Primary Osseous Inflammatory Malignant Fibrous Histiocytoma Masquerading as Chronic Osteomyelitis

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abstract

Inflammatory malignant fibrous histiocytoma, in addition to a mass lesion, may present with fever and other constitutional symptoms, mimicking an infectious process. This article presents an extremely rare and unique case of primary osseous inflammatory malignant fibrous histiocytoma, highlighting retrospectively the subtle clinical, radiologic, and pathologic features that can suggest this diagnosis. A 63-year-old woman with a history of nephrectomy for right kidney tuberculosis 20 years ago presented with slowly increasing left hip pain for 6 months. The relatively benign-appearing radiograph and biopsy report of chronic inflammation resulted in curettage and nailing of the lesion. The pathologic diagnosis was chronic osteomyelitis, but culture findings for bacteria and tuberculosis were negative. The patient remained well until 4 months later, when left thigh pain returned with fever and leukocytosis (white blood cell count as high as 20.7×10^9/L, 80% neutrophils). No source of infection was localized. The patient showed no response to broad-spectrum antibiotics and antituberculous drugs. Radiographs showed substantial enlargement of the femoral lesion and extraosseous extension; biopsy results and review of previous histopathologic findings led to a diagnosis of inflammatory malignant fibrous histiocytoma. The fever gradually resolved and the white blood cell count returned to normal within a few days after segmental resection of the proximal femur tumor and its soft tissue extension. However, deep venous thrombosis developed, resulting in left foot ischemia and toe gangrene, necessitating left below-the-knee amputation. Disseminated metastasis occurred 3 months after tumor resection. The patient declined further aggressive treatment and died 13 months after initial presentation.

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The authors have no relevant financial relationships to disclose.

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Received: February 3, 2014; Accepted: March 25, 2014; Posted: October 8, 2014.

doi: 10.3928/01477447-20140924-92

Figure: Plain anteroposterior radiograph of the left hip showing an osteolytic lesion involving the proximal diaphysis of the left femur. The border of the lesion is relatively well defined, but erosion into the cortex, especially the medial side, is seen. There is no significant periosteal reaction.
Malignant fibrous histiocytoma, first described by Ozzello et al. and O’Brien and Stout as a high-grade pleomorphic soft tissue sarcoma of late adult life, has been considered the most common adult mesenchymal malignancy, accounting for approximately 40% of cases. With the advent of modern sensitive immunohistochemical and molecular techniques, it is now widely accepted that most previously described cases of malignant fibrous histiocytoma represent a heterogeneous group of poorly differentiated malignant neoplasms, including specific subtypes of pleomorphic sarcomas as well as non-sarcomatous tumors. For instance, in an analysis of 159 cases of malignant fibrous histiocytoma, 63% were reclassified as specific types of pleomorphic sarcoma, such as leiomyosarcomas and liposarcomas; 12.6% were reclassified as nonmesenchymal malignancies; and only 13% were morphologically compatible with malignant fibrous histiocytoma. The designation malignant fibrous histiocytoma is thus currently reserved for those high-grade pleomorphic sarcomas showing no specific differentiation. The 2013 World Health Organization classification acknowledged this category, which is estimated to account for approximately 5% of all adult sarcomas and uses the term undifferentiated pleomorphic sarcoma as synonymous with malignant fibrous histiocytoma. According to this new classification, inflammatory malignant fibrous histiocytoma, the rarest subtype of malignant fibrous histiocytoma, has the additional alternative designation of undifferentiated pleomorphic sarcoma with prominent inflammation.

Primary malignant fibrous histiocytoma of bone accounts for approximately 2.5% of all primary bone tumors. As with its soft tissue counterpart, application of immunohistochemical and molecular techniques helps in the reclassification of traditional bone malignant fibrous histiocytoma into various specific subtypes. However, malignant fibrous histiocytoma remains a definite category under the alternative and more accurate label of undifferentiated pleomorphic sarcoma.

Primary osseous inflammatory malignant fibrous histiocytoma is extremely rare. This article describes a patient with primary inflammatory malignant fibrous histiocytoma arising from the left femur masquerading as chronic osteomyelitis, emphasizing in retrospect the subtle clinical, radiologic, and pathologic features that suggest this diagnosis so that timely and appropriate treatment can be instituted.

**Case Report**

**Clinical Course**

A 63-year-old woman presented with slowly increasing left hip pain for 6 months. The patient reported no fever, no swelling or redness around the area, and no antecedent trauma. She had a history of tuberculosis of the right kidney and underwent nephrectomy 20 years earlier. In addition, she underwent abdominal perineal resection with adjuvant chemotherapy and radiation therapy for carcinoma of the rectum 3 years earlier and underwent modified radical mastectomy and tamoxifen treatment for carcinoma of the right breast 2 years earlier.

