31st ANNUAL MEETING
OF THE HISTIOCYTE SOCIETY
ELECTRA PALACE HOTEL - ATHENS, GREECE
SEPTEMBER 28 - 30, 2015

MEETING PROGRAM AND ABSTRACTS
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## MEETING SPONSORS

- **Histioctytosis Association**: A Rare Community
- **CytoSorbents**:
- **Artemis Association**: On Histioctyoses
Dear Colleagues,

I am extremely pleased to welcome you to Athens, Greece for the 31st Annual Meeting of the Histiocyte Society.

Our main meeting venue, the Electra Palace Hotel, is located in the heart of Athens, only a few minutes away from the Acropolis, the home of the Parthenon, and many other beautiful historical sites. I hope you take some time to enjoy this wonderful city, its culture, its art, its history and its people.

The Board and the Program Committee have prepared a very exciting program that we hope will continue to represent the scientific advances made during the last year while facilitating interactions and development of new collaborations. In addition to our scientific sessions, we have prepared two symposia: one to discuss advances in our understanding of the neurodegenerative changes that occur in LCH and another to continue to define the spectrum of diseases that conform HLH. These two topics will also be highlighted in the plenary lectures; we have assembled a great group of speakers that I am sure will make the meeting memorable.

I am also thrilled to announce the launch of the first ever Annual Meeting mobile app, available on Android and Apple devices through your app store. Search “Histiocyte Society” to find and download the app or visit www.histiocytesociety.org/app. The full meeting program, special events, maps, and community engagement opportunities are included. You will also be able to get announcements and reminders about important happenings throughout the meeting.

As you know, a great deal of time, energy and resources go into planning the meeting each year. We are grateful to our annual key sponsor, the Histiocytosis Association, without whose generous support this meeting would not be possible. And special thanks to the Artemis Foundation and the Kontoyannis family for their support and inspiration.

As the President of the Histiocyte Society, I look forward to an incredible meeting in Athens.

Carlos Rodriguez-Galindo
President
Histiocyte Society
ABOUT THE HISTIOCYTE SOCIETY

The Histiocyte Society is a professional medical association comprised of more than 200 physicians and scientists from around the world. Members of the organization are considered to be the leaders in understanding and treating histiocytic disorders. The Society is committed to advancing knowledge about histiocytic disorders and improving outcomes for patients through the planning, development, sponsorship and oversight of clinical research.

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

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

NEW IN 2015 - ANNUAL MEETING MOBILE APP

The 2015 Histiocyte Society Annual Meeting has a FREE custom mobile app ready for downloading! The app is available on the App Store, Google Play and in HTML5 for Blackberries, Windows phones or older devices.

All of the information in the program book is also in the app, plus much more! Create your own custom agenda, provide feedback about sessions, see what your colleagues are saying, access maps of Athens, post pictures, and get the latest news and information right at your fingertips!

Find it in your app store or go to www.histiocytesociety.org/app on your mobile device.

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

ANNUAL MEETING PROGRAM

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The Road to Partnership

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

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

A True Partnership

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

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

The Histiocytosis Association Mission

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

The Histiocytosis Association Research Program

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

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

Since 1992, 166 individual awards have been made to date, representing more than $5.6 million to support critical research around the world. Grant amounts now average $50,000 per project but have been awarded in amounts up to $100,000 in the past. The Histiocytosis Association of Canada (HAC) has provided $265,000 of that funding.

Two Organizations, One Goal

The Histiocytosis Association and the Histiocyte Society have been committed partners for over 25 years. Though separate organizations, they share a common goal that binds their continued partnership - to find better treatments and, ultimately, a cure leading to a world free of histiocytic disorders.

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

HISTIOCYTE SOCIETY EXECUTIVE BOARD
President .................................................. Carlos Rodriguez-Galindo
2013-2016
President Elect ........................................... Milen Minkov
2014-2016
Treasurer .................................................. Itziar Astigarraga
2014-2016
Secretary ................................................... Michael Jordan
2014-2016
Member-at-Large ...................................... Anna Carin Horne
2014-2017
Member-at-Large ....................................... Kim Nichols
2014-2017

HISTIOCYTE SOCIETY EDUCATION COMMITTEE
Kimo Stine, Chairperson ..................................... 2014-2016
Oussama Abla ............................................ 2014-2016
David Dix ................................................. 2013-2015
Anna Carin Home ....................................... 2013-2015
Michael Jeng .............................................. 2013-2015
Kai Lehmberg ............................................ 2013-2015
Rebecca Marsh .......................................... 2013-2015

HISTIOCYTE SOCIETY SCIENTIFIC COMMITTEE
Carl Allen, Chairperson .................................... 2013-2015
Yenan Bryceson .......................................... 2013-2015
Stephan Ehl ............................................... 2014-2016
Caroline Hutter .......................................... 2013-2015
Akira Morimoto .......................................... 2013-2015
Barrett Rollins .......................................... 2014-2016
Kejian Zhang ............................................. 2013-2015

HISTIOCYTE SOCIETY STUDY GROUP CHAIRPERSONS
Adult Histiocytosis ........................................ Michael Girschikofsky
Epidemiology/Late Effects ..................... Riccardo Haupt / Vasanta Nanduri
LCH-IV .................................................... Milen Minkov / Carlos Rodriguez-Galindo

HLH STEERING COMMITTEE
Gritta Janka, Chairperson .............................. 2013-2016
Maurizio Aricò ............................................. 2013-2016
Itziar Astigarraga ......................................... 2013-2016
Yenan Bryceson .......................................... 2013-2015
Stephan Ehl ............................................... 2014-2018
Lisa Filipovich ........................................... 2014-2018
Jan-Inge Henter .......................................... 2014-2018
Anna Carin Home ....................................... 2013-2015
Eiichi Ishii ............................................... 2014-2017
Michael Jordan ......................................... 2013-2017
Kim Nichols .............................................. 2013-2015

RARE HISTIOCYTIC DISORDERS STEERING COMMITTEE
Oussama Abla, Chairperson .......................... 2013-2016
Jorge Braier .............................................. 2013-2016
Ron Jaffe ................................................... 2013-2015
Marian Malone .......................................... 2014-2018
Jim Whitlock ............................................. 2013-2015

LCH STEERING COMMITTEE
Cor van den Bos, Chairperson ......................... 2013-2015
Carl Allen .................................................. 2013-2016
Karim Beutel ............................................. 2013-2017
Jean Donadieu ......................................... 2013-2017
Michael Girschikofsky .................................. 2013-2015
Rima Jubran ............................................. 2013-2017
Milen Minkov ............................................ 2014-2018
Vasanta Nanduri ......................................... 2013-2016
Carlos Rodriguez-Galindo ............................. 2014-2018
Kimo Stine .............................................. 2014-2018
Johannes Visser ......................................... 2013-2015
Sheila Weitzman ....................................... 2013-2016

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

ATHENS 2015
ACKNOWLEDGEMENTS AND RECOGNITIONS

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

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

HISTIOCYTE SOCIETY GOLDEN PIN Recipients
Sheila Weitzman.............................................................2014
Shinsaku Imashuku ........................................................2010
Helmut Gadem .......n .....................................................2008
Jon Pritchard ...............................................................2006
Giulio D’Angio ...............................................................2002
Sally Kivilis .................................................................2001
Elizabeth Kontoyannis ..................................................2000
Paul Kontoyannis ..........................................................2000
Jeffrey M. Toughill ........................................................1998

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

TRAVEL SCHOLARSHIP Recipients
Congratulations to the Histiocyte Society’s 2015 Travel Scholarship recipients:

Alia Ahmad
for the abstract titled,
“OUTCOME OF LANGERHANS CELL HISTIOCYTOSIS AMONG CHILDREN IN DEVELOPING COUNTRIES: CHILDREN’S HOSPITAL LAHORE PAKISTAN EXPERIENCE”
This abstract will be presented during the Poster Presentation Session on Tuesday, September 29, 2015.

Prabhas Prasun Giri
for the abstract titled,
“INFECTION-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: RISK STRATIFICATION CRITERIA & RISK-GUIDED LOW INTENSIVE THERAPY: AN EXPERIENCE FROM INDIA”
This abstract will be presented during Scientific Session III on Tuesday, September 29, 2015.

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

SATURDAY • SEPTEMBER 26, 2015
0800 – 1330 Executive Board Meeting* ................................................................. Lefkothea – Mezzanine
1400 – 1600 HLH Steering Committee Meeting* .................................................. Lefkothea – Mezzanine
1600 – 1700 Rare Histiocytic Disorders Steering Committee Meeting* .............. Lefkothea – Mezzanine
1800 – 1900 LCH Steering Committee Meeting* ..................................................... Lefkothea – Mezzanine

SUNDAY • SEPTEMBER 27, 2015
0800 – 0900 LCH-IV Discussion Session* ............................................................. Ballroom - Basement
0900 – 1030 LCH Disease Discussion Session* ...................................................... Ballroom - Basement
1030 – 1100 Coffee Break ...................................................................................... Ballroom Foyer
1030 – 1130 LCH Adult Disease Discussion Session* .......................................... Ballroom - Basement
1130 – 1230 Rare Histiocytic Disorders Discussion Session* ............................. Ballroom - Basement
1230 – 1330 Lunch ................................................................................................. Motivo Restaurant - Lobby at Electra Palace Garden
1330 – 1800 HLH Disease and MAS Discussion Session* .................................... Ballroom - Basement
1600 – 1630 Coffee Break ...................................................................................... Ballroom Foyer
1900 – 2100 Artemis Association Concert with the Van Gool Family* .................... Theocharakis Foundation for the Fine Arts and Music

MONDAY • SEPTEMBER 28, 2015
0800 – 1700 Meeting Registration and Check-In ................................................. Ballroom Foyer
0800 – 0930 Education Committee Meeting* ...................................................... Lefkothea - Mezzanine
0930 – 1045 Opening Ceremonies ...................................................................... Ballroom - Basement
0945 – 1030 Guest Speaker Presentation: Sergio Lira ........................................ Ballroom - Basement
1030 – 1100 Coffee Break ...................................................................................... Mezzanine
1100 – 1230 LCH Symposium ............................................................................... Ballroom - Basement
1230 – 1330 Lunch ................................................................................................. Mezzanine
1330 – 1500 LCH Meet the Expert Lunch Session* .............................................. Lefkothea - Mezzanine
1330 – 1515 HLH Meet the Expert Lunch Session* ............................................ Alikioni - Mezzanine
1500 – 1530 Coffee Break ...................................................................................... Mezzanine
1530 – 1700 Scientific Session II: Presidential Symposium ................................. Ballroom - Basement
1700 – 1800 General Assembly Business Meeting* ............................................. Ballroom - Basement
1845 – 2000 Welcome Reception* ....................................................................... The Acropolis Museum

TUESDAY • SEPTEMBER 29, 2015
0800 – 1300 Meeting Registration and Check-In ................................................. Ballroom Foyer
0800 – 0930 Poster Presentation Setup ............................................................... Electra/Alikioni - Mezzanine
0800 – 0900 Clinical Studies and Registries Update ............................................ Ballroom - Basement
0900 – 0930 Coffee Break ...................................................................................... Mezzanine
0930 – 1015 Guest Speaker Presentation: Alain Fischer ..................................... Ballroom - Basement
1015 – 1230 HLH Symposium ............................................................................. Ballroom - Basement
1230 – 1330 Lunch ................................................................................................. Mezzanine
1330 – 1500 Rare Meet the Expert Lunch Session* ............................................ Lefkothea - Mezzanine
1500 – 1700 Poster Presentation Session ........................................................... Electra/Alikioni - Mezzanine
1900 – 2400 Histiocyte Society Annual Banquet ............................................. The Ble Pavilion

WEDNESDAY • SEPTEMBER 30, 2015
0800 – 1200 Meeting Registration and Check-In ................................................. Ballroom Foyer
0800 – 0845 Executive Board Meeting* ............................................................... Lefkothea - Mezzanine
0800 – 0845 Education Committee Meeting* ..................................................... Lefkothea - Mezzanine
0900 – 1000 Jon Pritchard Lecture on the Nicolas Symposium ........................ Ballroom - Basement
1000 – 1030 Coffee Break ...................................................................................... Mezzanine
1030 – 1200 Scientific Session IV: Oral Presentations ........................................ Ballroom - Basement
1200 – 1215 Closing Ceremonies: Awarding of Scientific Prizes ...................... Ballroom - Basement

* Indicates closed session
* Indicates that advance registration was required

WWW.HISTIOCYTESOCIETY.ORG
R. Maarten Egeler is an internationally recognized expert in the treatment and research of stem cell transplantation and histiocytoses. After graduation in 1985 at the University of Leiden Medical School, the Netherlands, he was awarded a research fellowship at the University of Minnesota. Subsequently he was a staff-member of the Division of Pediatric Hematology and Oncology at the Erasmus University of Rotterdam (5 years), at the Southern Alberta Children's Cancer Program of the University of Calgary, Canada (3 years), before he was appointed Director of the Division of Pediatric Immunology, Hematology, Oncology, Bone Marrow Transplantation and Auto-immune disease at the Leiden University Medical Center. After 11 years, Dr. Egeler moved back to Canada, to accept the position of Medical Director of Stem Cell Transplantation in the Division of Hematology/Oncology at The Hospital for Sick Children in Toronto. Dr. Egeler was a Board-member of the international Histiocyte Society for 12 years including being the President. For over 10 years he was a Trustee of the Histiocytosis Association and he has served for over 2 decades as co-organizer in the Nikolas Symposium Steering Committee. For 6 years Dr. Egeler served as the President of the Dutch Childhood Oncology Group (DCOG) and the President of the International Society of Pediatric Oncology (SIOP) for 3 years. Dr. Egeler has authored more than 250 manuscripts and chapters in national and international text-books and journals.

Alain Fischer studied medicine with a specialization in pediatrics and pediatric immunology at the Université de Paris, where he received his medical and doctoral degrees. After completing a postdoctoral fellowship at the University College London, he started independent research in a unit of the National Health Institute of Medical Research (INSERM) at the Necker Hospital in Paris. Since 1991, he has been the director of an INSERM unit for “normal and pathological development of the immune system.” Since 2009, he is the director of the Institute for Genetic Diseases (Imagine) at Necker University Hospital. Dr. Fischer also served as a professor of pediatric immunology at the Université Paris Descartes. From 1996 to 2012, he has served as the director of the pediatric immunology department at the Necker Hospital. Dr. Fischer is presently Professor at College de France (Chaire de Médecine Expérimentale). Dr. Fischer’s main research interests are in gene therapy, genetics of immunological disorders, primary immunodeficiency diseases, and the development of the lymphoid system. He has been the author or co-author of over 600 publications on these topics. Dr. Fischer received the Louis Jeantet Prize for Medicine in 2001 and the Grand Prix Inserm in 2008. Since 2002, Dr. Fischer has been a member of the French Academy of Science and the European Molecular Biology Organization.

Anna Carin Horne is a Swedish paediatrician working at the Karolinska Hospital, Stockholm. She has previously worked as a clinical associate at the paediatric oncology/coagulation unit. In 2011 she transferred to paediatric rheumatology where she holds a staff position. Dr. Horne’s research focus lies in clinical studies and she currently holds a Post Doc position at the Karolinska Institute working on CNS involvement in HLH. Over the last few years Dr. Horne has conducted research on macrophage activation syndrome (MAS) on behalf of the Histiocyte Society. The aim of this work is to define the clinical criteria for diagnosis of this rare entity and to develop international guidelines for treatment. These efforts have resulted in a major contribution to ongoing research within the rheumatology field. Dr. Horne’s leadership in the MAS working group has been key in establishing a solid bridge of communication and collaborative research between the Histiocyte Society and the pediatric oncology and rheumatology fields.

Michael Jordan’s interest in histiocytic disorders started during his training in Pediatric Hematology/ Oncology in the mid-90’s when he was amazed by the varied and mysterious nature of both LCH and HLH. When the first gene underlying familial HLH was discovered in 1999, he began to study the development of HLH. These studies led to the groundbreaking publication in 2004 first demonstrating that perforin-deficient mice develop HLH after viral challenge. They defined the critical role of T cells and interferon gamma in this disease process, shaping subsequent scientific and clinical thinking. He have continued to focus on understanding and treating HLH, publishing a series of papers better defining its development and treatment in our experimental model. These studies have served, in part, as the basis for ongoing clinical trials (HIT-HLH) and new drug development for patients with HLH (Novimmune, NI-0501). His clinical focus has remained on patients with histiocytic disorders and his efforts have contributed to improvements in salvage therapy for HLH (alemtuzumab) and marrow transplantation for these patients. He has been active within the Histiocyte society for over a decade, serving in several capacities.

Kai Lehmberg did his undergraduate medical training in Kiel, Essen, and London. He is a physician at the Department of Paediatric Haematology and Oncology at University Medical Centre Hamburg Eppendorf, where he has been introduced into the field of histiocytoses by Prof. Gritta Janka. He has since dedicated his scientific interest to clinical research with a focus on HLH. Dr. Lehmberg managed the European CureHLH project in 2010 and 2011. He is the contact person for clinical matters of HLH in the German Society of Paediatric Oncology and Haematology and coordinates the HLH-2004 and EURO-HIT-HLH studies in Germany, in close co-operation with Prof. Stephan Ehl, Freiburg. His particular interests are acquired forms with infectious, rheumatological, and malignant triggers. He chairs the HS study group on HLH subtypes and leads the development of guidelines on Malignancy-associated HLH.

Biographical information provided by guest speakers.
**GUEST SPEAKER HIGHLIGHTS**

**Sergio Lira** received his M.D. from the Universidade Federal de Pernambuco in Brazil and his Ph.D. in Physiology and Pharmacology from the University of California at San Diego. He did his postdoctoral training at the Roche Institute for Molecular Biology in Nutley, NJ. After his postdoctoral training he worked for 11 years in the pharma sector, first at Bristol-Myers Squibb and then at Schering-Plough. He is currently the Leona M. and Harry B. Hemsley Charitable Trust Professor of Immunology at the Icahn School of Medicine at Mount Sinai in New York, where he is the Director of the Immunology Institute. His research focuses on the role of immune cells and the microbiome in mucosal inflammation and cancer. He has organized international meetings in this field, including the 2003 Keystone Symposium on Chemokines and the 2006 Gordon Research Conference on Chemotactic Cytokines. He was elected to the Henry Kunkel Society in 2006 and to the Association of American Physicians in 2008. He is a member of the Board of Scientific Advisors of the National Cancer Institute and Visiting Professor at the Southern Medical School in Guangzhou, China.

**Kenneth McClain** 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 150 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 and clinical prognostic factors in Hemophagocytic Lymphohistiocytosis.

**Milen Minkov** is currently a Professor of Pediatrics and Head of the Clinic of Neonatology, Pediatrics and Adolescent Medicine at the Rudolfstiftung Hospital, Vienna, Austria. He is a Consultant for Pediatric Hematology and Chair of the International LCH Study Reference Center at St. Anna Children’s Hospital, Medical University of Vienna. Dr. Minkov graduated from the Russian State Medical University, Moscow in 1991 and had his residency and fellowship in pediatrics and pediatric hematology/oncology at the Russian Federal Institute for Pediatric Hematology in Moscow and later in St. Anna Children’s Hospital in Vienna. Between 1996 and 2012, he worked in St. Anna Children’s Hospital, where he provided clinical care, supervised trainees, administered the Department of Outpatient Hematology/Oncology, and conducted clinical research at the Children’s Cancer Research Institute. He has been actively involved in teaching and supervision of medical students at the Medical University of Vienna since 1997 (Assistant Professor 1997-2007; Assoc. Professor 2007-2012; Professor of Pediatrics since 2012). Since 2012, he has been a mentor at the Open Medical Institute of the American-Austrian Association and a member of the Honorary Board of the Armenian Association of Hematology and Oncology. Dr. Minkov’s clinical experience covers the full spectrum of pediatrics and pediatric hematology/oncology, with a particular expertise in non-malignant hematology. His research has mainly been focused on LCH. He has more than 80 published papers in peer-reviewed medical journals and contributed to a number of book chapters, guidelines and consensus papers. Dr. Minkov was the first awardee of the Mark Nesbit Award for Clinical Science (1997). He is a member of several professional societies and networks and a medical advisor of patients and parent organizations.

**Kim Nichols** is a pediatric oncologist whose research focuses on understanding the molecular and cellular mechanisms that predispose to Epstein Barr Virus (EBV)-induced hemophagocytic lymphohistiocytosis (HLH). Dr. Nichols was among the first to identify the gene defective in X-linked lymphoproliferative disease (XLP), a rare primary immunodeficiency associated with increased risk for EBV-induced HLH, B cell lymphomas and progressive hyogammaglobulinemia. For the last 15 years, Dr. Nichols and her research group have worked to dissect how the XLP gene product SAP regulates immune cell development and function and coordinates host immunity to EBV. Through these efforts, she and her collaborators have identified key roles for SAP during regulation of T cell cytokine production, natural killer (NK) and invariant NKT (iNKT) cell cytotoxicity, and iNKT cell development. Dr. Nichols has also explored the use of B-cell directed therapies such as rituximab, as well as other targeted approaches in the treatment of children and adults with EBV-HLH. Dr. Nichols is a past member of the Scientific Committee and a current member of the HLH Steering Committee of the Histiocyte Society, where she also participates in several of the HLH working groups and serves as a Member-at-Large on the Histiocyte Society Executive Board.

**Jennifer Picarsic** is an Assistant Professor at the University of Pittsburgh School of Medicine and a Pediatric Pathologist at the Children’s Hospital of Pittsburgh of UPMC in the USA. She graduated from the University of Pittsburgh School of Medicine in 2007 and entered residency in Anatomic and Clinical Pathology at UPMC where she served as Chief Resident from 2009-2011. She completed a fellowship in Pediatric Pathology at Children’s Hospital of Pittsburgh in 2012 and has since continued on as a faculty member. As a clinically oriented pediatric pathologist, she has defined a focus in the study of Langerhans cell histiocytosis (LCH) and other rare histiocytic disorders. She and Dr. Ron Jaffe have recently written an updated review on the pathology of LCH for the Hematology/Oncology Clinics of North America: Congenital and Acquired Disorders of Macrophages and Histiocytes, which is currently in press. Other recent peer-reviewed publications include the Histologic patterns of thymic involvement in Langerhans cell proliferations, published in Pediatric and Developmental Pathology. She has also given a workshop on the pathology of histiocytic disorders at the annual meeting of the Society for Pediatric Pathology (SPP) in Boston and is an invited member to the Nikolas Symposium on the Histiocytosis in Greece.
MEETING AGENDA: SATURDAY, SEPTEMBER 26, 2015

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

0800 – 1330  Executive Board Meeting* ................................................................. Lefkothea – Mezzanine
1400 – 1600  HLH Steering Committee Meeting* ......................................................... Lefkothea – Mezzanine
1600 – 1700  Rare Histiocytic Disorders Steering Committee Meeting* ...................... Lefkothea – Mezzanine
1800 – 1900  LCH Steering Committee Meeting* .......................................................... Lefkothea – Mezzanine

MEETING AGENDA: SUNDAY, SEPTEMBER 27, 2015

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 – 0900  LCH-IV Discussion Session* ........................................................................ Ballroom - Basement
             Session Moderator: Milen Minkov, Carlos Rodriguez-Galindo
0900 – 1030  LCH Disease Discussion Session* ............................................................... Ballroom - Basement
             Session Moderator: Cor van den Bos
1030 – 1100  Coffee Break ............................................................................................... Ballroom Foyer
1030 – 1130  LCH Adult Disease Discussion Session* ...................................................... Ballroom - Basement
             Session Moderator: Michael Girschikofsy
1130 – 1230  Rare Histiocytic Disorders Discussion Session* ......................................... Ballroom - Basement
             Session Moderator: Oussama Abla
1230 – 1330  Lunch ........................................................................................................ Motivo Restaurant - Lobby at Electra Palace Garden
1330 – 1800  HLH Disease and MAS Discussion Session* .............................................. Ballroom - Basement
             Session Moderator: AnnaCarin Horne, Gritta Janka
1600 – 1630  Coffee Break ............................................................................................... Ballroom Foyer
1900 – 2100  Artemis Association Concert featuring the Van Gool Family* .................... Theocharakis Foundation for the Fine Arts and Music

* Indicates Closed Session
+ Indicates that advance registration was required

Group will depart, on foot, promptly at 1845 from the Electra Palace Hotel Lobby

9, Vassilissis Sofias Avenue & 1, Merlin St,
Athens 106 71 Greece
Tel: +30 210 3611206 • Website: www.thf.gr
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<tr>
<th>Time</th>
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<tr>
<td>0800 – 1700</td>
<td>Meeting Registration and Check-In</td>
<td>Ballroom Foyer</td>
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<td>0800 – 0930</td>
<td>Education Committee Meeting*</td>
<td>Lefkothea - Mezzanine</td>
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<td>0800 – 0930</td>
<td>Scientific Committee Meeting*</td>
<td>Alkioni - Mezzanine</td>
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<td>0930 – 0945</td>
<td>Opening Ceremonies</td>
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<td>0945 – 1030</td>
<td>Guest Speaker Presentation</td>
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<td>DEFINING A CELL-OF-ORIGIN FOR LCH IN MICE</td>
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<td>Sergio Lira</td>
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<td>Icahn School of Medicine at Mount Sinai, New York, NY USA</td>
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<td>1030 – 1100</td>
<td>Coffee Break</td>
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<td>1100 – 1230</td>
<td>LCH Symposium</td>
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<td>Session Moderator: Vasilios Papadakis</td>
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<td>LANGERHANS CELL HISTIOCYTOSIS OF THE CENTRAL NERVOUS SYSTEM: CLINICAL PRESENTATION, IMAGING FINDINGS AND DISEASE COURSE</td>
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<td>Milen Minkov</td>
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<td>1230 – 1330</td>
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<td>LCH Meet the Expert Lunch Session*</td>
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<td>Hemophagocytic Syndromes</td>
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<td>Karolinska Institutet, Stockholm, Sweden</td>
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<td>1330 – 1500</td>
<td>Scientific Session I: Oral Presentations</td>
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<td>Session Moderators: Patrick Campbell, Michael Jeng</td>
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<td>STUDIES ON THE PATHWAY OF DIFFERENTIATION OF LCH CELLS</td>
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<td>Matthew Collin, Paul Milne, Naomi McGovern, Marie-Luise Beres, Duan Kaibo, Venetia Bigley, Muzlifah Haniffa, John M Hicks, Amanda Shin, Michael Poidinger, Kenneth McClain, Miriam Merad, Carl E. Allen, Florent Ginhoux</td>
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<td>1330 – 1500</td>
<td>LANGERHANS CELL HISTIOCYTOSIS: INTRINSIC IMMUNOEEDITING PROPERTIES</td>
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<td>Zdenka Krenova, Eliska Tvrlikova, Jaroslav Sterba, Leos Kren</td>
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<td>MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS (MS-LCH): PREDICTIVE VALUE OF SCORING SYSTEM BASED ON RISK-ORGAN INVOLVEMENT (RO) AT DIAGNOSIS</td>
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<td>Ulirike Pötschger, Maurizio Arico, Itziar Astigarraga, Jorge Braier, Jean Donadieu, Helmut Gadner, Nicole Grois, Jan-Inge Henter, Gritta Janika-Schaub, Kenneth McClain, Elfriede Thiem, Sheila Weitzman, Kevin Windebank, Stephan Ladisch, Milen Minkov</td>
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* Indicates closed session

