Case Report

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Multicentric Epithelioid Angiosarcoma of Bones Showing Angiotropic Spread: A Case Report

뼈에 발생한 혈관성 파종 양상을 보이는 다발성 상피상 혈관육종: 증례 보고

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Epithelioid angiosarcoma is a rare variant of angiosarcoma characterized by an epithelioid morphology that mimics carcinoma. Therefore, multicentric epithelioid angiosarcoma is easily misdiagnosed as bone metastasis from carcinoma and has an aggressive clinical course. Here, we present a rare case of a 61-year-old male with multicentric epithelioid angiosarcoma of the bone. Plain radiography, CT, and MRI revealed multiple osteolytic lesions in both femurs; some lesions showed soft tissue extension with cortical bone destruction. Interestingly, PET-CT revealed that the lesions were only distributed along the bones of the lower extremities, including the pelvic bones, femurs, and tibiae. Despite histological analysis initially suggesting metastatic carcinoma, after additional immunohistological staining, including that for vascular markers (CD31 and ERG), the final diagnosis was epithelioid angiosarcoma. A better understanding of the clinicoradiological features of this disease may help eliminate diagnostic confusion and provide better management.

Index terms Sarcoma; Hemangiosarcoma; Magnetic Resonance Imaging; Bone; Pathology

INTRODUCTION

Angiosarcoma of bone is rare and accounts for < 1% of primary skeletal malignancies (1). Similar to hemangiomas and hemangioendotheliomas, angiosarcomas of the bone may be solitary or multicentric and can originate in intraosseous blood vessels (2). Multicentricity is observed in 20% to 50 % of cases and consists of multiple lesions in a single bone, in the same extremity, or throughout the skeleton (2). Furthermore, angiosarcoma of bone is characterized by aggressive biological behavior, resulting in a high local recurrence rate, lymph node metastasis, and systemic metastasis (3). The term "epithelioid angiosarcoma" refers to a variant of angiosarcoma composed of neoplastic cells with an epithelioid morphology. These tumors are usually poorly differentiated epithelial-like cells arranged in a carcinoma-like fashion that still form identifiable vascular channels (4).

Herein, we report a case of multicentric epithelioid angiosarcoma of the bone, characterized by an aggressive clinical course. Cases with multicentric bone lesions tend to suggest bone metastases from carcinoma, both clinically and radiologically. This case report aimed to describe the clinical, imaging, and pathological features of a multicentric contiguous epithelioid angiosarcoma of the bone to better understand its biological behavior.

CASE REPORT

A 61-year-old male developed right hip pain three days before our institution's initial evaluation. He had tenderness over the hip, and the pain worsened with weight bearing. The patient had no history of radiotherapy. No laboratory data abnormalities were detected, except for an increased white blood cell count (14.41×10^9/L) and elevation of the inflammatory marker C-reactive protein (7.79 mg/dL). Plain radiographs showed multiple osteolytic lesions with ill-defined margins located both centrally and eccentrically (Fig. 1A). Cortical bone destruction was observed in both femurs, particularly in combination with pathological fractures of the right femur. In contrast, the periosteal reaction was minimal in some lesions. Lower extremity CT revealed multiple ill-defined osteolytic lesions with epicenters located in both the medullary space and cortex (Fig. 1A). Furthermore, some lesions showed cortical bone destruction with extraosseous soft-tissue extension. MRI of both femurs revealed multiple lesions measuring less than 3.7 cm in longitudinal diameter, some of which were associated with extraosseous soft tissue mass formation (Fig. 1B). The representative lesion displayed iso-to-hyperintensity on T1-weighted images and heterogeneous hyperintensity on T2-weighted images. Moreover, gadolinium enhancement was heterogeneously observed on T1-weighted images (Fig. 1C). Notably, the enhanced solid portion of the lesion showed diffusion restriction with an apparent diffusion coefficient of 772 μm^2/sec on the diffusion-weighted image (DWI) (Fig. 1C). Finally, a ^{99m}Tc bone scan showed multiple radionuclide uptakes involving the L3 vertebra, both pelvic bones, both femurs, and the left tibia (Fig. 1D).

