Clinical Case Report

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Erdheim–Chester disease (ECD)

Case report, clinical and basic investigations, and review of literature

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Abstract

Background: Erdheim–Chester disease (ECD) is an uncommon aggressive, multisystem form of non-Langerhans' cell histocytosis, which was firstly reported by Jakob Erdheim and William chester in 1930. The disease pathological features encompass an aberrant multiplication, overproduction and accumulation of white blood cells called histiocytes within multiple tissues and organs. Herein, we present a case of ECD owing to the rarity of this disease (roughly 550 cases have been described in the literature to date).

Methods: We discussed the clinical course, diagnostic evaluations, and the possible treatments. Our case was encountered in an Arab male in his 30's who has suffered from an ongoing bones pain for years.

Results: At our rheumatologic department we compiled his recent medical history, which consisted of diagnosis of central diabetes insipidus, hyperprolactinemia and secondary hypogonadism along with the previously conducted laboratory evaluations and imaging which brought to our mind the possibility of an infiltrative disease such as ECD. The diagnosis of ECD was done based on the combinations of pathognomonic radiographic osteosclerosis, neuroimaging, bones biopsies along with a careful clinical evaluation. Given the protean clinical manifestations, interferon-α was considered as our first line treatment of ECD, consequently our patient improved noticeably.

Conclusion: Clinical presentation, imaging studies, distinctive pathological findings, followed by bone biopsy showed a non-Langerhans cell histiocytosis, supported by immunohistochemistry exams are essential for the diagnosis. Radiation therapy and Bisphosphonates in addition to cladribine, anakinra, infliximab and vemurafenib (BRAF Inhibitors) are currently advocated as promising second line treatment for patients whose response to interferon-α is unsatisfactory.

Abbreviations: ACD = Erdheim–Chester disease, Anti-CCP = anti-cyclic citrullinated peptides, B27 = human leukocyte antigen, CDI = central diabetes insipidus, CDI = immunohistochemical, CNS = central nervous system, CRP = C-reactive protein, IFN-α = interferon-α, LCH = histiocytosis X, RF = rheumatoid factor, Th1 = T-helper 1.

Keywords: Erdheim–Chester disease, multisystem disease, non-Langerhans' cell histocytosis

1. Introduction

Erdheim–Chester disease (ECD) is a rare foamy non-Langerhans' cell, lipid-laden histiocytosis distinguished by cardinal histological finding such as xanthogranulomatous and xanthomatous infiltration of tissues with a numerous spumous histiocytes,[1] frequently surrounded by fibrosis with distinct diagnostic radiological features illustrated by symmetrical patchy osteosclerosis involving the diametaphyseal but sparing the epiphyses portion of the long bones of the extremities, mainly affecting the distal femur and proximal tibia and fibula.[2,3]

These radiological characteristics are pathognomonic and important for the diagnosis. In fact, the diagnosis of ECD depends on the combination of clinical presentations and imaging features which are confirmed with histopathologic findings.[4]

In addition, in ECD to skeletal involvement is highly pronounced, and it occurs in up to 96% of ECD patients. Notwithstanding the fact that bone pain prevails as the presenting symptom, but it occurs only in 50% of cases.[5]

Other clinical spectrum encompasses extraskeletal and internal organs involvement (>50% of cases) causing exophthalmos, papilledema, xanthelasmas and papulonodular skin lesions, diabetes insipidus, severe lung disease (progressive dyspnea), renal failure, retroperitoneal region involvement, cardiomyopathy, and central nervous system (CNS) disorders such as pyramidal syndromes, cognitive impairment, seizures, sensory disturbances, headaches, and the presence of bilateral typical cerebellar and pontine signals changes on T2- weighted images. In fact, today PET scans are vital for the assessment of disease activity.[6–9]

ECD prevalence is unknown; roughly 550 cases have been described in the literature since the first publication by the

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Austrian pathologist Jakob Erdheim (1874–1937) and the American pathologist William Chester (1903–1974).[10,11]

The disease usually becomes apparent in adulthood (between 40 and 60 years, average age of onset 53 years), with a 3-fold frequency in males than females.[2,12]

The underlying etiology and pathogenesis of ECD is still ambiguous yet speculated to be associated with an intense T-helper 1 (Th1) immune response. The high levels of IFN-alpha, interleukin-7, interleukin-12, monocyte chemoattractant protein-1, and reduce concentrations of interleukin-4 found in ECD patients may explain the associated systemic immune TH-1 intense activity. Other investigators considered ECD to be inflammatory non-neoplastic condition as well as a clonal neoplastic disease.[13–16]