* Indicates that advance registration was required
LONG-TERM (>3 YEARS) IVIG TREATMENT IN AN ATTEMPT TO PREVENT THE PROGRESSION OF CNS NEURODEGENERATIVE DISEASE IN PATIENTS WITH LCH
Yoko Shioda, Ryuta Tanaka, Naoto Fujita, Haruyoshi Noma, Shiro Seto, Toshinori Minato, Kazuo Sakashita, Nobuhiro Ito, Ryoji Kobayashi, Toshihiko Imamura, Akira Morimoto, Shinsaku Imashuku, and Japan LCH Study Group (JLSG)

CLINICAL RESEARCH OF PULMONARY LANGERHANS CELL HISTIOCYTOSIS IN CHILDREN: ANALYSIS OF 117 CASES
Rui Zhang (Corresponding Author), Dong Wang, Li Zhang, Hong-yun Lian, Hong-hao Ma, Tian-you Wang

INFLAMMATORY PLASMA PROTEINS PREDICT DISEASE SEVERITY AND RESPONSE TO THERAPY IN PATIENTS WITH LCH
Daniel Zinn, Howard Lin, Albert Shih, Brooks Skull, Miguel Cantu, Harshal Abhyankar, Rikhia Chakraborty, Karen Lim, Stephen Simko, Tricia Peters, Sergio Lira, Kenneth McClain, Miriam Merad, Tsz-Man, Carl Allen

1500 – 1530 Coffee Break

1530 – 1700 Scientific Session II: Presidential Symposium
Session Moderator: Carlos Rodriguez-Galindo

PRESENTATIONS NOMINATED FOR THE NESBIT PRIZE IN CLINICAL SCIENCE (see page 58 for more information)

CLINICAL AND BIOLOGICAL RESISTANCE ASSOCIATED WITH A NOVEL, ACTIVATING MUTATION OF MEK1
David Azorsa, Robert Arceci, David Lee

INCREASED RISK OF CANCER IN FEMALE RELATIVES OF PATIENTS WITH PRIMARY DEFECTS IN LYMPHOCYTE CYTOTOXICITY
Alexandra Löfstedt, Samuel C.C. Chiang, Erik Onelöv, Yenan T. Bryceson, Marie Meeths, Jan-Inge Henter

HYDROXYUREA HAS ACTIVITY IN RELAPSED/REFRACTORY LANGERHANS CELL HISTIOCYTOSIS
Daniel Zinn, Amanda Grimes, Carl Allen, Kenneth McClain

PRESENTATIONS NOMINATED FOR THE NEZELOF PRIZE IN BASIC SCIENCE (see page 58 for more information)

DIVERSE KINASE MUTATIONS AND FUSIONS DRIVE NON-LANGERHANS CELL HISTIOCYTOSES
Benjamin Durham, Eli Diamond, Zhan Yao, Jing Ma, John Choi, Eunhee Kim, Stanley Lee, Yijun Gac, Jean-Baptiste Micol, Patrick Campbell, Michael Walsh, Joy Nakitandwe, Juvallee Estrada-Veras, Mario Lacouture, Young Rock Chung, Rajit Rampal, Janine Pichardo, Samuel Briggs, David Hyman, Baselga, Filip Janku, Barry Taylor, Christopher Park, Jean-Francois Emile, Julien Haroche, Neal Rosen, Tanja Gruber, Omar Abdel-Wahab

INHIBITION OF DIACYLGLYCEROL KINASE ALPHA RESTORES SENSITIVITY TO TCR-INDUCED CELL DEATH AND LESSENS IMMUNOPATHOLOGY IN A MURINE MODEL OF XLP-ASSOCIATED HEMOPHAGOCYTIC LYMPHOPHISTIOCYTOSIS
Kim E. Nichols, Elvis Ruffo, Valeria Malacarne, Sasha Larsen, Rupali Das, Laura Patrussi, Christoph Wülfing, Christoph Biskup, Pamela Schwartzberg, Cosima Baldari, Ignacio Rubio, Andrew Snow, Gianluca Balduini, Andrea Graziani

LCH REACTIVATION RISK IS AFFECTED BY LESIONAL CD8+ T CELL PERCENTAGE BUT NOT BY BRAF MUTATIONAL STATUS
Astrid van Halteren, L. Blijleven, E. Steenwijk, Vincent van Unen, Willemin Quispel, Ronald van Eijk, Judith Bovee, Maarten Egeler, Oussama Abla, Cor van den Bos

1700 – 1800 General Assembly Business Meeting*

1845 – 2000 Welcome Reception* The Acropolis Museum
Group will depart, on foot, promptly at 1815 from the Electra Palace Hotel Lobby
Dionysiou Areopagitou 15, Athens 117 42 Greece
Tel: +30 21 0900 0900
Website: www.theacropolismuseum.gr/en

* Indicates closed session
* Indicates that advance registration was required

MEETING AGENDA: MONDAY, SEPTEMBER 28, 2015
MEETING AGENDA: TUESDAY, SEPTEMBER 29, 2015

0800 – 1300  Meeting Registration and Check-In ................................................................. Ballroom Foyer
0800 – 0930  Poster Presentation Setup ................................................................................ Electra/Alkioni - Mezzanine
0800 – 0900  Clinical Studies and Registries Update ............................................................... Ballroom - Basement
             Session Moderator: Jim Whitlock
0800 – 0815  Clinical Studies Update
0815 – 0900  Proposal for New Classification of Histiocytic Disorders

0900 – 0930  Coffee Break ......................................................................................................... Mezzanine
0930 – 1015  Guest Speaker Presentation ............................................................................... Ballroom - Basement
             Session Moderator: Michael Jordan

GENE THERAPY OF T CELL IMMUNODEFICIENCIES
Alain Fischer
Institute for Genetic Diseases (Imagine), Necker University Hospital, Paris, France

1015 – 1230  HLH Symposium ................................................................................................. Ballroom - Basement
             Session Moderator: Jan-Inge Henter

HLH: WHAT ARE WE REALLY TALKING ABOUT?
Michael Jordan
Cincinnati Children's Hospital, Cincinnati, OH USA

MACROPHAGE ACTIVATION SYNDROME IN THE ERA OF BIOLOGIC THERAPY
AnnaCarin Horne
Karolinska Institutet, Stockholm, Sweden

EPSTEIN-BARR VIRUS INDUCED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: CURRENT INSIGHTS INTO CLINICAL PRESENTATION, MECHANISMS OF DISEASE AND TREATMENT
Kim Nichols
St. Jude Children's Research Hospital, Memphis, TN USA

HLH IN MALIGNANT CONDITIONS INCLUDING IATROGENIC HLH
Kai Lehmb erg
University Medical Centre Hamburg Eppendorf, Hamburg, Germany

1230 – 1330  Lunch ....................................................................................................................... Mezzanine
1230 – 1330  Rare Meet the Expert Lunch Session* ................................................................. Lefkothea - Mezzanine
             Attendees should bring lunch from the Mezzanine into the meeting room.

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

1330 – 1500  Scientific Session III: Oral Presentations ............................................................ Ballroom - Basement
             Session Moderator: Gritta Janka, Rebecca Marsh

WHOLE EXOME SEQUENCING AS A NEW MODULE IN THE DIAGNOSTIC EVALUATION OF PATIENTS WITH HLH: 2010-2014 EXPERIENCE
Sandra Ammann*, Kai Lehmb erg*, Sebastian Bode, Carsten Speckmann, Udo zur Stadt, Gritta Janka, Hans Christian Hennies, Mirzokhid Rakhmanov, Ilka Fuchs, Stephan Ehl
*equal contribution

NEUTRALIZATION OF INTERFERON-Γ IS EFFICACIOUS IN A MOUSE MODEL OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS SECONDARY TO CHRONIC INFLAMMATION
Fabrizio De Benedetti, Principe Giusi , Ivan Caiello, Cristina de Min

IFNγ DRIVES DISEASE IN TLR9-MEDIATED SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (sHLH) IN MICE. RATIONALE FOR A NEW THERAPEUTIC TARGET IN HLH SECONDARY TO INFECTION IN HUMANS
Cristina de Min, Vanessa Buatois, Laurence Chatel, Laura Cons, Sabrina Lory, Françoise Richard, Claudia Bracaglia, Fabrizio De Benedetti, Marie Kosco-Vilbois, Walter Ferlin

* Indicates that advance registration was required
MEETING AGENDA: TUESDAY, SEPTEMBER 29, 2015

INFECTION-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: RISK STRATIFICATION CRITERIA & RISK-GUIDED LOW INTENSIVE THERAPY: AN EXPERIENCE FROM INDIA
Prabhas Prasun Giri, Priyankar Pal

NEW MECHANISMS OF HLH PATHOGENESIS REVEALED FROM A NOVEL MOUSE MODEL
Gang Huang, Yoshihiro Hayashi, Xiaomei Yan, Michael B. Jordan, Alexandra H. Filipovich

HLH DIAGNOSIS IN THE GENOMIC ERA
Kejian Zhang, Rebecca Marsh, Diane Kissell, Christopher Walipe, Xia Li, C. Alexander Valencia, Alexandra Filipovich

1500 – 1700 Poster Presentation Session ............................................................ Electra/Alkioni - Mezzanine

BASIC LCH POSTER PRESENTATIONS

Poster Location #1 OUTCOME OF LANGERHANS CELL HISTIOCYTOSIS AMONG CHILDREN IN DEVELOPING COUNTRIES: CHILDREN’S HOSPITAL LAHORE PAKISTAN EXPERIENCE
Alia Ahmad, Fauzia Shafi Khan, Ahsan Waheed Rathore, Ghazala Hanif, Nayla Asghar

Poster Location #2 CNS INVOLVEMENT IN PULMONARY LANGERHANS CELL HISTIOCYTOSIS - MRI IMAGING
Katarzyna Blasinska-Przerwa, Elzbieta Radzikowska, Malgorzata Sobiecka, Lucyna Opoka, Jakub Ptak, Iwona Bestry, Jan Kuś, Elzbieta Wiatr, Kazimierz Roszkowski-Śliż

Poster Location #3 THE ROLE OF T CELLS IN THE IMMUNE REGULATION OF LANGERHANS CELL HISTIOCYTOSIS (LCH)
Jenée Mitchell, Jennifer West, Sharon Olsen, Ross Priddle, Jennifer Luke, Selma Olsson Akefeldt, Jan-Inge Henter, Christopher Turville, Stuart Berzins, George Kannourakis

Poster Location #4 INCREASED TYRO3 AND PROTEIN S EXPRESSION IN CIRCULATING MONOCYTES AND T CELLS SEEM TO CORRELATE WITH ACTIVITY OF LCH
Diego Rosso, Licina Tessone, Graciela Elena, Antonio Carrera Silva, Andrea Errasti

CLINICAL LCH POSTER PRESENTATIONS

Poster Location #5 CLINICAL IMPROVEMENT OF ADULT ONSET LANGERHANS CELL HISTIOCYTOSIS WITH DIFFUSE SKIN AND LYMPH NODES INVOLVEMENT WITH VINBLASTIN AND PREDNISONE
Rami Ahmad, Thamer Sartawi, Seneviratne Chandula, Gerardo Capo

Poster Location #6 OUTCOME OF LANGERHANS CELL HISTIOCYTOSIS IN CHILDREN RECEIVING TREATMENT ACCORDING TO HISTIOCYTE SOCIETY GUIDELINE-2009
Ferdousi Begum, Chowdhury Yakub Jamal, Md Anwarul Karim, Momena Begum, Lutfur Rahman Molla, Zannat Ara, Md Bani Yeamin

Poster Location #7 OPTIMAL THERAPY FOR ADULTS WITH LANGERHANS CELL HISTIOCYTOSIS
Minakshi Taparia

Poster Location #8 BISPHOSPHONATE THERAPY IN LANGERHANS CELL HISTIOCYTOSIS: AN INTERNATIONAL RETROSPECTIVE DESCRIPTIVE STUDY
Deepak Chellapandian, Polyzois Makras, Gregory Kaltas, Cor van den Bos, Anne-Sophie Carret, Sheila Weitzman, Maarten Egeler, Oussama Abla

Poster Location #9 CHILDREN AND ADOLESCENTS WITH LANGERHANS CELL HISTIOCYTOSIS IN BELARUS
Viktoria Efremova, Olga Aleinikova

Poster Location #10 REFRACTORY LCH PRESENTING WITH FEVER, LEUKOCYTOSIS AND THROMBOCYTOSIS RESPONDING TO DABRAFENIB
Anthony Chuang, Lilibeth Tomo
MEETING AGENDA: TUESDAY, SEPTEMBER 29, 2015

Poster Location #11
THE USE OF PREVENTIVE PLEURODESIS IN A PATIENT WITH LANGERHANS CELL HISTIOCYTOSIS WITH LUNG INVOLVEMENT
Dmitry Evseev, Irina Kalinina, Uskova Natalya, Samarin Alexey, Salimova Tatyana, Baidilidina Dina, Maschan Mikhail, Maschan Alexey

Poster Location #12
CLINICAL STUDY OF HEMAPHAGOCYTIC LYMPHOHISTIOCYTOSIS SECONDARY TO LANGERHANS CELL HISTIOCYTOSIS
Xiaodong Shi, Lei Zhang, Rong Liu, Tao Hu, Juanjuan Li
Presented by: Junhui Li

Poster Location #13
CLINICAL RESEARCH OF 6 CASES OF PEDIATRIC THYROID LANGERHANS CELL HISTIOCYTOSIS
Hong-hao Ma, Li Zhang, Hong-yun Lian, Dong Wang, Tian-you Wang, Rui Zhang

Poster Location #14
TEENAGE AND YOUNG ADULTS WITH LCH MODEL OF CARE
Maria Michelagnoli, Louisa Wright, Johann Visser, Vasanta Nanduri

Poster Location #15
INTENSIFIED AND PROLONGED THERAPY DID NOT IMPROVE THE OUTCOME IN LANGERHANS CELL HISTIOCYTOSIS WITH SINGLE-SYSTEM MULTIFOCAL BONE LESIONS: RESULTS OF JLSG-02 PROTOCOL STUDY
Akira Morimoto, Yoko Shioda, Toshihiko Imamura, Kazuko Kudo, Eichi Ishii, Keizo HORibe, Fumio Bessho, Yukiko Tsunematsu, Shinsaku Imashuku

Poster Location #16
BONE LESIONS IN LANGERHANS CELL HISTIOCYTOSIS: “SPECIAL SITES” AND OUTCOME
Michaela Nikolaou, Kalliopi Stefanaki, Christiana Hadjigeorgi, John Nikas, Neophytos Prodromou, Maria Moschovi

Poster Location #17
CLINICAL PRESENTATION AND OUTCOME IN CHILDREN WITH JUVENILE XANTHOGRANULOMA
Michaela Nikolaou, Kalliopi Stefanaki, Christiana Hadjigeorgi, John Nikas, Maria Moschovi

Poster Location #18
LANGERHANS CELL HISTIOCYTOSIS: ONE CENTER EXPERIENCE
Nihal Ozdemir, Tiraje Celkan, Gulen Tuysuz, Hilmi Apak, Ibrahim Adaletli, Metin Hallac, Murat Hiz, Serap Yildiz, Inci Yildiz

Poster Location #19
SIMULTANEOUS VULVAR AND PARENCHIMAL BRAIN LANGERHANS CELL HISTIOCYTOSIS: ASSOCIATION OR COINCIDENCE?
Giovannella Palmieri, Margaret Ottaviano, Vincenzo Damiano, Irene Tucci, Luigi Insabato, Umberto Malapelle, Caterina De Luca, Roberta Sgargi, Giancarlo Troncone

Poster Location #20
ISOLATED SUPRASELLAR LESIONS WITH PROGRESSIVE PITUITARY DYSFUNCTION AND NEGATIVE TUMOR MARKERS: CLINICAL COURSE AND MANAGEMENT
Vassilios Papadakis, Elpis Vlachopapadopoulou, Panagiotis Nomikos, Spyridon Sgouros, Sophia Polychronopoulou

Poster Location #21
A CASE REPORT OF PULMONARY LANGERHANS CELL HISTIOCYTOSIS DIAGNOSED USING CD1A IMMUNOSTAINING OF BRONCHOALVEOLAR LAVAGE CELLS
Jeong A Park, Mi Jin Kim, Jin Ho Yoo, Young Wook Cho, Seong Soo Jang, Chan Jeong Park, Gwang Nam Kim, Jin Kyung Suh, Seong Wook Lee, Kyung-Nam Koh, Ho Joon Im, Jong Jin Seo

Poster Location #22
ANALYSIS OF DIAGNOSIS DELAY IN PATIENTS WITH PLCH WHO HAD PNEUMOTHORAX AS A FIRST SYMPTOM
Elzbieta Radzkowska, Elzbieta Wiatr, Katarzyna Blasinska-Przerwa, Kazimierz Roszkowski-

Poster Location #23
NORTH AMERICAN CONSORTIUM FOR HISTIOCYTOSIS (NACHO) - PROVIDING A MECHANISM TO ENHANCE CLINICAL AND TRANSLATIONAL RESEARCH IN LANGERHANS CELL HISTIOCYTOSIS (LCH)

* Indicates that advance registration was required
POSTER LOCATION #24
LANGERHANS CELL HISTIOCYTOSIS AND PULMONARY INVOLVEMENT: LONG TERM FOLLOW UP IN 22 PEDIATRIC
PATIENTS HAVING PULMONARY FUNCTION TESTS
Claudia Sampor, Verónica Aguerre, Yasmine Esquivel, Jorge Braier, Claudio Castañes

POSTER LOCATION #25
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Sandra Ammann, Christian Klemann, Sebastian Fuchs, Hans Fuchs, Claudia Roll, Thomas Vraet, Brigitte Strahm, Jan Rohr, Klaus Schwarz, Stephan Ehl

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AND ASSOCIATED IMMUNODEFICIENCIES: CASES REPORTED IN SPAIN
Itziar Astigarraga, Susana Garcia-Obregon, Juana Gil-Herrera, Antonio Pérez-Martínez, Montserrat Melo, Cristina Mata, Elena Mateos, Cristina Díaz-de-Heredia, Ana Sastre, Marta Gonzalez-Vicent, Isabel Bedell on behalf of GETMON (Grupo Español de Trasplante de Médula ósea en Niños) and SEHOP (Grupo histiocitosis, Sociedad Española de Hematología y Oncología Pediatricas)

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ANTI INTERFERON-GAMMA (IFNγ) MONOCLONAL ANTIBODY TREATMENT IN A CHILD WITH NLRC4-RELATED DISEASE
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Francescii De Benedetti, Claudia Bracaglia, Giuse Prencipe, Antonio Gatto, Manuela Pardeo, Geneviève Lapeyre, Luigi Raganelli, Emiliano Marasco, Walter Ferlin, Robert Nelson, Cristina de Min

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Michael Jordan, Lisa Filipovich, Walter Ferlin, Cristina de Min

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Zeynep Karakas, Ismail Yildiz, Serap Karaman, Selime Aydogdu, Demet Demirkol, Kemal Nisli, Ilmay Bilge, Hacer Aktürk, Agop Citak, Sema Anak, Aysegul Unuvur, Gulyuoz Ozdem, Omer Devecioglu

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* equal contribution

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HYPERFERRITINEMIA DOES PLAY A ROLE IN DIAGNOSING WITH HLH FOR ADULT POPULATIONS WITH FEVER, CYTOPENIAS, AND HEPATIC DYSFUNCTION (OR) HEPATOSPLENOMEGALY
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Presented by: Jia Zhang, Fu Li

Poster Location #45
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Jia Zhang, Jianhang Chen, Yini Wang, Jingshi Wang, Lin Wu, Ruijun Pei, Zhao Wang

Poster Location #46
TREATMENT OF ADULT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS PATIENTS WITH ETOPOSIDE, A SYSTEMATIC REVIEW
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RARE HISTIOCYTIC DISORDERS POSTER PRESENTATIONS

Poster Location #47
JUVENILE XANTHOGRANULOMA WITH HEPATOSPLENOMEGALY AND PERI-PORTAL / PERI-CELIAC LYMPHADENOPATHY
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MEETING AGENDA: TUESDAY, SEPTEMBER 29, 2015

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MAPK1 MUTATION IN AN AGGRESSIVE CASE OF DISSEMINATED NON-LANGERHANS CELL HISTIOCYTOSIS
Rikhia Chakraborty, Oliver A. Hampton, Harshal Abhyankar, Daniel J. Zinn, Amanda Grimes, Brooks Skull, Karen Phaik Har Lim, Kenneth L. McClain, David A. Wheeler, D. Williams Parsons, Carl E. Allen

Poster Location #49
CHARACTERISTICS OF MACROPHAGE ACTIVATING SYNDROME (MAS) WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (sJIA) OF A TERTIARY REFERRAL HOSPITAL IN AN-YANG, KOREA
Kwang Nam Kim, Si Nae Eom

Poster Location #50
DENDRITIC CELL NEOPLASM: 2 CASE REPORTS AND REVIEW OF LITERATURE
Minakshi Taparia

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CEREBELLAR SYNDROME AND COGNITIVE DEFICITS IN ERDHEIM CHESTER DISEASE: JUST ACCUMULATION OF HISTIOCYTES OR SECONDARY METABOLIC/ENDOCRINE DEFICIT?
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Poster Location #52
ORAL MANIFESTATIONS OF ERDHEIM CHESTER DISEASE
Juvenile Estrada-Veras, Pamela J. Gardner

Poster Location #53
WHEN TWO CONDITIONS WITH SIMILAR FEATURES MEET: A CASE OF ERDHEIM CHESTER DISEASE IN A PATIENT WITH A COMMON GENETIC DISORDER
Juvenile Estrada-Veras, Kevin O'Brien, William Gahl

Poster Location #54
A CASE OF JUVENILE XANTHOGANULOMA DEVELOPED DURING ACUTE LYMPHOCYTIC LEUKEMIA TREATMENT
Jun Eun Park, Kyu Jung Park, Eun Jae Cheon, Il Soon Park, Eunjoo Lee, Chuhl Joo Lyu

Poster Location #55
ROSAL-DORFMAN DISEASE - A CHALLENGING CONDITION
Santanu Sen, Kashmira Jain, Vasanta Nanduri

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INTERDIGITATING DENDRITIC CELL NEOPLASM PRESENTING IN THE CONJUNCTIVA
Nicholas Whipple, Matthew Wilson, Casey Mickler, Evangeline Brown, John Choi, Patrick Campbell

1815
Group Transportation to Histiocyte Society Annual Banquet .......................................................... Electra Palace Hotel Lobby
Group will depart, on foot, to bus pick up location

1900 – 2400
Histiocyte Society Annual Banquet ......................................................................................................... The Bie Pavilion
Buses will return to the Electra Palace at 2200, 2300 and 2400
174 55, Leof. Posidonos 70
Tel: +30 210 894 6625
Website: www.theble.gr
MEETING AGENDA: WEDNESDAY, SEPTEMBER 30, 2015

0800 – 1200  Meeting Registration and Check-In.............................................................................. Ballroom Foyer

0800 – 0845  Executive Board Meeting* ......................................................................................... Lefkothea - Mezzanine
Executive Committee Meeting* ........................................................................................................ Ballroom - Basement
Scientific Committee Meeting* ........................................................................................................ Ballroom - Basement

0900 – 1000  Jon Pritchard Lecture on the Nikolas Symposium......................................................... Ballroom - Basement
Session Moderator: Kim Nichols

25 YEARS OF THE NIKOLAS SYMPOSIUM – HISTIOCYTE SOCIETY CONNECTION: HOW HAS THIS ADVANCED THE KNOWLEDGE OF LANGERHANS CELL HISTIOCYTOSIS

In memory of Bob Arceci, Ralph Steinman and Jon Pritchard
R. Maarten Egeler
The Hospital for Sick Children, Toronto, ON Canada

1000 – 1030  Coffee Break ................................................................................................................... Mezzanine

1030 – 1200  Scientific Session IV: Oral Presentations........................................................................ Ballroom - Basement
Session Moderators: Itziar Astigarraga, Kimo Stine

INCREMENTAL VALUE OF F18-FDG PET/CT IN THERAPEUTIC DECISION-MAKING IN CHILDREN UNDERGOING CHEMOTHERAPY FOR LANGERHANS CELL HISTIOCYTOSIS
Anne-Sophie Carret, Raymond Lambert, Amélie Damphousse, Natalie Patey, Sophie Turpin

