Primary Epithelioid Angiosarcoma of the Femur and Tibia: A Rapidly Aggressive Course

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ABSTRACT

We report the rare case of a primary epithelioid angiosarcoma of the femur and tibia. Only a small fraction of primary angiosarcomas occur in bone, and even more so, a rarity is the presence of the epithelioid variant in bone. The epithelioid variant consists of large cells with epithelioid features that can easily be mistaken histologically for a poorly differentiated carcinoma due to the epithelioid microscopic appearance of the neoplasm, as was the case with the initial diagnosis for the patient presented. As such, immunostains are imperative to making the correct diagnosis of an epithelioid angiosarcoma.

A relatively healthy 76 year old male presented to the emergency department with hypercalcemia and left knee pain that had progressively worsened over a few months. A magnetic resonance imaging (MRI) scan obtained five days prior had revealed a mass in the knee suspicious for malignancy; notably, no mass was visible on MRI imaging obtained about a month prior. Further evaluation revealed the diagnosis of a primary epithelioid angiosarcoma of the knee with metastases to the lungs. The patient underwent palliative radiotherapy with a plan to undergo systemic chemotherapy. His mental status deteriorated within a month of presentation due to obstructive hydrocephalus caused by metastasis to the pineal gland. The patient passed away shortly thereafter under hospice care.

The rapid deterioration of our patient demonstrates the aggressive nature of the epithelioid variant of angiosarcoma, with high rates of widespread systemic metastases. The diagnosis is difficult to make considering the rarity of the tumor in bone and the epithelioid microscopic appearance of the neoplasm, which may mistakenly suggest a poorly differentiated carcinoma. A low threshold of clinical suspicion and proper histological examination with immunostains is necessary to correctly diagnose this uncommon malignancy.

CASE PRESENTATION

A 76 year old Caucasian male with a history of chronic deep venous thromboses (DVTs), peripheral arterial disease, hyperlipidemia, and multiple rib fractures was referred to the emergency department (ED) by his primary care physician for hypercalcemia and progressively worsening severe left knee pain unresponsive to oxycodone, tramadol, and gabapentin. A month prior to emergency department presentation, he received an MRI that was significant only for...
degenerative changes consistent with osteoarthritis. Reconstruction and total knee arthroplasty were considered as options to treat the presumed arthritis, but poor circulation to the knee required that revascularization around the knee joint via bypass surgery be performed first. While awaiting completion of preoperative testing for vascular bypass, the patient was given an intra-articular steroid injection for interim symptomatic relief. Two days after the injection, he was seen in clinic and found to have a new palpable left knee effusion which was concerning for septic arthritis. Knee aspiration was performed and 22 mL of bloody fluid was sent for analysis. He also had a repeat knee X-ray that showed a large area of cortical destruction in the medial femoral condyle and tibial plateau. Repeat MRI the day after preoperative labs were drawn (five days prior to ED presentation) revealed a large knee mass in the distal femur and proximal tibia. Given the MRI findings, the revascularization procedure was held by vascular surgery pending a distal femur biopsy. Preoperative laboratory test results revealed an elevated calcium level, which prompted the patient’s primary care physician to refer him to the ED.

Upon arrival to the ED, the patient was a poor historian with apparent memory deficits, including an inability to recall recent events, timelines, and tasks, thus requiring him to constantly record reminders. His friend who accompanied him provided much of the history, noting that the memory issues of the patient had started a couple of months prior despite the patient’s previous excellent memory capacity and literacy. He also stated that the patient had recently become confined to a wheelchair due to the knee pain and could not take care of himself at home. In addition to memory loss, the patient had experienced episodes of hemoptysis over the preceding month with small amounts of blood lost in each episode (exact quantity could not be ascertained). Additionally, he complained of chills and night sweats during the previous week, but denied fevers or significant weight loss in the past year. He also denied shortness of breath, abdominal pain, or dysuria. The review of systems was otherwise negative.

Significant past medical history included peripheral arterial disease, hyperlipidemia, and chronic DVTs controlled with an inferior vena cava filter and chronic anticoagulation with warfarin. Other home medications included gabapentin, oxycodone, tramadol, and simvastatin. Surgical history was remarkable for right and left inguinal hernia repair, appendectomy as a teenager, and abdominal surgery after a motor vehicle collision, from which he also incurred several rib fractures that later healed. Family history was negative for
diabetes, hypertension, or cancer. The patient denied previous or current tobacco, drug, and alcohol abuse. He stated that before his knee pain he maintained a very active lifestyle as a competitive athlete.

