10th International Erdheim-Chester Disease Medical Symposium

27 May 2025 | Barcelona, Spain

Program Guide

ERDHEIM-CHESTER DISEASE GLOBAL ALLIANCE

Bellvitge Hospital Universitari

Agenda

Welcome to Barcelona!

Dear Colleagues, Friends, and Members of the ECD Community,

It is my honor and great pleasure to welcome you to the 2025 Erdheim-Chester Disease Global Alliance Medical Symposium here in the vibrant city of Barcelona, hosted at the highly-regarded Bellvitge University Hospital.

Barcelona is a city unlike any other—where centuries of history blend with innovation and forward-thinking science. It's a city with culture, collaboration, and creativity—an ideal setting for bringing together global minds dedicated to understanding and treating Erdheim-Chester Disease. Within Barcelona, the Bellvitge University Hospital stands as a pillar of excellence in clinical care and research—a place where breakthroughs are made and lives are changed.

When I was first approached about hosting this symposium, I did not hesitate. The opportunity to welcome our global ECD family to my home institution felt deeply personal. I believe that hosting this conference here not only elevates awareness of ECD across Europe but also creates space for new research partnerships and perspectives to flourish. For me, this symposium is more than a meeting of minds—it is a gathering of hearts united by a common purpose.

This event is vital to the global ECD community. It provides a rare and powerful chance for clinicians, researchers, and advocates to come together in one room—to learn from one another, to challenge each other, and to strengthen the network of expertise that patients so deeply rely on. Together, we move closer to clarity, to compassion, and to a cure.

Personally, this conference is also a reminder of why we do what we do. Each session, each case study, each conversation reaffirms my commitment to not only advancing the science of ECD, but to supporting the human beings behind the diagnosis—the patients, families, and caregivers who inspire our every step.

I hope you leave this symposium enriched with knowledge, empowered with new ideas, and most importantly, reminded that we are together in this journey. Together, we are building something lasting—something meaningful—for those living with Erdheim-Chester Disease today, and for those yet to be diagnosed.

With deep appreciation,

Xavier Solanich, MD, PhD
Bellvitge University Hospital
xsolanich@bellvitgehospital.cat

Welcome: 10th Annual ECD Medical Symposium

Dear ECDGA Medical Community,

On behalf of the Board of Directors of the Erdheim-Chester Disease Global Alliance (ECDGA), we are honored to welcome you to the 10th Annual ECD Medical Symposium.

This meeting represents a cornerstone of our organization's mission. The ECDGA is deeply committed to fostering collaboration across disciplines, institutions, and continents. By convening this annual symposium, we aim to advance understanding, accelerate research, and support the medical professionals working to improve outcomes for individuals affected by Erdheim-Chester Disease and related histiocytic disorders.

We believe that progress in rare disease research happens when diverse perspectives unite. Since our founding in 2009, the ECDGA has remained devoted to building an inclusive community—bringing together clinicians, scientists, and allied professionals alongside patients and families. Through this collaboration, we have witnessed the powerful breakthroughs that occur when rigorous science and lived experience converge for the benefit of all.

The achievements of recent years stand as a testament to this collective effort. We have seen the identification of underlying mutations and the development of targeted therapies to address them. The ECD Referral Care Center Network has grown to include 41 institutions across the globe. And more research than ever is being dedicated to improving our understanding and management of ECD. These advancements have been driven by the passion and dedication of the medical and research communities, in partnership with the strength and resilience of patients and families.

As we gather in Barcelona, we celebrate how far we've come—and look with hope to all that lies ahead. We believe this symposium will continue to serve as a catalyst for deeper learning, new collaborations, and bold ideas that will shape the future of ECD care and discovery.

Thank you for your commitment to the field and for the vital role you play in helping us move forward—together.

With appreciation on behalf of the ECDGA Board of Directors,

Kathy Brewer
President/Founder, ECDGA
Kathleen.Brewer@erdheim-chester.org

Diane Schriner
President Elect, ECDGA
Diane.Schriner@erdheim-chester.org

Schedule at a Glance

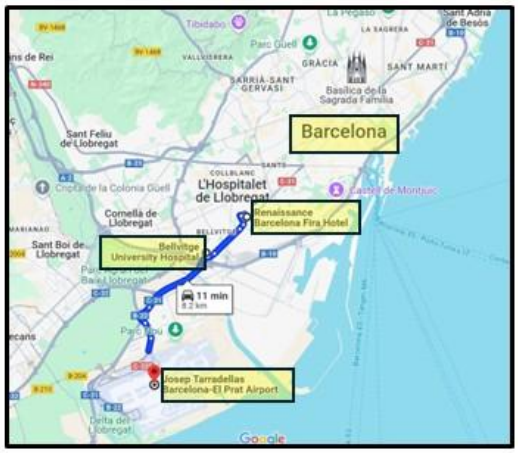
Sunday, May 25, 2025 | Pre-conference		
5:00 pm – 6:00 pm	Catholic Mass	Renaissance Barcelona Fira; Floor – 1; Room Fira Father Charles Balnaves
Monday, May 26, 2025 | Patient & Family Gathering *Light breakfast, lunch, and dinner are provided.*		
8:00 am – 8:30 am	Registration & Light Breakfast	Bellvitge University Hospital, Main Building, Street Level, Auditorium
8:30 am – 4:30 pm	Patient & Family Gathering Meeting	Bellvitge University Hospital, Main Building, Street Level, Auditorium
6:00 pm – 8:00 pm	ECD Global Alliance Celebration Dinner	Renaissance Barcelona Fira; Floor -1; Room Fira
Tuesday, May 27, 2025 *Light breakfast, lunch, and evening snacks are provided.*		
8:00 am – 8:30 am	Registration & Light Breakfast	Bellvitge University Hospital, Main Building, Street Level, Auditorium
8:30 am – 5:00 pm	ECD Medical Symposium	Bellvitge University Hospital, Main Building, Street Level, Auditorium
6:00 pm – 8:00 pm	ECDGA Medical Reception	Skyfall Cocktail Club, Hyatt Regency Barcelona Tower
Wednesday, May 28, 2025 *Light breakfast is provided.*		
8:00 am – 11:00 am	ECD Referral Care Center Network Meeting	Bellvitge University Hospital, Small Conference Room

Volunteers will be in the Renaissance Barcelona Fira hotel lobby from 7 – 7:45 am on May 26-28 to escort attendees to the hospital via Metro. The estimated travel time 10 minutes. The last escorted group will leave the hotel at 7:45 am. Those with mobility issues may want to consider a taxi or ride-sharing service.

Volunteers will be available to escort attendees from the Bellvitge University Hospital to Skyfall Cocktail Club following the meeting on May 27. Estimated walk time is 10 minutes.

Conference Maps

Barcelona Map



Barcelona Area

Barcelona Airport, Bellvitge Hospital, Renaissance Barcelona Fira Hotel

Barcelona Metro

DIRECTIONS

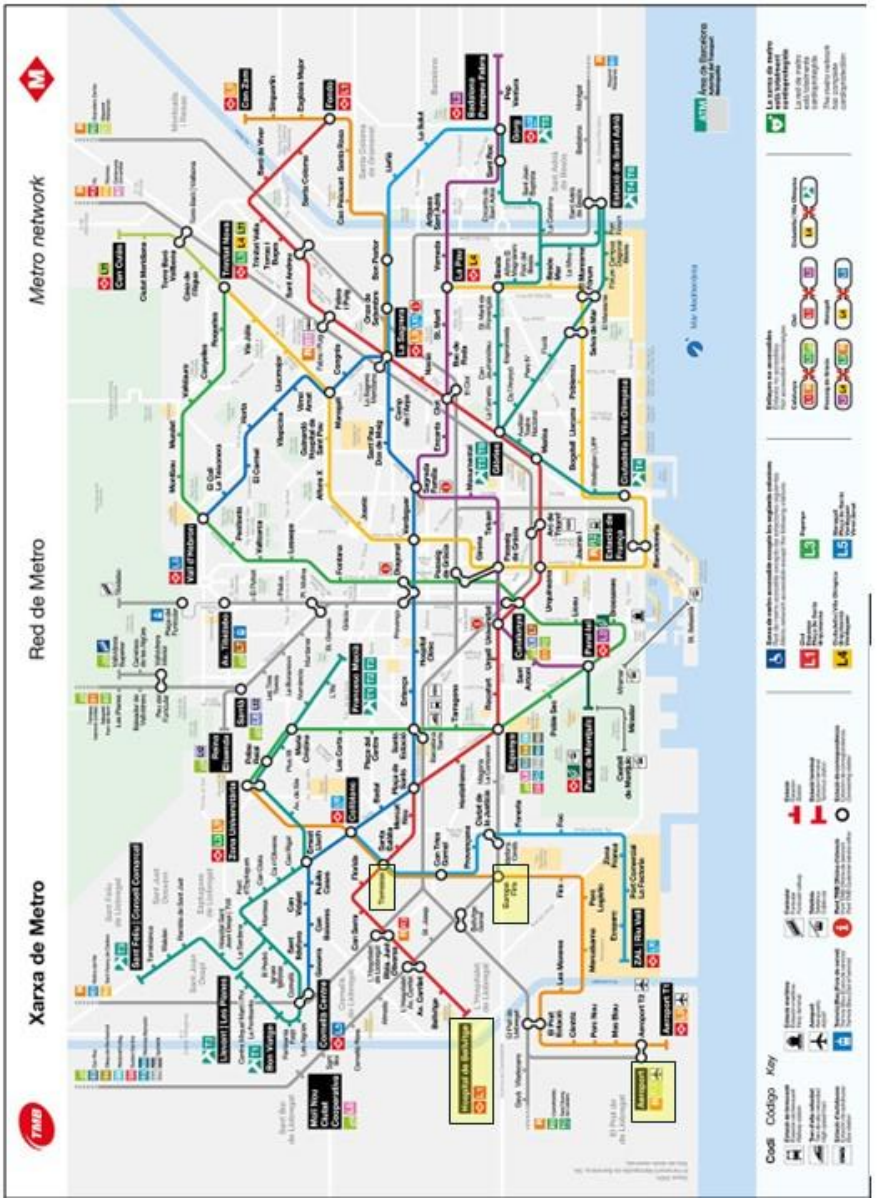
Airport to Renaissance Hotel - Metro
Line 9 to Europa Fira Station

Hotel to Bellvitge Hospital - Metro
Line 9S to Torrassa Station, then
Line 1 to Hospital Bellvitge

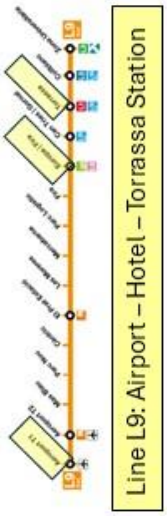
Hospital to Renaissance Hotel - Metro
Line 1 to Torrassa Station, then
Line 9 to Europa Fira Station

Also Available
- Uber/Cabify (fastest option)
- Buses

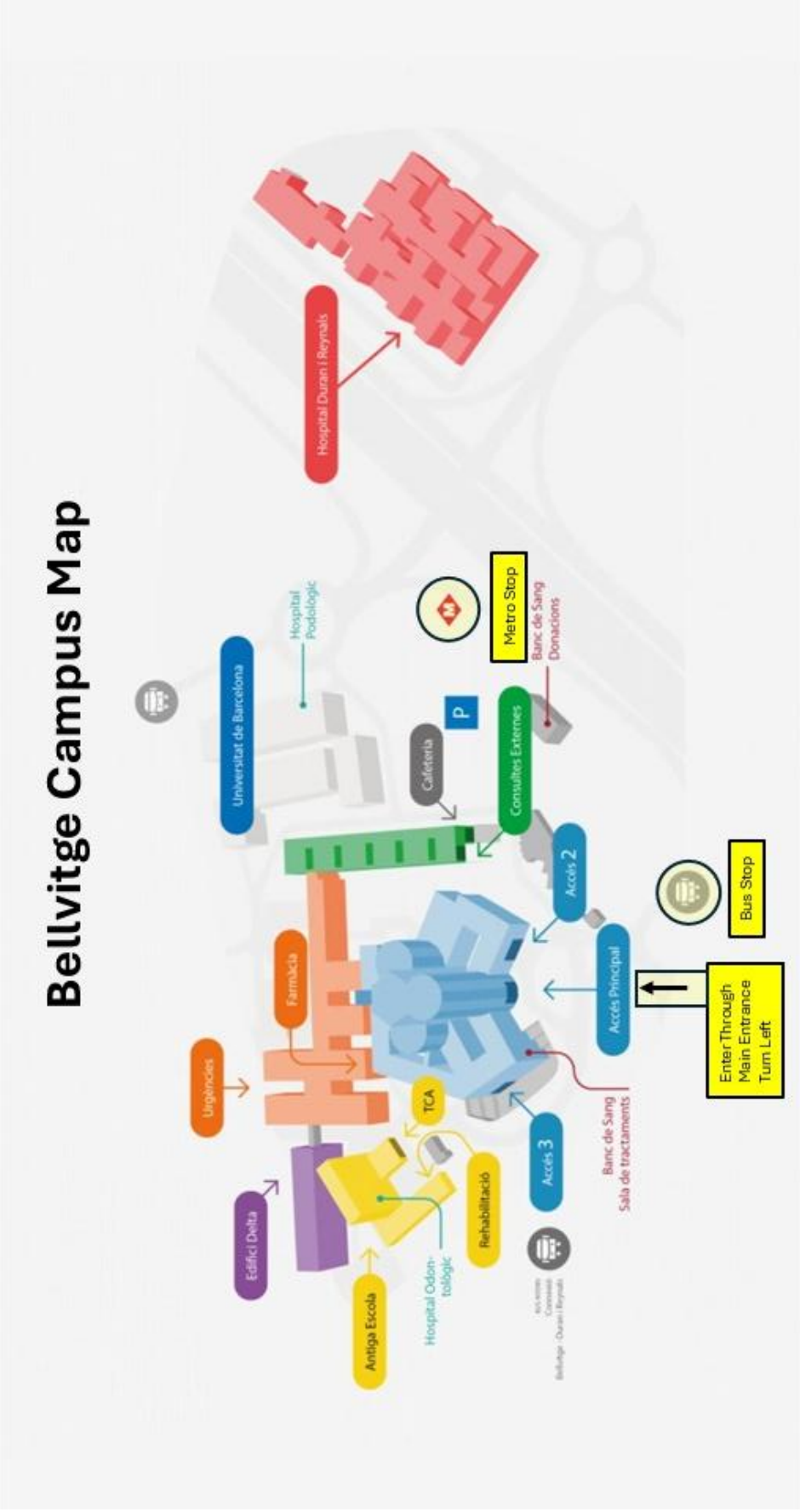
Metro line runs:
- 5 am - midnight (M-F);
- 5 m – 2 am (S-S)



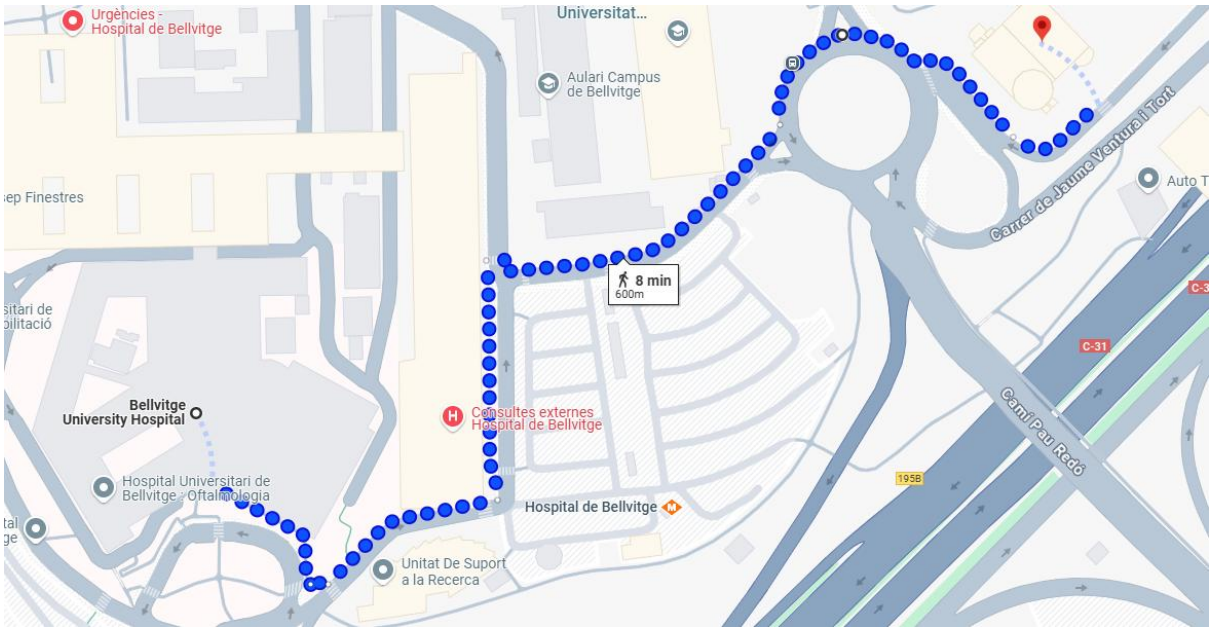
Line L1: Torrassa Station - Hospital



Line L9: Airport – Hotel – Torrassa Station


Bellvitge Campus Map
Hospital Duran i Reynals
Universitat de Barcelona
Hospital Podològic
Metro Stop
Banc de Sang Donacions
Cafeteria
P
Consultes Externes
Accés 2
Accés Principal
Enter Through Main Entrance Turn Left
Bus Stop
Farmàcia
Urgències
TCA
Banc de Sang Sala de tractaments
Accés 3
Edifici Delta
Rehabilitació
Hospital Odontològic
Antiga Escola

Walking Map - Bellvitge to Skyfall Cocktail Club



Medical Symposium Agenda

Emcee: **Matthew Collin**
Newcastle University
Newcastle upon Tyne, UK

Time	Subject	Presenter
8:00 am	Registration & light breakfast	
8:30 am	Welcome to Barcelona and the 10th Annual Erdheim-Chester Disease International Conference	**Xavier Solanich** Event Host, Internal Medicine, Bellvitge University Hospital, Barcelona, Spain **Paul Hendrie** Past Event Host, Hematologist, Fred Hutch Cancer Center, Seattle, WA USA
Keynote Address		
8:45 am	CAR-T-cell Immunoherapies: driving therapies beyond Hematological Cancers, through the Barcelona model.	**Manel Juan** Head of Immunology Service, *Hospital Clínic Barcelona, Barcelona, Spain, and Research Leader at The* Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (FCRB-IDIBAPS), Barcelona, Spain
9:25 am	Break	
Morning Abstract Presentations Session 1: Biology		
9:35 am	1. Advanced proteomic profiling for biomarker discovery in Erdheim-Chester Disease	**Oshrat Hershkovitz-Rokah** Ariel University & Assuta Medical Center, Tel Aviv, Israel
9:50 am	2. RAF-independent MEK mutations drive refractory histiocytic neoplasms but respond to ERK inhibition	**Benjamin Durham** Rutgers Cancer Institute, New Brunswick, NJ USA
10:05 am	3. BCL-2 immunohistochemistry expression in patients with histiocytosis	**Julien Haroche** Hôpital Pitié-Salpêtrière, Paris, France
10:20 am	4. Comparative Genetic Analysis of Primary versus Secondary Histiocytic Sarcoma: A Single Institution Case Series	**Lindsay Hill** University of Texas Southwestern Medical Center, Dallas, TX USA
10:35 am	Networking Break	

