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To patients diagnosed with a histiocytic disorder (if children, their parents or legal guardians): Please seek the advice of a physician or other qualified health provider with any questions you may have regarding a medical condition and do not rely on the information within the Meeting Program to serve as medical advice. The Histiocyte Society is an organization for medical professionals and does not provide individualized medical care or treatment.

To physicians and other healthcare providers: The Meeting Program is not intended to replace your independent clinical judgment, medical advice, or to exclude other legitimate criteria for screening, health counseling, or intervention for specific complications of treatment for the histiocytic disorders. Neither is the Meeting Program intended to exclude other reasonable alternative follow-up procedures. The Meeting Program is provided as a courtesy, but not intended as a sole source of guidance in the evaluation of patients diagnosed with a histiocytic disorder. The Histiocytosis Association recognizes that specific patient care decisions are the prerogative of the patient, family, and healthcare provider.

No endorsement of any specific tests, products, or procedures is made by the Meeting Program, the Histiocyte Society, the Histiocytosis Association, or any other organization, institution, or individual.
Dear Colleagues,

It is with great pleasure that the Histiocyte Society welcomes you to Vienna for its 27th Annual Meeting. Vienna has long held a special place in the hearts of Society members; it is home to St. Anna Kinderspital and the Children’s Cancer Research Institute (CCRI), host of the Society’s Statistics and Data Center, as well as Professor Helmut Gadner, Director of the CCRI and former president of the Society, and several other long-contributing members of the Society. St. Anna Kinderspital has also been the host to many Society Board and LCH Committee meetings.

This year’s invited speakers include Dr. Julien Haroche of the Hôpital Pitié-Salpêtrière, who will discuss his group’s investigations into Erdheim-Chester disease; and Dr. Barrett Rollins, who will present this year’s Jon Pritchard Lecture on the Nikolas Symposium regarding his lab’s ongoing work into the role of BRAF mutations in the pathogenesis of LCH. Drs. Yenan Bryceson and Stephan Ehl will discuss new ideas about the pathogenesis of HLH. Dr. Michael Girschikofsky has organized an outstanding Symposium on Adult LCH that includes several members of the Society. Other educational sessions include updates of ongoing Society-sponsored clinical trials and the interactive and always-entertaining poster session. This year’s social events include a Welcome Reception at the Liechtenstein Museum and the Annual Banquet at the historical Colosseum XXI.

While you are in Vienna, we hope that you will sample the many outstanding cultural opportunities conveniently located near the meeting site such as the soaring spaces of St. Stephen’s Cathedral (Stephansdom); the superb Klimt and Schiele collections housed in the Upper Belvedere and Leopold Museums; the magnificent displays and architecture of Kunsthistorisches Museum (Museum of Art History), the Albertina Museum and the Secession Building; the joys of the Vienna Opera House and other revered musical venues; and the delicate pastries and other culinary delights of this magnificent and historic city.

We are very grateful to Milen Minkov, our local organizer, for his many hours of hard work in planning and organizing this year’s meeting. Special thanks are also extended to our sponsors, without whose generous support this meeting would not be possible.

Welcome to Vienna!

Jim Whitlock, MD, President, Histiocyte Society

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ACKNOWLEDGEMENTS AND RECOGNITIONS

**Histiocyte Society Executive Board**
President .................................................. Jim Whitlock
Past-President .............................................. Alexandra Filipovich
Treasurer ..................................................... Alexandra Filipovich
Secretary ................................................... Carlos Rodriguez-Galindo
Member-at-Large .......................................... Milen Minkov
Member-at-Large .......................................... Sheila Weitzman

**Histiocyte Society Education Committee**
Rima Jubran, Chair
Karim Beutel .............................................. Kenneth McClain
Anna Canin Home ......................................... Diego Rosso
Naoko Kinugawa .......................................... Kimo Stine

**Histiocyte Society Scientific Committee**
Michael Jordan, Chair
Karl Allen .................................................. Matthew Collin
Itziar Astigarraga .......................................... Michelle Hermiston
K. Scott Baker ............................................ Johannes Visser

**Histiocyte Society Study Group Chairpersons**
Adult Histiocytosis ......................................... Maurizio Aricò
Epidemiology/Late Effects .............................. R. Haupt/V. Nanduri
HLH .............................................................. Jan-Inge Henter
LCH-III ....................................................... Helmut Gadner
LCH-IV ....................................................... Milen Minkov/Carlos Rodriguez-Galindo
LCH-S .......................................................... Jean Donadieu
Rare Histiocytic Disorders ............................. Oussama Abla

**Histiocyte Society Past Presidents**
Alexandra Filipovich ........................................ 2007 - 2010
Jan-Inge Henter ............................................ 2004 - 2007
R. Maarten Egeler ......................................... 2001 - 2004
Kenneth McClain ........................................... 1998 - 2001
Göran Elinder .............................................. 1996 - 1998
Helmut Gadner ............................................. 1992 - 1996
Stephan Laidisch ........................................ 1989 - 1992
Blaise Favara .............................................. 1987 - 1989
Christian Nezelof ......................................... 1985 - 1987

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**Meeting Sponsors**
Histiocytosis Association
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**Nesbit Prize in Clinical Science Awardees**
Rebecca Marsh ............................................. 2010
Rebecca Marsh ............................................. 2009
Jorge Braier ............................................... 2008
Kenneth McClain ......................................... 2007
Loretta Lau ................................................. 2006
Anna Canin Home ........................................ 2005
Marie Ouchée-Chardin ................................... 2004
Manuel Steiner ............................................ 2003
Jorge Braier ............................................... 2002
Wolfgang Holter ........................................... 2001
Kazuhiro Kogawa .......................................... 2000

**Nezelof Prize in Basic Science Awardees**
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

**Histiocyte Society Golden Pin Recipients**
Giulio D’Angio ............................................... Jeffrey M. Toughill
Helmut Gadner ............................................. Elizabeth Kontoyannis
Sally Kivilis ................................................ Paul Kontoyannis
Jon Pritchard .............................................. Shinsaku Imashuku

**Histiocyte Society Honored Members**
Valerie Broadbent ...................................... Grita Janka
Blaise Favara ........................................... Mark Nesbit
Helmut Gadner ........................................... Christian Nezelof
Shinsaku Imashuku
AT-A-GLANCE MEETING AGENDA

PRE-MEETING SESSIONS
Attendance at pre-meetings is limited to members of the Histiocyte Society who have registered in advance. Meetings will take place in the Olympia Mancini 3A Room (ground floor) unless otherwise noted. Lunch will be served in the Prinz of Savoyen Restaurant (1st floor).

FRIDAY, OCTOBER 14, 2011
0900 - 1800  Histiocyte Society Executive Board Meeting (Johanna Room, 8th floor)

SATURDAY, OCTOBER 15, 2011
0830 - 1730  LCH Disease Committee Session
1800 - 1900  Histiocyte Society Database Oversight Committee Meeting
1930 - 2230  HLH Data Safety Monitoring Board

SUNDAY, OCTOBER 16, 2011
0830 - 1200  HLH Disease Committee Session
1300 - 1500  Rare Histiocytic Disorders Committee Session
1515 - 1645  MAS Discussion Session
1700 - 1800  Histiocyte Society Data Safety Monitoring Committee

GENERAL MEETING SESSIONS
Meetings will take place in the Olympia Mancini 2 Room (ground floor) unless otherwise noted.

MONDAY, OCTOBER 17, 2011
0800 - 1700  Meeting Registration and Check-In (Hotel Savoyen Lobby)
0800 - 0930  Education Committee Meeting (Wien Room, 1st floor)
             Scientific Committee Meeting (Paris Room, 1st floor)
0945 - 1000  Opening Ceremonies
1000 - 1115  Guest Speaker Presentation: Yenan Bryceson & Stephan Ehl
1115 - 1145  Coffee Break
1145 - 1315  Scientific Session I: Oral Presentations
1315 - 1415  Lunch (Prinz of Savoyen Restaurant, 1st floor)
1415 - 1545  Scientific Session II: Presidential Symposium
1545 - 1600  Coffee Break
1600 - 1800  Poster Presentation Viewing Session (Olympia Mancini 3A Room, ground floor)
2000 - 2300  Welcome Reception (depart from Hotel Savoyen lobby at 1900)

TUESDAY, OCTOBER 18, 2011
0800 - 1600  Meeting Registration and Check-In (Hotel Savoyen Lobby)
             Poster Presentation Viewing Opportunity (Olympia Mancini 3A Room, ground floor)
0830 - 1000  Clinical Studies and Registries Update
1000 - 1030  Coffee Break
1030 - 1130  Guest Speaker Presentation: Julien Haroche
1145 - 1315  Scientific Session III: Oral Presentations
1315 - 1415  Lunch (Prinz of Savoyen Restaurant, 1st floor)
1415 - 1645  Symposium on Adult LCH
1600 - 1630  Coffee Break
1630 - 1800  General Assembly Business Meeting
2000 - 0100  Histiocyte Society Annual Banquet (depart from Hotel Savoyen lobby at 1900)

WEDNESDAY, OCTOBER 19, 2011
0900 - 1045  Scientific Session IV: Oral Presentations
1045 - 1115  Coffee Break
1115 - 1215  Jon Pritchard Lecture on the Nikolas Symposium
             Guest Speaker: Barrett Rollins
1215 - 1230  Closing Ceremonies: Awarding of Scientific Prizes
GUEST SPEAKERS

YENAN BRYCESON, PhD
Dr Bryceson did his undergraduate training in immunogenetics at the University of Oslo, Norway, and later obtained his PhD from a graduate partnership program between the National Institutes of Health, Bethesda, MD, and the Karolinska Institutet, Stockholm Sweden in 2008. He did a postdoctoral fellowship in the lab of Hans-Gustaf Ljunggren at the Karolinska Institutet and is now heading a research group within the Center for Infectious Medicine at Karolinska Institutet.

Dr Bryceson’s research has mainly been focused on understanding the mechanisms of natural killer cell recognition and elimination of target cells. He has contributed to the understanding of how distinct receptors cooperate in order to induce target cell killing. More recently, research has focused on how defects in cytotoxic lymphocytes are related to human immunodeficiency disorders, with a particular emphasis on hemophagocytic lymphohistiocytosis and related syndromes.

STEPHAN EHL, MD
Dr Stephan Ehl received his MD from the Universities of Aachen, Erlangen and Munic. He currently works as the Scientific Director for the Centre of Chronic Immunodeficiency and Professor of Paediatrics Immunology at University Medical Centre Freiburg. He won the Kind-Phillip Prize of the German Society for Pediatric Oncology and Hematology in 2002.

Dr Ehl's main areas of research include T cell immunity to viral infections and pathogenesis of primary immunodeficiencies.

BARRETT ROLLINS, MD, PhD
Dr Rollins graduated from Amherst College, then received his MD and PhD from Case Western Reserve University. He performed his internal medicine training at Boston’s Beth Israel Hospital followed by a fellowship in Medical Oncology at Dana-Farber Cancer Institute. He has been a member of the faculty at Dana-Farber and at Harvard Medical School since 1987 where he is now the Linde Family Professor of Medicine. Dr Rollins also serves as Dana-Farber’s Chief Scientific Officer.

Biographical information provided by guest speakers.
PRE-MEETING SESSIONS

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Meeting Moderator: Alexandra Filipovich

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Meeting Moderator: Sheila Weitzman

1515 - 1645  MAS Discussion Session (HLH Disease Committee Session continued)
Meeting Moderator: Alexandra Filipovich

1700 - 1800  Histiocyte Society Data Safety Monitoring Committee
Meeting Moderator: Tom Gross, Chairperson
DETAILED MEETING AGENDA

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0800 - 0930  Education Committee Meeting (Wien Room, 1st floor)
             Scientific Committee Meeting (Paris Room, 1st floor)
             Poster Presentation Set-up (Olympia Mancini 3A Room, ground floor)

0945 - 1000  Opening Ceremonies
Jim Whitlock, Histioocyte Society President

1000 - 1115  Guest Speaker Presentation
Session Moderator: Alexandra Filipovich

MECHANISM OF NK CELL CYTOTOXICITY AND RELEVANCE TO HEMOPHAGOCYTIC DISORDERS
Yenan Bryceson, PhD
Karolinska Institutet, Stockholm, Sweden

THE USE OF DEGRANULATION AND CYTOTOXICITY ASSAYS IN THE DIAGNOSTIC EVALUATION OF HLH
Stephan Ehl, MD
Universitätsklinikum Freiburg
CCI - Centre of Chronic Immunodeficiency

1115 - 1145  Coffee Break

1145-1315  Scientific Session I: Oral Presentations
Session Moderators: Bengt Fadeel and Carlos Rodriguez-Galindo

COLONY STIMULATING FACTOR 1 RECEPTOR IS OVER EXPRESSED IN LANGERHANS CELL HISTIOCYTOSIS
Gayane Badalian Very, Jo-Anne Vergilio, Monica Calichio, Laura E Macconail, Matthew Meyerson, Barbara Degar, Mark D Fleming and Barrett J Rollins

DIAGNOSIS, INTERVENTIONS, AND OUTCOMES IN CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME
Tellen D Bennett, Mark Fluchel, Aimee O Hersh, Adam L Hersh, Thomas V Brogan, Rajendu Srivastava, Kristen Hayward, Bryan Stone, Kent Korgenski, Michael B. Mundorff, Charles Casper, Susan Bratton

FAVOURABLE OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANTATION AFTER MYELOABLATIVE CONDITIONING: A MULTI-CENTRE EUROPEAN EXPERIENCE
Karin Beutel, Roland Fischer, Elisabet Bergløf, Elena Sieni, Nizar Mahlaoui, Maurizio Aricò, Jan-Inge Henter, Gritta E Janka
USE OF THE ANTI-CD20 ANTIBODY RITUXIMAB IN THE TREATMENT OF EPSTEIN-BARR VIRUS-INDUCED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Susan Weiner, Kristin Zelley, Kim E Nichols

LCH, THE BELGIAN SURVEY
Leen Vangeebergen, Liesbeth Van Eycken, Stefaan Van Gool

AN EXPLORATORY EPIDEMIOLOGICAL STUDY OF LANGERHANS CELL HISTIOCYTOSIS IN A PREDOMINANTLY HISPANIC POPULATION
Rajkumar Venkatramani, Shira Rosenberg, Gitanjali Indramohan, Rima Jubran

1315 - 1415 Lunch (Prinz of Savoyen Restaurant, 1st floor)

1415 - 1545 Scientific Session II: Presidential Symposium
Session Moderator: Jim Whitlock

Presentations nominated for the Nezelof Prize in Basic Science:

FREQUENT BRAF V600E MUTATIONS ARE IDENTIFIED IN CD207+ CELLS IN LCH LESIONS, BUT BRAF STATUS DOES NOT CORRELATE WITH CLINICAL PRESENTATION OF PATIENTS OR TRANSCRIPTIONAL PROFILES OF CD207+ CELLS
Tricia Peters, Jeremy Price, Tsz-Kwong Man, Kenneth Heym, Miriam Merad, Kenneth L McClain and Carl E Allen

INTERFERON-GAMMA AND IL-10 FORM A COMPLEX SELF-REGULATING NETWORK THAT DETERMINES THE SEVERITY OF MACROPHAGE ACTIVATION SYNDROME
Scott W Canna, Katharine Slade, Sheila Rao, Portia A Kreiger, Michele Paessler, Edward M Behrens

SUBTLE DIFFERENCES IN CTL CYTOTOXICITY DETERMINE SUSCEPTIBILITY TO HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN MICE AND HUMANS WITH CHEDIAK-HIGASHI SYNDROME
Birthe Jessen, Andrea Maul-Pavicic, Heike Ufheil, Thomas Vraetz, Anselm Enders, Kai Lehmborg, Alfred Längler, Ute Gross-Wielsch, Ali Bay, Zuhre Kaya, Yenan T Bryceson, Ewa Koscielniak, Sherif Badawy, Graham Davies, Markus Hufnagel, Annette Schmitt-Gräff, Peter Aichele, Udo zur Stadt, Klaus Schwarz and Stephan Ehl

Presentations nominated for the Nesbit Prize in Clinical Science:

VARIANT ALLELES OF CYTOKINE GENES INFLUENCE THE RISK AND CLINICAL COURSE OF LANGERHANS CELL HISTIOCYTOSIS
Thomas Lehmbuecher, Emilia Salzmann-Manrique, Jan Sörensen, Karin Beutel, Gritta Janka, Helmut Gadner, Milen Minkov

CAMPATH 1H AS FIRST LINE TREATMENT IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: PRELIMINARY SINGLE CENTRE EXPERIENCE
Despina Moshous, Pierre Frange, Fabien Touzot, Jana Pachloupk-Schmid, Capucine Picard, Stéphane Blanche, Genevieve de Saint Basile, and Alain Fischer

GENETIC HETEROGENEITY OF FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Elena Sieni, Valentina Cetica, Francesca Brugnolo, Karin Beutel, Miriam Entesarian, Helena Trottestam, Daniela Pende, Gillian M Griffiths, Udo zur Stadt, Jan-Inge Henter, Gritta Janka, Maurizio Aricò
DETAILED MEETING AGENDA

1545 - 1600  Coffee Break

1600 - 1800  Poster Presentation Viewing Session (Olympia Mancini 3A Room, ground floor)
Session Moderators: K. Scott Baker and Tom Gross

Poster Location #1
HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR REFRACTORY EBV-HLH: REPORT OF TWO PEDIATRIC CASE
Oussama Abla, Michael Jordan and Sheila Weitzman

Poster Location #2
REAPPEARANCE OF POSTERIOR PITUITARY BRIGHT SPOT AND REVERSAL OF LCH-RELATED DIABETES INSIPIDUS WITH LOW-DOSE CHEMOTHERAPY
Oussama Abla

Poster Location #3
CENTRAL NERVOUS SYSTEM (CNS) JUVENILE XANTHOGANULOMA AFTER LANGERHANS CELL HISTIOCYTOSIS (LCH)
Oussama Abla, William Halliday and Sheila Weitzman

Poster Location #4
SIX CHILDREN WITH FAMILIAL HLH WHO UNDERWENT HSCT: A SINGLE CENTER EXPERIENCE
Gülyüz Öztürk, Aykan Özdüven, Ömer Devecioğlu, Sema Anak

Poster Location #5
MALIGNANCY-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS BEFORE AND AFTER MALIGNANCY
Itziar Astigarraga, Isabel Rios, Ana De Lucio, Alejandro Urberuaga, Aizpea Echebarria, Rosa Adan, Aurora Navajas

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BURQOL-RD PROJECT: SOCIAL ECONOMIC BURDEN AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH RARE DISEASES IN EUROPE
Itziar Astigarraga, Susana Garcia-Obregón, Eva Schaefer, Jean Donadieu, Renata Linertová, Manuel Posada, Julio López-Bastida

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ACUTE STIFF BACK IN A 12 YEAR OLD GIRL DUE TO PRIMARY LANGERHANS CELL HISTIOCYTOSIS IN THE THORACIC SPINAL ARCH
Carl Friedrich Classen

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INTERFERON-ALPHA MAINTENANCE THERAPY AND LANGERHANS CELL HISTIOCYTOSIS
Srdjana Culic, Dubravka Kuljis, Visnja Armanda

Poster Location #9
HISTIO NET – A REFERENCE NETWORK FOR THE CREATION OF ONLINE EXPERT SUPPORT FOR LCH AND ASSOCIATED SYNDROMES
Eva Schaefer, Itziar Astigarraga, Riccardo Haupt, Milen Minkov, Richard Price, Jean Donadieu

Poster Location #10
HEPARANASE EXPRESSION IN LANGERHANS CELL HISTIOCYTOSIS – A PRELIMINARY STUDY
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SUCCESSFUL TREATMENT OF MALIGNANCY-ASSOCIATED HEMOPHAGOCYTIC SYNDROME (MAHS) WITH ABATACEPT (CTLA4-Ig) AND HIGH DOSE CORTICOSTEROIDS IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
Lisa M Reaves, Bernice Pasut, Michael B Jordan, and Timothy P Garrington

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ON THE CONTRIBUTION OF C77G POLYMORPHISM IN EXON 4 OF CD45 GENE TO HLH
J Gil, J Modrego, A Diaz-Alderete, R Urrea, O Alvarez-Riego, C Rodríguez-Sainz, E Fernández-Cruz

Poster Location #13
DEFECTIVE NK GRANULE EXOCYTOSIS CORRELATES TO FHL3 IN PATIENTS RECRUITED THROUGH THE HLH-2004 PROTOCOL
J Gil, M Alonso-Martínez, YT Bryceson, Uzur Stadt, A Maul Pavicic, S Ehl, D Fernández, D Alecsandru, D Plaza, O Escobosa, E Fernández-Cruz, I Astigarraga

Poster Location #14
EXPRESSION OF COX-2 IN LANGERHANS CELL HISTIOCYTOSIS
Michael Henry, Paul Dickman

Poster Location #15
HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN THE NATIVE AMERICAN POPULATION – EXPERIENCE AT PHOENIX CHILDRENS HOSPITAL
Michael Henry

Poster Location #16
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Jan-Inge Henter, AnnaCarin Horne, Bo Magnusson, Stefan Hagelberg

Poster Location #17
THYMIC LANGERHANS CELL HISTIOCYTOsis: A NEGLECTED PRESENTATION OF AN ORPHAN DISEASE?
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BISPHOSPHONATE THERAPY FOR LANGERHANS CELL HISTIOCYTOSIS OF BONE
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G Bronin, GNovichkova, A Maschan

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Hisashi Wakiya, Hiroshi Kobayashi, Hirokazu Kanegane, Seiko Akiyama, Arinobu Tojyo, 
Toshikho Imamura, Shinsaku Imashuku

Poster Location #24
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Japanese Pediatric Leukemia/Lymphoma Study Group

Poster Location #26
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Yukiko Tsunematsu

Poster Location #31
CLADRIBINE THERAPY IN 2 PATIENTS WITH ERDHEIM-CHESTER DISEASE 
Petr Szutz, Zdeněk Adam, Renata Koukalová, Zdeněk Řehák, Jiří Neubauer, Jiří Prášek, 
Roman Hájek, Marta Krejčí, Luděk Pour, Lenka Zahradová, Viera Sandecká, 
Sabina Ševčíková, Hubert Mottl, Jiří Mayer
DETAILED MEETING AGENDA

Poster Location #32
NICHE-INDUCED PATHOGENESIS IN LANGERHANS CELL HISTIOCYTOSIS
Sarah Vaiselbuh, Kenneth McClain, Carl Allen, Andy Stahler and Shulim Willner

Poster Location #33
STXBP2 (MUNC18-2) MUTATIONS IN NORTH AMERICAN PATIENTS WITH FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Kejian Zhang, Judith Johnson, Diane Kissell, Kelly Huizenga, Rebecca Marsh, Michael Jordan, Udo zur Stadt and Alexandra H Filipovich

1900
Group departure for Welcome Reception from Hotel Savoyen Lobby

2000 - 2300
Welcome Reception
Liechtenstein Museum
Address: Fürstengasse 1, 1090 Vienna, Austria
Phone: +43 1 319 57 67–252
# DETAILED MEETING AGENDA

**TUESDAY, OCTOBER 18, 2011**  
Meetings will take place in the Olympia Mancini 2 Room (ground floor) unless otherwise noted.

