Unusual Presentation of Widely Metastatic Extraskeletal Osteosarcoma: Case Report

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ABSTRACT

Extraskeletal osteosarcoma is a highly aggressive malignant osteoid forming mesenchymal neoplasm arising from soft tissues which accounts for 1% of all soft tissue sarcomas. We report the case of a 46-year-old female with no significant past medical history presenting to an emergency department with a right lateral thigh mass following minor trauma. She was eventually found to have high grade extraskeletal osteosarcoma with rapid progression of disease resulting in patient demise. Differentiation of these lesions from alternative processes relies on specific imaging and pathologic features. Differential diagnoses include both benign and malignant etiologies such as myositis ossificans, soft tissue hemangiomas, and other malignant soft tissue neoplasms such as epithelial and synovial sarcoma.

CASE REPORT

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A 46-year-old female presented to her local emergency department with a 5-week history of a right lateral thigh mass after a minor trauma. There was no significant past medical history reported.

Upon initial presentation, a bedside ultrasound of the right thigh was performed demonstrating a suspected complex fluid collection (Fig. 1). A bedside incision and drainage was performed in the emergency department, the wound was packed, and the patient was discharged on antibiotics. Gram stain and cultures were negative.

Approximately one week later, she presented to her primary care provider with persistent 10/10 pain without resolution of the mass and was referred back to the emergency department. An AP radiograph of the right thigh was performed which demonstrated a soft tissue mass with dense amorphous mineralization (Fig. 2). Computed tomography (CT) of the right thigh was then performed demonstrating a complex space occupying mass lesion of the lateral thigh concerning for malignancy (Fig. 3). The mass initially was resected at the outside hospital with pathology concerning for "high grade mesenchymal neoplasm, extraskeletal osteosarcoma (ESOS)".

Approximately one month following surgery, the mass rapidly recurred with associated skin breakthrough; the patient was then referred to our institution for further management (Fig. 4). Upon presentation, contrast-enhanced magnetic resonance imaging (MRI) of the right thigh was performed.

MRI demonstrated a large heterogeneous fungating lateral thigh mass measuring 7.9 x 5.2 cm abutting and exerting mass effect upon the underlying fascia and thigh musculature with extensive surrounding peritumoral edema (Fig. 5). Imaging findings were concordant with previous diagnosis of osteosarcoma.

The case was presented at multidisciplinary sarcoma tumor board and, given increased risk for recurrence with surgery alone due to tumor size, grade, and rapid recurrence following initial resection, treatment recommendations included neoadjuvant radiation therapy (5000 cGy in 25 fractions) followed by surgical resection.

Unfortunately, re-staging examinations following radiation therapy demonstrated enlargement of the mass (Fig. 6) with interval development of inguinal lymphadenopathy and pulmonary metastatic disease (Fig. 7). Despite distant disease and need for systemic chemotherapy, the patient opted for palliative radical resection of the painful fungating thigh mass.

Histological examination of the tumor revealed round to spindle cells with abundant osteoid formation and focal chondrosarcomatous component consistent with osteosarcoma. There was tumor necrosis (85%) with 15% viable tumor cells consistent with extensive therapy changes (Fig. 8). Immunohistochemistry revealed no expression of pan cytokeratin, CD45, Mart1, SMA, S100 (polyclonal), desmin, MDM2 and CDK4; there was focal expression of CD10. The combination of histopathology and imaging findings were consistent with osteosarcoma.

Following surgery, the patient suffered from recurrent wound infections with poor wound healing, severe deconditioning, and marked progression of distant metastatic disease. As such, systemic chemotherapy was deferred and hospice care was recommended. The patient expired approximately 7 months after initial diagnosis.

DISCUSSION

Etiology & Demographics:

Sarcomas are rare mesenchymal neoplasms of soft tissues and bone accounting for just 1% of all adult malignancies [1,2]. Conventional intramedullary osteosarcoma represents a primary malignant bone tumor most commonly affecting long bones of the appendicular skeleton such as the distal femur, proximal tibia, and proximal humerus with several histological subtypes including osteoblastic, chondroblastic, fibroblastic, and telangiectatic among others. Surface osteosarcomas are juxtacortical osteoid forming malignancies consisting of parosteal and periosteal subtypes, of which the parosteal subtype has the best prognosis. ESOS (extraskeletal osteosarcoma) is a rare and highly aggressive subtype of conventional osteosarcoma arising in soft tissues rather than bone. ESOS represents approximately 4% of all osteosarcomas [3,4]. The majority of patients are diagnosed in the fifth or sixth decades of life, commonly presenting with a progressively enlarging painful soft tissue mass [5]. A small percentage of patients, approximately 12.5%, report antecedent trauma or radiation therapy [3]. ESOS most commonly metastasizes to lung, with bone and regional lymph nodes additional common sites of metastasis[6]. The prognosis is poor with a 5-year survival rate as low as 28% [7].