Considering the patient's age and tumor multiplicity, the clinical and radiological diagnoses were carcinoma-related bone metastases. To identify the primary carcinoma, neck, abdominal, and chest CT scans were performed. Gastrointestinal endoscopy and colonoscopy failed to detect a potential primary tumor. No other lesions, except for multifocal bone uptake in

Fig. 1. Multicentric epithelioid angiosarcoma of bone involving lower extremities in a 61-year-old male.
A. Plain radiograph of both femurs and lower extremity CT of the left thigh. Anteroposterior view shows multiple ill-defined osteolytic lesions in both centric and eccentric ways. Pathologic fracture is combined at the right femur (arrow). Note the cortical destruction with minimal periosteal reaction (arrowheads). Craniocaudally sequential axial CT images (bone and soft tissue windows) show cortical bone destruction and extraosseous soft tissue extension (arrowheads).
B. MRI of the left thigh. Coronal T2WFS (left) and T1WFS (right) with enhancement show an aggressive bony lesion with cortical destruction and extraosseous soft tissue mass (arrowheads).
C. MRI with DWI of the left thigh. Axial T2W FS image shows a heterogeneously hyperintense mass compared to signal intensity of adjacent muscles (arrowhead). The axial T1W FS image shows an iso-to-hyperintense mass with heterogeneous enhancement (arrowhead). Axial T1W FS image with enhancement shows an enhancing solid portion at the extraosseous area (arrowhead). DWI of b = 50 s/mm^2 shows this tumor area with hyperintensity. DWI of b = 800 s/mm^2 shows that this area remained hyperintense (arrowhead). ADC map shows this tumor area with hypointensity (arrowhead) and a mean ADC of 772 μm^2/sec.
D. ^{99m}Tc bone scan. Whole-body bone scintigraphy shows increased tracer uptake in the L3 vertebra, pelvic bones, femurs, and left tibia.
CE = contrast enhancement, DWI = diffusion-weighted image, FS = fat-suppressed, T1W = T1-weighted, T2W = T2-weighted

