A Rare Case of Osteosarcoma and Rhabdomyosarcoma at the Same Site 7 Years Apart

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Three decades ago, most patients with bone sarcomas underwent amputation for survival. Since then, advances in diagnostic techniques and imaging modalities, neoadjuvant chemotherapy, and radiation therapy have facilitated limb-salvaging procedures, which are being performed routinely. Survival has also improved, with 5- and 10-year disease-free rates of 60% and higher.[1-3] With improved survival, treatment-related late complications are more likely to occur.[4] One of the most significant complications in long-term survivors is development of a second malignant neoplasm (SMN).[4] It is estimated that approximately 3% of survivors will develop a second malignant tumor within 20 years.[1,4] It is hypothesized that this predisposition to additional malignancies may be related to type of treatment used for the first cancer or to the patient's genetic predisposition to malignancy.[1,4,5] Anthracyclines (eg, doxorubicin) have been associated with increased risk for developing a secondary soft-tissue sarcoma.[4] Radiation therapy is also known to contribute to malignant transformation, though the relationship between relative risk and radiation dose has not been established.[1,6,7] Genetic disorders, such as Li-Fraumeni syndrome, neurofibromatosis, and retinoblastoma, are well known to be associated with multiple neoplasms in different locations.[8]

Rhabdomyosarcoma is the most common soft-tissue sarcoma arising in children and adolescents.[2] Over the past 3 decades, multidisciplinary approaches to treating this cancer have raised the 5-year survival rate to more than 70%.[8,9] Several cases of a patient developing both rhabdomyosarcoma and osteosarcoma have been reported,[1,6,10] but each case involved radiation therapy in primary rhabdomyosarcoma subsequently leading to osteosarcoma in the radiation zone. Recently, Dagdemir and colleagues[11] reported the case of primary pleomorphic rhabdomyosarcoma developing 5 years after limb-sparing surgery and neoadjuvant chemotherapy for osteosarcoma. However, the osteosarcoma involved the femur, but the rhabdomyosarcoma occurred in the head of the humerus—that is, 2 separate and distinct anatomical locations.[11]

In this article, we report the case of a patient who underwent limb-sparing surgery and chemotherapy for primary osteosarcoma of the distal femur and presented 7 years later with primary alveolar rhabdomyosarcoma in the same anatomical location.

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Case Report

A 13-year-old girl presented with a 4-month history of swelling over the left anterior thigh. She complained of intermittent pain over the left thigh and walked with an antalgic gait. The pain was sharp and well localized, did not radiate to the hip or foot, and persisted despite a course of anti-inflammatory medications. There was no history of trauma, no other area of bone pain, and no associated swelling in other parts of the body. The patient denied fever, night sweats, and weight loss. There was a mass in the anteromedial aspect of the distal femur with soft-tissue extension. No erythema or other skin changes were noted. The area was cool to touch, nontender, and not fluctuant. There was no reactive effusion in the knee. The knee had full range of motion (0°-140°). Ipsilateral hip and ankle range of motion were full. Results from the systemic and neurovascular examinations were normal. Family history was negative for cancer, neurofibromatosis, retinoblastoma, and Li-Fraumeni syndrome.

Plain x-rays showed a 12-cm eccentric lytic lesion in the midshaft of the left femur (Figure 1), and magnetic reso-

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nance imaging (MRI) revealed a bony lesion with soft-tissue extension involving the vastus intermedius muscle but no obvious involvement of the neurovascular bundle (Figures 2A, 2B). Marrow involvement extended from the distal metaphysis to approximately 3 cm below the greater trochanter. Bone scan demonstrated increased uptake of the lesion without other hot spots in the skeleton (Figure 3). Results from an open biopsy confirmed this to be a high-grade osteosarcoma (Figure 4). After workup, the patient's cancer was staged Enneking IIB[12] (high-grade extra-compartmental lesion without metastasis). The patient underwent neoadjuvant chemotherapy followed by wide resection and limb salvage with allograft reconstruction and internal fixation. Preoperative chemotherapy included CCG 7921 with high-dose methotrexate/cisplatin and doxorubicin for 2 cycles. Postoperative chemotherapy involved 4 additional cycles of high-dose methotrexate/cisplatin and doxorubicin. Postoperative follow-up involved local imaging of the knee plus computed tomography (CT) scan of the lungs every 3 months for the first year, every 6 months for the next 2 years, and yearly thereafter.

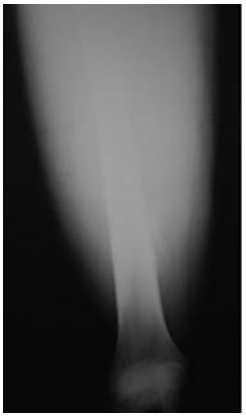


Figure 1. Plain x-ray of left femur. Periosteal reaction and the Codman triangle are apparent.

