

Osteosarcoma of the Distal Femur

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Introduction

Osteosarcoma is a malignant cancer which usually affects individuals in their teens and twenties, with 75% of tumors occurring in individuals under age twenty.¹ It is the most common primary malignant tumor of bone and accounts for 20% of primary bone cancers.¹ Men are more affected than women, with a ratio of 1.6 men to every one woman diagnosed with osteosarcoma.¹ Bone and joint cancers in general are rare in comparison to other cancer types, and there are only three thousand new cases in the United States every year (0.2% of all new cancers).² Of these, only a fraction are osteosarcomas. In individuals under age 25, there are just an estimated 450 osteosarcoma cases per year.²

The Surveillance, Epidemiology, and End Results Program of the National Cancer Institute determined that about 66.6% of patients with bone and joint cancers survive five years after diagnosis.² These numbers are similar for osteosarcomas, with 60-70% of patients surviving five years, but metastases (specifically pulmonary) occur in one to two out of ten patients. The average five-year survival rate for patients with complications (metastasis, recurrence, or secondary osteosarcoma to a previous condition) is less than 20%.¹

Osteosarcomas first present with a painful enlarging mass, typically at the metaphyseal region of long bones of the extremities.¹ The cancerous cells produce osteoid matrix or mineralized bone, and the neoplasms can be visualized on radiographs with both lytic and blastic areas of density.¹ A feature known as a Codman triangle, a triangular shadow between the periosteum and bone cortex, is indicative of an aggressive bone tumor but does not diagnose osteosarcoma specifically.¹ The triangle occurs when the periosteum lifts away from the bone during tumor expansion.¹ Subtypes of osteosarcoma are designated based upon the site of origin (within the bone cortex, medulla, or on the surface), whether or not a pre-existing condition was present before the neoplasm, and on the histologic features of the malignant cells. The most common subtype is "primary, intramedullary, osteoblastic, and high grade".¹

Acquired genetic mutations of tumor suppressors and oncogenes appear in 70% of osteosarcomas.¹ These genetic abnormalities usually appear in well-known genes, including RB, TP53, INK4a, MDM2, and CDK4.¹

Chemotherapeutic agents have had success in osteosarcoma cases. They are generally given preoperatively to reduce the size and aggressiveness of the tumor.¹ These drugs, specifically doxorubicin, cisplatin, and methotrexate, improved the 20% five-year survival rate of the 1960s and earlier to the 60% rate of the 1980s through today.³ However, even with improvement in surgical techniques and implants in recent years, we have reached stagnation with our five-year survival due to a lack of new chemotherapy options.³ This case study will introduce a patient who was treated for osteosarcoma, as well as the future of targeted drug therapies and the role of the pathologists' assistant (PA) in the documentation of treatment effectiveness.

Patient History

The patient is a 19-year-old male who presented with pain in his right distal femur which has been ongoing for the previous month. Pain medication was prescribed initially, but the pain returned upon stopping the medication. The patient denied any history of injury to the area and there was no new pain elsewhere in the body. The pain increases with moving the knee joint, but not with weight bearing. The patient has had no other symptoms like fever, chills, change in appetite, or weight loss. A brief review of the body systems determined there were no other remarkable issues.

Upon examination of the right distal femur and knee joint, a firm and immobile mass was palpated along the lateral aspect of the femur. The area was not tender, did not show warmth or erythema, and strength and range of motion were normal. Plain film radiograph displayed a mixed lytic and blastic lesion of the distal femur with a lateral Codman triangle.

Hospital Course

The attending physician determined that the lesion appeared to be an osteosarcoma, and recommended further imaging with an MRI and an open biopsy. The lesion was later diagnosed as a high grade osteosarcoma of the right distal femur.

Chemotherapeutic agents were given to the patient prior to surgical procedures. These drugs included inpatient doxorubicin and cisplatin, and outpatient Neulasta (pegfilgrastim). Antibiotics, antiemetics, laxatives, heartburn relief, and calcium and vitamin D supplements were prescribed for home use. Three weeks after the initial treatment, the patient was administered methotrexate. He received additional chemotherapy one week later, and had continuing hospital encounters until surgery.

