

Case Report

Multifocal Epithelioid Hemangioma with Reactive Bone Formation

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A healthy 16-year-old male patient presented with several weeks of right ankle pain on weight-bearing, worsened with sporting activities, and relieved with rest. Radiographs demonstrated multiple well-marginated lytic lesions in the right distal tibia, and talar head and neck, with a further small intracortical lesion in the mid-to-distal anterior tibia. MRI showed multiple rounded low T1 and high T2 signal intensity lesions within the distal tibia and talus, with marked associated bone marrow edema. The radiologic diagnoses included multifocal hemangioendothelioma, multifocal hemangioma, angiosarcoma, atypical infection, Langerhans cell histiocytosis, or osteoblastomatosis. Histology showed sheets of epithelioid cells lining vascular structures in a hobnailed “tombstone-like” arrangement, with additional areas containing trabeculae of osteoid and woven bone, with prominent osteoblastic rimming. The differential diagnosis at this point was either multifocal epithelioid hemangioma of bone or osteoblastomatosis. Immunohistochemistry showed strong expression of the vascular marker CD31, supporting a vascular neoplasm. The final diagnosis was multifocal epithelioid hemangioma with prominent reactive bone formation, an extremely unusual tumor with only one other similar case of multifocal disease reported in the literature. The patient was treated with curettage, cryosurgery, and bioceramic replacement and is currently doing well.

1. Introduction

Epithelioid hemangioma (EH) is a relatively common benign vascular tumor that usually occurs within the skin or subcutaneous tissues [1]. Less frequently, it can also occur in bone [2–9]. Radiographically, osseous EH lesions are seen as lytic lesions, or mixed lytic and sclerotic lesions within single or multiple bones. Histologically, the lesion is characterized by vascular channels lined with large cuboidal epithelioid endothelial cells that have abundant eosinophilic cytoplasm. The endothelial cells protrude into the vascular lumens in a characteristic “tombstone-like” manner. The differential diagnosis for benign EH includes intermediate-grade malignant epithelioid hemangioendothelioma (EHE), high-grade malignant epithelioid angiosarcoma (EA), and metastatic carcinoma. It can often be difficult to differentiate EH from these more malignant conditions, but since the prognosis for each of these diseases is different, accurate diagnosis is necessary to determine an appropriate therapeutic course. We describe a diagnostically challenging case of

multifocal EH with prominent osteoblastoma-like reactive bone formation.

2. Case Report

A healthy 16-year-old male patient presented with several weeks of right ankle pain on weight-bearing, worsened with sporting activities, and relieved with rest. He had no signs or symptoms of infection and no exposure to coccidiomycosis or tuberculosis. His past clinical history was unremarkable. His family history was notable for lupus in his mother, but it was otherwise negative for malignancy. Physical exam revealed slight tenderness to palpation around the right ankle and talus but no edema, joint effusion, or soft tissue mass. The patient had full range of motion in his ankle joint and no pain with movement. There was no popliteal or inguinal adenopathy, and his abdominal exam was normal without evidence of hepatosplenomegaly. Laboratory findings were unimpressive with a normal white

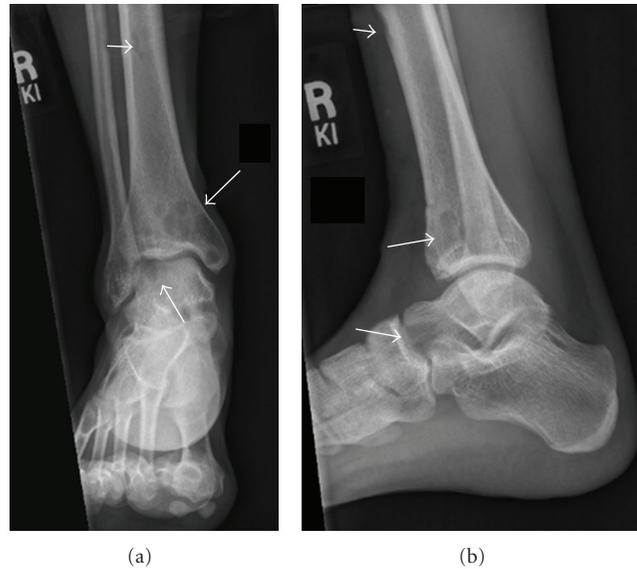


FIGURE 1: (a) AP and (b) lateral radiographs of the right ankle demonstrating multiple well-margined lytic lesions in the right distal tibia, and the talar dome, head, and neck (arrows). There is a further small intracortical lesion in the mid-to-distal anterior tibia with erosion of the cortex (small arrow).

blood cell count and normal erythrocyte sedimentation rate (ESR).

