Recurrent petit mal seizures in Erdheim-Chester disease mimicking an intra-axial brain tumor: illustrative case

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BACKGROUND Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis characterized histologically by foamy histiocytes and Touton giant cells in a background of fibrosis. Bone pain with long bone osteosclerosis is highly specific for ECD. Central nervous system involvement is rare, although dural, hypothalamic, cerebellar, brainstem, and sellar region involvement has been described.

OBSERVATIONS A 59-year-old man with a history of ureteral obstruction, medically managed petit mal seizures, and a left temporal lesion followed with serial magnetic resonance imaging (MRI) presented with worsening seizure control. Repeat MRI identified bilateral amygdala region lesions. Gradual growth of the left temporal lesion over 1 year with increasing seizure frequency prompted resection. A non-Langerhans cell histiocytosis with a BRAF V600E mutation was identified on pathology. Imaging findings demonstrated retroperitoneal fibrosis and long bone osteosclerosis with increased fluorodeoxyglucose uptake that, together with the neuropathologic findings, were diagnostic of ECD.

LESSONS This case of biopsy-proven ECD is unique in that the singular symptom was seizures well controlled with medical management in the presence of similarly located bilateral anterior mesial temporal lobe lesions. Although ECD is rare intracranially, its variable imaging presentation, including the potential to mimic seizure-associated medial temporal lobe tumors, emphasizes the need for a wide differential diagnosis.

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KEYWORDS Erdheim-Chester disease; non-Langerhans cell histiocytosis; seizures

Erdheim-Chester disease (ECD) is a rare, idiopathic non-Langerhans cell histiocytosis characterized histologically by xanthogranulomatous infiltrate and on imaging by osteosclerosis of long bones.1,2 Erdheim-Chester disease most commonly affects middle-aged adults and is considered nonfamilial.3 Symmetric, bilateral osteosclerosis of long bones is a highly specific finding for ECD, but cardiovascular, pulmonary, central nervous system (CNS), retroperitoneal, and adrenal involvement is seen in half of patients with ECD.1 Clinical symptomatology can range from systemic disease to focal, asymptomatic processes.

Central nervous system involvement is rare in ECD, most commonly manifesting as diabetes insipidus, orbital lesions, cerebellar syndromes, or extra-axial masses involving the dura.4 Only a third of patients with ECD report neurological symptoms.5 In most cases, patients already have systemic disease by the time an intracranial lesion is identified.3 We present the unique case of a middle-aged patient with bilateral anterior mesial temporal lobe ECD presenting with chronic adult-onset seizures. The nearly 5 years of medical management and imaging follow-up in this patient prior to surgery highlights the indolent nature of ECD and the need for a wide differential diagnosis for intracranial lesions.

Illustrative Case

A 59-year-old man with a past medical history of hypertension, rheumatoid arthritis, retroperitoneal fibrosis, bilateral ureteral obstruction

ABBREVIATIONS CNS = central nervous system; CT = computed tomography; ECD = Erdheim-Chester disease; FDG = fluorodeoxyglucose; LCH = Langerhans cell histiocytosis; MRI = magnetic resonance imaging; PET = positron emission tomography; RDD = Rosai-Dorfman disease; SUV = standardized uptake value.

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requiring bilateral ureteral stents, and type 2 diabetes mellitus presented for treatment consultation of a known “brain tumor.” Four years earlier, the patient had experienced a grand mal seizure, and magnetic resonance imaging (MRI) showed a left temporal lesion. The patient was placed on mycophenolate for autoimmune encephalitis and levetiracetam and was advised to follow the lesion’s growth with serial imaging. Two years passed, and the patient began experiencing petit mal seizures. Lamotrigine was added to his medication regimen, and watchful management given the lack of lesion growth was continued.

One year later, in June 2020, 4 years since the first seizure event, the patient presented to our institutional clinic. He was still taking mycophenolate, levetiracetam, and lamotrigine; however, the medications in combination were sedating, impairing his quality of life and only resulted in partial seizure control. The frequency of seizures ranged from 1 or 2 per week to several months, and the majority were characterized as petit mal seizures.

