genes, and other genes such as CUBN, NCF2, TYK2 in Chinese children with pHLH. The polygenic inherited patterns or dominant-negative monoallelic mutations maybe existed in pHLH.

**Poster Location #43**

**NEUROLOGICAL ABNORMALITY COULD BE THE FIRST AND ONLY SYMPTOM OF FAMILIAL HEHOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: REPORT OF 2 FAMILIES**

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a severe disease, which always leads to impairment of the central nervous system (CNS). Furthermore, neurological symptoms could be the first onset or the only symptom of HLH patients in the early stage, which leads to a delay of HLH diagnosis. Methods: We reported two cases of HLH children who had CNS symptoms at the first onset and visited neurological department repeatedly for a long term, and were diagnosed as HLH eventually. PRF1 compound heterozygous mutations of c.1349G>A (p.T450M) and c.218C>T (p.C73Y) was found in the first case, and the second site was reported firstly with a positive family history. In the second family, compound heterozygous mutations of c.1349C>T (p.Thr450Met) and c.853_855del (p.285del) in PRF1 had been reported. The level of PRF1 protein was decreased in both NK cells and CTL cells by 47.3% and 18.2% respectively in the second case. Results: PRF1 compound heterozygous mutations of c.1349G>A (p.T450M) and c.218C>T (p.C73Y) was found in the first case, and mutation of c.1349G>A (p.T450M) might related to the involvement of CNS. Conclusion: Doctors should pay more attention to patients who have CNS symptoms and extensive or multi-focal white matter changes in cranial MRI, combining with mildly decreased blood cells and splenomegaly while fever in the course. These patients are prone to misunderstand as other neurological diseases such as leukodystrophy.
Purpose -The goal of our research is to improve our understanding of Langerhans Cell Histiocytosis (LCH). To this end, we are investigating the composition and development of this disease at the cellular and molecular level. Methods - We have used single-cell RNA-sequencing of a primary LCH biopsy sample to dissect intraleSIONal heterogeneity. In addition, we have analyzed RNA expression and DNA methylation on bulk LCH samples, dendritic cells, and epidermal Langerhans cells to delineate inter-patient heterogeneity. Results - We have identified different LCH cell populations with distinct pathway signatures, including a stem-cell-like, proliferative state and a transformative state. Functional chromatin mapping inferred distinct regulatory signatures discriminating both cell states. Furthermore, by employing a combination of single-cell transcriptome and epigenome profiling assays we discovered a continuum of dendritic- and Langerhans-cell-like signatures in LCH patients. Conclusion: We propose that LCH is comprised of different LCH cell subsets that arise in an intrinsic developmental process within the lesions.

CD1a and TNF were overexpressed in LCH CD1a+/CD207+cells. Interestingly, we also found two genes that previously were described to be restricted to epidermal Langerhans cells, HLA-DQB2 and HLA-DQA2 that were highly expressed in LCH CD1a+/CD207+cells. HLA-DQB2 and HLA-DQA2 expression was absent from peripheral blood and tonsil cells from healthy controls. However, HLA-DQA2 and HLA-DQB2 were also expressed at lower levels in peripheral blood CD1c+ cells, with BRAF-V600E mutation highly enriched in HLA-DQB2 peripheral blood CD1c+ cells from patients with high risk LCH. Conclusions: HLA-DQA2 and HLA-DQB2, previously described to be exclusively expressed by epidermal Langerhans cells, are highly expressed in LCH lesion CD1a+/CD207+ cells. Previous study also describe ability of HLA-DQA2 and HLA-DQB2 in human normal skin Langerhans cells to mediate staphylococcal superantigen stimulation of T cells. The expression of these two MHCII antigens may therefore play a role in T cell recruitment and activation in LCH lesions and may represent novel diagnostic and therapeutic targets for patients with LCH.

Purpose: Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia, characterized by accumulation of pathological CD1a+Langerin+ histocytes and eosinophils in affected tissues and formation of granulomas. We have previously observed that LCH blood monocytes produce Interleukin (IL)-17A and reported a correlation between IL-17A levels in plasma and CSF and LCH disease severity. Furthermore, we suggested that IL-17A could be used as an additional biomarker for monitoring neurodegenerative CNS-LCH. In this follow-up study, we explore the role of IL-23 signaling in LCH pathogenesis, since IL-23 is known to promote the initiation and maintenance of IL-17A-mediated inflammation. Methods and Results: Initially, we measured the plasma levels of IL-23 and of additional cytokines in LCH patients and healthy donors using ELISA assays and found significantly higher levels of all measured cytokines in LCH patients. The majority of patients with the highest IL-23 and/or IL-17A levels were untreated or had CNS involvement. In addition, analysis of several follow-up samples showed a correlation between activation of the IL-23/IL-17A signaling pathway and clinical deterioration or no clinical improvement. Analysis of fine needle lesional aspirates identified myeloid cells in LCH granulomas that produced those cytokines, while staining of affected tissues from patients with other granulomatous or inflammatory diseases was unable to detect the same cytokine-producing myeloid cells indicating that this phenomenon is more likely to be LCH-specific than related to inflammation per se. Conclusion: Our findings suggest that activation of the IL-23/IL-17A signaling pathway might have a key role in the initiation of LCH pathogenesis and likely in the maintenance of tissue inflammation. Further studies are required to assess the potential efficacy of cytokine inhibitors in resolving LCH granulomas.
Purpose: Tumor necrosis factor alpha (TNF-alpha) is produced in Langerhans cell histiocytosis (LCH) lesions and is elevated in active high-risk vs low-risk LCH vs control patient blood, where TNF-alpha has been reported at 12 pg/ml in juvenile rheumatoid arthritis (JRA). Anti-TNF therapeutic etanercept is used in TNF-mediated diseases, such as JRA, and was successfully used in one case of LCH. We therefore conducted phase II study for etanercept therapeutic efficacy for refractory or relapsed LCH patients. Methods: Luminex platform was used to assess patient blood TNF-alpha level. This phase II study was approved by the Baylor College of Medicine IRB with research support from Amgen/Immunex. Eligibility included LCH patients with progressive disease post-initial treatment and ≥1 salvage therapy. Etanercept was injected 0.4mg/kg subcutaneously twice/week for 12 weeks. Therapeutic response were evaluated at 4 and 8 weeks. Results: TNF-alpha is elevated in blood LCH high-risk (average 45pg/ml) vs low-risk (average 13pg/ml) vs control (average 13pg/ml). Five LCH patients (1.6-42 years) with multisystem involvement, 2 with high-risk disease were enrolled. A median of 5 doses of etanercept were administered (range 1-14). One high-risk patient died 18 days after the first dose from disease progression. At week 4 evaluation, one patient had stable disease and 3 progressed and all subjects progressed by week 8. Ultimately 0/5 patients had disease improvement with etanercept. Conclusion: Etanercept therapy, at JRA effective dose, in this trial did not improve LCH disease. It is possible that this may not be an effective strategy. Alternatively, it is also possible that drug dose or distribution was suboptimal. While anti-TNF therapies, including etanercept, are effective for treatment of RA, etanercept is not effective for granulomatous diseases such as Crohn's, sarcoidosis or Wegner's disease. Additional studies exploring potential efficacy of higher dose or alternative forms of TNF-alpha inhibition in LCH may be warranted.

Purpose: The extent of disease is an important prognostic factor for LCH. Current guidelines recommend the use of a plain radiography to assess skeletal involvement. Whole-body magnetic resonance imaging (WB-MRI) may represent a radiation-free alternative. The aim of the study is to prospectively evaluate the diagnostic performance of WB-MRI in comparison to plain radiography, as the reference standard, for staging patients with LCH. Methods: Paediatric and young adult patients with histological proven LCH were included (n=14), selected in the last 5 years. WB-MRI and plain radiography were performed within 2 weeks. The extent of disease was assessed by two blinded observers. Cohen's Kappa coefficient was applied to compare the agreement between WB-MRI and plain radiography. The sensitivity and specificity of WB-MRI were also determined. Results: Sixteen patients (median age: 9.5 years; range: 2 months, 21.6 years) were enrolled. Plain radiography showed 26 lesions in 15 patients: unifocal (n=11) and multifocal (n=4). WB-MRI identified additional 8 skeletal (hip and vertebral) lesions in 3/16 patients (19%) and extraskelatal (pulitary, lung, eyes) lesions in other 3/16 (19%) patients. Agreement between WB-MRI and plain radiography was 89% (k=0.89); sensitivity and specificity of WB-MRI were 99% and 86% respectively. Conclusions: WB-MRI is a high sensitive and radiation-free method to assess the skeletal extent of LCH and appears to be superior to plain radiography in detecting hip and vertebral lesions. In addition, WB-MRI can detect extraskelatal lesions of the disease. These results, in agreement with previous reports, support the introduction of WB-MRI for staging patients with LCH in the next clinical trials.
Purpose: Liver Transplantation (LT) is the sole curative option for severe SC-LCH but outcomes can be severely compromised by recurrence of the disease on the graft. We report the outcome of 2 patients who underwent LT for active BRAFV600E LCH-related sclerosing cholangitis (SC-LCH) and received BRAF +/- MEK inhibitors post LT to prevent disease relapse on the graft. Result: Case 1 presented LCH at 0.9 years with skin involvement initially treated with topical steroids. At 2.4 years of age, she presented with relapse including diabetes insipidus, SC-LCH, splenomegaly and skin lesions. VLB steroid therapy proved insufficient. At 4.3 years of age vemurafenib was initiated for presumed SC-LCH and a humerus lesion. The bone lesion improved but complications of portal hypertension worsened. LT was performed at age of 5.1 years with an unremarkable post-operative course on vemurafenib in addition to conventional immunosuppression protocol. There is no evidence of active disease at one-year follow up. Case 2 presented with LCH at 2.1 years with skin lesions, haematological dysfunction and SC-LCH. Vemurafenib was initiated 2 months after diagnosis as disease progressed after VLB and steroids. Cobimetinib was added for a new a bone lesion. Nonetheless, liver involvement worsened, leading to LT at age 4.9 years. Vemurafenib and Cobimetinib were continued after LT with no major drug interactions. There is no evidence of LCH recurrence at 3 months post LT, and liver function is normal. Conclusion: Vemurafenib and Cobimetinib were continued after LT with no major drug interactions. There is no evidence of LCH recurrence at 3 months post LT, and liver function is normal.
Purpose: To present the outcome of 53 children with refractory LCH bearing BRAFV600E mutation treated with Vemurafenib. Methods: Two groups of patients were considered. Active Refractory Disease (ARD) Group (n=47) included 38 patients with and 9 without Risk Organ (RO), all refractory to at least one induction of vinblastine and steroid. Symptomatic Neurodegenerative CNS (ND) Group (n=6), who all previously received vinblastine + steroid (>24 months) and retinoic acid; one also received intravenous immunoglobulins. After informed consent, Vemurafenib was provided off label at a dose of 20 mg/kg/day orally. Results: Median age at diagnosis was 0.9 and 1.6 years in ARD and ND groups respectively. In ARD patients Vemurafenib was initiated at median age of 1.9 years, all patients could be evaluated at week 6-8. Median duration of treatment was 9.1 months and median follow up was 1.6 years (1979 years person overall). Response was complete in 29 and partial in 18. No grade 3 or 4 side effect was observed and median follow up was 2.9 years. Shortly after onset, two patients withdrew therapy for grade 3 side effect (severe weakness in one, skin rash in one). When provided for long term (n=4) a limited subjective improvement was observed but SARA score remained stable in 3 and improved in one. Overall, therapeutic can be withdrawn in 23, pharmacokinetic parameters were analysed in 28, plasma Braf Load were till weeks 8. One death was observed in a patient who had a partial response was complete in 29 and partial in 18. No grade 3 or 4 side effect was observed and median follow up was 1.6 years (1979 years person overall). Response could be evaluated at week 6.

