Neuroradiologic manifestations of Erdheim-Chester disease

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Abstract

Background

We describe the neuroradiologic features of a cohort of patients with Erdheim-Chester disease.

Methods

We assessed patients at Mayo Clinic Rochester between January 1, 1990, and July 31, 2016, with pathologically confirmed Erdheim-Chester disease (n = 53).

Results

Neuroimaging, including head CT (n = 17), brain MRI (n = 39), orbital MRI (n = 15), and spine MRI (n = 16), was available for 42 participants. Median age at diagnosis was 55 years (interquartile range 46–66) with higher male prevalence (33:20). Neurologic symptoms were identified in 47% (25/53); BRAF^{V600E} mutation in 58% (15/26). Median follow-up was 2 years (range 0–20) with 18 patients deceased. Radiologic disease evidence was seen in dura (6/41), brainstem (9/39), cerebellum (8/39), spinal cord (2/16), spinal epidura (2/16), hypothalamic-pituitary axis (17/39), and orbits (13/42). T2 white matter abnormalities (Fazekas score ≥1) were present in 21/34 patients. Diabetes insipidus was present in 30% (16/53); 8 had abnormal hypothalamic-pituitary axis imaging. Radiographic evidence of CNS involvement (i.e., dural, brain, including Fazekas score >1, or spinal cord) occurred in 55% (22/40) and was unassociated with significantly increased mortality.

Conclusions

Erdheim-Chester disease commonly and variably involves the neuraxis. Patients with suspected Erdheim-Chester disease should undergo MRI brain and spine and screening investigations (serum sodium, serum and urine osmolality) for diabetes insipidus to clarify extent of neurologic disease.

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis with ~500 reported cases.¹ Diagnosis is based on histopathology demonstrating CD68+, CD1a-foamy histiocyte infiltration associated with fibrosis.² Characteristic skeletal abnormalities, including long-bone osteosclerosis, are frequently present.² Although the etiology of ECD remains uncertain, an activating oncogene mutation, BRAF^{V600E}, is found in 50%–70% of cases, with variation in sensitivity according to the method of detection.^{3,4} ECD is a multisystem disorder commonly involving perinephric fat (68%), the periaortic region (66%), lungs (43%),

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pericardium (42%), orbits (25%), and the neuroaxis (51%); 25% have diabetes insipidus (DI).^{1,5} We describe clinical and neuroradiographic features found in an ECD patient cohort.

Methods

Standard protocol approvals, registrations, and patient consents

The Mayo Clinic Institutional Review Board (IRB 16-006594) approved this retrospective study. No experiments on live vertebrates or higher invertebrates were performed in this study. Participating patients (or their legally authorized representatives) provided written consent to use medical information. No photographs, videos, or other recognizable information regarding participating patients has been submitted for publication.

We used our institution's medical record diagnostic linkage system to identify patients with pathologically confirmed diagnoses of ECD assessed at Mayo Clinic, Rochester, Minnesota, between January 1, 1990, and July 31, 2016. The search results were cross-referenced with a database of patients with histiocytic disorders maintained within the Mayo Clinic Department of Hematology. Diagnosis was based on histopathology demonstrating CD68+, CD1a-foamy histiocyte infiltration associated with fibrosis according to published guidelines.² Diagnosis date was date of first diagnostic biopsy. We extracted data by medical record review. All neuroimaging studies were initially reviewed by a neuroradiologist and subsequently reviewed by 2 neurologists (N.E.P., W.O.T.) using a standard checklist. Disagreements were resolved through consensus.

Kaplan-Meier survival curves of patients with and without radiographic involvement of the CNS were compared using the log-rank test with age adjustment performed using the Cox proportional hazards model. Chi-square statistics evaluated the relationship between BRAF status and radiographic CNS involvement. Radiographic CNS involvement was defined as evidence of dural, brain (including Fazekas score >1), or spinal cord involvement.

