Erdheim-Chester Disease

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CASE REPORT

A 51-year-old man presented after losing consciousness. Medical history was significant for hemiplegic migraines, asthma, and depression.

Physical examination showed right-side hemiplegia, aphasia, ecchymoses, and blisters on the right arm. Temperature was 38.7°C. Laboratory data were within normal limits, except for an elevated white blood cell count (20,800/mm³).

Axial computed tomography (CT) of the head showed no mass, hemorrhage, or focal infarction. Magnetic resonance imaging (MRI) of the head revealed T2-weighted signal abnormalities of the brain stem. The differential diagnoses included toxic metabolic insult, Wernicke’s encephalopathy, and lymphoma.

Plain radiographs of the right arm revealed ill-defined regions of medullary sclerosis and cortical thickening involving the diaphyses of the radius and ulna. Plain radiographs of the spine showed no fracture, but benign areas of sclerosis in both iliac bones. Further evaluation with a conventional radiographic skeletal survey demonstrated medullary sclerosis and cortical thickening involving the diaphyses of multiple long bones of the upper and lower extremities, including the radius and ulna and tibia and femur (Figure 1). The changes were most marked in the femurs, where in addition to dense medullary sclerosis and cortical thickening, thick periosteal new bone formation involving the diaphyses and metaphyses of both distal femurs with relative sparing of the epiphyses was observed. Cortical thickening of the skull was noted.

Plain chest radiograph showed soft-tissue density projected over the heart. Computed tomography of the chest and abdomen revealed a soft-tissue mass in the periaortic region that extended from the anterior mediastinum adjacent to the aortic arch, inferiorly to the retroperitoneum surrounding the abdominal aorta down to the aortic bifurcation. The mass involved both kidneys, resulting in mild bilateral hydronephrosis (Figure 2). The differential diagnosis included metastatic disease, lymphoma, or retroperitoneal and mediastinal fibrosis. A percutaneous CT-guided biopsy of the periaortic mass revealed dense fibrotic tissue with chronic inflammation. Bone marrow aspirate and biopsy were normocellular for the patient’s age.

During his 2-month hospitalization, the patient continued having fever of unknown origin, in addition to diabetes insipidus associated hypernatremia, dementia, neurologic bladder

Figure 1: AP radiographs demonstrate bilaterally symmetric medullary sclerosis and cortical thickening involving the diaphyses of the radii and ulnae (A), dense medullary sclerosis of the diaphysis and metaphysis of both femurs with coarsened trabecular pattern and thick periosteal new bone formation (B), and scattered medullary sclerosis in both tibiae (C).

Figure 2: Axial CT of the abdomen showing a soft-tissue retroperitoneal mass surrounding the aorta and both kidneys resulting in mild bilateral hydronephrosis.
complicated by enterococcal urinary tract infection, interstitial nephritis, ileus, asthma, normocytic anemia, and thrombocytosis.

With the presumptive diagnosis of Erdheim-Chester disease, the patient was discharged with improvement of his hemiplegia and aphasia. Residual weakness of all extremities was noted but the patient was able to stand up by himself and walk with minimal assistance. He required an indwelling urinary catheter because of his atomic bladder.

Three months postdischarge, due to continued back and right forearm pain, bone scan revealed increased radioisotope uptake of the radii, ulnae, distal femurs, and proximal tibiae bilaterally, as well as in the paranasal sinus region of the skull (Figure 3). A percutaneous CT-guided needle biopsy from the medial condydar region of the distal right femur was performed (Figure 4). Histological examination showed fragments of sclerotic bone and bone marrow containing clusters of foamy histiocytes, loose fibrosis, and scattered collections of lymphocytes. These findings were consistent with Erdheim-Chester disease (Figure 5).

At latest follow-up 1 year after symptom onset, the patient had significant functional limitations in his daily activities due to progressive neurological problems. Back and shoulder pain was mild. Joint range of motion was normal. Neurological examination was significant for aphasic speech, dementia, disorientation, increased right quadriceps reflex, and Babinski sign on the right. Examination of the cranial nerves, muscle strength, and sensation of the upper and lower extremities was normal.

**DISCUSSION**

In 1930, William Chester described the first two cases of unusual diffuse "lipogranulomatosis" associated with bone changes with fibrosis that was clinically and pathologically distinct from Hand-Christian disease and systemic lipodosis. In 1972, Jaffe reported a third patient and referred to this syndrome as "Erdheim-Chester disease" in recognition of Jakob Erdheim. Chester's mentor. Recognition of this entity allows better assessment of its true incidence, therapeutic options, and prognosis.

