

Erdheim-Chester Disease: MR and PET/CT Findings of a Rare Case with Extensive Bone Lesions and Review of the Literature

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Abstract: Erdheim-Chester Disease is a rare, non-Langerhans cell histiocytosis firstly described in 1930. It may effect all age groups, but more commonly in males between the 5th and 7th decades of life. The etiopathogenesis is not clear yet but in recent years, BRAF gene mutation is found at least 50% of cases. Clinical spectrum is protean and depends on the involved organs and systems. Since the skeletal system is commonly effected and bone pain is the most common symptom in presentation, orthopedists may encounter with those patients in routine practice. Bone scintigraphy and PET/CT are the most commonly used diagnostic tools and magnetic resonance imaging of bone may provide a valuable addition to the diagnosis. Treatment mainly depends on the extent of the organ damage. In this paper, we present magnetic resonance and PET/CT imaging findings of an Erdheim-Chester Disease case with extensive bone involvement and review the related recent literature.

Keywords: Erdheim-Chester Disease, magnetic resonance imaging, PET/CT, bone involvement, non-Langerhans cell histiocytosis.

INTRODUCTION

Erdheim-Chester disease (ECD) is a rare inflammatory, non-Langerhans cell histiocytosis characterized by xanthomatous infiltration of tissues and organs by CD68+, CD1a-/S100- foamy histiocytes. It is most commonly affects males who are in their 5th and 7th decade of life [1].

The disease is characterized by multiorgan involvement and the clinic depends on the extent of the lesions [2, 3]. Every tissue, organ or system can be effected by diseased histiocytes. However, skeletal and nervous system are the most common sites. The clinical spectrum ranges from asymptomatic bone lesions to multisystemic, lifethreatening forms [2].

Almost all radiological imaging methods can be used to detect the lesions and determine the extent of the disease. In recent years, magnetic resonance (MR) imaging and positron emission tomography/computed tomography (PET/CT) has gained a great importance among these methods.

In the current paper, we want to present the MR and PET/CT imaging findings of a rare case with ECD and review the related medical literature.

CASE REPORT

A 56-year-old female was admitted to the hospital with the complaints of high fever, dyspnea and bone pain in her both arms for 2 months. She had ankylosing spondylitis and was currently under treatment with TNF-alpha bloker and steroids. She was

followed up for retroperitoneal fibrosis, which was considered to be due to ankylosing spondylitis.

Thorax CT which was performed for her dyspnea and high fever revealed interlobular septal thickening, bilateral pleural effusion and associated passive atelectasis. A rheumatologic disease effecting lungs was suspected, primarily. Arm X-ray which was performed for the pain showed symmetric, geographic sclerotic areas effecting both proximal humerus. MR examination of both shoulders done for the further evaluation revealed bilateral patchy, symmetric heterogeneous signal which was hypointense on T1-weighted and hyperintense on fat saturated T2-weighted and proton density images representing osteosclerosis of medulla of both humerus. On PET/CT images, increased uptake of fluorodeoxyglucose (FDG) was detected on corresponding areas bilaterally which was primarily thought as inflammatory. Right knee MR examination also demonstrated patchy, heterogeneous signal effecting metaphyso-epiphyseal region of distal femur and proximal tibia on T1 and T2-weighted images (Figure 1 and 2).

In the lights of typical lesion distribution in long bones, MR and PET/CT features, ECD was

suspected and bone biopsy confirmed the diagnosis.