Recently an oncogenic alteration in this devastating disease was observed after the detection of a mutation in the BRAF proto-oncogen gene. This mutation has been identified in the majority of ECD patients (40–80%).[17–21]

The differential diagnoses of ECD are warranted, because they are a plethora of other conditions that may be characterized by certain symptoms and findings similar to those potentially associated with ECD. The differential diagnosis of ECD includes Histiocytosis X (LCH), multiple sclerosis, neurosarcoidosis, amyloidosis, metabolic diseases, mucopolysaccharidosies, Paget disease, Ormond's disease, cerebrotendinous xanthomatosis (CTX), Wegener's granulomatosis, Whipple's disease, Gaucher's disease, Rosai–Dorfman disease, chronic recurrent multifocal osteomyelitis, Takayasu arteritis, primary hypophysitis, cancers and mycobacterial infections.[22,23]

Historically ECD lacked effective treatments, but given the protean clinical manifestations, multifaceted, and the variability of the clinical symptoms, interferon-α is considered the first-line treatment of all forms of ECD, the dosages ranging from 3 million units 3 times per week for the mild-moderate cases to a 9 million units, 3 times per week in severe cases with the involvement of cardiac and cerebral tissues. Pegylated IFN-α is an alternative to standard interferon-alfa (IFN-α), and it is administered at dosages ranging from 135 to 200 μg per week.[24]

Other agent's treatments are based on anecdotal case reports and on the basis of biological rational. However, radiation therapy and bisphosphonates may be given to alleviate bone pain. Additionally, chemotherapy such as cladribine which is a new purine nucleoside analog, the effective administered dosages of 0.07 to 0.14 mg/kg/ for 5 consecutive days is useful treatment in moderate to severe cases, anakinra at dosages of 1 to 2 mg/kg/day for mild cases without CNS or cardiovascular involvements. Cladribine and Anakinra (IL-1 receptor antagonist), both can improve symptoms where IFN-α was unsuccessful. Lately, Infliximab is given at a dosage of 5 mg/kg/6weeks and Vemurafenib (BRAF Inhibitors), administered at a dosage of 960 mg/day, was given for patients whose histiocytes contains the V600-BRAF mutation and are currently advocated as promising second- and third-line treatments for patients whose response to IFN-α is unsatisfactory.[25,26]

Finally, secondary intervention and treatment modifications should be made based on proper assessment of the disease's progression as well as the patient's well being.[4,5]

ECD prognosis is poor mainly in those with CNS involvement; however, after the IFN-α treatments, the survival chances increase considerably, and 5-years survival is 70%.[27]

In this paper along with the presented case report, we will discuss this rare entity, including its clinical course, diagnostic evaluations, and the possible treatment options.

2. Case report

We report a case study of a 30-year-old Arab male patient living in Nazareth Metropolitan area after receiving his informed consent, and the study was approved by the ethics committee. The patient was admitted to our rheumatologic department due to diffused bone and articular pain. The pain was described as continuous, nonpulsatile, and exacerbating with physical activity. These complaints had been presented for the last 2 years with worsening reported in the previous month. In 2014, the patient underwent bone scanning, which had demonstrated diffused involvements of both the upper and lower extremities. A bone marrow biopsy was negative. Along with that, rheumatologic screening was negative for all serologic markers, including Rheumatoid factor (RF), the human leukocyte antigen B27 (HLA-B27), and anti- cyclic citrullinated peptides (Anti-CCP). Also, complement and inflammatory markers as C-reactive protein (CRP) were all in the normal range.

The patient's intriguing history is what drew our team attention to seek further investigations for the underlying condition. Looking for the past clinical history, in 2008 the patient was diagnosed with central diabetes insipidus (CDI), treated with nasal spray of desmopressin acetate (0.1 mg/mL) 3 times daily. Subsequent to that, in 2009, he was diagnosed with secondary hypogonadism, with low lab levels of Testosterone, which was contributed to a lesion demonstrated in the hypophysis gland by magnetic resonance imaging (MRI). Imaging was suspicious for hypophysitis with absence of demonstration of neurohypophysis. In 2015, the patient's Lab analysis revealed hyperprolactinemia with high levels of prolactin reaching 2053 ng/mL. A second MRI was performed in 2015, presenting infundibular changes with more pronounced swelling as compared with previous imaging.

Two months prior to his visit in our clinic, he was hospitalized in the surgical department after encountering diffused abdominal pain. Following initial work-up, an abdominal CT scan (2015) suggested the presence of mesenteric panniculitis; it was shown an enlargement of the mesenteric lymph nodes (12 mm) surrounded by adipose tissue, which was confirmed by a laparoscopic biopsy.

