ECD MEDICAL SYMPOSIUM

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ERDHEIM-CHESTER DISEASE

MAYO CLINIC

APRIL 27, 2023
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ECD GLOBAL ALLIANCE

Supporting those affected by
Erdheim-Chester Disease worldwide.
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April 26, 2023

2023 Annual International ECD Medical Symposium
Mayo Clinic
Rochester, Minnesota

Welcome!

It is great to have you join the 2023 Annual International Medical Symposium! We are very excited to meet in person once again, with this being our first international event since 2019. How wonderful it feels for the pandemic to be behind us, allowing us to meet again in person.

We are appreciative of all the work our clinicians and researchers do on behalf of the ECD community, and hope you are as excited as we are to learn about all the research and learning that has been going on this year. Our Mayo hosts, the ECD Global Alliance Board of Directors and staff, speakers, and volunteers trust that your time at this meeting will leave you feeling part of a strong community, working together to improve the lives of all who have been touched by ECD. We are very thankful to those members of our community who have made this event possible through their generosity, including private donors and industry sponsors.

Thank you for your attendance and involvement in this year's event. Your support shows that you find value in this experience. We will be very grateful if at the conclusion of this meeting you decide to become more involved in the work of the ECDGA to improve life for all ECD patients now and into the future. We truly believe with one another's help we will move forward to an even brighter future for all affected by ECD.

Please enjoy your experience!

With best wishes to you,

Ronald Go, MD
Mayo Clinic
Co-Host

Gaurav Goyal, MD
University of Alabama at Birmingham
Co-Host

Kathleen Brewer
ECD Global Alliance

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Schedule of Events | April 26-28, 2023

(See map of campus on page 2)

Date	***Time***	***Event***
Wednesday, April 26	6:00 pm – 8:00 pm	Medical Social *Marriott Ballroom 2*
Thursday, April 27	8:00 am – 5:00 pm	ECD Medical Symposium *Phillips Hall, Siebens Building, Mayo Clinic*
	6:00 pm – 8:00 pm	Banquet for Physicians, Patients, and Families *Marriott Ballroom 2*
Friday, April 28	7:30 am	Catholic Mass *Kahler Grand Regency Room*
	8:00 am	Registration & Continental Breakfast *Phillips Hall, Siebens Building, Mayo Clinic*
	8:45 am – 5:00 pm	ECD Patient & Family Gathering *Phillips Hall, Siebens Building, Mayo Clinic*

To support ECDGA's work, scan this

Map of Meeting Locations | April 27-28, 2023

*Phillips Hall is within Siebens Building shown above.

Presentation Agenda | Thursday, April 27 – 8:00 AM – 5 PM

Time	*Subject*	*Presenter*
8:00 am	Registration & Continental Breakfast	
8:30 am	Welcome & Meeting Overview	Ronald Go, MD Gaurav Goyal, MD
8:40 am	History of the ECDGA Focus on the Future	Kathleen Brewer, Founder Paul Hendrie, MD
Keynote Session		
8:50 am	*Understanding monocyte-related disorders including epigenetics and genomics*	Mrinal Patnaik, MBBS
Mutations Matter		
9:30 am	RAF-independent MEK mutations drive histiocytic neoplasms in vivo and are sensitive to single agent ERK inhibition in patients	Benjamin Durham, MD
9:45 am	Cluster analysis unveils the clinical spectrum of Erdheim-Chester Disease	Michelangelo Tesi, MD
10:00 am	Efficacy of MEK inhibitors of Erdheim-Chester disease	Aldo A Acosta Medina, MD
10:15 am	Neoplasms harboring class 3 MAP2K1 mutations, including novel treatment with the ERK inhibitor ulixertinib	Eli Diamond, MD
10:30 am	***Coffee Break and Poster Viewing***	
Epidemiology, Outcomes, and Survivorship		
10:50 am	Early changes in intermediate monocyte distribution correlate with relapse-free survival during follow-up in adult histiocytoses	Jerome Razanamahery, MD
11:05 am	Geographic clustering of Erdheim-Chester Disease in Italy and France	Francesco Peyronel, MD,
11:20 am	A multinational series of 26 patients with mixed histiocytic neoplasms highlighting a diverse mutational landscape and superior efficacy of targeted therapies	Eli Diamond, MD
11:35 am	A pilot study of patient-reported outcome measures among individuals with histiocytic neoplasm	Matt Slief, MD

Time	*Subject*	*Presenter*
Workshop		
11:50 am	Pathology mimics workshop	Karen Rech, MD Jennifer Picarsic, MD
12:20 pm	***Lunch and Poster Viewing*** ***Recognitions: Board, Medical Advisory Committee, Volunteer***	
It's All About the Organs		
1:20 pm	Abnormalities of pituitary imaging and associated endocrine disorders in Erdheim-Chester disease	Skand Shekhar, MD
1:35 pm	Longitudinal assessment of cardiac involvement in Erdheim-Chester disease using cardiac magnetic resonance imaging	Levi-Dan Azoulay, MD
Malignant Histiocytosis: The Forgotten Orphan		
1:50 pm	The phenotypic spectrum of malignant histiocytosis parallels the lineage subsets of monocytes, macrophages, and dendritic cells	Aishwarya Ravindran, MD
2:05 pm	Clinical features, molecular aberrations, treatments, and outcomes of malignant histiocytoses	Gordon Ruan, MD
Workshop		
2:20 pm	Radiology workshop	Corrie Bach, MD
2:50 pm	***Coffee Break and Poster Viewing***	
3:05 pm	Meet the Experts: Challenging situations and unanswered questions	Eli Diamond, MD Ron Go, MD Julien Haroche, MD Eric Jacobsen, MD
3:50 pm	ECD Global Alliance Mission Forward *Survey and Evaluations*	Kathy Brewer ECD Global Alliance
4:05 pm	Closing and Photograph	

Poster Sessions

	Poster	***Presenter***
1	CNS-restricted, BRAF-positive, Histiocytic Inflammation That Responds to MAP Kinase Inhibition	Rahul Dave, MD, PhD
2	Erdheim-Chester Disease with Rare Presentations of Tendon and Muscle Involvement	Kevin O'Brien, MS-CRNP
3	Introduction of a small molecule CSF1R and TAM tyrosine kinase inhibitor Q702 in hematologic malignancies	June Kim, MD
4	Uronephropathy Involvement in Erdheim-Chester Disease: Imaging Findings and Their Association with the BRAF Mutation	Kevin O'Brien, MS-CRNP
5	Identifying and responding to treatment failures in Erdheim-Chester Disease: A Case Study and Discussion on Histiocytic Molecular Heterogeneity	Samuel Reynolds, MD
6	Diagnostic and Therapeutic Challenges in Multi-Organ Erdheim-Chester Disease	Sabrina Wilcox, MD
7	Characteristics and Outcomes Associated with Cardiac Involvement in Erdheim-Chester Disease	Reema Tawfiq, MD
8	ECD Global Alliance	Kathy Brewer

Workshop and Panel Member Biographies

Pathology Mimics Workshop

Karen Rech Mayo Clinic, Rochester, MN, USA

Bio: Karen L. Rech practices in the Division of Hematopathology, with a special interest in the diagnosis of malignant lymphoma. She has expertise in diagnosis of hematolymphoid neoplasms and in integration of ancillary studies for diagnosis including immunohistochemistry, flow cytometry, molecular genetic testing, and amyloid typing by mass spectrometry. She is a member of the Mayo Clinic Histiocytosis Working Group and Medical Director of Immunostains Laboratory, providing oversight in clinical test development and diagnostic application. In addition to her clinical activities, Dr. Rech is active in research with particular emphasis on histiocytic neoplasms including Erdheim-Chester Disease, Rosai-Dorfman Disease and Langerhans Cell Histiocytosis.

Jennifer Picarsic Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Bio: As a pediatric pathologist, Dr. Picarsic studies cells specializes in histiocytic neoplasms, a rare group of white blood cell disorders that affect both pediatric and adult patients. She reviews pathology consultations from around the world at Cincinnati Children's Hospital Medical Center.

Radiology Workshop

Corrie Bach Mayo Clinic, Rochester, MN, USA

Bio: Dr. Corrie Bach earned her medical degree from New York Medical College. She subsequently completed radiology residency and nuclear radiology fellowship at Mayo Clinic, Rochester MN. She is a board-certified radiologist practicing at Mayo Clinic, Rochester MN. Her clinical interests include Erdheim-Chester Disease and histiocytic neoplasms.

Meet the Experts: Challenging Situations and Unanswered Questions

Eli Diamond Memorial Sloan Kettering Cancer Center, New York, NY, USA

Bio: Eli L. Diamond, MD is a neuro-oncologist who specializes in the care of patients with ECD and other histiocytosis, as well as brain tumors and neurologic complications of cancer. He did his neurology residency at the Massachusetts General Hospital and Brigham and Woman's Hospital and his neuro-oncology training at Memorial Sloan Kettering Cancer Center (MSK), where he is currently a staff neuro-oncologist. He conducts and has conducted several research studies for patients with ECD including the vemurafenib trial, the cobimetinib trial, a study looking for gene mutations in ECD tumors, a study to improve ECD biopsies, and a study about ECD and the brain. He is also the co-founder of the global ECD Patient Registry that has been supported by the ECD Global Alliance. At MSK, he works with a large team across many disciplines to offer the highest quality medical care and supportive care for patients with ECD, as well as to better our understanding and treatment of ECD with collaborative research.

