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Case Report

Radiation-induced osteosarcoma following treatment of Ewing's sarcoma

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ABSTRACT

Radiation-induced sarcomas are a known, rare, complication from prior therapeutic radiation therapy. Radiation-induced sarcomas have been reported to have poor associated prognoses with increased morbidity and mortality when compared to primary sarcomas. In this case report, we discuss a 27-year-old female who presented at the age of 17 during pregnancy with an inability to bear weight and was subsequently diagnosed with Ewing's sarcoma of her femur. Adequate response to treatment was obtained with the initial treatment and the patient presented with acute, severe pain of her femur at the site of prior Ewing's. Extensive workup demonstrated radiation-induced osteosarcoma at the site of her prior Ewing's sarcoma in the radiation field. Multidisciplinary teams including orthopedics, pathology, medical oncology, and radiology are vital for appropriate and efficacious diagnosis of radiation-induced sarcomas. Despite the rarity of radiation-induced sarcoma, the ability to recognize and diagnose recurrent sarcoma is important for radiologists, particularly considering the associated poor prognosis. Early diagnosis and aggressive multidisciplinary treatment is crucial to improving patient morbidity and mortality. In this case, the diagnosis of radiation-induced osteosarcoma allowed expedited workup and initial aggressive, lifesaving treatment for our patient.

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Case report

A 17-year-old female presented to her obstetrician 10 years prior with right leg pain and swelling with an inability to bear weight during her 6th month of pregnancy. Symptoms were initially attributed to pregnancy, although the inability to bear

weight persisted 2 months' postpartum. At this time, multiple imaging studies were performed including radiographs, MRI, and positron emission tomography (PET) imaging. Axial T1 pre- and postintravenous gadolinium administration demonstrated a cortically based, heterogeneous mass with a large and avidly enhancing soft tissue component involving the posterolateral aspect of the proximal femur (Figs. 1 and 2).

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The views expressed in this presentation are those of the author(s) and do not reflect the official policy of the Department of the Army, the Department of Defense, or the US Government.

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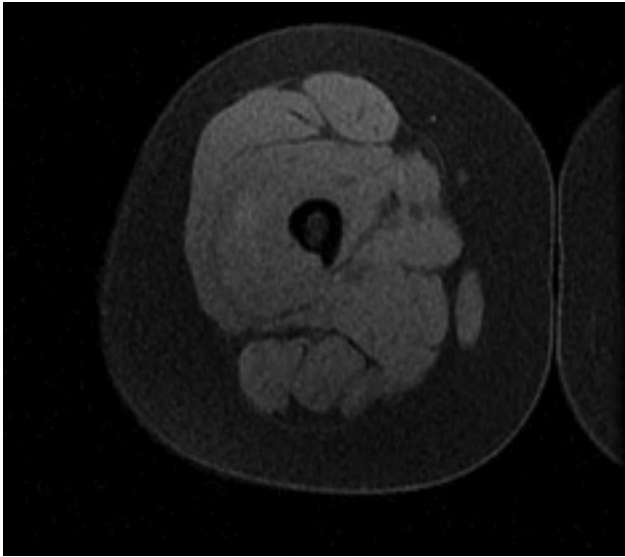


Fig. 1 – Axial T1 precontrast (2009). Focal cortical thinning of the posterolateral femur with a large surrounding T1 hyperintense soft tissue mass.

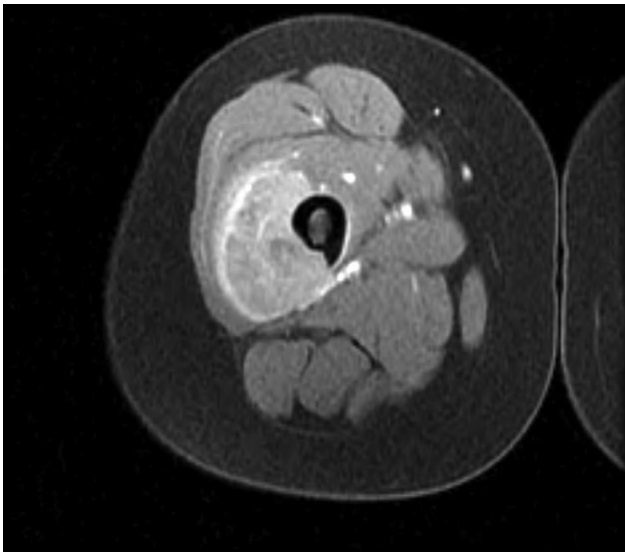


Fig. 2 – Axial T1 postcontrast (2009). Avid contrast enhancement is noted both of the cortex and the adjacent soft tissue mass.

