Bone marrow findings in Erdheim-Chester disease: increased prevalence of chronic myeloid neoplasms

Erdheim-Chester disease (ECD) is a rare subtype of non-Langerhans cell histiocytosis (LCH) that is diagnosed by histopathologic identification of a CD68 positive foamy histiocytic infiltrate in conjunction with established clinical and radiological criteria.[1,2] While the etiology remains uncertain, most ECD patients demonstrate activation of the mitogen activated protein kinase (MAPK) pathway (*RAS-RAF-MEK-ERK*) leading to immune dysregulation.[3] The cell of origin of ECD is elusive, although recent evidence suggests its origin from myeloid progenitor cells, monocytes or macrophages.[4] In the past few years, increasing evidence has mounted regarding the development of other myeloid malignancies in histiocytosis. A population-based study in LCH demonstrated an increased prevalence of acute myeloid leukemia.[5] Another recent study showed a high prevalence of myeloid neoplasms in ECD and other subtypes of non-LCH as well: 10.1% in the entire cohort, 7.8% in ECD, and 25% in mixed histiocytosis.[6] In this study, the most common myeloid neoplasm was chronic myelomonocytic leukemia (CMML). As ECD is a rare disease, more data are needed to establish the prevalence of concomitant or subsequent myeloid neoplasms to help device appropriate staging and monitoring strategies for these patients. In this study, we aimed to verify the findings and determine the prevalence of concomitant myeloid neoplasms in a large cohort of patients with ECD from our institution.

After obtaining institutional review board approval, we reviewed the records of ECD patients diagnosed and evaluated from January 1998 to December 2018. For this study, we specifically focused on patients who underwent bone marrow biopsy and reported the pertinent findings. Clinical and molecular data were abstracted, where available. To reduce bias, the charts were reviewed by two investigators independently (*GG and AR*). We also pursued molecular testing using whole exome sequencing (WES) or polymerase chain reaction (PCR) for patients who had concomitant myeloid neoplasms where the tissue was available. For WES, variants that met either of the below criteria were identified as high confidence somatic variants: 1. previously reported in the Catalogue Of Somatic Mutations In Cancer (COSMIC) databases with at least two supporting reports; 2. previously reported in COSMIC databases with only one supporting report but predicted to be 'deleterious' for at least two of these three mutation effect prediction algorithms (Polyphen2, Provean and SIFT).

We included 89 patients with clinicopathological features of ECD in this study, of which one had mixed ECD-LCH. The median age at diagnosis was 55 years (range: 34-80). Of the entire cohort, 23 (25.8%) had a bone marrow-biopsy done during the course of their disease. The indications for bone marrow biopsy were: i) an abnormal peripheral blood count to rule out hematologic malignancy (n=15), ii) clinical suspicion for ECD due to bone involvement on imaging studies (n=7) and iii) to rule out prostate cancer recurrence in one patient with a history of prostate cancer presenting with new osteosclerotic lesions. Of these 23 patients, seven (30.4%) had ECD involving the marrow (7.8% of entire cohort). We found the presence of a concomitant/subsequent myeloid neoplasm in 3 of 89 (3.3%) ECD patients.

Patient 1: A 75-year-old Caucasian male presented with chronic fatigue, unintentional weight loss of nine pounds, abdominal pain, and progressive ataxia to the clinic. He had a known history of CMML-0 for the past 5 years for which he was being monitored without therapy. He underwent a whole body fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scan that showed low level uptake throughout the abdominal mesentery, bone marrow, as well as bilateral orbital infiltrative process (Figure 1). He underwent orbital biopsy that showed atypical histiocytic proliferation suggestive of ECD, which was BRAF-

Table 1. Patients with Erdheim-Chester disease (ECD) and chronic myeloid neoplasms

	Patient 1	Patient 2	Patient 3
Age at ECD diagnosis, years	75	51	59
Age at myeloid neoplasm diagnosis, years	70	35	59
Myeloid neoplasm subtype	CMML-0	Essential thrombocythemia (initial) MPN, unclassifiable (subsequent)	CMML-0
ECD organ involvement	Orbit, mesentery, bone marrow	Bones, mesentery, liver, retroperitoneal	Skin, bones
Biopsy site ECD^{+}	Orbit	Perinephric	Skin
Molecular findings myeloid neoplasm	NA	*JAK2 V617F*$^{+}$	*KRAS* c.35G>A (VAF 42%) *ASXL1* c.1773C>G (VAF 42%)
Molecular findings ECD	*BRAF-V600E*	*JAK2 V617F*$^{+}$ *BRAF-V600*-wt	*KRAS* c.35G>A (VAF 28%) *ASXL1* c.1773C>G (VAF 9%)
Treatment and outcome	Corticosteroids, PD Anakinra, PD Vemurafenib, intolerance Dabrafenib, SD	Interferon alfa, intolerance Anakinra, PD Trametinib, PR	Hydroxyurea for CMML, PD
Vital status and overall survival from ECD diagnosis	Dead, 3 years	Dead, 3.5 years	Dead, 3.5 years

CMML: chronic myelomonocytic leukemia; MPN, NOS: myeloproliferative neoplasm, not otherwise specified; NA: not available; PD: progressive disease; SD: stable disease; PR: partial response.

