36TH ANNUAL MEETING OF THE HISTIOCYTE SOCIETY VIRTUAL

OCTOBER 1, 2020 @ 11:00AM EASTERN TIME (US)

NOVEMBER 5, 2020 @ 11:00AM EASTERN TIME (US)

ANNUAL MEETING PROGRAM AND ABSTRACTS

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WELCOME TO OUR VIRTUAL ANNUAL MEETING

Dear Colleagues,

I would like to cordially welcome you the 36th Annual Meeting of the Histiocyte Society being held virtually, split into two sessions on October 2 (Session I) and November 5 (Session II), 2020. Our meeting is not based in one city but is "Worldwide"-very appropriate for such an international society as ours! This year has been disrupted by the SARS-CoV2 pandemic in ways none of us have seen before or hope to ever see again. To avoid 'Zoom fatigue' the executive board decided to scale back our meeting this year to these two 90-minute sessions. We will still conduct our regular society business including elections and reports from the executive board and our committees. Members, don't forget to cast your vote before the November session of our meeting. Most importantly, we will still hear from YOU this year. We invited you to submit abstracts and have chosen the top six scoring abstracts, out of 54 submitted, to be presented during the two sessions of our meeting. Due to our limited meeting format and uncertainties about the abstract process, we elected to not award prizes this year (but they will be back next year!). Despite the fact that our meetings occur virtually in 2020, it still requires work. I would like to thank the Education Committee for scoring abstracts, Kathy for her organizational efforts, and our partner, the Histiocytosis Association, for assisting us in this endeavor.

This year I hope we all appreciate the special worldwide community we have developed and how much we have achieved over the years. Hopefully this year we will strengthen our bonds using technology such as through our virtual monthly Society sessions which will continue into the Spring of 2021. I hope we can all connect with each other in new ways this year including our newest effort, email discussion groups for members (please contact the secretariat if you haven't signed up and would like to participate).

Looking forward, we have elected to delay our return to Athens until 2021- mark your calendars, for October 10-12, 2021. After the 'long gap' of 2020 - the boredom of working from home, the tedium of social isolation measures, you won't want to miss our next meeting!

Wishing you all the best during this challenging year.

I look forward to seeing you all joyously in 2021, in Athens!

Sincerely,
Michael Jordan

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.

ANNUAL MEETING PROGRAM

VIRTUAL 2020

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HISTIOCYTE SOCIETY

Photography Consent

Registration for, attendance at, and participation in the 2020 Virtual Histiocyte Society Annual Meeting constitutes an agreement by the participant to allow the Histiocyte Society to use and distribute (both now and in the future) the registrant's or attendee's image and/or voice in photographs, video, electronic reproductions and audio of such events and activities.

HISTIOCYTOSIS ASSOCIATION AND HISTIOCYTE SOCIETY

Separate Organizations, One Goal

HISTIOCYTOSIS™ ASSOCIATION
A Rare Community

HISTIOCYTE SOCIETY

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 Founder Jeffrey Toughill offered the Association's business resources to help manage the Histiocyte Society. Thus began the partnership that still exists today.

A True Partnership

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

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

The Histiocytosis Association Mission

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

The Histiocytosis Association Research Program

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

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

Since 1992, nearly 200 individual awards have been made to date, representing more than $7 million to support critical research around the world. Grant amounts now average $50,000 per project but have been awarded in amounts up to $100,000 in the past. The Histiocytosis Association of Canada (HAC) has provided $265,000 of that funding.

Two Organizations, One Goal

The Histiocytosis Association and the Histiocyte Society have been committed partners for nearly 35 years. Though separate organizations, they share a common goal that binds their continued partnership - to find better treatments and, ultimately, a cure leading to a world free of histiocytic disorders.

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

ACKNOWLEDGEMENTS AND RECOGNITIONS

HISTIOCYTE SOCIETY EXECUTIVE BOARD

President	Michael Jordan 2019-2022
Past-President	Milen Minkov 2019-2020
Treasurer	Karin Beutel 2018-2020
Secretary	Kim Nichols 2018-2020
Member-at-Large	Carl Allen 2017-2020
Member-at-Large	Scott Baker 2017-2020

HISTIOCYTE SOCIETY EDUCATION COMMITTEE

Patrick Campbell, Chairperson	2019-2021
Itziar Astigarraga	2018-2020
Michael Henry	2019-2021
Melissa Hines	2019-2021
Vassilios Papadakis	2019-2021
Elena Sieni	2019-2021
Julie Talano	2018-2020

HISTIOCYTE SOCIETY SCIENTIFIC COMMITTEE

Ed Behrens, Chair	2018-2020
Rikhia Chakraborty	2018-2020
Benjamin Durham	2019-2021
Jean-Francois Emile	2019-2021
Julien Haroche	2019-2021
Michelle Hermiston	2019-2021
Caroline Hutter	2019-2021
Jennifer Picarsic	2019-2021f
Astrid van Halteren	2018-2020

HISTIOCYTE SOCIETY STUDY GROUP CHAIRPERSONS

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

HLH STEERING COMMITTEE

Kim Nichols, Chair	2019-2023
Rebecca Marsh, Vice-Chair	2019-2023
Itziar Astigarraga	2016-2020
Scott Baker	2018-2022
Ed Behrens	2019-2023
Stephan Ehl	2018-2022
Jan-Inge Henter	2018-2022
Gritta Janka	2016-2020
Michael Jordan	2017-2021
Kai Lehmberg	2017-2021
Rafal Machowicz	2019-2023
Elena Sieni	2019-2023
Zhao Wang	2019-2023

LCH STEERING COMMITTEE

Michelle Hermiston, Chair	2017-2021
Matthew Collin, Vice-Chair	2020-2024
Carl Allen	2016-2020
Karin Beutel	2017-2021
Patrick Campbell	2018-2022
Michael Girschikofsky	2019-2023
Rima Jubran	2017-2021
Milen Minkov	2018-2022
Vasanta Nanduri	2016-2020
Barrett Rollins	2017-2021
Kimo Stine	2018-2022
Johannes Visser	2019-2023

RARE HISTIOCYTIC DISORDERS STEERING COMMITTEE

Eli Diamond, Chair	2020-2024
Jean-Francois Emile, Vice-Chair	2017-2021
Oussama Abla	2016-2020
Jorge Braier	2016-2020
Eli Diamond	2015-2019
Benjamin Durham	2017-2021
Michael Girschikofsky	2017-2021
Julien Haroche	2018-2022
Eric Jacobsen	2019-2023
Zdenka Krenova	2019-2023
Akira Morimoto	2017-2021
Jennifer Picarsic	2019-2023
Sheila Weitzman	2016-2020

HISTIOCYTE SOCIETY PAST PRESIDENTS

Milen Minkov	2016-2019
Carlos Rodriguez-Galindo	2013-2016
Jim Whitlock	2010-2013
Alexandra Filipovich	2007-2010
Jan-Inge Henter	2004-2007
R. Maarten Egeler	2001-2004
Kenneth McClain	1998-2001
Göran Elinder	1996-1998
Helmut Gadner	1992-1996
Stephan Ladisch	1989-1992
Blaise Favara	1987-1989
Christian Nezelof	1985-1987

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ACKNOWLEDGEMENTS AND RECOGNITIONS

NESBIT PRIZE IN CLINICAL SCIENCE AWARDEES

Paul Kemps....2019
Jennifer Picarsic....2018
Elena Sieni....2017
Francesca Minoia....2016
Alexandra Löfstedt....2015
Vasanta Nanduri....2014
Carl Allen....2013
Stephen Simko....2012
Thomas Lehrnbecher....2011
Rebecca Marsh....2010
Rebecca Marsh....2009
Jorge Braier....2008
Kenneth McClain....2007
Loretta Lau....2006
AnnaCarin Horne....2005
Marie Ouachée-Chardin....2004
Manuel Steiner....2003
Jorge Braier....2002
Wolfgang Holter....2001
Kazuhiro Kogawa....2000

NEZELOF PRIZE IN BASIC SCIENCE AWARDEES

Lauren Meyer....2019
Lauren Meyer....2018
Hirofumi Shibata....2017
Edward Behrens....2016
Benjamin Durham....2015
Samuel Chiang Cern Cher....2014
Gayane Badalian-Very/Kim Nichols....2013
Edward Behrens....2012
Edward Behrens....2011
Michelle Hermiston....2010
Michael Jordan....2009
Matthew Collin....2008
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 Aricó....2001
Pieter Leenen....2000

ROBERT J. ARCECI AWARD FOR BEST POSTER

Hirofumi Shibata....2019
Amel Sengal....2018
Caroline Hutter....2017
Sandra Ammann....2016

HISTIOCYTE SOCIETY GOLDEN PIN RECIPIENTS

Jorge Braier....2017
Lisa Filipovich....2017
Gritta Janka....2016
Stephan Ladisch....2016
R. Maarten Egeler....2015
Sheila Weitzman....2014
Shinsaku Imashuku....2010
Helmut Gadner....2008
Jon Pritchard....2006
Giulio D'Angio....2002
Sally Kivilis....2001
Elizabeth Kontoyannis....2000
Paul Kontoyannis....2000
Jeffrey M. 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

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AT-A-GLANCE AGENDA

THURSDAY • OCTOBER 1, 2020 - SESSION 1 - VIA ZOOM WEBINAR

1100 – 1105	Welcome/Opening Remarks
1105 – 1115	Abstract Presentation #1 – Paul Milne
	MAPPING NON-BRAFV600E HEMATOPOIETIC CLONES IN MULTI-SYSTEM LANGERHANS CELL HISTIOCYTOSIS
1115 – 1125	Abstract Presentation #2 – Camille Bigenwald
	BRAFV600E-INDUCED SENESCENCE DRIVES LANGERHANS CELL HISTIOCYTOSIS PATHOPHYSIOLOGY
1125 – 1135	Abstract Presentation #3 – Jessica Velazquez
	CHARACTERIZATION OF DISTINCT T CELL RECEPTOR REPERTOIRES IN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS
1135 - 1145	Questions and Answers

Members Business Meeting*

1145 – 1150	Education Committee Chair Report
1150 – 1200	LCH-IV Update
1200 – 1210	Rare Histio Registry Update
1210 – 1220	HLH-2004 Update
1220 – 1230	Closing Remarks

THURSDAY • NOVEMBER 5, 2020 - SESSION 2 - VIA ZOOM WEBINAR

1100 – 11:05	Welcome/Opening Remarks
1105 – 1115	Abstract Presentation #1 – Randy Cron
	CHARACTERIZATION OF DOCK8 AS A NOVEL GENE ASSOCIATED WITH CYTOKINE STORM SYNDROME
1115 – 1125	Abstract Presentation #2 – Barbara Degar
	CLOFARABINE FOR RELAPSED/REFRACTORY LCH AND NON-LCH HISTIOCYTOSIS
1125 – 1135	Abstract Presentation #3 – Hamid Bassiri
	INFLAMMATORY PARAMETERS DISTINGUISH SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2) PEDIATRIC PRESENTATIONS, CORONAVIRUS DISEASE 2019 (COVID-19) AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)
1135 - 1140	Questions and Answers

Members Business Meeting*

1140 – 1150	President's Report
1150 – 1155	Treasurer's Report
1155 – 1200	Scientific Committee Chair Report
1200 – 1205	LCH Steering Committee Chair Report
1205 – 1210	HLH Steering Committee Chair Report
1210 – 1215	Rare Histiocytoses Committee Chair Report
1215 – 1225	Secretary's Report – Election Results
1225 – 1230	Closing Remarks

MAPPING NON-BRAFV600E HEMATOPOIETIC CLONES IN MULTI-SYSTEM LANGERHANS CELL HISTIOCYTOSIS

Paul Milne[1], Harshal Abhyankar[2], Brooks Scull[2], Preeti Singh[1], Rikhia Chakraborty[2], Matthew Collin[1*], Carl E Allen[2*],

[1]Newcastle University, Newcastle upon Tyne, United Kingdom
[2]Texas Children's Cancer Center, Texas Children's Hospital, , Houston, TX, USA
**Equal Contributions*

Activating mutations in MAPK pathway genes (BRAF or MAP2K1) have been identified in >85% of cases of Langerhans cell histiocytosis (LCH). Based on results obtained in patients harbouring BRAFV600E, the detection of mutated alleles in the peripheral blood holds considerable promise as a tool for diagnosis, risk stratification and assessment of response to treatment. Circulating mutated BRAFV600E alleles are associated with multi-system (MS) disease. In cases with BRAFV600E, the mutation is enriched in monocytes and myeloid dendritic cells (DCs) and found at similar or greater abundance in cell-free DNA. The purpose of this study was to determine whether activating MAPK pathway mutations other than BRAFV600E are detectable in similar compartments of the peripheral blood of MS-LCH patients. Peripheral blood mononuclear cells (PBMC) from thirteen patients with either BRAF in-frame exon 12 deletions (indel; p.N486_P490del), MAP2K1 mutations (p.Q56P, p.Q58_E62del, p.E102_I103del), or ERBB3 mutation (p.P921Q) were FACS sorted to obtain pure populations of monocytes, DCs, T and B cells. Genomic DNA was extracted and amplified using QIAGEN REPLI-g kits and analyzed by droplet digital PCR (ddPCR). As previously reported for BRAFV600E, mutations were only detected in the peripheral blood of patients with MS-LCH disease with the majority of mutated DNA residing within the CD14+ classical monocytes, CD16+ non-classical monocytes, and CD1c+ DC (BTLA+ DC2 and CD163+ DC3). A minor fraction of MAP2K1 mutations was also detected in the B and T cell compartments of 3 patients. These results suggest that mutant alleles of MAPK pathway genes follows a cellular distribution similar to that reported for BRAFV600E and will have clinical utility for LCH patients without BRAFV600E mutation. Sensitive detection reagents are available for many of these mutations, facilitating a personalised molecular approach to a wider spectrum of LCH patients, not just limited to those harbouring the BRAFV600E mutation.

BRAFV600E-INDUCED SENESCENCE DRIVES LANGERHANS CELL HISTIOCYTOSIS PATHOPHYSIOLOGY

Camille Bigenwald[1, 2], Jessica Le Berichel[1,2], Rikhia Chakraborty[3], Steven T. Chen[1,2], Guray Akturk[1,2], Alexandra Tabachnikova[1,2], Anahita Rafiei[4], Ilaria Laface[1,2], Howard Lim[3], Alessia Baccarini[1,2], Poulikos I. Poulikakos[2], Brian D. Brown[1,2], Sacha Gnjatic[1,2], Amaia Lujambio[1,2], Markus G. Man [4], Kenneth L. McClain[3], Jennifer Picarsic[5], Carl E. Allen[3*], Miriam Merad[1,2*]

[1]Precision Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA and the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [2]Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [3]Texas Children's Cancer Center, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA
[4]Department of Medical Oncology and Hematology, University Hospital and University of Zurich, Zurich, Switzerland; [5]Department of Pathology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA

Langerhans cell histiocytosis (LCH) is a difficult to treat condition leading to granulomatous lesions with characteristic clonal CD207+ CD1a+ mononuclear phagocytes (MNP) expressing somatic mutations in MAPK pathway genes, most notably BRAFV600E. We recently discovered that the BRAFV600E mutation can also affect multipotent hematopoietic progenitor cells (HPC) in multisystem LCH disease. Currently, front-line chemotherapy fails in more than 50% of patients with multisystem disease, highlighting the need for novel therapies for this group of patients. How BRAFV600E mutation in HPC leads to LCH is not known. Strikingly, we found that BRAFV600E mutations induce HPC to undergo senescence leading to growth arrest, overexpression of CDKN2A, and the production of a senescence-associated secretory phenotype (SASP). BRAFV600E-induced SASP skewed HPC differentiation towards the MNP lineage leading to excessive accumulation of senescent LCH-like cells in tissues and the formation of LCH lesions. Importantly, mTOR inhibition and elimination of senescent cells using INK-ATTAC transgenic mice improved LCH outcome in mice. These results provide a paradigm shift in our understanding of LCH pathophysiology and identify senescent cells as a major target for the treatment of systemic LCH.