Ronald S. Go Mayo Clinic, Rochester, MN, USA

Bio: Ronald S. Go, M.D. is a hematologist/oncologist and investigates the pathogenesis, diagnosis, and treatment of histiocytic disorders such as Erdheim-Chester disease, Rosal-Dorfman disease, and Langerhans cell histiocytosis. Since 2017, he has led the Mayo Clinic Histiocytosis Working Group, which is a multidisciplinary and dedicated team of physicians treating histiocytic disorders. Besides histiocytic disorders, Dr. Go's clinical and research interest include thrombotic microangiopathies, immune cytopenias, and monoclonal gammopathy of undetermined significance. He also performs health outcomes research in hematologic malignancies. Dr. Go leads an ECD Care Center at Mayo Clinic in Rochester, MN, including a multidisciplinary Histocyte Working Group, which meets monthly to discuss every case being studied within the collaborative tumor board. This has been very valuable to ECD patients, especially for those traveling from long distances.

Julien Haroche Hôpital Pitié-Salpêtrière, Paris, MN, USA

Bio: Julien Haroche is a professor in internal medicine, at Pitié-Salpêtrière, Paris, France. Since 2003, his main research field is Erdheim-Chester disease upon which he has acquired a world-renowned expertise. He has seen a vast number of patients at his institution. His other research fields are the other histiocytoses, such as Langerhans cell histiocytosis, mixed histiocytosis and Rosai-Dorfman disease. He is also interested in vasculitis, lupus and antiphospholipid syndrome. Dr. Haroche serves on the ECD Global Alliance Medical Advisory Board and is an ECD Care Center lead physician.

Eric Jacobsen Hematology - Oncology, Dana Farber, Boston, MA, USA
Bio: Dr. Jacobsen received his MD from the University of Connecticut School of Medicine in 1999. He completed postgraduate training in Internal Medicine at Johns Hopkins Hospital, followed by a fellowship in Medical Oncology and Hematology at Dana-Farber Cancer Institute. He joined the division of Hematologic Malignancies in 2005. He leads the ECD Care Center at Dana-Farber.

Abstract Presentations

RAF-INDEPENDENT MEK MUTATIONS DRIVE HISTIOCYTIC NEOPLASMS IN VIVO AND ARE SENSITIVE TO SINGLE AGENT ERK INHIBITION IN PATIENTS

Benjamin Durham durhamb@mskcc.org Memorial Sloan Kettering Cancer Center

Authors: Benjamin H. Durham[1,2], Michael Singer[1], Salima Benbarche[1], Caroline Erickson[1], Jahan Rahman[1], David B. Solit[3], Matthew Witkowski[4], Neal Rosen[1], Omar Abdel-Wahab[1,5], Eli L. Diamond[6]

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Histiocytic neoplasms are clonal, monocyte/macrophage lineage disorders encompassing Langerhans cell histiocytosis, Erdheim-Chester disease, and other histiocytoses with mutations activating MAP kinase (MAPK) signaling. Recent genomic studies across histiocytoses demonstrate that the most common alteration following BRAFV600E is MAP2K1E102_I103del. Unlike BRAFV600E, the biological impact of activating MAP2K1 mutations is unknown with no neoplastic MEK1/2 mutation having been modeled in vivo. MAP2K1E102_I103del is associated with allosteric MEK inhibitor resistance in vitro and in some histiocytoses patients. Therefore, these findings motivated us to generate Map2k1E102_I103del conditional knock-in mice within the endogenous locus of Map2k1, which represent the first genetically engineered mouse model of MEK1/2 mutations. We crossed Map2k1E102_I103del mice to Mx1-cre driver mice. By 5-6 weeks of age, Mx1-cre Map2k1E102_I103del knock-in mice developed 100% penetrant, lethal myelomonocytic neoplasms with suppression of B-lymphopoiesis and expansion of monocyte/macrophage subsets and Cd11b+ dendritic cells that also infiltrated hematopoietic organs, liver, and skin (common disease sites in LCH and ECD) while their littermate controls did not. Map2k1E102_I103del allele recombination occurred spontaneously and resulted in activation of phosphorylated ERK1/2 in hematopoietic cells. The Mx1-cre Map2k1E102_I103del disease was hematopoietic cell autonomous and propagated by serial transplantation, as well as using Vav1-cre Map2k1E102_I103del knock-in mice. Finally, restricting MEK1 mutant expression to monocyte/dendritic cell precursors using CD11c-cre resulted in a milder but similar disease as seen in the Mx1-cre and Vav1-cre models. Prior in vitro work has demonstrated that MEK1 p.E102_I103 activates MEK and ERK without requiring activated GTP-bound RAS and is associated with resistance to allosteric MEK inhibitors. Consistent with this, we identified nine histiocytosis patients with this MEK1 mutation three of which had de novo resistance to cobimetinib. These three patients, and one treatment-naïve patient, were treated with an oral ERK1/2 inhibitor, ulixertinib under the FDA single patient compassionate use program. Three of 4 patients had a clinical or radiological partial or complete response to ulixertinib. Overall, in vivo expression of Map2k1E102_I103del gave rise to disease reminiscent of human histiocytic neoplasms with more aggressive disease emerging with mutational expression earlier in hematopoietic development. Thus, these data identify the impact of oncogenic MAP2K1 mutations in vivo as found in histiocytoses patients. Importantly, MEK1 p.E102_I103del is resistant to MEK inhibition in some patients but responsive to ERK inhibition, which may be a promising therapeutic approach. Thus, this mouse model provides an avenue for studying other MAPK inhibitors in MEK-inhibitor-resistant histiocytoses and can inspire future clinical trials.

Bio: I am a molecular hematopathologist and experimental pathologist with American Board of Pathology certifications in anatomic pathology, clinical pathology, hematopathology, and molecular genetic pathology and am an Assistant Member Level 1 on the Molecular Diagnostics Service in the Department of Pathology and Laboratory Medicine at Memorial Sloan Kettering Cancer Center (MSKCC). I investigate the molecular pathogenesis and functional genomics of poorly characterized hematological malignancies driven by mitogen-activated protein kinase (MAPK) and receptor tyrosine kinase (RTK) signaling (histiocytic neoplasms and hairy cell leukemia (HCL)). I lead the biological and translational investigations into these disorders in the Omar Abdel-Wahab Laboratory in the Molecular Pharmacology Program and Center for Hematologic Malignancies at MSKCC. During this time, I applied my molecular hematopathology expertise to unravel the molecular bases of the BRAFV600-wild-type histiocytic neoplasms to identify potential molecular therapeutic avenues in these poorly characterized neoplasms without FDA-approved treatments. I pursued groundbreaking research on the molecular pathogenesis of the histiocytoses that led to the first description of kinase fusions; activating MAP2K1, ARAF, and CSF1R mutations; and clinical efficacy of MEK1/2, RET, and ALK inhibition in histiocytoses patients. This work inspired our phase II clinical trial using the MEK1/2 inhibitor cobimetinib for adults with BRAFV600-wild-type histiocytic neoplasms, which is now FDA-approved for this indication (11/02/2022). I have also generated the first xenotransplantation model of a histiocytic neoplasm with the first functional evidence that the cellular origins of a subset of histiocytoses occurs within the hematopoietic stem and progenitor cell compartment. I have also investigated the molecular pathogenesis of classical and variant HCL leading to our understanding of the first genetic mechanisms underlying clinical vemurafenib resistance in classical HCL Furthermore, I have extensively contributed to the development and characterization of multiple novel murine models of histiocytic neoplasms and other hematological malignancies resulting in >30 co-author manuscripts over the past 8 years.

CLUSTER ANALYSIS UNVEILS THE CLINICAL SPECTRUM OF ERDHEIM-CHESTER DISEASE

Michelangelo Tesi michelangelo.tesi@meyer.it **Meyer Children's Hospital, IRCCS**

Authors: Michelangelo Tesi, Francesco Pegoraro, Francesco Peyronel, Martina Mazzariol, Elena Gelain, Matthew J. Koster, Ronald S. Go, Gaurav Goyal, Matthew Collin, Paul Milne, Sarah Pagan, Juvianee I. Estrada-Veras, Roei D Mazor, Lorenzo Dagna, Eli L. Diamond, Fleur Cohen-Aubart, Matthias Papo, Augusto Vaglio, Julien Haroche

Background: Erdheim-Chester Disease (ECD) is a rare non-Langerhans cell histiocytosis characterized by tissue infiltration by foamy histiocytes. The disease is driven by mutations in proto-oncogenes such as BRAF, which activate mitogen-activated protein kinase (MAPK) pathways, while immune-mediated mechanisms contribute to disease development and progression. Clinical manifestations are extremely heterogeneous and virtually every organ system can be affected. In the present cohort study, we classified patients with ECD based on clinical presentation and mutational status using an unsupervised data-driven clustering approach.

Methods: This study was based on a dataset of 356 patients with ECD that contained data referred to demographics, clinical presentation, mutational status (BRAF and other relevant genes), and follow-up including treatment and outcome. Clinical features at presentation along with mutational status were included as twenty input variables in the clustering model. The dimensionality of the dataset was reduced through a principal component method, and then a hierarchical clustering approach was used. Each generated cluster was characterized by analyzing its summary features.

Results: The clustering algorithm produced two models, one with four clusters and one with five. The generated clusters were labeled with their prominent features or given a representative name. The clusters named "Digestive/Hematologic/Myelodysplastic Syndrome" (around 3% of subjects), "Testis/Lymph Nodes/MAP2K1 mutation" (8%), and "Limited Disease" (30%) were identical across the two models. The remaining patients showed a high rate of BRAF mutation (around 90%) and were aggregated in a single large cluster named "Widespread Disease" (59%) in the four-cluster model, whereas they were split into two different clusters - the "Hypothalamic/Pituitary/Associated Langerhans Cell Histiocytosis" (25%) and the "Cardiovascular/Perirenal"(34%) - in the five-cluster model.