INTERFERON-γ (IFNγ) IN MACROPHAGE ACTIVATION SYNDROME (MAS): CXCL9 LEVELS AS A BIOMARKER FOR IFNγ PRODUCTION IN MAS
Fabrizio De Benedetti, Claudia Bracaglia, Denise Pires Marafon, Ivan Caiello, Kathy De Graaf, Florence Guilhot, Walter Ferlin, Sergio Davi, Grant Schulert, Angelo Ravelli, Alexei Grom, Robert Nelson, Cristina De Min

DIFFUSE LOSS OF CEREBRAL GREY MATTER STRUCTURES IN ERDHEIM-CHESTER DISEASE
Eli L. Diamond, Vaios Hatzoglou, Sneha Pandya, Omar Abdel-Wahab, David M. Hyman, Raajit Rampal, Ashish Raj

ROSAI-DORFMAN-DESTOMBES DISEASE: A BROAD SPECTRUM OF A UNIQUE DISEASE? A NATIONWIDE COLLABORATIVE STUDY OF 47 PATIENTS
Julien Haroche, Fleur Cohen Aubart, Zahir Amoura, Mohamed Barkaoui, Frédéric Charlotte, Jean-François Emile, Abdellatif Tazi, Jean Donadieu

THE MINIMUM REQUIRED LEVEL OF DONOR CHIMERISM IN HEREDITARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS - A RETROSPECTIVE STUDY WITH 103 PATIENTS
Bernd Hartz, Rebecca Marsh, Kanchan Rao, Jan-Inge Henter, Gulsun Karasu, Michael Jordan, Lisa Filipovich, Sandra Ammann, Stephan Ehl, Gritta Janka, Ingo Müller, Kai Lehmberg

INTERLEUKIN-17A AS A BIOMARKER IN NEURODEGENERATIVE LANGERHANS CELL HISTIOCYTOSIS
Magda Lourda, Selma Olsson-Åkefeldt, Desiree Gavhed, Tatiana von Bahr Greenwood, Mattias Svensson, Jan-Inge Henter

1200 – 1215  Closing Ceremonies........................................................................................................ Ballroom - Basement
Carlos Rodriguez-Galindo, Histiocyte Society President
Awarding of Nesbit Prize for Excellence in Clinical Science
Awarding of Nezelof Prize for Excellence in Basic Science

* Indicates Closed Session
DEFINING A CELL-OF-ORIGIN FOR LCH IN MICE

Sergio Lira, M.D., Ph.D.
Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, NY USA

Langerhans cell histiocytosis (LCH) is associated with activating mutations in BRAF, but the cell-of-origin of the disease remains unclear. We tested the hypothesis that CX3CR1-expressing cells are involved in LCH pathogenesis. To generate mice that express BRAFV600E in CX3CR1+ cells, we crossed BRAFCA mice with mice expressing a tamoxifen inducible cre-recombinase (creER) and the reporter gene YFP in the CX3CR1 locus. After tamoxifen treatment, FRBRAF animals developed a syndrome that had neurological and hematological components. The neurological component was first observed at 12 weeks of treatment and consisted initially in mild hind limb weakness. By 20 weeks of treatment over 90% of the animals were affected and presented varying degrees of motor impairment and spasticity, which severely reduced their mobility. At this point, mice were hunched and had enlarged abdomens. Upon necropsy, the mice had marked hepatosplenomegaly, and inflammatory infiltrates were detected in the liver, lung, spleen, spinal cord and the brain. In most instances, granulomatous aggregates, rich in myeloid cells, multinucleated giant cells, and lymphocytes were detected in liver, spleen and the lungs. Remarkably, CD11b+MHCII+ Langerin+ cells, typically found within LCH lesions in humans, were also present in these infiltrates. Brain lesions consisted of inflammatory cells and clusters of activated microglia that were most evident in the white matter of the spinal cord and cerebellum. Transfer of CX3CR1+BRAFV600E cells from the liver into a healthy host induced development of CD207+ histiocytic clusters in the liver, lung and spleen, but not in the brain. Bone marrow transfer experiments confirmed that the disease-inducing cells originated from the bone marrow, rather than from a liver resident cell. Taken together these results suggest that CX3CR1-expressing cells are the cells of origin of systemic LCH in mice.

GUEST SPEAKER PRESENTATIONS

GENE THERAPY OF T CELL IMMUNODEFICIENCIES

Alain Fischer, M.D., Ph.D.
Institute for Genetic Diseases (Imagine), Necker University Hospital, Paris, France

Abstract text not available at time of publication.
LANGERHANS CELL HISTIOCYTOSIS (LCH) SYMPOSIUM

NEURODEGENERATIVE DISEASE IN LCH PATIENTS: NEW BIOLOGY AND NEW THERAPIES

Kenneth McClain, M.D., Ph.D.
Baylor College of Medicine/Texas Children's Cancer and Hematology Center, Houston, TX USA

The neurodegenerative condition associated with LCH was identified in 1993 by Gros et al. Since then there have been incremental advances in our understanding of the risk factors, clinical signs, radiologic findings, and treatment options based upon case series. Given the rarity of this condition it has been difficult to assemble a cohort of patients to compare different treatments. Our center has made the study of new therapeutic initiatives and biologic correlates of the neurodegenerative syndrome a priority. I will present new concepts about the biology of CNS ND LCH and treatment options.

LANGERHANS CELL HISTIOCYTOSIS OF THE CENTRAL NERVOUS SYSTEM: CLINICAL PRESENTATION, IMAGING FINDINGS AND DISEASE COURSE

Milen Minkov, M.D., Ph.D.
Rudolfstiftung Hospital/St. Anna Children's Hospital, Medical University of Vienna, Vienna, Austria

Langerhans cell histiocytosis (LCH) is a clonal disease characterized by proliferation of myeloid precursors resulting in granuloma formation and inflammatory response. It can affect virtually any organ of the human body, particularly, the central nervous system (CNS). Involvement of the hypothalamic-pituitary region (HPR) manifesting with diabetes insipidus (DI) and less frequently with dysfunction of the anterior pituitary, has long been recognized as one of the most common and characteristic presentations of LCH. Involvement of other structures of the CNS (CNS-LCH) attracted attention much later and became the object of systematic research just in the last twenty-five years. The spectrum of clinical manifestations of CNS-LCH is wide and ranges from acute presentation (headaches, seizures, symptoms of increased intracranial pressure) to insidious onset (cerebellar, cranial nerve, pyramidal, cognitive and memory deficits, as well as, emotional and behavioral problems) with variable course. Magnetic resonance imaging (MRI) has considerably improved our understanding of CNS-LCH and consistent imaging findings evolved into comprehensive classification. Based on correlation of clinical manifestations to imaging and pathology findings, two patterns of CNS-LCH have been defined for the reasons of clinical management. One is the so-called granulomatous or “tumorous” CNS-LCH. It usually manifests with seizures, increased intracranial pressure or other signs, depending on location of the lesions, which on biopsy reveal CD1a+ granulomas. The typical location on an MRI is extra-axial (meninges, choroid plexus, and the circumventricular organs, particularly the HPR and the pineal gland). The other pattern is called non-granulomatous or “neurodegenerative” CNS-LCH. It typically has an insidious onset with (ponto) cerebellar and bulbar symptoms. MRI signal alterations are consistent with degeneration (neuronal loss and demyelination) of the affected brain tissue. Biopsies of such lesions are usually non-diagnostic for LCH (lack of CD1a+, CD207+ cells) and reveal inflammatory changes with neuronal loss, demyelination and gliosis. The lesions are localized in the brain parenchyma of the cerebellum, pons, and the basal ganglia. The course can vary from spontaneous stabilization to rapid deterioration with loss of motor function and mental debilitation. Standardized neurological examination (i.e. EDSS, ICARS) and neuropsychological testing at regular intervals are essential for objective longitudinal judgment and clinical decision-making, apart from serial MRIs. Standardized disease assessment and follow-up, as well as, uniform evaluation of treatment response in the setting of large-scale controlled trials (e.g. LCH-IV) are essential for further progress on CNS-LCH.

LANGERHANS CELL HISTIOCYTOSIS OF THE CENTRAL NERVOUS SYSTEM: CHALLENGES IN PATHOLOGIC DIAGNOSIS

Jennifer Picarsic, M.D.
Children’s Hospital of Pittsburgh of UPMC/University of Pittsburgh School of Medicine, Pittsburgh, PA USA

The diagnosis of Langerhans cell histiocytosis (LCH) is relatively straightforward when the clinical, imaging, and pathologic findings are harmonious; however, this is not always the norm, especially in central nervous system (CNS) LCH. The initial diagnosis of LCH requires a tissue biopsy that shows a proliferation of abnormal histiocytic cells characterized by moderately large, (20-25 μm,) round to oval cells with a grooved nucleus. Immunohistochemistry (IHC) confirms the Langerhans cell phenotype with CD1a (membranous/surface), Langerin (cytoplasmic granular), and S100 (nuclear and cytoplasmic staining pattern) positivity. From the pathologist’s standpoint, a diagnosis of LCH is based both on the correct histologic pattern of involvement together with the confirmatory staining pattern, namely CD1a and Langerin positive LCH cells. The “pattern” of CNS-LCH involvement has been based on small case studies showing involvement of the meninges or choroid plexus, partial infiltration into the CNS parenchyma, and neurodegenerative (ND) lesions, which lack infiltration of CD1a+ cells.

The diagnostic challenges of CNS-LCH are multifaceted. Clinical and radiographic imaging may support a diagnosis, but obtaining adequate tissue for initial diagnosis may represent a challenge. This is especially true of hypothalamus-pituitary axis (HPA) lesions, which are a common site of involvement. Another pitfall is that CNS-LCH involvement may be obscured by a rich inflammatory response in which the diagnostic CD1a+Langerin positive LCH cells are not demonstrated in the biopsy material. Still other times, the biopsy may show only a xanthogranulomatous process during its regressive/healing phase, which may be difficult to distinguish from a reactive histiocytic process or even a juvenile xanthogranuloma (JXG) family of lesions, including Erdheim-Chester disease. Late CNS-LCH disease is a separate category and is not thought to be the result of an infiltrative LCH or “burnt-out” LCH, but rather a neurodegenerative, possible autoimmune/paraneoplastic-like process. However, very few ND cases are biopsied, so our understanding into the pathogenesis and pathology is limited. It is the hope that in the future, more predictive/prognostic markers of disease will enable better delineation of true LCH involvement, especially in those cases in which the clinical and radiographic findings are suggestive of active disease, but no CD1a/Langerin positive cells are demonstrated in the tissue biopsy.
HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) SYMPOSIUM

MACROPHAGE ACTIVATION SYNDROME IN THE ERA OF BIOLOGIC THERAPY

AnnaCarin Home, M.D., Ph.D.
Karolinska Institutet, Stockholm, Sweden

Macrophage activation syndrome (MAS) is an acute episode of overwhelming inflammation caused by a cytokine storm. Although increasingly recognized as a life-threatening complication of various rheumatic diseases, clinically MAS is strikingly similar to primary and secondary forms of Hemophagocytic lymphohistiocytosis (HLH). Not surprisingly, many prefer the term secondary HLH rather than MAS to describe these patients, and the effort to perhaps change the nomenclature is in progress. The pathophysiology of MAS remains elusive, but new observations in animal models, as well as new data on the effects of new anti-cytokine therapies on the rates and clinical presentation of MAS in patients with systemic juvenile idiopathic arthritis provide additional clues to understanding of this perplexing clinical phenomenon. Dr. Alexei Grom, Professor Fabrizio De Benedetti and I have recently written an article with the aim to review this new evidence and discuss the potential diagnostic challenges in the era of increasing use of biologics in this patient population. I will give a summary of this article in my talk.

HLH: WHAT ARE WE REALLY TALKING ABOUT?

Michael Jordan, M.D.
Cincinnati Children's Hospital, Cincinnati, OH USA

Hemophagocytic lymphohistiocytosis (HLH) is a well-described syndrome characterized by unusual immune activation and a range of distinctive clinical/pathologic features, thought to be driven by the immune system. Historically, HLH has been viewed as a disorder of macrophages, but in recent years increasing emphasis has been placed on T cells as central players and HLH as a disorder of immune regulation. The precise nature of the ‘HLH process’ remains an active area of research and newer experimental/translational efforts may further refine its definition.

Genetic defects of cytotoxic function underlie most cases of familial and/or recurrent HLH. However, there is a wide range of clinical phenotypes and many patients with HLH do not display a clear genetic (or consistent functional) defect of lymphocyte cytotoxicity. Such variation has led to the dichotomy of ‘primary’ and ‘secondary’ HLH, in which ‘primary HLH’ more clearly implies genetic defects and ‘secondary HLH’ is tied more closely to environmental insults such as malignancy, rheumatologic conditions, and various infections. However, increasing recognition of genetic and clinical complexity is blurring the line between these categories.

HLH is typically an episodic disorder which is often, but not always, associated with infections or malignancies. The syndromic definition of HLH and its association with other specific conditions has led to confusion, or at least imprecision, regarding what acquired conditions should be viewed as ‘triggers’ vs ‘mimics’ of HLH. Furthermore, newly defined genetic disorders and a new appreciation of HLH-like presentations of distinctive diseases have blurred the line between HLH and other conditions. A careful (re)consideration of what we mean when discussing HLH may lead to more precise/prompt diagnosis and more effective treatments for these challenging and diverse patients.

HLH IN MALIGNANT CONDITIONS INCLUDING IATROGENIC HLH

Kai Lehmberg, M.D.
University Medical Centre Hamburg Eppendorf, Hamburg, Germany

HLH can occur in the context of malignancies, with a higher prevalence in adults. Malignancy-triggered HLH should be regarded separately from HLH during chemotherapeutic treatment, which is frequently associated with an infectious trigger. The substantial overlap between the features of HLH and features of neoplasms makes the identification of Malignancy-triggered HLH difficult. In Malignancy-triggered HLH, there are two different diagnostic scenarios: First, in a patient with HLH an underlying malignancy must be excluded. Second, in a patient with a malignant condition and signs of hyperinflammation, the physician must decide whether these features go beyond the expected symptoms of the malignant condition and must thus be categorized as HLH. The optimal treatment of HLH in the context of malignancy remains controversial. A particular case of HLH in the context of malignancy is the iatrogenic cytokine-release syndrome triggered by T-cell engaging treatment of leukemia.

EPSTEIN-BARR VIRUS INDUCED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: CURRENT INSIGHTS INTO CLINICAL PRESENTATION, MECHANISMS OF DISEASE AND TREATMENT

Kim E. Nichols, M.D.
St. Jude Children's Research Hospital, Memphis, TN USA

Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a ubiquitous member of the herpes virus family that infects the majority of the world’s population. Primary infection of most immunocompetent hosts is asymptomatic or associated with a self-limited lymphoproliferative syndrome known as acute infectious mononucleosis (IM). In contrast, EBV infection of a subset of immunologically normal individuals, as well as those with acquired or inherited defects of the immune system, can lead to life threatening EBV-induced lymphoproliferative disorders such as hemophagocytic lymphohistiocytosis. During the last 2 decades, much has been learned about the clinical features and basic biology underlying EBV-induced HLH. These insights have led to increased awareness of the disorder, as well as earlier and improved treatment approaches. In this presentation, current insights into the demographic and genetic risk factors, clinical presentation, prognostic markers, disease pathogenesis and therapeutic modalities will be discussed.
Each year most physicians will only see a few patients with Langerhans cell histiocytosis (LCH), which provides us with ‘limited expertise’. Furthermore for years the collection and storage of affected tissue has hampered our knowledge of its pathophysiology. Collaborations within the Histiocyte Society (HS) has provided huge benefit and resulted in using one ‘histiocytic language’ and treating most of the patients through HS developed treatment protocols. Family associations like the Histiocyte Association have provided research funding for specific disease related problems. And over the last 25 years the ‘think tank’ meetings, entitled the Nikolas Symposia have concentrated in further understanding LCH by discussing certain topics and by initiating research collaborations. Twenty-five years ago Paul and Elizabeth Kontoyannis, whose son Nikolas had been diagnosed with LCH, wanted to give back to Nick’s physician (Dr. Jon Pritchard) and together they had a desire to promote more worldwide understanding of this sometimes awful disease. Dr Pritchard invited research minded physicians in the field and initiated the Nikolas Symposium (NS). These annual Symposia – 25 to date – have continued to provide a forum to bring together clinician scientists and a diversity of scientific experts to discuss the problems of LCH, to pinpoint research questions and carry out the research, and thus act like a catalyst for research on LCH. This has resulted by several symposium organisers and participants to interact worldwide, often in collaboration with the HS. To mention a few (a.) the biology and the origin of the Langerhans cell (Lc) within the disease versus to the physiologic Lc, (b.) clonality and what would this mean in LCH, (c.) the role of cytokines and chemokines in LCH and (d.) whether LCH is a immune dysregulation or a neoplasm. Current opinion is that the cells of origin are likely to arise from hematopoietic precursor cells although the stage of derailment remains unclear. Many of the signs and symptoms of LCH are driven by elevated cytokines and chemokines. The demonstration of the clonal nature of LCH in combination with the finding of a driver somatic mutation in BRAF in up to 60% of LCH patients, and related MAPK pathway activation in all, has provided compelling evidence for a neoplastic origin. Some of these findings have totally changed our view of the disease. This has led, that besides chemotherapy as standard of care, to explore the use of molecularly targeted therapies; the rational for a cure. Indeed ‘we’ came a long way!

Acknowledgements

I’d like to thank the entire Kontoyannis family, Peter Bienenstock and Dora Moustaka for the support of the Nikolas Symposia and all participants over the last 25 years.

References


STUDIES ON THE PATHWAY OF DIFFERENTIATION OF LCH CELLS
Matthew Collin1, Paul Mine1, Naomi McGovern2, Marie-Luise Berres3, Duan Kailb2, Venetia Bigley1, Muzlifah Haniffa1, John M Hicks2, Amanda Shin2, Michael Poidinger2, Kenneth McClain3, Miriam Merad4, Carl E. Allen5, Florent Ginhoux2

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Purpose: to analyse LCH cells, primary dendritic cells (DCs) and cultured cells by transcriptional profiling in order to map the most likely pathway of differentiation of LCH cells. Methods: RNA was isolated from sorted LCH cells (from skin, bone and lymph node) and other primary or cultured cells, processed with Illumina TotalPrep RNA Amplification Kit and hybridized to Illumina Human-HT12 Version 4 bead chips. Data were analysed by unsupervised hierarchical clustering and connectivity mapping (cMAP) to determine the relatedness of LCH cells to normal human DC, monocyte and macrophage subsets. Cultured DCs were also analysed by flow cytometry and electron microscopy for phenotypic markers of LCH cells. Results: unsupervised hierarchical clustering of a comprehensive database of human DCs monocytes and macrophages from blood and tissue, revealed that LCH cells were closest to CD1c+ dermal DCs. cMAP analysis also showed that the closest gene set enrichment to LCH cells was found in CD1c+ DCs, followed by LCs, while monocyte-derived cells or macrophages were unrelated. In culture with GM-CSF and TGFβ/BMP-7, CD1c blood DCs rapidly acquired high expression of langerin and CD1a. They also developed Birbeck granules and dense multilamellar bodies (thumbprint organelles) a unique pathological feature of self-resolving Hashimoto-Pritzker LCH. Conclusions: by mapping LCH gene expression to a comprehensive atlas of human blood and tissue resolving Hashimoto bodies (thumbprint organelles) a unique pathological feature of self-resolving Hashimoto-Pritzker LCH. 15% of patients with inferior survival in both study cohorts. Published data on LCH-III patients included 5-year survival rates (OS) of 76%, 80% and 91% in LCH-I, LCH-II, and LCH-III, respectively. In LCH-I/II, Cox-regression showed a significant impact of liver, spleen involvement on OS with hazard ratios (HR) of 4.4, 2.3 and 1.8. The resulting scoring system assigns 2 points to liver involvement and 1 point each to hema or spleen. In LCH-I/II a total score of 0,1,2,3 and 4 had an OS of 97%, 80%, 82%, 47% and 36%. Despite superior OS in LCH-III, the predictive value of the scoring system remains strong and patients with a total score of 0,1,2,3 and 4 had an OS of 98%, 100%, 96%, 76% and 64%. A significant impact of liver, hema, spleen involvement on survival could be confirmed in LCH-III, while lung involvement was not associated with inferior OS. Conclusion: In LCH-I/II and LCH-III cohorts, involvement of liver, hema and spleen at diagnosis had significant prognostic impact. A simple scoring system using the weighted impact of RO is able to identify a group of patients with inferior survival in both study cohorts."
LONG-TERM (>3 YEARS) IVIG TREATMENT IN AN ATTEMPT TO PREVENT THE PROGRESSION OF CNS NEURODEGENERATIVE DISEASE IN PATIENTS WITH LCH

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Japan LCH Study Group (JLSG)

Background: Outcome of LCH-related neurodegenerative CNS disease (ND-CNS-LCH) is very dismal. To date, limited information is available on the therapeutic experiences (IVIG, AraC and ATRA). We report here the therapeutic results of long-term IVIG treatment in 14 patients with ND-CNS-LCH in Japan. Patients and Methods: All patients showed typical MRI findings of ND-CNS and 11/14 patients had clinically active neurological symptoms. Of 14 patients, 8 were previously described (IJH 2015). The onset age of LCH was median 1.8 (range 0.2-4.9) years. The interval from MRI-based radiological diagnosis to the detection of neurological symptoms was median 2.2 (range 0.1-11.9) years. The ages when IVIG was initiated were median 8.0 (range 3.5-16.5) years. All patients received monthly IVIG longer than 3 years, of whom eleven patients have continued to receive IVIG for median 6+ (range 3+ -10+) years. There was no gender preference for PLCH. LCH was diagnosed between November 2006 and October 2013 at a single institution. Results: During the treatment and follow-up periods, 9/14 patients did not show progression of neurological deterioration and remained in stable condition. Of the 7 patients who had low EDSS scores (0-1.5) at the start of IVIG, 4 showed no progression while 3 did mild progression with elevated EDSS scores (2.0-3.5). On the other hand, even in 7 patients who started to receive IVIG with high EDSS scores (2.0-7.0), 5 showed no progression. At the latest evaluation, 12/14 were ambulatory with or without mild ataxia, with median values (ranges) of 2.8 (0-9.5) for EDSS scores, 5 (0-39) for SARA scores, 28 (3-30) for MMSE scores and below average for school performance in 12/14. Conclusions: Although this was not a controlled study, we found some efficacy of long-term IVIG treatment. IVIG starting at the early stage of ND-CNS-LCH could be useful to maintain the improved quality of life in these patients.

CLINICAL RESEARCH OF PULMONARY LANGERHANS CELL HISTIOCYTOSIS IN CHILDREN: ANALYSIS OF 117 CASES

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Purpose: The objective of this article was to characterize the clinical manifestations and features of pulmonary Langerhans cell histiocytosis (PLCH) by retrospectively analyzing clinical data of patients with PLCH. Methods: A retrospective analysis was performed in LCH patients registered between November 2006 and October 2013 at a single institute. They were stratified and treated according to Histioctye Society LCH-II protocol. Results: 117 PLCH patients were analyzed out of a total of 338 LCH patients (34.6%). There was no gender preference for PLCH. The age of PLCH children (mean age 25.2±5.7 years) was significantly lower than the non-PLCH group (mean age 53.8±39.2 months), P <0.001. Among the 117 PLCH children, Only 11 cases (9.4%) had clinical manifestations, which mainly included cough (8.5%), wheezing (0.9%) or shortness of breath (0.9%). All PLCH children had other organs involvement, mainly including rash, bone destruction, liver and spleen damage, while 56 cases (47.9%) had other “risk organs” involvement. The radiologic findings of PLCH children showed cysts (24.8%), ground glass like changes (21.4%), micronodular pattern (16.2%), emphysema (13.7%), etc. Pulmonary function abnormalities dominated in obstructive ventilatory dysfunction (82.9%). The overall survival rate of PLCH children was 96% and the progression-free survival rate was 61.3%, while among the children with disease progressed or relapsed, only 13.9% were mainly due to progression or recurrence of lung damage. Conclusions: Children with PLCH were mainly infants and young children, without obvious clinical manifestations. They generally had other “risk organs” involvement was the key point to improve progression-free survival.