A conventional radiograph demonstrated three well-margined lytic lesions in the right distal tibia, talar head, and talar neck (Figure 1). Furthermore, there was a small intracortical lesion in the mid-to-distal right anterior tibia. MRI showed multiple rounded low T1 and high T2 signal intensity lesions within the right distal tibia and talus, with marked associated bone marrow edema (Figure 2). The radiologic diagnoses included multifocal hemangioendothelioma, multifocal hemangioma, angiosarcoma, atypical infection, Langerhans cell histiocytosis, or osteoblastomatosis.

All biopsy tissues were fixed in 10% neutral-buffered formalin, dehydrated in graded alcohols, cleared in xylene, and embedded in paraffin. Histologically, there were two distinct areas within the tumor (Figure 3), the first containing irregular bony trabeculae, and the second with prominent cellular proliferation.

The bony portion of the tumor demonstrated numerous trabeculae of osteoid and woven bone, with prominent osteoblastic rimming (Figure 4).

The findings in this portion of the tumor were suggestive of osteoblastoma, and given the patient's history of multiple lytic lesions, these findings would be compatible with osteoblastomatosis of bone [10]. However, the cellular portion of the tumor demonstrated sheets of epithelioid cells lining vascular structures in a hobnailed "tombstone-like" arrangement (Figure 5). The background stroma was hypervascular with abundant osteoclast-like giant cells. There was no significant nuclear pleomorphism, mitotic activity (up to 1 mitotic figure/10 high-powered fields), necrosis, or dense lace-like osteoid to suggest a diagnosis of osteosarcoma.

Based on the histologic findings, the differential diagnosis included osteoblastomatosis of bone or epithelioid hemangioma. Whole tumor sections for immunohistochemistry were cut at 4 mm, deparaffinized in xylene, and rehydrated through graded to distilled water before undergoing antigen retrieval by heat treatment. Immunohistochemistry was performed and showed that these epithelioid cells lining the capillaries strongly expressed the vascular marker CD31 (DAKO clone JC70A, 1 : 150 dilution, EDTA pretreatment) (Figures 3(b) and 3(c)) with no expression of CD34 (clone My10, BD Biosciences, 1 : 20 dilution, EDTA pretreatment) or S100 (clone 16, BD Biosciences, 1 : 25 dilution, citrate pretreatment), providing support for a vascular neoplasm. Since no myxochondroid-like stroma or features typical of high-grade epithelioid vascular tumors were found, such as epithelioid hemangioendothelioma, the final diagnosis was multifocal epithelioid hemangioma with prominent osteoblastoma-like reactive bone.

The patient was then treated with curettage, cryosurgery, and bioceramic replacement (Figure 6) and is currently doing well 3 years later, with no evidence of recurrence.

3. Discussion

According to some experts, vascular tumors of the bone can be divided on the basis of histological and clinical features into three categories: benign hemangiomas, intermediate-grade malignant hemangioendotheliomas, and malignant angiosarcomas [11]. When epithelioid hemangioma (EH) of the bone is suspected, the differential diagnosis can include epithelioid hemangioendothelioma (EHE), epithelioid angiosarcoma (EA), and metastatic carcinoma.

