Erdheim-Chester disease diagnosed by $^{99m}$Tc-MDP bone scintigraphy and brief literature review

Abstract

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis with lipid-laden macrophages and fibrosis. Although ECD is a multisystemic disease, the most common finding is sclerotic bone involvement in the diaphyseal regions of bilateral distal femur and in proximal and distal tibia. We present a 40 years old woman who for the last two years had various systemic symptoms, especially knee pain, polyuria and polydipsia. Although a “hot knee” pattern was seen in bone scintigraphy (BS), a femur biopsy was performed, due to the preliminary diagnosis of haematologic malignancy. The biopsy specimen showed only intense fibrosis. One year later while the patient was in our clinic, BS showed characteristic for ECD bone involvement. Bone biopsy specimens stained in hematoxylin and eosin showed dense fibrosis but not histiocytosis. However, after immunohistochemical staining with CD-68, histiocytes were discerned. In conclusion, the authors underline that ECD was diagnosed at a second diagnostic attempt both clinically and by specific staining pathology specimens.

Introduction

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis characterized by xanthogranulomatous infiltration of both bone and soft tissue systems by lipid-laden histiocytes [1]. Erdheim-Chester disease was first described by Jakob Erdheim and William Chester in 1930 in two patients as a lipid granulomatosis [2]. H. Jaffe (1970) used the term “Erdheim-Chester disease” for the first time when about 100 patients were reported [3]. There has been a dramatic increase in the diagnosis of ECD in the past decade, reaching about 600-700 cases in the literature [1]. It is thought that this is due by the increased number of publications in recent years, along with physicians’ awareness.

Clinical diagnosis of ECD is very difficult because of its rarity and being a multisystem disease that can affect many organs. In addition the fact that the disease is also little known by physicians affects this situation. It usually takes about 4 years to diagnose ECD after the first symptoms occur [4]. Erdheim-Chester disease is diagnosed by identifying distinctive histopathologic findings in the presence of appropriate clinical, laboratory and radiologic findings. "Foamy" or lipid-laden macrophages are the most characteristic cytologic features, but their absence does not rule out ECD. The fibrosis seen in most cases is sometimes abundant. Even if lipid-laden histiocytes are not seen, a few “peculiar” histiocytes seen with fibrosis will favor the diagnosis. The immunohistochemical findings of ECD are the following: The positivity for CD68, CD163 and factor XIIIa which are non-Langerhans cells histiocyte markers and the negative CD1a. Protein S100 is found positive in 20% of the cases studied [4, 5]. This disease has no Birbeck granules found in Langerhans cells histiocytosis (LCH), while reactive lymphocytes, neutrophils, plasma cells and Touton giant cells are frequently present [6, 7].

The disease can occur in a very broad clinical spectrum depending on the severity and the organs involved. The most common presentation includes sclerosis and cortical thickening in the diaphyseal and metaphyseal regions of the distal femur, proximal tibia and fibula. This bilateral and symmetrical involvement pattern, also called “hot knee” is seen in 95% of patients and is nearly pathognomonic for ECD. Bone pain and fatigue are the most common symptoms. Approximately 50% of patients with ECD manifest extraosseous involvement including central diabetes insipidus, panhypopituitarism, cardiovascular and interstitial lung disease, renal failure, retroperitoneal fibrosis, xanthelasmas, exophi-
Case Report

A woman aged 40 years was referred to the Rheumatology Clinic of our Hospital with knee pain and was subsequently directed to our Nuclear Medicine Department for BS considering rheumatoid arthritis. Bone scintigraphy was performed three hours after an intravenous injection of 740MBq $^{99m}$Tc-MDP. The equipment used was a gamma camera (Siemens, Ecam-Signature, Germany) equipped with a low-energy high-resolution collimator. Whole-body bone imaging with $^{99m}$Tc-MDP revealed symmetrically increased $^{18}$F-FDG uptake in the bilateral proximal femur and proximal and distal tibia. There was also increased radioactivity in the left humerus, bilateral distal radius, maxillary, mandibular and the T9 vertebra (Figure 1). It was thought that the patient might have ECD because of the observation of the ‘hot knee’ involvement pattern. The clinical and laboratory findings were re-evaluated in this respect.

The patient had widespread bone pain for about two and a half years, which was more intense in the knees and ankles. In the previous year, symptoms of loss of appetite, nausea, burning in the stomach, weight loss, eye and mouth dryness, polyuria and polydipsia were added. The patient lost about fifteen pounds in the past year. Sometimes, she had fever, chill, and trembling. Due to these symptoms, the patient presented to various tertiary hospitals and was examined by specialists of physical therapy and rehabilitation, orthopedics, rheumatologists, hematologists, endocrinologists, general practitioners and others. During follow-up, infiltrative involvement was detected in the bone marrow of the long bones in the knee MR. The patient underwent BS one year ago in a university hospital. Increased radioactivity uptake was observed in the bilateral distal part of the femur and the bilateral proximal and distal parts of the tibia, similar to our BS images. Assuming hematologic malignancy, a biopsy was taken from the femur. Hypocellular intense fibrotic foci were observed and no pathology diagnosis was made. During this period, the patient was treated for subacute thyroditis and had a mild reduction of the knee and bone pain due to the steroid used for treatment.