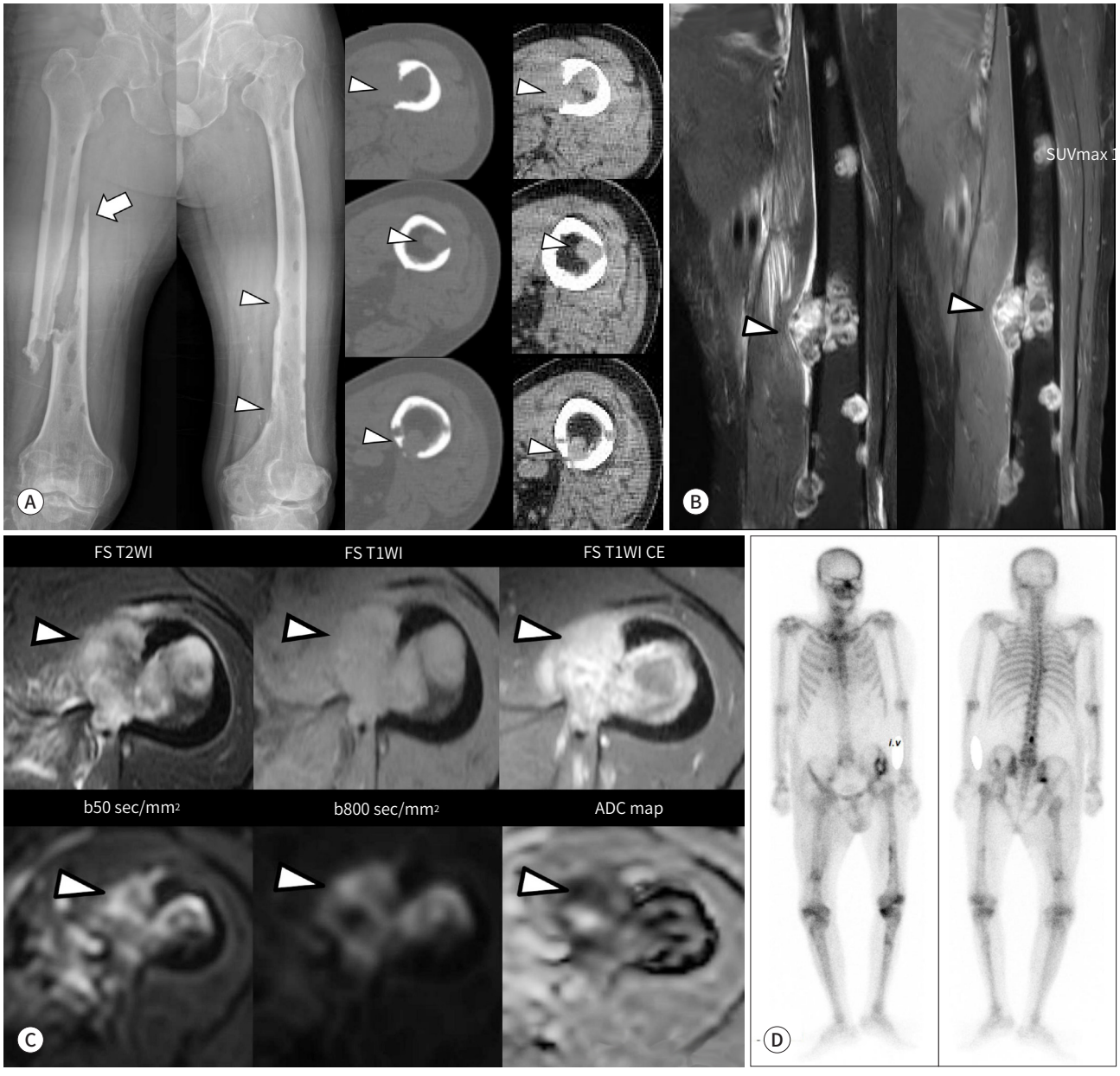
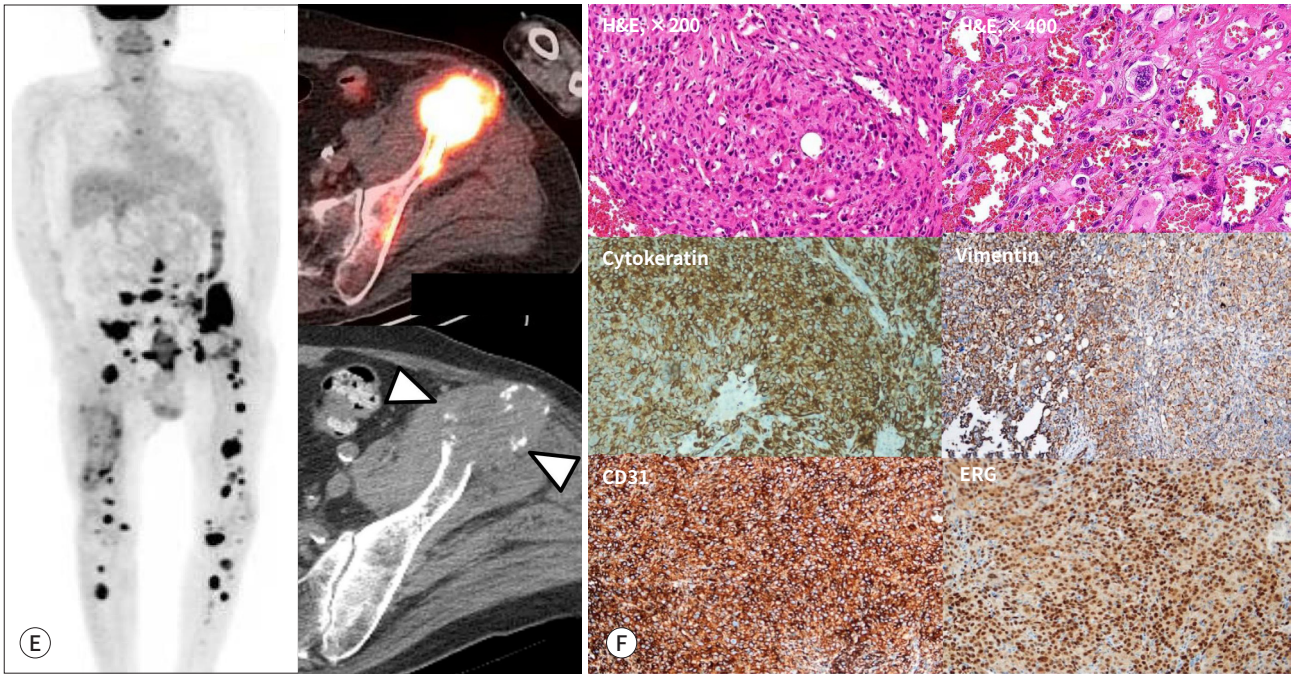