Erdheim-Chester disease is a rare, non-Langerhans form of histiocytosis characterized by infiltrates of foamy, lipid-laden histiocytes and bilateral symmetrical foci of sclerosis in appendicular long bones. Since Chester's initial description of Erdheim-Chester disease, <100 cases have been reported in the literature.

Although the etiology of Erdheim-Chester disease is still unknown, a pathologically high turnover of low-density lipoproteins seems to play an important role in the pathogenesis of this disease. It usually affects adults at an average age of 54 years (range: 21-76 years) and it has a 3 times higher incidence in men, predominantly in whites.

Clinical courses ranging from 5 months to 10 years after initial symptom onset have been described. Signs and symptoms are the result of histiocytic infiltration of various tissues. Clinical presentation is not specific and clinical and symptoms in Erdheim-Chester disease can lead to misdiagnosis or diagnosis of another histiocytic disorder. In a study of 59 cases, bone pain was the most common symptom (28 patients) and was sometimes isolated (7 patients). Bone pain is juxta-articular, mild but permanent. Knee pain is the most common symptom, affecting the femur and tibia. In the same study, general symptoms such as fever, weight loss, and weakness were present in 11 patients.

Hematological examination usually reveals abnormal lipid metabolism in a few cases (15%); moderate anemia and increased C-reactive protein and erythrocyte sedimentation rates are occasionally observed.

In the present patient, extraskeletal manifestations were more prominent. In approximately 40%-50% of reported cases, almost all of the organs are involved including the lungs, pericardium, skin, orbit, and retroperitoneum. Intramuscular lipogranuloma is a rare manifestation of Erdheim-Chester disease. Clinical features such as arterial hypertension, exophthalmos, and diabetes insipidus due to infiltration of the pituitary often are present. Chronic lipogranulomatous pyelonephritis, cardiac failure due to myocardial and pericardial lipid-laden histiocytic infiltration, histiocytic skin infiltration, chronic discharging sinus fistulas originating in bones, arthropathy, multiple brain masses, periodontitis, and hepatosplenomegaly have been reported. Pneumonia, nystagmus, paraparesis, urinary inconti-
nence, and loss of sight are also sometimes noted.\textsuperscript{4,8,13}

The skeletal manifestations of Erdheim-Chester disease characteristically involve the long tubular bones of the extremities and present radiographically with bilaterally symmetric medullary sclerosis with associated cortical thickening and coarsened trabecular pattern. As seen in this patient, the osseous changes typically involve the diaphyses and metaphyses of the long tubular bones with relative sparing of the epiphyses. However, a recent report by Bancroft and Berquist\textsuperscript{14} described a patient with Erdheim-Chester disease with partial involvement of the epiphyses. The findings of bilaterally symmetric medullary osteosclerosis and the histological features of the disease are characteristic.\textsuperscript{4,7}

As in the present patient, bone symptoms are mild or absent and bone scintigraphy may be valuable to disclose all sites of affected bone.\textsuperscript{15} Bone scintigraphy demonstrates intense, symmetrical radionuclide uptake corresponding to early bone lesions confined to the medullary cavity.\textsuperscript{16,17} Radioactive tracers \textsuperscript{99m}Tc and \textsuperscript{67}Ga accumulate in areas of radiographic abnormality, but on \textsuperscript{111}In chloride and \textsuperscript{99m}Tc sulfur colloid marrow scans, the affected areas show photopenia.\textsuperscript{18}

Magnetic resonance imaging is more sensitive than CT for evaluation of intra- and extra-osseous manifestations of the disease.\textsuperscript{19} On MRI, Erdheim-Chester disease presents with heterogeneous abnormal signal intensity in the long bones reflecting marrow infiltration with histiocytes and fibrosis. The imaging characteristics of the disease are nonspecific on MRI with low signal intensity on T1-weighted images and heterogeneous mixed low- and high-signal intensity on T2-weighted images. The fat suppressed proton- and T2-weighted images demonstrate mixed signal characteristics with lack of fat suppression in the infiltrated marrow and normal fat suppression of the uninvolved fatty (yellow) marrow.\textsuperscript{20} Correlation with conventional radiographs is valuable in formulating an appropriate differential diagnosis. The radiographic differential diagnosis includes mastocytosis; fluoride intoxication; myeloid metaplasia; lymphoma; metastatic disease; mucopolysaccharidoses; Paget's disease; toxic osteoarthropathy; lipid storage disease such as Gaucher's, Niemann-Pick, and Farby's disease; and adult progressive diaphyseal dysplasia (Engelmann's disease).\textsuperscript{7,13}