A surgical procedure was performed to remove the bone lesion. Eight frozen intraoperative consultation specimens were received, including subcutaneous tissue, synovium, iliotibial band, vastus lateralis margin, anterior and posterior cruciate ligaments, and lateral and medial collateral ligaments. Additionally, medial gastrocnemius and distal marrow margin specimens were submitted. The major specimen was the distal femur resection (see Figure 1).

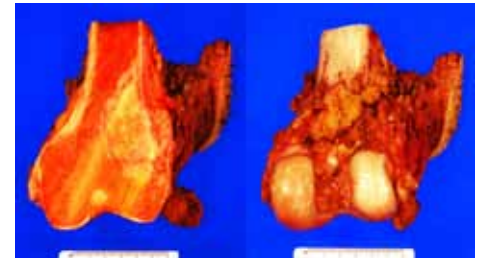


Figure 1: (distal femur resection): Once bisected, the tumor is revealed to be tan-yellow and ill defined. The protrusion of bone is visible on the right external surface of the specimen.

Diagnosis

Gross appearance of the lesion

The distal femur resection specimen with adjacent soft tissue and skin ellipse contained a 4.8 x 4.3 x 4.3 cm protrusion of bone located on the lateral femur. The protrusion was 3.5 cm from the bone resection margin. After bisecting the specimen, a variegated pink-tan to yellow-tan mass with ill-defined borders was visible, measuring 6.5 x 4.6 x 4.3 cm in size and 2.4 cm from the bone resection margin. The lesion grossly abutted the circumferential bone/soft tissue junction and was loosely adherent to the soft tissue resection margin. The mass was continuous with the external protrusion. The specimen was mapped out into 23 sections, which were illustrated on a bone diagram. Twenty seven sections were submitted for histologic processing. No lymph nodes were found or submitted for this specimen.

Histologic appearance and diagnosis

No evidence of malignancy was found in the intraoperative consultations, specimen bone margin, or additional tissue submissions. In the tumor, the WHO classification type was determined to be conventional osteosarcoma, chondroblastic, high grade, with 40-50% necrosis (Figure 2, 3). The greatest dimension of the neoplasm was 6.5 cm. The determined distance from the sarcoma to the bone resection margin was 2.4 cm. Treatment effect from chemotherapy was present in the bone tissue.

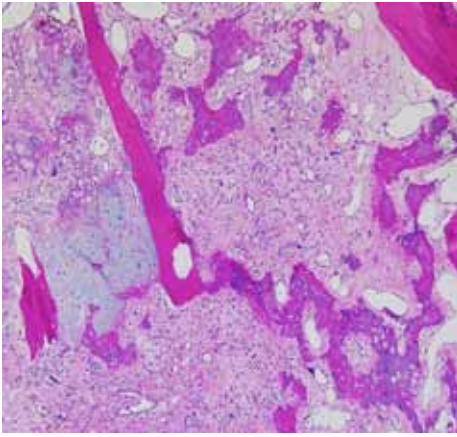


Figure 2: Under the microscope, the tumor displays the osteoid component which is diagnostic of osteosarcoma. Additionally, the chondroid component can be viewed, classifying the tumor as chondroblastic.

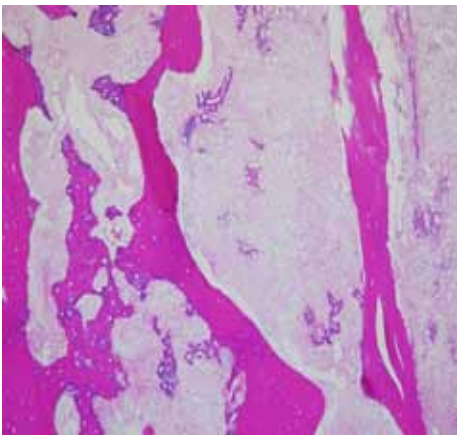


Figure 3: Necrosis of the malignant cells, estimated to be 40-50% of the tumor in this case, helps to evaluate the effectiveness of neoadjuvant chemotherapy. This percentage is obtained by microscopically analyzing the full face surface area of the bisected tumor and referring to the bone map created during prosection.

