of additional mutations, including structural variants or copy number alterations, confirms that the mutation in *CALR* is sufficient to develop ET.[14]

However, the factors influencing the latency of the disease are still unknown. Our results rule out genetic alterations as a mechanism involved in latency, as no additional mutations could be detected in any of the clonal cells evolving independently for >16 years. These data provide a basis for further studies aimed at identifying factors influencing disease latency, including epigenetic alterations or the influence of the microenvironment. These studies might lead to a better understanding of MPN evolution, as well as potential strategies to prevent or delay disease development. The recent finding of *JAK2* mutations in umbilical cord hematopoietic stem cells[15] might underestimate the number of MPN cases originated in utero. In addition, the finding that transplacental transfer can occur in myeloproliferative diseases is also relevant when a twin is diagnosed with this pathology at an early age, suggesting that examination of the other twin might result in an early diagnosis, facilitating a close surveillance of patient evolution.

*R.V.-M. and J.G.-A. contributed equally to this study.

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To the editor:

Anakinra as efficacious therapy for 2 cases of intracranial Erdheim-Chester disease

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Erdheim-Chester disease (ECD) is a myeloid neoplasm characterized by recurrent mutations in mitogen-activated protein kinase pathway genes, including *BRAF*, *ARAF*, *N/KRAS*, *MAP2K1*, and *PIK3CA* mutations and fusions in *ALK* and *NTRK1*.[1-4] Lesional ECD cells elaborate an array of pro-inflammatory cytokines,[5,6] and clinical disease in ECD is mediated by both tumorous infiltration and chronic systemic inflammation. Cytokine-directed therapies have been attempted in ECD treatment, including anakinra (an interleukin 1 [IL-1] receptor antagonist) and infliximab (a monoclonal antibody directed against tumor necrosis factor α),[7] as well as a clinical trial of tocilizumab (a monoclonal antibody against IL-6; NCT01727206). Anakinra has been reported in single cases and small series to be efficacious in the treatment of ECD-related bone pain and constitutional symptoms, perinephric infiltrates, skin

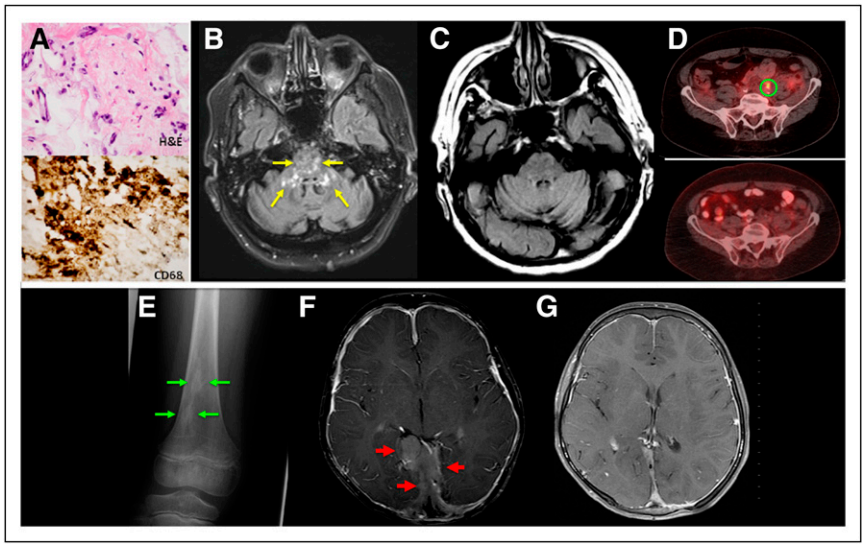

Figure 1. Perinephric tissue. Patient 1 with a CD68^{+} histiocytic infiltrate with admixed fibrosis (A). Axial T2-fluid attenuation inversion recovery MRI images demonstrate scattered lesions in the brainstem and cerebellar peduncles (yellow arrows) (B), and these are resolved after 6 months of treatment (C). A representative FDG-avid (SUV 3.1) periarterial lesion (D, upper) has resolved to background uptake (D, lower). Sclerotic lesions from the distal femur of patient 2 (E). Expansile meningeal infiltrations are demonstrated by axial postgadolinium T1-weighted MRI scan (red arrow) before treatment (F) and then are resolved 2 years into anakinra therapy (G).

lesions, and, in 1 case, a cardiac lesion.[8-13] Based on these reports and the unpublished experience of ECD-treating physicians, anakinra is listed as first-line ECD therapy in published guidelines, although it is not recommended for severe forms of disease such as cardiac or neurologic manifestations.[14]

In a recent Letter to the Editor in *Blood*, Cohen-Aubart et al reported the largest single-center retrospective series to date of patients with ECD treated with anakinra.[15] The authors presented a series of 12 ECD patients, previously treated with interferon-α-2a (IFN-α), with mixed but predominantly unfavorable responses to treatment with anakinra. Response to treatment defined by improvement in symptoms or diminished uptake by (^{18}F)-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan was seen in 3 patients, whereas the remainder stopped therapy because of toxicity or progressive disease. There were no favorable responses in patients with intracranial ECD, and, in 1, a new brain lesion developed during anakinra therapy, a manifestation of ECD independently associated with mortality.[16] Furthermore, another patient had progressive disease in the form of pericardial effusion and tamponade. The authors postulate that the patients in their series may have had unfavorable responses by virtue of having particularly refractory disease as evidenced by failure of IFN-α. On the basis of their series, they recommend against anakinra for intracranial ECD in favor of IFN-α or targeted therapies such as BRAF inhibitors. However, the potential response to anakinra for severe ECD that is naïve to IFN-α is unknown. We present here robust responses to anakinra in 2 patients with intracranial ECD without prior IFN-α treatment.

