

# Erdheim–Chester Disease: An Unusual Cause of Intracranial Vasculitis and Progressive Leukoencephalopathy

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Erdheim–Chester disease (ECD) is a non-Langerhans histiocytosis affecting multiple organs. Stroke as symptom onset of ECD with intracranial vasculitis is unusual. We report the case of a 64-year-old man who presented with an acute ischemic stroke associated with a moderate leukoencephalopathy and intracranial arteries stenosis. Four years later, he developed movement disorders with dysarthria and cognitive impairment. Neuroradiological findings demonstrated a rapidly progressive and diffuse leukoencephalopathy associated with brain atrophy and infiltration of the intracranial vertebral artery wall. Brain postmortem evaluation confirmed the diagnosis of ECD. This diagnosis should be evoked in patients with cryptogenic stroke, progressive leukoencephalopathy, and infiltration of the arterial wall. **Key Words:** Erdheim–Chester disease—stroke—diffuse progressive leukoencephalopathy—brain atrophy—vasculitis.

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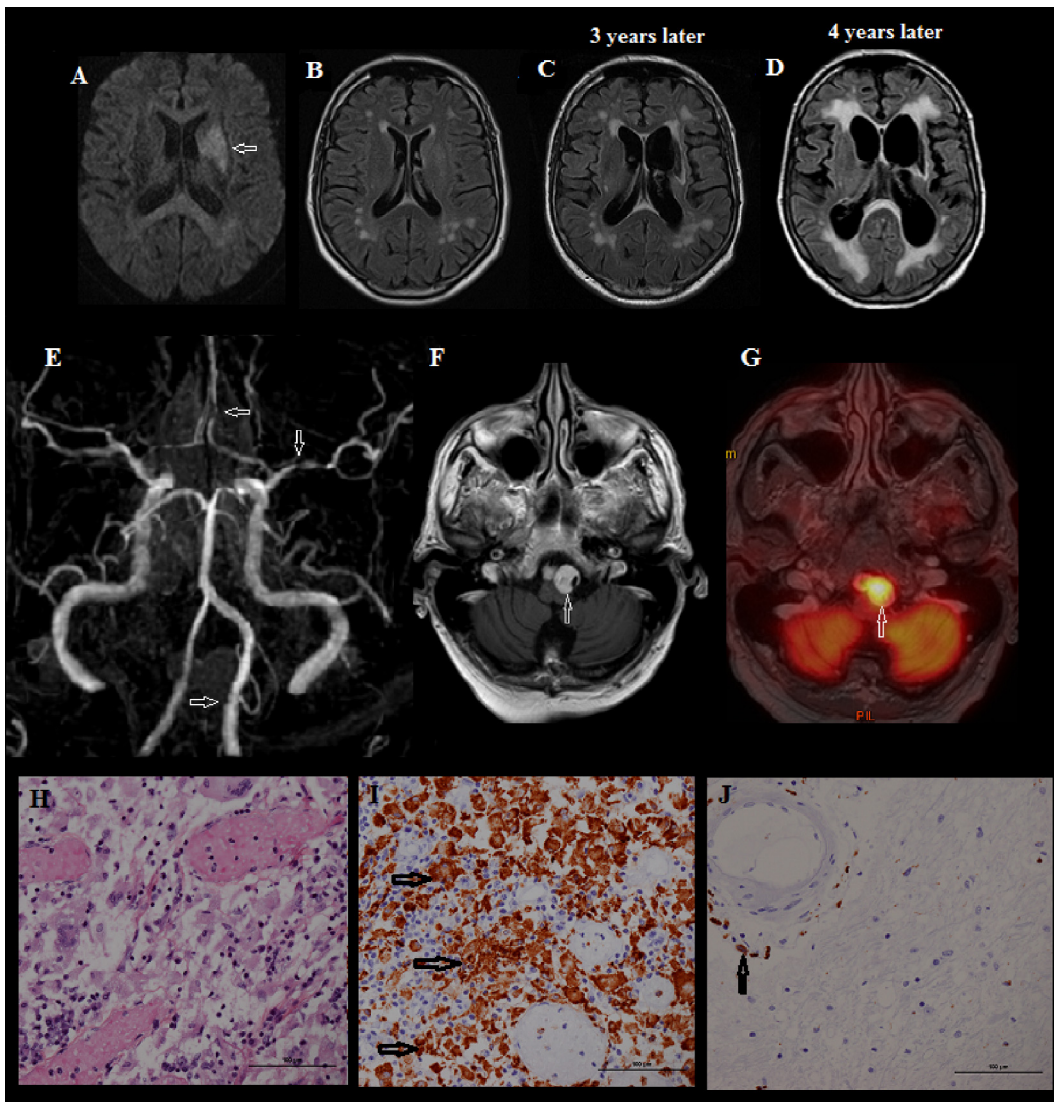
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## Introduction

Erdheim–Chester disease (ECD) is a non-Langerhans histiocytosis due to a clonal and inflammatory disorder most frequently related to *BRAFV600E* mutation<sup>1</sup> and exceptionally revealed by a stroke and brain vasculitis. The diagnosis of this rare disorder is frequently delayed, from 9 months to 12 years.<sup>2</sup> History of diffuse long bone pain and diabetes insipidus should lead clinicians to suspect the diagnosis of ECD,<sup>1,2</sup> but all organs can be affected, contributing to nonspecific symptoms such as asthenia or fever. The prognosis is reported to be poor but can vary according to the organs involved.