On admission, the patient was in moderate distress due to the knee pain and had a resting tremor of both hands. Physical exam of the left knee demonstrated joint swelling, mild erythe-

ma, and increased warmth to touch as well as extremely limited active and passive range of motion. The patient winced at the slightest touch of his knee or movement of his left leg. The physical exam was otherwise unremarkable. Labs revealed an elevated calcium level of 13.9 mg/dL and a white blood cell count of 26.7 x 10^9/L, with 88.8% neutrophils. A chest X-ray taken on admission revealed multiple old rib fractures and depression of the left lateral portion of the T12 vertebral body. MRI of the left knee obtained five days prior revealed a rapidly growing lobulated malignant mass centered in the posterior aspect of the medial femoral condyle with multiple additional smaller masses (Figures 1 and 2).

The patient's hypercalcemia was believed to be likely due to an underlying malignancy given the clinical history and MRI findings. He did not have any past medical history of parathyroid disease. The elevated calcium was resolved with normal saline hydration and zoledronic acid. His pain was managed with oxycodone/acetaminophen and morphine.

Initial assessment of the left knee mass led both malignancy and an atypical infectious process to be considered in the differential diagnosis. However, culture of the knee aspirate done before admission was negative. A pan-computed tomography (CT) scan with contrast was obtained in search of a primary malignancy. Results revealed multiple bilateral pulmonary nodules noted throughout the lungs, the largest measuring 1.4 cm in the lingula, all suspicious for metastasis. There was no intracranial malignancy noted on CT of the head nor was there thoracic, abdominal, or pelvic lymphadenopathy. No primary malignancy had been established at this point as the scan revealed only presumed metastatic lesions. Comparison of a repeat knee MRI to the MRI obtained 5 days prior to admission revealed no significant interval changes, with no additional masses seen in the distal tibial

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**Figure 3.** Cross section of MRI revealing pineal gland mass (arrow) representing metastasis of primary epithelioid angiosarcoma.

**Figure 4.** CT scan revealing prominent hydrocephalus of the lateral ventricles due to aqueductal obstruction secondary to pineal gland metastasis of the angiosarcoma.
shaft. At this point, a primary bone malignancy with metastases to the lungs was high on the differential diagnosis.

A left distal medial femur needle biopsy was then performed, and was initially read as squamous cell carcinoma. After further inspection, a malignant epithelioid neoplasm with necrosis was suspected, pending immunostains. The differential included a poorly differentiated melanoma, epithelioid angiosarcoma, or other poorly differentiated squamous cell carcinoma. A full body positron emission tomography (PET)/CT scan revealed a large multifocal hypermetabolic mass centered about the left knee joint, numerous hypermetabolic pulmonary metastases, and hypermetabolic mediastinal adenopathy. The patient was started on palliative radiation treatment to his left knee while awaiting the final pathology report, which confirmed an epithelioid angiosarcoma, high-grade (grade 3 of 3) with 30% necrosis, positive for CD31, ERG, and paracytokeratin. The plan was to complete radiation therapy followed by systemic chemotherapy.

While receiving inpatient radiotherapy, the patient’s hospital course was complicated by a decreasing hemoglobin level, supratherapeutic INR of 7.6 (trended down once anticoagulation was held), and choledocholithiasis requiring endoscopic retrograde cholangiopancreatography for stone removal. The patient also reported an episode of vomiting with streaks of blood and a few episodes of hemoptysis. The gastroenterology and pulmonary teams evaluated the patient and did not believe his symptoms represented true GI bleed or alveolar hemorrhage, respectively. The hemoglobin level continued to drop, to a level of 6.9 g/dL (from 10.1 g/dL on admission) after another episode of hemoptysis, at which point 2 units of blood were transfused. Thereafter, his hemoglobin remained stable.

In addition to these complications, the patient had episodes of altered mental status, with waxing and waning orientation throughout his hospital stay. A CT of the head revealed interval enlargement of the pineal gland since the previous CT of the head obtained as part of the initial workup. No hydrocephalus was noted, and the differential diagnosis included interval hemorrhage into the gland versus a tumor or other mass. A follow up MRI with contrast and dedicated pineal protocol revealed an enhancing 1.3 cm pineal mass, most likely representing pineal metastasis; no frank hydrocephalus was noted (Figure 3). While waiting to begin chemotherapy, the patient’s mental status acutely deteriorated. He was not oriented to person, place or time, but he opened his eyes spontaneously and followed commands. He could not, however, provide any verbal responses. Focal neurological deficits were not noted. A CT of the head showed new severe acute obstructive hydrocephalus secondary to aqueductal obstruction by the enlarging pineal mass, now increased to 1.8 cm (Figure 4). After discussion with his proxy, it was decided that the patient would not want any further invasive procedures, so he was transferred to hospice care, where he passed away a week later.