V600E+ by immunohistochemistry. He also underwent a bone marrow biopsy that showed a similar histiocytic infiltrate suggestive of ECD. He was treated with several agents, including corticosteroids, anakinra, vemurafenib and dabrafenib (Table 1). He was eventually lost to follow-up but subsequently was hospitalized for sepsis with pancytopenia culminating in multi-organ failure and death.

Patient 2: A 51-year-old Caucasian male with *JAK2*V617F^{+} essential thrombocytosis (ET) on hydroxyurea developed pericardial effusion and cardiac tamponade 17 years after ET diagnosis. He was also found to have bilateral pleural effusions, ascites, and retroperitoneal soft-tissue infiltration. He underwent a biopsy of the perinephric soft tissue that demonstrated histiocytic infiltrate, which in conjunction with knee osteosclerosis, was consistent with ECD (Figure 1). His tissue was tested for the *BRAF*-mutation and was *BRAF*-wild-type. He also underwent a bone marrow biopsy at this time and it was diagnosed as *JAK2*V617F^{+} myeloproliferative neoplasm, unclassifiable (MPN, unclassifiable). There was no involvement by ECD in the marrow, although it revealed a slight increase in CD163^{+} histiocytes with spindled morphology. He underwent treatment with interferon-α, anakinra, and later trametinib but unfortunately died three and a half years later due to progressive multi-organ failure resulting from fibrosis of the liver and kidney.

Patient 3: A 59-year-old Caucasian woman was seen in dermatology clinic for a slowly progressive skin rash for 3 years. The rash was in the form of yellowish-red papules that started around her eyelids but now involved her face, arms, trunk and legs. She had multiple skin biopsies that showed foamy histiocytes and Touton giant cells suggestive of ECD. She also had a technetium-99m bone scan that showed meta-diaphyseal osteosclerosis of the bilateral tibia and femur near the knee, confirming