INFLAMMATORY PLASMA PROTEINS PREDICT DISEASE SEVERITY AND RESPONSE TO THERAPY IN PATIENTS WITH LCH

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Purpose: Langerhans cell histiocytosis (LCH) is a myeloproliferative disorder with clinical manifestations ranging from single lesions to lethal multi-organ disease, and front-line therapy fails in the majority of patients. No histologic features of LCH lesions have yet been demonstrated to correlate with clinical outcomes. We hypothesize that function of differentiated CD207+, including interactions with recruited activated lymphocytes, results in plasma protein profiles that reflect disease burden and tissue-specific DC-lymphocyte interactions. Plasma proteins may therefore inform mechanisms of pathogenesis and serve to predict risk and follow disease burden in LCH patients. Methods: We evaluated inflammatory proteins in the plasma of LCH patients using the Luminex platform. We compared plasma concentrations of 121 analytes in 178 patients with LCH to 90 controls with discovery and validation sets. Comparisons were made based on disease status, age, and clinical risk categories. 152 samples collected from 78 patients at serial time points were also analyzed. Comparisons were made between diagnosis and cure, as well as multiple time points in therapy. Results: Thirty-one analytes were significantly different between all LCH and controls. Twenty-three analytes were significantly different when comparing adult vs pediatric LCH. When comparing LCH vs control by age groups, 5 were significantly different in adults and 23 were different in children. Twelve were different in pediatric low risk compared to high risk patients. Seven analytes predicted risk organ involvement with a sensitivity of 91.5% and a specificity of 87.5%. Seventeen analytes changed significantly after curative treatment. Conclusions: Distinct Plasma protein profiles exist in LCH, suggesting pathologic myeloid cells drive the inflammatory pathology of disease. Profiles are vastly different among children and adults with LCH, and differ based on burden of disease, suggesting separate inflammatory pathology. 7 analytes reliably predict high-risk disease and analysis of serial samples shows changes in protein profiles after cure.
we identified relatives of 79 Swedish primary HLH patients (diagnosed 1971-2011) using a multi-generation-registry. Relatives and matched controls were cross-linked with the Swedish cancer registry, and the cancer incidence rate and incidence rate ratio (IRR) were established for first- and second-degree relatives as well as separately for women and men. Additionally, NK-cell-mediated cytotoxicity was assessed in a subgroup of first-degree relatives. Results: Remarkably, a significantly higher incidence rate of malignancies was observed in first-degree relatives compared to controls (IRR=1.8; p=0.03) and first-degree female relatives (IRR=2.8; p<0.01), whereas no difference was seen among the male relatives. Despite this finding, functional analysis of heterozygous carriers of HLH-associated mutations did not display significantly reduced lymphocyte cytotoxicity as measured by current functional assays. Conclusion: In conclusion, our findings indicate that heterozygous mutations in HLH-associated genes represent a novel risk factor for cancer. The increased risk of developing cancer may imply haploinsufficiency of cytotoxic lymphocyte-mediated immunosurveillance of cancer in female carriers of HLH-causing mutations. Our results signify the impact of mutations in genes required for lymphocyte cytotoxicity to human health and may speak in favor of intensified screening for malignancies in female relatives of primary HLH patients.

**HYDROXYUREA HAS ACTIVITY IN RELAPSED/REFRACTORY LANGERHANS CELL Histiocytosis**

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Purpose: Langerhans cell histiocytosis (LCH) is a potentially fatal disease, clinically ranging from single bone lesions to diffuse multi-system involvement. Given incomplete understanding of LCH pathogenesis, optimal therapies remain uncertain. An emerging model of LCH pathogenesis suggests that pathologic CD207+ Langerhans cells arise from myeloid dendritic precursor cells, driven by activating mutations in the MAPK pathway. Therefore, we hypothesize that therapies directed against immature myeloid cells may be effective in treatment of LCH. Hydroxyurea is a myelotoxic therapy with proven efficacy in other myeloproliferative neoplasms, including CML. This study reports a single-center experience with hydroxyurea therapy in a cohort of LCH patients.

Methods: The charts of patients treated at Texas Children’s Hospital from December 2009 to present were reviewed in accordance with IRB-approved protocols at Baylor College of Medicine. Patients were selected for hydroxyurea therapy based on specific clinical characteristics, including low-risk single-system disease on presentation, recurrent/refractory disease following standard of care frontline therapy, and intolerance of other therapies. Treatment response was reported using the criteria established in the Histiocyte Society Evaluation and Treatment Guidelines. Results: 14 patients, ranging from 1 month to 66 years old, previously receiving 1-5 alternate regimens, have received hydroxyurea therapy. To date, patients have been on therapy for an average of 7.4 months. Results show better/regression in 8 patients, intermediate/stable in 2 patients, and worse/progression in 1 patient. One patient had anemia requiring dose reduction. Conclusion: Hydroxyurea demonstrated activity against LCH with minimal toxicity, meriting further investigation in clinical trials. Disease control improved in the majority of patients on hydroxyurea monotherapy. Chronic use of hydroxyurea is well tolerated, making it an ideal agent to investigate for the role of maintenance therapy. Furthermore, hydroxyurea may be useful in combination with other therapeutic strategies.
**PRESENTATIONS NOMINATED FOR THE NEZLEOF PRIZE IN BASIC SCIENCE**

**DIVERSE KINASE MUTATIONS AND FUSIONS DRIVE NON-LANGERHANS CELL HISTIOCYTOSIS**

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Purpose: The identification of BRAFV600E mutations in Langerhans Cell Histiocytosis (LCH), Erdheim-Chester Disease (ECD), and Juvenile Xanthogranuloma (JXG) has revolutionized our understanding and clinical management of these disorders. However, recurrent genetic alterations in the majority of BRAFV600E-wild type ECD/JXG patients are unknown, and the molecular bases for the phenotypic differences between LCH and non-LCH remain elusive. Therefore, we performed whole exome (WES) and whole transcriptome sequencing (RNA-seq) study. Fusions were validated using RT-PCR. Recurrence testing was performed in 43 BRAFV600E-wild type non-LCH samples. Results: Using combined WES/RNA-seq, activating kinase alterations were identified in 100% of patients. Of LCH cases, 60% and 40% had BRAFV600E and MAP2K1 mutations. Of ECD/JXG cases, 47%, 13%, 13%, and 7% were BRAFV600E, ARAF, MAP2K1, and NRAS mutant. RNA-seq with FISH confirmation revealed novel fusions involving BRAF, ALK, and NTRK1 in 20% of non-LCH patients. Expression of each fusion in Ba/F3 cells conferred cytokine-independent growth. Concomitant mutations affecting many cellular processes were also identified. Recurrence testing revealed the following mutually exclusive in ARAF, MAP2K1, NRAS, KRAS, and PIK3CA: 37%, 26%, 14%, 9%, and 7%. FISH screening failed to identify kinase fusions in 45 additional histiocytoses cases. Conclusions: This WES/RNA-seq study revealed activating kinase alterations in every patient and is the first description of kinase fusions and recurrent mutations co-existing with MAP kinase alterations in the histiocytoses. Non-LCH appears to harbor higher frequencies of MAP2K1 and ARAF mutations than described in any cancer. Future efforts to understand the clinical actionability of these mutations in histiocytoses is critical to improving therapy for the ~50% BRAFV600E-negative patients.

**INHIBITION OF DIACYLGLYCEROL KINASE ALPHA RESTORES SENSITIVITY TO TCR-INDUCED CELL DEATH AND LESSENS IMMUNOPATHOLOGY IN A MURINE MODEL OF XLP-ASSOCIATED HEMIPHAGOCYTIC LYMPHOHISTIOCYTOSIS**

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Purpose: X-linked lymphoproliferative disease (XLP) is a life-threatening disorder of the immune system that is caused by mutations in SH2D1A, the gene encoding a small adaptor protein known as SAP. XLP is perhaps best recognized for the unique vulnerability of affected male individuals to primary Epstein Barr virus (EBV) infection. Following EBV exposure, many patients develop and/or die from EBV-induced hemophagocytic lymphohistiocytosis (HLH). The purpose of this study was to identify novel treatments for XLP-associated EBV-induced HLH. Methods: XLP T cells fail to constrain the activity of diacylglycerol kinase alpha (DGKa), an enzyme that limits TCR signal strength. As a result, XLP T cells display significantly weakened TCR signaling. XLP T cells also exhibit marked defects in restimulation-induced cell death (RCD), an apoptotic program that curtails the accumulation of activated CD4+ and CD8+ T cells. Since a strong TCR signal is required to induce RCD, we hypothesized that by inhibiting DGKa, we might restore the sensitivity of XLP T cells to TCR-induced cell death. Results: Here we show that siRNA-mediated silencing or pharmacologic inhibition of DGKa in SAP-deficient T cells restores DAG signaling at the immune synapse and rescues RICD via induction of the pro-apoptotic proteins NUR77 and NOR1. Importantly, pharmacological inhibition of DGKa in vivo prevents the excessive CD8+ T cell expansion and IFNγ production that occur in Sap−/− mice following Lymphocytic Choriomeningitis Virus-infection. Conclusions: These findings underscore the role of SAP and DGKa as key regulators of T cell homeostasis and highlight DGKa inhibition as a rational and potentially more effective approach to treat XLP-associated EBV-induced HLH by promoting RICD in activated effector T cells.

**LCH REACTIVATION RISK IS AFFECTED BY LESIONAL CD8+ T CELL PERCENTAGE BUT NOT BY BRAF MUTATIONAL STATUS**

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Purpose: Langerhans Cell Histiocytosis (LCH) is a myeloid disorder with inflammatory features. BRAFV600E is frequently detected in CD1a+ LCH-cells. The impact of genetic aberrations on clinical presentation and outcome of LCH is unclear. We hypothesized that priming of CD8+ cytotoxic T lymphocytes (CTL) specific for neo-epitopes encoded by mutant genes is essential for immune-mediated clearance of neoplastic LCH-cells. By combining data on outcome, mutation status and immune signature of lesional cells, we expect to find a prognostic signature which may improve risk assessment and therapy decisions at LCH onset.

Methods: A Dutch-Canadian pediatric LCH patient cohort was established for this study. Archived formalin fixed paraffin embedded tissue biopsies were analyzed, in a blinded fashion, for the presence of the BRAFV600E mutation by microdissection and PCR. T cell numbers and subsets were assessed by triple immunofluorescent (IF) staining using CD3-, CD8- and CD1a-specific antibodies and ImageJ software. Low resolution Human Leukocyte Antigen (HLA) genotyping was used to assess the patients’ HLA-A, B and C genotype. Results: The median percentage of lesion-infiltrating CD3+CD8+ T cells (25.4%) as assessed in biopsies from Dutch patients (n = 84) was not affected by LCH manifestation form (MS vs SS) nor by BRAF mutation status (p=0.99). After stratification of 52 patients with known relapse status into a CD8high group (≥25.4%) or CD8low group (<25.4%) we observed that patients who remain LCH-free are more often confined to the CD8high group (26/36=72%) than those who reactivate (2/16=12.5%, p=0.0012). Conclusion: Data from this interim analysis indicate that high levels of lesional CD8+ T cells at LCH onset is associated with decreased LCH reactivation rates, independent of BRAF mutation status. Using peptide binding prediction models, we are currently mapping BRAFV600E protein-derived peptides in the context of HLA class I alleles (i.e. HLA-A*03) which seem more prevalent in patients who relapse.
WHOLE EXOME SEQUENCING AS A NEW MODULE IN THE DIAGNOSTIC EVALUATION OF PATIENTS WITH HLH: 2010-2014 EXPERIENCE

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening inflammatory syndrome with a heterogenous pathophysiological basis. Rapid disease classification is critical for treatment decisions. We review the performance of our diagnostic algorithm in reaching appropriate patient classification in a German cohort of patients referred for suspected HLH.

Methods: Patients referred for suspected HLH between 2010-2014 were analyzed for expression of perforin, SAP and XIP and for NK/CTL degranulation. Genetic analysis was performed if indicated by immunological or clinical clues, followed by whole exome sequencing in selected cases. Results: Of 405 referred patients, 174 fulfilled the clinical HLH criteria. Ninety-nine patients had mutations in cytotoxicity-related genes or XLP, including 31 patients with incomplete, atypical or no HLH. 15/15 patients with perforin mutations, 5/5 with SAP and 10/10 with XIP mutations were identified by intracellular protein staining. Among 69 patients with genetic degranulation defects, 60 had fresh NK cell degranulation <5%. The remaining 9 patients had 5-9% but in addition reduced degranulation after prestimulation. Eighty-six patients had active 2nd HLH, 17 of those had fresh NK degranation below 5%. Seven of these plus additional 8 patients with active or incomplete HLH and either abnormal immunological results, family history, consanguinity or relapses, but no mutation in known genes upon Sanger sequencing underwent whole exome sequencing (WES). WES revealed 1 mutation in a novel disease-causing gene (AP3D1), 3 unusual variations in known cytotoxicity-related genes (Perforin, MUNC13-4, RAB27A), 3 mutations in genes associated with different diseases (Wolman disease, Osteopetrosis, MVK) and 8 are still under investigation with no obvious candidates. Conclusion: The diagnostic screening algorithm proved highly effective. Genetic analysis including WES revealed that in our cohort most human genetic disorders of cytotoxicity predisposing to HLH have now been identified.

IFN\(\gamma\) DRIVES DISEASE IN TLR9-MEDIATED SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (sHLH) IN MICE. RATIONALE FOR A NEW THERAPEUTIC TARGET IN HLH SECONDARY TO INFECTION IN HUMANS

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Purpose: HLH is a life-threatening syndrome characterized by an overwhelming activation of immune cells presenting with a cytokine storm. Recently, increasing evidence of the central role of IFN\(\gamma\) has been gathered in patients with primary and secondary HLH. To study the role of IFN\(\gamma\) we used a mouse model that mimics TLR9 infection-driven sHLH.

Methods: In naive mice given repeated CpG-ODN injections and an anti-IFN\(\gamma\) monoclonal antibody, levels of total IFN\(\gamma\) and IFN\(\gamma\)-induced chemokines, CXCL9 and CXCL10, were measured. Serum levels of IFN\(\gamma\), CXCL9 and CXCL10 were also measured in 14 patients with sHLH.

Results: We found, for the first time, that total IFN\(\gamma\) levels originating within tissues (mainly liver and spleen) upon TLR9 stimulation are 500- to 2,000-fold higher than those measured in serum. The hyper-production of IFN\(\gamma\) in tissues was intimately associated to disease progression assessed as weight loss, splenomegaly, hyperferritinemia, cytopenia and liver inflammation. Ablation of IFN\(\gamma\) activity ameliorated HLH clinical and laboratory parameters, as well as significantly decreased CXCL9 and CXCL10 levels, both in serum and in tissues. These findings demonstrate in this model of sHLH that IFN\(\gamma\) and signature gene products, CXCL9 and CXCL10, strictly correlate with disease manifestations and severity. Importantly, in patients with sHLH sampled during active disease, IFN\(\gamma\), CXCL9 and CXCL10 levels (median 34.7pg/ml, IQR 23.9-170.1; 33,589pg/ml, 3,083-127,687; 4,420pg/ml, 799-8,226, respectively) were markedly higher compared to patients in remission (<3.5pg/ml, <3.5-6.5: 745pg/ml, 469-1,098; 132pg/ml, 74-157, respectively). Finally, a significant correlation of IFN\(\gamma\) with CXCL9 (r=0.65, p<0.002) and CXCL10 (r=0.54, p<0.02) levels was found also in sHLH patients. Conclusion: CXCL9 and CXCL10 levels unveil the amount of IFN\(\gamma\) present not only in circulation, but also, and most importantly, in tissues and could be used as surrogate markers of IFN\(\gamma\) production. Furthermore, IFN\(\gamma\) neutralization should be considered a valuable therapeutic option in infection-driven sHLH.

NEUTRALIZATION OF INTERFERON-GAMMA IS EFFICACIOUS IN A MOUSE MODEL OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS SECONDARY TO CHRONIC INFLAMMATION.

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Purpose: Macrophage activation syndrome is a term used to identify hemophagocytic lymphohistiocytosis secondary to rheumatic diseases (rheuHLH). It is part of secondary HLH forms, that are clinically and biochemically similar to primary HLH (pHLH), with generalized hypercytokinemia as a major feature. Based on data obtained in animal models of pHLH, showing that interferon-gamma (IFN\(\gamma\)) neutralization reverts the disease, we aim to demonstrate, in a murine model of rheuHLH, the role of IFN\(\gamma\) and the efficacy of an anti-IFN\(\gamma\) antibody.

Methods: A mouse model of rheuHLH (Strippoli R, Arthritis Rheum 2012), relying on an exaggerated response to toll-like receptor ligands in mice transgenic for interleukin-6 (IL-6TG), has been used to evaluate levels of IFN\(\gamma\) and the therapeutic potential of a neutralizing IFN\(\gamma\) antibody (XMG1.2, BioXcell, USA). Results: LPS-treated IL-6TG mice showed an exaggerated inflammatory response, with significantly increased serum IFN\(\gamma\) levels and higher IFN\(\gamma\) mRNA expression levels in liver, compared to LPS-treated WT mice. A significant increase in the expression of genes known to be induced by IFN\(\gamma\), such as CXCL9, CXCL10 and H2-Aa (class II antigen A, alpha) was observed in the liver from LPS-treated IL-6TG mice compared to WT mice. IFN\(\gamma\) neutralization studies have revealed that, in LPS-injected IL-6TG mice, anti-IFN\(\gamma\) treatment significantly improves survival and body weight recovery, compared to control antibody -treated animals. Furthermore, a significant reduction in ferritin levels was observed in mice treated with anti-IFN\(\gamma\) Ab, compared to control antibody-treated animals. Finally, a significant reduction in the mRNA expression of IFN\(\gamma\)-induced genes was observed in liver from mice treated with anti-IFN\(\gamma\) Ab. Conclusion: These results provide insights into the pathophysiology of rheuHLH. Further support the hypothesis that IFN\(\gamma\) is the common mediator of all HLH forms and provide the rationale for the therapeutic use of a monoclonal anti-IFN\(\gamma\) antibody in this fatal disorder.
Purpose: Infection associated HLH (IAHLH) develops as a result of immunological activation of the immune system triggered by an infection. In the last 6 years, we have encountered 75 patients of IAHLH, causative organism has been identified in 41 cases. Though in HLH 2004 protocol three tier therapies have been advocated, irrespective of the type and etiology, we invented a new risk stratification scoring system and score dependent treatment predominantly based on steroid with optional use of Intravenous immunoglobulin and Cyclosporine. Method: Clinical records of children of IAHLH admitted at Institute of Child Health, Kolkata were reviewed. The patients were classified in 4 groups with a scoring system depending upon 7 variables (Age, CNS symptoms, Absolute neutrophil count, coagulopathy, ferritin, fibrinogen, EBV positivity). Each variables given a score of 1 to 3 and the total score thus came out to be 7-21 with four subgroups (7-10, 11-14, 15-18, & 19-21). Treatment was individualised depending on the score like patient with a good score of 19-21 received only short course steroid for 4 weeks, whereas patients with less score of 7-10 received maximum therapy in the form of steroid, cyclosporine, etoposide and IV Ig. Results: Among 75 patients, 67 patients survived and those with the lowest score (7-10) had a significant high mortality of 84% despite most intensive therapy. Those with highest score (19-21) had 100% survival despite minimum therapy. Most of our patients were treated with novel steroid only protocol either for 4 weeks or traditional 8 weeks.

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. So we propose that IAHLH cases should be individualised depending upon the risk factors and those with low risk with high score can be treated satisfactorily with minimal therapy.

NEW MECHANISMS OF HLH PATHOGENESIS REVEALED FROM A NOVEL MOUSE MODEL

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Dysregulation of the immune system is a fundamental mechanism for hemophagocytic lymphohistiocytosis (HLH). Hyposa inducible factor-1α (HIF-1α) is a critical transcription factor for the hypoxic response, angiogenesis, normal hematopoietic stem cell regulation and cancer development. Accumulating evidence suggests the critical role of HIF-1α in the activation of both innate and adaptive immune cells. To elucidate the role of HIF-1α for the regulation of a broad spectrum of immune cells in a physiologic context, we generated inducible HIF-1α transgenic mice in which stable HIF-1α proteins can be induced in all hematopoietic cell lineages with Vav1-Cre/Rosa26-tTA drivers after doxycycline administration. Interestingly, in the FVB/J29/B6 mixed background, they developed myelodysplastic syndromes (MDS)/myeloproliferative neoplasm (MPN) phenotypes: abnormal self-renewal, cytopenias, megakaryocyte/myeloid dysplasia, iron overload and bone marrow fibrosis. We also observed that inflammatory monocytes, macrophages, peripheral blood T cell numbers, and type-1 polarized T cells were significantly increased. Similar immune activation has been reported in patients with MDS and MDS/MPN, and the critical roles of activated immunity for MDS/MPN have been discussed for several decades. Surprisingly, when we induced high level HIF-1α expression in the pure C57Bl/6 (type 1 biased) background, most mice developed HLH-like phenotypes: severe anemia, thrombocytopenia, multi-organ failure, splenomegaly, and hemophagocytosis. Most mice quickly appeared moribund within 3 weeks (median survival: 10 days). Since those mice had high levels of interferon gamma (IFN-γ), genetic deletion of IFN-γ receptor significantly attenuated HLH progression in this mouse model. In summary, we generated a novel mouse model which presents either an MDS/MPN or HLH phenotype depending on the genetic/immunologic background. This useful model will help us to identify new underlying mechanisms and potential new therapeutic targets, such as HIF-1α and IFN-γ pathways, for the lethal disorder HLH. This study also may shed light on the pathophysiological link between MDS/MPN, HLH, and other related disorders.

HLH DIAGNOSIS IN THE GENOMIC ERA

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a heterogeneous disorder. Defects in 17 genes (AP3B1, BLOC1S6, CD27, ITK, LYST, MAGT1, PRF1, RAB27A, SH2D1A, SLC7A7, STX11, STXBP2, UNC13D (MUNC13-4), XIAP (BIRC4)) have been associated with familial HLH and similar clinical conditions. A timely and cost effective diagnostic strategy is needed to support a more personalized treatment plan. Methods: We conducted a comprehensive review of the results form a HLH Next Generation Sequencing (NGS) testing panel along with protein expression and other clinical immunological testing (Perforin, SAP and XIAP by flow cytometry, NK function etc.) to evaluate a comprehensive testing algorithm for the diagnosis of HLH and associated disorders. Whole exome sequencing (WES) and deletion/duplication and X-inactivation analyses are also utilized in several NGS negative cases. Results: By reviewing the 17 gene HLH NGS panel in the first 370 clinically suspected HLH patients, we found 31 patients to have single or bi-allelic mutations in HLH related genes, 175 have variants with unknown clinical significance, 13 patients carried variants in more than two genes. In addition, gross deletions and duplications have been identified in 5 patients in several HLH genes. Interestingly, by WES, we found one female patient with one pathogenic mutation in BIRC4 and further study demonstrated she is also affected by X inactivation abnormalities. For the non-genetic studies, Perforin expression analyses detect 78% of patients and carriers with PRF1 variants. XIAP and SAP protein analyses by flow cytometry found 87% and 95% of patients with likely pathogenic variants in SH2D1A and BIRC4 genes respectively. Conclusion: To achieve a definitive diagnosis in patients with HLH, a comprehensive approach is desired which includes genetic and epigenetic studies as well as immunological work up. NGS panel and WES provide cost effective testing platforms with reasonable clinical sensitivity for patients with HLH.
OUTCOME OF LANGERHANS CELL HISTIOCYTOSIS AMONG CHILDREN IN DEVELOPING COUNTRIES: CHILDREN'S HOSPITAL LAHORE PAKISTAN EXPERIENCE

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Purpose: Langerhans Cell Histiocytosis is a relatively rare disease accounting for less than 2% of new cases each year enrolled in The Children’s Hospital Lahore. The purpose of this study was to analyze its clinical manifestations, course and outcome in resource limited settings lacking salvage therapy. Methods: Retrospective review of 27 patients enrolled between January 2011-December 2014 was done. Data regarding their age, sex, clinical classiﬁcation, course of therapy, and outcome analyzed. The therapy mainly comprised of prednisolone and vinblastine. Results: Total 27 patients with age ranging from< 1 to 6 years (30% <2 yrs) were included. M: F Ratio was 2:1. 20/27 (74%) patients presented with Multisystem-LCH (MS-LCH) with 7/7-100% mortality in MS-LCH group and 11/27 (41%) had Risk Organ involvement with 4/5(75%) mortality (p-value=0.079).19/27(70%) patients had bone lesions while 6/27(22%) patients presented with central nervous system (CNS) involvement. Total 6/27 (23%) have completed treatment, 9/27 (33%) are 6/27(22%) patients presented with CNS INVOLVEMENT IN PULMONARY LANGERHANS CELL HISTIOCYTOSIS - MRI IMAGING

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Introduction: Langerhans cell histiocytosis (LCH) is considered to be related to potential involvement of the central nervous system (CNS). Two major groups of CNS changes can be distinguished: tumors lesions and neurodegenerative changes. Pulmonary Langerhans cell histiocytosis (PLCH) in adults is usually a single-system disease, however the involvement of other organs is observed more than once. The most common CNS pathology location is the hypothalamus -pituitary axis (H-P) with diabetes insipidus (DI) as a clinical manifestation. Purpose: To analyse the frequency of CNS involvement in a group of patients with recently diagnosed PLCH. Materials and Methods: Between January 2012 to January 2015 a total group of 36 new diagnosed patients with PLCH, males 16 and females 20, ages ranging from 17 to 63, were examined. We performed a brain and dynamic, contrast enhanced pituitary MRI in all patients using the same scan protocol. Results: We identiﬁed 17 patients with H-P lesions and among them 9 with DI. We assessed the correlation between DI (N=9) and lack of posterior pituitary lobe high signal (N=7; P=0.006), inhomogeneous pituitary enhancement (N=7; P=0.006), empty sella (N=4; P=0.267), pineal cyst (N=4; P=0.267), pituitary continuous meningeal inﬁltration (N=1; P=0.257). No thickening of the infundibulum was observed. We identiﬁed 1 patient with neurodegenerative changes, 1 patient with meningial involvement and 7 patients with hyperintense white matter lesions presented with vascular pattern. Conclusion: The most common type of CNS pathology in our group was H-P lesion. DI in a group of patients with PLCH signiﬁcantly correlated with loss of high signal of posterior pituitary lobe and inhomogeneous pituitary enhancement. No statistically signiﬁcance between empty sella, pineal cyst and DI was observed. To assess the relevance of other CNS changes our study should be continued.