Clinical Features:

Benign and malignant musculoskeletal tumors derive from mesenchymal tissues – the embryologic precursor to fat, muscle, nerve, fibrous connective tissue, and blood vessels. The World Health Organization classifies musculoskeletal tumors based on their predominant tumor cell lineage; this includes adipocytic, myofibroblastic, and fibroblastic soft tissue tumors [8,9,10]. Primary bone tumors largely include hematopoietic, osteoid, chondroid and fibrous forming neoplasms. ESOS is a unique and rare osteoid forming malignancy arising in soft tissue rather than bone and is commonly composed of pleomorphic spindle or polygonal cells, with atypical mitotic figures and central necrosis [10]. They are infrequently seen in patients less than 30 years of age, as opposed to conventional intramedullary osteosarcoma which typically occurs in adolescents and young adults. The peak incidence of ESOS is the 5th and 6th decade of life with a male predilection [11]. The precise pathogenesis of ESOS remains unclear, likely due to its rarity with a reported annual incidence of approximately 2-3 per million [12]. However, there has been an association with prior radiation therapy in approximately 4-13% of cases [1]. A history of trauma is reported in up to 12.5%, though the significance of this association remains unclear [11]. ESOS may arise within superficial soft tissues and deeper musculature with thigh being the most common site of disease (48%) followed by the upper extremity [3]. They most commonly present as a palpable mass with pain and growth over several weeks to years [12]. The diagnosis of ESOS relies heavily on imaging appearance and correlation with pathology as there are no known serologic tests specific to the diagnosis.

Histopathology:

Osteosarcoma is a high grade mesenchymal neoplasm typically with active mitoses, infiltrative margins and occasionally satellite nodules [1] Necrosis and hemorrhage are common. Histologic diagnosis depends on three criteria: 1) the presence of a uniform morphological pattern of sarcomatous tissues excluding the possibility of a mixed malignant mesenchymal tumor; 2) production of malignant osteoid, bone, or both; and 3) exclusion of osseous origin [13]. Focal positivity for vimentin, S-100 and cytokeratin may be found [7].

Imaging Characteristics:

Diagnostic imaging plays an integral role in the diagnosis of ESOS; correlation between the imaging features and histopathology findings is critical to establish an accurate diagnosis. Radiographs typically demonstrate a large soft tissue mass with internal mineralization/osteoid, similar to the conventional subtype. On computed tomography (CT), ESOS typically presents as a large heterogeneous enhancing soft tissue mass with hemorrhage, necrosis, and intrinsic

mineralization representing osteoid or bone formation in approximately 50% of cases. These areas of mineralization can increase over time and are best demonstrated by CT [1]. As in this case, the underlying mass is separate from nearby osseous structures. On magnetic resonance imaging (MRI), ESOS typically demonstrates isointense signal to muscle on T1 weighted imaging and high signal on T2-weighted imaging. [11]. Hemorrhage may have variable signal intensity dependent on the age of blood products – hyperintense on T1- and T2-weighted sequences consistent with methemoglobin or hypointense with blooming artifact on T2-weighted sequences consistent with hemosiderin [1]. Soft tissue components typically demonstrate avid enhancement.

Differential Diagnosis:

The differential diagnosis for a space-occupying mass lesion with mineralization includes several benign and malignant etiologies. Diagnostic considerations may include myositis ossificans, soft tissue hemangioma with phleboliths, calcified metastasis, synovial sarcoma, epithelial sarcoma, pleomorphic sarcoma with metaplastic bone, and extraskeletal osteosarcoma [11,14,15].

Myositis Ossificans

Myositis ossificans (MO) is a benign process which is characterized by heterotopic ossification, usually within large muscles. This process can be seen at any age and is an important differential consideration when evaluating any new soft tissue mass with internal mineralization. The imaging appearance of MO varies in accordance with its stage of evolution. On radiographs, MO may present as nonspecific soft tissue swelling. As the underlying lesion evolves, mineralization becomes apparent at approximately 2-6 weeks, with the classic appearance of well-circumscribed peripheral mineralization at approximately 8 weeks [16]. CT demonstrates similar findings with an initial soft tissue mass which eventually develops a rim of peripheral mineralization and eventual mature trabeculae. The imaging appearance on MRI also varies depending on the stage of evolution. Lesions are typically isointense to adjacent muscle on T1 weighted imaging with heterogeneously hyperintense signal on T2-weighted imaging and post-contrast enhancement. There is often extensive edema within the surrounding soft tissues and musculature which may appear disproportionate to the size of the underlying lesion. This edema is unusual in most primary neoplasms and, along with the typical peripheral mineralized rim on radiographs/CT, allows for differentiation from malignant lesions.

Malignant Soft Tissue Sarcomas

Malignant soft tissue sarcomas other than ESOS may be difficult to differentiate preoperatively, as metaplastic bone formation with synovial, epithelial, and undifferentiated pleomorphic sarcomas may appear similar to ESOS. These lesions also demonstrate a variable appearance on CT and MRI related to necrosis and hemorrhage. However, there are some features which may guide in differentiation. Synovial sarcoma in particular may demonstrate the classic "triple signal" on T2-weighted imaging, with areas of high, intermediate, and low signal. In addition, these lesions are typically juxta-articular in location. However, close correlation between imaging findings and histopathology is important for accurate diagnosis, as these lesions lack the osteoid production of true ESOS.