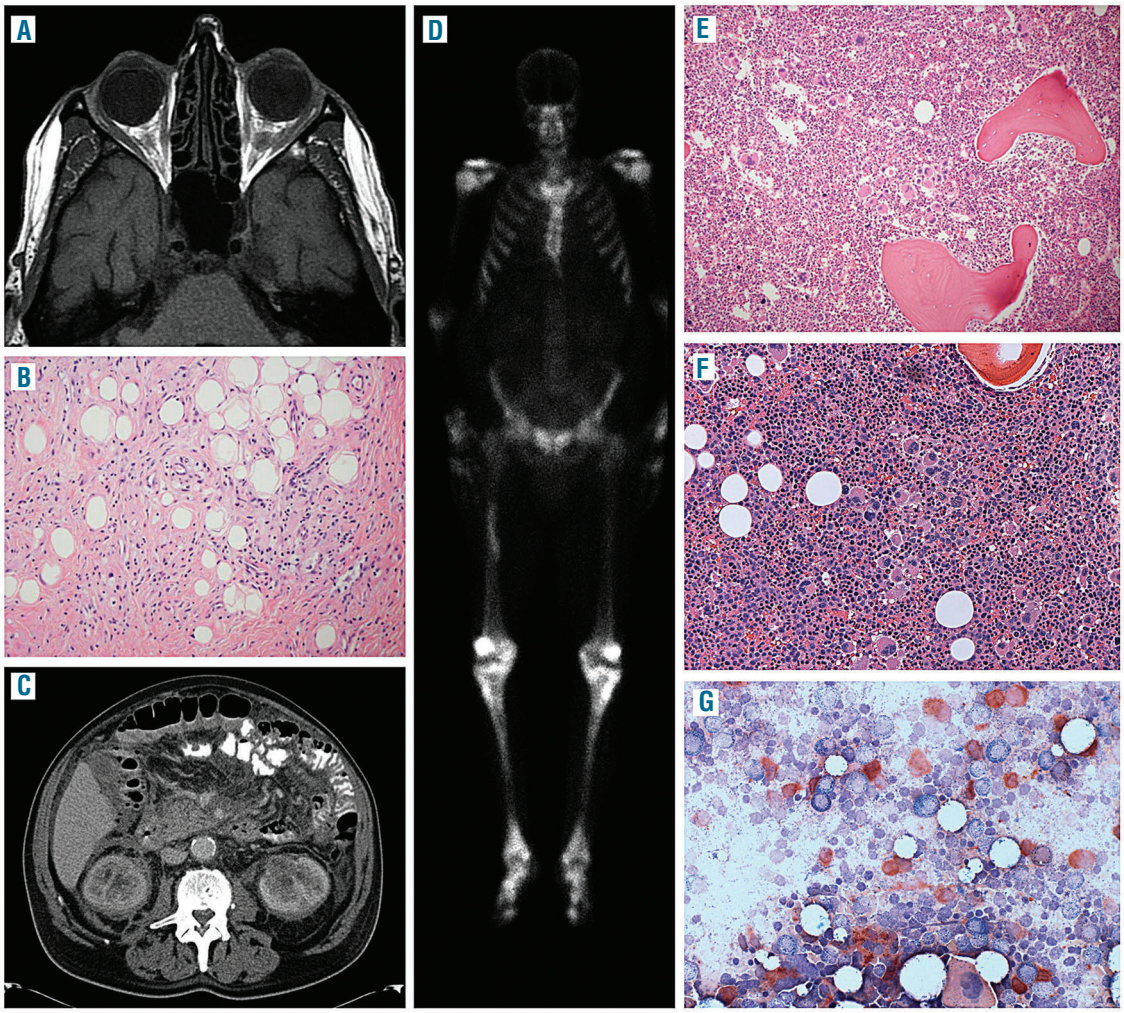

Figure 1. Radiographic and histopathological features of patients with Erdheim-Chester disease (ECD) and chronic myeloid neoplasms. (A) Axial gadolinium T1-weighed magnetic resonance imaging of orbit in patient 1 showing hyperintense orbital lesions of ECD. (B) Orbital biopsy from patient 1 demonstrating foamy histiocytic infiltrate in a background of fibrosis. (C) Computed tomography scan demonstrating perinephric infiltrate "hairy kidney" of ECD in patient 2. (D) Technitium-99m bone scintigram of patient 2 showing bilateral symmetric dia-metaphyseal osteosclerosis. (E) Bone marrow biopsy from patient 2 demonstrating hypercellular marrow with trilineage hyperplasia and megakaryocytic atypia with loose clusters. No involvement by ECD. (F) Bone marrow biopsy from patient 3 showing hypercellular marrow with trilineage hyperplasia and dysmegakaryopoiesis. No involvement by ECD. (G) Butyrate esterase/chloroacetate esterase stain on the bone marrow aspirate of patient 3 supports the diagnosis of chronic myelomonocytic leukemia with increased butyrate esterase positive monocytes (brown), and increased dual esterase positive cells (brown+blue).

the ECD diagnosis. Her peripheral blood counts showed mild leukopenia ($3.0x10^9$/L) and absolute monocytosis ($1.3x10^9$/L), which in conjunction with bone marrow findings, met the diagnostic criteria for CMML-0. We pursued WES on her bone marrow mononuclear cell DNA as well as the skin biopsy that showed mutations in *ASXL1* (c.1773C>G_p.Tyr591X, CMML VAF: 0.42, ECD VAF: 0.09) and *KRAS* (c.35G>A_p.Gly12Asp, CMML VAF: 0.42, ECD VAF: 0.28).[7] She was initially observed for 3 years, but then started on hydroxyurea due to her progressive symptoms of bone pain. She was admitted to the hospital six months later for weakness and abdominal pain, and developed respiratory failure from aspiration leading to her death.

We conducted a follow-up person-year analysis to circumvent any errors from loss to follow-up. Overall, the 89 ECD patients were followed for a cumulative duration of 265 years, resulting in a myeloid neoplasm in three cases. Therefore, the prevalence of myeloid neoplasms among ECD was 1.1 cases per 100 patient-years of follow up. Previous studies have not reported such a finding.

