

# Rare Dual Lesion: Extraskeletal Osteosarcoma Developing Within a Simple Lipoma

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## Abstract

Extraosseous osteosarcoma is a rare malignancy, but simple lipomas are common. This article is the first report of a case of radiation-induced extraosseous osteosarcoma that developed within a simple lipoma in a 72-year-old woman. We correlate the magnetic resonance imaging, computed tomography, positron emission tomography, and plain radiographic findings. The patient, treated with systemic therapy and wide surgical resection of the neoplasm, remained clinically free of disease during the first 22 months of follow-up.

## Take-Home Points

- Rare and histologically indistinguishable from osteosarcoma of bone.
- Most common presentation is an enlarging mass in the thigh or buttock.
- Secondary extraosseous osteosarcoma usually arises in the field of prior external beam radiation or brachytherapy.
- Radiographic pattern of mineralization is central amorphous or cloudlike.
- On cross sectional imaging, the soft-tissue mass is separate from the underlying bone and periosteum.

Aside from multiple myeloma, osteosarcoma is the most common primary malignancy of bone, but extraosseous osteosarcoma is rare and accounts for only 1% of soft-tissue sarcomas and only 4% of all osteosarcomas.<sup>1-3</sup> Benign mesenchymal tumors, such as lipomas, are common, and they are estimated to outnumber their malignant counterparts by more than a factor of 100. However, the true ratio is unknown, as many clinically benign lipomas are not biopsied.<sup>4</sup> Conventional lipoma is the most common lipoma and is biologically indolent. Conventional lipoma generally does not transform biologically into a more aggressive type of neoplasm—

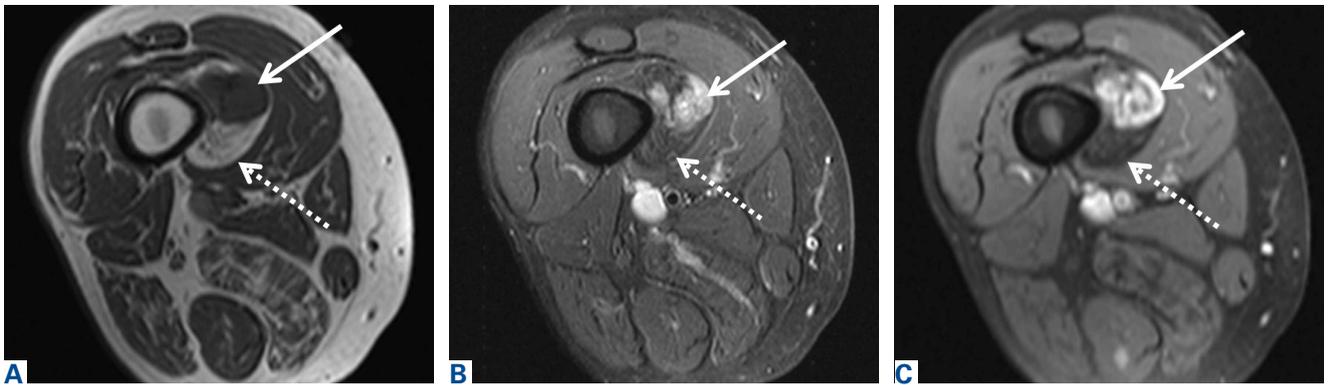
unlike atypical lipomatous tumors, which may demonstrate this type of evolution with multiple local recurrences.

This article is the first report of a case of radiation-associated extraosseous osteosarcoma that developed within a benign conventional lipoma. The patient provided written informed consent for print and electronic publication of this case report.