Poster Location #52

CLINICAL CHARACTERISTIC AND OUTCOME OF PEDIATRIC PATIENTS DIAGNOSED WITH LANGERHANS CELL HISTIOCYTOSIS IN PEDIATRIC HEMATOLOGY AND ONCOLOGY CENTERS IN POLAND BETWEEN 2010 AND 2017

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Purpose: In the study we aimed to summarize the clinical features, management and outcome of children with Langerhans cell histiocytosis (LCH) treated in Polish pediatric hematology-oncology centers in years 2010-2017. Methods: We retrospectively collected data from 14 out of 16 pediatric oncology centers in Poland. Between January 2010 and December 2017 182 children with LCH were included. Centers were requested to provide following data: demographic data, clinical data, local or systemic treatment data and outcome of the patients. Results: Majority of children 69% were classified as single system (SS). There were 61% boys, median age at diagnosis was 4.2 years however patients with SS were significantly older as compare to children with multisystem disease (MS) 6 years vs 2.3 years respectively (p=0.003). Bones were involved in 76% patients with SS and patients with MS disease presented with more than two organs involvement in 33 out of 56 cases (59%). Systemic treatment was applied to 112 patients: 47% children with SS disease and 98% with MS disease. 109 children received systemic chemotherapy according to Histiocyte Society Treatment Guidelines April 2009. Local therapy consisted of surgery with or without local steroids and radiotherapy in one case. Median follow-up time was 4.3 years. Six children were lost from follow-up and three patients were on treatment at the time of data collection. Overall survival (OS) in entire group with available follow-up (173pts) was 0.99 and event free survival (EFS) was 0.91. Two children died: one infant died before treatment introduction and one child died of progressive disease 6 months after diagnosis. Fourteen patients relapsed and are alive in second remission or remained on salvage therapy. Conclusion: Treatment of LCH according to Histiocytic Society Guidelines 2009 in Polish centers was effective but new approaches like mutation analyses are needed to identify patients with risk features.

Poster Location #53

GASTROINTESTINAL LANGERHANS CELL HISTIOCYTOSIS: IS IT UNDER-DIAGNOSED?

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Purpose: Gastrointestinal (GI) involvement in childhood Langerhans cell histiocytosis (LCH) is rare. We report a recent case, review the literature and raise questions regarding presentation and diagnosis. Methods- 1. Case report 2. Literature review 3. Retrospective data, iron status and albumin, from children with LCH treated at our institution between 2008-2017. Results- A 6-
month old boy with persistent generalized rash was diagnosed with LCH; no evidence of systemic involvement. Due to severe pruritis, prednisone/ vinblastine/methotrexate were initiated. After 12 months- still residual rash. During this period his weight dropped from 50th to 3rd percentile, with mild iron deficiency, but no vomiting/diarrhea/hypoalbuminemia. Endoscopy: gastric, esophageal, duodenal biopsies showed evidence of LCH, positive BRAFV600 mutation. PET-CT: no abnormal skin or GI tract FDG uptake. Literature search: 40 pediatric and 25 adult cases. Children: severe multisystem (MS) disease, 16/40 with risk organ involvement, 25/40 patients died. In all reported cases presenting symptoms included diarrhea, hematochezia, vomiting or significant hypoalbuminemia. Adults: 7/25 cases had multi-system involvement. Nine cases were asymptomatic, and were diagnosed on routine colonoscopy. Only one patient died of progressive disease. Iron status and albumin values at presentation were available for 59 of 80 childhood LCH patients treated at our center. Twenty-one patients (35%) had iron deficiency, low levels of iron (median 27 mcg/dl) and ferritin (median 14 ng/ml). Hypoalbuminemia was found in 5 of 14 cases (range 0.8-3.2 g/dl) with MS involvement. Conclusions- GI LCH may present with subtle clinical signs, or even asymptptomatically, and requires invasive methods for diagnosis. It is probably under-diagnosed. In a small cohort of LCH patients we found a significant percentage with iron deficiency anemia/hypoalbuminemia, raising questions regarding possible GI etiology. International collaboration is required to determine the outcome of this disorder. Whether GI resident dendritic cells have a pathogenic role in LCH remains to be determined.

Poster Location #56

CHOLESTASIS AND SCLEROSING CHOLANGITIS IN LANGERHANS CELL HISTIOCYTOSIS. CASE SERIES

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Background: Liver involvement (LI) in Langerhans cells histiocytosis typically occurs in infants with multisystem disease. A rare complication of LI is the development of sclerosing cholangitis (SC) with hepatic fibrosis (HF), which can result in the requirement of liver transplantation(LT). Purpose: To present the outcome of four patients with LCH, SC and HF. Material and methods-Results. Patient 1: One year-old-male, with skin and LI, mild conjugated hyperbilirubinemia, alkaline phosphatase (ALP) and elevated gamma-glutamyltransferase (GGT) with normal albumin. The patient had a good initial response to prednisone and vinblastine (PDN-VBL). After 5 months of maintenance therapy, patient had a skin reactivation with a
transient response to prednisone-cytarabine (PDN-ARAC). Complete response to cladribine (2CDa) was reached, with high toxicity. Liver biopsy (LB) and Magnetic Resonance cholangiography (MRC) confirmed HF grade 5/6. Currently is in evaluation to LT. Patient 2: Two years-old-male, with skin, bone, spleen and LI, conjugated hyperbilirubinemia, elevated ALP, GGT and a mild hypoalbuminemia. Transient response to PDN-VBL and PDN-ARAC was followed by skin reactivations. LB and MRC confirmed HF and SC. Currently under 2CDa therapy with esophageal variceal bleeding complication. Patient 3: One year-old-male with skin, bone, spleen and LI. Normal bilirubinemia with elevated ALP, GGT and a mild hypoalbuminemia were found. Patient had a mixed response to PDN-VBL. LB confirmed HF grade 5/6. Currently under 2nd line therapy without complications. Patient 4: One year-old-male with skin, spleen, hematopoetic and LI with risk organs dysfunction. Severe hyperbilirubinemia with ALP and GGT elevated were found. Currently under 2CDa-ARAC therapy without response yet. BRAF (v600E) mutations were not found. Conclusion: SC and HF are severe complications with high morbidity. Multilineage therapy may be required. The response to therapy and the interdisciplinary approach with early work-up for LT are important for the patient's survival.

Poster Location #57
SUCCESSFUL TREATMENT OF MASS LESIONS OF CENTRAL NERVOUS SYSTEM'S LANGERHANS CELL HISTIOCYTOSIS WITH 2-CHLORODEOXYADENOSINE CASES SERIE

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Background: Central nervous system Langerhans cell histiocytosis (CNS-LCH) may include mass lesions and/or a neurodegenerative disease (LCH-ND). No standard guidelines are available to treat patients with mass lesions. Two-chlorodeoxyadenosine (2-CDA) has shown some evidence of success. Purpose: To present the outcome of three patients with mass lesion's CNS-LCH treated with 2-CDA. Material and methods: Results: Patient 1: Ten years-old male with previous history of skin, bone, CNS-risk lesions and Diabetes insipidus (DI) at 3 years-old. Initially treated with prednisone-vinblastine (PDN-VBL) and prednisone-cytarabine (PDN-ARAC). He developed clinical evidence of LCH-ND, the Magnetic Resonance Imaging (MRI) showed nodular intraventricular choroid plexus and meningeal lesions. A stereotactic biopsy confirm the diagnosis of CNS-LCH and he received 10 courses of 2-CDA. A partial response was achieved with significant toxicity. Patient 2: Two year-old-female with skull vault osteolytic lesion and DI. The head MRI shows an extensive right hemispheric mass with significant edema. The biopsy of skull lesion confirms LCH. Six courses of 2-CDA were administered. A partial response was achieved. She is still under 2-CDA therapy. Patient 3: Two years-old boy with DI, cortisol deficiency and hypothyroidism. MRI revealed multiple tumor-like lesions on posterior fossa (PF) and supratentorial area. Biopsy of one lesion confirmed the diagnosis of LCH; He was initially treated with dexamethasone and etoposide, achieving stable disease. Five months afterwards he developed acute hydrocephalus and required a ventriculoperitoneal shunt while the MRI showed progressive disease. Methotrexate:vinblastine was given and Radiotherapy was performed (20 Gy) with no response. Two-CDA was then administered monthly through 1 year achieving no evidence of active disease, without significant toxicity. Conclusion: 2-CDA seems useful for these patients. More evidence and long-term follow-up are needed to confirm this fact and to evaluate helpfulness in prevention LCH-ND.

Poster Location #58
THE FINANCIAL BURDEN OF CARE FOR LANGERHANS CELL HISTIOCYTOSIS WITHOUT RISK ORGAN INVOLVEMENT

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Purpose: Therapies for Langerhans Cell Histiocytosis (LCH) vary depending on disease location and severity. While LCH without Risk Organ (RO)- involvement can be associated with significant morbidity, it is not considered to be life-threatening. However, current and forthcoming studies will investigate intensification and prolongation of therapy to reduce recurrence risk. While previous studies have investigated the financial burden of care associated with other life-threatening childhood cancers, little data exists regarding the financial burden of the treatment for RO- LCH. Methods: We conducted a cross-sectional survey of caregivers of RO- LCH patients at a tertiary children's hospital. Measures included the impact on relocation, employment and finances. Results: We surveyed 28 caregivers (72% mothers) of children (ages 0.8 : 14 years) with RO- LCH. Two-thirds of patients were privately insured while one-third had medicaid. Household income was less than $19,999 in 12%, $20,000-$39,999 in 23%, $40,000-$59,999 in 27%, $60,000-$79,999 in 8%, $80,000-$99,999 in 15%, and >$100,000 in 15%. Tissues involved with LCH included skin (5), single bone (8), multifocal bone (13), pultitary (2), brain (3), lung (1), and mediastinum (1). Twenty (71%) patients received some form of chemotherapy. Caregivers missed an average of 7 combined work days in the first month after diagnosis and 6 days per month over the first 6 months after diagnosis. Of 10 (36%) caregivers who reported moving residences since their diagnosis, 3 (30%) reported that the move was due to their child’s LCH. Eighteen percent (5) of caregivers reported quitting or changing jobs as a direct result of their child being diagnosed with LCH. One-fourth of caregivers felt that the financial burden was the "single greatest difficulty" associated with caring for an LCH patient. Conclusions: RO- LCH has an appreciable financial impact for caregivers. This should be considered as new treatment protocols are developed.

