CHAPTER 13

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Bone and Soft-Tissue Tumors

Pediatric bone and soft-tissue tumors are rare. Although uncommon, these tumors may impact significantly in the child's life, in terms of both survival and quality of life. Most musculoskeletal tumors seen in pediatric group are benign; however, malignancies do occur. The musculoskeletal primary malignancies that occur predominately in children are two bone sarcomas, namely osteosarcoma and Ewing sarcoma (EWS), and one soft-tissue sarcoma (STS), rhabdomyosarcoma (RMS). In addition, there are non-RMSs, such as congenital and infantile fibrosarcoma in young children and synovial sarcoma in adolescents. The orthopaedist must remain alert, because the malignant tumor is an unexpected event, and its infrequency can result in improper or delayed initial management. The orthopaedist who sees pediatric patients but is not prepared to manage a malignant or an aggressive benign musculoskeletal tumor needs to be comfortable with evaluating patients with these kinds of tumors and deciding which of them should be referred to an orthopaedic oncologist.

This chapter reviews the common bone and soft-tissue tumors of childhood; it discusses how the patients present, what physical findings to expect, and what the plain radiographs may show, and it suggests additional diagnostic and staging evaluations and treatment. This chapter is not intended to be a definitive text on musculoskeletal pathology, and tumor management, and includes only the most common tumors of childhood.

MOLECULAR BIOLOGY OF TUMORS

In the last 30 years, the use of adjuvant chemotherapy has led to dramatic improvement in the survival of children with previously lethal sarcomas. While 30 years ago, 80% of children with a primary bone sarcoma died, now at least that same number will survive (1, 2). One of the intriguing aspects of childhood sarcomas is that, despite similar histologies, stages, and prognostic factors, some patients respond well to treatment, whereas others seem to be resistant to chemotherapy. To date, patients with good prognoses cannot be distinguished from those with poor prognoses except by crude clinical characteristics, such as the presence of metastatic disease at diagnosis or the histologic response to preoperative chemotherapy (3). Recent molecular findings in sarcomas may shed light on their biologic behavior and their response to chemotherapy.

One method of looking for genetic alterations in tumors is to examine the chromosomes by karyotype analysis. The identification of recurrent chromosomal abnormalities provides clues regarding sites of potential gene mutations. Normally, there are 23 pairs of chromosomes in the nucleus of the human cell. Osteosarcomas in general have multiple, bizarre karyotypic abnormalities: some chromosomes are missing, some are duplicated, and some are grossly altered. To date, all studies of high-grade osteosarcomas have shown complex karyotypes and nonclonal chromosome aberrations superimposed on complex clonal events (4, 5). Low-grade juxtacortical osteosarcoma, on the other hand, is characterized by the presence of a ring chromosome accompanied by few other abnormalities or none at all (6). Although it is usually possible to distinguish high-grade from low-grade osteosarcoma by standard histology, the karyotype information may be diagnostically useful in the case of other tumors. In addition to possibly providing prognostic information, the specific chromosomal aberrations provide clues that assist molecular biologists who are looking for gene mutations (6).

In contrast to osteosarcoma, Ewing sarcoma (EWS)/peripheral neuroectodermal tumors (PNETs) and alveolar RMSs have single chromosomal translocations characteristic of their respective histologies. In these tumors, part of one chromosome is transposed to part of another chromosome through a breakpoint. A novel gene and gene protein product are created that presumably give the cell a growth advantage. The most common translocations for these tumors are listed in Table 13-1 (7, 8).

TABLE 13-1 Cytogenetic Findings in Pediatric Soft-Tissue Neoplasms

Tumor	Translocation	Genes
EWS/PNET	t(11;22)(q24;q12)	EWS-FLI1
	t(21;22)(q21;q12)	EWS-ERG
Clear cell sarcoma	t(12;22)(q13;q12)	EWS-ATF1
Synovial sarcoma	t(X;18)(p11;q11)	SYT-SSX1
		SYT-SSX2
Desmoid tumor, fibromatosis	Trisomy 20	
Congenital fibrosarcoma	t(12;15)(p13;q25)	ETV6-NTRK3 (Tel-TrkC)
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	COLIA1-PDGFβ
Lipoblastoma	8q rearrangement (8q11-q13)	
Alveolar RMS	t(2;13)(q35;q14)	PAX3-FHKR
	t(1;13)(p36;q14)	PAX7-FHKR
Alveolar soft parts sarcoma	t(X;17)(p11.2;q25)	ASPL-TFE3

EWS/PNET, Ewing sarcoma/peripheral (primitive) neuroectodermal tumor.