Seven years after the initial management of osteosarcoma, the patient noticed a new mass in the left thigh and complained of recurrent intermittent pain, which occasionally woke her up at night. The pain became persistent, was rated 8 to 9 on a scale of 1 to 10, and was well localized to the region of swelling with no radiation. There was no overlying skin erythema. The mass was diffuse, cool to touch, and nontender. The patient had full range of motion at the knee, hip, and ankle joints and no pain on active or passive motion. Neurovascular examination results for all extremities were normal. This concerning presentation was further investigated. Hematologic studies, including basic metabolic panel, complete blood cell count, and coagulation studies, were normal. Plain x-rays of the left femur provided no obvious evidence of any recurrent bony lesion. Allograft and hardware appeared stable. MRI revealed that a large lobulated soft-tissue mass in the vastus intermedius and medialis was completely surrounding the femoral vascular bundle (Figures 5A–5C). Also found were 2 enlarged (1.5 cm, 2 cm) left inguinal lymph nodes of the same signal intensity. It was decided to perform an incisional biopsy to rule out local recurrence of the sarcoma. Biopsy results revealed sheets of poorly differentiated cells infiltrating surrounding collagen and skeletal muscle, with numerous mitotic figures and marked atypia (Figure 6A). There was strong immunoreactivity with desmin, myogen, and Myo D-1 (Figure 6B). Polymerase chain reaction (PCR) for PAX 3/PAX 7-FKHR was negative. These findings were consistent with alveolar rhabdomyosarcoma. There was nothing histologically suggestive of recurrent osteogenic sarcoma.

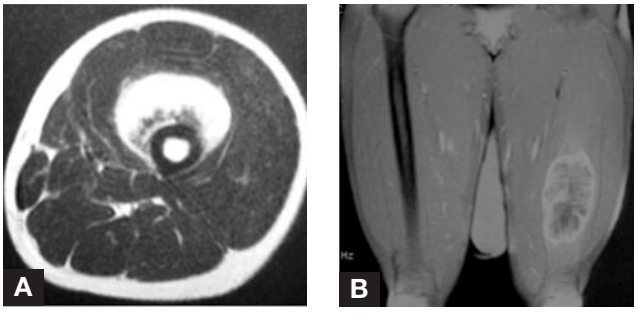


Figure 2. Left femur: (A) magnetic resonance imaging (MRI) axial scan (T_2-weighted contrast-enhanced) demonstrating soft-tissue enhancement and (B) MRI coronal scan (T_1-weighted) showing the extent of the lesion.

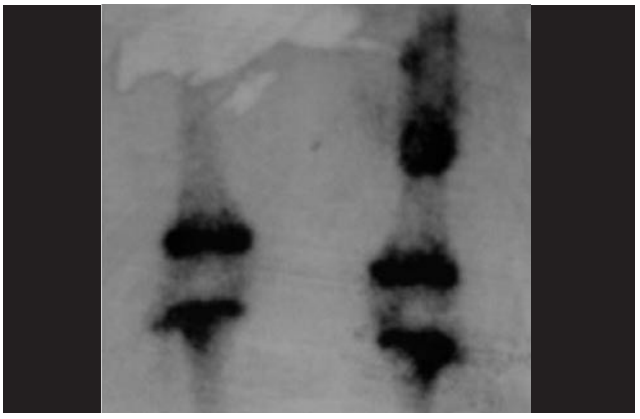


Figure 3. Bone scan showing the enhanced uptake in the left midshaft femur.

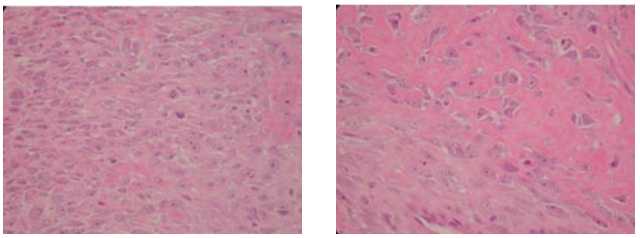
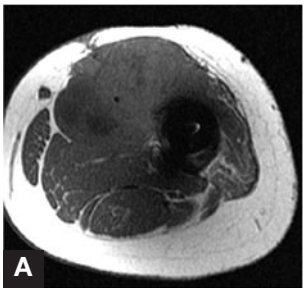
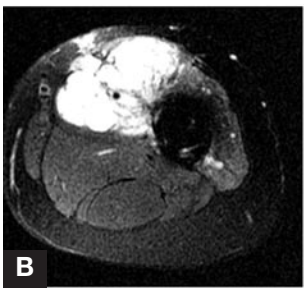


Figure 4. Biopsy slide of femur specimen (hematoxylin-eosin, original magnification ×40). Note the malignant spindle cells with immature osteoid formation.