In our cohort, myeloid neoplasms were present in 3.3% of ECD patients, most often manifesting as CMML. ECD involvement of the bone marrow has not been well characterized before. Our study shows that it may occur in ~8% of patients and contribute to peripheral blood count abnormalities as well. In the previous study evaluating this question, the prevalence of myeloid neoplasms in non-LCH patients was much higher at 10.1%.[6] There may be several reasons to account for this difference. The prior study included patients from a cancer center in the United States and a histiocytosis referral center in France, with a higher percentage of myeloid neoplasms from the former (15.3%) as compared to the latter (8.6%). This may reflect potential referral bias, with a higher proportion of myeloid neoplasm patients being referred to a tertiary cancer center. In contrast, our cohort includes patients seen at a tertiary referral center for all subspecialties, which includes several patients with incidentally discovered histiocytosis who don't have a concomitant myeloid neoplasm. The previous study also had a higher proportion of patients with mixed ECD-LCH histiocytosis, a subgroup that was found to have more significant association with a concomitant myeloid neoplasm than ECD alone. Nevertheless, even a smaller degree of association between two rare entities (ECD and CMML) is unlikely to be fortuitous, especially when demonstrated in three large independent institutional cohorts. Both ECD and CMML have been found to demonstrate perturbations in classical monocytes,[8-11] which may underlie their coexistence mechanisms. In our series, the molecular findings were similar in two of three cases, one with identical *KRAS* and *ASXL1* mutations in CMML and ECD, and another with *JAK2*V617F positivity in both the ECD and MPN. Previously, a case report demonstrated similar *BRAF, TET2*, and *SRSF2* mutations in LCH tissue as well as the $CD34^+$ progenitor cells in a case of mixed ECD-LCH and concomitant acute myelomonocytic leukemia.[4] Although the *JAK2*$V617F^+$ in skin biopsy in our patient could be a result of blood contamination of ECD skin lesion, the accumulating body of evidence from various studies suggests a common clonal origin for the myeloid and histiocytic neoplasms. Our study has several notable limitations. The bone marrow evaluations were not performed uniformly in all patients on a research protocol, which makes it difficult to ascertain the exact prevalence of myeloid neoplasms in ECD. Moreover, in the cases where molecular studies were pursued, we neither pursued an analysis of germline DNA or $CD34^+/CD38^-$ nor sorted $CD14^+$ bone marrow cells to ascertain mutational specificity in the myeloid neoplasms. Our study shows that chronic myeloid neoplasms occur at a higher than expected frequency in ECD patients, and almost always present with peripheral blood count abnormalities such as unexplained thrombocytosis, anemia, or monocytosis. Our findings suggest that bone marrow evaluation should be promptly undertaken in ECD patients with such unexplained abnormalities.

Gaurav Goyal,[1] Aishwarya Ravindran,[2] Yuanhang Liu,[3] Rong He,[2] Mithun V. Shah,[1] N. Nora Bennani,[1] Mrinal M. Patnaik,[1] Karen L. Rech[2] and Ronald S. Go[1] on behalf of the Mayo Clinic Histiocytosis Working Group

[1]Division of Hematology, Mayo Clinic; [2]Department of Laboratory Medicine and Pathology, Mayo Clinic and [3]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

Correspondence: RONALD S. GO/GAURAV GOYAL Go.Ronald@mayo.edu/GGoyal@uabmc.edu

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References

1. Diamond EL, Dagna L, Hyman DM, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. Blood. 2014;124(4):483-492.
2. Goyal G, Young JR, Koster MJ, et al. The Mayo Clinic Histiocytosis Working Group Consensus Statement for the Diagnosis and Evaluation of Adult Patients With Histiocytic Neoplasms: Erdheim-Chester Disease, Langerhans Cell Histiocytosis, and Rosai-Dorfman Disease. Mayo Clin Proc. 2019;94(10):2054-2071.
3. Diamond EL, Durham BH, Haroche J, et al. Diverse and targetable kinase alterations drive histiocytic neoplasms. Cancer Discov. 2016; 6(2):154-165.
4. Durham BH, Roos-Weil D, Baillou C, et al. Functional evidence for derivation of systemic histiocytic neoplasms from hematopoietic stem/progenitor cells. Blood. 2017;130(2):176-180.
5. Goyal G, Shah MV, Hook CC, et al. Adult disseminated Langerhans cell histiocytosis: incidence, racial disparities and long-term outcomes. Br J Haematol. 2018;182(4):579-581.
6. Papo M, Diamond EL, Cohen-Aubart F, et al. High prevalence of myeloid neoplasms in adults with non-Langerhans cell histiocytosis. Blood. 2017;130(8):1007-1013.
7. Goyal G, Liu Y, Ravindran A, et al. Concomitant Erdheim-Chester disease and chronic myelomonocytic leukaemia: genomic insights into a common clonal origin. Br J Haematol. 2019;187(2):e51-e54.
8. Itzykson R, Kosmider O, Renneville A, et al. Clonal architecture of chronic myelomonocytic leukemias. Blood. 2013;121(12):2186-2198.
9. Patnaik MM, Timm MM, Vallapureddy R, et al. Flow cytometry based monocyte subset analysis accurately distinguishes chronic myelomonocytic leukemia from myeloproliferative neoplasms with associated monocytosis. Blood Cancer J. 2017;7(7):e584.
10. Milne P, Bigley V, Bacon CM, et al. Hematopoietic origin of Langerhans cell histiocytosis and Erdheim-Chester disease in adults. Blood. 2017;130(2):167-175.
11. Bonnet P, Chasset F, Moguelet P, et al. Erdheim-Chester disease associated with chronic myelomonocytic leukemia harboring the same clonal mutation. Haematologica. 2019 Jun 20. [Epub ahead of print].