Chronic Ankle Pain and Swelling in a 25-year-old Woman

An Unusual Case

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Received: 16 October 2010 / Accepted: 23 February 2011 / Published online: 15 March 2011
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History and Physical Examination

A 25-year-old woman with no medical history presented with a 2-month history of nontraumatic ankle pain and swelling. She attempted ankle bracing and antiinflammatory medication, which decreased the pain but failed to resolve it. She denied any fevers or chills.

On physical examination, the ankle was mildly swollen anterolaterally without erythema. Her ankle was markedly tender over the lateral border of the talus. There was no warmth on palpation. She had full ROM at the ankle and had intact sensation, motor strength, and pulses. She had no signs of adenopathy.

Laboratory studies were negative. The patient was referred to our clinic because a lytic lesion of the talus was identified on initial radiographs (Fig. 1).

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

Imaging Interpretation

MR images showed a large lesion in the lateral aspect of the talus extending to the articular surface of the lateral talar dome (Fig. 2). This heterogeneous mass had low signal intensity on T1-weighted images and mixed intensity on T2-weighted images with mild to moderate heterogeneous postcontrast enhancement. Although there was mild perifocal edema surrounding the lesion, no bony expansion or discrete cortical destruction was identified.

Her CT scans (Fig. 3) showed a large intraosseous lesion measuring $3.2 \times 2.5 \times 2.0$ cm occupying approximately 40% of the talus. Some of the borders appeared slightly irregular and sclerotic. An open biopsy and histologic studies were performed (Fig. 4). Based on the history, physical examination, laboratory studies, imaging studies, and histologic picture, what is the diagnosis and how should this patient be treated?

Differential Diagnosis

Osteomyelitis
Bone cyst
Lymphoma
Giant cell tumor
Chondroblastoma
Clear-cell chondrosarcoma
Plasmacytoma
Rosai-Dorfman disease

Histology Interpretation

Microscopic analysis of the mass revealed a heterogeneous infiltrate of histiocytes, lymphocytes, and plasma cells with

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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.

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Fig. 1A–C (A) AP, (B) mortise, and (C) lateral views of preoperative ankle radiographs show a large cystic lesion in the lateral talus.

Fig. 2A–C (A) Coronal, (B) sagittal, and (C) axial T2-weighted MR images of the ankle show a large mixed signal intensity lesion in the lateral talus.

Fig. 3A–C (A) Coronal, (B) sagittal, and (C) axial CT images of the ankle show a large cystic lesion of the lateral talus with sclerotic margins.

some histiocytes showing intact lymphocytes in their cytoplasm (Fig. 4A). Immunohistochemical analysis had a positive S-100 stain (Fig. 4B). Cytologic touch

preparations stained with Diff-Quik (Baxter Diagnostics Inc, Deerfield, IL, USA) showed phagocytosis of intact lymphocytes (Fig. 4C).

Fig. 4A–C (A) A histologic section shows sheets of histiocytes with abundant foamy cytoplasm admixed with small lymphocytes (Stain, hematoxylin and eosin; original magnification, $\times 200$). Emperipolesis can be seen. (B) S-100 protein immunostain shows numerous positively staining histiocytes (Original magnification, $\times 200$). (C) Cytologic touch preparations stained with Diff-Quik (Baxter Diagnostics Inc, Deerfield, IL, USA) show numerous histiocytes intermixed with lymphocytes and plasma cells (Original magnification, $\times 1000$). Two histiocytes show emperipolesis (black arrows). An osteoclastlike giant cell is also present.

Diagnosis

Rosai-Dorfman disease of the talus (RDD)

Discussion and Treatment

The finding of emperipolesis, a phenomenon characterized by phagocytosis of intact lymphocytes or plasma cells by histiocytes, was diagnostic and was best observed on the cytology. The histiocytes in our biopsy specimen, as contrasted to reactive histiocytes typical of an infectious process, were characteristically positive for S-100 protein.

Although osteomyelitis was a possibility, it was unlikely given the patient's uneventful medical history and lack of local trauma near the talus. Although there was swelling, she did not have any warmth, erythema, fevers, or chills. Her laboratory tests were normal (including CBC, ESR, and CRP), which also is not consistent with osteomyelitis. Histologic analysis confirmed she did not have an infectious process.

Aneurysmal and unicameral bone cysts also were plausible given the lucent appearance of the lesion on radiographs. However, the lesion was not expansile. Typically, unicameral bone cysts are mildly expansile and aneurysmal bone cysts are more expansile. The MR images of aneurysmal bone cysts also will have fluid-fluid levels, which was not consistent with our patient's findings. Lymphoma was unlikely as it is associated with radiographs showing a permeative lesion and areas of cortical thickening, which was not seen in this patient. Her histologic specimens also did not have a large proliferation of blue, round cells typically seen in lymphoma. Giant cell tumor was higher on the differential given the age and gender of the patient, and the juxtaarticular location of the lesion. However, the histologic features of giant cell tumors will have multinucleated giant cells dispersed throughout a sea of mononuclear cells. This description did not resemble the findings for our patient. Chondroblastoma generally occurs in patients between 10 to 20 years old. Given the young age of our patient, this is certainly a plausible diagnosis. This lesion commonly arises in the proximal humerus, femoral condyles, and tibial plateau. However, it also may occur in the tarsal bones and the iliac crest. Radiographs show a radiolucent lesion with a thin rim of well-margined bone, which was seen in our patient. However, histologic analysis will reveal islands of hyaline cartilage and characteristic "chicken wire" calcification. This description did not match the histologic specimen taken from our patient. Clear-cell chondrosarcoma can occur in a wide age range of patients, and has a predilection for the proximal humerus and femoral head.

