REVIEW
VOLUME 68 | ISSUE 4 | OCTOBER - DECEMBER 2017

Erdheim-Chester disease. An update

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ABSTRACT

Erdheim-Chester disease is a rare non-Langerhans cell histiocytic disorder characterized by abnormal multiplication of histiocytes or tissue macrophages. It is most commonly characterized by multifocal osteosclerotic lesions of the long bones demonstrating sheets of foamy histiocytes, with or without histiocytic infiltration of extraskeletal tissues such as the skin, pituitary gland, retroperitoneum, kidneys and heart. Most cases are diagnosed in adulthood, between ages 40 and 60 years (mean, 53 years), with a 3-fold frequency in males than females. Sporadic cases in children have been reported. This review discusses the clinicopathological features, diagnosis and current treatment of this rare, non-Langerhans cell histiocytosis.

KEY WORDS: Erdheim-Chester disease; Non-Langerhans cell histiocytosis; Interferon A

Introduction

In 1930, Jakob Erdheim and William Chester described a "lipoid granulomatosis" disease that was subsequently named after them [1]. Since then, research showed that Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytic disorder characterized by abnormal multiplication of histiocytes or tissue macrophages. Although rare, the number of cases has dramatically increased in the last 10 years due to increased recognition and knowledge about ECD[1-6]. ECD is most commonly characterized by multifocal osteosclerotic lesions of the long bones demonstrating sheets of foamy histiocytes, with or without histiocytic infiltration of extraskeletal tissues such as the skin, pituitary gland, retroperitoneum, kidneys and heart [2,3]. ECD usually becomes apparent in adulthood, between ages 40 and 60 years (mean, 53 years), with a 3-fold frequency in males than females [5]. Sporadic cases of ECD in children have been reported (approximately 15 cases reported to date), however, none of them has displayed heart involvement, as opposed to adult patients [7,8].

Pathogenesis

The etiology and pathogenesis of ECD are unknown; it is considered an inflammatory or clonal neoplastic disorder [6]. The high levels of IFN-alpha, interleukin-7, interleukin-12, monocyte chemoattractant protein-1, and reduced concentrations of interleukin-4 observed in patients with ECD may explain the associated systemic immune TH-1 intense activity [5,9]. The detection of BRAFV600E mutations by Badalian-Very

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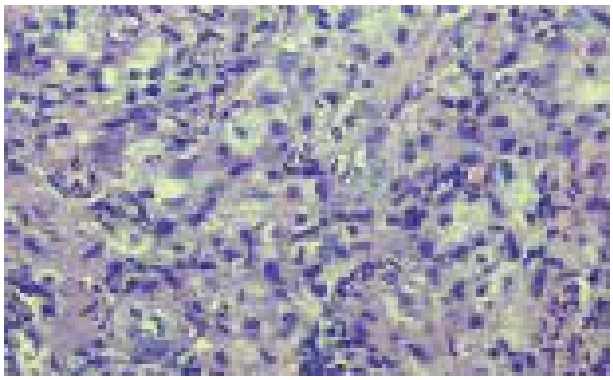

Fig. 1. *Histologic section of a bone tissue biopsy specimen from a patient with ECD shows intense fibrohistiocytic infiltrate with prominent proliferation of foamy histiocytes (stain, hematoxylin and eosin stain; magnification, 200x)*

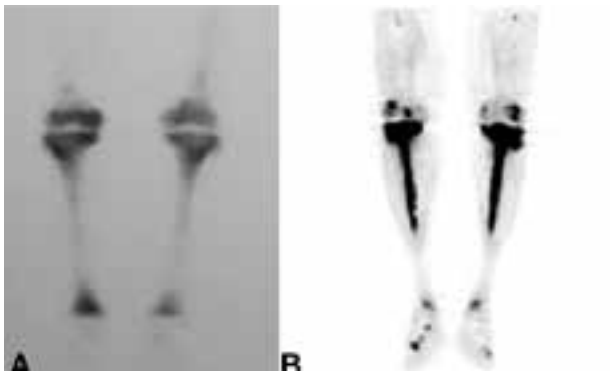

Fig. 2AB. ***(A)*** *Bone scan and* ***(B)*** *PET-CT of a patient with ECD show symmetrically increased uptake at the distal ends of the femurs and the proximal and middle tibia*

et al. [10] and NRASQ61R mutation by Diamond et al. [11] has changed the understanding of the pathogenesis of ECD. More than half the ECD patients carry the BRAFV600E mutation, while recurrent, somatic mutations of the MAP kinase and AKT pathways such as mutations of NRAS, MAP2K1 and PIK3CA have also been observed. It has been suggested that these mutations should lead to a new classification of histiocytic disorders such that Langerhans cell histiocytosis and ECD are classified as inflammatory myeloid neoplasms [2].

