4TH ANNUAL INTERNATIONAL ECD MEDICAL SYMPOSIUM PARIS | 2016

ERDHEIM-CHESTER DISEASE GLOBAL ALLIANCE

SUPPORTING THOSE AFFECTED BY ERDHEIM-CHESTER DISEASE

ECD medical symposia allow sharing of research findings, foster research collaborations, and provide a mechanism to educate ECD treating doctors. These meetings promote discussion of the complex problems facing the ECD community, allowing multiple disciplines to interact. The ECDGA has partnered with Hôpital Pitié-Salpêtrière this year to make this event possible.

Thank you to all presenters and participants for your dedication, time, and interest!

SHARE

COLLABORATE

LEARN

HÔPITAUX UNIVERSITAIRES
PITIÉ SALPÊTRIÈRE - CHARLES FOIX

ERDHEIM-CHESTER DISEASE GLOBAL ALLIANCE

ECD Global Alliance
P.O. Box 775
DeRidder, LA 70634 USA
337.515.6987
www.erdheim-chester.org

ECD Medical Symposium Attendees

September 16, 2016
Paris, France

Dear Attendees,

Welcome to Paris, France and the 4th Annual International ECD Medical Symposium! We are happy to be in Europe and are looking forward to meeting each of you. The ECDGA has partnered with Hôpital Pitié-Salpêtrière and Professor Julien Haroche to make this event possible.

Thank you for your attendance and participation in this year's event. We truly believe with one another's help we will move forward in increasing ECD studies and research, approving treatment options and aiding in the quality of life for each patient. Our ultimate goal is to find a cure for ECD. We are optimistic that you will find the diverse presentations about the ongoing studies, research and treatments from around the world helpful to your progress in this field.

There will be opportunities to interact with other researchers and physicians, to participate in open panel discussions, and also to review and discuss the poster presentations. Your collaboration with one another will help foster more research and better treatments to improve the lives of all ECD patients worldwide.

The ECD community is extremely grateful for your involvement and sharing of experiences with others. Please let us know how the organization can best serve you and if you are interested in getting more involved in the work of the organization. The contributions of you and others have proven to be instrumental in the success of this organization!

Please enjoy your visit!

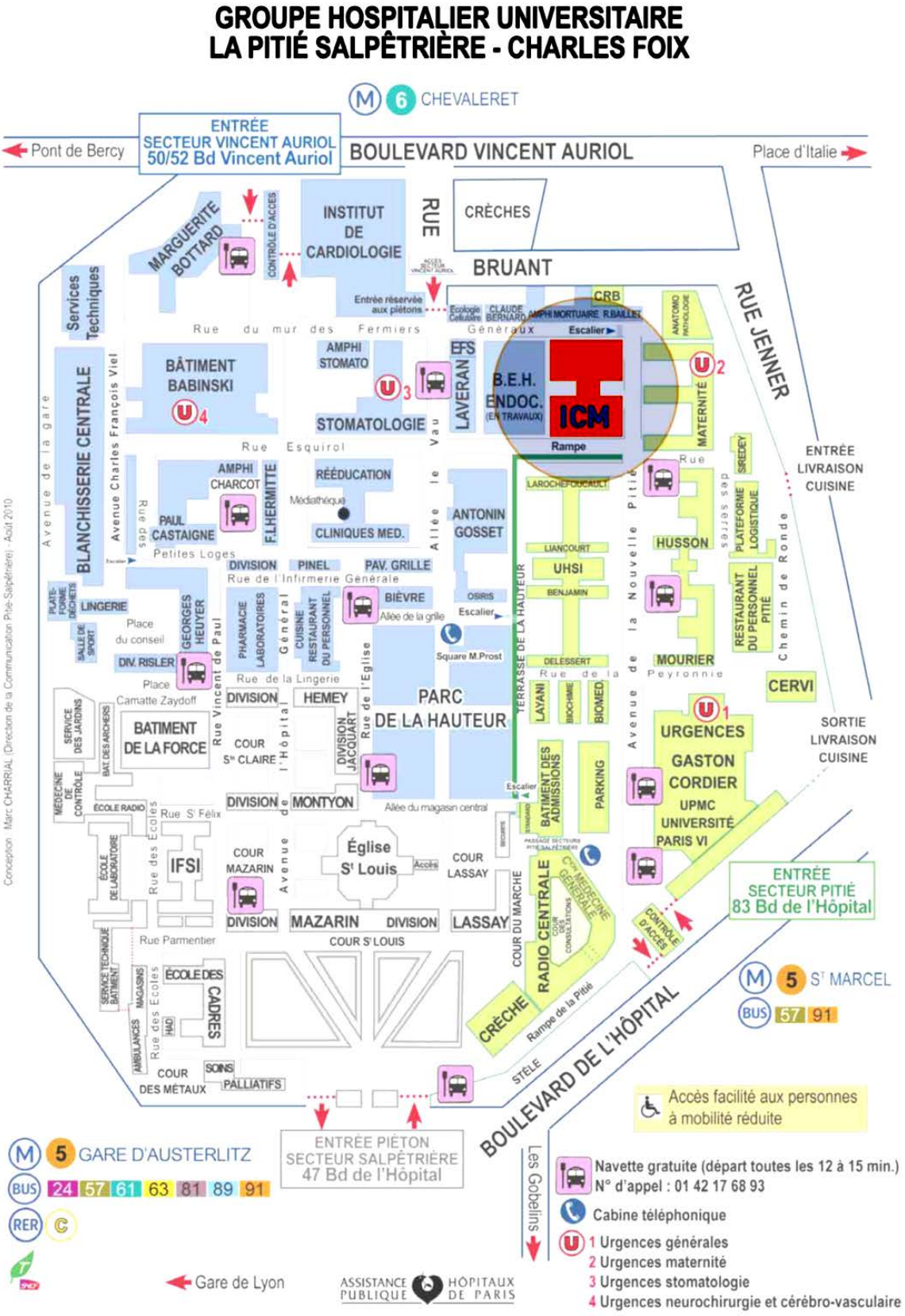
Sincerely,

THE ECDGA STAFF & BOARD OF DIRECTORS

SUPPORTING THOSE AFFECTED BY ERDHEIM-CHESTER DISEASE

TABLE OF CONTENTS

HOSPITAL MAP OF ICM BUILDING



PRESENTATION AGENDA

TIME	SUBJECT	TOPIC - CHAIR OR PRESENTER
8:15 – 8:45	**Registration**	
8:45 – 9:00	**Welcome**	Prof. Julien Haroche, MD, PhD Hôpital Pitié-Salpêtrière
9:00 – 10:30	**Basic Science**	Chair: Jean-François Emile, MD Hôpital Pitié-Salpêtrière
6 oral presentations *(10 min + 5 minute discussion)*	1. Insights into the Cell-of-Origin of the Histiocytoses Using Patient---Derived Xenograft Murine Models Omar Abdel-Wahab, MD, PhD and Benjamin Durham, MD; Memorial Sloan-Kettering Cancer Center	
	2. CCL18 in Erdheim-Chester Disease: Potential Implications in the Pathogenesis Prof. Lorenzo Dagna, MD, PhD; IRCCS H San Raffaele Scientific Institute and Vita-Salute San Raffaele University	
	3. The Hematopoietic Origin of Adult Histiocytosis Matthew Collin, MD; Newcastle upon Tyne Hospital	
	4. Erdheim-Chester disease is frequently associated with myeloproliferative neoplasms and myelodysplastic syndromes: a systematic clinical and molecular series of 189 patients followed at two centers Matthias Papo, MD, Hôpital Pitié-Salpêtrière	
	5. Tailoring Treatment for Erdheim-Chester Disease: Focus on ECD Marina Ferrarini, MD; Vita-Salute San Raffaele and IRCCS San Raffaele Scientific Institute	
	6. Marked alteration of circulating immune cells in Erdheim-Chester disease in a large single-center series of 46 patients Fleur Cohen-Aubart, MD & Wilfred Le Goff, MD, Hôpital Pitié-Salpêtrière	
10:30 – 10:45	*Break*	
10:45 – 11:30	**Pathology**	Chair: Omar Abdel-Wahab, MD, PhD Memorial Sloan-Kettering Cancer Center
3 selected oral presentations *(10 mins + 5 minute discussion)*	7. Evaluation of the Expression of Immune Checkpoint Modulators & BRAF expression in Biopsy Specimens of Erdheim-Chester Disease Patients Roei D. Mazor, MD; Sheba Medical Center	
	8. Clinical Molecular Profiling to Detect Targetable Alterations in Archival Tumor Tissue and Cell-free DNA from Patients with Erdheim-Chester Disease Filip Janku, MD, PhD, University of Texas MD Anderson Cancer Center	
	9. Elevated CSF Osteopontin and Circulating Cells with BRAF Mutations in Patients with Langerhans Cell Histiocytosis-Associated Neurodegeneration -A Model for ECD? Kenneth McClain, MD, PhD; Texas Children's Cancer Center	

TIME	SUBJECT	TOPIC - CHAIR OR PRESENTER
11:30 – 12:15	**Treatments (Part 1 of 2)**	Chair: Augusto Vaglio, MD, PhD Parma University Hospital
4 selected oral presentations (8 mins + 2 minute discussion)	10. Management of ECD Symptoms and Side Effects of Treatments Corrado Campochiaro, MD; IRCCS H San Raffaele Scientific Institute and Vita-Salute San Raffaele University	
	11. Efficacy of Cladribine (2-CdA) in the Treatment of Erdheim-Chester Disease (ECD) Ronald Go, MD; Rochester Mayo Clinic	
	12. A Single- centre Experience of Treating Adult Patients with Langerhans' cell Histiocytosis and Erdheim Chester Disease; Sustained Response to Oral Methotrexate in Frontline and Relapsed Disease Tahla Munir, MD; St James's Hospital	
	13. Superior Efficacy and Equivalent Safety of Double-dose Anakinra in Erdheim-Chester Disease Achille Aouba, MD, PhD; Université de Caen –Normandie	
12:15 –12:30	Group Photo of Attendees	
12:30 – 1:30	Lunch & Poster Presentations	
1:30 – 3:00	**Treatments (Part 2 of 2)**	Chair: Zahir Amoura, MD Hôpital Pitié-Salpêtrière
6 selected oral presentations (10 mins + 5 minute discussion)	14. Single Centre Experience of Treating Four Cases of Relapsed/Refractory BRAF Mutated Erdheim Chester Disease (ECD) / Langerhan's Cell Histiocytosis(LCH) with Oral BRAF Inhibitor Vemurafenib Tahla Munir, MD; St James's Hospital	
	15. The LOVE trial: preliminary results Prof. Julien Haroche, MD, PhD and Fleur Cohen-Aubart, MD, Hôpital Pitié-Salpêtrière	
	16. Dabrafenib and Trametinib as Potential Therapy in BRAF V600E Positive Erdheim-Chester Disease (ECD): Preliminary Results Juvianee Estrada-Veras, MD, National Institutes of Health	
	17. Encouraging activity of MEK inhibitor trametinib in patients with Erdheim-Chester disease irrespective of BRAF mutation status Filip Janku, MD, PhD, University of Texas MD Anderson Cancer Center	
	18. Phase 2 Trial of Single-Agent Cobimetinib for Adults with Histiocytic Disorders: Preliminary Results Eli L. Diamond, MD, Memorial Sloan-Kettering Cancer Center	
	19. Dabrafenib in combination with Trametinib is effective in treatment of refractory BRAF mutated mixed histiocytic disease- A Case report Tahla Munir, MD; St James's Hospital	
	20. Spectrum of Cardiovascular Involvement in Erdheim-Chester Disease Evaluated by Multimodality Imaging Diana Melo, MD; National Institutes of Health	