Our patient underwent a core needle biopsy and was subsequently diagnosed with Ewing's sarcoma.

Multiple cycles of chemotherapy and high-dose radiation therapy, total dosage of 66 Gray, were administered per oncologic guidelines. During routine post-treatment surveillance, a follow-up MRI was performed in 2012 and the Axial T1 pre- and postcontrast images demonstrated a residual T1 hyperintense cortical irregularity with no internal enhancement of the posterolateral right femur. The previously identified avidly enhancing soft tissue mass had completely resolved in the interim (Figs. 3 and 4). This was consistent with appropriate treatment response and cure of Ewing's sarcoma.

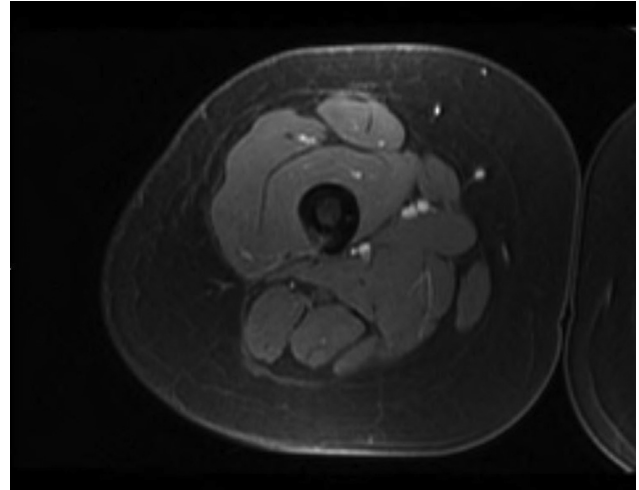


Fig. 3 – Axial T1 precontrast (2012). Interval absence of the previously seen soft tissue mass with residual cortical irregularity of the posterolateral femur.

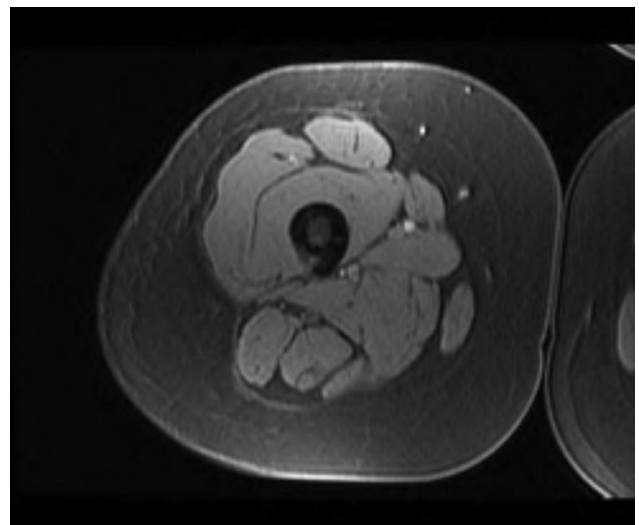


Fig. 4 – Axial T1 postcontrast (2012). No abnormal enhancement seen of the soft tissues or osseous structures consistent with appropriate treatment response.

Six years later, 10 years from initial diagnosis, our patient represented with new, severe, right-sided posterolateral thigh pain involving the same location as her previously diagnosed and treated Ewing's sarcoma.

Initial radiographs performed January 16, 2019 showed an ovoid, eccentrically located lucent focus involving the lateral right femur, at the site of prior Ewing's sarcoma, with a relatively narrow zone of transition, no loss of cortical integrity or evident soft tissue component (Fig. 5).

Due to her prior history of Ewing's sarcoma at this location, an MRI of the femur was ordered which showed a destructive cortical irregularity of the posterolateral femur at the site of prior radiation treatment for her prior Ewing's sarcoma. This juxtacortical irregularity demonstrated increased T2

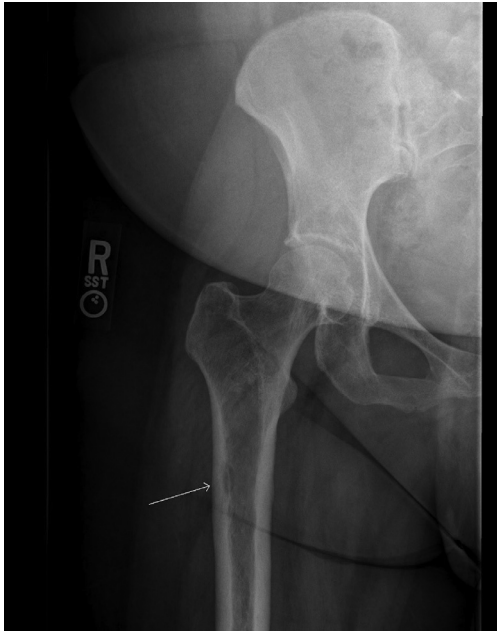


Fig. 5 – AP radiograph (2019). Small ovoid lucency of the posterolateral cortex at the site of prior radiation. No obvious soft tissue mass or definitive cortical break.