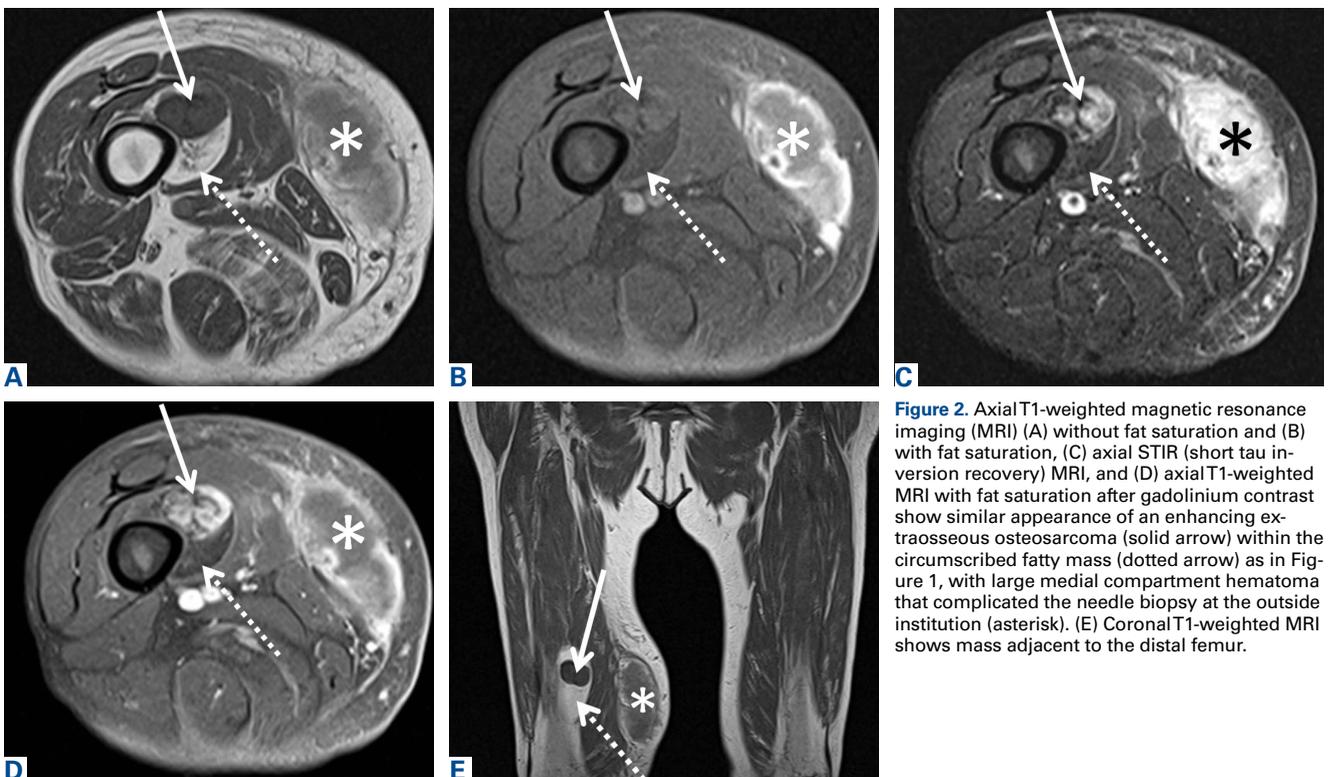
## Case Report

In March 2013, a 72-year-old woman presented to a general surgeon with a right thigh mass of several weeks' duration. The patient, who had a remote history of thyroid carcinoma, underwent thyroidectomy in 1991, excision of melanoma of the chest in 1998, and resection and adjuvant external beam radiotherapy (30 fractions) for Merkel cell carcinoma of the right proximal lateral leg (malignancy images unavailable) at an outside institution in 2003. Regional lymph node dissection at the time was negative. The patient remained disease-free the next 10 years. On presentation, magnetic resonance imaging (MRI) showed a 2.2-cm mass encircled by a tumor of lipomatous tissue within the vastus intermedius muscle, adjacent to but separate from the right distal femur (**Figures 1A-1C**). Clinical examination findings suggested the sarcoma had arisen at the margins of the radiation field, but more than 10 years had passed since initial treatment, and records were unavailable for confirmation. Results of a computed tomography (CT)-guided biopsy performed at an outside institution revealed a high-grade malignancy, either an extraosseous osteosarcoma or a dedifferentiated liposarcoma. After the biopsy, the patient developed a severe medial compartment hematoma that required angiography and embolization. She was then referred to the division of orthopedic surgical oncology at our institution.