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<td>Poster Presentation Viewing Opportunity (Olympia Mancini Room 3A, ground floor)</td>
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<td>0830-1000</td>
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<td>0830-0900</td>
<td>HLH 2004: Jan-Inge Henter</td>
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<td>0900-0930</td>
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<td>0930-0945</td>
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<td>Rare Histiocytic Disorders: Oussama Abla</td>
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<td>LCH-Adult: Maurizio Arico and Kenneth McClain</td>
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<td>1030-1130</td>
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<td>DIAGNOSTIC PATHOLOGY OF ERDHEIM-CHESTER DISEASE (ECD)</td>
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<td>Ronald Jaffe</td>
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<td>Denise Lee, Andrew Spencer, Andrew Grigg, Patricia Walker</td>
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<td>PULMONARY LANGERHANS CELL HISTIOCYTOSIS. CLINICAL PRESENTATION AND</td>
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<td>OUTCOME OF 60 CASES</td>
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<td>AND LONGITUDINAL FOLLOW-UP OF 40 CASES</td>
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<td>Malgorzata Sobiecka, Stefan Wesolowski, Jan Kus</td>
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<td>LENALIDOMIDE PROVED EFFECTIVE IN A PATIENT WITH RELAPSING MULTISYSTEM</td>
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<td>LANGERHANS CELL HISTIOCYTOSIS</td>
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<td>Jana Chovancová, Olga Stehlíková, Martin Klabusay, Jiří Mayer</td>
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DETAILED MEETING AGENDA

MEASURING DIFFUSE METABOLIC ACTIVITY ON PET/CT AS A NEW METHOD FOR EVALUATING PULMONARY LANGERHANS CELL HISTIOCYTOSIS ACTIVITY
Petr Szturz, Zdeněk Řehák, Zdeněk Adam, Renata Koukalová, Roman Hájek, Marta Krejčí, Luděk Pour, Lenka Zahradová, Hubert Mottl, Jiří Vaníček, Tomáš Nebeský, Jiří Mayer

1315 - 1415 Lunch (Prinz of Savoyen Restaurant, 1st floor)

1415 - 1600 Symposium on Adult LCH
Session Moderator: Michael Girschikofsky

1415 - 1420 INTRODUCTION
Michael Girschikofsky - Elisabethinen Hospital Linz, Austria

1420 - 1440 BONE AND SOFT TISSUE INVOLVEMENT
Kenneth McClain - Baylor College of Medicine, Houston, Texas USA

1440 - 1500 ENDOCRINE MANIFESTATIONS OTHER THAN DI
Polyzois Makras - Hellenic Air Force Hospital, Athens, Greece

1500 - 1520 Dermatological Aspects and Presentation of an Adult Clinic
Tony Chu - Imperial College of London, London, UK

1520 - 1540 ADULT PULMONARY LCH: A CLINICAL UPDATE
Abdellatif Tazi - Hôpital Saint Louis, Paris, France

1540 - 1600 SUMMARY OF THE EHN RECOMMENDATIONS
Claus Doberauer - Evangelische Kliniken Gelsenkirchen, Germany

CLOSING REMARKS
Michael Girschikofsky

1600 - 1630 Coffee Break

1630 - 1800 General Assembly Business Meeting
This session is open only to members of the Histiocyte Society

1900 Group departure for Annual Dinner Banquet from Hotel Savoyen Lobby

2000 - 0100 Histiocyte Society Annual Dinner Banquet
Colosseum XXI
Address: Sebastian-Kohl-Gasse 3-9
Gewerbepark, Objekt 24 A
Phone +43 / 1 / 272 50 50
DETAILED MEETING AGENDA

WEDNESDAY, OCTOBER 19, 2011

0900 - 1045  Scientific Session IV: Oral Presentations
Session Moderators: Itziar Astigarraga and Michael Jordan

IL-17A INDUCES BFL1, SURVIVAL AND CHEMoresistance in Monocyte-Derived Dendritic Cells: Consequences in Langerhans Cell Histiocytosis
Selma Olsson Åkefeldt, Carine Maisse, Alexandre Belot, Marlène Mazzorana, Giulia Salvatore, Mohamad Bachar Ismail, Nathalie Bissay, Béatrice Bancel, Françoise Berger, Jacques Tebib, Pierre Juridic, Maurizio Aricò, Chantal Rabourdin-Combe, Jan-Inge Henter and Christine Delprat

Infection Associated Hemophagocytic Lymphohistiocytosis: A Case Series Using Steroids Only Protocol for Management
Priyankar Pal, Prabhas Prasun Giri, Rajb Sinha, Apurba Ghosh

Evaluation of Radiographic Follow-Up Examinations in LCH Bone Lesions
Hubert Kogler, Helmut Prosch, Helmut Gadner, Milen Minkov, Karoly Lakatos

Discrimination of Acute Flares of Systemic Onset Juvenile Idiopathic Arthritis, Macrophage Activation Syndrome, and Other Forms of Haemophagocytic Lymphohistiocytosis
Kai Lehmberg, Isabell Pink, Karin Beutel, Thomas Vraetz, Gritta Janka

Locally Produced TGF-β Skews the Chemokine Receptor Expression Profile of LCH Cells
Willemijn T Quispel, Astrid G S van Halteren, R Maarten Egeler

Clinical Prognostic Markers for Pre-Transplant Outcome in Patients with Hemophagocytic Lymphohistiocytosis
Helena Trottestam, Elisabet Bergløf, AnnaCarin Horne, Karin Beutel, Kai Lehmberg, Elena Sieni, Thomas Silfverberg, Maurizio Aricò, Gritta Janka and Jan-Inge Henter

1045 - 1115  Coffee Break

1115 - 1215  Jon Pritchard Lecture on the Nikolas Symposium
Session Moderator: Kim Nichols

Therapeutic Target Discovery and Validation in Langerhans Cell Histiocytosis
Barrett Rollins, MD, PhD
Dana Farber Cancer Institute, Boston MA USA

1215 - 1230  Closing Ceremonies
Jim Whitlock, Histiocyte Society President
Awarding of Annual Scientific Prizes
Cytotoxic lymphocytes, such as CD8+ T cells and NK cells, contribute to defence against intracellular pathogens and infected cells. Congenital defects affecting lymphocyte cytotoxicity cause fatal hyperinflammatory syndromes associated with viral infections or predispose to hematological malignancies. To better understand how primary human NK cells discriminate target cells, we have employed reductionistic target cell systems. Moreover, through genetic and functional analysis of peripheral blood samples from patients suffering primary immunodeficiency syndromes, we have investigated the molecular mechanisms by which cytotoxic lymphocytes recognize and eliminate target cells. Results have revealed different contributions to synapse formation and activation by distinct receptors, specific pairwise cooperation among receptors for NK cell activation, and requirements for specific SNARE-proteins and Ca2+ influx for cytotoxic lymphocyte vesicle exocytosis. The biological and clinical significance of these findings will be discussed.

Erdheim-Chester disease (ECD) is a rare form of non-Langerhans histiocytosis first described by Jakob Erdheim and William Chester in 1930. By 2011, approximately 400 distinct cases have been reported in the medical literature. ECD is a systemic and heterogeneous disease mainly involving the bones, lungs, skin, retro-orbital tissues, central nervous system (CNS), pituitary gland, large-vessels, kidneys, retroperitoneum, and heart. The clinical course of ECD is largely dependent on the extent and distribution of the disease, which may range from asymptomatic bone lesions to multisystemic, life-threatening forms with poor prognosis, especially in case of specific CNS or cardiovascular involvements. ECD diagnosis is currently based on clinical, radiological and typical pathological features with biopsy specimen displaying infiltration by CD68+ CD1a- foamy histiocytes, which emphasizes the distinction from Langerhans cell histiocytosis. Untill recently, no treatment had been shown to improve survival in ECD patients, which was truly a critical issue due to the high overall mortality of the disease. We thoroughly analyzed the clinical presentation of 53 patients with biopsy-proven ECD seen in 2 french centers, and performed a survival analysis using Cox’s proportional hazard model. Multivariate survival analysis model revealed that CNS involvement was an independent predictor of death (Hazard Ratio, HR: 2.51, CI95%: 1.28-5.52; p=0.006) in our cohort. Conversely, treatment with interferon-alpha was identified as an independent predictor of survival (HR: 0.32, CI95%: 0.14-0.70; p=0.006). Although definitive confirmation would require a randomized controlled trial, these results suggest that interferon-alpha improves survival in ECD patients. This may be seen as a significant advance, as it is the first time a treatment is shown to improve survival in this multisystemic disease with high mortality.

We also conducted a study regarding ECD immunopathogenesis. In previous studies, various cytokines had been detected among ECD lesions, presumably orchestrating lesional...
histiocyte recruitment. Since ECD lesions are frequently associated with systemic symptoms, we postulated that underlying global immune perturbations might also be revealed. We quantitatively analyzed 23 cytokines in serum samples obtained from a large single-center cohort of 37 ECD patients, and studied the impact of treatment over cytokine production. Interleukin (IL)-6, IL-12, interferon-alpha (IFN-α) and monocyte chemotactic protein-1 (MCP-1) levels were significantly higher in untreated patients than in controls, while interferon-γ inducible protein-10 (IP-10), IL-12, MCP-1, IL-1 receptor antagonist (IL1-RA) were found significantly increased in interferon-alpha treated patients. A biomathematical approach was used to rationalize multiparameter data, in order to generate new hypotheses and identify global control pathways. Interestingly, cytokine profiles proved to be particularly stable at the individual level, and an “ECD signature” further distinguished patients from controls, based on their production of IFN-α, IL-12, MCP-1, IL-4 & IL-7. Altogether, our data underline the systemic immune Th-1 oriented perturbation associated with this condition, and provide clues for the choice of more focused therapeutic agents in this rare disease with non-codified therapeutic management.
COLONY STIMULATING FACTOR 1 RECEPTOR IS OVER EXPRESSED IN LANGERHANS CELL HISTIOCYTOSIS

Gayane Badalian Very 1,2,3, Jo-Anne Vergilio 3,4, Monica Calicchio 4, Laura E. Macconaili 3,5, Matthew Meyerson 3,5, Barbara Degar 1,3, Mark D. Fleming 3,4 and Barrett J. Rollins 1,2,3

1Department of Medical Oncology Dana Farber Cancer Institute 2Department of Medicine Brigham and Women’s Hospital 3Harvard Medical School 4Department of Pathology Children’s Hospital 5Center for Cancer Genome Discovery Dana Farber Cancer Institute

Introduction: Langerhans cell histiocytosis (LCH) is a disease caused by clonal proliferation of Langerhans cells (LC), a type of dendritic cell (DC). Cytokines influencing DC development include Granulocyte-Monocyte Colony Stimulating Factor (GM-CSF) and tumor necrosis factor alpha (TNF-α). Colony stimulating factor 1 (CSF-1, also known as M-CSF) is also associated with proliferation and maturation of DC’s. CSF-1 acts through its tyrosine kinase receptor CSF-1R. Moreover CSF-1R is overexpressed in several malignancies which led us to investigate the expression of CSF-1R in LCH.

Methods Immunohistochemistry analysis was performed on formalin fixed paraffin embedded (FFPE) tissue specimen from LCH patients. Antibodies were used against the total and phosphorylated (p-Tyr-723) forms of CSF-1R. LC’s were identified by CD1a staining and CSF-1R expression was detected using double staining techniques and immunofluorescence. mRNA and micro-RNA (miRNA) analysis was performed on CD1a-positive LC obtained by laser capture microdissection (LCM) from FFPE tissue. mRNA was quantified by qPCR. Micro-RNA analysis was performed using nuclease protection probes (NPP) which are synthetic biotinylated DNA probes complementary to micro-RNA species. The NPP probes were captured during an overnight incubation of the array plate and visualized using avidin-HRP. Cancer associated mutations of CSF1R and its downstream targets were interrogated using DNA isolated from FFPE tissue. Whole genome amplified DNA was used for multiplex PCR using primers from OncoMap 3 and OncoMap 3 Extended. Single base primer extension was performed using iPLEX Gold single base extension, and products were transferred to SpectroCHIPs for analysis by MALDI-TOF mass spectrometry. Allele peaks were flagged using a modified Sequenom algorithm followed by manual review by two independent reviewers.

Results: Immunohistochemistry analysis of CSF1-R demonstrated that it is overexpressed in LCs in LCH compared to LCs in normal skin and that it exists mostly in its active, phosphorylated state. mRNA expression of CSF-1R in our patient cohort did not differ from controls, however we detected dysregulation of micro-RNA involved in CSF-1R expression, namely hsa-miR-34-3p, hsa-miR-34-5p, hsa-miR-155, hsa-miR-449a and hsa-miR-449b. No cancer associated mutations were detected in CSF1R and its downstream kinases such as MAPK and PI3K.

Conclusion: In patients with LCH, over-expression of CSF-1R may be a factor contributing to the uncontrolled proliferation of LC’s. This could be due to epigenetic factors regulating the expression of this kinase. We propose that blocking these receptors could have therapeutic value for patients with active disease.
ABSTRACTS: SCIENTIFIC SESSION I

DIAGNOSIS, INTERVENTIONS, AND OUTCOMES IN CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Tellen D. Bennett, Mark Fluchel, Aimee O. Hersh, Adam L. Hersh, Thomas V. Brogan, Rajendu Srivastava, Kristen Hayward, Bryan Stone, Kent Korgenski, Michael B. Mundorff, Charles Casper, Susan Bratton

University of Utah, Salt Lake City, UT; University of Washington, Seattle, WA

Introduction and Purpose: Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) are rapidly progressive and life threatening conditions. Timely diagnosis and treatment with appropriate chemotherapy are essential for survival. While standards of care have been established by the HLH-94 and HLH-2004 protocols, it is unclear how these standards are implemented in practice and little is known about variation among treatment centers with respect to diagnostic workup, therapy and supportive care. This study describes coexisting diagnoses, supportive and therapeutic interventions, and outcomes in a cohort of children with HLH or MAS across 38 children’s hospitals in the United States using the Pediatric Health Information System (PHIS) database.

Patients and Methods: We performed a retrospective cohort study of the PHIS database, examining records from Oct 1, 2006 to September 30, 2010. Participants had an ICD-9-CM diagnosis code for HLH or MAS (288.4) without prior admission with the outdated, more generic, diagnosis code that included HLH and MAS (288.0). The primary outcome was hospital mortality. Secondary outcomes included intensive care unit (ICU) admission, critical care interventions, the presence of central nervous system (CNS) disease, and treatment with dexamethasone, cyclosporine, etoposide and hematopoetic stem cell transplant (HSCT).

Results: We evaluated 1,117 admissions at PHIS hospitals for HLH/MAS in 534 patients. Index admission mortality was 13% (71/534), and an additional 6% (32/534) of the patients died during subsequent admissions. Infants less than one year comprised 19.7% of the cohort with 29.8%, 27.0%, and 23.5% of patients being 1 to <5, 5 to <13, and 13 to <18 years at diagnosis, respectively. Less than half (225/534, 42%) of the patients had an underlying diagnosis known to be associated with HLH/MAS at presentation, with 20%, 9.6%, and 12.2% documented as having a concurrent rheumatologic, oncologic, or viral diagnosis, respectively. CNS disease was documented in only 9.7% of patients. HSCT was given to 7% (38/534) of the patients during the index admission, and to an additional 9% (49/534) during subsequent admissions. ICU admission (45%), mechanical ventilation (34%), and inotrope/vasopressor therapy (34%) were common during the index admission. After adjustment for treatment hospital, admission year, and coexisting diagnoses, age ≥ 13 years (adjusted hazard ratio [aHR] 0.5, 95% confidence interval [CI] 0.2-1.0) was independently associated with index admission survival. Treatment with etoposide without cyclosporine was independently associated with mortality (aHR 2.9, 95% CI 1.4-5.7).

Conclusions: Mortality and critical care interventions are common at the index admission in children with HLH and MAS. Younger children may be at higher risk for mortality and, in this cohort, those patients treated with etoposide without cyclosporine had poorer survival.
FAVOURABLE OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANTATION AFTER MYELOABLATIVE CONDITIONING: A MULTI-CENTRE EUROPEAN EXPERIENCE

Karin Beutel, Roland Fischer, Elisabet Berglöf, Elena Sieni, Nizar Mahlaoui, Maurizio Aricò, Jan-Inge Henter, Gritta E. Janka

Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Germany
Pediatric Hematology and Oncology, University Hospital Münster, Germany
Childhood Cancer Research Unit, Department of Women’s and Children’s Health, Karolinska Institutet, Stockholm, Sweden
Department of Pediatric Hematology and Oncology, Azienda Ospedaliero Universitaria A. Meyer, Florence, Italy
Hôpital Necker Enfants Malades and French National Reference Center for Primary Immune deficiencies (CEREDIH), Assistance Publique-Hôpitaux de Paris, Paris, France

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a rare genetic or acquired condition characterized by an immune dysregulation which is mostly fatal without treatment. In many cases definite cure can only be achieved with hematopoietic stem cell transplantation (HSCT). However, HSCT in HLH seems to be associated with specific risks regarding acute toxicity, graft failure and long-term sequelae. Reported survival rates range from 50-70%. We present a retrospective analysis of a large cohort of transplanted HLH patients which was intended to better define risk factors for adverse outcome and long-term sequelae. Patients and methods: Pseudonymized data on HLH patients who have been transplanted in a 15-year period were collected from 4 European reference centres on standardized questionnaires and stored in a central ACCESS-data base.

Results: Data from 187 evaluable patients have been analyzed who have undergone 212 HSCTs. Half of the patients were confirmed genetic cases. Median age at HSCT was 11,8 months, range 2,1-211 months. 86% of the HSCTs were performed after a Busulfan-based myeloablative conditioning (MAC). The donors were matched unrelated (MUD) in 37%, matched related (MRD) in 22%, haploidentical in 22% and mismatched unrelated donors (MMUD) in 18%. Primary graft failure occurred in less than 10%. After a median follow-up of 2,6 years the overall survival was 70%, being not significantly different after MRD, MSD or MMUD-HSCT. HSCT from a haploidentical donor was associated with a worse overall survival of 52%. Most patients died early, median 2,9 months after the first transplantation. Development of veno-occlusive disease (VOD) occurred in 30% of the transplantations. Busulfan-containing MAC conferred a significant risk for VOD compared to modified regimens. Severe GvHD was not a major problem.

Conclusion: This study includes the largest cohort of transplanted HLH patients reported so far. It demonstrates a superior outcome compared to previous reports. Haploidentical HSCT was an independent risk factor for transplant-related mortality. A Busulfan-based MAC was significantly associated with VOD. There is a need of modified conditioning regimens in order to prevent toxicity and early deaths without the risk of secondary graft failure which has been observed after reduced-intensity conditioning.
USE OF THE ANTI-CD20 ANTIBODY RITUXIMAB IN THE TREATMENT OF EPSTEIN-BARR VIRUS-INDUCED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Susan Weiner, Kristin Zelley, Kim E. Nichols
Division of Oncology, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a rare complication of Epstein-Barr virus (EBV) infection that is characterized by the proliferation of EBV-infected cells and the exuberant activation of T lymphocytes and macrophages. Current therapeutic approaches aim to curtail EBV-induced immune cell activation through the use of chemotherapy and/or immunosuppressive medications. The anti-CD20 antibody Rituximab targets EBV-infected B cells and reduces disease burden in individuals with EBV-associated post transplantation lymphoproliferative disorders. Its safety and efficacy in patients with EBV-HLH remain unknown.

Methods: To gather retrospective data regarding experience with the use of Rituximab in the treatment of EBV-HLH, we developed a questionnaire and distributed it to members of the Histiocyte Society who stated they had administered this medication to one or more patients. Anonymous clinical and laboratory data were gathered and analyzed for this report.

Results: This retrospective survey includes 36 patients with EBV-HLH who received treatment with Rituximab. The cohort consists of 25 boys and 11 girls, ranging in age from 1 to 44 years (median 5.75 years). All patients met criteria for HLH according HLH-2004 guidelines. A causal link to EBV was established in all patients based on positivity by monospot (n=9), EBV serology (n=25), EBV PCR (n=27) or a combination of these methods. Among the 33 patients for whom genetic data were available, 14 (42%) harbored germline mutations in distinct HLH-associated genes, including PRF1 (n=2), SH2D1A (n=8), XIAP/BIRC4 (n=1), UNC13D (n=2) and STXBP2 (n=1). On average, patients received a total of 3 infusions of Rituximab (range 1 to 10) at a dose of 375 mg/M2. The first dose of Rituximab was administered within 1 month from the date of HLH diagnosis in most patients, and it was always given in conjunction with other medications, including chemotherapy (n=32), steroids (n=35), cyclosporine (n=28), immunoglobulin (n=28) and/or anti-viral medications (n=23). Rituximab administration was associated with reversible immediate side effects in 7 patients (fever, n=5; allergic reaction, n=1; hypotension, n=1). Three patients experienced later side effects including 2 with neutropenia and 1 with hypogammaglobulinemia, although the reduced immunoglobulin levels may have been secondary to this patient’s underlying genetic mutation. In 28 of 33 (85%) patients for whom serial data are available, administration of Rituximab led to a reduction in EBV load and in 19 of 33 (58%) patients, Rituximab seemed to ameliorate the clinical and laboratory features of HLH with an average time to improvement of 11 days (range 1-28 days).

Conclusion: Rituximab is a well-tolerated medication with minimal side effects, even when administered to patients with HLH. Based on our data that Rituximab reduces viral load and improves patient status, we support the incorporation of this medication into future HLH therapeutic trials for patients whose disease is due to EBV infection.
LCH, THE BELGIAN SURVEY

Leen Vangheebergen, Liesbeth Van Eycken, Stefaan Van Gool

Pediatric hemato-oncology (LVG and SVG), University Hospital Leuven, Belgium, and the Belgian Cancer Registry (LVE).

Introduction: The determination of the true incidence of LCH in a population remains difficult. Moreover, most of the current studies do not include adults in their registry. We aimed to estimate the true incidence of LCH in Flanders and to provide an appropriate description and outcome of patients suffering from LCH. For this, the “LCH, the Belgian Survey” (LCH-BS) registry was initiated in 2001.