Soft Tissue Hemangioma

Hemangiomas are a type of slow-flow venous malformation which represent approximately 7% of all benign soft-tissue tumors [17]. If large enough, they manifest as a smooth, palpable soft tissue mass with some patients experiencing chronic pain. Radiographs of soft-tissue hemangiomas classically demonstrate a soft tissue mass with associated phleboliths. At nonenhanced CT, there may be a soft tissue mass which demonstrates similar attenuation to muscle. Phleboliths may again be identified. On MRI, soft tissue hemangiomas typically demonstrate a heterogenous appearance with avid post-contrast enhancement. On T1-weighted imaging, the overall signal is often intermediate to slightly high relative to skeletal muscle. If the lesion is intra-muscular, there may be associated areas of increased T1 signal around the periphery of the lesion representing fatty tissue due to muscular atrophy. T2 weighted imaging typically demonstrates marked hyperintensity with areas of thin hypointensity related to fibrous septa between intra-lesional vessels. There may be an associated feeding vessel visualized.

Calcified Metastasis

Common calcifying metastases include breast cancer, papillary thyroid cancer, ovarian cancer (mucinous types), and mucinous adenocarcinoma (especially colorectal carcinoma). Pre-operative staging evaluation utilizing a multi-modality approach when confronted with a mineralized soft tissue mass is important, as staging CT or MRI may suggest an alternative diagnosis to a primary soft tissue sarcoma and allow for workup of alternative etiologies. The presence of a dominant soft tissue mass with internal mineralization and distant calcified lesions would favor the diagnosis of ESOS over one of the common calcifying metastatic lesions described previously.

Treatment:

There is a paucity of evidence regarding standardized treatment options for extraskeletal osteosarcoma given the rarity of the disease [18]. Treatment plans are typically based on standard treatment options for conventional osteosarcoma, and include wide surgical resection or amputation with doxorubicin and ifosfamide-based chemotherapy regimens [11,19]. Radiation therapy has been postulated to have a positive effect on local tumor control [19].

Prognosis:

The prognosis of extraskeletal osteosarcoma is poor, even when compared with conventional osteosarcoma. The most common site of metastatic disease is lung, followed by liver, bones, regional lymph nodes, and soft tissues [1]. The duration from primary tumor resection to subsequent tumor recurrence can vary from 2 months up to 10 years [11]. Tumor size helps predict outcomes with poorer survival for tumors greater than 5 cm; however, Roller et. al suggest that lower grade tumors and absence of metastatic disease are more important prognostic features [14,20]. Reported five-year survival varies, from as low as 28% in older studies to close to 47% in more recent studies [7,21].

TEACHING POINT

Extraskeletal osteosarcoma (ESOS) represents an extremely rare aggressive mesenchymal malignancy with a poor prognosis which arises in soft tissues. ESOS typically presents as a palpable heterogenous mineralized soft tissue mass, most commonly arising in the thigh which may be associated with a history of prior trauma or radiation therapy. The main differential diagnosis of myositis ossificans typically demonstrates peripheral rather than internal mineralization and improvement on short interval follow-up imaging. Given rarity of the disease, precise etiology and standardized therapy remain uncertain, and most employ treatment regimens similar to conventional intramedullary osteosarcoma. Accurate diagnosis requires close correlation between diagnostic imaging and histopathology.