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**Figure 1.** (A) Axial T1-weighted magnetic resonance imaging (MRI), (B) axial STIR (short tau inversion recovery) MRI, and (C) axial T1-weighted fat-saturated postcontrast MRI show an enhancing T1 isointense mass with heterogeneously hyperintense STIR signal within the vastus intermedius corresponding to the extrasosseous osteosarcoma (solid arrow) within a circumscribed mass of white fat corresponding to the simple lipoma (dotted arrow).

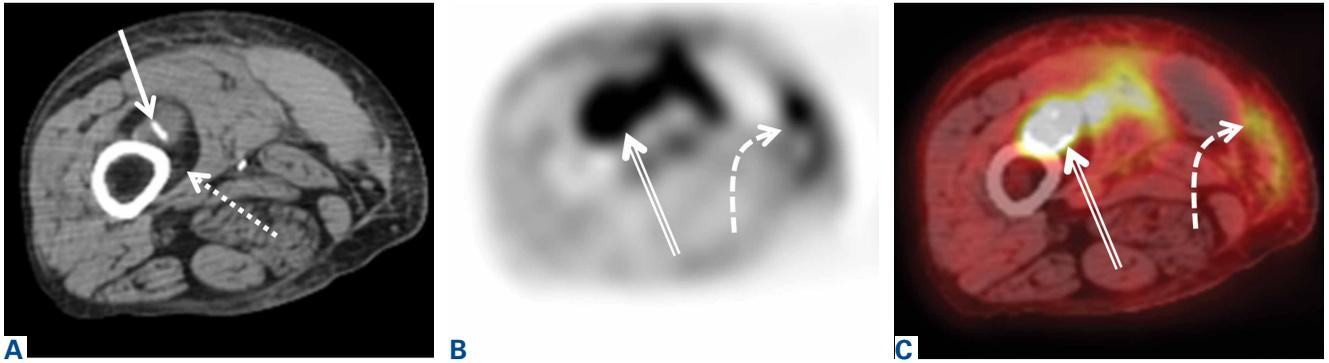


**Figure 2.** Axial T1-weighted magnetic resonance imaging (MRI) (A) without fat saturation and (B) with fat saturation, (C) axial STIR (short tau inversion recovery) MRI, and (D) axial T1-weighted MRI with fat saturation after gadolinium contrast show similar appearance of an enhancing extrasosseous osteosarcoma (solid arrow) within the circumscribed fatty mass (dotted arrow) as in Figure 1, with large medial compartment hematoma that complicated the needle biopsy at the outside institution (asterisk). (E) Coronal T1-weighted MRI shows mass adjacent to the distal femur.

Physical examination revealed marked ecchymosis of the left groin at the access site for embolization as well as massive ecchymosis and swelling along the right distal thigh, medial knee, and medial lower leg. The neurovascular structures were intact with full motor function and sensation distally, as well as normal distal pulses. No inguinal adenopathy was identified. The proximal portion of the prior radiation tattoo was at the inferior extent of the lesion on MRI.