## Observation

A 64-year-old man was admitted for sudden aphasia and paresis of the right arm and face (National Institutes of Health Stroke Scale score = 7). He only had history of chronic hypertension. Brain magnetic resonance imaging



**Figure 1.** Evolution of brain MRI and brain postmortem histopathological findings. Axial DWI sequence (A) demonstrates the infarct lesion in the left deep middle cerebral artery territory. Axial FLAIR sequences show the rapid progressive leukoencephalopathy and brain atrophy (B) after 3 (C) and 4 (D) years of evolution. TOF reconstructions of the polygon of Willis (E) demonstrates stenosis of the intracranial portion of the left vertebral artery associated with stenosis of the left middle and anterior cerebral arteries. Axial T1-weighted imaging shows intracranial periarterial sheathing of the vertebral arteries with gadolinium enhancement (F). Fusion between MRI and  $^{18}\text{F}$ FDG-PET imaging illustrates radiotracer uptake in the vertebral artery wall (G). Brain postmortem evaluation demonstrates fibrosis and infiltration of the vertebral artery wall by foamy histiocytes and giant cells (Hematoxylin Eosin Saffron [HES]) (H) that express CD68 (immunohistochemistry) (I). Immunohistochemistry with anti-CD68 antibody reveals also small foci of positive histiocytes in the splenium corpus callosum (J). In addition, periventricular white matter showed myelin and axonal loss, astrogliosis, interstitial edema, and microscopic infarctions. Abbreviations: DWI, diffusion-weighted imaging;  $^{18}\text{F}$ FDG-PET, 18-fluoro-deoxyglucose positron emission tomography; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; TOF, time of flight.

found a recent infarct in the left deep middle cerebral artery territory and a moderate leukoencephalopathy (Fig 1, A). Computed tomography angiography showed a not significant stenosis of the left middle and anterior cerebral arteries (M1 and A1). A diagnosis of stroke related to intracranial artery stenosis probably due to atherosclerosis was evoked. Three years later, he presented a vertebral-basilar transient ischemic attack with a slight progression of the leukoencephalopathy (Fig 1, C). One year later, his neurological status rapidly worsened, including dystonia, gait disturbances, dysarthria and cognitive

impairment. Brain magnetic resonance imaging demonstrated an extension of the leukoencephalopathy with brain atrophy, but without stroke recurrence. We observed the previously known intracranial stenosis together with a stenosis of the intracranial segment of the vertebral arteries, which were sheathed by a contrast-enhanced perivascular sleeve (Fig 1, E,F). Abdominal computed tomography demonstrated periaortic sheathing, infiltration of mesenteric and perirenal fat with a typical “hairy kidney” appearance, and technetium 99m bone scan showed moderate radiotracer uptake in the

metaphyseal area of the tibiae. 18-Fluoro-deoxyglucose positron emission tomography scan revealed a hypermetabolism of the aortic and vertebral artery walls (Fig 1, G). A leukocyte infiltrate with CD68-positive histiocytes was observed on perirenal fat biopsy. *BRAFV600E* sporadic mutation was positive.

Two courses of infliximab (5 mg/kg), a tumor necrosis factor alpha inhibitor, were administered intravenously at a 15-day interval without any significant improvement. The patient's condition rapidly became worse until he finally succumbed to his disease. Brain postmortem examination identified typical foamy histiocytes that expressed CD68 (Fig 1, H-J) but not S100 protein nor CD1a in the arterial wall of intracranial arteries and, to a lesser extent, in the brain parenchyma, confirming the diagnosis of ECD.

## Discussion

Central nervous system (CNS) manifestations of ECD are usually related to the infiltration of the brain parenchyma by abnormal cells, with a predominance of lesions occurring in the posterior fossa.<sup>1,3,4</sup> Stroke is an uncommon presentation and has never been described to our knowledge. In the present case, stroke was due to an intracranial periarterial infiltration, which is a rare and most often asymptomatic presentation in ECD.<sup>3</sup> While intracranial localization is unusual, other periarterial infiltrations are more typical, such as sheathing of the thoracic and abdominal aortas described in up to 60% of the patients.<sup>1</sup> We also observed a diffuse and progressive leukoencephalopathy probably due to a chronic hypoperfusion related to intracranial vasculitis rather than to an infiltration of foamy histiocytes that prevailed in the splenium corpus callosum. Leukoencephalopathy-like patterns involving periventricular white matter with brain atrophy are known lesions in Langerhans cell histiocytosis and are usually associated with poor outcome.<sup>5</sup> Similarly, our patient had rapid neurological deterioration. This is in accordance with previous studies that reported a poor prognosis in ECD patients with involvement of the CNS and the cardiovascular system.<sup>1,2,6</sup> In a large series of 53 patients, 14 patients died after a median follow-up of 55.9 months from disease onset, and four of them died from rapid or slow CNS involvement.<sup>6</sup>

To date, only interferon- $\alpha$  has been described to be a major predictor of survival,<sup>6</sup> and infliximab is consid-

ered as a second-line therapy.<sup>1</sup> Vemurafenib, a *BRAF* inhibitor actually in clinical trial, showed efficacy in patients with multisystemic and refractory ECD harboring the *BRAFV600E* mutation.<sup>7,8</sup> Unfortunately, this treatment was not started due to the rapid clinical worsening of the patient.

Finally, although stroke with brain vasculitis is uncommon in ECD, the more typical extraneurological signs found in our patient, including periaortic sheathing, hairy kidney appearance, and infiltration of the tibiae metaphysis, allowed the diagnosis. Such signs should alert the stroke clinician.

## Conclusion

This observation illustrates the variability of neurological involvement in ECD and reminds clinicians of the need to pursue etiologic investigations in the case of atypical stroke presentation.

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