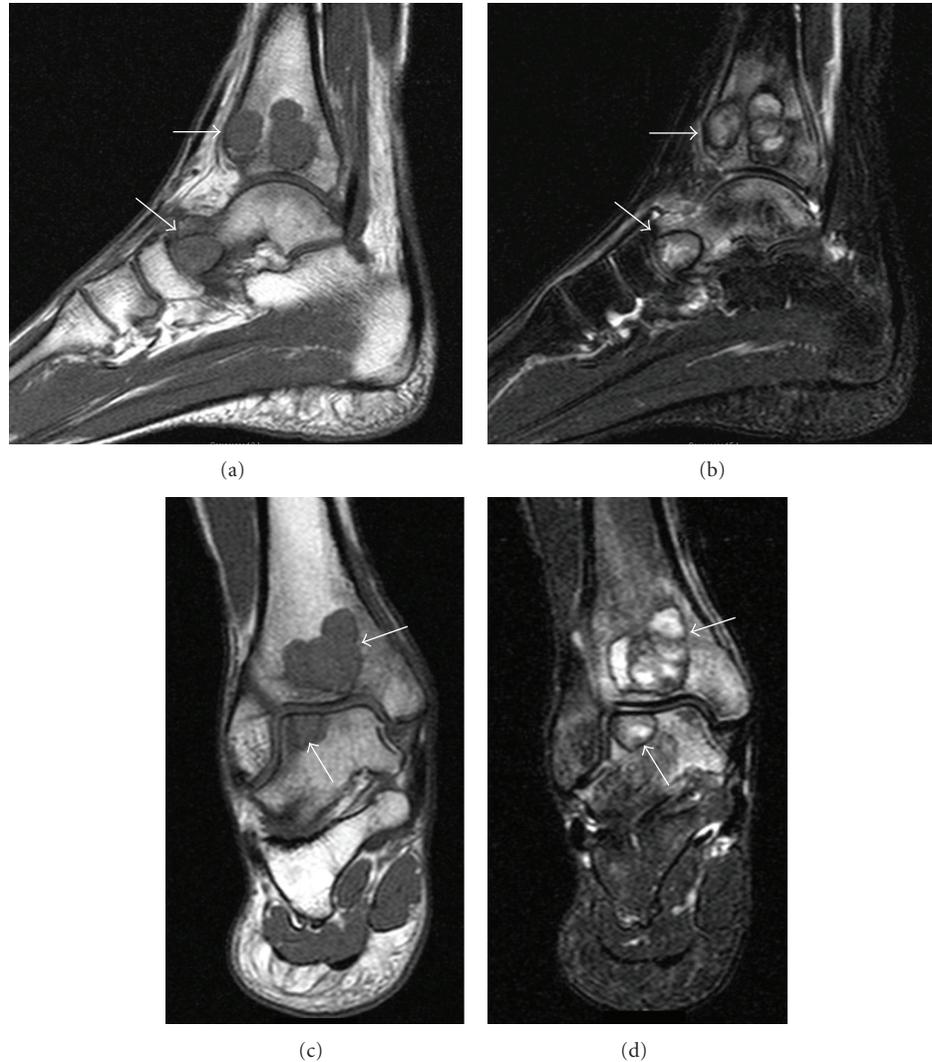


FIGURE 2: Sagittal T1-weighted (a), sagittal T2-weighted (b), and coronal T1- (c) and T2-weighted (d) images of the ankle demonstrate multiple lobulated lesions of low T1 and intermediate to high T2 signal intensity (arrows), with extensive surrounding bone marrow edema.

Epithelioid hemangioma of bone is typically found in adult patients, presenting most commonly as a solitary lesion, but approximately 25% may be multifocal, as in our patient [11]. EH is most frequently seen in the femur followed by the tibia, the hand and foot bones, and finally the bones of the axial skeleton [10, 11]. Our patient presented with increasing pain in his left ankle on weight-bearing. Although pain is the most common presenting symptom, occasionally EH may be discovered incidentally [10]. Radiographically, EH is predominantly lytic with well-defined sclerotic margins. Some may have a lytic or sclerotic appearance with prominent reactive bone formation. Although the prominent areas of reactive bone demonstrated histologically in our patient, the lesions appeared lytic on X-rays, with no visible regions of sclerosis. EH does not commonly cause cortical bone destruction. However, when the cortex is involved, there is usually focal cortical destruction associated with thick reactive periosteal bone formation [10]. The

prognosis of EH is unknown, but surgical excision is usually curative. However, recurrence has been reported in two cases: 5 years after excision of a sacral lesions and 2 years after excision of a femoral lesion [6, 12, 13].

