A 76-year-old woman who had been diagnosed with rheumatoid arthritis (RA) sought further treatment at Beth Israel Medical Center. The patient had suffered from pain over her arms and legs for several years. She had difficulty raising her right arm over her head. She had previously been evaluated at another institution and had been treated as RA with weekly oral methotrexate. She did not report any joint swelling or morning stiffness. There was no history of nodule, skin rashes, or dryness of the eyes or mouth. She had a past medical history significant for coronary artery disease requiring stent placement, hypertension, and hypercholesterolemia. Two years before this evaluation she had undergone a total knee replacement at another institution. Her medications included furosemide, telmisartan, metoprolol, simvastatin, and Plavix. She was taking acetaminophen and tramadol as needed for pain. She had not known medication allergies. Review of systems was negative for fevers, weight loss, or night sweats. She did not have chest pain but noted some exertional dyspnea. Her family history was negative for rheumatic diseases. On physical exam her blood pressure was 130/70, her chest was clear, and cardiac sounds were normal. Her abdominal exam did not revealed organomegaly. Her skin did not have rashes or nodules. Her hands did not have tender or swollen joints and no deformities or evidence of synovitis was observed. Her grip was normal. Her right shoulder had a forward flexion and abduction limited to 90°. The rest of the joints had normal range of motion, and no pain was elicited during the exam. Left knee revealed a well healed midline scar. There was no muscle tenderness or weakness and no gross neurological deficits were noted. Laboratory findings were significant for mildly elevated leukocyte count (11,400 mm³), 59.4% polymorphonuclear cells, 26.8% lymphocytes, and 2% eosinophils. Her hemoglobin was 13 g/dL and hematocrit was 39.7%. Her electrolytes were within normal limits. Her inflammatory markers were normal (erythrocyte sedimentation rate of 25mm/h and C-reactive protein < 0.5). Her creatinine was 1.26 mg/dL, glucose 99 mg/dL, AST 26 U/L, ALT 27 U/L, alkaline phosphatase 142 U/L (38-126). Her rheumatoid factor was positive (39.3) normal 0-19, and anti-CCP was 2 (normal < 20). Hepatitis B surface antigen and hepatitis C antibody were negative. Chest radiograph revealed cardiomegaly (Fig. 1). Radiographs of her hands showed bilateral medullary sclerosis of the distal radii and ulnae, with no erosive changes (Fig. 2). A long bone survey demonstrated patchy intramedullary sclerosis in symmetric distribution affecting the shafts and metaphyseal portions of the bilateral radii, ulnae, femurs, tibiae, and fibulae with bilateral humeral sparing (Fig. 3). Left knee prosthesis and osteoarthritis of the right knee noted.

A previously obtained specimen from the knee replacement was obtained and reviewed.

Differential Diagnosis

Sclerosis of the bone represents a response to a slow focal aggression by reactive bone formation. The differential diagnosis of medullary sclerosis is broad, including malignancies (osteosarcoma, lymphoma, osteoblastic metastasis), benign tumors (osteoid osteoma), infections (chronic osteomyelitis), and other conditions (osteonecrosis, Paget’s disease, eosinophilic fasciitis). In this case, the patient’s clinical presentation, radiographic findings, and laboratory results suggested a diagnosis of Erdheim-Chester disease. This rare condition is characterized by the triad of mediastinal mass, polyserositis, and polyarthritis, often with a prominent radiographic feature of medullary sclerosis involving long bones. The differential diagnosis includes other conditions that may present with similar radiographic findings, such as metastatic disease, lymphoma, or eosinophilic granuloma. Additional workup, including bone biopsy and immunostaining, may be necessary to confirm the diagnosis and exclude other potential causes of medullary sclerosis.
tis), trauma (healing stress fractures), metabolic disorders, several sclerosing bone dysplasias, and acquired syndromes with increased bone density that include Erdheim-Chester disease, myelofibrosis, and sickle cell disease. Characteristic radiological findings that suggest malignancy are periosteal new bone formation and soft-tissue extensions, while small radiolucent nidus are often seen in benign tumors, all of which are absent in the case presented. Infections and trauma can also be discarded given the lack of classic clinical history. Metabolic disorders, such as hypervitaminosis A, pseudohypoparathyroidism, and renal osteodystrophy, could be excluded based on their radiological appearance of periosteal new bone formation in diaphysis with sparing of the medullary cavity (hypervitaminosis A) and generalized osteosclerosis (pseudohypoparathyroidism, and renal osteodystrophy) along with laboratory abnormalities (i.e.,

Figure 1 Chest radiograph. It shows marked cardiomegaly with no signs of pulmonary congestion.