TIME	SUBJECT	TOPIC - CHAIR OR PRESENTER
3:00 – 3:45	**Organ Involvement**	Chair: Eli L. Diamond, MD Memorial Sloan-Kettering Cancer Center
4 selected oral presentations *(8 mins + 2 minute discussion)*	21. Adult-onset (Infratentorial) Leukoencephalopathy as Presenting Manifestation of Erdheim-Chester Disease Giulio Cavalli, MD; IRCCS H San Raffaele Scientific Institute and Vita-Salute San Raffaele University	
	22. MRI evidence of cardiac involvement in Erdheim-Chester disease Davide Gianfreda, MD; Parma University Hospital	
	23. Endocrine manifestations in Erdheim-Chester disease Carine Courtillot, MD, Hôpital Pitié-Salpêtrière	
3:45 – 4:00	*Break*	
4:00 – 4:45	**Panel discussion**	Moderator: Mark Heaney, MD Columbia University
ECD Patient Registry: Community Tool for Retrospective Multi-Center Outcome Analyses	Prof. Julien Haroche, MD, PhD Hôpital Pitié-Salpêtrière	
	Eli L. Diamond, MD Memorial Sloan-Kettering Cancer Center	
	Matthew Collin, MD Newcastle upon Tyne Hospital	
	Prof. Lorenzo Dagna, MD, PhD IRCCS H San Raffaele Scientific Institute and Vita-Salute San Raffaele University	
4:00 – 4:45	**Panel discussion**	Moderator: Augusto Vaglio, MD, PhD Parma University Hospital
Proposed ECD GWAS Study	Juvianee Estrada-Veras, MD National Institutes of Health	
	Filip Janku, MD, PhD University of Texas MD Anderson Cancer Center	
	Omar Abdel-Wahab, MD, PhD Memorial Sloan-Kettering Cancer Center	
	Prof. Javier Martin, MD, PhD Instituto de Parasitología y Biomedicina López Neyra Consejo Superior de Investigaciones Científicas,	
5:30 – 5:45	**Symposium Closing**	
	Prof. Julien Haroche, MD, PhD Hôpital Pitié-Salpêtrière	
	Kathleen Brewer ECD Global Alliance	

POSTER PRESENTATIONS

1. Plasma Chromogranin A as a marker of cardiovascular involvement in Erdheim-Chester disease

Marina Ferrarini, Angelo Corti, Julien Haroche*, Daniela Belloni, Barbara Colombo, Alvise Berti, Giulio Cavalli, Corrado Campochiaro, Antonello Villa**, Fleur Cohen-Aubart*, Zahir Amoura*, Claudio Doglioni, Lorenzo Dagna, and Elisabetta Ferrero

From: Università Vita-Salute San Raffaele and IRCCS San Raffaele Scientific Institute, Milan, Italy; *Pitié-Salpêtrière Hospital, Université Pierre et Marie Curie, Paris, France; **Università Milano Bicocca, Milan, Italy

Background. Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis (LCH) characterized by tissue infiltration with CD68+CD1a- foamy histiocytes. TNF-related chronic inflammation and mutations in the MAP kinase signaling pathway in histiocytes are recognized as the two major pathogenic events. Among pleomorphic clinical manifestations, cardiovascular involvement is frequent and prognostically relevant. Evaluation of ECD clinical course and response to treatment is, however, still challenging.

Objective. Taking advantage from the two largest cohorts of ECD patients worldwide, we investigated the relevance and the potential of circulating Chromogranin A (CgA), a pro-hormone involved in cardiovascular homeostasis and inflammation, as a biomarker of response to therapy in ECD.

Methods. Plasma levels of CgA, soluble TNF-receptors (sTNF-Rs) and TNF- were determined by immunoassays in 37 ECD patients and in matched controls; in four patients, serial determination of these parameters was obtained and correlated to response to therapy. The expression of CgA in a cardiac lesion was determined by immunohistochemistry.

Results. sTNF-Rs, TNF- and CgA plasma levels were significantly increased in ECD patients compared to controls. CgA, but not sTNF-Rs, discriminated cardiovascular involvement in ECD patients and correlated with pro-Brain Natriuretic Peptide (pro-BNP). In a single case where a cardiac biopsy was obtained for diagnostic purposes, CgA was found expressed by cardiomyocytes but not by infiltrating histiocytes. In the four ECD patients analyzed, the kinetics of sTNF-Rs and CgA overall paralleled response to therapy; specifically, sTNF-Rs overlapped TNF- variations, while CgA, together with pro-BNP, closely mirrored response of cardiac disease.

Conclusion. Our data indicate that both sTNF-Rs and CgA are linked to ECD pathophysiology. Moreover, CgA, in concert with pro-BNP, can be further exploited to fulfill the unmet clinical need of non-invasive reliable biomarkers of cardiac disease in these patients.

2. BRAF V600E+ ECD: the Last Great Masquerader. Acute Coronary Syndrome as the Initial Presentation

Julio Hajdenberg, MD, FACP. UF Health Cancer Center at Orlando Health, Orlando, Florida.
Julio.hajdenberg@orlandohealth.com

Background: periarterial involvement or both left and right coronary arteries was described by Haroche et al. (Circulation, 2009) in 27% and 5% of patients, respectively, in an imaging series of 37 subjects. We present the case of a patient without a prior diagnosis of ECD that presented to a local hospital with acute coronary syndrome, and discuss his diagnosis and outcome after initiation of systemic therapy with vemurafenib and opportune cardiac intervention.
Case Description: A 60-year old male presented to a local hospital with acute chest pain. He was treated at a local hospital for acute coronary syndrome, and underwent placement of a RCA stent with initial resolution of pain. 24 hours later he developed very severe acute bilateral lower extremity pain. A bone scan showed bilateral tibial uptake and a biopsy confirmed the diagnosis of Histiocytosis, with ECD features. Additional chest pain developed, and he obtained a second opinion with us. Because of the temporal association of chest pain and tibial pain, we performed a cardiac MRI

Cardiac findings: the MRI confirmed infiltration and enhancement of the ventricular septum and inferior wall. Coronary angiogram showed mild non-occlusive CAD of the right and left coronary arteries. Subsequent EKGs showed no defect and the LVEF remain at 60%. The angiographic luminal findings were thought not to explain the clinical presentation. In addition, non-sustained Ventricular Tachycardia was diagnosed.

Other findings: BRAFV600E assessment on the bone biopsy was negative, but urine liquid biopsy (Trovera) was positive.

Patient course: treatment with vemurafenib at 480mg po bid led to complete resolution of bone and chest pain within 2 weeks. An implantable defibrillator was placed. Follow up with PET and blood liquid biopsies is planned.

Conclusion: This is the first case, that we know of, of a patient with ECD presenting with acute coronary syndrome. In this case, likely the result of coronary spasm. Thus, we emphasize that cardiac symptoms in patients with a diagnosis of ECD must be evaluated by a team of physicians familiar with the pattern of cardiac involvement of this disorder. Prompt attention and treatment of the cardiac findings and treatment with a BRAF inhibitor can lead to rapid improvement of symptoms and prevention of acute life threatening complications. The utilization of less commonly used technologies, such as cardiac MRIs and liquid biopsies greatly accelerates the necessary diagnostic and therapeutic decisions.

3. Facing the Challenges of the Erdheim Chester Disease in Israel

Roei D. Mazor(1,5), Joab Chapman(2), Ilan Goldberg(3), Elena Ribakovski(4) and Yehuda Shoenfeld(1,5,6)
The Zabludowicz Center for Autoimmune Diseases (1), Sheba Medical Center, Tel Hashomer, Israel.
Department of Neurology (2), Sheba Medical Center, Tel Hashomer, Israel.
Department of Dermatology (3), Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.
Department of Hematology, Hemato-oncology Unit (4), Sheba Medical Center, Tel Hashomer, Israel.
Sackler Faculty of Medicine (5), Tel Aviv University, Tel Aviv, Israel.
Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases (6), Tel-Aviv University, Israel.

Exactly 4 years have passed since Asher and colleagues published the first case report on an Israeli ECD patient in the Israeli Medical Association Journal. Since then, awareness of the Erdheim Chester Disease has rocketed in Israel and culminated in the same patient from 2012 appearing smiling on the center page of a popular nonprofessional newspaper appealing to the general public. As for today, 15 ECD patients are being treated in Israel by dedicated teams of medical professionals from a variety of medical centers. We would like to propose presenting a brief overview of the Erdheim Chester Disease in Israel, to update the global ECD community as to our ongoing evolving clinical services at the Sheba Medical Center and to share some of the pivotal clinical challenges we faced with our newest patients – topics relating to issues such as establishing diagnosis, tissue retrieval, drug delivery and paramedical support.

4. BRAF/MAPK inhibition in non-langerhans histiocytosis Erdheim-Chester

Thierry M. Nordmann1, Freimut Jüngling2, Mike Recher1, Christoph Berger1 Gieri Cathomas3, Alexandar Tzankov4, Thomas Daikeler5

[1] Medical Outpatient Clinic, University Hospital Basel, Switzerland.
[2] Institute of Radiology, Clara Hospital, Basel, Switzerland
[3] Institute of Pathology Liestal, Cantonal Hospital Baselland, Liestal, Switzerland
[4] Institute of Pathology, University Hospital Basel, Basel, Switzerland
[5] Rheumatology, University Hospital Basel, Switzerland.

Major advances have been made in treating non-langerhans histiocytosis including Erdheim-Chester disease. Targeted therapies such as BRAF inhibition have shown a significant impact on disease management, emphasizing the importance of activated mitogen-associated protein kinase pathway in this disease. However, incomplete responsiveness and potentially limiting side effects caused by BRAF inhibition indicate that a more detailed understanding of the involved molecular components is crucial for the development of further successful therapeutic strategies. Here we report that the addition of the MEK-inhibitor trametinib to BRAF-inhibiting dabrafenib, is able to overcome acquired partial resistance after initial response, in a patient suffering from Erdheim-Chester disease positive for somatic mutations in both BRAF and KRAS.

