Erdheim-Chester disease among neuroinflammatory syndromes: the case for precision medicine

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Erdheim-Chester disease (ECD) is a rare, non-Langerhans histiocytosis characterized by xanthogranulomatous infiltration typically affecting long bones, cardiovascular system, retroperitoneum, and lung, and that involves the CNS in 25%–50% of patients (table).1,2 Historically, establishing the diagnosis has been challenging, particularly in the absence of systemic abnormalities. Recent genomic studies have uncovered that approximately 50% of ECD tissue samples harbor a mutation in the BRAF gene,3 termed BRAFV600E, and that pointed to a neoplastic, rather than inflammatory, nature of the disease.4,5

We describe a case of ECD with isolated CNS presentation emphasizing the diagnostic challenges and how a precision medicine approach provided a path to successful treatment.

Clinical case

A 51-year-old right-handed man presented with a 3-month history of diplopia and falls. Neurologic examination revealed right VI nerve palsy and mildly ataxic gait, with no other findings. A brain MRI revealed multifocal FLAIR hyperintensities mainly in the posterior fossa, with nodular enhancement (figure 1, A and B). Extensive workup was unrevealing (lactate dehydrogenase, erythrocyte sedimentation rate, B2-microglobulin, angiotensin-converting enzyme, CSF analysis with flow cytometry, spine MRI, HIV, syphilis, and rheumatologic/inflammatory panels). Whole body fluorodeoxyglucose-positron emission tomography showed minor increased uptake within the pons and no systemic abnormalities. CT of the legs was normal.

The patient underwent stereotactic needle biopsy of a leading cerebellar lesion. Pathology showed fragments of normal cerebellum and no mutations on next-generation targeted sequencing of 422 genes (NGS). High-dose steroids were tried without clinical improvement. ECD was considered but felt unlikely because of the absence of systemic involvement.

Three weeks after corticosteroid tapering, an open biopsy was performed, but pathology and NGS were again unrevealing. Given mild but continuous worsening of symptoms, a decision was made to perform a third cerebellar biopsy. Pathology showed non-granulomatous lymphohistiocytic infiltrates, with CD3-labeling T cell infiltrates, no loss of pan-T antigen expression, and rare B cells. A very large number of CD163-labeling, CD1a/Langerin-negative mononuclear elements were present. Findings were reviewed by 3 pathologists; the possibility of an infection was raised, and infectious diseases genomic studies suggested. However, given normal CSF, and on discussions with an experienced pathologist (M.R.), tissue was prioritized for genomic studies focusing on neoplastic etiologies and ECD. Immunohistochemistry for BRAFV600E mutation and RNA sequencing...
panel (ARCHER) showed no abnormalities (no BRAF/ KIAA gene fusions). NGS was initially reported as negative, but review of results and comparison of pathology accession numbers indicated DNA had been inadvertently extracted using tissue from a previous biopsy. NGS was repeated using the correct tissue and finally demonstrated a BRAFV600E mutation, as well as mutations in CHEK2, DOT1L, KDM5A, and MSH6 and deletions in ROS1 and ATXN2. The integrated pathology diagnosis was ECD. The disease course timeline was summarized in figure 2.

Further staging included normal echocardiogram and cardiac MRI; repeat fluorodeoxyglucose-positron emission tomography/CT showed right knee mild hypermetabolism, questioning osseous involvement. Treatment with vemurafenib, an Food and Drug Administration-approved drug for ECD, was considered. However, based on the literature on BRAFV600E melanoma suggesting improved efficacy and decreased toxicity with combined BRAF and MEK1/2 inhibition, a regimen with dabrafenib and trametinib was favored. After insurance denial and a successful appeal process supported by the genomic findings, treatment was initiated, resulting in significant and early clinical and radiographic improvement (figure 1, C and D). The patient was still in remission 18+ months later.

### Discussion

This report illustrates how a combination of precision medicine, perseverance, and clinical judgment may result in successful diagnoses and treatments of rare diseases. Although this patient’s MRI did show findings suggestive of ECD, these are not pathognomonic and differential was broad. The absence of systemic findings further confounded the diagnosis.

