CLINICAL NOTE

Erdheim-Chester Disease: The Effect of Bisphosphonate Treatment—A Case Report

Sibel Eyigör, MD, Yeşim Kirazlı, MD, Ayşenur Memis, MD, Gülçin Başdemir, MD

ABSTRACT. Eyigör S, Kirazlı Y, Memis A, Başdemir G. Erdheim-Chester disease: the effect of bisphosphonate treatment—a case report. Arch Phys Med Rehabil 2005;86:1053-7.

Erdheim-Chester disease is a distinctive pathologic and radiographic entity characterized by bilateral symmetric sclerosis of the diametaphyseal regions of long bones and infiltration of foamy lipid-laden histiocytes. It is a rare histiocytic disease of unknown etiology that is characterized pathologically by xanthogranulomatous infiltrates of multiple organs. We present a patient in her early sixties with bilateral mild knee and leg pain. The patient showed a typical bilateral symmetric medullary sclerosis at the diametaphyseal portions of long bones of the lower extremity. The diagnosis was confirmed by a bone biopsy, and bisphosphonate (alendronate, 70mg/wk) was given to the patient. After 9 months of treatment, biochemical markers of bone turnover, which were high at baseline, decreased to normal ranges. However, the radiographs showed that bone lesions had changed to lytic lesions. We propose use of bisphosphonates, such as alendronate, to decrease the biochemical markers of bone turnover. But we suggest that it is premature to conclude that bisphosphonates have any effect on lytic lesions and the progression of the disease as shown by changes in radiographs. Further studies with long-term follow-up and ultrastructural evaluation are needed.

Key Words: Bisphosphonates; Case report; Densitometry; Histiocytosis, non-Langerhans-cell; Rehabilitation.

ERDHEIM-CHESTER DISEASE (ECD) is a rare disorder with specific clinical and histologic features that has been reported fewer than 100 times in the literature.[1,2] It may be difficult to diagnose because it is rarely seen and has a broad spectrum of clinical manifestations. The diagnosis is based on radiologic findings of striking, patchy medullary sclerosis in the diametaphyseal region, which is mostly confined to the appendicular skeleton in a symmetric fashion.[3] Radiologic findings should be confirmed with the computerized tomography, bone scans, and histopathologic features. Although the histologic examination is important for diagnosis, it may not be precise enough to ensure the accuracy of diagnosis.[4]

Knee and leg pain are the most common symptoms because the disease affects mainly the long bones of the lower extremity.[5] Extraskeletal manifestations occur in the retroperitoneum, the lungs, the central nervous system, the orbits, and the other internal organs in more than 50% of patients.[6]

Treatment options for ECD include corticosteroids, radiotherapy, chemotherapy, and immunotherapy or combination therapy, although none have been highly effective.[1]

We report on a patient with ECD who presented with a nonspecific medical history of mild knee and leg pain and radiologic findings unique to the disease. Bisphosphonate treatment was tried, and its effect is discussed in relation to biochemical markers, bone densitometer, and radiologic progression.

CASE DESCRIPTION

A woman in her early sixties who was physically fit presented with bilateral, mild knee and leg pain that had developed in the past year. She had a history of hypoactive nodules of the thyroid and had had surgery for a gingival cyst. Physical examination revealed bilateral slight tenderness over both tibia on palpation and xanthelasma of the left eyelid.

Plain films of the knees and lower legs revealed symmetric medullary sclerosis at the diametaphyseal portions of the tibia, irregular cortical thickening, and bilateral focal lytic lesions within the tibia (fig 1). In addition, increased density was seen in the radius and distal ulna diametaphyseal area. Radiographs of the cranium and both hands were normal.

A bone scan indicated sites of symmetrically increased radionuclide uptake, including the bilateral tibia, both distal femurs, the fibulas, both radii, ulnae, the metatarsal bones, and the mandible (fig 2).