The patient had recently consulted elsewhere, and brain MRI showed a nodular-enhancing lesion without significant surrounding edema or mass effect in the left anterior mesial temporal lobe. The differential diagnosis included a low-grade glioma or glioneuronal tumor such as a ganglioglioma, pleomorphic xanthoastrocytoma, or dysembryoplastic neuroepithelial tumor. However, further review of imaging revealed a second similar, but smaller, nodular-enhancing lesion in the contralateral right anterior mesial temporal lobe. The possibility of brain metastases was proposed but considered unusual given the nearly symmetric locations of the lesions and chronic seizure history (Fig. 1).

Further imaging was performed for lesion characterization and staging. Brain and whole-body positron emission tomography (PET)/computed tomography (CT) showed avid fluordeoxyglucose (FDG) uptake (standardized uptake value [SUV] 9.7) of the dominant nodular-enhancing lesion in the left anterior mesial temporal lobe concerning for malignancy but no other significantly increased FDG uptake in the brain. Mildly increased FDG uptake (SUV 3.0–4.8) was noted in the long bones of the bilateral upper and lower extremities in addition to sclerotic bone lesions interpreted as indeterminate for benign versus malignant etiologies, although no definitive primary cancer was identified. Brain proton magnetic resonance spectroscopy of the left anterior mesial temporal lesion showed mildly increased choline, mildly decreased N-acetylaspartate, and no identifiable lactate or lipid peak, which was nonspecific but suggested high-grade glioma as unlikely. Magnetic resonance perfusion showed minimally increased cerebral blood flow in the left anterior mesial temporal lobe.

Results of neurocognitive testing indicated difficulties on several left hemisphere tasks, including verbal intelligence, naming to confrontation, and 3 of 4 episodic verbal memory tasks, although all right hemisphere functions were intact. Options including continuing conservative management with serial scans, stereotactic radiosurgery, laser interstitial thermal therapy, or open surgical excision of the left-sided lesion were discussed. The patient believed his current medication regimen was making him worse; however, concern for surgery worsening his deficit and the potential that the seizures were not exclusively left-sided in origin prompted continued conservative management. The patient returned for follow-up serial scans in January.
and July 2021, which revealed gradual growth of the dominant left-sided lesion (Fig. 2). Interestingly, the lesion on the right appeared slightly decreased in size. As there were 2 consecutive scans indicating growth of the dominant left-sided lesion, craniotomy and left-sided biopsy versus resection, depending on frozen pathology, was planned.

During this time, the patient continued follow-up with his nephrology and primary care teams for his history of ureteral obstruction requiring ureteral stent placement. Computed tomography and MRI of the abdomen and pelvis were notable for complications of retroperitoneal fibrosis (Fig. 3). A review of PET/CT scans obtained earlier indicated FDG uptake in the region of retroperitoneal fibrosis.

In December 2021, 4 months since imaging confirmation of growth of the dominant left-sided lesion, the patient underwent left temporal craniotomy. Several abnormal regions were encountered in the tract to the main lesion, with frozen sections demonstrating inflammatory infiltrates. A distinct, firm, yellowish, and rubbery mass was attached to the very anterior aspect of the temporal horn located within the medial temporal lobe. Multiple frozen sections (7) were performed, and the frozen-section diagnosis in the most pathologic focus was “inflammatory lesion with histiocytes, lymphocytes, and multinucleated giant cells.” Additional pieces from the same anatomical focus were requested for permanent section evaluation and molecular studies. Frozen sections excluded the presence of a neoplasm, which was in the radiological differential. A gross-total excision was achieved.

Further neuropathologic evaluation showed foamy histiocytes and multinucleated Touton-type giant cells in a background of lymphocytic inflammation (Fig. 4). These foamy histiocytes were positive for CD68, CD163, and factor XIIIa, as are characteristic of ECD. No Langerhans cells or eosinophils were identified, and CD1a was negative, excluding a Langerhans cell histiocytosis. S100 staining was negative in histiocytes, and engulfment of lymphocytes by histiocytes (emperiplois) was not identified, excluding Rosai-Dorfman disease (RDD). Special stains for organisms were negative, and there was no granulomatous inflammation. Electron microscopy studies of the biopsy showed histiocytes with cytoplasmic vacuoles, including lipid, lysosomes, and dense granules, as well as invaginated nuclei. No Birbeck granules were noted, further excluding the presence of Langerhans cells. A BRAF V600E mutation was subsequently confirmed using next-generation sequencing, as well as immunohistochemistry for mutant BRAF V600E protein. Based on these findings, a pathologic diagnosis of “non-Langerhans cell histiocytosis, BRAF V600E-mutated” was made.

