Diffuse Osteosclerosis in Hairy Cell Leukemia

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We describe two patients with a new clinical pathologic syndrome of diffuse osteosclerosis in association with hairy cell leukemia. In both patients bone marrow biopsies could not be obtained due to extremely hard bones and inability to insert the biopsy needle; neither patient had a history of bony pain or fracture. The osteosclerotic process in one patient stabilized after successful treatment of her hairy cell leukemia with interferon alpha and deoxycoformycin suggesting that the osteosclerosis observed was related to the underlying malignant disease. Possible etiologic mechanisms are discussed.

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Hairy Cell Leukemia is an indolent lymphoproliferative disorder of B-lymphocyte origin. The disease typically involves the peripheral blood, bone marrow, and spleen and patients usually present with pancytopenia and splenomegaly. Clinical involvement of other organs has been reported but is less common. Bony infiltration by hairy cells is particularly unusual but when it occurs, it can result in painful lytic or mixed blastic/lytic bone lesions usually in the thoracic or lumbar spine, femoral neck, or femoral head. Diffuse bony sclerosis in association with hairy cell leukemia has not been reported previously. In this report, we describe two patients with hairy cell leukemia and diffuse bony sclerosis. The disease process did not appear to be caused by direct infiltration of the bone by hairy cells. The diffuse nature of the process suggested that a humoral factor was responsible for the widespread bony thickening.

CASE REPORTS

Patient no. 1. A 39-year-old white woman presented in 1981 with progressive fatigue, splenomegaly, and pancytopenia. A marrow biopsy revealed a diffuse hairy cell infiltrate and a splenectomy was performed 4 months after presentation. The spleen weighed 900 g. There was a diffuse infiltration of the red pulp with a uniform population of small lymphocytes with prominent cell membranes, clear cytoplasm, round nuclei, and occasional small nucleoli. Peripheral blood counts normalized after splenectomy. In mid-1984 her hemoglobin began to fall progressively and she developed recurrent fatigue. In January 1986, a bone marrow biopsy was attempted but could not be obtained.

The patient was referred to the National Cancer Institute in February 1986 and was found to have a hemoglobin of 8.8 g/dL, a granulocyte count of 660/mm$^3$, and a platelet count of 171,000/mm$^3$. A small percentage of peripheral blood cells had the morphologic appearance of hairy cells and were positive on staining for tartrate resistant acid phosphatase (TRAP). Posterior iliac crest marrow biopsies could not be performed because of our inability, despite several attempts, to penetrate the cortical bone. The biopsy needle broke off in the bone and could not be retrieved, even under direct visualization in the operating room. An open bone marrow biopsy revealed markedly thickened bony trabeculae. Very little medullary space was observed but that which was present was filled with dense fibrous tissue containing large numbers of hairy cells (Fig 1). Very little normal hematopoietic tissue was present. Radiographs (Fig 2) revealed diffuse osteosclerosis of the ribs, vertebral bodies, pelvis, and proximal femora. Treatment began on March 20, 1986 with alternating monthly cycles of deoxycoformycin (dCF) and recombinant interferon-alpha 2a (rIFN-α2a) as described previously. Within 6 months, there was normalization of peripheral blood counts and the patient completed 14 months of therapy uneventfully. A repeat open bone marrow biopsy after the completion of therapy again revealed markedly thickened bony trabeculae and little medullary space filled predominantly by fat and hemorrhage. No hematopoietic tissue was present. Serum levels of soluble IL-2 receptor, a recently described tumor marker in hairy cell leukemia, normalized during the course of therapy. The patient has been followed at 3-month intervals since the completion of therapy and has done well. Soluble IL-2 receptor levels have remained normal. Peripheral blood counts 18 months after the completion of therapy remain normal but there has been no change in the x-ray appearance of her bones since the completion of therapy.

Patient no. 2. A 48-year-old white man presented with fatigue and lethargy in August 1974. Examination revealed splenomegaly and the absence of lymphadenopathy. His hemoglobin was 8.7 g/dL, total leukocyte count 2,700/mm$^3$, with 42% granulocytes, 5% band forms, 48% lymphocytes, 2% eosinophils, 2% basophils, and 1% hairy cells. His platelet count was 97,000/mm$^3$ and a reticulocyte count was 1.9%. Buffy-coat cells were TRAP positive. A bone marrow biopsy showed myelofibrosis and hairy cell leukemia. Radiographs of the skull, pelvis, lumbar, and thoracic spine revealed diffuse osteosclerosis. A bone scan showed increased uptake in both proximal femora. In March 1975, repeat percutaneous bone marrow biopsies were unsuccessful because the bones were so hard that two needles were broken during the biopsy procedure. On April 21, 1975, the patient underwent an open bone marrow biopsy, axillary lymph node biopsy, and splenectomy. Microscopic examination of all three specimens revealed involvement with hairy cell leukemia. After splenectomy, peripheral blood counts normalized until December 1978 when the hemoglobin again began to progressively decline. He began to require red blood cell (RBC) transfusions in January 1979 and developed hepatomegaly. Transfusion dependency developed in October 1979. Evaluation included liver biopsy, lymph node biopsy,
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Fig 1. Hematoxylin and eosin stain of bone biopsy of patient no. 1 showing osteosclerosis (A) and hairy cell infiltration (B) (original magnifications: A, x 32; B, x 128).