Histologically, EH is characterized by its distinctive architecture and cytology [6, 7, 10, 14]. The vessels are organized in a lobulated fashion, and are well-differentiated with open lumina. The endothelial cells lining the vessels have abundant eosinophilic cytoplasm. The nuclei of the endothelial cells are round to oval and small nucleoli may be present. The characteristic “tombstone” appearance of the epithelial cells results from endothelial cells with prominent cytoplasm and nuclei protruding into the vascular lumina. The stroma surrounding the vessels does not show hyalinization, which is more typically seen in EHE. This patient’s tumor lacks the background inflammatory component including eosinophils, plasma cells, and lymphocytes typically seen in epithelioid hemangiomas identified in the skin and soft

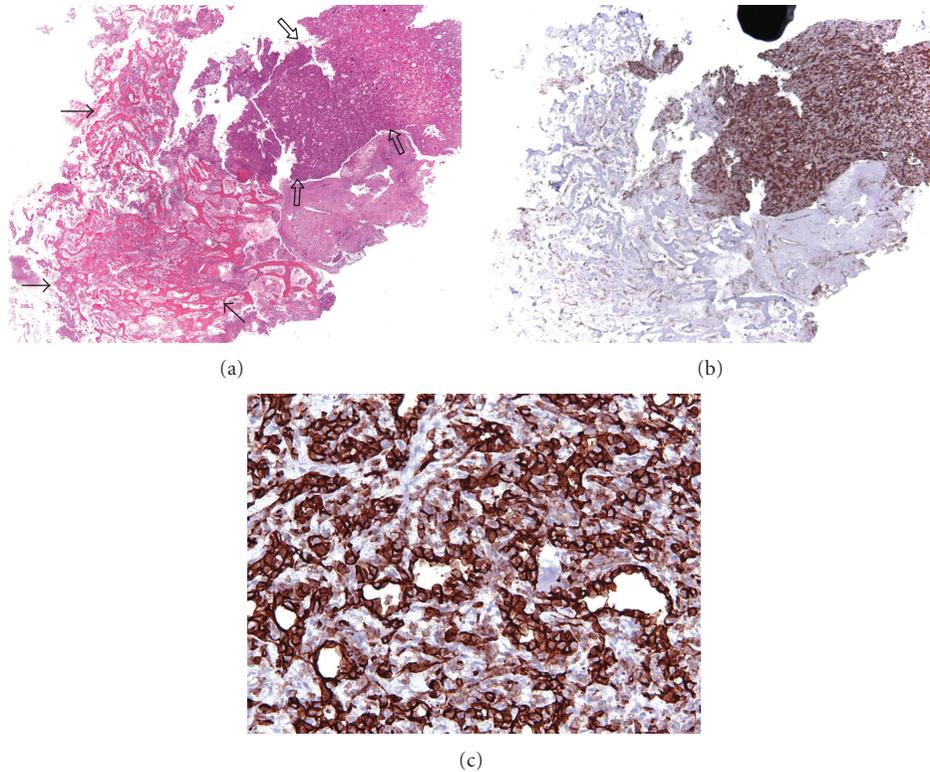


FIGURE 3: (a) The biopsy specimen demonstrates two distinct areas. Prominent bony trabeculae are seen on the left of the image (arrows), and cellular proliferation is seen on the right (open arrows). (b) The corresponding immunohistochemistry stain demonstrates strong expression of the vascular marker CD31 in the cellular areas, supporting a vascular neoplasm. (c) High-powered image of immunohistochemistry stain demonstrates strong expression of the vascular marker CD31 in the endothelial cells lining the vascular spaces, highlighting the areas of vascular proliferation supporting a vascular neoplasm.

tissue. However, recent literature has demonstrated that only a subset of epithelioid hemangiomas of bone display the characteristic inflammatory background typically observed in soft tissue epithelioid hemangiomas [14].