THE ROLE OF T CELLS IN THE IMMUNE REGULATION OF LANGERHANS CELL HISTIOCYTOSIS (LCH)

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Purpose: LCH is characterized by lesions containing CD1a+ and or CD207+ histiocytes as well as inﬁltratory cells, including lymphocytes. Immune regulation is important in cancer and many groups (including the Kannourakis group) believe that it may be important in the pathogenesis of LCH. Immune regulation can potentially affect recruitment, activation and function of other immune cells, and possibly the regression of LCH lesions, but this mechanism remains poorly deﬁned. We are especially interested in the role of CD3+CD1a+ T cells, previously reported by our group, in the pathogenesis of LCH. The role of other T cells with a known regulatory function, such as FOXP3+ regulatory T cells (Tregs), mucosal associated invariant T (MAIT) cells and natural killer T (NKT) cells is not clear in LCH. Methods: This project has used tissue samples from healthy blood donors, and LCH lesions stored in the Fiona Elsey Cancer Research Institute’s Tissue Bank facility. The samples were studied using 13-colour ﬂow cytometry analysing intracellular and surface antigens, as well as in vitro assays of T cell function. Results: We have detected mature colour flow cytometry analysing intracellular and surface antigens, as well as in vitro assays of T cell function. Results: We have detected mature
INCREASED TYRO3 AND PROTEIN S EXPRESSION IN CIRCULATING MONOCYTES AND T CELLS SEEM TO CORRELATE WITH ACTIVITY OF LCH

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Background/Purpose: The TAM receptor tyrosine kinases (RTKs), TYRO3, AXL, and MERTK, together with their cognate agonists GAS6 and Protein S (PROS1) play an essential role in the resolution of inflammation. Additionally, TAM receptors are aberrantly expressed in multiple haematological and epithelial malignancies promoting survival, chemo-resistance and motility. Our aim was to explore the role of the TAM system in the immunological dysregulation of pediatric LCH. Methods: We analyzed the expression of TAM receptors and their ligands in peripheral blood monocyte and T lymphocyte lineage (PBMC) of three LCH children (LCH1-3) by FACS analysis. At sampling, LCH1 was an 8 month old (m.o.) boy untreated with a bulky mediastinum mass and multiple skin lesions; LCH2 was a 3 year old girl treated during the first year of life, with a non-active cutaneous disease and LCH3 was a 10 m.o. girl with active skin disease and under non-systemic therapy. PBMC of LCH1 was analyzed again after 6 weeks of vinblastine and meprednisone treatment. Results: Remarkable, LCH1 who presented systemic compromise showed increased circulating CD11b+ cells (27%) compared with LCH2 (2%) and LCH3 (8%). Furthermore, PROS1 and TYRO3 were much more expressed in the monocytes and T cells compartment of LCH1 compared with LCH2 and LCH3 patients. Interestingly, after 6 weeks of treatment LCH1 showed a reduction of circulating CD11b+ cells (14%) concomitant with lower levels of PROS1 (14-fold decrease) and TYRO3 (3-fold decrease) expression in the CD11b+ population. Conclusion: Our results show that higher levels of TYRO3 and PROS1 are associated with LCH activity and could be an indicator of systemic compromise in pediatric LCH.
Objective: Langerhans Cell Histiocytosis is the most common type of childhood histiocytic disorder in children under age of 15 years. The study was conducted to see the outcome of Langerhans Cell Histiocytosis treating according to Histiocyte Society guideline-2009. Methods: This prospective observational study was conducted from January 2013 to January 2015 at BSMMU, Dhaka, Bangladesh. A total of 10 children with diagnosis of Langerhans cell histiocytosis (LCH) included in the study. Diagnosis of LCH was done according to clinical, radiological and histopathological examination. Immunohistochemistry could done only in 50% cases. After preclinical evaluation, disease was stratified according to guideline-2009. Systemic chemotherapy were given according to indication of guideline. Results: Age range of studied children were 3 months to 13 years with M: F was 3:2. Among 10 studied cases 7 children were straffied as multisystem (MS)-LCH, 2 were as single system( SS)-LCH with CNS-risk lesion and 1 children was SS-LCH with multifocal involvement. After enrollment 1/10 (10%) patient refused treatment. Total 6 cases completed full 1 year therapy, 2 patients are on maintenance therapy, 1 patient died before completing course-1. After completion of initial 6 weeks induction therapy, 88.9%(8/9) children showed excellent response.Among the 6 cases who completed treatment, 2/6 (33.3%) patient maintaining remission, 1/6 (16.7%) patient died, 3/6 (50%) patient developed relapse (2 in lymph node and 1 in bone). Conclusion: The study found high rate of relapse after completion of full one year therapy, though 88.9%(9/10) children showed excellent response to initial 6 weeks induction therapy.

Poster Location #6

OUTCOME OF LANGERHANS CELLS HISTIOCYTOSIS IN CHILDREN RECEIVING TREATMENT ACCORDING TO HISTIOCYTIC SOCIETY GUIDELINE-2009

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Purpose: Bisphosphonates are osteoclast inhibitors that can be effective in treating bone Langerhans cell histiocytosis (LCH). We aimed to evaluate the efficacy and safety of bisphosphonates in treating bone LCH and extra-osseous disease. Methods: An international multicenter retrospective chart review was conducted in children and adults with LCH who received bisphosphonates between 1995 and 2014. Results: Eighteen patients were identified from 4 centers. All received bisphosphonates therapy either at diagnosis or at ≥ 1st reactivation. Median age at start of bisphosphonates was 23.7 years (range 5.7-38.3 years), and median follow-up time post bisphosphonate therapy was 2.8 years (range 0.9-5.0 years). Patients had either SS or MS LCH with or without risk organ involvement. Patients were treated with different bisphosphonates with majority received zoledronic acid (n=10), followed by pamidronate (n=4) and alendronate (n= 3); one patient received both pamidronate and zoledronic acid. All patients reported significant reduction in pain, to either no or mild pain after administration of bisphosphonates, with none having moderate/severe pain. Thirteen of 18 patients (72%) achieved complete remission (CR) in the bone lesions, including lesions in skin (n=1), lung (n=1) and pituitary (n=1); 2 had partial response and 3 had no response. Among the 13 CR patients, 12 had no active disease for a median of 4.1 years (range 2.8 - 5.1 years) and 1 developed radiographic neurodegeneration after 2 years. Bisphosphonates were well tolerated by all patients with no major toxicity. Progression-free survival (PFS) was 75 ± 11% at 3 years, with a trend favoring better PFS (P=0.24) in patients with no or first reactivation compared with those having ≥ 2 reactivations. Conclusion: Bisphosphonates significantly improved bone pain in patients with bone LCH, and may be effective in treating extra-osseous disease. A prospective randomized trial evaluating the role of bisphosphonates in multifocal bone LCH is warranted.

Poster Location #9

CHILDREN AND ADOLESCENTS WITH LANGERHANS CELL HISTIOCYTOSIS IN BELARUS

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Langerhans cell histiocytosis (LCH) is a disorder with highly variable clinical presentation and biological behavior. Purpose: the aim of the study was to analyze the morbidity and mortality of LCH the age group (0-18). Methods: due to the children’s cancer sub-registers of the Republic of Belarus (Belarus) the extended epidemiological analysis of the incidence of LCH became possible. Diagnosis was carried out in accordance to generally accepted international standards. Statistical analysis was performed using Statistica 6.0. During the period of 1987-2014 (27 years ) 127 cases of LCH in children (0-18 ) were reported. Among them 73 boys (57.5%) and 54 girls (42.5%). Median follow-up was 10.6 years. In the analyzed group there were 46 children under the age of 2 years (36%). The annual increase of the incidence of LCH is 5.21%, that is probably due to the improved awareness of health professionals about the disease and the use of immunohistohemical techniques in the diagnosis. Peak of incidence is October- November. Results: In the overall structure of malignant tumors LCH is 1.17%. 93 patients (73%) received chemotherapy protocols DAL-HX-90, LCH-I, LCH-II, LCH-III, an individual treatment program, 34 patients (27%) - observed. Overall survival was 97% ±2%. Event-free survival 78% ±4%. The protocol LCH-III involved 69 patients. 37 of them received chemotherapy. The 5-year overall survival was 96%±4%, event-free survival 62%±9%. Group I (high risk, 9 patients ) - 56%±17%. Group II (low risk, 11 patients ) - 51%±16%. Group III ((multifocal bone disease, 17 patients )- 88%±8%. According to the results of cooperative research LCH-III 5-year overall survival was 84%, event-free in the respective risk groups 46%, 54%, 63%. According to the Japan LCH Study Group (JLSG-98) overall survival was 78-95%.

Poster Location #11

THE USE OF PREVENTIVE PLEURODESIS IN A PATIENT WITH LANGERHANS CELL HISTIOCYTOSIS WITH LUNG INVOLVEMENT

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Introduction: spontaneous pneumothorax is a well-described complication of pulmonary LCH in children. Surgical strategy in pulmonary LCH is usually reactive and includes thoracostomy, passive aspiration and, rarely pleurodesis. We describe a case of preventive pleurodesis in a patient with multi-system LCH and severe pulmonary involvement. Case report: Eleven month-old boy presented with skin rash at 2.5 months. External otitis, fever and pneumonia with respiratory compromise developed at 8.5 months. The diagnosis of non-specific immune deficiency syndrome was established in a regional hospital. Antibacterial therapy and prednisolone 3 mg/kg/day were initiated. Seven days later spontaneous pneumothorax
developed. It resolved after thoracic drainage. On admission: skin and nail lesions, bone lesions, dyspnea, distant crepitations. LCH diagnosis was confirmed by skin biopsy (mononuclear histioctye-like cells with expression of CD1a+, Langerin+, S-100+, CD68+). CT scan showed multiple irregular-shaped thin-wall cysts forming a massive bulla (7x5 cm) in the right lung apex. Due to the high risk of recurrent pneumothorax we elected to perform preventive pleurodesis of the right lung. The bulla was cut, its capsule was excised and defect was sutured. On subpleural bullas, electrocaugulation was performed in all parts of the right lung and pleurectomy from apature up to VI-VII intercostal spaces on front lateral and posterior surfaces. Histological examination of the extracted pleura’s part was performed and LCH was confirmed. Patient was treated according to LCH-IV protocol. The response to IC was rated as AD-better. On the follow-up CT lungs scan: new bullas in left lung upper lobe (47x19x29 mm) and in the lower lobe (26x13x19 mm). Considering negative dynamic, left lung pleurodesis was performed. At present the child is free from all active disease signs and dyspnea and is receiving continuation therapy. Conclusion: Elective pleurodesis can be considered to prevent recurrent pneumothorax in cases of LCH with disseminated cystic/bullous lung involvement.

Poster Location #12

CLINICAL STUDY OF HEMAPHAGOCYTIC LYMPHOHISTIOCYTOSIS SECONDARY TO LANGERHANS CELL HISTIOCYTOSIS

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Purpose: To improve the knowledge about the clinical manifestation of Langerhans cell histiocytosis (LCH) and secondary hemophagocytic lymphohistiocytosis (HLH), and to improve the stratified therapy of LCH. Methods: Retrospective study of 5 cases of HLH secondary to LCH, investigate the cytokine storm in LCH. Results: All patients were diagnosed with LCH by biopsy and pathological examination of skin, and met the revised diagnostic criteria of HLH 2004. Persistent fever, extremely hepatosplenomegaly, and refractory pancytopenia unresponsive to transfusion were the common characteristics of all cases. Infection of EB virus coexisted in 2 cases. HLH was the main manifestation of 1 case and the LCH was neglected for about 7 months. 2 cases died in 6 months. Conclusion: LCH is a highly heterogeneous disease and requires stratified therapy. Cytokine storm coexists with LCH complicated the condition and is related to negative prognosis.

Poster Location #13

CLINICAL RESEARCH OF 6 CASES OF PEDIATRIC THYROID LANGERHANS CELL HISTIOCYTOSIS

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Purpose: The aim of the study was to elucidate the clinical characteristics of pediatric thyroid Langerhans cell histiocytosis (LCH). Methods: A retrospective analysis was performed in pediatric thyroid LCH patients registered between July 2007 and July 2014 at a single institute in China, with LCH grouped and treated as LCH-III protocol. Results: A total of 387 patients (225 boys, 58.1%) with a median age of 53.8 months at diagnosis of LCH were analyzed, including 6 thyroid LCH (1.55%), 2 thyroid LCH had thyroid tissue biopsy. The proportion of male and female in thyroid LCH (2:1) was higher than the non-involved ones (1.38: 1), but no statistical significance (P=0.669). The age of thyroid LCH (mean age 90 months) was significantly higher than the non-involved ones (mean age 52.8 months). All of them suffered other organ involvement, lung (6 cases), liver (3 cases), skeleton(2 cases), and skin (1 cases). On thyroid ultrasound, thyroid enlargement and abnormal lobulated hypoechoic tissue was identified in all thyroid LCH with (2 cased, 33.3%) or without increased vascularity, while only 3 cases (no pituitary gland involved) had subclinical hypothyroidism (elevated TSH only). After chemotherapy as LCH-III protocol, thyroid ultrasound changes of the ones without hypothyroidism became normal (still in the maintenance treatment), the ones with hypothyroidism had no effect (both thyroid function and thyroid ultrasound changes) and one gave up. But after two courses of treatment of 2CDA, thyroid ultrasound changes of the two with hypothyroidism improved and TSH decreased (still in the chemotherapy of 2CDA) Conclusions: Thyroid LCH remains uncommon with invisible clinical manifestations, but usually part of a multi-systemic disease in children. The patients are mainly elder children but not associated with sexual predilection. Thyroid function and ultrasound is an important examinational basis, for 2CDA maybe the key point of the treatment for those with not only thyroid ultrasound changes but also hypothyroidism, as they do not have responding to conventional treatments.
Poster Location #15

INTENSIFIED AND PROLONGED THERAPY DID NOT IMPROVE THE OUTCOME IN LANGERHANS CELL HISTIOCYTOSIS WITH SINGLE-SYSTEM MULTIFOCAL BONE LESIONS; RESULTS OF JLSG-02 PROTOCOL STUDY

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Background: Patients of Langerhans cell histiocytosis (LCH) with single-system multifocal bone (MFB) lesions are rarely fatal but may experience reactivations and develop permanent consequences as represented by diabetes insipidus (DI). In our previous JLSG-96 study conducted from 1996 to 2001, 97% of patients responded to the therapy, while around 30% of patients experienced reactivation. To further improve the quality of life in patients of LCH with MFB lesions, we performed a modified treatment protocol (JLSG-02) from 2002 to 2009. Patients and Methods: All patients were newly diagnosed children of LCH with single-system MFB lesions and treated initially by protocol A, which consisted of 6 weeks’ Induction A with cytosine arabinoside/vincristine (VCR)/ prednisolone (PSL), followed by 48 weeks’ maintenance therapy. Poor responders to Induction A were switched to intensive salvage regimen, which consisted of adriamycin/cyclophosphamide/VCR/PSL. JLSG-02 has been revised from JLSG-96 as that; increase of PSL dosage at the induction phase and extension of maintenance therapy duration from 24 weeks to 48 weeks. Results: Eighty-two patients were eligible and median follow-up duration was 7.0 (range; 2.6-11.9) years. At 6 week, 76 (92.7%) patients responded to Induction A and 79 (96.3%) were in no active disease at last follow-up. OS rates were 100%; however, 22 (26.8%) patients experienced at least one reactivation and 2 (2.4%) patients developed DI. Reactivation rate and DI developing rate were not different between JLSG-02 and -96 cohort (27.3±5.0% vs. 27.6±9.3% at 5-years; p=0.805 and 10.5±8.6% vs. 6.9±4.7% at 10-years; p=0.565, respectively). In JLSG-96, all reactivations occurred within 3 years, while 5/22 reactivations occurred late beyond that in JLSG-02. Conclusions: Modification of treatment from previous protocol has not contributed to reduction of reactivation in LCH with single-system MFB lesions.

Poster Location #16

BONE LESIONS IN LANGERHANS CELL HISTIOCYTOSIS: “SPECIAL SITES” AND OUTCOME

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Purpose: Bone involvement is the most frequent manifestation of pediatric (LCH). “Special Sites” are bone lesions with soft tissue extension that are located in critical anatomic sites in which lesions may cause immediate morbidity. Prognosis varies markedly by age and disease sites at presentation. The site of bone lesions and the outcome the aim of our study. Methods: Thirty two children were diagnosed with LCH and bone involvement and treated in our Unit. All patients are enrolled in this study. The age ranges from 6 months to 11 years (mean: 5 11/12 years). Patients who received chemotherapy were treated according to the LCH protocol. All patients remain in follow-up. Results: Eleven cases (34%) had multiple and twenty one cases (66%) had single bony lesions. The sex ratio (M:F) was 1.9:1. Lytic lesions in skull are found in 19 cases. Five patients (16%) had lesions in spine found in C1-C2, C1-C2-C3, C1, T4, and L3 respectively. Long bones involvement was found in 5 cases, pelvic involvement in 6 cases. Three patients (9%) presented with “Special Sites” lesions. Fifteen cases received chemotherapy according to the LCH protocol. Four cases (12%) had a reactivation within 1-3 years from the diagnosis. They achieved second remission. All cases remain in remission, apart from one case with lost follow up. Conclusion: LCH with bone involvement had a higher incidence in males. Lesions in “Special Sites” have a risk of morbidity but chemotherapy eliminates the risk. The LCH protocol gives a good outcome in cases with bone lesions in “Special Sites”.

Poster Location #17

CLINICAL PRESENTATION AND OUTCOME IN CHILDREN WITH JUVENILE XANTHOGRANULOMA

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Purpose: Juvenile xanthogranuloma (JXG), is an uncommon histiocytic disorder. It is usually benign, infiltrating the skin, with high incidence in infants. JXG with systemic (extracutaneous) involvement has significant morbidity and occasional deaths. Aim of our study is the spectrum of clinical presentation and the outcome of JXG in childhood. Methods: Six children, who were diagnosed with JXG first and treated in our Unit, were enrolled in this study. The diagnosis of JXG confirmed with biopsy. All patients were treated according to the LCH protocol. All patients remain in follow-up. Results: Three cases (50%) had systemic JXG while the other 3 cases (50%) presented only with skin lesions. Two cases (33%) with systemic disease had abnormalities in blood counts and liver while one case presented only with brain involvement. Patients with skin lesions had infiltrations in the scalp, trunk, arms and legs. The age of diagnoses ranged from 30 days to 5 years (median: 7.5 months). Two cases with systemic JXG were diagnosed at the age of 30 days and 3 months respectively while case with brain involvement diagnosed at the age of 5 years. Patients with skin lesion diagnosed under the age of two years. All patients with systemic JXG received chemotherapy. Five out of six cases remain in first remission. Reactivation of the disease was not noted. Patient with brain involvement died from the disease. Conclusion: The onset of JXG is early in life, with exception the case with brain infiltration which occurred in older age. Our study highlights the clinical heterogeneity of JXG. There is a favorable outcome even in severe cases of systemic disease while the brain involvement has a fatal outcome.
LANGHERHANS CELL Histiocytosis: one center experience

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Purpose: Diagnosis and follow-up of Langerhans cell histiocytosis (LCH) patients at our center were evaluated in this study. Material and Methods: Retrospectively the files of the LCH patients treated at our center were analyzed. Results: During the 23 year of follow up, 80 patients (56 boys and 24 girls) were diagnosed with LCH. Seventy of these patients were treated at our center. Fourteen patients with one system organ involvement and 4 patients with one system multifocal involvement were treated with curretage-excision of the tumour; one of these patients had a local nux and treated successfully with re-excision. Three patients received systemic chemotheraphy (prednisolone and etoposide) after curretage; no relapse occurred. Five patients with one bone involvement received radiotherapy to the involved side; relapsed occurred at 3 of these patients but all had gone into remission with treatment (1 patient received systemic chemotheraphy an 2 had excision of the lesion). Remission was achieved at patients with soft tissue involvement with local intralesional steroid therapy (n:1) and local steroid (n:3) treatment. One patient had regression of the tumour spontaneously. Twenty seven of the patients with systemic involvement received prednisolone + vinblastine, 13 received prednisolone + vinblastine + etoposide and 3 patients received prednisolone + vinblastine + methotrexate. Respectively 7, 4 and 1 of these patients had relapse. Six of these patients had 2, 4 of these patients had 3 and 2 of these patients had 4 times of relapses. One of these patients died after the second relapse. The rest 11 patients are in remission. Four patients with multi system involvement died during treatment due to progression of the disease. Conclusion: Langerhans cell histiocytosis is a disease that involves multiples organs. Systemic or local treatment has a good response but 20-25 % of patients might have relapses.

Poster Location #20

Isolated suprasellar lesions with progressive pituitary dysfunction and negative tumor markers: clinical course and management

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Purpose: isolated suprasellar lesions without elevated tumor markers (alpha-fetoprotein -α-FP/ beta-human chorion gonadotropin -β-HCG) nor other Langerhans cell histiocytosis (LCH) peripheral lesions are difficult to manage. Obtaining biopsy material carries significant risks and slow progression is not indicative of a “benign” diagnosis. We report 3 cases where prompt biopsy lead to definitive diagnosis and appropriate treatment. Methods: Case 1: A prepubertal 8yo girl was evaluated for short stature (height percentile decline from 50-<5% / 3years). Diabetes insipidus (DI), growth hormone deficiency (GHD) and adrenocorticotropic hormone (ACTH) deficiencies were diagnosed. Magnetic resonance imaging revealed mass in the sella turcica and suprasellar region with heterogeneous, intense contrast enhancement, displacing the optic chiasm. Case 2: An adolescent 15.5yo girl was followed for 2.5 years for DI and irregular menses, with a known slow-growing upper pituitary stalk thickening (3.8mm, pre-surgery 5.5mm). Hypogonadotropic hypogonadism, central hypothyroidism, DI, GHD and hyperprolactinemia were noted. Case 3: A 2.5 y/o girl with new onset DI, developed central hypothyroidism and ACTH deficiency over a 9 month period, together with a 0.6cm (fast-growing: pre-surgery 1.4cm) lesion of the upper pituitary stalk. Results: All patients in excellent clinical status had no other lesions on extensive imaging. Repeated serum/cebrospinal fluid (CSF) α-FP and β-HCG measurements were low. Their families were under the impression that they had a “benign” condition. Following repeated consultations, they were persuaded to proceed to transsphenoidal biopsy (Case 1&2, postmenopausal period referred to our Rare Tumors Center (CRTR) in October and November 2014 respectively. Material and Methods: The first patient is a 43 years old woman presenting a multisystemic progressive involvement disease, started in 2005 with lung site. After thyroid progression she was referred to our centre where we observe a potential vulvar involvement confirmed by pathological examination. The second patient is a 59 years old woman monitored for a suspected parenchimal brain lesion never histologically analyzed, which underwent to a vulvar biopsy for local discomfort. In both of them the microscopic findings revealed ulcerated, keratinized stratified squamous epithelium and, under this, neoplastic cell infiltration both in the superficial and deep dermis. Immunohistochemistry showed strong positivity for S-100, vimentin, CD1a, and CD68 and weak positivity for Ki-67 in these cells. BRAF V600E mutation was found in the second patient by gene test, negative the result for the first one. They were started to chemotherapy according to schedule Vinblastine plus prednisolone for 18 months. Overall response rate and local disease control were evaluated. Results: After 18 months of chemotherapy, brain disease was stable and vulvar disease had complete response in the second patient, only a symptomatic relief was obtained in the first patient. Conclusion: These two case reports demonstrate that vinblastine plus prednisolone single-agent is an efficacy treatment for local control and symptomatic relief for vulvar LCH advanced with an acceptable toxicity and an improved patientsâ€™ compliance. Further studied are needed to establish the correlation between this two rare sites of LCH.

Poster Location #19

Simultaneous vulvar and parenchial brain Langerhans cell histiocytosis: association or coincidence?

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Background: Vulvar and parenchial brain are very rare sites of Langerhans cell Histioctyosis (LCH) and there is still no universally accepted treatment protocol available both for vulvar and brain LCH. We present two interesting case reports of two female patients in
uneventful) or endoscopic biopsy (Case 3, improving hemiparesis). Pathology results: malignant germ cell tumor (Case 1&2) and LCH (Case3). Resolution of the masses followed appropriate etiological treatment. Conclusion: Suprasellar lesions, without positive serum/CSF markers nor accompanying imaging findings can be biopsied promptly. Age, degree of pituitary impairment or velocity of symptom/mass evolution cannot accurately elucidate the diagnosis. Histologically proven diagnosis benefits patients’ long-term health with prompt etiological treatment.

Poster Location #21

A CASE REPORT OF PULMONARY LANGERHANS CELL HISTIOCYTOSIS DIAGNOSED USING CD1A IMMUNOSTAINING OF BRONCHOALVEOLAR LAVAGE CELLS
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Purpose: Pulmonary Langerhans Cell Histiocytosis (PLCH) is a rare interstitial lung disease that occurs in approximately 10% of all LCH patients. The signs and symptoms of PLCH are nonspecific and characteristic radiographic findings is the most valuable clue for diagnosis. Although an open lung biopsy is needed for definite diagnosis, it is invasive and can yield a non-specific result. Here, we report a case of PLCH diagnosed using bronchoalveolar lavage (BAL) cytology. Methods: A 5-month-old girl was transferred due to incidental finding of a huge cystic mass in her left upper lobe (LUL) on chest x-ray and multiple cystic lesions on chest CT scans. She didn’t have any respiratory symptoms, fever, weight loss or abnormal finding on physical examination except for a right PLCH diagnosis.

Pneumothorax is one of the main and very suggestive symptoms of lung involvement in PLCH patients. However in some patients in spite of this event patients were not correctly diagnosed or were expecting diagnosis for a long time. In PLCH, stopping of cigarette smoking is the most important advice, and immediate, right diagnosis can not be overestimated. Material and Methods: Out of 90 patients with PLCH collected in our database 29(30%) had a pneumothorax as a symptom of pulmonary lesions preceding diagnosis. In this group, 18(62%) patients (ND) were diagnosed usually in a period of month, but 11(38) patients (D) expected diagnosis for 4 to 120 months (mean 38 months) Results: Persistent leak of air, resulted in subsequent surgical procedures and diagnosis, was observed in 4(14%) patients in ND group (p=0.007). Recurrent pneumothorax was the most frequently diagnosed in ND group than in D group (9 vs. 5 patients : p= 0.009) and was observed 1-72 months from the first episode (mean 32 months). Computer tomography was performed in all patients in ND group but in no case in D group (p=0.0009). Wrong diagnosis influenced on very long time of diagnosis delay in two patients. Patients who had pneumothorax as a first symptom were younger (27.7 vs. 39.9; p=0.0001), smoked less (8.4 vs.19 pack/years; 0.003), had significantly lower mean values of FVC (77.96 vs. 89.2;p=0.015), FEV1 (68.5 vs. 79.4 ; p= 0.03, and TLC (90.6 vs. 104.7; p= 0.007) than patients who had no pneumothorax. Conclusions: Patients who had pneumothorax as a first symptom of PLCH in spite that they were younger displayed the higher respiratory impairment than patients who had no pneumothorax. CT in patients with pneumothorax significantly influence right PLCH diagnosis.