Abnormal laboratory findings included increased C-reactive protein (CRP) (5.1mg/dL) and erythrocyte sedimentation rate (ESR) (70mm/h), and decreased hemoglobin (10.6g/dL) and hematocrit (32%) values. Alkaline phosphatase and thyroid-parathyroid hormone levels were within referent levels. Proteinuria was negative. Cholesterol and triglyceride values were normal. According to the dual-energy x-ray absorptiometry (DXA) scan, the L4 spine T score $\pm$ standard deviation was $-2.7\pm.822 g/cm^2$ and T score of the trochanter was $-1.5\pm.551 g/cm^2$. Bone turnover was increased: urinary deoxypyridinoline was 19.5 nmol/mmol (referent range, 3–7.4nmol/mmol) and osteocalcin was 19ng/mL (referent range, 3–10ng/mL). Medical treatment for osteoporosis consisted of 70mg of alendronate weekly, 600mg of calcium carbonate daily, and 400IU of vitamin D daily. After 9 months of treatment, the osteocalcin value was evaluated at 9ng/mL, deoxypyridinoline was 7nmol/mmol, ESR was 34mm/h, and CRP was 3.31mg/dL.

Evaluated as normal were baseline chest radiographs, mammography, abdominal and pelvic ultrasonography, serum protein electrophoresis, cranial computed tomography (CT) scanning, thoracic high-resolution CT scanning, bone marrow biopsy, and aspiration of the iliac crest. Open bone biopsy of the tibia revealed foamy lipid-loaded histiocytes, incipient local inflammatory reaction, giant cells, and osteosclerosis with medullary fibrosis. Immunohistochemically, foamy histiocytes were positive for CD68 and negative for the S-100 protein, CD1a. This histopathologic appearance is a typical finding in

From the Departments of Physical Therapy and Rehabilitation (Eyigör, Kirazlı), Radiology (Memis), and Pathology (Başdemir), Ege University Medical Faculty, Izmir, Turkey.

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the authors(s) or upon any organization with which the author(s) is/are associated.

Reprint requests to Yeşim Kirazlı, Dept of Physical Therapy and Rehabilitation, Ege University Medical Faculty, 35100 Bornova, Izmir, Turkey, e-mail: *ykirazli@med.ege.edu.tr.*

0003-9993/05/8605-9038$30.00/0
doi:10.1016/j.apmr.2004.05.005

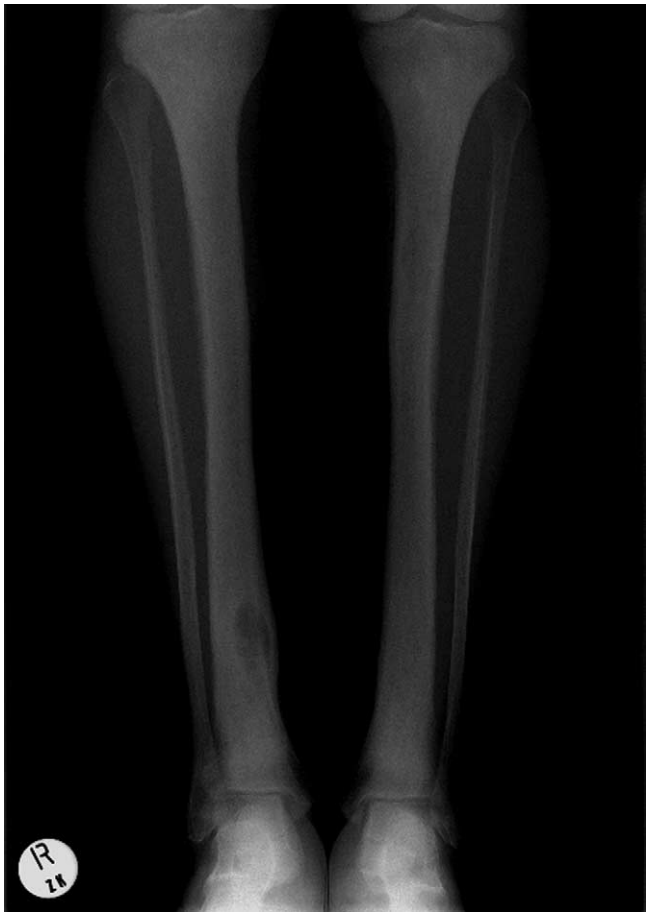

Fig 1. Baseline radiographs of the lower legs (anteroposterior [AP] view).

ECD patients (fig 3). Our patient continues to feel well and is seen regularly every 6 months. After 1.5 years, there are no signs of suspected systemic involvement.