CHARACTERIZATION OF DISTINCT T CELL RECEPTOR REPERTOIRES IN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS

Jessica Velazquez[1,2], Jing Wang[3], Ankita Das[3], Amel Senegal[1,2], Derek Vargas[3], Vasumathi Kode[3], Niyati Thosani[3], Nitin Mandloi[3], Olive Eckstein[1,2], Miriam Merad[4,5], Carl Allen[1,2], Rikhia Chakraborty[1,2]

[1]Texas Children's Cancer Center, Texas Children's Hospital, Houston, TX, USA; [2]Division of Pediatric Hematology-Oncology, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA; [3]MedGenome Inc, Foster City, CA, USA; [4]Department of Oncological Sciences, Tisch Cancer Institute, New York, NY, USA; [5]Department of Dermatology, Icahn School of Medicine, New York, NY, USA

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia characterized by granulomatous lesions containing clonal pathological CD207+ dendritic cells (DCs) with persistent mitogen-activated protein kinase (MAPK) pathway activation along with a large inflammatory infiltrate that do not carry MAPK mutations. Properties of lesion-infiltrating T-cells in LCH are poorly understood; it is likely that the pathogenic DCs in LCH mediate some of the pathologic manifestations through DC-T cell interactions. Antigen-dependent T-cell activation depends on the interaction between the antigen-major histocompatibility complex (MHC) and the αβ T-cell receptor (TCR). There is increasing evidence that deep sequencing-based T-cell repertoire can serve as a biomarker of immune response in cancer patients; however, the characteristics of T-cell repertoire as well as its prognostic significance in LCH remain unknown. In this study, we performed bulk TCR αβ repertoire profiling to identify the CDR3 clonotypes in sorted lesion-infiltrating CD8+, CD4+, and CD4+CD25+ cells as well as from matching peripheral blood. We found that in the sorted CD8+ and CD4+ cells from all patient lesions, there was a characteristic clonality shift where-in the repertoire in the lesions were clonally expanded, and interestingly some of the TRBV genes were shared among the patient lesions. We also observed evolution of new-clonotypes post-chemo and radiation therapy. In addition, we performed bulk transcriptome analyses to characterize the functional nature of the T-cell infiltrates, which revealed genes responsible for epigenetic modification, calcium mobilization and mitochondrial metabolism are significantly downregulated in LCH lesion-infiltrating T-cells. Our findings suggested that TCR repertoire might be a potential indicator of immune monitoring and a biomarker for predicting the prognosis of LCH patients. Although further functional studies of T-cell populations are clearly required, this study has expanded our understanding of T-cell immunity in LCH and provided an experimental basis for further studies on its pathogenesis and immunotherapy.

CHARACTERIZATION OF DOCK8 AS A NOVEL GENE ASSOCIATED WITH CYTOKINE STORM SYNDROME

Randy Quentin Cron[1], Remy Reese Cron[1], Devin Absher[2], Thomas Prescott Atkinson[1], Walter Winn Chatham[1], Anshul Varecha[3], Shannon Lozinsky[3], Suchitra Acharya[3], Carolyn Fein Levy[3], Mingce Zhang[1]

[1]University of Alabama at Birmingham, AL, USA; [2]HudsonAlpha Institute for Biotechnology, Huntsville, AL, USA; [3]Cohen Children's Medical Center of New York, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

PURPOSE: Cytokine storm syndrome (CSS), also known as hemophagocytic lymphohistiocytosis (HLH), is a life-threatening condition presenting with fever and shock-like multi-organ dysfunction (MOD). Familial CSS/HLH results from homozygous defects in genes critical to perforin-mediated cytolysis by cytolytic lymphocytes. 30-40% of CSS cohorts possess heterozygous defects in familial CSS/HLH genes resulting in decreased cytolysis, prolonged interaction with antigen presenting cells, and subsequent increased pro-inflammatory cytokines resulting in MOD. Since NK cell dysfunction is common in CSS, there are likely other genes contributing to CSS via decreased cytolysis. METHODS: CSS patients at UAB, and children with SARS-CoV-2 multisystem inflammatory syndrome in children (MIS-C) at Northwell were screened for mutations via genome sequencing or a commercial immunodeficiency panel. Seven patients (3 with MIS-C) had mutations in the guanine nucleotide exchange factor DOCK8 critical to NK cell function. DOCK8 mutations, or wild-type (WT) sequence controls, were introduced into human NK-92 cells by FOAMY virus (FV) transduction. FV-transduced WT and mutant DOCK8-expressing NK-92 cells were incubated with K562 target cells and compared for cytolytic activity, degranulation (CD107a), and cytokine [interferon-g (IFNg), tumor necrosis factor (TNF)] production by flow cytometry. RESULTS: Four patients had rare heterozygous missense DOCK8 mutations, and 2 had the same DOCK8 polymorphism (Asp63Asn, 12% of population). One splice acceptor variant (c.54-1G>T, 0.03%) disrupted RNA splicing by exon-trapping. One novel (Ala261Val) DOCK8 mutant decreased NK cell lytic activity (n=3, decreased ~50% versus WT, p=0.007) and degranulation by >50% (n=3, p=0.013). During incubation with K562 targets, NK cells expressing the novel DOCK8 mutant increased IFNg and TNF expression by >200% (p=0.019 and p=0.003, respectively). The DOCK8 polymorphism decreased lysis and degranulation to a lesser degree. CONCLUSION: Heterozygous mutations in DOCK8, a novel CSS/HLH-associated gene, contribute to CSS pathology through a partial dominant-negative or hypomorphic effect resulting in decreased cytolysis and increased pro-inflammatory cytokine production.

CLOFARABINE FOR RELAPSED/REFRACTORY LCH AND NON-LCH HISTIOCYTOSIS

Barbara Degar[1], Patrick Campbell[2], Carl Allen[3], Michael Henry[4], Oussama Abla[5], Michelle Hermiston[6], David Ebb[7], Michael Hogarty[8], Stephan Ladisch[9], Rima Jubran[10], Kimo Stine[11], Ashish Kumar[12], Pei-Chi Kao[13], Wendy London[14], Eric Jacobsen[15], Carlos Rodriguez-Galindo[16]

[1]Dana-Farber Cancer Institute/Boston Children's Cancer and Blood Disorders Center, Boston, MA USA; [2]St. Jude Children's Research Hospital, Memphis, TN, USA; [3]Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA; [4]Phoenix Children's Hospital, Phoenix, AZ, USA; [5]The Hospital for Sick Children, Toronto, ON, Canada; [6]University of California San Francisco Medical Center, San Francisco, CA, USA; [7]Massachusetts General Hospital, Boston, MA, USA; [8]The Children's Hospital of Philadelphia, Philadelphia, PA, USA

[9]National Medical Center, Washington, DC, USA; [10]Children's Hospital Los Angeles, Los Angeles, CA, USA

[11]Arkansas Children's Hospital, Little Rock, AR, USA; [12]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [13]Boston Children's Hospital/ Dana-Farber Cancer Institute, Boston, MA, USA;[14]Boston Children's Hospital/ Dana-Farber Cancer Institute, Boston, MA, USA; [15]Dana-Farber Cancer Institute, Boston, MA, USA; [16]St. Jude Children's Research Hospital, Memphis, TN, USA

Langerhans Cell Histiocytosis (LCH) and non-LCH Histiocytosis are rare neoplastic diseases with highly variable behavior. Although chemotherapy is usually effective, many patients experience disease recurrence and are at risk for permanent consequences. This prospective, multicenter, phase II study evaluated the efficacy and toxicity of clofarabine in two strata: recurrent/refractory (R/R) LCH (stratum 1) and Non-LCH Histiocytosis (stratum 2). Objectives were to estimate response rate, progression-free (PFS) and overall survival (OS), and to describe toxicities. In stratum 1, a two-stage design required 14 "responders" (disease regression/resolution after cycle 2) of 20 evaluable (≥1 dose clofarabine) participants to warrant further investigation of clofarabine. All participants received clofarabine 25 mg/m2/d IV on days 1-5 of each 28-day cycle. Radiographic response was assessed after 2 cycles. Participants without evidence of disease progression after 2 cycles received 4 additional cycles. Twenty-five participants consented and enrolled: 20 in stratum 1, five in stratum 2. Seventeen stratum 1 participants (85%; 95% CI: 62%, 97%]) were responders, and three had stable disease after cycle 2. Four stratum 2 participants (80%; 95% CI: [28%, 99%]) had partial metabolic response. Nineteen stratum 1 participants completed 6 treatment cycles; one withdrew after cycle 3; none progressed during treatment. Three participants in stratum 1 had residual or recurrent disease after cycle 6 and received subsequent LCH-directed treatment. One-year PFS/OS was 82%/100% in stratum 1 (n=20) (median follow-up: 0.8 years (range: 0.1, 3.5)). Overall, 19/25 (76%) experienced grade ≥3 hematological toxicity; 9/25 (36%) non-hematological. 80% (20/25) of participants had one or more grade ≥3 toxicities attributed to protocol therapy. In patients with R/R LCH, clofarabine is active and tolerable, with a sufficiently high response rate to justify a future larger trial of clofarabine. In patients with Non-LCH Histiocytosis, clofarabine efficacy appears promising; further study in phase II is needed.

INFLAMMATORY PARAMETERS DISTINGUISH SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2) PEDIATRIC PRESENTATIONS, CORONAVIRUS DISEASE 2019 (COVID-19) AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

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PURPOSE: Pediatric SARS-CoV-2 infections result in at least three distinct disease manifestations. Most children infected acutely remain asymptomatic or develop only mild symptoms of COVID-19; however, small proportion of acutely infected children, develop progressive respiratory illness, multi-organ involvement, and an associated hyperinflammatory syndrome. These COVID-19 presentations are contrasted by MIS-C, a post-infectious hyperinflammatory condition characterized by fever, shock, and multi-organ dysfunction. We sought to characterize the hyperinflammatory syndromes of SARS-CoV-2 infections, in order to identify biomarkers that may distinguish the hyperinflammation seen in these conditions from that of HLH. METHODS: We enrolled children admitted to the Children's Hospital of Philadelphia who had positive SARS-CoV-2 RT-PCR tests or met clinical criteria for MIS-C. We measured plasma levels of 10 cytokines on a MesoScale Discovery platform and correlated these values with available clinical parameters of inflammation. RESULTS: Fifty patients were classified into asymptomatic/mild COVID-19 (amC19; N=18), severe COVID-19 (sevC19; N=11), or MIS-C (MIS-C; N=21). Five cytokines (IL-1beta, IL-2, IL-4, IL-12p70 and IL-13) were excluded from further analyses, as their levels were not abnormal. Of the remaining (IL-6, IL-8, IL-10, TNF-alpha and IFN-gamma) that were often elevated, we found statistically significant elevations in IL-10 in both sevC19 and MIS-C, when compared to amC19 patients. Some patients in each cohort had markedly elevated IFN-gamma, but the cohort means were not statistically different. While the maximal C-reactive protein levels were elevated in both sevC19 and MIS-C, these were not statistically different, while maximal ferritin levels differentiated sevC19 from amC19 and MIS-C. CONCLUSION: While the pathogenesis of pediatric COVID-19 and MIS-C are not fully elucidated, differences between observed biomarkers suggest that the immune pathogenesis of the hyperinflammation in these syndromes is likely to be mechanistically different, although overlap may exist with HLH in some patients.

CD8+ T CELLS FROM PATIENTS WITH HEMOPHAGOCYTIC LYMPHO-HISTIOCYTOSIS DISPLAY A DISTINCTIVE ACTIVATION PROFILE IN CONTRAST TO THOSE FROM PATIENTS WITH SEPSIS.

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a rare and fatal immune regulatory disorder caused by defects of perforin dependent cytotoxicity. Early diagnosis is challenging because of the rarity of the disease, nonspecific symptoms which often overlap with other illnesses such as bacterial sepsis. Our understanding of HLH is largely based on experimental studies in mice which have linked its pathophysiology to excessive antigenic activation of CD8+T cells. However, the role of these immune cells in human patients is not well characterized. We investigated whether patients with active HLH, displayed a distinct, activated CD8+ T cell phenotype in the periphery and the tissues. METHODS: We use flow cytometry to characterize, compare and contrast the T cell in patients with HLH from those of patients with sepsis. RESULTS: Patients with HLH displayed a prominent population of activated CD8+ T cells. The activated cells were CD38high/HLADR+ cells. The bulk of the activated CD8+T cells were T effector memory (TEM) (CD45RA- CCR7-) cells and also displayed cytolytic differentiation (Granzyme+) and produced cytokines such as interferon gamma and tumor necrosis factor alpha upon stimulation. This is in striking contrast to the CD8+ T cells in patients with bacterial sepsis which are CD38lowHLADRlow and were enriched in TEMRAs (CD45RA+CCR7-). CONCLUSION: Our data show that the CD8+ T cell profiles in these two diseases with overlapping clinical manifestations are highly distinct.

NOTES

HYPERFERRITINEMIA IS A BAD PROGNOSIS FACTOR IN COVID-19 PATIENTS AND IT IS NOT SPECIFIC FOR HLH IN ADULTS

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A fulminant multi-organ failure with hypercytokinemia is observed in severe cases of SARS-Cov-2 infection. This exaggerated inflammatory response share findings with hemophagocytic lymphohistiocytosis (HLH) such as hyperferritinemia and activated macrophages. Aim: to review the ferritin levels in COVID-19 confirmed patients and analyze the data of cases with hyperferritinemia higher than 10,000µg/L in a tertiary hospital between March and June 2020, focusing on HLH diagnostic criteria. 5,863 ferritin determinations were done in 2,396 COVID-19 patients (1,491: <400µg/L, 606: 400-1,000µg/L, 270: 1,000-5,000µg/L, 19: 5,000-10,000µg/L and 10 patients >10,000µg/L). Mortality rate in patients with ferritin over 5,000µg/L is 50% and it goes up to 70% if ferritin>10,000µg/L. We analyzed 10 adults (8males/2females; median age=67 years-old). Six patients had previous illness (1 T-cell lymphoma, 2 chronic lymphoid leukemia, 1 gastric adenocarcinoma, 1 acute lower limb ischemia and 1 chronic renal insufficiency). Ferritin levels were determined in plasma (n=6; median=13,905µg/L) or serum (n=4; 20,401µg/L). All but one had fever but only one hepato-splenomegaly. Other HLH observed parameters: 7 cytopenia (hemoglobin<90g/L or platelets<100x103/mm3), 7 hypertriglyceridemia (>175mg/dL), 1 hypofibrinogenemia (<150mg/dL). No bone marrow studies, sCD25 levels or NK cell activity were performed. All patients showed high levels of C-reactive protein (CRP) (>11mg/L) and D-Dimer (>500ng/mL) and 9 had increased procalcitonin (PCT) levels (>0.5ng/L). IL-6 was only evaluated in 3 patients, showing levels below 40pg/mL. All patients had respiratory involvement and half required mechanical ventilation. Other organ failures were: 2 renal, 2 heart, 1 hepatic and 0 neurological. In this study we observed that hyperferritinemia is common in COVID-19 patients and highly elevated ferritin is not specific for HLH in adults. Ferritin >5,000µg/L is associated with bad prognosis and mortality rate is 70% when levels >10,000µg/L. Most patients with highest ferritinemia share HLH diagnostic criteria, but although COVID-19 resembles some HLH features there are many differences.