Figure 2 Hands radiograph. Bilateral medullary sclerosis of the distal radii and ulnae. No erosive changes.

Figure 3 Long bone survey. There is patchy intramedullary sclerosis in symmetric distribution affecting the shafts and metaphyseal portions of the bilateral radii, ulnae, femurs, tibiae, and fibulae with bilateral humeral sparing.
Sclerosing bone dysplasias are a heterogeneous group of genetic disorders resulting in errors of bone metabolism that often present with pain of the extremity involved. Camurati-Engelmann disease occurs in the first decade of life, is an autosomal-dominant inherited disorder seen symmetrically in long bones, that occasionally involves the skull. In contrast, Ribbing disease is an autosomal recessive disorder that usually presents after puberty, commonly found in women, where skull is spared, and asymmetric intramedullary diaphyseal scleroses of long bones is seen. Intramedullary osteosclerosis is clinically and histologically indistinguishable from Ribbing disease (osteoblastic activity and new bone formation), but it is nonhereditary condition.

Osteopetrosis (Albers-Schönberg disease) is a hereditary disease, manifesting during childhood (autosomal-recessive form) or adolescence (autosomal-dominant form). It is characterized by osteoclasts dysfunction and excessive mineralization, with subsequent anemia due to bone marrow infiltration. Features such as hypocalcemia and elevated alkaline phosphatase can also be observed. Given the age of the patient and the lack of hypocalcemia, this disorder can also be excluded.

Erdheim-Chester disease is a systemic histiocytic disorder diagnosed on the basis of a characteristic pattern of symmetric intramedullary sclerosis of long bones. It often manifest with chronic bilateral bone pain. Pericardium, lungs, and retroperitoneum can be affected.

Rheumatoid arthritis is a chronic inflammatory disease that typically presents as a symmetrical polyarthritis. The diagnosis of RA is based on the combination of symptoms, signs, serologic tests (RF and anti-CCP), and radiologic findings. RF is found in 60% to 80% of RA patients. However,
it is not specific and may be detected in other autoimmune diseases, in chronic infections, and in approximately 10% of healthy individuals.

In conclusion, this 76-year-old patient with bilateral medullary sclerosis of long bones, mildly elevated RF, the most likely diagnosis is Erdheim-Chester disease.

Pathological Discussion
The analysis of the pathology specimen showed an irregular articular surface with progressive thinning of the cartilage and eburnation of the underlying bone which is consistent with osteoarthritis. These changes are seen on the medial femoral condyle and medial tibial plateau. Moderate peripheral osteophyte formation is present particularly in the medial condyle. Abundant foamy histiocytes were observed on cut surface with a grossly yellow appearance (Fig. 4a). On microscopy, large aggregates of histiocytes with clear to pale cytoplasm that stain positively for CD68 and negatively for S100 and CD1a immunomarkers were observed (Fig. 4b). Bony trabecules near the histiocytic areas showed secondary sclerotic changes. There was no evidence of RA. The differential diagnosis of these findings includes Langerhans cell histiocytosis (CH), which would stain positively for CD68 and also S100 protein.

A diagnosis of ECD was made.

Discussion
ECD is a non-Langerhans cell histiocytosis described by the American pathologist Chester and the Viennese pathologist Erdheim in 1930.9 It is a nonhereditary disorder that affects long bones in the region of the metadiaphyses, sparing the epiphyses and axial skeleton. It is a disease of adults and the incidence is reported to be more in women. The xanthogranulomatous lesions can infiltrate the soft tissues, central nervous system, retroperitoneum, and viscera. Therefore, clinical manifestations could include exophthalmos, interstitial lung disease, diabetes insipidus, retroperitoneal fibrosis, and pericardial thickening.

Radiographically, it is characterized by a symmetric pattern of diffuse or patchy increased density, medullary sclerosis, and cortical thickening. The gross bone biopsy contains yellow areas of lipid accumulation. The most distinctive feature is the positive staining for CD68 and negative staining for S100 and CD1a.

In terms of treatment, there are no randomized control trials given the small number of cases worldwide. By January 2010, there were 350 cases published in the literature; none of them had a positive RF.

There are anecdotal reports of patients responding to interferon alpha therapy,10,11 and a recently published study of 24 ECD patients who received interferon alpha therapy and were followed for a median of 19 months.12 In the latter, the response to treatment was successful in most of the patients (67%), and it correlated with organ involvement.

Disclosure Statement
None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References