29th ANNUAL MEETING
OF THE HISTIOCYTE SOCIETY
GRAND HYATT - WASHINGTON, DC USA
OCTOBER 21 - 23, 2013

MEETING PROGRAM AND ABSTRACTS
For Informational Purposes Only:

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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.

All abstracts not presented at this meeting have been removed from the program for the security of unpublished information.

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MEETING SPONSORS

HISTIOCYTOSIS ASSOCIATION
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HISTIOCYTOSIS ASSOCIATION OF CANADA

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BOEDECKER FOUNDATION

Children’s National Medical Center

Sponsor of the 2013 Welcome Reception
Dear Colleagues,

It is with great pleasure that the Histiocyte Society welcomes you to Washington, D.C., for its Twenty-Ninth Annual Meeting. In addition to housing the offices of the United States government, Washington is home to many popular national monuments and museums as well as Children’s National Medical Center, recognized as one of the nation’s best pediatric hospitals.

This year’s invited speakers include Dr. Stephen Groft, Director of the NIH Office of Rare Diseases Research, who will discuss opportunities for research in rare diseases such as the histiocytic disorders; Dr. David Teachey of Children’s Hospital of Philadelphia, who will discuss recent developments in the biology and management of hypercytokinemias following T-cell activation; and Dr. Adeline Vanderver of Children’s National Medical Center, who will participate in a symposium on CNS inflammation in histiocytic disorders with Society members Drs. Kenneth McClain and Jan-Inge Henter. A symposium on malignant histiocytosis will feature Society members Drs. Diego Rosso, Marian Malone and Johannes Visser. Other educational sessions include the Presidential Symposium, updates on ongoing Society-sponsored clinical trials and a poster session.

Two features introduced at last year’s London meeting will return this year: “Meet the Expert” lunch sessions and a poster discussion session preceding the poster presentations. The “Meet the Expert” sessions on Monday are designed to provide an opportunity for trainees and other attendees new to the field of histiocytosis to interact with an international expert in a small-group, informal setting that fosters discussion. This program is a part of the Society’s ongoing effort to attract and engage younger members and investigators. Drs. Jan-Inge Henter of the Karolinska Institute and Kenneth McClain of Texas Children’s Hospital will serve as this year’s session leaders. Participation is limited in order to keep the number of participants to a size optimal for small-group discussion and registration is required. The poster discussion session, also introduced at last year’s meeting in London, will feature Drs. Tom Gross and Maarten Egeler providing analyses and perspectives on the meeting’s poster presentations.

This year’s social events include a welcome reception at Children’s National Medical Center and the Annual Banquet at the National Museum of Women in the Arts, housed in the former Masonic Temple, listed on the U.S. National Register of Historic Places and featuring works by Mary Cassatt, Frida Kahlo and Élisabeth Louise Vigée-Le Brun.

While you are in Washington, we hope that you will sample the many outstanding cultural opportunities conveniently located near the meeting site, such as a visit to the Washington Mall, featuring the National Art Gallery and its architecturally stunning East Wing (soon to close for 3 years of renovations), and the Lincoln Memorial, site of Martin Luther King’s inspirational “I Have a Dream” speech.

We are very grateful to our sponsors, without whose generous support this meeting would not be possible.

Welcome to Washington!

Jim Whitlock
President
Histiocyte Society
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ABOUT THE HISTIOCYTE SOCIETY

The Histiocyte Society is a professional medical association comprised of more than 175 physicians and scientists from around the world. Members of the organization are considered to be the leaders in understanding and treating histiocytic disorders. The Society is committed to advancing knowledge about histiocytic disorders and improving outcomes for patients through the planning, development, sponsorship, and oversight of clinical research.

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

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

True Partners
For more than 20 years, the Histiocytosis Association has served as a partner, secretariat and the primary source of funding for the Histiocyte Society. The Association’s support of the Society includes:

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

Conducting these activities alleviates the Society’s leadership of the administrative duties associated with running a volunteer-based, nonprofit organization and allows them to focus solely on research and treatment.
Each year the Histiocyte Society awards one scholarship based on the applicant's demonstration of need for financial assistance in order to attend the Annual Meeting. Scholarships are awarded in the amount of $1,000 US and based on the availability of funds.
All 29th Annual Meeting Sessions will be held on Constitution Level.
AT-A-GLANCE MEETING AGENDA

SATURDAY • OCTOBER 19, 2013
0900 – 1430  Executive Board Meeting* ................................................................. Washington Board Room, Constitution Level
1600 – 1700  Rare Histiocytic Disorders Steering Committee Meeting* .................... Washington Board Room, Constitution Level
1700 – 1800  LCH Steering Committee Meeting* ........................................................ Washington Board Room, Constitution Level

SUNDAY • OCTOBER 20, 2013
0800 – 1030  LCH Disease Discussion Session* ......................................................... Room CDE, Constitution Level
1030 – 1130  LCH Adult Disease Discussion Session* ................................................. Room CDE, Constitution Level
1130 – 1230  Rare Histiocytic Disorders Discussion Session* .................................. Room CDE, Constitution Level
1230 – 1330  Lunch ........................................................................................................ Room B, Constitution Level
1330 – 1830  HLH Disease and MAS Discussion Session* ........................................ Room CDE, Constitution Level

MONDAY • OCTOBER 21, 2013
0800 – 1700  Meeting Registration and Check-In ....................................................... Registration Desk, Constitution Level
0800 – 0930  Education Committee Meeting* ............................................................. Arlington, Constitution Level
0945 – 1000  Opening Ceremonies ............................................................................ Room AB, Constitution Level
1000 – 1100  Special Presentation: Opportunities in Rare Disease Research ............ Room AB, Constitution Level
1100 – 1130  Coffee Break ......................................................................................... Room AB, Constitution Level
1130 – 1300  Scientific Session I: Oral Presentations ................................................ Room AB, Constitution Level
1300 – 1400  Lunch ........................................................................................................ Room CDE, Constitution Level
1400 – 1530  LCH Meet the Expert Lunch Session* .................................................... Arlington, Constitution Level
1445 – 1530  HLH Meet the Expert Lunch Session* ................................................... Cabin John, Constitution Level
1530 – 1600  Scientific Session II: Presidential Symposium ......................................... Room AB, Constitution Level
1600 – 1800  Coffee Break ......................................................................................... Room AB, Constitution Level
1900 – 2100  Welcome Reception* ............................................................................. Children’s National Medical Center

TUESDAY • OCTOBER 22, 2013
0800 – 1300  Meeting Registration and Check-In ....................................................... Registration Desk, Constitution Level
0830 – 1000  Clinical Studies and Registries Update .................................................. Room AB, Constitution Level
1000 – 1030  Coffee Break ......................................................................................... Room CDE, Constitution Level
1030 – 1145  Malignant Histiocytosis Symposium ...................................................... Room AB, Constitution Level
1145 – 1245  Scientific Session III: Oral Presentations .............................................. Room AB, Constitution Level
1245 – 1315  Guest Speaker Presentation: David Teachey .......................................... Room AB, Constitution Level
1315 – 1415  Lunch ....................................................................................................... Room CDE, Constitution Level
1415 – 1530  CNS Inflammation in Histiocytic Disorders Symposium ...................... Room AB, Constitution Level
1530 – 1600  Coffee Break ......................................................................................... Room CDE, Constitution Level
1600 – 1730  General Assembly Meeting* ................................................................. Room AB, Constitution Level
1900 – 2400  Histiocyte Society Annual Banquet ....................................................... National Museum of Women in the Arts

WEDNESDAY • OCTOBER 23, 2013
0800 – 1200  Meeting Registration and Check-In ....................................................... Registration Desk, Constitution Level
0900 – 1000  Jon Pritchard Lecture on the Nicolas Symposium .................................. Room AB, Constitution Level
1000 – 1030  Coffee Break ......................................................................................... Room CDE, Constitution Level
1030 – 1145  Scientific Session IV: Oral Presentations .............................................. Room AB, Constitution Level
1145 – 1200  Closing Ceremonies: Awarding of Scientific Prizes ............................... Room AB, Constitution Level

* Indicates closed session
* Indicates that advance registration was required

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GUEST SPEAKER HIGHLIGHTS

STEPHEN C. GROFT, Pharm.D, is the Director of the Office of Rare Diseases Research (ORDR) in the National Center for Advancing Translational Sciences at the National Institutes of Health (NIH). His major focus is on stimulating research with rare diseases and developing information about rare diseases and conditions for health care providers and the public. To help identify research opportunities and establish research priorities, the Office has co-sponsored over 1200 rare diseases-related scientific conferences with the NIH research Institutes and Centers and the extramural research community, including patient advocacy groups. Current and recent activities include establishing common data elements and patient registries for rare diseases, developing an inventory of available bio-specimens from existing bio-repositories, developing an educational module on rare diseases for middle school children, maintaining a public information center on genetic and rare diseases, developing an international rare diseases research consortium, maintaining the Rare Diseases Clinical Research Network, and assisting in the development of a special emphasis clinic with senior clinical staff for patients with undiagnosed diseases at NIH’s Clinical Research Center Hospital. Steve received a B.S. degree in Pharmacy in 1968 and a Doctor of Pharmacy degree from Duquesne University in 1979.

JAN-INGE HENTER earned an MD from Uppsala University in 1980 and after internship in Uppsala he completed a fellowship in Pediatrics (1987) in Stockholm and defended a PhD-thesis at the Karolinska Institutet in 1990, with a focus on hemophagocytic lymphohistiocytosis (HLH). He specialized in Pediatric Hematology and Oncology and was named Professor at Karolinska Institutet in 2004. His research interest in the histiocytoses remains and in addition to developing the first diagnostic criteria for HLH, he also was PI of HLH-94 as well as HLH-2004. He also analysed the underlying biological and genetic defects in HLH, and another interest is the secondary forms of HLH. He is also increasingly interested in understanding the biology of Langerhans cell histiocytosis (LCH), with the ultimate aim to reduce morbidity. In addition, he is running studies in many other fields, including End-of-Life Care. He was President of the Histioyte Society 2004-2007 and the Founding President of the International Conference for Rare Diseases and Orphan Drugs (ICORD). He has received numerous prizes and co-authored more than 170 publications. He describes himself as a curious and enthusiastic explorer of the World and everything in it.

MARIAN MALONE is a paediatric pathologist and Head of Laboratories at Great Ormond Street Children’s Hospital, London, UK. She qualified with Honours in Medicine in Dublin, Ireland in 1977. After internship in the Mater Misericordiae Hospital, Dublin she moved to London. She received her general pathology training at The Royal London Hospital, Whitechapel and King’s College Hospital, Denmark Hill and her specialist paediatric pathology training at Great Ormond Street Children’s Hospital. She was appointed consultant pathologist at Great Ormond Street in 1986. She engages in collaborative clinical research and has over 100 publications in peer-reviewed journals. In 2004, she was co-applicant on a research grant for £80,000 and co-supervised the resultant MD thesis. She is a member of the Children’s Cancer and Lymphoma Group (CCLG) Histiocytosis Special Interest Group and a member of the Steering Group of the Nikolas Symposium. In June 2013, she was appointed to the Rare Histiocytoses Steering Committee of the Histioyte Society. She is Clinical Director for Paediatric Pathology for London and is a member of the London Clinical Senate which is a forum for discussion on issues that are key to the development of London’s health services. Since January 2012 she has chaired the national Clinical Reference Group which advises NHS England on Paediatric Cancer Services. In August 2013 she was appointed to the National Institute for Clinical Excellence (NICE) Highly Specialised Technologies Evaluation Committee which evaluates the benefits and costs of a small number of medicines aimed at treating patients with very rare diseases and very complex healthcare needs.

KENNETH MCCLAIN, M.D., Ph.D. is a Professor of Pediatrics at Baylor College of Medicine. He graduated from the University of Chicago School of Medicine in 1973 as a trainee in the Pediatric Medical Scientist program. From 1973-76 he did a pediatric residency at the Johns Hopkins Hospital in Baltimore followed by post-doctoral research at the National Institutes of Health in the Laboratory of Molecular Genetics of the Child Health Institute from 1976-1979. He completed his pediatric oncology fellowship at the University of Minnesota School of Medicine (1979-81) and was then on the faculty for 5 years. Since 1986 he has been an attending physician in the Texas Children’s Cancer and Hematology Center and a Professor of Pediatrics since 2003. Dr. McClain is a member of the Histiocytic Diseases/Lymphoma clinic team. In 2001, he developed a Histiocytosis Center which now sees over 135 new patients a year including children and adults with Langerhans cell histiocytosis, Hemophagocytic Lymphohistiocytosis, Juvenile Xanthogranuloma, Rosai Dorfman Disease, Multifocal Reticulohistiocytosis, and Erdheim Chester Disease. He and Dr. Carl Allen have done ground-breaking work on the biology of Langerhans cell histiocytosis, clinical prognostic factors in Hemophagocytic Lymphohistiocytosis and improved treatments for adult patients with histiocytic diseases.

Biographical information provided by guest speakers.
DIEGO ROSSO graduated from the University of Buenos Aires Medical School with an Honors Diploma in 1991. After completing a pediatrics residency and a fellowship in Pediatric Hematology/Oncology at the National Pediatric Hospital Garrahan, he performed a fellowship in medical research for three years in the field of cytokines and histiocytosis under the supervision of Dr. Jorge Braier. The results of these investigations were the basis of his thesis to obtain a PhD degree at the University of Buenos Aires. In 1989, Dr. Rosso started as a student instructor of Pharmacology and after continuing teaching, in 2012 was named Adjunct Professor. He has attended the Histiocyte Society Annual Meetings since 1998 and currently serves as the chair of the Education Committee. He is attending at the pediatric hemato-oncology sections of the Hospital de Niños “Dr Pedro de Elizalde” and Hospital de Clinicas “Jose de San Martin” of Buenos Aires, Argentina.

DAVID TEACHEY is a physician/scientist working in pediatric hematology and oncology at the Children’s Hospital of Philadelphia (CHOP). He completed his training in pediatrics at the Children’s National Medical Center in Washington, D.C. and his fellowship training at CHOP. He remained at CHOP after training and is currently an Assistant Professor of Pediatrics at the University of Pennsylvania School of Medicine. Dr. Teachey’s research focuses on leukemia stem cell biology and lymphoproliferative disorders. His clinical interests include childhood leukemia, lymphoproliferative and histiocytic disorders, as well as hematopoietic stem cell transplant.

ASTRID G. S. VAN HALTEREN, after graduating from the University of Amsterdam (M.Sc. in Biomedical Sciences) in 1992 and obtaining a PhD degree at the Faculty of Medicine of the Vrije Universiteit Amsterdam in 1996, worked as a junior postdoctoral fellow at the Vrije Universiteit Amsterdam (2 years) and as a senior postdoctoral fellow at the Department of Immunohematology and Blood Transfusion at the Leiden University Medical Center (7 years). During these years, she became a specialist in Immunology (SMBWO accredited) and was extensively trained in human T-cell biology. Six months pregnant (the girls are now 5 and 3-year-old), Dr. van Halteren joined Professor Egeler’s research group at the Department of Pediatrics at the Leiden University Medical Center in May 2008. As a senior research associate, Dr van Halteren is (co) PI on two distinct research lines: unravelling the process of inflammatory lesion formation in Langerhans Cell Histiocytosis (LCH) and unravelling alloimmune T-cell mediated complications associated with female-to-male allogeneic hematopoietic stem cell transplantation. The LCH research program is sponsored by grants from the Histiocytosis Association, the 1000 Kaarsjes voor Juultje Foundation and the KinderenKankervrij Foundation. In addition to her research activities, Dr. van Halteren is a (key) lecturer in two distinct educational programs of the Leiden University (Medicine and Biomedical Sciences) and R&D project manager working 1 day/week at Immunobank n.v.

ADELINE VAN DER VER is a child neurologist with special expertise in biochemical genetics. Clinical research interests include undiagnosed neurogenetic disorders and leukodystrophies, with research protocols aimed at providing diagnosis. In addition, she provides molecular diagnosis of Alexander disease, megalencephalic leukodystrophy with subcortical cysts, and eIF2B disorders (vanishing white matter disease), as well as a rapid cerebrospinal fluid test for eIF2B related disorders. She is also exploring abnormal protein production in eIF2B related disorders and the etiology of hypomyelinating (or pelizaeus merzbacher-like disorders) leukodystrophies.

JOHANNES VISSER is a Consultant Paediatric Oncologist based at the Leicester Children’s Hospital in the United Kingdom. He is also Clinical Service Director of the Children’s and Young Persons’ Integrated Cancer Service in the East Midlands. Dr. Visser received his primary medical degree from the University of Stellenbosch in South Africa in 1992. He trained in paediatrics in the United Kingdom and at the University of Stellenbosch, completing his general paediatric training in 2001. In 2005 he completed his paediatric oncology/haematology fellowship at the British Columbia Children’s Hospital in Vancouver and joined the paediatric oncology team in Leicester. He has a special interest in histiocytic disorders, sarcomas and the design and conduct of clinical trials. Dr. Visser is a current member of the Histiocyte Society Scientific Committee and a trustee of the Histiocytosis Research Trust.

Biographical information provided by guest speakers.
MEETING AGENDA: SATURDAY, OCTOBER 19, 2013

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

0900 – 1430  Executive Board Meeting* ..............................................................Washington Board Room, Constitution Level
1600 – 1700  Rare Histiocytic Disorders Steering Committee Meeting* ..............................Washington Board Room, Constitution Level
1700 – 1800  LCH Steering Committee Meeting* ............................................................Washington Board Room, Constitution Level

MEETING AGENDA: SUNDAY, OCTOBER 20, 2013

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

0800 – 1030  LCH Disease Discussion Session* ...............................................................Room CDE, Constitution Level
Session Moderator: Cor van den Bos

1030 – 1130  LCH Adult Disease Discussion Session* .........................................................Room CDE, Constitution Level
Session Moderator: Michael Girschikofsy

1130 – 1230  Rare Histiocytic Disorders Discussion Session* .................................................Room CDE, Constitution Level
Session Moderator: Oussama Abla

1230 – 1400  Lunch (on your own) .........................................................................................Room B, Constitution Level

1400 – 1900  HLH Disease and MAS Discussion Session* ..................................................Room CDE, Constitution Level
Session Moderators: Gritta Janka, AnnaCarin Horne

* Indicates Closed Session
+ Indicates that advance registration was required
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<td>Education Committee Meeting*</td>
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<td>Scientific Committee Meeting*</td>
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<td>0945 – 1000</td>
<td>Opening Ceremonies</td>
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<td>Special Presentation: Opportunities in Rare Disease Research</td>
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<td><strong>OPPORTUNITIES IN RARE DISEASE RESEARCH</strong></td>
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<td>Stephen C. Groft, Pharm. D.</td>
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<td>Director, NIH Office of Rare Diseases Research, Washington, DC USA</td>
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<td>1100 – 1130</td>
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<td>1130 – 1300</td>
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<td><strong>ADOLESCENTS AND YOUNG ADULTS WITH HLH WHO UNDERGO ALLOGENEIC HCT ARE AT INCREASED RISK OF MORTALITY COMPARED TO YOUNGER PATIENTS</strong></td>
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<td>LCH Meet the Expert Lunch Session*</td>
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<td>Kenneth McClain, MD, PhD</td>
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<td>Texas Children's Hospital, Pediatric Hematology-Oncology, Houston, TX USA</td>
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1300 – 1400  HLH Meet the Expert Lunch Session* ........................................................................................................................................Cabin John, Constitution Level
Hemophagocytic Syndromes
Jan-Inge Henter, MD, PhD
Childhood Cancer Research Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden
Lunch will be served to session attendees in meeting room.