Results

We identified 53 patients with pathologically confirmed ECD and reviewed the clinical, radiographic, and pathologic characteristics (table 1) with a focus on neurologic disease.

Clinical

Neurologic symptoms were identified among 47% (25/53) of participants, including imbalance (17), headache (11), cognitive change (6), dysarthria (6), diplopia (5), dysphagia (4), focal sensory deficit (4), and focal motor deficit (2). Patients with neurologic symptoms underwent MRI brain. Of the patients with neurologic symptoms (25 patients), the initial diagnostic impressions were histiocytic disorder (5),

Table 1 Clinical characteristics of the Erdheim-Chester disease cohort

	Values (total n = 53)
Age at diagnosis, y, median (IQR) ^a	55 (46–66)
Sex, male:female	33:20
BRAF ^{V600E} mutation, n (%)	15 (58) ^b
Radiographic long-bone osteosclerosis, n (%) ^c	41 (77)
Any neurologic symptom, n (%)	25 (47)
Diabetes insipidus, n (%)	16 (30)
Duration follow-up, y, median (range)	2 (0–20)
Modified Rankin Scale score, median (range)	
Presentation	1 (0–4)
Last follow-up	3 (0–6) ^d
Dead, n	18
Medication, n (%)	40 (75)
Steroid	26
Cladribine	17
Interferon	12
BRAF inhibitor	11
IL-1 receptor antagonist	5
Other	14

Abbreviations: IL = interleukin; IQR = interquartile range.

^a Date of diagnostic biopsy.

^b Available for 26 patients.

^c Determined using available imaging including x-ray, PET-CT, bone scan, and skeletal survey.

^d Available for 48 patients.

retroperitoneal fibrosis (2), idiopathic mesenteritis (1), leukemia (1), sarcoidosis (1), polymyalgia rheumatica (1), Paget disease (1), cerebellar ataxia (1), right atrial thrombus (1), large vessel vasculitis (1), pinkeye (1), primary brain tumor (1), periorbital pseudotumors (1), autoimmune pancreatitis (1), DI (1), and unknown (5).

Spinal fluid analyses were available for 8 patients, 5 of which were abnormal. Median white cell count was 1/μL (range 1–29). Median protein was 59 mg/dL (range 31–137). Only 1 patient had oligoclonal bands detected in CSF (3 bands).

Treatment protocols included medication (40 patients) and radiotherapy (19) (table 1). Medications included corticosteroids (26), interferons (12), cladribine (17), vemurafenib (10), anakinra (5), methotrexate (8), infliximab (3), azathioprine (2), ifosfamide (1), etoposide (1), cisplatin (1), cyclophosphamide (1), vinblastine (1), dabrafenib (2), imatinib (1), trametinib (1), etanercept (1), and mycophenolate (1). No patient had a stem cell transplant.

(A) T2-hypointense gadolinium-enhancing dural mass lesions involving the tentorium cerebelli (A.a and A.b [arrow], A.e) and falx cerebri (A.c and A.d [arrow], A.f) resulting in obstructive hydrocephalus with dilated temporal horns (A.e [arrow]) and 3rd ventricle (A.f [arrow]). (B) T2-hyperintense infratentorial infiltration affecting the pons (B.a and B.c) and cerebellum (B.a, B.c, and B.e) with variable gadolinium enhancement (B.b, B.d, and B.f). (C) Periventricular Fazekas score 1–3 (C.a–C.c). None of the fluid-attenuated inversion recovery lesions depicted demonstrate gadolinium enhancement. (D) Deep Fazekas score 3 (D.a) with limited region of gadolinium enhancement (D.b [arrow]). Cortical laminar necrosis with left temporo-parieto-occipital cortical T2 hyperintensity (D.c [arrow]) associated with gadolinium enhancement (D.d [arrow]). Mesial temporal lobe T2 hyperintensity (D.e [box]) associated with punctate gadolinium enhancement (D.f [box]).