Fig. 1. Multicentric epithelioid angiosarcoma of bone involving lower extremities in a 61-year-old male.
E. ^{18}F-FDG PET with CT. Whole-body PET imaging shows multifocal bone uptake in the sacrum of lumbar segments 3, 4, and 5, pelvic bones, femurs, tibiae, and left fibula. The SUVmax is 18.82 in the left iliac bone. The lesion shows severe cortical bone destruction with prominent extraosseous soft tissue extension (arrowheads).
F. Histopathology of a biopsy specimen. H&E × 200 image and × 400 image show high cellularity with epithelioid cells and spindle cells lining abnormally dilated vascular channels. Tumor cells show evidence of abnormal mitotic figures. Cytokeratin and vimentin staining are positive, CD31 and ERG staining are highly positive. The Ki-67 index was 53.72% (not shown). The final pathological diagnosis was an epithelioid angiosarcoma.
ERG = ETS-related gene, H&E = hematoxylin and eosin, SUVmax = maximum standardized uptake value



lumbar segments 3, 4, and 5, the sacrum, pelvic bones, both femurs, both tibiae, and left fibula, were identified by ^{18}F-FDG PET (Fig. 1E). The maximum standardized uptake value (18.8) was detected in the left iliac bone, which was the largest lesion, with prominent extraosseous soft tissue extension and severe cortical bone destruction. Despite these negative findings, bone metastasis from carcinoma was considered the most likely diagnostic possibility, although primary bone tumors were included in the differential diagnosis. We considered that the lesion originated from primary malignant bone tumors, such as angiosarcoma, with the primary site in the left iliac bone.

Internal fixation with intramedullary nail insertion was performed for the pathologic fracture of the right femur with extended intralesional excision. Subsequently, an incisional biopsy of the left iliac bone was performed. Microscopically, the resected specimen appeared to have high cellularity, with epithelioid and spindle cells lining the abnormally dilated vascular channels (Fig. 1F). The tumor cells had vesicular nuclei with prominent nucleoli. An abundant eosinophilic cytoplasm was conspicuous in the intraluminal tumor cells. Immunohistochemically, the tumor cells expressed cytokeratin and vimentin, suggesting a poorly differentiated carcinoma. However, additional immunohistochemical staining (Fig. 1F), including that for CD31 and ERG, was highly positive, and the Ki-67 index was 53.72%. The final pathological diagnosis was an epithelioid angiosarcoma. The patient died four months postoperatively.

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The Institutional Review Committee of our institution (IRB No. VC23ZISI0013) approved the study, and the requirement for informed consent was waived owing to the retrospective nature of the study.

DISCUSSION

Epithelioid angiosarcoma is a rare variant of angiosarcoma characterized by large cells with epithelioid features. Epithelioid angiosarcoma most often arises in the deep soft tissue of the extremities, and the bone is an extremely rare site of origin for this malignancy. Because of its rarity, the exact incidence rate is not available, and instead, only a few case series have been reported in bone and soft tissue. Deshpande et al. (5) reported 10 cases of epithelioid angiosarcoma of the bone, and Chen et al. (6) reported four epithelioid angiosarcomas of bone and three cases of soft tissues. Additionally, there were almost five single-case reports, but none of them included multimodal imaging findings, such as bone scans, PET-CT, and DWI. Clinically, epithelioid angiosarcoma of the bone is highly aggressive, with frequent local recurrence, lymph nodes, and early distant metastasis, including that of the lung, skin, soft tissue, and bone, and usually affects the elderly, with a mean age of 62 years (5, 6); specifically, it occurs more frequently in males and primarily manifests in the lower extremities (6). Moreover, common clinical symptoms include localized pain and tenderness (6). The treatment includes wide surgical resection, sometimes requiring amputation, postoperative adjuvant chemotherapy, and radiotherapy. Prognosis is mostly poor, with a five-year-overall survival rate of 20% (5, 7).

Owing to its rarity, the radiologic features of epithelioid angiosarcoma of the bone have not been described diagnostically except with regard to its aggressiveness. As this tumor originates from the medullary vascular channels and infiltrates the cortex and soft tissue (8), plain radiography and CT may reveal ill-defined marginated osteolytic lesions located in either eccentric or centric ways (1). Furthermore, its aggressiveness may vary from endosteal erosion to cortical destruction with tumor extension, involving a minimal periosteal reaction (1).

