Orthopaedic Case of the Month

Recurrent Thigh Pain in a 44-Year-Old Man

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History and Physical Examination

A 44-year-old man presented with progressively worsening left thigh pain of 8 years' duration. The patient's medical history was significant for a diagnosis of osteoid osteoma of the left femur treated elsewhere 24 years previously. At that time, the patient underwent open incisional biopsy (Fig. 1), curettage, and autogenous iliac crest bone grafting without stabilization. The patient had no complications after surgery and was in good health until 8 years before this visit when he began to experience intermittent left

thigh pain which gradually increased in frequency and severity. By the time the patient presented to us, he described a dull pain present most of the time punctuated by intermittent sharp pain. The patient could not identify any particular palliative or provocative factors for the pain. Acetaminophen provided minimal relief. He had experienced some decrease in his energy level but denied any fevers, chills, night sweats, skin changes, abdominal pain, diarrhea, unintentional weight loss, or decrease in appetite.

On physical examination, the patient appeared healthy and had a normal gait. He had full active and passive ROM of the left hip, knee, and ankle without limitation. Motor testing and sensation in the left lower extremity were normal. Distal pulses were present and normal in the left lower extremity. There was exquisite tenderness to palpation over a several-centimeter diameter region of the anterior and lateral left mid-thigh, but there was no palpable mass in that extremity or any skin lesions at this site or elsewhere. The patient had increased thigh pain with provocative testing, including resisted hip flexion, extremes of hip rotation, and with full passive hip flexion.

One month before presentation to our institution the patient had sought care from his primary care physician. The physician ordered radiographs (Fig. 2). A CT scan (Fig. 3) and bone scan (Fig. 4) were obtained subsequently and the patient was sent to us for additional orthopaedic care.

Based on the history, physical examination, and imaging studies, what is the differential diagnosis at this point?

Imaging Interpretation

The radiographs (Fig. 2) and CT images (Fig. 3) of the left femur showed a geographic 3-cm diaphyseal radiolucency

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All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research* editors and board members are on file with the publication and can be viewed on request. Each author certifies that his or her institution approved the reporting of this case report, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained. This work was performed at Upstate Medical University.

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Fig. 1 A histologic section from the nidus of the originally curetted lesion shows haphazardly arranged bone trabeculae with osteoblastic rimming and surrounded by a background of loose vascular tissue. These features are consistent with the nidus of an osteoid osteoma given the accompanying radiographic findings.

Fig. 2A–B (A) AP and (B) lateral radiographs of the femur show a radiolucent lesion in the diaphysis with expansion of the bone but with intact cortices.

Fig. 3A–B (A) Axial and (B) coronal CT images of the femur show a 3-cm diaphyseal lesion with intracortical and intramedullary involvement.

with slight expansion of the bone but intact cortices. The epicenter of the lesion was intracortical, but with some intramedullary involvement. There was no calcification or substantial periosteal reaction. The bone scan revealed modest increased uptake at this site but nowhere else in the skeleton (Fig. 4).

Differential Diagnosis

Osteoblastoma

Recurrent osteoid osteoma

Fig. 4 A full skeletal bone scan shows slight increased uptake in the left femur.

Brodie's abscess
 Langerhans' cell histiocytosis
 Solitary plasmacytoma
 Lymphoma
 Rosai-Dorfman disease
 Extracutaneous mastocytoma

An open biopsy with frozen section was performed. The biopsy revealed a friable, soft, cherry-red area of tissue subcortically. Based on the intraoperative histologic evaluation (Fig. 5), curettage, grafting, and prophylactic plate stabilization were performed.

Based on the history, physical examination, imaging studies, and histologic picture, what is the diagnosis and how should this patient be treated?

