Multiple Diffuse Fibrosarcoma of Bone Associated with Extramedullary Hematopoiesis

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We report a case of multiple diffuse fibrosarcoma of bone. The patient, a 38-year-old man, was referred to our hospital with knee pain, anemia and thrombocytopenia. No solid mass was seen on radiographic examination of the knee joint, but magnetic resonance imaging showed hypointensity of the distal femur. Femoral biopsy revealed proliferation of long spindle-shaped fibrosarcoma cells, while a bone marrow biopsy of iliac bone (which appeared normal on radiographic examinations) showed replacement of hematopoietic cells by fibroblast-like spindle cells. A diagnosis of multiple diffuse fibrosarcoma of bone was therefore made. Autopsy revealed tumor invasion into multiple bones and several visceral organs and extramedullary hematopoiesis in the liver, spleen and lymph nodes. As this patient had leukoerythroblastic anemia with poikilocytosis, splenomegaly exhibiting extramedullary hematopoiesis, and apparent fibrotic change in his bone marrow, we suggest that this extremely rare disease should be considered in the differential diagnosis of myelofibrosis.

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Key words: spindle cells, leukoerythroblastic anemia, myelofibrosis

Introduction

Fibrosarcoma is a malignant tumor of fibroblasts which can occur in almost all tissues including bone. Most cases of fibrosarcoma of bone are unifocal, with less than 1% being multifocal (1, 2). Steiner (3) reported the first case of multiple diffuse fibrosarcoma of bone in 1944, and an additional four cases have since been reported (4–7). As multiple diffuse fibrosarcoma of bone is extremely rare, it remains poorly characterized, especially with regard to hematological findings. We present a case of multiple diffuse fibrosarcoma of bone associated with extramedullary hematopoiesis, leukoerythroblastic anemia with poikilocytosis, and apparent fibrotic change in the bone marrow, and discuss the associated hematologic and histologic features.

Case Report

A 38-year-old Japanese man was admitted to Ehime University Hospital in November 1993 with right knee pain, severe anemia and liver dysfunction. He had experienced right knee pain for two years. Plain radiograph examination of the knee joint was normal, but magnetic resonance imaging revealed hypointensity of the right distal femur on T1 and T2 weighted images with inhomogeneous contrast enhancement. Computed tomographs of the brain, chest and abdomen showed no abnormality except mild splenomegaly. The patient had no lymphadenopathy or skin lesion. Laboratory tests revealed a hemoglobin concentration of 6.8 g/100 ml with poikilocytosis; the white blood cell count was 8,400/mm3 with 52% neutrophils, 1% monocytes, 3% eosinophils, 1% basophils, 38% lymphocytes, 3% myelocytes, 1% metamyelocytes, 1% blasts and 9 erythroblasts per 100 white blood cells. The platelet count was 10.6×10^9/mm³. On testing liver function, asparate aminotransferase was 59 IU/L, alanine aminotransferase, 31 IU/L, lactate dehydrogenase, 764 IU/L and γ-glutamyl transpeptidase 419 IU/L. Renal function and electrolytes were within normal limits. Serum C-reactive protein was 2.3 mg/100 ml, and serum protein electrophoresis showed polyclonal gammopathy with immunoglobulin (Ig)G 3,248 mg/100 ml, IgA 560 mg/100 ml and IgM 169 mg/100 ml.

A bone marrow scintigram showed decreased bone marrow...
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Figure 1. Bone marrow biopsy specimen of posterior iliac crest. The bone marrow has been replaced by fibroblasts (HE stain, x400).

activity, but increased activity in the liver and spleen. Bone marrow aspiration resulted in a dry tap. Bone marrow biopsy of the posterior iliac crest revealed hematopoietic cell replacement by fibroblast-like spindle cells, which were arranged in a storiform pattern (Fig. 1). No hematopoietic cells were observed in the biopsy specimen. Giant cells with multiple nuclei were rarely observed. These findings led to a diagnosis of suspected fibrosarcoma of bone.

