

## BACKGROUND

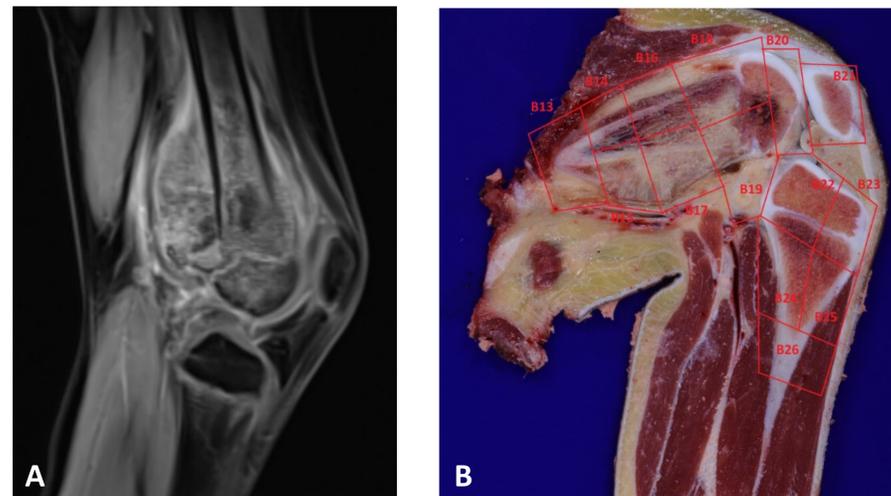
Osteosarcoma is an aggressive malignant bone forming tumor. It is the most common primary malignant tumor of the bone and the third most common cancer of adolescence.<sup>1</sup> The most common locations are the metaphysis of long tubular bones, such as the proximal humerus, the distal femur, and the proximal tibia. Patients typically present with localized pain and swelling. MRI is a useful tool for local staging, particularly for evaluation of intraosseous tumor extension and soft-tissue involvement.<sup>2</sup> Though most cases of osteosarcoma are sporadic, Rothmund-Thomson Syndrome (RTS) is an autosomal recessive disorder, often seen with pathogenic variants in *RECQL4*, that is associated with an increased risk of osteosarcoma development. Poikiloderma, small stature, sparse or absent scalp hair, skeletal dysplasia, and/or juvenile cataracts can also be seen in this disorder.<sup>3</sup> Patients with RTS and other genetic predisposition syndromes usually present at a younger age and the tumor may involve multiple sites.<sup>3</sup> Synchronous Multicentric Osteosarcoma (SMOS) is a rare variant of osteosarcoma characterized by tumors in multiple osseous sites at diagnosis in the absence of pulmonary metastasis.<sup>4</sup> To make an accurate diagnosis of SMOS, primary osteosarcoma with bone seeking-metastasis and direct extension from the primary tumor must be ruled out. Both solitary primary osteosarcoma and SMOS are typically treated with neoadjuvant chemotherapy and surgical excision, however patients with SMOS have a much worse prognosis.

## CLINICAL HISTORY

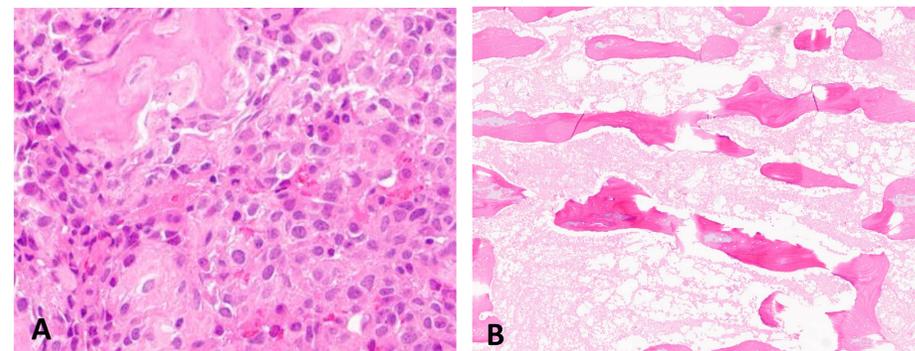
An 8-year-old male with RTS presented with 2-3 days of left knee swelling, pain, and limp. X-ray showed an area of mixed lucency and sclerosis at the medial margin of the left femoral metaphysis and geographic sclerosis along the medial margin of the proximal tibial metaphysis. MRI showed a mass with a large soft tissue component (4.1 x 5.2 x 6.2 cm) centered in the left femoral metaphysis and a contusion in the medial aspect of the tibial metaphysis (**Fig. 1a**). The PET scan was negative for metastatic disease. A left femur needle biopsy showed neoplastic bone produced by tumor cells with high nuclear to cytoplasmic ratio and hyperchromatic nuclei. Given the radiographic and histological appearance, a diagnosis of high grade (G3) osteogenic conventional osteosarcoma was made. Following neoadjuvant chemotherapy, the patient underwent above-the-knee amputation. Pre-surgical MRI showed that the lesion in the distal femoral metaphysis was overall mildly increased in size (4.3 x 3.1 x 7.2 cm) compared to the prior study while the medial proximal tibial metaphysis showed stable geographic sclerosis along the medial margin.