Poster Location #59
NON-LANGERHANS CELL HISTIOCYTOSIS

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A 6-year old girl was admitted with new-onset headache, right sided hemiparesis and generalised seizure. Cranial MRI revealed a left frontal mass of 44x50 mm. The mass was partially resected. Pathologic examination revealed lymphocytic and histiocytic infiltration with no specific diagnosis. The residula mass was resected and the final diagnosis was non-langerhans cell histiocytosis, juvenile xanthogranuloma. BRAF mutation was negative. Bone graphs, abdominal USG and PET-CT was negative for additional systemic involvement. The diagnosis was Non-Langerhans Cell Histiocytosis, with isolated CNS involvement She was given vincristin and cytarabine for every 4 weeks. A recurrent mass was seen on cranial MRI at the end of the first year and cefotaxime was started. After 6 courses of the treatment, cranial MRI was normal. She was on regular follow-up with no evidence of disease for 2 years after completion of the therapy. Isolated involvement of CNS with Non-LCH is very rare in children. Diagnosis and treatment is difficult with need to multidisciplinary approach.
INCIDENCE AND CLINICAL CORRELATIONS OF SOMATIC MAPK PATHWAY MUTATIONS IN PEDIATRIC AND ADULT LANGERHANS CELL HISTIOCYTOSIS

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Purpose. Neoplastic Langerhans Cell Histiocytosis (LCH)-cells are characterized by constitutive activation of the mitogen-activated protein kinase (MAPK) signaling pathway, mostly as the result of somatic mutations. The incidence and clinical correlations of distinct MAPK pathway mutations remain unresolved, especially in adults. We therefore collected a large retrospectively genotyped Dutch-Canadian LCH-patient cohort, including adults and children, with long-term follow-up. Methods. Archived formalin-fixed-paraffin-embedded tissue biopsies were analysed for the presence of the BRAFV600E mutation by microdissection and real-time PCR. BRAFV600E negative (BRAFWT) samples were subjected to Sanger sequencing (BRAF exon 12&15, MAP2K1 exon 2&3) and/or an AmpliSeq™ next-generation-sequencing panel containing primers to detect established LCH-associated mutations in ARAF, BRAF, MAP2K1, MAP3K1, KRAS, NRAS and mutations in many other cancer-associated genes. Clinical data were obtained using standardized case report forms. Results. To date, 204 LCH-patients with a median follow-up of 6.4 years (range:0-40 years) were successfully genotyped for BRAFV600E, comprising 155 children (n=76+49%) and 49 adults (n=20+41%). MAP2K1 mutations were detected in 22/62 (35%) effectively genotyped BRAFWT children and in 7/14 (50%) successfully tested BRAFWT adults. Alternative genetic alterations in MAPK pathway genes were detected in 12 patients. BRAFV600E correlated with high-risk LCH and reduced event-free survival in children (p=0.04), but not in adults (p=0.99). Moreover, BRAFV600E positive pediatric patients had significantly reduced event-free survival compared to BRAFWTMAP2K1WT patients (n=40,p=0.02), but not compared to MAP2K1 mutated patients (p=0.42). Conclusions. Our study confirms earlier reported findings on BRAFV600E in pediatric LCH. In addition, BRAFWTMAP2K1WT patients appear to have the most favorable prognosis in children with LCH. Our study currently lacks sufficient power to address genotype-phenotype correlations in adult LCH, emphasizing the importance of collecting robust genotype data on these patients before findings may be translated. We therefore encourage the integration of molecular genotyping in routine pathology work-up of all LCH-biopsies, regardless of clinical presentation.
Background: It has not yet been evaluated in large cohort whether laboratory data at diagnosis reflect the outcomes in pediatric LCH patients, though the impact of risk organ (RO: liver, spleen and/or hematopoietic system) is well recognized. We performed data analyses affecting on overall survival (OS) in patients enrolled to JLSG-02 trial. Patients and Methods: Data were collected for laboratory data at diagnosis and involved organs in a total of 147 cases (75 males; median age 1y6m) with multi-system LCH, registered during a period of 2002 to 2009. Continuous variables of laboratory data were divided into two categories by analysis with ROC curve. Cox proportional hazards model and Kaplan-Meier method were employed for analysis. P<0.05 was considered significant. Results: In this cohort, actually, 71/147 (4.8%) patients died and OS rate at 5 years were 95.2% (95%CI: 91.8-98.7). RO(+) patients had significantly lower OS rate compared to RO(-) patients (90.0% (95%CI: 83.0-97.0) vs. 100%, p=0.005). Analyses showed that patients with low levels of Hb (<8.0), platelet (<200K), total protein (<5.5), albumin (<3.5), WBC (<5,000), as well as high levels of total bilirubin (T-bil) (>0.55), C-reactive protein (>4.5) and lactic dehydrogenase (LDH) (>350) had significantly low OS rate (HR=41.5, 34.8, 22.1, 13.1, 8.5, 11.7, 5.3, and 5.2, respectively). Among them, four variables; namely low Hb, high T-bil, high LDH and low WBC were extracted by multivariate analysis with stepwise selection method (HR=15.0, 10.3, 5.5 and 5.5, respectively). The OS rate was extremely lower in patients with 3 or more of these four variables (n=7), in whom all belonged to RO(+) and 5/7 to fatal cases, than the others (28.6% (0.0-62.0) vs. 98.6% (96.6-100), p<0.001). Conclusions: These data demonstrate that pediatric LCH patients with extremely poor outcome could be extracted with accuracy by a combination of routine laboratory examinations at diagnosis.

Poster Location #63
LANGERHANS CELL HISTIOCYTOSIS-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
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Objective: To investigate the clinical features and treatment of patients with Langerhans cell histiocytosis-associated hemophagocytic lymphohistiocytosis (Lc-HLH). Methods: The clinical data of two cases of Lc-HLH were retrospectively analysed and the relevant literatures were reviewed. Results: Two cases of Langerhans cell histiocytosis (LCH) were pathological diagnosis. Hemophagocytic lymphohistiocytosis (HLH) was presented as initial manifestation occurred in the patient No. 1. However, one year after the treatment of HLH-2004 regimen, the patient No. 1 developed bone lesions. LCH was diagnosed by the bone biopsy. Then the patient No. 1 received JLSG02 regimen. Patient No. 1 currently is alive followed up for 18 months. Patient No. 2 developed HLH in the remission period of LCH. HLH was triggered by sepsis. One heterozygous mutation (c.953C>T) of STXBP2 was found. The patient No. 2 received the treatment of HLH-2004 regimen. Patient No. 2 currently is alive followed up for 17 months. Conclusion: HLH can be the initial manifestation of LCH. The prognosis of Lc-HLH may be better than other malignancies-HLH. The standard treatment scheme of Lc-HLH is unavailable and future multicenter and large sample studies are needed to optimize the treatment regimen for Lc-HLH.

Poster Location #64
A CHILD WITH BOTH LANGERHANS AND LANGERHANS CELL HISTIOCYTOSIS
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An 18 months-old-girl was first admitted with paleness and abdominal distention. Physical examination revealed hepatosplenomegaly with no additional skin or bony changes. Laboratory examination was consistent with normocytic anemia. Bone marrow aspiration was non-diagnostic. With a diagnosis of non-immune hemolytic anemia she had been transfused repeatedly in addition to immunosuppressive treatment. During follow-up, she admitted with right parietal mass. Radiologic evaluation revealed multiple lytic bone lesions and bilateral nephromegaly with parenchymal nodular lesions and megacalculi. Biopsy of the parietal lesion was consistent with Langerhans Cell histiocytosis. LCH-IV chemotherapy was started with a diagnosis of LCH, multisystem disease. At he end of the induction therapy as there is progression of the renal nodular lesions, a renal biopsy was performed and the diagnosis was reported to be non-Langerhans cell histiocytosis. Both specimen (bone and kidney) were positive for BRAF V600E mutation. She was diagnosed as both LCH and non-LCH disease with multystem involvement. Because of the clinical progression during the diagnostic work-up, clofarabine was started with partial clinical response after 3 cycles. The patient is still on follow-up waiting for the evaluation of the response. Vemurofenib was scheduled for the continuation of the treatment. The presence of LCH and Non-LCH lesions in the same patient is very rare in children. Especially renal parenchymal involvement is exceptional. The diagnosis and treatment of this complex disease pattern is very challenging.

Poster Location #65
RACIAL AND ETHNIC DISPARITIES IN INCIDENCE OF LANGERHANS CELL HISTIOCYTOSIS DIFFER ACROSS AGE GROUPS
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Purpose: Langerhans cell histiocytosis (LCH) is a myeloid neoplasia with median diagnosis age of 30 months. We recently reported an increased risk for LCH in children of Hispanic parents using data from the Texas Cancer Registry. However, less is known about racial/ethnic disparities among adults diagnosed with LCH. Therefore, we sought to compare the incidence of LCH by race/ethnicity in the United States among pediatric, adolescent/young adult (AYA), and adult cases using Surveillance, Epidemiology, and End Results (SEER-18) program data. Methods: LCH incidence data were obtained from the SEER-18 program, 2000-2015. Race/ethnicity was categorized as: non-Hispanic white (NHW); non-Hispanic black (NHB); non-Hispanic Asian (NHA);
and Hispanic. Age-specific incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were generated in SEER-STAT (v3.3.5). Results: Data on LCH cases ages 0-14 (n_children=777), 15-39 (n_AYAs=214), and 40+ (n_adults=261) were abstracted. Compared to NHW children, Hispanic children experienced significantly elevated LCH IRRs (IRR_Hispanic_children=1.30, 95% CI: 1.11-1.52). However, this trend was not observed among AYAs (IRR_Hispanic_AYAs=0.62, 95% CI: 0.43-0.89) or adults (IRR_Hispanic_adults=0.60, 95% CI: 0.37-0.95) where lower IRRs compared to NHWs were evident. While not statistically significant, this trend was also suggested among NHAs. Compared to NHW children, IRRs for NHAs were slightly elevated (IRR_NHA_children=1.06; 95% CI: 0.81-1.38), whereas among AYAs a trend toward lower incidence was suggested (IRR_NHA_AYAs=0.59, 95% CI: 0.32-0.101) and became stronger among NHA adults (IRR_NHA_adults=0.56, 95% CI: 0.31-0.96). NHBs experienced lower IRRs compared to NHWs in all age groups: (IRR_NHB_children=0.36, 95% CI: 0.25-0.51; IRR_NHB_AYAs=0.47, 95% CI: 0.26-0.79; and IRR_NHB_adults=0.41, 95% CI: 0.21-0.74). These reported estimates remained similar after adjusting for sex and SEER registry using Poisson regression. Conclusion: These contrasts in incidence by race/ethnicity suggest differences in underlying LCH etiology across the age spectrum. While limitations of registry data exist, future studies characterizing molecular components in adults compared to children is warranted.

Poster Location #66

PULMONARY LANGERHANS CELL HISTIOCYTOSIS - CLINICAL PRESENTATION, TREATMENT AND OUTCOME OF 110 ADULT CASES

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Pulmonary Langerhans cell histiocytosis (PLCH) is a rare sporadic cystic lung disease of unknown etiology that is characterized by the infiltration and destruction of the lung parenchyma by CD1a+ Langerhans-like cells. It is seen as part of multisystem LCH or as an isolated form of the disease. The clinical spectrum of the PLCH varies widely and its course is unpredictable. It may resolve after smoking cessation but in other cases progression in spite of treatment is observed. Material and methods: In a period of 20 years, 111 adults (52 women and 59 men in age 15 to 69 years) with PLCH, confirmed by histological examination, have been diagnosed and treated in our Department. The median follow-up period was 132 months (range 6 to 320 months). Out of 3 patients who were nonsmokers, 97% of patients were smokers. Results: Twenty seven (25%) patients had multisystem disease, 2 (2%) multifocal bone disease, one (1%) isolated mucosal lesions and 74% isolated PLCH. Diabetes insipidus was diagnosed in 14 patients. Clinical and radiological features, pulmonary function tests, and outcome will be discussed. Chemotherapy according to LCH-Adult protocol was administered in 11(10%) patients, 13(12%) patients received Cladribine, and 10(9%) patients prednisone. Local steroid treatment was applied to 4(4%) patients, radiotherapy in one, and a surgical excision of bone lesions was performed in 6(6%) patients. Two men underwent unilateral lung transplantation. Conclusions: PLCH is a rare, polycystic lung disease; early diagnosis, accurate staging, smoking cessation, and adequate treatment are considered critical in PLCH management.