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FIGURES

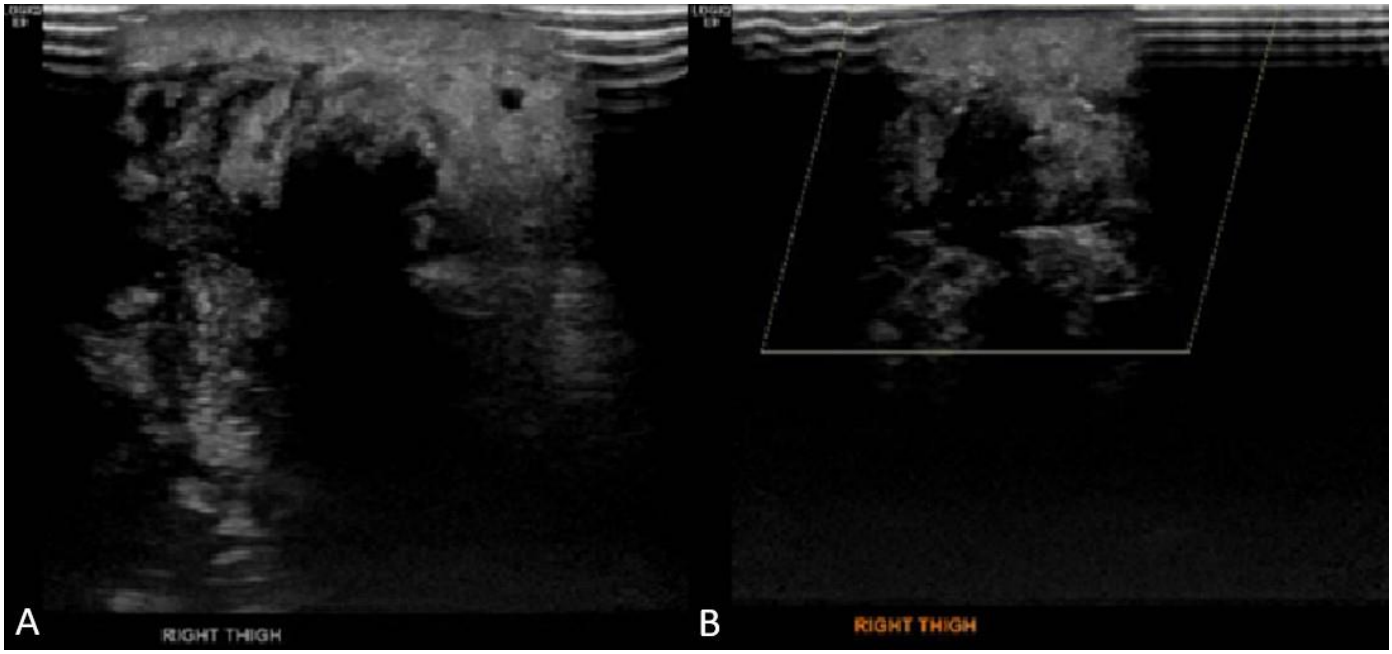

Figure 1: 46-year-old female with extraskeletal osteosarcoma of the right thigh.

Findings: Figure 1 A (Transverse B mode) and B (transverse duplex mode) ultrasound scan demonstrating an ill-defined heterogenous mass-like lesion correlating to the patient's area of clinical palpable concern. The sampled area demonstrates no significant internal vascularity.

Technique: Real-time ultrasound images of the right thigh soft tissues acquired on GE healthcare with 8-10 MHz linear probe.

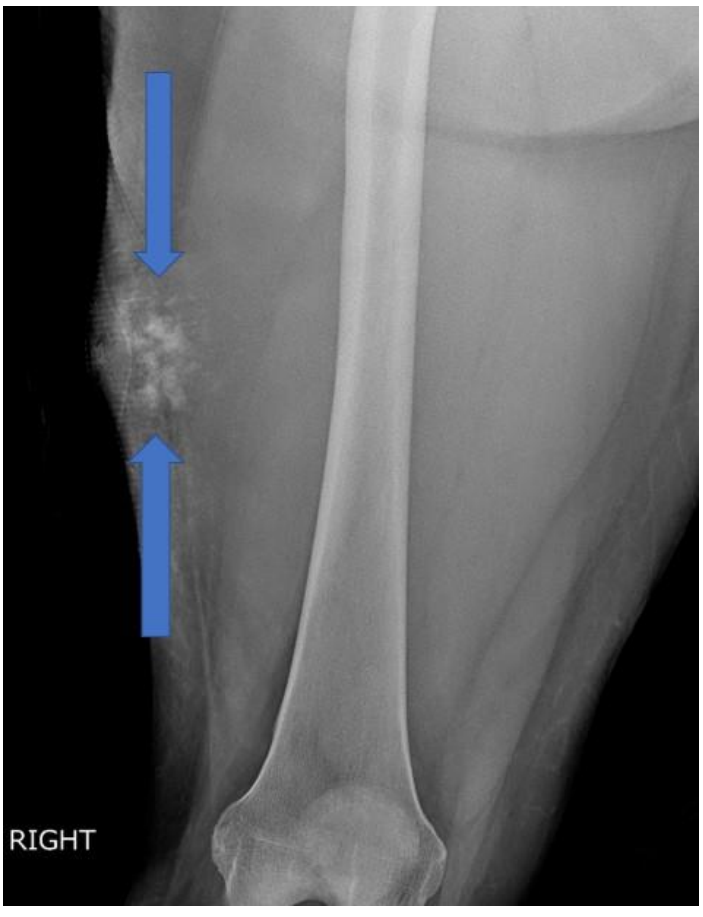

Figure 2 (left): 46-year-old female with extraskeletal osteosarcoma of the right thigh.

Findings: AP radiograph of the distal right thigh demonstrates a soft tissue mass (arrows) involving the lateral thigh with amorphous and cloud-like internal mineralization. The mass extends beyond the skin border which correlates to the fungating mass seen in figure 1. The mineralized portion of the mass does not appear to extend to the underlying femur.

Technique: Frontal radiograph of the distal thigh, 446 mA, 76 kV.