Diagnosis

The diagnosis of ECD is based on histopathologic findings (**Fig. 1**) within an appropriate clinical and radiological context. ECD has a specific immunohistochemical profile with xanthomatous foamy histiocytes that stain positive for CD68, negative for CD1a, and either positive or negative for S100 [12]. In addition to lymphocytes, plasma cells and occasional eosinophils, ECD characteristically shows the Touton giant cells, which are enlarged histiocytes that contain large amounts of clear eosinophilic cytoplasm and peripherally displaced nuclei [13].

In addition to the typical histologic features, the radiographic finding of symmetric diaphyseal and metaphyseal osteosclerosis in the legs is present in almost all patients (96%)[14,15]. This is one of the iconic features of ECD, best seen on 99-mTc bone scan compared to positron emission tomography (PET) scan (**Fig. 2**). Bone scan shows increased radioisotope uptake at the distal ends of the femurs and the proximal and distal tibia [14,15]. Bone lesions may be missed on radiographs but can be visualized more sensitively on computed tomography (CT) or magnetic resonance (MR) imaging. CT of the abdomen may show dense infiltration of perinephric fat ("hairy kidneys") in 57% of cases [16,17].

Clinical manifestations

Patients with ECD may present with bone pain, diabetes insipidus, exophthalmos, constitutional symptoms, interstitial lung disease, ureteral obstruction, renal impairment, heart dysfunction and/or tamponade, cerebellar or pyramidal symptoms, and xanthelasmas.

Bone involvement

Bone lesions in ECD are described as osteosclerosis or polyostotic sclerosis as evident in imaging studies [6,18-23]. Bone involvement is extremely frequent (96% of the patients) [14,15] but only 39% of patients experience bone pain that is, nevertheless, the most common clinical symptom of the patients with ECD [15]. Bone pain is usually mild, may start at any time during the course of the disease and mostly affects the legs. Radiographs show a patchy or diffuse osteosclerosis involving the medullary canal, a feature most

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prominent in the diaphysis and metaphysis; bone cortices are also thickened due to periosteal new bone deposition, and skeletal involvement is multifocal and usually symmetrical [17,19,20]. Lytic lesions are reported in 5-8% of patients [19]. MR imaging of the long bones may show epiphyseal involvement, periostitis and replacement of the normal fatty marrow [23].

Cardiovascular involvement

The most common cardiovascular sign in patients with ECD is the circumferential periaortic sheathing of the thoracic or abdominal aorta and its branches [5,20]. Renal artery involvement is associated with renovascular hypertension in 16% of cases [20]. In contrast, infiltration of the pericardium, right heart and coronary arteries may result in cardiac tamponade, myocardial infarction and valvular dysfunction in 17% of cases [20,24]; however, even in patients with symptomatic heart valve disease, valve replacement is rarely required [20,25].

Central nervous system, orbital, and neuroendocrine involvement

Endocrine involvement is very frequent in ECD and should carefully be evaluated at diagnosis and during follow-up [26-31]. Exophthalmos, often bilateral, may occur in 25% of the patients with ECD due to infiltration of the retro-orbital soft tissues [26,27]. Infiltration may be massive in a small number of cases, rendering it refractory to medical therapy, and requiring surgical debulking of the involved orbit. Diabetes insipidus, due to pituitary gland infiltration, is the most frequent endocrine manifestation of ECD (26% of cases). The hypothalamic-pituitary axis is the most common central nervous system (CNS) site affected [28]. Rare cases of pituitary or hypothalamic infiltration with other endocrine consequences such as hyperprolactinemia, gonadotropin insufficiency and abnormally low levels of IGF-1 have also been reported [29,30]. A single-center observational study, [31] reported a 33.3% incidence of diabetes insipidus, a 91.3% incidence of anterior pituitary dysfunction, a 78.6% incidence of somatotropic deficiency, a 44.1% incidence of hyperprolactinemia, a 22.2% incidence of gonadotropic deficiency, and a 9.5% and 3.1% incidence of thyrotropic and corticotropic deficiency, respectively. No patient in that series was free of endocrine hormonal or morphological involvement [31].

