INTERNATIONAL
Erdheim-Chester Disease Events

6TH ANNUAL | ORLANDO | 2018

SUPPORTING THOSE AFFECTED BY ERDHEIM-CHESTER DISEASE

WELCOME TO THE ANNUAL ECD SYMPOSIUM

ECD medical symposia allow sharing of research findings, foster research collaborations, and provide a mechanism to educate physicians. These meetings promote discussion of the complex problems facing the ECD community, allowing multiple disciplines to interact. Thank you to the host, presenters, and participants for your dedication, time and interest!

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ERDHEIM-CHESTER DISEASE GLOBAL ALLIANCE

ERDHEIM-CHESTER DISEASE GLOBAL ALLIANCE

ECD Global Alliance
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DeRidder, LA 70634 USA
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www.erdheim-chester.org

6th Annual International ECD Medical Symposium

November 15, 2018
Orlando, FL

Dear Attendees,

Welcome to the 6th Annual International ECD Medical Symposium! Thank you for your attendance and participation.

This year, the ECD Global Alliance has partnered with Dr. Julio J. Hajdenberg and Orlando Health UF Health Center, to make this year's event possible.

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

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

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

Best regards,

THE ECDGA STAFF & BOARD OF DIRECTORS

SUPPORTING THOSE AFFECTED BY ERDHEIM-CHESTER DISEASE

Orlando Health Meeting Wi-Fi:

Network: *Orlando Health Guest* | Password: *guest1*

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*ORMC – meeting location

Orlando Health Downtown Campus

- **Emergency Department and Level One Trauma Center** 29 W. Sturtevant St.
- **Children's Emergency Department and Trauma Center** 92 W. Miller St.
- **Orlando Regional Medical Center (ORMC)** 52 W. Underwood St.
- **Arnold Palmer Hospital for Children** 92 W. Miller St.
- **Winnie Palmer Hospital for Women & Babies** 83 W. Miller St.
- **UF Health Cancer Center – Orlando Health** 1400 S. Orange Ave.
- **Orlando Health Heart Institute** 1222 S. Orange Ave.
- **Ambulatory Care Center** 22 W. Underwood St.

① Arnold Palmer Hospital Specialty Practices
83 W. Columbia St.

② Clifford E. Graese Library
1414 Kuhl Ave.

③ Occupational Health
77 W. Underwood St.

④ Hubbard House
29 W. Miller St.

⑤ Human Resources
85 W. Gore St.

⑥ Winnie Palmer Hospital Surgical Pre-Testing
1301 Sligh Blvd.

⑦ Medical Education Administration
86 W. Underwood St.

⑧ Medical Education Outpatient Clinic
89 W. Copeland Dr.
Access from Underwood St.

⑧ UF Health Neurosurgery – Orlando Health
89 W. Copeland Dr.
Access from Underwood St.

⑨ Orlando Health Medical Pavilion
32 W. Gore St.

⑩ Obstetrics/Gynecology
21 W. Columbia St.

⑪ Rehabilitation, Children
925 S. Orange Ave.

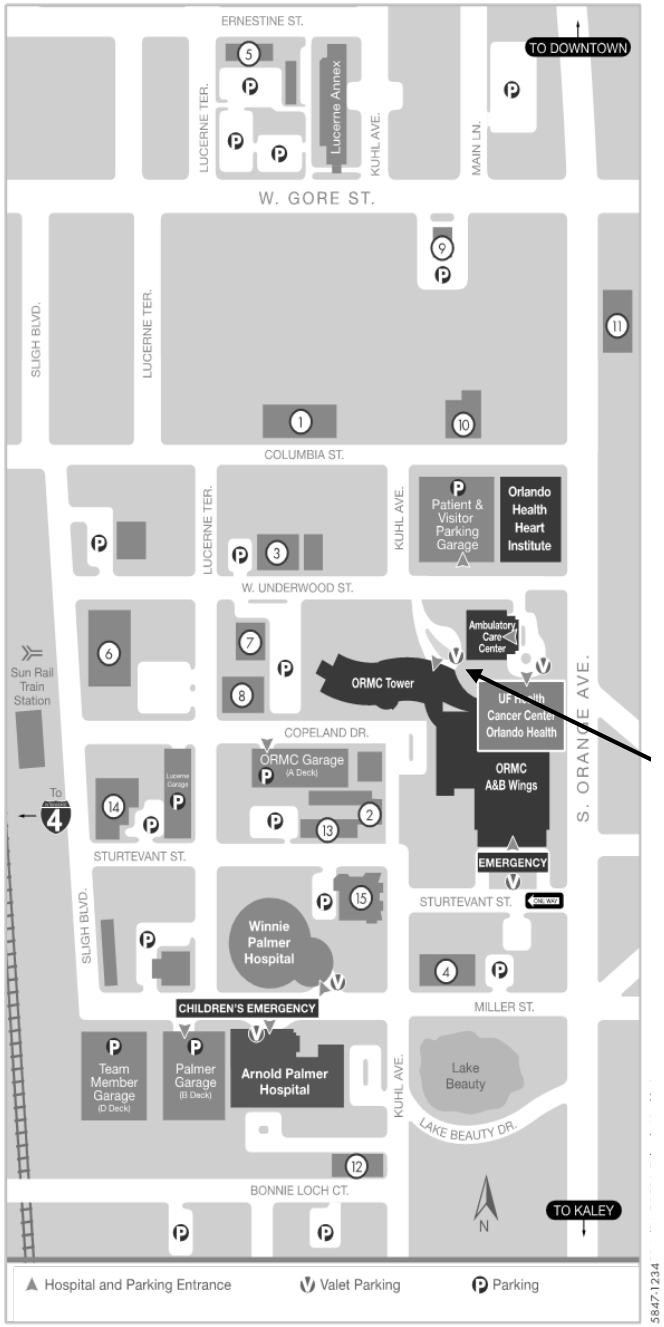
⑫ Ronald McDonald House
1630 Kuhl Ave.

⑬ Thorsen Building
65 W. Sturtevant St.

⑭ Healthy U Fitness Center
119 W. Sturtevant St.

