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Case Report
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A Rare Cause of Progressive Cerebellar Ataxia and Dementia

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Abstract

Erdheim-Chester Disease (ECD) is a rare histiocytic multisystem disease, affecting bones, heart, aorta, lungs, skin, retroperitoneum and Central Nervous System (CNS), caused by a mutation in the MAPK signaling pathway, often the BRAF proto-oncogene. We report the case of a 42-year-old man presenting with cognitive impairment and progressive cerebellar ataxia due to the CNS involvement of his ECD.

Keywords: Erdheim-Chester disease; Ataxia; Dementia; Neuroimaging

Introduction

Erdheim-Chester Disease (ECD) is a rare non-Langerhans cell histiocytosis characterized by tissue infiltration with CD68+, CD1a – foamy histiocytes [1]. ECD is a systemic disease that almost invariably affects bones, particularly the long bones of the lower extremities. Extra-skeletal manifestations may include cardiovascular, pulmonary, cutaneous, retroperitoneal, neurological, endocrine and retro-orbital involvement [2]. ECD often occurs in adults with male predominance, and is caused by various mutations in proto-oncogenes namely BRAF and MEK [2,3].

We report a case of ECD, with slowly progressive cerebellar and brainstem dysfunction with brain resonance imaging (MRI) findings, over 10 years of evolution. To the best of our knowledge, it is first case reported in Lebanon. The study was approved by the ethical committee of the Faculty of Medicine at the Saint Joseph University of Beirut, Lebanon. Written informed consent was obtained from the patient to report this case and accompanying images.

Case Presentation

A 42-year-old man presented in 2015 with severe aggravation of ataxia, dizziness and dysarthria.

He was diagnosed with Erdheim Chester Disease (ECD) in 2004. Microscopic exam was obtained on a right knee lesion that demonstrated an intense CD68+, CD1a-, and S100-infiltrate of histiocytes with foamy cytoplasm, in favor of the diagnosis of ECD. Initial MRI of the head was reported normal. Treatment with high dose methylprednisolone was ineffective. Afterwards, interferon alpha treatment was given but did not result in significant clinical improvement and was discontinued due to intolerance.

Otherwise, he has a history of bilateral cataract, a thyroid adenoma resected in 2001, type 2 diabetes mellitus treated with insulin, and diabetes insipidus secondary to pituitary infiltration by his disease. The patient was seen in 2009, when he presented for recent ataxic gait, dysarthria, dysmetria and dysdiadochokinesia. The rest of physical examination was normal. At that time, he had no cognitive impairment. Cranial Magnetic Resonance Imaging (MRI) (Figure 1) showed hyperintense, non-contrast enhancing lesions within the bilateral dentate nuclei as well as within the posterior medulla bilaterally. Multiple enhancing extra-axial masses were noted along the falx cerebri and the cerebellar tent. Thickening of the pituitary stalk was also present with an absent posterior pituitary bright spot. There was mild cerebral and cerebellar volume loss. Over the next year, the patient developed gradual increase in ataxia with limb weakness and difficulty with speaking. He became wheelchair-bound in 2012. In the subsequent 2 years, he developed mild cognitive impairment with short-term memory loss. Routine blood tests were performed to rule out reversible causes for cognitive impairment such as vitamin B12 deficiency, HIV and thyroid function tests and were normal. Repeat MRI of the head (Figure 2) showed interval development of severe cerebellar volume loss with marked signal abnormality within the dentate nuclei, bilateral middle

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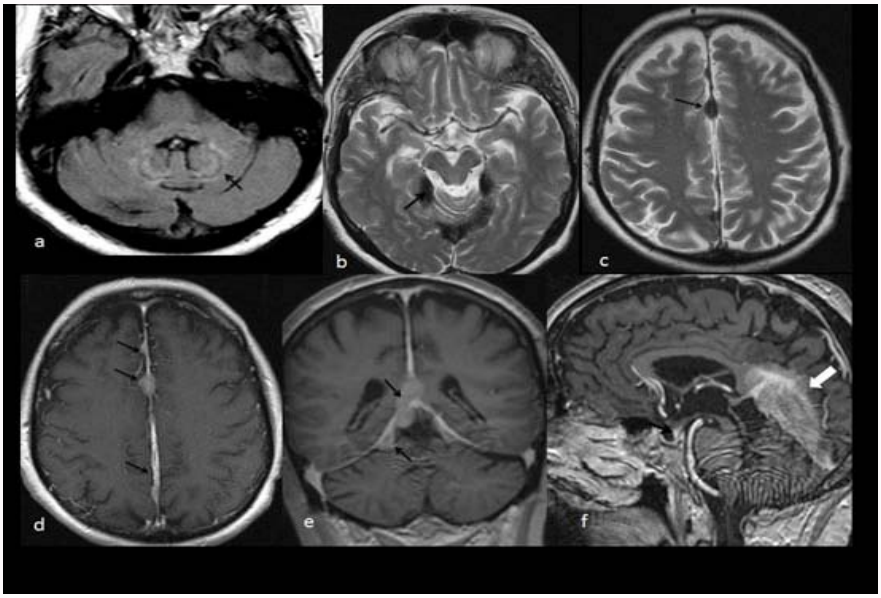