1400 – 1530  Scientific Session II: Presidential Symposium .........................................................................................................................Room AB, Constitution Level
Session Moderator: Jim Whitlock

PRESENTATIONS NOMINATED FOR THE NEZELOF PRIZE IN BASIC SCIENCE (see page 59 for more information)
GENETICALLY ENGINEERED MOUSE MODELS OF BRAF V600E EXPRESSION IN LANGERHANS CELLS
Gayane Badalian-Very, Jo-Anne Vergilio, Kristen Stevesen, Roderick Bronson, Mark Fleming, Barrett Rollins

JANUS KINASE INHIBITION AS A NOVEL TREATMENT FOR MACROPHAGE ACTIVATION SYNDROME

DESCRIPTIVE EPIDEMIOLOGY OF LANGERHANS CELL HISTIOCYTOSIS
Carlos Rodriguez-Galindo, Barbara Degar, Celia Antonelli, Barrett Rollins, Karina Ribeiro

PRESENTATIONS NOMINATED FOR THE NESBIT PRIZE IN CLINICAL SCIENCE (see page 59 for more information)
HEMATOPOIETIC STEM CELLS AND CIRCULATING MYELOMONOCYTIC PRECURSORS WITH BRAF-V600E ARE IDENTIFIED IN HIGH-RISK PATIENTS AND DEFINE LCH AS A MYELOID NEOPLASIA

INFECTION ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A NOVEL SHORT COURSE STEROID ONLY PROTOCOL
Prabhas Prasun Giri, Priyankar Pal

SOMATIC ARAF MUTATIONS IN LANGERHANS CELL HISTIOCYTOSIS
Barrett Rollins, David Nelson, Willemijn Quispel, Gayane Badalian-Very, Astrid van Halteren, Paul van Hummelen, Matthew Ducar, Laura MacConnail, Mark Fleming, Maarten Egeler

1530 – 1600  Coffee Break ..............................................................................................................................................................................Room CDE, Constitution Level

1600 – 1800  Poster Presentation Session .........................................................................................................................................................Room AB, Constitution Level
Please note that the second hour (1700 - 1800) of this session will take place in Room CDE, Constitution Level.
Session Moderators: R. Maarten Egeler, Thomas Gross

CLINICAL LCH POSTER PRESENTATIONS
Poster Location #2
CENTRAL NERVOUS SYSTEM LESIONS COMPATIBLE WITH NEURODEGENERATIVE INVOLVEMENT IN LANGERHANS CELL HISTIOCYTOSIS
Jorge Braier, Soledad Monges, Constanza Pasteris C, Elisa Vaiani, Carlos Rugilo, Viviana Lopez

Poster Location #3
A RARE PRESENTATION OF LCH WITH SOLID BONE MASS: CASE REPORT
Devecioglu O, Koc BS, Uysalol E, Karaman S, Unuvar A, Karakas Z, Anak S

Poster Location #4
PITFALLS IN THE DIAGNOSIS OF GASTROINTESTINAL TRACT LANGERHANS CELL HISTIOCYTOSIS
Rieko Ito, Akina Matsuoka, Toshihiro Tomii, Kyogo Suzuki, Hironobu Kitaizawa, Taemi Ogura, Masayuki Okada, Yasuo Horikoshi, Kazuko Kudo

* Indicates that advance registration was required
MEETING AGENDA: MONDAY, OCTOBER 21, 2013

Poster Location #5
THE RESULTS OF TREATMENT WITH VINBLASTINE, PREDNISONE AND MERCAPTOPURINE IN ADULT PATIENTS WITH MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS
Elżbieta Radzikowska, Elżbieta Wiatr, Iwona Beatty, Ewa Szczepulska-Wójcik, Piotr Rudzinski, Kazimierz Roszkowski-Śliż

Poster Location #6
INDOMETHACIN WAS EFFECTIVE IN TWO PATIENTS WITH LCH IN “SPECIAL SITES”
Diego Rosso, Stella Balestrini, Valeria Santidrian, Ezequiel Recondo

Poster Location #7
CONGENITAL ANOMALIES IN CHILDREN AND YOUNG PEOPLE WITH LANGERHANS CELL HISTIOCYTOSIS: A POPULATION-BASED RECORD LINKAGE STUDY
Jane Salotti, Peter Tennant, Kevin Windebank, Judith Rankin

Poster Location #8
FAVORABLE OUTCOMES OF REFRACTORY OR REACTIVATED LANGERHANS CELL HISTIOCYTOSIS TREATED WITH SALVAGE CHEMOTHERAPY OF 2-CHLORODEOXYADENOSINE AND CYTOSINE ARABINOSIDE: A SINGLE CENTER EXPERIENCE IN KOREA
Jong Jin Seo, Kyung-Nam Koh, Jin Kyung Suh, Hye Ran Shin, Ho Joon Im

Poster Location #10
ANALYSIS OF PERMANENT CONSEQUENCES IN PEDIATRIC PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS: DATA OF THE JLSG-96 AND JLSG-02 STUDIES IN JAPAN
Yoko Shioda, Akira Morimoto, Toshihiko Imamura, Kazuko Kudo, Shinsaku Imashuku

Poster Location #11
THE OPTIMAL IMAGING TECHNIQUE FOR EVALUATION OF BONE LESIONS IN LANGERHANS CELL HISTIOCYTOSIS AT DIAGNOSIS: A SYSTEMATIC REVIEW
Sebastiaan Somers, Eline Deurloo, Raquel Dávila Fajardo, Jan Booij, Anne Smets, Cor van den Bos

BASIC LCH POSTER PRESENTATIONS

Poster Location #13
ANALYSIS OF SERUM OSTEOPONTIN LEVELS IN PEDIATRIC PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS
Akira Morimoto, Yukiko Oh, Yoko Shioda, Toshihiko Imamura, Kazuko Kudo, Shinsaku Imashuku

Poster Location #14
PULMONARY LANGERHANS CELL HISTIOCYTOSIS: THE INCIDENCE OF ALPHA-1 ANTITRYPSINE (A1AT) DEFICIENCY ALLELES
Elżbieta Radzikowska, Radosław Struniawski, Joanna Chorostowska-Wynimko, Agnieszka Jarzemska, Kazimierz Roszkowski-Śliż

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BONE MARROW NECROSIS, LEUKEMIA AND HEMOPHAGOCYTOSIS: IS THE UNDERLYING CAUSE EBV?

Poster Location #16
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Poster Location #18
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AnnaCarin Horne, Francesca Minoia, Sheila Weitzman, Ed Behrens, Alexei Grom, Randy Crohn and Angelo Ravelli

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A CASE OF EPSTEIN BARR VIRUS (EBV)-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) AND SUBSEQUENT EBV-ASSOCIATED PRIMARY CNS LYMPHOMA (PCNSL)
Caroline Yingwen Hu, Steven Diamond
THE RESPONSE OF PATIENTS WITH EPSTEIN-BARR VIRUS-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS TO HLH-2004 PROTOCOL IN THE INITIAL THERAPY
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PRENATAL DEMISE OF A FETUS WITH GENETICALLY CONFIRMED FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (FHLH)
Karen Mandel, Lauren Higgins, Julie Richer

NEUROLOGIC AND NEUROIMAGING FEATURES OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN ADULT PATIENTS
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HEMOPHAGOCYTIC SYNDROME DURING INDUCTION THERAPY FOR AMBIGUOUS LINEAGE (B/My) ACUTE LEUKEMIA
Diego Rosso, Stella Balestrini, Candelaria Serrano, Lucia Diodied, Ezequiel Riecondo

ANAPLASTIC LARGE CELL LYMPHOMA PRESENTING WITH SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Meaghann Weaver and Patrick Campbell

IDENTIFYING FAMILIAL ASSOCIATIONS IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) USING THE UTAH POPULATION DATABASE
Mark Fluchel, Michael Hogarty, Jim Whitlock, Richard Pimental, Geri Mineau

R65Q MUTATION IN STXBP2 SHEDS LIGHT ON THE MOLECULAR MECHANISMS THAT CONTROL LYTIC GRANULE RELEASE
Claudio G. Giraudo, Waldo A. Spessott, Maria L. Sanmillan, Kim E. Nichols

PATHOGENESIS AND OUTCOME OF CHEDIAK-HIGASHI SYNDROME: A LYTIC GRANULE DISORDER OF LYMPHOCYTES IN JAPAN
Kozo Nagai, Eiichi Ishii, Masaki Yasukawa and the Histioctosis Committee of the Japanese Society of Pediatric Hematology/Oncology

WHOLE EXOME SEQUENCING IDENTIFIES THE MOLECULAR DEFECTS IN 3 PATIENTS WITH PARTIAL ALBINISM AND IMMUNODEFIENCY
Bianca Tesi, Marie Meeths, Samuel C.C. Chiang, Miriam Entesarian, Waleed Al-Herz, Ekrem Uinal, Magnus Nordenskjoeld, Jan-Inge Henter and Yenan T. Bryceson

ACTIVATING MUTATIONS IN NRAS IN ERDHEIM-CHESTER DISEASE
Eli L. Diamond

A SURVEY OF DISSEMINATED JUVENILE XANTHOGRANULOMA IN JAPAN
Miho Maeda, Eiichi Ishii, Yasushi Ishida, Shigeru Ohta, Takayuki Okamura, Hirokazu Kanegane, Toshiyuki Kito, Kazuhiro Kogawa, Nobuhiro Suzuki

SPONTANEOUSLY REGRESSING NON-LANGERHANS CELL HISTIOCYTOMA WITH RETICULOHISTIOCYTOMA MORPHOLOGY: A REPORT OF TWO CASES
Marian Malone, Penelope Brock, Johannes Visser
MEETING AGENDA: MONDAY, OCTOBER 21, 2013

Poster Location #35
CEREBELLAR DEGENERATION IN A PATIENT WITH HISTIOCYTIC DISEASE
Karen Mandel, Kandice Mah, Daniel Keene

Poster Location #37
ERDHEIM-CHESTER DISEASE (ECD) IN A 3-YEAR-OLD CHILD: A DIFFICULT DIAGNOSIS
Elena Sieni, Anna Maria Buccoliero, Chiara Azzari, Massimo Resti, Maurizio Aricò

Poster Location #38
TWO CASES OF NEONATAL DISSEMINATED JUVENILE XANTHOGRANULOMATOSIS TREATED WITH LCH-BASED THERAPY
Thomas Y. Merola P, Phelps R, Rosenberg H and Wistinghausen B

Poster Location #39
REFRACTORY, ATYPICAL ROSAI-DORFMAN DISEASE SUCCESSFULLY TREATED WITH A CYTARABINE-CONTAINING LANGERHANS CELL HISTIOCYTOSIS TREATMENT REGIMEN: A CASE REPORT
Johannes Visser, Martin JS Dyer

1900 – 2100
Welcome Reception at Children’s National Medical Center*
Sponsored by Children’s National Medical Center
111 Michigan Avenue, NW, Washington, DC 20010
Phone: +1 202-476-5000

Buses will pick up guests at 1830 from the Grand Hyatt Washington Lobby Level Main Entrance (1000 H Street, NW, Washington, DC USA)

* Indicates that advance registration was required
MEETING AGENDA: TUESDAY, OCTOBER 22, 2013

0800 – 1300  Meeting Registration and Check-In.................................................................Registration Desk, Constitution Level

0830 – 1000  Clinical Studies and Registries Update.........................................................Room AB, Constitution Level
   Session Moderator: Riccardo Haupt

   0830 – 0900  LCH-IV: Milen Minkov
   0900 – 0915  Pediatric Trial of Dabrafenib, an Oral BRAF Inhibitor: Jim Whitlock
   0915 – 0930  HIT-HLH: Michael Jordan
   0930 – 0945  Pilot Study of Ni-0501, an Anti-IFN Monoclonal Antibody: Maurizio Aricò
   0945 – 1000 Reduced-Intensity Conditioning for HLH and Select Immune Deficiencies: Carl Allen

1000 – 1030  Coffee Break........................................................................................................Room CDE, Constitution Level

1030 – 1145  Malignant Histiocytosis Symposium .................................................................Room AB, Constitution Level
   Session Moderator: Oussama Abla

CASE ON MALIGNANT HISTIOCYTOSIS  
Diego Rosso, PhD  
Hospital Elizalde, Pediatric Hemo-oncology, Buenos Aires, Argentina

THE PATHOLOGY OF HISTIOCYTIC MALIGNANCIES  
Marian Malone, MD  
Great Ormond Street Children’s Hospital, Pediatric Pathology, London, UK

EXPLORING THE EPIDEMIOLOGY, TREATMENT AND OUTCOME OF THE MALIGNANT HISTIOCYTOSIS  
Johannes Visser, MD  
University Hospitals of Leicester, Leicester Children’s Hospital, Pediatric Oncology, Leicester, UK

1145 – 1245  Scientific Session III: Oral Presentations.........................................................Room AB, Constitution Level
   Session Moderators: Lisa Filipovich, Akira Morimoto

   INTERFERON GAMMA (IFNG) AND TOLL-LIKE RECEPTOR 9 (TLR9) PROVIDE COLLABORATING AND NON-REDUNDANT SIGNALS TO INHIBIT B-CELL DEVELOPMENT IN CYTOKINE STORM SYNDROMES  
Edward Behrens, Kim Nichols, Sheena Baratono

   AGGRESSIVE LANGERHANS CELL HISTIOCYTOSIS FOLLOWING T-ALL: CLONALLY RELATED NEOPLASMS WITHOUT BRAF V600E MUTATION AND SUFFICIENT EXPRESSION OF ASPARAGINE SYNTHETASE  
Kitoh T, Akiyama M, Taki T, Shimomura Y, Hori T, Tsurusawa M, Terashima T and Yokoi T

   IL-17A PRODUCTION BY BLOOD MONOCYTES IS TIGHTLY RELATED TO THE DEGREE OF ACTIVITY OF LANGERHANS CELL HISTIOCYTOSIS  
Magda Lourda, Selma Olsson Åkefeldt, Désirée Gavhed, Niels Clausen, Ulf Hjalmars, Magnus Sabel, Abdellatif Tazi, Maurizio Aricò, Christine Delprat, Mattias Svensson and Jan-Inge Henter

   SYNERGISTIC DEFECTS OF DIFFERENT MOLECULES IN THE CYTOTOXIC PATHWAY LEAD TO CLINICAL FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS  
Kejian Zhang, Shanmuganathan Chandrakasan, Ammar Husami, Diane Kissell and Alexandra H. Filipovich
### MEETING AGENDA: TUESDAY, OCTOBER 22, 2013

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<td>1245 – 1315</td>
<td><strong>Guest Speaker Presentation</strong> .................................................</td>
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<td>Session Moderator: Michelle Hermiston</td>
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<td><strong>BIOLOGY AND MANAGEMENT OF CYTOKINE RELEASE SYNDROME AFTER T-CELL ACTIVATING THERAPIES</strong></td>
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<td>David Teachey, MD</td>
<td>Department of Oncology, Children's Hospital of Philadelphia, Philadelphia, PA USA</td>
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<td>1315 – 1415</td>
<td><strong>Lunch</strong> .........................................................................................</td>
<td>Room CDE, Constitution Level</td>
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<td>1415 – 1530</td>
<td><strong>CNS Inflammation in Histiocytic Disorders Symposium</strong> ..................</td>
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<td>Session Moderator: Carl Allen</td>
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<td><strong>NEURODEGENERATIVE CNS LCH: HAVE WE MADE ANY PROGRESS?</strong> ...............</td>
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<td>Kenneth McClain, MD, PhD</td>
<td>Texas Children’s Hospital, Pediatric Hematology-Oncology, Houston, TX USA</td>
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<td><strong>CNS INVOLVEMENT IN HLH</strong></td>
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<td>Jan-Ingell Henter, MD, PhD</td>
<td>Childhood Cancer Research Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden</td>
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<td><strong>HERITABLE DEGENERATIVE DISORDERS OF THE WHITE MATTER: LEUKODYSTROPHIES AND GENETIC LEUKOENCEPHALOPATHIES</strong></td>
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<td>Adeline Vanderver, MD</td>
<td>Principal Investigator, Children's Research Institute, Children's National Medical Center, Washington, DC USA</td>
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<td>1530 – 1600</td>
<td><strong>Coffee Break</strong> ...............................................................................</td>
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<td>1600 – 1730</td>
<td><strong>General Assembly Meeting</strong>* ..........................................................</td>
<td>Room AB, Constitution Level</td>
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<td>1900 – 2400</td>
<td><strong>Histiocyte Society Annual Banquet</strong> ...........................................</td>
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<td>National Museum of Women in the Arts</td>
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<td>1250 New York Avenue, NW Washington, DC 20005-3970</td>
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<td>Group will depart, on foot, promptly at 1830 from the Grand Hyatt Washington Lobby Level Main Entrance (1000 H Street, NW, Washington, DC USA)</td>
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* Indicates Closed Session
MEETING AGENDA: WEDNESDAY, OCTOBER 23, 2013

0800 – 1200  Meeting Registration and Check-In ................................................................. Registration Desk, Constitution Level

0900 – 1000  Jon Pritchard Lecture on the Nikolas Symposium .................................................. Room AB, Constitution Level
Session Moderator: Robert Arceci

CXCR4 EXPRESSION BY LANGERHANS CELL HISTIOCYTOSIS CELLS IS ASSOCIATED WITH POOR DISEASE OUTCOME
Astrid van Halteren, PhD
Willem Alexander Children’s Hospital / LUMC, Leiden, The Netherlands

1000 – 1030  Coffee Break ............................................................................................................. Room CDE, Constitution Level