⑮ Outpatient Center I
50 W. Sturtevant St.
- Audiology (Pediatric and Adult)
- NICU Follow-Up Wellness Center
- Radiation Oncology TomoTherapy

ORLANDO HEALTH



ORLANDO HEALTH CAMPUS MAP

*ORMC – meeting entrance

PRESENTATION AGENDA

TIME	SESSION / SPEAKER	
8:00	*Registration & Hot American Breakfast*	
8:30	WELCOME ADDRESS	**Julio Hajdenberg, MD** *UF Health Cancer Center*
8:45	KEYNOTE Erdheim Chester Disease: Cancer, but not as we know it.	**Matthew Collin, MD, PhD** *Newcastle University*
9:15	Patient-reported outcomes in adults with Erdheim-Chester Disease: Early findings from the ECD Registry	**Eli L. Diamond, MD** *Memorial Sloan Kettering*
BASIC SCIENCE		
9:45	**Benjamin Durham, MD** Novel Activating Mutations in CSF1R and Additional Receptor Tyrosine Kinases in Histiocytic Neoplasms	
10:05	**Ran Weissman, M.Sc** The role of microRNAs in the Pathogenesis of Erdheim-Chester Disease and their Potential Use as Biomarkers for Diagnosis and Prognosis of the Disease	
10:30	*Break & Poster Display*	
ORGAN INVOLVEMENT		
10:55	**Julien Haroche, MD, PhD** Imaging aspect of cardiac involvement in Erdheim-Chester disease: cardiac CT and MRI of 188 patients	
PATHOLOGY		
11:15	**Gaurav Goyal, MD** Tumor mutational burden and other immunotherapy markers in Erdheim-Chester disease and other histiocytic neoplasms	
11:35	**Anaïs Roeser, MD** Auto-immunity in L-group histiocytoses	
11:55	*Group Photo of Speakers & Attendees*	
12:10	*Lunch & Poster display*	***Resume meeting at 1:25***

TREATMENTS	
1:30	**Roei Mazor, MD** Efficacy of Dual BRAF/MAP2K1 Blockade in BRAF mutant Erdheim Chester Disease Patients
1:50	**Fady Hannah-Shmouni, MD** Hypothyroidism in Erdheim-Chester Disease: Experience from the National Institutes of Health
2:10	**Gordon Ruan, MD** Acute Pancreatitis from treatment with BRAF-inhibitors in patients with Erdheim-Chester Disease
2:30	*Break & Poster Display*

PANEL DISCUSSIONS		
2:55	TOXICITY OF ECD THERAPIES	*Moderator:* **Eli L. Diamond, MD**
3:40	COMPLEX CASE STUDIES	*Moderator:* **Julio Hajdenberg, MD**
4:25	ECDGA ANNOUNCEMENTS	**Kathleen Brewer**
4:45	CLOSING	**Julio Hajdenberg, MD**

POSTER PRESENTATIONS

TITLE	Presenter
Erdheim-Chester Disease Global Alliance Achievements & Statistics	**Kathleen Brewer** *ECD Global Alliance*
Sick-Day and Emergency Rules for Adrenal Insufficiency in Subjects with Erdheim-Chester Disease	**Fady Hannah-Shmouni, MD** *National Institutes of Health*
MTOR Inhibition in Erdheim-Chester Disease	**Julian Haroche, MD, PhD** **(On behalf of Augusto Vaglio, MD, PhD)** *Parma University Hospital, Parma, Italy*
Effects of Testosterone Supplementation on Hypogonadism Associated with ECD	**Kevin J. O'Brien, RN, MS-CRNP** *National Institutes of Health*
Erdheim-Chester Disease: Expanding the Spectrum of Cutaneous Manifestations	**Adam Schmitt, MD** *Mayo Clinic*
Cognitive Dysfunctions in Erdheim-Chester Disease	**Charlotte Soumet-Leman, MD** *Pitie-Salpêtriere Hospital*

ABSTRACTS

1. Erdheim Chester Disease: Cancer, but not as we know it.

Matthew Collin, MD, PhD

Newcastle University, Human Dendritic Cell Laboratory, Institute of Cellular Medicine, Newcastle upon Tyne, UK

The histiocytic disorders are rare diseases caused by somatic mutation in the MAP kinase pathway leading to the accumulation of dendritic cells, macrophages and monocyte-derived cells. Although neoplastic in origin, histiocytic lesions are also dependent upon inflammation, properties that confer unique biological characteristics and unusual clinical challenges. Systemic histiocytosis is traceable to the haematopoietic stem cell in many cases, however the burden of mutation is often low and new models of pathogenesis must be developed to explain how a haematopoietic clone of 1% or less can lead to a life-threatening multi-system disorder. The impact of targeted therapy, while often dramatic, also requires new therapeutic paradigms in order to understand how to achieve the most benefit for patients.

2. Patient-Reported Outcomes in Adults with Erdheim-Chester Disease (ECD): Early Findings from The ECD Registry.

Katherine Panageas, [1] Anne Reiner, [1] Justin Buthorn, [2] Thomas Atkinson, [3] Raajit Rampal, [4] David Hyman, 4 Omar Abdel-Wahab, [4] Benjamin Durham, [5] Mario Lacouture, [4] Jasmine Francis, [6] and Eli Diamond

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Purpose: Erdheim-Chester disease (ECD) is a rare L-group histiocytosis in adults. Patients with ECD endure widely varying and disabling symptomatology. However, the spectrum of disease-related symptoms, quality of life, mood, and unmet care needs have not been examined in ECD.

Methods: The Memorial Sloan Kettering (MSK) ECD Registry is a prospective longitudinal study of adult patients with ECD. Patients report demographic and treatment characteristics and complete a battery of patient-reported outcomes (PROs) at the time of enrollment and then at regular subsequent time points. The PRO battery includes an ECD-specific symptom scale, FACT-G, Brief Pain Inventory (BPI), Brief Fatigue Inventory (BFI), and Hospital Anxiety and Depression Scale, and Supportive Care Needs Survey.