The patient was treated with doxorubicin and

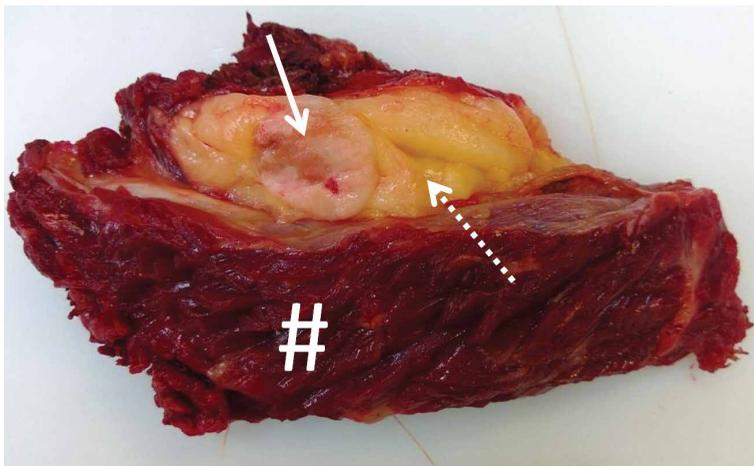
ifosfamide (2 cycles) while waiting for the hematoma to shrink. Contrast-enhanced MRI showed a 2.2-cm enhancing mass with isointense T1 signal and heterogeneously hyperintense STIR (short tau inversion recovery) signal surrounded by a circumscribed nonenhancing lipomatous tumor within the vastus intermedius muscle, adjacent to the distal femoral cortex. There was no invasion of the bone, and a fat plane between the enhancing mass and the femoral cortex was identified (**Figures 2A-2E**). Fluorine 18 (<sup>18</sup>F) fluorodeoxyglucose (FDG)



**Figure 3.** (A) Noncontrast axial computed tomography (CT) for attenuation correction, (B) axial fluorine 18 (<sup>18</sup>F) fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT (FDG-PET/CT), and (C) axial fused FDG-PET/CT show mineralization within the soft-tissue mass (straight solid arrow) within a circumscribed mass of fat density (dotted arrow), with marked FDG avidity (maximum standardized uptake value, 7.0) indicating hypermetabolism (double arrow). There is also expected FDG avidity at the hematoma (curved dotted arrow).



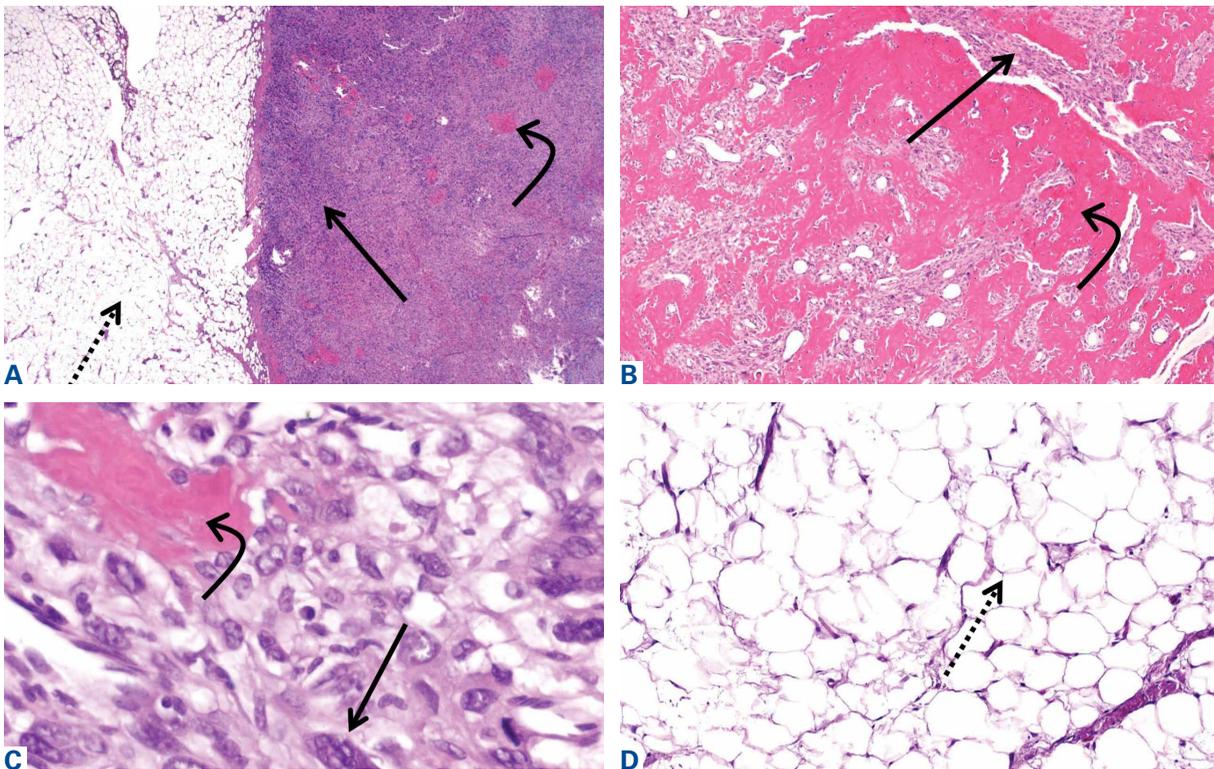
**Figure 4.** (A) Anteroposterior and (B) lateral radiographs show mineralization of the soft-tissue mass adjacent to the femur (straight arrow) and coil embolization material (curved arrows).