Conclusions: Hierarchical clustering on principal components subdivided the ECD patient sample into clusters which reflect what has often already been observed in the clinical practice, with regard to the widespread disease

phenotype as opposed to the limited one, and to the phenotypes of ECD associated with other types of histiocytosis or myelodysplastic syndrome.

Bio: Michelangelo Tesi obtained a bachelor's degree in Biotechnology (2019) with his thesis project in bioinformatics on the subject of genome-scale metabolic network reconstruction. He is now a Research Fellow at Meyer Children's Hospital, Florence. He is interested in computational biology, biostatistics and bioinformatics.

EFFICACY OF MEK INHIBITORS IN ERDHEIM CHESTER DISEASE

Aldo A Acosta Medina AcostaMedina.Aldo@mayo.edu **Mayo Clinic**

Authors: Aldo A. Acosta-Medina MD, Saurabh Zanwar MD, Gordon Ruan MD, Jithma P. Abeykoon MD, Karen Rech MD, Aishwarya Ravindran MBBS, Nora Bennani MD, Caroline J Davidge-Pitts MBBCh, Matthew Koster MD, Jay Ryu MD, Mithun V. Shah MD PhD, W. Oliver Tobin MB BCh, Robert Vassallo MD, Jason R. Young MD, Gaurav Goyal MD and Ronald Go MD

Introduction: Erdheim Chester disease (ECD) is known to be driven by recurrent mutations in the MAPK pathway. Increased understanding of ECD resulted in the study of MEK inhibitors (MEKi) in cases not harboring the BRAFV600E mutation, ultimately leading to approval of cobimetinib for BRAFV600E negative histiocytic neoplasms. We aimed to describe characteristics and outcomes of the largest cohort of ECD patients treated with MEKi outside of a clinical trial.

Methods: We included all patients with ECD seen at Mayo Clinic and treated with available MEKi (cobimetinib, trametinib, or binimetinib) between 2019-2021. Tumor MAPK pathway mutation status was determined with next-generation sequencing (NGS) or, if unavailable, immunohistochemistry (IHC) or allele-specific PCR was used to determine BRAF mutation status.

Results: A total of 22 patients with ECD were included. Median follow up was 19 months (95% CI 10 – 28 months) and 55% (n=12) were female. Median age at diagnosis of ECD was 52 years (IQR 35.8 – 70.8 years). NGS data was available in 82% (n=18). The 4 remaining patients had assessment of BRAFV600E by IHC or PCR. Within the 22 patients, 29 instances of MEKi initiation were observed as 6 patients (27%) received 2 MEKi throughout follow up. MEKi used included: cobimetinib (n=22, 76%), trametinib (n=4, 14%), and binimetinib (n=3, 10%). Median time on a MEKi was 7.1 months (IQR 3 – 18.9 months) and it was used as 1st line therapy in 68.2% (n=15). Median EFS was 28 months (95%CI 16 – 39 months). Tumor genomic profile demonstrated non-BRAFV600E mutations in 16 patients (72.7%) and BRAFV600E was identified by IHC in 1 patient. All others had no mutation identified (n=2) or did not have successful NGS (n=3; Patients 3, 4, and 15). Among 19 with assessable mutation status, overall response rate (ORR) was 78.9% (n=15). A MAPK pathway mutation was present in 14 (73.7%), while the remaining 5 had either non-MAPK mutations (n=3, 15.8%) or no variants (n=2, 10.5%) identified. ORR was significantly improved amongst those with MAPK mutations as compared to those without (ORR 92.9% vs. 40%, p=0.013). Non-responders included all those with non-MAPK mutations in addition to a patient with a BRAFV471F variant. At last follow-up, all patients were alive and 10 (52.6%) remained on MEKi. Reasons for therapy discontinuation included intolerable side effects (n=2), drug holiday after response achievement (n=4), disease progression (n=2), and change to other kinase inhibitors (n=1).

Conclusions: MEK inhibitors are a highly efficacious treatment in patients with ECD. Main limitations of our study include its retrospective nature and sample size. Not all patients will respond to MEKi; however, our study suggests that identification of non-MAPK pathogenic variants may predict response to MEK inhibition. Further research to guide individualized therapies is needed.

Bio: Aldo A Acosta Medina is an international medical graduate from Mexico City, MX and current PGY-2 with the Internal Medicine program at Mayo Clinic Rochester. With intents of a future career in Hematology, his main research focus has included the study of histiocytic disorders, thrombotic microangiopathies, and clinical outcomes and survivorship in allogeneic stem cell transplantation.

CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES IN PATIENTS WITH HISTIOCYTIC NEOPLASMS HARBORING CLASS 3 MAP2K1 MUTATIONS, INCLUDING NOVEL TREATMENT WITH THE ERK INHIBITOR ULIXERTINIB

Eli Diamond diamone1@mskcc.org **Memorial Sloan Kettering Cancer Center, New York, NY**

Authors: Eli L. Diamond[1], Marc Rosenblum[1], Mariko Yabe[1], Kseniya-Petrova-Drus[1], Jasmine H. Francis[1], Raajit K. Rampal[1], Mario E. Lacouture[1], Veronica M. Rotemberg[1], Vaios Hatzoglou[1], Robert Young[1], Gary A. Ulaner[2,3], Ryan Reddy[1], Omar Abdel-Wahab[1], and Benjamin H. Durham[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY
[2]Hoag Family Cancer Institute, Newport Beach, CA
[3]University of Southern California, Los Angeles, CA

Purpose: The second most frequently mutated gene driving HN is *MAP2K1*, with broad responsiveness to MEK inhibition reported. The most common *MAP2K1* variant observed is the exon 3 p.E102_I103 in-frame deletion, among the Class 3 *MAP2K1* mutants predicted to be resistant to allosteric MEK inhibition. We present clinical and treatment characteristics of HN patients with Class 3 *MAP2K1* mutations.

Methods: Patients with HN and p.E102_I103del or similar mutations were included. Sites of disease were captured. First- and later-line treatments were categorized as observation, chemotherapy, immune modulation, MEK inhibition (MEKi; trametinib/cobimetinib/binimetinib), or ERK inhibition (ulixertinib). Clinical and radiologic responses were captured as partial response (PR), complete response (CR), stable disease (SD) or progressive disease (PD) by PET/CT.

Results: 16 patients were identified. 8 (50%) were female, and median age at histiocytosis diagnosis was 31 (range 22-58). 10 patients had Langerhans cell histiocytosis (LCH), 4 had Erdheim-Chester disease (ECD), 2 had mixed histiocytosis. Most frequent sites of HN were bone (16; 100%), lymph node (8; 50%), brain (8; 50%), and skin/subcutaneous (4; 25%). Mutations were MEK1 p.E102_103del (13; 81%), p.L101_103delinsF (1; 6%), p.P105_I107delinsL (1; 6%), and p.I103_A106del (1; 6%). Of 11 patients treated with chemotherapy or immune modulation, 9 had CR/PR, 1 SD, 1 PD. 7 of these 9 with CR/PR/SD had subsequent progression. Of 8 patients treated with MEKi, 8/8 (100%) had CR/PR, however 4 (50%) had subsequent progression. 3 of these, plus one treatment-naïve patient, were treated with an oral ERK1/2 inhibitor, ulixertinib, on prospective protocols. 3 of 4 had clinical or radiologic CR/PR.

Conclusions: HN with Class 3 MAP2K1 mutations represent a diverse spectrum of disease characterized by frequent bone, nodal and neurologic involvement, and poor responses to chemo/immunomodulatory therapy. This entity demonstrates resistance to MEKi in some patients, a phenomenon previously undocumented, and response to ERK inhibition.

Bio: Eli L. Diamond, MD is a neuro-oncologist who specializes in the care of patients with ECD and other histiocytosis, as well as brain tumors and neurologic complications of cancer. He did his neurology residency at the Massachusetts General Hospital and Brigham and Woman's Hospital and his neuro-oncology training at Memorial Sloan Kettering Cancer Center (MSK), where he is currently a staff neuro-oncologist. He conducts and has conducted several research studies for patients with ECD including the vemurafenib trial, the cobimetinib trial, a study looking for gene mutations in ECD tumors, a study to improve ECD biopsies, and a study about ECD and the brain. He is also the co-founder of the global ECD Patient Registry that has been supported by the ECD Global Alliance. At MSK, he works with a large team across many disciplines to offer the highest quality medical care and supportive care for patients with ECD, as well as to better our understanding and treatment of ECD with collaborative research.

EARLY CHANGES IN INTERMEDIATE MONOCYTE DISTRIBUTION CORRELATE WITH RELAPSE-FREE SURVIVAL DURING FOLLOW-UP IN ADULT HISTIOCYTOSES.

Jerome Razanamahery razanamahery.jerome@hotmail.fr **Institution: Dijon University Hospital**

Authors: Jerome Razanamahery, Maxime Samson, Julien Guy, Jessica Racine, Celine Row, Barbara Nicolas, Stephanie Francois, Jean-Francois Emile, Fleur Cohen-Aubart, Sylvain Audia Julien Haroche and Bernard Bonnotte

Background: Our data on the distribution of monocytes subsets in histiocytoses showed that a decrease in the intermediate fraction was associated with a metabolic response. However, no study has evaluated its significance for disease activity staging during follow-up.