Results: 34 participants have complete PRO assessments at the time of Registry enrollment. 17 (50%) are men. Neurologic or psychiatric symptoms were reported by 33 (97%), gastrointestinal symptoms by 22 (65%), pain by 20 (59%), vision problems by 11 (32%), breathing problems by 12 (35%), and other uncategorized symptoms by 33(97%). The five most common symptoms were fatigue (74%), trouble with balance or walking (56%), aching bones or joints (56%), depression/sadness (50%), and stress/anxiety

(50%). The average overall QOL score was 67.82, comparable to cancer patients requiring bed rest for up to 50% of the waking day. Of 12 participants who reported pain, mean total pain score assessed by the BPI was 4.85 (1.66), ranging 1.18-6.91, and of 25 who reported fatigue, mean total fatigue score assessed by the BFI was 5.08 (2.12), ranging 1.13-8.67. 11 (32%) reported mild to severe anxiety, and 9 (26%) reported mild to severe depression.

Conclusions: Patients with ECD endure frequent and varied symptomatology as well as diminished quality of life and mood. Further research is needed to identify disease-related and treatment-related determinants of symptom burden.

3. Novel Activating Mutations in CSF1R and Additional Receptor Tyrosine Kinases in Histiocytic Neoplasms

Benjamin H. Durham [1,2] , Estibaliz Lopez-Rodrigo [3] , Jennifer Picarsic [4] , David Abramson [5] , Alessandro Pastore [2] , Diana Mandelker [1] , Michael Walsh [3] , David Solit [2] , Michael Berger [1,2] , David M. Hyman [6] , Michelle Ki [2] , Ira Dunkel [3] , Frederic Geissmann [7] , Eli L. Diamond [8] , Omar Abdel-Wahab [2,9]

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Background: Genomic analyses of Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD) have revolutionized our understanding of these disorders as clonal hematopoietic malignancies driven by MAP kinase signaling and led to FDA approval of vemurafenib for BRAF V600E -mutant ECD. Nonetheless, several questions about the pathogenesis of the histiocytoses remain unanswered. For example, the cellular origins of the histiocytoses are not definitively known. Furthermore, the genetic alterations across the histiocytic neoplasms (ECD, LCH, juvenile xanthogranuloma (JXG), Rosai-Dorfman disease (RDD), and histiocytic sarcoma (HS)) have not been comprehensively evaluated.

Moreover, although histiocytoses usually occur as sporadic disorders, familial clustering has been well documented, which suggests a hereditary component of these diseases. However, germline genetic causes are unknown. Here we performed comprehensive genomic analyses of 222 patients, including monozygotic twins, with diverse histiocytic neoplasms that uncover a novel series of CSF1R and other activating receptor tyrosine kinase (RTK) alterations, as well as differences in the kinase alteration spectrum across histiocytoses.

Methods: We performed whole exome sequencing (WES) of skin lesions, blood, and fingernails from monozygotic twins with systemic JXG. We then sequenced 93 ECD (42%), 61 LCH (27%), 50 JXG (23%), 12 RDD (5%), and 6 HS (3%) lesions using WES and targeted DNA and RNA sequencing.

Results: We identified in-frame deletions in CSF1R (CSF1R Y546_K551del) in the JXG lesions of both twins that was absent in their blood and fingernails. This supports recent data from murine models suggesting that CSF1R-expressing yolk sac derived precursors of tissue-resident macrophages may be a cell-of-origin of the histiocytoses (Mass et al. Nature 2017). Interestingly, 8 additional patients had CSF1R mutations, most commonly CSF1R Y546_K551del, which conferred cytokine-independent growth when expressed in Ba/F3 cells and sensitized these cells to inhibition by the CSF1R-specific inhibitors pexidartinib and BLZ945. Additionally, mutations in CSF3R, KIT, ALK, MET, JAK3, CRAF, and MAP2K2, as well as a RET fusion were discovered (in addition to previously described mutations in BRAF V600E, MAP2K1, N/KRAS, and ARAF, as well as BRAF, NTRK1, and ALK fusions). Furthermore, we uncovered the following differences in the spectrum of kinase alterations across the histiocytoses: BRAF V600E was the most common kinase alteration in ECD and LCH but was not seen in JXG or RDD in our cohort; ARAF and CSF1R mutations were most frequently seen in ECD and JXG, respectively; BRAF deletions were only noted in LCH; BRAF fusions were predominantly found in LCH and JXG; and NTRK1 and ALK fusions were most common in JXG and ECD, respectively. Meanwhile, as evidence of the direct therapeutic implications of these findings, an ALK-rearranged ECD patient required therapy with crizotinib that resulted in profound therapeutic improvement.

Conclusion: Here we identify activating mutations in CSF1R, the RTK required for monocyte/macrophage development, and other novel activating RTK alterations in the histiocytoses, many of which have direct therapeutic importance (such as the first demonstration of ALK inhibitor efficacy in ALK+ histiocytosis). In addition, the discovery of somatic, activating CSF1R mutations in identical twins with histiocytosis raises the possibility that tissue-resident macrophages may serve as a cell-of-origin for the histiocytoses.

4. The role of microRNAs in the pathogenesis of Erdheim-Chester Disease and their potential use as biomarkers for diagnosis and prognosis of the disease

Ran Weissman [1,2], Nir Pilar [3], Benjamin H Durham [4], Michelle Ki [5], Roei D Mazor [6], Omar I Abdel-Wahab[5], Noam Shomron [3], Ofer Shpilberg [6,7], Eli L Diamond [8] and Oshrat Hershkovitz-Rokah [1,2].