Bone densitometer scan, bone scan, and radiographs of both tibiae (fig 4) were obtained after 1 year. Current radiographs revealed symmetric medullary sclerosis at the diametaphyseal portions of the tibia and bilateral focal lytic lesions within the tibia as with the baseline films. However, the size of the lytic lesions in the right tibia had enlarged, whereas the number of the lytic lesions in the left tibia had increased. According to the DXA scan from the first year, L4 spine T score was $-2\pm.900 g/cm^2$ and T score of the trochanter was $-1.3\pm.567 g/cm^2$. DXA scans of the distal radius were also evaluated. Density at the distal radius had increased dramatically. Distal radius total T score was $10.3\pm1.087 g/cm^2$. There was a significant difference in the favor of lytic lesions at the end of the first year; therefore, radiographs were repeated after 18 months (fig 5) and appeared similar to the radiographs from the first year (see fig 4, 5).

DISCUSSION

ECD is a rare form of non-Langerhans histiocytosis of unknown etiology, which characteristically affects long bones, especially the lower limbs bilaterally and symmetrically, in adults. Bone pain that is usually described as juxtaarticular, mild but permanent, and noninflammatory is the most common presenting symptom of ECD,[1] which was the case presented here. Other common symptoms and signs include fever, weight loss, exophthalmos, dyspnea, and neurologic signs, with central diabetes insipidus being the most common neurologic manifestation.[7] Presence of visceral foci of variable localization and extension determine both the clinical diagnosis and the prognosis.[8] The eventual outcome of cases found in the literature was often not reported.[9] The prognosis for ECD is related to the extent of visceral involvement; of those with significant systemic disease in whom it was detailed, most showed gradual progression and many died within 2 to 3 years after diagnosis from congestive heart failure, lung fibrosis, or renal insufficiency as a result of the disease.[1,5,10] Involvement of the kidney or retroperitoneum leads to kidney disorders, whereas involvement of the lung, pericardium, skin and orbita leads, respectively, to lung fibrosis, cardiac failure, and exophthalmos.[11] Sustained improvement seems unusual.[9] In our patient, mild bone pain was the only symptom at baseline and our 1-year follow-up indicated that there was no suspected systemic involvement. The physical examination and extensive investigations supported this theory.

The only signs specific to ECD are radiologically confirmed osteosclerosis and histologic features. Radiographs show bilateral and symmetric cortical osteosclerosis of the diaphyseal and metaphyseal regions in the long bones having a clear-cut limit between the involved portion of the bone and the epiphyseal region, which is usually spared.[1,3] Our patient showed osteosclerotic bony lesions in the diametaphyseal portions of the tibia, radius, and distal ulna, with an osteolytic component within the tibia. Although bilateral symmetric osteosclerosis has been regarded as a pathognomonic feature of ECD, an osteolytic component has also been described in approximately one third of cases, affecting both the long bones and the flat bones such as the skull.[1,12]

A bone scan showing all sites of bone involvement in one diagnostic procedure can be valuable because clinical symptoms are usually mild or absent.[13] Common to all reported cases, including ours, is the symmetric and abnormally increased labeling of the distal ends of the long bones of the lower limbs and sometimes the upper limbs, the orbits, the maxillary sinuses, the mandible, and the ribs.[1,13] Symmetric involvement almost excludes diseases such as osteomyelitis, Paget's disease, lymphoma, and sclerotic sarcoidosis.[14] Bone scanning is an effective diagnostic method to detect sites of osseous infiltration in patients with known ECD. It may also provide valuable information about patients with unclear diagnoses. But the histologic examination of the biopsy material is the only way to make a definite diagnosis.

ECD exhibits negative S-100 staining and is considered distinct from Niemann-Pick disease, Farber's disease (lipogranulomatosis), and Langerhans cell histiocytosis (LCH) (formerly, histiocytosis X). Pathophysiologically, ECD and LCH are grouped together as reactive histiocytoses as distinguished from the primary lipid storage disorders and histiocytic malignancies.[6] ECD differs from LCH in its age distribution and immunochemical and radiologic characteristics.[3,4] Histologically, ECD is characterized by a diffuse infiltration with large, foamy lipid-laden histiocytes, rare Touton-like giant cells, lymphocytic aggregates, reactive bone sclerosis, and fibrosis. Open bone biopsy of our patient's tibia also revealed foamy lipid-loaded histiocytes, incipient local inflammatory reaction, giant cells, and osteosclerosis with medullary fibrosis. The histiocytes in ECD differ from the Langerhans cell group in ontogenesis, immunohistochemistry (positive for CD68, negative for CD1a and S100 protein), and ultrastructural ap-