The demonstration of translocations has been useful in the differential diagnosis of round cell tumors. Under the light microscope, there is little to distinguish one of these tumor types from another, and although immunohistochemistry helps to a certain extent, it is at times difficult to be sure of the diagnosis. Demonstration of these characteristic karyotypic findings makes pathologists more secure in their diagnosis and has helped with the classification of these tumors. To perform a karyotype analysis, short-term cultures and metaphase spreads are necessary, but these are labor- intensive and require fresh tissue (7). Fluorescent *in situ* hybridization and reverse transcriptase–polymerase chain reaction (RT-PCR) allow rapid analysis for the presence of translocations; these techniques can be performed on frozen tissue and sometimes even on paraffin-embedded tissue (8–10). Therefore, it is important to give the pathologist appropriate fresh tissue to be snap frozen to preserve messenger ribonucleic acid (mRNA) and allow these studies to be performed (11).

These translocations have significance beyond merely establishing the diagnosis. These rearrangements lead to novel proteins that give the tumor cell a growth advantage. In EWS/PNET, for instance, a fragment of the EWS gene contains DNA-binding domains of the FLY1 gene. The protein acts by disrupting pathways that regulate DNA transcription (12). For several years, it was difficult to make the distinction between EWS and PNET, and clinicians were not sure whether to treat them differently. The observation that both EWS, a poorly differentiated mesenchymal tumor of uncertain cell lineage, and PNET, a tumor believed to be of neural crest origin, shared the same chromosomal translocation led pathologists to believe that both were related neuroectodermal tumors (13). As noted in Table 13-1, further studies revealed other translocations in several of these tumors, each such translocation specifying a different novel protein. There is debate regarding whether one or the other of these is associated with a better prognosis, but the treatment strategies used today are the same for both tumors. While some authors suggest that tumors with the type 1 transcript (EWS-FLY1) are associated with a better prognosis than those with other transcripts, others have disputed this (14, 15).

More recently, these markers have been used in staging and follow-up of high-risk patients (16). Using RT-PCR technology, one can detect small numbers of tumor cells in a bone marrow or a peripheral blood cell population (17). This makes the interpretation of bone marrow aspirates more precise and may provide a method for the earlier detection of relapses after treatment. It is hoped that the gene products of these translocations can also be used in treatment strategies. Because the novel genes formed from the translocation make a novel protein that normal cells do not make, antibodies or targeted T cells can be generated to specifically kill tumor cells. This is being tried in early-phase trials of relapsed patients with RMS and EWS/PNET, and if it works, it may be a way of treating patients who fail standard drug therapy.

Genetic alterations in the DNA of sarcomas have been well demonstrated. Mutations in genes, called *oncogenes*, give some evidence about the pathogenesis of these tumors and may have some prognostic and therapeutic import (4, 18, 19). Oncogenes are normal cellular genes (*protooncogenes*) that are necessary for the normal development and functioning of the organism (20). When they are mutated, they may produce a protein that is capable of inducing the neoplastic state. Oncogenes act through a variety of mechanisms to deregulate cell growth. This is obviously a very complex process and may involve more than one genetic event.

There are two categories of oncogenes: *dominant oncogenes* and *tumor-suppressor genes* (20). The cumulative effect alters proteins that function as growth factors and their receptors, kinase inhibitors, signal transducers, and transcription factors (12). The dominant oncogenes encode proteins that are involved in signal transduction, that is, in transmitting an external stimulus from outside the cell to the machinery that controls replication in the cell nucleus. Mutant cellular signal transduction genes keep the cell permanently "turned on." The protein products of oncogenes also function as aberrant growth factors, growth factor receptors, or nuclear transcription factors. These types of genes seem to have less of a role in osteosarcomas. One exception is amplification of the *HER-2/NEU/ERBB-2* protooncogene in patients with breast cancer, which confers a poorer prognosis. Patients with this amplification are treated with a monoclonal antibody to this protooncogene [MAb45D5, trastuzumab (Herceptin)]. Overexpression of *HER2-NEU* in osteosarcoma has been reported and is associated with advanced disease and poorer prognosis (21, 22). Although this has been disputed by some studies (23, 24), it provides the potential for treatment strategies in patients with osteosarcoma who have amplification of HER2-NEU.