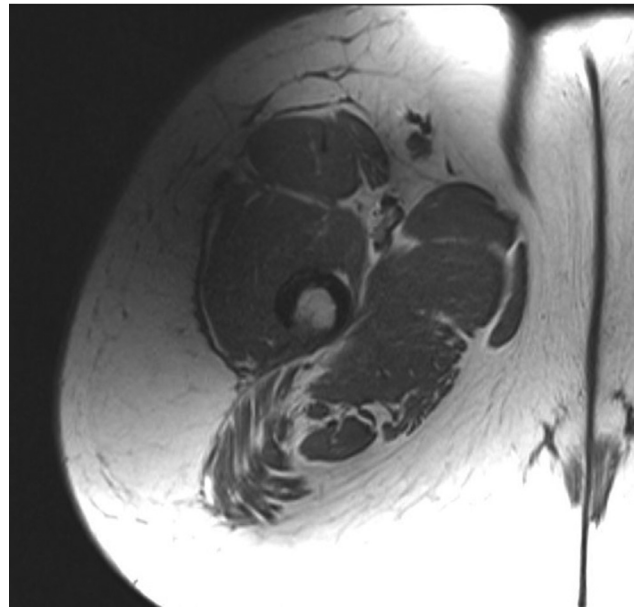


Fig. 7 – Axial T1 precontrast (2019). Increased conspicuity of the cortical irregularity of the posterolateral femur compared to 2012. No definitive soft tissue component.

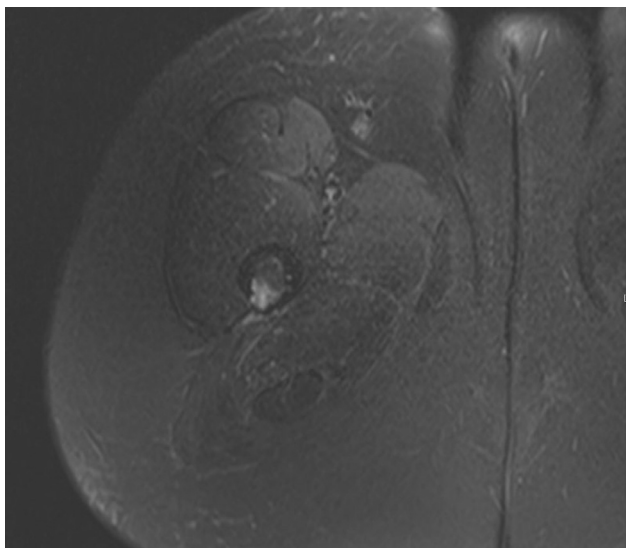


Fig. 6 – Axial T2 fat saturation (2019). Increase T2/fluid signal at the site of prior cortical thinning involving the posterolateral femur. Subtle increased T2 signal within the adjacent soft tissues.

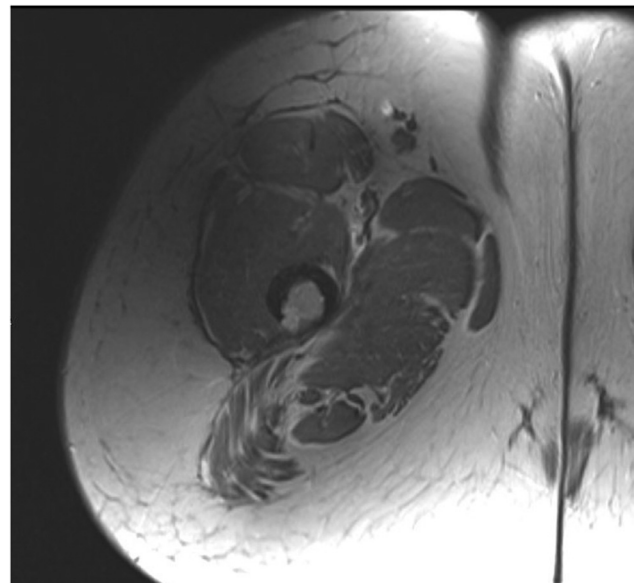


Fig. 8 – Axial T1 postcontrast (2019). Avid cortical enhancement at the site of cortical irregularity with no definitive soft tissue enhancement.

signal and avid cortical contrast enhancement without a significant soft tissue component (Figs. 6–8). These findings were concerning for a new, aggressive neoplastic process.