Follow-up data were available on 48 patients (39 treated, 9 untreated). Patients treated with medications had a median increase in disability of 1 (interquartile range [IQR] 0–4) compared to 2 (IQR 0–3.5, $p = 0.7$, Wilcoxon rank sum test) in patients who did not receive medication as measured by a change in modified Rankin Scale (mRS). Only one patient had an improved mRS score from 1 to 0 at follow-up.

Radiographic

Cranial imaging was obtained for 42 patients with head CT (17), brain MRI (39), orbits MRI (15), and sella MRI (13). Spine MRI was obtained for 16 patients including cervical (9), thoracic (8), and lumbar (11) views. Radiographic evidence of CNS involvement was defined as abnormal dural, brain (including Fazekas score >1), or spinal cord imaging (table e-1, <http://links.lww.com/CPJ/A9>). Among 22/40 patients with radiographic CNS involvement, 6 were asymptomatic; the 16 symptomatic patients included 14 with ataxia. Radiographic CNS involvement was not associated with an increased risk of death following age adjustment (hazard ratio 2.1, $p = 0.3$).

Twenty-eight patients had whole body PET-CT with 25/28 being abnormal. Bony abnormalities were seen in 19 patients and extraosseous PET-CT abnormalities were seen in 24 patients. Bone involvement was present without extraosseous disease on PET-CT in only 1 patient, while 6 patients had extraosseous PET-CT abnormalities without bone involvement. Of 32 bone scans obtained, 28 were abnormal. Of the skeletal surveys performed, 28/30 were abnormal.

Dura

Enhancing dural masses (6/41) occurred as solitary (3) and multiple (3) lesions in infratentorial and supratentorial regions (figure 1A). Among those with abnormal T2 appearance (4/5), all were hypointense. In a single case, multiple infratentorial dural masses resulted in obstructive hydrocephalus.

CNS parenchyma

Infratentorial T2-hyperintense lesions occurred in the brainstem (9/39) and cerebellum (8/39) (figure 1B). All cases with brainstem involvement affected the pons. Two patients with cerebellar involvement did not have pontine involvement.

Supratentorial T2-hyperintense white matter changes (Fazekas score ≥ 1) occurred among 21/34 patients. Median periventricular and deep Fazekas score was 1 including 5 patients with periventricular Fazekas score grade 2–3 (figure 1C). Among these 5, 3 had a deep Fazekas score of grade 2–3. Only 2 patients exhibited gadolinium-enhanced white matter including one patient with deep Fazekas score 1 exhibiting enhancement of a juxtacortical lesion and one patient with deep Fazekas score 3 with a single small enhancing area despite extensive deep white matter T2 hyperintensity (figure 1D).

Additional supratentorial changes included cortical laminar necrosis (1/39) and mesial temporal lobe T2 hyperintensity (4/39) with (3) and without (1) gadolinium enhancement (figure 1D). Three patients experienced an ischemic stroke, each of different etiology including large vessel, small vessel, and watershed mechanism. In the case of the watershed infarct, there was biopsy-proven cardiac involvement by ECD.

Enhancement-associated intramedullary spinal cord lesions occurred among 2/16 patients; one had multiple T2-hyperintense cervical lesions, and the other had a single T2-hypointense mass in the conus medullaris (figure 2A). T2-hypointense epidural infiltration penetrating the lateral foramina around nerve roots occurred in 2 patients with a single occurrence in the thoracic (1/16) and sacral (1/16) region (figure 2, B and C).

Orbital

Orbital involvement occurred among 13/42 patients including intraconal (8), extraconal (2), globe (3), and

Radiographic CNS involvement was not associated with an increase in mortality in the present study.

extraocular muscle (1) involvement (figure e-1, <http://links.lww.com/CPJ/A8>).