The patient was referred to hematology-oncology for treatment. At the 1-month follow-up, the patient was seizure free on lamotrigine and levetiracetam with further improvement in cognitive function. A follow-up MRI bone survey was significant for low T1-weighted marrow signal in the mid- and distal femoral shaft and midportion of the humerus, suggestive of a marrow proliferative or dysplastic process, although the patient still had no complaints of bone pain. Magnetic resonance imaging of the lower extremity identified a benign fibro-osseous lesion in the proximal femoral intertrochanteric region on the left. Additionally, symmetric hypointense cortical hypertrophy within the mid- to distal femoral shaft with epiphysis sparing supported the MRI bone survey’s suggestion of an atypical red marrow conversion or other marrow proliferative process (Fig. 5). These findings supported a prior PET/CT, which had revealed mild FDG uptake and sclerosis within the long bones of the bilateral upper and lower extremities. However, an initial bone survey completed in 2018, 2 years into the patient’s treatment for seizures, had been negative for aggressive osseous lesions. Thus, there was progression over this nearly 4-year span.

From the combination of imaging and pathological findings, the patient’s final diagnosis was ECD, a rare form of non-Langerhans cell histiocytosis identified on pathology by xanthogranulomatous infiltrate and on imaging by osteosclerosis with FDG uptake of long bones, retroperi-toneal involvement with hairy kidney sign, and ureteral obstruction. The patient is currently being treated with trametinib and dabrafenib.

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Non-Langerhans cell histiocytosis is a diagnostic category that includes RDD, xanthogranuloma, and ECD. In addition to RDD, Langerhans cell histiocytosis (LCH) and sarcoidosis are 2 other histiocytic disorders rarely characterized by a single mass lesion. Immunohistological and microscopic characteristics of histiocytes differentiate ECD from LCH, with histiocytes in ECD positive for CD68 and negative for CD1a, S100 protein, and OKT6. In contrast, LCH is CD1a and S100 positive, and Birbeck granules can be found on electron microscopy. Histopathology with immunohistochemistry paired with the clinical findings of long bone sclerosis confirmed ECD in this patient, and notably showed BRAF V600E protein, which was further confirmed by next-generation sequencing studies.

Neurological symptoms such as seizures are rare in ECD and can lead to severe disability and death. Lachenal et al. reported 6 cases of ECD with neurological symptoms and identified 60 additional cases
on literature review. In 22% of patients, as in our patient, neurological symptoms were the first manifestation of ECD. Unlike our case, the majority of the 66 cases had multiple neurological symptoms, whereas our patient presented with just 1 symptom, seizures.

Isolated craniocerebral involvement is reported in fewer than 50% of patients with ECD. Even when CNS lesions are present, the majority of patients are asymptomatic, with diabetes insipidus and ataxia being the most common clinical manifestations in symptomatic cases.
patients. Jain et al. reported a case of biopsy-conﬁrmed ECD with recurrent, secondarily generalized seizures. Unlike this case, where os-
teosclerosis in the long bones was identiﬁed, Jain et al. reported no extracranial involvement even after 12 years of follow-up, and the os-
teolytic lesions isolated to the skull vault resolved spontaneously.

Rushing et al. reported a case of isolated intracranial ECD mimicking
a primary brain tumor. As in our case, the patient had seizures as his
primary symptom, a temporoparietal mass was identiﬁed on imaging,
and skeletal involvement was not identiﬁed until a postoperative bone
scan.