Poster Location #67

EFFICACY OF INDOMETHACIN AS SALVAGE THERAPY IN CHILDREN AND ADULTS WITH LANGERHANS CELL HISTIOCYTOSIS WITH BONE INVOLVEMENT

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Purpose: The aim of this study was to analyze the results of treatment with indomethacin in children and adults with recurrent Langerhans cell histiocytosis (LCH) with bone involvement. Methods: Between 1992 and 2014, 17 patients (median age 37 years, range 1-53) with recurrent LCH and active bone lesions were treated with indomethacin 2 mg/Kg/day (maximum dose 150 mg/day) for a minimum of 3 months. Indomethacin was given alone or in combination with surgery/chemotherapy in 10 (59%) and 7 patients (41%), respectively. BRAF mutation analysis was available in 5 patients. Median follow-up was 24 months. Results: All patients were evaluable for response. Median duration of treatment was 6 months. Fourteen of 17 (82.5%) patients obtained a response, that was complete (CR) in 12 (70.5%) and intermediate (IR) in 2 (17.5%) patients. Concerning the disease status at the time of treatment with indomethacin, a CR was obtained in 4/6 (66.6%), 3/4 (75%) and in 5/7 (71%) patients in first, second and in ≥3 recurrences, respectively; an IR was achieved in 1 patient in first and 1 patient in ≥3 recurrences. Three patients (1 in first and 2 in ≥3 recurrences) had a poor response. Five of 14 responding patients (36%) had a disease recurrence after a median time of 4 months from treatment suspension. Two of 17 patients presented a BRAF mutation; they were treated with indomethacin as a single agent at the third recurrence obtaining a CR, but all of them had a disease recurrence. No side effects were observed. All patients are alive. Conclusions: In our experience indomethacin is effective as salvage regimen in recurrent LCH, also in patients with multiple recurrences. Prospective studies are needed to identify patients with advanced LCH and bone involvement who can optimally benefit from treatment with indomethacin.

Poster Location #68

INDOMETHACIN AS FIRST LINE TREATMENT OF LANGERHANS CELL HISTIOCYTOSIS (LCH). A 20-YEAR EXPERIENCE OF A SINGLE CENTRE

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Purpose: The aim of this study was to analyse the results of treatment with indomethacin as first line treatment in children and adults with Langerhans cell histiocytosis (LCH). Methods: Between 1999 and 2018, 47 patients with a diagnosis of LCH (CD1a+, S100+, CD207+) with a median age of 29 years (range 1-66) were treated with indomethacin 2 mg/Kg/day (maximum dose 150 mg/day) as first line (21 in combination with surgery and/or chemotherapy). Twenty-seven patients (57.5%) had single system diseases (SS-LCH), 20 unilateral (74%) and 7 multifocal, and 20 (42.5%) presented multi-system involvement (MS-LCH). BRAF mutation analysis was available in 8/47 patients. Results: Thirty-eight of the 47 patients (81%) were evaluable for response. Two patients (4%) discontinued indomethacin due to toxicity. Considering patients evaluable for response, the median treatment duration was 3 months. All patients obtained a response, that was complete (CR) in 23
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Poster Location #69

NEURODEGENERATIVE CNS DISEASE IN PEDIATRIC LANGERHANS CELL HIATOCTYSIS (LCH): IDENTIFIED DURING LONG TERM FOLLOW-UP IN THE JLSG 96/02 STUDY

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Purpose: Neurodegenerative disease in the central nerve system (ND-CNS) is a dismal complication of patients with LCH. To date, the incidence of ND-CNS was reported as 7%~25%; however, radiological ND-CNS (rND-CNS) without neurological symptoms and clinical ND-CNS (cND-CNS) were included. In this study, we assessed the incidence of cND-CNS as well as risk factors for the development of cND-CNS among pediatric patients treated with the JLSG-96/02 protocol. Also, the progression from rND- to cND-CNS in evaluable cases were analyzed. Methods: A total of 317 patients with LCH (111 with multifocal bone; MFB and 206 with multisystem; MS) treated with JLSG-96/02 protocol from 1996 to 2009 were studied. Results: Overall, 15 (MFB: 4, MS: 11) of 317 patients developed cND-CNS with median follow-up of 10.1 (range 10.5: 21.5) years. The 10-year and 15-year cumulative incidence of cND-CNS were 4.1% and 5.9%, respectively. Patients diagnosed as cND-CNS were at 7.9 (range 4.0 : 14.5) years of age. Time interval to cND-CNS from the diagnosis of LCH was 6.0 (range 1.2 : 11.9) years. Ten of the 15 cND-CNS accompanied with central diabetes insipidus (CDI), and as risk factors for CDI, CDI was a most significant (CDI hazard ratio 8.13, 95%CI, 1.89-33.31, p< 0.01) by multivariatate analysis. In this cohort, MRI was taken for detection of rND-CNS in 194/320 (60.6%). Of 13 patients initially identified as rND-CNS, 8 progressed to cND-CNS with an interval of 3.7(range 1.2 : 10.6) years while the other 5 remain without symptoms over 12.1 (range 11.0-20.1) years. Conclusions: In JLSG cohorts, the 10-year cumulative incidence of cND-CNS was 4.1% with CDI as a most significant risk factor. In view of preventive measures for cND-CNS, early detection of rND-CNS.

Poster Location #70

PROGNOSTIC SIGNIFICANCE OF THE COMBINATION OF LIVER INVOLVEMENT, SPLEEN INVOLVEMENT AND YOUNGER AGE AT DIAGNOSIS IN THE PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS

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Background: Pediatric LCH patients with risk organ involvement or low age have been reported to have poor prognosis. However, it has not been evaluated in large cohort whether a combination of these factors holds worse effect on the outcomes. We performed data analyses assessing overall survival (OS) of pediatric LCH patients enrolled in the JLSG-02 trial. Patients and Methods: Data were collected for involved organs and age at diagnosis in a total of 147 cases (75 males; median age 1y6m) with multi-system LCH, registered during a period of 2002 to 2009. Age at diagnosis was divided into two groups (<8m or 8m) by ROC curve analysis. Kaplan-Meier method was employed for analysis. P<0.05 was considered significant. Results: In this cohort, actually, 7/147 (4.8%) patients died and OS rate at 5 years were 95.2% (95%CI: 91.8-98.7). The OS rate in patients with spleen involvement (n=27), with liver involvement (n=42) and with hematopoietic system involvement (n=54) was significantly lower than that in patients without it (74.1% (95%CI: 57.5-90.6) vs. 100%, p<0.001, 83.3% (72.1-94.6) vs. 100%, p<0.001 and 88.9% (80.5-97.3) vs. 98.9% (96.8-100), p=0.006, respectively). Younger patients (n=31) also had significantly lower OS rate (80.7% (66.7-94.6) vs. 99.1% (97.5-100), p<0.001). However, lung involvement (n=22) did not affect OS rate (95.5% (86.8-100) vs. 95.2% (91.5-99.0), p=0.95). Analysis of the effect of combination of these factors on survival revealed that the combination of liver involvement and spleen involvement (n=24) had the highest sensitivity (100%); all of 7 fatal cases had this combination. While, the combination of liver involvement, spleen involvement and younger age (n=10) had the highest specificity (97.1%); only 4 of 140 survivors had this combination. Conclusion: Data demonstrate that the combination of liver involvement, spleen involvement and diagnostic age is useful for predicting outcome of pediatric LCH.

Poster Location #71

A HOLE IN THE HEAD: DOES PRESENCE OF BRAF V600E MUTATION INDICATE CNS RISK IN CHILDREN WITH SINGLE SYSTEM SKULL BONE LCH?

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Purpose: Langerhans Cell Histiocytosis (LCH) is a predominantly paediatric inflammatory myeloid neoplasia with a remarkably heterogeneous range of behaviour & severity. As we have recently understood that LCH exhibits BRAFV600E mutations in approximately 50-60% of patients, BRAFV600E mutation is now routinely screened for in all newly diagnosed patients, although the clinical significance remains to be understood. From clinical observations, we postulated that presence of BRAFV600E mutation in children with single-system skull-bone LCH would be significantly higher in children with CNS risk features than in those without. Methods: Children
diagnosed with LCH between 2008-2018 at a large tertiary UK paediatric oncology centre were classified into disease subtypes according to the 2014 UK LCH Treatment Guidelines for Children & Adolescents. BRAFV600E mutation status was recorded & associations analysed between BRAFV600E status, demographic data, clinical presentation & presence of CNS risk lesions in children with single-system skull-bone LCH. Results: Initial results showed 50 children diagnosed with boney LCH: 28 male (56%) & 22 female (44%); average age at diagnosis 35 months (2 months-10 years 2 months). 18/50 (36%) children had multi-system LCH, & 32/50 (64%) single-system LCH. Patients with multi-system LCH were excluded from analysis. 21 (66%) of 32 patients with single-system bone LCH had skull bone lesions; 8/21 (38%) unifocal & 13/21 (62%) multifocal. Of the 21 skull-bone LCH patients, 12/21 (57%) had CNS risk features: 4/12 (33%) BRAFV600E mutation positive, 5/12 (42%) BRAFV600E mutation negative, 3/12 (25%) BRAFV600E mutation awaited. Only 1/9 (11%) non-CNS risk patients expressed BRAFV600E positivity. Outstanding BRAFV600E mutation statuses awaited. Conclusion: Preliminary results suggest BRAFV600E mutation positivity is higher in children with CNS risk lesions than in those without, but outstanding data is awaited to further investigate a potential link between BRAFV600E mutation positivity & CNS risk in paediatric skull-bone LCH.

Poster Location #72
REFRACTORY LANGERHANS CELL HISTIOCYTOSIS TREATED BY BRAF AND MEK INHIBITORS AND ALLOGENEIC BONE MARROW TRANSPLANTATION, TWO CASE STORIES

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Purpose: We describe 2 cases of patients with refractory Langerhans cell histiocytosis (LCH) treated by vemurafenib, dabrafenib, trametinib and allogeneic bone marrow transplantation (BMT). Methods: Two case reports. Results: First: Twelve months old boy presented with multi-system LCH with skin, liver and spleen involvement. Therapy according to LCH-IV protocol was started; active disease worse at week 6. Treatment with vemurafenib was initiated (22.8mg/kg/day). Three months later, the dose of vemurafenib was doubled for LCH reactivation (fever, splenomegaly). BMT from matched unrelated donor was scheduled, shortly before, LCH reactivated again. BMT conditioning: fludarabine, thiopeta, melphalan, alemtuzumab. Day 100 after BMT, vemurafenib was stopped, LCH reactivated within 5 days; the therapy changed to dabrafenib. For mixed chimerism, 2 doses of donor lymphocyte infusions and rituximab were given. Ten months after BMT, LCH reactivated, trametinib was added to dabrafenib. Fifteen months after BMT, the patients is clinically stable with mixed chimerism, no chronic graft versus host disease (cGVHD), no clinical signs of active LCH, treated with dabrafenib and trametinib, BRAF free circulating DNA (BRAFcDNA) is almost constantly positive in peripheral blood (PB). Second: 15 months old boy presented with multi-system LCH; bone, mucous membranes and bone marrow involvement. The patient was treated according to LCH-III protocol. He reactivated during maintenance therapy and 2-chlorodeoxyadenosine (2-CDA) was commenced. However, LCH further progressed; therefore vemurafenib (10-15mg/kg/day) was started. BMT conditioning: fludarabine, thiopeta, melphalan, alemtuzumab; sibling donor. Vemurafenib was stopped on day 29 after BMT. Ten months after BMT, LCH reactivated in bones and vemurafenib was re-started. The patients is clinically stable with mixed chimerism 19 months after BMT, no cGVHD, no clinical signs of active LCH, treated with vemurafenib, BRAFcDNA is almost constantly positive in PB. Conclusion: BMT and targeted therapy did not eradicate refractory LCH clone measured by BRAF positivity in PB.