HEMOPHAGOCYTIC LYPHOHISTIOCYTOSIS IN CHRONIC GRANULOMATOUS DISEASE- A SERIOUS CAUSE OF MORTALITY

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PURPOSE: Chronic granulomatous disease (CGD) is a primary immune deficiency due to defects in phagocyte respiratory burst leading to severe and life-threatening infections. Patients with CGD also suffer from disorders of inflammation and immune dysregulation including colitis and granulomatous lung disease, among others. Additionally, patients with CGD may be at increased risk of systemic inflammatory disorders such as hemophagocytic lymphohistiocytosis (HLH). The presentation of HLH often overlaps with symptoms of systemic inflammatory response syndrome (SIRS) and therefore can be difficult to differentiate, delaying diagnosis, especially in patients with a primary immune deficiency in which incidence of infection is increased. METHODS: We conducted a retrospective evaluation of patients with CGD who also met the diagnostic criteria for HLH based on HLH 2004 guidelines. Data gathered includes clinical course, genotype, infectious history, laboratory parameters treatment, and where appropriate, cause of death. RESULTS: Four patients were identified with X-linked CGD with underlying CYBB mutation. The age of the patients ranged from 4.5 weeks to 17 years. All patients developed HLH secondary to or with concurrent CGD-related infection. In two patients, CGD was a known diagnosis prior to development of HLH and in the other two CGD was diagnosed as part of the evaluation for HLH. HLH was fatal in three; one case was successfully treated, ultimately receiving hematopoietic stem cell transplantation. CONCLUSION: HLH in CGD is most often secondary to infection and therefore poses a particular challenge in treatment. Concurrent treatment of infection with antimicrobial agents and inflammation with immunosuppression is necessary to blunt the inflammatory response. Physicians and other care providers should maintain a high level of suspicion for HLH in patients with immune deficiency as these patients may develop sudden and ultimately fatal decline.

MALIGNANCY-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN CHILDREN: A 10-YEAR EXPERIENCE OF A SINGLE PEDIATRIC HEMATOLOGY CENTER

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PURPOSE: Malignancy-associated hemophagocytic lymphohistiocytosis (M-HLH) in children is a relatively rare but life-threatening secondary hemophagocytic lymphohistiocytosis(sHLH). Until now, there has been a limited number of reports regarding children with M-HLH. METHODS: We conducted a retrospective study of 27 children with M-HLH, admitted to our center between July 2007 and October 2019. The clinical data and laboratory data were analyzed. RESULTS: The median age of the children with M-HLH was 7 years. Underlying diseases included acute myeloid leukemia (AML, n=4), myelodysplastic syndrome-refractory anemia with excess blasts (MDS-RAEB-II, n=2), acute lymphoblastic leukemia (ALL, n=5), and different types of lymphoma (n=16). The one-year mortality rate was 56%. All patients had persistent fever. The clinical manifestations included hepatomegaly (89%), splenomegaly (67%) and central nervous system symptoms (56%). Thirteen children (48%) had Epstein-Barr virus (EBV) infection. No significant differences were observed between EBV-positive and negative M-HLH patients in terms of most clinical indicators. However, EBV-positive M-HLH patients showed prolonged activated partial thromboplastin time (APTT) and more hemophagocytosis in the bone marrow (BM) than that seen with EBV-negative patients. Eighteen patients (67%) received the HLH-94/04 regimen as the initial treatment. There were no significant differences in the overall survival (OS) between EBV-positive and negative patients. Patients with prolonged APTT had a significantly poorer OS than other patients (p=0.012).CONCLUSIONS: The M-HLH

children with EBV infection are more likely to have prolonged APTT and more hemophagocytosis in BM. The children with M-HLH had poor prognosis, especially those with prolonged APTT.

THE EFFECT OF EPSTEIN-BARR VIRUS INFECTION IN CENTRAL NERVOUS SYSTEM ON PROGNOSIS OF PATIENTS WITH EPSTEIN-BARR VIRUS-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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PURPOSE: This study was conducted to investigate the effect of EBV infection in the central nervous system(CNS) on the prognosis of Epstein-Barr virus associated hemophagocytic lymphohistiocytosis (EBV-HLH) patients. METHODS: Clinical information of 88 EBV-HLH patients diagnosed and treated in our medical center was included. All 88 patients had completed EBV-DNA testing in lumbar puncture and cerebral spinal fluid. RESULTS:The 88 patients were divided into 2 groups based on whether the result of their first cerebrospinal fluid EBV-DNA testing was positive. Statistical difference in survival time was found between the two groups(P=0.035). The 88 patients were divided into two groups for survival time analysis based on whether the results of EBV-DNA tests of their cerebrospinal fluid were positive, and statistical difference in survival time was found between the two groups(P=0.049). The 44 EBV-HLH patients who were EBV-DNA-positive in their cerebrospinal fluid were divided into two groups for survival time analysis based on the highest copy number of EBV-DNA in the cerebrospinal fluid, using 1.0E + 04 copies/ml as the cutoff, and statistical difference in survival time was found between the two groups(P=0.030). The 27 patients who underwent multiple lumbar puncture tests and also had a positive result of the first EBV-DNA test of their cerebrospinal fluid were divided into two groups based on whether the EBV-DNA tests of their cerebrospinal fluid changed from positive to negative,and statistical difference in survival time was found between the two groups(P=0.038). CONCLUSIONS: EBV infection of the central nervous system was found to be a poor prognostic factor in EBV-HLH patients. The changes in EBV-DNA in cerebrospinal fluid and the EBV-DNA copy number were found to affect the prognosis of EBV-HLH patients. Monitoring the changes in EBV-DNA copy number in the cerebrospinal fluid was of great significance.

POPULATION PHARMACOKINETIC (PK) ANALYSIS OF EMAPALUMAB, A FULLY HUMAN, ANTI-INTERFERON GAMMA (IFNγ) MONOCLONAL ANTIBODY, IN PATIENTS WITH PRIMARY HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

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PURPOSE: IFNγ is considered key to the hyperinflammation of HLH. Thus, IFNγ neutralization could help control the disease until haematopoietic stem cell transplantation, the only curative treatment. Emapalumab, which binds to and neutralizes IFNγ, is the first and only approved (FDA) treatment for primary HLH. METHODS: To characterize the PK of emapalumab, a population PK (PopPK) analysis was performed using data from patients with primary HLH administered emapalumab in a phase 2/3 clinical trial (NCT01818492) and as part of a compassionate use programme. RESULTS: Emapalumab PK was adequately described by a two-compartment model. Central and peripheral volumes of distribution were 0.059 and 0.079 L/kg, respectively. Exploratory graphical analysis showed that (i) IFNγ production varied significantly between and within patients as a function of time; (ii) the higher the IFNγ production, the faster the elimination of emapalumab due to target-mediated drug disposition; and (iii) the higher the IFNγ production, the higher the dose of emapalumab required to reach the neutralizing concentration of IFNγ. Only body weight and total IFNγ (free and bound) levels were found to significantly influence emapalumab PK. The allometric exponents of body weight for the volume of distribution and clearance were 1 (fixed) and 0.886 (95% confidence interval 0.68, 1.09), respectively. At values of total IFNγ 10^3-10^6 pg/mL, total clearance (linear + target mediated) of emapalumab was 0.0012-0.0140 L/h for a bodyweight of 5 kg, with corresponding terminal half lives of 17.5-2.3 days. This wide variance in clearances and half-lives partly explains the emapalumab dose adaptations that are required for treating primary HLH patients. CONCLUSION: The PopPK model reliably predicted serum concentrations of emapalumab in patients with primary HLH. The expected dynamics of IFNγ biology was confirmed and included in the PopPK model and supported the proposed dosing scheme of emapalumab in patients with primary HLH.

OVERALL RESPONSE RATE (ORR) WITH EMAPALUMAB, A FULLY HUMAN, ANTI-INTERFERON GAMMA MONOCLONAL ANTIBODY, IN PATIENTS WITH PRIMARY HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH): RESULTS OF A SENSITIVITY ANALYSIS

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PURPOSE: There are currently no validated endpoints for efficacy assessment to guide clinical trials in primary HLH. Therefore, clinical objective response criteria were used to define the primary endpoint of ORR in the emapalumab pivotal study of primary HLH (NCT01818492). We report the findings of a sensitivity analysis of the ORR to emapalumab using various assessment criteria. METHODS: ORR at end of treatment with emapalumab were analyzed as per the protocol definition in treatment-experienced patients, and several pre-specified and post hoc sensitivity analyses were performed to pressure test the data. RESULTS: 63% (95% confidence interval [CI], 0.42-0.81) of 27 treatment-experienced patients had a response according to the pivotal study protocol ORR definition. Pre-specified sensitivity analysis of 22 patients treated with additional HLH therapies other than dexamethasone during the study were imputed as non-responders and showed a similar magnitude of response to that observed in the protocol-defined primary analysis (59.3%; 95%CI 0.39-0.78). Utilizing the response criteria defined by Marsh et al. (2013) in a retrospective analysis of primary HLH patients also resulted in a similar response to the protocol-defined primary endpoint in 27 treatment-experienced patients (70.4%; 95%CI 0.50-0.86). When platelet count was added to the analysis, the percentage of emapalumab responders increased to 74.1% (95%CI 0.54-0.89). Pre-specified analysis of physician-reported response rates was also in line with the primary analysis, with 70.4% (95%CI 0.50-0.86) of 27 treatment-experienced patients deemed to have a response to emapalumab. CONCLUSION: The current analyses support the primary analysis by having a numerically comparable point estimate to the primary endpoint and also support the use of the clinically objective ORR as a primary endpoint, and may represent a significant improvement over methodology applied so far in this research area. The current analyses confirm the positive benefit of emapalumab in patient's refractory or intolerant to conventional HLH therapies.

EFFICACY AND SAFETY OF EMAPALUMAB, A FULLY HUMAN, ANTI-INTERFERON GAMMA MONOCLONAL ANTIBODY, DESCRIBED IN TREATMENT-NAIVE PATIENTS WITH PRIMARY HEMOPHAGOCYTIC LYMPHOHISTOCYTOSIS

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PURPOSE: Current conventional therapy for HLH comprises immunochemotherapies, which are associated with opportunistic infections, toxicity, and high morbidity and mortality. Emapalumab, a fully human, anti-IFNγ monoclonal antibody that neutralizes IFNγ, is approved by the FDA for the treatment of primary HLH patients who have failed or are intolerant to conventional HLH therapy. Here we describe the efficacy and safety of emapalumab in a sub-population of 7 treatment naïve primary HLH patients. METHODS: Efficacy and safety of emapalumab were assessed in the pivotal study of 34 pediatric patients with active primary HLH at a database cutoff of July 2017 [1]. Initial emapalumab dose was 1 mg/kg given intravenously every 3 days. Subsequent doses could be increased up to 10 mg/kg, based on predefined laboratory and clinical response parameters. Treatment duration was up to 8 weeks. A primary analysis of the predefined efficacy and safety endpoints was conducted in 7 patients who had received emapalumab as their first treatment. RESULTS: Overall response rate at end of treatment in the treatment-naïve patients was 71.4% (95% confidence interval [CI] 0.29, 0.96), similar to that seen in previously treated patients (63.0%; 95% CI 0.42, 0.81). Three treatment-naïve patients achieved a partial response and 2 achieved HLH improvement. Six patients (85.7%) had at least one response during the study. There were no apparent differences in the incidence of serious adverse events from the overall study population of 34 patients. CONCLUSION: These data support that targeting IFNγ with emapalumab in both treatment-naïve and treatment-experienced primary HLH patients, emapalumab is effective in controlling hyperinflammation, demonstrating that IFNγ neutralization is a relevant therapeutic objective in primary HLH [1].

Reference: 1. Locatelli et al. N Engl J Med 2020;382:1811-22.

SAFETY OF EMAPALUMAB IN PEDIATRIC PATIENTS WITH PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH): FINDINGS FROM THE PRIMARY ANALYSIS OF THE PIVOTAL PHASE 2/3 STUDY

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PURPOSE: Current conventional therapy for HLH comprises immunochemotherapies, which are associated with opportunistic infections and toxicity. Emapalumab, a fully human, anti-interferon gamma (IFNγ) monoclonal antibody that neutralizes IFNγ, is approved by the FDA for the treatment of primary HLH patients who have failed or are intolerant to conventional HLH therapy. We report on the safety of emapalumab in primary HLH seen in the open-label, pivotal phase 2/3 study and investigate the relationship of adverse events (AE) to treatment dose and duration. METHODS: Efficacy and safety of emapalumab were assessed in the pivotal study of 34 pediatric patients with active primary HLH at a database cutoff of July 2017 [Locatelli et al. NEJM 2020]. Initial emapalumab dose was 1 mg/kg given intravenously every 3 days. Subsequent doses could be increased up to 10 mg/kg, based on predefined laboratory and clinical response parameters. Treatment duration was up to 8 weeks. The relationship of AE to emapalumab treatment was reported by the study investigator. RESULTS: Overall, 29% of patients had at least one AE deemed related to emapalumab, most (90%) of which were infusion-related reactions that were mild to moderate in nature and resolved. No severe or serious hypersensitivity reactions were reported. Infections caused by pathogens potentially favored by IFNγ neutralization occurred in 1 patient during emapalumab treatment (disseminated histoplasmosis) and resolved with appropriate treatment. There was no increase in AE frequency or the number of viral, bacterial, or fungal infections with increased dose or duration of emapalumab treatment. CONCLUSION: Neutralization of IFNγ with emapalumab in patients with active primary HLH was associated with a favorable and manageable safety profile across all doses and treatment durations assessed, allowing for flexible and tailored use based on patient clinical response, and may possibly offer an advantage over conventional HLH therapies.