Secondary to this concern, a PET scan was performed January 23, 2019 that demonstrated an increased uptake in fluorodeoxyglucose (FDG) with a maximum standardized uptake value (SUV) of 2.2 (Fig. 9). No other findings concerning for metastatic disease were found on PET.

CT-guided biopsy by interventional radiology was performed on February 25, 2019. Pathologic evaluation demonstrated a moderately differentiated, high-grade radiation-associated osteosarcoma (Figs. 10 and 11), which originated from the site of her prior irradiated Ewing's sarcoma of femur. Ten weeks of neoadjuvant chemotherapy was initiated in July 2019.

After completion of the initial chemotherapeutic regimen, she went on to receive a radical resection of the right proximal

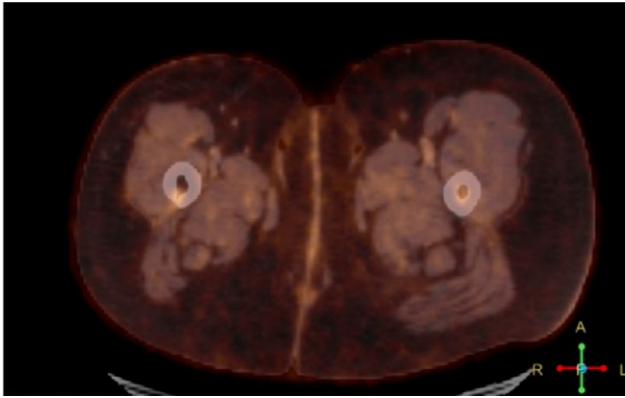


Fig. 9 – PET (2019). Increased FDG avidity (SUV 2.2) of the posterolateral right femur corresponding to the location of enhancement on MRI.

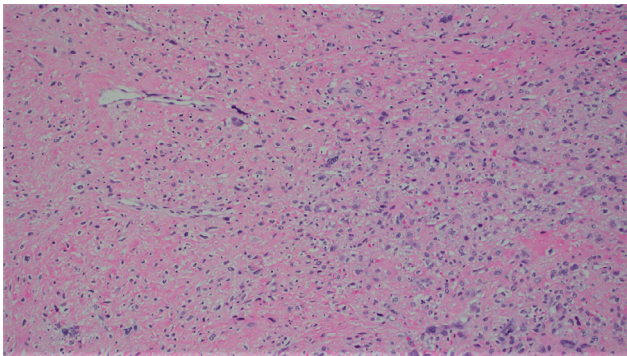


Fig. 10 – Hematoxylin and eosin stained section demonstrating hypercellularity with abundant pleomorphic spindled cells with marked pleomorphism and an osteoid matrix in the background. The cells demonstrate a high nuclear to cytoplasmic ratio, irregular nuclear contours, and vesicular chromatin.

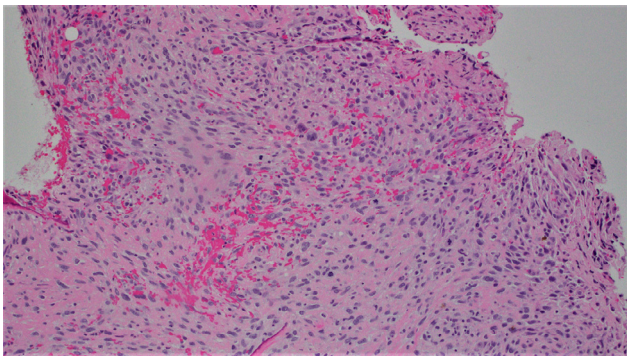


Fig. 11 – Hematoxylin and eosin stained section demonstrating a hypercellular spindle cell proliferation with marked pleomorphism and hemorrhage. Highly mitotic areas are present with numerous atypical mitotic figures. A background osteoid matrix is present.