Time	Subject	Presenter
Morning Abstract Presentations Session 2: Clinical		
10:50 am	1. Comparative Efficacy of Frontline Targeted Therapies Versus Chemotherapy in MAPK-Pathway Altered Histiocytic Neoplasms	**Carla Isabel Borre** Mayo Clinic, Rochester, MN USA
11:05 am	2. Second cancer in Erdheim-Chester disease	**Francesco Pegoraro** Meyer Children's Hospital IRCCS, Florence, Italy
11:20 am	3. Glomeruloid angioma in Erdheim-Chester disease: an atypical skin manifestation associated with elevated VEGF-A	**Jerome Razanamahery** Dijon University Hospital, Dijon, France
11:35 am	4. Treatment Holidays in Patients with Erdheim-Chester Disease Receiving Vemurafenib: A Prospective Pilot Study	**Francesco Catamerò** Meyer's Children Hospital IRCCS, Florence, Italy
11:50 am	5. Don't Dish Out Old Therapies: Use of Pegylated-Interferon-Alpha in a case of Erdheim-Chester Disease with congestive heart failure	**Brinda Shukla** University of Alabama at Birmingham, Birmingham, AL USA
12:05 pm	Group Photo	
12:20 pm	Lunch	
Afternoon Abstract Presentations Session 1: Data		
1:20 pm	1. Symptoms, unmet needs, and quality of life in Erdheim-Chester disease: A longitudinal registry-based analysis	**Eli Diamond** Memorial Sloan Kettering Cancer Center, New York, NY USA
1:35 pm	2. Diagnostic Impact of 18F-FDG PET/MRI over PET/CT in Histiocytoses: A Prospective Comparative Study	**Pudis Michal** Hospital Universitari de Bellvitge, Barcelona, Spain
1:50 pm	3. Natural history of Erdheim-Chester disease. A preliminary analysis on 1044 patients within the ECDGA network	**Francesco Pegoraro** Meyer Children's Hospital IRCCS, Florence, Italy
2:05 pm	4. Erdheim-Chester Disease: Evolving Insights and Improved Survival Over Time	**Mia Poleksic** Mayo Clinic, Rochester, MN USA
2:20 pm	5. Real-World Efficacy and Toxicity of MEK Inhibitors in Histiocytic Neoplasms	**Gaurav Goyal** University of Alabama at Birmingham, Birmingham, AL USA
Afternoon Abstract Presentations Session 2: Biology		
2:35 pm	1. MAPK-kinase mutations and aortic lesions are associated with the distribution of circulating monocytes in histiocytosis	**Jerome Razanamahery** Dijon University Hospital, Dijon, France

Time	Subject	Presenter
2:50 pm	2. Deciphering ALK-positive histiocytosis and mimickers using single cell RNA-sequencing	**Abdou Malik Da Silva** Research unit EA4340-BECCOH at the University of Versailles SQY, University Paris-Saclay, Paris, France
3:05 pm	3. The clonal origin and evolution of high-risk multisystem histiocytosis in adults	**Matthew Collin** Newcastle University, Newcastle upon Tyne, UK
New Registry for ECD Patients		
3:20 pm	Mapping Erdheim-Chester Disease in Europe through the Core Registry	**Polyzois Makras MD, PhD** 251 Hellenic Airforce & VA General Hospital, Athens, Greece
Poster Presentations and Networking		
3:30 pm	1. Anti-IL-6 Therapy in Rare Histiocytic Disorders: Erdheim-Chester and Rosai-Dorfman Disease	**Laura Eurelings** Erasmus University Medical Centre, Rotterdam, Netherlands
	2. Global Utilization of the National Comprehensive Cancer Network Clinical Practice Guidelines for Histiocytic Neoplasms	**Guneet Janda** Mayo Clinic, Rochester, MN USA
	3. Navigating the Challenges of Erdheim-Chester Disease Associated with Myeloid Neoplasm: The Uncharted Territory of Hepatobiliary Involvement and The Double-Edged Sword of Steroids – a case report	**Rudy Mirad** University of Texas Southwestern Medical Center, Dallas, TX USA
	4. Rare Dual Diagnoses: Rosai-Dorfman and Lhermitte-Duclos Disease in a Patient with PTEN Hamartoma Tumor Syndrome	**Rudy Mirad** University of Texas Southwestern Medical Center, Dallas, TX USA
	5. Clinical and molecular features of cutaneous involvement in adults histiocytoses	**Jerome Razanamahery** Dijon University Hospital, Dijon, France
	6. Identification of overlapping clinical and molecular features of patients with abdominopelvic Rosai Dorfman disease with KRAS mutated diseases: A case series	**Samuel Reynolds** Moffitt Cancer Center, Tampa, FL USA
	7. A survey of Spanish internists to assess where patients with Erdheim-Chester disease receive care and what resources are available	**Gemma Rocamora Blanch** Hospital Universitari de Bellvitge, Barcelona, Spain
	8. Success of Second Allogeneic Stem Cell Transplant in a Patient with Erdheim-Chester Disease and Myelodysplastic Syndrome	**Shireen Usman** University of Rochester, Rochester, NY USA

Time	Subject	Presenter
Challenging Case Study		
4:10 pm	Layers of Complexity: ECD Diagnosis and management in the presence of confounding comorbidities	**Jerome Razanamahery** Dijon University Hospital, Dijon, France
Closing Remarks & Student Abstract Award		
4:40 pm	ECD Global Alliance into the Future	**Kathy Brewer** Founder/President, ECD Global Alliance, DeRidder, LA USA **Diane Schriner** President-Elect, ECD Global Alliance, Coloma, MI USA
4:55 pm	Junior Investigator - Best Presentation Award	**Oshrat Hershkovitz-Rokah** Ariel University & Assuta Medical Center, Tel Aviv, Israel

Speaker Introductions

Event Host: Xavier Solanich, MD, PhD

Xavier Solanich, MD, PhD
Internal Medicine
Bellvitge University Hospital, Barcelona, Spain
ECD Care Center Lead Physician
xsolanich@bellvitgehospital.cat

Xavier Solanich, MD, PhD is an internal medicine physician at Bellvitge University Hospital (BUH), where he specializes in the treatment of patients with immunological disorders and rare diseases, including histiocytosis. In addition to his clinical work, he serves as a professor at the University of Barcelona and as principal investigator at the Bellvitge Biomedical Research Institute (IDIBELL). Dr. Solanich has contributed to numerous national and international research projects focused on autoimmune diseases, immunodeficiencies, and other rare disorders.

As the lead physician at the ECD Care Center at BUH, Dr. Solanich oversees the care of patients with ECD, a condition historically viewed as a multisystem inflammatory disorder. Recent breakthroughs in the genetics and immunology of the disease have revolutionized its understanding and treatment, prompting physicians to update and refine their protocols accordingly.

As host of the 10th ECDGA meeting he would like to help physicians stay on top of new research and treatment options and provide the opportunity for European patients and families to contact world experts on the disease.

Keynote Speaker: Manel Juan, MD, PhD

Dr. Manel Juan, MD, PhD
Head of Immunology Service | Assistant Professor | Researcher
University of Barcelona, Barcelona, Spain
mjuan@clinic.cat

If we accept that the system in place is good enough and that pharmaceutical companies alone should manage gene and cell therapies, then many patients with rare conditions, like paediatric or infrequent cancers, will be left out."

– Dr. Manel Juan, MD, PhD

Dr. Manel Juan is an immunologist with a career spanning clinical practice, research, and education. He earned his degree in Medicine and Surgery in 1988, followed by a doctorate in 1994. Specializing in immunology, he has dedicated his career to advancing immunogenetics and immunotherapy. He is part of the team behind the development of European CAR-T-cell therapies to treat leukemia and multiple myeloma.

Dr. Juan has been an Assistant Professor since 2011 at the University of Barcelona (UB), where he coordinates the Master of Autoimmune Diseases program and has mentored 14 doctoral theses. His previous teaching roles include serving as an Assistant Professor of Immunology at the Autonomous University of Barcelona (1997-2007).

Serving as the Head of the Immunology Service since 2020, Dr. Juan oversees key programs in cell immunotherapy, including Dendritic Cells (DCs), Tumor-Infiltrating Lymphocytes (TILs), and Chimeric Antigen Receptor T-cells (CART), along with immunochemistry applications.

As a research leader at The Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (FCRB-IDIBAPS), Dr. Juan heads the Immunogenetics and Immunotherapy in Autoinflammatory and Immune Responses group. His contributions include 237 peer-reviewed publications (234 international) with a total impact factor exceeding 692.060. He has played a pivotal role in securing over €16 million in research funding across 42 projects, including both competitive and non-competitive grants, and holds nine licensed patents (six PCT).

Dr. Juan is an active member of multiple scientific and technical committees and has contributed to the organization of 13 research and development activities. Through his extensive work in immunology, he continues to drive advancements in the field, bridging fundamental research with clinical application.

New Registry for ECD Patients: Polyzois Makras, MD, PhD

Polyzois Makras MD, PhD
Endocrinologist
251 Hellenic Air Force &VA General Hospital, Athens, Greece
ECD Care Center Lead Physician

Polyzois Makras is Director of the Endocrinology Department, the Department of Medical Research, and of the National expert center for Langerhans Cell Histiocytosis (LCH) and Erdheim Chester Disease (ECD) of 251 Hellenic Air Force &VA General Hospital. He received his MD from the University of Thessaloniki, Greece in 1994, and his PhD Degree from the University of Thrace, Greece, and he served as a clinical fellow at the Department of Endocrinology and Metabolic Diseases of the Leiden University Medical Center, The Netherlands between 2006- 2007.

During the last seventeen years he has been engaged in research in disorders of calcium and bone metabolism as well as in rare diseases. He co-founded the LCH adult clinic which became the National expert center for LCH and ECD in 2019 and joined the ERN – EuroBloodNet in 2022. He is founding member of the European Consortium for Histiocytosis (ECHO) and head of the Adult ECHO working group.

He is former President of the Hellenic Society for the Study of Bone Metabolism, and member of the Committee of Scientific Advisors of the International Osteoporosis Foundation (IOF) since 2020. He is the leading author of all diagnostic and therapeutic guidelines for osteoporosis and parathyroid disorders in Greece during the last 12 years.

Challenging Case Study: Jerome Razanamahery, MD

Jerome Razanamahery, MD
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ECD Care Center Lead Physician
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Jerome Razanamahery is an internal medicine practitioner in the Department of Internal Medicine and Clinical Immunology at Dijon University Hospital. He has led the multidisciplinary effort at Dijon University Hospital to study and treat histiocytic neoplasms. He has established a center of competence for histiocytic disorders recognized by the French Ministry of Health, where we offer comprehensive diagnostic and treatment services for individuals afflicted with histiocytic disorders. His ongoing research endeavors primarily revolve around the study of monocytes in hematological conditions, with a special emphasis on histiocytic disorders.

Abstracts

Morning Abstract Presentations Session 1: Biology

1. Advanced proteomic profiling for biomarker discovery in Erdheim-Chester Disease

Oshrat Hershkovitz-Rokah, Ariel University & Assuta Medical Center, Tel-Aviv, Israel
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Dr. Rokah is the head of the Molecular Research Lab at Assuta Medical Center, located in Tel Aviv, Israel. She holds a PhD from the Department of Genetics in the Faculty of Medicine at Tel Aviv University. Dr. Rokah's group were pioneers in studying microRNA expression in Erdheim-Chester Disease, contributing to a better understanding of the molecular mechanisms underlying the development of the disease and opening new avenues for therapeutic treatment. She works in close cooperation with clinical professionals, physicians, and scientists to target real clinical needs and deficiencies. As part of the dedicated clinic at Assuta Medical Center for histiocytic neoplasms, her lab is investigating the role of epigenetic mechanisms in these neoplasms.

Authors: Refael Meyuchas[1,2], Mali Salmon-Divon[1,3,] Ofer Shpilberg[2,3,4], May Basood[4], Benjamin H. Durham[5], Matthias Papo[6], Fleur Cohen-Aubart[6], Omar Abdel-Wahab[5], Eli L. Diamond[7], Julien Haroche[6], and Oshrat Hershkovitz-Rokah[1,2]

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[4] Institute of Hematology, Assuta Medical Center, Tel-Aviv, Israel
[5] Molecular Pharmacology Program, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[6] Service de Médecine Interne, Hôpital Universitaire Pitié Salpêtrière-Charles Foix, Sorbonne Université, Faculté de Médecine, Paris, France
[7] Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

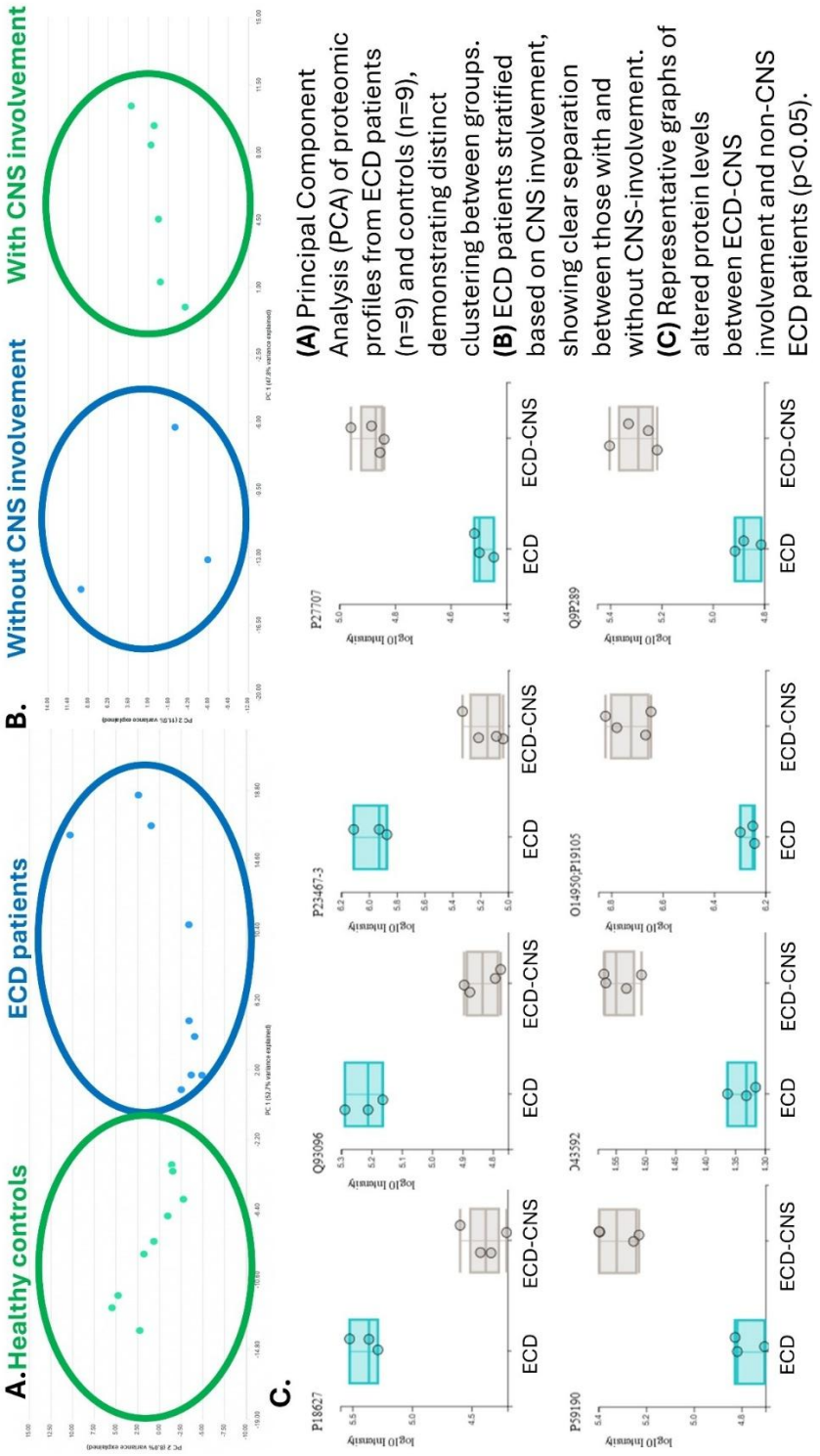
Background: Studies elucidating the pathogenesis of Erdheim-Chester Disease (ECD) have primarily focused on inflammatory cytokines, genomic alterations, and recently, epigenetic modifications. However, proteomic studies remain largely unexplored. Proteins serve as key regulators of molecular pathways; thus, their expression analysis is crucial for identifying potential biomarkers for diagnosis, prognosis, and therapeutic targeting. With advancements in technology, deep, unbiased proteomic profiling is now possible using highly sensitive platforms like Seer's Proteograph XT Assay. This technology enables the discovery of proteins involved in disease pathogenesis and the identification of potential biomarkers.

Methods: We conducted a pilot study utilizing Seer's Proteograph XT Assay for proteomic profiling on plasma samples from nine ECD patients and nine healthy controls. This advanced technology enables unbiased, high-throughput protein quantification, allowing for in-depth potential biomarker discovery. Proteomic data were analyzed to identify differentially expressed proteins between groups, with further stratification of ECD patients based on central nervous system (CNS) involvement.

Results: Proteomic analysis identified 7,630 protein groups and 91,014 peptides across samples, demonstrating clear differential clustering between ECD patients and controls (Figure 1A). Additionally, we observed distinct proteomic signatures differentiating ECD patients with CNS involvement from those without, highlighting potential biomarkers for non-invasive disease monitoring (Figure 1B-C). These

findings suggest that plasma proteomics can provide valuable insights to aid in biomarker discovery, particularly for inaccessible tissues such as the brain.

Conclusions: This study serves as proof of concept that advanced proteomic profiling may identify clinically relevant biomarkers. The ability to distinguish patients with CNS involvement using blood-based biomarkers has significant clinical implications, potentially reducing the need for invasive biopsies. Future studies with larger cohorts are warranted to validate these findings and translate them into clinical applications.



(A) Principal Component Analysis (PCA) of proteomic profiles from ECD patients (n=9) and controls (n=9), demonstrating distinct clustering between groups. **(B)** ECD patients stratified based on CNS involvement, showing clear separation between those with and without CNS-involvement. **(C)** Representative graphs of altered protein levels between ECD-CNS involvement and non-CNS ECD patients ($p<0.05$).

2. RAF-independent MEK mutations drive refractory histiocytic neoplasms but respond to ERK inhibition

Benjamin Durham, Rutgers Cancer Institute, New Brunswick, NJ USA
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Benjamin H. Durham, M.D. is a hematopathologist and molecular genetic pathologist with American Board of Pathology certifications in anatomic pathology, clinical pathology, hematopathology, and molecular genetic pathology who has recently transitioned to an Assistant Professor (tenure-track) in the Department of Pediatrics, Division of Hematology/Oncology Research, and the Department of Pathology and Laboratory Medicine at Robert Wood Johnson Medical School and Rutgers Cancer Institute. His new and emerging independent research program investigates the molecular pathogenesis, functional genomics, cancer immunology, and molecular pharmacology of poorly characterized hematological malignancies driven by mitogen-activated protein kinase (MAPK) and receptor tyrosine kinase (RTK) signaling.