**Figure 5.** Gross pathology specimen shows an intramuscular (hashtag) encapsulated lobulated mass of adipose tissue (dotted arrow) containing a tan-white calcified solid component corresponding to the extraskeletal osteosarcoma (solid arrow).

positron emission tomography (PET)/CT (FDG-PET/CT) showed marked hypermetabolic activity within the soft-tissue mass (maximum standardized uptake value, 7.0), surrounded by metabolically nonactive fat. No hypermetabolic lung, bone, or soft-tissue metastases were seen. CT and plain radiographs showed the nonfat portion of the tumor had soft-tissue density and contained a central and peripheral curvilinear pattern of mineralization (**Figures 3A-3C, 4A-4B**). The primary differential diagnosis included myositis ossificans, chondrosarcoma, lipoma, parosteal lipoma (ossifying variant), liposarcoma with metaplastic bone, and dedifferentiated liposarcoma with osteosarcoma or chondrosarcoma component (see Discussion section).

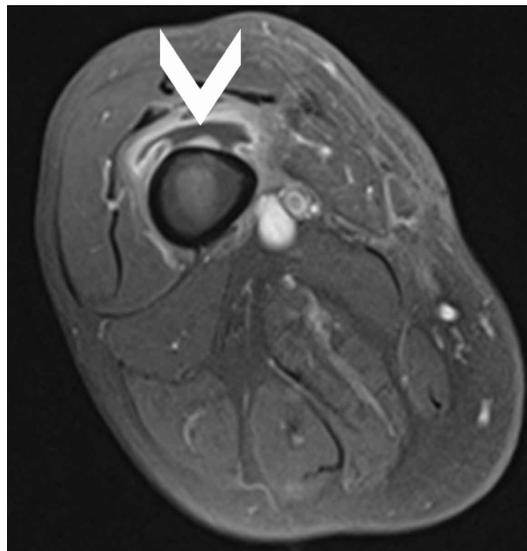
After 3 cycles of neoadjuvant chemotherapy with doxorubicin and ifosfamide, MRI showed a marked reduction in hematoma size, to 2.4 cm × 0.7 cm × 3.2 cm (estimated volume, ~3 mL), from 10 cm × 3.4 cm × 7.3 cm (estimated volume, ~130 mL), so the decision was made to proceed with surgery, excising the hematoma and sarcoma separately. First, wide resection of the hematoma yielded a 7-cm × 4-cm resection specimen with negative margins on frozen section. Subsequently, definitive radical resection of the tumor with wide margins yielded a 13-cm × 9-cm × 4-cm specimen. The resection specimen contained an intramuscular, mobile, encapsulated 2.0-cm × 1.5-cm × 1.0-cm mass with 2 components. The first was a tan-white solid mass containing thin deposits of calcified matrix, and the second, which surrounded the first, was composed of well-circumscribed soft yellow lobulated adipose tissue (**Figure 5**). Microscopic evaluation revealed that the tan-white mass consisted of a hypercellular proliferation of malignant spindle and polyhedral cells that exhibited marked pleomorphism and hyperchromasia and