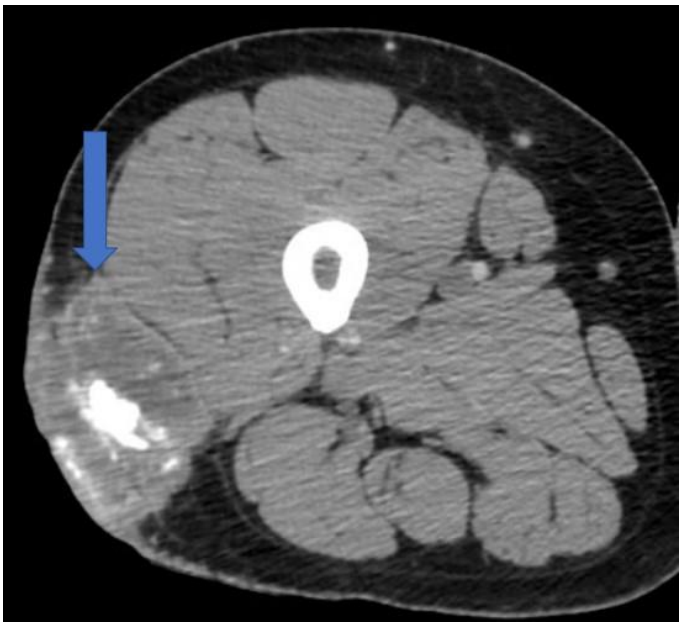

Figure 3: 46-year-old female with extraskeletal osteosarcoma of the right thigh.
Findings: Axial enhanced lower extremity CT demonstrates a heterogenous predominantly low density soft tissue mass (blue arrow) with central mineralization and mass effect upon the underlying investing fascia and lateral quadriceps muscle. The mass appears to extend to the skin surface with associated skin thickening. There is minimal peripheral lesional enhancement.
Technique: Axial CT of the thigh with contrast, 240 mAs, 140 kV, 2 mm slice thickness, 75mL of Isovue 370 contrast.

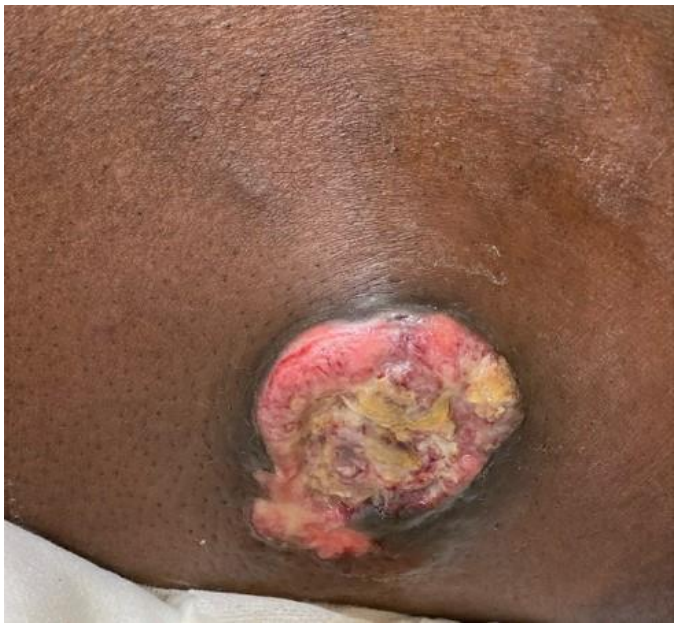

Figure 4: 46-year-old female with extraskeletal osteosarcoma of the right thigh.

Clinical picture which demonstrates a heterogenous fungating mass arising from the patient's lateral right thigh.