Patient 1, a 68-year-old man, had developed diabetes insipidus 10 years prior, although cranial imaging was not performed at that time. Later, he was evaluated for ataxia and dysarthria as well as progressive bone pain in both legs, fatigue, and night sweats. Enhanced magnetic resonance imaging (MRI) of the brain was performed and demonstrated (Figure 1B) scattered areas of T2-prolongation in the pons and middle cerebellar peduncles bilaterally. Computed tomography and FDG-PET demonstrated hypermetabolic infiltrations in the perinephric, periaortic, and perisplenic regions as well as avid, symmetric, sclerotic lesions in the femurs and tibia. Percutaneous needle biopsy of perinephric soft tissue demonstrated a mixed nonxanthomatous inflammatory/histiocytic infiltrate with marked CD68 immunoreactivity (Figure 1A), and admixed fibrosis. Biopsy of a tibial lesion demonstrated a xanthomatous histiocytic infiltrate, consistent with ECD. CD1a immunohistochemistry was not performed in light of the clinical phenotype highly consistent with ECD and also to preserve material for genotyping. Targeted sequencing demonstrated a *MAP2K1*^{C121S} mutation in lesional tissue. Treatment with IFN-α was deferred because of the patient's wish to avoid its known toxicities; therefore, treatment was initiated with anakinra, 100 mg injected daily. Clinical symptoms (constitutional and neurologic) improved over the coming weeks, and sequential MRI scans of the brain up to 6 months on treatment demonstrated resolution of T2 hyperintensities in the brainstem (Figure 1C). FDG-PET demonstrated reduction in hypermetabolism of abdominal and osseous infiltrates (Figure 1D). No toxicities have been observed, and the patient continues anakinra therapy, currently for 9 months.

Patient 2, a 7-year-old boy, presented with several weeks of lethargy, dizziness, worsening hearing loss, and facial asymmetry. He was found to have a left facial palsy on physical examination. Postgadolinium MRI of the brain revealed hydrocephalus and an extensive, multicentric, enhancing dural-based tumor in the anterior and posterior interhemispheric region with extension to the cavernous sinuses and sellar/suprasellar regions (Figure 1F). A biopsy was performed and interpreted as a non-Langerhans histiocytosis, rendering a diagnosis of juvenile xanthogranuloma. He underwent a craniotomy for tumor debulking and brainstem decompression, although the lesion regrew within months, symptomatic with seizures. The lesion grew despite successive treatment with (1) vinblastine and prednisone (per Langerhans cell histiocytosis III protocol) for 6 weeks, (2) cladribine for 6 cycles, and (3) clofarabine for 2 cycles.

The diagnosis of ECD was considered in light of this refractory disease and a skeletal survey was done and demonstrated bilateral sclerosis in the extremities (Figure 1E). A biopsy of a tibial bone lesion demonstrated a histiocytic infiltrate harboring the *BRAF*^{V600E} mutation, establishing an ECD diagnosis. Anakinra treatment was initiated at 2 mg/kg daily. Over the following 2 years, successive MRI scans have shown continued improvement of the dural thickening and lesional enhancement (Figure 1G). Osseous surveys showed gradual improvement and resolution of the sclerotic bone lesions over 2 years of therapy.

These are 2 cases of intracranial ECD with robust clinical and radiologic responses to treatment with anakinra, 1 a treatment-naïve patient and the other with disease refractory to chemotherapy. Efficacy of cladribine has been reported in a limited number of ECD cases,[17,18]

and clofarabine has been reported to be efficacious as salvage therapy in juvenile xanthogranuloma, but not in ECD.[19] Our patients did not endure intolerable local reactions, cytopenias, or complications of immunosuppression. In 1 prospective trial of anakinra, administered in the context of traumatic brain injury, the drug was found to have both reasonable penetration into the brain parenchyma and to lead to demonstrable reduction of cerebral IL-1 levels.[20] Therefore, the blood-brain barrier should not, in theory, impose limitations upon effectiveness of anakinra for intracranial ECD as compared with other sites of disease. The most salient difference between our patients and those from the reported treatment failures is that our patients were not treated previously with IFN-α. It is not clear why ECD refractory to IFN-α would be refractory to anakinra. The mechanism of IFN-α's activity in ECD is not well-understood; therefore, mechanisms of resistance to IFN-α are unclear as well. IFN-α is thought to have a variety of antineoplastic and immunomodulatory effects, including promoting differentiation of host immune cells to possess antitumor immunity or antiviral immunity.[21] A variety of resistance mechanisms to IFN-α have been postulated in the context of hematologic neoplasms and viral infections, such as upregulated expression of MAL[22] and JAK[23] family genes, as well as enhanced levels of IL-8.[24] It is possible that ECD resistant to IFN-α would not be sensitive to IL-1 blockade alone, but further study is certainly required.

In conclusion, we present 2 cases of intracranial ECD with marked radiologic and clinical response to initial treatment with anakinra. The clinical experience that anakinra is ineffective in certain localizations of ECD (brain and heart) may be explained by refractory manifestations of disease in those cases rather than by the organs involved. Although there have been advances in targeted therapies for ECD, particularly with vemurafenib for disease harboring the $BRAF^{V600E}$ mutation, treatment with therapies such as RAF inhibitors is not feasible or desirable in all cases for reasons of patient comorbidities as well as for reasons of limited access to such agents in many contexts. The poor outcomes that have been reported with central nervous system and cardiac ECD must remain a consideration, even in light of our 2 cases; however, further clinical experience may demonstrate that anakinra could be an alternative first-line therapy for severe forms of ECD, regardless of mutational status.

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