Poster Location #22

ANALYSIS OF DIAGNOSIS DELAY IN PATIENTS WITH PLCH WHO HAD PNEUMOTHORAX AS A FIRST SYMPTOM
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Purpose: NACHO was formed to advance the care of patients with LCH and related disorders through the integration of cooperative etiological, mechanistic, and clinical research. NACHO’s aims are to: 1) Develop a network for the advancement of clinical, translational, and basic research in LCH; 2) Advance research through the implementation of high-impact clinical trials and organized collection of well annotated clinical data and biology specimens; and 3) Define LCH pathogenesis and develop risk-stratification strategies with tissue samples from patients treated on
NACHO trials. Methods: NACHO is developing an infrastructure that leads to good organizational management, leadership and sustainability and will integrate the 12 member institutions. Steering, Clinical Studies, and Scientific Committees have been established. There is an Operations Center at Dana-Farber Cancer Institute and a center for biology studies at Texas Children’s Hospital. NACHO held its first meeting in October 2014 at the Histiocyte Society Annual Meeting and has monthly conference calls. Results: A Master Agreement for NACHO sites has been completed; riders for all NACHO studies will be written and executed, streamlining the process for initiating studies that were once a challenge to open at institutions in North America. Two studies, the LCH-IV and LCH-CLO (phase II study of clofarabine), have been activated, and the biology study ‘LCH-BIO: Protocol for the Advancement of LCH Biology’ will open as a companion study to the clinical trials. Conclusions: The general structure of the consortium has been established, key personnel have been hired, two clinical trials are being activated, and a biology initiative, including a protocol for collection of specimens that will be linked to the clinical trials, has started. St. Baldrick’s Foundation’s generous funding has allowed NACHO to take the initial steps to establishing a solid organizational foundation and towards opening a number of high-impact clinical trials.

Poster Location #24

LANGERHANS CELL HISTIOCYTOSIS AND PULMONARY INVOLVEMENT: LONG TERM FOLLOW UP IN 22 PEDIATRIC PATIENTS HAVING PULMONARY FUNCTION TESTS

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Purpose: To report the results of pediatric patients with Langerhans cell Histiocytosis (LCH) and pulmonary involvement (PI) with a long term follow up (FU) having pulmonary function tests (PFT). Methods: Since 1987 to 2009, 124 patients with multisystem (MS) LCH were diagnosed and 50 of them had PI. Twenty two of these patients performed clinical exam, chest X-ray, CT scan evaluation and PFT (Spirometry, Diffusion Lung Capacity and Plethysmography). Median age at diagnosis was 2.6 years. Results: Nineteen patients had multisystem LCH and 3 had isolated PI at diagnosis (13 female and 9 male patients). Ten out of 22 patients had bullous PI and 6 of them presented pneumothorax at diagnosis (3 of them had isolated PI). The other 12 patients had a mild to moderate diffuse interstitial pattern. Median FU since the diagnosis was 14.1 years (1.7-17.6 years) and all patients were still alive and without active disease at last FU. Fourteen patients had PI at diagnosis of LCH, and 8 patients had PI during FU. At last FU visit, 12 patients had chest X-ray and CT scan without evidence of disease while 10 patients still had a mild pulmonary sequel at last CT scan. Median interval between diagnosis and last PFT was 9 years. PFT were performed during FU and only 5 patients demonstrated a mild restrictive and/or obstructive pattern (all of these had previous bullous PI and 1 of these had mild respiratory symptoms with physical efforts). Four patients had abnormal PFT at diagnosis that became normal during FU. PFT were always normal in the other 13 patients. Conclusion: Good outcome with low incidence and severity of lung sequel was found in the 22 patients with PI evaluated with CT scans and PFT, with a long term FU.
Women with HLH Carry Genetic Variants Affecting Protein Expression of X-Linked BIRC4 and SH2D1A Genes

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Purpose: Defective X-linked inhibitor of apoptosis (XIAP) and SLAM-associated protein (SAP) can cause hemophagocytic lymphohistiocytosis (HLH) in male patients. Recent reports show female patients diagnosed of HLH as well as with incomplete forms of the disease carrying heterozygous mutated BIRC4 (XIAP) or SH2D1A (SAP) genotypes. We aimed to analyse these two X-linked genes in women with late-onset HLH. Methods: 8 women from 13 to 56 years-old fulfilling HLH diagnosis. Coding exons and exon-intron boundaries of XIAP/BIRC4 and SH2D1A genes were amplified and sequenced. Single nucleotide variation (SNP) identification, position in the coding sequence and allele/genotype frequencies data were obtained from dbsNP database and Ensembl project. In silico tools SIFT and POLYPHEN-2 were used. Results: We founded the SNP rs5956583 (c.1268A>C; Q423P) is 5/8 patients; 2 homozygous and 4 heterozygous for this polymorphism. Allele frequency for C nucleotide is 0.325 and female frequencies for A/A, A/C and C/C genotypes are 0.24, 0.21 and 0.07, respectively. Q423P is located close to the UBA domain of XIAP and predicted to be a tolerated change. Genetic analysis of SH2D1A revealed a novel point mutation in the gene encoding ORAI1, the pore-forming subunit of the Ca2+-release-activated Ca2+ (CRAC) channel. Interestingly, early T cell activation (CD25/CD69) functioned normally, but CD40L-upregulation was severely impaired. In line with the few other reported cases of CRAC channelopathies, our patient suffers from muscular hypotonia, mydriasis, and anhydrotic ectodermal dysplasia. Conclusion: This instructive case illustrates that the full clinical picture of HLH including functionally impaired cytotoxicity can develop in patients with a TINK cell activation defect. It provides further evidence that lymphocyte activation is not needed in all forms of this heterogeneous syndrome.

Poster Location #27

CMV-Associated Hemophagocytic Lymphohistiocytosis as Presenting Sign of SCID Due to ORAI-1 Mutation

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a heterogeneous, hyperinflammatory syndrome defined by the HLH-2004 diagnostic criteria. These criteria aim at identifying patients with familial HLH, but the syndrome can also occur in other primary immunodeficiencies without genetic defects typically predisposing to HLH. Purpose of this case report is to elucidate the necessity of lymphocyte activation in this syndrome. Methods: We report on a case of HLH in a patient with a lymphocyte activation defect due to ORAI1 mutation. Patients’ lymphocytes were functionally analyzed by flow cytometry. Results: The patient presented with a severe, postnatally acquired cytomegalovirus (CMV) infection and developed clinical features of HLH with fever, cytopenia, splenomegaly, elevation of ferritin, triglycerides and sCD25. NK cells from the child displayed defective cytotoxic granule exocytosis, pointing towards a primary form of HLH. However, genetic testing revealed no mutations in known familial HLH genes. Upon steroid treatment HLH symptoms ceased, but the CMV infection remained poorly controlled. Additionally, the patient developed pneumocystis jiroveci pneumonia, prompting further immunological studies. T cells were present in normal numbers, but poorly activated despite severe CMV infection. Moreover, they showed an impaired proliferative response in vitro. We identified impaired Ca2+-flux as the cause of abrogated T cell activation. Genetic analysis revealed a novel point mutation in the gene encoding ORAI1, the pore-forming unit of the Ca2+-release-activated Ca2+ (CRAC) channel. Interestingly, early T cell activation (CD25/CD69) functioned normally, but CD40L-upregulation was severely impaired. In line with the few other reported cases of CRAC channelopathies, our patient suffers from muscular hypotonia, mydriasis, and anhydrotic ectodermal dysplasia. Conclusion: This instructive case illustrates that the full clinical picture of HLH including functionally impaired cytotoxicity can develop in patients with a TINK cell activation defect. It provides further evidence that lymphocyte activation is not needed in all forms of this heterogeneous syndrome.

Poster Location #28

Allogeneic Hematopoietic Stem Cell Transplantation in Hemophagocytic Lymphohistiocytosis (HLH) and Associated Immunodeficiencies: Cases Reported in Spain

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Purpose: Allogeneic hematopoietic stem cell transplantation (HSCT) is the definitive therapy for some primary immunodeficiency syndromes, such as familial hemophagocytic lymphohistiocytosis (FHLH). Associated life-threatening complications have been reduced but they remain significant. AIM: To review HSCT performed in children diagnosed with FHLH and other immunodeficiencies related to HLH (ID-HLH) in Spain. Methods: Review of epidemiological and clinical data, conditioning and GVHD therapies, complications and evolution of transplanted FHLH and ID-HLH children registered in GETMON and Spanish HLH-2004 database. Analysis was performed by using SPSS. Results: In the last 15 years (2000-2014), 32 HSCT were performed in patients with HLH (17M/15F) in 7 Spanish hospitals. FHLH in 27 and associated syndromes: 3Chediak-Higashi, 2Griscelli-type2. Median age at HLH diagnosis was 0.53 years-old and median age at HSCT was 2.05 year-old. Time between diagnosis
and HSCT varies from 2.3 months to 6.89 years with median of 0.84 years. Stem cells sources were 18 bone marrow, 9 umbilical cord blood and 5 peripheral blood. Five HSCT were related and 27 from unrelated donors. Conditioning regimes varied in different hospitals. Mortality was high (16 cases) and complications included infections, hemorrhages, GVHD, VOD. Follow-up time: from 1 m to 13.89 years. Outcome: 16 patients died and 15 are alive. Mortality rate was higher when cord blood or peripheral blood SCT was used comparing to bone marrow.

Conclusions: Although the definitive cure of FHLH, Griscelli and Chediak-Higashi is only achieved by HSCT, the mortality remains too high (50%) in our country. Time between diagnosis and HSCT is longer in Spain than recommended, so we need to start donor search, select source and referral to HSCT reference centers earlier. Results were worse in cord blood and peripheral blood SCT. Specific recommendations should be disseminated in Spain; HLH diagnosis and HSCT should be performed in reference and accredited hospitals.

Poster Location #29

ANTI INTERFERON-GAMMA (IFNγ) MONOCLONAL ANTIBODY TREATMENT IN A CHILD WITH NLRC4-RELATED DISEASE AND SEVERE HEMOPHAGOCYTIC LYMPHOMA (HLH)

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Purpose: Animal and humans data suggest that IFNγ plays a pathogenic role in HLH. A pilot trial in primary HLH with NI-0501, an anti-IFNγ monoclonal antibody, is ongoing. Mutations in NLRC4 have recently been reported to cause recurrent macrophage activation syndrome and increased production of IL-18, that is known to induce IFNγ. Methods: We report safety and efficacy of NI-0501 in a patient, carrying an NLRC4 mutation with severe recalcitrant HLH. Results: The patient presented at 20 days of age with fever, hepatosplenomegaly, pancytopenia, hypofibrinogenemia, hypertriglyceridemia, hyperferritinemia and sCD25 levels (6 pg/ml) and high tissue levels of CXCL9 (5670pg/ml) and CXCL10 (4400pg/ml). NI-0501 allowed control of all HLH features, while enabling glucocorticoid tapering. No safety concern emerged.

Poster Location #30

PRF1 MUTATION VERSUS PERFORIN EXHAUSTION: TWO DIFFERENT SETTINGS FOR HLH DEVELOPMENT

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Purpose: Mutations in PRF1 gene may lead to defective perforin-mediated cytotoxicity and hemophagocytic lymphohistiocytosis (HLH). However, a loss of perforin content and diminished cytotoxicity is also associated to serial killing and exhaustion of normal NK-cells. We describe two HLH pediatric patients with different clinical and genetic features but a similar pattern of perforin expression. Methods: NK-cells and perforin expression were measured by flow cytometry (BD-Bioscience). NK-cell cytotoxicity was analyzed using Cr51labelled-K562 target-cells. Genomic DNA was amplified and directly sequenced. Results: Patient#1: non-consanguineous 17 months-old male with HLH and Leishmania donovani infection. At diagnosis, NK-cell counts were 2% with 93 cell/µl (normal-age ranges: 3-16%; 100-1400 cell/µl). Perforin expression (mean fluorescence intensity, (mfi): 14) was within normal range (11-54) albeit lower than the daily control, with null cytotoxic function. PRF1 sequencing found no pathogenic mutations. Following HLH-2004 and antimicrobial treatment, perforin expression and NK-cytotoxicity were restored. 8 years after diagnosis, he remains asymptomatic. Patient#2: consanguineous 3 years old male with atypical, neurological HLH presentation. NK-cell counts were 9%, 288 cell/µl (normal-age ranges: 4-23%; 100-1000 cell/µl) with detectable perforin (mfi: 22) although lower than the daily control. NK-cytotoxicity was absent. PRF1 sequencing showed P459L, a pathogenic mutation allowing protein expression and maturation. The patient underwent HLH-2004 protocol and hematopoietic transplantation and he is currently alive. Conclusions: Perforin exhaustion is described as part of the immune hyperactivation during infectious diseases and cancer. Patient#1 demonstrates that a transient perforin reduction can lead to HLH, and how graded differences in cytotoxic molecules and functions complicate clinical phenotype and genotype correlations. Therefore, a dull protein expression may be found in perforin exhausted NK-cells from wild-type PRF1 carriers as well as in patients with deleterious (L459P) or hypomorphic (A91V) PRF1 genotypes. A complete laboratory workout is essential for an accurate diagnosis and a better understanding of HLH pathogenesis.

Poster Location #31

HEMOPHAGOCYTIC LYMPHOMA. EIGHT ADULT CASES WITH DYSPLASIA IN A PUBLIC GENERAL HOSPITAL IN SPAIN

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome that can be either primary or secondary. In adults it is usually secondary, and associated to other causes. Its clinical manifestations are nonspecific and the diagnosis should be actively pursued. Patients often have rapid
failure of multiple organs and systems with fatal outcome if untreated. Pathophysiology focuses on cytokine dysfunction resulting in accumulation of activated macrophages and lymphocytes on multiple organs. Hemophagocytosis is the key pathological finding, although not essential for diagnosis. Prognosis is poor, but early diagnosis and aggressive use of protocols with etoposide seems to improve survival. Material and methods: eight patients were diagnosed with HL since 1989 in our Hospital. They were all adults, median age 73 (21-83), male/female ratio 1/1. Associated cause could be established in six cases: two T-peripheral lymphocytis, one Hodgkin’s lymphoma, one Kaposi associated Herpes Virus Type 8 infection, one Crohn’s disease and one necrotizing infanadensitis. Five patients died soon after diagnosis. Clinical evolution was very aggressive in patients with lymphoma. Almost all patients showed a very significant reduction of erythroid precursors and dysplastic features, particularly striking in erythroid lineage. Two cases treated with HLH-94 protocol are alive 10 and one month after diagnosis. One case responded to empiric steroid, and remains asymptomatic after 12 years. Conclusions: HL syndrome is poorly understood, very aggressive, and it diagnosis can be challenging. The presentation, with fever, cytopenia, organomegaly, quick progressive involvement of multiple organs, should clinicians be aware of HL diagnosis, specially when hemophagocytosis is founded on histological samples. Once diagnosis is established, supportive treatment and underlying search of associated diseases should be initiated. If patients are critical, intensive treatment with specific chemotherapy protocols should be started, within a clinical trial when available. It is necessary to determine the significance of dysplastic features observed in our cases.

Poster Location #32

RESPONSE TO NI-0501, AN ANTI-IFNγ MONOClonAL ANTIBODy, IN A PATIENT WITH REFRACTORY HLH AND MULTIPLE INFECTIOUS COMPLICATIONS

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Purpose: Refractory HLH carries a very poor prognosis. Though therapy with agents such as alemtuzumab has been reported effective, it carries significant risks related to profound immune suppression. Targeted therapy against interferon gamma (IFNγ) is a potentially promising approach for HLH. Methods: A 2 year old boy was transferred to our hospital with severe, refractory HLH. He presented 2 months earlier with acute EBV-associated HLH. He initially received etoposide, dexamethasone, and rituximab, but continued to be persistently febrile, severely pancytopenic, coagulopathic, with unrelenting elevation of inflammatory markers. By the time of transfer to our hospital he had multiple infectious complications: EBV viremia consistently > 1 million copies/ml, new onset CMV viremia >10,000,000 copies/ml, adenoviremia, and bacteremias. He was also experiencing gastrointestinal and CNS bleeding. Soon after transfer, he experienced fungal sepsis with Trichosporon, complicated by worsening CNS hemorrhage and renal failure. Withdrawal of care due to futility was discussed, but family refused. NI-0501, administered under an FDA-granted emergency IND, was started along with anti-fungal and anti-viral medications. Results: Within hours of the first dose of NI-0501 he defervesced, and within 10 days he displayed notable improvement of all HLH indices. Remarkably, within 2 weeks of starting NI-0501, the patient experienced resolution of persistent fungemia, a dramatic decreases of multiple viremias, and was extubated. Gluocorticoids were rapidly discontinued. Over the ensuing 3 months the patient had a complete resolution of HLH features, recovery of renal function (GFR>60), and displayed intact neurologic/developmental status. The patient is currently off NI-0501, with genomic studies pending. Pharmacodynamic studies revealed remarkably elevated IFNγ levels which responded to NI-0501 therapy. Conclusion: The dramatic response to treatment, associated with resolution or substantial improvement of all active infections, and the favorable safety profile, strengthen the rationale for targeting IFNγ in HLH, in first and second line.

Poster Location #33

SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: ISTANBUL PERSPECTIVE

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Background: Secondary hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hematologic condition resulted from many diseases such as infections, malignancies, immune deficiency syndromes, and rheumatologic and metabolic disease. Clinical and laboratory findings are fever, splenomegaly with and without hepatomegaly, cytopenias, elevated liver enzymes, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia. Aims: To evaluated the clinical profile and the treatment of secondary hemophagocytic lymphohistiocytosis in children. Methods: Secondary HLH, who were admitted to the Istanbul Faculty of Medicine, Department of Pediatrics from January 2003 through December 2014, were retrospectively evaluated. Results: There were 38 secondary HLH cases, of that 49 % were females and the mean age was 6.7±4.2 (range: 1-17.0) years. Primary causes were determine rheumatological diseases in sixteen, malignancies in eleven, infectious diseases in seven, metabolic disorder in one, epilepsy in one, hemolytic anemia in one, and chronic granulomatous disease in one cases. Mean ferritin value was 22939.8 ± 28312.3 (range: 1114-100 000) ng/mL. Six cases (7.9%) were treated with high dose methylprednisolone (HDMP), three (7.9%) with intravenous immunoglobulin (IVIG) only; four (10.5%) with HDMP+plasma exchange (PE); 10 (%26.3) with HDMP+PE+IVIG; 12 (31.5%) with HDMP+IVIG; 2 (5.2%) PE+IVIG, and one (2.6%) with standard steroid treatment. Conclusion: HDMP is a very effective treatment especially for severe cases with secondary HLH. In case of progressive disease adding PE + IVIG is an important issue.

Poster Location #34

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN ADULTS: RESULTS OF THE GERMAN HLH REGISTRY

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POSTER PRESENTATIONS - CLINICAL HLH

Purpose: Hemophagocytic Lymphohistiocytosis in adults (aHLH) is a diagnostic challenge. The absence of valid diagnostic criteria for adults often delays diagnosis. Since data on aHLH in Germany are not available, a national multicenter registry was initiated (www.hlh-registry.org). Methods: Patients (pts) with suspected aHLH were recruited from 19 institutions. To diagnose HLH, five out of eight pediatric HLH-2004 criteria had to be fulfilled. HLH diagnosis was validated by using the diagnostic H-Score (http://saintantoine.aphp.fr/score/). Clinical characteristics, laboratory findings, treatment and outcomes were collected. Results: From August 2010 to April 2015, 76 pts (33 female), median age 49 (17-81) years were enrolled. 57 pts fulfilled the HLH-2004 criteria. 52/57 pts achieved a probability of having HLH higher than 90% using the H-Score. Trigger diseases were neoplasia in 19/57 pts (lymphoma n=14, acute leukemia n=4, other malignoma n=1), infections in 20/57 pts (EBV: 14/20). In 4/14 pts, EBV-HLH developed after allogeneic stem cell transplantation (allo-SCT) for AML (n=2) and severe aplastic anemia (n=2). Two pts were co-infected with EBV and H1N1 or HIV respectively. Other viral triggers were HIV, Parvovirus B19, HHV8 and CMV. 10/57 pts developed acquired HLH due to AID. The underlying trigger could not be identified in 8 cases. In 2 pts with infection-associated HLH and 1 pt with unknown trigger genotyping revealed hereditary HLH. 37/57 pts were treated with corticosteroids, 22/57 pts with etoposide and 22/57 pts received i.v. immunoglobulins. Allo-SCT was performed in 1/57 pts. Conclusions: Trigger diseases identified are in accordance with the literature, with infections and neoplasia among the main causes for aHLH in Germany. Diagnostic accuracy using the HLH-2004 criteria was 75%, and even lower using the H-Score. The German aHLH web-based registry aims to improve on diagnostic vigilance and accuracy, and is open for cooperative registry studies.

Poster Location #35

TOTAL BODY IRRADIATION-BASED MYELOABLATIVE CONDITIONING REGIMENS FOR ALLOGENEIC PERIPHERAL BLOOD STEM CELL TRANSPLANTATION: A NOVEL TREATMENT MODALITY FOR ADULT HEMOPHAGIC LYMPHOHISTIOCYTOSIS

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Purpose: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective therapeutic measure for curing hemophagocytic lymphohistiocytosis (HLH) through immune reconstitution and hematopoietic reconstitution. Total body irradiation (TBI)-based myeloablative conditioning was reported in treating adult HLH. Methods: We conducted a retrospective study of 22 adult HLH transplanted for primary HLH (n=6), tumor-associated HLH (n=7), Epstein-Barr virus-associated HLH (n=8) and underlying disease-unknown HLH (n=1) using TBI-based myeloablative conditioning and peripheral blood stem cells (PBSCs) as the graft source. Results: 10 patients were in nonremission and 12 were recurrent at time of HSCT. 16 patients were transplanted from HLA-haploidentical family donors, 5 from HLA-identical sibling donors and 1 from a matched unrelated donor. The conditioning regimen was TBI/etoposide /cyclophosphamide ± anti-thymocyte globulin. After transplantation, 4 patients with haploidentical pairs were mixed chimerism and 18 were full donor myeloid chimerism by day +30; no patient presented with graft failure. The cumulative incidence of grades II-IV and III-IV acute graft-versus-host disease (aGVHD) were 27% and 9%, respectively. The cumulative incidence of chronic GVHD (cGVHD) was 36%. The incidence of posttransplant lymphoproliferative disorders was high up to 23%. With a median follow-up of 13.5 months, the relapse cumulative incidence was 9.1%, the nonrelapse mortality was 27.3% and the estimated 2-year overall survival (OS) was 63.8%. Compared with the 225 adult HLH patients who had the same etiology and did not receive transplant at the same period, 22 patients had a significantly higher 2-year OS ($\chi^2=9.064$, P=0.003). Conclusion: TBI-based myeloablative conditioning for allo-PBSCT is a safe and effective treatment for adult HLH to achieve cure and long-term survival. The ability to advance HSC engraftment makes TBI-based myeloablative conditioning a promising transplantation platform for the integration of postgrafting strategies to reduce rate of graft failure.

Poster Location #36

UTILITY OF MARKED HYPERFERRITINEMIA IN DIAGNOSING HEMOPHAGIC SYNDROME IN ADULTS

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Purpose: Hemophagocytic syndrome (HLH, hemophagocytic lymphohistiocytosis) is a devastating hyperinflammation, which without treatment leads to death. In adults it is highly underdiagnosed, due to the resemblance of other inflammatory states. Hyperferritinemia >500 µg/L is one of the eight HLH-2004 diagnostic criteria, but typically it reaches higher values: even around 10,000 µg/L or in some cases up to 100,000 µg/L. Such marked hyperferritinemia can sometimes be effect of other causes like Still’s disease or extreme cases of acute liver failure. While diagnostic utility of extreme hyperferritinemia in HLH in adults is questioned by some authors, we addressed this problem by analyzing the ferritin concentrations in two large clinical centers: Medical University of Warsaw (WUM) in Poland and University Medical Center Hamburg-Eppendorf (UKE) in Germany. Results: In our cohorts marked hyperferritinemia was a relatively rare finding. In the recent years at WUM for which the number of all ferritin evaluations was available, ferritin levels above 10,000 µg/L were found in only 57/3,404 (1.6%) patients, while at UKE it was even less: 83/17,685 (0.5%). At WUM in patients with marked hyperferritinemia strong overrepresentation of HLH patients was observed: 17% (6/35) over a threshold of 15,000 µg/L and 36% (4/11) over 50,000 µg/L. Additional 6 patients had unconfirmed suspicion of HLH fulfilling 4/6 available diagnostic criteria. Data from UKE revealed another cause of high hyperferritinemia - the period around hematopoietic stem cell transplantation (SCT). In this center over one third of patients (30/83) with ferritin above 10,000 µg/L was hospitalized at SCT Unit while only one of them had lymphoma-induced HLH. Conclusion: Marked hyperferritinemia, combined with clinical picture, can indicate high risk of hemophagocytic syndrome and should always cause assessment of other diagnostic criteria.
Poster Location #37

ACCURACY OF FLOW CYTOMETRIC PERFORIN SCREENING FOR DETECTION OF PATIENTS WITH FAMILIAL HLH DUE TO PRF1 MUTATIONS

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Purpose: There is no literature to describe the diagnostic accuracy of flow cytometric screening for perforin deficiency due to PRF1 mutations. In this study we present our experience with flow cytometric screening in over 750 patients suspected to have PRF1 mutations. Methods: We reviewed the results of clinical samples submitted to our Institution for perforin testing between August, 2009 and December, 2014. Samples were classified as having Absent, Low, or Normal expression of perforin based on the MCF of perforin in NK cells. Flow cytometric results were correlated with genetic sequencing results. Results: We observed absent or low perforin expression in 213/751 samples. We excluded carriers and patients with PRF1 sequence variants of uncertain significance. Approximately one-third of the remaining samples with abnormal perforin expression were found to have biallelic disease-causing mutations (positive predictive value [PPV] 32%). Of 50 samples with bi-allelic disease causing mutations, 48 had absent to low perforin expression (96% sensitivity). Among 584 patients with normal PRF1 sequencing, 483 had normal perforin expression (83% specificity). Conclusion: The flow cytometric measurement of perforin has greater than 80% diagnostic accuracy with regard to detection of patients with PRF1 mutations and is a robust screening tool.

