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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 $BRAF^{V600E}$, 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 $BRAF^{V600E}$ mutation and RNA sequencing

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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 meningioma

Abbreviation: ECD = Erdheim-Chester disease.

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 $BRAF^{V600E}$ 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 $BRAF^{V600E}$ 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.

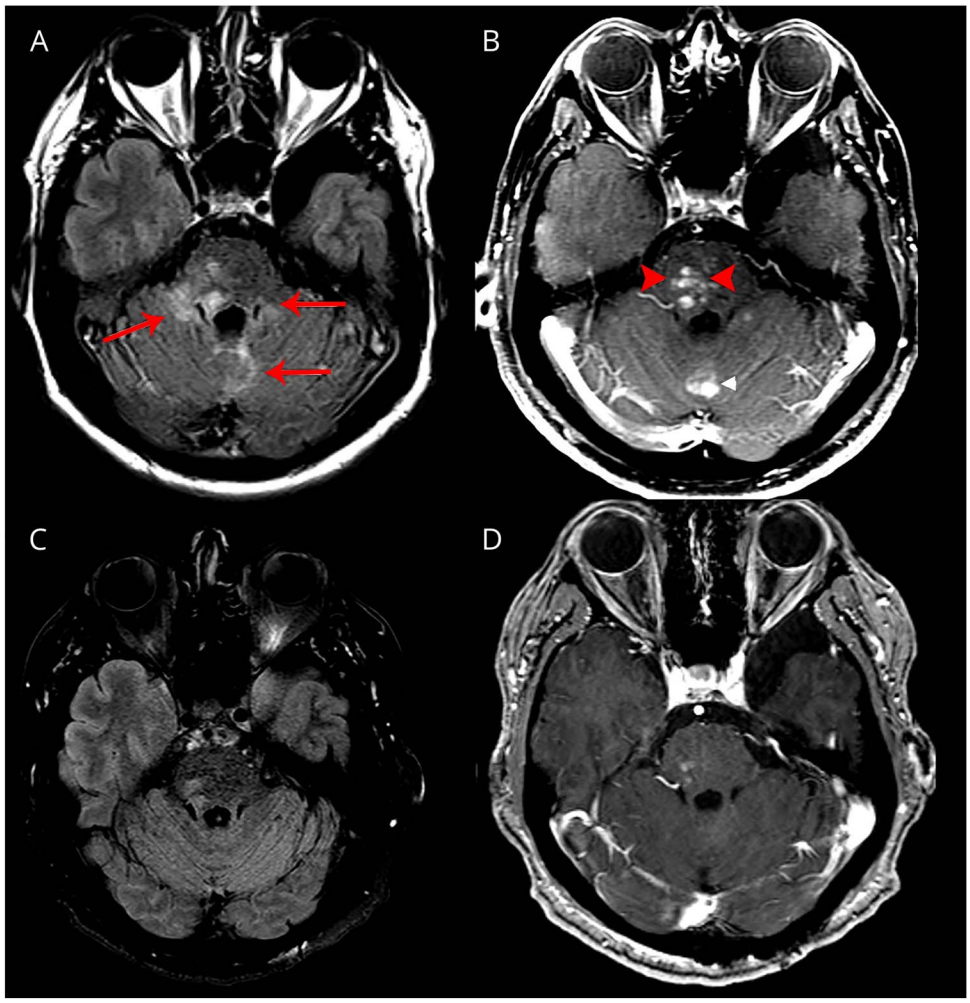
Discussion

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, $BRAF^{V600E}$ 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

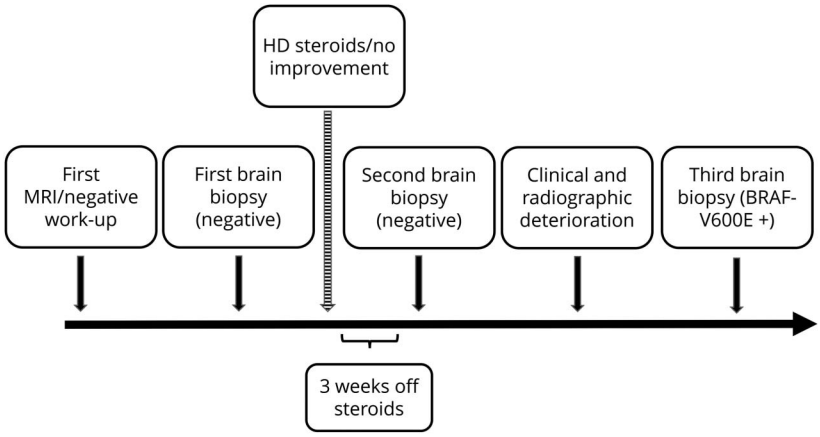
Figure 1 MRI imaging



(A and B) Baseline MRI. Axial FLAIR (A) sequence showing FLAIR signal hyperintensity lesions in the pons, middle cerebellar peduncles, and cerebellum (arrows), with corresponding solid enhancement on T1 postcontrast images (arrow heads). A follow-up MRI (C and D) performed 10 weeks into treatment, showing near complete resolution of the lesions.

patient reported in the literature.[2] 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.

Figure 2 Disease course timeline



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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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