5. ECDGA – The Patient Population

Kathy Brewer; ECD Global Alliance, DeRidder, LA USA

ABSTRACTS

1. Insights into the Cell-of-Origin of the Histiocytoses Using Patient-Derived Xenograft Murine Models

Benjamin H. Durham1, Akihide Yoshimi2, Matthias Papo3, Young Rock Chung2, Neval Ozkaya1, Ahmet Dogan1, David M. Hyman4, Raajit Rampal5, Eli L. Diamond6, Jean---Francois Emile7, Julien Haroche3, Omar Abdel---Wahab2,5

1. Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, United States
2. Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, United States
3. Internal Medicine Service, Hôpital Pitié---Salpêtrière, Paris, France
4. Developmental Therapeutics, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, United States
5. Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, United States
6. Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, United States
7. Pathology Service, Hôpital universitaire Ambroise Paré, Paris, France

The identification of the BRAFV600E mutation and mutations in other kinases in Langerhans cell histiocytosis (LCH) and Erdheim---Chester disease (ECD) has revolutionized our understanding and clinical management of these disorders. In addition, remarkable parallels have emerged in the genetic alterations driving LCH, ECD, and the ECD/LCH overlap disorder, which suggest that LCH and ECD might have a shared cell---of---origin. Recently, Berres et al. detected the BRAFV600E mutation in bone marrow (BM) CD34+ cells, a heterogeneous population of hematopoietic stem and progenitor cells (HSPCs), from a proportion of patients with high---risk LCH. However, the BRAFV600E mutation has not been detected in the CD34+ compartment of all LCH patients. Moreover, whether or not HSPCs from histiocytosis patients have functional self---renewal potential is unknown. We therefore attempted to understand the cell---of---origin of ECD using xenotransplantation of HSPCs purified from ECD patients.

CD34+ cells were purified from cryopreserved bone marrow mononuclear cells (MNCs) from 8 patients with ECD (n=5), LCH (n=1), and ECD/LCH (n=2) using immunomagnetic selection. These cells (range of 0.1---0.8x106 cells/animal) were then delivered by intrafemoral injection into sublethally irradiated "NSGS" (NSG---SGM3; NSG mice with transgenic expression of human SCF, GM---CSF, and IL---3) mice. Human engraftment was monitored by monthly flow cytometric analysis of peripheral blood (PB) until mice became moribund. Thereafter, animals were sacrificed and bone marrow, spleen, liver, lung, and peripheral blood were analyzed using flow cytometry, histology, immunohistochemistry, and sequencing analysis for the donor patient's original kinase alteration. Human CD34+ cells were then enriched from BM and spleen of engrafted mice and serially transplanted into secondary NSGS recipient mice.

Thus far, transplanted mice have been observed for a mean of 70 days (30---120 days). During this time, one animal engrafted from a KRAS---mutated ECD patient developed severe pancytopenia and macrocytic anemia at 90 days. At this time, there was clear evidence of human engraftment due to the presence of human CD45+ (hCD45) cells in the PB (0.73%), BM (8.84%), spleen (4.52%), liver (19.8%), lung (9.17%), and kidney (0.66%). Many of the hCD45+ cells co---expressed human monocyte lineage markers hCD33 and hCD14: bone marrow (18.7%), spleen (14.7%), liver (52.6%), lung (53.8%), and kidney (45.8%). Histologically, tissues were infiltrated by a hCD45+/hCD163+ mononuclear cell population with a foamy histiocyte infiltrate characteristic of ECD. Furthermore, genomic analysis of the DNA from the engrafted animal's bone marrow and spleen revealed the same KRAS p.G12S mutation found in the donor patient's ECD.

This study identifies that the CD34+ compartment in ECD has functional self---renewal potential and can initiate histiocytosis. Furthermore, this study demonstrates the first successful patient-- derived xenograft of a human histiocytic neoplasm. Further work will be needed to determine the frequency of successful engraftment of ECD CD34+ cells and what exact cell type(s) among the CD34+ cells gives rise to LCH and ECD, and what proportion of cells in the CD34+ compartment contain kinase alterations.

2. CCL18 in Erdheim-Chester Disease: Potential Implications in the Pathogenesis

Greta Pacini, Giulio Cavalli, Guido Pacini*, Alessandro Tomelleri, Corrado Campochiaro, Alvise Berti, Elisabetta Ferrero, Marina Ferrarini, Claudio Doglioni, Lorenzo Dagna

From IRCCS H San Raffaele Scientific Institute and Vita-Salute San Raffaele University, 20132 Milan, Italy; *Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia

Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cells histiocytosis characterized by multisystemic xanthogranulomatous infiltration by CD68+ and CD1a- foamy macrophages, accompanied by fibrosis. The clinical spectrum of ECD is particularly broad since the disease may involve virtually every organ with variable clinical manifestations, ranging from asymptomatic to multisystemic and potentially life-threatening forms.
The pathogenesis of ECD has not yet been fully clarified. Our group and others demonstrated the presence of a pro-inflammatory cytokine network in ECD lesions responsible for the recruitment and activation of histiocytes. More recent findings indicate that ECD is a clonal disorder characterized by somatic mutations in the MAP kinase genes (most frequently in BRAF). This observation led to new therapeutic strategies based on selective inhibition of such kinases. One of those drugs, vemurafenib, has been used in a significant number of ECD patients not responsive to first-line treatments with interferon α or anti-cytokine agents. In our study we analyzed the pathways associated to fibrosis in ECD with particular interest towards TGF-β1 and CCL18, two cytokines involved in pathological fibrosis and to date not specifically studied in this disease.
We evaluated a cohort of 20 patients with histologically confirmed ECD and 20 age- and sexmatched healthy controls. In all patients we gained full clinical data, complete radiological evaluation, and analyzed the basal serum level of CCL18 and TGFβ1. In 12 of them we could also evaluate in multiple serial samples the serum levels of those two cytokines during follow-up. We also evaluated the expression of CCL18 and TGF-β1 on biopsies from those patients.
We finally studied the potential effects of drugs that may be used as a treatment for ECD by means of a specific ex vivo assay based on RCCS™ bioreactor technology. There were no statistically significant differences between the serum levels of TGF-β1 between controls and ECD patients. Accordingly, it was not possible to demonstrate a significant production of TGF-β1 in biopsies from ECD patients. On the contrary, CCL18 serum levels were markedly elevated in patients with ECD, with statistically significant differences between both treated and untreated patients and controls. No significant differences were found among the treated and untreated patient groups. CCL18 was also found in biopsies from ECD patients and it was mainly produced by the foamy histiocytes. CCL18 serum levels positively correlated with the presence of multi-systemic disease, and with neurologic involvement in particular.
Finally, with the experiments exploited by means of the RCCS™ bioreactor, we found that CCL18 production was strongly inhibited by infliximab treatment, as evaluated by the marked reduction in CCL18 levels in culture supernatants and in the CCL18-producing cells in tissue fragments. On the contrary, we observed an up-regulation of CCL18 production upon vemurafenib treatment. Collectively taken, these data suggest that CCL18 plays an important role in the pathogenesis of ECD through the induction of an unconventional fibrotic pathway that is independent of those typically associated with TGF-β1. CCL18 seems to parallel the extension of the disease and elevated levels of this chemokine may be considered as another potential clue for the diagnosis of ECD.
To our knowledge, this is the first report describing an association between CCL18 and fibrotic disorder not confined to the lung. Further investigations will be needed to elucidate the mechanisms of CCL18-induced fibrosis and to better interpret our experimental results on the effects of specific pharmacological treatments on this pathway. Current studies on long-term effects of vemurafenib in ECD may be helpful in clarifying the full pharmacological implications of this drug and its paradoxical effects observed on CCL18 secretion.

3. The Hematopoietic Origin of Adult Histiocytosis

Matthew Collin, MD, Newcastle upon Tyne Hospital, Newcastle, UK, Paul Milne, Venetia Bigley, Antoine Neel, Muzlifah Haniffa, Eli Diamond, Omar Abdel-Wahab

Purpose: to understand the origin and differential development of Langerhans Cell Histiocytosis (LCH) and Erdheim Chester Disease (ECD) in adults.
Methods: 49 patients with LCH, ECD or LCH/ECD cross-over and 5 patients with hairy cell leukemia (HCL). Tracking of BRAFV600E mutated bone marrow progenitor fractions, peripheral blood cells and lesional cells by allele-specific PCR. In vitro differentiation of dendritic cells (DCs) and monocytes into histiocyte-like cells using defined growth factors and conditioned media. Comparative analysis of gene expression in in vitro derived and primary histiocytosis lesions.
Results: BRAFV600E localized to the hematopoietic stem cell (HSC) in multi-system LCH, ECD and HCL and was

enriched in myeloid progenitors in multi-system LCH and ECD. In peripheral blood, the pattern of BRAF mutant alleles was indistinguishable between LCH and ECD, involving predominantly monocytes and myeloid DCs. In HCL, mutant alleles were only detectable in HCL cells and B/NK lymphocytes. Detection of BRAFV600E alleles in the blood was more likely in MS-LCH than SS-LCH (p = 0.004) but no correlation with disease stage was observed in ECD. LCH-like cells differentiated from CD1c+ DCs in response to GM-CSF, TGFbeta or BMP7 and co-culture with primary keratinocytes. In contrast, CD68+ macrophages were formed by co-culture of monocytes with fibroblasts. Gene expression studies during differentiation in vitro confirmed that CD1c+ DCs and monocytes remained distinct and did not trans-differentiate despite the expression of similar surface markers.

4. Erdheim-Chester disease is frequently associated with myeloproliferative neoplasms and myelodysplastic syndromes: a systematic clinical and molecular series of 189 patients followed at two centers

Matthias Papo, MD, Hôpital Pitié-Salpêtrière, Paris, France, Fleur Cohen-Aubart, Jean-François Emile, Claude Baillou, Damien Roos-Weil, Zofia Helias-Rodzewicz, Omar Abdel-Wahab, Eli Diamond, Benjamin Durham, Olivier Bernard, Zahir Amoura, François Lemoine, Julien Haroche