1030 – 1145  Scientific Session IV: Oral Presentations ................................................................. Room AB, Constitution Level
Session Moderators: Kimo Stine, Stephan Ladisch

AN ORAL PAN-AKT INHIBITOR IN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS SHOWS SIGNS OF CLINICAL ACTIVITY
Robert J. Arceci, Carl Allen, Ira Dunkel, Eric Jacobsen, James Whitlock, Robert Vassallo, Ivan Borrell, Shannon Morris,
Beth Ann Reedy, Alison Portnoy, Bob Noble, Amy Murnane, Stephen Szabo, Carlos Rodriguez-Galindo, Kenneth McClain,
Sarah Vaiselbuh

PATTERN AND COURSE OF MULTIFOCAL BONE DISEASE (MFBD) IN LANGERHANS CELL HISTIOCYTOSIS (LCH): DATA FROM THE LCH III STUDY
Bernhard Fahrner, Ulrike Pötschger, Evgenia Glogova, Elfriede Thiem, Gritta Janka, Nicole Grois, Helmut Gadner,
Milen Minkov for the LCH III Study Group

PATIENT OUTCOMES OF LANGERHANS CELL HISTIOCYTOSIS INVOLVING SKIN
Benjamin Garmezy, Stephen J. Simko, Harshal Abhyankar, Karen Phaik-Har Lim, Albert Shih, Munu Bilgi, Rachel Bingham,
Kenneth L. McClain and Carl E. Allen

NEURODEGENERATIVE LANGERHANS CELL HISTIOCYTOSIS (ND-LCH): CORRELATION WITH AGE AT DIAGNOSIS AND IDENTIFICATION OF MARKERS OF DISEASE PROGRESSION
Elena Sieni, Carmen Barba, Marzia Mortilla, Sara Savelli, Cecilia Cecchi, Claudio Fonda, Renzo Guerrini, Maurizio Aricò

THE OPTIMAL IMAGING TECHNIQUE FOR RESPONSE EVALUATION OF BONE LESIONS IN LANGERHANS CELL HISTIOCYTOSIS: A SYSTEMATIC REVIEW
Sebastiaan Somers, Elise Deurloo, Raquel Dávila Fajardo, Anne Smets, Cor van den Bos

1145 – 1200  Closing Ceremonies .................................................................................................... Room AB, Constitution Level
Carlos Rodriguez-Galindo, Histioyte Society President
Awarding of Annual Scientific Prizes
THE PATHOLOGY OF HISTIOCYTIC MALIGNANCIES

Marian Malone, MD
Pediatric Pathologist and Head of Laboratories
Great Ormond Street Children’s Hospital, Pediatric Pathology, London, UK

Before the age of immunohistochemistry and molecular biology, histiocytic lymphoma was a relatively common diagnosis. Cases previously reported as such almost all represent large cell lymphomas of B or T lineage or anaplastic large cell lymphoma. Histiocytic malignancies are now recognised to be extremely rare, representing less than 1% of tumours presenting in lymph nodes. There are few series, and most are single case reports. The clinical presentation is commonly as a mass, either in lymph node, soft tissue or skin and the mean age of presentation is 44-55 years.

The histiocytic malignancies are classified according to their cell of origin from the dendritic or mononuclear phagocyte systems based on the immunophenotypic profile.

**Histiocytic sarcoma** is characterised by a proliferation of large cells with abundant eosinophilic cytoplasm and large oval to round vesicular nuclei. A variable number of reactive small lymphocytes, plasma cells, eosinophils and benign histiocytes may be present. The overall appearance may be indistinguishable from a diffuse large B cell lymphoma or an anaplastic large cell lymphoma. Immunostaining must be negative for specific B and T cell markers. Tumour cells are positive for CD45 and show granular staining for CD68, and membrane and cytoplasmic staining for CD163. Lysozyme shows fine granular cytoplasmic staining with accentuation of the Golgi apparatus. CD14 is strongly expressed on the cell membrane. S100 expression is variable; if expressed it is weak and focal. HLA-DR is usually positive as well as CD4. Follicular dendritic markers CD21 and CD35 are negative as well as CD1a. CD30 is not expressed. The Ki67 index is variable ranging from 10 to 90% with a mean of 20%.

**Langerhans cell sarcoma** consists of large, oval to spindle shaped tumour cells with nuclear pleomorphism and atypical mitoses. Nuclei may be grooved or folded. Cells have abundant eosinophilic cytoplasm. Tumour cells show CD45, CD1a, S100 and Langerin positivity with small amorphous deposits of CD68. Lysozyme, CD21 and CD35 are negative.

**Interdigitating dendritic cell sarcoma (IDCS)** has the appearance of a paracortical spindle cell neoplasm with sparing of residual follicles. Tumour cells form fascicles and whorls with occasional sheets of round cells. There are numerous small T lymphocytes in between the tumour cells. Tumour cells are weakly positive for CD45and strongly positive for S 100, vimentin, HLA DR and fascin. Expression of CD68 is variable. CD163, CD1a, CD21 and CD35 are negative and the proliferative index with Ki67 is low (about 10%). These tumours carry a wide differential diagnosis of spindle cell tumours depending on the site of clinical presentation, and many immunohistochemical stains may need to be employed to exclude these diagnoses before reaching the conclusion of a histiocytic malignancy.

**Follicular dendritic cell sarcoma (FDS)** consists of spindle cells in fascicles and whorls in a serpiginous growth pattern. Individual tumour cells have prominent eosinophilic cytoplasm. The cytological features are usually bland. Tumour cells are positive for CD21, CD35, CD23, CD68 and fascin. They are negative for CD1a and S100. As with IDCS, these tumours have a wide differential diagnosis depending on the site of presentation and are a diagnosis of exclusion.

(04/2010) A 14-year-old boy presented with a huge right cervical mass (>10cm). The two biopsies performed confirmed the Histiocytic Sarcoma diagnosis. A FDG-PET showed high activity and mediastinum involvement of the tumor. (11/2010) There had been marginal response to two cycles of cladribine (5 mg/m2 x 5 days each). (01/2011) 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). (03/2011) 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. (05/2011) A high dose metrotexate (5g/m2 in 24hs) infusion did not show a favorable response. (07/2011) The patient received localized radiation therapy without evidence of response. In June of 2012, Alemtuzumab (anti-CD52, 10mg/day x3, 9 cycles) was started. Distal femur involvement was observed. (07/2013) He goes to school every day, without major complaints, he is on thalidomide therapy.
MALIGNANT HISTIOCYTOSIS SYMPOSIUM

EXPLORING THE EPIDEMIOLOGY, TREATMENT AND OUTCOME OF THE MALIGNANT HISTIOCYTOSIS

Johannes Visser, MD
Consultant Paediatric Oncologist
University Hospitals of Leicester, Leicester Children’s Hospital, Pediatric Oncology, Leicester, UK

The malignant histiocytoses include a range of rare macrophage and dendritic cell related malignancies. These conditions include histiocytic sarcoma, Langerhans cell sarcoma, interdigitating dendritic cell sarcoma, follicular dendritic cell sarcoma, indeterminate dendritic cell sarcoma and fibroblastic reticular cell tumours. The malignant histiocytoses may present as localized or as disseminated disease. It has been reported in adults and in children.

The study of the epidemiology of these conditions is hampered by the small number of cases and by changes in the classification, nomenclature and ICD coding over time. These factors limit the value of cancer registry data, especially data from smaller regional cancer registries. Using pooled European population-based cancer registry data, the ‘Surveillance of Rare Cancers in Europe’ (RARECARE) project estimates the crude incidence of histiocytic and dendritic cell neoplasms as a group, to be less than 1/100 000 per year. It estimates the incidence of histiocytic sarcoma, interdigitating dendritic cell sarcoma and follicular dendritic cell sarcoma, each to be <0.01/100 000 per year. Information on any possible sex, race or geographic predilection is lacking.

The optimal treatment for the different malignant histiocytoses are not known. Due to the rarity of these conditions there are no clinical trials to inform treatment decisions and there is limited data available to help predict outcome. A range of different treatments have been reported in the form of case reports and small case series. These reports provide some limited insight into the potential role of different treatments and the long term outcome of these patients. Histiocytic sarcoma, Langerhans cell sarcoma and interdigitating dendritic cell sarcoma often behave aggressively with the majority of patients succumbing to the disease despite treatment. Patients with disseminated disease appear to have a particularly poor prognosis. Follicular dendritic cell sarcoma often has a more indolent course.

Clinicians, patients and their families find the lack of robust information about the clinical course of these diseases and the absence of reliable treatment strategies very frustrating. I will present a summary of the published data and reflect on current efforts to close these gaps in our knowledge.

BIOLOGY AND MANAGEMENT OF CYTOKINE RELEASE SYNDROME AFTER T-CELL ACTIVATING THERAPIES

David Teachey, MD
Assistant Professor of Pediatrics, Dept. of Oncology
Department of Oncology, Children’s Hospital of Philadelphia, Philadelphia, PA USA

Recently, a number of novel therapies have been developed that use the host immune system to target malignant cells. T-cells engineered with a chimeric antigen receptor directed at CD19 have shown remarkable efficacy in patients with relapsed and refractory chronic lymphocytic leukemia and acute lymphoblastic leukemia (Porter, et. al NEJM 2011 and Grupp, et. al NEJM 2013). In addition, blinatumomab, a CD19/CD3-bispecific T-cell receptor-engaging antibody has shown marked activity in patients with relapsed and refractory CD19+ malignancies. Many patients treated with these non-physiological T-cell activating therapies develop clinically significant cytokine release syndrome (CRS), primarily driven by IL-6, IL-10, and INF-g. Based on the clinical presentations and cytokine profiles, our group hypothesized and established that these patients were in fact developing abnormal macrophage activation with subsequent hematophagocytic lymphohistiocytosis (HLH) (Grupp, et. al NEJM 2013 and Teachey, et al. Blood 2013). We further hypothesized and demonstrated that IL-6 receptor-directed therapy with tocilizumab is effective at reversing the clinical symptomatology from the CRS. This presentation will review the biology, pathophysiology, and management of CRS and HLH after T-cell activating therapies.
Neurodegenerative CNS LCH (ND-LCH) is a syndrome that results from damage to neurons primarily in the cerebellum, pons, basal ganglia, dentate nuclei, and cerebral peduncles. Histopathologic examination of brain tissue shows infiltration of CD8+ lymphocytes with neuronal and axonal degeneration and secondary loss of myelin. No CD1a+ dendritic cells are found in this form of CNS LCH. It is not known whether neuronal damage is a direct effect of cytokines or other factors elaborated by the lymphocytes, antibodies to neurons, or other causes. Patients present with ataxia, dysarthria, tremors, dysmetria, learning difficulties, and often psychological problems. The true incidence of this syndrome is unknown, but case series from single institutions suggest that radiologic features may occur in 10% to 76% of patients with diabetes insipidus and 4% of all LCH patients. The key radiologic features are T1 hyperintense signal in the dentate and basal ganglia, increased FLAIR signal in the cerebellum, T2-weighted hyperintense signal in the horns of the lateral ventricles, increased Virchow-Robin spaces, and cerebellar atrophy. Patients most at risk for this syndrome are those with LCH lesions of the craniofacial bones and diabetes insipidus. A variety of CSF markers of neurodegeneration have been identified and new findings from our laboratory will be discussed in this presentation. Therapy for these patients remains a challenge. Treatment with trans-retinoic acid and intravenous immunoglobulin seem to stabilize the neurodegenerative findings. Intravenous cytosine arabinoside therapy of 7 ND-LCH patients from a single center was reported to provide clinical benefits in 5 with 4 of these having sustained clinical benefit for 5-10 years. New treatments are needed for children and adults who don’t respond and are suffering from the devastating effects of progressive neurodegeneration.

Although survival in hemophagocytic lymphohistiocytosis (HLH) has increased markedly, CNS involvement is still a major clinical problem. It causes meningoencephalitis and significant neurologic sequelae. In addition, CNS involvement is itself a poor prognostic sign.

We have previously examined the relationship between neurological symptoms and cerebrospinal fluid (CSF) at diagnosis, and long-term outcome, in 193 children enrolled in the HLH-94 study for whom information on CSF at diagnosis was available (Horne et al, Br J Haematol 2008). At diagnosis, neurological symptoms were reported in 72/193 (37%) (seizures=23); abnormal CSF in 101/193 (52%), and either or in 122/193 (63%). Altogether 18/107 (15%) survivors had neurological sequelae at follow-up (median 5.3 years). Adjusted odds ratios (OR) for mortality were 2.05 (1.13-3.72) for children with neurological symptoms and abnormal CSF, as compared to children with no neurological symptom and normal CSF. Moreover, sequelae were more frequent in children with neurological symptoms and abnormal CSF [7/21, 33%] compared to other children [9/86, 10%] (p=0.015). Children with abnormal CSF at diagnosis had significantly increased mortality [OR=1.78 (CI=1.08-2.92), p=0.023]. Thus, a substantial proportion of HLH survivors suffer sequelae. Moreover, children with abnormal CSF have increased risk of mortality and neurological sequelae. Prompt treatment of HLH at onset or relapse may reduce these complications.

In the final report from the HLH-94 study altogether 249 patients fulfilled inclusion criteria and started HLH-94 therapy, and at a median follow-up of 6.2 years the estimated 5-year probability of survival was 54±6% (Trottestam et al, Blood 2011). In this cohort altogether 33% of patients had neurological symptoms prior to therapy start, abnormal CSF was found in 53%, and any of these signs of CNS disease in 127/203 (67%). Notably, and in line with previous reports, presence of neurological symptoms and abnormal CSF at diagnosis was a poor prognostic sign, and in this group (n=52), 5-year-survival was 40±14% as compared to 67±11% in the patients with no neurological symptoms and normal CSF (n=76) (p<0.01). Finally, the rate of neurological late effects was 19% at last follow-up.

In a separate study, 29 of 46 of children with HLH (63%) displayed neurological symptoms at diagnosis (Deiva et al, Neurology 2012). Altogether 23 (50%) had pathological CSF but only 15 (33%) had abnormal brain MRI. At follow-up (3.6±3.6 years), 11 of 28 surviving patients (39%) had mild (21%) or severe (18%) neurologic dysfunction.

There are numerous current challenges in the field of CNS-LHL. With regard to therapy, less reduction of systemic steroids as compared to HLH-94/HLH-2004 may be considered for children with mutations associated with severe HLH. CNS-directed therapy may be increased, and alertness on CNS reactivations improved. Moreover, the association between CsA, posterior reversible encephalopathy syndrome (PRES) and HLH needs to be better understood. Another question worth considering is if patients with HLH are particularly prone to CNS bleedings. Finally, it is also important to be aware of the risk of severe CNS involvement in patients with secondary HLH.
CNS INFLAMMATION IN HISTIOCYTIC DISORDERS SYMPOSIUM

HERITABLE DEGENERATIVE DISORDERS OF THE WHITE MATTER: LEUKODYSTROPHIES AND GENETIC LEUKOENCEPHALOPATHIES

Adeline Vanderver, MD
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Children’s National Medical Center, Washington, DC USA

Heritable disorders of the CNS white matter, as an aggregate, are as or more common than the pediatric acquired demyelinating disorders, such as multiple sclerosis. However, individually, these disorders remain poorly understood and often unrecognized in individual patients. This presentation is a review of pediatric heritable disorders of the CNS white matter, with a special emphasis on those that might be included in a differential diagnosis of histiocytosis involving the central nervous system.

GUEST SPEAKER PRESENTATIONS

WEDNESDAY, OCTOBER 23, 2013 • 0900
ROOM AB, CONSTITUTION LEVEL

JON PRITCHARD LECTURE ON THE NIKOLAS SYMPOSIUM

CXCR4 EXPRESSION BY LANGERHANS CELL HISTIOCYTOSIS CELLS IS ASSOCIATED WITH POOR DISEASE OUTCOME

Willemijn Quispel1, Janine Stegehuis-Kamp1, Susy Santos-Boeij1, Cor van den Bos2, Astrid van Halteren1 and Maarten Egeler1,3

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Purpose: Langerhans cell histiocytosis (LCH) manifestation varies from a single tissue lesion to multiple lesions present in various organs. We analyzed expression levels of migration promoting chemokine receptors, and their ligands, in relation to LCH manifestation and outcome.

Methods: CXCR4, CCR6, CCR7, CXCR7 and CXCL12 co expression by Langerin+ histiocytes (LCH-cells) was visualized by immunohistochemistry in 30 diagnostic LCH biopsies.

Results: CXCR4+Langerin+ LCH-cells were detected in 20/30 (67%) samples. CXCR4 expression coincided more with CCR6 than with CCR7, but never with CXCR7. CXCL12, which binds to both CXCR4 and CXCR7, was expressed by histiocytes as well as by blood vessels in 29/30 lesions. The presence of CXCR4+LCH-cells at diagnosis was constrained to patients with LCH manifestation at multiple sites (10/11) and also identified, retrospectively, 10/20 patients who developed new lesions after an initial response to treatment. To substantiate that CXCR4-CXCL12 interactions are involved in hematogenous migration of LCH-cells, we analyzed the frequency and migration capacity of CD1a+ cells present in paired peripheral blood (PB) or bone marrow (BM) samples collected from several LCH patients. HLA-DR+CD1a+CD11c+CXCR4+ cells were only detected in samples collected at disease onset, but not in samples collected after treatment initiation. CXCR4+CD1a+ cells migrated towards CXCL12 in trans-well experiments and this migration could be abrogated using the CXCR4-antagonist AMD3100/Plerixafor®. Parallel analysis of BRAF mutation status of paired blood-borne and lesional CD1a+ cells derived from the same patient is expected to reveal whether these cells are related.

Conclusion: Although alternative functions of CXCR4-CXCL12 signaling in LCH pathology remain to be studied, this study provides the first evidence that CXCR4 expression is correlated with poor disease outcome. To confirm the putative clinical relevance of these data, a second cohort of LCH patients is currently analyzed.
ADOLESCENTS AND YOUNG ADULTS WITH HLH WHO UNDERGO ALLOGENEIC HCT ARE AT INCREASED RISK OF MORTALITY COMPARED TO YOUNGER PATIENTS

Shanmuganathan Chandrakasan, Rebecca A Marsh, Denise Bellman, Michael Grimley, Jack Blessing, Michael Jordan, Alexandra Filipovich

Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH USA

Purpose: Allogeneic hematopoietic cell transplantation (HCT) is the only curative therapy available for primary Hemophagocytic Lymphohistiocytosis (primary HLH). There is limited data on HCT outcome for adolescents and young adults with HLH.