Hypothalamic pituitary axis

Radiologic hypothalamic pituitary axis (HPA) abnormalities were seen in 44% (17/39) with thickening of the infundibular stalk (16) and hypothalamic mass (1) (figure e-1, <http://links.lww.com/CPJ/A8>). DI was present in 30% (16/53) including 8 with abnormal and 7 with normal HPA imaging on MRI brain while a single patient had normal imaging on CT head. DI onset typically preceded ECD diagnosis with 13 patients diagnosed with DI before the diagnosis of ECD (median 4 years) while 3 patients were diagnosed with DI after the diagnosis of ECD. In addition, 9 patients had abnormal HPA imaging without DI. Cavernous sinus infiltration occurred among 2 patients, although neither had DI.

Pathology

Diagnostic tissue was obtained from CNS parenchyma/dura (4), orbit (9), abdomen (5), retroperitoneum (8), thorax (13), bone (21), and other tissues (8) with 23% (12/53) having multiple biopsy-confirmed sites of involvement.

Figure 2 Spinal manifestations of Erdheim-Chester disease

(A) Conus medullaris T2-hypointense (A.a [arrow]) gadolinium-enhancing (A.b [arrow]) lesion. (B) Extensive posterior thoracic T2-hypointense (B.a and B.b [arrow]) epidural infiltration without associated enhancement (B.c [arrow]). (C) Sacral T2-hypointense (C.a [arrow]) epidural infiltration with enhancement (C.b [arrow]).

Higher rates of radiographic involvement might have been found if specific imaging studies had been performed in all patients.

The patient who underwent dural biopsy demonstrated marked macrophage infiltrate of the dura with xanthomatous features and rare giant cells. BRAF^{V600E} mutation analysis was not performed in this patient. Of the 3 patients with brain parenchymal biopsy, 1 demonstrated an inflammatory xanthogranulomatous pseudotumor (BRAF^{V600E} mutation analysis not performed), 1 demonstrated a foamy macrophage infiltrate (BRAF^{V600E} mutation positive), and 1 demonstrated KP1 positive foamy histiocytes and xanthomatous cells with myelin loss and decreased axonal density (BRAF^{V600E} mutation negative). Langerin stains were negative.

BRAF mutation analysis was performed using whole blood PCR in 12 patients (8/12 BRAF^{V600E} mutation positive), urine PCR in 3 patients (3/3 BRAF^{V600E} mutation positive), immunohistochemistry in 9 patients (2/9 BRAF^{V600E} mutation positive), Sanger sequencing in 1 patient (BRAF^{V600E} mutation positive), and next-generation sequencing in 1 patient. Next-generation sequencing identified a BRAF^{V471F} mutation, 2 NF1 splice sites (1641+1G>A, 7189+2T>G), along with MCL1 amplification mutation in 1 patient. No additional mutations were identified.

BRAF^{V600E} mutation status was not associated with increased risk of radiographic CNS involvement ($p = 0.8$).

Discussion

CNS involvement in ECD was common and consistent with prior case series.⁵⁻⁹ Asymptomatic neurologic involvement

was present in >10% of cases. Although asymptomatic lesions have been described previously, the present study estimates the relative frequency of asymptomatic lesions.^{6,10} Neuroimaging did not identify an HPA abnormality in half of patients with DI, despite MRI brain being performed for most patients with DI. This was seen in a prior study in which HPA lesions that might explain DI were “rarely found.”¹⁰

A variety of neuroimaging abnormalities were seen, similar to previously.⁵⁻⁹ Obstructive hydrocephalus and spinal root compression, both due to dural involvement, are important to identify as they may be amenable to surgical intervention for symptomatic relief. Stellate-pattern extra-axial lesions and ependymal enhancement along the lateral ventricle with deep linear extension to the lentiform nucleus were not seen.⁸

Radiographic CNS involvement was not associated with an increase in mortality in the present study. Previously, CNS involvement was shown to be an independent predictor of mortality using Cox proportional hazards regression analysis.⁵ In a systematic review where the definition of neurologic involvement included the presence of DI, no association existed between neurologic involvement and survival.⁹

