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Erdheim–Chester disease: A systematic review

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Abstract

Erdheim–Chester disease (ECD) is a rare form of non-Langerhans-cell histiocytosis, associated in more than 50% of cases to *BRAF*^{V600E} mutations in early multipotent myelomonocytic precursors or in tissue-resident histiocytes. It encompasses a spectrum of disorders ranging from asymptomatic bone lesions to multisystemic, life-threatening variants. We reviewed all published reports of histologically-confirmed ECD and explored clinical, radiological, prognostic and therapeutic characteristics in a population of 448 patients, including a unique patient from our Department. To find a clinically relevant signature defining differentiated prognostic profiles, the patients' disease features were compared in relation to their CNS involvement that occurred in 56% of the entire population. Diabetes insipidus, visual disturbances, pyramidal and extra-pyramidal syndromes were the most recurrent neurological signs, whereas concomitant pituitary involvement, retro-orbital masses and axial lesions in the presence of symmetric bilateral osteosclerosis of long bones depicted the typical ECD clinical picture. Patients

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with CNS infiltration showed a lower occurrence of heart involvement and a higher incidence of bone, skin, retro-peritoneal, lung, aortic and renal infiltration. No difference in the therapeutic algorithm was found after stratification for CNS involvement. A better understanding of the disease pathogenesis, including *BRAF* deregulation, in keeping with improved prognostic criteria, will provide novel suggestions for the management of ECD.

Keywords: Erdheim–Chester disease; CNS involvement; Histiocytosis; $BRAF^{V600E}$; Vemurafenib

1. Introduction

Erdheim–Chester disease (ECD) is a non-Langerhans-cell form of histiocytosis characterized by xanthomatous infiltration of tissues by CD68-positive, CD1a-/S100-negative foamy histiocytes [1]. It is a rare disorder accounting for up to 600 cases to date, which primarily affects male patients between their 5th and 7th decade of life [2]. Although, according to the WHO classification, ECD is a neoplasm deriving from histiocytes, there is a long standing debate as to whether the disorder is of malignant or polyclonal reactive nature [3]. Clinical manifestations of ECD at presentation are protean and encompass bone pain, diabetes insipidus, neurological and constitutional symptoms, although retroperitoneal, cutaneous, cardiovascular and pulmonary involvement have also been described [4,5]. Since the clinical picture of ECD arises as a slowly forming mosaic with sequential manifestations, the diagnosis is often challenging. However, X-ray peculiar aspects such as symmetric diaphyseal osteosclerosis or parallel scintigraphy uptake in long bones of both extremities provide a striking signature of the disease and may favor the diagnosis [2].

Recently, the discovery of activating mutations of *BRAF* in 54% of ECD patients, along with the role of tumor microenvironment in its development, has modified the traditional interpretation of the disease, supporting novel therapeutic potential in adopting the targeted therapy [6–8]. In particular, the *BRAF* inhibitor Vemurafenib [9], the anti-TNFα moAb Infliximab [10], and the IL-1R antagonist Anakinra [11] have been used with variable though promising results. However, the 5-year survival occurs in less than 70% of patients [12].

Based on the availability of new drugs, some of which exceeding the blood–brain barrier, optimized treatments for patients with CNS lesions are urgently needed. Here, we report a single case of ECD and systematically revisit all published, reliably diagnosed cases of ECD.

2. Case report

A 28-year-old man with a 5-year history of diabetes insipidus, vespertine fever, dyspepsia, nausea and vomiting was admitted in 2010 at our Department complaining of paresthesia and weakness of the lower extremities. Physical examination demonstrated mild left hand dysmetria, ataxic gait as well as the presence of bilateral eyelid xanthelasmas and well-defined papules on the thoracic wall. The results of extensive serum laboratory analyses were otherwise unremarkable. The brain MRI documented a homogeneous intense enhancement of infundibular stalk (Fig. 1A) after gadolinium administration and the presence of white matter lesions in the pons and in the right middle cerebellar peduncle (Fig. 1B). Spinal cord involvement was also detected, since several lesions with moderate contrast enhancement on T1 sequence were diagnosed at level of C2, D1, D8 and D10–D11 (Fig. 1G). The ^{99}Tec-bone scan showed increased uptake in the proximal epiphysis and metaphysis of long bones (Fig. 1D), while 18FDG-PET/CT demonstrated high glucose avidity of the brain lesions with a SUV up to 7.3 in the pituitary gland (Fig. 1C). The patient was subjected to rachicentesis, but the cerebrospinal fluid analysis was unremarkable, showing only rare lymphocytes and histiocytes. Treatment with desmopressin and prednisone was started, but neurological symptoms exacerbated. A skin lesion biopsy revealed the presence of small nucleated foamy histiocytes (CD1a−, CD68+, S100−) and Touton-like multinucleated giant cells along with lymphocytic and eosinophilic infiltration (Fig. 1I–J). These findings suggested the diagnosis of ECD, and therapy with cyclophosphamide was initiated. After one year of treatment, ataxia, paresthesias and weakness of lower extremities worsened with raising of dizziness, diplopia and blurred vision. A new brain MRI showed additional areas of increased contrast-uptake in the right cerebellar hemisphere (Fig. 1E), in the left parietal lobe in close proximity to the ipsilateral lateral ventricle and in the splenium of the corpus callosum (Fig. 1F) in concomitance with worsening of the multiple spinal lesions, while a new sclerotic area involving the L2 vertebra was detected (Fig. 1H). Cyclophosphamide was discontinued and the patient started the treatment with alfa-2b Peg-interferon at 120 μg/week. Since this single-drug therapy did not improve the neurological symptoms, the interferon dosage was increased to 180 μg/week, in conjunction with low dosage of prednisone and cyclophosphamide. At the last follow-up, in June 2013, a partial regression of the brain lesions was detected by both MRI and 18FDG-PET/CT, and the treatment was maintained. Based on the study by Haroche et al. [6], analysis of *BRAF* mutational status was performed by pyrosequencing, and the V600E mutation was detected.

3. Literature review and methods of analysis

We searched the English-language literature indexed in PubMed using the keyword “Erdheim–Chester disease” and