Methods: We reviewed the allogeneic HCT outcomes of 19 adolescents and young adults with HLH (12 male and 7 female). The median age at transplantation was 19.2 years (range: 15.2-27.2). The majority (15/19) underwent reduced-intensity conditioning (RIC) consisting of alemtuzumab, fludarabine, and melphalan. Thirteen patients received transplants from HLA matched donors (10 MUD and 3 MSD). The HCT outcome of this group was compared to outcome of children with HLH less than 15 years of age.

Results: Median follow up of adolescent and young adult patients following HCT is 280 days (range 9-1643 days). Mixed donor chimerism was noted in 20% (3/15) of patients who received RIC. Acute GVHD grade II-IV was noted in 4 patients. Overall survival was 42.1% (8/19). In patients who received RIC, Kaplan Meier analysis revealed a long term estimated survival of 57%, compared to 75% for children less than 15 years of age (p=0.03). Cox proportional hazard modeling revealed a reduced risk of mortality in young patients undergoing RIC HCT compared to adolescent and young adult patients (HR 0.379 [0.154-0.933], p=0.035), controlling for donor match and source. Deaths in adolescent and young adult patients occurred from days +9 to +568 following HCT. The causes of death varied from fulminant bacterial sepsis (n=4), acute refractory GVHD (n=2), disseminated Aspergillus and fungal sepsis (n=2), viral infection (n=2), and refractory chronic GVHD (n=1).

Conclusion: Adolescents and young adults with HLH who undergo allogeneic HCT are at increased risk of mortality compared to younger patients. Further study is warranted to better identify risk factors which may be modified to improve outcomes for adolescents and young adults.

TREOSULFAN-BASED CONDITIONING REGIMEN FOR CHILDREN AND ADOLESCENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Kai Lehmburg1, Michael H. Albert1, Karin Beutel1, Bernd Gruhn4, Nicolaus Kröger2, Roland Meisel1, Ansgar Schulz2, Daniel Stachel1, Rita Beier3, Thomas Vraetz4, Wilhelm Woessmann1, Gritta Janka1 and Ingo Müller1

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Purpose: The high incidence of veno-occlusive disease (VOD) and transplant related mortality after busulfan-based myeloablative regimens in hemophagocytic lymphohistiocytosis could be reduced with melphalan-based reduced intensity conditioning (RIC), however, at the cost of high rates of mixed chimerism. We hypothesised that treosulfan may be more myelosuppressive than melphalan and still produce less adverse effects than myeloablative doses of busulfan.

Methods: Rates of survival, engraftment, donor chimerism, reactivation, and serious adverse events after HCT (06/2010 - 12/2012) were retrospectively determined in 19 HLH patients from 9 German centers. The conditioning regimen contained fludarabine (150 mg/m²), treosulfan (42 g/m²; 36 g/m² if <12kg), and alemtuzumab (1.0 mg/kg for unrelated donors; 0.3 mg/kg for matched related donors (MRD)). Thiopeta (10 mg/kg; 7 mg/kg if <12 kg) was added in patients at risk (n=14), depending on center preference.

Results: The cohort included 4 FHHL3, 2 FHHL4, 6 FHHL5, 1 Griscelli syndrome, 1 XLP1 (x-linked lymphoproliferative syndrome 1), 3 XIAP deficiencies, and 2 undiagnosed degranulation defects; median age 3.9y (range 0.3-22y) at HCT. Donors were HLA-mismatched (9/10) in 7 patients, matched unrelated in 6, matched related in 5, and haploidential in 1. Seven patients were not in full remission. Both, overall and disease-free survival were 100% (follow-up 3-31 m, median 16 m). Two patients required secondary transplants (1 after haploidential HSCT). In 5 patients, the degree of mixed chimerism prompted donor lymphocyte infusions, stabilizing donor chimerism. Interestingly, all 5 had a mismatched donor and 4 had not received thiopeta. One veno-occlusive disease, 1 graft versus host disease III after DLI, and 2 severe viral infections occurred (1 influenza, 1 EBV).

Conclusion: A combination of fludarabine, treosulfan, and alemtuzumab, is an effective conditioning regimen with low toxicity in HLH patients. Modification of serotherapy and inclusion of thiopeta may reduce the rate of mixed chimerism after mismatched HCT.

TREATMENT AND OUTCOME IN MALIGNANCY-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A SINGLE CENTER RETROSPECTIVE STUDY

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Purpose: The prognosis of malignancy-associated hemophagocytic lymphohistiocytosis (MHLH) is dismal, and knowledge on its etiology and treatment is limited. The aim of this study was to review treatment and outcome of patients with M-HLH.

Patients and Methods: Between January 2008 and March 2012, 56 adult patients were referred to the Hematology Center Karolinska with suspicion of HLH. Medical records were retrospectively evaluated with respect to malignancy, clinical and laboratory features, therapy and outcome. Hemophagocytosis was re-evaluated cytohistologically.
Results: Of the 56 evaluated patients, 31 fulfilled at least four HLH-2004 criteria and had a concomitant malignancy. Eleven patients (35%) suffered from myeloid malignancies, eleven from B-cell malignancies, eight from T/NK-cell malignancies, whereas one had an endocrine carcinoma. Eight patients debuted with HLH, of which six were later diagnosed with T/NK-cell malignancy. The majority of patients developed HLH subsequently to immunosuppressive therapy. At initial evaluation, hemophagocytosis was found in 17 patients (55%). However, reevaluation performed by an experienced hematopathologist confirmed hemophagocytosis in 28 patients (90%). All patients displayed hyperferritinemia (max-value range: 1,442 – 645,291 μg/L). Twenty-one patients received HLH-targeted therapy with IVIG and corticosteroids. Etopoide and cyclosporine were administered in 10 and 8 patients, respectively. Overall survival was 16% (mean follow-up 218 days) and 40-day survival was 58%. The worst prognosis was noted for patients with T-cell malignancies (overall follow-up 0%, mean survival 58 days). There was no difference in survival between patients that fulfilled four versus five or more HLH criteria.

Conclusions: Malignancy-associated HLH occurs in patients with hematological malignancies of all cell lineages and occasionally in patients with solid tumors. In patients with T/NK-cell malignancies HLH often preceded the diagnosis of malignancy, whereas in other malignancies HLH predominately followed immunosuppressive therapy. Survival rates were dismal, especially in patients with T/NK-cell malignancies, highlighting the need for improved treatment of adults with M-HLH.

AN INTERMEDIATE ALEMTUZUMAB SCHEDULE REDUCES THE INCIDENCE OF MIXED CHIMERISM FOLLOWING ALLOGENIC HEMATOPOIETIC CELL TRANSPLANTATION OF PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS DISORDERS

Rebecca Marsh1, Mi-Ok Kim2, Chunyan Liu2, Denise Belman1, Laura Hart1, Michael Grimley1, Parinda Mehta1, Ashish Kumar1, Sonata Jodele1, Kasiani Myers1, Tom Leemhuis1, Jack J. Bleesing1, Stella M. Davies1, Michael B. Jordan1, Alexandra H. Filipovich1

1Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children’s Hospital, OH USA
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Reduced intensity conditioning (RIC) is known to improve the allogeneic hematopoietic cell transplant (HCT) outcomes of patients with hemophagocytic lymphohistiocytosis (HLH) compared to myeloablative conditioning regimens. However, proximal (close to graft infusion) dosing of alemtuzumab is associated with a high incidence of mixed chimerism (MC). Distal (more distant from graft infusion) dosing is associated with less MC, but higher incidences of acute GVHD. We hypothesized that an intermediate alemtuzumab schedule would reduce MC yet maintain a low incidence of acute GVHD. Twenty-four consecutive transplants were performed in patients with HLH disorders using a novel intermediate alemtuzumab schedule of 1mg/kg beginning on day -14. The cumulative incidences of MC and acute GVHD grades II-IV were compared to HLH disorder patients treated with distal (n=15) or proximal (n=33) alemtuzumab schedules. All patients received fludarabine 150mg/M2 (1mg/kg if <10kg) and melphalan 140mg/M2 (4.7mg/kg if <10kg). The cumulative incidence of MC was 34% in the intermediate alemtuzumab cohort, versus 72% in the proximal and 40% in the distal cohorts (p=0.004). The regimen maintained a low incidence of overall acute GVHD grades II-IV at 12%, versus 16% and 27% in the proximal and distal cohorts (p=0.57). This 14 day RIC regimen reduces the incidence of MC and maintains a low incidence of acute GVHD.

REVIEW OF DECEASED CHILDREN WITH HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS ON A NATIONAL CANCER REGISTRY BETWEEN 1978-2007

Vasanta Nanduri, Harriet Holme, Robin Dowse, Jane Salotti, Charles Stiller, Johannes Vissers, Kevin Windebank

UCL Cancer Institute, London, United Kingdom; Department of Haematology, Maidstone Hospital, Kent, United Kingdom; Institute of Health & Society, Newcastle University, Sir James Spence Institute, Newcastle upon Tyne, United Kingdom; Childhood Cancer Research Group, University of Oxford, United Kingdom; Leicester Royal Infirmary, Leicester, United Kingdom; Institute of Health & Society, Newcastle University, Newcastle upon Tyne, United Kingdom; Paediatric Department, Watford General Hospital, Watford, Herts, United Kingdom

Purpose: To review causes of death amongst children with haemophagocytic lymphohistiocytosis (HLH) in England, Scotland and Wales.

Methods: The National Registry of Childhood Tumours records children with neoplasms and histiocytosis treated at paediatric oncology centres affiliated to the Children’s Cancer and Leukaemia Group. Registry records of children (<15 years) diagnosed with HLH, between 1978-2007 were reviewed and causes of death extracted from death certificates.

Results: Of 149 children registered, 103 died (69%). 3 with incomplete data were excluded from analysis. Of the remaining 100, 56 male, 44 female (ratio 1.0:1.78) the primary cause of death was HLH (95%), with one death occurring from malignancy (acute eosinophilic leukaemia, aged 5 years). The median age at death in completed years was 1 year (range 0-23 years). Forty-eight patients had primary HLH. The median age at diagnosis was <1 year (range 0-8 years) with a median survival time of 0.1 years (range 0-9.4 years). Fifty-two patients had secondary HLH, with a median age at diagnosis of 1 year (range 0-23 years) and median survival of 0.3 years (range 0-10.7 years). Thirty-one cases were diagnosed before trials began in 1994. However, only 31 of a possible 68 were subsequently registered (30/50 on HLH94, 1/19 on HLH 2004). For those registered pre-1994, 1994-2004 and 2004-2007, median survival from diagnosis was 0.1, 0.4 and 0.2 years respectively. Patients on trial had a median survival of 0.5 years (range 0-2.5 years), compared with 0.2 years (range 0-10.8 years) for those not on trial.

Conclusions: This study represents the longest follow-up of children with HLH to date. It is notable that the median time from survival to death for both primary and secondary HLH is very similar. It is recognized that recruitment onto trials was relatively poor and seems to have been worse for HLH 2004 than 94.
REVIEW OF DECEASED CHILDREN WITH LANGERHANS CELL HISTIOCYTOSIS ON A NATIONAL CANCER REGISTRY BETWEEN 1978-2007

Vasanta Nanduri, Harriet Holme, Jane Salotti, Charles Stiller, Johannes Visser, Kevin Windebank

UCL Cancer Institute, 72 Huntley Street, London, WC1E 6DD, United Kingdom; Institute of Health & Society, Newcastle University, Sir James Spence Institute, Floor 4, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, United Kingdom; Childhood Cancer Research Group, University of Oxford, New Richards Building, Old Road Campus, Oxford, OX3 7LG, United Kingdom; Leicester Royal Infirmary, Leicester LE1 5WW, United Kingdom; Institute of Health & Society, Newcastle University, Sir James Spence Institute, Floor 4, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, United Kingdom; Paediatric Department, Watford General Hospital, Vicarage Road, Watford, Herts, WD18 0HB, United Kingdom

Purpose: Review of causes of death amongst children with Langerhans cell histiocytosis (LCH) on the National Registry of Childhood Tumours (NRCT).

Methods: NRCT records children with neoplasms and histiocytoses treated at paediatric oncology centres in England, Scotland and Wales. Records of children (<15 years) diagnosed with LCH between 1978-2007 were reviewed, and causes of death were extracted from death certificates.

Results: 78/821 registered children died - 49 male, 29 female (ratio 1.7:1). Primary causes of death included; LCH 62; malignancy 4; accidental/misadventure 4; infection 3; cardiac 2; other 3. For those with LCH as the primary cause (n=62), the median age at death was 1 year, range (0-38 years), compared with a median of 3 years (range 0-33 years) for those who died of other causes. Of these 62 children, 34 died of disseminated disease, 16 respiratory causes, 4 bone marrow failure, 4 hepatic, 1 macrophage activation syndrome, 3 other causes; the median survival time was 0.6 years (range 0-29 years). Of the total number of deaths, 59 had multisystem disease; the median survival time was 0.5 years (range 0-25 years). The majority (65%) were diagnosed before 1991 and only 15/27 possible cases were registered on a trial (5 LCH I, 10 LCH II). 19 (24%) were reported to have single system disease. Deaths in this group were due to: 6 disseminated LCH, pulmonary histiocytosis 4, infection 2, 1 each had LCH-related cardiac failure, splenic rupture, gastrointestinal haemorrhage, congenital cardiac disease, mediastinitis and misadventure 2; median age at death was 3 years (range 0-33 years).

Conclusions: This study represents the longest follow-up of children with LCH to date. It is notable that 19 patients (24%) with single system disease died, the majority reported as being due to LCH. It is recognized that recruitment onto trials was relatively poor, although improved with time.
Purpose: The activated oncogene BRAF V600E appears in the abnormal histiocytes of nearly 60% of Langerhans cell histiocytosis (LCH) samples suggesting that it may be a driver of this neoplastic disease.

Methods: We developed two mouse models in which a conditional, mutated BRAF allele was expressed in either normal LCs (using Langerin-Cre) or in all somatic cells including some stem cell populations (using MX1-Cre).

Results: In the first model BRAF V600E expression is activated by the Langerin promoter. Most of the mice of the desired genotype suffer early postnatal death. But some mice do survive and have the following characteristics: smaller body mass; fewer LC-like cells and more macrophage-like cells in lymph nodes. Their lymph nodes also show evidence for frequent apoptosis which may explain the decreased number of LC-like cells. In the second model, BRAF V600E expression is activated by the MX-1 promoter, mice develop a systemic proliferative disease characterized by accumulation of histiocytic cells in multiple organs accompanied by multinucleated giant cells. These mice also demonstrate reduced CD207 cells along with increased F4/80 cells and less frequent apoptosis compared to the first model.

Conclusions: The Langerin-cre model suggests that BRAF V600E expression in mature LCs by itself is insufficient to cause an LCH-like disease. This suggests that additional molecular abnormalities may be necessary for the development of LCH. Alternatively, our data are also consistent with the suggestion made by other groups that LCs are not the target of transformation in LCH. The MX1-cre model has features that are reminiscent of disseminated LCH. The expression patterns of MX1 are consistent with a model in which hematopoietic stem cells may be the relevant transforming target in LCH.

**Presentations nominated for the Nezelof Prize in Basic Science**

**Genetically Engineered Mouse Models of BRAF V600E Expression in Langerhans Cells**

Gayane Badalian-Very1,2, Jo-Anne Vergilio1, Kristen Stevensen1, Roderick Bronson1, Mark Fleming1, Barrett Rollins1,2

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Purpose: The activated oncogene BRAF V600E appears in the abnormal histiocytes of nearly 60% of Langerhans cell histiocytosis (LCH) samples suggesting that it may be a driver of this neoplastic disease.

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Conclusions: The Langerin-cre model suggests that BRAF V600E expression in mature LCs by itself is insufficient to cause an LCH-like disease. This suggests that additional molecular abnormalities may be necessary for the development of LCH. Alternatively, our data are also consistent with the suggestion made by other groups that LCs are not the target of transformation in LCH. The MX1-cre model has features that are reminiscent of disseminated LCH. The expression patterns of MX1 are consistent with a model in which hematopoietic stem cells may be the relevant transforming target in LCH.

**Janus Kinase Inhibition as a Novel Treatment for Macrophage Activation Syndrome**

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Purpose: The macrophage activation syndromes (MAS) are rare inflammatory disorders typified by excessive T-cell and macrophage activation and secretion of high levels of pro-inflammatory cytokines, including interleukins (IL)-6, 12, 10 and interferon (IFN)-y. Many of these cytokines bind to receptors that signal via the Janus kinases (JAKs).

Based on the central role for cytokines as mediators of MAS pathogenesis, we hypothesized that pharmacologic inhibition of the JAKs would serve as a rational and potentially more effective treatment for this disorder.

Methods: C57BL/6 mice received repeated i.p. injections of CpG DNA, which engages TLR9 and leads to many of the cardinal manifestations of human MAS. Mice were treated orally with the JAK inhibitors (JAKinibs) tofacitinib or ruxolitinib starting 1 day before or 4 days after initiation of CpG injections. On day 10, mice were euthanized and evaluated for signs of MAS.

Results: Regardless of whether started before or after CpG injections, treatment with the pan-JAK inhibitor tofacitinib lessened splenomegaly, improved cytopenias and lowered proinflammatory cytokine levels, but did not ameliorate liver inflammation or reduce serum ferritin levels. In contrast, preliminary studies using the JAK1/3 inhibitor ruxolitinib reveal significant reductions in splenomegaly and serum cytokine levels and no evidence of tissue inflammation.

Conclusion: The JAKinibs diminish signs of hyperinflammation in CpG-induced MAS. Studies are ongoing to: 1) optimize dosing and schedule of administration; 2) determine mechanism of action; 3) assess efficacy in LCMV-induced murine HLH; and 4) evaluate for cooperativity with more traditional MAS therapies such as steroids and etoposide. The JAKinibs are FDA approved agents with minimal toxicity. By characterizing their effects in MAS, these studies will define whether and how the modulation of JAK function can be incorporated into future clinical trials to ameliorate inflammation and improve the cure rate for children and adults with MAS.

**Descriptive Epidemiology of Langerhans Cell Histiocytosis**

Carlos Rodriguez-Galindo, Barbara Degan, Celia Antonelli, Barrett Rollins, Karina Ribeiro

Dana-Farber Cancer Institute and Boston Children’s Hospital, Harvard Medical School, Boston; Faculdade de Ciências Médicas da Santa Casa de São Paulo, Department of Social Medicine, São Paulo, Brazil

Purpose: Langerhans cell histiocytosis (LCH) is a rare disease, which etiology is not well understood. Population-based studies may contribute to etiologic research by defining incidence patterns. This study was designed to evaluate the descriptive epidemiology of disseminated LCH in the United States, using data from population-based cancer registries.