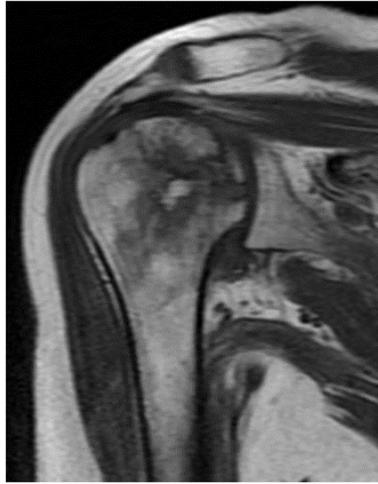


Fig-1a

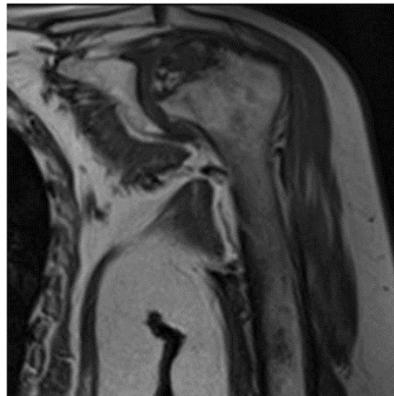


Fig-1b

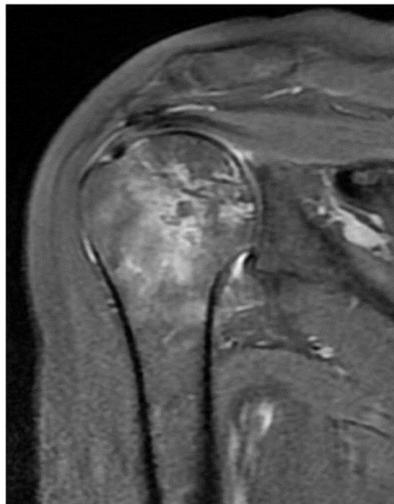


Fig-1c

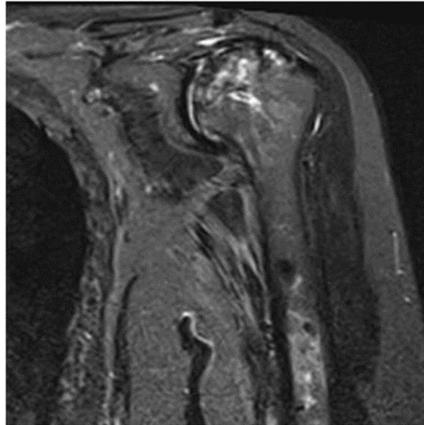


Fig-1d

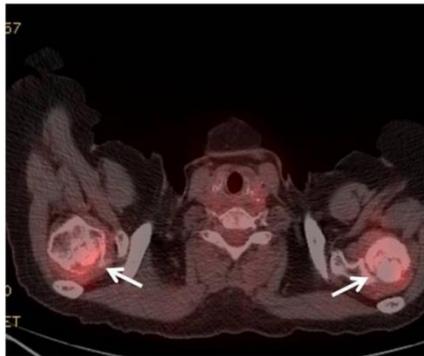


Fig-1e



Fig-1f

Fig-1: T1-weighted (a and b) and fat saturated T2-weighted coronal images (c and d) show bilateral, symmetric, patchy, and heterogeneous signal in both humerus. Lesions are hypointense on T1-weighted and hyperintense on fat saturated T2-weighted images representing osteosclerosis which is the pathognomonic finding of the bone involvement of Erdheim-Chester Disease. Axial (e) and coronal (f) PET/CT images demonstrate increased FDG uptake at corresponding sites in both proximal humerus (arrows).

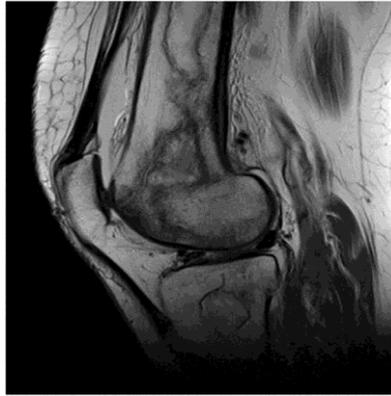


Fig-2a

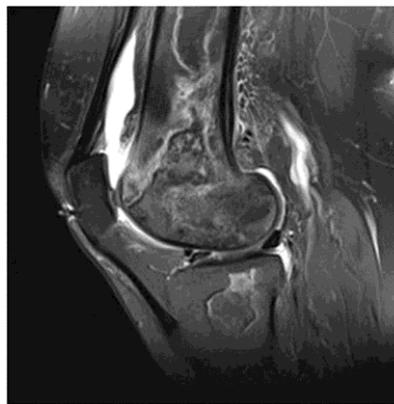


Fig-2b

Fig-2: Sagittal T1-weighted (a) and fat saturated proton density (b) images demonstrate abnormal, heterogeneous signal similar to the ones in humerus located in distal femur and proximal tibia. Additionally, suprapatellar bursal effusion and soft tissue edema in popliteal fossa are also seen

DISCUSSION

ECD is a rare type of non Langerhans cell histiocytosis [1, 4] and chiefly characterized by the migration and infiltration of lipid laden histiocytes to various target organs. This infiltration causes deterioration in tissue architecture and results in fibrosis that initiates the organ disfunction and often bone pain [5]. The disease is firstly described by Jakob Erdheim's pupil William Chester in 1930 and since that time only several hundred patients have been reported in medical literature [4].