The most remarkable radiological feature of epithelioid angiosarcoma is multifocality; the presence of multifocal lesions may be the only indication of a vascular tumor of the bone (9). The multifocal contiguous variant reported by Mirra (9) is an angiosarcomatous lesion involving the adjoining bones. In this variant, contiguous bones show multiple lesions, whereas all other bones appear normal. In our case, the tibia, fibula, femur, and pelvic bones were involved as adjoining bones. Interestingly, the lesions spread to the contiguous bones in both a retrograde and antegrade manner in multicentric contiguous variants (9, 10). These variants show a unique feature, so-called angiotropic spread, which occurs through vascular channels from the bone without evidence of systemic metastases (10).

Pathologically, epithelioid angiosarcoma is characterized by poorly differentiated tumor cells composed of epithelioid cells that share histological features with metastatic carcinoma, which leads to misdiagnosis. While both can express epithelial markers on immunohistochemistry, epithelioid angiosarcoma expresses vascular markers, including ERG and CD31, which are different from those of metastatic carcinomas and are useful for the final diagnosis. Notably, CD31 is the most sensitive (5). Additionally, metastatic carcinoma can be distinguished from epithelioid angiosarcoma based on the histological features of neoplastic vas-

cular structures, including abnormally anastomosing vascular channels lined by pleomorphic epithelioid cells and cytoplasmic vacuoles that contain red blood cell fragments (5).

This case highlights two important messages regarding epithelioid angiosarcoma. First, if radiological findings show multiple osteolytic lesions with aggressive features contiguously involving more than one bone, multicentric angiosarcoma should be included in the differential diagnosis of metastatic carcinoma. The presence of contiguous distribution along the adjacent bones was an indication for the consideration of multicentric angiosarcoma in our case. Second, to avoid misdiagnosis, when imaging findings do not correlate with pathological findings, immunohistochemical staining can be used for a definitive diagnosis of epithelioid angiosarcoma.

In conclusion, we report an epithelioid angiosarcoma of the bone characterized by its aggressive nature. These tumors can show a multicentric contiguous pattern known as angiotropic spread. To differentiate these tumors from metastatic tumors, careful histological examination using the immunoexpression of vascular markers is critical because of the significant differences in the treatment and clinical outcomes of these entities.

Author Contributions

Conceptualization, L.S.K.; supervision, L.S.K., K.J.Y.; visualization, C.W.S., L.S.K.; writing—original draft, C.W.S., L.S.K.; and writing—review & editing, L.S.K., K.J.Y., K.J.H.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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뼈에 발생한 혈관성 파종 양상을 보이는 다발성 상피상 혈관육종: 증례 보고

최우석[1] · 이슬기[1]* · 김지영[1] · 김준호[2]

상피상 혈관육종은 혈관에 생기는 육종 중 드문 변이이다. 이 종양은 대개 연부조직에서 발생하고, 뼈에서 발생하는 경우는 특히 드물다. 다발성으로 발생한 경우 이 종양은 이차성 골전이와 혼동될 수 있으며, 매우 치명적인 임상 진행을 보일 수 있다. 우리는 61세의 남성에서 다발성으로 발생한 상피상 혈관육종의 증례를 보고하고자 한다. 이 종양은 혈관성 파종으로 인해 발생한 것으로 추정된다. 엑스선 단순 촬영, CT 및 MRI에서 양쪽 하지 장골에 여러 개의 골융해성 병변이 관찰되었다. 이 중 일부는 골피질을 파괴하면서 연조직성 병변도 동반되었다. 초기 영상의학적 검사 결과로는 전이성 암종이 의심되어, PET-CT를 촬영하였다. 흥미롭게도, PET-CT에서는 이러한 병변들이 양쪽 하지 뼈의 반골, 장골, 경골을 따라 분포하고 있어, 혈관을 따라 파종할 가능성이 있는 혈관육종의 가능성도 확인되었다. 병리학적 소견에서 또한 처음에는 전이성 암종의 가능성을 고려하여 추가적인 면역 화학 염색 검사를 시행하였다. 그러나, 혈관성 표지자인 CD31, ERG 등의 검사 결과 강한 양성 소견을 보여 최종적으로 이 병변은 상피상 혈관육종으로 진단되었다. 이번 증례를 통해 뼈에 일차성으로 발생한 상피상 혈관육종에 대한 임상적, 영상의학적 특징을 정리하여, 진단적 혼동을 줄이고 더 나은 치료 방법을 제공하는데 도움이 될 것이다.

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