Methods: We analyzed the incidence and survival of disseminated LCH in children and adolescents (0-19 years) from 18 SEER registries during 2000-2009. Age-standardized incidence rates (ASIR) per million and rate ratios (RR) were calculated by gender, race, ethnicity, age, and socioeconomic variables (crowing, rural/urban, education, and poverty level) using the SEER*Stat software 8.0.1. Relative survival (RS) estimates were calculated according to the Ederer II method.

Results: 145 cases of disseminated LCH were recorded; ASIR was 0.6/ million per year. ASIR was higher in female children (<1 year, 5.3/ million). Lower ASIR was observed for blacks (vs. whites) (RR=0.43, 95% CI 0.19-0.84), while higher ASIR was noted for Hispanics (vs. non-Hispanics) (RR=1.62, 95% CI 1.14-2.29). ASIR was higher in crowded counties (ASIR= 0.47 vs. 0.84 in less crowded counties RR=1.77, 95% CI 1.26-2.48). Higher ASIR was observed in areas with lower educational level degree (ASIR 0.67 vs. 0.45 in >16.6% vs. <16.6% with less than high-school; RR=1.50, 95% CI 1.03-2.25). No significant differences were found for rural/urban location or poverty level. Five-year relative survival for the cohort was 90.0% (95% CI 83.0-94.2%). Important differences in survival rates were noted according to gender (male RS=96.0 vs. female RS=83.4%, p=0.029) and age (<1 year RS=78.5, 1-4 years RS=95.6%, 5-19 years RS=100%, p=0.004).
Conclusions: This population-based study shows significant variations in the incidence of disseminated LCH by race and ethnic group, as well as the possible influence of environmental factors. These data may provide clues to causation and point toward the need for dedicated epidemiology studies.

**PRESENTATIONS NOMINATED FOR THE NESBIT PRIZE IN CLINICAL SCIENCE**

**HEMATOPOIETIC STEM CELLS AND CIRCULATING MYELOMONOCYTIC PRECURSORS WITH BRAF-V600E ARE IDENTIFIED IN HIGH-RISK PATIENTS AND DEFINE LCH AS A MYELOID NEOPLASIA**

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Purpose: Langerhans Cell Histiocytosis (LCH) is a clonal lymphoproliferative disorder characterized by inflammatory lesions with characteristic CD207+ dendritic cells (DCs). LCH has variable clinical presentations ranging from single lesions to potentially fatal multi-system “High Risk” disease. The etiology of LCH remains elusive, with debate of LCH as an inflammatory versus malignant disorder unresolved. The first recurrent somatic genetic mutation in LCH, BRAF V600E, was recently reported in 57% of LCH lesions (Badalian-Very et al., 2010). In this study, we investigate the clinical significance of BRAF V600E and identify cells carrying the mutation to determine the origins of LCH.

Methods: Lesions, peripheral blood, peripheral monocyte/dendritic cell populations, and hematopoietic stem cells from were genotyped for the BRAF V600E mutation, which was correlated with clinical variables.

Results: Lesions from 100 patients with LCH were genotyped, and 64% percent carried the V600E mutation, which localized to the infiltrating CD207+ DCs. In 16 patients with more than one lesion, BRAF status remained fixed, suggesting somatic mutation is an early event. BRAFV600E did not define specific clinical risk groups or impact overall survival, but it was associated with approximately two-fold higher risk of relapse (p=0.04). Furthermore, the cellular compartment carrying the mutation correlated with disease severity: The ability to detect BRAFV600E in circulating mononuclear cells defined High-Risk LCH with 100% sensitivity/87% specificity. The ability to detect BRAF-V600E in circulating blood cells in patients with High-Risk LCH defined clinically detectable disease with 97% sensitivity/100% specificity. Analysis of sorted populations localized the BRAF-V600E to CD11c+ and CD14+ fractions in peripheral blood, and to CD34+ hematopoietic stem cells in bone marrow.

Conclusion: We therefore hypothesize that High-Risk LCH arises from somatic mutation of an immature myelomonocytic precursor cell, where Low-Risk disease arises from somatic mutation of tissue-restricted DC precursors. Based on these results, we propose classifying LCH as an “inflammatory myeloid neoplasia”.

**INFECTION ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A NOVEL SHORT COURSE STEROID ONLY PROTOCOL**

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Introduction: Infection associated Hemophagocytic Lymphohistiocytosis (IAHLH) 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, we are using the Steroid only protocol for last 5 years (Dexamethasone only for 8 weeks). But recently we treated 32 selected cases of IAHLH with short course (4 weeks) steroid only protocol and had a very good outcome.

Patients & Method: The patients of IAHLH were divided into two categories depending on the risk factors. Those with risk factors (age<1 year, severe CNS symptoms, Coagulopathy, severe neutropenia with ANC<500, hyperferritinemia with Ferritin>20,000 and with EBV serology positive) received 8 weeks steroids with or without additive therapies and those without the above mentioned risk factors received the short course steroids for 4 weeks. A total 32 patients were enrolled in the short course steroid therapy between the time period of January 2011 to April 2013. They received Dexamethasone only in a dose of 10 mg/m2 for 7 days and the dose tapered rapidly over the next 3 weeks (a total 4 weeks course). These patients also received supportive therapy in the form of blood component transfusion and antibiotics. No other chemotherapeutic agent was used in these 32 patients.

Results: In 82% of cases fever subsided within 48 hours to 72 hours of starting steroids. Reversal of cytopenias and regression of hepatosplenomegaly occurred over the next 5 to 7 days. Serum Ferritin started normalising within a week. One patient expired on day 6 of 10 mg/m2 of Dexamethasone and ultimately found to be EBV positive while another relapsed on day 18 of steroid and put on additive therapies.

Conclusion: Though traditionally perceived as a near fatal disease requiring aggressive chemotherapy, our selective low risk patients did remarkably well with the use of only 4 weeks Dexamethasone and supportive therapy without necessitating the use of further chemotherapy. Observing this encouraging response to a short course steroid only protocol, we propose that IAHLH cases should be individualised depending upon the risk factors and those without the risk factors can be treated satisfactorily with the short course steroid only protocol.
SOMATIC ARAF MUTATIONS IN LANGERHANS CELL HISTIOCYTOSIS

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Purpose: The abnormal histiocytes in most patients with Langerhans cell histiocytosis (LCH) harbor activating mutations of BRAF and reports indicate that these patients respond to vemurafenib. However, LCH cells in all patients show activation of ERK pathway signaling, including those whose histiocytes have wild type BRAF alleles. To identify other genetic causes of ERK activation, we performed whole exome sequencing on patient samples.

Methods: Massively parallel sequencing using the Illumina platform was performed on DNA from CD1a-positive cells and normal cells from three patients with LCH.

Results: Sequencing revealed somatic BRAF V600E in one patient and wild type BRAF alleles in the remaining two. One of those with wild type BRAF had compound mutations in the kinase domain of ARAF: a six nucleotide deletion leading to the loss of two amino acids (Q347_A348del) and a single nucleotide change producing an amino acid substitution (F351L). Unlike wild type ARAF which has little MEK kinase activity, the compound ARAF mutant was a potent MEK kinase in vitro kinase assays, with activity comparable to BRAF V600E. Incorporating a third mutation which inactivates RAF kinases destroyed the MEK kinase activity of the compound mutant indicating that the two mutations directly enhanced the kinase activity of ARAF. Expressing the compound mutant in 3T3 cells induced their anchorage independent growth indicating that this mutant had transforming activity. Variant ARAF kinase activity was inhibited by vemurafenib.

Conclusion: We describe a case of BRAF wild-type LCH containing novel somatic activating mutations in ARAF reflecting the strong selective pressure to activate the ERK pathway in this disease. To our knowledge, this is the first report of an activating ARAF mutation in a neoplasm. Importantly, defining eligibility for vemurafenib treatment by the presence of BRAF V600E would have excluded this patient although our data suggest a possible therapeutic benefit.
Posters

**Posters Location #2**

**CENTRAL NERVOUS SYSTEM LESIONS COMPATIBLE WITH NEURODEGENERATIVE INVOLVEMENT IN LANGERHANS CELL HISTIOCYTOSIS**

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*Purpose:* To describe the clinical, neuropsychological, and radiological features of patients with lesions compatible with neurodegenerative (ND) involvement of the central nervous system (CNS) in Langerhans cell histiocytosis (LCH).

*Materials/Methods:* Three hundred and ninety patients with LCH were seen between October 1987 and April 2013; 64 patients had diabetes insipidus and eight (2.1%) had ND-LCH. We reviewed the clinical records, MRI, neuropsychological and endocrinological tests of seven patients with ND-LCH. One patient was excluded because of missing data.

*Results:* Median age at LCH diagnosis was 2.3 years (r: 1.1-3.9), five patients were male. Median time of follow-up was 8 years (r: 4-21). Six patients had multisystem involvement. Before diagnosis of CNS involvement five patients had CNS-risk bone lesions (Histiocyte Society criteria). Four patients were initially treated less than 6 months, four had disease reactivation, and six had diabetes insipidus. Median time from diagnosis to the first ND lesions was 7 years (r: 5-15.7). All patients had cerebellar white matter involvement and four also had brain white matter involvement. In three patients hyperintense signal changes on T1 restricted to the dentate nucleus and basal ganglia were observed. At ND diagnosis four patients were asymptomatic and three had headache. One of them developed progressive ataxia and other tremor. Six patients presented with neuropsychological impairments in executive functions after the first MRI.

*Conclusions:* In agreement with other reports, most of our patients with ND-LCH had: multi-systemic involvement, CNS-risk lesions, short treatments, reactivations and DI at diagnosis or during follow-up. The frequency of ND-LCH is lower than in other studies. Systematic prospective multidisciplinary studies should be performed in CNS-risk patients with LCH.

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**Posters Location #3**

**A RARE PRESENTATION OF LCH WITH SOLID BONE MASS: CASE REPORT**

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Langerhans’ cell histiocytosis (LCH) is a rare disease of childhood. LCH commonly involves bone and bone lesions are mostly lytic on radiological examination. Solid lesion of bone is an unusual presentation of LCH. We report a rare case of LCH presenting with solid mass on the scapula.

*Case:* A nine-month-old child had been admitted to a local hospital with orbital mass. After clinical and laboratory evaluation he was categorized as multi-system risk patient with LCH and had received the initial course with continuation treatment according to LCH-III protocol. Unfortunately, the continuation treatment was stopped at the sixth month. Seven months after the cessation of therapy, he presented with swelling, pain and functional disability of the left shoulder. Magnetic resonance imaging showed a 7 x 6.5 x 5.5 cm solid mass on the left scapula. Tru-cut biopsy of the lesion revealed LCH. As the disease had bone marrow involvement, he received the same protocol according to LCH III. After two initial courses, anemia disappeared but the mass did not resolve and the functional disability of the left arm remained. The disease was resistant to chemotherapy and he was too young for the radiotherapy. The solid mass was removed with surgical excision. The symptoms resolved after the operation. The child is on continuation treatment since three months and the continuation treatment is planned for one year.

*Conclusion:* Bone lesion of LCH is mainly lytic, but rarely it may be present as a solid tumor. LCH should be considered in the differential diagnosis of solid masses of bone in children.

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**Posters Location #4**

**PITFALLS IN THE DIAGNOSIS OF GASTROINTESTINAL TRACT LANGERHANS CELL HISTIOCYTOSIS**

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*Background:* Langerhans cell histiocytosis (LCH) is rarely noted in the gastrointestinal tract as initial presentation, thus, the diagnostic delay occurs. We report here a patient, who was initially diagnosed as eosinophilic gastritis, and needed endoscopic biopsy twice to reach the diagnosis of LCH.

*Case:* An 18-months-old girl of mixed Japanese/Brazilian presented with vomiting, diarrhoea and poor oral ingestion. She was first suspected for protein losing enteropathy. Upper gastrointestinal endoscopic study revealed mucosal edema from the duodenal bulb to third portion. The histopathological findings of the duodenal biopsy was provisionally diagnosed as eosinophilic gastritis. With intravenous prednisolone, her digestive tract symptoms were improved; however, exacerbated again following the tapering of prednisolone. Seven months after initial presentation, diabetes insipidus and renal dysfunction occurred. The MRI findings revealed disappearance of bright signal of the pituitary posterior lobe. Skull as well as risk organ (liver and bone marrow) involvements appeared. Repeat duodenal biopsy showed mucosal infiltration with mononuclear cells strongly positive for CD1a. Eventually, the patient was diagnosed as multisystem LCH. Treatment the JLSG-02 protocol was started; however the response at 6 week was poor. Accordingly, she underwent U-CBT with the conditioning of melphalan, fludarabine and low dose TBI, following one course of intensive chemotherapy with 2-CdA and high dose cytarabine. Post-transplant hemophagocytic syndrome occurred, which was manageable with intravenous prednisolone. Currently, she has had chronic skin GVHD, with no active disease of LCH at 13 months after transplantation.

*Conclusion:* The symptoms of gastrointestinal tract LCH are nonspecific, thus, if initially presented, correct diagnosis often delays. Although repeat digestive tract biopsy may be required as illustrated in this case, caution must be exercised to search for the LCH lesions outside the gastrointestinal tract. In case of refractory digestive diseases, LCH should be included in the differential diagnosis.

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THE RESULTS OF TREATMENT WITH VINBLASTINE, PREDNISONE AND MERCAPTOPURINE IN ADULT PATIENTS WITH MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS

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Purpose: Multisystem Langerhans cell histiocytosis (MLCH) in adult patients is a rare disease. The combination of vinblastine, prednisone, with mercaptopurine given in a 12-month course was suggested by Histioctye Society in the last decade and now it is no longer recommended. However only limited data has presented the results of this treatment.

Patients and Methods: Eleven patients with multisystem Langerhans cell histiocytosis (all patients had pulmonary lesions), 6 women and 5 men in mean age 31.3 y. (range 15-56 y.) were treated according to LCH ADULT-1 protocol.

Results: Patient received treatment for mean 8, 6 months (range 1-12 m.). In 9 cases stabilization of the disease was observed and in 2 cases progression during initial phase of treatment was noticed. There was no influence of treatment on mean value of pulmonary function parameters; however in 2 patients significant improvement of FVC, FEV1, DLCO was shown. After the median follow-up period of 32 months (range 4-72 months) one patient relapsed (after 12 months). The most common adverse event was granulocytopenia (10 episodes of granulocytopenia grade 1 in 7 patients). Hepatic toxicity-grade 2, neurotoxicity-grade 1, episode of upper respiratory infection was noticed in 1, 3, and 3 patients respectively. Two patients died, one after 4 months from beginning of the treatment in the course of disease progression, and other one year after termination of the therapy, because of pulmonary infection.

Conclusions: LCH ADULT 1 protocol is not sufficiently effective; however toxicity profile of this treatment is acceptable.

INDOMETHACIN WAS EFFECTIVE IN TWO PATIENTS WITH LCH IN "SPECIAL SITES"

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Purpose: Patients with LCH in “special sites” (facial bone or anterior or middle cranial fossa bones involvement) are usually treated with corticosteroids and vinblatine. There are positive experiences in the usefulness of indomethacin (IND) in single system boney disease. The aim is to describe the effectiveness of IND in LCH patients with special sites involvement.

Methods: Retrospective analysis of clinical data and images at diagnosis and at 8 weeks of IND therapy (2mg/kg/day) was done in two patients.

Results: Case 1: A previously healthy 2-year-old girl presented with a left orbital tumor. The diagnosis of LCH was done by biopsy. The parents preferred to avoid chemotherapy, so the patient was treated with IND. After 8 weeks of therapy, the images showed a good response (regression of soft tissue mass and signs of bone repair), so the girl continued under IND. After one year of therapy the orbital lesion was in complete resolution. Case 2: A 9-month-old baby presented chronic antibiotic resistant aural discharge, the images showed an expansive process in the right temporal bone. Partial surgical excision of the mass was done and LCH was confirmed. After a new set of images the patient started IND therapy. At the 8 week evaluation, the MRI revealed favorable changes in comparison with the previous one.

Conclusions and Comments: These observations are in favor of the usefulness of IND as treatment for this group of patients with special sites involvement, avoiding chemotherapy adverse effects.
FAVORABLE OUTCOMES OF REFRACTORY OR REACTIVATED LANGERHANS CELL HISTIOCYTOSIS TREATED WITH SALVAGE CHEMOTHERAPY OF 2-CHLORODEOXYADENOSINE AND CYTOSINE ARABINOSIDE: A SINGLE CENTER EXPERIENCE IN KOREA

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Background: 2-chlorodeoxyadenosine (2-CdA) can be used in combination with cytosine arabinoside (Ara-C) in various dosing schedules for refractory or reactivated Langerhans cell histiocytosis (LCH). The aim of this study was to assess the efficacy and tolerability of combination chemotherapy of 2-CdA and Ara-C.

Methods: We retrospectively reviewed medical records of 14 patients, with a median age of 2.2 years at diagnosis, who were treated with 2-CdA and Ara-C for reactivated or refractory LCH between November 2008 and March 2013 at Asan Medical Center.

Results: At initial diagnosis, 6 had multisystem disease with risk organ (RO) involvement, 3 multisystem disease without RO involvement, and 5 multifocal bone disease. At initiation of 2-CdA and Ara-C therapy, 2 had refractory disease in RO, 4 refractory disease in low-risk organ, and 8 reactivations in low-risk organ after vinblastine/prednisone-based chemotherapy. Salvage chemotherapy was comprised of 2-CdA of 9 mg/m²/day for 5 days and Ara-C of 1,000 mg/m²/day for 5 days every 3 to 4 weeks in 4 patients (group A), and 2-CdA of 5 mg/m²/day for 5 days and Ara-C of 200 mg/m²/day for 3 days every 3 to 4 weeks in 10 patients (group B). In group A, 1 stopped chemotherapy due to poor tolerance, 2 were switched to group B due to infectious complications, and 1 completed 3 courses of chemotherapy followed by maintenance therapy. In group B, 7 were treated with 4 to 6 courses of chemotherapy followed by maintenance therapy, 1 stopped chemotherapy due to infectious complication, and 2 are still on 2-CdA. All the patients are surviving without event for median follow-up period of 29 months. Of 12 evaluable patients, 6 (50%) showed no active disease and 6 (50%) regression. In group A, all 4 showed grade IV neutropenia for median 8 days and grade IV thrombocytopenia, while in group B all 10 showed grade IV neutropenia for median 4 days, and 2 of 10 (20%) grade IV thrombocytopenia. Infectious complications included bacterial sepsis (n=1) and pulmonary aspergillosis (n=1) in group A, and pulmonary tuberculosis (n=1) in group B.