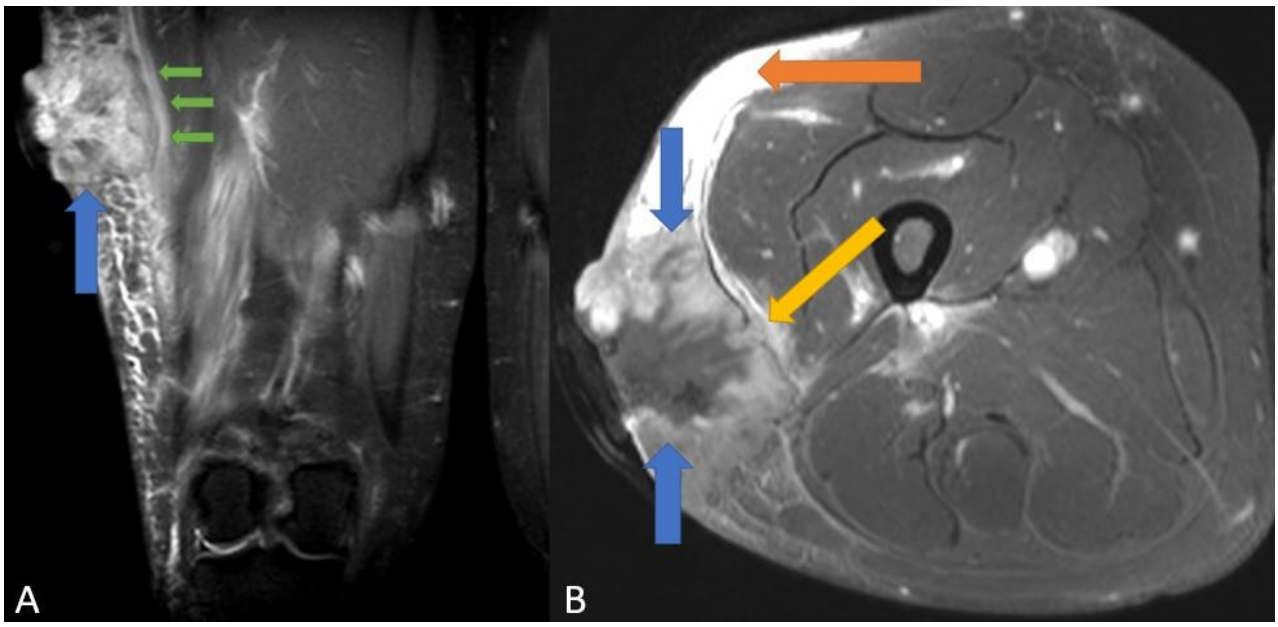

Figure 5: 46-year-old female with extraskeletal osteosarcoma of the right thigh.
Findings: (A) Coronal STIR thigh MR image demonstrates a 7.9 x 5.2 cm superficial soft tissue mass (blue arrows). The central portion of the mass demonstrates predominantly high T2 signal. There is surrounding reticular high T2 signal within the soft tissues consistent with edema. There is also intramuscular edema (green arrows).
(B) Axial post-contrast T1 subtraction image demonstrates a lobular superficial soft tissue mass which extends to the skin surface. There is predominantly peripheral enhancement of the lesion with central signal which appears isointense to muscle. The tumor exerts mass effect on the adjacent underlying musculature with apparent extension through the bordering fascia (yellow arrow). Note the inhomogeneous fat suppression anterior to the soft tissue mass (orange arrow).
Technique: MRI of the right thigh performed with contrast, 1.5 T, coronal STIR (TR 5378, TE 20), coronal T1 post contrast (TR 566, TE 20), 9.6 cc Gadavist contrast.

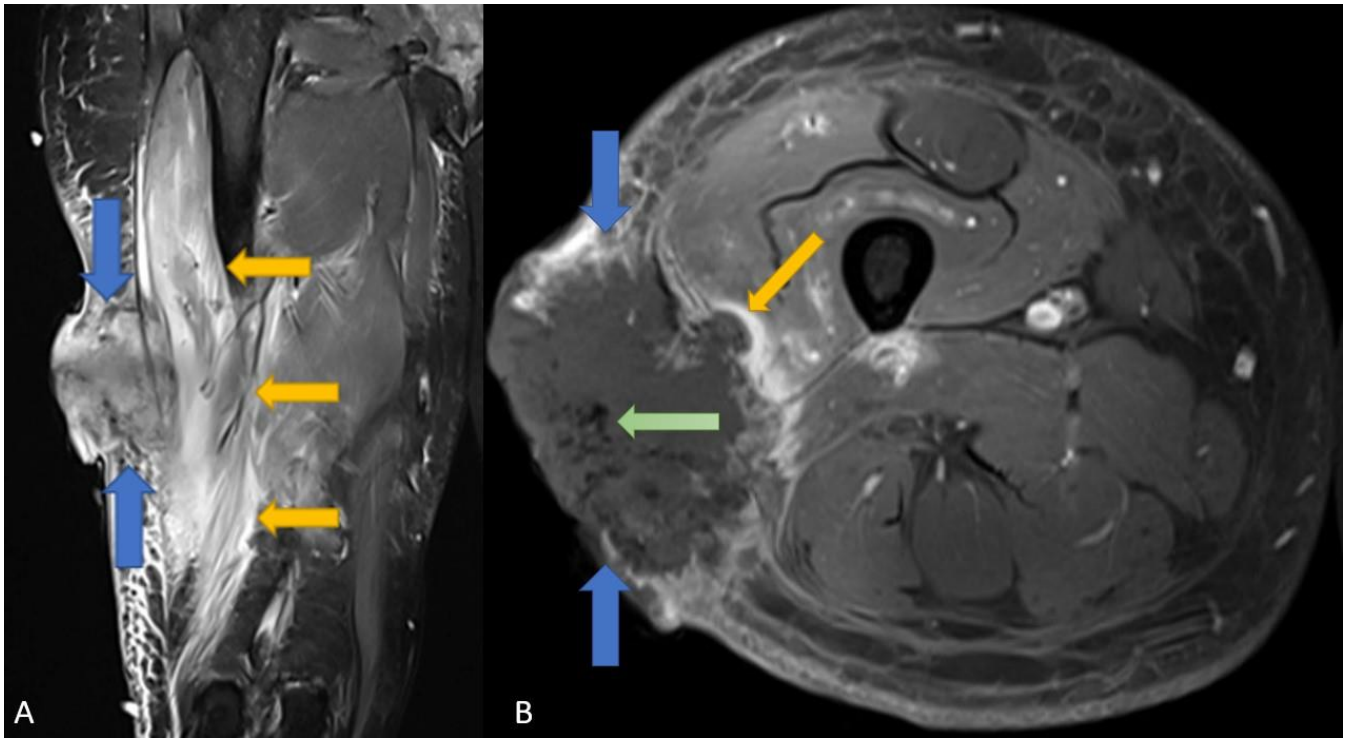

Figure 6: 46-year-old female with extraskeletal osteosarcoma of the right thigh.

