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Treatment of Erdheim-Chester Disease with High Dose Pegylated IFN-α: a Case Report and Literature Review

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Abstract

Erdhein-chester disease is a rare non-Langerhans histocytes that can involve multiple systems, with bone involvement as the most common. We reports a 39-year-old female who visited the hospital due to pain in both lower limbs, combined with clinical manifestations, imaging, and laboratory tests, Erdhein-Chester disease was prelimi narily diagnosed. The diagnosis was confirmed by the presence of BRAF V600E mutation and tissue cells on biopsy of the right tibia. We discussed the disease based on literature review, aiming to improve the understanding of clinicians.

Keywords: Erdheim-Chester disease; Non Langerhans Cell Histocytes; Aching Bones; Treatment

Introduction

Erdheim-Chester disease (ECD) is a clinically rare non-Langerhans histiocytosis characterized by foamy CD68 + CD1a - Histiocytes infiltrate the tissue and 1500 cases have been reported since 1930 [1]. Mutations activating the MAPK pathway have been identified in over 80% of ECD patients, mainly BRAFV600E activating mutations in 57% to 70% of cases, followed by MAP2K1 approaching 20% [2-4]. Trivial Ten percent of ECD cases are associated with myeloproliferative neoplasms and/or myelodysplastic syndromes [5]. In this paper, we report a case of ECD in an adult with pain in both lower limbs as the main manifestation and review the relevant literature to improve the understanding of ECD.

Case presentation

This is a 39-year-old female patient who was admitted due to "pain in both lower limbs for more than 1 year". The patient perfected the relevant examinations after admission and underwent a right femoral biopsy under local anesthesia on May 31, 2020. The surgery went smoothly. Postoperative examination showed: (right femoral biopsy tissue) a large number of foamy histiocytes accumulated in the bone marrow cavity with fibrosis and scattered lymphocyte and plasma cell infiltration, bone hyperplasia, and irregular adhesiveness. The diagnosis of "ECD" was considered because ECD can involve multiple systems, and relevant examinations were further improved. These include follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), testosterone (T), free T3 (FT3), free T4 (FT4), thyroid-stimulating hormone (TSH), thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb), adrenocorticotropic hormone (ACTH), cortisol (COR), and insulin-like growth factor (IGF-1) in the normal circumference. Prolactin (PRL) 36.79 mU/L (86 ~ 324 mU/L). Interleukin 6 (IL-6) was 35.39 pg/mL (0 to 7 pg/mL) and interleukin 8 (IL-8) was 92.63 pg/mL (0 to 62 pg/mL). Brain MRI and cardiac MRI, CT of the chest, abdomen, and pelvis, CTA of the whole aorta, and cardiac ultrasound showed no abnormalities. On July 6, 2021, bone marrow biopsy and aspiration showed no significant abnormality of bone marrow. PET-CT showed 1. There was multiple bone changes/destruction in the middle and lower segments of the femur, the upper end of the fibula, and tibia (especially in the upper and lower segments), with different degrees of increased metabolism, which was considered to be consistent with the signs of Erdheim-Chester disease infiltration. 2. Multiple decreased bone density and partially increased metabolism in the mandible, slightly more significant at the junction of the right proximal branch, not excluding Erdheim-Chester disease infiltration, and observation is recommended. On July 12, 2021-12, the patient was given 180 μg SC/wk (high dose) pegylated IFN-α subcutaneously once a week for treatment, and the patient's pain in both lower limbs was reduced than before.

Discussion

ECD, first described by Jakob Erdheim and William Chester in 1930, is a rare non-Langerhans histiocytosis characterized histologically by foamy, lipid-rich CD68+ and CD1a – histiocytic infiltrates [1,6-8]. ECD mainly affects patients between the ages of 40 and 70 years and is reported to be predominantly male (male: female =1.5 to 3:1), with a reported average diagnosis time of 4.2 years [9-11]. In the 2011 proposed revised classification, Langerhans cell histiocytosis (LCH), ECD, and extra dermal juvenile xanthogranuloma (JXG) are included in a group of patients called "group L" because they have certain molecular and clinical characteristics and can coexist in the same group of patients. Nearly 20% of ECD patients have associated LCH lesions [12-15].

The underlying etiology of ECD has long been uncertain, and it is considered a non-neoplastic inflammatory disease as well as a clonal neoplastic disease [16-18]. Badalian-Very [3] et al found the BRAF V600E mutation in LCH, as well as studies, found that ECD histiocytes express a proinflammatory cytokine and chemokine that is responsible for the local activation and recruitment of histiocytes [19,20]. Based on these studies, ECD can now be defined as a clonal disorder characterized by frequent hyperactivation of mitogen-activated protein kinase signaling, in which the inflammatory milieu is important in the pathogenesis and clinical presentation of the disease. At present, important questions such as cells of ECD origin, somatic genetic changes present in ECD patients without BRAF V600E mutation, and recent causes of immune dysregulation in ECD have not been fully answered and still need further study.

The clinical presentation of ECD is extensive and complex, depending mainly on the distribution and extent of the diseased tissue. Bone infiltration is the most prevalent symptom in patients with ECD and is found in more than 90% of cases. It mainly affects the bones of the extremities and usually leads to symmetrical diaphyseal and metaphyseal osteosclerosis, which can be detected on X-ray, CT, MRI, and is most sensitive on PET-CT [21,22]. Extraskeletal involvement of ECD may include the central nervous system, pituitary, cardiovascular system, lung, retroperitoneum, kidney, skin, and retro-orbital tissues [23-27]. Cardiovascular involvement, along with pulmonary and neurological systems, is associated with poor prognosis [28-30]. Cardiovascular manifestations are the leading cause of death in patients with ECD, as approximately 60% of patients die due to cardiac complications [31].