Physical examination showed no abnormality other than scars from previous surgery. Plain radiograph showed an osteolytic lesion with fairly well-defined borders in the proximal diaphyseal region of the left femur, with erosion into the medial cortex (Figure 1A). Magnetic resonance imaging (MRI) scan showed that the lesion was mildly expansile and was 2.2 cm deep, 1.9 cm wide, and 3.8 cm long. It showed inhomogeneous contrast enhancement. Endosteal scalloping and ostitis were noted and were more severe in the anterior aspect, where surrounding mild parosteal edema was noted. No definite invasion through the cortex or soft tissue extension was seen. The clinical and radiologic diagnosis was a benign bony lesion, probably fibrous dysplasia, and the differential diagnosis was chronic infection. Percutaneous needle biopsy showed reactive bone in a background of fibroblastic tissue, with infiltrates of small lymphocytes and histiocytes, suggestive of chronic inflammation. Curettage of the lesion with nailing was performed; the pathologic diagnosis was chronic osteomyelitis. Results of staining for acid-fast bacilli and fungus were negative. Results of polymerase chain reaction and culture of the lesional tissue for bacteria and tuberculosis were negative.

The patient was well until 4 months after curettage, when she was readmitted because of recurrent left thigh pain and fever. Results of blood, urine, and bone marrow cultures were negative. Echocardiogram showed no vegetation, and no source of infection could be localized. She was treated empirically with broad-spectrum antibiotics and later with antituberculous drugs, with no response. The fever was swinging in pattern and persisted occasionally up to 40°C. It was associated with leukocytosis, and the white blood cell count was as high as 20.7×10^9/L, with 80% neutrophils. Radiographs, positron emission tomography scan, and computed tomography (CT) scan showed substantial enlargement of the femoral lesion, with extraosseous extension anteriorly into the upper thigh and superolaterally into the left buttock. Biopsy of the left femoral lesion showed moderately pleomorphic spindle cells closely associated with inflammatory infiltrates. The previous slides and the entire clinical picture were reviewed; the features were most compatible with inflammatory malignant fibrous histiocytoma. Fever and leukocytosis were thus attributed to the tumor, and treatment with antibiotics and antituberculous drugs was stopped. The fever was controlled with antipyretics.

Segmental resection of the left proximal femur, including the tumor and its soft tissue extension, was performed. Pathologic examination of the tumor...
showed features of inflammatory malignant fibrous histiocytoma. The fever gradually resolved and the white blood cell count returned to normal within a few days after tumor resection. However, the postoperative course was complicated by deep venous thrombosis involving the left common femoral, upper superficial femoral, and popliteal veins. Left foot ischemia and toe gangrene developed, necessitating left below-the-knee amputation. Three months after tumor resection, CT scan showed subcutaneous nodules in the right lower chest and upper abdominal wall and right lung base, consistent with disseminated metastasis. The patient declined further aggressive treatment and finally died 13 months after initial presentation.

Pathologic Examination
The core of bone and the curettage specimen showed similar histologic features, although the curettage specimen included much more cortical bone. A spindle cell lesion infiltrated the surrounding cortical bone (Figure 1B), with focal reactive woven bone formation at the edge (Figure 1C). The spindle cells had elongated nuclei and a small to moderate amount of eosinophilic cytoplasm (Figure 1C). These cells were supported in a fibroblastic stroma and were associated with dense infiltrates of small lymphocytes and epithelioid histiocytes, but no granuloma formation was seen (Figures 1B-C). Some of the spindle cells showed moderate nuclear pleomorphism, with prominence of nuclear chromatin and nucleoli (Figure 1D). However, these cells were interpreted as reactive inflammatory atypia and the conclusion was chronic inflammation.

The biopsy specimen obtained during the second admission showed histologic features similar to those seen in the curettage specimen, but the pleomorphic spindle cells were more prominent and focally fairly closed packed (Figure 2A). They showed negative reactivity to CKAE1, CKAE3, epithelial membrane antigen, CD45, CD15, CD30, S-100 protein, HMB45, Melan-A, actin, desmin, myogenin, CD34, CD99, chromogranin, and synaptophysin. The proliferative marker Ki67 showed positive nuclear staining in approximately 30% of the spindle cells (Figure 2B). Because of the history of progressive enlargement of the lesion and persistent fever and leukocytosis in the absence of a source of infection, a diag-