Introduction: Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytosis of unknown, characterized by polymorphic granulomas infiltrated with foamy histiocytes CD68+, CD163+, CD1a-, Langerin (CD207)-, S100- at immunohistochemical staining. Recently, an international multidisciplinary group of expert published the "revised classification of histiocytoses and neoplasms of macrophage-dendritic cell lineages" in Blood, with a particular focus on recurrent mutations in the MAP kinase pathway. In this suggested classification, ECD is now listed in a Langerhans or "L" group, which also includes Langerhans cell histiocytosis (LCH). The pathogenesis of ECD has been greatly improved by the discovery of recurrent BRAF-V600E mutations in 55-70 % of cases depending on the techniques used. A consecutive study also reported PI3KCA and NRAS mutations; a more recent study with transcriptome and whole exome analysis reported had at least one mutation involving the MAP kinase pathway was found in each patient tested. To the best of our knowledge, hematological disorders, such as myeloproliferative neoplasms (MPN), myelodysplastic syndrome (MDS), lymphomas, myelomas or auto-immune cytopenias have never been described in ECD. The aim of this study is to describe clinical, pathological and molecular features of the hematological disorders associated with ECD.
Methods: We performed a two-center retrospective study, with biopsy-proven ECD who were referred at least once in the Internal Medicine Department of Pitié-Salpêtrière Hospital in Paris, France and to the Memorial Sloan-Kettering Cancer Center (MSKCC), New-York, United States. A total of 189 cases of ECD were reviewed. ECD was diagnosed according to published criteria. Clinical parameters, biological features and outcome were obtained from digital or paper medical records. Mutational status regarding the MAP kinase pathway was also recorded.
Results: Hematological disorders were reported in 25 patients (13.2%). Apart from a few lymphoproliferative or auto-immune disorders, hematological malignancies associated with ECD were mainly represented by MPN and MDS (n=19; 10.0 %), represented by 7 cases of chronic myelomonocytic leukemia (CMML), 2 cases of essential thrombocythemiae (ET), 3 cases of MDS, 2 cases of myelofibrosis (MF), 1 case of polycythemia vera (PV) and 1 case of acute myeloblastic leukemia (AML). Twelve patients (63.2%) harbored the BRAF V600E mutation in histological samples, while seven (36.8%) tested positive for JAK2 V617F, and four patients (23.5%) had both mutations. One patient with ET had a calreticulin mutation as well as BRAF mutation. Others MAP kinase pathway mutations (NRAS, MAP2K1) were described in a few patients in the histiocytic pathology as well as in the myeloid malignancies, which also harbored mutations of tumor suppressor genes (TET2, IDH2, ASXL1). Patients received vemurafenib or dabrafenib in 7 cases (36.8%). Other patients also received MEK inhibitors (trametinib) and JAK inhibitors (ruxolitinib).
There were no major statistical differences between patients with or without MDS/MPN. Patients from the MDS/MPN group were significantly older (68 vs 56.5, p=0.0005), and a larger number of death was recorded in that same group (36.8 vs 19.4) with no statistical significance (p=0.07)
Conclusion: The high prevalence (10 %) of myeloid neoplasms (MPN and MDS), and especially Chronic Myelomonocytic Leukemia (CMML), found in patients with ECD or mixed histiocytoses, suggests that such patients should systematically be screened at diagnosis for these disorders. Since all these diseases share a common pathogenesis, involving mutations of genes associated with signaling pathways and proliferation, we formulate the hypothesis that several mutations of intracellular signaling, at different stages of myeloid cell differentiation, may lead to induce either MPN, MDS, ECD, LCH or association of these disorders.

5. Tailoring Treatment for Erdheim-Chester Disease: Focus on ECD

Marina Ferrarini, MD; Daniela Belloni, Antonello Villa*, Claudio Doglioni, Lorenzo Dagna,

From: Università Vita-Salute San Raffaele and IRCCS San Raffaele Scientific Institute, Milan, Italy; *Università Milano Bicocca, Milan, Italy

Background - Erdheim-Chester disease (ECD) is a systemic non-Langerhans' cell histiocytosis, characterized by tissue infiltration by foamy CD68+CD1a- histiocytes, surrounded by fibrosis. The identification of two major pathogenic events, i.e., a full-blown chronic inflammation and mutations in the MAPK-kinase pathway in histiocytes, prompted the development of effective therapies for ECD patients. Indeed, treatment with the BRAFV600E inhibitor vemurafenib results in sustained albeit partial responses in most ECD patients carrying the mutation. Improved therapeutic options for BRAFV600E-negative ECD patients, as well as for patients unsuitable or partially responsive to vemurafenib treatment, are however still needed. In this regard, harnessing the inflammatory ECD microenvironment by interfering with specific molecules and/or adaptive responses may represent an alternative strategy.
The assessment of drug efficacy in ECD is hampered by both the extreme rarity of the disease, and the lack of suitable in vitro or in vivo models. 3-D tissue culture systems are emerging as an invaluable tool for drug testing. In particular, the Rotary Cell Culture System (RCCSTM) bioreactor allows for 3-D dynamic culture of samples by optimizing mass and gas transfer. We have recently validated the system for culture of human biopsies, showing the maintenance of their viability, histo-architecture and functions, thus anticipating the unprecedented possibility to assess the impact of drugs on human tissues.
Objectives – Aim of the study was to determine the pathogenic role of the inflammatory microenvironment expressed in ECD lesions. We also exploited the 3-D dynamic culture in RCCSTM bioreactor as a preclinical model for drug testing for ECD.
Methods – The impact of exudates (pericardial fluid) from patients, used as surrogate ECD microenvironment, was tested in vitro on monocyte/macrophage and endothelial cell functions/morphology. Tissue fragments (two xanthelasmas and one pleural biopsy) from three ECD patients were kept in parallel cultures in bioreactor in the presence of cytokine- or BRAF-inhibitors. Cytokines and chemokine levels in culture supernatants were assessed through Multiple-Cytokine Assays. Proliferation/apoptosis, expression of inflammatory molecules, extracellular matrix components and senescence markers were assessed by immunohistochemistry on tissues.
Results – Pericardial fluid from ECD patients affected monocyte migration, differentiation and conversion into foamy cells; the contribution of specific pro-inflammatory molecules and intracellular pathways is currently under investigation. Supernatants obtained from untreated ECD samples cultured in bioreactor showed a progressive accumulation of inflammatory cyto-chemokines, indicating that histiocyte functions are retained. Cytokine release was substantially impaired upon treatment with cytokine-inhibitors in all cases, while the efficacy of vemurafenib varied according to the frequency of BRAF-mutated histiocytes inside the lesions. At variance with BRAF-mutated melanoma cells, vemurafenib did not induce histiocyte death in short-term culture (up-to 1 week). We are currently investigating alternative mechanisms promoted by vemurafenib on histiocytes and their microenvironment.
Conclusions – ECD microenvironment is endowed with pathogenic activities that can be potentially targeted by therapeutic interventions. The RCCSTM bioreactor system is a well-suited tool for preclinical drug testing in ECD and allows both to compare the efficacy of drugs and to explore their in situ mechanisms of action/resistance, possibly leading to the identification of combination strategies for the disease.

6. Marked alteration of circulating immune cells in Erdheim-Chester disease in a large single-center series of 46 patients

Fleur Cohen-Aubart2, Lucie Poupel1, Maryse Guérin1, Zahir Amoura2, Philippe Lesnik1, Julien Haroche2 & Wilfried Le Goff1

1. Sorbonne Universités, UPMC Univ Paris 06, INSERM, ICAN, Institute of Cardiometabolism and Nutrition (UMR_S1166), Integrative Biology of Atherosclerosis team, 91 boulevard de l'hôpital, F-75013, Paris, France.

2. Assistance publique-Hôpitaux de Paris, hôpital Pitié-Salpêtrière, université Pierre-et-Marie-Curie Paris 6, institut E3M, centre de référence des maladies rares auto-immunes et systémiques, service de médecine interne 2, Paris, France.

Erdheim–Chester disease (ECD) is a rare, non-Langerhans form of histiocytosis of unknown origin which is characterized by the xanthomatous or xanthogranulomatous infiltration of tissues by spumous histiocytes, lipid-laden macrophages or histiocytes, surrounded by fibrosis. Immune cells and pro-inflammatory cytokines were detected in lesions testifying of immune cell recruitment in ECD. However, although a systemic cytokine Th-1-oriented signature was detected in ECD, the immune cell network orchestrating the immune response in ECD was not described. To address this question,

phenotyping of circulating leucocytes (including mononuclear phagocytes and lymphocytes) in ECD was analyzed by flow cytometry in a large single-center cohort of 46 ECD patients (69% carriers of the V600E BRAF mutation) and compared with a group of 16 control individuals. While number of circulating classical (CD14++/CD16-) and intermediate (CD14++/CD16+) monocytes was not altered in ECD patients, a marked decrease of non-classical monocytes (CD14+/CD16++) was observed in ECD patients carrying the V600E BRAF mutations (-70%, p<0.05). This latter was restored by treatment with pegylated IFN and vemurafenib. Moreover, a drop of circulating plasmacytoid (-75%, p<0.0005) and myeloid 1 (-50%, p<0.05) & 2 (-70%, p<0.005) dendritic cells was detected in ECD patients regardless of the status of the mutation in comparison to control individuals. Treatment with pegylated IFN or vemurafe rescued amounts of myeloid 2 dendritic cells in V600E BRAF carriers. Analysis of lymphocytes subsets revealed a profound reduction of naïve T helper (-50%, p<0.05), cytotoxic (-80%, p<0.0005) and B (-65%, p<0.005) lymphocytes counts whereas those of T regulatory and natural killer lymphocytes were unchanged in both mutated and non-mutated ECD patients. Only treatment with pegylated IFN tended
Taken together, those results demonstrate that ECD is characterized by a marked immunodeficiency which is only partially overcome by current therapeutic agents, highlighting the need to reinforce the pharmacological arsenal available in this rare pathology.

7. Evaluation of the Expression of Immune Checkpoint Modulators & BRAF expression in Biopsy Specimens of Erdheim-Chester Disease Patients

Roei D. Mazor(1,5), Iris Barshak(2), Joab Chapman(3), Ilan Goldberg(4), Elena Ribakovski(5) and Yehuda Shoenfeld(1,6,7)

1. The Zabludowicz Center for Autoimmune Diseases (1), Sheba Medical Center, Tel Hashomer, Israel.
2. Department of Pathology (2), Sheba Medical Center, Tel Hashomer, Israel.
3. Department of Neurology (3), Sheba Medical Center, Tel Hashomer, Israel.
4. Department of Dermatology (4), Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.
5. Department of Hematology, Hemato-oncology Unit (5), Sheba Medical Center, Tel Hashomer, Israel.
6. Sackler Faculty of Medicine (6), Tel Aviv University, Tel Aviv, Israel.
7. Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases (), Tel-Aviv University, Israel.

Background: The Erdheim-Chester Disease (ECD) is a multi-systemic histiocytic myeloid neoplasm predominantly dependent on impaired Ras/Raf/MEK/ERK signaling. Treatment of BRAF mutant patients with the BRAF inhibitor vemurafenib is reported to yield satisfactory clinical responses. Conversely, treatment options for BRAF wild-type patients are limited. Positive expression of various immune checkpoint modulators for which targeted therapy is indicated in other malignant diseases, could solidify the rationale for immune checkpoint inhibition as a potential strategy for the treatment of BRAF wild-type ECD patients, especially those whose driver mutation has yet been identified.

Objectives: To identify expression patterns of various candidate proteins involved in cellular signaling and modulation of immune checkpoints in ECD specimens and the correlations between their expressions in specimens originating from different foci.

Methods: A retrospective analysis of the medical records of patients with biopsy proven ECD was performed. Involvement sites, clinical status, BRAF status and treatment timelines were noted. FFPE biopsy specimens were collected from 3 tertiary medical centers in Israel. Samples were stained for various candidate proteins, among them, CD3, CD68, CD1a, the V600E mutant BRAF protein, ALK, and PD-L1. PD-L1 staining of ECD specimens in particular was performed using a harmonized assay comprised of multiple PD-L1 binding antibodies. Stained ECD specimens were compared to PD-L1 stained tonsillar paracortical macrophages enveloping germinal centers which served as positive controls.