Histology Interpretation

Microscopy of the excised mass revealed trabecular bone with patchy areas of fibrosis with lymphoid aggregates and clusters of cells with spindle- to oval-shaped nuclei and clear cytoplasm. Some of these cells had cytoplasmic granules consistent with typical mast cells. The mast cell aggregates, comprising 30% of the cellularity and occupying 10% of the marrow, were located adjacent to bony trabeculae and surrounded by a rim of small lymphocytes (Fig. 5A). Immunohistochemistry revealed strong expression of tryptase (Fig. 5B), CD117 (Fig. 5C), CD25 (Fig. 5D), and CD68 in the mast cells. Toluidine blue highlighted the presence of sparse cytoplasmic granules [11, 15]. Staining for CD1a and S-100 protein (Langerhans' cell markers) [3], and CD38 and CD138 (plasma cell markers) [24], were negative. The small aggregates of lymphocytes were positive for B and T cell markers (CD20 and CD3, respectively). Because of the slight predominance of B cells, the possibility of systemic mastocytosis with associated clonal hematologic nonmast cell lineage disease (SM-AHNMD, WHO Classification) [1] was considered. However, subsequent flow cytometry of a bone marrow biopsy obtained a month later showed no evidence of leukemia or lymphoma.

Diagnosis

Extracutaneous mastocytoma.

Discussion and Treatment

This rare occurrence of extracutaneous mastocytoma was made based on the characteristic pathology findings of aggregates of mast cells with characteristic

intracytoplasmic granules confirmed as such by immunohistochemistry. Although there is nothing specific about the clinical and radiographic presentation in this patient, the occurrence of mastocytoma as an isolated bone lesion is a rare but described entity. This is an unusual case that emphasizes the importance of maintaining a broad differential diagnosis when dealing with patients with solitary bone lesions.

The patient's prior diagnosis of osteoid osteoma, albeit remote but confirmed by review of the original slides, combined with clinical symptoms of nonspecific femoral bone pain, made recurrent osteoid osteoma or osteoblastoma candidates in the differential diagnosis. The radiographic evidence of a radiolucent diaphyseal lesion with intact cortex was consistent with either of these diagnoses [12]. However, local recurrence after surgical treatment of osteoid osteoma is rare, and given the self-limited nature of its growth, it is not believed to progress to osteoblastoma, the latter being distinguished by its larger size and greater growth potential [12]. Osteomyelitis also was included in the differential diagnosis owing to the similarity in clinical picture and radiographic appearance and could have resulted from seeding at the previous operative site at the time of the remote procedure or subsequently. Local tenderness with a lack of systemic symptoms is the hallmark for Brodie's abscess, and the radiographic appearance is notoriously difficult to distinguish from neoplastic bone lesions [17]. Radiographically solitary lytic lesions with associated bone pain have been described in cases of plasmacytoma [18]. In these cases, there is a predilection for male patients and involvement of the axial skeleton with absence of hypercalcemia, anemia, or renal impairment [8]. Langerhans' cell histiocytosis could not be ignored as patients with bone involvement present with pain and swelling of the affected area. Lymphoma of bone often involves the diaphysis and presents with localized bone pain, but it typically appears radiographically as a more diffuse, permeative lytic process, often with an associated soft tissue mass [14]. Rosai-Dorfman disease typically presents with bilateral cervical lymphadenopathy, but in 2% of cases can present as isolated extranodal bone disease [16, 19]. In cases with bone involvement, osteolytic lesions predominate [16, 19]. Histologically, Rosai-Dorfman disease is characterized by large histiocytes showing emperipolesis (lymphocytophagocytosis).

Radiographically, lesions of mastocytosis appear lytic with poorly defined margins, making them difficult to distinguish from malignancy. Although any bone may be affected, $\frac{1}{3}$ of lesions involve long bones, and the metaphysis is most commonly affected [3]. Finally, mastocytosis, although rare, can present with isolated bone pain and solitary osteolytic lesions on radiographs [9]. This would not usually be included in the differential given the

Fig. 5A–D (A) A histologic section shows bone with patchy areas of fibrosis with lymphoid aggregates and a proliferation of clusters of plump spindle- and oval-shaped cells, some of which exhibit clear cytoplasm. Adjacent to these areas, eosinophils and myeloid cells are present (Stain,

hematoxylin and eosin; original magnification, $\times 20$). (B) Tryptase stain highlights the abundance of mast cells (original magnification, $\times 50$). Immunohistochemistry reveals strong expression of (C) CD117 and (D) CD25 by mast cells (original magnification, $\times 50$).

lack of systemic involvement. However, given the histologic findings, it was included.