Authors: Eli L. Diamond[1,*], Jean-Francois Emile[2,*], Julien Haroche[3], Maxim I. Maron[4], Jahan Rahman[4], Anne S. Reiner[5], Dana Bossert[1], Marc Rosenblum[6], Mariko Yabe[6], Kseniya Petrova-Drus[6], Jasmine H. Francis[7], Veronica Rotemberg[8], Raajit K. Rampal[9], Sonia Mahajan[10], Vaios Hatzoglou[10], Robert Young[10], Gary A. Ulaner[11], Wiebke Rösler[12], Oshrat Hershkovitz-Rokah[13,14], Ofer Shpilberg[13,14], Roei D. Mazor[13,14], Luke Y.C. Chen[15], Michael Singer[4], Takeshi Fujino[4], Alexander M. Lewis[4], Kenyon Weis[4], Salima Benbarche[4], Nina Fox[4], Cynthia Castro[4], Steven Tittley[4], Matthew Witkowski[16], Fleur Cohen-Aubart[3], Louis Terriou[17], Maher Hanoun[18], Nicolas Schleinitz[19], Gabriela Sosa[20], Timo Hautala[21], Laure Farnault De Lassus[22], Neal Rosen[5], Omar Abdel-Wahab[4,**], Benjamin H. Durham[4,6,23,**]

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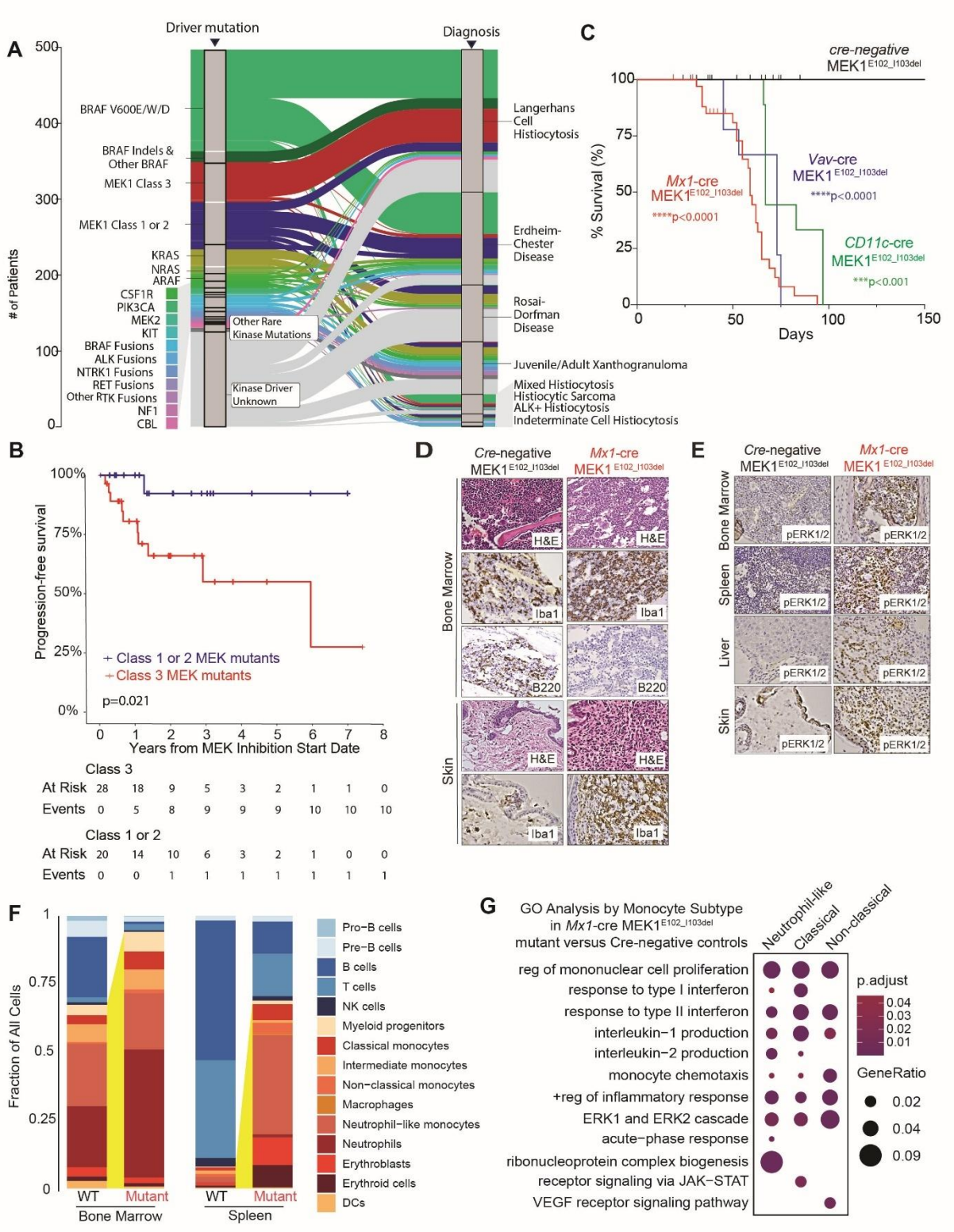
Background: Histiocytic neoplasms are clonal disorders of the monocyte/macrophage lineage defined by mutations activating MAP kinase signaling, including BRAFV600E mutations in ~50% of patients, which confer robust responses to BRAF inhibition. More recently, the MEK inhibitor cobimetinib was FDA-approved for BRAFV600-wild-type histiocytosis patients. Here following genomic analysis from a prospective registry of children and adults with histiocytoses (clinicaltrials.gov NCT03329274), across 500 patients with diverse histiocytoses the most common alteration following BRAFV600E was MEK1E102_I103 in-frame deletion. MEK1E102_I103del (Figure A) and related RAF-independent MEK1 mutants were associated with an aggressive multi-system clinical phenotype and worse progression-free survival with MEK inhibition compared to patients with other classes of MEK1/2 mutations (Figure B). Given that cancer-associated MEK1/2 mutations have not been modeled in vivo and the clinical importance of MEK1/2 mutations, we generated Map2k1E102_I103del conditional knock-in mice, which represent the first genetically engineered mouse model of activating MEK1/2 mutations.

Methods: Map2k1E102_I103del conditional knock-in mice were generated within the endogenous locus of Map2k1 and crossed with Mx1-cre, Vav-cre, and CD11c-cre mice. Primary mutant and control mice were characterized using flow cytometric, histological, biochemical, single-cell, and digital spatial molecular analyses.

Results: By approximately 6 weeks of age, Mx1-cre Map2k1E102_I103del knock-in mice developed a 100% penetrant, lethal myelomonocytic neoplasm with suppression of B-lymphopoiesis and expansion of monocyte /macrophage subsets and Cd11b+ dendritic cells that also infiltrated hematopoietic organs, liver, and skin while their littermate controls did not. Furthermore, immunophenotypic and scRNA-sequencing analyses of MEK1-mutant mice reveal distinct myeloid skewing and expansions of mature monocyte and macrophage subsets with transcriptional profiles consistent with a hyperinflammatory state and a relative depletion of lymphoid cell types, which is consistent with an inflammatory myeloid neoplasm reminiscent if human histiocytic neoplasms. Also, Map2k1E102_I103del allele recombination resulted in activation of phosphorylated ERK1/2 in hematopoietic cells (Figure C-G). MEK1-mutant mice were sensitive to treatment with the ERK inhibitor ulixertinib. We consequently treated five MEK1E102_I103del-mutant patients with ulixertinib on prospective IRB-approved Single Patient Use Expanded Access protocols, four of whom were refractory to MEK inhibition. Four of five patients experienced objective clinical and/or radiological responses to ulixertinib.

Conclusions

Overall, in vivo expression of Map2k1E102_I103del gave rise to disease reminiscent of human histiocytic neoplasms. These data reveal the impact of oncogenic MEK1 kinase mutations in vivo, identify patients with likelihood of resistance to MEK inhibition, and nominate ERK inhibition as a therapy to overcome resistance to MEK1/2 inhibition in histiocytoses. Furthermore, this model provides a pre-clinical avenue for studying optimal single-agent or combinatorial therapeutic regimens for MEK1/2 inhibitor-resistant histiocytoses and can inspire future clinical trials.


A
Driver mutation
Diagnosis
# of Patients
BRAF V600E/W/D
BRAF Indels & Other BRAF
MEK1 Class 3
MEK1 Class 1 or 2
KRAS
NRAS
ARAF
CSF1R
PIK3CA
MEK2
KIT
BRAF Fusions
ALK Fusions
NTRK1 Fusions
RET Fusions
Other RTK Fusions
NF1
CBL
Other Rare Kinase Mutations
Kinase Driver Unknown
Langerhans Cell Histiocytosis
Erdheim-Chester Disease
Rosai-Dorfman Disease
Juvenile/Adult Xanthogranuloma
Mixed Histiocytosis
Histiocytic Sarcoma
ALK+ Histiocytosis
Indeterminate Cell Histiocytosis
C
cre-negative MEK1E102_I103del
Mx1-cre MEK1E102_I103del
****p<0.0001
Vav-cre MEK1E102_I103del
****p<0.0001
CD11c-cre MEK1E102_I103del
***p<0.001
% Survival (%)
Days
B
Progression-free survival
Class 1 or 2 MEK mutants
Class 3 MEK mutants
p=0.021
Years from MEK Inhibition Start Date
Class 3
At Risk 28 18 9 5 3 2 1 1 0
Events 0 5 8 9 9 9 10 10 10
Class 1 or 2
At Risk 20 14 10 6 3 2 1 0 0
Events 0 0 1 1 1 1 1 1 1
D
Cre-negative MEK1E102_I103del
Mx1-cre MEK1E102_I103del
Bone Marrow
Skin
H&E
Iba1
B220
E
Cre-negative MEK1E102_I103del
Mx1-cre MEK1E102_I103del
Bone Marrow
Spleen
Liver
Skin
pERK1/2
F
Fraction of All Cells
WT
Mutant
Bone Marrow
Spleen
Pro−B cells
Pre−B cells
B cells
T cells
NK cells
Myeloid progenitors
Classical monocytes
Intermediate monocytes
Non−classical monocytes
Macrophages
Neutrophil−like monocytes
Neutrophils
Erythroblasts
Erythroid cells
DCs
G
GO Analysis by Monocyte Subtype in Mx1-cre MEK1E102_I103del mutant versus Cre-negative controls
Neutrophil-like
Classical
Non-classical
reg of mononuclear cell proliferation
response to type I interferon
response to type II interferon
interleukin−1 production
interleukin−2 production
monocyte chemotaxis
+reg of inflammatory response
ERK1 and ERK2 cascade
acute−phase response
ribonucleoprotein complex biogenesis
receptor signaling via JAK−STAT
VEGF receptor signaling pathway
p.adjust
GeneRatio

3. BCL-2 immunohistochemistry expression in patients with histiocytosis

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Background: The role of BCL-2 has been extensively studied in cancer pathogenesis, especially in hematologic malignancies. Various mechanisms are involved in BCL-2 overexpression, such as chromosomal rearrangement involving chromosome 18 or epigenetic mechanisms (1). Histiocytosis represents a spectrum of diseases with diverse clinical presentations. While the involvement of the MAPK pathway in the pathophysiology of histiocytic neoplasms has been long recognized, recent research by Salmon-Divon et al. suggests a significant role for the epigenetic landscape in their development (2). Additionally, they demonstrated that epigenetic signature correlates with the overexpression of BCL2 gene transcription and BCL2 protein expression in histiocytic neoplasms (3). The objective of this study was to investigate the immunohistochemical expression of the BCL2 protein in a cohort of patients diagnosed with histiocytosis and to determine the clinical and molecular phenotype of ECD patients according to BCL2 status.

Methods: We performed additional immunohistochemical staining on tissue sections to evaluate the expression of BCL2 protein in a cohort of French patients diagnosed with various forms of histiocytosis (Erdheim-Chester disease (ECD), Langerhans cell histiocytosis (LCH), Rosai-Dorfman disease (RDD), and malignant histiocytosis (MH)). Two experienced pathologists evaluated BCL2 expression, classifying it as either negative or positive based on the immunohistochemistry (IHC) staining of BCL2 and the percentage of histiocytic cells showing BCL2 expression. Expression was deemed positive if more than 50% of histiocytes exhibited BCL2 expression. Clinical and molecular data were collected retrospectively. Differences between the groups were tested using the Mann–Whitney test for the continuous data and Fisher's exact or chi-square test for the qualitative data.

Results: We studied BCL2 expression by immunohistochemistry in 75 patients diagnosed with histiocytosis. BCL2 expression was positive in 19/33 ECD, 12/23 MH, 4/6 LCH and 13/13 RDD. Among the cohort of ECD patients, only pulmonary/pleural involvement was associated with the absence of BCL2 expression in IHC.However, several non-significant variables appear to suggest a potential association with the presence of BCL2 expression, namely the presence of a BRAF mutation ($p = 0.14$) and bone involvement ($p = 0.11$).

Conclusions: In our sample, all patients followed for Rosai-Dorfman disease express BCL2, as well as half of the patients with malignant histiocytosis. Our study suggests that BCL2 could also be associated with specific clinical phenotypes (such as pulmonary/ pleural involvement and absence of BCL2 expression). Continuing statistical analysis on a larger sample will help determine whether a specific clinical or molecular phenotype is associated with the expression of BCL2 in patients with Erdheim-Chester disease. The ultimate goal would be to study the use of BCL2 inhibitors like venetoclax in severe forms of histiocytosis, in combination with BRAF or MEK inhibitors, or as an alternative in case of toxicity from these treatments.

4. Comparative Genetic Analysis of Primary versus Secondary Histiocytic Sarcoma: A Single Institution Case Series

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Introduction: Histiocytic sarcoma (HS) is a rare and aggressive malignancy with heterogeneous molecular underpinnings. Primary HS (pHS) develops de novo with distinct genetic features, while secondary HS (sHS) typically shares a clonal relationship with, and is postulated to arise from the transdifferentiation of, an underlying hematologic malignancy. This study compares the molecular profiles of pHS and sHS to elucidate differences in pathogenesis and therapeutic implications.

Case Presentations: Patient 1 was a 68-year-old Caucasian female with pHS of the hard palate. She had a history of low-grade salivary gland adenocarcinoma treated with surgery and radiation 13 years prior. She presented with a rapidly enlarging right oropharyngeal mass causing airway obstruction. Imaging confirmed tumor extension crossing the midline, with nasal cavity obstruction (Fig 1) and significant hemorrhagic episodes. Next-generation sequencing (NGS) of the tumor revealed PIK3CA (p.His1047Arg), ABL2, DIS3, STAG2 mutations, loss of chromosomes 7 and 9 leading to SAMD9 and CDKN2A/B loss, and chromosome 2q and 7 gain leading to BRAF gain. She received one cycle of nivolumab with ifosfamide, carboplatin, and etoposide (Nivo-ICE) but developed mixed-shock and airway compromise. Due to rapid decompensation, the family transitioned to comfort care. Patient 2 is a 26-year-old Hispanic male with multifocal pHS. He presented with fever and night sweats, and was found to have a large mediastinal mass, masses in the liver and spleen, extensive lymphadenopathy, and lytic bone lesions (Fig 2). NGS identified mutations in NRAS (Q61H), PTEN (P281fs*17), TP53 splice site mutation (375+5G>T), and PDL1 expression at 40%. Given symptomatic disease burden, he was started urgently on ICE. Nivo was added in cycle 2 given PDL1 expression. He continues to tolerate treatment with mixed response on imaging and is undergoing allogeneic stem cell transplant evaluation. The MEK inhibitor cobimetinib +/- salvage chemotherapy is being considered as second-line treatment given his NRAS mutation. Patient 3 was a 66-year-old Caucasian female with an 11-year history of chronic lymphocytic leukemia (CLL) who developed sHS while on ibrutinib, presenting with dyspnea, fatigue, and lymphadenopathy. Biopsies confirmed HS with diffuse lymph node and bone marrow (BM) infiltration, with residual CLL on BM core (Fig 3). NGS identified NOTCH1 (p.Pro2514fs), TP53 (p.His193Arg), KRAS (p.Lys117Asn), PTPN11 (p.Glu76Lys), POT1 (p.Ile49fs), SETD2 (p.Leu1755fs) mutations, and KRAS copy number gains. NOTCH1 and TP53 alterations

signify an underlying unfavorable CLL signature. The patient was treated with ICE chemotherapy but succumbed to disease and treatment complications.

Conclusion: While our cohort is small, our analysis confirms the central role of the RAS/MAPK and PI3K-AKT-mTOR pathways in HS pathogenesis. The genomic landscape of pHS and sHS reveals key differences in oncogenic drivers. Our pHS cases demonstrate genetic alterations in the PI3K-AKT-mTOR pathway, expanding its molecular profile and potential therapeutic avenues. Concomitant mutations in PTEN and NRAS (patient 2), affecting RAS/MAPK and PI3K-AKT-mTOR pathways, have not been previously reported in pHS. KRAS mutagenesis in sHS arising from CLL, as in patient 3, has previously been described, but concurrent KRAS and PTPN11 mutations have not. Anti-PD1 immune checkpoint blockade did not result in significant clinical responses in our cohort and needs further exploration. This study highlights the need for prospective, collaborative trials guided by comprehensive genomic profiling to individualize treatment strategies in these rare disease entities.

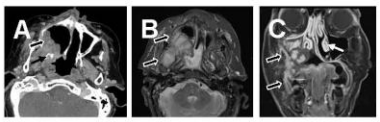

Figure 1. Radiographic evidence of an obstructive oropharyngeal mass, biopsy confirmed as primary HS in Patient 1. (A) Axial cross-section of contrast-enhanced CT head, (B) axial T2-weighted FLAIR MRI, and (C) coronal cross-section of contrast-enhanced T1-weighted MRI demonstrate an infiltrating mass with heterogeneous polypoid-like components (thick black arrows) at the right oral mucosa extending into the right maxillary sinus and masticator space and infiltrating the pterygoid muscles and right pterygoid plate (thin black arrow). T1-weighted MRI further shows mucosal enhancement of the right maxillary sinus, bilateral nasal cavity, and nasopharynx (C, thin white arrow).

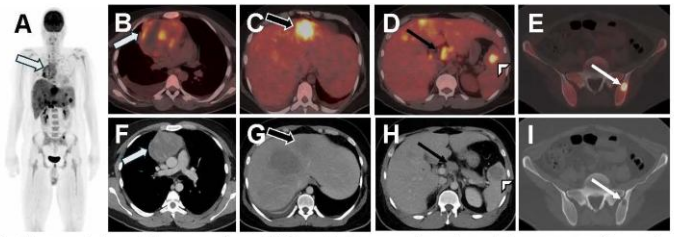

Figure 2. Radiographic evidence of multi-focal disease burden, biopsy confirmed as primary HS in Patient 2. FDG PET/CT demonstrates diffuse avidity in the axial and proximal appendicular skeleton and an FDG avid 10 cm anterior mediastinal mass on maximum intensity projection (A). Axial cross-sections from FDG/PET (B-E) and contrast-enhanced CT (F-I) further demonstrate that the mediastinal mass is heterogenous and partially necrotic (B, F) and show a hypodense FDG-avid hepatic mass (C, G), enlarged FDG-avid periportal node (D, H), and an FDG-avid lytic lesion in the left iliac bone (E, I).

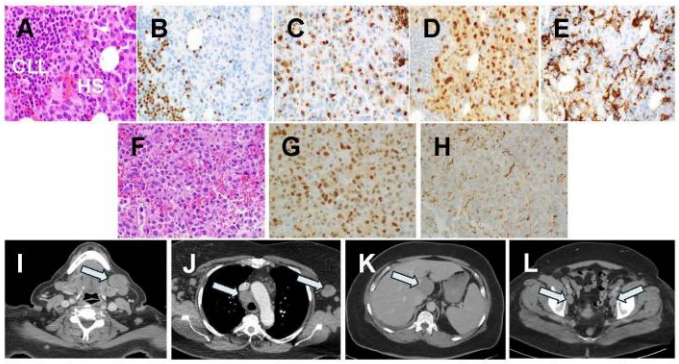

Figure 3. Pathologic and radiographic evidence of concurrent CLL and secondary HS in Patient 3. Bone marrow core biopsy reveals small round CLL cells and large, pleomorphic cells with irregular nuclei and abundant cytoplasm (A) that are PAX5- (B), lysozyme+ (C), cyclin D1+ (D), and rarely CD163+ (E), consistent with HS. Submandibular lymph node biopsy is also consistent with HS, without evidence of CLL, showing large pleomorphic cells (F) that are cyclin D1+ (G), and CD68+ (H). Axial cross-sections of contrast-enhanced CT demonstrate multi-station lymphadenopathy (white arrows), including cervical (I), mediastinal and axillary (J), periportal (K), and pelvic nodes (L). The largest lymph node is 4 cm in short-axis at the porta hepatis (K). Mild splenomegaly is also seen (K).

Morning Abstract Presentations Session 2: Clinical

1. Comparative Efficacy of Frontline Targeted Therapies Versus Chemotherapy in MAPK-Pathway Altered Histiocytic Neoplasms

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Carla Isabel Borre, MD, MPH, is an Internal Medicine resident at Mayo Clinic in Rochester, MN, with a dedicated focus on Hematology-Oncology and rare diseases. Driven by a passion to improve patient care for rare diseases, her research investigates histiocytic disorders, specifically comparing the efficacy of targeted therapy versus traditional chemotherapy. Dr. Borre's goal is to establish evidence-based treatment strategies that optimize patient outcomes. She holds an MD from Universidade Federal de Ciências da Saúde de Porto Alegre (Brazil) and an MPH in Global Health from Yale University.

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Background: Erdheim-Chester Disease (ECD) and Langerhans Cell Histiocytosis (LCH) are rare, histiocytic neoplasms (HN) with ~90% of patients demonstrating MAPK pathway alterations. BRAF and MEK inhibitors show promising outcomes, but treatment interruptions due to adverse effects (AE) are common. Limited access to targeted therapies complicates global care. The comparative efficacy of continuous targeted agents versus (vs.) fixed-duration chemotherapy in MAPK-altered HN remains unclear.

Methods: A retrospective cohort analyzed adult patients with BRAFV600E or MAP2K (gain-of-function) mutated HN consecutively seen at Mayo Clinic MN, AZ, and FL between 2007–2024. Patients received targeted therapy with either BRAF inhibitors (for BRAFV600E) or MEK inhibitors (for MAP2K alterations), or chemotherapy, as frontline treatment. Data on disease, treatments, and outcomes were collected and analyzed using JMP software.

Results: Among 95 patients (LCH=25, ECD=63, Mixed=7; median age 56 years [range: 18–83], 56% male), 77 (81%) received targeted therapy (TT) and 18 (19%) chemotherapy (CT): cladribine (n=7), cytarabine (n=8), etoposide (n=1), cyclophosphamide and vincristine (n=1), and methotrexate (n=1). Baseline characteristics are in Table 1. Median follow-up was 3.6 years (95% CI: 2.7–4.2); 3.4 years (95% CI: 2.4-4.2) , and 4 years (95% CI: 2.1-5.3) for TT and CT cohorts, respectively, p=0.7. The overall response rates (ORR) were similar: 70% for TT (complete response [CR] 10%) and 73% for CT (CR 13%), p=0.78. The median time to best response was 3 months (95% CI: 2.6-3.6) for TT and 4 months (95% CI: 1.1-6.5) for CT, p=0.68. Progression-free survival (PFS) at 4 years was 76% vs. 77% for TT and CT, respectively, p=0.92. Targeted therapy was discontinued in 34% (n=26) of patients: AE (n=20) and disease progression (n=6). In comparison, 17% of CT cohort (n=3) prematurely discontinued treatment: AE (n=1), suboptimal response (PR after 2 cycles, n=1), and disease progression after 2 cycles (n=1), p=0.1. Median time-to-next therapy was not reached in both cohorts and at 4 years, 74% of patients receiving targeted therapy and 63% receiving chemotherapy were free from receiving next line of therapy, p=0.24 . Four-year overall survival (OS) was 92% and 100% for TT and CT, respectively, p=0.15.