Results: 15 ECD patients from 6 different medical centers in Israel were audited by our team. Adequate FFPE biopsy specimens were collected from the pathological archives of 9 patients. 22 specimens were obtained from 6 different biopsy sites (bone marrow – 11, skin – 5, cerebellum – 3, other – 3). Upon interim analysis following staining and interpretation of samples from more than half of the patients in our cohort, all specimens were validated as CD68 (+) and CD1a (-). All stained specimens were found to be negative to PD-L1. In selected cases, diffuse and weak ALK staining of the membrane and nuclear compartments was noted. Staining of the remainder of specimens will be completed in the following month.

Conclusions: In contrast to recent published results, PD-L1 may not be ubiquitously expressed on ECD histiocytes. Analysis of larger patient cohorts is necessary to determine whether this marker should be of any therapeutic or prognostic value in ECD.

8. Clinical Molecular Profiling to Detect Targetable Alterations in Archival Tumor Tissue and Cell-free DNA from Patients with Erdheim-Chester Disease

Filip Janku, MD, PhD, University of Texas MD Anderson Cancer Center, Houston, TX USA, Tamara G. Barnes, Debra L. Andrews, Takeo Fujii, Helen J. Huang, Razelle Kurzrock

Background: Discovery of BRAF mutations and other targetable kinase alterations has brought new therapeutic options to patients with Erdheim-Chester disease (ECD). Conventional molecular testing of tumor tissue can be challenging due to small amount of DNA in archival tissue samples. Novel approaches utilizing liquid biopsies are being explored.
Methods: Samples of archival tumor tissue, plasma cell-free (cf) DNA and urine cfDNA were tested prior to treatment initiation for BRAF mutations and other molecular alterations of clinical importance with CLIA-compliant assays, which included tumor tissue PCR, tumor tissue targeted next-generation sequencing (NGS), plasma cfDNA targeted NGS and urine cfDNA PCR. Success rate for each method, their concordance and turnaround times have been evaluated.
Results: Total of 25 patients had at least one type of molecular testing before treatment initiation (tumor tissue PCR, n=14; tumor tissue targeted NGS, n=15; plasma cfDNA targeted NGS, n=7; urine cfDNA PCR; n=3), which produced at least one valid result in 19 (76%) of them. Molecular testing was successful in 10/14 (71%) cases tested with tumor tissue PCR, in 8/15 (53%) tested with tumor tissue targeted NGS, in 7/7 (100%) cases tested with plasma cfDNA targeted NGS and 3/3 (100%) cases tested with urine cfDNA PCR. Due to high failure rate with tumor tissue testing only 6 patients had valid results from tumor tissue DNA and cfDNA molecular profiling before therapy, which were 100% concordant for key targetable alterations. The median turnaround times for tumor tissue PCR, tumor tissue targeted NGS, plasma cfDNA NGS and urine cfDNA PCR were 8 (5-41) days, 37 (19-116) days, 15 (13-18) days and 12 (7-25) days, respectively. Of 20 patients, who had at least one or more successful molecular testing, 13 (65%) had targetable molecular alteration of whom 10 received appropriate targeted therapy. Of interest, 4 patients with BRAF mutations from tumor tissue had plasma cfDNA targeted NGS while on therapy with BRAF inhibitors, which failed to confirm the presence of BRAF mutation plausibly because of favorable therapeutic effect.
Conclusions: Clinical molecular testing in patients with ECD identifies targetable molecular alterations in majority of patients. Liquid biopsy approaches appear to have higher success rate, short turnaround time and excellent concordance with results of conventional tumor tissue testing as long as they are used prior to initiation of systemic therapy.

9. Elevated CSF Osteopontin and Circulating Cells with BRAF Mutations in Patients with Langerhans Cell Histiocytosis-Associated Neurodegeneration -A Model for ECD?

[1]Kenneth L. McClain, [2]Jennifer Picarsic, [1]Howard Lin, [1]Harshal Abhyankar, [1]Brooks Scull, [1]Rikhia Chakraborty, [1]Daniel Zinn, [1]Albert Shih [1,3]Karen Lim, [1]Stephen Simko, [1]Amanda Grimes, [1]Olive Eckstein, [1,4]Tricia L. Peters, [1]Walter Olea, [1]Thomas Burke, [1]Nabil Ahmed, [1,5]D. Williams Parsons, [1,4]M. John Hicks, [6]Huy D. Tran, [6]Jeremy Jones, [7]Robert Dauser, [8]Michael Jeng, [9]Robert Biaocchi, [10]Deborah Schiff, [11,12]Stuart Goldman, [13]Kenneth Heym, [14]Ashish Kumar, [9]Craig Okata, [15]Simon Heales, [16]Marian Malone, [17]Randy Woltjer, [17]Joseph Quinn, [18]Paul Orchard, [19]Michael Kruer, [20]Ronald Jaffe, [21]Sergio Lira, [21,22]Miriam Merad, [1]Tsz-Kwong Man, [1]Carl E. Allen.

1. Texas Children's Cancer Center Histiocytosis Program; Department of Pediatrics Baylor College of Medicine, Houston, TX
2. Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA
3. Program of Translational Biology and Molecular Medicine, Baylor College of Medicine, Houston, TX
4. Texas Children's Cancer Center Histiocytosis Program; Department of Pathology, Baylor College of Medicine, Houston, TX
5. Department of Human Genetics, Baylor College of Medicine, Houston, TX
6. Department of Radiology, Baylor College of Medicine, Houston, TX
7. Department of Neurosurgery, Baylor College of Medicine, Houston, TX
8. Department of Pediatrics, Stanford University School of Medicine, Paulo Alto, CA
9. Department of Internal Medicine, The Ohio State University, Columbus, OH
10. Department of Pediatrics, University of California-San Diego, La Jolla, CA
11. Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL
12. Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL
13. Department of Pediatrics, Cook Children's Medical Center, Fort Worth, TX
14. Department of Pediatrics, The Ohio State University, Columbus, OH
15. Chemical Pathology, Great Ormond Street Hospital for Children, London, UK
16. Laboratory Medicine, Great Ormond Street Hospital for Children, London, UK

17. Layton Aging and Alzheimer's Disease Center, Oregon Health Sciences University, Portland, OR
18. Department of Pediatrics, University of Minnesota, Minneapolis, MN
19. Departments of Pediatrics, & Neurosciences, Sanford School of Medicine of the University of South Dakota, Sioux Falls, SD
20. Department of Pathology, Magee-Women's Hospital of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, PA
21. Immunology Institute, Icahn School of Medicine, New York, NY
22. Department of Oncological Sciences, Tisch Cancer Institute, Icahn School of Medicine, New York, NY
23. Rady Children's Hospital, San Diego, CA
24. Medical City Dallas Hospital, Dallas TX

Background: Langerhans cell histiocytosis (LCH) is characterized by inflammatory lesions with pathologic CD207+ dendritic cells. Brain involvement may include mass lesions or a progressive neurodegenerative syndrome (LCH-ND). Differentiating isolated pituitary lesions from other conditions is difficult due to risks of biopsy. LCH-ND may arise years after LCH is presumed cured, mechanisms of pathogenesis are unknown, and no standard approaches to surveillance or therapy exist.
Methods: CSF biomarkers including inflammatory proteins and extracellular BRAF-V600E were evaluated in 40 patients with LCH brain lesions and/or LCH-ND. Peripheral blood and brain biopsy specimens were tested for the presence of cells harboring BRAF-V600E.
Results: Osteopontin was significantly elevated and S100B was decreased in CSF from patients with LCH compared to patients with brain tumors and other neurodegenerative conditions. While extracellular BRAF-V600E was detected in CSF of only 2/25 patients with LCH CNS lesions or LCH-ND, circulating cells with BRAF-V600E were detected in 12/37. Brain biopsies of patients with LCH-ND demonstrate diffuse infiltration by cells with BRAF-V600E. Three of four patients with LCH-ND treated with BRAF inhibitors experienced significant clinical and radiologic improvement.
Conclusions: These results support a model of LCH lesions and LCH-ND arising from a common hematopoietic precursor. This revised model of pathogenesis further supports change in current practice to evaluate serial CSF and blood biomarkers prospectively along with long-term clinical surveillance to identify patients at risk for LCH-ND who may benefit from early initiation of therapy directed against the clonal reservoir of myeloid precursors with activated ERK. Given the parallels in cell of origin in ECD and LCH, evaluation of ECD patients with neurologic involvement for the same biomarkers could be informative.

10. Management of ECD Symptoms and Side Effects of Treatments

Corrado Campochiaro MD, Giulio Cavalli MD, Alvise Berti MD, Lorenzo Dagna MD

Erdheim-Chester disease (ECD) is a rare inflammatory disorder of unknown etiology, characterized by organ infiltration by CD68+, CD1a- non-Langerhans foamy histiocytes. ECD clinical spectrum is particularly broad, and depends on the distribution and extent of the lesions [1]. According to the recently published guidelines [2] and the newer data about ECD pathogenesis [1] many different therapeutic approaches for ECD have been explored so far, but still no randomized controlled trials are available. Three main approaches are currently being used in the management of patients affected by ECD: interferon-α-2a and pegylated interferon-α, anticytokine directed therapy (anakinra, infliximab, tocilizumab) and serine/threonine kinase inhibitors (vemurafenib and imatinib). Unfortunately all these treatments have noteworthy side effects that can sometimes limit their use. It is therefore important for the practicing clinician to discuss the possible side effects with patients and take them into consideration before starting the treatment. Aim of our presentation will be to discuss about the most common symptomatic treatments for the many of the protean manifestations of the disease. We will also focus on the main side effects of the currently available treatments, and discuss how they should be prevented and treated, taking also advantage of our clinical experience with such drugs.

References:
[1] Campochiaro C et al. Erdheim-Chester Disease. Eur J Intern Med. 2015 May
[2] Diamond EL et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. Blood. 2014 Jul 24

11. Efficacy of Cladribine (2-CdA) in the Treatment of Erdheim-Chester Disease (ECD)

Ronald S. Go, Mithun Vinod Shah, Timothy G. Call, Karen L. Grogg, and C. Christopher Hook
Divisions of Hematology and Hematopathology, Mayo Clinic, Rochester, MN

Background: While cladribine is best known for its activity in hairy cell leukemia and other lymphoid malignancies, it also has activity against myeloid neoplasms such as Erdheim-Chester Disease (ECD). We reviewed our institutional experience of using cladribine in the treatment of ECD.

