Sarcomas of the Upper Extremity in Children

Mark C. Gebhardt, MD*†

Abstract: Bone and soft tissue sarcomas of the upper extremities in children are rare, but the practicing pediatric orthopaedist should be aware of their presentation, biology and treatment. This report presents a brief review of the presentation, diagnostic findings and treatment of osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, synovial sarcoma and infantile fibrosarcoma of the upper extremity in the pediatric population.

Key Words: Bone neoplasms/pediatric, soft tissue neoplasms/pediatric, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, synovial sarcoma, infantile fibrosarcoma, upper extremity sarcomas


Sarcomas in children are rare and none have a specific predilection for the upper extremity. Despite their rarity, they may present as a hand or arm mass and the upper extremity and pediatric surgeon should be aware of them. Malignant tumors in this age group include bone sarcomas, osteosarcoma, and Ewing sarcoma/peripheral neuroectodermal tumor (PNET) and soft tissue tumors, the common ones being rhabdomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors. In babies and infants, congenital and infantile fibrosarcomas are seen.1

OSTEOSARCOMA

Osteosarcoma is the most common bone sarcoma in childhood2 and the proximal humerus is the third or fourth most common site of presentation. It may also occur in the radius and ulna and rarely in the digits. They are seldom seen before the age of 5 years and are most common in adolescents. Symptoms include pain and a mass and there are no specific laboratory studies. The alkaline phosphatase and lactic dehydrogenase may be elevated and portend a worse prognosis. The plane radiographs show a destructive tumor with areas of increased radiodensity usually in the metaphysis with poor margination and incomplete periosteal response (Codman triangle). There is usually a soft tissue mass that may contain mineralization (Fig. 1A). A staging workup to include magnetic resonance imaging of the affected site (including the entire bone of involvement to look for skip metastases), a bone scan and a computed tomogram of the chest should be obtained. About 10% to 20% of patients will have demonstrable metastases in the chest or another bone at site, but all are suspected of having micrometastases at diagnosis, which is the rationale for the use of adjuvant chemotherapy. A biopsy is necessary to establish the diagnosis and can be accomplished by either open or needle techniques, but should be directed by the surgeon who will perform the definitive surgery.

The pathology shows a high-grade sarcoma that directly forms tumor osteoid or bone. Grossly, the tumor does not cross the articular cartilage, but may cross open growth plates. The adjacent joint should be carefully evaluated on magnetic resonance imaging as the tumors may enter the joint by extending along capsular structures and ligaments. Cytogenetics shows multiple anomalies such as duplication of aberrant chromosomes and losses of parts or all of certain chromosomes (unlike Ewing sarcoma that has clonal translocations of chromosomes 11 and 22).3

Treatment involves a multidisciplinary team composed of surgeons, pediatric oncologists, radiologists, pathologists and at times radiotherapists. Experience with the diagnosis and treatment of these highly lethal and rare sarcomas is essential to maximize the treatment effectiveness. Treatment consists of adjuvant chemotherapy and

FIGURE 1. A, Anteroposterior (AP) radiograph of an osteosarcoma of the proximal humerus in an adolescent girl. B, AP radiograph after chemotherapy, resection, and reconstruction with an osteoarticular allograft.
wide surgical resection.\textsuperscript{2,4–7} Chemotherapy is most often begun after the biopsy results are known and given in the neoadjuvant setting followed by resection and more chemotherapy. The active drugs are high-dose methotrexate, doxorubicin, and cisplatin. Ifosfamide is another active agent, but has not been documented to increase survival beyond that achieved with standard protocols. Event-free survival is approximately 70\% and overall survival (OS) is 80\% in current multicenter trials.\textsuperscript{5} The Children's Oncology Group has done several trials in this country, which have proven the effectiveness of chemotherapy in osteosarcoma that there is no survival advantage to neoadjuvant chemotherapy (although it likely makes resection safer), and that the addition of ifosfamide does not further improve the survival.\textsuperscript{4,5} Multi-institutional cooperative studies are currently being conducted together with European cooperative groups looking to see whether more intensive treatment of patients with a poor histologic response to neoadjuvant chemotherapy will lead to better survival of those patients.