According to additional studies, including chest CT and bone scans, there was no evidence of distant metastasis. The T2bN1M0 stage IV cancer was treated with 3 cycles of vincristine/actinomycin/cyclophosphamide with no obvious benefit, followed by 3 cycles of ifosfamide/VP-16 with a clinical response. During the later therapy, the patient also underwent radiation therapy with 5000 cGy in 25 fractions over the course of 35 days. Wide resection with limb salvage was then performed. Intraoperatively, the tumor was found to involve the vastus lateralis laterally and the adductors medially. The femoral artery and vein were also involved, and they were resected and reconstructed using the contralateral saphenous vein. The specimen margins





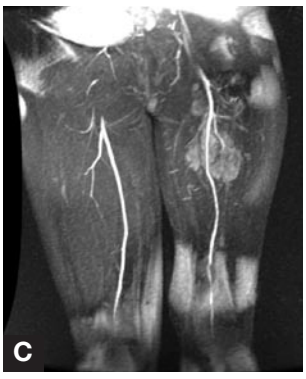
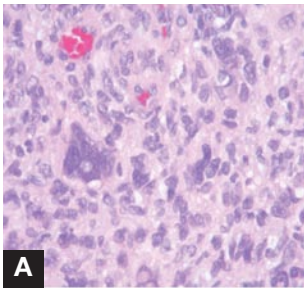


Figure 5. (A) Magnetic resonance imaging (MRI) axial scan (T_1-weighted) of rhabdomyosarcoma shows the lobulated soft-tissue mass. (B) MRI scan (T_2-weighted contrast-enhanced) of rhabdomyosarcoma shows enhancement of the lobulated soft-tissue mass. Note the vascular-bundle involvement. (C) Angiogram of left femur demonstrates the vascular-bundle compromise in the area of the lesion.



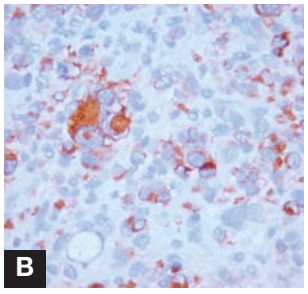


Figure 6. Biopsy slides: (A) Removed specimen (hematoxylin-eosin, original magnification ×100). Note the sheets of pleomorphic and atypical cells surrounded by collagen and skeletal muscle. (B) Operative specimen (desmin, original magnification ×100) showing strong positivity of the atypical cells.

appeared clinically tumor-free, though pathology review showed positive margins and less than 25% tumor necrosis/fibrosis. The 2 inguinal nodes noted to be enlarged on MRI were resected, and no tumor was found.

In view of this unique case of 2 sarcomas developing and the high likelihood of recurrence, a decision was made to start chemotherapy and radiation therapy after surgery. The patient received CPT-11/vincristine alternating with ifosfamide/VP-16 along with radiation to the left inguinal area (3.5 cycles of CPT-11/vincristine, 1 cycle of ifosfamide/VP-16, 4500 cGy delivered in 25 fractions). At the last follow-up, 16 months after surgery, there was no clinical or radiographic evidence of local recurrence or distant metastasis. However, the patient discontinued her second cycle of oral VP-16 despite being aware that noncompliance is associated with a high probability of recurrence and possible metastasis.

Discussion

Soft-tissue and bone sarcomas are rare, accounting for only 1% of new malignancies diagnosed in the United States each year.[13] Osteosarcoma is the most common solid malignancy in children; it occurs in approximately 5.6 per 1 million children each year.[14] Peak frequency is in the second decade of life, and there is a slight male predominance but no racial preference. Rhabdomyosarcoma is the most common soft-tissue sarcoma in children and young adults; annual incidence in the United States is approximately 4.5 cases per 1 million, accounting for 5% of all childhood cancers.[2] Therefore, the chance that these 2 independent tumors would occur in a patient lacking obvious risk factors is extremely low (~1 in 40 billion).

Historically, the sole treatment for osteosarcoma without systemic spread was amputation, and up to 90% of patients died from subsequent metastatic disease.[3] Metastases can occur regionally in the same extremity or systemically, most commonly to the lungs. Induction and adjuvant chemotherapy, which are associated with the best outcome, have become a vital part of treatment. Some studies have shown that the best prognosis is predicted if more than 90% necrosis is found in the resected tumor. The chemotherapeutic agents found to be most effective include doxorubicin (Adriamycin), cisplatin (Platinol), ifosfamide (Ifex), etoposide (VP-16), and high-dose methotrexate (Rheumatrex). Multiagent therapy is most effective, and most standard protocols include doxorubicin and cisplatin with or without high-dose methotrexate.