EVALUATION OF INFLAMMATORY BIOMARKERS FOR EARLY DISCRIMINATION OF SEVERE BACTERIAL INFECTION AND HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN PEDIATRIC PATIENTS

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PURPOSE: The goal of this study was to identify optimal parameter for early discrimination of severe bacterial infection from hemophagocytic lymphohistiocytosis (HLH) for avoiding excessive diagnosis and treatment. Study design A prospective study was performed on pediatric patients with severe bacterial infection (SI) and HLH. The diagnosis of SI required fulfillment of microbiological and clinical evidence with infection and organ dysfunction or shock. The diagnosis of HLH required fulfillment of 5 of 8 criteria proposed in the HLH-2004 protocol. Patients' clinical and laboratory findings and inflammatory biomarkers, including Th1/Th2 cytokines, C-reactive protein (CRP) and procalcitonin (PCT), were collected and analyzed. RESULTS: A total of 152 patients from our hospital during January 2011 through December 2016 were enrolled in this study. All SI (90 cases) and HLH (62 cases) patients presented with fever, but various degrees of splenomegaly, neutropenia, anemia, thrombocytopenia, hypertriglyceridemia, hyperferritinemia, and hemophagocytosis in bone marrow. HLH patients had higher levels of interferon-γ (IFN-γ), and interleukin-10 (IL-10), but lower levels of interleukin-6 (IL-6), PCT and CRP levels. IL-6 was the best discriminator for SI with AUC of 0.920 (95% confidence interval: 0.89-0.96; P<0.001). At the optimal cutoff value for discriminating SI from HLH, IL-6 >478.3pg/mL presented 95.2% of specificity and 79.3% of sensitivity, respectively. In addition, high levels of TNF-α , and CRP were found to had the intermediate discriminating power for SI from HLH with AUC of 0.812 and 0.712, respectively, while high levels of IFN-γ favored the diagnosis of HLH with AUC of 0.851. CONCLUSIONS: Patients with high levels of IL-6 and CRP but not IFN-γ reveal the discrimination power for SI from HLH, while high level of IFN-γ favors the diagnosis of HLH. This findings may be used for the stratification therapy for the patients with severe bacterial infection and true HLH.

TREATMENT OF PEDIATRIC PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS WITH THE HLH-94/2004 REGIMENTS AND HEMATOPOETIC STEM CELL TRANSPLANTATION IN CHINA

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PURPOSE: We aimed to clarify the clinical characteristics, prognostic factors, and effectiveness of the HLH-94/2004 regimens and hematopoietic stem cell transplantation (HSCT) in pediatric patients with primary hemophagocytic lymphohistiocytosis (pHLH) in China. METHODS: A retrospective analysis was performed on 38 patients with pHLH at Beijing Children's Hospital. RESULTS: PRF1 (34.2%) and UNC13D (31.6%) were the most common mutations in the pHLH. Thirty-eight patients were treated with the HLH-94/2004 regimens after diagnosis. Twenty-six patients (72.2%) responded to first-line treatment (complete response: 55.5%, partial response: 16.7%). The median survival time was 23 months. The overall survival (OS) rate at 3 years was 74.7%. There was no significant difference in the response rate (72% vs. 63.6%, P=0.703) or 3-year OS (83.6% vs. 66.7%, P=0.443) between the patients treated with the HLH-94 regimen and those treated with the HLH-2004 regimen. The incidences of all side effects in patients treated with the HLH-94 or HLH-2004 regimen were 32.0% and 18.2%, respectively (P=0.394). Among 15 patients treated with HSCT, neither the preconditioning regimen nor the donor type affected patient prognosis (P=0.205 and P=0.161, respectively). The disease status (remission or nonremission) before preconditioning did not affect prognosis or the incidence of GVHD. Furthermore, a higher bilirubin level (≥ 30 μmol/L) was correlated with a poorer prognosis in pHLH patients (P=0.026). CONCLUSION: The effectivenesses of the HLH-94 and HLH-2004 regimens, chemotherapy and HSCT were similar in pHLH patients. A bilirubin level ≥ 30 μmol/L might be an adverse prognostic factor in pHLH.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN PEDIATRIC PATIENTS: A SINGLE INSTITUTION EXPERIENCE

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH), is a rare life-threatening syndrome of excessive immune activation. A high index of suspicion is required to make the diagnosis. The objective was identify the etiology of HLH and prognostic factors associated with severity. METHODS: Retrospective study at Federico Gómez Mexico Children's Hospital in patients aged 0-18 years diagnosed with HLH from January 1st 2010 to December 30th 2019. Data collected incuded, age at diagnosis, gender, family history, cause of HLH, symptoms, laboratory testing, bone marrow pathology, mortality, diagnostic suspicion and treatment. Descriptive analysis and x2 statistics were used. RESULTS: A total of 47 patients were included. The median age at the time of diagnosis was 68 months (2-192 months). 44.6% were females and 55.5% were males. The most frequent symptom was fever (97.9%). Underlying triggers of HLH were as follows: infections in 28(59.57%), human inborn error of immunity in 6(12.76%) 1 of them patients in the setting of X-linked Agammaglobulinemia, autoimmune diseases in 5(10.63%), malignancies in 4(8.5%), drugs in 2(4.25%), Graft versus host disease in 1(2.12%) and 1 without known trigger. The median time of diagnosis was 24 days(2-210 days). 44(93.6%) had ferritin levels >500 and 44(93.61%) had some degree of hepatic dysfunction. Bone marrow biopsy demonstrated hemophagocytosis in 85.1%. Factors associated with severity were cutaneous involvement(p=0.05), ferritin >2,000 (p=0.01) and respiratory symptoms(p=0.000025). Overall, the mortality rate was 40.42%. Mortality was higher among patients with a longer hospital staying in the intensive care unit(p=0.04). 27 (57.44%) were treated HLH 2004 protocol, 11 (23.4%) with dexamethasone and cyclosporine A, 6 (12.76%) with dexamethasone and intravenous immunoglobulin and the rest with another treatment. CONCLUSION: The respiratory symptoms, cutaneous involvement and ferritin >2,000 had a statistically significant increased severity.

CHARACTERISTIC OF ADULT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS DEPENDING ON CANCER STATUS

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PURPOSE: In adults, most Hemophagocytic lymphohistiocytosis (HLH) cases are reported in patients with cancer or inflammatory conditions. Identification of an underlying condition is essential for specific treatment and improvement of survival. We aimed to compare characteristics and outcomes of secondary HLH depending on cancer status among adults. METHOD: We have retrieved database of HLH patients between 2005 and February 2019 in Besancon university hospital. Diagnosis of HLH was retained according to Histiocyte Society criteria. Patients with solid cancer/ hematological malignancy were classified in cancer group if diagnosis of neoplasia was performed in the 6 months prior or following the HLH diagnosis. RESULTS: Twenty nine patients were included in the study (15 patients in "malignancy-associated HLH (M-HLH)" and 14 in "other secondary HLH (S-HLH)"). Mean age of patient was 61.0 years [43.0; 75.0] and a 1:1 sex ratio. The most frequent condition in "M-HLH" was hematological malignancy (n=12); and in the "S-HLH", it was adult-onset Still disease. Weight loss over than 10 % , headache and enlarged lymph nodes were more frequent in M-HLH group (p=0.012, p= 0.042 and p=0.039 respectively). Biological tests were similar between groups except higher phosphatase alkaline level (160 (±79.5) vs 477 (±716) p= 0.014) and CRP level (189 (±121) vs 112 (±86.9); p= 0.085) in M-HLH. Infections at diagnosis was frequent (n= 27/29) with mostly virus replication (n=21). Almost half of patient (41%) were hospitalized in intensive care unit with similar proportion between groups (p= 0.88). Mortality rate tended to be higher in M-HLH group at the first month and during the two years follow-up (p=0.25 and p=0.065 respectively). CONCLUSION: Few clinical features (i.e. weight loss, headache and enlarged lymph nodes) and biological abnormalities (elevated alkaline phosphatase) are associated with an increased probability of malignancy in secondary HLH among adults.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: CLINICAL, LABORATORY CHARACTERISTICS AND OUTCOMES OF TWENTY-ONE PATIENTS IN A SINGLE INSTITUTION

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PURPOSE: The hemophagocytic lymphohistiocytosis (HLH) comprises a systemic hyperactivation of macrophages that requires prompt recognition of symptoms and early treatment. In this meaning, we described clinical and laboratory characteristics, therapeutic modality and outcome of patients with HLH treated in a pediatric oncology hospital. METHOD: We reviewed the medical records of 21 patients with HLH between January 2000 and February 2019 in a single institution. Survival curves were adjusted by Kaplan-Meier and compared with Log-Rank or Breslow test. RESULTS: HLH mainly affected females (ration of 1:1,33) with a mean age of 5,89 years. Seven patients had primary HLH (involving PFR1 mutation, STXBP2 mutation, UNC13D mutation, Chediak-Higashi, ataxia-telangiectasia, consanguineous parents). Eight had secondary disease (caused by leishmaniasis; chemotherapy; immunosuppression in liver transplantation; fungal peritonitis; EBV infection) and 6 patients were not tested for genetic mutations. Fever was the most frequent clinical sign and hyperferritinemia was the most prevalent laboratory abnormality. The protocols used were HLH - 94 in 4 patients (19%) and HLH - 04 in 16 patients (76.1%), one patient did not follow protocols. Twenty patients were admitted to the intensive care unit (ICU) at some point. Fifteen (71,4%) patients presented resolution criteria and eight (53,3%) of them presented reactivation. The mortality rate was 52,3% and the mean time between diagnosis and death was 9,98 months. 5-year overall survival (OS) was 39,5%. There was no difference between OS according to type of HLH. We observed a significant difference in prognosis associated with reactivation of HLH. These patients demonstrated an estimated 5-year OS of 25%, while all patients that did not reactivate were alive until the end of follow-up. CONCLUSION: HLH mainly affects children under 6 years old and the secondary type is the most common. ICU is necessary in most cases. The prognosis is poor, especially in patients who reactivate.

A NOVEL INFLAMMATORY INDEX IS SUFFICIENT TO IDENTIFY HEMOPHAGOCYTIC LYMPHIHISTIOCYTOSIS IN ADULT PATIENTS WITH HEMATOLOGIC MALIGNANCIES

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyper-inflammatory syndrome which may occur in adult patients with hematologic malignancies (HM). The diagnosis of HLH in this context (HM-HLH) is hampered by a number of factors. The diagnostic criteria are derived from a very different population, pediatric patients with familial HLH. Furthermore, many of the HLH diagnostic parameters are directly impacted by the underlying HM and may reflect processes other than hyperinflammation. We aimed to determine the discriminatory value and optimal cutoffs of currently used HLH diagnostic criteria in patients with HM-HLH versus patients with HM alone. METHODS: We conducted a multi-center retrospective study of 212 adults with HM +/- HLH, in whom testing for HLH was performed. We analyzed a discovery cohort to establish the optimal cutoffs for laboratory parameters used for the diagnosis of HM-HLH using receiver operating curves (ROC) and validated their performance in a validation cohort. RESULTS: While all parameters apart from fibrinogen were able to distinguish patients with HM-HLH versus those with HM without HLH, ferritin and sCD25 had the greatest discriminatory power. ROC demonstrated optimal cutoff of >5,600 U/mL for sCD25 (sensitivity/specificity 76%/78%, AUC=0.83) and a cutoff of >1,300 ng/ml for ferritin (sensitivity/specificity 76%/76%, AUC=0.83). Combining the two markers to create a novel inflammatory index (HLH-INFL) yielded superior diagnostic ability (AUC =0.86) for identifying the full syndrome of HLH. With these optimized cutoffs, HLH-INFL demonstrated a specificity of 92% and a positive predictive value of 90%, making it a clinically useful confirmatory criteria. CONCLUSION: HLH-INFL, an index comprising only ferritin and sCD25 at optimized cutoff levels is highly specific and sensitive for diagnosing HLH in HM patients. These findings further support that HLH in the context of HM is an intrinsically inflammatory condition which may be viewed as an immune complication of malignancy.

NOTES

A 15-MONTH OLD CHILD PRESENTING WITH HIGHLY AGGRESSIVE BRAF+ MULTISYSTEM LCH WITH CNS INVOLVEMENT: IMMUNE CELL AND CYTOKINE PROFILES

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A 1.5 year old boy presented with very high risk LCH and massive infiltration of the cerebellar middle fossa. Monthly pulses of low dose cytarabine plus MEK inhibitor were initiated. Our patient experienced increasingly severe fever, and fatigue during infusions of cytarabine, Despite the premedication with indomethacin and corticosteroids we could not prevent unbearable symptoms so we terminated treatment with cytarabine completely after 4th cycle. (initially ment to last 12 months).Our patient achieved the complete resolution of LCH lesions at four months evaluation. Repeatedly documented BRAF positivity in CSF cleared completely at 4 months evaluatuion as well. Positivity of BRAF-V600E in bone marrow is lasting and is reason why he is still on BRAF+MEK inhibitors. Clinical symptoms of cytokine storm were accompanied with high CRP and very high presepsin.We analyzed monocyte subsets and their maturation markers within peripheral blood mononuclear cells isolated from whole blood, as well as we detected cytokines by multiplex cytokine array in plasma and liquor samples. We found a high degree of fluctuation in monocyte subset frequencies in peripheral blood across multiple timepoints in patient with severe LCH after initiation of treatment when compared to two patients in remission. We observed that innate immune parameters including monocytes maturation, phagocytic capacity increased by cytarabin treatment initiation, while frequency to phagocytes remains stable after 7 months post treatment initiation resembling the level of patients in remission. However, the amount of phagocyted material remains lower compared to patients in remission. Cytokine analysis revealed, that the treatment with BRAF/MEK inhibitors decreased the amount of many pro- and anti-inflammatory cytokines present in plasma. These results highlight the fluctuation of monocyte and cytokine production profiles during the course of therapy. Observed strong increase of presepsin (sCD14) levels after the cytarabin administration will be further analysed in context in changes of innate immune markers.

HYPER MAPK/ERK SIGNALING IN DCS CAUSES INCREASED LPS-INDUCED TNFA AT THE POST-TRANSCRIPTIONAL LEVEL

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PURPOSE: Increasing evidence suggests Langerhans Cell Histiocytosis (LCH) has a reactive nature. LCH is driven by abnormal mononuclear phagocytes closely related to dendritic cells (DCs) with hyper-MAPK/ERK signaling, most commonly due to BRAF-V600E mutation. Since DCs are poised with Toll like Receptors (TLRs), which signal through the MAPK/ERK pathway to incite an immune response, we hypothesize that LCH cells have a hyper-TLR response. METHODS: To address this, we measure LPS-induced TNFa production using an animal model of LCH, the CD11c-Cre:BRAFV600E flox mouse which expresses BRAF-V600E in DCs. Mice were injected with LPS before measuring levels of serum TNFa and tnfa transcripts of CD11c+ splenocytes. To determine if the TNFa phenotype is reversible, cultured BMDCs and CD11c+ splenoctyes were pre-treated with a V600E inhibitor and stimulated with LPS. We measured intracellular TNFa by flow cytometry, secretion and reuptake of TNFa, tnfa and tlr4 transcripts, NFkB signaling, and TACE activity. RESULTS: LCH mice have increased LPS-induced circulating TNFa compared to WT. V600E-BMDCs and splenic-DCs have a reversible LPS-induced increase in TNFa secretion and intracellular accumulation. V600E-BMDCs and CD11c+ splenocytes have decreased LPS-induced tnfa transcripts compared to WT. Levels of tlr4 mRNA and downstream NFkB signaling are decreased in the LCH model. There is no difference in TACE activity or TNFa reuptake. CONCLUSION: Hyper MAPK/ERK signaling in DCs causes a hyper LPS-induced TNFa response, despite diminished LPS signaling. Decreased tlr4 transcripts at baseline could be responsible for the decreased LPS-induced NFkb signaling and tnfa transcription. Increased secretion of TNFa from LCH cells is not due to increased TACE activity or decreased reuptake. Increased intracellular TNFa indicates a cell intrinsic, post-transcriptional mechanism. Current experiments are analyzing the rate of degradation and translation of TNFa, both of which are implicated by MAPK/ERK signaling. These data indicate novel effects of BRAF-V600E on LPS-induced TNFa production.