Fig 2. Plain radiographs of the pelvis (A) and chest (B) of patient no. 1. demonstrating diffuse osteosclerosis. Arrow indicates broken bone marrow biopsy needle, inside circle, from previous bone marrow biopsy attempt.
and open bone marrow biopsy. The liver and lymph nodes were infiltrated with TRAP positive lymphocytes. The open bone marrow biopsy revealed markedly thickened bony trabeculae, myelofibrosis, and an infiltrate of hairy cells. In November 1979, therapy began with clorambucil but the patient continued to require frequent RBC transfusions. Lithium carbonate was added in June 1981 without improvement in peripheral blood counts. Chlorambucil and lithium carbonate were both discontinued in December 1981 and oxymethalone was commenced in March 1982. In April 1982, the patient was hospitalized for bilateral pneumonia and an open lung biopsy revealed nonspecific pneumonitis and hairy cell infiltration into the lung parenchyma. He died in May 1982 of progressive pulmonary involvement with hairy cell leukemia.

COMMENTS

Bone involvement in hairy cell leukemia is a rare complication that usually manifests itself clinically by pain in involved skeletal areas. Pathologic fractures due to infiltration of the cortical bone by hairy cells have been reported. Radiographically these lesions have been predominately lytic in nature; however, bone scans are frequently positive suggesting that some osteoblastic activity is also present. This is the first report of diffuse osteosclerosis, without a lytic component, as a manifestation of bone disease associated with hairy cell leukemia. Both cases reported here had extensive bony sclerosis on radiographs, which in both cases was confirmed pathologically.

Both patients described here presented with hairy cell leukemia and diffuse bony osteosclerosis. Initially, it was possible to perform percutaneous bone marrow biopsies but as the hairy cell leukemia progressed this became impossible in both patients. This progressive “hardening” of the bone suggests that the sclerotic process was active and progressing in the early years of these patients’ disease. The sclerotic process in the second patient showed radiographic worsening that correlated with his progressive hairy cell leukemia and the first patient demonstrated radiographic stabilization after remission of hairy cell leukemia with effective therapy. Thus, in both patients the osteosclerotic process appears to have worsened as the patient’s hairy cell leukemia progressed and in one patient has stabilized after remission of the hairy cell leukemia. This suggests a causal relationship between hairy cell leukemia and the osteosclerosis.

Multiple myeloma, another B-cell neoplasm, classically results in osteolytic bone lesions with or without osteosclerotic involvement. The neoplastic cells of multiple myeloma are arrested at a more mature stage of differentiation than hairy cells, which are malignant counterparts of pre-plasma cells. Bone involvement has not been reported in chronic lymphocytic leukemia, a B-cell neoplasm characterized by a proliferation of cells arrested at a stage of differentiation that is less mature than in hairy cell leukemia. Thus, the degree of cellular maturity may be an important variable in the development of bony complications in these B-cell disorders.

The development of bone disease in hairy cell leukemia may be related to the platelet dysfunction known to exist in this disease. The α-granules of platelets contain, among other things, platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β). PDGF stimulates both DNA and protein synthesis in organ cultures of rat calvariae and has also been shown to stimulate bone resorption. TGF-β enhances bone DNA synthesis and the cells of the osteoblastic lineage appear to be the most sensitive to its mitogenic activity. Thus, both PDGF and TGF-β are growth factors that by themselves or in conjunction with other growth factors exert a major effect on bone remodeling. The α-granules of platelets in hairy cell leukemia have been shown to decrease in number and to have lower concentrations of these growth factors. The platelets in hairy cell leukemia appear to be intrinsically normal in that the storage pool deficiency-like abnormality has been observed to resolve with effective hairy cell leukemia treatment. These data are consistent with the notion that in hairy cell leukemia an “exhausted-platelet” or storage pool deficiency-like state occurs, which leads to aberrant release of these growth factors. These locally released factors could result in the sclerotic or lytic bone lesions observed in our patients. The diffuse osteosclerosis seen in our patients included bony sites not usually thought to be active in hematopoiesis in adults and is certainly more extensive than the bone involvement previously reported in hairy cell leukemia. Therefore, it seems likely that the pathogenesis of osteosclerosis in hairy cell leukemia involves a humoral mechanism.

Treatment of the lytic bone complications in hairy cell leukemia can be accomplished by systemic therapy with α-interferon or dCF but local radiation therapy is also often required. The first patient reported here responded to combination therapy with both dCF and α-INF with an improvement in peripheral blood counts and normalization of soluble IL-2 receptor levels and her bone disease radiographically has remained stable. If the bone complications are indeed due to abnormal platelet release of growth factors, it would be anticipated that the bone disease might improve or stabilize with correction of the functional platelet abnormality. Further studies of growth factor release and bone cell activation by platelets in hairy cell leukemia and other B-cell neoplasms are needed.

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