Figure 1: Plain anteroposterior radiograph of the left hip showing an osteolytic lesion involving the proximal diaphysis of the left femur. The border of the lesion is relatively well defined, but erosion into the cortex, especially the medial side, is seen. There is no significant periosteal reaction (A). Curettage specimen showing infiltration of the spindle cell lesion into the cortical bone. The spindle cells are supported in a fibroblastic stroma with dense infiltrates of small lymphocytes (hematoxylin and eosin, original magnification ×100) (B). There are areas in which the spindle cell lesion is associated with both lamellar bone erosion and reactive woven bone formation (hematoxylin and eosin, original magnification ×200) (C). High-power magnification showing moderate nuclear pleomorphism of the plump spindle cells that are supported in a fibroblastic stroma. A mitotic figure is seen (green arrow) (hematoxylin and eosin, original magnification ×400) (D).
nosis of inflammatory malignant fibrous histiocytoma was made.

The resected segment of the left proximal femur was 18 cm long. A light gray-pink fleshy tumor was seen in the proximal diaphysis. It invaded through the cortex and extended into the surrounding soft tissue (Figure 2C). The tumor showed similar histologic features as were seen in the biopsy specimen, consisting of fairly closely packed pleomorphic spindle cells with prominent interspersed small lymphocytes and histiocytes supported in a fibroblastic stroma (Figure 2D). There was infiltration and destruction of the cortical bone, with focal reactive bone formation. The diagnosis was primary inflammatory malignant fibrous histiocytoma of the left proximal femur.

DISCUSSION

Inflammatory malignant fibrous histiocytoma, also known as inflammatory undifferentiated pleomorphic sarcoma, is a rare tumor that was first described in 1976 by Kyriakos and Kempson9 as inflammatory fibrous histiocytoma to highlight the intense inflammatory infiltrates in the tumor in the absence of infectious agents. In a description of a similar case in the abdomen of a 13-year-old girl in 1980, Merino and LiVolsi10 coined the term inflammatory malignant fibrous histiocytoma to designate its aggressive nature. This sarcoma is characterized histologically by close association of the tumor cells with a diffuse and intense inflammatory infiltrate that consists of neutrophils and/or small lymphocytes and variable numbers of eosinophils in the absence of tissue necrosis and any recognized source of infection.9 Although the retroperitoneal cavity is the most common site, the tumor occurs very rarely in almost any part of the body, including the kidney,11-12 colon,13 gallbladder,14 and thymus.15 In addition to the typical local symptom of a rapidly growing painful mass, many patients present with fever and other constitutional symptoms mimicking an infectious process. Further, these tumors usually are large and pursue a highly aggressive clinical course characterized by multiple local recurrences, metastasis, and ultimately death.9

Primary inflammatory malignant fibrous histiocytoma of bone is extremely rare. To the authors’ knowledge, only 1 case has been reported.16 A 29-year-old man had severe back pain 17 weeks after the initiation of chemotherapy for acute lymphoblastic leukemia. The pain lasted for 2 weeks and was associated with fever...
of 38.5°C, nausea, vomiting, and restless-ness. Findings on lumbar spine radiograph were normal, but gallium isotope scan showed an area of increased uptake at L1-L2. With the presumptive diagnosis of paravertebral abscess, the patient was given broad-spectrum antibiotic therapy, with resolution of the fever. However, pyrexia and back pain returned 4 weeks later, despite continued antibiotic therapy. Plain radiographs showed destruction of the right lateral part of the body, pedicle, and transverse process of L1. Gallium scan showed significant enlargement of the previous area of increased uptake. Surgical exploration was undertaken, and a tumor involving L1 was found but was only partially resectable. The tumor was histologi-cally diagnosed as inflammatory malign-ant fibrous histiocytoma. The patient was given local radiation therapy and systemic chemotherapy but had metastatic lesions in both knees and ankles 8 months later.

The relatively long history of progres-sive left knee pain for 6 months in the current patient, coupled with the fairly well-circumscribed nature of the oste-lytic lesion on both plain radiographs and MRI scan, misled the orthopedic surgeon and radiologist to the diagnosis of benign bone lesion, probably fibrous dysplasia. In the percutaneous biopsy and curettage specimen, the lower-power pattern of a fibroblastic lesion with evenly admixed small lymphocytes and histiocytes, together with a history of previous kidney tuberculosis in the authors’ locality, where such disease was still prevalent, misled the pathologist to the conclusion that the patient had a chronic inflammatory lesion for which tuberculosis needed to be excluded. When the lesion continued to enlarge and resulted in pyrexia and leukocytosis that did not respond to broad-spectrum antibiotics and antituberculous drugs, and in the absence of detectable infection, the possibility of inflamma-tory malignant fibrous histiocytoma was recognized in the second percutaneous biopsy specimen. In that specimen, the more closely packed plump spindle cells with moderately pleomorphic nuclei, the absence of specific differentiation, and the high mitotic index on Ki67 staining made the diagnosis of inflammatory malignant fibrous histiocytoma most likely.