GENOTYPING OF BRAF WILD-TYPE LANGERHANS CELL HISTIOCYTOSIS AND IDENTIFICATION OF A NOVEL MAP2K1 INDEL

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Langerhans cell histiocytosis (LCH) has a wide range of clinical presentations from self-resolving single-organ lesions to potentially lethal multi-organ disease. Molecular profiling has become an important aspect of clinical care through the identification of new risk strata and to direct the use of targeted therapy. All patients demonstrate hyperactivation of the MAPK/ERK pathway and a causative mutation has been identified in up to 90%. BRAFV600E mutation is the most frequent, occurring in about 50-65% of LCH patients, but BRAFwild-type cases comprise a wide range of other abnormalities. In this study, we used amplicon-based targeted next generation sequencing (NGS) of FFPE-derived DNA to describe these mutations in a cohort of 22 BRAF wild-type children and adults referred to a single UK institution (median age 9 years, age range 0.6-49 years, 12 females and 10 males). A median coverage of 2500 variant reads was obtained across the panel. 8/22 (36%) samples had poor target coverage (<700 reads, ROC, $p<0.002$) probably due to poor quality of DNA isolated from FFPE tissue. Potentially causative mutations were found in 7/22 (32%) patients including MAP2K1 mutations in two SS-LCH patients and BRAF in-frame deletions (p.486-491NVTAPT>T, exon 12) in two MS-LCH patients. Two MS-LCH patients presented with somatic mutation in ARAF and a single KRAS (G12S) mutation was found in a patient with SS-LCH. All of these mutations have been previously described in LCH except for the novel in-frame deletion of MAP2K1 (p.40-53LELDEQQRKRLEAF>L, exon 2). This was validated by Sanger sequencing. The remaining 7/22 samples with no mutation were sent for analysis of fusion transcripts but none were detected. As reported by others, amplicon-targeted NGS is able to detect mutations in a substantial proportion of BRAF wild-type LCH patients, although the quality of nucleic acids accessible from FFPE-fixed specimens was limiting in about one-third of cases.

ARE JUVENILE XANTHOGRANULOMA IN LANGERHANS CELL HISTIOCYTOSIS PATIENTS A POSSIBLE SIGN OF RELAPSE? PRELIMINARY DATA FROM A SYSTEMATIC REVIEW OF THE LITERATURE

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PURPOSE: to analyze the clinical features and outcome of pediatric patients diagnosed and treated for Langerhans cell histiocytosis (LCH) subsequentially developing juvenile xanthogranuloma (JXG). METHODS: We performed a systematic review of the literature in accordance to the PRISMA guidelines. Search was performed in March 2020. Queried terms include a combination of "LCH" and its synonyms with "xanthogranuloma". We analyzed and selected only paper describing pediatric patients developing histologically proved JXG after having received chemotherapy for a previous LCH. RESULTS: We collected 10 paper, describing 13 different patients. Median age at diagnosis of LCH was 3 years. 8/13 patients were males. All but one patients developed a multisystem LCH (including 3 LCH with neurologic degeneration), treated with a combination of corticosteroid and vinblastine with complete or partial response in all cases. The median time to JXG diagnosis was 33,5 months. The JXG involved the skin only in 12 cases and the both bones and skin in one case. Two patients were tested for BRAF mutations and both bear a V600E mutation. After a median of 42 months from diagnosis of JXG, 9/12 patients experienced a progressive disease, relapse or partial remission. No patient died. CONCLUSIONS: The association of LCH with other histiocytoses (mixed histiocytosis) is rarely reported in the literature and represent an under investigated field in histiocytosis research. Development of JXG after treatment for a previously diagnosed LCH is a matter of clinical interest giving the possible biological association between the two disorders. LCH may show a histological spectrum of maturation (also with JXG-like pictures) caused by aging of the lesions or possibly histological response to therapy. Therefore, the development of JXG in LCH patients may represent a form of disease relapse and deserve more attention. Case-control studies are needed to identify the biological and clinical significance of this phenomenon.

INCREASED ANGIOGENESIS CHARACTERISES CUTANEOUS LANGERHANS CELL HISTIOCYTOSIS

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PURPOSE: TGFβ is an important factor in cancer progression, promoting both ECM remodelling and angiogenesis. Increasing evidence shows that Langerhans cell histiocytosis (LCH) exhibits many of the "hallmarks of cancer", and in this study we sought to evaluate TGFβ expression, angiogenesis and matrix disruption in biopsies of cutaneous disease. METHODS: Eleven formalin-fixed patient samples (5 SS-LCH; 6 MS-LCH) were subjected to immunohistochemistry or special staining (picrosirius or Herovici) to investigate CD1a, CD207, TGFβ1, CD31 and ACTA2 expression, as well as matrix perturbation. Slides were evaluated under bright-field or cross-polar microscopy by two independent assessors to allow semi-quantitative assessment of angiogenesis and fibrosis. RESULTS: Co-localisation with CD207 confirmed TGFβ production by lesional Langerhans-like cells. Special staining revealed ECM remodelling, but not frank fibrosis. Semi-quantitative analysis revealed increases in vessel formation in ten out of 11 samples (either within or closely associated with lesions). This analysis did not, however, discriminate single- from multi-site disease. CONCLUSION: While ECM remodelling and angiogenesis are normal physiological process, their disruption promotes tumour progression. Herein, we report localised angiogenesis and tissue remodelling in LCH, providing further evidence that LCH does indeed display features of cancer. Critically, we identified lesional Langerhans cells as a source of TGFβ that could drive these processes. That LCH is truly a malignant disorder (with implications for management) remains to be established. Moreover, we did not detect histological differences between single- and multi-site disease, which are known to have different outcomes. We hope that further investigation of LCH lesions will yield information of prognostic value.

INDOMETHACIN IS AN EFFECTIVE TREATMENT IN ADULTS WITH BONE LANGERHANS CELL HISTIOCYTOSIS (LCH)

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PURPOSE: The aim of this study was to analyze the results of treatment with indomethacin in adults with Langerhans Cell Histiocytosis (LCH) and bone involvement, managed over a 20-year period. METHODS: Between 1999 and 2019, 54 adults with a median age of 39 years (range 20-66) with bone LCH (30 unifocal and 24 multifocal diseases), were treated with indomethacin, at a dose ranging from 1 to 2 mg/kg/day, as first line in 39 patients, and after multiple disease reactivations in 15 patients. Indomethacin was given as a single agent in 49 patients (91%) with isolated bone disease, and combined with vinblastine and prednisone in 5 patients with recurrent multisystem disease. RESULTS: Overall response to indomethacin was achieved in 53/54 (98%) patients, in 25 (47%) of them it was complete. The median time to response was 9 months (range 1-23). All 39 (100%) untreated patients, and all but one of the 15 (93%) patients with recurrent disease achieved a response, that was complete in 20/39 (51%) and in 5/14 (36%), respectively. The median duration of treatment was 17 months. Reactivation occurred after a median time of 36 months (range 17.5-65.7) in 9 patients treated for advanced disease, most of them with multisystem, or multifocal disease. Side effects, observed in 17 patients, were limited, and led to treatment discontinuation in one case only. The 5-year reactivation free survival was significantly higher in patients given indomethacin as first line treatment (81.2%, IC 95% 78-84, p=0.01), and in those with unifocal bone disease (87.5%, IC 95% 86-90, p=0.007). To date, all patients are alive. CONCLUSIONS: Our results showed that indomethacin was an effective drug in adults with single-system, unifocal or multifocal bone LCH, mainly as front-line treatment. In addition, indomethacin was well tolerated, both in older patients and in those heavily pretreated.

DISCREPANCIES BETWEEN F-18-FDG PET/CT FINDINGS AND CONVENTIONAL IMAGING IN PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS PATIENTS

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PURPOSE: Accurate risk stratification of LCH is essential as management can range from conservative in single system, low-risk for CNS involvement lesions to intensive chemotherapy for multi-system or high-risk disease. Additionally, being able to differentiate active from inactive lesions is essential for both prognostic reasons and to avoid potentially unnecessary treatment. METHODS: A retrospective review was performed on all patients with histopathology confirmed LCH at CCHMC between 2009 and 2019. PET/CT's at either the time of diagnosis or the first available scan were compared to other imaging modalities performed within 1 month as long as no major medical or surgical intervention had taken place in the interim. RESULTS: 101 PET/CT's were included in the review. A discrepancy between PET/CT and conventional imaging occurred on 41 occasions. On 14 occasions, increased uptake was observed on PET in an area with no identifiable lesion on conventional imaging. On 27 occasions, lesions were found on conventional imaging where no increased uptake was observed on PET. On 7 skeletal surveys, 1 radiograph, 6 diagnostic CT's, 1 MRI, and 5 CT portions of the PET/CT, no lesion was identified in an area with increased F-18-FDG uptake. This occurred on 12 instances in bone and 1 in the thymus. On 10 skeletal surveys, 3 diagnostic CT's, 13 MRI's, 2 bone scans, and 3 CT portions of the PET/CT, a lesion was identified in a location without increased F-18-FDG uptake. This occurred on 24 instances in bone, 6 in the CNS, and 1 in the lungs. CONCLUSION: F-18-FDG PET/CT is vital in the evaluation of LCH lesions given its ability to detect LCH lesions not detectable on conventional imaging modalities, as well as its ability to distinguish active from inactive disease. MRI and diagnostic CT are still useful adjunctive tests for identification of CNS and lung lesions.

OUTCOMES OF CHILDREN WITH BIOPSY PROVEN LANGERHANS CELL HISTIOCYTOSIS(LCH)TREATED AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL(RCWMCH) FROM 1998 - 2017

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PURPOSE: To measure the outcomes of children diagnosed with LCH at Red Cross War Memorial Children's Hospital (RCWMCH) from 1998 to 2017. METHODS: A retrospective review of all children diagnosed with LCH at RCWMCH over 20 years. Data was collected from patient folders, entered into Microsoft Access and analysed in Statistica. Where two groups were compared using the log rank test, a p value of 0.05 was significant. RESULTS: There were 30 patients between the ages of 1 month and 12 years with a median age of 2 years. Seventeen patients (56.7%) presented with multisystem disease with risk organ involvement (MS RO LCH). Twelve patients (40%) had single system LCH (SS LCH) and only one patient had multisystem disease with no risk organ involvement. The patients were treated with modified versions of serial HS LCH-protocols. The 5-year overall survival (OS) for the whole group was 83% with a 5-year event free survival (EFS) of 58%, but SS-LCH patients fared better with OS of 100% and EFS of 90%. Considering the whole group, OS was lower for patients <1 year of age (43.7% versus 100% with a p value of 0.002), as was EFS (15.1% versus 77.3% with a p value of 0.008). CONCLUSION: Patients with MS RO LCH had a poorer outcome despite more intensive therapy. The 5-year OS and EFS were consistently lower in those patients less than 1 year of age at diagnosis.

LONGITUDINAL MONITORING OF PERIPHERAL BLOOD BRAFV600E IN CHILDREN WITH HIGH RISK LANGERHANS CELL HISTIOCYTOSIS [TREATED ACCORDING TO UK INTERIM GUIDELINES FOR USE OF MAP KINASE INHIBITORS]

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Patients with refractory multisystem Langerhans cell histiocytosis (LCH) are conventionally treated with high dose salvage chemotherapy. When salvage fails, BRAF inhibitors can induce dramatic clinical improvement of BRAFV600E disease. Within the spectrum of refractory LCH, the clinical utility of longitudinal monitoring of circulating mutated alleles, is undefined. In particular, it is not known whether suppression or clearance of mutation is associated with durable treatment-free responses. To define the relationship between disease activity and mutation burden, we report longitudinal monitoring of eight high risk patients over a median of 24 months (range 10-47). Three patients responded to conventional chemotherapy with cytarabine and cladribine followed by allogeneic transplantation or maintenance. One RO+ patient cleared BRAFV600E and remains in a durable clinical remission. The second RO+ patient did not clear their mutation with chemotherapy, received allogeneic transplantation, and remains clinically well but with a high level of mutation despite full donor engraftment. The third patient was RO- and transiently cleared BRAFV600E but mutation remains detectable on maintenance therapy, with continuing clinical remission. Five patients received targeted therapy. All had excellent clinical responses but BRAFV600E persisted at up to 0.1 mutated allele fraction. Neither concomitant high dose conventional chemotherapy or slow weaning was successful in clearing their mutation. Abrupt withdrawal of targeted treatment was associated with rapid relapse within days. One patient progressed to ALL with clonal BRAFV600E mutation (0.11% BM; 0.162% PBMC). Mutation was highest in cell-free DNA compared with mononuclear cells, particularly in patients receiving conventional treatment. Urinary cell-free DNA provided the least sensitive level of detection. In conclusion, targeted therapy induces dramatic clinical responses in the face of a high level of mutation. Similar high-risk patients treated conventionally may also achieve clinical responses while apparently failing to clear mutation. Longer follow up is required to determine whether these patients will relapse.

INDETERMINATE CELL HISTIOCYTOSIS IN PAEDIATRIC POPULATION: A REVIEW OF THE LITERATURE

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PURPOSE: Indeterminate Cell Histiocytosis (iCH) is a rare entity thought to derive from precursor of Langerhans Cells, although these cells have never been clearly identified. iCH express markers of both Langerhans Cells Histiocytosis (LCH) and macrophages, S100 protein and CD1a, but in contrast to LCH, do not present Birbeck granules by electron microscopy (EM). Since the first description, several case reports have supported the concept of iCH as a distinct clinico-morphologic entity, presenting mostly as skin lesions and often associated to second hematopoietic malignancy. Aim of this work is summarize the main features of iCH in paediatric patients. METHODS: Comprehensive literature review of case reports, published since 1991 to 2018, on the clinical, morphological, histopathological findings of iCH in paediatric population. RESULTS: The literature describes 13 cases of iCH, although in 3 of them the diagnosis is not confirmed based on the revised WHO classification. Cutaneous affection was always described and mostly in the form of papules and/or nodules involving the head/neck, limbs and trunk. Only 1 patient presented extracutaneous manifestations in bone and kidney. When described, iCH principally exhibited a dense atypical histiocytoid infiltrate with a strong CD1a and CD68 positivity while the staining pattern and intensity for S100 varied widely. EM demonstrated an absence of Birbeck granules. A clonal relationship between iCH and an associated hematopoietic malignancy was demonstrated in only 1 case for trisomy 8 in the setting of juvenile myelomonocytic leukaemia. Various therapeutic approaches have been reported, such as phototherapy with narrowband ultraviolet B and several chemotherapeutic strategies with clinical benefit. Only 1 death due to iCH was reported on a new-born with systemic disease. CONCLUSION: Some iCH may show overlapping features with other subtypes of histiocytoses but the awareness of this entity is crucial to prevent misdiagnoses and prompt investigation of possible associated haematological malignancies.