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**DISCUSSION**

As isolated findings, hypercalcemia or bone pain can lead to a broad differential, but the combination of the two is more suggestive of a malignant etiology. In regards to hypercalcemia, more than 90% of cases are in fact due to primary hyperparathyroidism or malignancy, with the former being more prevalent in the outpatient setting and the latter more prevalent in the inpatient setting. Other causes of hypercalcemia may include familial disorders, secondary hyperparathyroidism as a result of chronic kidney disease, chronic granulomatous disorders, medications, and disorders such as hyperthyroidism.
Patients with hypercalcemia of malignancy typically have significantly high calcium concentrations (above 13 mg/dL), concentrations that are uncommon with primary hyperparathyroidism. The mechanisms underlying hypercalcemia of malignancy include osteolytic bone metastases, increased 1,25-dihydroxyvitamin D (calcitriol) production via activation of extrarenal 1-alpha-hydroxylase, and the action of parathyroid–related protein (PTHrP); these mechanisms vary with different types of malignancies. Increased production of calcitriol is more common with lymphomas. Osteolytic metastases, the etiology of 20% of cases of hypercalcemia of malignancy, often result from solid tumors that metastasize to bone, most commonly breast cancer, and also from multiple myeloma (MM); these malignancies result in bone destruction and resorption via osteoclast stimulation by tumor factors. The most common etiology of hypercalcemia of malignancy is humoral hypercalcemia of malignancy (HHM) with production of PTHrP, which typically occurs in squamous cell carcinomas, and renal, bladder, breast, or ovarian carcinomas.

Given our patient’s severe knee pain, it was more likely that a metastatic lesion or primary malignancy of bone was the underlying cause of his hypercalcemia. Given his gender, unremarkable family history for cancer, and lack of a smoking history, breast and lung cancer were lower on the differential. Multiple myeloma was a possibility as it most commonly presents with bone pain, but the lesions of MM are typically lytic unlike those seen in the MRI of this case; furthermore, the patient did not exhibit other manifestations of MM such as pathologic fractures or renal failure. A primary tumor of bone thus seemed more likely.

Primary bone malignancies are an important cause of cancer morbidity and mortality, particularly in young individuals. Epidemiologically, the most common primary bone malignancy, excluding myeloma, is osteosarcoma, which occurs most often in the extremities of children. The second most common bone malignancy is chondrosarcoma which occurs in cartilage tissue and is often found in adults over the age of 50; it often presents in the pelvis, proximal femur, and proximal humerus. Other primary bone neoplasms include Ewing sarcoma and giant cell tumor, both of which most often occur in children and young adults, and bone angiosarcoma, which occurs in the second to seventh decades of life. Soft tissue sarcomas are also a possibility when considering tumors of the bone (or regions near bone). In the case of our patient, it was not until a biopsy was performed that the definitive diagnosis was made.

Angiosarcomas are aggressive mesenchymal neoplasms composed of rapidly proliferating anaplastic cells derived from blood vessels and the lining of vascular spaces. These malignancies often recur locally and have a high rate of both lymph node and systemic metastasis. Angiosarcomas more commonly originate in the skin and soft tissue, but have also been reported to occur in the liver, breast, spleen, heart, and bone. As was reported in this specific case, primary angiosarcoma of the bone is rare as only 6% of all angiosarcomas originate in bone. Additionally, only 1% of primary malignant neoplasms in bone are primary angiosarcomas. The epithelioid variant of angiosarcoma is even more rare as a primary tumor in bone. This variant has been reported more commonly in deep soft tissues of the extremities, with some cases in the thyroid gland, skin, and adrenal glands; very few cases of primary bone epithelioid angiosarcomas have been reported. A series of 10 cases of bone epithelioid variant included 8 men and 2 women, ages ranging from 26 to 83 years old, three of which were located in the femur, as was the case with our patient. The epithelioid variant consists of large cells with epithelioid features that can easily be mistaken for a poorly differentiated carcinoma on microscopic analy
sis, and can present with multifocal (25% of cases) or solitary lesions (75% of cases). In the case of this patient, the initial diagnosis was a poorly differentiated carcinoma due to the histologic appearance of the tumor cells. Histopathological recognition is notably an issue in the diagnosis of angiosarcomas.