In this case, PET/CT imaging identiﬁed both CNS and long bone
lesions, even in the absence of bone pain, and retrospectively corre-
lated the histopathologic diagnosis of ECD with prior imaging ﬁndings.
In a review of 32 patients with 18F-FDG PET/CT imaging, Young et al. found that PET/CT imaging impacted patient management in
half of the patients, especially in those with CNS involvement. Sioka et al. used PET/CT imaging in a patient with ECD previously treated
with interferon alpha-2b to retrospectively identify lesions in the heart,
mediastinum, abdomen, and brain, including, as in this patient, a left
medial temporal lobe lesion, thus illustrating the idle, silent progres-
sion of ECD.

Observations
It is important to note the progression of differential diagnoses in
this case alongside the serial imaging ﬁndings, with many conclusions
considered in retrospect. Seizure activity prompted the initial clinical
and imaging workup of the patient. The identiﬁcation of 2 enhancing
brain lesions on serial imaging 4 years after the initial presentation
raised concern for metastatic disease. However, the location of these
lesions in the symmetric opposite anterior mesial temporal lobes, the
lack of association with any signiﬁcant T2 ﬂuid-attenuated inversion
recovery (FLAIR) signal abnormality or mass effect, and a 3-year sei-
zure history made this less likely. As a primary brain tumor was on the
differential, surgery for resection and immunohistopathologic analysis
was a topic of signiﬁcant discussion. However, the location of the le-
sion in the left temporal lobe raised concerns for worsening language
and verbal memory diﬃculties with surgery. Thus, an initial watch-
and-wait approach was chosen given the presence of bilateral le-
sions, the risks of surgery, and the well-controlled seizures. Later
growth of the dominant left-sided lesion on serial imaging, combined
with the risk of continued growth and transformation into a more ag-
gressive pathology, hastened the need for diagnosis and was the indi-
cation for surgery. Concerns for worsening function in this patient
following surgery fortunately did not materialize. After 1 month of post-
operative follow-up, the patient did not have signiﬁcant deﬁcits and
continued the treatment regimen of trametinib and dabrafenib.

Lessons
This case of biopsy-proven ECD is unique in that the patient pre-
sented with bilateral symmetric temporal lobe lesions and a singular
symptom of seizures controlled for years with medical management.
While most cases of ECD that present with neurological ﬁndings have
cerebellar, brainstem, or pituitary involvement on imaging, this patient’s
intracranial lesion was restricted to bilateral anterior mesial temporal
FIG. 5. Erdheim-Chester disease skeletal changes. Coronal CT (A) shows a 2.0-cm sclerotic lesion in the left femoral neck (arrow). Axial T2WI with fat saturation (B) and axial T1WI (C) show a T2-hyperintense and T1-hypointense irregular lesion (arrows) centered at the left femoral neck corresponding to the CT ﬁnding. Coro-
nal T1WI (D) shows diffuse symmetric T1 hypointensity involving bilateral mid-distal femurs and proximal tib-
iae, sparing the epiphysis. A frontal radiograph (E) of the bilateral knees shows bilateral symmetric metaphyseal and diaphyseal sclerotic changes of the tibiae, ﬁbulae, and femurs with epiphyseal sparing. A frontal radiograph (F) of the right ankle shows similar sclerotic changes of the distal tibia and ﬁbula, sparing the epiphysis. Symmetric ﬁndings were seen on the contralateral ankle. The constellation of ﬁndings is con-
sistent with sclerotic changes secondary to ECD.
lobes. Although ECD is rarely found intracranially, its potential to mimic brain tumors emphasizes the need for a wide differential in patients presenting with a suspicious lesion or lesions on MRI. A biopsy with established mutational and immunohistopathologic confirmation is required to confirm ECD diagnosis and guide targeted therapy.

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Conception and design: Baskin, Stuebe, Jenson, Cykowski, McClain. Acquisition of data: Baskin, Stuebe, Jenson, Lines, Cykowski, McClain. Analysis and interpretation of data: Stuebe, Lines, Cykowski, Fisher, McClain. Drafting of the article: Stuebe, Jenson, Holloman, Cykowski, Fung, McClain. Critically revising the article: Baskin, Stuebe, Holloman, Cykowski, Fung. Reviewed submitted version of the manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Baskin. Administrative/technical/material support: Baskin, Jenson. Study supervision: Baskin.

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