On admission to our department (2016), the patient's general appearance was normal and hemodynamically stable. Vital signs were all in the normal range including blood pressure, heart rate, and pulse oximetry. There was no evidence of swelling, erythema, or movement restrictions in all his joints. Despite the described bone involvements, the rest of his physical examination was normal without any significant alterations.

Lab examinations presented normal values of blood cell count, including hemoglobin and leukocytes. Also, his serum creatinine, liver enzymes, and electrolytes were in the normal range. Inflammatory markers, including C-reactive protein (CRP), were above the normal range, (8.89 mg/dL), along with that, rheumatologic screening was negative for other serologic markers, including rheumatoid factor (RF), the human leukocyte antigen B27 (HLA-B27), and anti-cyclic citrullinated peptides (anti-CCP).

Following his initial evaluation and the review of the patient past imaging which showed inconclusive diagnosis, our team decided to perform additional bone scan using [(Technetium-99m-Methylene Diphosphate bone scan (99m-Tc-MDP)]. This radioisotope bone scans technique revealed remarkably increased pathologic uptake of Tc-99m-MDP and especially diffused uptake involving the elbow joints bilaterally; the distal half of

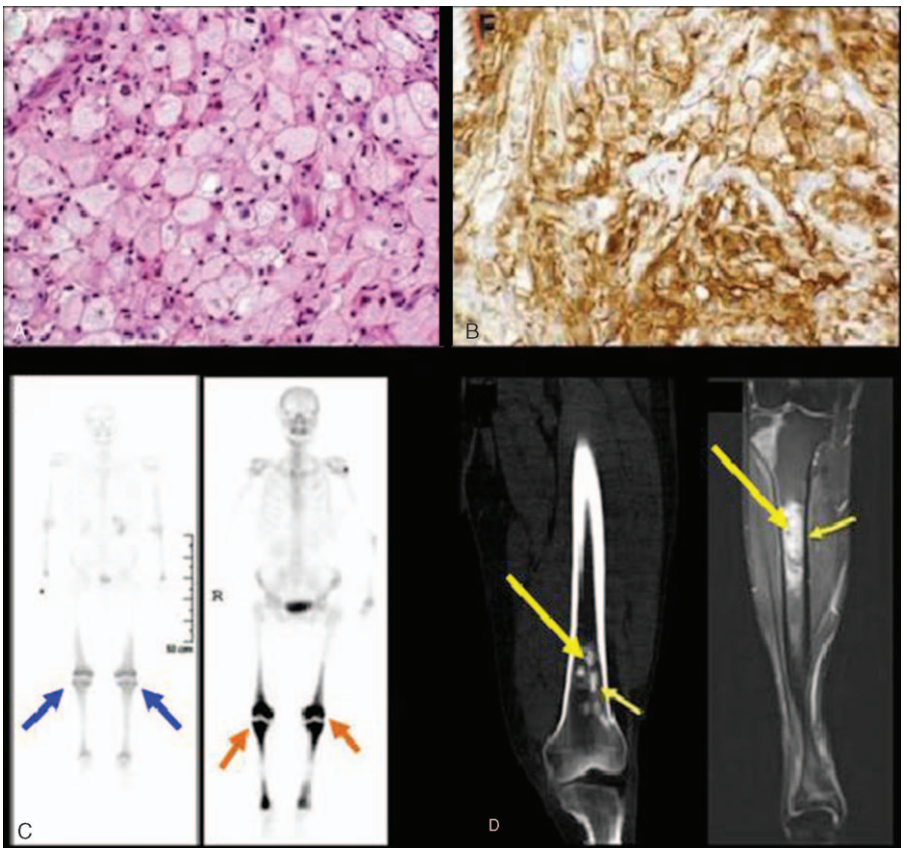

Figure 1. Histopathologic and radiographic findings of ECD. (A) Hematoxylin-eosin–stained biopsy section of ECD lesion revealing lipid-laden histiocytes characteristic of ECD. (B) IHC stain for CD68 revealing positivity of histiocytes. (C) Tc 99m-methylene diphosph, demonstrating symmetric diametaphyseal radiotracer uptake and diffused uptake involving: the long bones of the legs (arrow), elbows, along the distal half of humerus, knees, the distal half of the femur and tibia around the orbital cavity. CT-scan and MRI scan represented respectively in (C) and (D) showing sclerotic lesions of the metaphyses of femur and tibia (arrows). CT = computed tomography, ECD = Erdheim–Chester disease (ECD), IHC = immunohistochemical.