An open biopsy of the right distal femur showed spindle cell proliferation in a storiform pattern without osteolytic and osteoplastic changes. Hematopoietic cells in the bone marrow had been replaced by fibroblasts and abundant collagen (Fig. 2). These findings were identical to those of the posterior iliac crest biopsy. Extensive examinations were carried out to find a solid tumor of a visceral organ. However, there was no evidence of such a tumor. These findings were suspected to be multiple diffuse fibrosarcoma of bone. But a differential diagnosis of fibrosarcoma is malignant fibrous histiocytoma (MFH). Histological findings of MFH comprise fibroblasts, histiocytes, myofibroblasts and primitive mesenchymal cells in some extents. But, these specimens were monotonous spindle cells. In addition, the immunohistochemical and enzymatic characteristics of histiocytes, such as CD68, lysozyme and antichymotrypsin were negative in these specimens. Multiple diffuse fibrosarcoma of bone was therefore diagnosed.

The tumor failed to respond to chemotherapy with prednisone, adriamycin and cyclophosphamide and in September 1994, the patient’s right knee joint radiograph showed osteolytic change and multiple liver masses were detected by echography. The patient died of liver failure in February 1995.

On autopsy solid white-grayish tissues were seen in femur, tibia, pelvis, thoracic and lumbar vertebrae, and ribs. Round and

Figure 2. Open biopsy specimen of right distal femur. A) Low-power view showing a prominent storiform pattern of fibroblastic cells (×100). B) High-power view showing spindle-shaped tumor cells admixed with rare multinucleated forms (HE stain, ×300).

Figure 3. Autopsy specimen of spleen showing macrokaryocytes and erythroblasts (HE stain, ×800).
well-defined multiple nodules were observed in the liver, spleen and kidney. No primary neoplastic focus was found elsewhere. The histologic findings of these tissues were the same as those of the bone marrow and right distal femur biopsies. Immunohistochemically the tissues did not stain for neuro-specific enolase, S-100, smooth muscle actin or osteocalcin. There were many megakaryocytes and erythroblasts in the spleen (Fig. 3), indicating extramedullary hematopoiesis. The same changes were also observed in the liver and portal hepatic lymph nodes.

Discussion

This report describes a patient with fibrosarcoma of bone in which tumor cells had diffusely infiltrated the bone marrow of the whole body and had led to solid organ metastasis. Fibrosarcoma showing such infiltration has been designated as multiple diffuse fibrosarcoma of bone. Steiner described the first case of multiple diffuse fibrosarcoma of bone (3) in which the neoplastic growth in multiple bones (e.g. spine, sternum, ribs, clavicles and pelvis) had completely replaced the bone marrow. The patient had severe anemia, but white blood cell and platelet count were normal. The tumor destroyed the trabeculae and cortex of the bone, eroding through the latter in many places. In such places the tumor sometimes caused a slight periosteal elevation, but did not stimulate periosteal new bone formation. Histologic examination showed that the tumor cells had completely replaced the hematopoietic cells in the bone marrow in multiple regions. The histopathologic and clinical findings of the present case were consistent with those of Steiner's case.

Since fibrosarcoma of bone has been diagnosed as MFH (8), it is likely that recent cases of fibrosarcoma of bone have been regarded as MFH. However, few cases of multifocal MFH have been reported. Chen reported four patients with MFH and multicentric lesions (6). Dahlin and Unni (9) observed multiple MFH in only one of 52 cases of MFH, while Mirra found no cases of multiple MFH among 62 cases (10). Huvos et al reviewed 130 reported cases and noted synchronous multiple MFH in three and metachronous multiple MFH in 13 (11). Multiple diffuse fibrosarcoma of bone therefore appears to be a rare disease even if cases of multiple MFH are included.