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Background: Erdheim-Chester disease (ECD) is a rare hematological malignancy, belonging to the L-group histiocytoses. ECD is characterized by multi-systemic proliferations of mature histiocytes in a background

of inflammatory stroma. The inflammatory and neoplastic characteristics of the disease comprise a complex medical challenge for its diagnosis and treatment. MicroRNAs (miRNAs/miRs) are short non-coding RNAs (~22 nucleotides) that regulate gene expression in a sequence specific manner and play an important role in cancer development and progression. Since miRNAs are released into the blood by tumor cells, they may be used as biomarkers to distinguish between cancer patients and healthy individuals and to assist in determining treatment response. Moreover, miRNA-mRNA interactions can determine the molecular mechanism by which miRNAs and their target genes are involved in ECD and may suggest novel therapeutic options for these patients. To date, this is the first study elucidating the role of miRNA in ECD. Aims: The main focus of this study is to identify miRNAs that are differentially expressed in ECD patients compared to healthy controls and any clinical utility they have as potential biomarkers in ECD diagnosis, as well as to investigate their role in ECD pathogenesis, which may lead to new therapeutic options.

Preliminary results: Using the nCounter Human miRNA Expression Assay (NanoString Technologies), we analyzed the plasma miRNA expression profiles of 6 ECD patients (BRAF V600E) compared to 6 healthy individuals. Of the 800 mature miRNAs analyzed, 234 miRNAs showed different expression levels in these samples. Principal component analysis (PCA) was applied to experimental quality control. The miRNAs from healthy donors were clustered separately from the ECD samples indicating a distinct miRNA expression pattern between these groups (Fig. 1A, 1B). Among the 131 miRNAs remaining in the final analysis (FDR<0.05),110 miRNAs were downregulated in ECD patients compared to those of healthy controls, and 21 miRNAs were upregulated in ECD samples compared to those of the controls. We validated the analysis method by quantitative real-time polymerase chain reaction (qRT-PCR) and found a positive correlation between miRs-15a, 16, 125a, 223, 21, 34a, 155 and miR-630 expression obtained by the NanoString array. This may indicate the potential use of miRNAs as biomarkers in ECD. To determine potential target genes and signaling pathways implicated in ECD, we analyzed the predicted pathways of the top 30 downregulated miRNAs that were differentially expressed between the two groups using the Ingenuity® Pathway Analysis (IPA) and DIANA-miRPath v3.0 database. Reassuringly, the analysis identified cancer, inflammatory disease, and inflammatory response (p<0.01) as the main disease and disorder related with the miRNA expression pattern, as well as oncogenic pathways such as MAPK, PI3K-AKT, RAS, ErbB, Hippo, and mTOR as the main molecular pathways related to the differentially-expressed miRNAs (p<0.009). This finding suggests that low expression of miRNAs results in up regulation of target genes that participate in cell survival signaling. These augmented pathways may be inhibited by novel therapeutic treatments such as PI3K inhibitors, mTOR pathway inhibitors, and MEK inhibitors in ECD patients. Next, we examined if there is any correlation between the predicted target genes of the miRNAs (obtained by IPA) and the experimentally validated gene expression pattern in ECD patients. To that end, we downloaded RNA-seq results of ECD patients from the GEO database (GSE74442 deposited by Diamond et al) and compared this list to our predicted miRNA targets in ECD patients, using Gene Set Enrichment Analysis (GSEA). We found a positive correlation between the gene expression reported in the literature and the predicted target of our deregulated miRNAs (Fig. 2), indicating that the predicted target genes are enriched in this data set, suggesting that the differentially expressed miRNAs might have a crucial role in the pathogenesis of ECD.

Conclusions: Our preliminary data highlight the unique inflammatory and neoplastic features characteristic of ECD. These deregulated miRNAs may highlight new candidate gene targets allowing for a better understanding of the molecular mechanisms underlying the development of ECD and propose novel therapeutic treatments for these patients.

5. Imaging aspect of cardiac involvement in Erdheim-Chester disease: cardiac CT and MRI of 188 patients

Julien Haroche, Marine Bravetti, Fleur Cohen-Aubart, Zahir Amoura, Philippe Cluzel

[1]*Hôpital Pitié-Salpêtrière, Paris, France*

Objectives: Describe the radiological aspects of cardiac involvement of Erdheim-Chester disease (ECD). Identify complications and repercussions on cardiac function.
Introduction: ECD is a rare (less than 1500 known cases worldwide), non-Langerhans cell histiocytosis characterized by tissue infiltration of CD68 + CD1a - histiocytes in various organs. Cardiovascular involvement in ECD is common but not always clinically evident, underdiagnosed and often associated with a poor prognosis.

Material and Methods: This retrospective study was conducted between 2004 and 2018 in hôpital Pitié-Salpêtrière with 217 patients followed for a histologically proven ECD. 188 had cardiac imaging (181 MRIs and 7 CT-scans when MRI was contraindicated). We have identified the types of lesions (infiltration, pseudo mass, effusion), localization of lesions (pericardial, myocardial, valvular, posterior mediastinum) and consequences on cardiac function (coronary stenosis, atrial wall dyskinesia, alteration of diastolic and systolic functions).

Results: Cardiac involvement was present in 93 patients (49%). Among these, 73 had an impairment (pseudo mass) of the right atrioventricular groove (74%), 65 of the right atrium wall (69%), 29 (15%) of the left atrioventricular groove. Alteration of Tricuspid Annular Systolic Excursion (TAPSE) was found in 15% and correlated with the size of the pseudo mass. Pericardial involvement (effusion, thickening or contrast enhancement) was found in 53 patients (54%).

Conclusion: Cardiac involvement in ECD is very frequently seen (49% of all cases). The typical infiltration is the “iconic” pseudo mass located in the lateral wall of the right atrium (35%) and in the right atrioventricular groove (15%).

6. Tumor mutational burden and other immunotherapy markers in Erdheim-Chester disease and other histiocytic neoplasms

Gaurav Goyal, MBBS [1], Robert Vassallo, MD [2], Karen L. Rech, MD [3], Jay H. Ryu, MD [2], Caroline J. Davidge-Pitts, MBBCh [4], W. Oliver Tobin, MBBCh, PhD [5] , Matthew J. Koster, MD [6], Nabila Nora Bennani, MD [1], Mithun Vinod Shah, MD, PhD [1], Minetta C Liu, MD [7] and Ronald S. Go, MD [1]

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[6]*Division of Rheumatology, Mayo Clinic, Rochester;*
[7]*Department of Medical Oncology, Mayo Clinic, Rochester*

Introduction: Histiocytic neoplasms (HNs) are rare hematological neoplasms that can pose significant management challenges. Over the last 5 years, immune checkpoint inhibitors such as programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors have shown significant improvement in outcomes among patients with several malignancies. Evidence from solid tumors has suggested a favorable response to checkpoint inhibitor therapy with higher tumor mutational burden (TMB), with no response among tumors with TMB of < 5 mutations/megabase (mut/Mb). In addition, high levels of PD-1/PD-L1 expression and microsatellite instability (MSI) are also correlated with response to therapy. In this study, we report the results for these biomarkers using NGS in patients with ECD and other HNs.