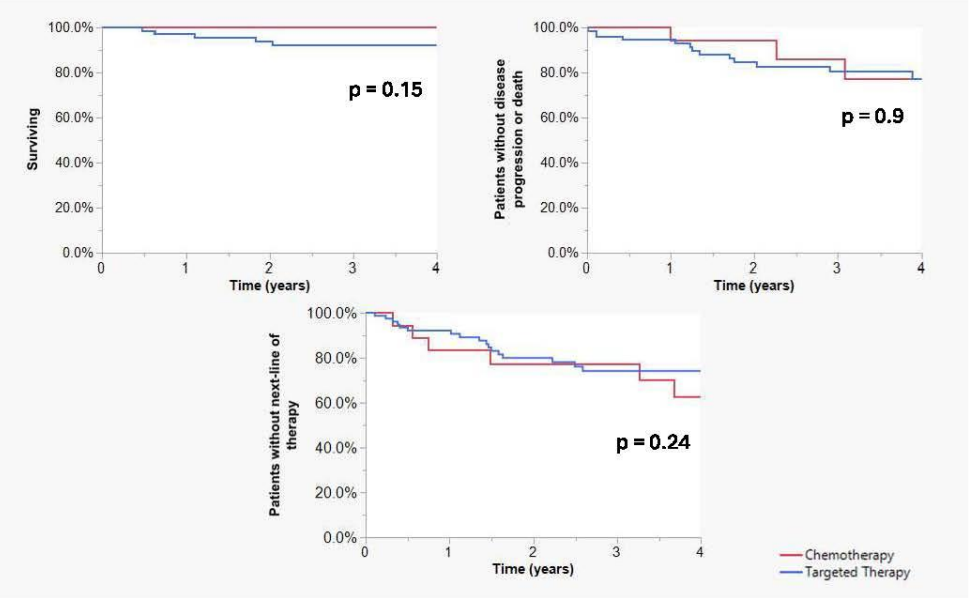
Conclusions: Fixed-duration chemotherapy achieves outcomes comparable to continuous targeted therapies in patients with MAPK-altered ECD and LCH. The selection of therapy should consider patient preferences, comorbidities, and resource availability while carefully considering the comparable efficacy and toxicity.

Table 1: Baseline Characteristics and Outcomes of Patients Receiving Targeted Therapy and Chemotherapy

Variable	Targeted Therapy (n = 77)	Chemotherapy (n = 18)	p-value
Age (median, y, range)	58 (19-83)	43 (18-72)	0.006
Sex (M, %)	61	33	0.03
Multisystem disease (%)	94	67	0.004
Risk organ involvement (%)	35	22	0.3
BRAF^{V600E}(%)/*MAP2K* (%)	83/17	83/17	1.0
Outcomes			
Median Follow-up y, (95% CI)	3.4 (2.4-4.2)	4 (2.1-5.3)	0.7
Median Time to Best Response months (95% CI)	3 (2.6-3.6)	4 (1.1-6.5)	0.7
ORR (CR, PR), %	70 (10, 60)	73 (13, 60)	0.8
4Y OS, %	92	100	0.15
4Y PFS, %	76	77	0.9
TTNT, %	74	63	0.24

ORR = overall response rate; PFS = progression-free survival; OS = overall survival; TTNT = time to next therapy.

Figure 1: Overall Survival, Progression-Free Survival, and Time to Next Therapy



2. Second cancer in Erdheim-Chester disease

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Dr. Francesco Pegoraro, is a clinical researcher and pediatrician specializing in ECD and other histiocytic disorders. During his residency, he joined the Histiocytosis clinic, caring for adults and children affected by ECD and other histiocytic disorders, and he actively participated in several scientific projects focused on histiocytosis and other hematologic conditions. Currently, Dr. Pegoraro is a part-time MD at the Department of Hematology/Oncology of the Meyer Children's Hospital (Florence). Additionally, he is pursuing a Ph.D. at the University of Florence, as a second-year student. His doctoral research is dedicated to elucidating the genetic predisposition underlying histiocytosis, with the aim of expanding our understanding of these complex diseases.

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[11] Hematology Clinic, Pitié-Salpêtrière Hospital, Sorbonne University, Assistance Publique-Hôpitaux de Paris, Paris, France
[12] EA4340 BECCOH, Versailles SQY University, Pathology Department, Ambroise Paré Hospital, Assistance Publique-Hôpitaux de Paris, Boulogne, France
[13] Desbrest Institute of Epidemiology and Public Health, Univ Montpellier, INSERM, Montpellier, France
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Background: Erdheim-Chester disease (ECD) is a histiocytic disorder driven by somatic mutations in myeloid precursors and often associated with clonal hematopoiesis. The disease has a heterogeneous clinical spectrum, requiring deep exploration of cancer risk and outcome in patients with ECD. Here, we aimed to evaluate the prevalence and incidence of associated cancers in ECD, compare cancer risk between ECD patients and the general population, and assess survival outcomes and clinical features linked to second malignancies.

Methods: This retrospective study analyzed data from two referral centers in France (Paris) and Italy (Florence). It included patients with ECD diagnosed and followed between 2000 and 2023. Patients were screened for second malignancies, including both hematologic and solid cancers, alongside ECD-related

clinical features. Primary outcomes included the incidence and types of cancers associated with ECD, standardized incidence ratio (SIR) compared to the general population, survival, and clinical predictors of second malignancies.

Results: Among 515 ECD patients, 146 (28%) had a history of cancer, including hematologic malignancies in 73 patients (14%) and solid cancers in 87 (17%); 14 patients (3%) had both solid and hematologic neoplasms. The cancer standardized incidence ratio (ECD vs. general population), assessed in the French cohort, was 4.835 (95%CI 4.106-5.623). Multivariable analysis showed an association between the increased risk of second cancers after ECD and age (OR 1.039, 95%CI 1.018-1.061), male gender (OR for females 0.377, 95%CI 0.193-0.736), multisystem involvement (OR 1.883, 95%CI 1.059-3.348), and absence of hypothalamic/pituitary involvement (OR 0.364, 95%CI 0.160-0.830). After a median follow-up of 66 months (IQR 56-74), 156 patients (30%) died, with deaths primarily attributed to ECD (n=87, 56%) or second cancers (n=24, 15%).

Conclusions: Second cancers occur in nearly 30% of patients with ECD, a frequency significantly higher than in the general population. These malignancies are more prevalent in older males with multisystem disease. Regular cancer surveillance and tailored management strategies are essential to improve outcomes in this high-risk population.

3. Glomeruloid angioma in Erdheim-Chester disease: an atypical skin manifestation associated with elevated VEGF-A.

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Jerome Razanamahery graduated in internal medicine and immunology in 2017. He is a physician in the internal medicine department of Dijon University Hospital. He is particularly interested in immunology and oncology. During his residency at Pitié-Salpétrière Hospital, he researched histiocytic disorders, especially ECD and RDD, with Professor Haroche. He led an internal multicentric project with Eli Diamond, Gaurav Goyal, Jean-Francois Emile, and Julien Haroche, describing the overlapping forms between ECD and RDD in adult patients. His current research focuses on monocyte disturbance in histiocytic disorders and the significance of their modification in the disease's course.

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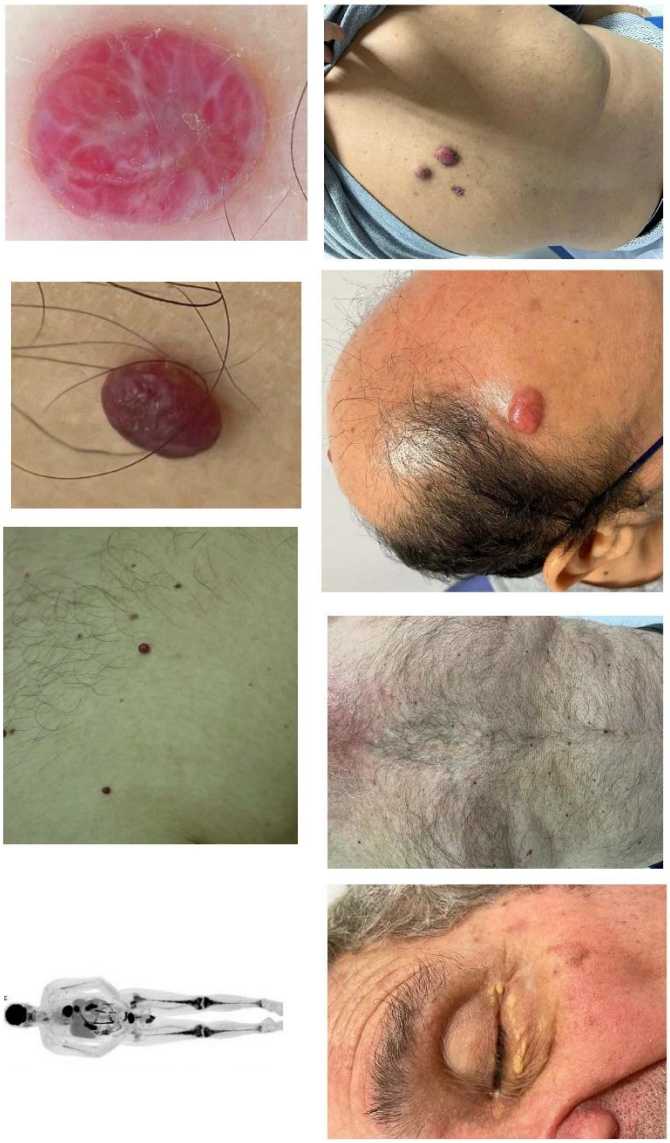
Background: Erdheim-Chester Disease (ECD) is a rare, clonal histiocytosis characterized by distinct clinical and histological features, including long bone osteosclerosis, peri-renal infiltrates, and vascular sheathing. Cutaneous manifestations, such as eyelid xanthelasma, are observed in some patients. ECD pathogenesis is driven by constitutive activation of the mitogen-activated protein (MAP) kinase pathway, predominantly through the BRAFV600E mutation, promoting cellular proliferation and resistance to apoptosis. Vascular Endothelial Growth Factor-A (VEGF-A), a pro-angiogenic factor, is elevated in ECD patients, correlating with vascular involvement. VEGF-A levels are also elevated in POEMS syndrome, a hematological condition associated with glomeruloid hemangiomas and bone lesions. However, hemangiomas have been reported in one ECD patients. This study presents the first case series of ECD patients with hemangiomas associated with elevated VEGF-A levels, without criteria for POEMS syndrome.

Methods: Data were retrospectively analyzed from three ECD care centers: Dijon, Pitié Salpêtrière Hospital, and Florence Hospital. Patients with skin involvement were identified from a cohort of 574 ECD cases, focusing on individuals presenting with hemangiomas and lacking POEMS syndrome criteria. Clinical, molecular, and biological data, as well as treatment responses, were analyzed. The study adhered to the declaration of Helsinki, with ethics committee approval from all institutions.

Results: Among 574 ECD patients, 189 patients (32%) had skin involvement. Five male patients (median age: 64 years; IQR: 47-77) presented with hemangiomas at diagnosis. All had multisystemic disease, with a median of five organs affected (IQR: 3.5-7). The most commonly involved organs were bones (5/5), cardiovascular system (3/5), and peri-renal regions (3/5). Cutaneous hemangiomas were reddish, well-circumscribed, and predominantly located on the trunk (4/5 patients). One patient exhibited extensive cephalic lesions with skull involvement. The lesions were painless, non-pruritic, and showed increased vascularization in two cases. Only one patient exhibited peri-orbital xanthelasma-like lesions. Molecular analysis identified MAP kinase pathway mutations in four patients: BRAFV600E (2/5) and MAP2K1 c.388T>C (2/5). Blood tests revealed elevated C-reactive protein (CRP) levels in all patients (median: 46 mg/L; IQR: 10-51) with normal blood counts. VEGF-A levels were markedly elevated in four patients

(median: 751 pg/ml; IQR: 271-1364; normal: <115 pg/ml). None exhibited IgM gammopathy or elevated kappa light chains, excluding POEMS syndrome. Two patients had clonal hematopoiesis with TET2 mutations. PET-CT confirmed typical ECD bone lesions, with no lytic lesions suggestive of POEMS syndrome. Biopsies of hemangiomas (n=3) revealed glomeruloid angiomas. Two biopsies demonstrated histiocytosis associated with BRAFV600E (n=1) and MAP2K1 mutations (n=1). Treatment with targeted therapies (3/5) achieved metabolic responses in most patients, though hemangiomas persisted in all but one case. Cephalic lesions resolved with MEK inhibitor therapy.

Conclusions: This study identifies hemangiomas as a novel cutaneous manifestation in ECD, associated with elevated VEGF-A levels, distinct from POEMS syndrome. VEGF-A likely plays a critical role in their pathogenesis. Clinicians should consider ECD in cases of hemangiomas without POEMS criteria. Persistent VEGF-A-driven lesions despite metabolic responses highlight the potential need for VEGF-A-targeted therapies.



4. Treatment Holidays in Patients with Erdheim-Chester Disease Receiving Vemurafenib: A Prospective Pilot Study

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Dr. Catamerò graduated in Medicine and Surgery in 2022 from Vita-Salute San Raffaele University, Milan, Italy with a thesis on Erdheim-Chester Disease and new therapeutic frontiers in the disease. During his studies, he had the opportunity to actively participate in the ECD Clinic of UniRaR at San Raffaele, where he began to develop various projects related to the disease. Subsequently, since 2022, he has become a resident at Meyer's Children Hospital IRCCS, Florence, Italy, a role he still holds, which allows him to attend different clinics, including the Histiocytosis Clinic, carrying out various projects mainly concerning therapeutic, diagnostic, and genetic strategies for ECD.

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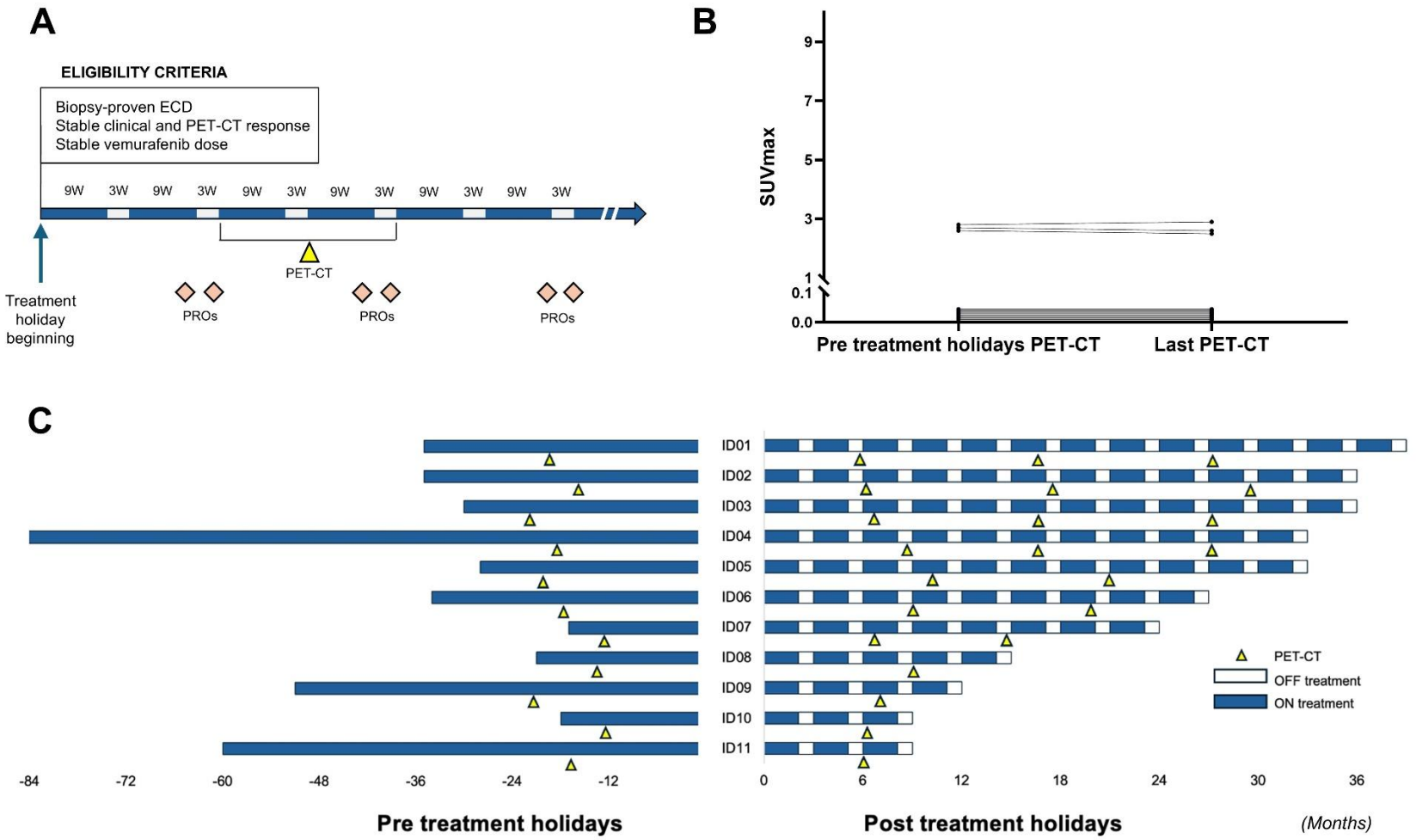
Background: Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis driven by MAPK pathway mutations. Its clinical spectrum is heterogeneous, ranging from organ-limited to diffuse, life-threatening forms. Prognosis has improved with MAPK inhibitors (BRAFi/MEKi), but their toxicity often limits their use. The LOVE study found that stopping BRAFi after metabolic response led to relapse in most cases, highlighting the need for better strategies to balance efficacy and tolerability. Proposed approaches include gradual dose reduction or alternative therapies like mTOR inhibitors. Given ECD's slow progression, we tested a vemurafenib 'treatment holiday' protocol—3-week breaks every 12 weeks—reducing dosage by 25%. We report its efficacy and safety in 11 patients recruited at the Meyer's Children Hospital, Florence, Italy.

Methods: Patients with ECD were diagnosed based on the latest consensus guidelines. All had a biopsy-proven diagnosis, received vemurafenib as a single agent (480 mg bid in eight cases and 240 mg bid in the remaining three) and started the treatment holiday protocol only after achieving sustained metabolic responses for over 6 months. Dosage remained unchanged unless toxicity or inefficacy. Disease activity was monitored through clinical, laboratory, and imaging assessments, including PET-CT at baseline, months 6–12, and thereafter annually. We also assessed quality of life (QoL), symptom burden, and drug toxicity using the FACT-G QoL questionnaire, the ECD-Symptom Scale, and the NCI-PRO-CTCAE® items. These were first administered after the second 'on' and 'off' treatment cycles, then biannually.

Results: All patients had the BRAFV600E mutation and long-bone involvement. Central nervous system and peri-renal infiltration were detected in 8 patients (73%) each. Cardiac involvement was detected in 5 patients (46%), whereas 4 (36%) had coated aorta. Other manifestations were less frequent. Before starting the treatment holiday protocol, patients had been on vemurafenib monotherapy for a median of 34 months. At the time of protocol initiation, 8 (73%) were experiencing a sustained complete metabolic response, and 3 (27%) a sustained partial metabolic response. All completed at least 3 treatment holiday cycles, with a median protocol duration of 23 months. PET-CT scans showed no disease reactivation or progression. Inflammatory markers and lab results remained stable. Patient-reported outcomes (PROs) indicated reduced toxicities without worsening ECD symptoms. Though toxicity improvement was of

borderline significance (NCI-PRO-CTCAE® scores: on-treatment 19 vs. off-treatment 10, p=0.094), 8 patients reported relief from therapy-related side effects, particularly nausea, fatigue, and photosensitivity. QoL scores (FACT-G) improved in 3 patients and remained stable in 6, while the ECD-Symptom Scale showed no significant changes.