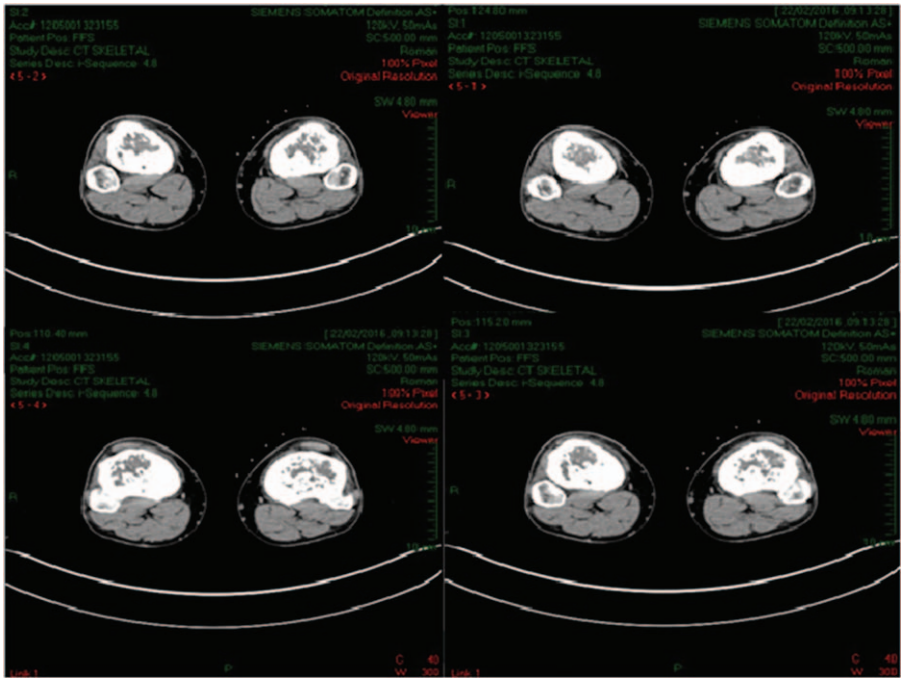

Figure 2. The figure shows a CT-scan with a multiple and diffuse bone lytic lesions. CT = computed tomography.

humerus and the knees surrounds area. Symmetrical increase uptake in distal half of the femur and tibial condyles was shown to be bilateral. Additionally, involvements and enhanced uptake was seen around the orbital cavity. On (2016) head MRI was performed using different techniques (TSET2, Diffusion, Fair, and T1 with and without contrast) and was compared to the previous MRI scan, (Fig. 1C and D). The results showed no remarkable changes comparing to the previous imaging but small changes where shown in the posterior hypophysis and in the suprasellar region of the pituitary gland.

Based on the patient's past clinical history, specifically that of central diabetes insipidus, continuous bone pain complaints, along with his physical examination, and the imaging results presented on CT and bone scanning, the possibility of ECD was first suggested (Figs. 2 and 3). Therefore, a diagnostic bone biopsy was performed with CT guidance obtained from the medial proximal end of the left tibia.

The histopathologic findings revealed a feature compatible with non-Langerhans' cell histocytosis. Lesional tissue demonstrates infiltration of typically foamy or lipid-laden histiocytes with admixed or surrounding osteonecrosis with fibrosis (Fig. 1A and B).

Part of the histiocytes had shown extended cytoplasm within the adipose tissue, almost all of histiocytes were diffuse, but it was possible to see part of them in a 0.1 diameter. On immunohistochemical (IHC) staining, the histiocytes had plentiful pale staining and foamy cytoplasm and were positive for CD68. Staining for S-100 was positive in a part of histiocytes but the CD1a was negative. On the light of these findings, the diagnosis of ECD was confirmed, and recommendation to begin treatment with subcutaneous IFN-α (3 million units 3 times per week) was under way. Consequently, treatment with (pegylated IFN-α) will be considered according to the patient's medical development. It is worthy to mention, that prior to beginning the treatment by (IFN-α), it was recommended to carry out complete blood count (TT3, FT4, TSH, Testosterone, prolactin, FSH, LH, vit.B12, serum creatinine, uric acid, and C-reactive protein) and other necessary exams such as hepatitis profile (Anti-HCV, Anti-HBS, Anti-HBS, HBsAg), in addition to lung function exams and lung diffusion. These exams give a clinical picture for the possibility of ECD related pituitary insufficiency, renal, lung, and liver involvement. The patient clinical situation after the treatment with IFN-α has noticeably ameliorated and his condition

