Movement Disorders
CLINICAL PRACTICE
CASE REPORT

Choreo-Athetosis and Ataxia as Leading Features in a Case of Erdheim-Chester Disease

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Erdheim-Chester disease (ECD) is a rare non-Langerhans cells histiocytosis that presents with multifocal osteosclerotic bone lesions; although tissue infiltration can occur in almost every organ, skeleton, retroperitoneum (mainly the kidney and aorta) and orbit involvement is common.[1] Being a multiorgan disease accounts for the protean clinical manifestations, of which bone pain is the most frequently reported, whereas neurological symptoms are rare and include ponto-cerebellar dysfunction associated with hypopituitarism and seizures.[1] The described brain magnetic resonance imaging abnormalities consist of proliferative tissue invasions of the hypophysis, cerebellum, and brainstem.[2] Here we report an atypical ECD presentation manifesting with movement disorders.

Case Report

A 67-year-old man with a longstanding history of Paget's disease, chronic bronchitis and recurrent cardiovascular events presented to our clinic for the evaluation of subtle dysarthria and dysphagia. The patient's personal history also included mild depression, obsessive thoughts, and vocal stereotypies, whereas his Montreal Cognitive Assessment score, performed as part of the routine clinical evaluation, was 18/30, with a prevalent impairment of executive tasks. Clinical examination showed the presence of ataxia and involuntary choreo-athetoid movements of trunk, head, and limbs (Video S1) that had appeared 1 year before this evaluation and had been considered to be of cerebrovascular origin by another neurologist. Brain magnetic resonance imaging was performed, showing the presence of brainstem and cerebellar atrophy, with a remarkable overload of ferromagnetic substances especially in striatum, red nucleus, and substantia nigra. Moreover, serpiginous images extending from ventricular ependymal zone to diencephalon were reported and interpreted as perivascular space enlargements (Fig. 1). A full biochemical and cerebrospinal fluid examination excluded secondary causes of chorea, ataxia, and brain metal overload. The exams were inconclusive except for the presence of antinuclear antibodies 1:640, but negative anti-dsDNA and clinical criteria ruled out lupus erythematosus chorea. Despite a negative family history, and in the suspect of a dominant disease with reduced penetrance, we performed a first line of genetic tests looking for hereditary causes of progressive chorea. This included Huntington's disease (CAG 16/26) and the phenocopies spinocerebellar ataxia type 17 (CAG/CAA 34/37), dentatorubral-pallido-luysian atrophy, and *C9orf72* gene expansions (G3C2 2/7); however, all of these investigations came back negative. A later next-generation sequencing panel for neurodegeneration with brain iron accumulation syndromes excluded mutations of *PANK2*, *PLA2G6*, *WDR45*, *FA2H*, *COASY*, *ATP13A2*, *C19orf12*. Aceruloplasminemia, neuroferritinopathy, and Wilson's disease were also excluded on the basis of biochemical/genetic exams and clinical findings, whereas brain computed tomography excluded calcification (Fahr and related diseases). We then decided to perform a fluorodeoxyglucose–positron emission tomography scan to further characterize the cognitive impairment. This showed a loss of cerebellar metabolism with the integrity of cortical structures. Because of the chronic bronchitis, we performed chest computed tomography, revealing the presence of aortic wall thickening. Therefore, the study was extended to the abdominal region, showing retroperitoneal fibrosis with a massive accumulation of fibrotic tissue encasing kidneys. After biopsy, the histological analysis enlightened the presence of foamy histiocytes (CD68+, CD163+, S100−, IgG4−), later resulting positive for a BRAFV600E mutation—compatible with a diagnosis of ECD. A bone scintigraphy later