Findings: (A) Coronal STIR image demonstrates soft tissue mass measuring approximately 10.3 x 5.3 cm (blue arrows). The mass demonstrates predominantly high T2 signal. There is extensive surrounding high T2 signal consistent with soft tissue and intramuscular edema (orange arrows). The overall size of the mass and degree of intramuscular edema is increased when compared with the original study performed approximately 4 months prior.
(B) Axial T1 contrast-enhanced thigh MR image demonstrating a superficial soft tissue mass (blue arrows). The central portion of the mass demonstrates predominantly low T1 signal which likely reflects a combination of necrosis and hemorrhage. There are additional foci of markedly hypointense T1 signal (pale green arrow) representing mineralization. Increased T1 signal in the surrounding soft tissues likely reflects edema and neovascularity. There is increased involvement of the adjacent fascia and muscular compartment compared with the original exam (yellow arrow).

Technique: MRI of the right femur performed with contrast, 1.5 T, coronal T1 post contrast (TR 533, TE 16), coronal STIR (TR 5351, TE 20), 9.6 cc Gadavist contrast.

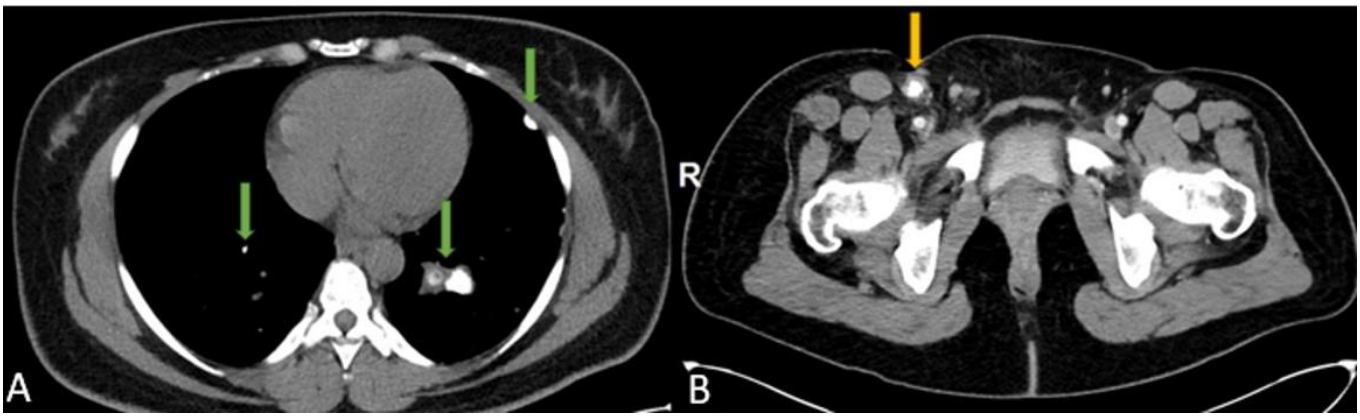

Figure 7: 46-year-old female with extraskeletal osteosarcoma of the right thigh.

Findings:
(A) Axial unenhanced chest CT demonstrates bilateral mineralized lung nodules (green arrows) suspicious for metastatic disease.
(B) Axial contrast-enhanced pelvic CT demonstrates an enlarged calcified right inguinal lymph node with abnormal morphology and size (orange arrow) concerning for metastatic lymphadenopathy.

Technique: Axial CT of the thorax without contrast and axial CT of the pelvis with contrast, 91 mAs (Figure 6a), 290 mAs (Figure 6b), 120 kV, 3 mm slice thickness, 125 cc Isovue 370 contrast.

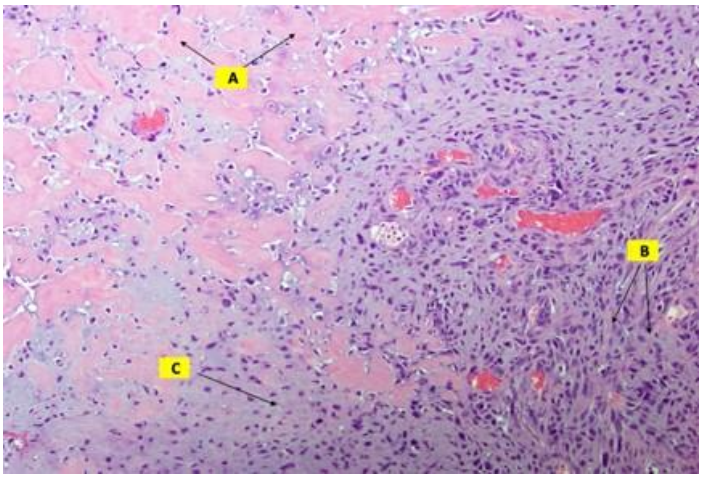

Figure 8 (left): 46-year-old female with extraskeletal osteosarcoma of the right thigh.