Methods: We utilized Tempus TM NGS platform to analyze the tissue specimen. The Tempus xO Assay (Tempus Labs; Chicago, IL) combines a 1,711 gene targeted somatic and germline DNA sequencing panel with RNA-sequencing to detect both germline and somatic single nucleotide polymorphisms, indels, copy number variants, and gene rearrangements causing chimeric mRNA transcript expression in a wide array of solid tumor types. The assay utilizes formalin-fixed paraffin-embedded tumor samples and matched blood samples. TMB was calculated and reported as somatic mutations in tumor tissue per million base-pairs or mut/Mb. Both PD-L1 and PD-1 gene expressions were reported as percentiles. DNA mismatch repair status was predicted by analysis of alterations in five common mismatch repair genes in somatic and germline DNA (MSH2, MSH6, MLH1, PMS2, and EPCAM), and lack of alterations was predicted as microsatellite stable (MSS).

Results: A total of 13 patients were included in the study. The distribution of individual HNs was as follows: ECD (n=3), and LCH (n=1), and RDD (n=9). The median TMB for ECD and RDD patients was 0.17 mut/Mb. For the one patient with LCH, the TMB level was 0.51 mut/Mb. Compared to normal reference sets, the PD-L1 expression was elevated in one patient each with ECD and RDD, and PD-1 expression was elevated in two patients each with ECD and RDD. For both ECD patients with higher PD-1 expression, NGS also showed presence of BRAF-V600E in the tumor tissue. The LCH patient had a low level of PD-L1 and PD-1 expression. For patients where evaluation of DNA mismatch repair was feasible on the tissue specimen (n=4), none showed related somatic or germline alterations.

Conclusion: In our series, ECD and other HNs (RDD, LCH) demonstrated low TMB. None of the ECD patients were found to have alterations in DNA mismatch repair genes. Other markers of immunotherapy such as PD-L1/PD-1 expression appeared to be higher in ECD patients with BRAF-V600E, but in only a small subset of RDD patients. The low TMB seen in our study suggests that ECD and other histiocytic neoplasms may be less likely to respond to immune checkpoint inhibitors such as anti-PD-1 and anti-PD-L1 agents as compared to the tumors with high TMB.

7. Auto-immunity in L-group histiocytosis

Anaïs Roeser, MD, Fleur Cohen Aubart, MD, PhD, Makoto Miyara, MD, Paul Breillat, MD, PhD, Jean-François Emile, MD, PhD, Zahir Amoura, MD, PhD, and Julien Haroche, MD, PhD

Internal Medicine Department, French National Reference Center for Histiocytoses, Hôpital Pitié-Salpêtrière, Sorbonne University, Paris, France

Background: Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis characterized by tissue infiltration of CD68 (+), CD1a (-) histiocytes in various organs. It has been recently re-classified as a myeloid neoplasia, since the discovery of the RAS-RAF-MEK-ERK pathway alterations in almost all cases. Langerhans cell histiocytosis (LCH), also belonging to the group L histiocytosis, is characterized by the presence of CD1a (+) histiocytes in bone marrow, bones, skin, nervous system, and lungs. Both diseases are sometimes associated, in so-called “mixed histiocytosis”. Histiocytes play an important role in the pathophysiology of inflammation and the regulation of immunity. Autoimmunity is present in a wide spectrum of diseases where the histiocytes are altered. It has never been evaluated in L-group histiocytoses, although some cases of autoimmune disease associated with ECD or LCH have been reported. Targeted therapies, namely BRAF and MEK inhibitors, have been recently used in the treatment of ECD and LCH. We aimed to determine the prevalence of autoimmunity in L-group histiocytoses, and to evaluate the impact of BRAF and MEK inhibitors on clinical and laboratory autoimmunity in these patients.

Methods: We evaluated L-group histiocytoses seen in the French National Reference Center for Histiocytoses. Patients had histologically confirmed L-group histiocytosis, and had at least one determination of antinuclear antibodies. Some of them had been tested for other autoantibodies, such as anticardiolipid (ACL) and antibeta2glycoprotein I (B2GP1) antibodies, and/or had lupus anticoagulant (LA) testing. Antiphospholipid antibodies (APL) were considered positive if ACL, antiB2GP1 or ACC were positive on at least 2 successive determinations separated at least by 12 weeks. The presence of autoimmune disease was systematically evaluated through medical charts, in which a systematic questionnaire for 19 autoimmune diseases was collected.

Results: Two hundred and thirty-one patients were included, including 167 ECD, 35 LCH, and 29 mixed histiocytosis patients. The overall prevalence of autoimmunity was 40.1% in ECD, 48.3% in mixed histiocytosis and 20.0% in LCH (p=0.04). The prevalence of autoimmune diseases was 12.0% in ECD and 8.6% in LCH (p=0.77). The clinical features and BRAF status of ECD patients with and without autoimmunity were not different. The prevalence of autoimmunity was not statistically different in

patients with ECD who received interferon-alpha (n = 144) and those who did not receive interferon-alpha (44.4% versus 36.5%, p=0.41), or between those who received infliximab (n = 19) and those who did not receive infliximab (42.1% vs. 42.3%, p=1.0). Seventy-five ECD patients received targeted therapy. Of these, 8.0% had autoimmune disease, 22.7% had antinuclear antibodies, and 24% had persistent antiphospholipid biology. The ACL titers decreased significantly under treatment. One patient with systemic lupus erythematosus did not experience flare during the treatment.