Two biopsies and NGS were negative, and it would be tempting to categorize this case among unspecified CNS inflammatory disorders. However, the mismatch between MRI suggesting an active process and histology showing no signs of active inflammatory or neoplastic diseases suggested biopsies and NGS were not representative of the ongoing process. The lack of response to corticosteroids was another red flag for an inflammatory disease or CNS lymphoma diagnosis, prompting a third, and eventually representative biopsy. Histology remained inconclusive after multiple reviews, but genetic analysis finally provided the crucial missing information. Interestingly, BRAFV600E was negative by immunohistochemistry.6,7 IHC is a sensitive and specific tool for detection of BRAF-V600E. However, negative or low staining cases should undergo genetic analysis, based on clinical and histopathologic features. It is also noteworthy that the first 2 gene sequencing attempts were negative because the tissue was not representative of the active process, containing normal cerebellum and no neoplastic cells to allow for detection of this somatic mutation.8 The genomic findings provided a path for utilization of dabrafenib and trametinib, possibly a better treatment of ECD than single-agent vemurafenib, but that is not Food and Drug Administration-approved, with only one treated

| Table: Clinical manifestations of ECD |
|-------------------------------------|
| **Organ involved** | **Manifestation** | **Incidence, %** | **Comment** |
| Bone | Long bone osteosclerosis | 80–95% | Presents with pain or asymptomatic. |
| Cardiovascular | Periaortic infiltration | 46–62% | Usually asymptomatic |
|  | Right atrium pseudotumor | 9–57% | |
|  | Coronary infiltration | 27% | Risk for coronary stenosis and myocardial infarction |
|  | Pericardial involvement | 10–31% | Risk for tamponade |
| Pulmonary | Involvement of pleura, lung parenchyma or both | 25–50% | Asymptomatic or manifest as dyspnea and/or cough |
| Retroperitoneum | Mass-like, perirenal infiltrative lesion | 58–65% | “Hairy kidneys” |
| Central nervous system | Periorbital involvement | 22–27% | Exophthalmos |
|  | CNS involvement | 37–38% | Cognitive impairment, neuropsychiatric and pyramidal syndrome |
|  | Pituitary involvement | 28–47% | Central diabetes insipidus |
|  | Cerebellar involvement | 17% | |
|  | Dura involvement | | Differential diagnosis with meningo |

Abbreviation: ECD = Erdheim-Chester disease.
We provide a second case successfully treated off-label with this combination. Overall, our patient illustrates how precision medicine can result in successful diagnosis and therapies for previously untreatable conditions, although clinical judgment remains irreplaceable for realizing the full potential of emerging technologies.
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Disclosure
M.I. de la Fuente served as a member on an ad hoc scientific advisory board for Puma Biotechnology, Agios Pharmaceuticals, and Forma Therapeutics and as a consultant for Foundation Medicine. M.K. Rosenblum has nothing to disclose. E.L. Diamond has nothing to disclose. V.S. Tabar is a scientific cofounder of Blue Rock Therapeutics and receives research support from the same. She is a scientific advisor for Robeauté. A. Omuro served as a member on an ad hoc scientific advisory board for BTG and Merck. Go to Neurology.org/NN for full disclosures.

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Appendix Authors

| Name                  | Location                          | Contribution                                                                 |
|-----------------------|-----------------------------------|------------------------------------------------------------------------------|
| Macarena I. de la Fuente, MD | University of Miami                | Data acquisition; drafting/revising the manuscript; analysis or interpretation of the data |
| Marc K. Rosenblum, MD  | Memorial Sloan-Kettering Cancer Center | Data acquisition; drafting/revising the manuscript; analysis or interpretation of the data |
| Eli L. Diamond, MD     | Memorial Sloan-Kettering Cancer Center | Drafting/revising the manuscript; analysis or interpretation of the data     |
| Viviane S. Tabar, MD   | Memorial Sloan-Kettering Cancer Center | Data acquisition                                                             |
| Antonio Omuro, MD      | Yale Brain Tumor Center            | Data acquisition; drafting/revising the manuscript; study concept or design; analysis or interpretation of the data |

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