CNS involvement in patients with ECD ranges from 25% to 50% (mean, 40%) [4,28,32]. The most common neurological signs are cerebellar and pyramidal syndromes (41% and 45% of cases, respectively), followed by seizures, headaches, neuropsychiatric signs or cognitive impairment, sensory disturbances, cranial nerve paralysis, and asymptomatic lesions [32]. Parenchymal CNS lesions have been reported as an independent predictor of death [5]. The most damaging and difficult to treat neurological condition is pseudodegenerative involvement of the cerebellum [28].

Skin involvement

The most common skin involvement in ECD includes xanthomalike papules and periorbital xanthelasmalike skin lesions [19,33]. Red-brown papular lesions at the extremities and trunk have also been described [34,35].

Renal and urinary tract involvement

Renal and Urinary tract involvement in ECD accounts for approximately 30% of cases [4,19,36,37]. Manifestations vary and occur secondary to direct invasion of sheets of histiocytic infiltrate into the retroperitoneum, causing upper ureteral obstruction, encasement of the kidneys, adrenal insufficiency and chronic renal failure [4,19,36,37].

Pulmonary and other organs involvement

Pulmonary involvement has been reported in 15-35% of patients with ECD [19,38]. Patients with lung involvement by ECD typically present with progressive dyspnea over a period of months to years [19]. Imaging findings include an interstitial process characterized by smooth interlobular septal thickening and centrilobular nodular opacities, fissural thickening, and pleural effusions [38]. Autopsy studies have demonstrated involvement of the testes, thyroid, lymph nodes, breasts, and macrophage activation syndrome [39-42].

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Differential diagnosis

Parietal aortic wall thickening with diffusion to the main aortic branches can be observed in Takayasu arteritis, which mainly affects young women. However, the imaging and histologic findings of Takayasu arteritis and ECD are different; the entire arterial wall is affected in Takayasu arteritis, whereas the adventitial and periadventitial periaortic spaces but not the wall itself is affected in ECD patients. ECD can also be differentiated from mediastinal and retroperitoneal fibrosis based on imaging; typically, retroperitoneal fibrosis is not circumferential and infiltrates the anterior and the lateral sides of the aorta, sparing the posterior side, while retroperitoneal fibrosis but not ECD may involve the inferior vena cava that may be stenosed or occluded, or the pelvic ureters [20]. Extravascular involvement common in ECD but not in retroperitoneal fibrosis such as bilateral infiltration of the perirenal space ("hairy kidneys") is useful for differential diagnosis. The differential diagnosis of ECD should also include relapsing polychondritis (via periaortitis), hyper IgG4 syndrome with some overlap forms with Rosai-Dorfman disease, and mesenteric panniculitis [20].

Treatment

Initial treatment for ECD was empirical, mainly based on chemotherapeutic or immunosuppressive agents; mortality rates were as high as 60% within 3 years of diagnosis [19]. Currently, treatment options for ECD include interferon alpha (IFN-a), IL1-receptor antagonists, BRAF and MEK inhibitors, with mortality rates significantly improved. However, ECD remains an orphan disease that is a disease for which no treatment has been developed because of its rarity.

IFN-a treatment for ECD had a positive impact on patients' outcome [5,43-45]. Braiteh et al. reported rapid, marked and persistent regression of retro-orbital infiltration, and progressive improvement of bone lesions, pain and diabetes insipidus in patients in whom IFN-a was administered [43]. However, IFN-a efficacy differed according to the involved sites, especially for CNS, cardiovascular and multiorgan involvement; in these cases, higher doses of INF-a were recommended [44,45]. IFN-a appears to be the best choice for the initial treatment of ECD, however, it should be administered for long. A prospective study of 24 patients with extensive ECD involving the CNS with or without cardiac involvement who had suboptimal response to standard IFN-a dosing reported improved disease in 46% of patients, stable disease in 21% of patients, and worsened disease in 25% of patients at a 3-year follow-up with increased IFN-a and pegylated IFN-a doses [45].