Poster Location #73
A RARE COMPLICATION OF A RARE DISEASE : CHALLENGES IN STUDYING LANGERHANS CELL HISTIOCYTOSIS NEURODEGENERATION IN UK AND IRELAND

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Purpose: Langerhans cell histiocytosis associated neurodegenerative disease (LCH-ND) is a rare, potentially devastating complication of LCH. Treatment outcomes have been unsatisfactory but recent reports suggest that some patients respond to BRAF inhibitors. We sought to explore the challenges of undertaking a prospective treatment trial. Methods: An electronic survey was sent to 115 paediatric oncologists in the 20 principal treatment centres in the UK who are members of the Children’s Cancer and Leukaemia Group. The survey requested the number of patients under their care with LCH-ND, their current age, MRI findings, clinical signs/symptoms, whether improving/stable/progressing, current or previous treatment for LCH-ND and BRAFV600E status. Results: 30/115 (26%) paediatric oncologists in 15/20 (75%) centres responded; 9 patients with LCH-ND were identified, under the care of 9 different clinicians, in 6 centres (1-3 centre); age range 5-21 years (median 13 years); MRI findings consistent with LCH-ND were reported in all cases and neurological symptoms present in 7/9 cases; 6 patients received chemotherapy +/- immunoglobulins for LCH ND in the past; the BRAFV600E mutation was present in 4, absent in 1 and untested in 4; 2 patients with the BRAFV600E mutation are receiving the BRAF inhibitor, dabrafenib (both patients showed clinical and radiological improvement); 1 patient is awaiting treatment with dabrafenib; 6 (67%) patients were classified as stable, 2 (22%) as improving (the patients receiving dabrafenib) and 1 was not specified as responding; 9 patients with LCH-ND were diagnosed in the past; 8 patients have never been considered for BMT; 5 patients have a LP and 3 patients have an MRI skull. Conclusion: This survey identified only a small number of patients with LCH-ND, their current age, MRI findings, clinical signs/symptoms, whether improving/stable/progressing, current or previous treatment for LCH-ND and BRAFV600E status but may provide insight for future treatment trials. International collaboration is essential.
RETROSPECTIVE ANALYSIS OF EFFICACY AND SIDE-EFFECTS OF DABRAFENIB IN TREATMENT OF 21 BRAF-V600E MUTATION POSITIVE LCH CHILDREN

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Objective: We sought to investigate the efficacy of dabrafenib in children with BRAFV600E-mutated Langerhans cell histiocytosis (LCH) Methods: Retrospective analysis of efficacy and side-effects of dabrafenib in treatment of 21 BRAFV600E-mutation positive LCH patients who were refractory to traditional therapy or intolerance to chemotherapy. Quantity of BRAFV600E-mutation in blood cell free DNA (cf-DNA) was performed before and during the treatment. Results: The disease of 13 out of 21 patients got improvement (61.9%), while 6 patients were in stable condition. One case was refractory. One patient died of progression. BRAFV600E quantity of 4 patients were negative at the beginning of treatment but with progression. One patient didn’t detect the mutation regularly. 3 patients were treated less than 3 months. Among the 13 patients with regular monitoring and follow-up time more than 3 months, the mutated gene couldn’t be detected in 9 patients within 3 months (69.2%). One patient turned negative between 3 to 6 months (7.7%). 3 patients still had BRAFV600E positive after 6 months’ treatment (23.1%). There were no late side-effects in 13 patients (61.9%), while the remaining 8 patients all presented skin rash. Two of the 8 patients had fever and one presented photophobia, blurred vision and limbs pain. Five of them had minor side-effects subsided spontaneously, while 3 patients required anti-allergy treatment. Although one patient had skin relapse in 7 months after drug withdrawal (4.8%), the rash disappeared quickly after reuse of dabrafenib. Six cases complicated with HLH were all improved quickly after dabrafenib treatment (100%). Conclusion: The efficacy of dabrafenib in BRAFV600E-mutated LCH children was notable, especially for the patients with concomitant HLH. The negative conversion ratio of BRAFV600E-mutation was high within the 3 months’ treatment of dabrafenib along with high safety and slight short-term adverse effects. Relapse rate need further investigation with long term follow-up.

LANGERHANS CELL HISTIOCYTOSIS OF THE GASTROINTESTINAL TRACT: RISK ORGAN STATUS

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Langerhans cell histiocytosis (LCH) is currently treated with chemotherapy determined by the risk status of involved organ systems. Risk organs are associated with higher mortality and if affected by LCH, patients are assigned more intense and longer courses of chemotherapy. Gastrointestinal tract (GIT) involvement is rare and the high mortality described in published LCH-GIT. However, LCH-GIT is not currently a risk organ. We performed this study to evaluate the independent "risk status" of LCH of the GIT (LCH-GIT). A cohort of subjects with histologically diagnosed LCH-GIT from clinical database and the medical literatures was identified (Group A). An age matched control cohort (except LCH-GIT) was developed from a clinical database (Group B). 5-year overall survival (OS) and refractory/recurrent disease were compared between Groups A and B using Kaplan Meier curves. Group A (n=43) had significantly lower 5-yr OS compared to Group B (n=43) [45.3% vs. 94.6%; p=0.001]. To minimize confounding factors, we excluded of patients with RO involvement and diagnosed before 2000. Finally, Group A+ (n=6) had a lower OS when compared to Group B- (n=31), [75% vs. 100%; p=0.012]. Group A+ had a 4-fold increased association with risk organ involvement. [Odds Ratio of 4.359, 95%, CI, 1.75 : 10.82, p=0.001]. Similar to other risk organs which are not cumulative or independent of one another, LCH-GIT did not affect 5-yr OS when other risk organs were involved (Group A+ (n=27) 41.3% vs. Group A- (n=16) 53.6%; p=0.370). From this limited, retrospective study, GIT is a risk organ associated with higher mortality, and appears to be similar to other risk organs. Larger prospective studies to confirm the risk status for LCH-GIT are indicated and published information of clinical trials which include LCH:GIT patients may need re-interpretation.
BASIC RARE HISTIOCYTIC DISORDERS POSTER PRESENTATIONS

Poster Location #76

ROSAI-DORFMAN DISEASE WITH EGFR MUTATION ON METACHRONOUS LESIONS

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Purpose: We describe a previously unreported mutation detected metachronously in a 37 years-old, HCV+ Rosai-Dorfman Disease patient with subsequent parotideal, nasal mucosa and nodal involvement. Methods: we analyzed by high resolution melting and further validated by direct sequencing, the mutational hot spot regions of K/NRAS, BRAF, MAP2K1, ERK1, PIK3CA, AKT1, KIT, PDGFRa, EGFR and SLC29A3 genes, from microdissected FFPE specimens. Therefor we used SIFT and PolyPhen-2 bioinformatic tools to predict the likelihood fo pathogenicity of all unreported mutations. Results: we detected the presence and predicted the pathogenicity of EGFR A702G missense mutation on the salivary gland and the lymph node, subsequently involved by RDD in our patient. Such mutation is, to the best of our knowledge, unpublished for the whole spectrum of histiocytic disorders, as the occurrence of RDD in an HCV+ patient. No further mutations of the MAPK or PIK3CA pathways were detected. Conclusion: The unusual presence of HCV-related chronic inflammation in our patient could have boosted the RDD proliferation causing the gain of upstrem signaling regulator EGFR mutation and therefore the maintanance of a monoclonial histiocytic expansion. This would add a new tessera in the pathogenic mosaic of histiocytoses.

CLINICAL RARE HISTIOCYTIC DISORDERS POSTER PRESENTATIONS

Poster Location #77

RETICULOHISTIOCYTOSES, GENERALIZED ERUPTIVE HISTIOCYTOSIS AND MYELOID NEOPLASM: A SYSTEMATIC REVIEW

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Purpose: We investigate the frequency and features of the association between rare non-foamy, C-group, non-langerhans-cell histioctyes (NF-C-NLCH) and myeloid neoplasms (MN) from the scientific literature. Methods: We performed a literature search of published papers, with last query in May 2018, using four retrieval systems: PubMed, Scopus, Web of Science and Open Grey. The search included each combination of MN related terms and names of the NF-C-NLCH (Generalized Eruptive Histioctysis, Reticulohistioctysis and Benign Cephalic Histioctysis). The obtained papers (526) were deduplicated via Mendeley (246), selected by title and abstract and finally filtered according to clinical-pathological descriptions. We collected 12 case reports: 5 cases diagnosed with Generalized Eruptive Histioctysis and 7 with Reticulohistioctysis. No cases of Benign Cephalic Histioctysis associated with MN were found. Just one patient presented with multisystem disease. Most patients (11/12) were male, with a median age of 59 years. The associated myeloid neoplasms was Acute Myeloid Leukemia in 4 cases, Chronic Myelomonocytic Leukemia in 3 cases, Myelodysplastic syndrome with ring sideroblasts in 2 cases, Primary Myelofibrosis in 2 cases and Chronic Eosinophilic Leukemia in the last one. A clonal relation between histioctysis and MN was proved in two reports. Results: Despite the exceeding rarity of NF-C-NLCH, the number of papers describing their association with myeloid neoplasms is relatively high. Most patients present synchronously with hematological abnormalities and generalized poplar skin eruption, revealing an epithelioid histiocytic infiltrate CD68+, CD1a- with ground-glass cytoplasm. Conclusions: NF-C-NLCH result often associated and sometimes clonally related to MN. For some instance, NF-C-NLCH skin eruption may also be expression of a systemic myeloid dyscrasias more than a purely histiocytic dermatosis. Therefore, a complete hematological evaluation is mandatory for all histioctysis patients, even in single-system conditions, and bone marrow biopsy is highly recommended at the onset of hematological abnormalities.