Conclusion: Autoimmunityis more common in ECD (including mixed histiocytosis) than in LCH, and appears to be independent of the previous treatments (interferon, infliximab). In ECD patients under targeted (anti BRAF or anti MEK) therapy, the ACL titers decrease under treatment.

8. Efficacy of Dual BRAF/MAP2K1 Blockade in BRAF mutant Erdheim Chester Disease Patients

Roei D. Mazor [1], Ran Weissman [1,2], Judith Lockman [3], Liran Domachevsky [3,4], Shirley Shapira [5], Oshrat Hershkovitz-Rokah [1,2], David Groshar [3,4] and Ofer Shpilberg [1,6].

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Background: Erdheim Chester Disease (ECD), a rare inflammatory myeloid neoplasm, is known to be fundamentally reliant on the constitutive activation of the MAPK signaling pathway in the majority of patients. Consequently, pharmacological inhibition of the V600E mutant BRAF kinase has proven to be a safe and efficacious long term therapeutic strategy for BRAF mutant ECD patients. Nevertheless, in a subset of these patients, the efficacy of long term treatment may diminish, thus facilitating disease progression.

Patients & Methods: Herein, we retrospectively describe three BRAF mutant ECD patients whose treatment with Vemurafenib was upgraded to Vemurafenib/Cobimetinib dual therapy due to progression of their disease. The patients were primarily evaluated using Magnetic Resonance Imaging (MRI) in order to assess their CNS response to therapy. Routine clinical and neurological evaluations, comprehensive laboratory investigations and whole body 18 F Fludeoxyglucose Positron Emission Tomography/Computed Tomography (PET/CT) were also utilized.

Results: Three patients with a mean age of 52.6 years were treated with Vemurafenib monotherapy for a mean duration of 26.6 months (range: 6-52). Monotherapies were upgraded to Vemurafenib/Cobimetinib dual therapy due to signs of disease progression (2/3) or inability to withstand treatment related toxicities at effective doses (1/3). The combination therapy was administered for a mean duration of 12 months (range: 10-14). All three patients exhibited clinical and neurological improvement. Regression of

lesions on MRI was noted in two patients. Both patients characterized by a PET avid disease responded to the biological treatment regimen with complete metabolic remissions.

Conclusion: Dual pharmacological inhibition of both BRAF and downstream MAP2K1 may be a safe and effective therapeutic strategy for BRAF mutant ECD patients exhibiting clinical and/or radiological evidence of disease progression. This strategy may also be appropriate in the settings of a rapidly progressing, aggressive disease phenotype, as well as for patients who cannot tolerate effective doses of a BRAF inhibitor.

9. Hypothyroidism in Erdheim-Chester Disease: Experience from the National Institutes of Health

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Background: Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis affecting multiple organs, including the endocrine system. While endocrine involvement in ECD is well characterized, infiltration of the hypothalamic-pituitary-thyroid axis may cause either primary or central hypothyroidism that is often underdiagnosed. The prevalence of hypothyroidism and the occurrence of isolated central hypothyroidism in ECD has not been thoroughly investigated.

Methods: A prospective cohort study of biopsy-confirmed cases of ECD was conducted at the National Institutes of Health. Clinical, radiographic, and biochemical characteristics were assessed. All subjects underwent baseline evaluation with a thyroid function test, including TSH, free thyroxine (fT4) and total thyroxine (T4).

Results: Sixty-one subjects with ECD (46 males, 54.3 ± 10.8 years) were evaluated. Seventeen subjects (28%) had hypothyroidism and were receiving thyroid hormone supplementation before enrollment, with a mean TSH 2.00 ±1.63 mcIU/mL (normal 0.27-4.20 mcIU/mL), fT4 1.52 ±1.51 ng/dL (normal 0.9-1.7 ng/dL), and T4 7.42 ±2.15 mcg/dL (normal 4.5-11.7 mcg/dL). The prevalence of hypothyroidism was higher than general population estimates (28% vs. 3.7%, P<;0.05). No subject presented with myxedema coma or thyrotoxicosis. One subject (1.6%), a 61- year-old Caucasian female with ECD-related cerebellar dysfunction, retroperitoneal fibrosis, and osteosclerosis, harbored the BRAF V600E pathogenic variant and had a biochemical pattern suggestive of isolated central hypothyroidism: TSH 0.16 mcIU/mL, fT4 1.2 ng/dL and a normal baseline pituitary function test. She did not report symptoms suggestive of clinical thyroid disease and her physical examination was unremarkable. Pituitary MRI showed a small hypoenhancing lesion in the posterior aspect of the pituitary gland that is clinically insignificant. Dynamic TSH-secretion testing with a thyrotropin releasing hormone (200 µg IV synthetic TRH with serial TSH

testing) demonstrated a blunted response in keeping with central hypothyroidism; baseline TSH 0.35 mcIU/mL, peak 2.90 mcIU/mL (ΔTSH <7 mcIU/mL).

Conclusion: The prevalence of hypothyroidism (1 in 4) is high in subjects with ECD. Clinicians should have a low threshold to screen for hypothyroidism in this at-risk population. Central hypothyroidism is a rare manifestation of ECD and should be suspected in the setting of pituitary disease with a fT4 level below the laboratory reference range or low-normal levels in conjunction with a low, normal, or mildly elevated TSH.

10. Acute Pancreatitis from treatment with BRAF-inhibitors in patients with Erdheim-Chester Disease

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Introduction: Vemurafenib and dabrafenib are tyrosine kinase inhibitors that are used to treat patients with BRAF-V600-mutant Erdheim-Chester disease (ECD). Common adverse effects of these agents include arthralgias, fatigue, rash, and skin papillomas. Acute pancreatitis from dabrafenib has only been reported in post-marketing studies while pancreatitis from vemurafenib has a prevalence of 0.2% (6 out of 3,603 patients) in clinical trials among patients treated with vemurafenib for metastatic melanoma. In the landmark VE-BASKET trial, there were no reported cases of acute pancreatitis in ECD patients treated with vemurafenib. In this study, we report BRAF-inhibitor-associated acute pancreatitis in three patients with ECD.