Findings: Hematoxylin and eosin stain demonstrating abundant osteoid formation and associated malignant spindle cells. Therapy changes include fibrous to hyalinized stroma and individual tumor cell necrosis. Magnification x200.
Annotations. A: osteoid matrix; B: Spindle Cell; C: tumor necrosis with fibrous to hyalinized stroma.

Etiology	Unknown but some cases have been linked to prior trauma or radiation.
Incidence	Sarcoma represents 1% of all adult malignancies. ESOS represents 4% of all adult sarcomas.
Symptoms	A progressively enlarging mass with pain
Gender and Age	No gender predilection. Peak incidence is the 5th to 6th decade of life.
Treatment	Wide surgical excision, chemotherapy, and radiation.
Prognosis	The prognosis is poor with 5-year survival rate can reach as low as 28%
Findings on Imaging	CT: soft-tissue attenuating lesion with calcification or osteoid matrix formation. MRI: Intermediate to low T1 signal with heterogeneously high signal on T2. There may be focal areas of decreased T1/T2 signal relative to skeletal muscle corresponding to areas of mineralization on CT. Solid regions typically demonstrate avid enhancement. US: solid heterogeneously hypoechoic to isoechoic mass with increased vascularity and posterior acoustic shadowing from calcification/osteoid matrix. FDG PET/CT: peripheral uptake with relative central photopenia representative of intralesional hemorrhage or necrosis.

Table 1: Summary table of extraskeletal osteosarcoma.

Diagnosis	Symptoms	CT Findings	MRI Findings	US Findings
Extraskeletal Osteosarcoma	Typically presents with an enlarging palpable painful mass.	Heterogeneous soft tissue mass with variable calcification/ ossification. May exert mass effect on surrounding structures. Distinctly separate from the skeleton.	Heterogeneously enhancing mass with intermediate to low T1 signal and high T2 signal. Intralesional hemorrhage and necrosis are common	Predominantly hypoechoic mass with internal calcification/osteoid matrix and associated posterior acoustic shadowing.
Synovial Sarcoma	Usually presents in the first three decades of life with a history of painless enlarging nodule.	Most commonly visualized as a heterogenous deep-seated mass which is isodense or hypodense to muscle. Areas of necrosis or hemorrhage are common. Calcification can be seen in approximately 27-41% of cases.	Heterogeneously lobulated soft tissue mass. May demonstrate isointense to slightly hyperintense T1 weighted signal to muscle. Classically associated with the "triple sign" on T2 weighted imaging with high signal in areas of necrosis/cystic degeneration, isointense signal due to soft tissue components, and low signal due to dystrophic calcifications and fibrotic bands.	Commonly seen as a focal, solid, hypoechoic soft tissue mass which can demonstrate irregular margins in a minority of cases.
Epithelioid Sarcoma	Typically presents as a painful subcutaneous or deep-seated nodule in the distal extremities of young adults.	Heterogenous lobulated mass which may demonstrate speckled calcifications. Osseous remodeling may be evident.	Variable appearance on MR imaging. Most commonly manifests as isointense to hypointense on T1 and T2 with variable enhancement depending on degree of necrosis and hemorrhage.	Usually homogenous hypoechoic solid mass with a well-defined border and positive color flow
Myositis Ossificans	Commonly presents with a history of specific injury or minor trauma with persistent muscular pain.	Variable appearance on CT depending on the timing of injury; will see low attenuating mass in the weeks after the initial trauma with eventual peripheral mineralization which gradually matures.	Presents early with isointense T1 weighted and heterogeneously hyperintense signal T2 weighted signal. There is typically surrounding muscular edema with diffuse contrast enhancement. Surrounding edema decreases over time with eventual signal close to bone in the late stage.	Variable appearance depending on stage, initially visualized as a hypoechoic mass which demonstrates eventual peripheral mineralization.
Soft Tissue Hemangioma	May present as palpable soft tissue mass associated with chronic pain.	On nonenhanced CT, soft tissue hemangiomas will demonstrate an ill-defined mass with phleboliths. Significant enhancement is typical after administration of contrast material.	Heterogenous on T1 and T2 weighted imaging. May demonstrate a peripheral high signal T1 rim which corresponds to muscular fatty atrophy. A feeding vessel may be visualized, best seen on T2.	Variable appearance, but classically presenting as a complex mass. If phleboliths are present, there may be acoustic shadowing.

Table 2: Differential diagnosis table for extraskeletal osteosarcoma.

ABBREVIATIONS

CT = Computed tomography
ESOS = Extraskeletal osteosarcoma
MRI = Magnetic resonance imaging
US = Ultrasound

KEYWORDS

Extraskeletal osteosarcoma; mesenchymal tumor; sarcomatous tumors; soft tissue sarcoma; spindle cell neoplasm; extraosseous osteogenic sarcoma; sarcoma; cancer