Conclusions: Combination chemotherapy of 2-CdA (5 mg/m²/day for 5 days) and low-dose Ara-C was effective with excellent response rate and tolerable in refractory or reactivated LCH, while outcome result with higher dose of 2-CdA combined with high-dose Ara-C was limited by poor tolerability and infection. Further investigation is warranted to determine optimal dose and combination of 2-CdA and Ara-C for refractory or reactivated LCH.
THE OPTIMAL IMAGING TECHNIQUE FOR EVALUATION OF BONE LESIONS IN LANGERHANS CELL HISTIOCYTOSIS AT DIAGNOSIS: A SYSTEMATIC REVIEW

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Purpose: The number of bone lesions detected at diagnosis of Langerhans Cell Histiocytosis (LCH) has an impact on treatment and prognosis. Skeletal survey is still the gold standard for the evaluation of bone lesions at diagnosis. Other imaging techniques have been studied. The value of these techniques is, however, still unknown. Therefore, a systematic review was performed to study the value of these other total-body imaging techniques at diagnosis of LCH. The optimal technique should identify all relevant bone lesions during staging, without detecting too much false-positive lesions.

Methods: A PubMed search was performed to identify articles comparing different full-body imaging techniques for the identification of bone lesions in pediatric patients with LCH. Two authors independently selected studies for this review. Articles with an English abstract were accepted; studies with less than 5 patients were excluded.

Results: Out of 416 articles, 4 articles that met the criteria for evaluation were identified. Due to different approaches in analysis, pooling was not possible. Two studies assessed concordance between skeletal scintigraphy and skeletal survey. In both studies, skeletal survey was superior in identifying bone lesions, although a few lesions were only detected on bone scintigraphy. One study compared total-body magnetic resonance imaging (MRI) and skeletal survey. MRI detected more lesions than skeletal survey. Finally, one study compared positron-emission tomography (PET-CT) with full skeletal survey. PET-CT detected additional lesions compared to skeletal survey.

Conclusions: Only a few comparative studies have been performed on full-body imaging during work-up at diagnosis of LCH. Skeletal scintigraphy might be less sensitive than skeletal survey, as demonstrated in previous research. Total-body MRI or PET-CT seem to be more promising for staging. As only few studies have been published on this topic, a well-designed prospective trial evaluating the role of these full-body imaging techniques in LCH diagnosis is urgently needed.
ANALYSIS OF SERUM OSTEOPONTIN LEVELS IN PEDIATRIC PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS

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Purpose: LCH has a character of clonal disease as well as inflammatory disease. Previously, we showed that serum levels of inflammatory cytokines/chemokines in LCH patients were significantly elevated. It has been reported that osteopontin (OPN) is expressed abundantly in LCH cells. In this study, we investigated whether serum OPN levels correlate with the disease severity of LCH.

Methods: Forty eight newly diagnosed LCH patients as well as controls were studied. Of these, 8 patients had multi-system disease with liver, spleen or hematopoietic system involvement (MS+), 20 multi-system disease without such involvements (MS-), 20 single-system disease (SS) and 26 controls had non-inflammatory diseases. Ages (median; ranges) of these 4 groups were; 12 (0.5-2.0) in MS+, 3.0 (0.4-12.0) in MS-, 5.4 (0.9-19.0) in SS and 4.0 (0.3-17.0) years old in controls. Serum OPN levels were measured by using human OPN ELISA kit (R&D systems). Data were analyzed by Mann Whitney U test and multiple regression analysis. P values less than 0.05 were considered to be significant.

Results: Levels of serum OPN (median; IQR) were 240.3 (131.4-501.3) in MS+, 67.3 (43.6-119.0) in MS-, 63.8 (36.9-103.0) in SS and 47.6 (24.1-89.1) ng/ml in controls, respectively. Between MS- and SS and SS and controls, serum OPN levels did not differ (p=0.646 and p=0.184, respectively). However, the values in MS+ were significantly higher than MS-, SS and controls (p=0.003, p<0.001 and p<0.001, respectively). Multivariable analysis revealed that MS+ was the most significant factor on serum OPN levels (p<0.001).

Conclusion: Serum OPN levels appear to correlate with the disease severity of LCH. OPN is a multifunctional protein which plays as osteoclast activator, proinflammatory cytokine and chemokine attracting histiocytes. OPN may be involved in tissue destruction of LCH lesion and could become a therapeutic target in patients with MS+ LCH.

PULMONARY LANGERHANS CELL HISTIOCYTOSIS: THE INCIDENCE OF ALPHA-1 ANTITRYPSINE (A1AT) DEFICIENCY ALLELES

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Introduction: Inherited alpha-1 antitrypsin deficiency (A1ATD) is one of the three most common genetic disorders in Caucasians. It considerably increases the risk of progressive obstructive lung diseases, mostly chronic obstructive pulmonary disease. There is no data regarding A1ATD prevalence in patients with pulmonary Langerhans cell histiocytosis (PLCH). PLCH in adults is strongly connected with cigarette smoking and the polycystic lung lesions are observed in the course of the disease.

Material and Methods: A1AT serum concentration was measured by nephelometry and Pi phenotype identified by isoelectrofocusing in blood samples of 34 adult patients (14 women and 20 men) with histologically confirmed PLCH. The Pi’S and Pi’Z alleles were confirmed by real-time PCR.

Results: Deficiency alleles Pi’Z and Pi’S were present in 3 patients (one woman and 2 men), respectively in 5.88% and 2.94%. Estimated incidence of deficiency alleles was 29.4/1000 (95% CI; 10-69.5) for Pi’Z and 14.7/1000(95% CI; 13.9-43.3) for Pi’S. Our previous screening data in newborn shown the incidence of deficiency alleles was 13.7/1000 (95% CI 5.8-21.5) for Pi’Z and 7.6/1000 (95% CI 1.7-13.5) for Pi’S.

Conclusions: Incidence of A1AT deficiency alleles in patients with PLCH was 2 times higher than in unselected population of newborns.
Introduction: Bone marrow necrosis is a rare, clinicopathologic condition defined in the course of diagnosis and remissions of malignant diseases like leukemia. Also infections, drugs, sickle cell disease and hyperparathyroidism may accompany. In our case, the role of coexistence of EBV both in diagnosis and remissions of leukemia in the etiology of bone marrow necrosis and hemophagocytosis. 

Case: A one-and-half-year-old boy referred to the Emergency Department with fever and fatigue. On his physical examination he had hepatosplenomegaly. Hematologic examination revealed leukocytosis, lymphocytosis (16900/13000/mm3) and anaemia (Hb 6.6 g/dl). No atypical cells were seen on peripheral blood smear examination. Among all infection markers, EBV IgM was positive, EBV DNA was negative. Bone marrow aspirate showed L1 type cells (%90 t (12:21) positive). He underwent ALL BFM 2000 chemotherapy. On the 16th week of the maintenance therapy, he began to suffer widespread leg and back pain. Hematologic examination revealed neutropenia. Sedimentation 54/h, LDH 785Ü, Alkalen phosphatase 213, CRP 81 mg/L, PPDtuberculin gold and infection markers, EBV IgM was positive, EBV DNA was negative. Bone marrow biopsy showed widespread bone marrow necrosis and no malignant cells. His kraniospinal MRG showed necrosis and sclerosis in both in diagnosis and remissions of leukemia in the etiology of bone marrow necrosis and hemophagocytosis.

Conclusion: In our case the association between EBV and leukemia, hemophagocytosis and bone marrow necrosis is open to discussion but should not be ignored. By this means, patients who have other conditions accompanying leukemia, underlying EBV should be monitored carefully.
Poster Location #18

CLINICAL AND THERAPEUTIC FEATURES OF 362 PATIENTS WITH MACROPHAGE ACTIVATION SYNDROME ENROLLED IN A MULTINATIONAL SURVEY

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Aim of the Study: To describe the demographic, clinical, laboratory, histopathologic, therapeutic and prognostic features of 362 children with macrophage activation syndrome (MAS) complicating systemic juvenile idiopathic arthritis (sJIA) collected as a part of a multinational project.

Method: Investigators from paediatric rheumatology societies and the Histiocyte Society were asked to enter the information of their patients with MAS collected retrospectively in a web-based database, managed by the coordinating center (Gaslini, Italy).

Results: 362 patients with sJIA-associated MAS were entered in the study website by 95 investigators (78.2% paediatric rheumatologists, 21.8% paediatric hemato-oncologists) from 33 countries. 208 patients (57.5%) were females. Median age at onset of sJIA was 5.3 years (IQR 2.7-10.1 years) and median disease duration at onset of MAS was 3.5 months (IQR 0.1-2.6 years); MAS occurred at onset of sJIA in 77 patients (22.2%). The most frequently observed clinical features were fever (96%), liver enlargement (70%) and spleen enlargement (58%); CNS involvement was reported in 122 patients (35%) and haemorrhagic manifestations in 71 patients (20%). The main laboratory abnormalities were: hyperferritinemia, increased D-dimer and liver enzymes, falling platelet count, hypertriglyceridemia and increased LDH. The most frequently reported trigger of MAS was sJIA flare (53.8%), followed by infections (37.8%) and medication toxicity (4.3%). Hyperferritinemia, increased liver enzymes, LDH, triglycerides and D-dimer and falling platelet count were the sole laboratory parameters that showed a percentage change greater than 50% between pre-MAS visit and onset of MAS. Histiocytosis was seen in 2/3 of patients who underwent bone marrow aspirate. Therapeutic interventions included corticosteroids (97.7%), cyclosporine (61.2%), IV Ig (36.3%), biologic medications (15.2%), etoposide (11.8%), other immunosuppressants (7.1%) and plasma exchange (4.1%). CNS involvement was required in 34.9% of patients; the mortality rate was 8.1%.

Conclusions: This multinational study can provide the so far largest cohort of patients treated for MAS. Further comparisons with control-groups are planned. This will hopefully enable us to create a suggestion for new diagnostic criteria in this life-threatening condition.

Poster Location #19

A CASE OF EBV-ASSOCIATED HEMOPHAGOCYTIC LYMPHOMA (HLH) AND SUBSEQUENT EBV-ASSOCIATED PRIMARY CNS LYMPHOMA (PCNSL)

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Purpose: To describe a case of EBV-associated HLH followed by EBV-associated PCNSL, which has not previously been described in the literature.

Methods: A 21-year-old male initially presented with fever, malaise, and hallucinations. His physical exam was remarkable for dehydration and enlarged exudative tonsils. A CBC revealed thrombocytopenia (platelets 45x10^9/L). His lumbar puncture demonstrated a normal cell count, glucose, protein and negative cultures. His serum and cerebrospinal fluid (CSF) EBV PCRs were 44,000 and 400 copies/ml, respectively. He had a brain MRI and electroencephalography which were normal. After admission, the patient decompensated rapidly with multiorgan failure (respiratory, renal and hepatic) requiring a prolonged intensive unit stay.

Results: He fulfilled seven of eight criteria for HLH, including fever, splenomegaly, cytopenias, hypofibrinogenemia, low NK-cell activity, elevated ferritin (6250 ng/mL), and elevated soluble CD25 (17,517 units/mL). Testing for mutations associated with HLH was negative. He was treated as per the HLH-2004 protocol with methylprednisolone and etoposide. After completing the initial therapy, his soluble CD25 and ferritin levels decreased to normal levels and his neurologic status improved significantly. Four months later he had a seizure. His serum and CSF EBV PCRs were positive (348 and 700 copies/ml, respectively). MRI revealed multiple supratentorial lesions. He underwent a brain biopsy that was positive for EBV-encoded RNA(+) and CD20(+) consistent with an EBV-driven B-cell CNS lymphoma. His metastatic disease work up was negative. He was treated with high-dose methotrexate, rituximab, and temozolomide. His brain MRI after induction chemotherapy showed a complete response and his CSF EBV PCR was undetectable. For definitive treatment of his HLH he will receive an allogeneic transplant from a matched sibling donor.

Conclusion: This is the first documented case of EBV-associated PCNSL occurring in the setting of EBV-associated HLH.

Poster Location #20

THE RESPONSE OF PATIENTS WITH EPSTEIN-BARR VIRUS-ASSOCIATED HEMOPHAGOCYTIC LYMPHOMATOYICHTOSIS (HLH) TO HLH-2004 PROTOCOL IN THE INITIAL THERAPY

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Objectives: To determine the rate of response of patients with Epstein-Barr virus (EBV)-associated HLH (hemophagocytic lymphohistiocytosis) to HLH-2004 protocol, and to evaluate the courses of clinical signs as well as laboratory data during the first 8 weeks of therapy.

Methods: This was a prospective case series report consisting of 13 patients younger than 16 years old, diagnosed with EBV-associated HLH and admitted to the Children Hospital 1 in HCMC from August 1st, 2011 to May 31st, 2012.

Results: Of these patients, 54% (7/13) were classified as response group and 23% (3/13) as non-response group and 23% (3/13) as mortality group. The median (range) of EBV DNA loads in plasma of the mortality group, response group and non-response group were respectively 7.3 x 10^7 copies/ml (7.0-7.3 x 10^7 copies/ml), 6.9 x 10^7 copies/ml (5.7-7.5 x 10^7 copies/ml) and 5.0 x 10^7 copies/ml (2.7-7.3 x 10^7 copies/ml). Immunochemotherapy were used as followed: dexamethasone in 100% (13/13) cases, cyclosporine A in 100% (13/13) cases, etoposide in 46%
Familial hemophagocytic lymphohistiocytosis (FHLH) is a rare, genetically heterogeneous condition that is inherited in an autosomal recessive manner. Five genetic loci have been associated with FHLH (FHL1 - FHL5). While the onset of FHLH is typically within the first few months of life, reports of prenatal presentation have been documented in the literature. Such case reports have described hydrops without or without hydrocephalus, oligohydramnios and hepatosplenomegaly as possible prenatal manifestations of FHLH. These cases were ascertained via complications of pregnancy rather than by family history, and for the majority, molecular testing was not available. We present a pregnancy of a woman with a history of rheumatoid arthritis, presented with fever and malaise followed by an acute encephalopathy with focal seizures and multiorgan failure leading to intubation. MRI demonstrating increased signal within the bilateral thalamus and left temporal lobe and hippocampus.

Case 3: 73-year-old man with a history of rheumatoid arthritis presented with progressive confusion and unexplained falls. He developed hematemesis, cytopenia, fever, and worsening delirium. MRI demonstrated diffuse pachymeningeal enhancement.

Conclusion: Adult-onset HLH can be associated with focal and diffusely localizing neurological syndromes and abnormal findings on neuroimaging. It is important to consider HLH in the differential diagnosis of sub-acute neurological disorders particularly when associated with other features of the disease. Awareness of the neurologic presentations of HLH is important to ensure prompt diagnosis and treatment.
HEMOPHAGOCYTIC SYNDROME DURING INDUCTION THERAPY FOR AMBIGUOUS LINEAGE (B/My) ACUTE LEUKEMIA

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Purpose: The presence of hemophagocytic syndrome (HS) in a patient with an acute leukemia (AL) could be difficult to recognize.

Methods: Clinical and laboratory parameters were recorded from the chart. HLH-04 protocol criteria were used to evaluate the patient.

Case Report: A 16-year-old girl with an ambiguous lineage AL (BLASTS: CD38+, CD19+, CD58+, CD10+, MPO+, HLA-DR+ and t(2;11)) developed fever, jaundice, hepatosplenomegaly, thrombocytopenia, while receiving the last doses of chemotherapy (L-ASA) of the induction phase of the ALL IC-BFM 2009 protocol. Bone marrow aspiration on Day 33 of induction showed hypocellularity and hemophagocytosis of platelets. During the next days, the CBC values progressively decreased and triglycerides, ferritin and amylase increased. The patient was successfully treated with dexamethasone 10 mg/m2/day for two weeks. The laboratory values and the bone marrow aspirations progressively improved and normalized in 1 month approximately. Clinical and laboratory evaluation showed no evidence of infectious cause to HS.

Conclusion: An unexplained fever, cytopenia, hepatosplenomegaly in a patient with an AL, must aware us about a possible HS, in order to be diagnosed and treated. Dexamethasone could be a useful therapy for this condition.

ANAPLASTIC LARGE CELL LYMPHOMA PRESENTING WITH SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) results from an uncontrolled activation of lymphocytes and NK cells resulting in a marked hyperinflammatory state. Untreated, HLH typically progresses rapidly to death from multi-organ failure. Prompt and aggressive therapy aimed at suppressing inflammatory cytokines has improved prognosis of HLH. Secondary HLH can present in patients with various malignancies. Management of these patients is complicated by the need to balance treatment of the underlying malignancy with HLH therapy. This poster presents a case of secondary hemophagocytic lymphohistiocytosis (HLH) in the setting of anaplastic large cell lymphomas (ALCL).

Case Report: An 8-year-old African American male presented with a two week history of daily fever to 40 degrees Celsius, pancytopenia, adenopathy with a mediastinal mass compressing the vena cava, and massive hepatosplenomegaly. Laboratory data showed elevated ferritin, hypertriglyceridemia, decreased NK-cell activity and markedly increased soluble IL2 receptor. Bone marrow and lymph node biopsies showed only rare hemophagocytosis, but both tissues contained lymphocytes strongly positive for CD30 and ALK, confirming a primary diagnosis of ALCL.

The patient’s initial therapy followed the BFM ALCL99 protocol, however he clinically worsened after pre-phase dexamethasone and cyclophosphamide with direct hyperbilirubinemia, increased hepatosplenomegaly, worsening pulmonary effusions and respiratory distress. In order to better treat the progressive HLH, BFM therapy was modified with increased dexamethasone dose and intensification of etoposide. The patient showed clinical and laboratory improvement after HLH-directed therapy. After clinical stabilization, he was able to safely continue with standard ALCL-directed therapy.

Conclusion: Secondary HLH is an uncommon complication of newly diagnosed lymphoma and has rarely been described with ALCL. This case illustrates the treatment challenges associated with this combination of diagnoses and the importance of prioritizing management of the hyperinflammatory HLH. Careful selection of ALCL treatment plans and subsequent modification of therapy makes it possible to effectively control both diseases.
Purpose: Hemophagocytic Lymphohistiocytosis (HLH) is considered familial in patients with an underlying predisposing genetic mutation. Acquired HLH occurs in patients without a known genetic predisposition, often as a disordered immune response to infection, malignancy or autoimmune diseases (macrophage activation syndrome, MAS). However, only a very small minority of patients with these possible underlying conditions get HLH, raising the possibility of unknown predisposing genetic mutations in patients with presumed “acquired” HLH.