Methods: This was a retrospective study of ECD patients treated with vemurafenib or dabrafenib from January 1998 to July 2018. All patients had a diagnosis of ECD made by using clinical criteria in conjunction with histopathologic findings.

Results: A total of 89 adults with ECD were identified. Forty-four patients were tested for the BRAF-V600E mutation and 25 (57%) were positive. Among the cohort who tested positive, 21 patients were treated with either vemurafenib (90%) or dabrafenib. The median age at diagnosis was 57 years (range 32-76) and 12 (57%) were male. The most common side effects were fatigue (29%) and skin papillomas (14%). Three patients (14%) developed acute pancreatitis. Among the subgroup of patients who developed acute pancreatitis, the median age at diagnosis was 52 years (range 34-64) and 2 were male. Primary organs affected by ECD included bone (100%), CNS (67%), skin (67%), kidneys (67%), retroperitoneal structures (67%), and bone marrow (33%). All patients had first-line therapy with prednisone, methotrexate, and/or infliximab before starting a BRAF- inhibitor. Two patients were treated with vemurafenib (1440 mg/day and 960 mg/day, respectively), while one patient was treated with dabrafenib 150 mg/day. The median time to onset of acute pancreatitis was 4 days (range 1-365). Two patients had characteristic abdominal pain, 3 had elevation in serum lipase (range 224 14,905 Units/Litre), and 3 had positive CT findings. All patients had resolution of their acute pancreatitis after discontinuing their BRAF-inhibitor. None of the patients had other risk factors for pancreatitis. Two patients were restarted on

different BRAF-inhibitors after progression of disease. One patient was started on dabrafenib 75 mg/day and trametinib 2 mg/day nine months after discontinuation of vemurafenib with no recurrence of acute pancreatitis since her last day of follow up (1.5 months). Another patient was started on vemurafenib 240 mg/day eleven months after discontinuation of dabrafenib with no recurrence of acute pancreatitis since her last day of follow up (27 months).

Conclusion: The temporal relationship between BRAF-inhibitor exposure and the onset of acute pancreatitis, and resolution of symptoms on drug discontinuation suggests that this was a true adverse effect to BRAF- inhibitors. Developing acute pancreatitis from one BRAF-inhibitor may not be a contraindication to starting another BRAF-inhibitor in the future. Acute pancreatitis as a side effect of BRAF-inhibitors appears to be more common in ECD compared to melanoma, though the mechanism remains unclear.

POSTER PRESENTATIONS

1. Erdheim-Chester Disease Global Alliance Achievements and Statistics

Kathleen Brewer

ECD Global Alliance, Louisiana, USA

The ECD Global Alliance (ECDGA) has been registering Erdheim-Chester Disease patients since the organization's inception in 2008. Contact information for patients is captured, but little medical information has historically been recorded. The information available provides insight into the number of ECD patients and where they are located. The ECDGA has funded seven research projects and an ECD dedicated patient registry, totaling over $650,000. This has aided in effective treatment and mutation discoveries that have drastically improved care for patients. Thirty-three ECD Care Centers have been identified to more effectively provide care to patients across the globe. Support has been provided to over 530 families from 54 countries through the organization's website, events, and more.

2. Sick-Day and Emergency Rules for Adrenal Insufficiency in Subjects with Erdheim-Chester Disease

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Background: Erdheim-Chester disease (ECD) is a rare multi-organ non-Langerhans cell histiocytosis characterized by chronic and uncontrolled inflammation resulting in fibrotic tissue damage. Infiltration of the hypothalamic-pituitary-adrenal (HPA) axis that may cause adrenal insufficiency (AI) is often underdiagnosed in ECD. Sick-day and emergency rules for AI in subjects with ECD have not been investigated.

Methods: A prospective cohort study of ECD was conducted at the National Institutes of Health. Clinical, radiographic, and biochemical characteristics were assessed. All subjects underwent evaluation of AI using a paired serum morning cortisol and adrenocorticotropic hormone as a preliminary test. Sick-day and emergency rules pattern were recorded.

Results: Sixty-one consecutive subjects with ECD (46 males, 54.3 ± 10.8 years) were evaluated; 56% (32/57) harbored BRAF V600E. Adrenal gland and pituitary/stalk infiltration were present in 18/57 (31.6%) and 9/57 (15.8%) on CT or MRI, respectively. Twelve subjects (12/61, 21%) had a prior diagnosis of AI due to ECD. No subject presented with an adrenal crisis as the initial manifestation of ECD, although all subjects with AI (100%) reported lack of education toward sick-day and emergency rules before their first visit. No subjects with AI carried medical identification jewelry, and none had a written emergency care plan for AI.

Conclusions: To our knowledge, this is the first study investigating the importance of sick-day and emergency rules in relation to AI and ECD. ECD patients with AI are at significant risk of morbidity and mortality during an adrenal crisis. Therefore, clinicians should familiarize themselves with the signs and symptoms of AI, and should periodically screen patients. Clinicians should refer patients to an endocrinologist, with whom they can partner to develop an emergency care plan outlining the management of AI during an acute illness (e.g., flu or fever). Patients and their caregivers should receive ongoing education about how to manage steroid dosing during illness, and all ECD patients with AI should wear medical identification jewelry.