A tissue biopsy confirms the presumptive clinical and radiographic diagnosis of Erdheim-Chester disease. Bone or retro-orbital tissue have been the most useful sources of diagnostic biopsies. Tissue biopsies contain clusters of lipid-laden, foamy histiocytes with variable amounts of chronic inflammation and fibrosis. In addition, bone biopsies typically show sclerotic bone. The histiocytes in Erdheim-Chester disease express CD 68, supporting a histiocytic phenotype. Unlike Langerhans cell histiocytosis, they do not contain electron microscopic evidence of Birbeck granules and they lack CD1a expression. However, S-100 protein expression is variable.\textsuperscript{4,5,11,21}

The relationship of Erdheim-Chester disease to Langerhans histiocytosis (formerly known as Histiocytosis X, which includes Letterer-Siwe and Hand-Schüller-Christian disease and eosinophilic granuloma) has been studied.\textsuperscript{7} Langerhans histiocytosis affects children and young adults, whereas Erdheim-Chester disease affects adults (average age at presentation: 54 years).\textsuperscript{10,14,22} Osseous lesions accompany both diseases. Erdheim-Chester disease typically involves the long bones, with bilaterally symmetric primarily sclerotic lesions. Langerhans histiocytosis also occurs in the long bones, but also commonly involves the flat and axial bones, and lesions usually are osteolytic and asymmetrical.

Nevertheless, Langerhans histiocytosis and Erdheim-Chester disease overlap in several respects radiographically. It has been reported that Langerhans histiocytosis, which initially exhibits osteolysis on radiographs, may subsequently exhibit sclerosis. On the other hand, bone resorption was found in a radiograph demonstrating osteosclerosis in a case of Erdheim-Chester disease, indicating a histological similarity to Langerhans histiocytosis.\textsuperscript{21}

Miller et al\textsuperscript{24} reported a patient with Erdheim-Chester disease who initially exhibited osteolytic lesions and then went on to exhibit sclerosis approximately 4 years later. Dalinka et al\textsuperscript{25} reported three cases of Erdheim-Chester disease with limited foci in the ribs, without any lesions in long bones. Waite et al\textsuperscript{17} presented radiographs of typical Erdheim-Chester disease with bilateral osteosclerosis in the femora and tibiae, and stated that these cases were diagnosed as conventional Langerhans histiocytosis through biopsy.
were found to have Langerhans granules when examined with an electron microscope and to be S-100 protein positive immunohistochemically. Thus, the criteria for Erdheim-Chester disease require further investigation.5

Clinical trials for treatment of Erdheim-Chester disease have not been conducted; thus, therapeutic options are based on anecdotal experience and generally do not provide information about the effects on disease outcome. Systemic corticosteroids, chemotherapy (vinblastine, vincristine, cyclophosphamide, doxorubicin), immunotherapy (interferon alpha), and radiation treatment have been used.4,5 The efficacy of the various treatments is difficult to evaluate because of the rarity of the disease. None have been highly effective, and the disease is typically relentless in its course.

Information regarding the natural history and prognosis of Erdheim-Chester disease is limited.5 In general, the clinical course of patients with this disease is variable, and the prognosis is poor, despite treatment. The prognosis depends largely on the extent and distribution of extraosseous disease.13 In a review of 59 patients, Veyssier-Belot et al4 reported death related to the disease in 59% of cases, including 36% in <6 months. Most patients die within 2-3 years after diagnosis due to lung fibrosis, congestive heart failure, or renal insufficiency.13

Whether histiocytic proliferations represent monoclonal neoplastic populations or are part of a polyclonal reactive process also is unclear. In a recent report investigating the clonality of non-Langerhans’ cell histiocytes, using the human androgen receptor gene assay, no evidence was found that these cells represent a monoclonal population.26 Further clinical research on the pathogenesis and natural history of Erdheim-Chester disease may enhance understanding of this rare multisystem histiocytosis and thereby contribute to the development of effective treatment.

REFERENCES


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