## GROSS DESCRIPTION

The specimen is received fresh and consists of an above-the-knee amputation measuring 18.4 cm from heel to toe, 36.5 cm from heel to knee, and 14.4 cm from knee to skin and soft tissue resection margin. The specimen displays 5 intact toes with nails. Protruding from the proximal margin is a 0.6 cm in length segment of femur surrounded by muscle, vasculature, and nerve. There is a 0.6 x 0.6 cm healed lesion on the medial aspect of the thigh, consistent with previous biopsy site. The site is located 0.1 cm from the proximal margin. The specimen is frozen at -70 degrees Celsius and subsequently sectioned from lateral to medial into 8 slices to show a 5.5 x 2.5 x 1.0 cm tan-white firm area with infiltrative borders in the medullary cavity of the distal diaphysis extending into the metaphysis. Extension through the cortex, the periosteum, and into the soft tissue is seen anteriorly and posteriorly. In the proximal medial tibia, an intramedullary 2.0 x 1.0 x 1.0 cm area of hemorrhage is seen in the medial diaphysis. Both tumors are greater than 5 cm from the skin, soft tissue, and proximal femur margin. Involvement of the joint space and vasculature is not grossly identified. Tumor necrosis is not grossly evident in the area between the two lesions.



**Figure 1:** Correlation of radiographic imaging and specimen. **A.** MRI of left knee. **B.** Slice through the long axis of the specimen with mapped histological sections.



**Figure 2:** Microscopic appearance before and after treatment. **A.** Left femur biopsy shows lacelike pattern of neoplastic bone produced by anaplastic malignant tumor cells. **B.** Tumor bed with extensively necrotic cellular tissue

## PATHOLOGIC FINDINGS

Microscopically, both lesions showed 99% extent of treatment effect. The femoral tumor consisted of extensively (60%) necrotic cellular tissue (**Fig. 2b**) with small foci of malignant osteoid. Within the marrow space, both the tumor and residual benign bony trabeculae were necrotic. In the tibia, hemorrhage as well as thick bony trabeculae, treatment effect changes, and rare residual markedly atypical cells are seen. The vascular, proximal femur, skin, and soft tissue margins were negative for tumor. Lymphovascular invasion was not identified. No tumor necrosis or treatment effect changes such as fibrosis, hemosiderin deposition, or chemotherapy-induced pleomorphism were seen in the sections between the two lesions on histological examination, further supporting the notion that the tibial lesion is not a result of direct extension. Based on this finding and the patient’s genetic predisposition, the lesion in the tibia is favored to represent a second site of primary tumor rather than metastasis. In accordance with the AJCC Cancer Staging Manual, both the femoral and tibial tumors were given a Pathological Tumor-Node-Metastasis (pTNM) of ypT1(m)pN0pM0. The “y” prefix is applied to cases that are classified during or following initial multimodality therapy. The “m” suffix indicates the presence of multiple primary tumors. Both treated tumors occurred in the appendicular skeleton and were less than 8 cm in greatest dimension. One lymph node was collected and was negative. A PET scan confirmed that distant metastasis was absent. By correlating the TNM definitions and high grade (G2 or G3) appearance of the tumor, the prognostic stage group was determined to be IIA. Ancillary studies were not performed.

## DISCUSSION

The inherent genetic mutation in *RECQL4* may play a role in the pathogenesis of multicentric osteosarcoma. It is thought that the various skeletal dysplasias seen in RTS may undergo sarcomatous transformation.<sup>6</sup> Because patients with RTS have greater risk of multicentric disease, the appearance of one or more additional osteosarcomas in a young patient should draw attention to a possible genetic predisposition of the patient involved. The determination of multiple foci of osteosarcoma as synchronous primary tumors or bony metastasis is significant as pathologic staging pTNM will vary with each disease. Separate primary tumors will be staged individually. Bone metastasis would be defined as M1b and upstage the tumor to IVB disease. Stage IVB disease is defined by any tumor size (T), either positive or negative lymph node metastasis (N), spread to bone or sites other than lung (M1b), and any grade (G).<sup>2</sup> Because of this patient’s genetic predisposition to osteosarcoma, the lesion seen in the tibia is favored to represent two synchronous separate primary tumors rather than rapidly appearing bone-seeking metastasis. Approximately 20% of patients with osteosarcoma present with metastatic disease at the time of diagnosis, most often in the lungs via hematogenous dissemination.<sup>5</sup> Because metastasis to extrapulmonary sites is infrequent, it is highly unusual that metastasis to another bone would occur in the absence of lung metastasis.

This case emphasizes the importance of a close working relationship of pathology and radiology. Review of not only the most recent imaging, but also the imaging prior to treatment before cutting was critical in giving the pathologists’ assistant an idea of the anatomic location of tumor and if soft tissue involvement of the tumor was present before treatment. In this case, the imaging highlighted the distinct tibial lesion. Choosing to cut full sections through the long axis of the bone allowed for macroscopic and microscopic identification of any treatment effect changes between the femoral and tibial lesions, and thus identification of evidence of direct extension. Mapping of histologic sections is especially useful in osteosarcoma for calculation of tumor necrosis, as tumors showing 90% therapy response are associated with a favorable prognosis.<sup>12</sup> Bone mapping served an additional value in this case, as it documented the exact locations of the tumor, which allowed the pathologist to determine the relationship between the femoral and tibial lesions (**Fig. 1b**). Ultimately, grossing this bone resection case in the context of a patient history of Rothmund-Thomson Syndrome and a close review of pre- and post-treatment imaging allowed for the diagnosis of synchronous multicentric osteosarcoma to be made.

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