Objective: To establish if blood circulating monocytes can predict disease activity during follow-up.

Methods: Peripheral blood cells were obtained from patients with histiocytoses during a follow-up period of one year (baseline, month 6, month 12). Blood samples included complete blood count with flow cytometry analysis, liver, kidney function tests, C-reactive protein, complete lipid test, and VEGF-A. For disease staging, patients were considered as "responder" when a complete or partial metabolic response was achieved on PET-CT, while "non-responders" had stable or progressive metabolic disease. Disease progression on PET-CT or worsening on skin assessment for isolated cutaneous histiocytoses defined a relapse.

Results: Nineteen patients were prospectively included. Eight patients had ECD (4 BRAFV600E), 6 LCH (2 BRAFV600E), one BRAF-mutated mixed "LCH/ECD" and 4 RDD (2 MAP2K1 mutation). At baseline, responder patients had a lower percentage of "intermediate" monocytes (3.5% [2.00-5.00] vs. 7.0% [4.00-13.00]; p= 0.04) and lower CRP levels (3.0 [1.1-8.75] vs. 33.65 [5.33-59.5] mg/L; p=0.04) Seven patients (4 LCH, 2 ECD, and one mixed "ECD/LCH") experienced a relapse during follow-up. The relapsers were treated more frequently with conventional therapy at baseline (36% vs 63%; p=0.05). At six months, relapsing patients had lower lymphocyte counts (g/L) (1.95[1.37-2.95] vs 1.18[0.34-1.67]; p=0.04), while all characteristics were similar at one-year. The only factor associated with relapse free-survival was the decrease in intermediate monocytes during the first six months (Mean Diff.-2.756.IC95%[-4,468 to -1,043]; p=0.004]), while no factor was associated with relapse. With the Pearson correlation model, relapse-free survival was only associated with LCH (-0.567. IC 95%[-0,81 to -0,15];p=0.011]). Our data showed that repeated flow cytometry analysis can be a valuable tool for predicting relapse-free survival in histiocytoses. These data need to be confirmed in a larger cohort to establish the significance of intermediate monocyte changes as an early marker of relapse-free survival.

Conclusion: The reduction of intermediate monocytes during histiocytoses is associated with relapse-free survival and may be an interesting marker to help managing patients.

Bio: I am a physician in the internal medicine department of Dijon University Hospital, particularly interested in immunology and oncology. During my residency, I have reached experience in histiocytic disorders with teaching from Pr Haroche in Pitié-Salpétrière hospital. I was lucky enough to lead an internal multicentric project with Eli Diamond, Gaurav Goyal, Jean-Francois Emile, and Julien Haroche, reporting the mixed 'ECD/RDD' forms in adult patients. My current researches focus on monocyte disturbance in histiocytic disorders and the significance of their modification during the disease's course.

GEOGRAPHIC CLUSTERING OF ERDHEIM-CHESTER DISEASE IN ITALY AND FRANCE

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Background: Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis in which somatic mutations involving MAPK and PI3K-AKT pathways play a crucial pathogenic role. The geoepidemiology of the disease is still unknown. Our study aimed at assessing the geographic origin of adult ECD patients in Italy and France.

Methods (Italian cohort): Data of 139 patients diagnosed from 1996 to 2022 were obtained from clinical charts of Italian ECD Referral Care Centres (i.e., IRCCS Meyer, Florence, and IRCCS San Raffaele, Milan) and of other Centres belonging to the Italian ECD Network (ItalECD). Patients with childhood-onset ECD (n=5), born in other countries (n=13), or lacking data (n=4) were excluded (N=117). Metrics regarding Italian Region demographics (i.e., resident

adult population) were obtained from public reports produced by the Italian national institute of statistics (ISTAT) and used to normalise the number of ECD diagnoses.

Methods (French cohort): Data of 354 patients diagnosed from 1982 to 2022 were obtained from clinical charts of the French ECD Referral Care Centre (i.e., Hôpital Universitaire Pitié Salpêtrière - Charles Foix, Paris). Patients with childhood-onset ECD (n=4), born in overseas French Regions (n=5), born in other countries (n=96), or lacking data (n=11) were excluded (N=238). Metrics regarding French Region demographics (i.e., resident adult population) were obtained from public reports produced by the French national institute of statistics (INSEE) and used to normalise the number of ECD diagnoses.

Methods (statistical analysis): The test described and validated by Ohno Y et al. to assess significance for geographic clusters of disease (Int J Epidemiol. 1979;8(3):273-80) was used to analyse observed clustering of ECD diagnoses in Italian and French Regions. The number of diagnoses per 1'000'000 adult residents for each Region was classified according to their ratio over national average, which was taken as 100: (1) above national average ratio (>120), (2) in line with national average ratio (80-119.9), (3) below national average ratio (<80).

Results: The Italian Regions showing a frequency of ECD diagnoses over national average (i.e., 2.35/1'000'000 adult residents) clustered in Southern Italy, whereas French Regions exhibiting a rate of diagnosis over national average (i.e., 4.68/1'000'000 adult residents) clustered in the central area of the country. Statistical analysis demonstrated that such geographic aggregations were statistically significant (P-value < 0.01 for Italy and < 0.05 for France).

Conclusion: The significant geographic clustering of ECD diagnoses, with higher incidences in Southern Italy and central Regions of France, suggests the potential role of genetics and/or environmental exposures in the development of the disease. Further epidemiological studies are required to highlight specific risk factors.

Bio: PhD Student at the Department of Experimental and Clinical Medicine of the University of Florence, Florence, Italy. Nephrologist at Meyer Children's Hospital, Florence, Italy. Have worked in the team of Prof. Augusto Vaglio for several years. Clinical research focused on rare diseases involving kidneys, particularly systemic lupus erythematosus, ANCA-associated vasculitides, retroperitoneal fibrosis and Erdheim Chester disease.

A MULTINATIONAL SERIES OF 26 PATIENTS WITH MIXED HISTIOCYTIC NEOPLASMS HIGHLIGHTING A DIVERSE MUTATIONAL LANDSCAPE AND SUPERIOR EFFICACY OF TARGETED THERAPIES

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Purpose: Patients with mixed histiocytosis comprise a small minority of patients with histiocytosis, and limited observations exist regarding the spectrum of this entity.

Methods: Retrospective series of patients with pathologically-confirmed mixed Erdheim-Chester disease (ECD)/Langerhans cell histiocytosis (LCH), ECD/Rosai-Dorfman-Destombes disease (RDD), RDD/LCH, and ECD/RDD/LCH. Clinical variables collected included demographics, sites of disease, and tumor sequencing. Treatments were dichotomized to conventional (corticosteroid/immunosuppressive/chemotherapeutic) versus targeted therapy (BRAF/MEK inhibitor) modalities. Modalities were compared with respect to (1) frequency of complete or partial

response (CR, PR) and stable disease (SD) by PET/CT or CT/MRI and (2) proportion of those with CR/PR/SD experiencing subsequent disease progression despite therapy, considering all instances of each modality.

Results: 26 patients were studied. 19 (73%) were male. The median age was 53.6 with a range of 18.0 to 74.1 years. Mixed subtypes were ECD/LCH in 19 (73%), ECD/RDD in 5 (19%), RDD/LCH in 1 (4%), and ECD/RDD/LCH in 1 (4%). 17 (65%) patients were diagnosed with histiocytosis subtypes asynchronously, 14 (82%) with LCH or RDD first. Somatic mutations were identified in 25/26 patients: BRAFV600E in 15 (58%), MAP2K1 in 4 (15%), and one each of MAP2K2, MAPK3, KRAS, non-V600 BRAF, RAF1, and BRAF fusion. 37 instances of conventional therapy led to CR in 5 (14%), PR in 8 (22%), SD in 6 (16%). However, 18 of these 19 (95%) had subsequent progression. 29 instances of targeted therapy led to CR in 10 (34%), PR in 15 (52%), SD in 2 (7%). 4 of these 27 (15%) had subsequent progression ($p<0.0001$ versus conventional therapy).

Conclusions: Mixed histiocytosis represents a diverse spectrum of mutational entities with nearly invariable progression following conventional therapies. Patients with histiocytic neoplasms should be evaluated with meticulous attention to the possibility of mixed disease to improve outcomes with early implementation of targeted therapies.

A PILOT STUDY OF PATIENT-REPORTED OUTCOME MEASURES AMONG INDIVIDUALS WITH HISTIOCYTIC NEOPLASMS

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Introduction: Histiocytic neoplasms are a rare group of hematopoietic malignancies, primarily including Erdheim-Chester disease (ECD), Langerhans cell histiocytosis (LCH), and Rosai-Dorfman disease (RDD). The discovery of targetable mutations in most of these cases has led to improved disease prognosis, resulting in a growing survivor population. There is a lack of studies examining physical, mental, and social domains of health in people living with histiocytic neoplasms. In this pilot study, we used PROMIS® (Patient-Reported Outcomes Measurement Information System) to assess functioning and well-being in a cohort of individuals with diverse histiocytic neoplasms.