EPSTEIN-BARR VIRUS INFECTIONS IN PATIENTS WITH BRAFV600E+ MULTISYSTEM RISK ORGAN INVOLVEMENT LANGERHANS CELL HISTIOCYTOSIS

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PURPOSE: Langerhans cell histiocytosis (LCH) is a heterogeneous disease, characterized by accumulation of dendritic cells in organs such as the skeleton, the skin and the pituitary. LCH is treated with chemotherapy and gene targeted therapy. Treatment can result in long term side effects such as secondary malignancies, endocrine disorders, and cardiomyopathies. Additionally, there have been case reports of Epstein-Barr virus (EBV) lymphoproliferative disease (LPD) as a long-term effect from treatment. METHODS: Here we present two cases with BRAFV600E+ MS RO+LCH who developed EBV complications while undergoing treatment. RESULTS: 6-month-old diagnosed with multisystem risk organ LCH (MS RO+ LCH) involvement (lymph node, skull, mediastinal mass) in August 2013, by a lymph node biopsy. The tumor was found to be BRAF V600 E+. The patient underwent treatment per LCH stratum III with vinblastine and prednisone, followed by a short course of cladribine, and clofarabine. In May 2014, she started Debrafenib, until November 2016 when she developed EBV positive non-Hodgkin's lymphoma. EBV DNA PCR at that time was elevated to 3739 copies/mL. She started ANHL 1131 on December 2016. She had disease progression and was switched to ADVL1412. She eventually succumbed to her disease. The other case was a 5-year-old male with MS RO+ LCH BRAF V600 E+ diagnosed on 6/3/2015 and treated on Trametenib for 2.5 years. Five years from diagnosis he presented with the sudden development of significant hepatosplenomegaly and persistent pancytopenia. EBV quantitative titers were sent and they were elevated to 815 copies/mL. He continued to have EBV reactivation and was treated with Rituximab and intravenous immunoglobulins. CONCLUSION: Though EBV infections can be attributed to multiple causes in these patients such as immunosuppression, BRAF/MEK inhibition or underlying genetic predisposition, it is important to have EBV infection on the differential in patients with LCH presenting with adenopathy, prolonged fevers and cytopenias.

CELL FREE BRAFV600E: A SURVEILLANCE MARKER PEDIATRIC LANGERHAN CELL HISTIOCYTOSIS (LCH) DISEASE?

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BACKGROUND: Langerhans cell histiocytosis (LCH) is a heterogeneous disease, characterized by accumulation of dendritic cells with features similar to epidermal Langerhans cells in organs such as the skeleton, the skin and the pituitary. The clinical course can vary from a self-limiting disease to a rapidly progressive one leading to death. Reactivation can occur after a long period of disease control. The BRAFV600E mutation has been the mainstay of targeted therapy and disease management. The BRAFV600E allele can be detected in circulating cell-free DNA (cfDNA) and be used to mirror response to treatment or detect disease. METHODS: We followed cfBRAFV600 in a cohort of patients with BRAFV600E mutated LCH throughout different time points of therapy. We sought to correlate these levels with disease recurrence confirmed by clinical presentation and imaging. RESULTS: Median age at time of diagnosis was 2 years of age [6 months-13 years] in a predominantly male sample. In patients with RO-LCH bone involvement LCH, cfBRAFV600E was used as a marker for surveillance. All had undetectable cfBRAFV600E and without clinical evidence of disease. In one patient with RO+MS LCH, cfBRAFV600E became minimally detectable with onset of clinical symptoms (Level of detection (LOD): 0.07%, 3 mutant copies/mL), and became fully detectable at time of recurrence of disease (LOD: 0.5-0.01%). In another symptomatic patient with recurrence of RO+MS LCH, cfBRAFV600E was detectable in urine (greater than or equal to 0.107 LOD) and not detectable in blood (LOD 0.17). Both these patients were on targeted therapy with a MEK or B-RAF inhibitor. CONCLUSION: cfBRAFV600E is a good marker to use to both detect disease response while a patient is undergoing therapy and after end of therapy as a surveillance marker. Future studies will focus on standardized testing and further categorizing the threshold of detection at which point patients become clinically symptomatic.

LANGERHANS CELL HISTIOCYTOSIS AND ULCERATIVE COLITIS: ON SAME INFLAMMATION SUBSTRATUM? A CASE REPORT.

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PURPOSE: Langerhans cell histiocytosis (LCH) and Ulcerative colitis (UC) are rare diseases, in childhood. LCH associates myeloid cell recruitment and survival in inflammatory conditions with tissue destruction and bone resorption. It occurs predominantly in children and multiple organs may be affected including bone (80% of the patients). LCH lesions are heterogeneous and form aggressive granulomas containing CD1a+ CD207+/−cells cells mixed with macrophages, T cells and eosinophils. The etiology of LCH remains controversial between an inflammatory disorder, a neoplasm, or even both since induction of long-term dendritic cells survival by inflammation may license accumulation of mutations. Recent data support the hypotheses that a combination of cytokines/growth factors may be important in varying LCH clinical presentations. Ulcerative colitis likewise has also a mild inflammation ground. METHODS: We present a 7 year old girl who was diagnosed at the age of 5 with low risk LCH, on the lower jaw. RESULTS: The LCH lesion resolved after biopsy, without chemotherapy. Two years later at the age of 7, she presented with diarrhea and hemorrhagic stool. A colonoscopy was performed and biopsy for a possible gastrointestinal involvement of LCH. It was negative for LCH and a diagnosis of ulcerative colitis was set. CONCLUSION: It is known that LCH may have a reactivation in the first two years after diagnosis. In the presenting case, there was a second inflammatory disease (UC) in the first two years after LCH diagnosis. It was a reactivation of the immunological dysfunction? It is of great importance that under a possible same inflammatory substratum, the two diseases co-exist.

USE OF METHOTREXATE IN REFRACTORY AND RELAPSED LANGERHANS CELL HISTIOCYTOSIS

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PURPOSE: To evaluate the use of intermediate dose methotrexate (ID-MTX) in refractory and relapsed Langerhans Cell Histiocytosis (LCH), as currently used agents have not been shown to be consistently effective and are associated with significant adverse events. Outcomes include progression free survival (PFS) and adverse events. METHODS: Retrospective chart review of all LCH patients receiving ID-MTX at a large, academic-affiliated pediatric hospital. RESULTS: A total of 17 patients were included. Mean age at diagnosis was 2.5 years. Single system disease (SS) was found in 3 patients (17%): one with neurodegenerative disease, one with multifocal bone disease and CNS risk lesions (CNS+), and one with multifocal bone disease without CNS risk lesions (CNS-). Multi-system disease (MS) was found in 14 patients (82%): four without risk organ involvement (RO-)/CNS-, six with RO-/CNS+, one with risk organ involvement (RO+)/CNS-, and three with RO+/CNS+ disease. All patients received at least one cycle of 500 mg/m2 methotrexate intravenously. End of therapy response of non-active disease or better, active disease was found in 12 patients (71%), two of whom subsequently relapsed. Disease progression occurred in 6 patients (35%). One-year PFS for the MS RO- group and MS RO+ group were 60% and 75%, respectively ($p = 0.92$). One-year PFS for the MS CNS+ group and MS CNS- group were 78% and 50%, respectively ($p < 0.05$). Occurrence of neutropenia was lower with ID-MTX as compared to clofarabine ($p < 0.05$). Occurrence of febrile neutropenia was lower with ID-MTX as compared to cladribine ($p < 0.05$). CONCLUSION: ID-MTX was shown to be beneficial in the treatment of MS CNS+ LCH. ID-MTX has a favorable side effect profile and can be considered in patients with prior treatment failures, difficult to treat disease, or contraindications to other therapy.

LANGERHANS CELL HISTIOCYTOSIS (LCH): UKRAINIAN PROSPECTIVE STUDY IN A REAL-LIFE COHORT

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PURPOSE: Clinical characteristics and molecular alterations (MAPK/ERK pathways) in identifying high-risk group patients, and the correlation of these factors with treatment outcome. METHOD: 17 patients with LCH (range 1-58, median age 29.5) were treated at the NCI Department of Oncohematology (Kyiv, Ukraine). Six and eleven pts had SS-LCH and MS-LCH histiocytosis stratification type, respectively. The detection of 23 mutations in BRAF (V600E) and NRAS (12, 13, 61 codons) genes was performed using a real time PCR analysis with TaqMan Probe-Based Assays (Applied Biosystems, USA). RESULTS: The ORR was 46.6%, with a 66.6% relapse rate during follow-up (median duration - 31.9 months). 50% vs 75% of relapse cases were diagnosed in SS-LCH vs MS-LCH groups, respectively ($p<0.05$). There was no significant difference in the EFS between LCH stratification types (25% in SS vs 20% in MS type, respectively $p=0.6$). A 3-year EFS rate in patients with early relapse was 14% vs 33% in patients with late relapse with HR of 4.9 [95% (CI) 1.3-18.7, $p=0.009$]. The BRAF c.1799T>A, p.V600E mutation was detected in 46.1% (6/13) of cases: 3 patients had an early relapse and 3 patients had a stable disease. We noticed no significant independent effect of BRAF mutation on the LCH clinical outcome, except NRAS (2/13), which appeared to be a strong and independent marker of LCH prognosis. A multivariate analysis showed the NRAS Q61R mutation presence is associated with poor event free survival in LCH patients with HR of 6.1 [95% (CI) 0.2-12.6, $p=0.008$]. CONCLUSION: Our study showed that patients with NRAS mutation should belong to a high-risk group with poor clinical outcome. Whereas BRAF mutation status had no impact on disease progression and clinical outcome.

LANGERHANS CELL HISTIOCYTOSIS (LCH) CENTRAL NERVOUS SYSTEM (CNS) NEURODEGENERATION DESPITE LONGSTANDING BRAF INHIBITION

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PURPOSE: To highlight the development of LCH CNS Neurodegeneration (LCH-ND) in a 6-year- old boy who had been on a BRAF inhibitor, uninterrupted for 3.5 years. METHODS: This boy presented at the age of 18 months with bloody discharge from his right ear, posterior auricular swelling, recurrent ear infections, persistent nappy rash and prolonged cradle cap. Head CT showed abnormalities in the mastoid bilaterally; the intracranial appearances were normal. Biopsy of the right mastoid mass demonstrated BRAF V600E mutation positive LCH. Staging revealed him to have multi-system LCH (bone, skin, bone marrow). He was started on standard first line treatment with vinblastine and prednisolone but failed to respond to initial 12 weeks of therapy. He was therefore started on 5.25mg/kg/day dabrafenib. RESULTS: The dabrafenib was well tolerated and there was excellent compliance throughout. During the first 12 months of therapy all the symptoms

and signs of LCH resolved. He continued to grow normally and developed no LCH reactivation. After 3.5 years on dabrafenib, surveillance MRI revealed LCH-ND with signal changes involving the cerebellar peduncles, tegmentum of the brain stem and globus pallidi. He is clinically well, apart from longstanding slow speech development (noted at age 3 years). He is currently undergoing detailed assessments to establish if, in addition to radiological LCH-ND, he has also developed clinical LCH-ND. CONCLUSION: Clinical LCH-ND is a rare (overall 10-year cumulative incidence 4·1%; 7·8% if pituitary or skull base or orbit bone involvement; 33·1% if also BRAFV 600E+), often progressive, complication of LCH. Despite longstanding, ongoing treatment with daily dabrafenib (and control of refractory multisystem LCH), this child developed at least radiological LCH-ND. This suggests that prophylactically treating patients at high risk of LCH-ND with ongoing BRAF inhibition to prevent LCH-ND, may not be a worthwhile strategy.

HIGH PREVALENCE OF BRAFV600E IN PATIENTS WITH CHOLESTASIS, SCLEROSING CHOLANGITIS OR LIVER FIBROSIS SECONDARY TO LANGERHANS CELL HISTIOCYTOSIS

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PURPOSE: BRAFV600E mutation has emerged as a pathology defining marker for patients with Langerhans Cell Histiocytosis (LCH). Targeted therapies with RAF inhibitors have demonstrated in several studies the modulation of the pathological manifestations in high risk LCH patients with active disease. However, BRAFV600E assessment in LCH liver sequelar manifestations have not been addressed yet. Since Hospital Garrahan possess a considerable number of tissue samples, we decided to explore the presence of the BRAFV600E mutation in our cohort of patients with multisystem-LCH (MS-LCH) and liver involvement. (cholestasis, sclerosing cholangitis and liver fibrosis). METHODS: The presence of BRAFV600E mutation in formalin fixed paraffin embedded (FFPE) samples from patients with cholestatic patterns and/or liver fibrosis was assessed by high sensitivity digital droplet PCR. BRAFV600E assessment was correlated to clinical overall survival, CD1a immunostaining and histopathological parameters. RESULTS: BRAFV600E mutation was present in 9/10 diagnosis biopsies. When liver samples of patients with SC were analyzed by ddPCR, 3/10 biopsies displayed the BRAF mutation, even though CAST-PCR was not sensitive enough to detect the presence of those mutations in any sample. CONCLUSION: We found a high prevalence of BRAFV600E mutation through ddPCR but not by the conventional CAST-PCR in cases of severe liver involvement of patients with MS-LCH. BRAFV600E mutation was found even in samples that were considered histologically as LCH sequelae and did not present CD1a staining and histiocyte-like cells.

DEVELOPMENT OF BRAF V600E-POSITIVE AML IN A PATIENT ON LONG-TERM DABRAFENIB THERAPY FOR MULTISYSTEM LCH

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PURPOSE: Langerhans Cell Histiocytosis (LCH) is an inflammatory myeloid neoplasm known to develop secondary to acquired, activating mutations in the RAS/RAF/MEK pathway, most commonly the BRAF V600E mutation. We present a case of a child with recurrent high-risk LCH complicated by secondary hemophagocytic lymphocytic histiocytosis (HLH). Subsequently, while in long-term remission on targeted therapy with dabrafenib, the patient developed treatment-related acute myeloid leukemia (t-AML) with additional, acquired somatic mutations. RESULTS: The patient presented at 12 months of age with BRAF V600E positive LCH (skin, gastrointestinal tract, liver, and bone marrow). At age 3, while in remission following front-line therapy, the patient developed HLH in the setting of a multisystem LCH relapse (including neurodegenerative LCH). Despite intensive therapy for LCH and HLH, the patient had critical progression of neurologic symptoms. Dabrafenib monotherapy was initiated leading to a rapid and complete recovery. After 3.5 years on dabrafenib, the patient developed t-AML marked by BRAF V600E, monosomy 7, NRAS, and KRAS mutations and diabetes insipidus with MRI findings consistent with pituitary LCH. The patient received AML induction chemotherapy followed by matched sibling donor bone marrow transplant (BMT) as consolidative therapy in first complete morphologic remission. The patient is now >100 days post BMT and remains in clinical remission with 100% donor chimerism and no detectable BRAF V600E cell free DNA in the peripheral blood. CONCLUSION: Numerous reports have demonstrated the effectiveness of MAPK pathway inhibition in the treatment of relapsed, refractory LCH. However, little data is available of its long-term risks and curative potential. This case demonstrates the potential for malignant transformation of the LCH clone and the need for close monitoring of patients receiving MAPK inhibitors long-term. Additional research is necessary to determine the proper use of targeted therapy in LCH and to better understand its associated toxicities.