Methods: We retrospectively reviewed the medical records of ECD patients evaluated at Mayo Clinic from January 2001 to October 2014 who received cladribine (2-CdA). In all cases, the diagnosis of ECD was made by using clinical criteria in conjunction with histopathologic findings. Since the post-therapy response assessment was not uniformly performed, we used two response criteria: clinical and radiographic. For clinical response, we used the following criteria: complete response (CR; complete resolution of symptoms attributed to ECD); partial response (PR; incomplete resolution of symptoms); stable disease (SD; no change in symptoms); progressive disease (PD); or intolerance to therapy. Radiological response were categorized as (CR; complete resolution of proven or suspected lesion due to ECD); partial response (PR; incomplete resolution of proven or suspected lesion due to ECD); stable disease (SD; no significant change in proven or suspected lesion due to ECD); and progressive disease (PD; progression/worsening of proven or suspected lesion due to ECD).
Results: A total of 61 adult patients with ECD were identified. The median age at diagnosis was 54 years (range, 18-80) and most (n=42, 68%) were males. 2-CdA was the most commonly used chemotherapeutic agent with 13 patients (21%) receiving 2-CdA over the period of the study. Cladribine was used as the first line therapy in 7 patients, as the second line therapy in 5 patients, while one patient received 2-CdA as the 5th line of therapy. The median number of cycles of therapy was 2 (range 1-4). The clinical responses were 0% CR, 44% PR, and 22% SD, and 33% PD. Two patients had infections during 2-CdA therapy, while 1 had significant hyponatremia (likely unrelated to 2-CdA), and 1 had significant fatigue. The radiographic responses were 0% CR, 29% PR, 14% SD, and 57% PD. In those who responded to cladribine therapy, the median duration of response was 21 months (range 4-129).
Conclusions: Cladribine has a moderate clinical activity in ECD. It is generally well tolerated and may result in durable responses.

12. A Single- centre Experience of Treating Adult Patients with Langerhans' cell Histiocytosis and Erdheim Chester Disease; Sustained Response to Oral Methotrexate in Frontline and Relapsed Disease

Talha Munir1, Morag Griffin1, Roger Owen1, Anita Hill1, Anne Critchley1, Caroline Overvoode1, Paul Evans2, Chirag Patel3, Peter Hillmen1

1. Haematology department, St James's Hospital Leeds UK
2. Haematology malignant and diagnostic service, St James's Hospital Leeds UK
3. Radiology and Nuclear Medicine department, St James's Hospital Leeds UK

Langerhans' cell histiocytosis and Erdheim Chester disease are multisystem histiocytic diseases characterized by distinct clinical, radiographic and histological features. We report our single tertiary centre experience of treating histiocytic disorders with continuous weekly oral methotrexate in both frontline and relapsed settings. 17 patients treated at St James's Hospital Leeds between January 2000 to June 2016 with histological diagnosis of Langerhans' cell histiocytosis or Erdheim Chester disease were evaluated retrospectively. FDG PET/CT was performed in most patients at baseline prior to commencing treatment and 6-12 months thereafter to assess treatment response. Pulmonary function tests, cardiac MRI, MRI brain, echocardiograms were used to assess organ-specific response, as clinically appropriate. The median age was 63.9 years (45-86yrs) with male predominance (11 males/ 6 Females). 11/17 cases were diagnosed with ECD; 4/17 with LCH; one had co-existent disorder and one case had progressive Rosai Dorfmann disease. 5/17 cases had BRAFV600E mutation detected whereas MAP2K1 mutation was detected in one patient. Three cases had mutation detected in morphologically normal bone marrow. The common clinical presentations included; Nodal or soft tissue masses (78%), osteosclerosis and/or lytic lesions (77%), diabetes insipidus (30%), hypoadrenalism (14%), pulmonary involvement (28%), skin rash (14%) and anaemia (12%). Abnormal lung function tests were recorded in 5/17 patients with predominant restrictive pattern. All patients were treated with methotrexate with maximum tolerated dose of 40mg per week (Range 10-40mg/week). There was 24% complete metabolic response rate; 35% partial response; 17% stable disease. Two patients were unable to tolerate methotrexate due to liver impairment. The average duration of treatment was 16.1 months (Range 2-72 months). Three patients with BRAFV600E mutation have progressed on methotrexate but all have responded to BRAF inhibitor Vemurafenib. Three patients have died; Two due to progressive disease and the other due to inoperable oesophageal cancer. Grade 1/2 liver toxicity (33%) was reversible in all cases and was managed by concurrent use of folic acid. To conclude, this largest case series reports the efficacy of continuous oral methotrexate in the management of histiocytic diseases.

13. Superior Efficacy and Equivalent Safety of Double-dose Anakinra in Erdheim-Chester Disease

Fréderic Franconieri,[1] Hubert de Boysson,[1] Salim Trad,[2] Nicolas Martin Silva[1], Benjamin Terrier,[3] Boris Bienvenu,[1] Françoise Galateau-Salle,[4] Jean-François Emile,[5] Alison Johnson,[6] Achille Aouba[1]

1. Department of Internal Medicine, CHU de Caen, Université de Caen -Normandie, Avenue de la Côte de Nacre, 14000 Caen, France
2. Department of Internal Medicine, CHU Ambroise Paré, Université Paris Ouest, 9 Avenue Charles de Gaulle, 92104 Boulogne-Billancourt cedex, France
3. Department of Internal Medicine, Hôpital Cochin, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France
4. Department of Pathology, CHU de Caen, Université de Caen, Basse Normandie, Avenue de la Côte de Nacre, 14 000 Caen, France
5. Department of Pathology, CHU Ambroise Paré, Université Paris Ouest, 9 Avenue Charles de Gaulle, 92104 Boulogne-Billancourt cedex, France
6. Department of Oncology, François Baclesse Cancer Center, Caen France

Corresponding author: Dr Achille Aouba, 1Department of Internal Medicine, CHU de Caen, Université de Caen-Normandie, Avenue de la Côte de Nacre, Caen, France, Tel : + 33 2 31 06 45 79 Fax : + 33 2 31 06 49 54 E-mail: achille.aouba@gmail.com

Conflicts of interest: none

Introduction. Anakinra has been shown to be safe and efficient in Erdheim-Chester disease (ECD). However, the daily subcutaneous single dose (SD) of 100 mg is empirical in this setting and it has been hypothesized that doubling the dose (100mg x2/day) of this immunotherapy in cases of partial response or failure could improve outcomes.

Methods. Retrospective analysis of the outcomes with double-dose (DD) of anakinra in 4 out of our cohort of 10 ECD patients who did not exhibit a complete response (CR) under the initial SD. Early and long term tolerance, including renal function, were also studied. Responses were assessed as CR, failure (FL), partial response (PR; 50%≤PR<75%) and very good partial response (VGPR; 75%≤VGPR<100%).

Results. Anakinra SD was the fist-line treatment in 1/4 patients, and the second or third line treatment in the others, after failure of interferon-therapy. Genetic analysis found a BRAF-V600E mutation in patient 3, both BRAF and NRAS mutations in patient 1, a minority BRAF mutated clone (at the threshold of 20%) in patient 2, and no mutation in patient 4. With SD, three patients presented CR and one patient presented VGPR for constitutional symptoms, bone and lumbar pains. With DD, all patients achieved CR in terms of these symptoms, although only transiently for patient 2. With SD, patients 1 and 2 showed CR on right atrial masses, but only PR and FL on massive pericardic and/or pleuritic seritis, respectively. With DD, they achieved sustained VGPR and transient PR, respectively. Two patients with xanthelasma achieved CR and VGPR, respectively, with SD, followed by CR with DD. Patient 2 was the only patient with active retro-orbital/neurologic involvement: he presented bilateral exophthalmos and achieved PR with SD and CR with DD. Bone and retroperitoneal imaging showed improvement with both SD and DD, which produced CR in two patients. Interestingly, two patients exhibited disseminated intraperitoneal nodules with seritis mimicking appendicitis in one of them, which responded completely to both SD and DD. Finally, in terms of global outcomes, patients 3 and 4 achieved long term CR and patient 1 achieved long term VGPR with the ongoing DD treatment. Patient 2 presented FL and severe sides-effects, respectively with DD and the full dose of vemurafenib, then finally achieved sustained CR with SD associated with the half dose of the target therapy. All patients with moderate renal insufficiency improved their renal function and exhibited identical minor side-effects under the two doses, consisting mainly of transient reactions at injection sites.

Conclusion. Doubling the conventional dose of 100 mg/d of anakinra was tolerated as well as the SD, and improved global outcomes in 3/4 patients, including two long term CRs. Failures were essentially related to cardiac and pleuritic massive seritis. These outcomes do not seem to be correlated with detected molecular defects. Doubling the dose of anakinra and/or its association with targeted therapies should be assessed in treatment-refractory ECD.

14. Single Centre Experience of Treating Four Cases of Relapsed/Refractory BRAF Mutated Erdheim Chester Disease (ECD) / Langerhan's Cell Histiocytosis (LCH) with Oral BRAF Inhibitor Vemurafenib

Talha Munir1, Morag Griffin1, Roger Owen1, Anita Hill1, Anne Critchley1, Caroline Overvoode1, Paul Evans2, Chirag Patel3, Peter Hillmen1

1. Haematology department, St James's Hospital Leeds UK
2. Haematology malignant and diagnostic service, St James's Hospital Leeds UK
3. Radiology and Nuclear Medicine department, St James's Hospital Leeds UK

Malignant histiocytic disease characterized by multiorgan infiltration by abnormal histiocytes. BRAFV600E mutation is detected in 50-60% of cases. We report our single centre experience of treating four patients with relapsed/refractory BRAF mutated ECD/LCH with oral BRAF inhibitor, Vemurafenib. Fifty-five years old male diagnosed with BRAF mutated ECD progressed on oral methotrexate with widespread lymphadenopathy, osseous disease, bilateral lung disease, right atrial mass. peri-aortic thickness of entire thoracic aorta, peri-renal soft tissues and diabetes insipidus. Vemurafenib (480mg twice a day) was initiated with complete metabolic response achieved on FDG PET/CT within a month. Lung function tests and cardiac appearances improved with marked improvement in patient's symptoms. The patient continues to be in complete remission after 30 months of treatment on the lower dose of Vemurafenib (240 mg once a day). Forty-four years old lady presented with extensive osseous disease, widespread skin rash, pancreatic and splenic disease. BRAF mutated ECD was confirmed on mastoid biopsy. The patient was intolerant to oral methotrexate due to liver toxicity. Vemurafenib resulted in excellent clinical response and has achieved complete metabolic response within a month and continued on treatment for four months. The patient developed skin toxicity and the disease relapsed on lower dose of Vemurafenib. The patient has subsequently been refractory to Interferon-alpha and Cladrabine. However, the patient has now achieved partial metabolic remission on combination of Dabrafenib and Trametinib. Seventy-one years old male diagnosed with ECD two years ago with extensive respiratory disease. The patient was treated with oral methotrexate for one year with minimal response. Vemurafenib used as second line treatment has resulted in good clinical response and improvement in radiological appearances. The patient continues on the drug for more than one year now at a lower dose of 240 mg twice a day and is no longer oxygen therapy dependent. Fifty-three lady was diagnosed with Langerhans' cell histiocytosis involving multiple bones, nodal disease and pituitary involvement. Initial oral methotrexate treatment achieved complete metabolic remission but patient relapsed after one year whilst on therapy. Vemurafenib resulted in complete metabolic remission and patient continues at a dose of 240 mg once a day. The patient developed significant skin toxicity but this has improved on reduction of the dose.