Methods: The Utah Population Database (UPDB) is a unique and powerful tool for population-based research that provides information on more than 7,000,000 individuals dating back several generations. It includes medical records, demographics, birth and death records which are linked to an extensive set of family pedigrees. We used the UPDB to evaluate the degree-of-relatedness amongst a cohort of HLH patients diagnosed over a 15-year period at a tertiary children’s hospital.

Results: Linkage data was available for 35 HLH patients. Distantly related HLH patients were identified in three pedigrees. Pedigree 1: Patients #25 (HLH secondary to lymphoma) and #2 (MAS secondary to juvenile rheumatoid arthritis) had a common ancestor dating back six generations. Neither patient had a known familial HLH mutation. Pedigree 2: Patients #5 (HLH secondary to EBV with no known genetic predisposition) and #28 (HLH with two separate heterozygous MUNC13-4 mutations) had a common ancestor dating back five generations. Pedigree 3: Patients #10 (MAS with Still’s disease), #14 (HLH), and #26 (MAS) had a common ancestor dating back five generations and no known HLH mutation.

Conclusions: A minority of patients in this cohort with “acquired” HLH are distantly related. This raises the possibility of the existence of poorly penetrant genetic mutations that might predispose patients to HLH.

Poster Location #27
IDENTIFYING FAMILIAL ASSOCIATIONS IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) USING THE UTAH POPULATION DATABASE
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Purpose: To characterize the cellular and molecular defects leading to HLH in a patient bearing a monoallelic STXBP2 mutation (194 G>A; R65Q).

Methods: CD8+ T and NK cells were isolated by negative selection from PBMCs from normal healthy controls or from the patient, who exhibited classical features of HLH. STXBB2 protein levels were analyzed by Western blotting. Subcellular localization was determined by super-resolution Stimulated Emission Depletion (STED) microscopy. The physical interaction between STXBP2 and STX11 was assessed by immunoprecipitation (IP). The cytolytic activity of CTLs and NK cells was evaluated using a non-radioactive target cell-killing assay.

Results: STXBP2, STX11 and MUNC13-4 protein expression levels were comparable in cells from the FH5 patient and normal controls. The subcellular localization of STXBP2, STX11, MUNC13-4, RAB27A, Perforin, Granzyme A and Lamp1 under resting and activated conditions were not affected. Activated CTLs from the patient displayed a normal surface phenotype but exhibited a significant and >60% reduction in target cell killing compared to control cells. Preliminary IP experiments revealed that endogenous STX11 co-immunoprecipitated the same amount of STXBP2 in patient and control cells; however, further experiments are underway to precisely determine whether the stability or other features of the physical interaction are affected.

Conclusion: The R65Q mutation causes a severe defect in cytolytic activity in CTL and NK cells, which could have led to the symptoms of HLH in this patient. This effect was not mediated by a reduction in the expression or obvious mis-sorting of STXBP2 or relevant cytolytic proteins. Since the R65 residue lies in the STXBP2 central cavity, we propose this mutant acts as a dominant negative that interferes with SNARE complex assembly rather than functioning to promote interaction with monomeric STX11. Experiments are underway to examine the effects of the R65Q mutation on SNARE complex formation.

Poster Location #29
PATHOGENESIS AND OUTCOME OF CHEDDIK-HIGASHI SYNDROME: A LYtic GRANULE DISORDER OF LYMPHOCyTES IN JAPAN
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Background: Lytic granule disorder has been characterized by cytotoxic dysfunctions of lymphocytes or NK cells followed by several immunodeficiencies including hemophagocytic lymphohistiocytosis (HLH). In the current study, we performed nationwide survey of Chediak-Higashi syndrome (CHS), one of the lytic granule disorders, in Japan.

Methods: We first sent questionnaires to 287 institutes in Japan that employ pediatric or adult hematologist, asking for experience of diagnosis of lytic granule disorders. Then we sent second questionnaire to where had experience diagnosis, asking for information on clinical feature, treatment, and outcome of each patient. In patients with available DNA samples, sequencing of possible candidate genes were performed. Cytotoxicity and degranulation activity of cytotoxic T lymphocyte (CTL) were analyzed in patients with or without genetic mutations.

Results: We collected 15 patients with CHS who were registered and treated in 12 institutions of Japan, whereas no patients with Griscelli syndrome or Hermansky-Pudlak syndrome were detected. Giant granules in neutrophils were observed in 15 (100%), ocuculocutaneous albinism in 14 (93%), recurrent bacterial infection in 9 (64%), and life-threatening HLH ‘accelerated phase’ in 4 (36%). Five patients including three patients with HLH underwent hematopoietic stem cell transplantation. Ten patients were still alive. Sequencing of LY7 gene was performed in 10 patients.
Seven mutations were found in 7 but not in other three; 3 were siblings with heterogenous mutation (5541-5542delAA/), and the other 4 had 3944insC/-, 7982C>G/8281A>T, 1044-1045insA/- and 10445-10446insCA/7207C>T, respectively.

Cytotoxicity and degranulation activity of CTL were analyzed in two patients. In the patient with LYST nonsense mutation who developed HLH, CTL activity was significantly decreased, whereas in the patient without mutation and HLH development, CTL was mildly impaired. Degranulation of CTLs showed significantly low activity in both patients.

Conclusions: These findings suggest the correlation between CTL activity and development of HLH in CHS. Genetic and functional analysis of CTLs also indicates the presence of other CHS subtype by unknown causative gene. Data analysis from other CHS patients could clarify the appropriate diagnosis and treatment of CHS in the future.

Poster Location #31
WHOLE EXOME SEQUENCING IDENTIFIES THE MOLECULAR DEFECTS IN 3 PATIENTS WITH PARTIAL ALBINISM AND IMMUNODEFICIENCY

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Griscelli syndrome type 2 (GS2), Chediak-Higashi syndrome (CHS), and Hermansky-Pudlak syndrome type 2 (HPS2) are autosomal recessive disorders characterized by oculocutaneous albinism and immunodeficiency due to defects in secretory lysosome biogenesis and trafficking. The genes affected in these disorders are RAB27A, LYST and AP3B1, respectively. Here we report our experience with whole exome sequencing (WES) as a tool to discover molecular defects in patients with partial albinism and immunodeficiency. We performed WES on three unrelated patients suffering from partial albinism and immunodeficiency. In two patients, both from Kuwait and with a clinical diagnosis of Chediak-Higashi syndrome, homozygous LYST mutations were identified. The first patient harbored a novel LYST c.2311C>T (p.Gln771X) mutation leading to a truncated protein. The second patient harbored a previously reported c.1902dup (p.Ala635Serfs*4) mutation also giving rise to a truncated protein. In the third patient, referred from Turkey with a clinical suspicion of GS2, two novel compound heterozygous mutations in AP3B1 were identified, establishing a molecular diagnosis of HPS2. A c.2626C>T (p.Arg876X) nonsense mutation and a c.1254dup (p.Gln419Thrfs*22) 1-bp duplication gave rise to a truncated protein.

In conclusion, we report three novel mutations associated with partial albinism and immunodeficiency and confirm the usefulness of WES for genetic studies of rare disorders. This work also served as test for our WES data analysis pipeline, which can now be applied for studying patients with defects in cytotoxic lymphocyte function and a less clear phenotype.
Poster Location #32

ACTIVATING MUTATIONS IN NRAS IN ERDHEIM-CHESTER DISEASE

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Purpose: There is a high frequency of activating mutations in proteins of the Ras/Raf/MEK/ERK pathway in melanoma and other solid tumors. The BRAF V600E mutation has recently been found to be highly prevalent in Erdheim-Chester disease (ECD), a rare non-Langerhans cell histiocytosis with poor prognosis, as well as Langerhans cell histiocytosis (LCH). Treatment of BRAF V600E mutant ECD patients with vemurafenib has been associated with unprecedented and dramatic response in a few cases.

Methods: We present the case of a 66-year-old man evaluated for several months of cognitive and motor decline. He was found to have multifocal enhancing lesions in the cerebral meninges, multiple soft-tissue masses in the abdomen and sacrum, and abnormal scintigraphic uptake in the long bones of the legs.

Results: Biopsy of a renal mass demonstrated a xanthomatous CD68+ CD1a- histiocytic infiltrate, consistent with ECD. Interrogation of tumor tissue with the Sequenom MassArray system demonstrated absence of the BRAF V600E mutation but presence of the NRAS Q61R mutation. Sanger sequencing confirmed the presence of the NRAS mutation in the tumor and wildtype NRAS in the germline. Immunohistochemical staining of the effected tissue for pERK1/2 revealed clear activation of RAS-RAF pathway in the NRAS mutant histiocytes.

Conclusion: This is the first report of an activating NRAS mutation in ECD. The finding of an oncogenic NRAS mutation in ECD further supports the hypothesis that this disease is driven by activation of the Ras/Raf/MEK/ERK pathway. Studies are currently underway to identify recurrent somatic mutations in RAF and RAS in patients with ECD, LCH, and other histiocytic disorders.

Poster Location #33

A SURVEY OF DISSEMINATED JUVENILE XANTHOGRANULOMA IN JAPAN

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Background: Juvenile xanthogranuloma (JXG) is the most common histiocytic disorder in children. However, we lack epidemiological data for Japan.

Methods: We sent questionnaires regarding experience with JXG to 280 hospitals with doctors belonging to the Japanese Society of Pediatric Hematology. Fifty one patients with JXG were found among 232 hospitals. Then we inquired into characteristics and pathology of the disease, therapies, and prognosis of about 51 patients through a second questionnaire.

Results: Twenty one (12 males, 9 females) of 51 patients were diagnosed with disseminated juvenile xanthogranuloma (DJXG). Twelve (57.1%) were diagnosed during the first year of life, and 8 of 12 patients (38.1%) had symptoms at birth. No neurofibromatosis or JMML patients were in this series. Three incidences of DI, 2 GHD, 1 dysfunction of pan-putitary glands, and 1 schizophrenia were seen as coexisting diseases. Eight of the 21 patients had CNS lesions, 9 of 21 had skin lesions, and 4 of 21 had lung lesions. Nine of 15 patients had Trouton-type giant cells, 9 of 13 patients had foamy histiocytes. All of 16 patients had positive anti-CD68. Nine patients received chemotherapy, 2 only tumor resection, and 6 no therapy. Twenty of 21 patients were alive. Four patients suffered from DI, 2 dysfunction of pan-putitary glands, 2 had visual dysfunction, and 3 experienced skin disorders as late effects.

Poster Location #34

SPONTANEOUSLY REGRESSING NON-LANGERHANS CELL HISTIOCYTOMA WITH RETICULOHISTIOCYTOMA MORPHOLOGY: A REPORT OF TWO CASES

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Purpose: We present two unusual cases of spontaneously regressing histiocytoma in infants.

Methods: The pathology findings, clinical presentation and course are described.

Results: Case 1 is of an otherwise well 6-week-old baby girl who presented with a non-progressive firm swelling over the right ankle since birth. X-ray showed thickening of the distal fibula but no lytic lesion. Magnetic resonance imaging (MRI) showed a poorly defined mass in the lateral muscle group of the lower limb with underlying bony invasion of the fibula. There were no distant sites of disease. Needle biopsy showed sheets of large epithelioid histiocytic cells with numerous associated inflammatory cells including many eosinophils. Mitoses were inconspicuous. Immunohistochemically the cells were positive for CD68, CD14, CD163, fascin and Factor XIIIa. CD1a, S 100 and Langerin were negative. Case 2 is of a 9-month-old girl who presented with a non-progressive swelling anterior to the right tibia. She was systemically well but had bilateral cervical lymphadenopathy. MRI revealed a lobulated mass arising from the soft palate, infiltrating the pterygoid muscle and tibia, and confirmed the cervical lymphadenopathy. Histology showed sheets of large epithelioid histiocytic cells with numerous eosinophils. Immunohistochemistry showed the cells to be positive for CD68 and CD163, with weak staining for Factor XIIIa. S100 staining was also positive. CD1a and Langerin were negative. A cervical lymph node showed extensive sinusoidal infiltration by a similar infiltrate. The lesions in both cases regressed spontaneously.

Conclusion: Morphologically, the appearances are of non-Langerhans cell histiocytomas, similar to that of reticulohistiocytoma. The non-cutaneous nature and aggressive imaging characteristics at presentation are not typical of solitary reticulohistiocytoma/epitheloid histiocytoma or multicentric reticulohistiocytosis. These lesions expand the morphological category of spontaneously regressing non-Langerhans cell histiocytomas and demonstrate that in infants, histiocytomas with aggressive clinical features may regress spontaneously.

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CEREBELLAR DEGENERATION IN A PATIENT WITH HISTIOCYTIC DISEASE

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Langerhans cell histiocytosis (LCH) is a CD1a-positive monoclonal disorder with the potential of late onset neurodegeneration. Rosai Dorfman disease (RDD) is a CD1a-negative polyclonal disorder with no reported late onset neurological sequelae. We describe a child originally diagnosed with LCH who then developed RDD, who then presented with late-onset cerebellar degeneration.

The patient first presented at 22 months of age with LCH involving the right parietal bone. He continued to have multiple bony recurrences. At 6 years post diagnosis he developed a large left submandibular lymph node and recurrent skin lesions on his extremities. Biopsy of the lymph node and a skin lesion were consistent with RDD.

As a teen, he was noted to have an ataxic gait. MRI of the brain showed changes consistent with late onset cerebellar degeneration. Later on, his neurological status had worsened with the development significant cerebellar dysfunction. The MRI was unchanged. He was started on IVIg infusions. After 6 months of IVIg therapy, he had significant improvements in his symptoms.

At 15 months into IVIG therapy, he had improved back to his baseline level. This case questions the natural history of histiocytic disorders and the role of IVIg in the management of cerebellar degeneration. This case has features that diverge from the previously understood natural history of LCH and RDD. Most cases of coexisting LCH and RDD had both LCH and RDD occurring in the same lesion. What causes this difference and why this patient developed both diseases is still unclear.

There is no definitive treatment for neurodegenerative changes in LCH. IVIg has been shown to be beneficial and was administered in this patient with surprisingly great results. This case provides supports the benefit of IVIG in late onset cerebellar degeneration.

ERDHEIM-CHESTER DISEASE (ECD) IN A 3-YEAR-OLD CHILD: A DIFFICULT DIAGNOSIS

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Purpose: ECD is a rare non-Langerhans cell histiocytosis, exceptionally described in children. Here we report a case of ECD with retroperitoneal, bone, skin and lymph node involvement diagnosed at 3 years of age.

Case Report: The patient developed skin lesions, lymphadenopathy, fever and anemia at the age of 4 months. She was first seen at the pediatric department of our hospital at 11 months. Bone morrow aspiration was normal. A cervical lymphnode was biopsied and found to be reactive. Infectious and autoimmune diseases, autoimmune lymphoproliferative syndrome and familial hemophagocytic syndrome were ruled out. In the suspicion of a systemic inflammatory disease, immunosuppression with steroids and cyclosporine was started, with rapid improvement. During the following months, cyclosporine was stopped but at steroid tapering adenomegaly and anemia reappeared. At 2.6 years Rapamicine was added to prednisone with transient improvement. Soon after, the child developed retroperitoneal fibrosis with bilateral hydronefrosis and renal failure. We saw the child at this stage. X-ray screening showed multiple osteolytic lesions of the skull, with typical bilateral femoral sclerosis of the diaphysal and metapysal regions. Bone biopsy showed infiltration by foam cells CD68+ and CD1a-, confirming the diagnosis of ECD. Mutation analysis of BRAF turned to be negative for V600E. PEG-IFN-α therapy was started.

Conclusions: The diagnosis of ECD in a child may be challenging. The clinical course may remain undefined for months or even years. Retroperitoneal fibrosis and asymptomatic characteristic bone lesions may represent the clue to the diagnosis.
Juvenile Xanthogranuloma (JXG) is the most common form of non-Langerhans cell histiocytosis. Its cutaneous form generally follows a benign course with spontaneous resolution over a period of a few years. However, the extracutaneous disseminated forms are exceedingly rare and can be associated with considerable morbidity if not treated promptly. Currently, there is no standard chemotherapeutic regimen for disseminated JXG. We report two cases of disseminated JXG in the neonatal period treated with LCH-based protocols. The two patients had immunohistochemical characterization of the infiltrating histiocytes that showed strongly positive staining for CD68, CD163, and Factor IIIa. Patient A presented at 3 weeks of age with dermal nodules on scalp, face, arm, and scrotum and then subsequently was found to have pulmonary, liver and bone marrow involvement. Biopsies for this patient were obtained from the skin, bone marrow and liver. He was initially treated with vinblastine and prednisone based on LCH-II. Even though the patient clinically improved he had persistent bone marrow and liver involvement and his treatment was modified to include high dose methotrexate. Currently, patient A remains disease-free after 4 years without chemotherapy. Patient B also presented in the neonatal period treated with LCH-based protocols. He completed the induction phase with vinblastine and showed a good clinical response. The initiation of therapy was modified to include high dose methotrexate.

Currently, there is no standard chemotherapeutic regimen for R-Dorfman disease. As atypically, only had moderately enlarged lymph nodes while suffering debilitating systemic symptoms.

Methods: A case report.

Results: A 42-year-old, previously well, gentleman presented with enlarged (1-2 cm diameter) supraclavicular lymph nodes and subcutaneous palmar nodules. Biopsies of supraclavicular nodes and palmar nodules showed typical features of R-DD. He also had marked systemic symptoms including progressive night sweats, episodic fever, rigors, headaches and lethargy, but had no organ involvement. Blood results revealed raised inflammatory markers, marked polyclonal increase in serum immunoglobulins and severe CD4 T-cell lymphopenia. After a 3 year watch-and-wait strategy he was no longer able to work and the debilitating nature of his symptoms dictated the need for treatment. His symptoms and inflammatory markers did not improve, or only briefly improved, on a number of different treatments including single agent rituximab, prednisolone, azathioprine and 2-chlorodeoxyadenosine, as well as combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, etoposide and prednisolone (CHOEP). His symptoms however did resolve and the inflammatory markers normalised after treatment with a childhood Langerhans cell histiocytosis treatment regimen containing cytarabine, prednisolone and vincristine. After 6 months therapy he was switched to oral 6-mercaptopurine and methotrexate for 18 months to consolidate his disease control. Twelve months after completing therapy he is back at work, his inflammatory markers remain normal and his symptoms have not returned. His serum immunoglobulins have normalised and his CD4 count has improved.