EXTENSIVE PULMONARY LCH TREATED WITH ECMO

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PURPOSE: Isolated lung LCH is rare amongst paediatric population. We describe an infant with extensive isolated pulmonary LCH who has survived with prompt placement on ECMO. PATIENT AND RESULTS: 10 months old boy presented to the Paediatric Unit with 6 weeks history of fever and respiratory symptoms culminating in rapid deterioration with pneumothorax requiring intubation, ventilation and bilateral chest drain insertion. The CXR

and CT scan of the chest show multiple large cystic structures in both lungs obliterating parenchyma. Two days later he was placed on ECMO due to progressive hypoxemia. Clinical and radiological diagnosis was of Langerhans cell histiocytosis (LCH). Screening and examination of the skin failed to show any other system involvement. Serum did not contain BRAFV600E. The LCH was diagnosed on lung biopsy. He was started on prednisolone and vinblastine 2 days post biopsy. He remained on ECMO for 24 days and developed several further pneumothoraces requiring repeated surgical interventions. After clinical, ventilatory and radiological improvement he was decannulated and started on cPAP and proceeded to be self ventilating after 6 days, initially with supplemental oxygen and then in air. BRAFV600E was negative in the tumour tissue. He was started on MEK inhibitor Trametinib, following approval for compassionate use. He was discharged home after 3 months of inpatient stay. He continues on combined therapy with vinblastine/ prednisolone/Trametinib, tolerating treatment without any significant side effects and continues to be clinically well 8 months after initial presentation. CONCLUSION: Patients with extensive pulmonary cystic disease due to LCH can have a curative outcome. Patients with pulmonary compromise and extensive disease due to LCH should have every opportunity to be placed on ECMO as this procedure allows bridging to lung recovery while appropriate LCH directed treatment is put in place.

SIROLIMUS PLUS INTRATECHAL METHYLPREDNISOLONE AND SUBCUTANEOUS ANAKINRA IN A PATIENT WITH LCH AND A NOVEL GERMLINE MUTATION ON FAS GENE

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PURPOSE: We report on the efficacy of sirolimus associated with intratechal methylprednisolone and anakinra in a patient with Langerhans Cell Histiocytosis (LCH) and a germline mutation of FAS gene causative of an autoimmune lymphoproliferative syndrome-like disorder (ALPS-likeD). METHODS: A boy with an unremarkable clinical history was diagnosed at the age of 8 with bone unifocal single system BRAFV600E-positive LCH and treated with removal of the lesion and instillation of steroid. At the age of 9 he was diagnosed with Neurodegenerative Central Nervous System-LCH (ND-CNS-LCH) and treated with Intravenous Immunoglobulin. While on treatment patient developed an acute neurological syndrome associated with longitudinally extensive spinal cord lesion as shown by MRI. He was sequentially treated with 2-Chlorodeoxyadenosine, Clofarabine and Vinblastine because of progressive clinical and neuroradiological disease. Cerebrospinal fluid showed very high cellular count, immunoglobulin and protein levels. Spinal cord biopsy showed nonspecific BRAFV600E-negative inflammatory infiltrate. NGS analysis revealed a novel germline mutation of FAS gene (p.Thr319Ile) whose functional analysis made on patient's EBV-immortalized B cells treated with FAS-ligand showed an impairment of apoptosis. Treatment with subcutaneously daily anakinra, the antagonist of IL -1, the prototypical inflammatory cytokine, was started. Subsequently we added two immunomodulators: weekly then monthly intrathecal methylprednisolone and oral daily sirolimus. Therapy lasted one year. RESULTS: Halting of clinical deterioration promptly occurred following the beginning of therapy. Cerebrospinal fluid markers of inflammation rapidly decreased in one month and stabilized in one year. CONCLUSION: Sirolimus plus intratechal methylprednisolone and subcutaneous anakinra was an effective therapy to stop disease activity, but unable to improve severe neurological sequelae and neuroradiological signs of disease. Mutation of FAS gene might have caused disruption of immune system and a spectrum of clinical manifestations overlapping with LCH. The interaction between LCH and defects of apoptosis secondary to FAS gene mutations needs to be elucidated.

CLINICAL PREDICTORS OF ADVERSE OUTCOMES IN 135 CHILDREN WITH BRAFV600E-MUTATED LANGERHANS CELL HISTIOCYTOSIS

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OBJECTIVE: To explore clinical predictive indicators of adverse outcomes in Langerhans cell histiocytosis (LCH) children with BRAFV600E mutation. METHODS: We retrospectively reviewed all newly diagnosed LCH patients with BRAFV600E mutation detected from biopsy tissues or plasma, who admitted to Beijing Children's Hospital from August 1, 2015 to November 1, 2019. Survivors were followed up until May 31, 2020. Adverse outcomes were defined as disease progression, recurrence or death. RESULTS: We enrolled 135 patients in this study. The ratio of male to female was 1.25:1. The median age at disease onset was 1.8 (0.8, 4.2) years old, and the median follow-up time was 1.6 (1.0, 2.1) years. Forty patients (29.6%) had liver, spleen or hematopoietic involvement, i.e. risk organs involved. One hundred and twenty patients (88.9%) were treated with first-line chemotherapy, 42 patients (31.1%) with second-line chemotherapy, and 41 patients (30.4%) with target therapy. A total of 49 patients (36.3%) suffered from progression or relapse, of which 1 patient died. The median event-free survival time was 1.0 (0.5-1.6) years. The results of survival analysis showed that more adverse outcomes could be observed in patients younger than 3 years old, with involvement of risk organs, skin, lung, or CNS risk sites at diagnosis, secondary hemophagocytic lymphohistiocytosis (HLH), fever, the value of circulating cfBRAFV600E >0.55%, IL-10 >4.89pg/ml, or elevated IFN-γ before specific treatment of LCH, or with persistent positive cfBRAFV600E after treatment ($P<0.05$). In Cox analysis, fever [HR (95% CI)=2.302 (1.282-4.136), P=0.005], lung involvement [HR (95% CI)=3.088 (1.647-5.788), $P<0.001$), CNS risk lesions [HR (95% CI)=3.417 (1.759-6.636), $P<0.001$], the value of IL-10 >4.89pg/ml [HR (95% CI)=2.506 (1.306-4.807)), P=0.006] were independently associated with adverse outcomes. CONCLUSIONS: In LCH children with BRAFV600E mutation, Fever, lung involvement, CNS risk lesions and the value of IL-10 > 4.89pg/ml were independent risk factors for adverse outcomes.

THE ASSOCIATION OF INDETERMINATE CELL HISTIOCYTOSIS AND HEMATOLOGICAL MALIGNANCIES

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PURPOSE: to analyze the clinical, pathological and molecular features patients diagnosed with indeterminate cell histiocytosis (iCH) developing hematological neoplasms. METHODS: We performed a systematic review of the literature in accordance to the PRISMA guidelines searching for papers containing description of iCH patients developing myeloid or lymphoid neoplasms. RESULTS: We collected 17 paper, describing 17 different patients. Median age at diagnosis of iCH was 49 years (range 0-87). Fifteen patients were males. In 12 cases, the iCH involved the skin with a generalized eruption and in four, it displayed multisystem involvement (skin, bone and risk-organ involvement). All cases showed a monomorphous proliferation of medium-sized cells positive for CD1a and S100 protein and negative for CD207/langerin. In three cases, analysis of BRAF mutation tested negative. 13 patients developed myeloid neoplasms after iCH diagnosis (including 6 acute myeloid leukemia. 4 myelodysplastic/myeloproliferative neoplasm, 2 myelodysplasia and 1 mast cell neoplasm) and the remaining four patient developed a lymphoid neoplasm (including 2 acute lymphoblastic leukemia, 1 T-cell lymphoma and 1 B-cell lymphoma). The hematological malignancy presented with B-findings, cytopenia and/or leukocytosis. Fourteen patients were treated with different combination of chemotherapy drugs. After a median of 15 months of follow up (range 3-72 months) 13 patients died of disease. CONCLUSIONS: iCH is a rare condition, classified in the L-group of the 2016 revised classification of histiocytosis. The literature describes around a hundred cases and a fifth of these, associates with a hematological malignancy. As the association of histiocytoses and hematological malignancies is estimated to occur in around 10% of patients, iCH seem to represent a category of histiocytic disorders with higher risk of developing secondary hematological tumors. The biological relationships between the two disorders have never been investigated.

SHEDDING LIGHT TO THE CLINICAL SPECTRUM OF MIXED HISTIOCYTOSES AND ITS POSSIBLE CLASSIFICATION: A SYSTEMATIC REVIEW OF THE LITERATURE

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PURPOSE: to analyze the clinical, pathological and molecular features of mixed histiocytoses (MH). METHODS: We performed a systematic review of the literature in accordance to the PRISMA guidelines. Queried terms include a combination of “Langerhans cell histiocytosis”(LCH) and its synonyms with all diagnostic categories of histiocytoses included in the L-, C- and R-groups of the 2016 Revised Classification. We analyzed and selected only paper describing histologically proved association of LCH and non-LCH. RESULTS: We collected and studied 62 paper, describing 105 different patients. According to the clinical history and histopathological results, we divide patients into 3 groups. The first (Type-1 MH) included patients with multisystem disease presenting as a synchronous or methachronous association of LCH and non-LCH. The second group (Type-2 MH) included patients treated with chemotherapy for a LCH, subsequentially developing a non-LCH. The last group (Type-3 MH) included patients with single-system, single-focal disease, histologically characterized by two immunohistochemically and morphologically distinct population with LCH and non-LCH features. The 3 groups showed a clinical profile discernible from each other and from other histiocytoses. Type-1 MH was represented by young adults developing a multisystem LCH/Erdheim-Chester disease overlap. 89% of patients were BRAFV600E-mutated and 14.3% of patients died after a median of 7 months. Type-2 MH included pediatric patients developing cutaneous xanthogranuloma after being treated for a multisystem LCH. 80% were BRAFV600E-mutated. No patient died, but most were in progression or experienced a partial remission. Type-3 MH was represented by patients developing single cuteaneous lesions with mixed LCH and Rosai-Dorfman disease histopathological features. A third of patients was mutated for BRAF. A single patient died, two years after diagnosis. CONCLUSIONS: MH are a heterogeneous group of condition. A clinical classification of MH allow differentiating patients with different clinical histories, disease burden and outcome.

SPECTRUM OF HISTIOCYTIC NEOPLASMS ASSOCIATED WITH DIVERSE HEMATOLOGICAL MALIGNANCIES BEARING THE SAME ONCOGENIC MUTATION

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Histiocytic disorders are a spectrum of rare diseases characterized by the accumulation of macrophage-, dendritic cell-, or monocyte-differentiated cells in various tissues and organs. The discovery of recurrent genetic alterations in many of these histiocytoses has led to their recognition as clonal neoplastic diseases. Moreover, the identification of the same somatic mutation in histiocytic lesions and peripheral blood and/or bone marrow cells from histiocytosis patients has provided evidence for systemic histiocytic neoplasms to originate from hematopoietic stem/progenitor cells (HSPCs). Here, we investigated associations between histiocytic disorders and additional hematological malignancies bearing the same genetic alteration(s) using the nationwide Dutch Pathology Registry. By searching on pathologist-assigned diagnostic terms for the various histiocytic disorders, we identified 4602 patients with a putative histopathological diagnosis of a histiocytic disorder between 1971 and 2019. Histiocytosis-affected tissue samples of 187 patients had been analyzed for genetic alterations as part of routine molecular diagnostics, including from nine patients with an additional hematological malignancy. Among these patients, we discovered three cases

with different histiocytic neoplasms and additional hematological malignancies bearing identical oncogenic mutations, including one patient with concomitant KRAS p.A59E mutated histiocytic sarcoma and chronic myelomonocytic leukemia (CMML), one patient with synchronous NRAS p.G12V mutated indeterminate cell histiocytosis and CMML, and one patient with subsequent NRAS p.Q61R mutated Erdheim-Chester disease and acute myeloid leukemia. These cases support the existence of a common hematopoietic cell -of-origin in at least a proportion of patients with a histiocytic neoplasm and additional hematological malignancy. In addition, they suggest that driver mutations in particular genes (e.g. N/KRAS) may specifically predispose to the development of an additional clonally related hematological malignancy or secondary histiocytic neoplasm. Finally, the putative existence of derailed multipotent HSPCs in these patients emphasizes the importance of adequate (bone marrow) staging, molecular analysis and long-term follow-up of all histiocytosis patients

NOTES

SUCCESFULL TREATMENT OF A CEREBRAL KIF5B-ALK-FUSION POSITIVE NON-LANGERHANS CELL HISTOCYTOSIS WITH THE ALK TYROSINE-KINASE-INHIBITOR ALECTINIB

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PURPOSE: To present the successful treatment of a patient with a cerebral, ALK-driven non-Langerhans cell histiocytosis with an ALK-inhibitor. METHODS: A 13 year old Yazidish girl presented with a speech arrest and a secondary generalized seizure. MRI disclosed a 3 x 3 x 2.5 cm, contrast-enhanced cerebral lesion of the left insula, as well as contrast-enhancement of several cranial and spinal nerve roots and the pituitary stalk. Subtotal resection war performed. Histology analyses revealed a non-Langerhans cell histiocytosis (group L) with overexpression of ALK1 and positive staining for S100 and CD68. Molecular analyses disclosed a KIF5B-ALK fusion transcript. There were no BRAF V600E or NPM1 mutations. At the first follow-up ten weeks after surgery, the patient presented with a local relapse of 2.3 x 1.8 cm, but with only minor clinical symptoms. Repeat surgery was considered as potentially harmful and of limited benefit due to the disseminated state of the disease. Instead, treatment with the ALK tyrosine-kinase-inhibitor alectinib was started at a dose of 2 x 600 mg/day and reduced to 2 x 450 and 2 x 300 mg/day after 12 and 18 months, respectively. Alectinib was chosen because of its superior penetration into the central nervous system. RESULTS: MRI scans after two and six months of treatment showed a quick and profound regression of the primary tumor as well as the disseminated disease of the nerve roots and the pituitary stalk, which lasts now for 18 months. The treatment is well tolerated and the patient has no clinical restrictions. CONCLUSION: In ALK-activated histiocytosis, specific treatment with an ALK-inhibitor can be considered as an alternative to surgery and/or cytotoxic chemotherapy in selected cases. The necessary duration of treatment and the optimal long-term dosing remain challenging questions for further investigations.

MAP2K1-MUTATED ECD/RDD-OVERLAP NON-LANGERHANS CELL HISTIOCYTOSIS RESPONDING TO COBIMETINIB

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PURPOSE: Non-Langerhans cell histiocytoses represent a large group of heterogeneous, rare diseases. Overlapping disorder of Erdheim Chester (ECD) and Rosia-Dorfman disease in childhood has not yet been reported. METHODS: A 16 year old male presented with cervical lymphadenopathy for 4 weeks, in combination with night sweat, malaise and weight loss of 10 kg within 6 months. Ultrasound showed intraabdominal lymphadenopathy, hepatosplenomegaly and testicular infiltrates. Lab results showed a marked inflammatory reaction with CRP of 66 mg/dl and erythrocyte sedimentation rate of 68/119 mm/30 min. Cervical lymph node biopsy revealed an overlap Non-Langerhans cell histiocytosis showing properties of ECD and RDD, with an activating mutation in the exon 2 of the MAP2K1 gene (p.Phe53Leu). PET/CT demonstrated multiple lymph node enlargements plus numerous subcutaneus/osseous lesions. RESULTS: Initially, dexamethasone 3 x 4 mg p.o. was given, with moderate clinical improvement and shrinkage of lesions. However, dexamethason reduction led to rapid disease reactivation including appearance of new lesions. PEG-Interferon alpha, being escalated up to 180 Âµg s.c./ week was associated with further progress. Finally, a targeted therapy with the MEK inhibitor Cobimetinib was initiatied. This led to continuous normalisation of laboratory values and regredient lymphadenopathy. CONCLUSION: Overlap syndromes in histiocytoses are a rare condition, and targeted treatment still represents an individual and new approach. Publications are largely based in individual experience; only one case collection of 13 adult patients with overlap histiocytosis has been published. Here, most patients had MAP2K1 mutation. Different therapeutical regimes were initiated (anakinra, methotrexate, cladribin, PEG-interferon). Four poor responders received Cobimetinib, leading to regression. Today, targeted therapy should be considered in all cases of ECD in children or adolescents; this is currently off-label in Germany. Treatment duration is still undefined. In conclusion, sequencing should be performed in all patients with rare histiocytoses, since targeted therapies represent a valuable treatment option.