Method: The registry started in 2001. In a first step, retrospective data were recruited through hospital-based registries and questionnaires. From 2001, data were prospectively sampled. Since 2003, we relied on the Belgian Cancer Registry (BCR) for sampling data coming from Flanders. For each diagnosis in the ICD catalogue, the pathologist in Flanders reports the diagnosis to the BCR. As such, new and accurate LCH diagnoses were reported centrally and were collected prospectively. These data included also basic data of the patients. Through the pathologist, the referring physician was contacted, and further patient data were collected after informed consent. An update of the ongoing project is reported.

Results: In total, 256 patients with LCH are included in LCH-BS (56% males). Between 2004 and 2006, 53 patients were collected via BCR, giving a global incidence of 0.3/100000/year. These data are comparable to the data sampled prospectively in the registry from 2001 to 2006. The latter cohort includes 61 adults and 67 patients <20y, resulting in an incidence of 0.22/100000/y for adults and 0.83/100000/y for children. There were no major differences between the regions in Flanders. The incidence remained stable over the years of study. Of this group, 61% were single system and 17% were multisystem patients, mostly children, while 22% were adults with isolated lung disease. Of 119 patients in the registry, we were able to contact the general physician to obtain survival data. The 10y survival was 87%. The 10y survival in patients with single system lung disease was 74% (n=24), while only 45% of the multisystem risk patients were alive at 10y follow up (n=13). In the single system unifocal (n=53), single system multifocal (n=18) and multisystem low risk (n=12) subgroups, the survival after 10 years was 100%.

Conclusion: Our registry LCH-BS includes adult patients besides children. A unique method has been developed for prospective sampling of population-based data via the pathological diagnostics. These two features makes the “LCH, the Belgian Survey” registry unique and accurate. Although keeping its own accent and methodology, the registry will participate in the Euro-Histio-Net project.

This work is supported by the patient organization LCH Belgium.
AN EXPLORATORY EPIDEMIOLOGICAL STUDY OF LANGERHANS CELL HISTIOCYTOSIS IN A PREDOMINANTLY HISPANIC POPULATION

Rajkumar Venkatramani, Shira Rosenberg, Gitanjali Indramohan, Rima Jubran

Children's Hospital Los Angeles, Los Angeles, California, USA, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

Purpose: Maternal urinary tract infection during pregnancy, family history of thyroid disease, neonatal infection and lack of immunization have been described as risk factors for Langerhans cell histiocytosis (LCH) in epidemiological studies in which subjects were predominantly white. The purpose of our study was to explore the risk factors for LCH in Los Angeles, a predominantly Hispanic population.

Methods: Sixty children with Langerhans cell histiocytosis treated at oncology clinic (cases), and 150 random patients (controls) visiting pediatric ambulatory clinic at Children’s Hospital Los Angeles were interviewed. The questionnaire consisted of 22 questions about demographic factors, family history, parent’s occupation, parent’s and patient’s exposure to smoking, alcohol, metals, granite, wood, pesticide, immunization status of the child, problems during pregnancy and, infections during first year of life. Clinical data on cases was abstracted from the medical record.

Results: The median age of cases and controls were 3.6 years and 5.1 years respectively. 43% of both cases and controls were male. 53% of cases and 67% of controls were Hispanic. More than half of cases and controls were first generation immigrants to the United States. LCH was restricted to skeletal system in 41 cases; monostotic in 20 and polyostotic in 21. Five cases presented with single organ involvement and multiple organs were involved in 14. There was not a statistically significant difference between cases and controls in the following; family history of thyroid disease, smoker in family, maternal problems during pregnancy, pesticide exposure. Cases were 2.5 times more likely to report cancer diagnosis in a first degree relative. Parents of cases were 2.75 times more likely to drink alcohol when compared to controls. Cases were more likely to report (OR 2.76) having infections as an infant.

Conclusions: While this is a small case controlled study of children with LCH in Los Angeles and their families, we found significant unreported associations between family history and environmental exposures and the development of LCH. A larger study is needed to validate our findings.
FREQUENT BRAF V600E MUTATIONS ARE IDENTIFIED IN CD207+ CELLS IN LCH LESIONS, BUT BRAF STATUS DOES NOT CORRELATE WITH CLINICAL PRESENTATION OF PATIENTS OR TRANSCRIPTIONAL PROFILES OF CD207+ CELLS

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Background: Very little is known about the cell of origin or the pathogenesis of LCH. There remains debate regarding LCH as a malignant disorder or the result of immune dysregulation. While multiple studies in the past failed to identify significant genetic lesions, an activating mutation (V600E) in the serine/threonine kinase BRAF was recently described in LCH biopsy samples (Badalian-Very et al., 2010).

Objective: This study was designed to evaluate the frequency of BRAF mutations in LCH lesions, to identify the cells within the lesions carrying the mutation, and to evaluate the clinical and biological significance of the mutation.

Design/Methods: Fresh LCH biopsy samples were collected, cells were sorted into CD3+ and CD207+ fractions, and RNA was purified then amplified into cDNA. Sanger sequencing as well as BRAF allele-specific PCR were performed for each sample. Categorical clinical data was compared to BRAF genotype to evaluate clinical significance of the mutation. Transcriptomes of CD207+ cells were also compared (wild-type BRAF vs V600E) to determine the impact of the BRAF mutation on global gene expression.

Results: The BRAF V600E mutation was consistently identified in cDNA generated from CD207+ cells in 17 of 32 (52%) LCH biopsy samples. Only the wild-type allele was detected in purified T (CD3+) cells from LCH lesions, epidermal (CD207+) Langerhans cells, and tonsil T (CD3+) cells. In two cases of recurrent disease, BRAF status was consistent in the presenting and the relapse CD207+ cells: wild-type BRAF in one case and V600E BRAF in another. However, mutation status did not correlate significantly with age, extent of disease, or recurrent/refractory disease in this series. Furthermore, unsupervised clustering of gene expression profiles among CD207+ cells (wild-type BRAF vs V600E) did not segregate datasets based on BRAF status. Using standard statistical analysis, there were no genes identified as significantly up- or down-regulated as a result of the V600E mutation.

Conclusion: The BRAF V600E point mutation is the first reproducible molecular abnormality identified in LCH. In this study, we validate the observation that it occurs with high frequency, and definitively localize the pathologic CD207+ cell as the source of the mutation in LCH lesions. Interestingly, while the frequency of the mutation implies some functional significance, in this series there is no statistically significant clinical difference between patients with wild-type or mutated BRAF lesions, and the transcriptomes of LCH CD207+ cells with wild-type or V600E BRAF are indistinguishable. It is possible that the mutation affects LCH pathogenesis at earlier stages in tumorigenesis, or there may be other routes of Ras pathway activation in LCH lesions with wild-type BRAF. While the role for BRAF in LCH pathogenesis remains to be defined, this is an important molecular foothold from which to investigate the biology of LCH.
INTERFERON-GAMMA AND IL-10 FORM A COMPLEX SELF-REGULATING NETWORK THAT DETERMINES THE SEVERITY OF MACROPHAGE ACTIVATION SYNDROME

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Introduction: Macrophage Activation Syndrome (MAS) is a hemophagocytic disorder seen secondary to a number of rheumatologic conditions. We recently described a novel murine model of MAS, induced by repeated stimulation of Toll-like Receptor 9 (TLR9). Both IFNg and IL-10 are important cytokines in regulating the disease severity. IFNg is critical for the development of many of the elements of TLR9 induced MAS, while IL-10 protects against the development of more severe disease, including the development of hemophagocytosis. We now show that these two cytokines regulate each other’s expression during the progression of the disease, as well as which cells are responsible for this production.

Methods: MAS was induced by repeated injection of CpG1826 every other day for 10 days. YFP reporter mice for IFNg and IL-10 were used to track cytokine producing populations by flow cytometry. IL-10 signaling was blocked via administration of 1B1.3A, a monoclonal antibody against the IL-10 receptor (IL-10R). Cytokines were measured by ELISA. Histology was reviewed, blinded, by trained pathologists.

Results: IL-10 in TLR9 induced MAS is produced predominantly by hepatic CD4 and CD8 T-cells, natural killer cells, plasmacytoid dendritic cells and lymphoid dendritic cells. Depletion of either lymphocytes using Rag2-/- mice, or dendritic cells using mice expressing Diphtheria Toxin Receptor in CD11c bearing cells, results in a significant reduction of serum IL-10 levels with an enhancement of liver inflammation. IL-10 producing T-cells have a surface phenotype of recent T-cell receptor activation (CD69hiCD62LloCD44hi) despite the absence of exogenous antigen in this model. Blockade of IL-10R during disease induction results in a dramatic increase in serum IFNg, IL-6 and IL-12, as well as IL-10 itself. The increase in IFNg is correlated with an increase in hepatic IFNg producing NKT cells, but not in other IFNg producing populations. Elimination of IFNg using IFNg-/- mice for disease induction results in decreased IL-10, but not IL-12 or IL-6. IFNg responsive IL-10 production depends on a radiosensitive marrow cell, since irradiated wild type mice transplanted with IFNg receptor deficient marrow and treated with repeated CpG also show a decrease in serum IL-10. Surprisingly, IL-10R blocked IFNg-/- mice treated with repeated CpG only had minimal improvement in their disease parameters, with similar mortality to mice with intact IFNg.

Conclusions: IL-10 and IFNg counter-regulate each other’s production in TLR9 induced MAS. While IFNg mediates most of the pathogenicity in states of intact IL-10 signaling, other cytokines may be mediating disease in states of low or absent IL-10 signaling. These results have implications for cytokine blocking and cell depletion therapies for MAS. Investigation into the specific biochemical mediators of the reciprocal regulation of IFNg and IL-10 in MAS is ongoing.
SUBTLE DIFFERENCES IN CTL CYTOTOXICITY DETERMINE SUSCEPTIBILITY TO HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN MICE AND HUMANS WITH CHEDIAK-HIGASHI SYNDROME

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Perforin-mediated cytotoxicity is important for controlling viral infections, but also for limiting immune reactions. Failure of this cytotoxic pathway leads to hemophagocytic lymphohistiocytosis (HLH), a life-threatening disorder of uncontrolled T cell and macrophage activation. We studied susceptibility to HLH in two mouse strains (sours and beigeJ) and a cohort of patients with partial defects in perforin secretion due to different mutations in the LYST gene. Although both strains lacked NK cell cytotoxicity, only souris mice developed all clinical and histopathological signs of HLH after infection with lymphocytic choriomeningitis virus (LCMV). The two strains showed subtle differences in CTL cytotoxicity in vitro that had a large impact on virus control in vivo. While beigeJ CTL eliminated LCMV infection, souris CTL failed to control the virus which was associated with the development of HLH. In LYST-mutant patients with Chediak-Higashi syndrome (CHS), CTL cytotoxicity was reduced in patients with early-onset HLH, while it was retained in patients who later or never developed HLH. Thus, the risk of HLH development is set by a threshold that is determined by subtle differences in CTL cytotoxicity. Differences in the cytotoxic capacity of CTL may be predictive for the risk of CHS patients to develop HLH.
VARIANT ALLELES OF CYTOKINE GENES INFLUENCE THE RISK AND CLINICAL COURSE OF LANGERHANS CELL HISTIOCYTOSIS

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Background: A dysregulation of cytokines may play an important role in the pathogenesis and clinical course of Langerhans cell histiocytosis (LCH). It is well known that variant alleles (polymorphisms) of cytokines may influence functional characteristics and/or serum concentration of the molecule, and that host genetic factors may modify the risk as well as the clinical course of various malignancies and immune-mediated diseases. We therefore hypothesized that polymorphisms within genes encoding pro- and anti-inflammatory cytokines may contribute to the risk, severity and prognosis of LCH.

Methods: Based on altered cytokine production, clinical outcome, or both in various disease populations, five polymorphisms of candidate genes encoding pro- and anti-inflammatory cytokines were selected: interleukin (IL)-6 (G-174C), IL-8 (A-352T), IL-1α (G-889T), IL-1 receptor antagonist (intron 2) and tumor-necrosis factor α; (G-308A). Variant alleles were assessed in 202 patients with confirmed LCH and associated with risk and clinical course of the disease.

Results: A total of 82 girls and 120 boys (median age: 24 months) were included in the study. The patients presented with single-system (n=113) or multi-system LCH (n=89; 56 and 33 patients with and without involvement of risk organs such as liver, spleen, hematopoietic system, and lung, respectively). When comparing patients with LCH with healthy individuals, we found a significant overrepresentation of heterozygotes of IL6-174 in LCH patients, whereas the IL8-251 heterozygous genotype was significantly more often observed in the control group (P=0.0026 and P<0.00001, respectively). Whereas no association was found between any of the variant alleles analyzed and age at diagnosis or gender, the heterozygote genotype CG of IL6-174 was also significantly overrepresented in the more aggressive MS-disease as compared to patients with SS-LCH (P=0.00198). In addition, heterozygotes for the IL-8 (A-352T) promoter polymorphism were significantly overrepresented in patients reaching a non-active disease status, both at the first follow-up at 6 weeks and over time (P=0.027 and P=0.03, respectively).

Conclusion: The results of this analysis on the largest cohort of LCH patients published to date suggest that specific cytokine polymorphisms may affect susceptibility to and clinical course of LCH and may ultimately help to design treatment protocols tailored individually for each patient.

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ABSTRACTS: SCIENTIFIC SESSION II

CAMPATH 1H AS FIRST LINE TREATMENT IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: PRELIMINARY SINGLE CENTRE EXPERIENCE

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Introduction: Familial hemophagocytic lymphohistiocytosis (FHLH) are autosomal recessive primary immune deficiencies affecting granule-mediated cytotoxicity. Known genetic causes include mutations in PRF1, UNC13D, STX11, and STXBP. HLH is rapidly fatal in the absence of appropriate treatment. Survival and cure include specific treatment in order to achieve and maintain remission from overwhelming HLH, followed by allogeneic hematopoietic stem cell transplantation (HSCT), which is the only curative approach. A major breakthrough was achieved through the HLH-94 protocol, a combined chemo- and immunotherapy, that greatly improved the survival of children with HLH.

Rationale: As HLH is a primary T (NK) cell immunodeficiency with massive CD8 T lymphocyte infiltration and macrophage activation, immunotherapy may be a valuable treatment option. This approach may be less toxic by targeting directly the T cells that are primarily involved in triggering the HLH condition while sparing myeloid cells. So far, Anti T cell polyclonal Antibodies, (“Antithymocyte globulins” or ATG) associated to steroids and cyclosporine have been used successfully in FHLH, as previously reported by our group.

The humanized anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) efficiently depletes T cells in vivo, as well as B cells and other lymphoid subsets. As alemtuzumab does not activate T cells, we hypothesized, that it may be better tolerated than ATG, notably in infants. However, very little information has been available regarding direct comparison of ATG and alemtuzumab in first line treatment of FHLH.

Purpose of the study: to analyze retrospectively our experience regarding the first 10 patients with severe forms of FHLH who have received alemtuzumab (instead of ATG) combined with steroids as first line therapy.

Results: The patients presented HLH with early onset (0-527 days, median 33 days of life). Four patients had CNS disease at onset. Mutations in the known FHLH genes were found in all but one patient (PRF1 in 6, UNC13D in 1, STX11 in 1 and STXBP2 in 1 patient respectively). The patients received a total dose of 2.5 to 5 mg/kg. A complete remission allowing HSCT was obtained in 7 patients (time to achieve remission: 15-35 days, median 30) and 6 of 7 patients are alive. A partial remission was observed in 2 patients, who then received ATG and proceeded to HSCT. One of these 2 patients died. Only one out of 10 patients did not respond to alemtuzumab (nor to VP16 as second line treatment) and died. Detailed information on these patients and the treatment will be presented.

Conclusion: These preliminary results on the use of alemtuzumab in FHLH are encouraging. We observed acceptable toxicity and excellent response rates. Even if the exact dose and the administration schedule may still require further refining, our preliminary data suggest that immunotherapy with alemtuzumab may represent a valuable alternative to ATG in the treatment of FHLH.
GENETIC HETEROGENEITY OF FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Background: Familial hemophagocytic lymphohistiocytosis (FHL) is a genetically heterogeneous disorder characterized by a hyperinflammatory syndrome with fever, hepatosplenomegaly and cytopenia. A similar clinical picture may result from mutations in different genes involved in the granule-dependent exocytosis pathway. To date, five independent loci implicated in FHL have been identified and the underlying genetic defect described for four of these. We compared the four genetic subtypes of the disease and explored genotype-phenotype correlations.

Methods: The consortium established between Italy, Germany and Sweden planned to compare data from previously reported FHL2 and FHL3 cohorts with the current analyzed data on mutations, presenting features and cytotoxic function of FHL4 and FHL5 patients. Statistical analysis with regard to age at diagnosis was performed with the Kruskal-Wallis test, and with regard to consanguinity and CNS involvement by the chi-square.

Results: 257 patients were reported with the following genetic diagnoses: FHL2 (n=124), FHL3 (n=84), FHL4 (n=15) and FHL5 (n=34). The age at the onset was different in the four groups (p=0.001), with FHL2 and FHL3 having a younger age (3.0 and 4.1 months respectively) than FHL4 (12.2 months) and FHL5 (6.0 months). Consanguinity was more frequent in FHL4 (n=14/15, 93%) compared to FHL2 (n=43/86, 44%) [p=0.001], FHL3 (n=28/80, 35%) [p=0.001] and FHL5 (n=16/33, 48%) [p=0.008]. The ethnic origin was different in the four groups of patients: FHL2, FHL3 and FHL5 were found in many ethnic groups while FHL4 was restricted to the Turkish population; ethnic-specific mutations were previously reported for FHL2 and now for FHL5 with the c.1430C>T mutation being most frequent in Arabian patients. The presenting features were similar in the four groups, except for gastrointestinal symptoms, hypogammaglobulinemia and bleeding disorders that were reported in 8/34 (23%) patients with FHL5 and not reported in the other groups. The proportion of CNS involvement was significantly higher in FHL3 patients (n=49/81, 60%) compared to FHL2 (n=31/86, 36%) [p=0.003], while no statistically significance was found comparing FHL3 with FHL4 (n=4/13, 31%) or FHL5 (n=15/31, 48%). The combination of fever, splenomegaly, thrombocytopenia and hyperferritinemia was found in 63% of patients with FHL2, 71% of FHL3, 85% of FHL4 and 76% of FHL5. Granule release capacity was reduced in 29/30 patients with FHL3 and 14/15 patients with FHL5 (FHL4 not reported). Perforin expression was reduced in 32/33 FHL2 patients and normal in patients from other groups. NK cell activity was defective in all the patients with FHL4 and FHL5, 44/45 patients with FHL3 and 66/70 patients with FHL2.

Conclusions: Despite some specificities on presenting features, FHL subtypes are not easy to discriminate on a clinical basis. Flow-cytometry screening of perforin expression and degranulation supported by evaluation of cytotoxicity confirms to be a very sensitive tool for diagnosis of FHL.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #1

HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR REFRACTORY EBV-HLH: REPORT OF TWO PEDIATRIC CASES

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Epstein-Barr virus (EBV) is a frequent trigger of secondary hemophagocytic lymphohistiocytosis (HLH). The clinical features of EBV-HLH vary from mild to severe, and successful treatment with HLH-94/2004-type immunochemotherapy has been reported. No consensus exists regarding the treatment of refractory EBV-HLH, although HCT has resulted in remission in some reports. We report the treatment course of two children with refractory EBV-HLH.

Case 1: A 17 year old male was admitted to ICU with fever, shock and laboratory evidence of HLH. He had a semi-quantitative EBV load > 1000 copies/million mononuclear cells, normal NK function and normal perforin, syntaxin-11 and Munc-13.4 genes as well as normal XLP genes (SH2D1A and BIRC4). Despite an initial excellent response to dexamethasone, etoposide and cyclosporine he had recurrence of the EBV load and HLH when an attempt was made to discontinue his therapy and despite addition of Rituximab (375 mg/m²) to his therapy. Lymphocyte subtyping after rituximab showed zero CD20+ cells despite recurrence of a high EBV load, suggesting that EBV was proliferating in other cell types (such as T cells, as previously reported by Japanese groups). The patient eventually underwent reduced intensity unrelated allogeneic HCT with Fludarabine, Melphalan and Alemtuzumab in Cincinnati. He remains without evidence of HLH at 30 months post-transplant but with grade 2-3 GVHD and osteonecrosis.

Case 2: A 5 yr old male of Vietnamese descent, presented with atypical Kawasaki and EBV-HLH. Despite initial response to HLH therapy, his EBV load continued to increase. He received 2 doses of Rituximab with transient drop in EBV load. His XLP and FHLH genes were normal. Due to recurrent episodes of HLH, and a persistent increase in EBV load, he underwent unrelated cord blood transplant with Busulfan, Etoposide, Cyclophosphamide and Alemtuzumab conditioning. His transplant was complicated by hepatic veno-occlusive disease and gut GVHD. The EBV load increased again 2 months post-transplant and he was restarted on ganciclovir and cytogam for a few weeks. He is now clinically well with no signs of HLH or EBV at 21 months post HCT.

Conclusion: Secondary EBV-HLH may continue to recur in some patients despite absence of abnormality of known FHLH and XLP genes, requiring HCT for resolution. These patients may have FHLH due to as yet undescribed genes, or there may be as yet unknown genes which result in the XLP phenotype.
Diabetes insipidus (DI) is the most common central nervous system manifestation of Langerhans cell histiocytosis (LCH). Once established, DI associated with LCH is usually not reversible although there are some reported cases of reversal with chemotherapy. We report the case of a girl with LCH-related DI who had reversal of her symptoms with prolonged low-dose chemotherapy.

A 13 year old girl was diagnosed with LCH of the right tibia, with no other bony or skin lesions and no MS disease. She was treated with curettage, but two months later she developed symptoms of DI and started Desmopressin (DDAVP) with good control. A brain MRI showed a thickened pituitary stalk with enhancement of the pituitary gland and nonvisualization of the posterior bright spot, compatible with pituitary LCH. She received 6 months of vinblastine (6 mg/m²) and prednisone (60 mg/day), followed by low-dose weekly methotrexate (20 mg/m²) for 18 months. One year after the end of therapy, she stopped the DDAVP spontaneously and experienced good control of her symptoms. A repeat MRI revealed a bright signal in the posterior pituitary gland with no abnormal enhancement of the anterior pituitary gland. She continues to be clinically well and off DDAVP at 18 months off therapy.

A number of cases have been reported in which LCH-related DI remitted either spontaneously or with chemotherapy, such as cladribine or etoposide, or after hypothalamic-pituitary radiation therapy. Prolonged and intensive therapy used in the DAL-HX studies reduced the incidence of DI to 19% in patients with MS LCH as opposed to 36% when a more conservative approach was used.