Patients and Methods: This study enrolled patients diagnosed with histiocytic neoplasms from two referral centers (Mayo Clinic; Rochester, MN and University of Alabama at Birmingham; Birmingham, AL) from August 2022-December 2022. Study participants were administered the PROMIS-29+2 profile v2.1. This patient reported outcome (PRO) measure captures 8 domains (physical function, pain interference, fatigue, anxiety, depression, sleep disturbance, ability to participate in social roles and activities, and cognitive function) in addition to pain intensity (measured on a numeric rating item scale of 0-10). Internal consistency of the PROMIS subscales was evaluated using the Cronbach's coefficient α, with values >0.70 considered adequate. Each domain is scored as a T-score, which has been calibrated against the health of the general US population (mean, 50; standard deviation [SD], 10). A higher score indicates more of the domain being assessed. We also calculated summary scores for physical and mental health domains. A mean PROMIS T-score difference of 3 (SD 0.3) from the general US population mean of 50 was considered clinically meaningful. Descriptive statistics were calculated using JMP software, and T-score means were compared between subcohorts using bivariate analysis.

Results: The pilot cohort included 47 individual with histiocytic neoplasms with disease distribution as follows: ECD (n=13), LCH (n=18), RDD (n=15), and mixed ECD/LCH (n=1). Median age at diagnosis was 49y and median age at completing the instrument was 52y. Most cases were multisystem (n=30, 63.8%). Organs involved included bone (53.2%), kidney (27.7%), skin (30.0%), lymph nodes (19.1%), and CNS (17.0%). The subscales showed high internal

consistency (α >80%). Several mean PROMIS T-scores were worse in individuals with histiocytic neoplasms than general US population. Particularly affected domains included physical function in ECD (T-score 44.9, SD 0.51) and LCH (T-score 46.0, SD 0.40), cognitive function in ECD (46.9, SD 0.31), pain interference in ECD (54.5, SD 0.45) and LCH (56.0, SD 0.60), sleep disturbance in LCH (54.3, SD 0.43), fatigue in LCH (54.0, SD 0.40), and anxiety in LCH (56.9, SD 0.69) and RDD (53.3, SD 0.33). The T-scores for depression and ability to participate in social roles and activities were not significantly different than the general population, while those for sleep disturbance were better among ECD. For the one patient with mixed ECD/LCH, the T-score was worse in all domains. Composite physical function scores were lower than general population for ECD (45.3, SD 0.47) and LCH (45.7, SD 0.43), while mental health score was worse for LCH (45.6, SD 0.44). When evaluating by organ involvement, individuals with central nervous system (CNS) involvement had worse scores than reference population for physical function (42.3, SD 0.77), cognitive function (45.8, SD 0.42), depression (53.1, SD 0.31), and the ability to participate in social roles and activities (46.3, SD 0.37). The T-score for fatigue was especially high among those with pituitary involvement (55.0, SD 0.50).

Conclusions: In our pilot study evaluating PROs in people living with histiocytic neoplasms, we found impaired multi-domain functioning and well-being compared to the general U.S. population. Disease subtype and organ involvement appeared to be associated with specific PRO domains. Further enrollment of participants on the study is ongoing, and a larger cohort will allow for analysis of the effect of therapeutic and demographic factors.

Bio: Matt is a second year internal medicine resident at the University of Alabama at Birmingham. He intends to pursuing a career in hematology/oncology. His interests include healthcare outcomes research and medical education.

ABNORMALITIES OF PITUITARY IMAGING AND ASSOCIATED ENDOCRINE DISORDERS IN ERDHEIM-CHESTER DISEASE

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Introduction: Erdheim-Chester disease (ECD) is a rare histiocytic neoplasm that is commonly associated with hypothalamic-pituitary gland dysfunction leading to endocrine derangements. However, the exact nature and frequency of hypothalamic-pituitary remains poorly understood.

Methods: We conducted a cross-sectional descriptive analysis of a natural history cohort study diagnosed with ECD at a tertiary care academic research center. Baseline endocrine tests of anterior and posterior pituitary function and dedicated pituitary gland MRI scans were performed. Moreover, the frequency of various pituitary imaging abnormalities in ECD, and its relationships with age, sex, BMI, BRAF V600E status, high sensitivity CRP, ESR, pituitary hormone deficits and number, diabetes insipidus (DI), and panhypopituitarism was assessed in this cohort. We employed fisher's exact test or t-test/Wilcoxon tests to compare patients with and without abnormal pituitary imaging (API).

Results: We included a total of 61 subjects diagnosed with ECD [mean age (SD): 54.3 (10.9)yrs, 46 males/15 females] in this study. API was noted in 47.5% (29/61) of our ECD cohort. Furthermore, thickening of the pituitary stalk (24.6%), abnormal enhancement of the pituitary (18.0%) and pituitary atrophy (14.8%), were the most frequent abnormalities. Diabetes Insipidus and panhypopituitarism were present with a higher frequency in subjects with API. There were no differences in age, sex distribution, hsCRP, ESR, and BRAF V600E status in API compared to normal pituitary imaging.

Conclusion: A high burden of API and endocrinopathies was present in ECD. Specifically, API was highly associated with the presence of panhypopituitarism and DI. Thus, a comprehensive radiological and endocrine assessment of the hypothalamic-pituitary unit is warranted in subjects with ECD.

Bio: Skand Shekhar, M.D., D.A.B.I.M., is a clinician investigator in endocrinology and reproduction with a special interest in studying the relationship between metabolism and reproductive disorders. As the deputy leader of the Reproductive Physiology and Pathophysiology group at NIEHS, Dr Shekhar cares for patients with metabolic and genetic disorders of reproductive function, including idiopathic hypogonadotropic hypogonadism (IHH), Kallmann

syndrome, puberty disorders, menstrual disorders, and polycystic ovarian syndrome (PCOS). His research involves studying the interaction between lifestyle, sleep, diet, and the hypothalamic-pituitary gonadal axis in humans. With a keen interest in neuroendocrinology, he studies the interaction between stress (cortisol), thyroid, and reproductive axes. He is developing clinical trials to enhance our understanding of sleep, metabolism, and reproductive endocrinology interplays. Some of his published work in this field has studied rare neoplasms such as Cushing syndrome and Erdheim-Chester disease. In addition, he serves on several NIH intramural committees and is a core faculty member of NIH's Inter-institute Endocrinology Training Program and an attending physician on the endocrinology and diabetes consult service at NIH Clinical Center. Dr Shekhar completed his clinical and research training in adult endocrinology at NIH, focusing on reproductive endocrinology, under Hall's mentorship. Previously, Dr Shekhar attended medical school at the University of Delhi, India, followed by residency training in internal medicine and chief medical residency at Saint Peter's University Hospital/Rutgers Robert Wood Johnson Medical School in New Jersey. He is board-certified in internal medicine and endocrinology, diabetes, and metabolism by the American Board of Internal Medicine. Additionally, he serves as a peer-reviewer for several scientific journals and holds active memberships in the Endocrine Society, the American Association of Clinical Endocrinologists, and the American College of Physicians.

LONGITUDINAL ASSESSMENT OF CARDIAC INVOLVEMENT IN ERDHEIM-CHESTER DISEASE USING CARDIAC MAGNETIC RESONANCE IMAGING.

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Background: Erdheim-Chester disease (ECD) is a rare multi-systemic non-Langerhans cell histiocytosis that affects the heart in nearly half of patients1. Atrial infiltration and pericardial effusion are the hallmarks of cardiac involvement and can lead to clinical complications (conduction disorders, coronary artery stenosis, tamponade, constrictive pericarditis)2,3,4,5. Evolution under treatment is poorly studied.

Purpose: To investigate the evolution of cardiac involvement in ECD using cardiac magnetic resonance (CMR) imaging.

Methods: All ECD patients with a CMR imaging disclosing a cardiac involvement and who underwent at least one follow-up CMR imaging between 2005 and 2020 at a French tertiary center were retrospectively included. First and last CMR imaging were compared. Multivariable analysis was performed to search for independent predictors of cardiac involvement resolution. Variables were included in the model if their P-value was < 0.1 on univariable analysis.

Results: Overall, 46 patients were included. Median age at first imaging was 63 years [53-69]. Median delay between the first and the last imaging was 4 years [2-7]. BRAFV600E mutation was present in 43 patients (94%). Patients received a median of 2 [1-3] treatments. All patients (100%) had cardiac involvement at baseline. Right atrio-ventricular sulcus (RAVS) was infiltrated in 38 patients (83%) and was the main cardiac feature. Overall, complete regression was observed in 6 patients (13%), partial regression in 26 patients (56%), stable imaging in 12 patients (26%), and worsening in 2 patients (5%). In patients with RAVS infiltration, complete regression was observed in 5 patients (16%) and partial regression was seen 22 patients (58%) regression. Proportion of regression, stability and worsening according to the type of cardiac involvement lesion are reported in Figure 1. Serial CMR images of a patient with complete regression of RAVS infiltration under vemurafenib is shown in Figure 2. On univariable analysis, patients with regression of their infiltration had a lower rate of death (16% versus 64%, P=0.002), a higher rate of atrial infiltration late gadolinium enhancement (LGE) (97% versus 71%, P=0.01), a higher rate of hydronephrosis (50% versus 14%, P=0.03) and a lower rate of interferon prescription (69% versus 100%, P=0.02). A similar rate of vemurafenib use was observed in both groups (69% versus 54%, P=0.3). On multivariable analysis, death remained significantly associated with follow-up imaging status (ß=-2.3 P=0.01), while atrial infiltration LGE (ß=2.7, P=0.06), hydronephrosis (ß=1.6, P=0.1) and treatment with interferon (ß=-16, P=1) were no longer significantly associated with imaging status.

Conclusion: Partial or complete resolution of cardiac involvement was observed in 69% of patients with ECD and was significantly associated with a lower rate of death on multivariable analysis.