3. mTOR Inhibition in Erdheim-Chester disease

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Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis with an often progressive, life-threatening course. We tested the efficacy and safety of mammalian target of rapamycin (mTOR)-inhibitors in 14 patients with ECD. Ten of the 14 patients had been enrolled in a previous trial testing sirolimus (SRL) and prednisone (PDN) for ECD (Gianfreda D et al. *Blood*. 2015); we here report the results of their extended follow-up. The remaining 4 patients were treated with everolimus (EVE) monotherapy. Long bones and retroperitoneum were involved in 12 patients (86%), large vessels in 8 patients (57%), heart, lungs, skin, hypothalamic-pituitary axis in 5 patients (36%), CNS and maxillary bones in 3 patients (21%). The V600E-BRAF mutation was present in 5/8 tested patients while NRAS, KRAS, PIK3CA mutations were absent in 4/4 tested patients. Three patients were previously non-responders to other treatments

(alpha-interferon, cyclophosphamide and prednisone plus colchicine). The median follow-up was 32.5 months (interquartile range, 9.5-69.5). Two patients died for progression of the disease and one for small-cell lung cancer (21%). Eleven patients (79%) achieved stable disease or objective responses. Interestingly, the responses observed in the patients treated with EVE monotherapy were comparable to those of patients treated with SRL+PDN, suggesting that mTOR inhibition is efficacious *per se*. The treatment was generally well tolerated. One patient withdrew SRL for infectious panniculitis and another patient temporarily withdrew it for 3 months for interstitial pneumonitis and then resumed it at a lower dose. The most common side-effects were hypertension, dyslipidemia, worsened pre-existing type 2 diabetes.

mTOR inhibitors induce objective responses or disease stabilisation in patients with ECD; they are well tolerated and may be considered a feasible therapeutic option for ECD patients, particularly for those who have no indication to BRAF inhibitors or who cannot tolerate or have access to targeted therapies.

4. Effects of Testosterone Supplementation on Hypogonadism associated with ECD

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Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis characterized by the abnormal accumulation of foamy histiocytes, resulting in chronic inflammation, fibrosis, and eventually organ dysfunction. Patients often present with bone pain and fatigue, but ECD can manifest with multisystem involvement, including endocrinopathies. Previously, we demonstrated that 60% of the ECD cohort studied at the National Institutes of Health (NIH) presented with hypogonadism confirmed by the presence of characteristic signs and symptoms in conjunction with decreased total or free testosterone levels. The purpose of this study is to characterize how testosterone supplementation modulates symptoms of hypogonadism in ECD patients, and how it affects 18F-FDG activity in the testes. Clinical data from patients was extracted from NIH records, and18F-FDG activity was quantified using an SUV-threshold based semi-automated approach with MIM Vista workshop. Preliminary results have shown that testosterone supplementation improves some of the signs and symptoms of hypogonadism like sexual dysfunction and fatigue, and decreases 18F-FDG activity in the testes. Our study warrants further analysis of how testosterone supplementation regulates the gonadotropin response and affects the symptoms of hypogonadism in Erdheim-Chester disease patients.

5. Erdheim-Chester Disease: Expanding the spectrum of cutaneous manifestations

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Importance: Erdheim-Chester disease (ECD) is a rare condition with limited information available regarding cutaneous manifestations.

Objective: To describe the clinical and histopathologic features of cutaneous involvement in ECD. Design, Setting, Participants: Single center retrospective analysis that included patients 18 years and older with clinically and histopathologically confirmed diagnosis of ECD between January 1990 and April 2017. From this cohort, patients were screened for cutaneous involvement.

Outcomes and Measures: Primary outcomes included cutaneous manifestations (morphology and topography of lesions), BRAF mutation status, and response to drug therapy.

Results: Of 71 patients with ECD, 15 (21%; median age 52; 60% male) presented with cutaneous manifestations. The most common finding was xanthelasma-like lesions (XLL) seen in eight patients. Two patients had non-facial cutaneous xanthomas. Seven patients presented with non-xanthoma cutaneous involvement, with the most common finding being subcutaneous nodules (n=5). A single patient presented with granuloma annulare-like lesions. Another patient with mixed ECD and Langerhans cell histiocytosis presented with lightly scaling, pink-red macules. BRAF-V600E mutations were seen in 50% of ECD patients with cutaneous involvement compared to 56% of patients in the whole ECD cohort. Cladrabine use showed improvement in skin findings in two of three patients treated for non-xanthelasma lesions. Vemurafenib was beneficial for one patient with BRAF-V600E mutation.

Conclusion: The most common skin finding associated with ECD is periorbital XLL. Other presentations include non-facial cutaneous xanthomas, panniculitis-like lesions, and granuloma annulare-like lesions. Treatment of ECD is challenging and target therapy should be utilized when possible.

6. Cognitive dysfunctions in Erdheim-Chester disease

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Objectives: Although neurological manifestations and changes in brain volumes have been described in Erdheim-Chester disease (ECD), it remains unknown whether the disease may be associated with subtles cognitive dysfunctions. Here, we conducted a descriptive study aiming to describe the neuropsychological manifestations associated with ECD.

Method: This study involved the completion of a 60-minute neuropsychological assessment in patients younger than 70 years old, who were not treated with Interferon in the last 6 months, and did not have other serious illnesses. The neuropsychological tests used were: Wisconsin Card Scoring Test (cognitive flexibility), D2 (attention processes), Stroop (selective attention, inhibitory processes), California Verbal Learning Test (episodic verbal memory), Lexical and Categorical Fluence, Digit span, Trail Making Test a and b (working memory). For each neuropsychological test, the individual score was compared to French population norms according to age and education level. Results were converted to standard scores (Z-scores; i.e. number of standard deviations above or below the mean) as follows: {[individual score]-[population mean]/ [standard deviation of the population]}. Z-scores were then compared to the reference. Bonferroni's correction was applied to adjust p-values for multiple analyses.

Results: 32 ECD patients were included (15 women, mean age = 59 years). The results highlighted the attentional and mnemic features: The productivity and concentration indices of D2 were significantly reduced (GZ: $t = 16.12$, $p < 0.0001$, GZ-F: $t = 15.99$, $p < 0.0001$, KL: $t = 37.01$ $p < 0.0001$). Long-term recall and short-term indexed recall capabilities were also significantly lower (STIR: $t = -3.01$, $p = 0.006$, LTFR: $t = -2.87$, $p = 0.008$, LTIR: $t = -3.63$, $p = 0.001$). Performances in other neuropsychological tests did not statistically differ from normal ranges.

Conclusion: This study argues for some specific neuropsychological dysfunctions in EDC patients. It remains to clarify whether these cognitive changes may impact the quality of life of EDC patients and require specific treatments such as cognitive remediation therapy.

INVITATION TO ATTEND PATIENT AND FAMILY SOCIAL

Thank you for your attendance and participation!

Special thanks to this year's co-host!

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