Patients with LCH and new onset DI could benefit from low dose systemic chemotherapy in order to prevent secondary consequences of DI, such as neurodegenerative disease and anterior pituitary dysfunction.
Juvenile xanthogranuloma (JXG) is an uncommon histiocytic disorder that is usually limited to the skin, although systemic JXG may occur. We report a 7 year old girl treated for multisystem LCH with diabetes insipidus who subsequently developed CNS JXG lesions. Five years after the initial presentation of LCH, on routine brain MRI, dural-based lesions were noted, some compressing the cerebral venous sinuses. Review of the previous MRI, in retrospect, showed one lesion although much smaller. She was considered to have CNS-LCH and treated with cladribine (9 mg/m²) and dexamethasone for 2 cycles without benefit, except possibly prevention of further growth. Cytarabine was added to cladribine for 2 cycles and once again brain MRI remained unchanged. Brain biopsy then revealed Touton giant cells, Factor XIIIa, CD163, CD68 and Fascin positivity, while CD1a, Langerin and S100 were negative, compatible with JXG. She was started on weekly vinblastine with an initial slight decrease in the CNS lesions, but after one year of weekly therapy, her MRI shows no further decrease in the lesions. She remains clinically neurologically normal and well on DDAVP.

Progression of LCH to JXG has been previously documented, but no case of progression to CNS JXG has been published. The treatment of CNS JXG remains challenging. Possible therapeutic options including imatinib or dasatinib will be discussed.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #4

SIX CHILDREN WITH FAMILIAL HLH WHO UNDERWENT HSCT: A SINGLE CENTER EXPERIENCE

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Primary hemophagocytic lymphohistiocytosis (HLH) is a rare and fatal genetic disorder characterized by hyperinflammation effecting bone marrow, liver and central nervous system. Remission can be induced by conventional chemotherapy (etoposide (VP-16), corticosteroids, intrathecal methotrexate) and immunosuppressive therapy (antithymocyte globulins (ATG) and cyclosporin A). But the only curative treatment modality is hematopoietic stem cell transplantation (HSCT), otherwise the disease will recur. But optimal HSCT regimen for patients for HLH remains to be defined whether it should be myeloablative or non-myeloablative.

The purpose of our study to analyze six children with HLH who undergone myeloablative high dose chemotherapy and allogeneic HSCT in a single center.

Six consecutive patients with primary HLH underwent HSCT from fully matched related donors between April 2008 and Feb 2011 in our institution. We retrospectively analyzed the epidemiological characteristics, clinical and laboratory data, pre-SCT organ dysfunction and primary endpoints of these patients.

Five male (84%) and 1 female (16%) (male/female ratio:5) patients with HLH underwent allogeneic HSCT. Median age at the diagnosis was 5 months (range, 2–19 months) and only one patient had central nervous system involvement at diagnosis. The family history of the parental consanguinity was in 5 of 6 patients (83%). Only four of the 6 patients could be assessed in terms of the genetic mutations and these analysis showed that two patients had detectable perforin mutation and one patient had UNC 13D mutation. The remaining patient had no detectable mutation. The median age at transplantation was 22 months (range, 9 – 38 months). Hematopoietic stem cell transplantation was performed at a median 16 months from diagnosis (range, 6 – 20 months). Three of 6 were in complete remission and 2 in partial remission and 1 in active disease before HSCT. All patients were conditioned with busulfan 0.8- 1 mg/kg/dose q 12 hour for 4 days (days -8 to -5) and etoposide 30 mg/kg/day (day -4) and cyclophosphamide 60mg/kg/day (days -3 to -2). Only one patient received antithymocyte globulin (ATG) 5 mg/kg for 5 days (day -5 to -1). Three patients who were in CR before HSCT have 100% donor cells one month after HSCT and they are alive and two of them are full chimeric now, but one of them developed mixed chimerism 8 months later, on the other hand he is in remission also. One patient who was in PR before HSCT had rejected donor lymphocytes and donor chimerism could not be achieved, so he has been in partial remission for 6 months. The remaining two patients who were in PR or active disease before HSCT died due to VOD and gram negative sepsis.

Our observation confirmed the previous studies that active disease in HLH before HSCT is a poor prognostic factor. So consideration should be given to the remission status of HLH patients before starting conditioning regimen and HSCT, otherwise all efforts can be failed. But further prospective studies concerning specifically to HLH disease status immediately before HSCT are needed for the precise decision. The second remarkable point is mixed chimerism in HLH patients that seems to be enough to maintain remission status.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #5
MALIGNANCY-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS BEFORE AND AFTER MALIGNANCY

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Malignancy-associated Hemophagocytic Lymphohistiocytosis (HLH) is a rare disease in children and has the worst prognosis among HLH forms. In leukemic patients, HLH diagnosis is usually delayed due to unspecific clinical presentation, presence of a documented infection and lack of reliable markers. Treatment decisions are controversial because both HLH and cancer directed therapies are necessary for cure. We report our experience with 4 Caucasian boys diagnosed of HLH and leukaemia, one prior to diagnosis of acute myeloid leukaemia (AML) and three during maintenance chemotherapy of acute lymphoblastic leukaemia (ALL).

HLH prior to AML was diagnosed in a 20-month-old boy. He presented with a 2 week history of fever, hepatomegaly, pancytopenia and hyperferritenemia with positive IgM EBV and hemophagocytosis in bone marrow. Perforin expression was normal and genetic studies showed heterozygosity for A91V in perforin gene. Spontaneous HLH remission was observed. Due to persistent neutropenia, bone marrow was repeated and AML was revealed. He successfully completed treatment and is in remission 12 months after AML diagnosis.

HLH during maintenance chemotherapy of B precursor-ALL was diagnosed in 3-, 14- and 12-year-old boys, the latter having Down syndrome, at 2, 4 and 12 months since maintenance had been started with Methotrexate/6-Mercaptopurine. They suffered from infections (diarrhea, anal abscess and pneumonia, respectively) with microbiology documented infections (salmonella, respiratory syncytial virus, metapneumovirus and EBV reactivation). They received microbiological treatment but fever persistence, clinical symptoms and laboratory data progression made us suspect HLH. Although initially they don't fulfill all diagnostic criteria and hemophagocytosis was just found in bone marrow of 2 patients, they were treated according to HLH therapy (corticosteroid, etoposide and cyclosporine) due to the severe clinical progression with good initial responses. The first boy had ALL relapse 6 months after finishing leukaemia treatment and died of disease progression. The second case had HLH reactivation 7 months later while on maintenance, which resolved. However, he suffered from bone marrow and testicular relapse 1 month after the end of ALL treatment and died of sepsis during second induction (necropsy showed HLH). The Down-syndrome boy is being tapered from HLH drugs and continues on ALL maintenance with a very short follow-up.

COMMENTS: HLH was the first manifestation of an as yet unrecognized leukemia in one case and occurred during maintenance of three ALL patients. Leukaemia-associated HLH recognition is often delayed due to misdiagnose with complicated bacterial and viral infections in immuno-compromised children. HLH should be ruled out in ALL children who have clinical progression, such as fever or organic failure. Repeated laboratory tests and bone marrow samples are recommended for diagnostic confirmation. Prognosis was fatal in the 2 cases with longer follow-up, so we wonder the role of stem cell transplantation in these secondary HLH patients.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #6

BURQOL-RD PROJECT. SOCIAL ECONOMIC BURDEN AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH RARE DISEASES IN EUROPE

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BACKGROUND: BURQOL-RD is a 3 year project under the Second Programme of Community Action in the field of Public Health, promoted by DG Sanco in Europe that started in April 2010. The main aim is to generate a model to quantify the socioeconomic costs and Health-related Quality of Life (HRQOL), of both patients and caregivers, for 10 rare diseases (RD) in 8 European countries (Spain, France, United Kingdom, Italy, Sweden, Germany, Hungary and Bulgaria). The associated partners of BURQOL-RD Group* are: FUNDIS; IIER; Istituto Superiore di Sanita, Italy; London School of Economics an Political Science, UK; Bulgarian Association for Promotion of Education and Science, Bulgaria; Federación Española de Enfermedades Raras, Spain; Leigniz University Hannover, Germany; The Swedish Institute for Health Economics, Sweden; Universita Commerciale “Luigi Bocconi”, Italy; University Paris Val de Marne, France; Centre for Public Affairs Studies Foundation, Hungary; Mario Negri Institute for Pharmacological Research, Italy.

One of the rare diseases targeted in the pilot study of BURQOL-RD is histiocytosis.

METHODS: The main partner of this European project is Canary Foundation of Investigation and Health (FUNCIS) in Spain. The coordinator, Julio Lopez-Bastida, is a health economist who is supported by the 11 associated partners and 10 collaborating partners. Among these partners, Euro-Histio-Net, an international reference network for Langerhans Cell Histiocytosis and associated syndromes has contributed to the work related to histiocytosis. The collaboration of national patients associations and federations for the specific rare diseases is fundamental to ensure that all the objectives are successfully reached and ACHE (Asociación española contra la Histiocitosis) has also participated in the initial development of this project.

RESULTS: The project is divided in different work packages headed by groups from 8 European countries. The first work was related to the selection of the 10 rare diseases targeted in the pilot study: Cystic fibrosis, Prader-Willi Syndrome, Haemophilia, Scleroderma, Epidermolysis Bullosa, Histiocytosis, Juvenile Idiopathic Arthritis, Mucopolysaccharidosis, Fragile X Syndrome and Duchenne Muscular Dystrophy. The published methods to measure socioeconomic burden and instruments of HRQOL evaluation for each disease have been reviewed and the information available is insufficient or null for most of these RD. For Histiocytosis, we are preparing and validating the questionnaires for patients under 17 and over 16 years-old and their caregivers, in order to develop tools to measure the HRQOL and direct and indirect costs of this RD for the families and the society.

COMMENTS: The expected outcomes of BURQOL-RD is an integrated and harmonized set of instruments to assess and monitor socio-economic burden and health-related quality of life of patients affected by histiocytosis and their caregivers as well as the impact of new national policies and treatments. The tools developed by BURQOL-RD will build on the ongoing EUROPLAN project and will also improve Rare Diseases awareness and literacy among European citizens.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #7

ACUTE STIFF BACK IN A 12 YEAR OLD GIRL DUE TO PRIMARY LANGERHANS CELL HISTIOCYTOSIS IN THE THORACIC SPINAL ARCH

Carl Friedrich Classen
University Children’s Hospital Rostock, Rostock, Germany

Here, we report on a 12 year old girl who first presented with a stiff back that manifested itself after a sporting contest; the symptom was due to a single histiocytosis lesion in the thoracic spine. The girl is the second of two daughters of healthy unconsanguinous parents. Pregnancy and birth were uneventful, the girl had always been healthy. After taking part in a sporting contest including high jumping and running, the girl suddenly suffered from back pain. The clinical examination revealed a stiff back involving the complete thorax.

The girl was not able to bend forward her head. Trying to bend forward, the girl experienced pain and a marked asymmetric protrusion of the ribs at the right side became apparent. No neurological deficits, with regard to movement, sensitivity, or coordination were observed. While X-ray of the spine showed mild unspecific torsion scoliosis only, MRI of the thoracolumbar spine showed a contrast medium uptaking space occupying lesion at the dorsal side of the left pedicle, laminar bone and transverse processus of the vertebral arch of the 8th thoracic vertebra. The lesion led to narrowing of the spinal canal and the neuroforamen. The spinal nerve was swollen. Besides, a contrast medium uptaking infiltration of the surrounding soft tissue was observed. Blood count, laboratory examinations, tumor markers and hormone tests were normal, as was abdominal ultrasound. Whole body MRI showed no additional lesion, especially in the skull, spine or brain. Since surgical exploration of the region was impossible, a trephine biopsy from the involved tissue was taken. Histopathological analysis of the tissue revealed infiltrates of a Langerhans cell histiocytosis. Both an operative resection of the lesion or a local steroid instillation appeared impossible without induction of major damage to the spine. Thus, a chemotherapy strategy was chosen. The girl received a low risk - single site, special site - adapted chemotherapy according to the therapy protocol LCH III of the Histiocyte Society, using Vinblastin and Prednisolon as induction treatment. After 6 weeks of treatment, an involution of the soft tissue infiltrating part of the lesion was observed, thus the patient was regarded as responder, and treatment went on as continuation therapy. Clinically, the patent did very well.

While Langerhans cell histiocytosis involving the vertebral body has been repeatedly described, especially in adults, involvement of the vertebral arch leading to a severely stiff back is an uncommon presentation. Since operations in this area close to the spinal joints may be harmful, we report successful medical treatment in this case.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #8

INTERFERON-ALPHA MAINTENANCE THERAPY AND LANGERHANS CELL HISTIOCYTOSIS

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Introduction: There is increasing evidence that cytokines are involved in pathogenesis of Langerhans cell histiocytosis (LCH). The efficacy of interferon-alpha (IFN-α) therapy in LCH coincides with the expression and activation of the protein kinase C alpha signaling pathway in LCH histiocytes. Our report (Pediatr Hematol Oncol 2001) presented 3 patients with multisystem LCH who were treated with IFN-α as the maintenance therapy. All 3 patients belonged to high-risk group and 10 year after our first report they are still in remission (patient 1 - 19 years; patient 2 - 17 years; patient 3 -15 years.

Material and Methods: The purpose of our report is to present 5 more patients successfully treated with IFN-α; maintenance therapy after chemotherapy regiment.

Patients: BM 2-year old female with polypoid LCH tumor in external auditory meatus. With AIEOP-ICL 89 regiment achieved partial remission. IFN-α maintenance therapy proceeded for 1 year. Two years later local relapse occurred. With LCH III regiment for risk patients achieved partial remission. After 7 months IFN-α maintenance therapy complete remission was achieved. Follow up 10 year. FL diagnosis was performed in Germany at age of 1 year. He was treated with Vinblastine and had two relapses. At age of four after second relapse was admitted to our department. After treatment with AIEOP ICL 89 achieved a remission. IFN-α maintenance therapy for 1,5 year was performed. Follow up 10 year. JV six-month-old male with enlargement of inguinal lymph nodes. After chemotherapy with LCH III complete remission was achieved. Follow up 7 year. ZE 6-month-old female was admitted at intensive care unit in seriously damaged general condition, enormous enlargement of the liver and spleen, diffuse maculopapular rash and oedema of lower legs and feet. After LCH III risk regiment only partial remission was reached. IFN-α maintenance therapy 1 year proceeded and achieved a complete remission. Follow up 1 year. ÐT 4-year-old boy admitted after operation of skull tumor and pathhistologically approved LCH with multifocal bone lesions. LCH III protocol was performed and he did not reach the remission, even new bone lesions were found. After 5 months of IFN-α therapy partial remission achieved. He is still on every day IFN-α regimen.

Conclusion: IFN-α maintenance therapy after chemotherapy regiment may induce remission and prevent relapses of LCH. Prospective randomized studies are required to confirm this hypothesis.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #9

HISTIO NET – A REFERENCE NETWORK FOR THE CREATION OF ONLINE EXPERT SUPPORT FOR LCH AND ASSOCIATED SYNDROMES

Eva Schaefer¹, Itziar Astigarraga², Riccardo Haupt³, Milen Minkov⁴, Richard Price⁵, Jean Donadieu⁶

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BACKGROUND: According to the incidence, each year 1,400-2,500 children and adults in the European Union develop Langerhans cell histiocytosis (LCH) and associated syndromes. In several cases, patients have to wait many weeks, months or even years until diagnosis. Once confirmed, patients and treating physicians have to deal with histiocytosis, searching for scientifically approved information concerning adequate diagnosis, therapy and follow-up. The situation in many other countries worldwide is even far more difficult.

METHODs: 30 international partners have contributed to create a secure multilingual web portal for histiocytosis specialists, attending doctors, patients, and other people concerned with LCH and associated syndromes. This project called Euro-Histio-Net has received European funding.

RESULTS: The project partners are 20 international physicians with high experience in LCH and associated syndromes in their respective countries and 10 international patient associations for histiocytosis. Based on their experience, the established web portal “Histio Net” provides scientifically approved information about histiocytic diseases as well as about rare diseases in general. In combination with technical tools for online communication, the web portal is a “histiocypedia” as well as an operative instrument of exchange. The core elements are medical guidelines, lists of frequently asked questions, separate for patients and for professionals, maps of experts, contact forms for patients and contact forms for case presentations and requests of professionals. Due to a sophisticated language administration, the contents can easily be translated. At present, 13 languages in three different alphabets are available.

CONCLUSION: The Histio Net web portal is the first internet presence providing information about histiocytoses in many different languages. It is expected to support histiocytosis specialists in their daily work and to enable patients and treating physicians to easily find scientifically established information. It therefore will be an important contact point for everyone worldwide who is concerned by or interested in Langerhans cell histiocytosis and associated syndromes.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #10
HEPARANASE EXPRESSION IN LANGERHANS CELL HISTIOCYTOSIS – A PRELIMINARY STUDY

Tel-Aviv Sourasky Medical Center, Israel Sackler Medical School, Tel-Aviv University Rappoport institute of Medical Sciences, Thechnion, Haifa

Introduction: Heparanase is an endo-beta D-glucuronidase capable of cleaving heparan sulfate side chains, yielding heparan sulfate fragments. Heparanase activity has been correlated with the metastatic potential of tumor-derived cells that facilitate cell invasion as well as with angiogenesis, autoimmunity, and inflammation. Heparanase release by degranulation has been implicated in diapedesis and extravasation of a number of immune cells, including neutrophils, macrophages, and lymphocytes. It has also been shown that heparanase is a key enzyme in normal dendritic (and Langerhans) cell transmigration through the extra cellular matrix. Its role in dendritic cell derived pathologies i.e. LCH has not been previously studied.

Aims: Performing a preliminary study of heparanase expression in specimens obtained from LCH patients.

Materials and Methods: Heparanase was demonstrated by immunohistochemistry of paraffin embedded slides from LCH patients. LCH diagnosis was confirmed by morphology and immunohistochemistry for Langerin, CD1-a and S-100.

Results: 26 specimens from LCH patients were examined. 17 males,9 females. 9 had multifocal LCH disease, and 4 had multisystem disease. 22/26 patients had positive heparanase staining in LC, and 4 had non specific staining.

Conclusions: Heparanase is expressed in specimens from LCH patients. Recent evidence has linked LCH with BRAF mutations. A possible connection between BRAF mutations and heparanase has been recently documented and suggests that BRAF kinase activation plays an important role in regulating heparanase expression. Increased heparanase expression may contribute to the aggressive behavior of BRAF-mutated cancer. Further studies are required to clarify the role of heparanase in the pathogenesis of LCH.
SUCCESSFUL TREATMENT OF MALIGNANCY-ASSOCIATED HEMOPHAGOCYTIC SYNDROME (MAHS) WITH ABATACEPT (CTLA4-Ig) AND HIGH DOSE CORTICOSTEROIDS IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Lisa M. Reaves¹, Bernice Pasut¹, Michael B. Jordan², and Timothy P. Garrington¹

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INTRODUCTION: Secondary hemophagocytic lymphohistiocytosis (HLH) in association with malignancy is a rare and often fatal disease process. We describe the case of an 8 year old Hispanic male who developed malignancy-associated hemophagocytosis during ALL induction therapy, leading to a prolonged delay in his leukemia treatment. Treatment of the MAHS with a regimen including Abatacept and high-dose corticosteroids led to eventual resolution of the disease process.

CASE SUMMARY: The patient was diagnosed with precursor B-cell acute lymphoblastic leukemia and started on standard 3-drug induction therapy. No hemophagocytosis was noted on his diagnostic marrow. One week later, his marrow was hypocellular with 4% lymphoblasts and erythrophagocytosis. At the completion of induction, the marrow remained hypocellular with significant hemophagocytosis but no lymphoblasts and <0.1% minimal residual disease, indicating remission. Over subsequent weeks, he failed to recover counts sufficiently to resume therapy, and his marrow continued to show hemophagocytosis. Additional labs included a ferritin of 487 ng/mL and a triglyceride level of 170 mg/dL. EBV, CMV, and Varicella titers indicated past infection. EBV, HHV-6, and Parvovirus B19 PCRs were negative. Liver transaminases and bilirubin levels were normal. The patient was hypofibrinogenemic. Perforin and granzyme B expression was normal to increased. NK cell activity was not measurable due to the patient’s low absolute lymphocyte count. No genetic testing for HLH was done. After 3 weeks, despite failure of count recovery, consolidation therapy was initiated, in hopes of treating the underlying cause for his hemophagocytosis. He remained pancytopenic and became red blood cell and platelet transfusion dependent. Two weeks later, he was begun on treatment for HLH with Dexamethasone and Etoposide according to HLH 94, with little clinical response. A follow-up ferritin level was 6739 ng/mL. An IL-2 receptor level was 1280 U/mL (reference range: <970). With continued failure to show a clinical response after 4 weeks, he was treated with a 3-day burst of methylprednisolone (10 mg/kg/day), along with Abatacept (CTLA4-Ig) 20 mg/kg IV weekly. Following the methylprednisolone burst, he resumed treatment with Dexamethasone 10 m/m2/day. His marrow continued to show hemophagocytosis, but his clinical parameters improved, and he resumed treatment for his leukemia two months following initiation of treatment with Abatacept. The Abatacept was continued at a dose of 20 mg/kg weekly for a year, then tapered until discontinuation after 22 months total therapy. The Dexamethasone was tapered over another 7 months. His ferritin level remained highly elevated for a year following initiation of treatment with Abatacept, then gradually dropped toward the normal range. He completed treatment for his leukemia and is now thriving 15 months off therapy.

CONCLUSIONS: This case indicates a potential role for Abatacept combined with high dose steroids to treat MAHS.
ON THE CONTRIBUTION OF C77G POLYMORPHISM IN EXON 4 OF CD45 GENE TO HLH

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Introduction: Single nucleotide polymorphisms play an important role in the determination of individual susceptibility and severity of human diseases. CD45 protein is a tyrosine-phosphatase expressed on the surface of all human leukocytes with multiple isoforms generated by alternative splicing of the exons 4 (also named A), 5 (B) or 6 (C). A point mutation in the exon 4, C to G transversion at position 77 (C77G) results in aberrantly high inclusion of exon 4 with abnormal coexpression of CD45RA and CD45RO isoforms on memory T-cells, which might contribute to a hyperactive immune system. C77G allelic frequency varies from <0.16 to 6.7% in healthy individuals depending on the ethnic background. Hemophagocytic lymphohistiocytosis (HLH) has been described in several C77G patients, but functional citotoxicity assays are lacking in such reports.

Aim: To study the impact of C77G on lymphocytotoxic function.

Patients and methods: A male patient aged 67 years with an indolent LGL/NK lymphocytosis and a 48 year-old woman with IgG mild hypogammaglobulinemia were identified as possible C77G carriers by flow cytometry (BD Bioscience). Detection of C77G polymorphism was performed by PCR with primers on either site of the mutation within exon 4 and further direct sequencing with the same primers. NK cytotoxic function was evaluated by a standard Cr 51 release assay.