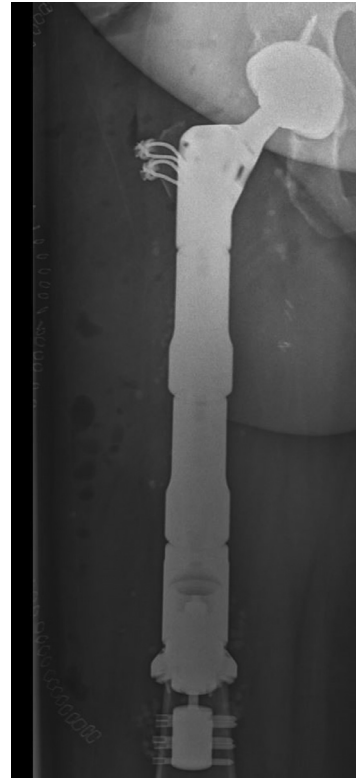


Fig. 12 – AP radiograph (2019). Interval proximal femoral replacement status post tumoral resection. Expected postoperative edema and subcutaneous emphysema noted in the surgical bed. Antibiotic beads noted within the surgical bed as well.

femur with proximal femoral replacement on October 30, 2019 [Figure 12](#).

Follow-up

Surgery was tolerated well without complications. Pathology demonstrated negative margins with complete tumoral excision of a 3.7 cm lesion. Patient will likely continue chemotherapy postoperatively at the discretion of her medical oncologist.

Discussion

Radiation-induced sarcomas (RIS), including soft tissue and bone sarcomas are a known, albeit rare, complication of primary radiation therapy. The definition for RIS has undergone multiple changes throughout the years, initially Cahan et al [1] established the definition for a RIS as a histologically confirmed sarcoma in a prior irradiated field, where there was either no microscopic lesion or a radiographically proven non-malignant lesion, and diagnosed after a latency period of at least 5 years. This definition has been revised several times,

most notably by Arlen et al [2], which has included preirradiation malignant tumors devoid of osteoblastic activity and shortened the latency interval to 3–4 years. The latency period has been shown to traverse a wide range, cases have been seen to develop anywhere from 6 months to 64 years after initial radiation treatment [3–5].

As above, RIS is a rare occurrence. A large Finnish study demonstrated that RIS in all treated parts of the body with prior radiation led to development of malignancy in approximately 0.05% of all treated patients. Furthermore, the risk of developing a bone sarcoma in the setting of prior radiation was approximately 0.004% [6]. However, in the setting of radiation-induced bone sarcomas, osteosarcoma accounts for 50%–70% of all diagnoses [7,8].

Secondary RIS have, for the most part, demonstrated worse prognoses than primary sarcomas. Reasons for these reported poor prognoses of RIS are multiple and include late diagnosis with metastatic disease, high/advanced grade of tumor at diagnosis, surgical difficulty due to tumor size/location, inability to provide full dose radiation therapy in a previously irradiated field and limited chemotherapy options after prior chemotherapeutic regimens [9–13].

Studies have demonstrated that the prognosis of RIS has significantly improved over time with early detection and aggressive surgical and chemotherapeutic regimens. For example, a study performed in the 1970s by Sim et al [14] showed a mean survival time of 1.1 years after the diagnosis of RIS. Recently, multiple studies have shown 5-year survival rates ranging from 10% to 50% [3,5,7,11]. Contrarily, other studies have shown that RIS demonstrates similar prognosis to primary bone sarcomas, with 5-year disease-free survival ranging from 50% to 70% when treated with aggressive surgical and chemotherapy regimens in the setting of no metastatic disease [3,8]. Additional factors affecting long-term survival include RIS location, with limb sarcomas demonstrating a 60%–70% 5-year survival versus a 10%–20% 5-year survival when compared to centrally located sarcomas. Wide, local resection is the mainstay of treatment in RIS. Peripheral lesions are more amenable to wide, local resection versus surgically difficult and/or impossible central lesions [7,15]. The study by Kalra et al [7] showed that wide, local resection with aggressive chemotherapy led to a 41% survival rate at 5 years compared to a mean survival time of 8.8 months with palliative treatment.

Adjuvant and neoadjuvant chemotherapy are not well described in the literature given the relative rarity of RIS without any randomized control trials addressing the risks and benefits. Mixed data are currently presented in the literature with some studies showing chemotherapy providing no significant benefit in disease-free survival [16]. Meanwhile, other studies have demonstrated 65% complete remission with aggressive chemotherapy before and after wide local surgical resection [17].

The literature is limited in regards to reirradiation treatment these cases. One study in particular demonstrates a median survival time of 15.5 months with reirradiation treatment and hypothermia, although this notably involved nonresectable tumors of the chest wall [18]. More literature and data are needed in the future to determine the utility of radiation therapy for these patients.

In summary, RIS are a rare, but well-documented entity with associated high morbidity and mortality for patients receiving prior therapeutic radiation, even radiation received several years prior. Aggressive cancer surveillance postradiation is vital to improving patient morbidity and mortality. Surgical intervention with negative margins is the most important factor affecting long-term survival with more data needed to be obtained for reirradiation and chemotherapy.

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