Conclusion: This case demonstrates that debilitating systemic symptoms may dictate the need for an effective treatment in some R-DD patients. As far as the authors are aware this is the first report of successful treatment of R-DD with the combination of cytarabine, prednisolone and vincristine.
INTERFERON GAMMA (IFNG) AND TOLL-LIKE RECEPTOR 9 (TLR9) PROVIDE COLLABORATING AND NON-REDUNDANT SIGNALS TO INHIBIT B-CELL DEVELOPMENT IN CYTOKINE STORM SYNDROMES

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Purpose: There are multiple reports of hypogammaglobulinemia in patients across the spectrum of hemophagocytic syndromes (HPS). We considered that B-cell lymphopenia might be impaired in hemophagocytic syndromes and studied this process using murine models.

Methods: B-cell lymphopenia was examined using flow cytometric characterization of B-cell precursor subsets both in vivo and the OP9 culture system in vitro. Various genetically altered mice were used to dissect the immune regulation of this process. CpG1826 and recombinant IFNg were used to explore the effects of these signals in these systems.

Results: We found defects in B-cell lymphopenia in all of these in vivo models of HPS. Using a combination of in vivo models, in vitro OP9 culture systems, and mixed bone marrow chimeras, we show that TLR9 signals impair B-cell development at multiple stages, starting from the Common Lymphoid Progenitor (CLPs), in both cell intrinsic and extrinsic manners. This is true both in terms of number of CLPs as well as the per cell potential of CLPs to form B-cells. Later stages of development including Pro- and Pre-B-cells are also impaired by TLR9 signals. IFNg acts in a synergistic manner to impair CLP function, but only in an additive manner to impair later stages. Interestingly, TLR9 signals do not affect T-cell development, while IFNg profoundly affects T-cell development.

Conclusions: Systemic inflammation in HPS impairs B-cell development via multiple interacting mechanisms. IFNg, a central cytokine in HPS, has profound effects on both B- and T-cell development. Future studies should be directed to see whether these defects are indeed the causative link to hypogammaglobulinemia in HPS, and might suggest possible therapeutic interventions to overcome this complication.

AGGRESSIVE LANGERHANS CELL HISTIOCYTOSIS FOLLOWING T-ALL: CLONALLY RELATED NEOPLASMS WITHOUT BRAF V600E MUTATION AND SUFFICIENT EXPRESSION OF ASPARAGINASE SYNTHETASE

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Langerhans cell histiocytosis (LCH) is a proliferative disorder of Langerhans cell-like CD1a/CD207 (Langerin)-positive cell. Recently, the mutations of serine/threonine-protein kinase B-raf (BRAF) are frequently found in human tumors. BRAF V600E has been detected also in about 56% of LCH cases. We have previously shown that several cases of LCH lack asparaginase synthetase (ASNS) and might indicate effectiveness of L-asparaginase. A case of an irtractable skin LCH following T-ALL was reported. The relationship of BRAF V600E mutation and L-asparaginase sensitivity was explored.

Case Presentation: 7-year-old male, T-ALL was treated by TCCSG ALL07-16-2 HEX protocol. After achieving CR, maintenance therapy consisting of daily 6-MP and weekly MTX was added. Twenty months later, solitary, reddish, non-itchy exanthema appeared on extremities and invasively spread. Skin biopsy revealed LCH positive in CD1a, CD207 and S100. One month later, he died due to ARDS-like respiratory failure even with JLSG-02 induction A/B protocol and intensive care treatment.

Method: BRAF V600E mutation was analyzed by PCR amplification and direct sequencing. Immunohistochemical detection with anti-human BRAF V600E mAb (Clone VE1, Spring Biosciences), and anti-human ASNS mAb (Clone 3G3-2G8; U of Florida) was performed. Existence of BRAF V600E mutation ASNS positivity was explored in a small group of 3 SS and 2 SM and 2 MM lesion.

Result: TCR rearrangement analyzed by long-distance PCR and Southern blotting yielded the same clonal TCR gamma chain rearrangement in T-ALL and LCH. The BRAFV600E mutation was not detected by direct sequencing, or by immunohistochemistry in both lesions. LCH cases without BRAF V600E mutation expressed very low amount of ASNS.

Conclusion: The absence of BRAF V600E mutation was correlated with ASNS negativity. Immunohistochemical-result might indicate that negativity of BRAF V600E mutation might be related with ASNS negativity and L-asparaginase sensitivity and might suggest the possibility of L-asparaginase therapy for intractable LCH.

IL-17A PRODUCTION BY BLOOD MONOCYTES IS TIGHTLY RELATED TO THE DEGREE OF ACTIVITY OF LANGERHANS CELL HISTIOCYTOSIS

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Purpose: Interleukin (IL)-17A has been reported to promote long-term survival and chemoresistance of monocyte-derived dendritic cells (DC), as well as DC fusion and formation of multinucleated giant cells expressing tissue-destructive enzymes. Notably, IL-17A has also been implicated in many chronic inflammatory and autoimmune diseases and recently also in Langerhans cell histiocytosis (LCH). DC in LCH granulomas stain positive for IL-17A, implying that they may contribute to the high plasma IL-17A levels observed in LCH patients with active disease. Importantly, high levels of IL-17A receptor A have been detected in patients with multisystem LCH. The aim of our current study was to investigate whether IL-17A-producing cells could be identified in the blood of LCH patients and to explore possible correlation between IL-17A levels and LCH disease activity.
Methods: Blood samples from 22 LCH patients (16 active/6 inactive disease) and controls were studied. Peripheral blood mononuclear cells were stained with antibodies against markers defining monocytes, lymphocytes and cytokines and analyzed with flow cytometry. RNA levels were evaluated with qPCR. Plasma cytokine levels were measured with ELISA. Reagents for IL-17A detection from four companies were used.

Results: We report, for the first time, that circulating monocytes can produce IL-17A and this appears tightly related to LCH. In one-third of LCH patients, the majority of CD14high and CD14low monocytes stained positive for intracellular IL-17A, accompanied by increased expression of Retinoic acid orphan receptor C. Importantly, the patients with the highest levels of IL-17A in their plasma and IL-17A mRNA and protein in their monocytes were those with moderate or severe disease. No IL-17A+ lymphocytes were detected.

Conclusion: Our findings highlight a possible role for circulating monocytes in LCH pathogenesis. Identifying a correlation between IL-17A and the clinical course of LCH is important for the subgroup of patients that may benefit from novel therapeutic approaches.

SYNERGISTIC DEFECTS OF DIFFERENT MOLECULES IN THE CYTOTOXIC PATHWAY LEAD TO CLINICAL FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Purpose: More than half a dozen molecules (LYST, AP3, Rab27a, STX11, STXBP2, MUNC13-4 and PRF1) have been associated with the function of cytotoxic lymphocytes. The process involves polarizing, docking, priming, and fusing the cytolytic granules to the target cells, followed by penetration of the target cell, allowing the granzymes and granulolysin to diffuse into the target cells and trigger their apoptosis.

Biallelic defects in all of these molecules have been associated with Familial hemophagocytic lymphohistiocytosis (Familial HLH or FHL). FHL is typically characterized by fever, hepatosplenomegaly and cytopenias and described mainly in early childhood. However, there are many adult cases and atypical clinical presentations have been reported in patients with defects in these molecules. We provide evidence that the inheritance of uniallelic mutations in two different genes encoding molecules critical to the cytotoxic process result in the development of FHL and associated disorders.

Method: A retrospective chart review of patients with a clinical diagnosis of HLH was performed. Genetic tests for mutations and sequence variants in PRF1, MUNC13-4, STXBP2, STX11 and RAB27a, as well as immunologic studies were reviewed.

Results: We identified 27 patients with defects in two HLH associated genes. Age at presentation varied from 3 months to 28 years. NK cell function was decreased in 68.7% (11/16) of the patients. Decreased perforin expression by flow cytometry was noted in 44.5% (5/11) of the patients with combination defects involving PRF1 and degranulation pathway. In patients with combination defects involving two genes in the degranulation pathway, CD107a degranulation was decreased (2/2). However, the CD107a degranulation assay was normal in all patients with combination defects involving a gene in degranulation pathway and PRF1 (4/4).

Conclusion: Various digenetic defects of HLH associate genes are observed in patients with HLH. Farther functional studies are anticipated in order to dissect the biology behind this observation.
**AN ORAL PAN-AKT INHIBITOR IN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS SHOWS SIGNS OF CLINICAL ACTIVITY**

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Purpose: To evaluate efficacy of the oral pan-AKT inhibitor, afuresertib, dosed at 125 mg once daily, in adults and adolescents with relapsed/refractory Langerhans cell histiocytosis (LCH) or treatment-naïve LCH (adults). Secondary objectives included safety and pharmacokinetics.

Methods: Diagnosis was confirmed by pathology review of archival tissue. The Histiocyte Society criteria were used for response evaluation at three and six months. Safety and pharmacokinetic assessments were done at pre-specified intervals. BRAF status from archival tissue was evaluated by Sanger sequencing.

Results: 16 patients (15 adults, 9 females) were enrolled; median age was 36 years (15-70). 4/16 patients had isolated pulmonary disease, 1/16 had single-system, multifocal-bone disease, and 11/16 had multi-system disease. Eight patients were treatment-naïve; 8 were relapsed/refractory. The drug was well tolerated with only 2 drug-related ≥Grade 3 events reported (soft tissue necrosis; rash maculopapular). Eight patients had archival tissue available for BRAF testing from which DNA could be extracted and analyzed: 1 was BRAF V600E mutant and 7 were BRAF wild type. Of the 12 patients evaluable for efficacy at three months, 2 were classified as better and 9 had stable disease; of the 9 evaluable for efficacy at six months, 3 were classified as better and 4 had stable disease. Three additional patients withdrew prior to completion of the three month disease assessments due to progressive disease (1), investigator discretion (1), and withdrawal of consent (1); data is pending for one patient. Among the responders at months three and/or six, three were treatment-naïve and one had relapsed/refractory disease. The BRAF V600E patient had stable disease for 48 weeks.

Conclusion: The toxicity profile of afuresertib in patients with LCH was consistent with that observed in prior studies. Afuresertib was active in patients with both treatment-naïve and relapsed/refractory disease. Additional evaluation of afuresertib in the treatment of LCH may be warranted.

**PATTERN AND COURSE OF MULTIFOCAL BONE DISEASE (MFBD) IN LANGERHANS CELL HISTIOCYTOSIS (LCH): DATA FROM THE LCH III STUDY**

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Purpose: Single System skeletal LCH with MFBD is usually described in younger children and is associated with increased risk for reactivations and permanent consequences. Patients with MFBD were uniformly treated in the international LCH III study. Due to incomplete data, this stratum has not been published yet.

Methods: Patients with histologically verified MFBD (≥2 bone lesions) <18 years were enrolled into Group 3 of the LCH-III Study. The initial treatment consisted in a six-week PRED/VBL course. A second initial course was delivered depending on response. All patients received continuation therapy to total treatment duration of 24 weeks. We evaluated data completeness and preliminary results based on the cohort of the GPOH Sub-Center.

Results: 106 patients with MFBD were identified. Their median age at diagnosis was 5.7 years (0.2 – 18 years). The male to female ratio was 1.4:1.23% were < 2 years old. Overall 281 bone lesions were detected, 50% in the lower, 17% in the upper limb, 21% in the craniofacial region, and 12% in the vertebral bones. 65% of the patients reached non-active disease (NAD) within one year and 80 (90)% at 3 (5) years. Eighteen patients (21%) had disease reactivation within 1 year after achieving NAD. The long-term reactivation rate according to Kaplan-Meier was approximately 30%. Due to incomplete long-term data this has to be interpreted with caution. Reactivations were mainly localized in bones, 2/18 patients developed diabetes insipidus, 1/18 skin involvement. Reactivation rate between patients aged less than 2 years and over 2 years was identical (21%, p=0.331).

Conclusion: The overall outcome of patients with MFBD treated according to the LCH III protocol seems acceptable. However, the amount of missing follow up data is unacceptably high. Data completion particularly of the GPOH cohort is mandatory for a reliable final analysis.

**PATIENT OUTCOMES OF LANGERHANS CELL HISTIOCYTOSIS INVOLVING SKIN**

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Purpose: Langerhans cell histiocytosis (LCH) has protean clinical manifestations, from self-resolving skin involvement to potentially fatal multi-organ involvement. In order to characterize outcomes and biologic features of patients who present with skin LCH, we compared patients with skin-only disease to those with skin plus multisystem involvement.

Methods: We reviewed medical records of 64 LCH patients who presented to our institution between March 2005 and October 2011 with skin involvement. Log-rank analysis estimated progression free survival (PFS), and categorical data were compared using Fisher’s exact test. Quantitative real-time PCR was performed on peripheral blood DNA to detect circulating BRAFV600E mutation, a candidate marker of disease.
Results: Occult multi-system LCH was detected in 40% of patients referred for presumed skin only LCH. Skin disease in patients aged greater than 18 months at diagnosis predicted presence of disease in other organ systems (p = 0.026), but skin disease in early infancy did not exclude multisystem involvement. Six skin-only LCH patients (30%) had skin-limited disease requiring therapy due to progression. All but two had resolution with upfront therapy (often oral or topical) and none recurred in a different organ system. Patients with skin plus multifocal disease were likely to progress despite upfront treatment (estimated 3 year recurrence rate 72%). Circulating cells with the BRAF V600E mutation were detected in only 1/16 patients with skin limited disease, compared with detectable mutation in 8/11 skin plus multisystem patients (p = 0.0006).

Conclusion: Skin-limited LCH typically resolves with minimal or no intervention. Infrequent detection of circulating BRAF V600E in skin-limited patients compared to patients with multisystem disease suggests differential maturation of the cell of origin. Considering that patients with skin involvement in the setting of multisystem LCH respond poorly to initial therapy, thorough diagnostic measures to define extent of disease in patients who present with LCH skin lesions is essential.

NEURODEGENERATIVE LANCHEMS CELL HISTIOCYTOSIS (ND-LCH): CORRELATION WITH AGE AT DIAGNOSIS AND IDENTIFICATION OF DISEASE PROGRESSION

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Purpose: To propose a multidisciplinary diagnostic work up to early identify and follow-up patients potentially at risk to develop ND-LCH.

Methods: Between 2010-2012 patients with histologically proven LCH were prospectively enrolled in: group 1, ND-LCH verified by MRI; group 2, risk factors [craniofacial bone lesions (CFBL), diabetes insipidus (DI)] for ND-LCH without MRI alterations. All the patients underwent clinical, neurophysiological, neuropsychological and MRI evaluation.

Results: 28 patients, median age 12 years; group 1, n=17 (median 7 years); group 2, n=11 (median 11.5 years). The proportion of multisystem disease was not different in the two groups (74% vs. 64%); reactivations: 82% group 1, 54% group 2. All group 1 patients had DI (n=11) or CFBL (n=14). The median age at the diagnosis of LCH was significantly younger in group 1 (2 vs. 6.5 years; p=0.0448). Time elapsed between diagnosis and study entry was comparable (6 vs. 5 years); first evidence of ND-LCH in group 1 occurred at a median of 3.8 years after the disease onset. Neurological examination was abnormal in 8/17 group 1 patients, with overt clinical symptoms in 2/8. Somatosensitive evoked potentials (SEPs) were abnormal in 11/17 group 1 vs. 1/11 group 2 patients (p=0.02597). A reduction of the NAA/Cr ratio was detected by MRSpectroscopy in the cerebellum of 13/17 (76%) patients group 1, none group 2. At initial follow-up, 3/7 group 1 patients with discordant findings at first evaluation showed worsening at neurological examination and/or SEPs while MRI remained stable.

Conclusions: The combination of neurological examination, SEP and MR+MRS represents a sensitive diagnostic tool to screen cases with ND-LCH among patients at risk. Neurological examination and SEPs are more sensitive tests for the follow-up, thus representing a basis for selection of patient candidates for novel, experimental therapies. The observation that patients with ND-LCH have a significantly younger age at the diagnosis may provide an insight into pathogenesis and natural course of this devastating complication.

THE OPTIMAL IMAGING TECHNIQUE FOR RESPONSE EVALUATION OF BONE LESIONS IN LANGERHANS CELL HISTIOCYTOSIS: A SYSTEMATIC REVIEW

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Purpose: Different imaging techniques have been used for the response evaluation of bone lesions in Langerhans Cell Histiocytosis (LCH) patients. Classically bone lesions in LCH are evaluated with plain radiography. Clinically relevant issues include optimal timing of response evaluation and assessment of disease activity in stable lesions. In this review we studied the possible role of other whole-body imaging techniques in response evaluation of bone lesions in LCH.

Methods: A PubMed search was performed to identify articles studying full-body imaging during follow-up of pediatric LCH patients. Two authors independently selected studies for this review. Studies using one full-body imaging technique and comparing it with at least one other confirming imaging technique were included. Studies with less than 5 patients were excluded. An English abstract had to be available.

Results: Out of 416 articles, 3 articles were eligible for this review. Due to the comparison of different techniques and different approaches, pooling of data was not possible. One study compared bone scintigraphy with plain radiography. In this study, standard radiography was superior. No analysis was made for disease activity. One study assessed the use of total-body Magnetic Resonance Imaging (MRI), comparing it with skeletal scintigraphy. Total-body MRI detected changes in lesions earlier than scintigraphy. Finally, one study compared positronemission tomography (PET)-CT with radiography. PET-CT was earlier negative than radiography, possibly due to difference in detection of disease activity.

Conclusions: Only a few comparative studies have been performed using full-body imaging in the response evaluation of bone lesions in pediatric LCH patients. Total-body MRI and PET-CT seem to be promising techniques for evaluation, possibly evaluating disease activity as well as the size of the lesions. Because only a few studies have been published, a well-designed prospective trial is needed to assess the role of these techniques in terms of clinical relevant endpoints.
**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 (“Lymphocytopenie avec normogamma-globuline”). In the pediatric literature this condition became known as Nezelof’s syndrome.

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

Histiocytic disorders continue to be one of his major fields of interest. In 1982 Dr. Nezelof described the successful growth in nude mice of a tumor after injection of cells from the pleural effusion of a child with malignant histiocytosis. After this manuscript entitled: “Tumor cell line characterization of a malignant histiocytosis transplanted into nude mice” his team has described successful establishment in vitro of the Malignant Histiocytosis DEL cell line. The Society thought it entirely consistent with Dr. Nezelof’s great interest in new developments of basic pathophysiology, bridged with his key-role in supporting others that this prize be given in his honor. The awardee need not be a physician, but the focus of the work should be on some aspect of the pathophysiology of the histiocytic disorders.

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

**NESBIT PRIZE IN CLINICAL SCIENCE**

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

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

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

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

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

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

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

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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 Histioocyte 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 Histioocyte 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 Histioocyte 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 Histioocyte 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.
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.
ARTICLE VII: 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.

HISTIOCYTE SOCIETY CONSTITUTION

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

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

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

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