To conclude, Vemurafenib is a BRAF inhibitor with significant activity in BRAF mutated ECD/LCH. There is rapid improvement in clinical symptoms and FDG PET/CT appearances. However, the radiological abnormalities persist with the treatment. The main toxicity of the drug is photosensitivity and requires specific precautions. There is increased risk of skin malignancies and close monitoring for any growth or changes in mole appearance is necessary.

15. The LOVE trial: preliminary results

Prof. Julien Haroche, MD, PhD and Fleur Cohen-Aubart, MD, Hôpital Pitié-Salpêtrière, Paris, France

16. Dabrafenib and Trametinib as Potential Therapy in BRAF V600E Positive Erdheim-Chester Disease (ECD): Preliminary Results

Juvianee I. Estrada-Veras1, Kevin J. O'Brien2, Emily Huang2, William A. Gahl1, 2

1. Medical Genetics Branch, Section on Human Biochemical Genetics, NHGRI, NIH, Bethesda, MD;
2. Office of the Clinical Director, NHGRI, NIH, Bethesda, MD

Background. Erdheim-Chester Disease (ECD) is a rare, fatal, multi-organ non-Langerhans cell histiocytosis with variable clinical presentations and progression. The diagnosis is established by clinical, radiologic, and histologic findings; ECD tumors have foamy macrophages that are CD68+, CD163+, CD1a-, and S-100-. There is no approved therapy for ECD, but the association with mutations in BRAF and RAS provide potential targets for therapy.
Methods. Five patients with confirmed BRAF V600E ECD that met inclusion and exclusion criteria were enrolled in NHGRI protocol 15-HG-0006, "A Phase II Therapeutic Trial of the Use of Dabrafenib and Trametinib in Patients with BRAF V600E Mutation Positive Lesions in Erdheim Chester Disease" (NCT02281760). Patients began taking 150 mg of dabrafenib (a BRAF inhibitor) every 12 hours and 2 mg of trametinib (a MEK inhibitor) every 24 hours and have completed 6 cycles of therapy.
Results. Patients had at least one lesion that met RECIST 1.1 criteria for target lesions, and up to five lesions were selected for follow up. Lesions were followed at one, two, four, and six months. Eighty percent of patients (N=4) achieved

partial response in at least one diameter. Overall partial response at six months was seen in 40% of cases (N=2). Overall minor response (<30% reduction in size) occurred in the remainder. All patients reported improvements in their quality of life, activity level, and energy. The most common adverse event was pyrexia followed by skin exanthema. Skin cancer was not reported. Four cases required dose modifications.
Conclusions. BRAF inhibition in combination with MEK inhibition in patients with BRAF V600E ECD is a safe and promising therapy. Skin cancers are less likely to occur. This trial is still enrolling patients. Patients will complete 12 cycles of therapy and then be followed for 12 months to assess duration of response and disease progression.

17. Encouraging activity of MEK inhibitor trametinib in patients with Erdheim-Chester disease irrespective of BRAF mutation status

Filip Janku, MD, PhD, Tamara G. Barnes, University of Texas MD Anderson Cancer Center, Houston, TX USA

Background: Activation of the MAPK pathway through BRAF mutations or other molecular alterations is a hallmark of the Erdheim-Chester disease (ECD). Conventional clinical molecular testing of tumor tissue fails to identify targetable molecular alteration in about one third of patients with ECD. Targeting the MAPK kinase pathway in ECD with small molecule inhibitors can be effective in patients with BRAF or other MAPK molecular alterations and doses required for clinical effect are usually lower than these approved by FDA for other cancers.
Methods: Patients with ECD with unknown or pending molecular testing test (tumor tissue targeted next generation sequencing [NGS], plasma cell-free [cf] DNA targeted NGS) or without targetable molecular alteration were treated with trametinib, an oral inhibitor of MEK1/ 2 kinase at the dose of 1 mg daily (50% of FDA approved dose for melanoma).
Results: Total of 4 patients were started on trametinib 1mg po daily. Of these 4 patients, 2 patients were found not to have targetable alterations (tumor tissue PCR, plasma cfDNA targeted, urine cfDNA, cerebrospinal fluid cfDNA) and 2 patients were ultimately found to have BRAF V600E mutation (tumor tissue PCR, tumor tissue targeted NGS, plasma cfDNA targeted NGS). Patients with BRAF mutations were both treatment naïve while patients without targetable alterations received two lines of prior therapies (anakinra and anakinra in combination with everolimus). To date of 4 patients, 3 (BRAF V600E, n=1; wild-type BRAF, n=2) reported improvement (often rapid and dramatic) of their symptoms such as fatigue, pain, weakness, speech difficulties, problems with balance, fever and dyspnea. Of these 4 patients, only one had the first restaging scan after 4 months of therapy, which demonstrated significant reduction in FDG-avid disease. The only significant drug related toxicity was grade 2 erythematous rash (covering 10-30% of body surface) in two patients, which was manageable with supportive measures. Data on follow-up radiologic assessment and longitudinal plasma cfDNA analysis (in patients with BRAF mutation) will be presented at the meeting.
Conclusions: MEK inhibitor trametinib at 50% of the FDA approved dose demonstrated encouraging activity in patients with ECD irrespective of underlying molecular profile. Further studies perhaps focused on patients without targetable alterations are warranted.

18. Phase 2 Trial of Single-Agent Cobimetinib for Adults with Histiocytic Disorders: Preliminary Results

Eli L. Diamond, 1 Benjamin H. Durham2, Ahmet Dogan2, David M. Hyman3, Raajit Rampal4, Gary Ulaner, 5 Lynn Brody, Omar Abdel-Wahab4, 6

1. Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, United States
2. Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, United States
3. Developmental Therapeutics, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, United States
4. Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, United States
5. Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, United States
6. Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, United States

Background: The identification of recurrent BRAFV600E mutations in Erdheim-Chester disease (ECD) led to a breakthrough in treatment of refractory or severe forms of disease with BRAF inhibition. The finding that nearly all BRAF-wildtype ECD lesions harbor mitogen activated protein kinase (MAPK) pathway alterations has raised the possibility of treatment of BRAF-wildtype ECD with MEK inhibition.
Methods: This is an open-label, phase 2 trial of Cobimetinib 60mg daily, given for 21 days of a 28-day cycle, for patients with (1) BRAF-wildtype histiocytosis or (2) BRAFV600-mutated histiocytosis intolerant of or without access to BRAF inhibitor therapy. The primary study outcome is metabolic response by 18F-FDG PET scan performed every two cycles.
Results: 7 patients have enrolled: 4 ECD, 1 Rosai-Dorfman disease (RDD), 1 mixed ECD/RDD, and 1 Langerhans cell histiocytosis (LCH). Five patients (3 ECD, 1 RDD, and 1 LCH) have had response assessments. One patient died (Grade 5 respiratory failure, unrelated to drug, related to infection) before the first response assessment, and another has not yet

had a response assessment. The other serious adverse event was Grade 3 hyponatremia requiring hospital admission (possibly related to drug). Grade 3/4 toxicities observed have been hyponatremia (33%), lymphopenia (33%), hyperglycemia (33%), diarrhea (16%), and hypocalcemia (16%). The most common Grade 1-2 toxicities have been hypoalbuminemia (83%), acneiform rash (83%), nausea (67%), diarrhea (67%), and anemia (50%). Three patients have required dose reduction to 40mg. All evaluable target lesions have had a metabolic response, 20% a complete metabolic response and 80% a partial metabolic response. Organs involved have included brain, heart, skin, bones, retroperitoneum, and abdominal soft tissues. All patients have had clinical benefit.
Conclusions: Preliminary results from this trial demonstrate robust efficacy of single-agent Cobimetinib in BRAF-wildtype ECD, RDD, and LCH. Toxicities have been manageable and similar to those observed in previous trials of Cobimetinib.

19. Dabrafenib in combination with Trametinib is effective in treatment of refractory BRAF mutated mixed histiocytic disease- A Case report

Talha Munir1, Morag Griffin1, Roger Owen1, Anita Hill1, Anne Critchley1, Caroline Overvoode1, Paul Evans2, Chirag Patel3, Peter Hillmen1

1. Haematology department, St James's Hospital Leeds UK
2. Haematology malignant and diagnostic service, St James's Hospital Leeds UK
3. Radiology and Nuclear Medicine department, St James's Hospital Leeds UK

Forty-four years old lady presented with widespread skin rash, bony pains and symptoms of polyuria. FDG PET-CT scan showed extensive symmetrical metabolically active bony involvement in the axial and appendicular skeleton. There was further involvement of the kidneys, spleen and pancreas. The patient had confirmed diabetes insipidus with pituitary failure and was on replacement therapy. A widespread maculopapular rash was noticed and skin biopsy was consistent with Langerhans cell phenotype (CD163-, CD1a+, CD20-, CD3-, CD30-, CD4+, CD68-, Langerin+, S100+). Mastoid biopsy was performed due to diagnostic uncertainty at initial workup which confirmed ECD phenotype (CD1a-, CD68+, CD163+). However, BRAF V600E mutation was detected in both biopsies as well as peripheral blood. Cardiac MRI confirmed poor left ventricular function but no other characteristic features of ECD were found. The patient was intolerant to oral methotrexate due to liver toxicity and on-going pancreatitis. Vemurafenib was initiated at a dose of 480mg twice a day which resulted in excellent complete metabolic response within a month of starting Vemurafenib. However, the patient developed severe skin toxicity and the disease relapsed on lower dose of Vemurafenib. The patient was subsequently treated with 6 months of high dose Interferon-alpha resulting in no response and four cycles of Cladrabine with similar outcome. The patient progressed with worsening bony disease and neurological involvement confirmed on FDG PET-CT and MRI Brain.
The patient has now initiated oral BRAF inhibitor Dabrafenib (150 mg twice daily) along with MEK-1 inhibitor Trametinib (2mg once daily). After one month of therapy, the patient has achieved a partial response based on PET-CT appearances. The bony disease activity has completely subsided and the patient's analgesia requirements have reduced significantly. The combination has been tolerated well apart from few febrile episodes. These have been attributed to Dabrafenib as no obvious infection has been found.
In short, targeted therapies in form of BRAF and MEK-1 inhibitors are extremely effective in achieving remission in BRAF mutated histiocytic disease. Alternative BRAF inhibitors could be utilized especially in intolerant cases. As histiocytic diseases are extremely rare, we feel that it is important to report these cases.

20. Spectrum of Cardiovascular Involvement in Erdheim-Chester Disease Evaluated by Multimodality Imaging

Diana Melo1, Andrea Knab1, Jeannie Yu1, Sujata M. Shanbhag1, William A. Gahl2, Juvianee I. Estrada-Veras2, Marcus Y. Chen1

1. National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD
2. National Human Genome Research Institute, National Institutes of Health, Bethesda, MD

Background: Erdheim-Chester disease (ECD) is a rare, non-Langerhans cell histiocytosis, characterized by foamy macrophage-mediated accumulation and associated fibrosis in various organs. Clinical manifestations vary depending on the location and extent of disease. Cardiovascular and neurological involvement is associated with a poor prognosis, contributing to a mortality rate of 60% at three years after diagnosis. The presence of early cardiac manifestations may impact management strategy but are often clinically silent, and as such, advanced imaging techniques are frequently required to determine if there is cardiac involvement.