Figure 1: (a) Axial T2-Flair weighted image shows signal abnormality within the bilateral dentate nuclei (arrow); (b) Axial T2 weighted image shows extensive extra-axial lesions with T2 hypointensity (arrow) along the thickened cerebellar tent and (c) in several regions along the dura of the falx. T1-weighted postcontrast image reveals (d) on axial image a focal and homogeneous enhancing epidural lesion that is meningioma-like along the falx cerebri and (e) the cerebellar tent (coronal image); and (f) on sagittal sequence at the sella level, it indicates a thickened enhancing pituitary stalk (black arrow) and thickened irregular enhancement along the straight sinus (white arrow).

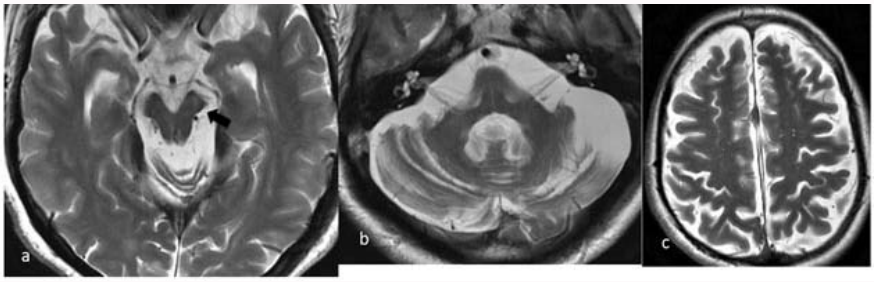

Figure 2: MRI of the brain, acquired 3 years later; axial T2-weighted image shows (a) signal abnormality and atrophy of the cerebral peduncles (arrow), (b) cerebellar atrophy and (c) moderate cerebral volume loss with hypointense nodular thickening along the falx cerebri.

and superior cerebellar peduncles as well as within the pons. New T2 hypointensity was noted lining the midbrain, pons and medulla without contrast enhancement. The multiple enhancing extra-axial masses along the falx and the cerebellar tent have decreased in size compared to the prior study.

Discussion

ECD is a rare disease caused by an activating mutation of the MAPK signaling pathway. The BRAF mutation is the most common, being incriminated in about 54% of ECD cases, followed by MAP2K1, NRAS, KRAS, ARAF and PI3K-AKT mutations as well as other rare mutations [4]. Clinical manifestations of ECD are heterogeneous. The most common manifestation is a symptomatic or asymptomatic osteosclerosis of long bones of the lower limbs, and sometimes the upper limbs [5]. Cardiovascular involvement is characterized by sheathing of the aorta, sheathing of the right coronary artery, right atrial pseudotumor, pericardial, myocardial or endocardial infiltration with conduction system defect [5]. Pulmonary manifestations are common, including interstitial lung disease and pleural involvement [6]. Other clinical manifestations include exophthalmos due to retro-orbital infiltration, hypopituitarism, retroperitoneal fibrosis and skin rash, namely xanthelasma-like lesions of the eyelids [5]. First line treatment includes an Interferon-α (IFN-α). BRAF and MEK inhibitors are recommended as second line therapy, after IFN-α failure or intolerance. The use of anti-cytokine biotherapies targeting Tumor Necrosis Factor (TNF)-α, Interleukin 1 (IL-1) or Interleukin 6 (IL-6) receptor may also be effective [4].

Central Nervous System (CNS) involvement occurs in up to 50% of ECD patients, and often presents with diabetes insipidus, cognitive dysfunction, cerebellar ataxia, focal neurological deficits due to cranial neuropathy, myelopathy or spinal cord compression, axonal neuropathy, headaches and seizures [5,7,8]. There are three patterns of CNS involvement: The infiltrative pattern, the meningeal pattern and the combined features [9]. Orbital infiltration and hypothalamic-pituitary axis involvement are common [9]. Brain imaging may reveal supratentorial or infratentorial T2-hypointense, gadolinium enhancing dural masses, or occasionally diffuse pachymeningeal thickening, symmetric T2-hyperintense, T1-hypointense lesions in the dentate nucleus of the cerebellum and brainstem particularly the pons [9,10]. Lesions may also be seen in the spinal cord, basal ganglia, periventricular and juxtacortical brain regions [9,10].

Cerebellar ataxia and dementia have been described in ECD. Our case supports the previously published literature as it shows dentate nuclei and cerebellar involvement by T2-hyperintense non-enhancing lesions, dural enhancing masses along the falx cerebri and the cerebellar tent as well as pituitary stalk involvement, in a patient presenting with typical clinical features of ECD. Involvement of the brainstem and the development of severe cerebellar atrophy on the subsequent MRI 3 years later, clearly demonstrate the role of ECD in development of brainstem and cerebellar symptoms particularly the progressive cerebellar ataxia.

Even though it is uncommon, ECD should be recognized as a cause of progressive cerebellar ataxia and should suspected when there are one or numerous dural lesions.

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