The etiopathogenesis of the disease is not fully clarified yet, but local and systemic pro-inflammatory cytokine-chemokine network, which seems to be responsible for the recruitment and activation of histiocytes are being blamed in recent years [6, 7]. A specific inflammatory cytokine signature of ECD that is characterized by elevated interferon (IFN)- α , interleukin (IL)-12, monocyte chemotactic protein-1 and decreased levels of IL-4 and IL-7 was discovered [6]. IL-6 has a critical role in the pathogenesis of ECD and various cells involving macrophages, endothelial cells, pneumocytes, and ECD histiocytes are positive for this interleukin. This interleukin participates in osteoclast differentiation that can finally result in

osteosclerosis which is one of the most important features of the disease. Furthermore, higher pericardial fluid IL-6 levels were detected in ECD patients, as well [7]. Recently, Emile *et al.* [8] showed that nearly half of their study group (19 out of 37) with ECD carried pathological histiocytes having a mutation in the proto-oncogene BRAF.

Clinical presentation is variable and mostly consists bone pain, diabetes insipidus, neurological and constitutional symptoms. However, rare symptoms such as retroperitoneal, cardiovascular, pulmonary or cutaneous have been identified [4, 9]. ECD primarily effects the bone, but every organ in the body may be effected. Proptosis, periorbital infiltration and even blindness may develop. ECD may also effect other organs and systems like kidney, adrenal glands, pancreas, and lung, as well [6]. Overall prognosis is poor, but growing interest to the disease and especially to the etiopathogenesis revealed new treatment strategies involving biologic agents and BRAF inhibitors [2].

ECD has usually typical imaging findings that considered pathognomonic. This entity mainly effects the long bones while axial skeleton is typically spared

[10]. Although ^{99m}Tc bone scintigraphy and PET/CT are most commonly used diagnostic tools, MR imaging of bone may provide a valuable contribution to the evaluation of the cancellous bone involvement [11]. However, most of the time, plain radiography is the initial imaging method. Plain radiographs usually demonstrate bilateral, symmetric cortical osteosclerosis of the diaphyseal and/or metaphyseal regions of the distal ends of lower and sometimes upper limbs. Bone scintigraphy may show ^{99m}Tc uptake in long bones of lower extremities [11]. Sometimes mixed lytic and sclerotic lesions may be seen [10]. Classical finding of PET/CT is bilateral and symmetric uptake of FDG in the long bones corresponds to the radiographic and scintigraphic pathologies [12, 13]. Osteosclerosis is the classical finding of bone involvement of ECD and involves extensive replacement of the fatty bone marrow. This appears as low signal on T1-weighted images and heterogeneous signal on T2-weighted and STIR sequences, and enhances after gadolinium administration. MR imaging is very beneficial to assess the medullary bone involvement and identify the associated osteonecrosis [11]. Our case also showed the classical MR imaging findings of ECD in both humerus and as well as in right knee.

Characteristic imaging findings are mostly enough to make the diagnosis with a near certainty. Bilateral diffuse or patchy symmetric osteosclerosis of the major long bones, with relative epiphyseal sparing, associated with perirenal disease or aortic perivascular thickening, is pathognomonic for ECD. However, for definitive diagnosis biopsy is necessary. Histopathological findings consists of diffuse xanthogranulomatous infiltration with foamy histiocytes, inflammatory and Touton giant cells surrounded by fibrosis [14].

For years, corticosteroids, cytotoxic agents involving vinca alkaloids and various immunosuppressive agents were used for the treatment of ECD. In recent years, IFN-based treatments gained importance and are used as a reliable option. Vemurafenib, a BRAF inhibitor shows promising results as the most recent treatment option [15, 16].

In conclusion, ECD is a rare disease mainly effecting the skeletal system. However, every organ or system may be effected and bone pain is the most common complaint. Osteosclerosis is the pathognomonic finding of bone involvement. MR imaging may readily show the medullary bone pathology with a great accuracy. On PET/CT, involved areas appear to have increased FDG uptake. If the radiologists and orthopedists are familiar with those classical imaging and clinical findings of ECD, the diagnosis can be made correctly.

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