In retrospect, although making a diag-nosis of inflammatory malignant fibrous histiocytoma might not have been feasible through examination of the initial biopsy and curettage specimen, inflammatory malignant fibrous histiocytoma should have been included in the differential di-aagnosis when all of the clinical, radiologic, and pathologic features were carefully analyzed. Although the lesion, with its relatively well-circumscribed radiologic appearance, had appeared to be a benign lesion of fibrous dysplasia, this diagnosis was not supported by the histologic biopsy findings. Likewise, interpretation of the fibroblastic lesion with evenly admixed small lymphocytes and histiocytes as chronic inflammation was not compatible with the clinical history of an afebrile pa-tient and the radiologic features of a well-circumscribed lesion with no periosteal reaction, sequestrum, or involucrum. In the context of an inflammatory lesion, the radiographic features are more suggestive of Brodie’s abscess. However, the typi-cal histologic features of central acute in-flammatory infiltrates, mostly neutrophils bordered by granulation tissue and reactive bone, were not seen in the biopsy specimen. These atypical features and discrep-ancies, especially the histopathologic features, should have prompted a critical review of the case. The moderate nuclear pleomorphism of the plump spindle cells, the presence of mitotic figures, and the finding of desmoplastic rather than loose edematous granulation stroma (Figures IC-D) suggested an intermediate-grade myofibroblastic neoplasm. In this case, segmental resection rather than curettage would be more appropriate for both diag-nosis and treatment.

Inflammatory malignant fibrous histo-cytoma in unusual sites, such as bone, in the current patient posed a formidable challenge to the diagnostic surgical pathologist. In a report by Singh et al., a 58-year-old patient with a left renal mass presented with left flank pain, fever, and leukocytosis of 29×10⁹/L. Radical left nephrectomy was performed, and the pathologic diagnosis was xanthogranulo-matous pyelonephritis. The patient gradually recovered, but had fever and left-sided chest pain 3 months after surgery. A CT scan showed left lower zone loculated empyema thoracis that was drained, with improvement of symptoms. The drainage tissue showed features of nonspecific chronic inflammation. However, the patient returned 2 months later with left flank pain, and CT scan showed tumor nodules in the left renal fossa, lesser sac, and left posterior thoracic cavity. Histopathologic examination of a biopsy specimen of the nodules and review of the previous renal tumor led to a diagnosis of inflammatory malignant fibrous histiocytoma. The tumor cells were masked by the intense inflammatory infiltrates.

Two pertinent clinical features of in-flammatory malignant fibrous histiocytoma are shown in the current patient: its association with pyrexia accompanied by significant leukocytosis and a second malignancy. The former is a result of the sys-temic effects of the various cytokines and growth factors elaborated by the tumor. Through these constitutional symptoms, including fever and malaise, and hiding of the neoplastic cells among heavy inflam-matory infiltrates, these tumors disguise themselves as inflammatory lesions. The association of malignant fibrous histiocytoma with a second malignancy was well recognized shortly after its description. In their analysis of 200 cases of malignant fibrous histiocytoma, Weiss and Enzinger found that 13% of patients had a second neoplasm, notably hematopoietic disease, including leukemia, Hodgkin’s disease, non-Hodgkin’s lymphoma, and multiple myeloma. Including the current patient, the 2 reported cases of primary
osseous inflammatory malignant fibrous histiocytoma were associated with a second malignancy. In the patient described by Woodcock et al., malignant fibrous histiocytoma presented 17 months after the initiation of chemotherapy for acute lymphoblastic leukemia, and the current patient had a history of carcinoma, including carcinoma of the rectum 3 years earlier and carcinoma of the breast 2 years before the current presentation. The short intervals between their occurrences do not lend support to a causal relationship between the effects of chemotherapy and radiation therapy and the development of inflammatory malignant fibrous histiocytoma.

Finally, as with its soft tissue counterpart, the clinical course of primary osseous inflammatory malignant fibrous histiocytoma is highly aggressive, resulting in bilateral lower-limb metastasis in the patient reported by Woodcock et al. 8 months after presentation and rapid local growth, disseminated metastasis, and death of the current patient 13 months after presentation.

CONCLUSION

Inflammatory malignant fibrous histiocytoma, despite its rarity, merits recognition and inclusion in the differential diagnosis in patients with atypical chronic inflammatory lesions. Timely wide local resection appears to be the best treatment for favorable long-term outcome.

REFERENCES