Results: CD45RA and RO isoforms showed a variant pattern of surface coexpression with absence of single CD45RO lymphocytes that correlated with C77G genotype. Intracytoplasmic perforin expression was normal. Peripheral blood mononuclear cells of both patients were able to kill target K562 cells as tested in different effector to target cells ratios when compared to healthy control samples.

Conclusions and discussion: C77G individuals do not show impaired NK cytotoxic activity; the contribution of this human polymorphism to the development of HLH could be looked further into a defective attenuation of T cell activity for the termination of the immune responses.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #13

DEFECTIVE NK GRANULE EXOCYTOSIS CORRELATES TO FHL3 IN PATIENTS RECRUITED THROUGH THE HLH-2004 PROTOCOL

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Introduction: Recognition of inherited defects in the granule exocytosis-dependent lymphocytotoxic pathway causing haemophagocytic lymphohistiocytosis (HLH) is needed for the final classification and therapy of the primary or familiar cases of this disease (FHL).

Aim: To standardize and validate a NK-cell degranulation assay as screening test for defects in FHL3, 4 and 5 causing genes, in a subgroup of patients included in the HLH-2004 therapy protocol.

Patients and Methods: 4 patients (Table), all of them fulfilled at least 5 HS diagnostic criteria and showed normal expression of perforin when studied.

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age at onset</th>
<th>Familial history</th>
<th>Consanguinity</th>
<th>NK cytotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 mo</td>
<td>No</td>
<td>Yes</td>
<td>Deficient</td>
</tr>
<tr>
<td>2</td>
<td>2.5 mo</td>
<td>Yes</td>
<td>Yes</td>
<td>n.t.</td>
</tr>
<tr>
<td>3</td>
<td>15 days</td>
<td>Yes</td>
<td>No</td>
<td>Deficient</td>
</tr>
<tr>
<td>4</td>
<td>2 mo</td>
<td>No</td>
<td>Yes</td>
<td>n.t.</td>
</tr>
</tbody>
</table>

Limitations in the number and/or viability of their NK peripheral lymphocytes prompted us to assess NK degranulation instead of cytotoxic activity in two out of the four samples. Peripheral blood mononuclear cells (PBMCs) were cultured overnight with or without IL-2 and then cocultured with K562 cells. CD107a expression was analysed within CD56+CD3- PBMCs. PRF1, UNC13D and STXBP2 genes were amplified by PCR from genomic DNA and analysed by direct sequencing.

Results:

<table>
<thead>
<tr>
<th>Pt.</th>
<th>CD107a expression</th>
<th>STXBP2 gene</th>
<th>UNC13D gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Defective</td>
<td>n.t.</td>
<td>Hom. deletion of 12 bp (c.del1828_1839) in exon 20</td>
</tr>
<tr>
<td>2</td>
<td>n.t.</td>
<td>n.t.</td>
<td>Het c.1208T&gt;C in exon 14 and c.2346-49delGGAG in exon 24.</td>
</tr>
<tr>
<td>3</td>
<td>Defective</td>
<td>wild type</td>
<td>Het c.766C&gt;T in exon 10 and c.2710 (-2) A&gt;G splice site exon 29.</td>
</tr>
<tr>
<td>4</td>
<td>Defective</td>
<td>wild type</td>
<td>Hom. c.1055(+1) G&gt;A splice donor site exon 12</td>
</tr>
</tbody>
</table>

Conclusions and discussion: We have observed an excellent correlation of defective CD107a expression with genetic defects affecting granule exocytosis that confirms this assay as a very sensitive and useful tool for FHL diagnosis. These defects have been found in very young infants (neonatal diagnosis or < 3 months of age) and are restricted to mutations in UNC13D gene in our patients. The high frequency of splicing mutations has been previously described in larger series of patients.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #14

EXPRESSION OF COX-2 IN LANGERHANS CELL HISTIOCYTOSIS

Michael Henry, Paul Dickman
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Background: Current treatment modalities of Langerhans cell histiocytosis (LCH) most often include surgical excision and curettage and/or low-intensity chemotherapy using prednisone and vinblastine, both of which can be regarded as medications aimed at decreasing inflammation. Medications that inhibit the inflammatory pathway involving cyclo-oxygenase (COX-2), such as celecoxib, are commercially available to treat pain and inflammation as a result of various musculoskeletal disorders. Celecoxib also has been used as anti-tumor therapy for a variety of neoplasms. This anti-tumor effect is thought to be exerted through its inhibitory action on COX-2, which possibly mediates angiogenesis and tumor growth. Prior studies have suggested a role of prostaglandins and thromboxane (mediators of inflammation) in the pathogenesis of histiocytic disorders. After a thorough review of the literature, there is only one report to date that demonstrated the expression of COX-2 in osteolytic lesions of LCH, although there was no attempted correlation of the degree of COX-2 expression with the extent of LCH lesions, measurable patient inflammatory parameters, or response to treatment. The present study seeks to correlate these specific parameters to the degree of COX-2 expression in LCH lesions.

Methods: Immunohistochemistry for COX-2 was performed on paraffin-embedded tissue specimens of lesions already excised from patients and diagnosed as LCH. Extent of COX-2 immunohistochemical expression was evaluated and correlated with disease site, patient outcome, and the results of available serum inflammatory markers performed on the patient at the time of diagnosis. Recent non-steroidal inflammatory drug (NSAID) use also was recorded. Chart review was performed to obtain the described information.

Results: Information relating to disease site, patient outcome, and the results of available serum inflammatory markers performed on the patient at the time of diagnosis was correlated with the degree of COX-2 immunostaining of the LCH tissue samples. The sample size, which was derived from the available number of patients in our institutional database, was 40 patients. Three patients experienced recurrent disease (mean time to recurrence = 18.3 months), although none of the recurrences were in “CNS risk” patients. All specimens expressed COX-2 to any extent, and 37/40 specimens (93%) expressed grade 2 or higher (grades 0 – 3 possible). There was no definite correlation between degree of COX-2 expression, outcome, level of inflammatory markers, or prior NSAID use.

Conclusion: COX-2 is expressed to a similar extent in LCH, regardless of the tumor site or presence of inflammatory markers. This is the first known study looking at COX-2 expression in multiple LCH patients. Though the sample size was small, these findings support the use of COX-2 inhibitors in future clinical trials aimed at impeding COX-2 mediated pathways leading to tumorigenesis in LCH.
HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN THE NATIVE AMERICAN POPULATION – EXPERIENCE AT PHOENIX CHILDREN’S HOSPITAL

Michael Henry
Phoenix Children’s Hospital

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a primary dysregulation of immunity that results in multiple organ failure and death in a large number of cases. HLH can present as an acquired or as a familial condition, and it can affect any race. Native Americans have a distinctly different genetic composition than other races. Little is known about the clinical presentation and disease course of HLH in the Native American population. This case review aims to describe the clinical presentation and disease course of Native American patients with HLH that were treated at Phoenix Children’s Hospital.

Methods: A retrospective case review was made of all patients diagnosed with HLH and treated at Phoenix Children’s Hospital between the years 2004 – 2011. Three male Native American patients were identified. Two patients were from the Apache Tribe, and one patient was from the Salt River Indian Community. Mean age at disease onset: 1.6 years (1.3 – 1.9). All three patients presented with pancytopenia and multiple organ failure. One of the patients had CNS disease.

Results: Mean WBC: 0.8 L/µl (0.3 – 1.7); Hgb: 8.0 gm/dl (6.9 – 9.5); platelets: 15 K/µl (9 – 20); fibrinogen: 235 mg/dl (163 – 310); ferritin: 42871 ng/dl (33663 – 60680); triglycerides: 312 mg/dl (183 – 425); sIL2r: 11392 U/L (10692 – 12779); AST: 1023 U/L (307 – 2157); ALT: 524 U/L (112 – 1336). Two patients had EBV-associated HLH with 4.7 x 107 copies/ml and 8920 copies/ml by PCR. No inciting agent was determined in the third patient. Natural killer cell function was absent in one patient, normal in another patient, and not performed in the third patient due to insufficient cells. None of the patients had mutations in perforin, syntaxin, MUNC 13-4, BIRC4, or SH2DIA. Two of the patients did not have mutations in Rab27a or ITK, and one of the patients presented before these tests were available. All three patients were treated according to a modified version of HLH-2004. The patient with CNS disease received four doses of intrathecal therapy with resolution of the CSF abnormalities. The patients with EBV-associated disease received one dose of rituximab each with elimination of serum EBV. All three patients experienced disease resolution after eight weeks of therapy. Two of the patients are still alive and well, but one of the EBV-associated HLH patients experienced recurrence of clinical HLH three weeks after discontinuation of initial therapy. He subsequently underwent a matched, unrelated, reduced-intensity bone marrow transplant, and he is now disease-free.

Conclusion: Native Americans with HLH demonstrate similar disease characteristics and disease course to other previously-described ethnic groups. More detailed investigations are needed to further describe the causes and the course of HLH in this unique subpopulation.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #16
ETOPOSIDE IN PATIENTS WITH RHEUMA-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (Rh-HLH)

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Introduction: Rheuma-associated hemophagocytic lymphohistiocytosis (Rh-HLH), also called macrophage activation syndrome (MAS), is a severe complication of systemic inflammatory disorders. It may occur spontaneously, as a complication of active underlying disease, or it may be triggered by an infection or a change in therapy. Rh-HLH has several clinical and laboratory similarities to other forms of HLH, and is potentially life threatening. Treatment of Rh-HLH has not been standardized yet, but it commonly includes a variety of agents such as high-dose corticosteroids, cyclosporine, intravenous immunoglobulin and, in severe cases, sometimes etoposide. Here we report on the experience of etoposide in two children with severe Rh-HLH admitted to the Karolinska Children’s Hospital over the 6 months July 2010 to Dec 2010.

Patients and Methods: 1) A 16-yr previously healthy boy with a 4-mo history of systemic lupus erythematosus (SLE) was referred from the local hospital because of accelerating inflammatory disease. Examination revealed pronounced muscular weakness, lupus-like erythema, nephritis, and moderate pericarditis. Initial laboratory evaluation revealed Hb 99 g/L, platelets 137 x10^9/L, WBC 1.6 x10^9/L, ESR 24 mm/hr, CRP 2 mg/L, albumin 27 g/L, AST 66 U/L, ALT 55 U/L, LD 1650 U/L, triglycerides 3.1 mmol/L, fibrinogen 2.3 g/L, creatinine 85 microg/L, ferritin 20778 microg/L, and sCD25 2172 U/ml. Antinuclear antibodies were negative, while SS-A and SS-B were positive. He was initially administered methyl-prednisolone (MP) pulses for 3 days followed by prednisolone 90 mg daily. While laboratory values improved, his CNS became increasingly affected and because of CNS-SLE, confirmed by MRI, and diagnostic criteria consistent with MAS, complementary treatment with etoposide 75 mg/m2 weekly was administered for a month. His CNS symptoms rapidly improved, he recovered fully and a subsequent MRI was normal. 2) A 9-yr old girl with systemic juvenile idiopathic arthritis (JIA) on treatment with tocilizumab and oral methotrexate was infected with EBV. She developed fulminant HLH with fever, splenomegaly, Hb 112 g/L, platelets 24 x10^9/L, WBC 9.6 x10^9/L, CRP 294 mg/L, albumin 23 g/L, AST 766 U/L, ALT 18 U/L, LD 6408 U/L, triglycerides 4.4 mmol/L, fibrinogen 0.7 g/L, creatinine 86 microg/L, ferritin 90839 microg/L, and sCD25 >7500 U/ml, and she was disoriented. The HLH-2004 criteria were fulfilled. She was initially administered MP-pulses. However, within 24 hours her cerebral function deteriorated further, and therapy was intensified with etoposide 100 mg/m2 (a total of 8 courses), rituximab 375 mg/m2 and dexamethasone. She also developed seizures and an abnormal MRI. She recovered fully, and a subsequent MRI was normal.

Summary: Two children with Rh-HLH and CNS affection both responded well and without severe side effects to weekly etoposide 75-100 mg/m2 as a complement to high-dose MP pulses.

Conclusion: Etoposide is worth considering in severe Rh-HLH.
Poster Presentation #17

THYMIC LANGERHANS CELL HISTIOCYTOSIS: A NEGLECTED PRESENTATION OF AN ORPHAN DISEASE?

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Introduction: Involvement of the thymus in Langerhans cell histiocytosis (LCH) was already documented in the original Letterer’s report. Half a century later Hamoudi et al. reported on prominent affection of the thymus at autopsy performed on 27/32 patients. In general, infants and toddlers are more severely affected by LCH than older patients. These facts raise the questions whether the disease severity parallels the level of maturity of the thymus and whether the thymus could play a role in the pathogenesis of LCH. Surprisingly, thymic involvement (TI) is rarely described in recent literature. We performed an exploratory retrospective study based on a large patient cohort.

Materials and methods: The database of the GPOH LCH Study Group containing 1348 patients (388 patients with multisystem LCH) registered onto the LCH I-III studies was screened for reported TI. The clinical characteristics and the course of LCH in patients with TI were studied by means of the descriptive statistics.

Summary: Thirteen patients (1% of the total cohort, 3% of the multisystem LCH), 7 males and 6 females, median age at diagnosis 7 months (7 days - 14 years), median observation time 4.5 years (2 months – 15 years) were encountered. Twelve had multisystem disease and 1 had isolated cutaneous LCH at initial presentation. In 11 patients thymic involvement was diagnosed at initial disease evaluation. In two cases it was diagnosed later (3 months and 14 months after LCH diagnosis) in the setting of disease progression. Eight patients (62%) had involvement of at least one risk organ. Two patients had severe progressive disease and were salvaged by stem cell transplantation. Most of the patients (6/13) responded to initial therapy. All patients survived but 9 of them (69%) experienced single or multiple reactivations during follow-up. Huge thymic mass causing compression of the airways led in one patient to complications during general anesthesia including neurological deficits and a tracheostomy for 3 years. Our analysis suggests that TI is an infrequent presentation in a rare disease. This is contradictory to earlier autopsy findings and appears to underestimate TI prevalence. The current international LCH guidelines for patient evaluation do not require specific imaging of the thymus. Hence, TI in young children can be easily either overlooked or misdiagnosed as thymic hyperplasia. Unrecognized TI can have fatal consequences in individual cases. Whether TI has an influence on the course of multisystem LCH has to be studied in a prospective study with appropriate imaging.

Conclusion: Imaging of the thymus by sonography should be included in the initial evaluation of young patients with LCH.
Poster Presentation #18

INCIDENCE AND CLINICAL FEATURES OF HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN UK AND IRELAND

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Introduction: Haemophagocytic lymphohistiocytosis (HLH) remains poorly understood by the majority of clinicians. We present the results of the first national survey of HLH in the United Kingdom (UK) and Ireland, using a prospective validated method of case ascertainment, the British Paediatric Surveillance Unit (BPSU). This study aimed to obtain epidemiological data, raise awareness of the condition, and assess treatment and outcome.

Methods: The BPSU provides an active case reporting system, which surveys rare childhood conditions. Orange cards are sent monthly with a selection of reportable disorders to over 1100 paediatricians throughout the UK and Ireland. Average response rate was 90%, and reported cases were followed-up according to study protocols.

Case ascertainment for 3 years from 1991 of all newly diagnosed cases of HLH aged 0-16 years in the UK and Ireland was undertaken using the 1991 Histiocyte Society diagnostic criteria.

Results: 36 cases were identified; incidence rate was 0.1/100,100 for 0-16 year-old children, sex ratio (M:F) was 2:1 and median age at diagnosis of 22 months. 24 (68%) were Caucasian, 8 Indian, Pakistani and Bangladeshi, 2 other, 1 black African and the ethnicity of 1 was unreported. 7 (19%) children were the product of a consanguineous relationship.

Length of time from presentation to diagnosis was a median of 0.5 months (range 0-12.6 months). The majority of children had hepatomegaly (72%), bruising or bleeding (61%), fever (61%) and splenomegaly (58%) at diagnosis. Phagocytosis was positively reported on the films of 6 (17%) children, negatively for 3 children, and not reported for 22.

Treatments were under-reported with a range of combinations. Most common first line treatments were etoposide (22%) and methylprednisolone (11%). Etoposide was most common second line therapy (14%).

One child received a fully myeloablative stem cell transplantation but died 2 months post transplantation. Another was awaiting transplantation, 17 were not transplanted during the study and the status of a further 17 was unknown. During the 3-year period studied, 7 children were reported alive, a further 4 reported to be in complete remission, 22 (61%) had died, and outcome of 3 was not reported. Time from diagnosis to death was a median of 1.0 month.

Conclusions: Incidence was lower than expected, probably due to complexity of the reporting definition and unfamiliarity. Since collection of this data, recognition has increased with better understanding of the underlying genetic mutations. Therapy with immuno-suppressive and cytostatic drugs, followed by stem cell transplantation in genetic cases, has changed prognosis from uniformly fatal to a cure rate of more than 50%. In view of revised diagnostic criteria, therapeutic guidelines and identification of genetic abnormalities, we propose to repeat this study. In addition, we aim to continue to improve early recognition and understanding of this potentially fatal condition.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #19

BISPHOSPHONATE THERAPY FOR LANGERHANS CELL HISTIOCYTOSIS OF BONE

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Bisphosphonate are synthetic analogs of inorganic pyrophosphate, which are not only potent inhibitors of osteoclast-mediated bone resorption, but also present an important inhibitory activity of angiogenesis. Bisphosphonates become, the standard of care in the management of patients with osteoporoses as well as bone metabolism alterations associated with neoplasias. The goal of therapy in Langerhans cell histiocytosis (LCH) is to decrease the activity and proliferation of histiocytes, lymphocytes and macrophages that cause the disease. Patients with disease that is localized to skin, bone and lymph node (defined as "nonrisk" organs) generally have a good prognosis and require minimal treatment. Here we present our experience using Aredia for the treatment of single and multi Langerhans cell histiocytosis of the bone.

The first patient was a 23 year old Bedouin male who presented with a painful left hip and limping. A single lesion of the left acetabulum.

LCH protocol using Vinblastine, Prednisone and 6-mercaptopurine had little effect and therefore the patient was started on 4 time once monthly infusions of Aredia (Pamidronate), 1mg/Kg. The patient has remained in remission from the past 19 months.

The second patient was a 13 year old male whose lesion was found at C5. The biopsy report showed a lesion at CDla+ and unifocal bone LCH was diagnosed. Bone scan showed a new lesion at T3. It was decided to treat him with four monthly doses of Aredia. The patient remained in remission for two years.

The third case is a 3 year old female. After a 3.5cm mass was discovered by CT exploratory surgery was conducted revealing destruction of the bone revealed multiple bone lesions of the spine, ribs and skull. LCH was diagnosed. Vinblastine, Prednisone, and 6_MP was given with minimal response...Methotrexate was added with no additional improvement, Aredia was started. She remained in remission for 6 months, and relapsed (the longest time she had maintained any sort of remission).

In conclusion: Bisphosphonate has activity in Cell Histiocytosis of bone. We need additional multisentrical studies in order to improve this concept and may be the part of chemotherapy protocol. We have had relatively good success and minimal side effects, with Nitrogen-Bisphonate in the treatment of single or multifocal Langerhans cell histiocytosis of the bone.
Poster Presentation #20

STUDIES ON IMMUNE CELLS AND INFLAMMATORY MARKERS IN CHILDREN WITH LANGERHANS CELL HISTIOCYTOSIS

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Introduction: Langerhans cell histiocytosis (LCH) is characterized by the abnormal distribution and accumulation of dendritic cells (DCs) in tissues, followed by granuloma formation and frequently also functional sequelae. Previously, our group proposed important inflammatory components as part of the disease mechanism and moreover reported that monocyte derived DCs (moDCs) from LCH patients spontaneously synthesize the inflammatory cytokine interleukin (IL)-17A, which leads to fusion of DCs and formation of multinucleated giant cells. We want to evaluate possible causes of LCH in children by studies on immune cells and various inflammatory markers in the blood.

Methods: Trucount stainings and flow cytometry were used to define the profile of cells in freshly isolated blood samples from LCH patients and healthy donors. Subsequently, the blood was subjected to Ficoll separation in order to retrieve the serum and the peripheral blood mononuclear cells (PBMCs). The levels of IL-17A in the serum were measured with ELISA assays, while a fraction of the PBMCs was intracellularly stained for IL-17A. The remaining PBMCs were enriched for CD14+ monocytes, which were left to differentiate to moDCs. moDCs were then stimulated with Toll-like receptor ligands (TLR-L) in order to mature.

Results: So far, we have successfully established a whole blood trucount staining for monocytes/DCs and lymphocytes. Differences in the profile of cells in the blood of LCH patients were noted and new IL-17A producing cell populations were identified. LCH patients with severe Central Nervous System (CNS) involvement had very high IL-17A amounts in their serum, while most patients exhibited low or moderate levels of expression. Furthermore, the levels of secretion of IL-17A during the in vitro differentiation of monocytes to moDCs were generally low, but in some cases increased with maturation.

In conclusion, IL-17A is produced by several types of blood cells and increased IL-17A expression is mainly observed in CNS-LCH patients. Analysis of more samples will help us define the profile of cells in the blood of LCH patients and this could be a valuable tool to monitor the disease and improve treatment.
ABSTRACTS: POSTER VIEWING ROUND

Poster Presentation #21

CENTRAL NERVOUS SYSTEM INVOLVEMENT IN HLH-CASE SERIES FROM POLISH PEDIATRIC HEMATOLOGY CENTERS

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INTRODUCTION: Hemophagocytic lymphohistiocytosis (HLH) is characterized typically by hepatosplenomegaly, fever, cytopenias, neurologic symptoms and blood coagulation disorders. Central nervous system (CNS) involvement at diagnosis has been reported in 10 to 73% of patients with HLH. It includes meningitis with spinal fluid abnormalities or neurological symptoms resulting from meningoencephalitis that can cause severe permanent neurological sequels.

AIM: We assessed the neurological manifestations in 12 patients with HLH treated in pediatric hematology centers in Poland between 2008-2011.

CASES: Seven out of 12 patients (58%) were diagnosed with CNS involvement at time of diagnosis of HLH. Six patients had abnormalities in CSF including pleocytosis and increased protein concentration, 1 patient had isolated abnormalities on MRI. Two additional patients, who did not present initially with CNS involvement developed CNS disease during first few weeks after diagnosis. One of them developed severe parenchymal changes without CSF abnormalities.

Clinical presentation of CNS involvement included seizure, developmental delay, lost of cognitive functions, changes in behavior (aggressiveness, sleep disturbances).