Conclusions: This study is the first approach to reduce vemurafenib dosage—and its associated toxicity—in ECD patients while maintaining efficacy. Given the high relapse rate reported after treatment withdrawal, the ECD community has been hesitant to discontinue vemurafenib, however, periodic PET-CT evaluations confirmed sustained metabolic response with our protocol. Additionally, PROs indicated improved QoL and reduced drug toxicity. The protocol prioritized patient safety with short off-therapy periods, though longer breaks could be considered for patients in stable remission. Future research should focus on optimizing the duration and frequency of treatment holidays and identifying ideal candidate patients. In conclusion, this study provides preliminary evidence that a structured treatment holiday protocol can lower vemurafenib drug exposure without compromising efficacy.


A
ELIGIBILITY CRITERIA
Biopsy-proven ECD
Stable clinical and PET-CT response
Stable vemurafenib dose
9W 3W 9W 3W 9W 3W 9W 3W 9W 3W 9W 3W
PET-CT
Treatment holiday beginning
PROs
PROs
PROs
B
SUVmax
9
7
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3
1
0.1
0.0
Pre treatment holidays PET-CT
Last PET-CT
C
ID01
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ID11
PET-CT
OFF treatment
ON treatment
-84 -72 -60 -48 -36 -24 -12
0 6 12 18 24 30 36
Pre treatment holidays
Post treatment holidays
(Months)

5. Don't Dish Out Old Therapies: Use of Pegylated-Interferon-Alpha in a case of Erdheim-Chester Disease with congestive heart failure

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Brinda is a fourth-year undergraduate student majoring in Cancer Biology at the University of Alabama at Birmingham (UAB). She is a Histiocytosis survivor herself and is a patient ambassador for the HA. Currently, she is a research assistant for the Histiocytic Disorder Survivorship Study which is being led by Dr. Gaurav Goyal. Brinda will be graduating from UAB in May 2025 and starting medical school.

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Introduction: Erdheim-Chester disease (ECD) is a rare histiocytic disorder with designation as a hematopoietic tumor as of 2016. Recent emergent therapies targeting the BRAF-V600E and other components of the MAPK signaling pathway have shown promise in the management and treatment of ECD, leading to regulatory approvals of BRAF (vemurafenib) and MEK (cobimetinib) inhibitors. These targeted treatments have largely replaced the conventional treatment options in the frontline recommendations for the management of ECD. The role of conventional treatments is unclear in the current era.

Case Presentation: Herein, we report a case of a 55-year-old male with a long-standing history of multiple sclerosis was suspected to have ECD by the neurologist. MRI scans depicted multiple enhancing brainstem/cerebellar and frontal lobe lesions. Full body PET CT did not reveal any bony or other organ involvement. Comprehensive skin exam revealed a small skin lesion on the thigh which was biopsied and showed xanthogranulomatous infiltrate. Therefore, he was diagnosed with ECD. NGS showed NOTCH1 and NOTCH2 mutations. He was initiated on trametinib resulting in partial response, however, was stopped due to dyspnea and edema, with trans thoracic echocardiogram showing low left ventricular ejection fraction (LVEF) at 25% and left bundle branch block (LBBB). Second-line treatment included intraarterial administration of melphalan led to grade 3 ocular complications prohibiting its further use, and eventually progressive disease. Ultimately, he was started on subcutaneous pegylated interferon-alpha (PEG-IFN-α) as a third-line treatment.

Outcomes: Brain MRI after 2 months of PEG-IFN-α therapy showed improvement in the prominence of the lesion in the pons, which persisted at the 4-month mark. Clinically, the patient improved in terms of ataxia and overall fatigue.

Conclusion: Our case report highlights the role of conventional treatment like PEG-IFN-α in the management of ECD when targeted therapies are prohibitive to use due to adverse events or other reasons.

Afternoon Abstract Presentations Session 1: Data

1. Symptoms, unmet needs, and quality of life in Erdheim-Chester disease: A longitudinal registry-based analysis

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Background: Measurement of patient-reported outcomes (PROs) and health-related quality of life (HrQOL) are crucial for comprehensive, patient-centered cancer care. PROs and HrQOL have been understudied in patients with Erdheim-Chester disease (ECD), a rare cancer with protean manifestations, dense symptomatology, and frequent diagnostic delay. We sought to evaluate the longitudinal evolution of symptom burden and unmet supportive care needs in patients with ECD, and to identify associations between these PROs and HrQOL.

Methods: A registry-based cohort of patients with ECD completed a PRO battery including the Functional Assessment of Cancer Therapy-General (FACT-G) and other validated PRO measures [Erdheim-Chester Disease Symptom Scale (ECD-SS), Brief Pain Inventory (BPI), Brief Fatigue Inventory (BFI), and Supportive Care Needs Survey (SCNS)]. Descriptive statistics were used to characterize the distribution of PROs and FACT-G scores; PROs were modeled by univariable linear regression with FACT-G total score as the dependent variable at (1) registry enrollment and (2) 12-month time points. Changes in FACT-G total score (the difference between the 12-month and enrollment scores) were correlated with changes in PROs using univariable linear regression analysis.

Results: 159 patients (59% male, average age 51.2 years) with a diagnosis of ECD or mixed ECD were enrolled into the study. Average duration of diagnosed ECD was 6.5 years. 59% of patients had a BRAFV600E mutation. In 158 patients, mean total FACT-G was 70.8 at enrollment, lower than observed across multiple cancer cohorts. Functional well-being was the FACT-G domain with the lowest average scores at enrollment (15.7 out of 28) and 12 months (16.8 out of 28). Neurologic symptoms were the most frequently endorsed category on the ECD-SS at enrollment (37% of patients) and 12 months (39% of

patients). Clinically relevant pain and fatigue were both associated with decreased HrQOL at enrollment (BPI estimate: -14.83; BFI estimate: -21.25) and at 12 months (BPI estimate: -10.86; BFI estimate -16.87). Reductions in pain (both in total BPI scores and shifting from clinically relevant pain to its absence) were significantly associated with improved HrQOL (estimate for BPI total change: -1.42). Reduction in fatigue as measured by total BFI scores was also significantly associated with improvement in HrQOL (estimate for BFI total change: -1.69). Meeting previously unmet needs in any category, except sexual needs, was significantly associated with improved HrQOL. Increasing total number of unmet needs was associated with reduction in HrQOL (estimate: -0.79).

Conclusions: There is a high burden of symptomatology and unmet needs in patients living with ECD; HrQOL for these patients is substantially diminished, even when considering other patients with cancer. In our cohort, higher levels of pain and fatigue, presence of neurologic symptoms, and greater number of unmet needs were all associated with worse HrQOL. Improvement in pain, fatigue, and unmet needs was significantly associated with improvement in HrQOL. Mitigation of symptoms and addressing unmet supportive care needs represent pressing and achievable opportunities for intervention to improve HrQOL for patients with ECD.

2. Diagnostic Impact of 18F-FDG PET/MRI over PET/CT in Histiocytoses: A Prospective Comparative Study

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Dr. Pudis holds a high school diploma from Skutt Catholic (Omaha, USA) and a Medical Doctor degree from the Autonomous University of Barcelona (UAB). He completed a postgraduate degree in Emergency Medicine from Barcelona University (UB) and a Master's Degree in Diagnostic Imaging from Francisco de Vitoria University (UFV). Currently, Dr. Pudis is a Nuclear Medicine and Molecular Imaging Specialist at Bellvitge University Hospital (HUB), with a special interest in patients with systemic histiocytosis. His department is a pioneer in Spain in applying PET/MRI technology in routine clinical practice.

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Background: Histiocytoses, including Erdheim-Chester Disease (ECD), Langerhans Cell Histiocytosis (LCH), and Rosai-Dorfman Disease (RDD), are rare multisystem disorders characterized by monocyte-derived cell infiltration. Accurate staging is essential for diagnosis, biopsy guidance, treatment planning, and monitoring. While 18F-FDG PET/CT is commonly used, 18F-FDG PET/MRI, with superior soft-tissue contrast, may offer improved lesion detection and characterization, though its role remains uncertain. This study aimed to compare the diagnostic performance of 18F-FDG PET/MRI and PET/CT in patients with systemic histiocytosis.

Methods: This prospective study, conducted at Bellvitge University Hospital (2022-2024), included patients with systemic histiocytosis (ECD, LCH, RDD, and mixed histiocytosis) who underwent sequential whole-body PET/CT and PET/MRI after a single 18F-FDG injection. A multidisciplinary team of nuclear medicine physicians and radiologists assessed lesion detection, anatomical definition, metabolic uptake, and disease extent, correlating findings with clinical presentation, laboratory markers, histopathology, and follow-up imaging. The primary focus was comparing the performance of PET/MRI and PET/CT.

Results: 15 patients were enrolled (mean age 58 years old [range 21–81], 8 females), including 9 with ECD, 2 with LCH, 2 with RDD, 2 with mixed histiocytosis. Concordance between PET/CT and PET/MRI was high at 93%: 12 patients demonstrated concordant pathological findings, while 2 showed no pathological findings on either modality. 1 patient showed a discordant result: PET/MRI detected an additional brainstem lesion not seen on PET/CT, influencing clinical management. Across the cohort, a total of 38 lesion regions were identified: brain (2), lymph nodes (6), cardiac (1), lung/pleural (2), renal/perirenal (4), bone marrow/bone (10), aortic/periaortic (2), retroperitoneal (1), articular (2), thyroid (2), skin/subcutaneous (2), mammary gland (1), pancreas (1), paranasal sinus (1), and orbital (1). Among these, 35 lesions (92%) were attributed to histiocytosis, while 3 were considered incidental findings. 68% of the histiocytosis-related lesions correlated with clinical manifestations. PET/MRI provided superior lesion and structural definition in 60% of cases, especially in complex areas like the brain, heart, kidneys, aorta, and bone. This improved visualization enabled better assessment of disease involvement. Additionally, PET/MRI enhanced lesion characterization in 33% of cases, particularly in the brain and heart, aiding treatment planning. It also detected additional lesions in 33% of cases, notably in the brain, lymph nodes, and bone marrow, facilitating a more comprehensive evaluation and guiding biopsy

decisions. PET/MRI showed higher metabolic uptake and greater lesion extension in 73% of cases, suggesting superior sensitivity in detecting active disease, likely due to better soft-tissue contrast and detection sensitivity. However, PET/CT was superior for characterizing certain lung lesions.

Conclusions: Our study demonstrates that 18F-FDG PET/MRI offers significant advantages over PET/CT in evaluating systemic histiocytosis, with better soft-tissue resolution, improved lesion delineation, and greater sensitivity in detecting disease burden. These features not only increase diagnostic confidence but also may influence clinical decision-making and treatment planning. Additionally, PET/MRI significantly reduces radiation exposure, making it particularly beneficial for patients requiring repeated imaging. These findings support integrating PET/MRI into histiocytosis diagnostic protocols, with further research needed to confirm its clinical utility.

3. Natural history of Erdheim-Chester disease. A preliminary analysis on 1044 patients within the ECDGA network

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Dr. Francesco Pegoraro, is a clinical researcher and pediatrician specializing in ECD and other histiocytic disorders. During his residency, he joined the Histiocytosis clinic, caring for adults and children affected by ECD and other histiocytic disorders, and he actively participated in several scientific projects focused on histiocytosis and other hematologic conditions. Currently, Dr. Pegoraro is a part-time MD at the Department of Hematology/Oncology of the Meyer Children's Hospital (Florence). Additionally, he is pursuing a Ph.D. at the University of Florence, as a second-year student. His doctoral research is dedicated to elucidating the genetic predisposition underlying histiocytosis, with the aim of expanding our understanding of these complex diseases.

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Background: Erdheim Chester disease (ECD) is a rare histiocytosis of the L-group driven by mutations in genes of the MAPK pathway such as BRAFV600E. The clinical presentation can be highly heterogeneous, and there is insufficient data on its natural history in large cohorts. Moreover, the impact of somatic

mutations on prognosis is unknown. Herein, we investigated the clinical presentation and outcome of a very large international cohort of patients with ECD.

Methods: We retrospectively investigated patients with ECD followed at 12 referral centers from Europe, the US, and Brazil. We included patients with ECD diagnosed between 1990 to 2024 who had available clinical and follow-up data (minimal follow-up duration of 6 months). In this preliminary analysis, we analyzed the clinical presentation, treatment, and survival. The study was conceived and conducted within the ECD Global Alliance network.

Results: A total of 1044 patients with ECD were included in the study. Their median age at diagnosis was 57 (IQR 46-66) years, with a median age of 55 (IQR 43-65) years at the first ECD manifestation. Bone pain (20%), renal abnormalities (18%), diabetes insipidus (11%), central nervous system (CNS) symptoms (9%) and skin lesions (9%) were the most frequently reported manifestations. The M:F ratio was 1.8. The median number of involved sites was 4 (IQR 3-6), and they more frequently included the long bones (n=768, 74%), the retroperitoneum, (n=605, 58%), the periaortic space (n=449, 43%), the CNS (n=368, 35%), the facial/orbit area (n=347, 33%), the heart (n=334, 32%), the hypothalamic/pituitary axis (n=277, 27%), the skin (n=274, 26%), and the lungs (n=242, 23%). One hundred and forty-one patients (14%) had mixed histiocytosis (114 ECD+Langerhans cell histiocytosis, 11%, and 27 ECD+Rosai-Dorfman-Destombes disease, 3%). The BRAFV600E mutation was found in 572 of 955 tested patients (60%), and MAP2K1 in 86 (9%). First-line treatment mostly included interferon-alpha (n=342, 33%) and targeted therapies (BRAF and MEK inhibitors; n=314, 30%), while chemotherapy (n=104, 10%) and immune-mediated drugs (n=76, 7%) were less frequent. Second- and third-line treatments mostly consisted of targeted therapies (55% and 63%, respectively). After a median follow-up of 51 months (IQR 20-89), 222 (21%) patients died; causes of death were related to ECD in almost half of the patients (n=101). The 5-year probability of survival in the whole cohort was 85%, and it was significantly reduced in patients harboring the BRAFV600E mutation (log-rank p=0.047).

Conclusions: Despite the introduction of effective treatments in the last decade, ECD remains burdened by significant mortality rates. The BRAFV600E mutation is associated with a lower probability of survival, regardless of treatment. Data on additional risk factors will be further analyzed.

4. Erdheim-Chester Disease: Evolving Insights and Improved Survival Over Time

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Mia Poleksic, M.D. is a first-year Internal Medicine resident at Mayo Clinic in Rochester, MN. She obtained her undergraduate degree in Biomedical Engineering at the University of Iowa and subsequently graduated from Roy J. and Lucille A. Carver College of Medicine in Iowa City, Iowa in 2024. Her research interests include histiocytic malignancies, cancer survivorship, and global health. Following residency, she hopes to pursue a fellowship in Hematology/Oncology.

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Background: Erdheim-Chester Disease (ECD) is a rare, incurable histiocytic neoplasm. Since its recognition in 1930, our understanding of ECD's pathophysiology has evolved. The identification of its clonal nature after 2015 established ECD as a cancer, prompting treatment advances. Targeted therapies show promising responses, but changes in ECD mortality over time are not extensively documented.

Methods: A retrospective cohort analyzed adults with ECD seen at Mayo Clinic MN, AZ, and FL between 2007-2024. Clinical and prognostic data were abstracted. Overall survival was estimated using the Kaplan-Meier method and compared to expected survival using US population data, matching age at diagnosis (by calendar year), date of diagnosis, and sex. Risk of death was compared by date of diagnosis (pre- and post- 2015) using Cox proportional hazards analysis. Statistical analysis was performed with R software.

Results: A total of 143 ECD patients were included (median age 59 years [range 19-82], 65% male). 47 patients were diagnosed between 1961-2014 and 96 between 2015-2024. Median follow-up for the entire cohort was 3.9 years (95% CI: 3.2-4.5). The 5-year overall survival rate was 81% (95% CI: 74-89). Compared to the general population, patients with ECD had an increase in mortality, with 25 deaths compared to an expected 10.4, a standardized mortality ratio (SMR) of 2.39 (95% CI: 1.62-3.54, $p<0.001$). Death was attributable to ECD in 10 patients (67%), secondary malignancy in 1 (7%), and unrelated causes in 4 (27%), with cause of death unknown in 10. Among deaths, 9 (36%) were treated with targeted therapy, 8 (32%) with chemotherapy, and 1 (4%) received both. 1 (4%) patient received steroids and 6 (24%) received no disease-directed therapy. For 47 patients diagnosed pre-2015, 14 deaths occurred during the follow-up, significantly higher than the expected 4.6 deaths based on U.S. population data (SMR of 3.06 [95% CI: 1.81-5.16, $p<0.001$]). Among those diagnosed between 2015 and 2024, 11 deaths occurred, compared to expected 5.9 (SMR of 1.87 [95% CI: 1.04-3.39]). In an age- and sex-adjusted Cox proportional hazards model, diagnosis after 2015 yielded a hazard ratio of 0.44 (95% CI: 0.19-1.03, $p=0.057$).

Conclusions: Advancements in ECD appear to have lowered mortality rates, especially among patients diagnosed after 2015. The age-adjusted mortality of ECD patients, though still higher than the general population, now aligns more closely. This demonstrates the potential evolution of ECD into a more manageable chronic disease, underscoring the importance of preventive care and cancer survivorship strategies.

Diagnosis Date	5 Year Kaplan-Meier Survival Estimates		Total Deaths During Follow-Up			
	Observed (95% CI)	Expected	Observed	Expected	SMR (95% CI)	p-value
Overall	81.3% (73.9, 89.4)	93.1%	25	10.4	2.39 (1.62, 3.54)	<0.001
1961-2014	72.8% (58.9, 90.1)	94.7%	14	4.6	3.06 (1.81, 5.16)	<0.001
2015-2024	85.4% (77.2, 94.4)	92.3%	11	5.9	1.87 (1.04, 3.39)	0.034

5. Real-World Efficacy and Toxicity of MEK Inhibitors in Histiocytic Neoplasms

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Dr. Goyal was born and raised in a small town in India. He obtained his medical school diploma from Smt. N.H.L. Municipal Medical College in Ahmedabad, India, followed by an Internal Medicine Residency from Creighton University Medical Center, Omaha, Nebraska, and a Hematology-Oncology Fellowship from the Mayo Clinic, Rochester, Minnesota.

At the Mayo Clinic, he developed a unique focus on histiocytic disorders, including Erdheim-Chester disease, Langerhans cell histiocytosis, and Rosai-Dorfman disease. He conducted multiple studies describing the epidemiology, treatments, and outcomes of patients with histiocytosis and helped establish the first-of-its-kind multidisciplinary Histiocytosis Working Group to improve the practice, education, and research for individuals with histiocytosis. He has led national and international guidelines on the diagnosis and management of these rare disease entities. He was recruited to join the Hematology-Oncology division at the University of Alabama at Birmingham as an Assistant Professor in 2019, where he established a histiocytosis program, including an ECD care center.

At UAB, Dr. Goyal continues to conduct multiple research studies in histiocytosis. He launched the Histiocytic Disorder Survivor Study at UAB in partnership with the ECDGA in 2023 to help understand the long-term health problems (health conditions, second cancers, mental health problems, and quality of life) and mortality among individuals with ECD and other histiocytic disorders.

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Background: The introduction of MEK inhibitors (MEKi) has revolutionized the management of histiocytic neoplasms (HN), but associated with dose reduction, drug withholding, or discontinuation. The strategies for management of these adverse events (AEs) have not been studied. In this real-world study, we aim to describe the efficacy and tolerability of MEKi therapy.

Methods: This retrospective study included patients (pts) with HN who received cobimetinib or trametinib. AEs were graded using the common terminology criteria for adverse events (CTCAE v5.0). Kaplan-Meier method was used to analyze event-free survival (EFS), progression-free survival (PFS), and overall survival (OS). The event was defined as time to drug discontinuation, disease progression, or death.