Bio: Lévi-dan Azoulay, MD, MSc is a resident doctor working at La Pitié-Salpêtrière Hospital in Prof. Zahir Amoura, Fleur Cohen-Aubart and Julien Haroche's team within the French Referral Center for Histiocytosis. He is an internal medicine and clinical immunology trainee, with a focus on histiocytosis, sarcoidosis and cardio-vascular involvement of systemic and autoimmune diseases.

THE PHENOTYPIC SPECTRUM OF MALIGNANT HISTIOCYTOSIS PARALLELS THE LINEAGE SUBSETS OF MONOCYTES, MACROPHAGES, AND DENDRITIC CELLS

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Malignant histiocytosis (MH), as defined by the Histiocyte Society, encompasses the diagnoses of histiocytic sarcoma, interdigitating dendritic cell sarcoma and Langerhans cell sarcoma. We analyzed the phenotypic spectrum of 22 MH cases seen at Mayo Clinic over a 13-year period, with genetic studies performed in 18 cases. Based on the phenotype by immunohistochemistry (IHC), we arranged the cases into 4 groups based on their lines of differentiation: i) Macrophage (n=5): CD68+, CD163+, CD14+, Factor XIIIa+; ii) Monocyte-Macrophage (n=5): CD68+, CD163+, CD14+, S100+, OCT2+; iii) Dendritic cell (n=6): CD68+, CD11c+, S100+, lysozyme+, ZBTB46+, CD1a/langerin <5%; and iv) Langerhans cell (n=6): CD68+, CD11c+, S100+, ZBTB46+, CD1a+, and langerin+. These phenotypic groups correspond to those seen in histologically low-grade histiocytic neoplasms (HNs): MH-macrophage type correlates with Erdheim-Chester disease phenotype; MH-monocyte-macrophage type with Rosai-Dorfman disease phenotype and MH-Langerhans cell type with Langerhans cell histiocytosis. MAPK pathway mutations were identified in 80% of MH cases; 29% had concurrent mutations in the PI3k-AKT-mTOR pathway. Activation of the MAPK pathway leads to phosphorylation of downstream targets (ERK and AKT) and upregulation of cyclin D1 expression. Strong cyclinD1 expression was present across all MH phenotypic subtypes, with variable p-ERK and p-AKT expression suggesting other mechanisms of cyclin D1 upregulation. Eight of 22 (36%) MH cases were proven to be clonally related to a prior B-cell lymphoma. In summary, the criteria for MH diagnosis include i) demonstration of high-grade cytologic features with marked nuclear pleomorphism and ii) expression of at least 2 macrophage or dendritic cell markers (CD11c, CD14, CD68, CD163, lysozyme, S100, CD1a, langerin), and strong and diffuse expression of cyclin D1. The more specific assignments of monocyte, macrophage, and dendritic cell lineage can be determined with IHC for OCT2, Factor XIIIa, and ZBTB46. Further study of the biological differences between these lineage subtypes is needed to develop therapies tailored to the phenotype and genotype of each patient's disease.

Bio: I (Aishwarya Ravindran) am an Assistant Professor of Pathology with a primary focus on Hematopathology at the University of Alabama at Birmingham (UAB) since July 2022. I completed my Anatomic/Clinical Pathology residency and Hematopathology fellowship at Mayo Clinic, Rochester, MN from 2017-2022. Prior to residency, I also pursued a two-year research fellowship at Mayo Clinic under the mentorship of Dr. Ronald S. Go (Hematology, Mayo Clinic), during which time I developed a special interest in studying histiocytic neoplasms, and subsequently also became a member of the Mayo Clinic-UAB Histiocytosis Working Group.

CLINICAL FEATURES, MOLECULAR ABERRATIONS, TREATMENTS, AND OUTCOMES OF MALIGNANT HISTIOCYTOSES

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Background: Malignant histiocytoses (MH) are extremely rare neoplasms of the macrophage-dendritic cell lineage. There is a paucity of data on treatments and outcomes in MH.

Methods: This is a retrospective study of patients with histologically confirmed diagnosis of MH of histiocytic sarcoma subtype (MH-H) and MH of Langerhans cell sarcoma subtype (MH-LC) from January 2000 to February 2022. The histopathologic findings of all cases were independently reviewed by three expert hematopathologists at both sites (K.L.R., D.M., and A.R.). Patients had unifocal disease if they had only one tumor at one site that was biopsy proven, while patients were categorized as having multifocal disease if they had more than 1 site of disease or had > 1 tumors in one site with at least one of the sites being biopsy proven and the remaining sites to be suspicious on radiographic studies. Kaplan-Meier and log-rank tests were used to perform overall survival (OS) analyses.

Results: We identified 35 patients with MH, of which 28 were MH-H and 7 were MH-LC. The median age at diagnosis was 62 years (range 3-83) and the most common sites of involvement were the lymph nodes (49%), lungs (29%), and bones (29%). 28 patients (80%) had multifocal disease while 7 had unifocal involvement. The tumor specimens from 17 patients (49%) underwent targeted next generation sequencing, and 16 out of 17 had at least 1 pathogenic mutation. Mutations involving genes of the RAS/MAPK pathway were identified in 14 out of the 17 sequenced cases (82%). The most common first-line treatment was chemotherapy and the median progression-free survival for frontline therapy for multifocal disease was 5 months (95% CI 1.7 – 10). The median overall survival (OS) among the entire cohort was 16 months (95% CI: 8 months – 51); the median OS for the multifocal cohort was 10 months (95% CI 7 months – 43 months) vs. not reached (95% CI: 11.7 months-not reached) for the unifocal cohort [p=0.16]. 3 patients were treated with MEK inhibitors; all had progressive disease within 3 months. 4 patients were treated with PD-1 inhibition. PD-1 inhibition as monotherapy was ineffective in all patients. However, in one patient, the addition of radiation therapy with continued PD-1 inhibition led to a near complete response that has been durable for more than 2 years

Conclusion: Our study shows that MH represents an aggressive neoplasm in which multifocal disease shows a trend towards worse outcomes compared with unifocal disease. Most patients had somatic oncogenic alterations involving the genes of the MAPK/ERK pathway. Chemotherapeutic regimens had variable response rates that were not durable. Targeted MEK-inhibitor therapies were associated with limited efficacy, suggesting a need to examine other treatment modalities. The role of PD-1 inhibitors in MH should be further studied as one of our patients had a sustained and durable response to pembrolizumab in combination with radiation therapy.

Bio: I am a hematology/oncology fellow and clinician investigator at the Mayo Clinic in Rochester, Minnesota. I am pursuing a career as an academic hematologist/oncologist. My current research interests include translational science and outcomes research in lymphoma and histiocytic neoplasms.

Poster Session

CNS-RESTRICTED, BRAF-POSITIVE, HISTIOCYTIC INFLAMMATION THAT RESPONDS TO MAP KINASE INHIBITION

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Authors: Adam Cohen, Kevin O'Brien, Mateo Ziu, Cheryl Robson, Juvianee I Estrada Veras, Rahul H Dave

Introduction: Erdheim Chester Disease is a multi-systemic disorder characterized by neoplastic histiocytes bearing activation mutations in the MAP kinase pathway, including BRAFV600E and others. Such mutations are hypothesized to drive the disease, and MAP Kinase inhibitors such as Vemurafenib and Cobimetenib have been FDA approved for the treatment of ECD and other malignancies bearing the BRAF muttations. and can result in reduction in tumor burden. Case reports have shown promise in reducing CNS tumor burden as well. Here, we describe a case of CNS histiocytic inflammation bearing BRAFV600E mutation that responded to Vemurafenib and Cobimetenib.

Case: The patient is a 46y/o healthy man with history of recurrent mild COVID infections who presented to the hospital with 4 months of dysarthria, ataxia and diplopia. Initial MRI revealed an enhancing tumefactive brainstem lesion compressing the 4th ventricle, along with other cerebral and short spinal cord lesions. He did not exhibit clinical signs of increased ICP. He did not respond to treatment with either IV methylprednisolone or IVIG. Immune serologies for rheumatologic disorders, CNS inflammatory disorders (NMO, MOG, autoimmune encephalitis) and infections were negative. CT chest, abdomen, pelvis was normal. CSF was initially deferred due to 4th ventricle compression, but was obtained via EVD and was essentially normal. Scant fungal elements without a clear infectious response was seen, and patient was given empiric antifungal without response, and the patient continued to decline clinically. Brain pathology revealed lymphocytes, vacuolated ('foamy') histiocytes, gliosis, demyelination and axonal loss. The histiocytes were positive on BRAFV600E staining and mutations were confirmed via Next-Gen RNA sequencing (NIH). He was evaluated for ECD. PET/CT scan revealed CNS uptake and a small intramuscular (paraspinal) focus, but no osteosclerosis, cardiac, perinephric involvement. Echocardiogram was unremarkable. The patient was started on vemurafenib 960mg bid and cobimetinb 40mg, resulting in improved clinical functioning and decreased size of brain lesions.

Diagnosis: 46y/o man with a novel tumefactive CNS inflammatory disorder bearing BRAFV600E mutation. He was assigned a forme fruste ECD diagnosis code, facilitating insurance approval of therapy.

Conclusions: (1) CNS inflammatory disorders can mimic ECD and histiocytic disease, not just clinically, but also radiologically and pathologically. We suggest that intractable CNS inflammatory disorders be evaluated for the presence of BRAFV600E and other targetable mutations. Such sequencing is now commercially available and is increasingly used at our institution (2) This case highlights the importance of considering ECD mimics or forme-fruste variants, particularly in patients who are experiencing intractable clinical courses (3) We will also highlight the real-world process of obtaining medication for ECD patients in the USA.