Poster Location #78

LANGERHANS CELL HISTIOCYTOSIS THERAPY FOR THE TREATMENT OF LIFE-THREATENING ROSAI DORFMAN DISEASE

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Purpose: Rosai Dorfman Disease (RDD), or Sinus histiocytosis with massive lymphadenopathy (SHML), is a rare condition of immune dysregulation of unknown etiology arising from the accumulation of non-Langerhans type, (CD1a-), S-100+(+)/CD68(+)), histiocytic cells inside lymph nodes. The disease can be self-limiting, but in cases with a chronic course or extranodal involvement, treatment may be necessary. This report describes a case of life-threatening, unresectable, recurrent RDD successfully treated with Langerhans Cell Histioctysis (LCH) 2009-inspired therapy. Methods: We searched PubMed, Ovid, and Google Scholar. We believe this to be the first reported case of using LCH therapy to successfully treat RDD. An 8-year-old male presented to an outside hospital with two years of massive neck swelling causing torticollis. Biopsy confirmed RDD. He was intermittently treated with antibiotics with partial response. Surgical removal was unsuccessful due to proximity to the spinal cord. Two years later, the patient presented to our institution. He was initially treated with prednisone with a fast tapering dose, but after a second relapse the decision was made to try chemotherapy following the LCH-2009 protocol of weekly vinblastine(6 mg/m2), 6-MP(75 mg/m2), and high-dose steroid bursts. He experienced two additional relapses off therapy, including CMV (+) associated septic shock and cytokine storm requiring rapid response, PICU admission, and inotropotrop support. An extended and slowly tapered maintenance therapy regimen of 2.5 years of daily 6-MP, monthly vinblastine and steroids has resulted in 36-months of continuous remission. Results: No similar cases were found. Literature search demonstrated no consensus regarding the most effective treatment of RDD, with no previous cases being successfully treated following LCH protocols. Conclusion: We hypothesize that the LCH-2009 therapy mitigates the immune dysregulation of RDD. This case suggests that LCH-2009 therapy can be used to treat cases of RDD that are not amendable to surgery or observation.
CORONARY ARTERY CALCIFICATION IS COMMON AND SEVERE IN ERDHEIM-CHESTER DISEASE BUT UNRELATED TO BRAF MUTATION STATUS

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Purpose: Erdheim-Chester disease is a rare, non-Langerhans cell histiocytosis, characterized by infiltration of CD68+/CD1a- foamy macrophages into various tissues with associated fibrosis. The clinical manifestations and prognosis vary depending on the location and extent of disease. Cardiovascular involvement most frequently results from neovascularization of the right coronary artery in the atrioventricular sulcus; however, the extent of intra-luminal coronary artery disease in the coronary vasculature has not been evaluated. The purpose of this study is to characterize the presence and extent of coronary artery calcification and disease in Erdheim-Chester Disease patients. Methods: A total of 58 consecutive patients (75% male, age 52±11 years, range 19-72 years) with biopsy-proven Erdheim-Chester Disease underwent cardiac CT on a 320-detector row scanner. Coronary calcium score was quantified utilizing the Agatston technique from non-contrast exams and compared to the Multi-Ethnic Study of Atherosclerosis reference values of >6,000 asymptomatic subjects. Results: Coronary calcium (median 61, interquartile range 10.5-384), was observed in 55.2% (32/58) of all subjects, with 40% (6/19) of females and 60% (26/43) of males being affected. When compared to age, gender and ethnicity matched controls, all women (6/6) with coronary calcium were greater than the 50th percentile (6/6) and 50% (3/6) were greater than the 75th percentile. Similarly, for men with coronary calcium, 73.1% (19/26) were greater than the 50th percentile and 61% (16/26) were greater than the 75th percentile. Overall, 34.4% (11/32) had significant coronary calcification defined as greater than 90th percentile for age, gender and ethnically matched controls. There was no association between the presence or severity of coronary calcification and BRAF mutation status, gender, smoking status, hyperlipidemia, diabetes or hypertension. Conclusion: In this cohort of Erdheim-Chester disease patients, coronary artery calcification is common and more severe than matched controls, and was unrelated to BRAF mutation status.

SPONTANEOUS RESOLUTION WITHOUT THERAPY OF SYSTEMIC JUVENILE XANTHOGranULOMA IN AN INFANT: CASE REPORT

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Juvenile xanthgranuloma (JXG) is a non-Langerhans cell histiocytic disorder (class C) which commonly presents as multiple cutaneous yellow orange papules mainly in young infants and has a benign outcome with frequent resolution of the papules over a period of months to years. Sometimes it is associated with neurofibromatosis 1 and juvenile myelo-monocytic leukemia (JMML). A rare systemic form of JXG has been described (class L JXG) and may include bone marrow, liver or central nervous system disease. The clinical course is variable from mild to severe disease with organ failure. There is no robust data regarding treatment guidelines. Some patients have responded to LCH based protocols. We present a 3 month old girl which developed three large ulcerating elevated skin lesions in the shoulder and flank. There was no fever or systemic manifestation. Two lesions were excised and pathology revealed JXG. Systemic workup displayed numerous hyper-echogenic lesions in the liver and a few similar lesions in the spleen. Their size was 1-1.5 cm. There was significant cervical lymphadenopathy without fever or rashes. Blood workup excluded infectious diseases. CBC, liver enzymes and LDH were within normal limits. The child developed well and received no therapy. A liver biopsy of a lesion was cancelled because of spontaneous decline in the size of the nodule. Now at three years of age the girl has normal development with no lymphadenopathy, hepatosplenomegaly or skin lesions. Abdominal ultrasound detected a normal spleen without any focal lesions and shrinkage of most of the hepatic lesions. We conclude that in absence of a severe systemic disease lesions of JXG in an infant can resolve spontaneously without therapy even in visceral organs. Careful conservative follow up is recommended.
with baricitinib. The treatment appears efficacious and safe in alleviating inflammation in the setting of this histiocytic disease. As the patient needs continued medication to maintain symptom control and as her scCD163 levels remain elevated, combination therapy may be needed to further improve the response.

Purpose: Erdheim-Chester Disease (ECD) is a life-threatening histiocytic neoplasm associated with retroperitoneal fibrosis (RPF), which can cause an obstructive uro-nephropathy and renal dysfunction. Treatment includes systemic ECD therapy or ureteral stenting, and rarely, nephrostomy tubes, ureterolysis, or renal transplantation. This poster 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. 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 = xx 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 21 patients (33%) with hydronephrosis/ureter had either bilateral or unilateral ureteral stents, and one of the 7 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. The stented patients had all been treated for ECD with various agents, but hydrenephrosis persisted and all required long-term ureteral and/or renal artery stenting to prevent further damage. Conclusion: ECD-associated RPF can cause an obstructive uro-nephropathy, leading to renal dysfunction. Despite therapy, some patients require stenting to maintain renal function.
Progressive nodular histiocytosis (PNH) is a rare non-Langerhans cell histiocytosis belonging to Xantogranuloma family (C group) of disorders. We present a 7 year-old male patient with widespread skin lesions starting before 1 year of age. Several resections were performed with the clinico-pathological diagnosis of multifocal Juvenile Xantogranuloma (JXG), BRAFV600-wildtypeby PCR. Clinical evaluation foundmore than 100 skin lesions in the face, arms, legs, trunk and perineal area, located in demis and subcutis, measuring up to 5 cm. He also had genu valgo, benign external hydroceles with neurological developmental delay, and bilateral cryptorchidism. CT scan, MRI, and abdominal ultrasound did not demonstrate non-cutaneous lesions in the body or nervous system. The patient received chemotherapy (induction with vinblastine and prednisone according to LCH III protocol), with no response, and treatment was discontinued. A second course of unsuccessful chemotherapy was attempted after an osseous lesion was identified and skin lesions progression. New lesions were resected in 2017, some of them in the folds of the skin with ulcerations. The deepness and storniform pattern of the lesions at the microscope raised the possibility of PNH superimposed upon JXG. Targeted-capture next generation sequencing was performed with MSK-IMPACT, identifying a hotspot oncogenic mutation (KRAS G12D). Treatment with MEK inhibition is anticipated and will be reported.

Poster Location #85
ROSARI DORFMAN WITH POSITIVE PHOSPHO ERK STAINING WITHOUT MAPKINASE MUTATIONS SUCCESSFULLY TREATED BY DABRAFENIB / TRAMETINIB ASSOCIATION IN A 11 YEARS OLD TEENAGER
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Purpose: To report the outcome of a patient with Rosai Dorfman disease (RDD) with massive adenopathy treated by dabrafenib & trametinib.

Method: Case report: Result: This female had presented at the age of 11 years, at age of 10 years, a massive enlargement occurred. Prednisone was proposed at 1 mg/kg/day with limited effect. Biological parameters showed inflammation. The size of cervical nodes was 13 x 6 x 5 cm. A new biopsy proposed at 1 mg/kg/day with limited effect. Biological parameters showed inflammation. The size of cervical nodes was 13 x 6 x 5 cm. A new biopsy showed similar histology and an extensive molecular NGS screening failed to detect any mutation in the MAPkinase pathway. Immunostaining showed an intense nuclear and cytoplasmic positivity with phosphoERK. As the steroid failed to control the nodes enlargement, Claudribine was proposed as monotherapy (6 courses: 5mg/m² 5 days / 4 weeks) with only a transient and limited effect. Two months after the end of the Claudribine, the nodes size was 13 x 10 x 5 cm (estimated volume 193 cm³) with a upper mediastinal extension and (18F)-fluorodeoxyglucose positron emission tomography / CT scan shown a high metabolic activity (SUV 13). This progression leads us to propose a targeted therapy combining Dabrafenib 75 mg BID and Trametinib 1.5 mg/day (Body weight of 61 kg). The nodes size begins to decrease by week 2 and was no more enlarged by week 6. Biological parameters return to normal value by week 6 and the PET Scan / CT scan decreased dramatically. Metabolic activity disappeared by 8 weeks and the nodes size was almost normal estimated < 15 cm³. Side effects were limited acne on the face. Conclusion: Targeted therapy against MAPkinase pathway is active in refractory RDD.
Imaging and laryngoscopy showed 50% occlusion of the right airway by a medical literature. We describe a localised case of subglottic ALK positive systemic histiocytic proliferative disorder of early infancy (Blood 2008; Purpose: ALK positive histiocytosis is a rare subtype of systemic histiocytosis. We report a case of disseminated MH in an infant with a favorable outcome.

Methods: a four-week baby girl was admitted with a right palsy of the brachial plexus and skull nodules. The magnetic resonance imaging showed perioveal lesions in the proximal humerus. 48 hours after her admission, she developed acute deterioration evolving to a shock, and required transfer to the intensive care unit. She subsequently developed hepatosplenomegaly, generalized edema, severe pancytopenia, and respiratory distress, remaining seriously ill through the diagnostic process. The abdominal computed tomography (CT) scan showed multiple nodules in the spleen, liver and kidneys. The chest CT evidenced diffused enlargement and multiple nodules in the thymus; lymph nodes in the supra, infracavicular and in the bilateral axillary regions; lytic lesions in clivus, scapula, ribs and thoracic vertebrae (T6-T8). A head CT showed bilateral symmetrical parietal and occipital hypodensity lesions. Bone marrow biopsy was normal. A biopsy of the humeral lesion showed prominent mitotic activity with atypical mitoses and cellular atypia, with large nucleus, reticular chromatin pattern and prominent nucleolus, infiltrating tissue bone. CD 68, CD 163 and lysozyme were positive and CD 1 was negative, and a reticular chromatin pattern and prominent nucleolus, infiltrating tissue bone. CD 68, CD 163 and lysozyme were positive and CD 1 was negative, and a diagnosis of malignant histiocytosis was made. She started chemotherapy based on an anaplastic large cell lymphoma protocol. Results: the patient received 6 cycles of chemotherapy, presenting many complications including episodes of cardiac arrests, and requiring aggressive antibacterial, antifungal and hematological support. Progressive improvement was noted, with marked regression of the disease activity after the fourth course. At the end of the treatment all the imaging exams, including blood tests were normal. At this time she is 15 months off therapy without evidence of disease. Conclusion: We report a case of disseminated MH in an infant with a favorable outcome.