It can resemble a giant cell tumor or chondroblastoma on radiographs with a radiolucent lesion with a thin rim of reactive bone. Microscopic features include lesional cells that are large and have clear cytoplasm. These cells are commonly admixed with clusters of benign-appearing giant cells. None of these histologic features are consistent with our case presentation. Plasmacytomas are more common in the 50- to 60-year-old age group and usually present in the vertebra, ribs, or pelvis. The patient denied any pain in any of these locations. Our patient had no systemic manifestations associated with plasmacytoma including anemia, renal insufficiency, hypercalcemia, or peripheral neuropathy. Moreover, there was no proliferation of plasma cells observed on histologic analysis.

RDD is a rare self-limited pseudolymphomatous disorder that can present with isolated osseous involvement, and has been reported in the skull, spine, femur, radius, ulna, metacarpals, and talus [10, 13]. The condition often is misdiagnosed, leading to delays in treatment. Initially described by Rosai and Dorfman [13] in 1969, RDD, also known as sinus histiocytosis with massive lymphadenopathy, is a rare nonneoplastic histiocytic disorder of unknown etiology. It most commonly presents as a bilateral, nontender, painless, cervical lymphadenopathy, which may be accompanied by fever, elevated sedimentation rate, weight loss, and immunologic abnormalities such as leukocytosis, polyclonal hypergammaglobulinemia, and anemia. Less frequently involved nodal sites are mediastinal and hilar (30%–40%), retroperitoneal and axillary (38%), and inguinal (44%) [2, 3, 11, 14]. Extranodal RDD occurs in 43% of patients, with 23% experiencing isolated extranodal disease [6].

The mean age of onset is 20.6 years among the 395 patients in the RDD database for which age was designated [6]. This condition is slightly more common in males than females by a ratio of 4:3 and has a higher prevalence in African Americans compared with Caucasians [3, 4, 14]. Hsiao et al. [9] reported a greater rate of extranodal involvement in Taiwanese patients along with a higher age of onset.

Definitive diagnosis of RDD, initially described by Goel et al. [7], is accomplished through detection of CD68 and S-100 protein positive histiocytes and by microscopic analysis showing emperipolesis. Compared with the presentation in lymph nodes, osseous RDD has less pronounced lymphophagocytosis and has more fibrosis [15].

Although only approximately 1000 patients have been reported with this disorder [2, 3, 14], less than 3% of those cases include isolated osseous involvement [6, 13]. In the registry of 423 patients reported by Foucar et al. [6], 8% had bone involvement, 2% had bone involvement without lymphadenopathy, and approximately 0.5% had isolated

bone involvement. The skull is the most common location of a solitary bone lesion [1].

The disease can affect extranodal sites in approximately 28% of patients [6]. The common sites of extranodal involvement include the orbit, eyelid, upper respiratory tract, salivary glands, skin, testes, and bone. As stated above, isolated osseous involvement is rare. In a review of the literature, 32 of 40 patients with RDD had spontaneous regression with nonoperative management [12], whereas three of nine patients treated with radiotherapy had regression. In eight of nine patients treated surgically there was no evidence of recurrence at the time of followup. Demicco et al. reported on the largest series of patients with primary intraosseous RDD [5]. This series included 15 cases. They had followup information for 12 patients. Five patients remained disease-free after an average followup of 51.6 months (range, 12–106 months). Five patients had extraosseous lesions develop, including testicular, lymph node, and subcutaneous manifestations. One patient had multiple lesions in the hand and wrist bones. Another patient had stable nonprogressive disease in the bone. We found two similar cases of extranodal RDD with primary lesions located in the talus and extending to adjacent bones. The first case, by Abdelwahab et al. [1] in 2004, involved a 63-year-old woman who complained of progressive pain in her left ankle and, after a biopsy early during the course of the disease, was misdiagnosed as having osteomyelitis and given antibiotics. She presented 25 years later on crutches with progressive swelling and intermittent flares of pain. MRI revealed a heterogeneous low-intensity signal on T1-weighted images of the talus with extension into the calcaneus, navicular, and surrounding soft tissue. The second case [8] is of a 64-year-old woman with a 6- to 8-month history of left ankle pain and swelling after a relapsing remitting course. After the initial evaluation, she was lost to followup for 4.5 years and presented once again with continued pain and swelling. MRI at baseline, 4.5 years, and 7 years showed progressive growth of multiple lesions with heterogeneous low-intensity signal on T1-weighted images eventually replacing the marrow of the talus, navicular, calcaneus, and portions of the cuboid and lateral cuneiform with extension into adjacent soft tissue.

After initial open biopsy, we performed an arthroscopy in our patient. We believed the arthroscopy was indicated because of the suggestion of pigmented villonodular synovitis on the pathology report. We débrided a moderate amount of reactive synovial lining from the anterior aspect of the ankle, then exposed the talus and used a high-speed burr to open a nonarticular portion of the bone. The defect was debulked and margins were extended with a high-speed burr followed by electrocautery. The wound was lavaged and subsequently packed with bone graft substitute. Cultures of the biopsy specimen were negative for

Fig. 5A–C (A) AP, (B) mortise, and (C) lateral radiographs taken at the 11-month followup show complete consolidation of the defect with bone.

any infectious process. At the 11-month postoperative followup, the patient was fully recovered and had returned to normal activities. She had no pain and was able to run. Radiographs revealed complete consolidation of the defect with bone (Fig. 5).

Acknowledgments We thank Michelle Collier MD for assistance with preparation and interpretation of the histologic specimens.

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