Table 1 summarizes the clinical features of the six cases of multiple fibrosarcoma including multiple MFH and the present case. Four of the patients were elderly females, and the common presenting symptoms were pain in the involved sites and anemia. The thoracic vertebrae, ribs and lower extremities were preferably involved. Visceral metastasis was present in five cases. The tumor cell invasion into the bone marrow was diffuse in two cases and multicentric in four cases. It is likely that hematopoiesis was most severely impaired in the cases showing diffuse tumor cell infiltration into the bone marrow. In fact, the present case had severe anemia and thrombocytopenia, and also showed extramedullary hematopoiesis. It remains unclear whether extramedullary hematopoiesis is characteristic of multiple diffuse fibrosarcoma of bone as there is no information about the presence of extramedullary hematopoietic lesions for the other cases. Further studies are needed to clarify the relationship between multiple diffuse fibrosarcoma and extramedullary hematopoiesis.

Table 1. Clinical Features of Multiple Fibrosarcoma of Bone

<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Patient Age</th>
<th>Symptoms</th>
<th>Involved lesions</th>
<th>Survival after demonstration of bone lesions</th>
<th>Metastasis</th>
<th>Bone marrow invasion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Steiner</td>
<td>43 M</td>
<td>Back pain</td>
<td>Thoracic and lumbar vertebrae, ribs</td>
<td>3 months</td>
<td>Multiple viscerae</td>
<td>diffuse</td>
<td>(3)</td>
</tr>
<tr>
<td>2</td>
<td>Nielsen and Poulsen</td>
<td>69 F</td>
<td>Leg pain</td>
<td>Tibia, femur</td>
<td>1.5 months</td>
<td>Adrenals</td>
<td>multicentric</td>
<td>(4)</td>
</tr>
<tr>
<td>3</td>
<td>Hernandez and Fernandez</td>
<td>61 F</td>
<td>Back pain</td>
<td>Thoracic vertebrae, ilium, pubic, ribs, skull</td>
<td>18 months</td>
<td>None</td>
<td>multicentric</td>
<td>(5)</td>
</tr>
<tr>
<td>4</td>
<td>Chen</td>
<td>60 F</td>
<td>Back pain</td>
<td>Thoracic vertebrae, skull, ribs, femur, ilium, ischium</td>
<td>8 months</td>
<td>Lung</td>
<td>multicentric</td>
<td>(6)</td>
</tr>
<tr>
<td>5</td>
<td>Gaetani</td>
<td>72 F</td>
<td>Back pain</td>
<td>Thoracic vertebrae, skull, ribs, femur, humerus, pelvic, tibia</td>
<td>8 months</td>
<td>Liver, spleen, lymph nodes</td>
<td>multicentric</td>
<td>(7)</td>
</tr>
<tr>
<td>6</td>
<td>Ninomiya</td>
<td>38 M</td>
<td>Knee pain</td>
<td>Femur, tibia, pelvic, thoracic and lumbar vertebrae, ribs</td>
<td>13 months</td>
<td>Liver, spleen, pancreas, lymph nodes</td>
<td>diffuse (present case)</td>
<td></td>
</tr>
</tbody>
</table>
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ullary hematopoiesis.

The hematologic findings of the present case of leukoerythroblastic anemia with poikilocytosis, splenomegaly with extramedullary hematopoiesis, and apparent fibrotic change in bone marrow resemble the findings of myelofibrosis (12). It may therefore be difficult to differentiate multiple diffuse fibrosarcoma from myelofibrosis unless there is a metastatic visceral lesion or osteolytic changes. In fact, our case had neither metastatic lesions nor osteolytic changes on admission. However, the storiform arrangement of fibroblastic cells and complete replacement of hematopoietic cells by fibroblastic cells suggested a diagnosis of multiple diffuse fibrosarcoma. A careful histologic examination of a bone marrow specimen is therefore required for an accurate diagnosis. The present case suggests that this extremely rare disease should be considered in the differential diagnosis of myelofibrosis.

References