**Figure 6.** (A, B) Low-power and (C, D) high-power hematoxylin-eosin microscopy reveals the conventional lipoma (dotted arrow) sharply demarcated from the extrasosseous osteosarcoma (curved arrow). Neoplastic bone (curved arrow) is eosinophilic and trabecular in architecture and is surrounded by sheets of cytologically malignant cells (straight arrow).

produced extracellular coarse lace-like neoplastic bone characteristic of a high-grade extraskeletal osteosarcoma (**Figures 6A-6D**). The sarcoma was sharply demarcated from the surrounding fatty component, which consisted of lobules of mature white adipocytes with no cytologic atypia, characteristic of a lipoma. An estimated 60% of the neoplasm was the lipoma, and the other 40% was the osteosarcoma. Immunohistochemistry revealed the tumor cells from both components to be negative for desmin, myogenin, CDK4, and MDM2. P16 showed cytoplasmic staining of the malignant cells, and these results helped exclude the possibility of dedifferentiated liposarcoma. All resection margins were negative, including the deep margin of the femoral periosteum. In addition, the resected hematoma did not contain malignant cells.

After surgery, the patient's dermatologist performed a shave biopsy of a lentiginous lesion anterior to the knee. Subsequently, the patient began having increasing knee pain and developed, on the lower extremity, small areas of erythema that were attributed to mild cellulitis. Four months after surgery, emergent contrast-enhanced MRI showed enhancement of thickened synovium of the knee joint (**Figure 7**). The patient underwent



**Figure 7.** Four-month follow-up axial gadolinium contrast-enhanced magnetic resonance imaging shows thick synovial enhancement (chevron). Aspiration yielded 51,000 white blood cells, highly suspicious for infection, despite no growth on fluid culture. Subsequent synovial biopsy yielded acute and chronic inflammatory cells compatible with infection, without malignant cells.

arthroscopic lavage and synovial biopsy for septic arthritis after knee aspiration yielded 51,000 white blood cells with a negative bacterial culture. The

biopsy yielded acute and chronic inflammatory cells compatible with infection. No malignant cells were identified, and the bacterial culture was negative.

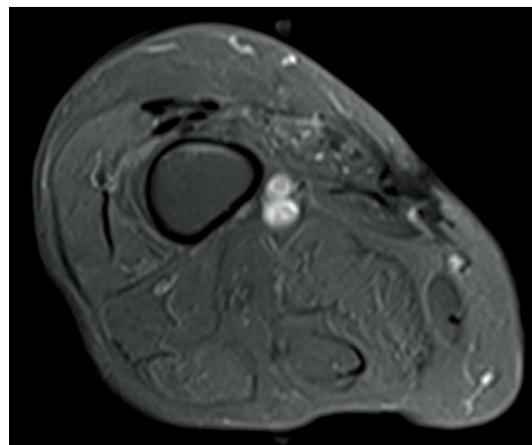
Since the lavage, the patient remained in good condition. There was no evidence of local recurrence on contrast-enhanced MRI (**Figure 8**), or metastases the first year, and she remained clinically free of disease the first 22 months of follow-up.

