Educational Case: Pediatric Osteosarcoma

Kelly M. Rogers, MRes¹ and Richard M. Conran, MD, PhD, JD¹

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

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Primary Objective

Objective MS1.2: Bone-Forming Sarcomas in Children.
Describe the most common benign and malignant bone-forming tumors in children and adolescents in terms of clinical presentation, radiologic findings, histologic features, treatment, and prognosis.

Competency 2: Organ System Pathology; Topic MS: Musculoskeletal System; Learning Goal 1: Bone Neoplasia.

Patient Presentation

A 16-year-old previously healthy male presents to his physician with worsening knee pain over the past 2 months. The pain began intermittently but is now persistent, severe, and localized to the swollen joint. There is no history of trauma to the knee. On physical examination, the affected area is swollen, erythematous, and tender with limited range of motion.

Diagnostic Findings, Part 1

Radiographs reveal a proximal tibial lesion with dense osteoid production and soft tissue involvement. (Figures 1 and 2).

Questions/Discussion Points, Part 1

What Is in the Differential Diagnosis for a Metaphyseal Tumor?
Metastatic disease is far more common than a primary bone neoplasm (Table 1) and must be ruled out first. Most tumors of bone and cartilage have been known to involve the metaphyses of long bones, with the exception of osteoma (more commonly found in flat bones) and chondroblastoma (epiphyses). Eighty percent of primary bone tumors occur about the knee in the distal femur or proximal tibial metaphysis.¹ The most common metaphyseal tumors seen in younger patients are osteochondroma, osteoid osteoma, primary osteosarcoma, and Ewing sarcoma. Patients older than the age of 40 with metaphyseal tumors are more likely to have a chondrosarcoma or secondary osteosarcoma.²,³

What Are the Most Common Benign Versus Malignant Childhood Bone Tumors?
Especially in the pediatric population, benign bone tumors are far more common than malignant tumors. Of the benign tumors of bone, osteochondroma is the most common variety followed by osteoid osteoma (10%-12% of all benign bone tumors) and osteoblastoma (3%). Other childhood benign tumors of bone include endochondroma and chondroblastoma. The most common malignant bone tumors in children are osteosarcoma (3.5% of all childhood malignancies) and Ewing sarcoma (2%-3%). Osteosarcoma is more common in adolescents

¹ Eastern Virginia Medical School, Norfolk, VA, USA

Corresponding Author:
Richard M. Conran, Department of Pathology & Anatomy, Eastern Virginia Medical School, 700 West Olney, Norfolk, VA 23501, USA.
Email: conranrm@evms.edu

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younger than 20 years; however, Ewing sarcoma is more prevalent in children younger than 10.

Based on the clinical picture, the patient was treated with neoadjuvant (preoperative) chemotherapy for 10 weeks and then referred to surgery for limb-sparing resection. The gross and histological features of the resected portion of the tibia are shown in Figures 3 to 5.

Diagnostic Findings, Part 2

What Is the Diagnosis Based on Pathological Examination of the Lesion?

The gross and microscopic features of the tumor are consistent with a conventional osteoblastic osteosarcoma post chemotherapy.

Questions/Discussion Points, Part 2

Describe the Gross and Microscopic Morphologic Features of Osteosarcoma

On gross appearance, osteosarcoma is classically coarse, granular and gray-white in color. On sectioning, the tumor has a mixed appearance with areas of hemorrhage, cystic degeneration, and neoplastic bone. On histology, malignant polygonal and spindled osteoblastic cells of various size are visible producing woven bone that is focally calcified. The neoplastic cells have large, pleomorphic, hyperchromatic nuclei. Numerous mitotic figures and atypical tumor giant cells are also present, as well as foci of malignant cartilage (Figure 6). Cells stain positively for alkaline phosphatase, osteocalcin, and osteonectin. At the advancing front of the tumor, nonneoplastic osteoclasts create areas of osteolysis. In patients treated with chemotherapy prior to resection, prominent necrosis may be seen grossly and on histologic examination which is important in staging the tumor (Figures 4 and 5).