Results: This study included total 31pts, diagnosed with Langerhans Cell Histiocytosis (LCH) (n=5,16.1%), Rosai Dorfman Disease (RDD) (17,54.8%), Erdheim Chester disease (ECD) (6,19.4%], mixed LCH/ECD (1,3.2%), xanthogranuloma family of HN (1,3.2%) and indeterminate cell histiocytosis (1,3.2%). Four pts were switched from one to another MEKi so total instances were counted as 35. The median age at the start of MEKi was 50.5 years (range 19-76). Among the cohort, 7 (22.6%) harbored BRAF V600E mutation, 20(64.5%) were BRAF-wild type, 7(22.6%) had MAP2K mutation, 5 (16.1%) had KRAS and 2(6.5%) had NRAS mutation. Echocardiogram and retinal examination were performed in 22(70.9%) and 14(45.1%) pts at baseline, and in all pts subsequently. The most prescribed MEKi was cobimetinib (87.1%) followed by trametinib (12.9%). The most common starting doses were 40 mg for cobimetinib and 1 mg for trametinib. Any grade AEs were noted in 91.4% of pts, with diarrhea (18,51.4%), acneiform rash (12,34.2%), fatigue (6,17.1%), and other rash (5,14.2%) being the most common AEs. Grade ≥3 AE was

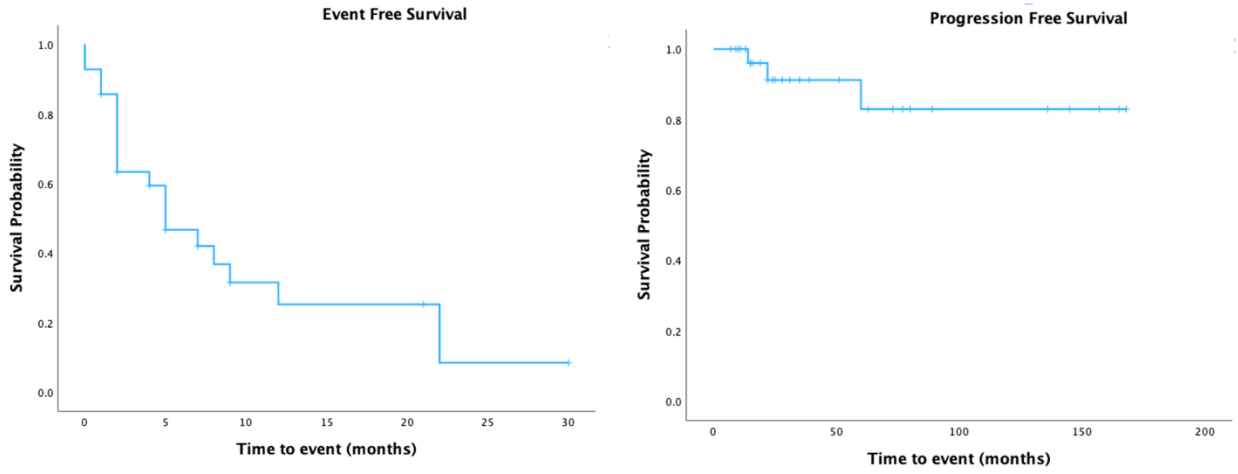
noted in 1 (2.8%) patient, was photosensitivity with cobimetinib. Other notable AEs included retinal change (2,5.7%), reduction in left ventricular ejection fraction (EF) (2,5.7%), hypertension (1,2.8%), constipation (1,2.8%), and hypertriglyceridemia (1,2.8%). Grade 1 retinal change were noted in retinal examination without any symptoms and were followed up with serial examination. Diarrhea was primarily managed with supportive care with antidiarrheal agents in 55.5% of cases, however 5 (14.3%) required dose reduction and 2 (5.7%) required drug discontinuation. The acneiform rash was managed by topical benzoyl peroxidase for grade 1 rash and minocycline or doxycycline for grade 2 rash allowing pts to stay on treatment. Reduction in EF was only seen with trametinib that required permanent discontinuation. Dose reduction was required in 31.4% of cases due to AEs such as diarrhea, vomiting, fatigue, photosensitivity, hypertension. Drug discontinuation occurred in 42.9% of pts, most commonly due to AEs (66.6%) such as diarrhea, fatigue and reduction in LVEF, headache and transaminitis, followed by lack of response (20%), insurance-related issues (6.7%) and drug holidays (6.7%). Diarrhea was the leading cause of dose reduction or discontinuation, followed by fatigue and leg edema. Among 27 pts with available response data, the overall response rate (ORR) was 81.5%, with 8(29.6%) achieving complete responses and 14 (51.8%) achieving partial responses. The median EFS was 22 months (95% CI: 14.56-29.44). Median PFS and OS were not reached. There was one death in the cohort of a ECD patient.

Conclusions: Our real-world study demonstrates that MEKi are highly efficacious but are associated with AEs requiring dose reduction and discontinuation. These findings emphasize the need for AE management strategies to optimize treatment adherence and improve long-term outcomes.

Table 1: Any grade and grade ≥3 adverse events with cobimetinib (total 28 instances) and trametinib (total 8 instances)

Adverse Events	Cobimetinib (Grade 1/2) N (%)	Cobimetinib (Grade ≥3) N (%)	Trametinib (Grade 1/2) N (%)	Trametinib (Grade ≥3) N (%)
Gastrointestinal				
Nausea/Vomiting	4 (14.3)	-	-	-
Diarrhea	14 (50.0)	-	4(50.0)	-
Constipation	1 (3.5)	-	-	-
Dermatologic				
Acneiform rash	10(35.7)	-	2(25.0)	-
Other rash	4(11.4)	-	1(12.5)	-
Photosensitivity	-	1(3.5)	-	-
Cardiovascular				
Reduction in Ejection fraction	-	-	2(25.0)	-
Hypertension	1 (3.5)	-	-	-
Metabolic				
Hypertriglyceridemia	-	-	1(12.5)	-
Neurologic				
Headache	1 (3.5)	-	-	-
Ophthalmologic				
Retinal change	2 (7.1)	-	--	-
Infection				
Pneumonia	-	-	1(12.5)	-
General				
Fatigue	4(14.3)	-	2(12.5)	-
Leg Edema	2(7.1)	-	2(12.5)	-

Figure1: Event Free Survival and Progression Free survival with MEKi



Afternoon Abstract Presentations Session 2: Biology

1. MAPK-kinase mutations and aortic lesions are associated with the distribution of circulating monocytes in histiocytosis.

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Jerome Razanamahery graduated in internal medicine and immunology in 2017. He is a physician in the internal medicine department of Dijon University Hospital. He is particularly interested in immunology and oncology. During his residency at Pitié-Salpétrière Hospital, he researched histiocytic disorders, especially ECD and RDD, with Professor Haroche. He led an internal multicentric project with Eli Diamond, Gaurav Goyal, Jean-Francois Emile, and Julien Haroche, describing the overlapping forms between ECD and RDD in adult patients. His current research focuses on monocyte disturbance in histiocytic disorders and the significance of their modification in the disease's course.

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Background: Histiocytosis represent a spectrum of rare myeloid neoplasms characterized by the proliferation of CD68+ histiocytes within organs; in which monocyte/macrophage system play a pivotal role. To characterize the impact of the clonal environment, the inflammatory syndrome, and vascular lesions on the distribution of monocyte subsets in histiocytosis, we compared this monocyte distribution in adult histiocytosis, giant cell arteritis (GCA), a vasculitis with an inflammatory pattern and frequent aortic lesions, and healthy donors (HD).

Methods: Peripheral blood samples were obtained from adult patients with histiocytosis (n=31 including 9 with aortic lesions), GCA before steroid initiation (n=21 including 7 with aortic lesions), and HD (n=21).

Results: Compared to GCA patients, patients with histiocytosis have a decrease in the intermediate subset (5.8% [4-8] vs 7.8% [5.8-16]]; p=0.04). Given the inflammatory nature of intermediate monocytes, these findings correlate with CRP levels analysis (4 mg/L [3.7-11.5] vs. 75 [46-99]; p<0.0001). To evaluate the impact of clonal environment, we have then analyzed patients according to their mutational status. Patients with MAP-kinase gene mutations had an increase in classical monocytes compared to GCA and HD (94% [89.5-96] vs 86% [78.9-91.9] and vs 85% [77-89]; p=0.02 and p=0.007, respectively), associated with a decrease in both intermediate monocytes (3.5% [2.25-4.75] vs 7.8% [5.8-16] with GCA and vs 6.6% [4.4-13.3] with HD; p=0.0017 and p=0.01, respectively), and in non-classical monocytes (2% [1-4.6] vs 6.1% [4.3-10] for HD; p=0.002). These pattern is mostly represent in BRAFV600E patients. Histiocytosis patients with aortic lesions had an increase in classical monocytes (92% [87–96] vs. 87% [82–90]; p=0.04) and a decrease in non-classical monocytes compared with those without aortic lesions (% [1-3.6] vs. 5.5% [2.6–9.2]; p=0.012) ; while no differences were observed in GCA patients. Histiocytosis patients with MAP-kinases mutations and aortic lesions had an increase in classical monocytes compared to GCA without aortic lesions (96% [93-96,5] vs 84% [68-89] p=0.072) and a decrease in intermediate monocytes

compared to GCA without aortic lesions (3% [2.5-4.5] vs 9,8%[6-15]; p=0.0042) These differences were not explained by a difference in CRP levels Finally, multivariate linear regression analysis revealed an association between aortic lesions and ECD (ß coefficient: 2.813; p=0.0066) and with CRP levels (ß coefficient: 2.885; p=0.0039).

Conclusions: In conclusion, MAP-kinase pathway gene mutations, mainly BRAFv600E, influence monocyte distribution in histiocytosis, leading to a distinct distribution pattern associated with a low-inflammatory state. Meanwhile, aortic lesions are associated with ECD.

2. Deciphering ALK-positive histiocytosis and mimickers using single cell RNA-sequencing

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Abdou Malik DA SILVA is presently a postdoctoral researcher in the research unit EA4340-BECCOH at the University of Versailles SQY, University Paris-Saclay. He previously completed a PhD in molecular parasitology in 2021 at the University of Bourgogne-Franche-Comté (France) and joined Prof. Jean-François Emile's lab in October 2022. His research focuses on understanding the molecular and cellular mechanisms underlying tumorigenesis, with a particular interest in oncogenic mutations and targeted therapies. He employs advanced bioinformatics, single-cell RNA sequencing, and high-throughput screening approaches to explore gene expression dynamics and disease progression.

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Background: ALK-positive histiocytosis is included as a new entity in the last WHO classification, but diagnosis can be difficult. Indeed, we shown that some tumors very rich in histiocytes and harboring a fusion of ALK are not ALK+ histiocytosis (Kemps Blood 2022). The majority of ALK-positive histiocytosis harbor the KIF5B::ALK fusion, but some other genes can be the ALK partners. Surprisingly, all the published cases of ALK+ histiocytosis harboring EML4::ALK fusion (n=7) are single lung nodules.

Methods: Inclusion criteria of patients: 1) case referred as ALK+ histiocytosis, 2) detection of a fusion of ALK by RNA sequencing, 3) Diagnosis of histiocytosis excluded by central review, despite abundant histiocyte infiltration. Among the 34 patients with criteria 1 & 2, three had a unique lung nodule with EML4::ALK fusion. Two of these patients (#Nr1 and #Nr2), and 2 control patients with typical ALK+ histiocytosis harboring KIF5B::ALK fusion (Nr3 & Nr4) were analyzed by single cell (sc) RNA-sequencing on nuclei extracted from FFPE fixed samples. Gene expression library was prepared using the Chromium Next GEM Fixed RNA kit (10x Genomics) targeting 10,000 cells/sample and sequenced on NovaSeq 6000 SP flow cell (Illumina) with read format configured as 28, 10, 10 and 90 bp for read1, i7-index, i5-index and for read 2 respectively. Sequencing reads were de-multiplexed with cellranger mkfastq and aligned to human genome GRCh38 using the cell Ranger software v7.1.0 (10x Genomics). Reads were processed with Seurat R package version 5.2.1. Cells with 2,500 genes, and >10% mitochondria genes were removed. All raw datasets and ALK+ filtered samples were log-normalized and the top 2,000 highly variables genes were used to perform the principal component analysis (PCA). The top 30 principal component from the PCA were used to perform Uniform Manifold Approximation and Projection (UMAP). The Seurat functions FindClusters (resolution = 0.3) and FindAllMarkers were used to identify clusters and cluster markers respectively. Cell types were manually assigned, based on marker expression (at significant adj. $p < 0.0001$) in Human Lung Cell Atlas database by using the ToppFun gene set tool.

Results: Patient Nr1 was a 19 years-old female with a single lung nodule of 70 mm. Nr2 was a 63 years old female with a subglottic tracheal tumor, 10 mm in diameter, bell-shaped, with a very fine pedicle base. Central pathologic review, performed before sc transcriptomic, classified these tumors as

“histiocyte-rich ALK-rearranged tumor” (Nr1), and inflammatory myofibroblastic tumors (IMT)(Nr2). Quality of data was excellent (Q30 value of seq: 88%), with at least 5,900 cells analyzed for each case, and a mean of 18,082 genes detected per sample. In the UMAP, Nr3 and Nr4 showed a total overlap, away from Nr1 and Nr2 (Figure 1). Unsupervised clustering of ALK positive cells from the 4 tumors revealed 8 clusters with one principal cluster per sample (Figure 3A). As expected ALK positive cells of both KIF5B::ALK patients (Nr3 & Nr4) clustered as macrophage/dendritic cell (clusters 0 and 2) (Figure 3B). By contrast, ALK positive cells of Nr1 and Nr2 clustered as adventitial cell/myofibroblasts (clusters 1 and 4) (figure 3B). Discussion: Although only 20% of IMT present as unique lung nodules, 75% of the published IMT with EML4::ALK (n=20) are localized to the lung.

Conclusions: Our data 1) confirm that diagnosis of ALK+ histiocytosis can be very difficult, 2) shows that single cell transcriptomic allows to classify some histiocyte rich tumors, and 3) suggest that most of the histiocyte-rich tumors with EML4::ALK (diagnosed as either ALK+ histiocytosis or IMT or histiocyte-rich ALK-rearranged tumor) could correspond to a unique entity derived from lung adventitial cells.

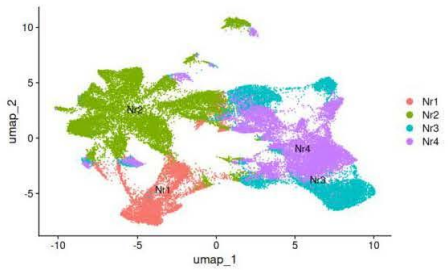


Figure 1. UMAP* plot of the 4 tumors

*Uniform Manifold Approximation and Projection

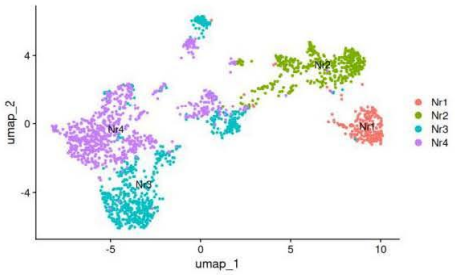
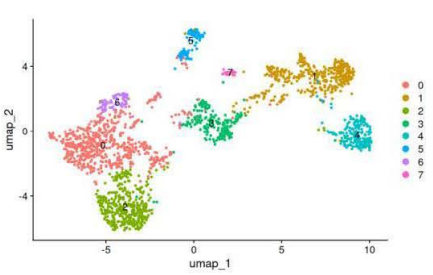


Figure 2. UMAP of the filtered ALK+ cells from the 4 tumors

A



B

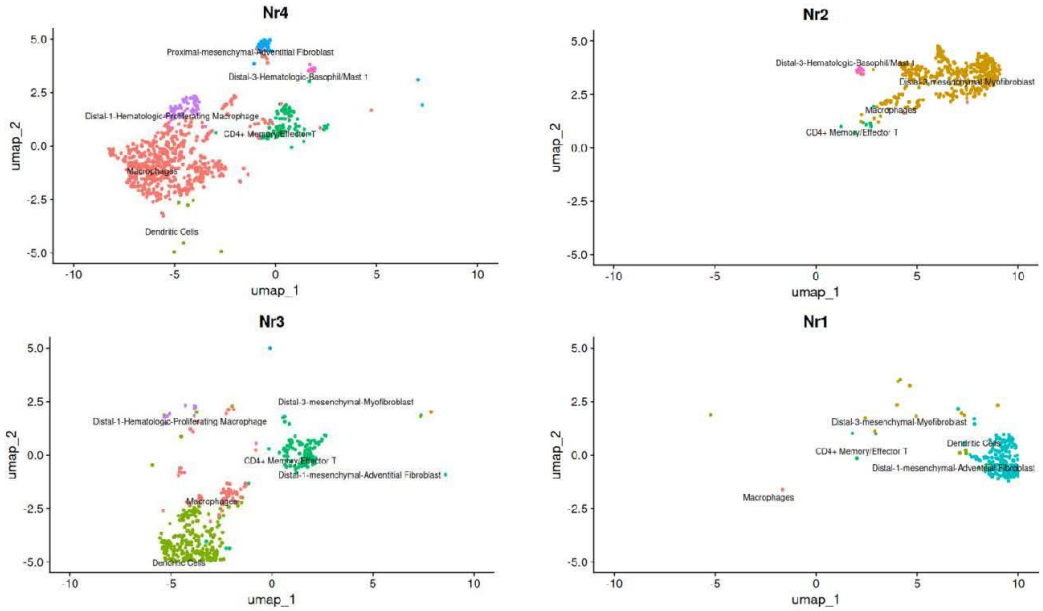


Figure 3. Unsupervised clustering (resolution = 0.3) of the ALK+ cells of the 4 tumors.

A) clusters identified from the 4 ALK+ filtered samples;

B) Cell types identified within each of the 4 tumors based on cluster markers

3. The clonal origin and evolution of high-risk multisystem histiocytosis in adults

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The authors are indebted to ECDGA and the Leukaemia and Lymphoma Society for funding. Matthew Collin is Professor of Haematology at Newcastle University and Newcastle Upon Tyne Hospitals. He obtained his PhD and Medical Degree in 1995 from Oxford University. His research focuses on the in vivo analysis of human monocytes, macrophages and dendritic cells, including studies genetic control of myeloid cell development, histiocytic disorders (Langerhans cell histiocytosis and Erdheim-Chester Disease) and graft versus host disease. His clinical expertise is in bone marrow transplantation and histiocytic disorders. He is currently a Wellcome Trust Investigator and receives funding from MRC, CRUK, the Histiocytosis Association and ECDGA and co-leads the MRC Rare Disease HistioNode.

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Background: Langerhans cell histiocytosis (LCH) and Erdheim Chester disease (ECD) are myeloid neoplasms driven by activating somatic mutation in RAS-MAPK genes including CSF1R, NRAS, KRAS, BRAF and MAP2K1. Aberrant dendritic cells and macrophages accumulate in a wide range of tissues causing inflammation, tissue destruction and fibrosis. These features obscured the true etiology of ECD for many decades and continue to thwart timely diagnosis in many patients. While single driver mutations in MAPK genes are often observed in children with LCH, adults with histiocytosis often have additional drivers associated with more common myeloid neoplasms such as myelodysplasia or myeloproliferative neoplasms. Defining the timing, sequence and landscape of clonal myeloid driver mutations in relation to RAS-MAPK pathway activation is a key step to developing precision medicine for patients and for understanding the pathogenesis of histiocytosis within the panoply of myeloid neoplasms.

Methods: CD34+ hemopoietic progenitors were isolated from two adults (aged 63 and 77) with multisystem LCH/ECD. Both patients presented with high-risk features including bone, cardiovascular and central nervous system involvement. Whole genome sequencing at 8-15x coverage was performed on >120 individual single-cell derived colonies expanded from CD34+ progenitors in each patient. Genome-wide single nucleotide variants and indels were called using CaVEMan and Pindel. ASCAT was used for copy number analysis. Somatic mutations were used to reconstruct phylogenetic trees to study clonal architecture, disease trajectory and timing, and mutational profiles.

Results: Phylogenetic trees of hemopoietic cells showed a remarkably similar pattern in both individuals. We observed parallel expansions of multiple independent clades harbouring mutant NRAS, KRAS and BRAFV600E, demonstrating strong convergent evolution of RAS-MAPK gene mutations. These mutations were acquired around a decade prior to clinical presentation. In both cases, MAPK gene mutation occurred in cells harbouring biallelic or hemizygous TET2 mutations thought to have arisen in the first half of life. Mutation signature analysis suggested rapid clonal outgrowth preceding clinical presentation.

Conclusions: In these patients, life-threatening histiocytosis caused by RAS-MAPK mutations arose within biallelic/hemizygous TET2 clonal hemopoiesis. This sequence of events is in stark contrast to children with multisystem LCH who appear to have only single gene mutations. It remains unknown if cell intrinsic or extrinsic forces drove the common secondary clonal evolutionary patterns following biallelic

TET2 mutation. Mutation of TET2 intrinsically links histiocytosis with much more common myeloid neoplasms including myelodsysplasia, CMML and MPN, suggesting that at least in some patients, the molecular evolution of histiocytosis resembles an unusual form of MPN, which also evolves to clinical disease over many decades.

Poster Presentations

1. Anti-IL-6 Therapy in Rare Histiocytic Disorders: Erdheim-Chester and Rosai-Dorfman Disease

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Dr. Laura Eurelings is a resident in Internal Medicine at Erasmus MC, pursuing a unique dual specialization in immunology and hematology. She completed her PhD in immunology and is now conducting postdoctoral research in the field of hematology, working at the intersection of both fields. She currently works under Dr. Jan A. M. van Laar on histiocytic disorders at Erasmus MC, which is part of the ECD Referral Care Center network. In 2024, she received the Abstract Achievement Award at the 66th ASH Annual Meeting. Through a personalized fellowship, she is training to become both a clinical immunologist and a medical hematologist. Her research is dedicated to unraveling the intricate mechanisms and the complex interplay of the immune system within hematological disorders.

