Cerebral Microvascular Erdheim-Chester Disease: A Perivascular Hematopoietic Vasculopathy

Michael Moussouttas^a Shanu Roemer^b Dennis W. Dickson^b

^aCerebrovascular Division, Department of Neurology, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA; ^bNeuropathology Laboratory, Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA

Keywords

Erdheim-Chester disease · Cerebral vasculature · Microvascular infiltrates · Perivascular microangiopathy · Infarction · Hemorrhage · Autopsy

Abstract

Erdheim-Chester disease (ECD) is a rare and elusive hematopoietic malignancy that may involve the nervous system in various ways. Cerebrovascular ECD involves the perivascular infiltration and compromise of any cervicocranial vessel by transformed proliferating histiocytes. Presented is the novel case of a patient with pathologically proven perivascular microangiopathy, manifesting in multifaceted fashion with ischemia, hemorrhage, mass lesions, and edema.

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Case Report

A 64-year-old man with hypertension, diabetes, hyperlipidemia, and non-Hodgkin's B-cell lymphoma in remission presented with acute onset dysarthria and hemi-paresis/hypesthesia. Head CT was normal, and CTA of the head/neck revealed only minor cervical carotid plaques. Tissue plasminogen activator was

administered for presumed acute cerebral ischemia. Clinical deterioration prompted repeat CT that revealed multiple acute punctate hemorrhages (Fig. 1a, b), for which cryoprecipitate was administered. Systems review indicated fatigue/malaise, arthralgias, abdominal pain, and urinary incontinence. In hospital, the patient experienced recurrent transient neurologic symptoms, a complex partial seizure, and two fevers >38°C, for which chest X-rays, urinalyses, and cultures were unrevealing. Cerebral MRI revealed the hemorrhages plus separate acute punctate infarcts (Fig. 1c, d). Trans-thoracic/esophageal echocardiograms were normal.

Review of the serologic, CSF, radiologic, and histologic investigations performed during this (and the later) hospitalization is presented in Table 1. Positive findings included elevated fibrinogen 577 mg/dL, ESR 83 mm/h, CRP 28 mg/L, and β 2-microglobulin 3.3 mcg/mL. Immunoglobulin subclass levels were low: IgM 26 g/L, IgA 54 g/L, and IgG 321 g/L. Based on the constitutional symptoms, recurrent fevers, serologic evidence of inflammation, recurrent neurologic symptoms, and new punctate ischemic foci on repeat MRI, the decision was made to pursue angiography and possibly biopsy. Cervicocranial angiography demonstrated no evidence for arterial or venous vasculitis or vasculopathy, and cerebral biopsy revealed no inflammatory, infectious, or neoplastic processes.

Four months later, due to persistent fevers and recurrent neurologic symptoms, the patient was readmitted, and cerebral MRI with contrast revealed circular enhancing lesions (Fig. 1e, f) with nodular widening of the infundibulum. CSF cytology was negative for malignant cells, but noted abundant macrophages/monocytes. Cytometry was negative for atypical lymphocytes. Repeat biopsy

Fig. 1. CT and MR imaging illustrating initial hemorrhagic and ischemic lesions, and later development of mass lesions and cerebral edema. **a, b** CT demonstrating linear pontine and multifocal subcortical hemorrhages post-tPA. **c, d** Diffusion MRI revealing

several acute punctate infarcts separate from areas of hemorrhage. **e, f** Contrast MRI sequences demonstrating several circular enhancing nodular mass lesions. **g, h** FLAIR imaging revealing extensive edema in the pons and subcortical hemispheric regions.

revealed no evidence of an inflammatory, infectious, or neoplastic process.

Later MRI revealed evolving confluent edema in the posterior fossa and in the subcortical hemispheric regions bilaterally (Fig. 1g, h). The patient continued to experience recurrent fevers and progressive neurologic deterioration, with decline in mentation, vision, articulation, and gait, and expired several months later.

Neuropathology

Histology demonstrated inflammatory cells along the convexity and basal leptomeninges composed of foamy histiocytes and T-cells. The histiocytic infiltration was also present in the thalamus and posterior fossa structures. The pituitary infundibulum had extensive perivascular infiltration with foamy histiocytes (Fig. 2a) that were positive for CD68 (Fig. 2b) and CD163 (Fig. 2c) but negative for S100 (Fig. 2d). CD3-positive T-cells accompanied the histiocyte infiltrate (Fig. 2e), with <50% being positive for the proliferative marker Ki67 (not shown). Stains for B-cell CD20 were negative (Fig. 2f). Subependymal microvasculature had extensive infiltration of

perivascular spaces by CD68 histiocytes (Fig. 2g) and CD3 T-cells (Fig. 2h). Pathologic findings were indicative of chronic meningoencephalitis and perivascularitis consistent with the non-Langerhans lymphohistiocytosis Erdheim-Chester disease (ECD). Additionally, multiple subacute infarctions were seen in the temporal lobe (Fig. 2i), thalamus, and posterior fossa structures, in which the histiocytes showed positivity with CD68 (Fig. 2j), but no reactivity for CD163 (Fig. 2k), and minimal reactivity for S100 positivity (Fig. 2l).