Bio: Rahul Dave is the medical director of the INOVA Multiple Sclerosis and Neuroimmunology Center. He is also a special volunteer at NIH, where he serves as Associate Investigator on studies related to ECD.

ERDHEIM-CHESTER DISEASE WITH RARE PRESENTATIONS OF TENDON AND MUSCLE INVOLVEMENT

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Background: Erdheim-Chester Disease (ECD) is a rare histiocytic multisystem disease, affecting bones, heart, aorta, lungs, skin, retroperitoneum and central nervous system. Only one case report of tendon involvement in patients with ECD was found in the databases, and there were only a few studies available for skeletal muscle involvement. Here,

we show a case of a patient with ECD who had involvement of the left Achilles tendon as well as a patient illustrating the multi-organ symptoms of ECD who had an unusual manifestation of involvement of the thigh musculature.

Cases presentation: First case was a 39-year-old man who initially presented with bone and pituitary involvement having positive CD 68 and negative S-100 protein, and CD 34. [18F] FDG PET imaging revealed a concentrated soft tissue mass that surrounds the left calcaneus and continues up the posterior ankle along the Achilles tendon. The second case was a 41-year-old man initially presenting with involvement of the cardiovascular system and retroperitoneum, having positive CD68, CD4, lysosome, and CD163, and negative CD1A and S100. An [18F] FDG PET scan showed a hypermetabolic destructive lesion in the left anterior acetabulum that spread to the musculature of the left anterior thigh. In the medial muscles of the thigh, a large multifocal hypermetabolic area of uptake was evident in the posterior side of the right proximal femur and extends into the muscle of the right posterior medial thigh.

Conclusion: Erdheim-Chester disease can present with rare manifestations including Achilles tendon and thigh muscles involvement. Due to its rarity and non-specific multi-systemic manifestations, there is often a diagnostic delay. It should be considered in patients presenting with tendinopathy and myositis alongside bony pain or other unexplained multi-systemic complaints.

Bio: I am a medical doctor graduated from Iran. I am interested in Radiology and imaging of rare diseases, and I am working in Radiology department at clinical center in NIH.

INTRODUCTION OF A SMALL MOLECULE CSF1R AND TAM TYROSINE KINASE INHIBITOR Q702 IN HEMATOLOGIC MALIGNANCIES

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Abstract Summary: Malignancies which stem from lymphoid and myeloid precursor cells are highly dependent on tumor associated macrophages (TAM) receptors. Stimulation of AXL receptors inhibit apoptosis in human dendritic cells and in Acute Myeloid Leukemia (AML). AXL overexpression conferred resistance to chemotherapy and AXL-mediated signaling induced activation of the AKT and ERK1/2 survival pathways, thus enabling tumor propagation. Overexpression of the AXL receptors and its stimulation by Gas-6 ligand could also enhance tumor survival through activating MAPK, PI3-AKT, and NF-KB pro-oncogenic pathways. In Non-Hodgkin's Lymphoma (NHL), including mantle cell l and T-cell lymphomas, AXL signaling is associated with the activation of MAPK and NF-KB pathways leading to tumor progression and resistance to SoC treatments. Another important receptor in TAM family is the MER receptor. In Mantle Cell Lymphoma (MCL), MER receptors are highly expressed in 50% of tumors. The MER receptor has an important role in modulating macrophage-mediated inflammation, immune response and a strong link exists between MER receptors and macrophage polarization of pro-tumor M2 subtype. Once macrophage MER and AXL receptors bind to phosphatidylserine on the apoptotic cells in the tumor microenvironment using Gas-6 ligand, polarization to the pro-tumor M2 subtype occurs, thus hindering its ability to clear tumor and apoptotic cells. Colony Stimulating Factor Receptor 1 (CSF1R) is another key molecule involved in tumor progression and pro-inflammatory cytokine production in hematologic malignancies. CSF1R is critical in pathobiology of Langerhans cell histiocytosis, as it is required for differentiation and migration of Langerhans cells. In NHL, CSF1R has been demonstrated to promote tumor survival through AKT and mTOR signaling. Recent studies have revealed that CSF1R expression in leukemic stem cells modulate the tumor microenvironment to facilitate the progression of leukemia. Due to the involvement of CSF1R in pathogenesis and tumor progression of acute leukemias, CSF1R has been proposed to be a therapeutic target in AML patients. In MCL, targeting CSF1R through a small molecular inhibitor induces significant antitumor effects both in vitro and in vivo. Q702 is a potent, orally available, selective small molecule inhibitor that targets AXL, MER, and CSF1R kinases. Nonclinical in vitro and in vivo pharmacology studies have demonstrated potent inhibition of AXL, MER together with CSF1R in biochemical assays, cell-based assays and in vivo xenograft tumor models with Q702. A phase 1, dose-escalation study (NCT04648254) of Q702 is currently ongoing to evaluate the safety, tolerability, pharmacokinetics (parent and active metabolites), and pharmacodynamics of orally administered Q702 in patients with advanced solid tumors. The proof-of-mechanism has been assessed using PD biomarkers. Increased expression of PD biomarkers in the 60 mg cohort showed a full target engagement of AXL and CSF1R. An increase in

IFN-g production mainly led by CD8 T cells has been observed. From the ongoing Q702 phase 1 study, the recommended phase 2 dose (RP2D) is estimated to be between 120 and 240 mg dose range. Given the pathobiology and the important role of TAM receptors and CSF1R in hematologic malignancies, Q702 would be an ideal candidate to be studied in patients with histiocytic malignancies, NHL, certain leukemias and dysproteinemias.

Bio: Dr. June Kim is an experienced project manager with over 10 years of experience in drug development from discovery clinical stage. He received his B.Sc. in pharmacy from Sungkyunkwan university. He completed a Ph.D. in pharmacokinetics. He started his career in LG Life Sciences from 2007 participating in number of new drug research and development programs. Starting from 2010 he joined Qurient participating as a clinical development team leader for inflammation, infectious, and oncology projects.

URONEPHROPATHY INVOLVEMENT IN ERDHEIM-CHESTER DISEASE: IMAGING FINDINGS AND THEIR ASSOCIATION WITH THE BRAF MUTATION

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Purpose: Erdheim-Chester Disease (ECD) is a rare histiocytic neoplasm. Perinephric histiocytic infiltration commonly occurs, creating a risk for obstructive uropathy and renal dysfunction. This descriptive study highlights the radiological manifestations of urologic involvement and looks for associations between imaging and urologic findings and the BRAFV600E mutation in ECD patients.

Methods: This prospective study included 62 ECD patients (47 men; mean age, 52) who gave informed consent for an approved protocol at the National Institutes of Health (NIH). Abdominopelvic images (45 MRI, 17 CT) were reviewed independently by two expert radiologists for signs of pre-, intra-, and post-renal ECD involvement. The Fisher's exact test and odds ratios (OR) with 95% confidence intervals (CI) were used to compare percentage differences in abdominal involvement between subjects with and without BRAFV600E mutation.

Results: Fourteen of 62 patients (23%) had no abnormal urologic imaging findings. Forty-one (66%) cases had some degree of perinephric histiocytic infiltration, also known as "hairy kidney". Twenty-three (37%) had hydronephrosis (17 bilateral), 13 showed hydroureter, and 4 had cystomegaly. Thirty (48%) had renal artery involvement, 10 with renal artery stenosis (3 bilateral, 7 unilateral), with 3 requiring renal artery stents. In patients with any of 5 urologic involvements, the mean estimated glomerular filtration rate was 89.5 mL/min, and the mean creatinine was 1.09 mg/dl. The BRAFV600E mutation was positive in 52% (32/59) of samples. Perinephric infiltration ($p= 0.003$, OR=7.27, 95%CI [1.99, 26.49]), renal artery stenosis ($p< 0.001$, OR=10.1, 95%CI [2.99, 33.83]), and hydronephrosis ($p< 0.001$, OR=8.71, 95%CI [2.40, 31.55]) showed significant association with the BRAFV600E mutation. However, hydroureter ($p= 0.35$, OR=1.87, 95%CI [0.44, 8.66]) and cystomegaly ($p= 0.617$, OR=0.38, 9 5%CI [0.001, 5.04]) were not associated with BRAFV600E mutation status. Two patients developed end-stage renal disease (ESRD) from urologic involvement and one of them underwent renal transplantation. Also, patients with positive BRAF mutation status had, on average, a lower eGFR compared to those without BRAF mutation ($p=0.03$).

Conclusion: ECD commonly manifests with urologic disease, which may manifest at different times in the course of the illness, and which may lead to renal dysfunction. Therefore, patients should be screened regularly for urological complications by medical history, exam findings, and laboratory and imaging studies. Despite adequate therapy, some patients require stenting to maintain renal function. BRAFV600E status used in conjunction with other molecular and clinical measures, could potentially help stratify patients, by detecting higher-risk sub-groups, for personalized screening/surveillance measures.

Bio: I am a Radiology resident in University of Alabama at Birmingham. I am interested in the role of imaging in rare diseases, and I am working with radiology department in NIH.