Methods: We sought to characterize the prevalence and spectrum of multimodality cardiac imaging findings in ECD patients. A total of 58 consecutive patients (75% male, age 52±11 years, range 19-72 years) with biopsy-proven Erdheim-Chester Disease underwent echocardiography and contrast-enhanced, ECG-gated, cardiac CT on a 320-detector row scanner. Eligible patients also underwent cardiac magnetic resonance (CMR).
Results: Overall, 40% (23/58) of the patients had cardiovascular involvement. The most common finding was that of a homogenous soft tissue density (or "pseudo-tumor") within the right atrioventricular groove, which was present in 91% or 21 of 23 patients [Figure 1]. Of note, ECD involvement of the right atrioventricular groove could also be detected with non-contrast CT. Other locations included the right atrium (87%; 20/23), interatrial septum (26%; 6/23), right ventricle (9%; 2/23), left atrium (4%; 1/23), and pericardium (4%; 1/23). Three subjects (5%) had a pericardial effusion. Six patients examined (10%) had circumferential peri-aortic thickening or a "coated aorta" in visualized portions of the descending aorta. While cardiac CT and CMR were equally sensitive in detecting ECD involvement, echocardiography was unable to visualize cardiac involvement in the majority of cases (78%; 18/23). In addition, 36% (12/33) of ECD patients had significant coronary calcification defined as greater than 90th percentile of age, gender and ethnically matched controls.
Conclusion: Cardiovascular involvement of Erdheim-Chester disease is common (40%), and the most prevalent feature is pseudo-tumor involvement of the right atrioventricular sulcus, with encasement of the right coronary artery. Given echocardiography's limited diagnostic value, advanced imaging with either cardiac CT or MRI should be performed to elucidate the degree of ECD heart involvement

21. Adult-onset (Infratentorial) Leukoencephalopathy as Presenting Manifestation of Erdheim-Chester Disease

Giulio Cavalli, MD; IRCCS H San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy, Ettore Salsano, Mario Savoiardo, Maria Luisa Chiapparini, Lorenzo Dagna

Introduction: Leukoencephalopathies are diseases characterized by degeneration of the white matter of the central nervous system (CNS). In most cases, leukoencephalopaties are hereditary diseases of childhood; however, they can also present in adulthood with a progressive, incurable course, resembling degenerative disorders of the CNS. The etiology of adult-onset leukodystrophies remains unknown in about 30–50 % of cases. Erdheim-Chester disease (ECD) is a rare histiocytosis characterized by tissue infiltration with foamy, lipid-laden macrophages. In this study, we report the clinical and radiologic features of 9 adult patients with leukoencephalopaty primarily affecting the cerebellum and brainstem, or 'infratentorial leukoencephalopathy' (ITL), attributable to CNS involvement by ECD.
Methods: We reviewed the clinical, laboratory and radiologic information of 9 patients with ITL and ECD and evaluated their brain MRIs. Patients also underwent spinal cord MRI. A diagnosis of ECD was established in the presence of typical imaging findings at Tc99m bone scintigraphy and compatible histology.
Results: All cases were isolated, with no evidence of autoimmune or hereditary diseases and unremarkable CSF examination. Clinical features included ataxia, spasticity, cranial nerve dysfunction, cognitive decline, neurogenic bladder, and diabetes insipidus. ECD-associated ITL has highly characteristic radiologic patterns of white matter involvement, with prominent signal abnormalities in the posterior fossa structures. Supratentorial white matter abnormalities and spinal cord lesions were present in 8 and 6 individuals, respectively. Brain involvement causing ITL may predate the onset of systemic manifestations of ECD.
Conclusions: ECD emerges as a cause of adult-onset ITL, a finding with relevant diagnostic and therapeutic implications. Investigations aimed at unveiling ECD are indicated in all patients with ITL, even in the absence of typical ECD manifestations. Diagnosing ECD enables therapeutic strategies in patients with ITL, an otherwise untreatable, chronically degenerative condition.

22. MRI evidence of cardiac involvement in Erdheim-Chester disease

Davide Gianfreda, MD1, Alessandro A. Palumbo, MD2, Enrica Rossi, MD2, Lorenzo Buttarelli, MD2, Gaia Manari1, Chiara Martini, RT2, Massimo De Filippo, MD2, Augusto Vaglio, MD PhD1 1Nephrology Unit, Parma University Hospital; 2Radiology Unit, Parma University Hospital, Parma, Italy

Background. Cardiovascular manifestations are common in Erdheim Chester disease (ECD), and mainly include infiltration of the myocardium, the pericardium and the aorta. ECD patients with cardiovascular involvement are reported to have a poorer prognosis and are therefore usually treated aggressively, although systematic studies are lacking. In addition, it is still unclear whether cardiovascular involvement only detected by imaging studies actually influences prognosis, and whether the purported adverse prognosis is due to cardiovascular lesions per se or to other factors.
Methods. We conducted a cross-sectional study on 23 consecutive patients using a standardized protocol of cardiac magnetic resonance imaging (MRI) and MR-angiography of the thoracic aorta and epiaortic arteries. All patients were referred to or diagnosed at our Unit between January 2007 and October 2015. They underwent cardiac MRI at first

evaluation at our centre; in 16, cardiac MRI was performed at the time of diagnosis, while in the remaining seven after a median time from diagnosis of 72 months (range, 19-180). All patients had a biopsy-proven diagnosis of ECD.
Results. Twenty patients (87%) were men; the median age at diagnosis was 48 years (range 22-72). Ten patients (43%) had MRI evidence of cardiac involvement, with myocardial involvement in nine and pericardial in nine. Six patients had thoracic large vessel involvement together with cardiac lesions, while only one patient had thoracic aorta involvement without cardiac disease. MRI revealed peculiar patterns of myocardial involvement: most patients had right atrial involvement, usually under the form of a pseudotumoral mass, mainly involving the posterior atrial wall and often protruding into the atrium; another common lesion was the infiltration of the right atrio-ventricular sulcus, where the tissue usually surrounded or infiltrated the right coronary artery. However, none of the seven patients with right peri-coronary infiltration had ECD-related ischemic cardiac lesions. Unlike other infiltrative disorders, ECD did not cause diffuse infiltration of the myocardium, a finding in line with the normal systolic or diastolic functions observed by MRI or echocardiography. Pericardial infiltration/thickening was common, often accompanied by pericardial effusion leading to tamponade in two cases and requiring pericardiocentesis in three cases. Unlike in other reports, we found no MRI evidence of ECD-related valvular disease.
Thoracic large artery involvement was generally characterised by perivascular thickening of the thoracic aorta and the origin of the epiaortic arteries, but no luminal narrowing or aneurysms were detected.
Six of the 10 patients with cardiac MRI abnormalities had cardiovascular symptoms during their disease course: in particular, three had peripheral edema and dyspnea (and one chest pain) due to pericarditis; one patient presented with edema and dyspnea due to acute cardiac failure, one had palpitations and dyspnea secondary to atrial flutter, and one angina and syncope likely secondary to atherosclerotic, non-ECD related, coronary artery disease. Cardiovascular symptoms were also found in patients without cardiac MRI abnormalities, secondary to ischemic heart disease (two patients) and uremic pericarditis (one patient).
The patients received different treatments; there were no significant differences in the distribution of the different therapies between patients with and without cardiac MRI abnormalities. Three patients died, one in the cardiac group and two in the non-cardiac group. No significant differences in overall survival were found between the two groups (figure 1), although it must be acknowledged that the mortality rate was low. Progression-free survival, defined as time from remission to disease progression, was also similar (figure 1). However, when we investigated disease extension by calculating the number of involved sites, we found that patients with cardiac MRI abnormalities had a significantly higher number of involved sites than those without cardiac lesions; in particular, all patients with disseminated disease (≥ 5 extracardiac sites) fell in the cardiac group (figure 2).
Conclusions. Our study demonstrates that ECD has peculiar patterns of cardiac involvement. MRI-detected cardiac disease does not seem to impact on survival, although this finding is limited by the low mortality rate observed. However, cardiac involvement on MRI is clearly associated with a greater disease burden.

23. Endocrine manifestations in Erdheim-Chester disease

Carine Courtillot, MD, Hôpital Pitié-Salpêtrière, Paris, France

Until last year, endocrine involvement in Erdheim-Chester disease had mostly been described in case reports. We performed a systematic endocrine evaluation in a large cohort of ECD patients in this single-center observational study, between October 2007 and May 2013.
Sixty-four consecutive ECD patients (SR 3.6, mean age 57.6 years [20-80]) were seen, among which 36 had follow-up assessments. We analysed clinical, biological and morphological evaluations of pituitary, gonadal, adrenal and thyroid functions, as well as metabolic evaluation. Diabetes insipidus was found in 33.3% of patients, frequently inaugural of ECD. Anterior pituitary dysfunction was found in 91.3% of patients with full anterior pituitary evaluation, including somatotropic deficiency (78.6%), hyperprolactinemia (44.1%), gonadotropic deficiency (22.2%), thyreotropic deficiency (9.5%) and corticotropic deficiency (3.1%). Thirty-five patients (54.7%) had ≥ 2 anterior pituitary dysfunctional axes, rising to 69.6% (16/23) when only considering patients with complete evaluation. Two patients had panhypopituitarism. Infiltration of pituitary and stalk was found on MRI in 24.4% cases. Testicular insufficiency was found in 53.1% patients, with sonographic testicular infiltration in 29% of men, mostly bilateral. TDM adrenal infiltration was found in 39.1% of patients, and one case of adrenal insufficiency was observed. No patient was free of endocrine hormonal or morphological involvement. Endocrine dysfunctions were most often permanent and new deficits appeared during follow-up.
Endocrine involvement is very frequent in ECD and should carefully be evaluated at diagnosis and during follow-up. Since the publication in JCEM in 2015, 73 ECD patients have been fully assessed for endocrine involvement.

THANK YOU FOR YOUR ATTENDANCE AND PARTICIPATION!

SUPPORTING THOSE AFFECTED BY ERDHEIM-CHESTER DISEASE

Kathleen Brewer
kathleen.brewer@erdheim-chester.org

Elizabeth Anderson
liz.anderson@erdheim-chester.org

Jessica Corkran
jessica.corkran@erdheim-chester.org

HÔPITAUX UNIVERSITAIRES
PITIÉ SALPÊTRIÈRE - CHARLES FOIX

Prof. Julien Haroche, MD, PhD
julien.haroche@aphp.fr

Funding for this conference was made possible (in part) by 1 R13 TR001695-01 from the National Center for Advancing Translational Sciences (NCATS). The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention by trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

NOTES

NOTES