Finally 9 (75%) patients had CNS involvement. Systemic and/or intrathecal therapies lead to resolution/improvement of CNS disease in 7 of them. In 1 patient despite the meeting the resolution criteria at week 8, the reactivation of the disease was diagnosed based on the development of new CNS symptoms and neuroradiological progression. The patient received Dexamethasone and IVIG and is under evaluation.

One patient with CNS involvement died on week 1 of initial therapy. Systemic and intrathecal therapy according to protocol HLH 2004 reduced the activity of CNS disease in 7 of 9 children with neurological manifestation of HLH.

CONCLUSION: There is a dilemma how to treat patients with HLH and deep parenchymal brain disease who do not respond to initial combined therapy. Published data indicates that bone marrow transplant is not likely to be successful in a setting of active CNS disease.
Poster Presentation #22

BRAF V600E MUTATIONS IN CHILDREN WITH LANGERHANS CELL HISTIOCYTOSIS

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Introduction: The etiology and pathogenesis of LCH have remained a topic of intensive research and discussion for decades. Recent evidence suggests that activating mutation BRAF V600E, a classic molecular event in a number of common cancers, might take part in the pathogenesis of LCH (Badalian-Very, Blood, 2010). The aim of the current study was to validate these results in an independent group of LCH patients.

Materials and methods: Archived biopsy specimens of children with LCH were collected. The diagnosis was confirmed by CD1a detection. Genomic DNA was extracted from macrodissected paraffin blocks. BRAF V600E detection was based on Real-time PCR with TaqMan fluorescent probe and direct sequencing. Overall 37 specimens from different clinics were available for analysis, clinical information was available for 30 patients. Eleven patients had multi-system disease with risk-organ involvement (MSRO+), 6 - multi-system disease without risk-organ involvement (MSRO-), 13 – single-system (SS). Median age at onset was 21 months (0-153).

Results: BRAF V600E mutation was detected in 9 (24%) specimens (7 by fluorescent probe, 9 by direct sequencing). Clinical characteristics of BRAF V600E-positive patients were as follows: age at disease onset – 28 months; SS disease - 2 (22%), MSRO+ – 4(44%), MSRO- - 3(33%). No statistically significant difference was detected between BRAF V600E +ve and –ve patients in terms of age, disease extent and organ involvement. The proportion of LCH cells in the diagnostic specimen and intensity of fluorescence did not correlate significantly.

Conclusion: The study suggests that BRAF V600E mutation can be detected in diagnostic specimens roughly in a quarter of LCH patients with low-sensitivity methods. The role of this molecular lesion in the pathogenesis of LCH and potential diagnostic and therapeutic applications remain to be established.
MULTIFOCAL LCH IN ADULT PATIENTS TREATED WITH SPECIAL C REGIMEN OF JLSG-02 PROTOCOL

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Background: LCH develops mostly in infancy to early childhood, however, about one third of LCH are adult onset. Besides smoking-related solitary pulmonary LCH, multifocal LCH occurring in adulthood needs more attention and effective treatment. A major obstacle to treat adult patients is that they are reluctant to have a leave of absence from their jobs for treatment, which often limits providing sufficient chemotherapy. Considering such adult-specific situation, JLSG planned Special C protocol available at the ambulatory basis for the treatment of multifocal LCH in adult patients.

Patients and Methods: 13 patients at age of median 29 (range; 16 to 69) yrs. with M/F=9/4 were enrolled, who had not received any previous cytoreductive agents for LCH. Three had multi-focal lesions but in single-system (SS) disease (skin 1, multi bones 2) while ten had multi-system (MS) disease, of which 5 had diabetes insipidus and one neurodegenerative disease already at the initiation of the treatment. Age at starting the treatment was median 40 (range; 20 to 70) yrs. All patients were treated with Special C regimen, consisting of VBL/PSL and MTX alternately every two weeks with daily 6-MP for 36 weeks. Time of the onset to treatment was median 2.3 (range; 0.1 to 32.7) years. Four had the history of malignant disease (T-LBL, renal cancer, DLBCL and uterine cervical cancer, respectively).

Results: At the end of the treatment, three SS patients attained no active disease, while 6 of the ten MS patients had response (no active disease in 3 and partial response in 3), two had no response, one had progressive disease and one died of bleeding during the treatment. At the follow-up of median 38 months, 10 of 13 patients are alive (8 without active disease and 2 with active disease). Of the 3 deceased, two died of infections in the course of subsequent salvage therapy. No adverse event which made it difficult to continue the C regimen was observed except for one bleeding death.

Conclusion: Effective treatment of adult patients with multifocal LCH was achievable on the ambulatory basis with our C regimen. It was shown to be effective for patients with all SS disease as well as half of MS disease, with acceptable adverse event. However, care is required for bleeding and infection.
Gene Expression Profiling of PTPN6 (SHP-1) Transfected Langerhans Cell-Like Cell Line (ELD-1) Compared with Open Data of LCH Subtype (GSE16395)

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Introduction: Langerhans cell histiocytosis (LCH) is a Langerhans cell-like cell proliferative disorder that encompasses two entities: LCH-SS (single-system LCH) and LCH-MS (multisystem LCH). From the point of therapy, LCH-SS cases are mostly controllable without chemotherapy; however, LCH-MS cases are not. Abnormalities in signal transduction pathways such as IL-17A-dependent pathway or BRAF mutation may be related to the severity of the disease. PTPN6 (SHP1) is a non-membranous protein tyrosine phosphatase that plays an important role in several signal transduction pathways. Down-regulation of SHP-1 has been reported for hematopoietic neoplasm such as lymphoma and leukemia, by contrast SHP-1 is over-expressed in epithelial tumor such as ovarian cancer. A higher level of expression of SHP-1 was previously shown in LCH-MS immunohistochemically (Murakami et al, Histiocyte Society Annual Meeting 2008) (Virchow Arch 2011, in press).

Materials and methods: In order to analyze the role of SHP-1 in development of LCH, a Langerhans cell-like cell line: ELD-1 (generously provided by Dr. Sanju Iwamoto) was transfected with SHP-1 gene. SHP-1 protein expression was confirmed by immunocytochemistry after G418 selection. Total RNAs of transfectedants were extracted and IVT (in vitro transcription) was done according to manufacturer's protocols. Total RNAs expressions of SHP-1 transfectant (S cell) were analyzed using GeneChip Human Gene 1.0 ST array (Affymetrix) compared with vacant vector transfectant (V cell). Analyses of the data were performed by Subio Platform software. Our data were compared with open LCH subclass data from the Gene Expression Omnibus web site (GSE16395).

Results: Analyses divided total RNAs into three groups such as increased level of expression, no change, and lower level of gene expression in S cells compared with that in V cells. Comparatively, open LCH subclass data (GSE16395) also provided three groups of expression profiles in LCH. Using Venn diagram in Subio platform software, several signal transduction pathways were delineated from both the SHP-1 transfectant and open data of LCH.

Conclusions: Higher expression level of SHP-1 was revealed in LCH-MS than in LCH-SS. By transfection of SHP-1 into a Langerhans cell-like cell line, ELD-1, several signal transduction pathways were delineated by expression array analysis. Expression profile obtained from the SHP-1 transfectant in comparison to open LCH data may assist to define the genomic features, which play an important role as the determinant(s) dividing LCH into LCH-SS and LCH-MS. (This work was partly supported by the Histiocytosis Association 2009 grant.)
Poster Presentation #25

MONITORING OF T-CELL RECEPTOR GENE REARRANGEMENT IN CHILDREN TREATED WITH HLH-2004 FOR EPSTEIN-BARR VIRUS-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Introduction: Epstein-Barr virus (EBV) infection is the most common trigger of secondary hemophagocytic lymphohistiocytosis (HLH) in children. Monoclonal proliferation of EBV-infected T cells and subsequent excessive cytokine release and activation of T cells/macrophages are responsible for the pathogenesis of EBV-HLH. Immunochemotherapy such as HLH-94/2004 protocol reduced recurrence and improved survival in EBV-HLH patients. However, markers capable of predicting therapeutic response are required to minimize the treatment intensity. Although TCR gene rearrangement can be detected in half of patients with EBV-HLH by Southern blotting or conventional PCR analyses, the clinical significance of T-cell clonality is obscure. In this study, sensitive BIOMED-2 multiplex PCR method in combination with GeneScan analysis was applied to detect the monoclonality of TCRβ; and/or TCRγ genes in children with EBV-HLH.

Materials and methods: The children with EBV-HLH who were treated with HLH-2004 protocol were eligible for the study. Rearrangements of TCRβ/γ genes and Viral load of EBV in PB were serially analyzed by BIOMED-2/GeneScan methods and quantitative PCR at onset, and 2, 4, and 8 weeks after the start of treatment.

Results: Total 36 patients with EBV-HLH were registered by December, 2010. EBV load at onset ranged from 3.3 x 102 to 2.2 x 106 (median, 1.5 x 105) copies in PB and 2.2 x 102 to 1.2 x 107 (median, 8.7 x 105) copies in serum. TCR clonality was detected in 21 of 34 patients at onset; rearrangement of TCRβ in 2, TCRγ in 10, and TCRβ/γ genes in 9. Interestingly, two with TCRγ rearrangement died of disease progression. However, close association between the presence of TCR rearrangement and prognosis in patients with EBV-HLH has not been clarified.

Conclusion: Presence and monitoring of T-cell clonality may be useful to predict therapeutic response in EBV-HLH.
STATISTICAL CHALLENGES IN THE DESIGN OF LCH-IV, STRATUM 1 FOR THE COMPARISON OF TWO DIFFERENT TREATMENT DURATIONS AIMING AT LONG-TERM OUTCOME

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The aim of this work is to describe statistical design issues of stratum 1 of the LCH-IV study. LCH-IV is an international randomised trial in children with the Langerhans cell histiocytosis (LCH). The intended design is 2x2 factorial, aiming to investigate 1) the role of the prolongation of therapy from 12 to 24 months and 2) the role of the addition of mercaptopurine to standard treatment on the long-term reactivation rate. A reduction of the long-term reactivation rate is the main aim of the study. Here, the comparison of two different treatment durations for the same treatment poses additional statistical challenges. When comparing identical treatments of different duration, then identical hazards are anticipated for the initial period. Furthermore, the prolongation of treatment duration may solely delay but not stop the occurrence of reactivations. Both result in time-dependent hazard ratios and Cox regression is inappropriate. In this situation, neither Cox-model nor log-rank test address the question of long-term outcome. Thus, for LCH-IV, mixture cure models are used to determine treatment differences. Without relying on the proportional hazards assumption, they explicitly allow to model the proportion of individuals who will not experience an event. As early differences in event rates may not necessarily translate in different long-term outcomes, early stopping is implemented in favour of the null-hypothesis only. Monte Carlo methods were used to evaluate the statistical power and interim-analysis. Appropriateness of Cox-regression and cure models are compared and discussed. Standard approaches are prone to misleadingly favour the arm with longer treatment duration. Cure models directly address the question of long-term outcome and correctly protect the type-I error rate. In the case of non-proportional hazards they can be more powerful. Apparently non-proportional hazard situations have to be addressed in the planning and design phase of a clinical trial. This includes, amongst others, the definition of the primary endpoint, statistical methods, power calculation and the implementation of interim-analyses. In summary, the use of cure models should be considered more often in the design of clinical trials.
PREGNANCY IN WOMEN WITH PULMONARY LANGERHANS CELL HISTIOCYTOSIS

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Pulmonary Langerhans cell histiocytosis (PLCH) is a rare disease in smoking women in child bearing age. In the course of the disease some patients require steroid treatment or chemotherapy but in other only cessation of smoking induce the regression of the disease.

In a period from 2000 to 2011, 29 women in age 15 to 69 years with PLCH have been observed in our Department.

The median follow-up period was 65 months (range 10 to 120 months). All patients were smokers. During that time 5 women were pregnant, one of them 2 times. One patient was pregnant in the time of diagnosis, two in the time of low doses of steroid treatment, one just after one year of the chemotherapy and one patient without any specific therapy. There was no significant problem in the time of pregnancy.

Four patients delivered on time, 5 healthy children (now they in age 9, 6, 3 years and 31 and 3 months). Spontaneous abortion in the 12th week of pregnancy was noticed in one patient without any treatment.

Conclusions: There was no significant complication of pregnancy and delivery in patients with PLCH.

Cesarean section is the preferable route of delivery.
HISTIOCYTIC SARCOMA. TWO CASES: SAME DIAGNOSIS, DIFFERENT RESPONSE TO THERAPY

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The rarity of histiocytic sarcoma (HS) continues to make its treatment challenging.

Objective: To describe clinical features and response to therapy of two patients with HS.

Case 1: A 9 year-old girl experienced cervical pain radiating to the right arm for two months. At the admission the girl had paralysis of the extremities without sensory loss. With the exception of motor involvement, physical examination and laboratory tests were not relevant. An MRI showed rectified cervical spine, a prevertebral soft tissue mass (6.7 x 6 x 3.4 cm) extended to the anterior epidural space compressing spinal cord at the C4/C5 level. These findings were evaluated by FDG-PET-CT scan. The mass was partially excised and the histology and immunohistochemistry revealed an HS. She started chemotherapy with CHOP-VP (cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide). After the first cycle of CHOP-VP, she began to move the upper limb and after completing six cycles she recovered from the paralysis completely. The final image evaluations are pending to be done.

Case 2: A 14 year-old boy presented with a huge right cervical mass (>10cm). The two biopsies performed confirmed the HS diagnosis. A FDG-PET showed high activity of the tumor. There had been marginal response to two cycles of cladribine (5 mg/m2 x 5 days each). Two cycles of CHOP-VP did not show effectiveness, on the contrary, progression could be noticed by a PET-CT (images in the abdomen and CNS). Then he received two courses CC (dexamethasone, cytarabine, etoposide) of the NHL-BFM group strategy. A scarce response was measured by PET-CT scan. Daily thalidomide was prescribed. The high dose metrotexate (5g/m2 in 24hs) was infusion did not show a favorable response. Now the patient is evaluating for localized radiation therapy.

Conclusion/comment: Therapy option for HS remains undefined. Multicenter international protocols must be established.
EXTRANODAL ROSAI DORFMAN DISEASE. FOUR PATIENTS: DIFFERENT TREATMENTS, DIFFERENT OUTCOMES

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Background. Rosai Dorfman Disease (RDD) is usually characterized by a persistent massive enlargement of the cervical lymph nodes and an inflammatory syndrome. Fewer than 10% of patients present with other than bilateral cervical lymphadenomegaly at diagnosis.

Aims. To present the different outcomes of four patients with RDD with extranodal involvement at diagnosis who received different therapeutic strategies.

Results. Patient 1. A 5 year-old boy presented 5 months before diagnosis with inflammatory bilateral cervical nodes involvement. Two months later he showed nasal obstruction and epistaxis. CT scan showed bilateral cervical adenopathy and an intranasal tumor. The MRI showed a nodular image in the antero-superior part of the nasal cavity with involvement of the ethmoidal cells. Exirpation of the nasal polyp was performed and histology revealed RDD. The treatment was prednisone and indomethacin with no evidence of active disease (NAD) after 5 years of follow-up (FU).

Patient 2. A 13 year-old boy presented 3 months before diagnosis with nasal obstruction, headaches and deficit of the visual acuity in the right eye with ipsilateral proptosis. MRI showed a mass involving the sella, right cavernous sinus, right medial and anterior fossa, ethmoid cells, nasal cavities, bilateral maxillary sinus and right orbit. Partial resection was performed and histology revealed RDD. Several treatments (dexamethasone, vinblastine, indomethacin and 6MP) were successively given without any response (FU: 2 years).

Patient 3. A 2 year-old boy presented with exophtalmos and a painless loss of motion. Skull CT scan showed an orbital mass and another one involving the maxilla, sphenoid sinus and the nasal cavity with bone destruction. The thoracic CT scan showed a node in the upper right lobe. In the CNS, 2 nodes were found in the frontal and the parietal-temporal lobes. The bone scan showed multiple lytic lesions. A biopsy of the orbit was performed and histology revealed RDD. Multiple episodes of progressive disease occurred, with bone, orbit, lymph nodes, parotid, skin (psoriasis), hematopoietic, renal (nephrotic syndrome) and lung involvement. The patient never achieved a complete response to different treatments (prednisone, 6MP, MTX, vinblastine, dexamethasone, etoposide, naproxene and cytarabine) (FU: 12 years).

Patient 4. A 7 year old boy presented with abdominal pain and diarrhea 3 months before diagnosis. Imaging studies showed a solid lesion in the right kidney. The evaluation did not show another organ involved. Complete tumor resection was performed and histology revealed RDD. The patient has NAD after 1.5 years of FU.

Conclusions. The 4 patients with RDD had an unusual disease presentation at diagnosis. They were treated with different strategies, with different responses and different outcomes. International collaborative studies need to be done to improve the understanding of the unpredictable response to treatment and outcome of this disease.
EXTRASKELETAL SOFT TISSUE INVOLVEMENT WITH LANGERHANS CELL HISTIOCYTOSIS (LCH): REPORT OF 3 PEDIATRIC CASES


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Introduction: In LCH, soft tissue mass not associated with bone lesions, i.e. extraskeletal soft tissue involvement is thought to be rare, but if these lesions occur, they may grow aggressively and invade into the adjacent organs. We describe 3 pediatric cases with such an unusual clinical presentation, which showed a dramatic response to chemotherapy.

Case reports: In our 109 cases of childhood LCH from 1965 to 2011, treated at our department, soft tissue involvement without bone lesions was found only in 3 cases, all females. [Case 1] In her early infancy, she had been successfully treated for multisystem LCH with multi-agent chemotherapy (prednisolone, etoposide, vinblastine and methotrexate). At age 2 yrs., DI was noted. At age 7 yrs., LCH recurred as the swelling of right iliac and inguinal area with heat and ulceration. Radiological study revealed the soft tissue involvement extending into the pelvic cavity. [Case 2] As initial presentation of LCH at age 12 yrs., she showed swelling of the lower neck. It was confirmed that cervical lymph nodes and thyroid were not involved. The soft tissue mass extended deeply into the mediastinum and the radiological and endoscopic study revealed esophageal fistula probably due to surrounding soft tissue LCH. [Case 3] She developed DI and panhypopituitarism due to the hypothalamic mass at age 11 and 14 yrs., respectively. At age 17 yrs., she presented with swelling of neck and chest wall with a 3 year history of goiter. The soft tissue mass was found in conjunction with thyroid, extended aggressively into the mediastinum and resulted in airway obstruction. [Case summary] In all cases, histologic evaluation of the soft tissue lesion revealed extensive involvement by LCH, confirmed by immunohistochemical analysis (positive for CD1a and S-100 protein). These lesions were clearly detected as high signal area with T2-weighted fat suppressed MRI images, also enhanced well with T1-weighted images. In all cases, the chemotherapy (a combination of prednisolone, vincristine, cytarabine or prednisolone, vinblastine, methotrexate) was effective for resolution of the huge soft tissue mass. In Case 1, recurrence of soft tissue mass occurred three times, but controlled well with the same chemotherapy. She has no evidence of disease for 5 years after the last chemotherapy.

Discussion and Conclusions: In literature review, soft tissue LCH of cervical area, similar to Case 3 was previously reported involving thyroid, parotid gland and lymph nodes. However, Cases 1 and 2 were unique, because the very invasive soft tissue lesions emerged seemingly soft tissue itself as primary site of LCH. Fortunately, these lesions could be manageable with chemotherapy. Further analysis is necessary to clarify the mechanisms, such as possible trigger(s) of development of extraskeletal soft tissue LCH lesions.
CLADRIBINE THERAPY IN 2 PATIENTS WITH ERDHEIM-CHESTER DISEASE

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Introduction: Erdheim-Chester disease is an uncommon disease with potentially life-threatening complications (pulmonary fibrosis, heart failure). Belonging to the non-Langerhans cell histiocytosis group, it is characterized by proliferation of foamy histiocytes and their infiltration into various tissues and organs, typically the long bones of the lower extremities. Because of the low prevalence, there is no standard therapy of this disorder. Herein we report on the follow-up and cladribine (2-chloro-2-deoxyadenosine, 2-CdA, Litak™)-based treatment in two patients with Erdheim-Chester disease and present an ample pictorial documentation of radiological and nuclear medicine imaging modalities, including X-ray, computed tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), positron emission tomography (PET) and hybrid PET/CT findings as well as those obtained by traditional bone scintigraphy.

Materials and Methods: Two male patients, one born in 1953, the other in 1965, were diagnosed with Erdheim-Chester disease in 2008 and 2009, respectively. Both suffered from diabetes insipidus, B-symptoms (fever or subfebrile temperatures, fatigue) and pains in the long bones of the lower extremities. In the first patient, a series of MRI scans of the brain showed multiple lesions gradually increasing in number. The radiological findings were accompanied by newly developed neurological symptomatology (dysarthria, hemiparesis and paresthesia). Both patients were treated with cladribine 5 mg/sqm SC, cyclophosphamide 150 mg/sqm IV (and dexamethasone 24 mg PO in the second patient) on days 1-5 of a 28-day cycle for 6 months in total. Bisphophonates (zoledronate 4 mg IV at 28-day intervals) as a long-term supportive therapy were administered.

Results: In the first patient, bone pains receded and MRI showed a significant regression of all brain infiltrates, however, the neurological symptomatology has remained and restaging PET/CT didn’t show a decrease of radiopharmaceutical uptake. Thus, partial remission has been achieved. In the second patient, remission of subjective symptoms as well as normalization of blood inflammatory markers and reduction of pathological hypermetabolism on restaging PET/CT examinations were achieved. We consider this therapy response as complete remission. No therapy related adverse events were observed in the first case. In the second male, lymphocyte and neutrophil counts were decreasing during the treatment and by this induced immunodeficiency led to shingles eruption 2 months after cessation of therapy with the necessity of hospitalization and antiviriotics prophylaxis initiation. Moreover, in our work we managed to document some of the typical manifestations of Erdheim-Chester disease like osteosclerosis, infiltration of the hypophysis, periaortic fibrosis (coated aorta) as well as retroperitoneal fibrosis reminding of Ormond’s disease.

Conclusions: Treatment with cladribine–based regimens in two patients with Erdheim-Chester syndrome led to disease stabilization and remission, respectively. Therefore, we recommend cladribine to be standard part of treatments for this disease.
Poster Presentation #32

NICHE-INDUCED PATHOGENESIS IN LANGERHANS CELL HISTIOCYTOSIS

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The pathogenesis of Langerhans Cell Histiocytosis (LCH) is yet unknown. We previously developed a mouse model of niche-induced pathogenesis in pediatric myeloid leukemia and used this model to study how microRNAs (miR) are involved in gene regulation of leukemic cells. We now propose to use this stromal niche model to investigate recruitment and retention of other myeloid lineage derived cells, i.e. dentritic cells (DC) as a model for LCH. Unique factors derived from the stromal niche might affect the LCH phenotype reflected in DC miR expression profiles. Investigation of the interaction of DC with the stromal microenvironment is the purpose of this study.