Histologically, the formation of bone by the tumor cells is diagnostic of osteosarcoma, and the chondroblastic subtype is declared when malignant cartilage is abundant within the mass.¹ However, the tumor stage is much more important to prognosis and treatment than the histologic grade and category. The AJCC staging of this tumor was determined to be ypT1 pNx pM:NA. This means that the tumor was considered stage 1, post treatment, with lymph node status unable to be determined, and metastasis was not applicable in this evaluation. In order for an osteosarcoma to be classified as tumor stage 1, it must be less than 8 cm in greatest dimension.⁴

Analysis of Treatment

It has now been about eight months since the patient underwent surgery for the removal of the osteosarcoma. He has had follow-up care including bone scans to locate possible metastasis or recurrence, and his quality of life after surgery is being monitored by his primary physicians. To date,

the patient has had no signs of recurrence of the osteosarcoma and reports no pain or hindrance during physical activity.

Discussion

This patient received the standard osteosarcoma chemotherapy regimen, which has been essential in increasing the five-year survival rate of patients since its development in the 1980s.⁵ These chemotherapies work to cause necrosis of the malignant cells in the tumor and are most successful when given prior to surgery. The effectiveness of the drugs directly correlates with the amount of necrosis in the tumor, but is not consistent for all cases due to variations in the genetic composition of the tumor cells. Recent research has found that high and low expressions of certain microRNAs are linked to metastasis versus positive chemotherapeutic response of osteosarcoma cells.⁶

The percentage of necrosis, and therefore the chemotherapeutic success, is able to be analyzed due to a team effort between the pathologists' assistant and the pathologist. The pathologists' assistant, while prosecting the specimen, creates a bone map of an entire slice through the center of the tumor and uninvolved bone. They first take a picture of the bisected specimen, and then use a saw to shave off a thin slice of the surface area of one half of the cut surface. The PA then blocks out the entire slice into pieces that will fit in the cassettes and draws out the cuts made onto the bone map image. After this, they write the corresponding cassette number for each piece on the image. When the pathologist examines the sections under the microscope, they are able to tell how much necrosis is present on each slide and match it up to the area on the bone map. By summing up all of the necrosis they see in each slide they are able to determine the percentage of necrosis for the entire tumor.

In addition to pro-metastatic miRNA expression, drug resistance to chemotherapy is another hurdle that must be overcome to improve the five-year survival of osteosarcoma patients. Resistance to the typical anticancer agents is associated with the DNA binding protein HMGB1 (high mobility group box 1), as recently determined by researchers. This protein regulates autophagy and could be targeted in future therapies.⁵

With molecular testing of patient specific osteosarcoma components and correlation to the amount of necrosis in the tumor after chemotherapy, targeted drug therapies may become possible for this aggressive cancer. Analysis of MicroRNA and other components within the osteosarcoma cells may inform the physician about the likelihood of chemotherapeutic success or metastasis, but currently targeted treatment is not available due to lack of alternative drugs.⁶

While the patient in this case study had success with the current drug and surgical options, there are many other patients who have encountered

metastasis or drug resistance. A lack of pharmaceutical options has caused stagnation in the survival rates of osteosarcoma patients since the 1980s when the 60% five-year survival rate was reached. Although we have greatly improved our surgical techniques in the last 30 years, it is unlikely that we can increase patient survival without new chemotherapies. Emerging research in nanoparticles may become useful for chemotherapy as the particles could encapsulate non-water soluble drugs, such as curcumin, and allow them to be delivered into the cells.⁷ This may open up the door for the use of drugs which have shown laboratory success, but are limited by their delivery systems in the human body.

Conclusion

Osteosarcomas are tumors of young healthy individuals and have relatively low survival rates, even without complications. Despite improvements in surgical techniques, there has been little advancement in chemotherapy since the 1980s, and survival rates have stagnated. Molecular analysis and nanoparticle technology may breathe new life into drug development for this disease. The effectiveness of chemotherapy can be measured by the percentage of necrosis of the tumor at resection, which is documented on a bone map by the pathologists' assistant. This data can be gathered and analyzed to gain a better understanding of the disease process and the success of new treatments.

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