Mastocytosis is a rare disease of abnormal growth and accumulation of mast cells in one or more organs that is diagnosed histologically by identification of proliferation of the characteristic mast cells in involved areas [22]. The disease most commonly involves the skin, but other organ systems such as the gastrointestinal tract, spleen, bone, bone marrow, liver, and lungs often can be involved [2, 13]. The clinical spectrum of mastocytosis is broad, ranging from a cutaneous form that may resolve spontaneously to an aggressive systemic form that may progress rapidly to leukemia [1]. As mast cells play an integral part in Type I hypersensitivity reactions, many of the clinical features of mastocytosis are related to the release of histamine and other mediators [15]. Urticaria, recurrent flushing, pruritis, cramping abdominal pain, palpitations, and vascular collapse have been reported as clinical manifestations of the disease [2]. The clinical presentation of systemic mastocytosis is diverse owing to the broad spectrum of the disease. Cutaneous disease is marked by the appearance of urticaria pigmentosa, the most common skin manifestation.

Skin lesions tend to be maculopapular with involvement of the trunk, abdomen, and extremities and may be solitary, multiple, or diffuse. Irritation through stroking or scratching these lesions induces local edema and urticaria, referred to as Darier's sign. The majority of cases, estimated at 65%, are seen in the pediatric population. Childhood onset of the disease portends a favorable prognosis with a majority of cases regressing spontaneously whereas adult-onset disease typically persists [20, 21]. Patients with systemic mastocytosis tend to present with symptoms related to the response of tissues attributable to mediators released by mast cells and the local mast cell burden. Pruritis, flushing, syncope, gastrointestinal distress, nausea, vomiting, diarrhea, bone pain, and neuropsychiatric symptoms have been described [5, 20].

The reported incidence of skeletal manifestations in patients with systemic mastocytosis ranges from 28% to 75% [4, 9, 21]. Skeletal manifestations rarely may be the first presenting symptom, as was the case in our patient. Typically, skeletal lesions result in poorly localized bone pain and tend to be most prevalent in the long bones [15]. However, they also may be discovered as incidental

findings in asymptomatic patients. Osteopenic, lytic, or sclerotic changes may be seen and may be misinterpreted as osteoporosis, metastatic disease, multiple myeloma, or Paget's disease of the bones [5]. Bone scans typically show increased uptake [7].

Mast cells are bone marrow precursors of myeloid lineage. The key player in inducing mast cell differentiation is the KIT ligand. Mast cells express a cell surface marker, KIT (CD117), the receptor for KIT ligand, and the interaction between the two promotes proliferation, maturation, survival, and enhanced mast cell activation [23]. Gain of function mutations in *KIT*, which allow it to become independently activated, have been found frequently in patients with mastocytosis. The most common is a substitution mutation at codon 816 of the c-kit protein sequence [10]. Other mutations exist as well, and the identification of *KIT* mutations has become a prognostic indicator for treatment. Protein kinase inhibitors, such as imatinib, provide limited symptom relief in patients with the D816 V mutation but are reportedly useful in controlling symptoms and disease progression in patients with other mutations [1]. Histologically, extracutaneous mastocytomas show perivascular accumulation of mast cells with spindle or spherical forms [6]. Special stains such as toluidine blue, Giemsa, and naphthol-AS-D-chloroacetate esterase are typically positive in mast cells. Immunohistochemistry offers more specificity [9, 15], however, and usually shows positive results for CD117, tryptase, and CD68. Chymase is observed only in a subpopulation of mast cells. Neoplastic mast cells exhibit an immunophenotype similar to typical mast cells but in addition are positive for CD25. In this case, morphologic features, along with positive results for CD117, tryptase, CD68, and toluidine blue, with negative staining for CD1a and S-100 protein, confirmed the diagnosis.

The treatment of extracutaneous mastocytoma is highly individualized. The main treatment of indolent cases is complete resection of the lesion and avoiding triggers of mast cell degranulation. Therapy is supportive with histamine 1 and histamine 2 receptor blockers for pruritis and gastric symptoms, and cromolyn sodium for gastrointestinal symptoms [9, 15]. Owing to the indolent nature of disease and lack of other systemic symptoms, our patient underwent resection with synthetic bone grafting along with stabilization. At last followup at 1.5 years, the patient was being treated with supportive therapies, experiencing no local pain, and showing no radiographic signs of local disease recurrence.

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