Identify the Populations at Risk for Osteosarcoma

Osteosarcoma is the most common primary malignancy of bone, excluding myeloma and lymphoma, and comprises around 20% of all primary bone neoplasms. Roughly 2000 cases of osteosarcoma are diagnosed per year in the United States. Males are more commonly affected than females (1.6:1), as are tall compared to short people.

There are 2 peaks of incidence, one in adolescents and the second in the elderly patients. Seventy-five percent of patients develop primary osteosarcomas between the ages of 10 and 20 years; the second cohort comprised of elderly patients who develop secondary osteosarcoma associated with comorbid conditions such as Paget disease, bone infarcts, and/or prior irradiation. Other preexisting bone lesions, such as fibrous dysplasia and osteomyelitis, can also increase the likelihood of developing osteosarcoma. Trauma has not been found to cause osteosarcoma.

Describe the Etiology and Pathogenesis of Osteosarcoma

Although osteosarcoma is not characterized by a specific gene translocation and has a highly variable genetic profile, several mutations have been consistently associated with higher risk of developing the neoplasm. Most significant, around two-thirds of patients with osteosarcoma have mutations in the retinoblastoma (RB1) gene. Germline RB1 mutations in particular, causing hereditary retinoblastomas, magnify the risk of developing osteosarcoma by 1000-fold. Patients with other germ line mutations causing familial Li-Fraumeni syndrome (TP53 inactivation), Rothmund-Thomson syndrome (RECQL4 inactivation), or Bloom or Werner syndrome (BLM or WRN inactivation, respectively) have also been found to have a higher incidence of osteosarcoma than the general population. Somatic mutations of the tumor suppressor gene TP53 have been linked to sporadic osteosarcoma, as have regulators of the cell cycle (cyclins, cyclin-dependent kinases, kinase
inhibitors), apoptosis, and growth signaling. Amplification of the oncogenes *PRIM1* (a DNA primase) and *CDK4* have also been associated with osteosarcoma, but the consequences of the increased copy number of these genes are still unclear.

Production of mineralized bone or osteoid by malignant cells is requisite for making a diagnosis of osteosarcoma. Vascular invasion of tumors and spontaneous tumor necrosis are both common phenomena in osteosarcoma. In most cases, the neoplastic bone invades and destroys the bone cortex, spreading widely through the medullary canal and replacing the marrow as it expands. In areas where tumor has burst through cortical bone, the periosteum may be elevated or perforated. Occasionally, but not commonly, the neoplasm penetrates the epiphysis and/or grows into the joint space.

Tumors tend to arise in areas of rapid bone growth and cell division, potentially due to the increased rate of mutation associated with cellular proliferation. Osteosarcoma is capable of metastasis and spreads hematogenously. Between 10% and 20% of patients have lung metastases at the time of diagnosis, as do 98% of patients who die from osteosarcoma. Other, less common areas of metastatic spread include other bones (35%), pleura (33%), and the heart (20%).

Describe the Common Clinical Features Associated With Osteosarcoma

Patients initially present with occasional mild pain in a certain region that intensifies over time. As pain progressively worsens, the affected area becomes tender and swells to the point of

Table 1. Classification of Bone Tumors.

| Behavior | Matrix          | Tumor Type           | Most Common                               | Long Bone Region                   |
|----------|-----------------|----------------------|------------------------------------------|------------------------------------|
| Benign   | Bone-forming    | Osteoma              | Craniofacial bones, skull                | Diaphysis, metaphysis              |
|          |                 | Osteoid osteoma      | Femur, tibia                             |                                    |
|          |                 | Osteoblastoma        | Vertebral column                         | Metaphysis                         |
|          |                 | Osteochondroma       | Long tubular bones                       | Metaphysis                         |
|          |                 | Enchondroma          | Small bones of hands and feet            | Metaphysis                         |
|          |                 | Chondroblastoma      | Proximal humerus, femur, tibia           | Epiphysis                          |
|          |                 | Giant cell tumor     | Distal femur, proximal tibia, distal radius, humerus, fibula | Epiphyseal–metaphyseal junction    |
|          |                 | Bone cysts           | Proximal humerus, femur, tibia           | Metaphysis adjacent to physis      |
|          |                 | Solitary             | Long bones, vertebral column             | Metaphysis                         |
|          |                 | Aneurysmal           | Distal femur, proximal tibia, humerus     | Metaphysis                         |
|          |                 | Primary              | Femur, humerus, pelvis                   |                                    |
|          |                 | Secondary            | Shoulder, pelvis, proximal femur, ribs   | Diaphysis, metaphysis, epiphysis   |
|          |                 |                     | Humerus, tibia, femur                    | Diaphysis, metaphysis              |
| Cartilaginous | Osteosarcoma | Primary, Secondary   | Distal femur, proximal tibia, humerus     | Metaphysis                         |
| Misc     |                 |                     | Femur, humerus, pelvis                   |                                    |
| Malignant| Bone-forming    |                     | Proximal humerus, femur, tibia           | Metaphysis adjacent to physis      |
|          |                 | Osteosarcoma         | Long bones, vertebral column             | Metaphysis                         |
|          |                 | Primary              | Distal femur, proximal tibia, humerus     | Metaphysis                         |
|          |                 | Secondary            | Femur, humerus, pelvis                   |                                    |
|          |                 |                     | Shoulder, pelvis, proximal femur, ribs   | Diaphysis, metaphysis, epiphysis   |
|          |                 |                     | Humerus, tibia, femur                    | Diaphysis, metaphysis              |