Surgical treatment consists of a wide resection of the involved bone and soft tissue with a cuff of normal tissue completely surrounding the tumor. Reconstruction either with is metallic prostheses or osteoarticular or intercalary allograft.\textsuperscript{8,9} An example of using an osteoarticular allograft for a proximal humerus osteosarcoma is shown in Figure 1B. The role of expandable prostheses in children is still uncertain, although they are being used in the lower extremity.\textsuperscript{7} Expandable prostheses for the proximal humerus add the complexity of maintaining the reduction of the shoulder during the times of expansion. Other novel techniques such as using vascularized fibular grafts with the blood supply to the epiphysis preserved may be useful for the proximal humerus or distal radius in children. Vascularized fibular grafts are also used to salvage fractured allografts or for intercalary reconstructions.\textsuperscript{10}

For lesions of digits, ray amputations are appropriate and at times amputation through the wrist, forearm, or arm may be necessary. Forequarter amputations are seldom performed in the primary setting but may be necessary for local recurrence. Resecting the humerus and scapula (Tikhoff-Linberg) even without reconstruction is preferable to amputation because there is no artificial prosthesis, that is, as good as a functional hand.\textsuperscript{11,12}

**EWING SARCOMA/PNET**

Ewing sarcoma/PNET is a primitive neuroectodermal tumor, which is one of the “round cell tumors” composed of malignant round blue cells. It occurs primarily between the ages of 5 and 30 years and is rare in African-Americans and children of Asian descent. Both Ewing sarcoma and PNET have a translocation of chromosomes 11 and 22 t(11;22)(q24;q12).\textsuperscript{13,14} Ewing sarcoma presents with pain and a mass, and is one of the tumors that may be associated with fevers, chills, and weight loss, although this is uncommon. They may occur in bone or soft tissue throughout the body, with the humerus being the most common site in the upper extremity. Radiographs show a “permeative” destruction of the bone with little if any matrix production and large, unmineralized soft tissue masses. The evaluation and staging are similar to osteosarcoma, with the exception that a bone marrow biopsy is performed to look for bone marrow metastases that occur in about 2\% of cases.

Treatment consists of neoadjuvant chemotherapy with doxorubicin, vincristine, and cytoxan. A recent study concluded that the addition of ifosfamide and etoposide improves the outcome of patients with Ewing/PNET and this 5-drug regimen is now the “standard” drug regimen. Event-free and OS rates for patients who presented without metastases were 69\% and 72\%, respectively.\textsuperscript{15} Current studies of the Children's Oncology Group are looking at methods of intensification of the therapy to improve outcome.\textsuperscript{16}

Treatment of the primary site may be by radiotherapy or surgical resection.\textsuperscript{13} Both modalities seem to give similar local control, but now that patients are surviving with their Ewing sarcoma, radiation sarcomas are a major issue in survivors.\textsuperscript{17,18} The exact incidence is not known for sure, but it may be as high as 5\% to 10\%. For that reason, most centers favor surgical resection over radiotherapy if a functional reconstruction is possible.

**Rhabdomyosarcoma**

The most common soft tissue sarcoma in childhood is rhabdomyosarcoma, which is much more common than other soft tissue sarcomas.\textsuperscript{19,20} It is one of the tumors that occurs in the Li-Fraumeni familial cancer syndrome and with the Beckwith-Wiedemann syndrome.\textsuperscript{21} Of the subtypes of rhabdomyosarcoma, only embryonal and alveolar rhabdomyosarcomas occur in the extremities. Sixteen percent of rhabdomyosarcomas occur in the upper extremity.