Poster Location #38

FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS TYPE 5 CAUSED BY A NOVEL MONOALLELIC STXBP2 MUTATION: CASE REPORT

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Purpose: Familial hemophagocytic lymphohistiocytosis type 5 (FHL5) is usually due to homozygous mutations in the STXBP2 gene, which encodes the syntaxin-binding-protein Munc18-2, thought to be involved in exocytosis of cytotoxic granules in killer T-cells. Spessott and colleagues (Blood, 2015) recently reported two novel, dominant-negative, STXBP2 mutations (194G>A; (R65Q) and 193C>T; (R65W)) resulting in FHL5. We report an additional, novel, dominant-negative mutation. Methods: We describe the case of a 20-month-old girl with hemophagocytic lymphohistiocytosis (HLH) found to have a previously unreported, monoallelic, missense mutation of STXBP2. Results: A 20-month-old girl with a history of chronic diarrhea and two weeks of fever was diagnosed with HLH in the setting of Esteinbarr virus viremia; meeting eight out of 10 criteria. The patient was successfully managed with steroid monotherapy, but had severe HLH reactivation one month later in the setting of parainfluenza virus. Testing revealed decreased neutral killer (NK) cell function, increased soluble interleukin-2 and decreased CD107a expression, indicating abnormal degranulation of NK cells. Next-generation sequence analysis revealed a monoallelic, missense variant in STXBP2 (1586G>C; (R529P)) which confirmed the diagnosis of FHL5, and explained her inflammatory bowel-like symptoms. She did not have a bleeding disorder or hypogammaglobulinemia, which may also be associated with FHL5. Following HLH reactivation, the patient was successfully managed with dexamethasone and etoposide, per the HLH-2004 protocol, and colitis was responsive to sulfasalazine. She is currently undergoing allogeneic bone marrow transplantation with a 9/10 matched-unrelated donor. Conclusion: This case adds to the list of recently described dominant-negative, STXBP2 mutations causing FHL5 and requiring hematopoietic stem cell transplantation for cure.

Poster Location #39

BEYOND SEPTIC SHOCK: A CASE OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A 62-YEAR-OLD MALE

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Hemophagocytic lymphohistiocytosis (HLH) is a relatively uncommon but potentially life-threatening condition brought about by excessive immune activation. Due to its similarity to the clinical syndrome of sepsis and septic shock, it is often underdiagnosed. We were presented with a 62-year-old male, known with laryngeal carcinoma, apparently well, until 4 months prior to admission when he developed fever, cough, easy fatigability, malaise and weight loss. He has had previous admissions during which he was treated with various antibiotics with no relief. During admission, patient was initially managed as sepsis but was noted to have clinical deterioration; the patient developed hypotension and multi-organ failure. Laboratory examinations later showed pancytopenia, hypertriglyceridemia, hypofibrinogenemia, and hyperferritinemia. Bone marrow aspirate were however, negative for hemophagocytosis. Together with other clinical criteria, a diagnosis of HLH was made for which he was given high dose dexamethasone and etoposide (HLH-94 protocol) with significant improvement thereafter. This case illustrates why HLH is underdiagnosed and emphasizes the significance not only of a good history and physical examination but also of a high index of suspicion especially among those with possible triggers. Although the specific trigger in this case is unclear, infection or his underlying malignancy, recognition of HLH was critical in initiating the appropriate therapy and pivotal in the patient’s recovery.

Poster Location #40

VALACYCLOVIR AS AN ADJUNCT TO RITUXIMAB IN THE TREATMENT OF EBV-RELATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A DIDACTIC CASE REPORT AND LITERATURE REVIEW OF ANTIVIRALS FOR EBV COMPLICATIONS

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Purpose: To discuss treatment aspects of hemophagocytic lymphohistiocytosis (HLH), a rare, underrecognized syndrome, usually fatal unless promptly treated and its trigger eradicated. Epstein-Barr virus (EBV) is one cause, also responsible for rare cases of encephalitis, lymphoproliferative diseases (LPD), neuropathies, nephropathies, hepatitis, blood dyscrasias, hypogammaglobulinemia, ARDS, myocarditis,
vasculitis. Methods: We present a 15 year old male with EBV-associated HLH treated with HLH-94 protocol, PLUS Rituximab+Valacyclovir (being investigational for HLH). Induction was successful, with rapid sustained viral clearance. We searched Pubmed terms rituximab+valacyclovir; hemophagocytic + valacyclovir; then replaced valacyclovir serially with valomaciolovir, ganciclovir, penciclovir, acyclovir, foscarnet, famciclovir. Results: In targeting EBV causing HLH without EBV-related LPD (where rituximab may have indication), there have been only five reports of antivirals used UNcombined with rituximab. Interestingly, likely not reflecting actual practice, we found no antivirals been combined with rituximab against EBV, for any aforementioned EBV /manifestation apart from LPD. Our patient with admission viral load 100,000 copies/ml had undetectable viral load post 17 days of therapy, one of the most rapid clearance rates reported. Conclusions: As guidelines for all treatment objectives do not exist here, we report a case where rituximab+valacyclovir were safe and effective, for future review. The much better than average viral clearance for this highly fatal syndrome, in which targeting the cause is pivotal, and the rarity of which makes an RCT extremely difficult, presently compels us suggest rituximab +valacyclovir therapy for consideration. Also, that practices need to get reported for such rare disorders. May we also suggest, for a child with unexplained septic shock /MODS, a ferritin level, D-dimers and triglycerides serve as a low-cost HLH screening; and if results warrant, more specific tests should run immediately. After induction, immunosuppression persists, and fever warrants multiple cultures, as it may mimic reactivation. Involving multiple consultants several times is pivotal in HLH.

Poster Location #41

THE SUCCESSFUL TREATMENT OF RECURRENT CNS DISEASE POST-HEMATOPOIETIC CELL TRANSPLANT (HCT) IN PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

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Purpose: HLH involves the CNS in 37-73% of patients and is associated with higher mortality rates. Current standard of care for CNS disease utilizes high dose dexamethasone therapy and intrastrach methotrexate/hydrocoristosine; however there is no standardized approach to post-HCT CNS monitoring and treatment. Methods: We conducted a single-center retrospective case series to describe the clinical course of five patients (age 2-17 mo) diagnosed with genetic HLH (PRF1 (n=2) Munc 13-4 (n=3)) who underwent HCT (4-UCB, 1-MUD) with myeloablative busulfan (BU) based conditioning regimens (BuCytoxanATG (4) BuFludarabineATG(1)) and had CNS involvement post-HCT. Results: All patients received a graft from an unrelated donor (UCBs (umbilical cord blood): HLA match 5/6 (n=2), 6/6 (n=2); MUD (matched unrelated donor): HLA match 10/10 (n=1) with a median TNC dose of 6.73 x 10^7/kg (range 3.6 x 10^7/kg - 12.8 x 10^7/kg). All patients were serially monitored with monthly surveillance lumbar punctures (LPs) and systemic dexamethasone was used to treat CNS disease. Systemic dexamethasone controlled CNS disease as a single agent in all five patients post-HCT. In three of the cases, CNS relapse was caught by routine LPs, prior to clinical symptoms. All patients are alive, a mean of 33 months post-transplant (range 12-60 months). Four patients have mild neurological deficits: mild speech delay (3) and one patient who exhibited brainstem herniation on day 0, due to CNS HLH, has made a substantial recovery with residual deficits of improving focal weakness on the right side with continued gains in developmental milestones. One patient has no deficits. Conclusion: There is limited literature on treatment and management strategies for CNS involvement post-HCT. This case review supports screening LPs post-HCT for occult CNS disease prior to the development of symptoms and the use of systemic dexamethasone for disease control. Future prospective clinical trials are needed to further evaluate this strategy.

Poster Location #42

CYTOKINE RELEASE SYNDROME (CRS) AFTER CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL THERAPY FOR ACUTE LYMPHOBlastic LEUKEMIA MIRRORS HEMOPHAGOCYTIC SYNDROME (HLH)

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Purpose: Dramatic responses with complete remission rates ~ 90% have been reported in children with relapsed/refractory ALL after treatment with CAR T cells directed against CD19 (CTL019; Maude, et. al NEJM 2014). Marked in vivo CAR T-cell proliferation leads to efficacy and the potential for toxicity, including CRS. To better understand CRS, we studied 39 children treated with CTL019. Methods: 44 cytokines were measured, using Luminex bead array. Results: 36/39 patients developed gr1-4 CRS (CRS1-4). 11 pts developed gr4 CRS (CRS4), defined as requiring high dose vasoactive medications and/or mechanical ventilation. These 11 pts along with 2 pts with gr3 CRS were treated with the IL-6 inhibitor tocilizumab, and all had rapid marked CRS improvement. We hypothesized and demonstrated patients with CRS4 develop clinical and laboratory manifestations similar to MAS/HLH. 5/10 CRS4 pts developed splenomegaly (1pt too obese to evaluate), and 7/10 developed hepatomegaly, whereas no CRS0-3 developed organomegaly. Fibrinogen (not tested in all) was decreased (<150mg/ml) in 9/10 with CRS4 and 2/15 CRS0-3. Ferritin and LDH were markedly clinically and statistically significantly elevated in all CRS4 as compared to CRS0-3. Of the 44 tested cytokines, 16 have been previously studied in pediatric primary HLH. We found an identical pattern of cytokines differentially elevated in HLH also in patients with CRS4 as compared to CRS0-3. Of the 44 tested cytokines, 16 have been previously studied in pediatric primary HLH. We found an identical pattern of cytokines differentially elevated in HLH also in patients with CRS4 as compared to CRS0-3. There was a clinically, statistically, and biologically significant difference in IFN-g, IL10, sIL2Ra, IL6, IL8, MCP1, and MIP1B in CRS 4 vs CRS0-3 and no clinically or biologically significant difference in IL1B, IL2, IL4, IL5, IL7, IL12, IL13, IL17, and TNF-a. IL6 and sIL6R were markedly elevated in CRS4 consistent with IL6 trans-signaling. Conclusions: These data represent the largest and most comprehensive profiling of the clinical and laboratory manifestations of CAR T-cell related CRS and provide novel insights into CRS biology.

Poster Location #43

ADULT EPSTEIN-BARR VIRUS ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IS A FATAL DISEASE: 68 CASES IN A SINGLE CENTER

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Purpose: In children, EBV-HELH had good outcomes, but outcome in adults was unclear. We presented data in our center to make further understanding and looking for an appropriate treatment in adult EBV-HELH.
Methods: 110 adult HLH cases with EBV-DNA positive at diagnosis were collected between March 2009 and January 2015. Exclude the malignancy and genetic ones, 66 cases were due to EBV infection only. Analyze clinical features, treatments and outcomes of them. Result: The median age was 27 years (14-78). Median EBV load at onset was 7.0E+05 (5.8E+03~6.4E+08) copies/ml. 75% patients used HLH-94/04 regimen as initial treatment. ORR was 68.2%, including CR 46%, PR 22.2%. The efficacy of HLH-94/04 regimen was superior to others (p=0.001). A recurrence was seen in 79.1% cases. The median PFS was 4.5 weeks (2-48). No long-time remission was seen in variable salvage regimens. ORR was 50% using HLH-94/04 regimen induced again. Interestingly, 8 refractory or relapse more than once cases were treated with asparaginase accompanying chemotherapy, ORR was 100%, including 3 CR, 5 PR. Nineteen were alive with a median duration 320d (30-920d). Twelve exhibited no evidence of active disease with negative EBV-DNA, while six with positive EBV-DNA were treatment-dependent. 1-year OS rate was 19% in all patients. The median OS time was 93.4d. Patients with low albumin (<25g/L) and fibrinogen (<1.0g/L) at diagnosis had poorer outcomes. Eight patients underwent allogeneic stem cell transplantation (allo-SCT), 4 got continuous remission. 3 died before engraftment, 2 in active, 1 in remission, 1 relapsed and died of CNS involvement. Conclusion: The prognosis of adult EBV-HLH is really poor. Although HLH-94/04 protocol improved rate of remission, high recurrence is still the main factor influencing OS. Asparaginase accompanying chemotherapy maybe an effective salvage regimen. Early identified poor factors and underwent allo-SCT in remission may improve outcomes.

Poster Location #44

HYPERFERRITINEMIA DOES PLAY A ROLE IN DIAGNOSING WITH HLH FOR ADULT POPULATIONS WITH FEVER, CYTOPENIAS, AND HEPATIC DYSFUNCTION (OR) HEPATOSPLENOEMAGLY

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Presented by: Jia Zhang, Fu Li

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Purpose: To discuss hyperferritinemia does play a role in diagnosing with HLH for adult populations with fever, cytopenias, and hepatic dysfunction (or) hepatosplenomegaly. Methods: A retrospective study was carried out in 231 adult patients with serum ferritin levels higher than 5,000 ug/L between January 2012 and December 2014 of Beijing Friendship Hospital, Capital Medical University; Peking University Third Hospital, and the 307th Hospital of Chinese People's Liberation Army. Patients were diagnosed with primary HLH according to the HLH-2004 criteria. Results: In the study, the patients ranged from 18 to 78 years with a median of 42 years. The patients were male in 130 cases (56.28%) and female in 101 cases (43.72%). Ferritin levels ranged from 5,041 to 299,800 ug/L. We identified 231 adult patients with ferritin levels above 5,000 ug/L, including patients were diagnosed with HLH in 103 cases (44.59%). For 231 cases, there were 126 cases with fever (T>38.5°C), cytopenias affecting 2 or more lineages (hemoglobin <90g/L, platelets <100×109/L, neutrophils <1.0×109/L), and hepatic dysfunction or hepatosplenomegaly that were suspected of HLH including patients were diagnosed with HLH in 93 cases (73.81%); patients were not suspected of HLH in 105 cases, including patients were diagnosed with HLH in 10 cases (9.52%). For 113 adult patients with ferritin levels above 10,000ug/L, there were 71 cases with fever, cytopenias, and hepatic dysfunction or hepatosplenomegaly including patients were diagnosed with HLH in 57cases (80.28%); for patients were not suspected of HLH in 42 cases, including patients were diagnosed with HLH in 6 cases (14.29%). Conclusion: Hyperferritinemia does play a role in diagnosing with HLH for adult populations with fever, cytopenias, and hepatic dysfunction (or) hepatosplenomegaly. Limitation: Beijing Friendship Hospital, Capital Medical University is long engaged in diagnosis and treatment of adult HLH that may cause a little data offset.

Poster Location #45

THE SAME MUTATION OF THE XLP-1(EBV-DRIVEN) RELATED GENE WILL CAUSE DIFFERENT AGES OF ONSET IN ONE FAMILY

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Purpose: X-linked lymphoproliferative disease (XLP) is a kind of EBV-driven primary hemophagocytic lymphohistiocytosis. We report the male onsets who are in different ages with the same mutation c.32T>G (p.I11S) of XLP-1 related gene (SH2D1A) in a family. Case report: A 32-year-old man presented to the hospital with intermittent fever (>38.5°C) more than 3 months. The laboratory work-up revealed pancytopenia, elevation of triglycerides (3.98mmol/L), ferritin (>15,000 ng/ml) and soluble interleukin-2 receptor (13,200 U/ml), and decreased NK cell activity. HBV-DNA quantification was 8.8 × 10^6 copies/ml. High-throughput sequencing of primary HLH related genes (PRF1, UNC13D, STX11, STXB2, RAB27A, LYST, AP3B1, SH2D1A, BIRC4, ITK, CD27 and MAGT1): Homozygous missense mutation c.32T>G (p.I11S) was found in SH2D1A. This mutation is novel, which has not been included in dbSNP database or reported. And it is predicted to affect protein function by SIFT and Polyphen2. The SAP expression of the patient was significantly decreased. Allogeneic hematopoietic stem cell transplantation was recommended after HLH-94 chemotherapy, but the patient refused and died after twice of relapses. Family survey of the patient had been performed. We found the patient’s maternal grandfather died at 30 years old with unknown reason. And his nephew (1 year old), who was EBV (+) with the same mutation c.32T>G (p.I11S), was diagnosed XLP-1 during the same period and died within a week after admission. Sanger sequencing was implemented in the patient’s three compatriot sisters, and all of them were found carrying the same heterozygous mutation. Conclusion: This mutation is novel and first reported. In one family, the same mutation of SH2D1A will cause different age of onsets due to EBV driving. The members without symptoms but have family history and carry the same pathogenic mutation, are still the high-risk groups and must be closely observed. SAP detection is a rapid screening method of XLP-1 for male.

Poster Location #46

TREATMENT OF ADULT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS PATIENTS WITH ETOPOSIDE, A SYSTEMATIC REVIEW

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is an immunological disorder in which an exaggerated immune response is ineffectively regulated. The subsequent cytokine storm causes severe septic
symptoms. The cause of HLH is either genetic (primary) or secondary to infections, malignancies or auto immune diseases. The most effective treatment includes etoposide, however solid data on adult patients lack. Therefore we employed a systematic literature study on the efficiency of etoposide in adult HLH patients. Methods: A systematic review is performed with regard to etoposide in adult HLH patients. All English literature in 7 databases has been studied. Two separate researchers assessed the titles and abstracts of the search results for relevant articles. These articles have been read as a whole and relevant data has been extracted. Results: In total 88 articles were judged as relevant. Twelve did not involve identifiable cases. The remaining 76 articles identified 255 evaluable patients. All these publications were case reports or small case series. On average a survival of 42% was found varying from 38% in patients with infectious causes to 51% with malignancies. Furthermore, one article stated that starting etoposide within 4 weeks after setting the diagnosis of HLH corresponds with a better survival. However, our analyses could not support this statement, since in the 57 patients (13% of all analyzed patients) registered to be treated within 4 weeks 51% survived, compared to an overall survival of 59% reported in the literature. These figures are undoubtedly biased. Conclusion: In this systematic review on adult patients with HLH treated with etoposide we determine a poor survival. Because our search results only include case reports and case series there is a high probability of bias in this study. More extensive and prospective research is needed to make a definitive conclusion on etoposide and its timing in HLH.
Whole exome sequencing was performed on the matched lesion and achieving remission only after ablative hematopoietic stem cell transplant. Persistent disease despite multiple courses of aggressive chemotherapy, CD163+CD1A liver, spleen, bone marrow, and lungs with a clonal population of CD207CD1A+histiocytes. The patient had persistent disease despite multiple courses of aggressive chemotherapy, achieving remission only after ablative hematopoietic stem cell transplant. Whole exome sequencing was performed on the matched lesion and normal tissue samples. Subsequent in vitro functional analysis was performed to define the functional consequences of identified mutation(s). Identified novel mutation in MAPK1 (ERK2) (c.961G>A) (p.D321N) is localized in the kinase domain of Ras/extracellular signal-regulated kinase 2 (ERK2). In silico analysis of the predicted 3-dimensional structures of wild-type and mutant proteins revealed changes in the catalytic pocket. In vitro analysis revealed that the mutation resulted in constitutive ERK activation. Stimulation of ERK pathway can modulate cell growth, proliferation, survival, and motility through phosphorylation and activation of the p90 ribosomal S6 kinases (RSKs) that lie at the terminus of the ERK pathway. In vitro assays revealed that the ERK2 p.D321N mutation significantly reduced RSK1 Threonine-359 phosphorylation, without exhibiting changes in RSK1 Throneine-573 or Serine-380 phosphorylation, thus suggesting a mechanism which would promote constitutive RSK1 activation by preventing the undocking of ERK from RSK1. The ERK2 p.D321N resulted in increased cyclic AMP response element binding protein (CREB) phosphorylation which might potentially cause increased nuclear translocation and activation of gene expression programs to promote cell proliferation and avoid apoptosis, which are being currently investigated. Recent evidence has highlighted role of somatic mutations in MAPK pathway in the pathogenesis of other histiocytosis disorders like LCH and ECD, highlighting the need to revisit and incorporate MAPK pathway inhibitors into therapeutic strategies for JXG as well as other ERK-associated neoplasias/malignancies.

**Poster Location #47**

**JUVENILE XANTHOGRANULOMA WITH HEPATOSPLENONEMALGY AND PERI-PORTAL / PERI-CELIAC LYMPHADENOPATHY**

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Purpose: Juvenile xanthogranuloma (JXG) is a rare disease often considered to be a type of non-Langerhans Cell Histiocytosis. Most patients present with a solitary cutaneous lesion; however, a group of patients can present with extracutaneous manifestations or even with systemic involvement. We present a 3-year-old male, initially diagnosed at 6-month-of-age, who during follow-up developed hepatosplenomegaly with peri-portal and peri-celiac adenopathy. The patient’s course of therapy is also described. Methods: We report the case of a 3-year-old child with JXG who during follow-up was noted for hepatosplenomegaly with peri-portal and peri-celiac lymphadenopathy on imaging. A review of pertinent literature and patient’s treatment course is also provided. Results: Our patient is a 3-year-old male who was initially diagnosed with JXG at 6-months-of-age by shave biopsy of his hyperpigmented facial lesions. During follow-up course patient was noted for hepatosplenomegaly with peri-portal and peri-celiac lymphadenopathy on imaging. Endoscopic ultrasound guided fine needle aspiration biopsy was performed and clinical picture was suggestive of JXG. Patient’s systemic liver, spleen and lymph node involvement led to administration of immunosuppressive treatment based on the Langerhans Cell Histiocytosis -IV (LCH-IV) protocol. Furthermore, persistence of patient’s disease with continued hepatomegaly and new onset facial lesions led to the transition of several chemotherapeutic medications including Cldarabine (2-CdA), Clofarabine and Cytarabine (Ara-C). Patient is presently on week 3 of the LCH-IV Salvage Therapy with Vincristine (VCR), Ara-C, and prednisone while closely being monitored. Conclusion: JXG is a rare type of non-Langerhans Cell Histiocytosis. Extracutaneous manifestations are rare and additional chemotherapy treatment with close follow-up is often warranted to ensure stability of the disease.

**Poster Location #48**

**MAPK1 MUTATION IN AN AGGRESSIVE CASE OF DISSEMINATED NON-LANGERHANS CELL HISTIOCYTOSIS**

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Juvenile xanthogranuloma (JXG) is a rare, non-Langerhans cell histiocytosis (LCH) that is usually benign and self-limiting. We present a highly unusual case of a pediatric patient with disseminated infiltration of liver, spleen, bone marrow, and lungs with a clonal population of CD163+CD1A+CD207-fascin-factorXIII+ histiocytes. The patient had persistent disease despite multiple courses of aggressive chemotherapy, achieving remission only after ablative hematopoietic stem cell transplant. Whole exome sequencing was performed on the matched lesion and normal tissue samples. Subsequent in vitro functional analysis was performed to define the functional consequences of identified mutation(s). Identified novel mutation in MAPK1 (ERK2) (c.961G>A) (p.D321N) is localized in the kinase domain of Ras/extracellular signal-regulated kinase 2 (ERK2). In silico analysis of the predicted 3-dimensional structures of wild-type and mutant proteins revealed changes in the catalytic pocket. In vitro analysis revealed that the mutation resulted in constitutive ERK activation. Stimulation of ERK pathway can modulate cell growth, proliferation, survival, and motility through phosphorylation and activation of the p90 ribosomal S6 kinases (RSKs) that lie at the terminus of the ERK pathway. In vitro assays revealed that the ERK2 p.D321N mutation significantly reduced RSK1 Threonine-359 phosphorylation, without exhibiting changes in RSK1 Throneine-573 or Serine-380 phosphorylation, thus suggesting a mechanism which would promote constitutive RSK1 activation by preventing the undocking of ERK from RSK1. The ERK2 p.D321N resulted in increased cyclic AMP response element binding protein (CREB) phosphorylation which might potentially cause increased nuclear translocation and activation of gene expression programs to promote cell proliferation and avoid apoptosis, which are being currently investigated. Recent evidence has highlighted role of somatic mutations in MAPK pathway in the pathogenesis of other histiocytosis disorders like LCH and ECD, highlighting the need to revisit and incorporate MAPK pathway inhibitors into therapeutic strategies for JXG as well as other ERK-associated neoplasias/malignancies.