Anakinra is an IL1-receptor antagonist approved for the treatment of rheumatoid arthritis and neonatal-onset multisystem inflammatory disease. Its mechanism of action in ECD is extrapolated from the knowledge that proinflammatory cytokines, including IL1, are produced after IFN-a stimulation [46-48]. However, response to anakinra varies; in a recent study of 12 patients with multiorgan ECD treated with anakinra, symptomatic improvement was reported in 50% of the patients in regard to fatigue, bone pain, fever and sinus disturbances, five patients had progression of disease, two had stable disease, one had a partial response and one had complete response [46].

Vemurafenib is a BRAF inhibitor approved in 2011 by the Food and Drug Administration for the treatment of advanced melanoma in patients harboring the BRAFV600E mutation. In 2012, a pilot study was conducted of vemurafenib treatment for three patients with the BRAFV600E mutation and multiorgan, refractory ECD after treatment with INF-a [49]. Vemurafenib treatment led to rapid, substantial clinical and biological improvement in all three patients as early as one month after the beginning of treatment. For one patient, serial PET assessments of the response to treatment showed continuous improvement during the first four months of treatment [50]. Darafenib and trametinib are similar drugs currently studied for the treatment of BRAF-mutated ECD.

Trametinib and cobimetinib are MEK inhibitors that have been used in few reported cases as either monotherapy or in combination with BRAF inhibitors in ECD with promising results [51,52].

Prognosis

The clinical course and prognosis of ECD depend on the extent and distribution of the disease; some patients present only asymptomatic bone lesions, where-

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as others have multisystemic, potentially life-threatening forms. Lesions accumulate in the affected organs and systems and rarely regress spontaneously. Serum C-reactive protein (CRP) levels are high in more than 80% of cases, but with little impact on patients' outcome. PET is particularly useful for the assessment of ECD activity [21]. PET scans can detect CNS and cardiovascular system involvement, and can reveal early responses to treatment, when no changes in such lesions are apparent on MR imaging. Two studies reported before the era of IFN-a provided evidence of poor prognosis of ECD [19,20]. Currently, high dose INF-a treatments and BRAF inhibitors have improved the prognosis of the patients with ECD [45,49,50].

Conclusions

ECD is a rare NLCH with potential for multiorgan involvement and dismal prognosis. Substantial progress has been made in recent years with the demonstration of efficacy for IFN-a, description of systemic proinflammatory cytokine signatures, recognition of the BRAFV600E mutation in more than 50% of the patients, and demonstration that BRAF inhibition is highly effective in severe cases of BRAFV600E mutation-associated ECD. However, ECD remains an orphan disease. Further studies of this disease and improvements in our understanding of its pathogenesis should lead to the development of better targeted, more effective treatments.

Conflict of interest

No benefits have been or will be received from a commercial party related directly or indirectly to the subject matter of this article.

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Antoniadou T, Archontakis G, Kapsimalis I, et al. Erdheim-Chester disease. An update. *Acta Orthop Trauma Hell* 2017; 68(4): 146-152.

ΠΕΡΙΛΗΨΗ

Η νόσος Erdheim-Chester είναι μία σπάνια μορφή ιστιοκύττωσης μη-Langerhans, την οποία διακρίνουμε από τον ανώμαλο πολλαπλασιασμό ιστιοκυττάρων ή ιστικών μακροφάγων. Η νόσος χαρακτηρίζεται από πολυεστιακές σκληρυντικές αλλοιώσεις στα μακρά οστά και την επίστρωση με αφρώδη ιστιοκύτταρα, ενώ μπορεί να υπάρχει διήθηση ιστιοκυττάρων σε άλλους εκτός του οστίτου ιστούς, όπως στο δέρμα, την υπόφυση, τον οπισθοπεριτοναϊκό χώρο, τους νεφρούς και το μυοκάρδιο. Η πλειονότητα των περιπτώσεων διαγιγνώσκονται στην ενήλικη ζωή, μεταξύ 40 έως 60 ετών (μέση ηλικία 53 ετών), με τριπλάσια συχνότητα στους άνδρες σε σύγκριση με τις γυναίκες. Έχουν ωστόσο αναφερθεί σπάνιες περιπτώσεις σε παιδιά. Η ανασκόπηση αυτή αναλύει τις διάφορες κλινικές μορφές, τη διαγνωστική προσέγγιση και την τρέχουσα θεραπευτική αντιμετώπιση αυτής της σπάνιας νόσου.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: νόσος Erdheim-Chester, ιστιοκύττωση μη-Langerhans, ιντερφερόνη Α