Rhabdomyosarcoma is a tumor of rhabdomyoblasts. There are 4 major subtypes: pleomorphic, botryoid, alveolar, and embryonal and the subtypes vary in presentation and outcome. Rhabdomyosarcomas appear as one of the small, round blue cell tumors under light microscopy, but can be differentiated by cytogenetics and immunohistochemistry from the other round cell tumors. Alveolar rhabdomyosarcoma has a chromosomal translocation of t(2,13) in 70\% of cases and t(1,13) in others.\textsuperscript{21} This translocation involves the PAX genes (PAX3 and PAX7) that are involved in muscle development in embryogenesis. Fusion of these genes with the FKHR gene results in a protein that influences tumor cell growth, apoptosis, differentiation, and motility. These translocations are helpful in establishing the diagnosis of alveolar rhabdomyosarcoma and may be of prognostic importance.\textsuperscript{22} Some evidence suggests that the presence of PAX3-FKHR in tumors may confer a worse prognosis than those patients whose tumors have PAX7-FKHR translocations. Embryonal rhabdomyosarcoma is not associated with a specific translocation but does have an allelic loss at 11p15.5.
Embryonal rhabdomyosarcoma is the most common soft tissue sarcoma of childhood, but the extremity is not a common site. They occur in children under the age of 12 years. Alveolar rhabdomyosarcoma occurs in older children and young adults, and 60% are in the extremity. They have a worse prognosis than embryonal rhabdomyosarcoma.

Treatment of rhabdomyosarcoma of the extremity is by chemotherapy and complete excision, if possible. Treatment most protocols call for radiation in addition to surgical excision as microscopic extension of this tumor is common. The OS is 72%, but those with favorable histology and a complete resection have a better prognosis. Lesions in the limbs have a worse prognosis probably because alveolar rhabdomyosarcoma is more common in extremities than the embryonal type and they may be unresectable. The outcome for alveolar rhabdomyosarcoma in the extremities is event-free survival and OS of 62% and 66%, respectively, at 3 years. The size and stage of tumors also influence outcome as does clinical stage.

SYNOVIAL SARCOMA

Of “nonrhabdomyosarcomas,” synovial sarcoma is the most common histologic subtype seen in children, although other sarcomas such as malignant peripheral nerve sheath tumors, alveolar soft parts sarcoma (Figs. 2A, B), and others may occur. Although the name suggests that they are in a joint, synovial sarcoma seldom involves the synovium but they are frequently located adjacent to joints. Another characteristic of synovial sarcomas is that they may be present for several months or years before they are recognized as a malignant mass. Synovial sarcomas have a translocation of chromosomes X, 18, t(X;18;p11;q11). This translocation is between the SYT gene and two areas of the SSX gene (SSX1 and SSX2). Therefore, the translocation can lead to 2 novel genes (the result of SYT-SSX1 or SYT-SSX2 translocation) and there is some evidence that these subtypes may vary in prognosis. Treatment is by surgical resection, although there may be a role for chemotherapy. In children whose lesion is located such that growth plates can be avoided, radiation is used to augment local control. Progression-free survival (PFS) is 40% and OS is 60%, but it varies by clinical group. Clinical groups 1 to 3 (localized) have PFS of 60% and OS of 80%, compared with group 4 (metastatic patients) whose PFS is 10% and OS is 20% at 5 years. Synovial sarcomas in general seem to have an OS better than other types of nonrhabdomyosarcomas and may be more responsive to chemotherapy than other soft tissue sarcomas.

INFANTILE FIBROSARCOMA

Infantile and congenital fibrosarcomas are rare soft tissue sarcomas presenting at birth or in very young children and may be difficult to distinguish from the various forms of fibromatosis. They appear as high-grade fibrosarcomas on histology, but, in general, the prognosis is better than the adult counterpart. Most have a chromosomal translocation leading to the TEL/TRKC fusion gene, which is useful in diagnosis. Cytogenetics or fluorescence in situ hybridization helps to distinguish infantile fibrosarcomas from other lesions. Treatment is surgical resection, which in many cases is curative. Chemotherapy may be useful as a neoadjuvant to make the lesion decrease in size and facilitate resection and at times avoid amputation. The role of chemotherapy for microscopic residual disease after excision is less clear.

In summary, the upper extremity is not a unique site for any of these sarcomas, but the hand or pediatric surgeon should be aware of their characteristics and treatment strategies. Many advances have been made in the diagnosis and treatment outcomes of these sarcomas.
that in the past were highly lethal neoplasms. With current multimodal therapy, survival rates are significantly better than in the past, but it is crucial that they be recognized early and treated by an experienced team.

REFERENCES