In our case, the differential diagnosis initially included multifocal osteblastomatosis (MO) [15] due to both the radiographic appearance and areas of reactive bone formation seen histologically. MO also manifests as intramedullary or intracortical lucent lesions, which can be indistinguishable from a primary vascular lesion of bone. On histology, the lesions in MO are composed of a spindle-cell stroma containing interconnecting irregular trabeculae of woven bone lined by prominent osteoblasts some of which have epithelioid features and scattered osteoclasts. Although the stroma may be well vascularized with capillaries, these are not as many as found in either a benign or malignant vascular tumor of bone. The vessels in MO are also lined with flat or inconspicuous endothelial cells, characterized by lack of stromal endothelial differentiation, in contrast to the rounded endothelial cells in a tombstone arrangement seen in our patient with MEH.

In comparison to benign EH, epithelioid hemangioendothelioma is described as an intermediate-grade malignant vascular neoplasm. It can occur at almost any age, but is more frequent in the second and third decades of life, and is slightly more prevalent in males [10, 11, 16]. The most

frequently affected bones are the tibia, femur, and humerus, and disease is multifocal in almost 50% of cases. EHE has a tendency to involve bones of the same region, for example the foot, or may exist as multiple foci within a single bone. Radiographically, it manifests as multiple lucent lesions, commonly with areas of peripheral sclerosis. EHE typically has a more aggressive clinical course. Wide surgical excision is recommended, but in some cases, local curettage with radiofrequency ablation has been used [17]. Radiation can also be used either alone or in combination with surgery, particularly in nonresectable lesions or metastatic disease.

Histologically, although vascular endothelial cells in EHE and EH are similar in appearance, EHE is best distinguished from EH by the appearance of its vessels. The vascular endothelial cells in EHE have abundant granular, eosinophilic vacuolated cytoplasm similar to those in EH. The vascular differentiation in EHE is more primitive than it is in EH. Instead of exhibiting the lobulated organization seen in EH, the vessels in EHE are more commonly arranged in cords or nests without lumina [6, 10]. The lumina are less conspicuous in EHE than they are in EH. Moreover, the stroma in EHE has a hyalinized or myxoid appearance, which is absent in EH.

Epithelioid angiosarcoma is an extremely rare high-grade malignant tumor. It predominantly occurs in the fourth and fifth decades of life, particularly in older male patients. EA

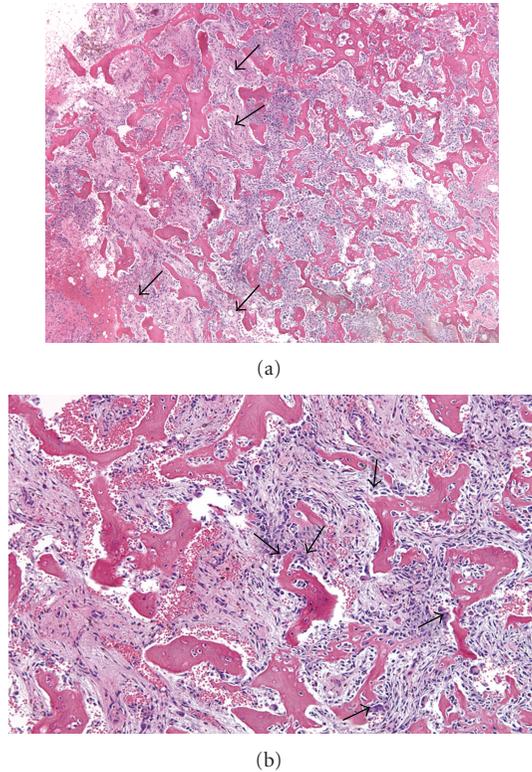


FIGURE 4: (a) Low-powered view of the bony portion of the tumor demonstrates numerous irregularly shaped bony trabeculae. In most areas, the bony trabeculae are associated with a mildly cellular spindle cell proliferation and small capillaries (arrows). (b) High-powered view demonstrates bony trabeculae rimmed by osteoblasts (arrows). These are associated with a mildly cellular fibrovascular stroma with no significant nuclear pleomorphism or mitotic activity. These findings raise the possibility of osteoblastoma.