IDENTIFYING AND RESPONDING TO TREATMENT FAILURES IN ERDHEIM CHESTER DISEASE: A CASE STUDY AND DISCUSSION ON HISTIOCYTIC MOLECULAR HETEROGENEITY

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Summary: Introduction Erdheim Chester Disease (ECD) is a non-Langerhans cell histiocytic disorder characterized by xanthogranulomatous infiltration into various tissues, where foamy histiocytes are surrounded by an inflammatory background of fibrous stroma. Clinic manifestations vary but scattered sclerotic foci affecting the dia-metaphyseal portions of appendicular long bones are common. On a molecular level, histiocytes are most commonly CD68+ and CD1a-, 80% of which harbor mutations within the mitogen-activation protein (MAP) Kinase signaling pathway. In patients with such mutations, targeted molecular therapy is now a standard of care, although treatment is challenging due to systemic effects of these novel agents.

Case Presentation: A 58 year-old male presented with new-onset headache, fever and visual impairment; MRI Brain that followed identified bilateral orbital masses and distant visceral involvement was absent by computed tomography of the chest and abdominopelvic regions. Plain radiography of the right leg, however, revealed a mixed lytic/sclerotic expansile osseous process involving the distal femoral metadiaphysis; nuclear bone scintigraphy confirmed bilateral symmetric lower extremity uptake. Tissue biopsies obtained from the orbital masses and right femur confirmed a diagnosis of Erdheim Chester histiocytosis, weakly positive for BRAF by immunohistochemistry. The patient was initiated on interferon (IFN) at a local center. He was switched to cobimetinib 3 months later but therapy was discontinued due to urticaria after less than two months; IFN was then reinitiated but permanently discontinued due to soft tissue edema and headache. A re-staging PET-CT now 10 months following treatment initiation exhibited new disease in the mediastinum with right atrial encasement. Sequential MEK 1/2 and BRAF kinase-inhibitor inhibitor therapy in trametinib and vemurafenib (respectively) were then instituted but were poorly tolerated, even with dose attenuation, ultimately leading to discontinuation and transition to orbital radiation therapy. One year later, he was treated with 2 cycles of cladribine for progressive osseous disease and today remains in a stable partial remission.

Discussion and Future Directions: Erdheim Chester Disease has a predilection for MAP Kinase mutations. Next generation sequencing is essential even in only localized disease so that physicians can predict treatment responses and plan for targeted molecular therapies as indicated. The true challenge is identifying the precise mechanisms of progression through such therapies, and one of the key theories here is in molecular heterogeneity, whereby ECD histiocytes harbor sub-clonal mutations outside of MAP Kinase pathway genes. When histiocytes are exposed to therapies such as MEK and BRAF inhibitors, the dominant clone is suppressed while subclones become increasingly more prevalent and later fulminant to drive progressive disease. A similar process known as clonal evolution occurs in acute myeloid leukemia and is felt to be a key driver of induction therapy failure and late disease relapse. Presently-developing analyses at our own institution will utilize transcriptomics via an RNA sequencing platform to better elucidate the complex mutational landscape underlying this rare disease state. It is through this understanding that we hope to identify new targets in ECD and, accordingly, begin developing novel therapies for the betterment of precision-based care.

Bio: Samuel Reynolds is a current second-year fellow in Hematology and Medical Oncology at The University of Michigan, where his primary clinical interests are in hematologic and myeloid neoplasms. He is also passionate about the clinical applications of MAP Kinase signaling in these disease states, specifically in histiocytic diseases such as Erdheim Chester and Rosai Dorfman Disease. His long-term goals in Hematology are in translational research and precision medicine.

DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN MULTI-ORGAN ERDHEIM-CHESTER DISEASE

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Abstract Summary: A 14-year-old female presented with progressive pain in her face and mandible, unresponsive to conservative pain management. Biopsy of the zygoma revealed foamy macrophage with fibroblasts and scattered lymphocytes that demonstrated features of both polyostotic fibrous dysplasia (PFD) and Erdheim Chester Disease (ECD). After two years of progressive proptosis and bilateral sensorineural hearing loss, imaging demonstrated sclerotic lesions in the pelvis, proximal femur, and thoracic vertebra with stable disease in facial bones and infiltrative ophthalmopathy. She then started pamidronate for PFD and continued it for 10 years. At age 31, she developed left upper quadrant abdominal and pleuritic chest pain. Labs showed a Hgb 9.3mg/dL (previously normal), ferritin 212mg/L, CRP 12.2mg/dL, and alkaline phosphatase of 491. CT and MRI identified extensive paraspinal, mediastinal, pericardial, pleural and mesenteric soft tissue prominences, as well as diffuse osseous lesions. A paravertebral lymph node biopsy and perinephric biopsy revealed CD163+, BRAF V600E, IgG4 and ALK rearrangement-negative foamy histiocytes with fibrosis, consistent with ECD. Next generation sequencing of the tissue characterized a t(1;7) RNF11-BRAF fusion, somatic diploid GNAS amplification, WT1 and WNT2 positivity. Whole exome sequencing reported a pathogenic variant of GJB2 gene, which is associated with non-syndromic sensorineural hearing loss. Absence of the GNAS mutation made McCune Albright Syndrome unlikely. Two months later, she started cobimetinib 40 mg daily, which was discontinued after one month due to diarrhea and an acneiform rash. PET CT after two months revealed a collective partial response. An MRI brain revealed cervical spinal meningeal disease involvement. It is unclear whether these findings were new, given the lack of baseline MRI brain imaging. She was then transitioned to bimetinib 15 mg twice daily; imaging that followed 3 months later revealed partial CNS and systemic response. Due to development of gastrointestinal side effects, therapy would be dose-attenuated and then ultimately discontinued. After 12 months off management while stable radiographic disease, peginterferon 90 mg was introduced due to ongoing bone pain, initially well-tolerated and then discontinued due to suicidal ideation. The patient was then monitored off therapy. After one year, imaging revealed mild progression of disease, prompting trametinib initiation. While NGS was not available to confirm ECD in our patient at the time of diagnosis, advancements in genomic studies have now led to the early utilization of targeted molecular therapies in MAP Kinase pathway. In this case, the identification of BRAF fusion suggests responsiveness to MEK inhibition but not to BRAF V600E inhibition. Molecular sequencing is crucial in identifying actionable mutations. Larger studies are essential to characterize the relationship between molecular heterogeneity and treatment response in ECD.

Bio: Sabrina Wilcox is a current internal-medicine and pediatrics second year resident at the University of Michigan. She plans to pursue a career in Adult Hematology and Oncology with a focus on adolescents/young adults and transitional medicine. Research conducted in residency thus far, has primarily been related to Erdheim Chester Disease and Rosai Dorfman Disease. Specifically, molecular heterogeneity within these rare diseases and exploring how this may correspond with treatment outcomes.

CHARACTERISTICS AND OUTCOMES ASSOCIATED WITH CARDIAC INVOLVEMENT IN ERDHEIM-CHESTER DISEASE

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Introduction: Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis. Cardiovascular involvement (CI) is present in about 40% of cases [2]. Given the limited literature on outcomes of ECD CI, we aimed to expand upon the current knowledge by characterizing ECD-related cardiovascular lesions and associated outcomes in one of the largest cohorts of patients (pts) with ECD and known CI published to date.

Methods: Records of pts diagnosed with ECD from Jan. 1990 to Dec. 2022, seen at Mayo Clinic were reviewed. The BRAF mutation status, CI and site involved, arrhythmias, cardiac comorbidities, as well as 1st line therapy received were captured, if available. All time-to-event analyses were performed from the 1st therapy initiation, using the Kaplan-Meier method.

Results: Among a total of 106 pts with ECD, 38% (n=40) of pts had CI. The mean age at diagnosis was 57 (range: 49-67); 61% were males. The median follow-up was 3.7 (95% CI: 3.1-5) years. 65% of pts with CI (n=26) had BRAF mutations compared to 39% of pts without CI (n=26), p=0.072. Of those with CI, cardiac imaging localized the compartment affected (pericardial n=17 (43%), myocardial n=29 (70%), coronary arteries (CA) n=21 (53%)). Myocardial localization was more frequent in the right atrium (right atrium n=29 (73%), left atrium n= 3 (8%), right ventricle n=2 (5%), left ventricle n=1 (3%)). Infiltration around the CA was greatest around the right CA (53%) (right n=21, left n=6). In addition, 17 of the 40 pts with CI had arrhythmias; of those pts, 11 had myocardial CI. Of those 11 pts, 10 had right atrial involvement, and one pt had biatrial CI. 6 of those 17 pts had pericardial CI. 8 pts with CI died; only 1 died from sudden cardiac death. Hypertension was present in 68% of pts (n=27) with CI compared to 36% in those without (n=32), p=0.056. Current or prior smoking was present in 43% of pts (n=18) with CI compared to 24% in those without (n=16), p=0.05. The estimated 5-year overall survival (OS) rate, approx. 80%, was not significantly different in those with CI compared to those without (p=0.68) (Figure 1). The time from diagnosis to treatment initiation was 0.2 years in those with CI compared to 0.15 years in those without (p=0.89). The time to next treatment from 1st line to 2nd line was 0.7 years in those without CI and 1.2 years in those with CI, p=0.76. Additional survival analysis including the progression-free survival (PFS) will be included in the final presentation.

Conclusion: We presented one of the largest cohorts of pts with CI published to date. Our data showed that the myocardium is the most commonly affected tissue layer in ECD CI and the RA is the mostly affected anatomic compartment. Smoking, hypertension, and BRAFV600E mutation were seen more commonly in patients with cardiac-involved ECD than in patients without. The OS in those with CI was not different compared to those without.

Bio: Reema Tawfiq is originally from Florida State and received her Medical Degree at Florida State University. She is completing her Internal Medicine residency at Mayo Clinic in Rochester, MN. Next year she will start her fellowship in Hematology-Oncology at Mayo Clinic in Jacksonville, FL.

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