Human skin biopsies are obtained from mammoplastic surgery and/or circumcision specimens via the Tissue Donation Program at the Feinstein Institute after informed consent. Skin biopsies are cut with a 2mm punch and digested with dispase to separate the epidermis. The obtained disk of dermis is further digested with 0.8mg/ml collagenase in RPMI with 10% FCS for 12 hrs and dispersed into a single cell suspension. Cells are washed and monocyte-derived DC generated from magnetically isolated CD14+ monocytes (Miltenyi Biotec) and cultured for 6 d with 50ng/ml GM-CSF and IL-4 (R&D Systems), followed by 24h activation with 0.1 ug/ml LPS (Sigma-Aldrich), 10ng/ml IL1-beta and 10ng/ml TNF-alpha (PeproTech). DC purity is confirmed by FACS analysis with following antibodies: CD1a FITC (NA1/34 Dako), CD11c APC (B-ly6 BD), CD14 PE (M5E2 BD) and FXIIIa (Enzyme Research Laboratories) with APC-conjugated donkey anti-sheep (Invitrogen) to exclude macrophage lineage. Monocyte-derived DC are also generated from peripheral blood ficolled buffy coats as controls. Obtained monocytes are cultured in RPMI 10% FCS for 18hr in presence of GM-CSF & IL-4.

We have created a myeloid leukemic stem cell niche model based on a mesenchymal stromal cell (MSC)-coated polyurethane scaffold that closely mimics the three dimensional structure of the bone marrow environment. In vitro, we confirmed by electron microscopy the intimate contact that takes place at a single cell level between a MSC and a myeloid leukemic blast cell, making this model suitable to study myeloid cell biology in the stromal niche and potential drug candidates that can result in niche-disruption. In vivo, in a NOD/SCID murine model, this artificial subcutaneously implanted stem cell niche can support growth of normal and leukemic hematopoiesis (1).

Moreover, we identified differentially pediatric leukemia-specific miR expression profiles induced by the leukemic stem cell niche. We applied this model to the study of dermal DC and PB-DC niche biology by inoculation of the MSC-coated polyurethane scaffold with DC to investigate the interaction of DC and the microenvironment. This model might shed light on niche-induced pathogenesis in Langerhans Cell Histiocytosis.

STXBP2 (MUNC18-2) MUTATIONS IN NORTH AMERICAN PATIENTS WITH FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Background: Familial hemophagocytic lymphohistiocytosis (Familial HLH or FHL) is an autosomal recessive disorder of immune regulation, characterized by defects in cell-mediated cytotoxicity that results in fever, hepatosplenomegaly and cytopenias. It typically occurs in early childhood, but many adult cases have also been reported. It is often rapidly fatal unless treated with chemotherapy, immune suppression and followed by bone marrow transplantation. Several genes are specifically associated with FHL including PRF1 (FHL2), UNC13D (FHL3), STX11 (FHL4) and STXBP2 (FHL5). Mutations in RAB27A have also been described in cases of FHL associated with Griscelli syndrome 2 as well as in isolated FHL. The purpose of this study is to characterize STXBP2 mutations in North American patients with Familial HLH.

Material and Method: PCR based sequencing of the entire coding region and exon/intron boundaries of the STXBP2 gene was undertaken in a total of 329 unrelated patients with the clinical diagnosis of HLH. The significance of missense variants were evaluated with a lab developed algorithm including database reviews (HGMD, NCBI etc.) as well as in silico analyses (PolyPhen, SIFT, Grantham Scale, etc.). This study was performed with the approval of Cincinnati Children’s Hospital Medical Center IRB.

Results: Bi-allelic STXBP2 mutations were found in 32 unrelated families. Heterozygous mutation and sequence variants were also identified in 22 additional symptomatic patients; the significance of these variants in the development of HLH in the heterozygous state is currently unknown. Fourteen novel mutations and 9 sequence variants were found in this cohort of patients. There are a few common mutations were observed. P477L is a mutation found frequently in patients with Arabic descent. 1247-1G>C and G541S are the two common mutations in Caucasian patients. G541S can be observed by itself or co-segregated with the 795-4C>T variant. While L130S and T345M are almost always observed together, T345M by itself also presented in about 2% of the local control population, and is likely a benign polymorphism. Thirty-five other sequence variants are also found in this cohort of patient and do not appear to result in aberrant protein.

Conclusion: Bi-allelic STXBP2 mutations are identified in approximately 10% of North American patients with FHL and sequencing analysis of STXBP2 gene should be included as part of the standard genetic evaluation of these patients. Further studies are necessary to characterize the role in the disease development of the novel missense and splicing site variants observed in this study.
DIAGNOSTIC PATHOLOGY OF ERDHEIM-CHESTER DISEASE (ECD)

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The pathologic diagnostic requirements for confirmation of Erdheim-Chester disease are not well defined, and most commonly are described as showing xanthomatous histiocytes that are CD68+/CD1a-.

METHOD: Tissues from 8 adult cases of clinically suspected ECD with multifocal lesions were subjected to conventional immunohistology. M=F, 38-64yrs. Bone, retroperitoneum, orbit, lung and meninges/brain were the preferred sites of involvement.

RESULTS: The pathology differed by site regarding local tissue response such as fibrosis. Histiocytes were the dominant population with cytoplasm-rich, and xanthomatous macrophages in varying proportion. Only 2/8 had Touton cells. An inflammatory component, mostly small lymphocytes was present in most. The phenotype was consistent, revealing CD14+/CD68+/CD163+ macrophages with high expression of F13a (only focal in one) and high fascin. S100 was either totally absent or light and focal in 3/8. No CD1a or langerin was present, though one patient had Langerhans' cell histiocytosis (LCH) elsewhere.

CONCLUSION: ECD has the JXG phenotype. Older, mostly xanthomatous lesions may lose some markers and have more sparse expression of CD163 and F13a, making diagnosis more tenuous. The main differential diagnosis of the full phenotype is systemic JXG in the young who may not demonstrate the usual ECD clinical pattern (skin, liver). The differential diagnosis of CD68+/CD1a- is wide, all xanthomatous inflammatory processes rich in macrophages will have this pattern, resolving abscesses, xanthomatous pyelonephritis, periappendicitis or cholecystitis for example.

The diagnosis of ECD rests on clinical and imaging features, complemented by a tissue diagnosis that reveals the full JXG phenotype. Although clearly different from CD1a+/Langerin+ LCH, there appears to be an association between the two conditions.
Langerhans cell histiocytosis (LCH) is a rare clonal disorder of Langerhans cells with a broad disease spectrum. Trialed therapies include steroids, chemotherapy, radiotherapy and stem cell transplantation, however these modalities often provide disappointing results for patients with refractory/relapsed disease.

We present the case of an adult patient with heavily pretreated, refractory multi-system disease who has remained in complete remission after treatment with an oral AKT-inhibitor (GSK2110183) as part of a phase I, open-label study.

A forty-four year old woman presented with a cough, loss of weight and sweats. CT & whole-body PET imaging revealed a large pulmonary and hilar mass accompanied by extensive mediastinal lymphadenopathy. Tissue biopsy confirmed LCH. Six cycles of conventional therapy consisting of 2-chlorodeoxyadenosine (0.14mg/kg/day for 5 days) and subsequent adjuvant local radiotherapy resulted in PET partial response. Within a year there was disease progression with additional mediastinal lymphadenopathy and pulmonary involvement. Treatment with the “Third International Study for Langerhans Cell Histiocytosis" protocol for six months resulted in partial PET response. Within half a year, disease progression was evident with dysphagia secondary to external compression on the gastro-oesophageal junction. At this stage the oral AKT-inhibitor was commenced (daily, over 28-day cycles). The patient had a rapid response with resolution of her dysphagia and cough after 2 cycles. This correlated with an improvement in her PET imaging. No significant adverse events were experienced. She has now completed 25 cycles with almost complete resolution of her disease.

AKT (a serine/threonine) protein kinase is involved in many oncogenic pathways. It is thought to have a key role in cellular survival and proliferation. AKT inhibition is a novel therapy in LCH. The dramatic and sustained improvement in the patient’s response yields new and exciting avenues of research into its pathogenesis. Further exploration of the AKT pathways will hopefully provide more insight and consequently more targeted treatment.
PULMONARY LANGERHANS CELL HISTIOCYTOSIS. CLINICAL PRESENTATION AND OUTCOME OF 60 CASES

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Pulmonary Langerhans cell histiocytosis (PLCH) is a disease of unknown etiology characterized by proliferation of phenotypically changed Langerhans cells. It is seen as part of multisystem LCH or as an isolated form of the disease. The clinical spectrum of the PLCH vary widely and course of it 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 13 years 60 adults (29 women and 31 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 72 months (range 2 to 216 months). All patients were smokers.

Results: Two patients had disseminated disease, 4 multifocal bone disease, 8 patients had mandible involvement, and in 3 patients skin lesions were revealed. Diabetes insipidus was diagnosed in 10 patients and in 2 of them central nervous system involvement was noticed. Clinical and radiological features, pulmonary function tests, will be discussed.

During the time of observation 36 patients were not treated (only stopped smoking) and regression or stabilization of pulmonary lesions were observed. Chemotherapy was administered to 13 patients and steroids to 10 patients, local steroid treatment was applied to 4 patients, radiotherapy in one and in one woman surgical excisions of bone lesions were performed.

One man underwent unilateral lung transplantation at the time of follow-up. Two deaths attributable to respiratory failure were noticed. No case of cancer was observed.

Conclusions: The spectrum of clinical, radiological, pulmonary function impairment and response to therapy in patients with PLCH vary widely.

Strong link with smoking was observed.

The treatment modalities in patients with progressive multiorgan disease are not satisfactory.
PULMONARY LANGERHANS’ CELL HISTIOCYTOSIS - CLINICAL CHARACTERISTICS AND LONGITUDINAL FOLLOW-UP OF 40 CASES

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Background: Pulmonary Langerhans’ cell histiocytosis (PLCH) is a rare interstitial lung disease characterized by the accumulation of Langerhans cells into the lung and occurs predominantly in young smoking adults.

Aim: To describe the clinical characteristics and to assess changes in pulmonary function test (PFT) during longitudinal observation in patients with PLCH.

Methods: Retrospective analysis of 40 patients (17 women and 23 men; 37 smokers with mean ± SD 17.1±12 pack years and 3 nonsmokers) with PLCH diagnosed between 1985–2011.

Results: Mean follow-up period was 41.3 months (range 0 – 331). Mean age at diagnosis of PLCH was 43.2 ±13.6 yrs and mean delay of diagnosis - 2.95 yrs (range 0 – 17 yrs). The most common presenting symptoms were cough (55%), dyspnea on exertion (55%), pneumothorax (22.5%), chest pain (7.5%), loss of weight (7.5%) and 6 cases (15%) were asymptomatic (diagnosed incidentally). Eight patients presented extrapulmonary lesions (bone – 4, pituitary gland – 4, skin – 3). An obstructive pattern was observed in 31% of cases, whereas 64% of patients had normal spirometric results. DLCO was reduced in 76% of patients. The serial biannual measurement of lung function revealed significant reduction in FEV1 after 4 yrs (n=9; 69.0±25.0 % pred. vs 83.3±17.8 % pred.; p=0.047). Thirteen patients (32.5%) were treated with prednisone alone or in a combination with cytotoxic drugs (metotrexate - 5, azatioprin – 2, cyclophosphamide - 2, etoposid - 1, vinblastine – 3). Spontaneous remission was observed in 4 patients (10%) after quitting smoking. Thirteen (11 treated) of the followed 30 patients had progressive disease. There were 5 deaths, including 4 from respiratory failure (after 12, 11, 11, and 2 yrs).

Conclusion: The diagnosis of PLCH was often delayed. PLCH is a slowly progressing disease with the first significant deterioration in PFT after 4 years of follow-up. Immunosuppressive treatment seems not to improve lung function in patients with PLCH.
LENALIDOMIDE PROVED EFFECTIVE IN A PATIENT WITH RELAPSING MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS

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Introduction: Lenalidomide is a derivate of thalidomide with anti-inflammatory, anti-angiogenic and immunomodulatory effects. Approved for treatment of multiple myeloma and myelodysplastic syndrome, its potential in Langerhans cell histiocytosis (LCH) hasn’t yet been described. Herein we are the first to report on a therapy effect of lenalidomide-based regimen in a patient with repeatedly relapsed aggressive form of multisystem LCH with lymph node involvement.

Materials and Methods: A male, born 1973, was diagnosed with multisystem LCH affecting the lymph nodes, skin and lungs at the age of 35. The symptoms reminded of a lymphoma with expressed B-symptoms (night sweats, fever, weight loss, fatigue) and generalized lymphadenopathy. Also present were productive cough, perianal itching and back pain. Initially, the patient was treated with 6 cycles of cladribine-based regimen combined with radiotherapy of the perianal area. This led to complete remission. However, in two months the disease relapsed, newly also with bone infiltration. The second line treatment consisted of 4 cycles of CHOEP regimen (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) completed in March 2010 with high-dose BEAM (carmustine, etoposide, cytarabine, melphalan) chemotherapy followed by autologous peripheral blood stem cell transplantation, which put the disease into complete remission again. Nevertheless, after 5 months the 2nd relapse was diagnosed and a PET/CT examination showed generalized lymphadenopathy with cervical, supraclavicular, axillary, mediastinal, retroperitoneal and inguinal involvement. The patient was then started on lenalidomide (25 mg orally days 1-21 of a 28-day cycle) with dexamethasone (40 mg orally once a week) treatment enhanced with etoposide (100 mg intravenous days 22-24, cycles 6-8) administration. Antithrombotic prophylaxis with low-molecular weight heparin was implemented. To date, 8 cycles have been carried out (10/2010-5/2011).

Results: Within several weeks of lenalidomide treatment, night sweats, fevers and back pain receded gradually, which was followed by a decrease of blood inflammatory markers (C-reactive protein, erythrocyte sedimentation rate) and normalization of haemoglobin levels. From the 2nd cycle on, fatigue has diminished and the patient has been feeling well. A restaging PET/CT examination during the 4th cycle showed reduction in the size of affected lymph nodes and their glucose uptake as well as generally reduced extent of the disease with physiological findings in some right-sided lymph node regions. Finally, pathological glucose hypermetabolism was detected only in the cervical lymph nodes on a PET/CT scan after 7 cycles. Moreover, through a series of 10 ultrasound examinations, gradual regression of enlarged lymph nodes was documented. No serious adverse events, including cytopenia or thrombosis, were observed during the therapy.

Conclusions: Lenalidomide–based regimen proved effective in a patient with the repeatedly relapsed aggressive form of multisystem Langerhans cell histiocytosis as demonstrated in the clinical, laboratory and radiological data enclosed.
MEASURING DIFFUSE METABOLIC ACTIVITY ON PET/CT AS A NEW METHOD FOR EVALUATING PULMONARY LANGERHANS CELL HISTIOCYTOSIS ACTIVITY

Petr Szturz; Zdeněk Řehák; Zdeněk Adam; Renata Koukalová; Roman Hájek; Marta Krejčí; Luděk Pour; Lenka Zahradová; Hubert Mottl; Jiří Vaníček; Tomáš Nebeský; Jiří Mayer

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Introduction: Langerhans cell histiocytosis (LCH) infiltrating pulmonary parenchyma is characterized by formation of nodules in active phase of the disease that evolve into non-active cystic lesions later on. A non-invasive evaluation of pulmonary LCH activity is routinely performed by means of high-resolution computed tomography (HRCT) imaging or pulmonary function tests. However, determining the number of nodules and cystic formations on HRCT scans is extremely difficult and time-consuming and pulmonary function tests cannot always distinguish between end-stage cystic disease and active LCH. Therefore, we developed a new method for measuring diffuse metabolic activity on fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) using a lung-to-liver activity ratio.

Materials and Methods: Nodules in pulmonary LCH often measure several millimeters (4 - 6 mm) and are below detectable levels of used PET scanners (about 7 mm), which precludes direct measurement of their activity. Thus, we tried to find these active lesions in a larger area on PET/CT scans. Considering the anatomical conditions and locations of predominant pulmonary LCH involvement, we chose the volume-of-interest shaped into spheres of 6 - 8 cm in diameter in the right upper and middle lung fields. To decrease the variability between single examinations as well as to compare examinations from different scanners, lung-to-liver activity ratio was established. In the liver parenchyma we chose the volume-of-interest shaped into spheres of 9 - 10 cm in diameter. For semiquantitative analysis of radiopharmaceutical (fluorodeoxyglucose) accumulation in a lesion, maximum Standardized Uptake Values (SUVmax) were calculated. SUVmax in the spherical volume in the right lung and SUVmax in the spherical volume in the reference hepatic parenchyma were measured and put into relation to set up the SUVmaxPULMO/SUVmaxHEPAR index. In our work we retrospectively studied a series of 4 FDG-PET and 23 FDG-PET/CT scans from 7 patients with pulmonary LCH, where index values were compared to the disease course in each patient. We also analyzed a sample of 100 randomly chosen FDG-PET/CT studies of patients free from any known lung or hepatic diseases.

Results: In patients with pulmonary LCH, a close correlation between the index values and the disease course was found in 7/7 subjects, where the increasing index values indicated disease activity, while the decreasing index values were observed after therapy administration. In the group of 100 healthy control subjects we found the index values lower than 0.3 in 80% and lower than 0.4 in 96% (median: 0.22, range: 0.14-0.43), which is in accordance with our observation that values about 0.5 bear high probability of pulmonary involvement in patients with Langerhans cell histiocytosis.

Conclusions: Measuring SUVmaxPULMO/SUVmaxHEPAR values represents a simple, non-invasive screening tool allowing an early diagnosis and monitoring of therapy effect in patients with pulmonary LCH.
IL-17A INDUCES BFL1, SURVIVAL AND CHEMORESISTANCE IN MONOCYTE-DERIVED DENDRITIC CELLS: CONSEQUENCES IN LANGERHANS CELL HISTIOCYTOSIS

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Langerhans cell histiocytosis (LCH) ranges from a self-resolving to a fatal course following tissue damage by granulomas, enriched in dendritic cells (DC) and multinucleated giant cells (MGC). Researchers debate whether LCH represents a malignancy or an inflammatory disease involving IL-17A and IFN-γ. We investigated DC survival and chemoresistance in an IL-17A-rich environment. Monocyte-derived DC from LCH patients spontaneously expressed BCL2A1 / BFL1, a pro-survival member of the Bcl-2 family. Anti-IL-17A antibodies impaired LCH DC survival, thus delineating IL-17A as an autocrine survival factor. BFL1 stained pathogenic myeloid cells in LCH biopsies. DC from healthy donors, treated with IL-17A and IFN-γ, mimic LCH DC in terms of survival, phenotype, cell fusion, BFL1 induction, broad chemoresistance established by cultures with 17 chemotherapy agents, and high sensitivity to cytarabine and vinblastine. Vinblastine killed DC and MGC after microtubule network disorganization, podosome destruction and MCL1 decrease, without affecting BFL1 expression. In vitro, anti-IL-17A biotherapy decreased BFL1 and synergized with chemotherapy to eradicate LCH DC. In conclusion, monocytes may be the precursors of pathogenic DC in LCH. BFL1 expression induced by IL-17A provides a molecular link reconciling pro-survival gene activation and inflammatory environment as well as new therapeutic targets for LCH and other IL-17A-related diseases.
INFECTION ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A CASE SERIES USING STEROIDS ONLY PROTOCOL FOR MANAGEMENT

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INTRODUCTION: Infection associated HLH develops as a result of strong immunological activation of the immune system triggered by any severe infection. Though in HLH-2004 protocol, three tier therapies have been advocated irrespective of the type and etiology, here we present a series of 19 cases of infection associated HLH diagnosed in our hospital within a time period of 3 years, treated only with a novel steroid only protocol.

PATIENTS AND METHODS: Clinical records of children fulfilling the diagnostic criteria of HLH admitted at the Institute of Child Health, Kolkata during the time period of July 2008 to July 2011 were reviewed. The diagnosis of HLH was based on the typical clinical findings supplemented with relevant laboratory investigations and exclusion of other diseases. The data collected included details of clinical and laboratory features, treatment and outcome. All the patients received only Dexamethasone(10mg/m2/day, then tapered over next 8 weeks) as a definitive therapy. But for the last 5 cases, we used a shorter course of steroids starting at a dose of 10mg/m2/day followed by rapid tapering over the next 4 weeks. The patients received supportive therapy in the form of blood component transfusions and broad spectrum antibiotics. Intravenous immunoglobulin (IVIG) was used in two patients as a rescue measure initially when we were hesitant to use only high dose steroids. Blood products were used in 11 patients. No chemotherapeutic agent other than steroids was used in all of our 19 patients.

RESULTS: In 84% cases fever subsided within 48 to 72 hours of starting steroids, reversal of cytopenias and regression of hepatosplenomegaly occurred over the next 7 to 10 days. Serum ferritin started normalizing within a week. We got the same clinical response in these two groups of patients receiving 8 weeks and 4 weeks of treatment. There was no mortality so far and 16 patients are on regular follow up and stable without any recurrence of the disease.

CONCLUSION: Though traditionally perceived as a near fatal disease requiring aggressive chemotherapy, our patients did remarkably well with the use of only corticosteroids and supportive therapy without necessitating the use of further chemotherapy. Observing this response to a corticosteroid only protocol, we propose a steroid only treatment for infection associated HLH. However further studies are required to substantiate the possibility of a shorter duration of treatment.
ABSTRACTS: SCIENTIFIC SESSION IV

EVALUATION OF RADIOGRAPHIC FOLLOW-UP EXAMINATIONS IN LCH BONE LESIONS

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BACKGROUND: Children with skeletal Langerhans cell histiocytosis (LCH) undergo serial X-ray examinations during the course of disease. Radiographic characteristics of the different bone lesions as well as the usually benign course of this disorder and the marginal influence of any form of treatment on the healing dynamics have been well described in literature. This knowledge changed the diagnostic guidelines so that monthly or bimonthly routine skeletal surveys are not considered state of the art anymore. However, there is still a lack of evidence in terms of optimal intervals for the follow-up X-ray examinations. Aims of this retrospective study were to review the imaging findings of LCH bone lesions at conventional X-ray images and to elaborate meaningful time points for radiographic follow-up examinations at which relevant changes would be visible in most of the patients.

PATIENTS AND METHODS: This retrospective study was carried out in patients with biopsy proven LCH and skeletal manifestation in the long bones or the skull. Only lesions with serial conventional X-ray images of adequate quality were included in the review process. Among 63 children (185 bone lesions) with the diagnosis of LCH seen in a single tertiary center from 1983 to 2010, 33 patients (61 bone lesions, 969 radiographs) met these criteria. The initial and the follow-up radiographs of the bone lesions were evaluated according to the following criteria: size, distinct/non-distinct margins, presence of sclerosis and a trabecular pattern. All the radiographs were reviewed by 2 experienced radiologists.

