



Head, Shoulders, Ankle, and Toes: De Novo Rearrangement of the LMO1 Gene in Osteosarcoma with Correction by Rotationplasty

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Abstract

In this case of an atypical osteosarcoma in a 5-year-old female, FoundationOne genomic testing found a de novo rearrangement of the LMO1 gene on exon 2. Prior to the finding, LMO1 translocations have mostly been associated with acute lymphoblastic T-cell leukemia, never osteosarcomas. Treatment of osteosarcoma and soft tissue sarcomas requires a multimodal approach of chemotherapy and surgical limb resection, which can be life-altering to patients. An alternative solution for biological reconstruction is the rotationplasty, an autograft surgery that allows for fine motor control of the reattached foot and fitting of a prosthesis, allowing patients to quickly return to independent movement.

Background

Osteosarcomas are aggressive malignant bone tumors, characterized by the production of osteoid matrix or immature bone. 75% of osteosarcomas occur in persons younger than 20, primarily during adolescent growth spurts, suggesting that regions of rapid bone proliferation are prime areas for neoplasm development. They typically arise along the metaphysis of long bones, like the distal femur or proximal tibia, and requires a multimodal approach in treatment consisting of neoadjuvant chemotherapy and surgical resection of the afflicted bone.

This poster focuses on an unusual case of pediatric high-grade sarcoma initially thought to be osteosarcoma. The patient was a 5-year-old female presenting with right knee pain. Needle core biopsy of the distal metaphysis of the right femur rendered a diagnosis of high-grade pleomorphic spindle cell sarcoma with smooth muscle differentiation (Figure 3). No osteoid was present upon histologic examination, which is typically pathognomonic for osteosarcoma. A radical resection of the tumor plus right femur rotationplasty was selected as the method of reconstruction following treatment with neoadjuvant chemotherapy.

The rotationplasty is an autograft surgery where the distal femur or proximal tibia containing the neoplasm is resected, the ankle joint and foot is salvaged, rotated 180° and reattached to the thigh by plates and screws to serve as a new knee joint (Figure 1).¹ Several studies report positive functional and psychological outcomes, allowing patients to rapidly to return to sports and independent movement within months of the surgery. Benefits to rotationplasty include autologous reconstruction that avoids immune reaction, minimal corrective surgery, and improved control of prosthesis.



Figure 1. Rotationplasty of left leg and custom prosthesis. Figure 2. Sagittal section of right distal femur, slice blocked in to measure treatment effect.

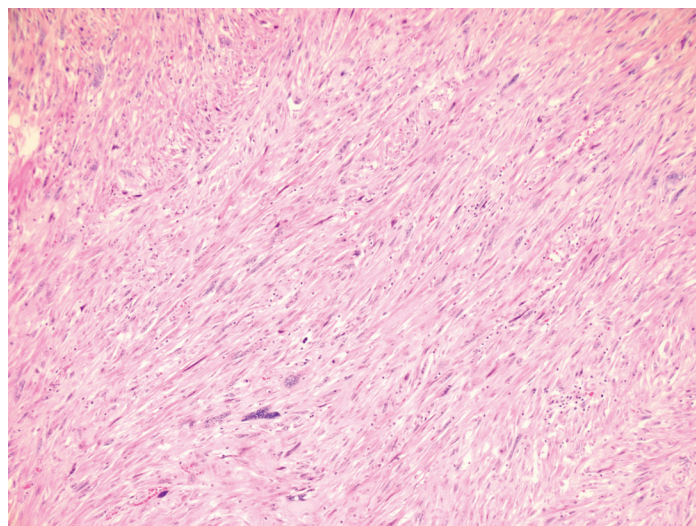


Figure 3. Spindled cells with eosinophilic cytoplasm consistent with high-grade sarcoma (H&E stain). No osteoid was seen in the tumor, but clinically it was most consistent with osteosarcoma.

Results

The specimen received designated "Right knee" was a 12.5 x 8.5 x 7.5 cm segment of upper leg and a 9.5 x 7.5 x 4.5 cm lower leg with a portion of skin and skeletal muscle absent from the posterior, lateral and medial aspects. The femur containing the tumor was removed from the surrounding soft tissue and sectioned in the sagittal plane, revealing a soft and fleshy tumor arising in the metaphysis and extending into the epiphysis (Figure 2). Histologic evaluation showed poor response to targeted chemotherapy with only 5% tumor necrosis, suggestive of an atypical presentation of osteosarcoma. Due to the lack of osteoid on additional gross sections, ancillary genetic sequencing through FoundationOne was called for. Heme molecular testing revealed a LMO1 rearrangement of exon 2. LMO1 translocations are mostly associated with acute lymphoblastic T-cell leukemia. LMO1 encodes Rhobotin -1, a protein that may be involved in gene transcription regulation of neural lineage cells. Mutations in LMO1 have been implicated in neuroblastomas, apoptosis of gastric epithelial cells, and T-cell ALL.

This genetic abnormality in combination with the unusual gross presentation of osteosarcoma, lack of osteoid, and poor response to chemotherapy may explain the atypical characteristics of the tumor and the challenges in treatment.

Despite the lack of osteoid seen in the tumor sample and presence of non-specific muscle markers, secondary pathology review concurs that the diagnosis is still thought to most favor osteosarcoma given the location of the tumor and pediatric age of the patient and was clinically treated as such.

Conclusion

- This de novo rearrangement of the LMO1 gene in the context of osteosarcoma has never been reported before, suggesting that the LMO family may have a propensity for promoting cancer when mutated.³
- The use of molecular testing in pathology is becoming more common with the desire to individualize treatment. The future of cancer treatment is likely to move towards deep sequencing, identifying specific biomarkers to personalize therapy and improve outcomes.

References

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