Generally, microscopic analysis of angiosarcomas reveals vascular spaces lined by tumor cells with atypia; low-grade lesions are more likely to contain large endothelial cells whereas high-grade lesions contain atypical cells and abnormal mitoses. In regards to the epithelioid variant, histologic features include well-formed vascular channels and cytoplasmic vacuoles that contain red blood cell fragments. These findings, however, are not necessarily specific for angiosarcomas and may be mistaken for other vascular tumors such as epithelioid hemangioendothelioma. The distinction of angiosarcoma can become even more difficult with the aggressive form of the tumor, in which sheets of anaplastic cells contain poorly defined vascular channels. This feature may result in a misdiagnosis of metastatic carcinoma, especially given the small amount of sample that is acquired with a biopsy that may not be representative of the entire lesion. Since identification of a primary angiosarcoma is difficult based on microscopic and histopathologic analysis, immunohistochemical staining for specific vascular marker expression patterns and for antibody markers of endothelial differentiation can distinguish an angiosarcoma from its histologic mimics. In the case presented, this staining procedure was required to confirm the diagnosis of an angiosarcoma with a multicentric presentation.

The majority of angiosarcomas express vimentin and factor VIII–related antigen, along with CD34 (74%), BNH9 (endothelial marker, 72%), and cytokeratin (35%). The most sensitive endothelial cell marker for angiosarcoma that is also highly specific is anti-CD31, which was notably positive in our case. The neoplasm in this case was also positive for ERG, another vascular tumor marker, and paracytokeratin. Since the epithelioid microscopic appearance of this variant is similar to that of a poorly differentiated carcinoma, other tumor markers may be screened to rule out a carcinoma. In this case, S100 and HMB-4, markers for melanoma, were tested and found to be negative, ruling out a poorly differentiated melanoma.

In the majority of angiosarcoma cases, the etiology is unknown. Certain risk factors and causes have been associated with the development of the neoplasm. These include chronic lymphedema, previous radiotherapy, trauma with introduction of foreign material such as shrapnel, and malignant transformation of a benign hemangioma. Angiosarcoma may also arise on a pre-existing benign lesion such as a bone infarct, pagetoid bone, or chronic osteomyelitis. Our patient did not have any history of previous irradiation or toxic exposures, lymphedema, or introduction of foreign material in the knee as far as he knew. He also had no previous trauma or infection in the left femur/tibia area. Our patient’s history and lack of risk factors were not suggestive of an angiosarcoma. This further emphasizes the importance of keeping in mind that a lack of risk factors does not necessarily exclude an angiosarcoma. The physical exam may also lack evidence to suggest an angiosarcoma, and the presentation of the patient often depends on the location of the tumor. For instance, worsening bone and joint pain refractory to many pain medications, including opioids, and steroid injections may indicate a bone neoplasm. The patient’s age and history should be factored in to narrow the differential of bone malignancies.
nancies rapidly proliferate yet are insidious in onset and may not cause any identifiable symptoms until advanced stages. Specifically, more than 50% of patients with the epithelioid variant die within 2 to 3 years of diagnosis.\textsuperscript{6,9,10} The patient in this case developed a visible mass in the span of approximately one month (based on the first MRI that revealed no mass compared to the repeat MRI a month later) and died within a month and a half of presenting to the hospital, with documented metastases to his lungs, mediastinal lymph nodes, right posterior gingiva, and pineal gland. With such advanced disease, treatment of choice is usually a combination of radiation therapy and chemotherapy, with simultaneous or sequential administration of ifosfamide and doxorubicin a common regimen for sarcomatous tumors. Evidence regarding the effectiveness of these therapies is uncertain, although Budd\textsuperscript{12} reports a good response with the doxorubicin and ifosfamide regimen. If the disease is localized, surgical resection and radiation therapy are standard.

The aggressive nature of angiosarcoma and high rate of metastasis presents a need for early detection, but this is difficult considering the potential lack of risk factors and specific physical findings. Diagnosis can be especially difficult in the case of the epithelioid variant due to the epithelioid microscopic appearance of the neoplasm, thus requiring a low threshold of suspicion from the clinician and careful pathologic review with immunostains.

2. Since epithelioid angiosarcoma is often mistaken for a poorly differentiated carcinoma due to the epithelioid microscopic appearance of the tumor, immunostains of a tumor sample are essential to properly diagnose the epithelioid variant.

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**REFERENCES**


**LEARNING POINTS**

1. Angiosarcoma should be considered in the differential diagnosis of a primary neoplasm of the bone.