* Common site for lesion.

Figure 3. Osteoblastic osteosarcoma of the tibia. The tan yellow necrotic tumor replaces much of the metaphyseal medullary cavity and extends to the physis. The tumor has extended through the cortex into the surrounding tissue.

Figure 4. Adjacent to spicules of cancellous (trabecular) bone (C), osteoid-producing tumor cells, which have undergone necrosis secondary to chemotherapy, are present in the matrix and the light pink osteoid stroma (S). Many of the tumor cells that were in the abundant arborizing osteoid matrix (M) have dropped out giving the false appearance of osteocytes in the neoplastic sclerotic bone (H&E, intermediate magnification).
An estimated 5% to 10% of patients are asymptomatic until a pathologic fracture reveals an underlying osteosarcoma. Serum alkaline phosphatase and lactate dehydrogenase are elevated in 40% and 30% of cases, respectively, but overall laboratory values are not reliable diagnostic tools for osteosarcoma.

Osteosarcomas arise most commonly in the metaphyses of long bones, with the incidence of craniofacial and axial tumors increasing with age. Seventy-five percent of tumors arise adjacent to the knee or shoulder, with the distal femur and proximal tibia or fibula being the most common sites and the proximal humerus the second most common. Radiographic evidence of a mass of lytic and blastic bone with indistinct infiltrating margins indicates an osteosarcoma, as well as the pathognomonic “Codman triangle.” A result of the tumor lifting the periosteum off the adjacent cortical surface, a Codman triangular shadow on X-ray may also have a superimposed “sunburst” periosteal reaction.

**Compare the Variants of Osteosarcoma**

Osteosarcomas are overall similar in behavior and prognosis but can be categorized into osteoblastic, chondroblastic, or fibroblastic tumors based on the dominant matrix-producing cell. Rare high-grade variants include telangiectatic, giant cell-rich, small-cell, and epithelioid osteosarcoma. The low-grade intramedullary variant known as low-grade central osteosarcoma is less likely to metastasize or to be fatal than conventional osteosarcoma.

Juxtacortical osteosarcomas are rare variants occurring on the surface of bone, often described as having a “stuck-on” appearance. Unlike classic osteosarcoma, most patients with juxtacortical sarcomas are older than 25 years and are more likely female than male. Seventy percent of cases occur in the lower posterior femoral metaphysis. The most common subtypes are parosteal and periosteal, the latter being more aggressive than the former. On the whole, juxtacortical osteosarcomas are slow-growing, low-grade lesions that may be surgically excised without adjunctive chemotherapy. Typical patients with this variant have 5-year survival rates of greater than 80%.