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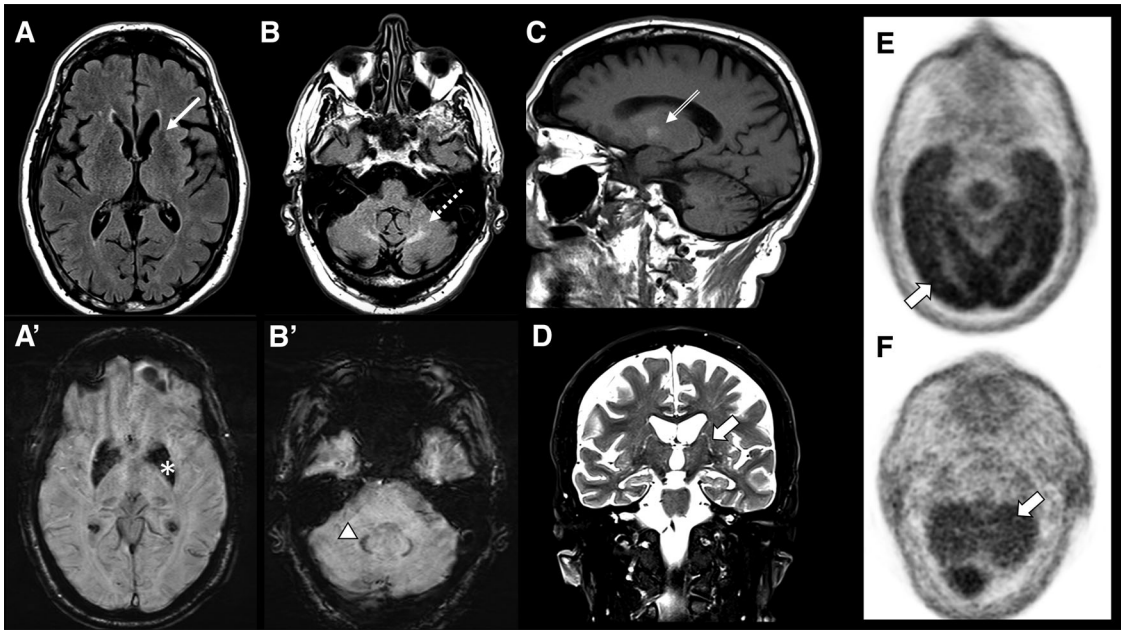

FIG. 1. Magnetic resonance imaging in Erdheim-Chester. Fluid-attenuated inversion recovery (**A,B**) and gradient-echo (**A',B'**): striatal (thin arrow) and cerebellar (dashed arrow) atrophy and caudate, pallidus, (*) and dentate ferromagnetic deposition. T1 hyperintense pallidus (double-body arrow; **C**) and T2 serpiginous images from ependyma to diencephalon (thick arrow; **D**).[1] Fluorodeoxyglucose–positron emission tomography (**E,F**): preserved cortex versus cerebellar diaschisis.