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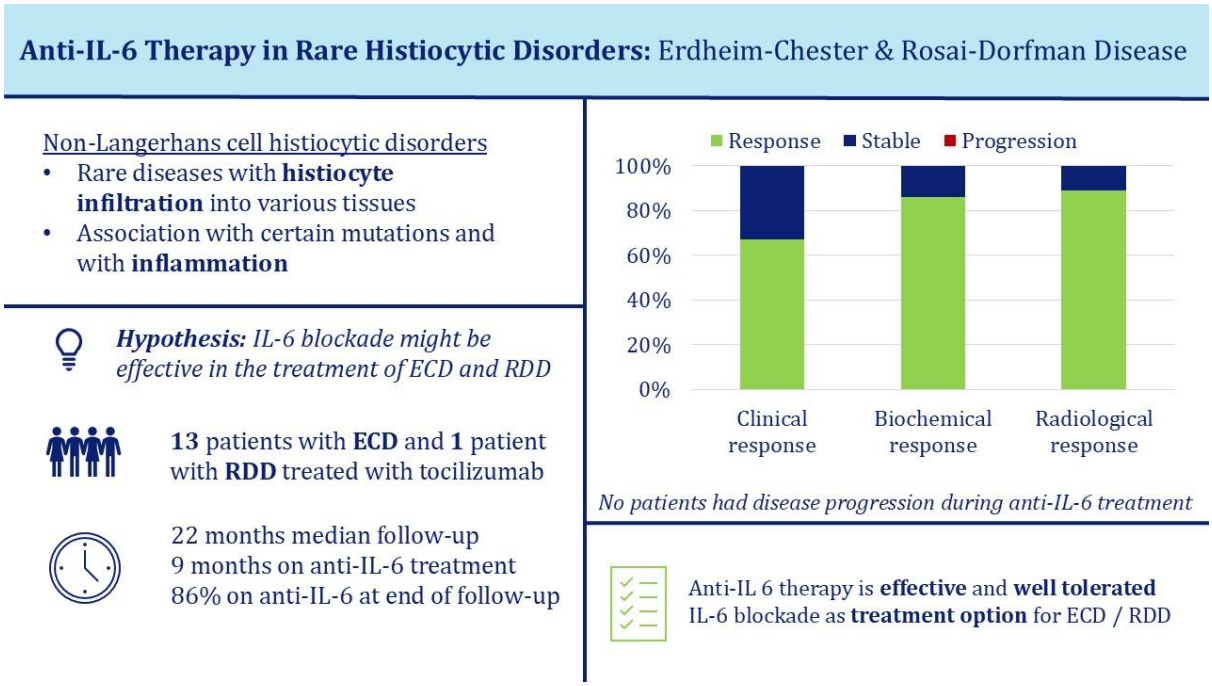
Background: Anti-IL-6 Therapy in Rare Histiocytic Disorders: Erdheim-Chester and Rosai-Dorfman Disease, L. E. M. Eurelings, J.A.M. van Laar Background: Non-Langerhans cell histiocytic disorders are rare conditions characterized by infiltration of histiocytes into tissues. Erdheim-Chester disease (ECD) often affects the long bones, skin, and large vessels, while Rosai-Dorfman disease (RDD) typically presents with lymphadenopathy and involvement of the skin and soft tissues. Therapeutic options for ECD include pegylated interferon alfa, targeted BRAF or MEK inhibitors, or therapies targeting inflammation, such as IFN or anakinra. In RDD, therapeutic options include surgical resection , radiation of lesions, or systemic therapies such as corticosteroids, sirolimus, cladribine or MTX. . Both disorders are associated with chronic systemic inflammation, and elevated IL-6 levels in ECD suggest that IL-6 blockade could be a promising therapeutic approach. This study aims to evaluate the effectiveness of anti-IL-6 therapy in ECD and RDD patients.

Methods: A retrospective chart review of ECD and RDD patients treated with anti-IL-6 therapy at the Erasmus Medical Centre Rotterdam between January 2021 and February 2025 was performed. Inclusion criteria included a diagnosis of ECD and/or RDD confirmed by clinical and histopathological findings. Clinical, biochemical, and radiological responses were assessed.

Results: Thirteen ECD patients and one RDD patient were treated with tocilizumab. Median age at diagnosis was 58 years, and the majority (64%) were female. Multisystem involvement was present in 93% of patients. The majority of patients (67%) showed a clinical response, while all other patients (33%) had stable disease. No patients showed disease progression while on tocilizumab treatment. Biochemical response, defined as a decrease in CRP, was observed in 6 out of the 7 patients with elevated CRP at the start of tocilizumab treatment. Radiological response, defined as a significant decrease in lesions on CT, PET-CT, or MRI, was noted in 8 of 9 patients assessed. The median follow-up duration of ECD and RDD patients was 22 months, with a median of 9 months on anti-IL-6 treatment. Previous therapies included corticosteroids, BRAF inhibitors, TNF inhibitors, and IL-1 receptor antagonists. Tocilizumab was well-tolerated in most patients, with only two serious infections reported: one soft-tissue infection and one submandibular abscess. Both patients recovered fully and resumed tocilizumab treatment. At the end of follow-up, 86% of patients remained on tocilizumab. Two patients were no longer on tocilizumab. In one patient, tocilizumab was switched to anti IL-1 therapy due to

activity of the comorbid psoriatic arthritis. The other patient had stopped 6 weeks after starting tocilizumab due to joint pains and muscle cramps.

Conclusions: This retrospective study supports the potential effectiveness of tocilizumab in patients with ECD and RDD, with the majority showing clinical, biochemical, and radiological improvements. Our findings support the use of IL-6 blockade as an effective therapeutic strategy for rare histiocytic disorders, especially for patients who are mutation-negative or ineligible for BRAF inhibitors.



2. Global Utilization of the National Comprehensive Cancer Network Clinical Practice Guidelines for Histiocytic Neoplasms

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Dr. Janda is a first-year Internal Medicine resident at Mayo Clinic. Originally from Ohio, he earned his undergraduate degree in biochemistry from Ohio State before attending Yale for medical school. He has research experience in structural biology, computational biology, and regulatory science. Some of his prior work has focused on deep learning for medical imaging, multi-omics analysis in immune-mediated diseases, and the utilization of real-world evidence. He is pursuing a career in hematology/oncology and is currently working on projects related to rare histiocytic diseases. Outside of work, he enjoys sports, outdoor activities, and spending time with his wife, an orthopedic surgery resident at Mayo, and their dog.

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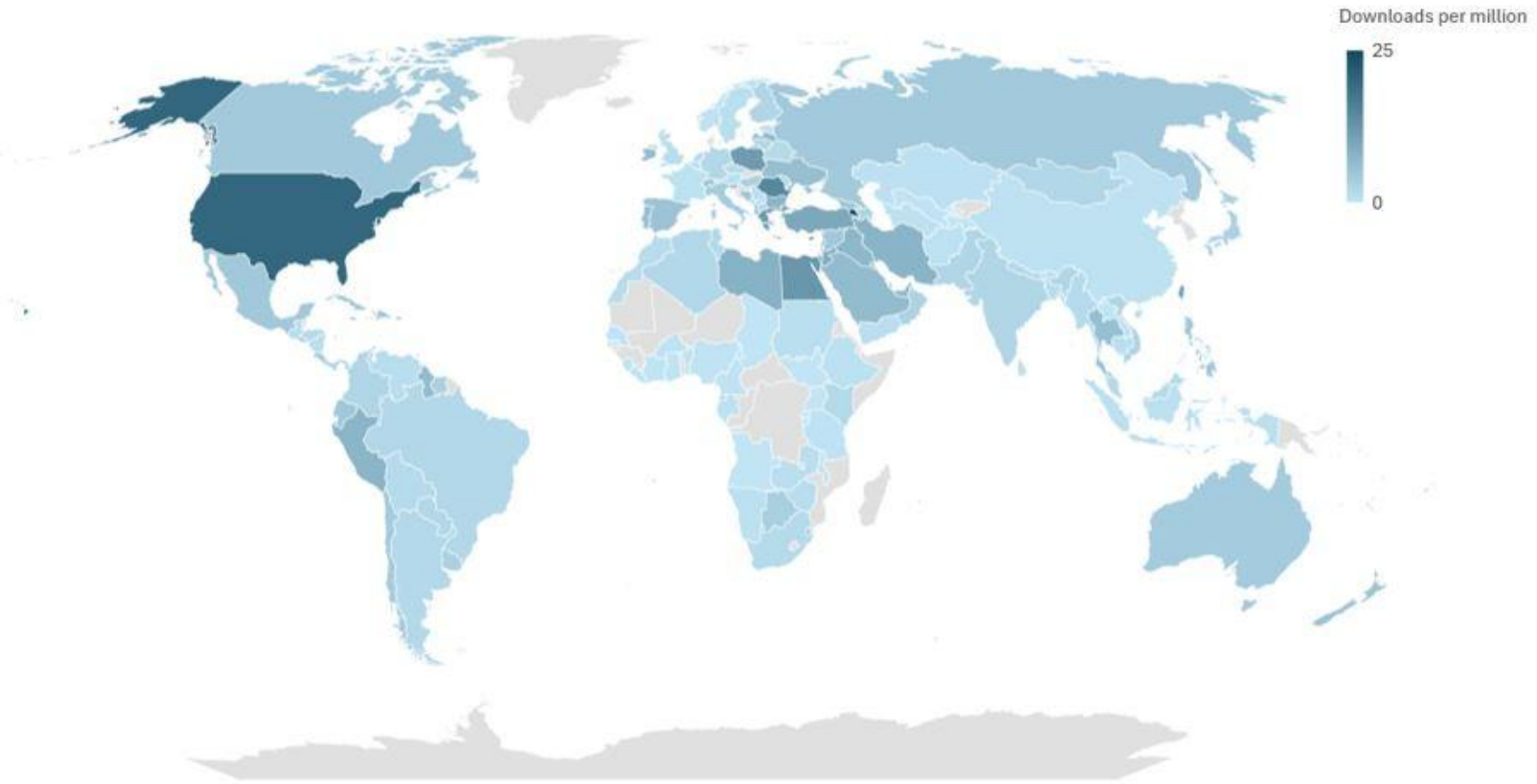
Background: Erdheim-Chester disease, Langerhans cell histiocytosis, and Rosai-Dorfman disease are the 3 major types of adult histiocytic neoplasms. In the US, we estimate a combined incidence of about 3 per million population or 1,000 cases annually. Due to the rarity of these disorders and the complexity in their diagnosis and management, the National Comprehensive Cancer Network (NCCN) convened a panel of experts and published the first clinical practice guidelines for histiocytic neoplasms in 2021. A major challenge in the field is estimating the worldwide burden of disease and level of disease awareness. Here, we report the global utilization of the NCCN clinical practice guidelines for histiocytic neoplasms as a proxy for disease burden and awareness.

Methods: We obtained the number of total downloads of the NCCN clinical practice guidelines for histiocytic neoplasms worldwide in 2024. Only countries with at least one download were included. For the US, we obtained the number of total downloads plus the number of unique downloads, defined as the number of unique NCCN accounts with at least one download, from all US states from 2021-2024. For all countries, we normalized these data points using the population for each country, obtained from either official national estimates or estimates from the United Nations. For the US, we also normalized the data using the number of licensed hematologists/oncologists from the American Board of Medical Specialties annual report from 2021-2024, respectively. We used a linear mixed model with clustered standard errors to analyze temporal trends in downloads while adjusting for state-level variations.

Results: In 2024, there was a total of 18,972 downloads of the NCCN clinical practice guidelines for histiocytic neoplasms across 152 countries and territories. The top 10 countries with the largest number of total downloads per million population were Armenia (24.8), US (20), Cyprus (15.2), Romania (14.7), Egypt (12.5), Greece (12.3), Mauritius (11.9), Poland (11.6), Taiwan (10.5), and Lebanon (9.8) (Figure 1). The countries with the fewest total downloads per million population were the Democratic Republic of the Congo (0.02), Chad (0.05), Angola (0.06), Uganda (0.07), South Sudan (0.07), Cote d'Ivoire (0.07), Burundi (0.08), Burkina Faso (0.09), Senegal (0.11), and Sierra Leone (0.11). In the US, there were a total of 6,798 non-unique downloads with 3,232 unique downloads. The states with the largest number of unique downloads per hundred licensed hematologists/oncologists were Idaho (33.8), Hawaii (29.8), Utah (29.1), Alaska (28.1), and Montana (26.1). The states with the fewest number of unique downloads per hundred hematologists/oncologists were Nevada (6), Maryland (7.1), North Dakota (7.6), New Hampshire (7.8), and Massachusetts (8.6). States with a National Cancer Institute comprehensive cancer center (CCC) had a median of 13 unique downloads per hundred hematologists/oncologists (interquartile range [IQR], 10.1-15.2), while states without a CCC had a median of 15.4 unique downloads per hundred hematologists/oncologists (IQR, 9-20.7). From 2021-2024, the number of downloads per hematologist/oncologists within the US significantly increased over time ($\beta = 3.65$, 95% CI: 3.12–4.18, $p < 0.001$). State-level effects were not statistically significant.

Conclusions: This report on the utilization of the NCCN guidelines for histiocytic neoplasms represents one of the first characterizations of global disease burden and clinician awareness of this group of rare disorders. We hope to use these data to focus educational efforts, inform practice needs, and develop a research agenda in collaboration with organizations serving patients with histiocytic neoplasms around the world.

Figure 1. Number of downloads of NCCN guidelines for histiocytic disorders by country.



3. Navigating the Challenges of Erdheim-Chester Disease Associated with Myeloid Neoplasm: The Uncharted Territory of Hepatobiliary Involvement and The Double-Edged Sword of Steroids – a case report

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Background: Erdheim-Chester disease (ECD) is a rare L-group histiocytic disorder with diverse manifestations. Skeletal, cardiovascular, renal, endocrine and nervous system involvement are well-documented, but hepatobiliary manifestations are poorly characterized. Prolonged steroid use, used to control inflammation, can lead to significant complications. We present a complex case of ECD with myelodysplastic syndrome (MDS) with a challenging clinical course.

Methods: A 45-year-old Caucasian male developed pan-hypopituitarism in 2013, including diabetes insipidus and hypogonadism. In 2016, he presented with fever, abdominal and left knee pain. Imaging showed rib and femur lesions, leading to an ECD diagnosis by femoral biopsy. He was started on trametinib monotherapy and then in combination with dabrafenib. In 2017, an acute myocardial infarction with cardiac arrest required urgent PCI/stent. After brief treatment halts for cardiac and renal dysfunction and infections, he continued trametinib until 2021. Due to intermittent abdominal pain and fever, prednisone (up to 40 mg qd) was given for nearly 6 years, causing steroid-induced diabetes, osteoporosis, renal dysfunction and hospitalizations for infections, including bacterial, COVID-19, and aspergillus pneumonias. In 2021, worsening cytopenias led to a diagnosis of MDS with multilineage dysplasia (MDS-MLD). Bone marrow (BM) biopsy revealed hypercellularity, 2% blasts with MLD, del(7q) and del(20q), and next-generation sequencing (NGS) showed ASXL1, SRSF2, NF1, U2AF1 and TET2 mutations- R-IPSS low-risk and M-IPSS moderate-risk (Fig 1, A-D). Due to multiple comorbidities, he was deemed very high-risk for allogeneic stem transplantation. He transitioned care to UTSW and was started on darbepoetin alfa for symptomatic anemia due to lower risk-MDS. Recognizing adverse effects of chronic steroid use, we initiated a slow steroid taper. Serial PET/CTs in 2022-2023 showed stable ECD. However, PET/CT in March 2024 revealed progressive hepatosplenomegaly, diffuse BM uptake, enlarged kidneys, and worsening perinephric/retroperitoneal stranding (Fig 2, A-C). Labs showed rising total/direct bilirubin (4/2.9 mg/dL) and alkaline phosphatase (711 U/L). MRI revealed peripheral biliary wall thickening and ductal dilation and peribiliary soft tissue enhancement, suggestive of ECD-related hepatobiliary involvement (Fig 2, D-E). Perinephric tissue biopsy confirmed CD68+/CD163+/CD1a-/S100- histiocytes (Fig 1, E-H), with BRAF V600E, ASXL1 and SRSF2 mutations per NGS. He was started on low dose cobimetinib (20 mg q21/28 days) in May 2024. PET/CT in November 2024 showed improving non-hypermetabolic retroperitoneal/perinephric stranding and stable hepatosplenomegaly. Liver function also stabilized on

cobimetinib. His multidisciplinary management team involves hematology-oncology, infectious disease, endocrinology, cardio-oncology, nephrology, pulmonary medicine, hepatology, and palliative care. The patient continues to need hospitalizations for recurrent bacterial and viral infections.

Conclusions: This case highlights several challenges and opportunities for multidisciplinary collaboration in ECD management. Mutational analysis supports a ASXL1/SRSF2-mutated ancestral clone with the acquisition of mutations in BRAF driving ECD and NF1, U2AF1, and TET2 driving MDS. Corticosteroids offer short-term relief, but chronic use leads to metabolic and infectious complications calling for provider and patient education. Hepatobiliary involvement in ECD is extremely rare and portends poor prognosis. This may be the first documented case of hepatobiliary ECD involvement with concurrent MDS. Optimizing the sequence of therapies is critical to improve long-term outcomes in ECD and overlapping myeloid neoplasms.

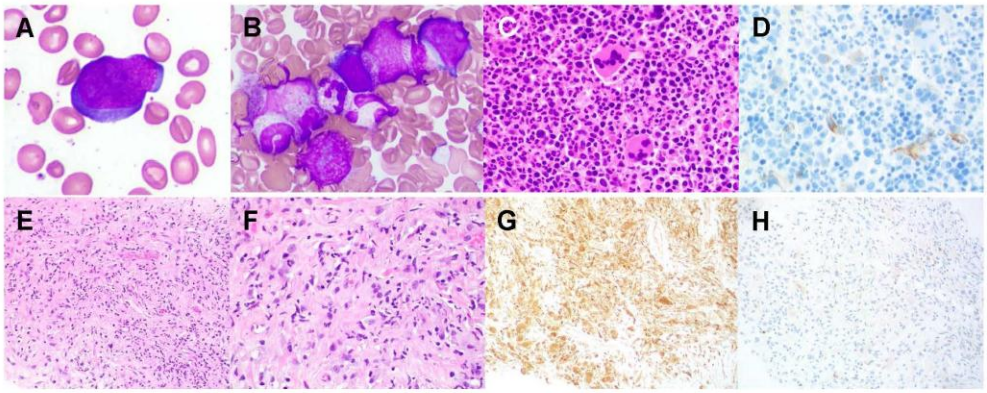

Figure 1. Histopathology of concurrent MDS (A-D) and ECD (E-F). (A) Blasts on peripheral blood smear. (B) Blasts and dysplastic/hypogranular neutrophils on bone marrow (BM) aspiration. Hypercellular BM core with dysplastic megakaryocytes (C) and 1-2% CD34 positive cells (D). Perinephric tissue biopsy with histiocytic infiltration admixed with small lymphocytes (E-F) where histiocytes are CD68 positive (G), S100 negative (H).

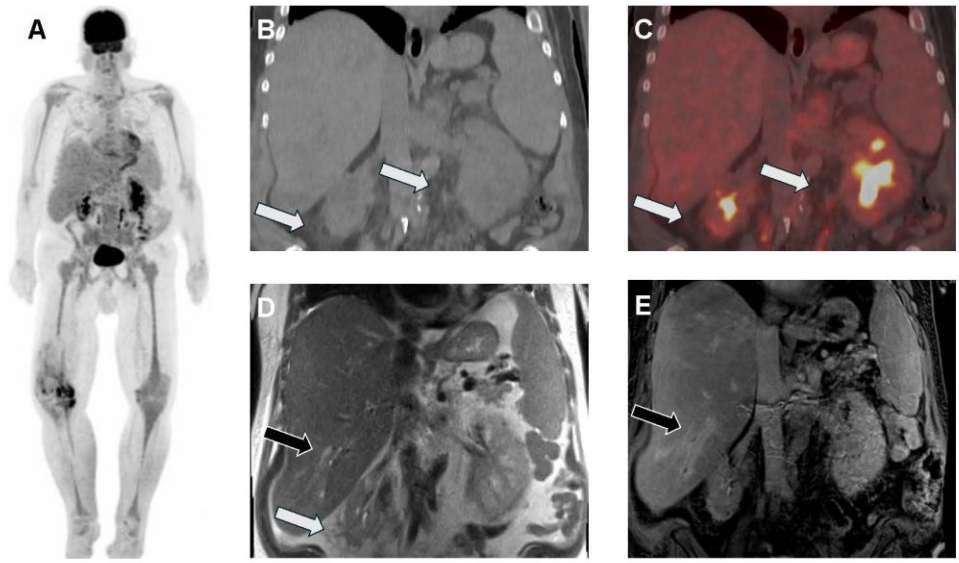

Figure 2. PET/CT and MRI of concurrent MDS and ECD. (A) FDG PET/CT maximum intensity projection demonstrating hepatosplenomegaly and diffuse FDG uptake in the bone marrow. Coronal slices from PET/CT reveal perinephric and retroperitoneal fat stranding (B) without FDG uptake (C). Coronal slices of T2-weighted MRI also show perinephric fat stranding (D, white arrow) and peripheral biliary dilation (D, black arrow) further detailed post-contrast with biliary wall thickening and enhancing peribiliary soft tissue (E, black arrow).