Purpose: ALK positive histiocytosis is a rare subtype of systemic histiocytosis. Three patients were initially described by Chan JKC et al., as a novel type of systemic histiocytic proliferative disorder of early infancy (Blood 2008; 112:2965-8), and only 4 other systemic cases have since appeared in the medical literature. We describe a localised case of subglottic ALK positive histiocytosis in a 3 year old boy presenting with respiratory distress. Methods: Imaging and laryngoscopy showed 50% occlusion of the respiratory airway by a solitary 9 mm subglottic nodule, 5mm below the true vocal cord. The excised mass was submitted for histopathologic, immunohistochemical and molecular analyses. Results: Microscopy showed a submucosa expanded by a diffuse infiltrate of histiocytes with mildly vacuolated pale eosinophilic cytoplasm without evidence of hemophagocytosis or emperipolesis. Most cells had small spherical nuclei without nuclear grooves and a few multinucleated cells were present. Immunohistochemistry showed the cells to be CD68+ve, CD163+ve, CD1a-ve, langerin-ve and S100-ve: nuclear, perinuclear or cytoplasmic dot like immunostaining with ALK-1 but not CD30. BFAV V600E staining was negative. Targeted RNA-seq (Trusight RNA fusion panel, Illumina, San Diego, CA) identified a KIF5B-ALK fusion gene. Conclusion: Two patients with ALK positive Erdheim Chester Disease with KIF5B-ALK fusion genes (involving skin in a 25 year old and liver in a 50 year old patient) were previously reported by Diamond et.al. (Cancer Discovery 2015;5(2):154-65). Herein, we present a novel clinical presentation of histiocytosis with a KIF5B-ALK fusion gene - a patient with localized extranodal disease and no evidence of regional or systemic disease after 6 months follow-up. These findings expand the clinical spectrum of this disease and raise the possibility that the site and extent of disease on presentation may represent an important prognostic factor.

Purpose: Histiocytic neoplasms harbor genetic aberrations that activate the RAF/MEK pathways. We present two pediatric histiocytic neoplasms spanning the "L" (Langerhans) and "M" (Malignant histiocytoses) groups with variable presentations, each with novel BRAF gene fusions. METHODS: Pathologic evaluation with immunohistochemistry (IHC) was performed. Neoplasms were analyzed on the CHOP Comprehensive Next Generation Sequencing Solid Tumor Panel, including RNA-seq for 106 fusion partner genes. RESULTS: Case 1: a 16 year-old female with 2.5 cm rapidly growing subcutaneous thigh mass. Resection showed atypical histiocytes (CD163/CD68/CD14/fascin/Factor XIIIa+); negative VE1. The Ki 67 index (20%), with scattered positivity for S100, CD1a and Langerin; negative VE1 (BRAF-V600E IHC), consistent with Langerhans cell sarcoma. RNA-seq identified a fusion of MTAP (NM_002451.3) exons 1-7 to BRAF (NM_004333.4) exons 9-18. Margins were negative and at two years post-resection, the patient is disease free. Case 2: a 12 year-old female with 5.3 cm rapidly enlarging heel mass, with lymph node, bone, and lung dissemination. Heel biopsy revealed bland histiocytes without malignant features (CD163/CD68/CD14/fascin/Factor XIIa+); negative VE1. The Ki-67 was focally increased up to 40%. RNA-seq identified a fusion of MS4A6A (NM_022349.3) exons 1-6 and BRAF (NM_004333.4) exons 11-18. Findings overall were consistent with histiocytic lesion of juvenile xanthogranuloma (JXG) phenotype with uncertain biologic behavior. The patient was treated with Clofarabine with tumor shrinkage over 4 months. CONCLUSION: While both neoplasms harbored novel BRAF-fusions, the L-group lesion with bland cytology and JXG phenotype had an increased proliferation rate and aggressive clinical behavior, while the M-group lesion with malignant cytology and a moderately elevated proliferation rate had indolent clinical behavior. A
combination of histologic, molecular, and clinical correlation are required for best diagnosis of these histiocytic neoplasms. Ongoing work should focus on the potential functional mechanisms of these novel BRAF-fusion partners/breakpoints, which may drive tumor biology.

Poster Location #90

GAIN OF FUNCTION MUTATIONS OF PIK3CD AS A CAUSE OF CHRONIC ACTIVE EPSTEIN-BARR VIRUS INFECTION

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Purpose: We report a case to provide some complements and experiences for chronic active Epstein-Barr virus infection (CAEBV) diagnosis and treatment.

Methods: Clinical retrospective analysis. Results: An 8 year old Chinese boy presented with infectious mononucleosis-like symptoms for more than 3 months. EBV antibodies and the EBV DNA copies in plasma were dramatically higher than the normal threshold during the course. Ganciclovir was employed, however, his symptoms repeatedly occurred many times. Bone marrow biopsy excluded the possibility of malignancy. Neck lymph node biopsy showed positive Epstein-Barr virus and T-cell abnormal lymphoproliferation. Immunological investigation revealed elevated serum IgM and a reduced CD4/CD8 T-cell ratio with the number of CD4+ T cells markedly decreased. Brain MR scanning suggested that lesions had involved the central nervous system. After pursuing a full diagnostic work-up, he was diagnosed with CAEBV. During the diagnosis, DNA sequencing was performed including all known primary immunodeficiency (PID) genes. The sequencing analysis showed that the patient had a c.3061G>A mutation in an allele of the PIK3CD gene, which is a heterozygous GOF mutation. After 2 cycles of a chemotherapy (PEG-asparagase, liposomal doxorubicin, etoposide, methylprednisolone [L-DEP]), he received allogeneic hematopoietic stem cell transplantation (allo-HSCT) during remission. The patient has been in good condition without relapse for 6 months after HSCT. Conclusion: This is the first report that PIK3CD gene mutation found in CAEBV patient. Genetic abnormalities for CAEBV have also been found in some other cases. Although these cases are not associated with the majority of CAEBV, it is possible that a defect in such a gene, essential for regulating lymphocyte activation and proliferation, may be a cause of CAEBV. Taken together, CAEBV may be an immunodeficiency disease in some cases and the genetic background should not be ignored in the diagnosis of CAEBV.
GENETIC AND MECHANISTIC DIVERSITY IN PEDIATRIC HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Purpose: The HLH-2004 criteria are used to diagnose hemophagocytic lymphohistiocytosis (HLH), yet concern exists for their misapplication, resulting in suboptimal treatment of some patients. We sought to define the genomic spectrum and associated outcomes of a diverse cohort of children who met the HLH-2004 criteria. Methods: Genetic testing was performed clinically or through research-based whole exome sequencing. Clinical metrics were analyzed with respect to genomic results. Results: Of 122 subjects enrolled over 17 years, 101 subjects received genetic testing. Biallelic familial HLH (fHLH) gene defects were identified in only 19 (19%) and correlated with presentation below 1 year of age (p < 0.0001). “Digenic” fHLH variants were observed but lacked statistical support for disease association. In 28 of 48 subjects (58%), research whole exome sequencing analyses successfully identified likely molecular explanations, including underlying primary immunodeficiency diseases, dysregulated immune activation and proliferation disorders, and potentially novel genetic conditions. Two-thirds of patients identified by the HLH-2004 criteria had underlying etiologies for HLH, including genetic defects, autoimmunity, and malignancy. Overall survival was 45%; increased mortality correlated with HLH triggered by infection or malignancy (p < 0.05). Differences in survival did not correlate with genetic profile or extent of therapy. Conclusions: “HLH” should be conceptualized as a phenotype of critical illness characterized by toxic activation of immune cells from different underlying mechanisms. In most HLH patients, targeted sequencing of HLH genes remains insufficient for identifying pathogenic mechanisms. Whole exome sequencing, however, may identify specific therapeutic opportunities and impact hematopoietic stem cell transplantation options for these patients.

ARE PROTEINS OF THE DEGRANULATION MACHINERY REQUIRED FOR RUBELLA VIRUS CONTROL IN THE SKIN?

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Background: Genetic deficiencies in perforin or proteins involved in the exocytosis of lytic granules such as MUNC13-4, MUNC18-2 or RAB27A impair lymphocyte cytotoxicity and predispose to primary hemophagocytic lymphohistiocytosis (HLH). In an index patient with RAB27A deficiency we observed unusual skin granulomas that harboured rubella virus. This unexpected observation has prompted us to investigate, whether lymphocyte cytotoxicity or other functions of RAB27A are required for Rubella virus control in the skin. Methods: Patients with mutations in genes important for lytic granule exocytosis such as MUNC13-4, MUNC18-2 and RAB27A were included. By immunohistochemistry and PCR we assessed for the presence of rubella virus by immunohistochemistry and PCR. Results: Among 30 primary HLH patients exposed to rubella vaccine in our German registry, 6 cases with skin abnormalities were observed, in 2/6 patients with RAB27A, 3/7 with MUNC13-4 and 1/9 patients with MUNC18-2 deficiency. By literature research we identified 7 additional patients with skin granulomas, 5 patients with RAB27A and 1 patient with MUNC13-4 deficiency. Skin biopsies of 4 patients with RAB27A and 1 patient with MUNC13-4 deficiency were analysed by immunohistochemistry and stained positive for rubella virus. In 2
patients, we confirmed the presence of Rubella vaccine virus by PCR. Conclusions: Mutations in RAB27A and UNC13D confer a risk for granuloma development following rubella vaccination. Vaccination of patients with these diseases and possibly with other cytotoxicity defects must be avoided. We are currently investigating functional defects of immune cells of RAB27 and UNC13D mutant mice that are relevant for the control of virus infections in the skin.

**CELL-SPECIFIC GENE EXPRESSION IN LANGERHANS CELL HISTIOCYTOSIS REVEALS DISTINCT PROFILES IN LESION CD207+ CELLS BASED ON BRAFV600E MUTATION**

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Purpose: Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia characterized by granulomatous lesions containing pathological CD207+ Langerhans cells (LCs). Approximately 60% of LCH patients harbor somatic BRAFV600E mutations localizing to CD207+ dendritic cells within lesions. This study was designed to define transcriptional differences in LCH lesion CD207+ cells harboring different MAPK gene mutations and from patients with variable extent of disease. Methods: We analyzed gene expression from FACS-sorted lesion CD207+ cells from pediatric LCH samples using the Affymetrix HTA 2.0 platform. We compared gene expression profiles in 86 patients with LCH, partitioning our cohort into single/organ involvement, single/multiple lesion or organ system, and somatic mutation (BRAF V600E+ vs BRAF-V600E-). Multivariate permutation test with confidence level FDR assessment 80% and maximum allowed proportion of false positive genes at 0.1 was used to determine significance. Genes were then validated in an independent cohort. Results: Interestingly, no differentially expressed genes (DEGs) were found between patients with high risk compared to low risk organ involvement, single lesions compared to multiple lesions, or single system compared to multisystem involvement. However, 75 DEGs were found between LCH CD207+ cells from BRAFV600E+ compared to BRAFV600E- lesions. Conclusion: Results show distinct profiles between lesion CD207+ cells from BRAFV600E+ vs BRAFV600E- lesions. Several new genes not previously associated with LCH may be useful diagnostic or therapeutic targets or elucidate further insight into disease biology and explain differences in clinical outcomes between patients with various somatic mutations.