The patient had not menstruated for the past three months and had chronic anemia. When the laboratory findings of the patient were examined, an increase inflammatory markers such as C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) were observed (65.9mg/L and 48/h, respectively). Kidney and liver function tests, calcium, phosphorus and alkaline phosphatase levels were normal. When present clinical and laboratory findings were evaluated together with bone scintigraphy, we thought that the existence of ECD in the patient was strongly probable. The biopsy material taken from the femur in another university hospital one year ago was re-examined in the pathology laboratory.
of our hospital in terms of ECD. In these specimens, intense fibrosis with storiform features was observed. In H&E-stained slides, a significant number of histiocytic cells was not seen histopathologically between connective tissue fibers but indistinct vacuole areas were seen (Figure 2). CD-68, an immunohistochemical histiocyte marker was used which supported ECD. CD68-positive histiocytes were present between the fibrous tissues (Figure 3). Periaortic and perinephric infiltration in the soft tissues were observed in CT which also supported the diagnosis of ECD. The PET/CT images of the patient also had the same pattern of involvement in the skeletal system as bone scintigraphy and additionally a linear pattern of $^{18}$F-FDG uptake in the descending aorta. In view of this information, the patient was diagnosed as having ECD.

Discussion

Erdheim-Chester disease was first described about 90 years ago [2]. This disease is uncommon but an increasing number of patients have been diagnosed in recent years. The majority of ECD patients are middle-aged or older patients, but pediatric cases have also been reported [11]. Erdheim-Chester disease is three times more common in males than in females [4]. Recent findings suggest that ECD is a clonal disease in which chronic uncontrolled inflammation can cause fibrosis and organ failure, which is an important mediator in the pathogenesis of the disease. More than half of all patients had recurrent BRAFV600E mutations. This change in the understanding of the pathogenesis of the disease allowed new treatment options to emerge [1, 15, 18].

The World Health Organization (WHO) classification of lymphoid neoplasms was revised in 2016 and ECD was also included in this classification. Erdheim-Chester disease was classified within the group of histiocytic and dendritic cell neoplasms as a provisional entity, and it was emphasized that it should be separated from the other members of the juvenile xanthogranuloma (JXG) family, which is associated with the BRAF mutation [1, 19].

Emile et al. (2016) also revised the classification of histiocytosis and included ECD in the ‘L’ (Langerhans) histiocytosis group. In this classification, it was proposed that LCH, ECD and extracutaneous JXG should be combined into a single group, “L” histiocytosis, due to their clinical and molecular similarities [11].

For the first time in 2014, a guideline was published for the diagnosis and clinical management of ECD. According to this guideline, in addition to clinical and radiologic features, characteristic histopathologic features should be added. Furthermore, additional biopsies should be taken if necessary to perform mutation analysis because the detection of BRAF and RAS mutations in patients with ECD is important for BRAF inhibition therapy [15].

Although the literature on ECD previously included more case reports or multicenter retrospective studies, prospective studies with a large number of patients have been published in the past decade [4, 20]. A group of researchers published a prospective study of 60 patients with ECD (45 males, 15 females) in 2017 to describe the clinical and molecular variability of the disease. They detected characteristic bone involvement in 95% of patients. Extraosseous manifestations, including DI, retro-orbital infiltration, cardiac, periaortic involvement, retroperitoneal, lung, central nervous system (CNS), skin involvement and xanthelasma were observed in one-third to two thirds of patients. Researchers also detected BRAF V600E in 51% of 57 biopsies [4].

Although the interest and research on ECD increased considerably in recent years, awareness of the disease has not yet reached a sufficient level. Therefore, even if the most characteristic feature of bone involvement is seen and biopsies are taken from appropriate areas, (as in our patient), the disease may not be diagnosed if proper histochemical staining is not performed. So in our case, a year ago, despite the present fibrosis seen in histopathology, the diagnosis of ECD was not made by the pathologist.

In conclusion, because of the rarity and broad clinical spectrum of ECD, the diagnosis is rather difficult and requires a multidisciplinary approach. Effective communication between physicians, radiologists, and pathologists is essential. Pathologists should be warned in terms of ECD when incidental characteristic bone involvement is seen in whole-body BS or in $^{18}$F-FDG PET/CT. Furthermore, in our opinion, even
if histiocytes are not seen in a bone biopsy in cases of excessive fibrosis, ECD should be suspected and a BS should be performed to investigate characteristic bone involvements.

The authors of this study declare no conflicts of interest

Bibliography


Antonio De Pereda. Nature Morte (1652). Oil in canvas. 80x94cm.