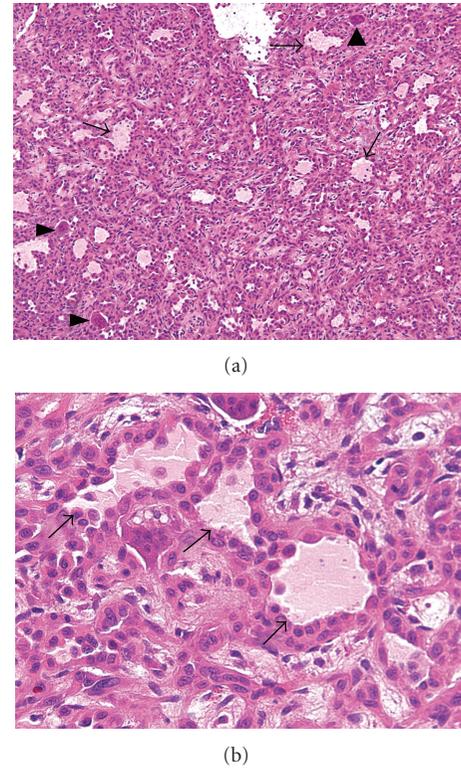


FIGURE 5: Low-resolution (a) and high-resolution (b) images of the cellular portion of the tumor demonstrate nests or sheets of epithelioid endothelial cells with abundant eosinophilic cytoplasm forming vascular spaces (arrows). The tumor cells line the spaces in a hobnail "tombstone-like" arrangement. Scattered multinucleated giant cells are also noted (arrowheads).

is often seen in the femur, tibia, and humerus and can be multifocal. Bony involvement is usually characterized by ill-defined permeative bony destruction, and involvement is polyostotic in 38%, often having a regional pattern. Radiologically, they are often considered metastatic carcinoma. EA is characterized by an aggressive clinical course with poor prognosis. Despite wide resection and adjuvant therapy, almost all patients diagnosed with EA die within 1–2 years of diagnosis [11].

Histologically, EA is distinguished from EH primarily by the architecture, mitotic activity, and degree of cytologic atypia [6, 11]. In EA, epithelioid endothelial cells almost always grow in large sheets with primitive branching vascular channels. Compared to the cells of EH, those of EA are larger with a greater nuclear-cytoplasmic ratio, large irregular nucleoli, and clumped chromatin. Atypical mitotic figures, necrosis, and neutrophilic infiltrate are frequently observed [6].

Although both EH and metastatic carcinoma can be multifocal, metastatic carcinoma can be differentiated from EH by the cytologic atypia associated with the carcinoma [6, 10]. Generally, endothelial cells with nuclear hyperchromasia or

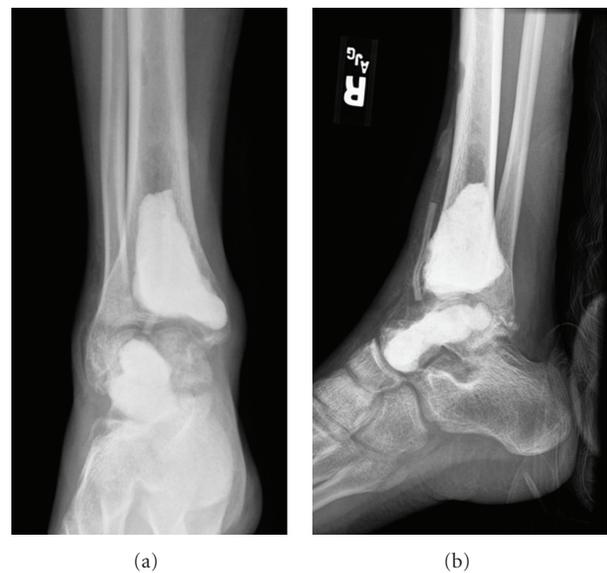


FIGURE 6: Follow up radiographs after curettage, cryosurgery, and bioceramic replacement of the lesion within the distal tibia and talus. The small lesion more proximally in the tibia was also subsequently curetted.

irregular chromatin patterns are more distinctive of metastases than EH.

In conclusion, we present a patient with multifocal EH with histological features reminiscent of osteoblastomatosis. To our knowledge, this is the first case of EH with such features. We emphasize the importance of careful attention to the histological features of EH which help distinguish it from other more aggressive vascular tumors of the bone.

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