ECD may overlap with Langerhans cell histiocytosis (LCH) (table 2), which is diagnosed by pathologic identification of Birbeck granules or CD1a+ immunohistochemistry, in ~20% of cases.¹¹ LCH is a multisystem disorder that frequently manifests with lytic bone lesions affecting the skull and HPA involvement including DI.¹² A study of 29 children with LCH demonstrated MRI signal abnormality in the brainstem and cerebellum (21%) primarily in the region of the dentate nucleus.¹² This suggests a similar distribution of neurologic involvement for LCH, although we excluded cases of pathologically confirmed LCH in the present study of ECD.

Treatment of ECD is not well-established.² A non-randomized, observational cohort study suggested that

Table 2 Comparison of histiocytic disorders¹¹

	Erdheim-Chester disease	Langerhans cell histiocytosis	Rosai-Dorfman disease
Typical age at presentation	Middle age	More common in children ¹¹	CNS involvement more common in middle age ¹⁸
Histopathology	Foamy histiocyte, CD68+, CD1a ^{-2,11}	Mononucleated dendritic cell, CD1a+, Birbeck granules ¹¹	Multinucleated histiocyte, CD68+, S100+, CD1a ⁻ ; may be associated with immunoglobulin G4-related disease ¹¹
Bone involvement	Common (long-bone osteosclerosis)	Common (osteolytic lesions including skull) ^{11,12}	Sporadic (osteolytic lesions) ¹¹
Neuroradiologic involvement	Brainstem/cerebellum T2 hyperintensity; cerebral white matter T2 hyperintensity; dural lesions	Globus pallidus/dentate nucleus T1 hyperintensity; brainstem/cerebellum T2 hyperintensity; dural lesion from intracranial extension of skull lesion ¹²	Isolated dural lesion ¹⁸
Diabetes insipidus, %	30	17 ¹²	Rare ¹⁸
Other common sites of involvement	Perinephric fat, periaortic region, lungs, pericardium, orbits ¹	Skin, bone marrow, lung, liver, spleen ¹¹	Lymph nodes ¹¹

interferon- α improved survival.⁵ BRAF inhibitors have been associated with dramatic improvement of CNS histiocytic infiltration in patients with BRAF^{V600E} mutation.¹³⁻¹⁵ BRAF is an oncogene involved in the RAS/RAF/MEK pathway. Among 3 patients with ECD with wild-type BRAF, the MEK inhibitor cobimetinib was associated with diminished lesion burden, including a single patient with dural lesions.¹⁶ Cladribine has recently been reported to have moderate clinical efficacy and may be considered for patients without BRAF mutation.¹⁷

Limitations of the present study include its retrospective nature. Imaging was performed as part of clinical care without a standardized procedure. Higher rates of radiographic involvement might have been found if specific imaging studies had been performed in all patients.

The present study demonstrates the range of CNS abnormalities present in patients with ECD. Some patients had lesions responsive to surgical intervention for symptomatic relief. DI was not always associated with neuroimaging abnormalities. We recommend MRI of the brain and spine along with screening laboratory investigations (serum electrolytes, serum osmolality, urine osmolality) for DI for all patients with ECD to clarify extent of neurologic involvement in addition to a bone scan or whole body PET-CT. Among individuals with symptoms suggestive of DI (including polydipsia or polyuria) or positive screening investigations, we recommend assessment by an endocrinologist for DI diagnosis and treatment.

Author contributions

N.E. Parks: study design, data collection/interpretation, drafting manuscript. G. Goyal: data interpretation, revising manuscript. R.S. Go: data interpretation, revising manuscript. J. Mandrekar: data analysis/interpretation, revising manuscript. W.O. Tobin: study design, data collection/interpretation, drafting manuscript, supervision.

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