**IMPACT OF A MULTIDISCIPLINARY TASKFORCE AND ELECTRONIC TRIGGER IN THE IDENTIFICATION AND TREATMENT OF PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS**

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Purpose: Hemophagocytic Lymphohistiocytosis (HLH) is a complex disease with a high mortality. Variable clinical presentations make HLH difficult to diagnose and often delays treatment. Early identification and prompt medical intervention is essential to reduce the morbidity and mortality associated with HLH. Methods: Members from various subspecialties at Children’s Medical Center of Dallas collaborated to create a taskforce with the goal of reducing the morbidity and mortality for patients with HLH. This multidisciplinary team created tools to aid in early identification and treatment of pediatric patients with HLH. One of the screening tools is a Best Practice Advisory (BPA) within the electronic medical record (EMR). This BPA utilizes the HLH diagnostic criteria with EMR data to actively screen all pediatric intensive care unit (PICU) patients and alert the provider to initiate further diagnostic testing. Results: Following the initiation of the HLH/MAS taskforce the number of patients correctly identified with HLH has increased with a corresponding decrease in the time to treatment. In a retrospective analysis prior to 2015 the time from development of symptoms to the initiation of treatment was 7 days. After the formation of the task force in 2015 the time decreased to 2.25 days. With the recent addition of the BPA trigger an HLH patient was accurately identified and treatment was initiated within 22 hours. Conclusion: Delayed or misdiagnosed HLH has a significant morbidity and mortality. The formation of the HLH/MAS taskforce and launch of the BPA has significantly impacted the time to diagnosis and treatment in patients with HLH.

**HISTOLOGY OF ROSAI-DORFMAN DISEASE IN A SUBSET OF PATIENTS WITH ERDHEIM-CHESTER DISEASE: A DISTINCT ENTITY MAINLY DRIVEN BY MAP2K1**

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Purpose: Diagnosis of Erdheim-Chester disease (ECD) relies on characteristic imaging of bone, retroperitoneal and/or cardiovascular involvement. Biopsy is mandatory to exclude differential diagnosis and might confirm infiltration of foamy histiocytes but histology is not specific. By contrast diagnosis of Rosai-Dorfman disease (RDD) is based on specific histology characterized by infiltration by CD68+ CD1a- S100+ histiocytes with large nuclei and abundant
lesions of emperipolesis. Up to 70% of ECD have BRAF or MAP2K1 mutation, which is rare in RDD. We investigated patients harboring an ECD phenotype but RDD histology. Method: We reviewed record of ECD patients from 2007 to 2018 followed in Pitie-Salpetriere hospital (Paris, France) and Memorial Sloan Kettering Cancer Center (New-York, NY, USA). Mutation in gene of MAP kinase pathway was performed on biopsy samples of all patients. Results: Among 210 patients with ECD, 11 patients (5.2%) had RDD histology. All patients had typical ECD presentation with bones (n=7), vascular (n=6), retro-peritoneal (n=7) and neurological involvement (n=6). Biopsies disclosing RDD histology were performed during the course of the disease involving testes (n=5), tibia (n=2), stomach (n=1), cheek (n=1) and omentum (n=1), peri-nephritic fat (n=1) except for 2 patients with RDD histology at diagnosis. All tissues showed infiltration by histiocytes with large nucleus and abundant lesions of emperipolesis. Histiocytes were CD68+ CD1a- S100+. Tests seems to be a privileged organ for development of RDD in ECD patients. Six patients harbored MAP2K1 mutation and one had PIK3CA mutation. None of the patients had BRAF mutation. MAP2K1 might have a pivotal role in development of RDD in patients with ECD. Conclusion: Some patients with ECD may also present the iconic histological lesions described by Destombes, Rosai and Dorfman. Overlap forms of such distinct histiocytoses between ECD and RDD are mainly driven by MAP2K1 but not by BRAF.

RUXOLITINIB FOR REFRACTORY/RELAPSED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a life threatening disease with uncontrolled immune activation leading to extreme inflammation. Current standard therapy has made great improvement in survival for HLH patient. But there are still about 30% patients make no response to current therapies. HLH is still a refractory disease with a significant risk of death. Recently, ruxolitinib, a Janus kinase (JAK) 1/2 inhibitor, has shown promise in mouse models of primary and secondary HLH. Methods: To gather data on the use of ruxolitinib in refractory or relapsed HLH, we performed a retrospective investigation involving 14 HLH patients who had received treatment with ruxolitinib. patients received ruxolitinib at a median dose of 0.3 mg/kg/d. Results: Ruxolitinib appeared well tolerated and improved clinical status in 71.4% of patients. Within 24 hours of starting ruxolitinib, 85.7% of our patient became afebrile. Examination of laboratory data obtained prior to and within 1-4 weeks after ruxolitinib revealed significant serum ferritin levels (median ferritin pre-ruxolitinib: 1,559.5 μg/l, median post-ruxolitinib: 832.5 μg/l, P=0.009). Seven of the 10 patients who achieved PR or CR survived to undergo subsequent chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT). Conclusion: This study suggests that ruxolitinib is a safe and effective salvage therapy prior to allo-HSCT for refractory/relapsed HLH and increases the possibility of such patients receiving allo-HSCT. A prospective multicenter large-scale clinical trial that aims to validate the DEP-ruxolitinib regimen for refractory/relapsed HLH is currently underway (ClinicalTrials.gov Identifier: NCT03533790).

DIFFERENT TH1/TH2 CYTOKINE PATTERNS BETWEEN PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) AND EBV RELATED HLH

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Purpose: The Th1/Th2 cytokine pattern with significantly elevated interleukin (IL)-10 and interferon (IFN)-γ and moderately elevated IL-6 was quite specific for the diagnosis of HLH. The aim of this study is to further investigate whether primary HLH (pHLH) and EBV-HLH present similar cytokine patterns. Methods: From Jan 2012 to March 2018, 54 patients with HLH and underwent genetic analysis of HLH-related genes were enrolled into this retrospective study. The Th1/Th2 cytokine concentrations when HLH was diagnosed were recorded for analysis. Results Of the 54 patients, 43 were diagnosed as EBV-related HLH, 7 as FHL, 4 as XLP, and 5 as others. The 7 patients with FHL were compound heterozygous, including 3 with PRF affected, 3 with UNC13D and 1 with STXBP2. Of the Th1/Th2 cytokines, IFN-γ were significantly higher in patients with EBV-HLH than those with FHL and XLP (median concentrations: 1221.9 pg/mL vs. 210.0 pg/mL vs. 7.5 pg/mL, P<0.001), while IL-10 were much higher in patients with FHL than those EBV-HLH and XLP (2238.0 pg/mL vs. 610.9 pg/mL vs. 77.0 pg/mL, P=0.002). IL-6 were not significantly different among the three groups (29.7 pg/mL vs. 37.0 pg/mL vs. 56.0 pg/mL, P=0.742). And the ratios of IL-10 to IFN-γ were different as well among the three group (FHL vs. EBV-HLH vs. XLP, 10.1 vs. 0.6 vs. 3.9, P<0.001). The AUC of IFN-γ to diagnose EBV-HLH was 0.851 (95% CI, 0.70-1.00), with a cut-off value of 650 pg/mL yielding a sensitivity of 64.2% and a specificity of 91.7%; while the AUC of ratio of IL-10 to IFN-γ to diagnose pHLH was 0.948 (95% CI, 0.89-1.00), with a cut-off value of 2.7 yielding a sensitivity of 83.3% and a specificity of 94.3%. Conclusion: EBV-HLH presents a cytokine pattern of IFN-γ higher than IL-10 while FHL presents much higher IL-10 concentration than IFN-γ. IL-10 and IFN-γ Patients are not significantly increased in XLP.

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

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

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

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

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

Judgment will be based on a written abstract describing work done by the candidate him/herself. It is understood that the winning abstract may have co-authors, but that the first author must be the major contributor who is awarded the Nezelof Award. The Program Committee will provide time during the Annual Meeting for presentation of the winning paper. The decision by a special committee of the Histiocyte Society will be based on originality, completeness, scientific accuracy, and contribution to science. The prize will consist of $1000 US and a certificate.

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

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

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

ARTICLE V
OFFICERS

Section 1. Officers. The officers of the Corporation shall consist of: (i) president (the "President"); (ii) president-elect (the "President-Elect"); (iii) immediate past-president (the "Past-President"); (iv) secretary (the "Secretary"); (v) treasurer (the "Treasurer"); and (vi) two (2) members-at-large (each, a "Member-at-Large" and together, the "Members-at-Large"). The Corporation shall have such other assistant officers as the Board may deem necessary in its sole discretion, and such officers shall have such authority as prescribed by the Board. One person may hold more than one office.

A. President. The President shall give active direction and have control of the business and affairs of the Corporation for a 3-year term. The President may be elected for no more than two terms, provided, however, that such terms shall not be consecutive. The President may sign contracts and other instruments, which the Board has authorized to be executed, and shall perform all duties incident to the office of President, as may be prescribed by the Board.

B. President-Elect. The President-Elect is an officer of the Corporation and assumes the office of President two (2) years following such individual's appointment as President-Elect. If for any reason, as determined by the Board, the President is unable to carry out the duties of such office, the President-Elect shall assume the office of President for the remainder of the President's term. The President-Elect shall be elected by the voting members of the Corporation at the time of the annual meeting of the members that occurs one year following the annual meeting of the members that elected the President. For the avoidance of doubt, the President-Elect shall remain vacant during the term that the Past-President serves in office.

C. Past-President. After serving one full term as President, such individual becomes the Past-President and remains an officer of the Board for one year immediately thereafter.

D. Secretary. The Secretary shall keep or cause to be kept the minutes of all meetings of the Board and shall perform such other duties and possess such other powers as are incident to the office of Secretary or as shall be assigned to such individual by the President or the Board. The Secretary serves a two year term with two additional terms permitted by re-election.

E. Treasurer. The Treasurer shall, subject to oversight by the Board, maintain general supervision over the financial affairs of the Corporation and shall cause to be kept accurate books of account. The Treasurer shall oversee the disbursement of funds of the Corporation and shall from time to time, or upon request from the Board, account for all the transactions undertaken as Treasurer, and of the financial condition of the Corporation. The Treasurer serves a two year term with two additional terms permitted by re-election.

F. Members-at-Large. Each Member-at-Large shall assist the other Board members in the conduct of their duties as directed by the President or by consensus of the Board. Candidates for a Member-at-Large position shall be ordinary members who have not served on the Board for at least two years prior to assuming a term as a Member-at-Large. The Members-at-Large shall serve for the unexpired portion of such term until their successors are elected and qualified, or their earlier removal, resignation or death.

Section 2. Election of Officers. The President-Elect, Secretary, Treasurer, and Members-at-Large shall be elected, as the case may be, by the voting members of the Corporation at an annual meeting of the members in
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 except at Section 1 of this Article V, or until their respective successors shall have been duly appointed 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 Corporation. Members of the Scientific Committee will serve two (2) year terms and may serve up to six (6) consecutive years if re-elected. The Scientific Committee will select its own chairperson within ten (10) days of the close of the annual meeting.

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 to 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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35th Annual Meeting

November 4-5, 2019
(Pre-Meetings on November 3)
St. Jude Children’s Research Hospital
Memphis, TN USA