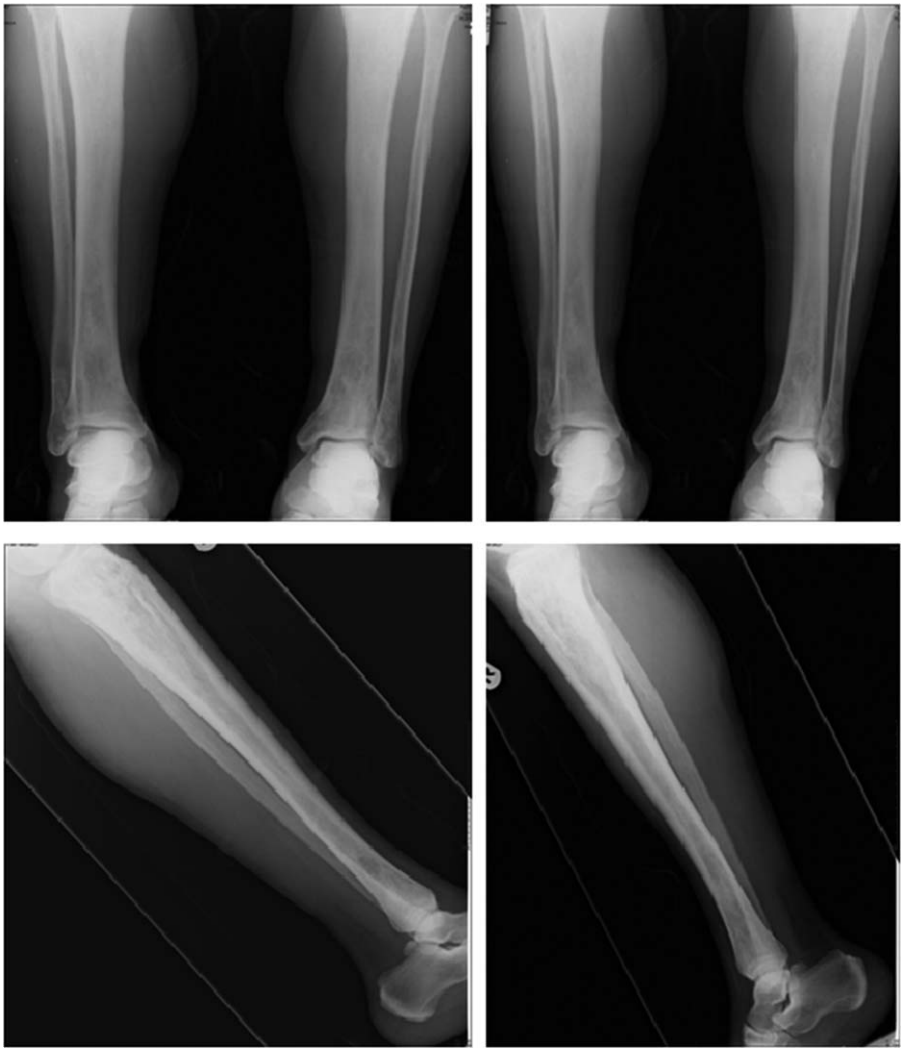

Figure 3. X-ray of the long bones of the lower limbs: osteosclerosis with focal osteolysis: Bone x-rays usually display bilateral and symmetric cortical osteosclerosis of the long bones, whereas technetium 99m bone scintigraphy shows almost constantly evidence of symmetric and abnormally strong labeling of the distal ends of the long bones of the lower limbs (and sometimes the upper limbs).

improved significantly, and he is currently under follow up in our rheumatologic clinic.

3. Discussion

Herein we have reported a rare multi-systemic disease with unknown etiology, where its both diagnosis and treatment are still challenging. In this presented case, clinical presentation, morphologic features, pathognomonic radiographic osteosclerotic findings, immunohistochemical profile, neuroimaging, bone marrow biopsies and ultrastructural features are all consistent with ECD.

Since no magic or definite treatment exists, the aims of the available cures will be prolonging survival and increasing the quality of life of the patients. Indeed, the treatment of this chronic condition necessitates patient support and full treatment adherence, in addition to management by a multidisciplinary collaboration of specialists in different medical fields associated with the clinical complications of the disease. Despite the progression in understanding the underpinning pathogenesis of ECD, we believe that more efforts should be dedicated for better comprehension of the underlying pathology and biology of the disease, which may open the door for novel therapeutic interventions and for persistent zealous hunt for future remedies.

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