Discussion

ECD is a rare, acquired, non-Langerhans histiocytic neoplasm associated with autoimmunity [1]. It is linked to somatic mutations of the MAPK pathway (usually BRAF proto-oncogene V600E) that enhance histiocyte proliferation and survival [2]. ECD results in the infiltration of tissues and organs by transformed histiocytes, and causes injury by inflammation and fibrosis [2]. Biopsy is required to confirm diagnosis [2]. The

Table 1. Summary of pertinent diagnostic investigations performed

<i>Serology</i>	
Coagulation	Protein C, protein S, antithrombin III, factor V mutation, PT20210 mutation, fibrinogen level; LAC, β 2-glycoprotein Abs and ACL IgM/IgG
Inflammatory	ESR and CRP
Immune	ANA, anti-ds DNA, RF, SS-A/SS-B, ANCA: MPO and PR3 Abs, C3 and C4 levels, CCP IgG, IgM/IgA/IgG levels, and β 2-microglobulin
Infectious	Procalcitonin; bacterial and fungal cxs; <i>Coccidioides</i> Ab, Fungitell B-D glucan; <i>Streptococcus pneumoniae</i> Ag; QuantiFERON, RPR; HIV-1 and HIV-2 Ag/Ab; PCR for RSV, adenovirus, rhinovirus, influenza and parainfluenza viruses, and metapneumovirus
Neoplastic	Flow cytometry
<i>CSF</i>	
Profile	Normal pressure; protein 53 mg/dL, glucose 68 mg/dL; erythrocytes 11/ μ L, leukocytes 4/ μ L
Immune	IgG synthetic rate and oligoclonal bands
Infectious	Fungal cxs, cryptococcal Ag, <i>Coccidioides</i> complement fixation; bacterial stains and cultures; AFB; VDRL, Lyme titer; IgM/IgG Abs for VZV, WNV, Eastern and Western equine encephalitis viruses, California virus and Saint Louis encephalitis virus; PCR for HSV-1 and 2, VZV, EBV, CMV, HHV-6, enteroviruses, polyomavirus, human parechovirus, <i>Streptococcus pneumoniae</i> and <i>Streptococcus agalactiae</i> , <i>Neisseria meningitidis</i> , <i>Haemophilus influenzae</i> , <i>Listeria monocytogenes</i> , <i>Escherichia coli</i> , and <i>Cryptococcus neoformans/gattii</i> ; <i>Cysticercus</i> Ab, <i>Toxoplasma</i> Ab
Neoplastic	Cytology $\times 2$ and flow cytometry $\times 2$
<i>Radiologic</i>	
Ultrasound	TTE and TEE
CT	CT head, CTA head, CTA neck, and CT body
MR	Cerebral MRI $\times 7$
Angiography	Cerebral angiography $\times 2$
<i>Pathology</i>	
Histology	Cerebral biopsy $\times 2$
Cxs, cultures.	

characteristic features of ECD include diffuse tissue infiltration with CD68-positive and CD163-positive, but S100-negative foamy histiocytes. Dense fibrosis, multinucleated (Touton) cells, and reactive lymphocytosis are often present [3]. Treatment with interferon- α constitutes first-line therapy [3], but prognosis remains guarded, with a 60% mortality rate 3 years after diagnosis [4].

Commonly involved organs include the bone, skin, eye, pituitary, heart, vessels, lungs, kidneys, liver, spleen, pleura, and retroperitoneum [3, 4]. Clinical symptoms may include fever, fatigue, bone pain, xanthelasmata, pituitary endocrine dysfunction, and manifestations of car-

diac, pulmonary, renal, and vascular compromise [3, 4]. Cardiac manifestations can include histiocytic invasion of the myocardium and pericardium, at times forming an intra-atrial mass [5]. Perivascular infiltration and fibrosis have been observed in the aortic, coronary, pulmonary, renal, visceral, and iliofemoral arterial systems [5].