**Discuss the Possible Treatments of Osteosarcoma and Associated Outcomes**

In the past, amputation or disarticulation of the affected limb was the only means used to treat osteosarcoma. Outcomes were generally poor, with the 5-year survival rate falling below 20%. Today, the standard of care is a preoperative chemotherapy regimen followed by limb salvage surgery and outcomes have vastly improved: 60% to 80% of patients are disease-free after 5 years. Greater than 90% necrosis post chemotherapy is a good prognostic sign. An 80% to 90% long-term survival is reported in cases achieving greater than 90% necrosis post chemotherapy. Additional resection of any pulmonary metastases may contribute to patient survival. Patients with secondary osteosarcoma do not respond as well to therapy and tend to succumb to their disease. Increased serum alkaline phosphatase may decrease following treatment but then climb again upon return of the tumor. In this way, fluctuations in serum alkaline phosphatase can be used to track future tumor recurrence or metastasis.

**Teaching Points**

- Most primary tumors of bone and cartilage are found in the metaphyses of long bones, of which osteosarcoma is the most common malignancy.
- On histology, osteosarcoma characteristically appears as polygonal and spindled osteoblastic cells of various size producing woven bone that is focally calcified.
neoplastic cells stain positive for alkaline phosphatase, osteocalcin, and osteonectin.1

- Osteosarcoma has 2 peaks of incidence: 75% of patients develop primary osteosarcoma under the age of 20, with the remainder developing osteosarcoma secondary to preexisting bone disorders at an older age.2
- Two-thirds of patients with osteosarcoma have mutations in the retinoblastoma (RB1) gene. Germ line RB1 mutations causing hereditary retinoblastoma increase the risk of developing osteosarcoma by 1000-fold.4
- Diagnosis of osteosarcoma requires the production of mineralized bone or osteoid by malignant cells. Tumors usually invade through the bone cortex and spread widely through medullary canals by replacing bone marrow.1
- Ninety-eight percent of people who die from osteosarcoma have lung metastases.1,2
- Clinical signs of osteosarcoma include progressively worsening regional pain and swelling with radiographic evidence of a mixed lytic and blastic bone lesion with indistinct infiltrating margins. Codman triangle shadow on X-ray is pathognomonic for osteosarcoma.1,2
- Current treatment of osteosarcoma involves perioperative chemotherapy followed by limb salvage surgery, with 60% to 80% of patients in remission after 5 years.1,2
- Secondary osteosarcoma does not respond well to therapy and is usually fatal.2

Authors’ Note

Figures 1 to 3 were provided by Dr Ellen Chung during her scope of US government employment. Figures 4 to 6 were obtained during the scope of US government employment for Dr Conran.

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References

1. Garcia RA, Demicco EG, Klein MJ, Schiller AL. Bones, joints and soft tissue. In Strayer DS, Rubin E, Saffitz JE, Schiller AL, eds. Rubin’s Pathology: Clinical Pathologic Foundations of Medicine, 7th ed. Philadelphia, PA: Wolters Kluwer Health; 2015:1305-1380.
2. Rosenberg AE. Bones, joints, soft tissue tumors. In Kumar V, Abbas AK, Aster JC, eds. Robbins and Cotran Pathologic Basis of Disease, 9th ed. Philadelphia, PA: Elsevier; 2015:765-796.
3. Reith JD. Bone joints. In: Goldblum JR, Lamps LW, McKenney JK, Myers JL, eds. Rosai and Ackerman’s Surgical Pathology. Philadelphia, PA: Elsevier; 2018:1748-1759.
4. Martin JW, Squire JA, Zielenska M. The genetics of osteosarcoma. Sarcoma, 2012;2012:627254.
5. Durfee RA, Mohammed M, Luu HH. Review of osteosarcoma and current management. Rheumatol Ther. 2016;3:221-243.
6. Dehner LP. Skeletal system. In: Stocker JT, Dehner LP, Husain AN, eds. Stocker & Dehner’s Pediatric Pathology, 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2011:1213-1217.
7. Geller DS, Gorlick R. Osteosarcoma: a review of diagnosis, management, and treatment strategies. Clin Adv Hematol Oncol. 2010; 8:705-718.
8. Vergara M. Bone-forming lesions. In: Horvai AE, ed. Bone and Soft Tissue Pathology. Philadelphia, PA: Elsevier; 2012;116-118.
9. Rosenberg AE, Cleiton-Jansen AM, dePinieux G, Deyrup AT, Hauben E, Squire J. Conventional osteosarcoma. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, eds. WHO Classification of Tumors of Soft Tissue and Bone. Lyon: IARC Press; 2013:282-288.