However, some authors have suggested that use of multiple chemotherapy agents can increase the chance that an SMN will develop.[4,15-17] In a review of 1511 patients over a 30-year period, Caglar and colleagues[16] found that 26 patients with childhood malignancies developed a second neoplasm. Eight of these 26 patients never received radiation therapy for the initial malignancy. In this cohort study, the overall risk was calculated to be 1.7%. In another retrospective cohort study, of 13,581 patients with childhood tumors, Neglia and colleagues[4] found that 314 SMNs occurred in 298 patients. Cumulative incidence of SMN at 20 years in patients with primary bone cancers was 3.28%. According to the investigators' statistical analysis, chemoagents associated with increased SMN risk included anthracyclines (eg, doxorubicin) and/or epipodophyllotoxins (eg, etoposide), particularly for leukemias with the latter. Our patient received 2 cycles of doxorubicin before limb-sparing surgery and another 4 cycles afterward.

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Concerning the risk for SMN after chemotherapy for osteosarcoma, Aung and colleagues[18] reported that SMN occurred in 14 (2.8%) of 509 patients. The central nervous system was the most common site of SMN (anaplastic meningioma, meningioma, high-grade glioma, maxillary astrocytoma). Two cases of acute myelogenous leukemia and 1 case each

of myelodysplastic syndrome, non-Hodgkin lymphoma, high-grade pleomorphic sarcoma, leiomyosarcoma, fibrosarcoma, breast cancer, and mucoepidermoid carcinoma were reported. Patients received different chemotherapy protocols during the study period but all received high-dose methotrexate and doxorubicin. Excluding the patients with known genetic risk factors, the incidence was calculated to be 2.5% (SD, 1.6%), similar to what Pratt and colleagues[17] reported in their follow-up of patients who survived osteosarcoma treated with chemotherapy (9 of 334 patients, overall cumulative 10-year incidence, 2%; SD, 1%). The patients in the study by Pratt and colleagues[17] also received high-dose methotrexate and doxorubicin alone or in combination with other agents.

Rhabdomyosarcoma is the most common childhood soft-tissue tumor. Histologically, it is one of the small blue cell tumors that must be distinguished from neuroblastoma, lymphoma, and Ewing sarcoma. Most tumors occur sporadically, and there are no associated risk factors. However, children with genetic anomalies (eg, neurofibromatosis, Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, Noonan syndrome, Costello syndrome) and children whose parents use cocaine and marijuana have been reported to have higher rates of incidence.[8] At diagnosis, microscopic metastasis is presumed to have occurred, and all patients need to be treated with chemotherapy. Advances in chemotherapy regimens over the past 3 decades have led to a reported cure rate of at least 70%.[8] Local control is achieved by surgical excision and radiation therapy, which are recommended for alveolar rhabdomyosarcoma and for regional lymph node spread.[8] Chemotherapeutic agents include vincristine and dactinomycin, and often cyclophosphamide is added to the combination. In some studies, ifosfamide has been substituted for cyclophosphamide, with similar effectiveness.[8]

Although osteosarcoma as an SMN after rhabdomyosarcoma treatment has been reported in several cohort studies,[4,16-18] to our knowledge the occurrence of rhabdomyosarcoma in the exact same anatomical location after chemotherapy for osteosarcoma has not been reported. Recently, Dagdemir and colleagues[11] reported a case of primary osteosarcoma of the femur presenting with primary rhabdomyosarcoma of the humerus on the same side 5 years after initial treatment. The osteosarcoma treatment included a T10 (high-dose methotrexate) protocol before limb-sparing surgery and T10A (cisplatin, bleomycin, cyclophosphamide, dactinomycin, doxorubicin) afterward. The investigators concluded that the SMN might have been related to chemotherapy. Another possible explanation is that patients with bone sarcomas may be predisposed to other cancers because of a genetic composition not yet identified. This view is supported by results from the cohort study by Neglia and colleagues,[4] who found increased risk for soft-tissue sarcomas in patients who originally had bone sarcomas with a negative history of Li-Fraumeni syndrome, retinoblastoma, or neurofibromatosis. However, our patient seemed not to have obvious genetic risk factors that could have contributed to the second sarcoma.

As an SMN can present more than a decade after an initial cancer,[4,16] we recommend scheduling follow-ups at regular intervals for all patients. In addition, any symptomatic patient in remission needs to be given thorough examinations and imaging workups, including MRI and CT and/or bone scans. Although the metal endoprosthesis used in treatment of the initial tumor may make MRI evaluation difficult, new MRI techniques with minimized image distortion can be used for appropriate evaluation of surrounding structures. Finally, physicians and patients need to be aware that sarcoma treatment requires close follow-up not only for recurrence but also for the possibility of a second lesion, even in the absence of the genetic predisposition.

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Richard D. Lackman, MD, is a consultant for Stryker Howmedica Osteonics. The other authors report no actual or potential conflict of interest in relation to this article.

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This paper will be judged for the Resident Writer's Award.