Diagnosing ECD is challenging because the most common clinical manifestations, such as skeletal, systemic, and even neurological symptoms, often lack sufficient specificity [1,3,32]. The diagnosis of ECD relies on established radiological and histological criteria to make a correct diagnosis by identifying pathological histiocytes in the appropriate clinical and radiological context.

Radiologic findings can provide valuable help, with the most specific and indicative results being: 1. Symmetrical diaphyseal and metaphyseal osteosclerosis of long bones on radiographs; 2. Increased radiotracer uptake in the tibia and distal and proximal femur on technetium Tc 99m bone scans or positron emission tomography (PET); 3. Perirenal fatty infiltrates ("hirsute kidneys") and periaortic soft tissue sheaths ("coated aortas"). However, the biopsy is required to confirm the diagnosis even when clinical and imaging features allow a high degree of suspicion [33].

Biopsies often show a typical foamy or histiocytic infiltrate, with mixed or surrounding fibrosis. Touton giant cells are often present. In immunohistochemical (IHC) staining, ECD histiocytes were positive for CD68, CD163, and factor XIIIa and negative for CD1a and CD207. Few positive results were observed for S100. This distinguishes ECD from LCH, in which Langerhans cells are positive for CD1a, S100, and Langerhans [15].

Currently, the most evidence-based supporting evidence for ECD treatment is IFN-α and pegylated IFN-α. Interferon-α provides sustained stable disease in most cases [34-38]. In the largest single series, a prospective, nonrandomized, observational cohort study of 53 patients with ECD, 46 of whom received IFN-α or PEG-IFNα interferon significantly improved overall survival compared with other therapies, and was an independent predictor of improved survival in multivariate analysis [39]. Although the optimal dose of IFN-α/PEG-IFN-α has not been established, 3 million units (mIU) of IFN-α 3 times/week has repeatedly been shown to reduce lesion burden [34-36]. The optimal duration of IFN-α in ECD is also unclear, but "long-term" (up to 3 years) treatment with high-dose "IFN-α (9 mIU 3 times/week [TIW]) or PEG-IFNα (180 μg/wk) found greater efficacy in ECD in 24 patients, stabilizing or improving 64% of central nervous system disease and 79% of heart disease [40]. IFN-α and PEG-IFN-α have multiple potential toxicities, including generalized (fever, fatigue, flu-like symptoms, myalgias, and arthralgias), neuropsychiatric and gastrointestinal symptoms, alopecia and pruritus, transaminases, and myelosuppression.

In cases of mild or non-severe ECD (e.g., no central nervous system and/or cardiac involvement) and contraindications or adverse effects of IFN-α, alternative treatments include replacement therapy including anakinra, infliximab [41], etc. Since IFN-α is thought to exert beneficial effects by inhibiting the action of IL-1, treatment with the recombinant IL-1R antagonist anakinra has been attempted and found to be effective in a few reported patients and more unreported experiences [42-45]. Its treatment is well tolerated and particularly effective for bone pain and systemic symptoms. However, its treatment of ECD involving the central nervous system has not been successfully reported. Common side effects include injection site reactions, headache, arthralgia, and nasopharyngitis.

Targeted therapies include: BRAF inhibitors (vemurafenib, dabrafenib, encorafenib), MEK inhibitors (kobayashi, trametinib, pimetinib) and their combinations. For ECD patients with BRAF V600E mutation, BRAF inhibitors as an alternative to IFNα, such as vemurafenib, have been approved by the FDA for ECD patients with BRAF V600E mutation [46]. Arthralgia, rash (photosensitivity, perifollicular keratosis, squamous cell carcinoma, eosinophilic dermatosis, and drug hypersensitivity syndrome), fatigue, or other toxic side effects often require a reduction in drug dosage during vemurafenib treatment, but the overall disease remission rate is

still 55% [47,48]. For patients without BRAF V600E mutation, especially some relapsed and or refractory cases, MEK inhibitors have some efficacy [49]. In addition, the combination of BRAF and MEK inhibitors is also applied in some patients with ECD, but their combination increases the risk of cardiomyopathy, which occurs at a higher rate than treatment with vemurafenib [50-52]. So far, there is no evidence that BRAF or MEK inhibitors induce prolonged application of ECD or complete clinical response, therefore, BRAF and/or MEK inhibitors are recommended as second-line treatment after ineffective or intolerant IFN-α, or as first-line treatment for ECD patients with life-threatening clinical symptoms [32]. Other targeted therapies also include: mTOR inhibitors (sirolimus, everolimus), and other tyrosine kinase inhibitors (imatinib, sorafenib) have also been reported [53-56].

In this case, the patient had bone pain. PET-CT showed multiple bone changes/destruction in the middle and lower femur, upper fibula and tibia (especially in the upper and lower segments), with different degrees of increased metabolism.

Laboratory tests showed the presence of multiple inflammatory cytokine abnormalities, and histopathological biopsy revealed a large number of foamy histiocytic aggregates with fibrosis and scattered lymphocyte and plasma cell infiltrates, bone hyperplasia, and irregular adhesiveness.

Conclusion

As an orphan multisystem disease, ECD is challenging to diagnose and treat. The treatment and management of the disease is more complex. Since no definitive cure exists, the goal of treatment should be to prolong life and maximize its quality. Over time, a better understanding of the immunology and molecular biology leading to this disease will eventually lead to the emergence of new therapeutic approaches.

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