**Poster Location #49**

**CHARACTERISTICS OF MACROPHAGE ACTIVATING SYNDROME (MAS) WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (sJIA) OF A TERTIARY REFERRAL HOSPITAL IN AN-YANG, KOREA**

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Purpose: MAS is potentially life-threatening complication of sJIA and characterized by fever, lymphadenopathy, hepatosplenomegaly, pancytopenia, coagulopathy an multiple organ failure. MAS is currently classified among the secondary hemophagocytic lymphohistiocytosis (HLH). The term has been recently proposed rheumatologic HLH. MAS is not a single feature and hard to distinguish from overlapping features flare of sJIA. So it is important to apply the reliable criteria. Recently new diagnostic definition was proposed on 2014. So we want to know that the new criteria can satisfy the our old data of MAS. Methods: The old data was applied to the new criteria. The old our data were applied and compared with the new criteria. The International consensus conference on MAS classification criteria was proposed on March 22, 2014 in Villa Quarata della Castagna, Genoa, Italy. The final definition is a febrile patient with sJIA is classified as having MAS if the patient has Ferritin > 700ng/L and at least 2 of the following 4 laboratory abnormalities: platelet < 180,000/mL, AST > 50U/L, Triglycerides > 160mg/dL, Fibrinogen < 360 mg/mL. Results: We analyzed 13 MAS with sJIA from 2011 thru 2015. All compared with the new criteria. The International consensus conference on MAS classification criteria was proposed on March 22, 2014 in Villa Quarata della Castagna, Genoa, Italy. The final definition is a febrile patient with sJIA is classified as having MAS if the patient has Ferritin > 700ng/L and at least 2 of the following 4 laboratory abnormalities: platelet < 180,000/mL, AST > 50U/L, Triglycerides > 160mg/dL, Fibrinogen < 360 mg/mL. Results: We analyzed 13 MAS with sJIA from 2011 thru 2015. All of them are performed by bone marrow biopsy and confirmed the hemophagocytic histiocytosis. Also CD 68 stained many positive cells. Age of onset 6.8 years. M:F=7:6. The geometric average means of WBC 13,981/mm³. Hb 10.5 g/L. Platelet 383,700/mm³. ESR 58mm/hr. CRP 88.8 mg/dL. Ferritin 4,950 ng/mL. Iron 49.4 TIBC 274. AST 627 IU/L. ALT 372 IU/L. Triglyceride 209 mg/dL. Procalcitonin 2.6 ng/mL. Conclusion: The performance of new guidelines for diagnosis of MAS with sJIA is more commode to diagnose the ambiguous and vague MAS of early stage. But there are some discrepancies of WBC and platelets. Because of sample size was small. This is the limitation of data.
Dendritic cell neoplasms are rare tumors that affect the lymphatic system as well as extra nodal sites. Diagnosis depends on an array of morphologic, histologic, electron microscopic and immunohistochemical studies. Here I describe 2 cases with 2 different types of dendritic cell tumors: Case 1- 72 year-old lady presented with dyspepsia and on investigations confirmed to have a mass in gastric cardia and underwent gastrectomy and biopsy confirmed interdigitating dendritic cell tumor (IDCT), has PET scan which showed residual disease in the area and no disease elsewhere, underwent local radiation treatment and continues to be in remission, to date. Case 2- 66 year-old lady with developmental delay, noticed to have a neck mass, had surgery with left total parotidectomy in June 2013. The biopsy confirmed follicular dendritic cell carcinoma. She had a recurrence at the same site in 2014, had undergone surgical resection again followed by radiation on this occasion and is in remission. Summary: A review and analysis and dendritic cell tumors published in the literature is provided to help guide physicians treating this disease.

CEREBELLAR SYNDROME AND COGNITIVE DEFICITS IN ERDHEIM CHESTER DISEASE: JUST ACCUMULATION OF HISTIOCYTES OR SECONDARY METABOLIC/ENDOCRINE DEFICIT?

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Background: Erdheim-Chester Diseases (ECD) is a rare non-Langerhans cell histiocytosis with up to 50% of cases having the BRAF V600E mutation in affected tissues. Its clinical characteristics range from asymptomatic to multisystemic. If left untreated, the disease progresses causing fatal outcomes. Diagnosis of ECD relies upon imaging studies and pathological findings. There is no standard treatment for ECD, but BRAF inhibitors are under study. Central nervous system (CNS) involvement is a predictor for increased morbidity and mortality. Neurological deficits are usually attributed to histiocytic accumulation in the pons, midbrain and cerebellum causing cerebellar syndrome and other CNS deficits. A subset of patients present with typical cerebellar-midbrain findings on exam and no evidence of disease on MRI. Methods: A 61 year old female with BRAF V600E positive ECD on interferon alpha was diagnosed at the NIH Clinical Center during a follow up visit secondary to old lady with developmental delay, noted to have a neck mass, had surgery with left total parotidectomy in June 2013. The biopsy confirmed follicular dendritic cell carcinoma. She had a recurrence at the same site in 2014, had undergone surgical resection again followed by radiation on this occasion and is in remission. Summary: A review and analysis and dendritic cell tumors published in the literature is provided to help guide physicians treating this disease.

ORAL MANIFESTATIONS OF ERDHEIM CHESTER DISEASE

Poster Location #52

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Objective: Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis characterized by xanthogranulomatous infiltration of tissues producing a wide range of systemic manifestations. Characteristically involving the long tubular bones of the extremities, other skeletal sites may also be affected. Very little is known about the oral manifestations of ECD with jaw involvement only documented in 10 case reports. This is the first time the clinical expression of ECD in the oral cavity has been reported on a cohort of patients. Methods: A detailed oral examination (radiographs, clinical images) was performed on 40 individuals with ECD participating in the NHGRI natural history study (11-HG-0207). The presence/absence of oral disease was observed. Results: 83% (33/40) male and 17% (7/40) female patients diagnosed with EDC were evaluated. Ages ranged from 19-72 years (mean 52 years). 45% (18/40) had radiographic lesions identified in the jaws with predominance for the mandible. All lesions were associated with the roots of teeth. No mucosal involvement, pain, swelling or tooth mobility was noted. While 88% (35/40) report regular access to routine dental care, 18% (7/40) presented with active dental decay and 20% (8/20) with broken teeth. 28% (11/40) had clinical evidence of periodontal disease (defined as probing depths greater than 4mm and moderate to severe alveolar bone loss on radiographs). 28% (11/40) presented with extracted teeth (excluding Third Molars). Conclusion: Jaw bone lesions are a unique radiographic characteristic associated with ECD. These mixed density lesions are found predominantly in the mandible and associated with the roots of teeth. Unlike jaw lesions assigned to Langerhans Cell Histiocytosis (painful swelling and loosening of teeth), ECD jaw lesions are asymptomatic, multiple, symmetrical, and may mimic dental pathology. The development and progression of ECD jaw lesions, including the impact of systemic therapy, is unknown at this time.

WHEN TWO CONDITIONS WITH SIMILAR FEATURES MEET: A CASE OF ERDHEIM CHESTER DISEASE IN A PATIENT WITH A COMMON GENETIC DISORDER

Poster Location #53

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Background: Hemochromatosis is the most common genetic disease in Caucasians causing iron overload. About 1:10 Caucasians carry one copy of C282Y in the HFE gene. Clinical manifestations such as fatigue, joint pain, weight loss, hypogonadism, diabetes insipidus, arrhythmia and liver disease may not manifest until age 50. Hemochromatosis has overlapping features with Erdheim-Chester Diseases (ECD) which can also manifest at age 50 with fatigue, hypogonadism, diabetes insipidus among other manifestations. Here we present a case of ECD that remained undiagnosed for 5 years since the initial manifestation was diabetes...
insipidus thought to be secondary to the patient’s known diagnosis of hemochromatosis. Methods: A 53 year old Caucasian male with diagnosis of hemochromatosis and ECD was evaluated at the NIH Clinical Center as part of ECD Natural History study. Clinical evaluations and images such as brain/pituitary/orbital/abdominal/pelvic MRI, CT scan of the heart and chest, FDG-PET and T-99 bone scans were performed. Results: Skin biopsy and imaging findings confirmed ECD. Molecular testing detected the BRAF V600E mutation. Excess iron was seen on brain MRI, but no other complications associated with hemochromatosis were seen. Presence of ECD was seen in bones, kidneys, heart, skin and pituitary stalk. Mild cerebral atrophy was reported. Endocrine abnormalities included hypogonadism and diabetes insipidus. Patient was treated with interferon (IFN) alpha, but because of side effects, therapy was modified to Anakinra. Today he is on BRAF-MEK inhibitors therapy. Conclusions: Having a common and a rare disorder that share clinical manifestations can also be rare, but not impossible. Having a diagnosis does not make one immune to other common or rare diagnoses. When manifestations sound similar, but there is something that doesn’t add up, keep looking and keep looking. New treatments are becoming available for rare diseases so it is important not to miss now treatable conditions.

Poster Location #54

A CASE OF JUVENILE XANTHOGRANULOMA DEVELOPED DURING ACUTE LYMPHOCYTIC LEUKEMIA TREATMENT

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Juvenile xanthogranuloma (JX) is characterized by multiple cutaneous nodules which resolves spontaneously or requires treatment. Sometimes patients with JX present systemic disease involving multiple organs which require chemotherapy treatment with LCH (Langerhans cell histiocytosis) like protocols. The patient was a 15-year old boy who was diagnosed as Acute lymphocytic leukemia (ALL), high risk. He had complete remission on day 28 after Induction chemotherapy, and continued consolidation and Interim maintenance therapy for ALL. During interim maintenance chemotherapy, he had persistent spiking fever with unknown origin with joint pain and bone pain, so he took bone scan which showed multiple uptakes on pelvis and skull area. Bone biopsy of uptake lesion on the pelvic bone and bone marrow biopsy on right posterior iliac crest was done. The bone marrow biopsy result showed diffuse infiltration of histiocytes, suggestive of benign tumor of histiocytes such as JX. The biopsy on uptake pelvic bone lesion of bone scan showed tiny cluster of mononuclear large cells with CD68 expression suggestive of benign tumor of histiocytes comparable with JX. All autoimmune work ups were within normal range. During delayed intensification treatment for ALL, he continued sufferings for undiagnosed bone pain and fever, whole body MRI was taken and to diagnose bone lesion, follow up bone marrow biopsy was done which proved also to be compatible with JX. We report our experience in the management of rare case of JX multiple bone involvement developed during Acute lymphoctytic lymphoma treatment. Even under ALL chemotherapy, we found JX which is still existed, so far.

Poster Location #55

ROSAI-DORFMAN DISEASE - A CHALLENGING CONDITION

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Purpose: We present a case of a 71-year-old female with Rosai Dorfman Disease (RDD). The clinical case, course of disease and outcome are discussed to highlight the difficulties of managing these rare disorders. Case History: The patient presented with left paranasal erythematous swelling for 3 months. CT scan showed infiltrative maxillary swelling invading the walls of the sinus with enlargement of the surrounding lymph nodes and cutaneous involvement over the side of neck and cheeks. A nasal biopsy and debridement was performed. Histopathology was diagnostic of RDD with infiltration by sheets of S-100 positive massive histiocytes and plasma cells. She was started initially on prednisolone at 40mg/m2 daily for 4 weeks and tapered over 2 weeks with weekly Vinblastine at 6 mg/m2 for 6 weeks. However she developed severe gastritis and a hypertensive crisis necessitating intensive care. Re-evaluation after this showed that the disease was still active with cutaneous and sinusosal infiltration. As her general condition precluded any aggressive therapy, we opted to continue her treatment with pulsed steroids and Vinblastine every three weeks and controlled her disease for 20 months. Her disease then progressed rapidly with enlargement of lymph nodes of the neck, axilla and supraclavicular region with massive cutaneous infiltration over her face, neck, scalp and chest. This very rapidly progressed to an extensive superficially eroding and infiltrating lesion over her entire upper chest and scalp which did not respond and had a fatal outcome. Conclusion: This case report highlights the severe clinical course and poor outcome of RDD in this patient. With such rare disorders, it is not possible to conduct randomized trials or produce evidence-based guidelines. Combining our experience in the International Rare Histiocytic Disorders Registry of the Histiocyte Society would be invaluable to learn more about these disorders and develop consensus treatment guidelines.

Poster Location #56

INTERDIGITATING DENDRITIC CELL NEOPLASM PRESENTING IN THE CONJUNCTIVA

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Purpose: We report an extranodal interdigitating dendritic cell neoplasm that does not subclassify well into currently recognized dendritic cell neoplasms, does not correspond to normal dendritic subtypes, and presents in the conjunctiva, a previously unreported site for dendritic cell neoplasms. Methods: A 10 year-old African-American male presented with a rapidly progressing right conjunctival tumor with initial biopsy diagnosis of inflammatory pseudotumor. Neither topical steroids nor subsequent systemic steroids and methotrexate slowed tumor growth. Review of initial biopsy and repeat biopsy of residual tumor by multiple pathologists revealed a dendritic cell neoplasm that did not fit well into the current classification system and was best classified as an interdigitating dendritic cell neoplasm. Magnetic resonance imaging (MRI) and positron emission tomography (PET) scan revealed no other organ system...
involvement. Systemic clofarabine treatment led to tumor regression. Results: Immunophenotyping indicated that these dendritic cells are HLA-DR positive but do not subclassify well into the recognized dendritic cell neoplasms. They lack expression of CD1a or strong S100 of Langerhans cell histiocytosis/sarcoma, CD4 or strong S100 of interdigitating dendritic cell sarcoma, CD21 or CD35 of follicular dendritic cell sarcoma, CD4 or strong CD68 or CD56 of blastic plasmacytoid dendritic cell neoplasm, and Factor XIIIa of juvenile xanthogranuloma. Hence a descriptive diagnosis of interdigitating dendritic cell neoplasm was rendered. Conclusion: Dendritic cell neoplasms have variable clinical presentations and are being recognized with increasing frequency. Novel tumor sites, such as the conjunctiva, must be reported to characterize disease biology and true incidence. Prompt reporting will assist the clinical community in timely diagnosis and treatment, preventing disseminated disease and unnecessary morbidity and mortality. Thorough diagnostic workup and consultation by experts may be necessary to distinguish disease subtypes and elucidate best treatment options.
INCREMENTAL VALUE OF F18-FDG PET/CT IN THERAPEUTIC DECISION-MAKING IN CHILDREN UNDERGOING CHEMOTHERAPY FOR LANGERHANS CELL HISTIOCYTOSIS

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Purpose: The aim of the study was to evaluate the influence of fluorine-18 fluorodeoxyglucose (F18-FDG) Positron Emission Tomography/ Computed Tomography (PET/CT) on treatment decision in children diagnosed with Langerhans Cell Histiocytosis (LCH) undergoing chemotherapy. Methods: This retrospective study included 13 patients with biopsy proven LCH and in whom F18-FDG PET/CT were performed during the course of the disease, including studies at diagnosis, at week 6 and week 12 of treatment. Patient evaluation also included clinical examination, blood work and multi-modality anatomical imaging. Patients were treated according to the LCH treatment guidelines pending opening of LCH IV protocol. The impact of PET/CT following was evaluated by reviewing the patient file and through a questionnaire to the referring physician. F18-FDG PET/CT was deemed to have significant impact if the patient treatment was modified based exclusively on PET/CT findings, partial impact if additional findings from the patient evaluation influenced therapy and no impact if F18-FDG PET/CT did not change treatment. Results: Six patients had multisystem LCH, five of them with risk organ involvement and one without. Six patients had bone disease and one isolated thymic involvement. F18-FDG PET/CT had impact in all patients. At the end of the first induction, a second course was started in 7 patients, 4 based exclusively on PET/CT findings. Six patients were switched to maintenance, 2 based exclusively on PET/CT findings. At completion of the second induction, F18-FDG PET/CT had partial impact on switching 6 patients to maintenance and one to salvage. The relapse of three patients, while on maintenance, were identified by F18-FDG PET/CT. Conclusion: The present study suggests that F-18-FDG PET/CT significantly influenced treatment response of LCH in about one half of patients However to confirm the real contribution of PET/CT, prospective multi-centric study is warranted.

INTERFERON-γ (IFNγ) IN MACROPHAGE ACTIVATION SYNDROME (MAS): CXCL9 LEVELS AS A BIOMARKER FOR IFNγ PRODUCTION IN MAS

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Purpose: A vast body of evidence in animals and humans points to a pivotal pathogenic role of IFNγ in primary HLH. The role of IFNγ in HLH secondary to rheumatic diseases, usually referred to as MAS, remains to be established. We have previously reported high levels of IFNγ and of the three IFNγ-related chemokines, CXCL9, CXCL10 and CXCL11 in patients with active MAS, in the context of systemic Juvenile Idiopathic Arthritis (sJIA). Indirect evidence in mice suggests that IFNγ is mostly produced in peripheral tissues and blood concentrations may be relatively low.
Rosai-Dorfman-Destombes disease (RDD) is a rare benign lymphoproliferative disorder of unknown cause histologically characterized by infiltration of lymph nodes or extranodal tissues by non malignant histiocytes exhibiting emperipolesis. We reviewed 47 cases of RDD (30 men and 17 women, median age at diagnosis of 20.3 years). Main areas of disease were: lymph nodes (n=32, 68%), bone (n=9, 19%), skin (n=7, 15%), central nervous system (CNS) (n=7, 15%), nasopharynx/ear/nose (n=5, 11%). Twenty-six patients (55%) had a typical pattern of RDD, defined by presence of enlarged lymph nodes, 14 (30%) had an atypical isolated form of RDD without lymphadenopathy, 7 of whom had an isolated involvement of the CNS, 4 an isolated bone involvement, 2 isolated skin and 1 isolated ear infiltration. Interestingly, 7 patients (15%) had an atypical form of RDD along with another histiocytic disorder (n=5) or with a hematologic malignancy (2 Hodgkins lymphoma). Patients were treated with corticosteroids (n=27, 57%), vinblastine (n=7, 15%), azathioprine (n=6, 13%), interferon-alpha (n=6, 13%), cladribine (n=5, 11%), methotrexate (n=5, 11%), rituximab (n=2, 4%), imatinib mesylate (n=1). Twenty patients (43%) were either untreated or had surgical or topical treatment. One patient developed a renal amyloidosis and died of a septic shock. In this multicenter study, half the patients had a clinical presentation similar to the princes description; although we observed frequent isolated bone and CNS involvements.

These patterns, as well as the association with other hematologic or histiocytic disorders are probably overlooked. To the best of our knowledge, we did not find any BRAF mutations within RDD tissue samples, as opposed to Erdheim-Chester disease and Langerhans cell histiocytosis. Finally, if RDD does the reputation of being a benign and reactive disorder, more than half of the patients from this series needed to receive immunosuppressive therapy among which corticosteroids were the best front-line therapy.

THE MINIMUM REQUIRED LEVEL OF DONOR CHIMERISM IN HEREDITARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS - A RETROSPECTIVE STUDY WITH 103 PATIENTS

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Purpose: Reduced-intensity conditioning has lead to an increase in the frequency of mixed chimerism after hematopoietic stem cell transplantation (HSCT) in patients with hereditary hemophagocytic lymphohistiocytosis (HLH). In a mouse model, 10-20% donor chimerism (DC) was considered sufficient to prevent reactivation. However, the required level in humans remains unclear. Methods: We performed a retrospective study in patients who had received an HSCT for hereditary HLH in 23 centers between 2000 and 2013. Patients with primary engraftment and a DC (overall, CD3, and/or CD56) permanently or transiently below 75% were eligible (n=103). Data on DC, flow cytometry and cytotoxicity results, occurrence of systemic reactivations (definition: ≥5/8 criteria), CNS reactivations and partial flares (<5 criteria, HLH-directed treatment), and management were correlated. Results: A reactivation occurred in 10, a partial flare in 5, and possible isolated CNS reactivations in 2 patients. Out of these 17 episodes, 10 occurred during the first 180 days (median overall DC 32%, range 1-100%), which renders a differentiation between post-HSCT hyperinflammation and HLH based on the genetic defect difficult. The other 7 episodes took place until 6.7 years after HSCT, at a median overall or CD3 DC of 10% (range 5-30%). Four patients died due to reactivations (including possible CNS). In 8 patients, overall, CD3, and CD56 DC was <15% for at least 6 months (median 4.4 years, range 0.7 - 10 years) without reactivation. A 2nd HSCT was performed in 18 patients, at a median overall DC of 4% (range 0-19%). Five patients died after 2nd HSCT. Flow cytometry and cytotoxicity results corresponded with the level of DC. Conclusion: Beyond day 180, a DC above 30% is protective against reactivation in most cases. However, lower levels do not inevitably result in reactivations. The risks of a preemptive 2nd HSCT must be weighed against the risk of reactivation.

INTERLEUKIN-17A AS A BIOMARKER IN NEURODEGENERATIVE LANGERHANS CELL HISTIOCYTOSIS

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Purpose: Langerhans cell histiocytosis (LCH) can affect various organs, including the central nervous system. At least 10% of the LCH patients encounter clinical symptoms of neurodegeneration (ND) and potential biomarkers in cerebrospinal fluid (CSF) indicative of ND have been suggested. Previous studies by our group have shown that increased levels of interleukin (IL)-17A in blood and lesions of LCH patients contribute to local and systemic inflammation in LCH. We therefore decided to further explore the role of the IL-23/IL-17A axis in the pathophysiology of ND-LCH. Methods: Cytokine plasma levels were measured in 28 LCH patients and 40 controls using Enzyme-linked immunosorbent assays. One of the patients presented with widespread ND-LCH affecting the basal ganglia, the cerebellum and the medulla. This patient was followed with consecutive magnetic resonance imaging and measurements of neurofilament protein light chain (NF-L) and cytokines in CSF over a 7-year period. Results: As presented previously, the LCH patients had overall significantly higher plasma cytokine levels compared to controls, particularly during disease progression. The ND-LCH patient was repeatedly found to have increased erythrocyte sedimentation rate and extraordinary high plasma IL-17A and IL-23 levels, indicative of an ongoing inflammatory reaction. While no IL-23 could be detected in CSF, high levels of both NF-L and IL-17A in CSF were found. Notably, the levels of NF-L correlated with the levels of IL-17A in the CSF and the clinical status of the patient. Conclusion: IL-17A may be used as a biomarker in ND-LCH, in both plasma and CSF.
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.

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 (“Lymphocytophthie avec normogamma-globulinemie”). In the pediatric literature this condition became known as Nezelof’s syndrome.
- In the field of histiocytosis, his seminal contribution was that Letterer-Siwe, Hand-Schuller-Christian and eosinophilic granuloma are linked to the same cell, having a common ultrastructural marker designated as the Langerhans body (Birbeck granule). In his paper “Histiocytosis X: Histogenetic arguments for Langerhans cell origin”, he noted the dendritic lineage of this disease. Not long afterwards the term Langerhans cell histiocytosis was introduced.

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

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

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

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

ARTICLE I: MEMBERSHIP

Section 1 – Definitions and eligibility

The membership of the Society shall consist of:

A. Ordinary Members

Ordinary Members are all health care professionals who are active in patient care, education or research in the histiocytic disorders. Ordinary Members pay dues, may participate in all activities of the Society, may hold office, are eligible to vote, receive all communications and publications of the Society, and have such special rights and privileges that may be decreed by the Board with the majority-vote consent and approval of the Ordinary Members.

B. Honored Members

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

C. Emeritus Members

Emeritus members are Ordinary Members who have retired from active involvement in the field. Emeritus Members enjoy all rights and privileges of Ordinary Members, but do not pay dues, may not hold office, and will not receive a copy of the Society’s official journal.

Section 2 – Appointment of members and termination of membership

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

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

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

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

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

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

ARTICLE II: DUES

Section 1

A. The annual dues for Ordinary Members shall be set by the Board and ratified by the General Assembly by a simple majority vote.

B. The annual dues shall be due and payable at the time of the annual meeting or by the date fixed by the Board for the payment thereof.

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

ARTICLE III: OFFICERS OF THE SOCIETY

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

A. President — Elected for a three-year term, and may be re-elected for one more term, but the second term may not be consecutive.

1. Presides over annual meetings, is Chairperson of the Board, appoints all members of committees not otherwise defined herein, organizes the agendas for Board and annual meetings, co-signs contracts and financial instruments on behalf of the Society, and serves as an ex-officio member of all standing and ad hoc committees of the Society.

2. Represents the Society in dealing with other organizations and media.

3. Becomes a member of the Board as the immediate past-president for the year immediately following his/her term of office.

4. When a member of the Board acts for the then president under the conditions of Article IV.1.B.

B. President-Elect — Elected for a three-year term as president. Succeeds to that office at the end of the term of the then-incumbent.

1. Becomes a member of the Board as the president-elect for the two years prior to assuming the presidency.

2. When a member of the Board acts for the then president under the conditions of Article IV.1.B.

3. Serves as chairperson of the nominating committee.

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

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

ARTICLE IV: THE EXECUTIVE BOARD

Section 1

The Executive Board (herein referred to as the “Board”) is the governing body responsible for operating the Society. It is composed of the immediate Past-President according to Article III.1.A.3., the President-Elect according to Article III.1.B.1., the other officers, and two Ordinary members-at-large elected by the membership for a three year term. All members serve without financial compensation.
A. The Board is required to meet no less than once each year, and it may enroll participation by others, without vote, as needed.

B. If for any reason, as determined by the Board, the president is unable to carry out his/her duties, then the President-Elect or the Past-President sitting on the Board at that time assumes the duties and responsibilities of the president.

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

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

ARTICLE V: FINANCES
Section 1 – Financing of the Society will come through membership fees and from other sources approved by the Board.

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

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

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

ARTICLE VI: COMMITTEES
Section 1
Standing Committees include the Nominating Committee, the Program Committee, the Scientific Committee, and the Education Committee. The president may, at his/her discretion, appoint other committees on an ad hoc basis. The President is responsible for all appointments to committees, with review by and approval of the Board, except as described below.

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

1. The committee will propose at least one more candidate than the number of vacancies to be filled by election.
2. This slate must be presented to the Board no later than one month prior to the upcoming relevant General Assembly.
3. The committee will be responsible for presentation of the slate, as approved by the Board, and for carrying out the election at the relevant General Assembly.
4. Elections for Secretary and/or Treasurer and the Board Members-at-Large shall be conducted at the meeting marking the beginning of the then-incumbents’ last year in office.
5. Elections for president shall be conducted at the meeting marking the beginning of the last two (2) years in office of the then-incumbent President. The president-elect thereupon becomes a member of the Board according to Article III.B.1.

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

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

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

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

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