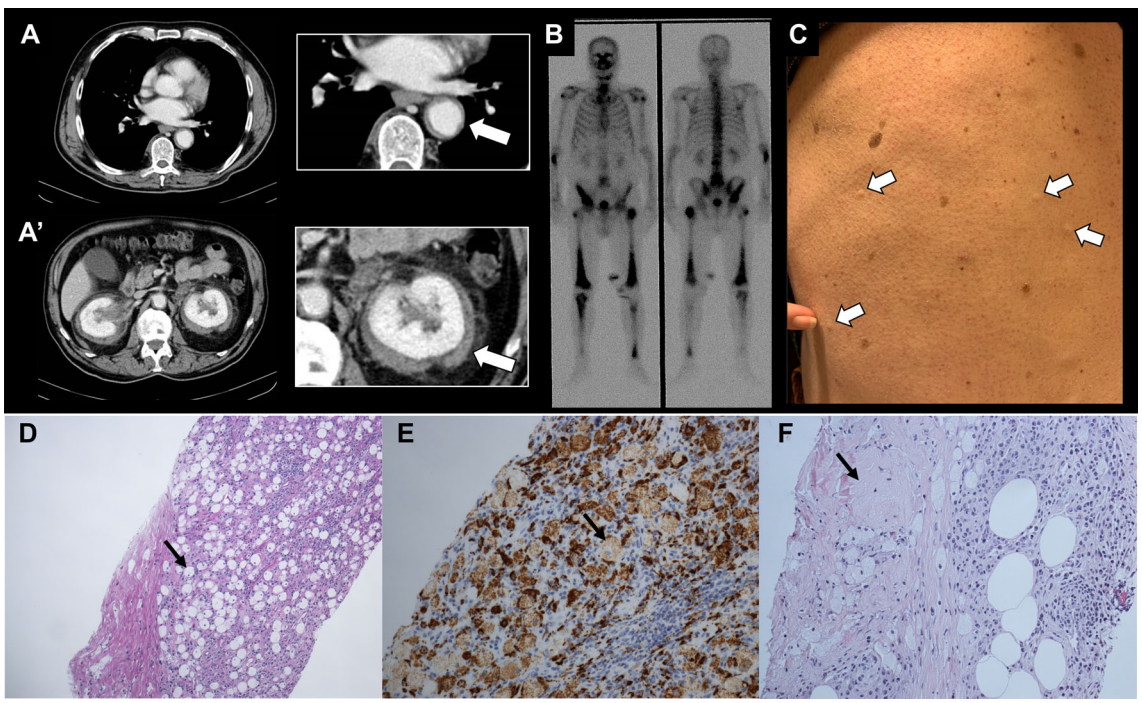

FIG. 2. (**A**) Computed tomography of aortic wall thickening and (**A'**) retroperitoneal fibrosis encasing kidneys (arrows); (**B**) multiple bone lesions (femoral epiphysis, pelvis, column; scintigraphy); and (**C**) skin nodules. Histological examination shows foamy macrophages (**D**; Periodic Acid-Schiff (PAS) reaction 40×), CD68+ macrophages (**E**; 100×), and extensive fibrosis (**F**; hemotoxylin and eosin, 10×).

reported multiple pathological disease localizations in various skeletal structures (Fig. 2). He is currently under hematological follow-up and has started therapy with vemurafenib at a dose of 960 mg (with a slow up-titration for 5 months). At present, no adverse events are reported, and his clinical conditions are stable. On a neurological standpoint, he showed an improvement of hand dexterity without significant changes in other neurological items including balance and gait. The latter is still possible with a cane, and the rate of falls is unchanged.

Discussion

Cerebral histiocytosis has been generally reported as a rare cause of ataxia as a result of brainstem and cerebellar involvement. However, here we specifically report of ECD (a non-Langherans histiocytosis) in whom ataxia and brain ferromagnetic substances deposition are neither predominant features nor diagnostic pointers. Chorea has been only recently reported as associated to ECD in a single case, who presented also with questionable ferromagnetic substances overload.[3] The presence of late-onset chorea, gait ataxia, and cognitive and psychiatric abnormalities in the elderly with chronic degenerative progression require several differential diagnoses, including Huntington's disease–like diseases, such as SCA17, DRPLA, and C9ORF72 and some inherited ataxias.[4] The former embraces late-onset phenotypes due to reduced penetrance or low-expanded mutations.[5] Also, autoimmune and paraneoplastic diseases, basal ganglia lesions, neurodegeneration with brain iron accumulation (disorders of mineral metabolism; i.e., aceruloplasminemia, neuroferritinopathy, Fahr and Wilson diseases), and lysosomal storage disorders should be considered (Supplementary Table S1). In our case, these etiologies of ataxia were excluded through genetic testing, neuroimaging, and blood tests.

Our patient had peculiar clinical picture and neuroimaging findings; the initial presentation of ECD could be traced back to the controverted diagnosis of "Paget's disease"—a common disease of bone recycling—and to the beginning of coronary and peripheral vascular ischemic events. The etiology is unknown, but ECD is strongly associated with somatic mutations of the *BRAF* gene, recently allowing the treatment with vemurafenib, a specific enzyme inhibitor and the only disease-modifying available therapy.[6] Albeit reported in less than one third of cases, the involvement of the central nervous system defines the prognosis in ECD patients as an independent predictor of death and poor response to conventional therapies (steroids, azathioprine, cyclosporine, interferon). This case highlights the importance of early recognition of ECD, as a newly discovered treatment with vemurafenib is currently changing clinical history and improving patients' quality of life and prognosis.

Finally, when dealing with rare diseases, a high index of suspicion is needed to make the correct diagnosis, especially if atypical or uncommon clinical findings are present.

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Author Roles

(1) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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A.T.: 1A, 1B
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Disclosures

Ethical Compliance Statement: Patient was informed and a signed consent was obtained. The authors confirm that the approval of an institutional review board was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Video S1. Movement disorders in Erdheim-Chester. First segment: jerky smooth pursuits, delayed/slow saccades, and hypomimia. Second segment: choreo-athetosis at neck and upper limbs. Mild impaired hand dexterity. Poor postural reflexes and mild dystonia of trunk and limbs. Third segment: wide based gait.

Supplementary Table S1. Causes of progressive choreo-athetosis in adult population.