### Discussion

Extrasosseous osteosarcoma, typically a high-grade malignant neoplasm of the soft tissues that produces osteoid or cartilaginous matrix, is histologically indistinguishable from osteosarcoma of bone. It usually occurs in the sixth decade of life, and there is a slight male predominance.<sup>1,3,5,6</sup> The most common presentation is an enlarging mass that may be painful. This mass often originates within the deep soft tissues of the lower extremities, especially the thigh and buttock, and less frequently in the upper extremity, retroperitoneum, and torso.<sup>6</sup> Secondary extrasosseous osteosarcoma accounts for 4% to 13% of extrasosseous osteosarcoma and usually arises in the field of prior external beam radiation or brachytherapy.<sup>1-3</sup>

Conventional lipoma, the most common subtype of lipoma, is a benign mesenchymal tumor. Other subtypes are hibernoma, fibrolipoma, angiolipoma, myelolipoma, spindle-cell lipoma, pleomorphic lipoma, and atypical lipomatous tumor.<sup>7</sup> Atypical lipomatous tumor and well-differentiated liposarcoma are distinguished from each other by location: The World Health Organization recommends the term *atypical lipomatous tumor* for tumors that arise in the extremities and trunk lesions and *well-differentiated liposarcoma* for neoplasms that develop in the retroperitoneum, peritoneum, mediastinum, spermatic cord, and thoracic cavity.<sup>8</sup> On PET, hypermetabolic activity is nonspecific and can be seen in malignant tumors and some benign reactive processes, such as evolving heterotopic ossification. However, simple lipomas, including those with mature ossification or dystrophic calcification, do not manifest increased FDG avidity.<sup>9</sup>

We are not aware of any published cases of extrasosseous osteosarcoma arising within a conventional lipoma. A limited number of cases of coexisting conventional lipoma and spindle-cell lipoma or liposarcoma have been reported.<sup>10-13</sup> Retroperitoneal liposarcoma with areas of dedifferentiation into osteosarcoma has also been described.<sup>14</sup> Development of malignant fibrous histiocytoma and liposarcoma have also been re-



**Figure 8.** One-year follow-up axial gadolinium contrast-enhanced magnetic resonance imaging shows no evidence of local recurrence.

ported within intraosseous lipomas.<sup>15</sup> One theory is based on premalignancy as a biological concept as opposed to a morphologic one. In other words, lesions that may be considered morphologically benign may already have the biological phenotype for malignancy that is not yet reflected morphologically.<sup>16</sup> However, it has been suggested that such findings may instead result from initial sampling error or histologic misdiagnosis.<sup>17,18</sup>

There is a spectrum of findings on imaging studies of extrasosseous osteosarcoma. Plain radiographs show a soft-tissue density with variable degrees of central calcification that reflects mineralization of deposited neoplastic bone. The pattern of calcification is characteristically amorphous or cloudlike, as opposed to the ring-and-arc observed in cartilage matrix. On CT, the soft-tissue mass of extrasosseous osteosarcoma is separate from the underlying bone and periosteum—a defining characteristic that distinguishes it from conventional intramedullary and juxtacortical osteosarcoma.<sup>6</sup> The central pattern of amorphous calcification helps to differentiate extrasosseous osteosarcoma from heterotopic ossification, which characteristically demonstrates zonation, with trabecular architecture and mature cortical bone peripherally.<sup>1</sup> Enhancement of extraskeletal osteosarcoma tends to be heterogeneous and depends on the quantity of necrosis. Extraskeletal osteosarcoma tends to be isointense on T1-weighted MRI and mildly hyperintense on T2-weighted MRI.<sup>1,6</sup> Areas of very low signal intensity on both T1- and T2-weighted MRI may reflect mineralization.<sup>19</sup> If intratumoral hemorrhage has occurred, there may be signal intensity of blood products of various ages.<sup>1,3</sup> Tumors with

abundant hemorrhage can be mistaken for hematoma. FDG-PET radiotracer accumulation tends to be intense peripherally with variable central activity depending on quantity of necrosis and hemorrhage.<sup>1</sup>