CNS involvement occurs in 25–50% of patients, [3] and may present as alterations in mentation/memory, seizures, cephalalgia, diplopia, dysarthria, dysphagia, hypacusis, sensory-motor deficits, and cranial/peripheral neuropathy [4, 6]. Imaging may reveal cerebral masses, transverse pontine enhancement, linear ependymal enhancement, pituitary nodules, meningeal lesions, gen-

Table 2. Conditions associated with cerebrovascular and cervicocranial perivascular leukocytic infiltrates [15–20]

Condition	Inflammatory cell(s)	Vessel type	Vessel size	Vessel locale	CNS focus
Inflammatory					
CLIPPERS [15]	Lymphocytes: CD4 > CD8 T-cells	Arteries and veins	Microvascular	Intracranial only	Predominantly pontine
Autoimmune GFAP astrocytopathy [16]	Lymphocytes: CD20 B-cells	Arteries and veins	Microvascular	Intracranial only	Periventricular and subpial
Inflammatory CAA [17]	Macrophages: multinucleated giant cells	Arteries	Microvascular	Intracranial only	Cortex and pia
Sarcoidosis [18]	Macrophages: epithelioid giant cells	Arteries and veins	Microvascular and macrovascular	Intracranial and extracranial	Variable
Behcet's disease [19]	Polymorphonuclear cells, lymphocytes, eosinophils, and macrophages	Arteries and veins	Microvascular and macrovascular	Intracranial and extracranial	Variable
TiPIC (carotidynia) [20]	Lymphocytes	Arteries	Macrovascular	Extracranial carotids	N/A
Proliferative					
ECD	Macrophages: CD68 and CD163 histiocytes and giant multinucleated (Touton) cells	Arteries	Microvascular and macrovascular	Intracranial and extracranial	Variable

CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; GFAP, glial fibrillary acidic protein; CAA, cerebral amyloid angiopathy; TiPIC, transient perivascular inflammation of the carotid artery; ECD, Erdheim-Chester disease.

Fig. 2. Histopathology of central nervous system ECD. Hypercellular pleomorphic histiocytic lesion (H&E) (**a**), positive for macrophage marker CD68 (**b**) and marker for peripheral macrophages (haptoglobulin receptor), CD163 (**c**), but negative for S100, a Langerhans cell marker (**d**). **e** Moderate to marked T-cell infiltrates (CD3) associated with the histiocytes. **f** No B-cell infiltrates

are apparent (CD20). **g, h** Subependymal vessels have perivascular histiocytes (CD68) and T-cells (CD3). **i–l** Subacute infarcts. **i** Histiocyte-rich subacute infarct (H&E) positive for macrophage-microglial marker CD68 (**j**) but negative for peripheral macrophage marker CD163 (**k**) and with sparse S-100 immunoreactivity (**l**). ECD, Erdheim-Chester disease.

eralized cerebral atrophy, orbital masses, and craniofacial osteosclerosis [7–9].

Cerebrovascular involvement by ECD is rare and, similar to systemic disease, demonstrates a predilection for the larger cervicocranial vessels. ECD has been associated with perivascular infiltration and stenosis of the cervical carotid [10], intracranial carotid [7], middle cerebral [11], vertebral [12], and basilar [13] arteries, with microvascular involvement implied in the presence of concurrent leukoencephalopathy [12, 14]. Previous reports documenting perivascular infiltrates of the microvasculature are lacking in ECD. Conditions analogous to ECD that may also demonstrate cervicocranial perivascular leukocyte infiltrates are provided in Table 2.

Conclusions

In summary, ECD is a rare and elusive hematopoietic malignancy that may involve the nervous system and cerebral vasculature in various ways. We believe this is the first reported case of cerebrovascular ECD that demonstrates the presence of perivascular microangiopathy. Our case also illustrates the multifaceted manner in which ECD may manifest in the central nervous system, including ischemia, hemorrhage, mass lesions, and cerebral edema. Importantly, our case illustrates the difficulty of diagnosing CNS involvement in myeloproliferative disorders, whereby CSF investigations are frequently unrevealing and require serial assessments [21]. As such, reliable biomarkers of CNS ECD are urgently needed to facilitate early diagnosis so as to permit timely initiation of treatment. It is notable that CSF cytology in our patient showed numerous macrophages, which raises the question whether increased S100-negative histiocytes in the CSF may serve as a marker for ECD in patients with CNS involvement. Finally, the dense infiltrate of proliferating subependymal CD3 T-cells raises the theoretical possibility of a secondary autoimmune process, steroid-treated B-cell lymphoma, or that of a secondary malignant T-cell transformation.

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Statement of Ethics

This work complies with internationally accepted standards. This research was conducted via the Mayo Clinic neurodegenerative brain bank which operates under an IRB. The study is exempt from Ethics Committee approval as it is a retrospective case report that entailed no active patient interventions.

Conflict of Interest Statement

The authors have no competing or conflicts of interest to declare.

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Author Contributions

Dr. Moussouttas researched the topic, reviewed the literature, obtained consent, and composed the manuscript. Drs. Roemer and Dickson performed histological evaluations and neuropathologic diagnosis, and assisted in the writing and review of the manuscript.

Informed Consent

Written informed consent was obtained from family members surviving the patient, who expired, for the collection and compilation of data, and for the publication of this case report and any accompanying images.

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