RESULTS: The appearance of sclerosis, which occurred at a median of 67 days and an arithmetic average of 83 days, was the first sign of healing in our patient population. After 4 months 51 of 61 lesions (82%) showed this finding. It took an average of 137 days (median: 88 days) to change from a non-trabecular to a trabecular pattern. Concerning their margin the lesions showed different healing characteristics. While the margin of the lesions of the long bones got more distinct, the skull lesions initially appeared with sharp borders and changed over to indistinct margins in the course of the healing. Healing changes of the margin occurred at a median of 84 days and an average of 102 days.

CONCLUSIONS: According to our findings the first radiographic follow-up examination of a clinically unapparent lesion should be performed not earlier than 4 months after the initial radiograph, when at least 1 healing characteristic is visible in 86.2% of the cases. This knowledge of the healing dynamics in X-ray will enable a more meaningful use of radiographic follow-up examinations and a reduction of the radiation burden in children with skeletal LCH.
ABSTRACTS: SCIENTIFIC SESSION IV

DISCRIMINATION OF ACUTE FLARES OF SYSTEMIC ONSET JUVENILE IDIOPATHIC ARTHRITIS, MACROPHAGE ACTIVATION SYNDROME, AND OTHER FORMS OF HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Background: Clinical and laboratory features of 1) macrophage activation syndrome (MAS) in systemic onset juvenile idiopathic arthritis (soJIA) substantially overlap both with 2) acute flares of soJIA and with 3) hereditary (FHL) and acquired forms of HLH. To differentiate 1) from 2), preliminary criteria for MAS have been established by Ravelli et al. (J Pediatr., 2005) that require evaluation. No routine parameters with cutoff values have been described that discriminate between 2) and 3). Both distinctions can be crucial for therapy choice.

Patients: In our cohort of patients referred for evaluation for HLH, we identified 27 patients (group 1) fulfilling the ILAR criteria for soJIA and the preliminary definition for MAS by Ravelli et al. and determined the number of patients fulfilling each single HLH2004 and preliminary MAS criterion. The dynamics of WBC, platelet count, fibrinogen, and CRP during the development prior to the diagnosis of MAS were quantified. For comparison, a cohort of 90 FHL patients and 42 patients (group 2) with definite acquired virus-associated HLH (acHLH) was identified. To test for statistical difference, an analysis of variance test (ANOVA) was performed. Cutoff values were determined by means of a receiver operating characteristic (ROC) curve.

Results: In group 1, 22 patients presented with MAS at the initial flare of soJIA, 5 of which did not have arthritis initially. 5 individuals had known soJIA at the manifestation of MAS. Only 16 fulfilled ≥5 of the HLH2004 criteria: Ferritin (25 out of 26), platelet count (21/27), splenomegaly (18/27), haemophagocytosis (17/23), sCD25 (17/19), fibrinogen (11/24), haemoglobin (10/27), bicytopenia (9/18), triglycerides (8/20), and neutrophil count (1/19). The preliminary criteria by Ravelli et al. in detail were platelet count (27/27), ASAT (25/27), hepatomegaly (18/27), WBC (16/27), fibrinogen (14/24), central nervous system dysfunction (9/27), and haemorrhages (4/27). Mean white blood count dropped from 17.4 to 9/nL (Δ 8d, n=20), platelet count from 310 to 120/nL (Δ 8d, n=20), and fibrinogen from 5.1 to 3.4 g/L (Δ 6d, n=7) prior to the diagnosis of MAS. In the comparison of group 1 and 2, haemoglobin (p<0.001), WBC (p=0.003), neutrophils (p<0.001), platelets (p=0.002), ferritin (p=0.003), and CRP (p<0.001) were higher, sCD25 (p<0.001) was lower in MAS than in FHL/acHLH. The parameters that best separated MAS from FHL/acHLH were CRP (cutoff value >90 mg/L, sensitivity 74%, specificity 89%), neutrophil count (>1.8/nL, 85%, 83%), and sCD25 (<7900 U/mL, 79%, 76%).

Conclusions: MAS is the presenting manifestation of soJIA in a relevant number of patients, both with and without initial arthritis. Falling WBC, platelet count, and fibrinogen may serve as additional parameters to distinguish MAS from acute bouts of soJIA. sCD25, CRP, and neutrophil count are parameters that may differentiate between MAS in soJIA and FHL/acquired virus-associated HLH.
ABSTRACTS: SCIENTIFIC SESSION IV

LOCALLY PRODUCED TGF-β SKEWS THE CHEMOKINE RECEPTOR EXPRESSION PROFILE OF LCH CELLS

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Introduction: Accumulation of CD1a+ cells in distinct tissues and organs is a hallmark of Langerhans Cell Histiocytosis (LCH). The failure of CD1a+ cells to differentially up or down regulate particular chemokine receptors could underlie the seemingly impaired migration capacity of these cells. We hypothesized that the chemokine receptor expression profile of Langerin+ cells is affected by cytokines produced in LCH lesions. To test this hypothesis, we analyzed the expression of a defined set of chemokine receptors which, according to a recently proposed two step process, facilitate migration of conventional Langerhans cells (LC) to skin-draining lymph nodes. These results were correlated to two cytokines typically present in LCH lesions, i.e. Transforming Growth Factor-beta (TGF-β) or Tumor Necrosis Factor-alpha (TNF-α).

Materials & Methods: To determine the chemokine receptor expression profile of lesional cells, triple immunofluorescent stainings were performed with antibodies specific for Langerin (CD207) in combination with CCR6, CXCR4, CCR7 and CXCL12 using paraffin embedded tissue sections (bone n=15; skin n=6, lung n=3 and LN n=3) prepared from n=27 LCH lesions. All biopsies analyzed were obtained at the time of diagnosis and before the start of treatment. Expression of TGF-β or TNF-α; was analyzed by enzymatic immunohistochemistry.

Results: Independently of the affected tissue site, the chemokine receptor expression by Langerin+ cells varied substantially. However, in line with the 2 step LC migration model, CCR6 and CCR7 never co-localized with Langerin on LCH cells present in 26 different LCH lesions, albeit that Langerin/CCR6/CCR7 triple positive cells were observed in a single osteolytic lesion. Like CCR6 and CCR7, CXCR4 expression, which is required for the transition of LC from the epidermis to dermis, seems heterogeneously expressed. Seven different chemokine receptor profiles could be deduced from the combined data set:

1) CXCR4neg CCR6pos (n=7)
2) CXCR4neg CCR7pos (n=2)
3) CXCR4pos CCR6neg (n=5)
4) CXCR4pos CCR6negCCCR7neg (n=7)
5) CXCR4pos CCR6pos (n=4)
6) CXCR4pos CCR7pos (n=1)
7) CXCR4pos CCR6pos CCR7pos (n=1)

Regardless of the corresponding chemokine receptor profile, the ligand for CXCR4, CXCL12, was expressed by 100% of Langerin+ cells present in n=27 lesions analyzed. LCH lesions in which the anti-inflammatory cytokine TGF-β dominated were characterized by complete absence of CCR7 as represented by profile 1, 3, 4 and 5. This observation suggests that CCR7-driven migration of LCH cells to regional lymph nodes is actively suppressed by TGF-β. The data on LCH lesions characterized by high levels of inflammation-prompting TNF-α are pending.

Conclusion: The observed heterogeneity in chemokine receptor profiles of LCH cells suggest that these cells accumulate during the different phases of migration. Combining information on the genetic and phenotypic make-up of LCH cells and their microenvironment may open new ways for targeted treatment of this disease.
CLINICAL PROGNOSTIC MARKERS FOR PRE-TRANSPLANT OUTCOME IN PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Background: Hemophagocytic Lymphohistiocytosis (HLH) is a life-threatening disturbance of immunoregulation. HLH comprehends primary and acquired forms with different disease severity. We investigated laboratory and clinical parameters before and two weeks into therapy for association with poor pre-transplant outcome.

Design and Methods: 232 children from Scandinavia, Germany or Italy, fulfilling diagnostic criteria and/or with familial disease and/or HLH-causing mutations, receiving HLH treatment 1994-2008 were included. The relation of clinical findings and pre-transplant death were examined using the Cox proportional hazards model, with a four month right-truncation of the outcome. Patients were censored at last follow-up or transplant. Predictors were adjusted for sex, age, missing values and inter-variance with other predictors.

Results: The following features were significantly associated with adverse outcome: hyperbilirubinemia (>50µmol/L; adjusted Hazard Ratio (aHR) 3.2; 95% CI 1.3-8.1, p 0.011), hyperferritinemia (>2000µg/L; aHR 3.2; 1.2-8.6, p=0.019), CSF pleocytosis (>100x10⁶/L; aHR 5.1; 1.4-18.5, p=0.012) at diagnosis, and thrombocytopenia (<40x10⁹/L; aHR 3.3; 1.2-9.5, p=0.024), and hyperferritinemia (>2000µg/L; aHR 10.0; 1.1-89.3, p=0.040) two weeks into therapy. Non-improvement of fever, anemia and/or thrombocytopenia also had adverse impact.

Conclusions: There are clinical predictors of poor pre-transplant outcome in HLH patients that may help to guide treatment decisions.
NEZELOF PRIZE IN BASIC SCIENCE

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

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

The many contributions by Dr. Nezelof include:

- Dr. Nezelof contributed significantly to the development of Pediatric Pathology as a subspecialty by creating a network of various specialties and also trained many clinicians and foreign pathologists. He has served as a consultant for the world of histiocytosis, always giving a friendly and illuminating answer to anyone's questions.

- In 1960, Dr. Nezelof played a key role in describing a clinical condition of immunodeficiency in childhood, in which the existence of a "split" in the human lymphoid system toward T and B-cells was recognized. An immune-deficient child was described as afflicted by a thymic hypoplasia, but with normal level of immunoglobulins ("Lymphocytotphie avec normogamma-globulinemie"). In the pediatric literature this condition became known as Nezelof's syndrome.

- In the field of histiocytosis, his seminal contribution was that Letterer-Siwe, Hand-Schuller-Christian and eosinophilic granuloma are linked to the same cell, having a common ultrastructural marker designated as the Langerhans body (Birbeck granule). In his paper "Histiocytosis X: Histogenetic arguments for Langerhans cell origin", he noted the dendritic lineage of this disease. Not long afterwards the term Langerhans cell histiocytosis was introduced.

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

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

Judgment will be based on a written abstract describing work done by the candidate him/herself. It is understood that the winning abstract may have co-authors, but that the first author must be the leader of the project and the one who is awarded the Nezelof Award. The Program Committee will provide time during the Annual Meeting for presentation of the winning paper. The decision by a special committee of the Histiocyte Society will be based on originality, completeness, scientific accuracy, and contribution to science. The prize will consist of $500US and a certificate.
The Histiocytosis Association, in conjunction with the Histiocyte Society, is offering an annual prize for the best clinical article at their Annual Meeting. It will be given in honor of Dr. Mark Nesbit, renowned pediatric oncologist, teacher, and supporter of the many families dealing with histiocytic disorders. The prize will be awarded to a physician or scientist who is carrying out clinical research to the therapy, biology or pathogenesis of one of the histiocytic disorders. The goal of the Award is to stimulate and promote the activities of clinical scientists from all around the world to study specific aspects of these puzzling diseases.

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

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

- Histiocytic disorders have been a continual interest from the onset of Professor Nesbit's career. His first publication was entitled: "Histiocytosis X".

- Dr. Nesbit played an important role in the organization of the Histiocyte Society. Besides his active input in the Epidemiology Study Group of the Histiocyte Society, he served on the Education Committee. His interest and initiative for increasing the activity and visibility of the Histiocyte Society has been an important part of the Society's evolution.

- Dr. Nesbit was a member and participant as a Board of Trustees member of the Histiocytosis Association. His activities in the Association made him a national source of information on the diagnosis and treatment of histiocytosis. In 1990, Professor Nesbit received the Outstanding Investigator Award from the Histiocytosis Association.

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

The Histiocytosis Association and the Histiocyte Society thought it entirely compatible with the support and the work of Dr. Nesbit within the world of the histiocytoses to offer this prize in his name. The candidates for this 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 is $500US and a certificate.
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.
HISTIOCYTE SOCIETY GOVERNING BY-LAWS

The Society shall be governed and guided by the principles set forth in these By-Laws.

ARTICLE I: MEMBERSHIP
Section 1 — Definitions and eligibility.
The membership of the Society shall consist of:

A. Ordinary Members
Ordinary Members are all 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 Society, may hold office, are eligible to vote, receive all communications and publications of the Society, and have such special rights and privileges that may be decreed by the Board with the majority vote consent and approval of the Ordinary Members.

B. Honored Members
Honored members are distinguished individuals, who in the view of the Board have made extraordinary contributions to the Society. Honored Members enjoy all rights and privileges of Ordinary Members, but do not pay dues, may not hold office, and will not receive a copy of the Society’s official journal.

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, may not hold office, and will not receive a copy of the Society’s official journal.

Section 2 — Appointment of members and termination of membership
A. A completed application for membership is to be submitted to the Secretariat of the Society for consideration by the Board prior to the General Assembly at the Annual Histiocyte Society Meeting. Applications should include a relevant curriculum vitae and/or supporting signature from an Ordinary Member. Applications approved by the Board must be ratified by the membership during the General Assembly of the Histiocyte Society Annual Meeting.

B. The Executive Board of the Society shall be the sole judge of moral, ethical and professional qualifications required for election to or termination of membership.

C. Applicants will be notified of action taken following the General Assembly in which their application has been considered.

D. Honored Members must be proposed to the Board by an Ordinary Member and accepted by the Board before ratification by the membership during the General Assembly of the Histiocyte Society Annual Meeting.

E. Emeritus Members must be proposed to the Board by an Ordinary Member or by themselves and accepted by the Board before ratification by the membership during the General Assembly of the Histiocyte Society Annual Meeting.

F. Membership shall be canceled on request of the member or on the grounds of: 1) nonpayment of dues for two successive years, 2) failure of the member to attend an Annual Meeting at least once in three years, or 3) unethical or unprofessional behavior by the member. Cancellation of membership must be approved by the Board.

ARTICLE II: DUES
Section 1
A. The annual dues for Ordinary Members shall be set by the Board and ratified by the General Assembly by a simple majority vote.
B. The annual dues shall be due and payable at the time of the annual meeting or by the date fixed by the Board for the payment thereof.

C. Membership may be canceled for failure to pay dues as set forth in Article I.

ARTICLE III: OFFICERS OF THE SOCIETY

The officers of the Society shall be the president, the immediate past-president, the president-elect, the secretary, and the treasurer. The offices of secretary and treasurer may be held by the same person. All officers must be Ordinary Members of the Society and serve without financial compensation. Terms begin and end at the end of the General Assembly of the Society as the final item of business.

A. President — Elected for a three-year term, and may be re-elected for one more term, but the second term may not be consecutive.
   1. Presides over annual meetings, is chairperson of the Board; appoints all members of committees not otherwise defined herein, organizes the agendas for Board and annual meetings, co-signs contracts and financial instruments on behalf of the Society, and serves as an ex-officio member of all standing and ad hoc committees of the Society.
   2. Represents the Society in dealing with other organizations and media.
   3. Becomes a member of the Board as the immediate past-president for the year immediately following his/her term of office.
   4. When a member of the Board acts for the then president under the conditions of Article IV.1.B.

B. President-Elect — Elected for a three-year term as president. Succeeds to that office at the end of the term of the then-incumbent.
   1. Becomes a member of the Board as the president-elect for the two years prior to assuming the presidency.
   2. When a member of the Board as the past-president acts for the then president under the conditions of Article IV.1.B.
   3. Serves as chairperson of the nominating committee.

C. Secretary — Elected for a two-year term with two additional terms permitted by re-election. Is responsible for communication with members and minutes of all meetings, and is ex-officio member of all committees. With the president, co-signs contracts and financial instruments on behalf of the Society. Oversees election of Scientific and Education Committee chairpersons following the annual General Assembly.

D. Treasurer — Elected for a two-year term with two additional terms permitted by re-election. Is responsible for all receipts and disbursements of money subject to direction from the Board. Such records as are necessary for auditing purposes must be kept. Recommendations concerning financial matters and the financial status of the Society are reviewed with the Board annually or more often as needed.

ARTICLE IV: THE EXECUTIVE BOARD

Section 1

The Executive Board (herein referred to as the “Board”) is the governing body responsible for operating the Society. It is composed of the immediate Past-President according to Article III.1.A.3., the President-Elect according to Article III.1.B.1., the other officers, and two Ordinary members-at-large elected by the membership for a three year term. All members serve without financial compensation.

A. The Board is required to meet no less than once each year, and it may enroll participation by others, without vote, as needed.
B. If for any reason, as determined by the Board, the president is unable to carry out his/her duties, then the President-Elect or the Past-President sitting on the Board at that time assumes the duties and responsibilities of the president.

C. Candidates for Board member-at-large shall be Ordinary Members who have not served on the Board in any capacity for at least two years prior to becoming at-large candidates.

D. A Board member-at-large may serve a second non-consecutive term permitted by re-election.

ARTICLE V: FINANCES

Section 1 — Financing of the Society will come through membership fees and from other sources approved by the Board.

Section 2 — Financial records will be audited by an external agency no less than every third year.

Section 3 — An annual budget and accounting of the previous year’s finances are to be presented by the Treasurer to the membership at each annual meeting.

Section 4 — Disbursements from the treasury in excess of $1,000US shall require prior approval of the Board.

ARTICLE VI: COMMITTEES

Section 1

Standing Committees include the Nominating Committee, the Program Committee, the Scientific Committee, and the Education Committee. The president may, at his/her discretion, appoint other committees on an ad hoc basis. The President is responsible for all appointments to committees, with review by and approval of the Board, except as described below.

A. Nominating Committee — This committee, composed of the most immediate Past-President, the President, and the president-elect (who will act as chairperson), shall be responsible for providing the Board with a slate of officers and candidates for at-large membership on the Board and members of the Scientific and Education Committees, the nominees having established a willingness to serve if elected.

1. The committee will propose at least one more candidate than the number of vacancies to be filled by election.

2. This slate must be presented to the Board no later than one month prior to the upcoming relevant General Assembly.

3. The committee will be responsible for presentation of the slate, as approved by the Board, and for carrying out the election at the relevant General Assembly.

4. Elections for Secretary and/or Treasurer and the Board Members-at-Large shall be conducted at the meeting marking the beginning of the then-incumbents’ last year in office.

5. Elections for president shall be conducted at the meeting marking the beginning of the last two (2) years in office of the then-incumbent President. The president-elect thereupon becomes a member of the Board according to Article III.B.1.

B. Program Committee — The President, Secretary, Chairperson of the Education Committee, Chairperson of the Scientific Committee, representative of Secretariat, and local representative(s) chosen by the Board among the members of the Society, if available, will act as a Program Committee for the upcoming annual meeting. The President shall act as chairperson. The committee shall be responsible for planning the meeting and for presenting plans to the Board for approval. It will organize and execute the
approved program. The committee will also be responsible for planning, organizing and executing other programs in which the Society is officially involved. The committee may recruit, at its discretion, assistance from others who may or may not be members of the Society.

C. **Scientific Committee** — Vacancies as they occur will be filled by election held at the General Assembly from a slate prepared by the Nominating Committee. Officers of the Society and members of the Nominating Committee are eligible to serve on this committee. Two-year terms will be staggered. A member may serve no more than six (6) consecutive years if re-elected. The committee will select its own chairperson from its membership within ten (10) days of the close of the annual meeting. The chairperson will lead the committee and liaison with the president.

The committee will:

1. Review proposals for research and related activities according to guidelines developed by the Board and make recommendations to the Board.
2. Present the Board with annual reports and plans concerning the Society’s research activities.

D. **Education, Constitution and By-Laws Committee** — Vacancies as they occur will be filled by election held at the General Assembly from a slate prepared by the Nominating Committee. Two-year terms will be staggered. A member may serve no more than six (6) consecutive years. The committee will select its own chairperson from its membership within ten (10) days of the close of the Annual Meeting. The chairperson will lead the committee and liaison with the president.

The committee will:

1. Suggest one or more topics to the Program Committee for an educational session to be conducted at the time of the General Assembly or such other times as are convenient and appropriate. The topics should be such as to attract not only physicians but also nurses, or psychologists or one of the other groups described in Article II. 4 of the Constitution.
2. Review abstracts and select those to be presented at the annual meeting.
3. a) Monitor the Constitution and By-Laws for needed amendments as circumstances dictate, and
   b) Be available to the Board for drafting of changes the Board deems advisable.
4. Present the Board with an annual assessment of the Constitution and By-Laws.

**ARTICLE VII: OPERATIONAL BASIS**

Section 1 — Business year

The Society’s official year will be January 1st through December 31st of each year.

Section 2 — Authority of procedure

“Robert’s Rules of Order, Revised” will guide all procedure, but where in conflict, these By-Laws shall prevail.

Section 3 — Quorum

Ten percent (10%) of the ordinary members shall constitute a quorum of the transaction of business at all General Assemblies of the Society.
HISTIOCYTE SOCIETY GOVERNING BY-LAWS

ARTICLE VIII: GENERAL MEETINGS

Section 1
The Society shall meet at least once annually in a combined business and scientific session (The Annual Meeting). The business meeting shall be termed the General Assembly. Special meetings may be called by the Board. Times and places thereof will be determined by the Board in consultation with the Scientific and Education Committees, and notice thereof shall be mailed to all members at least four (4) months prior to annual meetings and at least two (2) months prior to specially called meetings.

A. Scientific meetings
Scientific meetings will be open to all persons who are eligible for membership as defined in Article I and to others who share the objectives of the Society.

B. Business meetings
Business meetings (the General Assembly) are open only to members of the Society, consultants and guests invited by an officer of the Society.

Section 2
The agenda for the annual meeting shall be made available to the members no less than three (3) months prior to the meeting and will include:

1. Secretary’s report
2. Treasurer’s report
3. President’s report
4. Ratification of new members
5. Nominations and elections
6. Committee reports
7. Old business
8. New business
9. Other items

ARTICLE IX: AMENDMENTS AND REVISIONS

Section 1 — Amendments and revisions may be made by an affirmative vote of two-thirds (2/3) of a quorum at a General Assembly of the Society, provided proposed changes have been submitted to and approved by the Board and circulated among the members at least three (3) months prior to the General Assembly.

Section 2 — Proposed changes may originate with any Ordinary member of the Society. They should be submitted to the Secretary at least four (4) months prior to the General Assembly.

Section 3 — Changes properly proposed to the Board will be presented at the next General Assembly with the recommendation of the Board.
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