PROMISING OUTCOME OF L-DEP REGIMEN THERAPY FOR TREATMENT OF PEDIATRIC PATIENTS WITH CHRONIC ACTIVE EPSTEIN-BARR VIRUS INFECTION

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PURPOSE: We intended to clarify the clinical features and effectiveness of the L-DEP regimen in pediatric patients with chronic active Epstein-Barr virus infection (CAEBV) at Beijing Children's Hospital. METHODS: A retrospective analysis was performed on 21 patients with CAEBV in our center from January 2016 and June 2020. The efficacy and adverse events of the L-DEP regimen were evaluated on 3 and 6 weeks after treatment. RESULTS: The median age of 21 patients was 8.3 years (range 2.5-17.5 years). The overall response rate was 42.9% after L-DEP treatment. Median survival time was 35 months (11-50 months). The probability rate of survival at 4-year after CAEBV diagnosis were 55.9%. After L-DEP 1st treatment, the amount of EBV-DNA loads in blood and plasma were significantly reduced than diagnosis of disease (median: 4.20×105 vs. 1.35×106, Mann-Whitney U：P=0.036; 5.00×102 vs. 3.83×103, Mann-Whitney U：P=0.003). And, compared with liver and spleen size at diagnosis of CAEBV, the results showed that the size of liver and spleen shrank significantly after L-DEP 2st (mean 3.6cm vs. 1.6cm, P=0.003; 3.8cm vs. 1.5cm, P=0.008). In addition, the level of IFN-γ, TNF-α and IL-10 also decreased after L-DEP 1st and L-DEP 2st than at diagnosis(IFN-γ: 16.43pg/ml vs. 31.32pg/ml, P=0.002; 16.75pg/ml vs. 31.32pg/ml, P=0.001; TNF-α: 9.50pg/ml vs. 18.75pg/ml, P=0.009; 9.25pg/ml vs. 18.75pg/ml, P=0.007; IL-10: 17.42pg/ml vs. 27.58pg/ml, P=0.008; 10.54pg/ml vs. 27.58pg/ml, P=0.000). The major adverse effects of the L-DEP regimen were diarrhea, mild pancreatic injury, abnormal blood clotting, myelosuppression and high liver enzymes. With symptomatic treatment and most of the side events could be alleviated and disappeared. CONCLUSION: L-DEP regimen is a safe and effective therapy in treating CAEBV, and may be used as the first-choice treatment in early stage, for bridging allo-HSCT.

EXTRANODAL DISSEMINATED ROSAI-DORFMAN-DESTOMBES DISEASE WITH CUTANEOUS, ARTICULAR AND CARDIAC INVOLVEMENT

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PURPOSE: to report a case of extranodal Rosai-Dorfman-Destombes Disease, with cutaneous, articular and cardiac involvement. METHODS: A 46-year-old woman presented for a diffuse chamois-colored, papular eruption with sparing of the folds, bilateral symmetric polyarthritis and right atrial masses leading to pleural effusion and cardiac tamponade. Low-grade fever and symmetric arthralgias with morning stiffness alongside low-titer ANA positivity were documented, with articular ultrasound revealing tenosynovitis and minimal erosions. Whole-body PET-CT revealed right atrium and left distal femoral bone hypercaptation. Mild splenomegaly was appreciated, whereas lymph nodes appeared free of disease. Arthropathy showed good response to anti-TNF, while serous effusions were refractory to anti-IL1 targeting and drainage and heart debulking surgery was required, leading to resolution of the acute clinical picture. Two years later the patient is in good conditions and skin lesions are fading. RESULTS: Histopathological evaluation of skin and heart tissue revealed superimposable dense infiltrates consisting of S100+, CD68+, CD1a- large mononuclear cells, with emperipolesis of lymphocytes admixed with clustered plasma cells. BRAF and MAP2K1 were wild type. Considering the rheumatologic comorbidity, a diagnosis of extranodal disseminated-RDDD was made. CONCLUSIONS: Classified withing R group of 2016 revised classification of histiocytoses, RDDD is a clinically protean disorder, manifesting either in the classic nodal form with massive lymphadenopathies or as extranodal disease. It is typified by large pale histiocytes showing emperipolesis in a lymphoplasmacytic background. Interestingly, cutaneous involvement with erosive arthritis and immune dysregulation are characteristic features of multicentric reticulohistiocytosis, while peri-pyelocaliceal, distal femur and heart localizations are features of Erdheim-Chester Disease; emperipolesis being a possible finding in both. Moreover, recent reports of shared MAP2K1 driver mutations support the idea of a spectrum encompassing some MRH cases as well as “ECD with RDD features”. Our patient showed indeed an intermediate clinical picture between these entities that was not previously described.

GENERALIZED ERUPTIVE HISTIOCYTOSIS MIMICKING DISSEMINATED MOLLUSCUM CONTAGIOSUM: A CASE REPORT

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PURPOSE: To describe a rare case of generalized eruptive histiocytosis (GEH) mimicking disseminated molluscum contagiosum. METHODS: A 39-year-old man with a history of syphilis and gonococcal proctitis presented at the Sexually Transmitted Infections (STI) service of our Dermatology clinic with a diffuse, slightly itchy, papular-nodular eruption. On physical examination, numerous, pruriginous, well-delimited, reddish to violaceus, dome-shaped papules and nodules were appreciated over the abdominal region and proximal thighs. A disseminated molluscum contagiosum or a lichenoid variant of sarcoidosis were considered in the differential diagnosis. However, HIV-infection as well as other causes of immunodeficiency were ruled out and therefore a biopsy was obtained. The overall clinical-pathological picture was consistent with a diagnosis of GEH. Spontaneous resolution of the majority of the lesions was appreciated one month later, with only residual brown macules. Ten months after presentation the patient is in clinical remission and good health. RESULTS: Histopathological evaluation showed a diffuse dermal infiltrate made of pleomorphic CD163+, CD68R/PGM1+, fXIIa+, S100 protein+/-, CD1a- medium to large-sized, mononuclear histiocytes, with scant vacoulated eosinophilic cytoplasm, admixed with lymphocytes and few eosinophils. No Touton’s nor foamy cells were observed. CONCLUSIONS: First described in 1963 by Winkelmann and Muller and categorized in C-group of 2016 revised classification of histiocytoses, GEH is a cutaneous, non-lipidic histiocytosis affecting more frequently young adult males. It is characterized by an asymptomatic widespread papular eruption with self-resolution usually occurring after few months. Histologically is characterized by a monomorphous dense histiocytic infiltrate composed by mononuclear, vacuolated, CD163+, CD1a- histiocytes with no foamy or multinucleated giant cells. The etiopathogenesis of GEH is unknown. However, it has been hypothesized that GEH may represent a primitive form of other C-group histiocytoses, such as xanthogranuloma. The literature reports an association with myeloid neoplasms in five case with a shared loss of Y chromosome in one report.

SYMPTOMATIC SCLEROSING MESENTERITIS REVEALING ERDHEIM-CHESTER DISEASE: A RARE CONDITION MEDIATED BY BRAF

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PURPOSE: Sclerosing Mesenteritis (SM) refers to a spectrum of digestive inflammatory disorders. Diagnosis is based on imaging showing an increase of fat attenuation displacing bowel loops and is rarely symptomatic. Several conditions (abdominal trauma, neoplasia, infectious and inflammatory diseases) are responsible for SM. Among neoplasia, Erdheim-Chester disease (ECD) is a rare histiocytosis in whom SM is exceptionally described. No series of patients presenting both pathologies has been reported. METHOD : We reviewed the database of patients in Besancon University Hospital. Patient required one imaging showing sclerosing mesenteritis and ECD diagnosis to fulfill the inclusion criteria. RESULTS: Four patients suffered from SM and ECD. The mean age at ECD diagnosis was 68 years old (61-72). All patients described abdominal pain and the mean duration between first symptoms and ECD diagnosis was 12 months (4-19). The mean CRP level at diagnosis was 40.75 mg/L (5-117). Two patients presented myeloid neoplasms (chronic myelomonocytic leukemia and essential thrombocythemia) concurrent with ECD diagnosis. Regarding imaging, all patients had a mesenteric mass associated with hyper-attenuated mesenteric fat and a “fat halo sign”. One patient had ascites and one had splenomegaly but no patient had enlarged lymph nodes. CT also demonstrated peri-nephric fat infiltration (4/4), vascular sheathing of aortic branches (3/4), adrenal hypertrophy (1/4) or ureter dilation (1/4). Mean SUVmax of the mesentery was 7.5 (4.1-10.9) at diagnosis on 18FDG-PET. Three patients underwent mesentery fat biopsy and all samples exhibited ECD histology. 75% (3/4) patients had BRAFV600E mutation. After

initiation of therapies for ECD (targeted therapies for ¾ patients), all patients had improvement of digestive symptoms and decreased of SUVmax on evaluation 18 FDG-PET. CONCLUSION: ECD should be investigated in patient with symptomatic SM especially if it is associated with peri-nephric fat infiltration. This condition is rare and might be driven by BRAF.

PEDIATRIC RECURRENT ROSAI-DORFMAN DISEASE WITH GERMLINE HETEROZYGOUS SLC29A3 AND SOMATIC MAP2K1 MUTATIONS

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PURPOSE: Rosai-Dorfman disease (RDD) is a rare non-Langerhans cell histiocytosis and mutually exclusive somatic mutations in KRAS and MAP2K1 have been reported in a third of patients. Homozygous germline mutations in SLC29A3 are associated with Faisalabad histiocytosis and familial RDD. We report a child with recurrent RDD and germline heterozygous SLC29A3 and somatic MAP2K1 mutations. CASE REPORT: A currently 7-year-old African-American male patient presented with cervical lymphadenopathy at 19 months of age. Lymph node biopsy was consistent with RDD. Due to progression, he was treated on oral steroids with improvement. He presented 2 1/2 years later with recurrent RDD. A sizeable population of CD5-dim T cells and T-cell receptor (TCR) rearrangement pattern suggested clonal T-cell large granular lymphocyte (T-LGL) expansion. He failed steroids and has had two debulking surgeries due to progressive nodal disease. He has had dysgammaglobulinemia and elevated inflammatory markers correlating with disease activity. Vitamin B12 levels have been persistently elevated. Tumor tissue 596 gene mutational analysis revealed a known pathologic somatic MAP2K1 gain of function mutation (c.159T>A p.F53L), along with overexpression of MAP2K1, NFBK1, and NFBK2 mRNA; whole-exome sequencing showed likely-pathogenic germline heterozygous mutation in SLC29A3 (c.45delC) and ACSF3 (c.1075G>A) genes. DISCUSSION: Despite the known link between autoimmune lymphoproliferative syndrome (ALPS) and RDD and elevated vitamin B12 levels documented, he did not have increased double-negative TCR alpha/beta T-cells or any known ALPS-related mutations ruling out ALPS. An increase in clonal T-LGL expansion likely reflects persistent immune dysfunction. Homozygous germline SLC29A3 mutations are not reported in sporadic RDD. This patient has heterozygous SLC29A3 mutation, which might have made him prone to RDD and somatic MAP2K1 mutation has led to RDD development. Similarly, the inflammation process could be contributed by SLC29A3 mutation. CONCLUSION: This case raises the possibility of complementary germline and somatic mutations in the development of RDD.

NOTES

HISTIOCYTE SOCIETY GOVERNING BY-LAWS

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

ARTICLE I
OFFICES, REGISTERED OFFICE, AND REGISTERED AGENT

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

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

ARTICLE II
PURPOSES AND MISSION

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

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

ARTICLE III
MEMBERSHIP

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

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

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

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

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

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

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

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

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

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

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

ARTICLE IV
BOARD OF TRUSTEES

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

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

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

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

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

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

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

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

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

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

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

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

ARTICLE V
OFFICERS

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

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

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

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

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

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

F. Members-at-Large. Each Member-at-Large shall assist the other Board members in the conduct of their duties as directed by the President or by consensus of the Board. Candidates for a
Member-at-Large position shall be ordinary members who have not served on the Board for at least two years prior to assuming a term as a Member-at-Large. The Members-at-Large shall each serve a three year term with one additional term permitted by re-election.

Section 2. Election of Officers. The President-Elect, Secretary, Treasurer, and Members-at-Large shall be elected, as the case may be, by the voting members of the Corporation at an annual meeting of the members in

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

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

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

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

ARTICLE VI
COMMITTEES

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

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

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

C. Scientific Committee. The Scientific Committee shall be composed of no less than five (5) and no more than nine (9) Ordinary Members. The Scientific Committee shall review proposals for research and related activities according to guidelines developed by the Board, make recommendations to the Board, and present the Board with annual reports and plans concerning the Corporation's research activities. Members of the Scientific Committee will be elected by voting members of the Corporation at the time of the annual meeting. Members of the Scientific Committee will serve two (2) year terms and may serve up to six (6) consecutive years if re-elected. The Scientific Committee will select its own chairperson within ten (10) days of the close of the annual meeting.

D. Education Committee. The Education Committee shall be composed of no less than five (5) and no more than none (9) Ordinary Members. The Education Committee will oversee the educational activities of the Corporation, and review and score the abstracts to be presented at the annual meeting of members. The Education Committee will also present the Board with annual reports and plans concerning the Corporation's educational activities. Members of the Education Committee will be elected by voting members of the Corporation at the time of the annual meeting of the member. Members will serve two (2) year terms and may serve up to six (6) consecutive years if re-elected. The Education Committee will select its own chairperson within ten (10) days of the close of the annual meeting.

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

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

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

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

ARTICLE VII
AGENTS

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

ARTICLE VIII
MISCELLANEOUS PROVISIONS

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

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

ARTICLE IX
INDEMNIFICATION

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

HISTIOCYTE SOCIETY GOVERNING BY-LAWS

expenses or, where appropriate, may itself undertake the defense of any officer or agent. However, such officer or agent shall repay such expenses if it should be ultimately determined that such individual is not entitled to indemnification under this Article IX.

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

ARTICLE X
DISTRIBUTION OF ASSETS UPON DISSOLUTION

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

ARTICLE XI
AMENDMENTS TO BYLAWS

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

HISTIOCYTE SOCIETY CONSTITUTION

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

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

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

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

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37TH ANNUAL MEETING OF THE HISTIOCYTE SOCIETY









OCTOBER 10-12, 2021
ATHENS, GREECE

REGISTRATION OPENS APRIL 2021

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