The radiologic differential diagnosis includes myositis ossificans, chondrosarcoma, parosteal lipoma (ossifying variant), liposarcoma with metaplastic bone, dedifferentiated liposarcoma with osteosarcoma or chondrosarcoma component, and malignant mesenchymoma. Other common soft-tissue sarcomas, such as fibrosarcoma, leiomyosarcoma, and pleomorphic undifferentiated sarcoma, are excluded by the presence of fat within the tumor. The radiographic pattern of osteoid matrix produced by the tumor in our patient may be seen in heterotopic ossification, but the absence of mature ossification with zonation was evidence against heterotopic ossification, and microscopically it was neoplastic rather than reactive osteoid. In addition, it is possible that, because of the small size of the soft-tissue component, it was difficult to appreciate the less mature osteoid matrix peripherally. The lack of characteristic rings and arcs helps exclude benign and malignant cartilage containing neoplasms. Malignant mesenchymoma is a diagnosis of exclusion, and such tumors are usually better classified as sarcomas that have undergone heterologous differentiation.

The histologic diagnosis of extraosseous osteosarcoma requires identification of malignant mesenchymal cells that secrete neoplastic osteoid that may or may not mineralize. It is important to exclude the possibility that the malignant bone-forming tumor is part of a different type of sarcoma, the most common being dedifferentiated liposarcoma. Immunohistochemistry can be helpful in this situation, as dedifferentiated liposarcomas demonstrate nuclear expression of MDM2, CDK4, and p16, a constellation of findings rare in conventional and extraosseous osteosarcoma.<sup>20-23</sup> Osteosarcoma has not previously been reported as arising in a lipoma; in our patient's case, we excluded the possibility that the fatty component represented an underlying atypical lipomatous tumor/well-differentiated or dedifferentiated liposarcoma on the basis of morphology and lack of expression of MDM2, CDK4, and p16.

Although histologically identical to osteosarcoma of bone, extraosseous osteosarcoma is treated differently because of its relatively decreased chemosensitivity and radiosensitivity. Treatment tends to be focused on limb-sparing wide local excision, and local recurrence complicates about 50% of cases.<sup>1</sup> Neoadjuvant or adjuvant treatment with radiation

or chemotherapy is often provided.<sup>6</sup> Platinum and doxorubicin chemotherapeutic agents, which are first-line treatments for osteosarcoma of bone, tend to be less effective in extraosseous osteosarcoma, and ifosfamide is more often used instead.<sup>5</sup>

Primary extraosseous osteosarcoma classically has a poor prognosis, with 2- to 3-year mortality of 50%, and prognosis tends to be worse for secondary radiation-induced sarcomas than for primary sarcomas.<sup>2,6</sup> However, with there being improved treatment protocols involving surgery and chemotherapy, more recent 5-year survival rates without metastatic disease are between 60% and 80%, though there is no definite consensus regarding the optimal systemic therapy regimen.<sup>1,24</sup> In a 2014 review of 53 patients who presented with localized disease, Choi and colleagues<sup>25</sup> identified a 3-year cumulative 39% incidence of death caused by disease, and in 2016 Sio and colleagues<sup>26</sup> reported that 55% of patients, most of whom had stage 3 disease, were alive at median follow-up of 45 months. Similar to osteosarcoma of bone, metastases may develop up to 10 years after primary treatment and are most commonly to the lung (80%-88%). Because extraosseous osteosarcoma is rare, no definite prognostic factors have been determined, but metastases at presentation and large tumor size (>5 cm) likely portend a worse prognosis.<sup>2,3,27</sup> Fibroblastic and chondroblastic subtypes may have a slightly better prognosis.<sup>6,28</sup>

## Conclusion

Extraosseous osteosarcoma is a rare malignancy that should be considered in the appropriate clinical and imaging scenario. This article is the first report of a case of a radiation-associated extraosseous osteosarcoma that developed within a lipoma with preoperative and postoperative multimodality imaging.

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