4. Rare Dual Diagnoses: Rosai-Dorfman and Lhermitte-Duclos Disease in a Patient with PTEN Hamartoma Tumor Syndrome

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Background: Rosai-Dorfman Disease (RDD) is a non-Langerhans cell histiocytosis that classically presents with lymphadenopathy, though it can present with extranodal disease and be associated with autoimmune, hereditary and malignant diseases. PTEN encodes a phosphatase that acts as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway, a key regulator of cell proliferation and survival. Loss of function mutations and copy number loss of PTEN are associated with cancer progression. PTEN Hamartoma Tumor Syndrome (PHTS) is a spectrum of highly variable conditions with overlapping features. The PHTS spectrum includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and PTEN-related autism spectrum disorder. PHTS predisposes patients to hamartomatous growths, vascular malformations, and increased risk of malignancies including breast, thyroid, kidney, colon and endometrial cancers. We present the case of a 26-year-old female with dual diagnoses of RDD and PHTS, complicated by a dysplastic cerebellar gangliocytoma (Lhermitte-Duclos Disease) and vascular malformations, highlighting the diagnostic and therapeutic complexity of her disease.

Case Presentation: This Guyanese American woman was initially diagnosed with RDD at 12 years of age in 2011 when her mother noted a lump on her scalp while brushing her hair. Imaging identified a right parietal extra-axial dural-based mass with osseous extension. She underwent subtotal resection of the mass and pathology revealed extranodal RDD. This surgical intervention was complicated by infection requiring washout and titanium mesh cranioplasty and a third surgery for resection of residual disease in 2012. She was then treated with chemotherapy with cladribine for 6 cycles. She also has a history of arterio-venous malformations (AVMs) of her left foot since age 7 (Fig 1) for which she has undergone multiple sodium tetradecyl sulfate (STS) and bleomycin sclerotherapy treatments. Additionally, she underwent thyroidectomy in 2017 for a multinodular goiter. In 2023, she developed right-sided headaches. Imaging showed a right cerebellar lesion, with the classic “tigroid” appearance on MRI suggestive of a dysplastic cerebellar gangliocytoma (Fig 2). She was referred to our institution and, due to the concern for Lhermitte-Duclos Disease, underwent genetic testing and was found to harbor a germline PTEN mutation (c.634+5G>A). The same PTEN mutation was also detected on next-generation sequencing of the 2011 dural RDD specimen. Given the stable nature of the cerebellar lesion on imaging, urgent neurosurgical intervention was deferred. Over the past several months, she has experienced

progressive, disabling headaches and visual disturbances. Despite trials of multiple migraine therapies, she has experienced no significant relief. Serial imaging showed stable size of the cerebellar mass with mild increase in perilesional vasogenic edema, prompting initiation of the mTOR inhibitor (mTORi) sirolimus as first-line therapy for PHTS. She is also undergoing guideline-directed cancer screening by our genetic counseling team.

Conclusion: This case underscores the complex interplay between RDD and malignancy. PTEN mutations are rare in RDD. The extranodal dural RDD in this case was likely an epiphenomenon of her underlying PHTS, emphasizing the need for a multidisciplinary approach to diagnosis and management. Targeted therapy with mTORi like sirolimus have been effective in PHTS, including management of vascular malformations, but its effectiveness in symptom relief and regression of Lhermitte-Duclos disease will need to be discerned. Continued surveillance and early intervention for malignancies is a priority in optimizing long-term patient outcomes in PHTS.

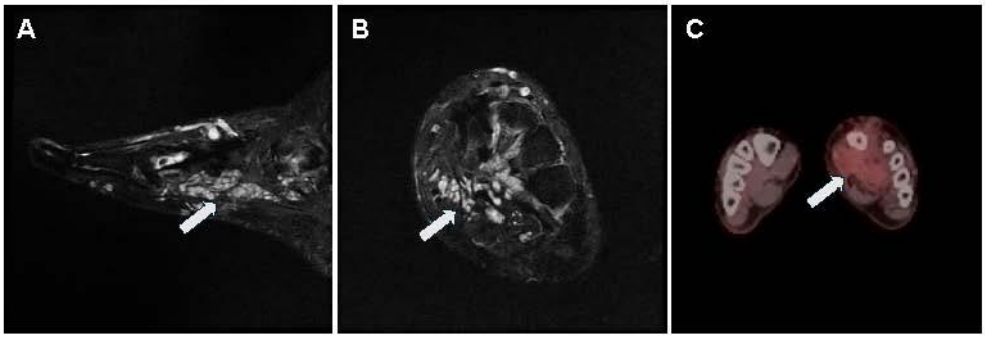

Figure 1. Radiographic evidence of PHTS-associated arteriovenous malformations of the left foot. Sagittal (A) and axial (B) cross-sections of MRI of the left foot demonstrate a large nidus of vessels (white arrows) in the deep flexor compartment of the medial two-thirds of the foot with numerous small radiating tributary vessels extending superficially, most consistent with a cavernovenous malformation. (C) Axial cross-section of FDG PET/CT through the mid-foot reveals mild FDG uptake in a poorly defined soft tissue density of the left plantar region (white arrow), likely related to the left foot vascular malformation following sclerotherapy treatments.

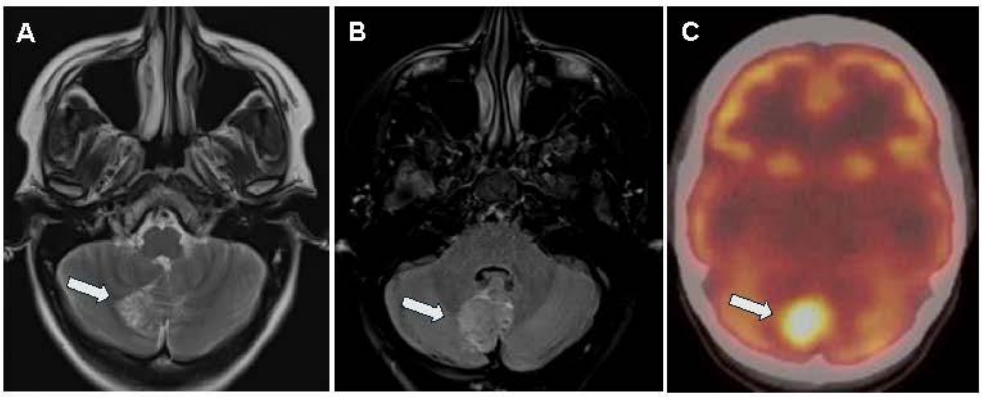

Figure 2. Radiographic evidence of Lhermitte-Duclos Disease in the setting of *PTEN* Hamartoma Tumor Syndrome. Axial cross-sections of T2-weighted MRI of the brain demonstrating a hyperintense mass centered in the inferior vermis and right cerebellar hemisphere (white arrows) consistent with a dysplastic cerebellar gangliocytoma (Lhermitte-Duclos Disease) (A) with perilesional vasogenic edema as shown on T2-weighted Fluid Attenuated Inversion Recovery (FLAIR) imaging (B). Axial cross-section of FDG PET/CT confirms a highly FDG-avid right cerebellar mass.

5. Clinical and molecular features of cutaneous involvement in adults histiocytoses.

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Jerome Razanamahery graduated in internal medicine and immunology in 2017. He is a physician in the internal medicine department of Dijon University Hospital. He is particularly interested in immunology and oncology. During his residency at Pitié-Salpétrière Hospital, he researched histiocytic disorders, especially ECD and RDD, with Professor Haroche. He led an internal multicentric project with Eli Diamond, Gaurav Goyal, Jean-Francois Emile, and Julien Haroche, describing the overlapping forms between ECD and RDD in adult patients. His current research focuses on monocyte disturbance in histiocytic disorders and the significance of their modification in the disease's course.

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Purpose: Histiocytoses are a group of clonal diseases characterized by tissue infiltration by CD68+ histiocytes harboring somatic activation in the MAP-kinase pathway. Clinical presentation is heterogeneous according to disease widespread, and aggressiveness which is associated with mutational status, in particular BRAFV600E mutation. In theory, histiocytoses can affect every organs including the skin. Skin lesions are well reported in several adults histiocytosis(i.e. Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), Rosai Dorfman disease (RDD), Indeterminate cell histiocytosis (IHC), or juvenile xanthogranuloma(JXG)). However, all this lesions have been reported separately and the aim of the study is to report the epidemiology, clinical, and molecular features of patients with skin lesions from a cohort of adult histiocytosis.

Methods: We retrieved data from adult patients with histiocytosis followed at Dijon University Hospital from 2015 to 2024, comparing their characteristics based on the presence of cutaneous involvement.

Results: Among 45 adult patients (17 LCH, 14 ECD, 6 RDD, 3 mixed ECD/LCH, 3 IHC, and 2 JXG), 17 (38%) had cutaneous involvement. These patients were more frequently female (n=11). At histiocytosis onset, patients with skin lesions were older (mean age: 68 years, IQR [49–76] vs. 53 [26–67]; p= 0.05) at histiocytosis onset. They also have frequent ICH (3/17 vs. 0/28; p = 0.04), and less commonly ECD (2/17 vs. 12/28; p = 0.04). Histiocytosis was also more limited among these patients (mean organ involved: 1.47 vs. 2.42; p= 0.0365); with in particular less bone (7/17 vs. 22/28; p= 0.02) and peri-renal (0/17 vs. 11/28; p= 0.01) lesions. Regarding the mutational status, there is a trend towards more prevalent BRAF deletion in patients with skin lesions (3/17 vs. 0/28; p= 0.06). Thereafter, we have delved deeper into the characteristics of patients with cutaneous lesions (n=17). There was no difference according to the frequency of elementary dermatologic lesions or mutational status. Nevertheless, patients with unicentric skin lesions had frequent trunk (3/7 vs. 3/10; p = 0.0498) and neck (5/7 vs. 0/10; p = 0.00034) lesions. The presence of cutaneous involvement had no impact on relapsing status or overall survival. Interestingly, multiple regression analysis showed a negative correlation between skin involvement and ECD (OR: -3.733, 95% CI [-7.38 to -1.28]; p = 0.01).

Conclusions: Cutaneous lesions are frequent in adults with histiocytosis. They mostly affect old patients with limited disease, and is localized in neck and trunk. Nonetheless, these lesions remains rare among ECD patients.

6. Identification of overlapping clinical and molecular features of patients with abdominopelvic Rosai Dorfman disease with KRAS mutated diseases: A case series

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Introduction: Rosai Dorfman Disease (RDD) is a rare non-Langerhans cell histiocytic disorder occurring in both children and adults characterized by S100 and variable CD68 and CD163 positive sinus histiocytosis with emperipolesis. Mutations within the Ras/MAP Kinase pathway are well-described in RDD but their precise subtype and distribution in patients with primary extra-nodal abdominopelvic disease remains elusive. Herein, we present a short case series of 4 patients with peri-colonic/abdominal soft tissue RDD and a discussion to follow on overlapping clinical features with other related KRAS-mutated diseases.

Case Series: Case 1: 64-year-old female with progressively worsening abdominal discomfort over the course of 6 months was identified by conventional computed tomography (CT) imaging to have multifocal abdominal pelvic soft tissue lesions with collective encasement of the rectosigmoid colon and right ureteral compression. After unsuccessful surgical debulking locally, a mutation in KRAS (variant K117N, variant allele frequency (VAF) 7.2%), was identified and cobimetinib initiated. Therapy has been well-tolerated to-date and response assessments are forthcoming. Case 2: 70-year-old male with extensive cardiac history, including coronary artery disease with prior stenting, experienced right-sided hip discomfort, prompting imaging that identified a soft tissue mass adjacent to the sigmoid colon. Subsequent whole-body positron emission tomography (PET) identified fluorodeoxyglucose (FDG)-avid disease at this site along with numerous hypermetabolic osseous lesions. Biopsy of the pelvic mass confirmed extra-nodal RDD and sequencing revealed a mutation in KRAS, variant A146P, VAF 1.5%. Ras/MAP Kinase pathway-targeting therapy is now being instituted. Case 3: 64-year-old male with worsening discomfort in his right lower inguinal region underwent abdominopelvic imaging and was identified to have an enlarged right inguinal lymph node as well as a cystic lesion in the pancreatic head. RDD was confirmed on subsequent biopsy of the node. Fluid from the pancreatic lesion was also sampled by fine needle aspiration and confirmed as a mucinous lesion with mutated KRAS, variant G12R, VAF 6%. Case 4: 63-year-old female with known diverticulosis who presented with lower abdominal discomfort to the emergency department, where CT imaging revealed multiple peritoneal soft tissue masses, including around the cecum, biopsy from which confirmed RDD. Molecular characterization is underway.

Conclusion and Discussion: Rosai Dorfman Disease is known for its clinical heterogeneity but, even within the context of an already-rare disease state, isolated soft tissue lesions in the peritoneum, including those in the pancreas or encasing the small bowel, are uncommon (lesions are more routinely observed in the skin or cervical lymph nodes). Moreover, diagnoses in these regions are often missed due

to the dense, fibrotic tissue surrounding histiocytic conglomerate lesions and less emperipolesis being present. The concurrence of KRAS variants in patients with pancreatic and/or peri-colonic lesions is an important finding even within this limited cohort. KRAS mutations are more heavily represented in primary gastrointestinal, specifically colonic and pancreatic malignancies but their proclivity for extra-luminal/glandular soft tissue surrounding visceral structures is virtually unreported in adult histiocytic disease. Further investigations into extraluminal soft tissue abdominopelvic RDD, specifically pertaining to KRAS alterations, is warranted in future studies as molecular characterization of this rare entity in an already-rare disease is under-reported/represented in the field.

7. A survey of Spanish internists to assess where patients with Erdheim-Chester disease receive care and what resources are available

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Dr. Gemma Rocamora is a physician specializing in Internal Medicine, having graduated in 2020. She currently focuses on clinical practice at a tertiary care hospital, with a particular interest in rare and autoimmune diseases. Dr. Rocamora is working on her doctoral thesis regarding Erdheim-Chester disease, with a focus on improving the clinical management of patients affected by this condition. Participation in this symposium presents a valuable opportunity to expand her knowledge and engage with diverse perspectives in the field.

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Background: Erdheim-Chester disease's (ECD) rarity and the involvement of multiple organ systems contribute to the difficulty in establishing a standard care pathway in this disease. In Spain, there is a lack of knowledge about the specialists responsible for the care of patients with ECD. It is also unknown what resources are available or how these patients are currently being treated. The aim of this study is to assess which internists are treating patients with ECD in Spain, evaluate the clinical condition of these patients, and identify the available resources.

Methods: In February 2025, an online survey was sent to all Spanish internists to determine which hospitals are treating patients with ECD, the current status of these patients, and the resources (imaging, molecular diagnostics, treatments, etc.) available at each treating center.

Results: Fourteen Spanish centers responded to the survey (11 tertiary care hospitals and 3 secondary care ones), representing the most densely populated areas of the country. Overall, 41 patients are currently being treated, 30 of them in three centers. The mean experience of the treating physicians in ECD was 8.4 years (range 1-20). Most physicians always perform PET-CT (79%), echocardiogram (86%), and brain MRI (64%) on their patients. Only one of the centers is organized as a multidisciplinary unit for systemic histiocytosis. In nine (64%) centers, these patients are jointly managed by hematology, in four (29%) by cardiology, in two (14%) by endocrinology / oncology / urologists, and only in one (7%) by neurology. Six of these centers have pathologists with experience in histiocytosis. In 10 centers, the BRAFV600E variant can be determined, and in 9 of them other somatic variants can be also identified. Half of the centers have difficulties in prescribing targeted therapies as the first-line, although all but one of them can prescribe these therapies in severe forms and in case of refractoriness to other drugs. Most physicians use full or intermediate doses to induce remission, while for maintenance, they use intermediate or low doses. 17 patients are currently receiving a BRAF inhibitor, 6 a MEK inhibitor, 6 corticosteroids (usually associated with other medications), 5 cytokine-blocking drugs, 2 interferon, 1 cladribine, and 6 patients are not receiving treatment. All centers, except one, report that there is not enough training on ECD. Only 4 of the treating physicians are aware of associations for the study of histiocytosis.

Conclusions: Our results highlight the need for a more structured approach to the diagnosis, treatment, and management of ECD in Spain.

8. Success of Second Allogeneic Stem Cell Transplant in a Patient with Erdheim-Chester Disease and Myelodysplastic Syndrome

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I am a third year hematology/oncology fellow at the University of Rochester Medical Center in Rochester, New York. I have an interest in blood and marrow transplantation.

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Background: Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytic disorder characterized by infiltration of foamy CD68+CD1a- histiocytes with about 1500 known cases reported to date. Patients with ECD typically present with sclerotic long bone lesions and may have additional cardiovascular, pulmonary, renal, cutaneous, neurologic or endocrine manifestations. Activating MAPK pathway mutations are found in more than 80% of cases with BRAF V600E being the most common. Little is known about the outcomes of allogeneic stem cell transplant (SCT) in adult patients with ECD. Here, we present the case of a 62-year-old male with ECD and relapsed myelodysplastic syndrome (MDS) who underwent two allogeneic SCTs. **Case Presentation**

Case Presentation: Our patient was diagnosed around age 42 after biopsies from hernia repair surgery incidentally revealed histology consistent with ECD. Bone imaging and presence of BRAF V600E mutation further supported the diagnosis. He was also found to have renal involvement, pituitary microadenoma, and gynecomastia. He was treated with interferon alpha and dabrafenib, a BRAF inhibitor, for several years until MDS diagnosis. At the age of 55, he was noted to have progressive thrombocytopenia followed by neutropenia. Bone marrow biopsy (BMbx) 2 years later confirmed diagnosis of MDS with 5q deletion. He was treated with lenalidomide and IFN-α was briefly held. His MDS progressed after about 2 years of therapy. Repeat BMbx demonstrated 9% blasts with ongoing 5q- and new monosomy 7. He was treated with single agent azacitidine (aza) initially followed by combination with venetoclax (ven) leading to morphologic but not cytogenetic remission after 1 year. He proceeded with reduced intensity conditioning (RIC) fludarabine/busulfan matched sibling donor transplant and received post-transplant cyclophosphamide, tacrolimus, and mycophenolate for GVHD prophylaxis. His MDS relapsed 1 year after transplant and BMbx showed scattered CD68+ histiocytes with 5q-, monosomy 7, and EZH2/TET2 mutations. He restarted aza/ven and achieved MRD+ remission 1 year later. He underwent second transplant using a 10/10 matched unrelated donor with fludarabine/melphalan conditioning and the same GVHD prophylaxis as prior. Course was complicated by engraftment syndrome and acute grade 2 gastrointestinal GVHD. Day +100 BMbx showed full donor chimerism with normal cytogenetics. Molecular studies done at Day +30 showed no evidence of EZH2, TET2, or BRAF mutations. Repeat PET/CT showed no bony lesions and MRI pituitary showed decreased size of prior microadenoma. Clinically, he reported improvement in gynecomastia and bony pains after transplant. He remains in remission at Day +315.

Discussion: ECD is associated with increased incidence of additional myeloid neoplasms (reported in 10% of cases). Advances in targeted therapies such as BRAF/MEK inhibitors have improved survival in this population and use of SCT for ECD is limited. There are few reports on the use of double autologous SCT in refractory ECD with mixed efficacy as well as the use of allogeneic SCT in pediatric patients. However, to our knowledge, this is the first reported case in an adult patient.

Acknowledgments

Volunteers

We are thankful for all the generous members of the ECDGA community who provide financial support to allow the organization to work on behalf of all those affected by Erdheim-Chester Disease (ECD) worldwide.

In addition, the ECD Medical Symposium would not be possible without community volunteers - patients, family, friends, physicians, and scientists - who give of their time and knowledge so freely to help all in the community. By working together we are stronger and we can see the advancements in the management of ECD that brings us all hope.

Finally, we thank all the medical professionals who devote their time to the study and clinical support to help individuals living with ECD and adult histiocytosis, to include patients and their families.

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