A second class of genes are the tumor-suppressor genes, which encode proteins whose normal role is to restrict cell

proliferation (25, 26). They act as brakes rather than as accelerators of growth. Their normal role is to regulate the cell cycle and keep it in check. The retinoblastoma gene (*RB*) was the first gene recognized in this class (27). Osteosarcomas are very frequent in patients with hereditary retinoblastoma (1000× increased chance), both in the orbit and in the extremities, and are unrelated to irradiation. It was subsequently learned that osteosarcoma in these patients, as well as spontaneously occurring osteosarcomas, carries mutations or deletions of the *RB* gene. It was one of the first clues to the finding that osteosarcomas have a genetic cause. It is estimated that approximately 60% to 75% of sporadic osteosarcomas either have an abnormality of the *RB* gene or do not express a functional RB product (19). The *RB* gene is located on the long arm of chromosome 13 (13q14) and is 200 kb in length. Its product is a 105- to 110-kDa nuclear phosphoprotein (pRB) that appears to have a cell cycle regulatory role. The retinoblastoma protein acts as a signal protein, or a gatekeeper, to regulate the cell cycle through the transcription of genes that mediate the cell cycle. Deactivation of the *RB* gene or absence of pRB allows cells to enter the cell cycle in an unregulated fashion, a condition that imparts a growth advantage to the affected cell. It should be noted that one copy of the gene is sufficient for a normal phenotype. A child born with a normal allele and a mutant or an absent allele will not manifest retinoblastoma until some event occurs in retinoblasts to alter the normal allele. If both copies become deranged, the normal check on the cell cycle disappears, and the conditions for the neoplastic state are met. There are several other mechanisms by which the function of the RB protein can be altered; for instance, viral proteins may bind to the RB protein and inactivate it (5).

The second tumor-suppressor gene to be identified was the *p53* gene (28–30). Located on the short arm of chromosome 17 (17p), its product is a nuclear phosphoprotein that has a cell cycle–regulatory role similar to that of the RB protein. As in the case of *RB*, inactivation of p53 gives the cell a growth advantage, probably because of loss of cell cycle regulation. The p53 phosphoprotein may be inactivated by a variety of mutations, including a single base change (point mutation) that increases the half-life of the protein, allelic loss, rearrangements, and deletions of the *p53* gene. Each of these mechanisms can result in tumor formation by loss of growth control. The p53 protein functions as an extremely important cell cycle checkpoint that blocks cells with DNA damage until they can be repaired or directs damaged cells into apoptosis (programmed cell death) if they cannot be repaired. Cells lacking this checkpoint can accumulate successive genetic abnormalities and possibly become malignant. It is estimated that approximately 25% of osteosarcomas have detectable mutations of the *p53* gene (31).

The p53 protein is a transcription factor, meaning that it binds to regions of other genes (DNA) and controls the expression of genes responsible for cell cycle control (cell growth), apoptosis (programmed cell death), and other metabolic functions, such as control and repair of DNA damage. In concert with RB and a variety of other proteins, p53 acts to regulate the cell cycle through a complex cascade of enzymes, in which RB probably plays the central role. Apoptosis has recently become recognized as an important mechanism by which chemotherapy and radiotherapy kill cancer cells. p53 is involved in this process and appears to arrest cell division after sublethal damage (e.g., by radiation), to give the cell time to repair DNA defects before the next division (32–34). If repair does not take place, the cell undergoes apoptosis and dies. If p53 is not functional, the cell may survive and accumulate genetic defects, leading to malignant transformation. Osteosarcomas have been shown to have a variety of mutations of the *p53* gene (35–37). Preliminary evidence suggests that overexpression of mutant p53 protein (detected by immunohistochemistry) or loss of heterozygosity of the *p53* gene is related to human osteosarcoma (38, 39).

In sarcomas, genetic defects other than p53 and RB have also been detected. One example is a gene called *mdm-2*, which is a zinc finger protein that is amplified in some sarcomas (28, 40, 41). It inactivates p53 protein by binding to it, preventing its transcription factor activity. Cordon-Cardo et al. (42) studied 211 adult STSs by immunohistochemistry, using monoclonal antibodies to mdm-2 and p53, and demonstrated a correlation between overexpression of mdm-2/p53 and poor survival rates. Patients without mutations in either gene (mdm-2/p53–) had the best survival rates, those with one mutation (either mdm-2+/p53– or mdm-2–/p53+) had intermediate rates of survival, and those with mutations in both genes (mdm-2+/p53+) had the lowest survival rates. Another mechanism in which p53 protein can be inactivated is by viral proteins that bind and inactivate both RB and p53 protein (43).

Not only are genetic mutations found in the tumors of patients with sarcomas, but mutations may also be present in all somatic cells (*germ-line mutations*) in patients with heritable cancer (44–46). Although such defects do not appear to be common in the general population, germ-line p53 mutations are present in patients who are part of a familial cancer syndrome. These families have a variety of cancers, often at an early age, and osteosarcomas and STSs are a fairly common occurrence in these kindred. Identification of patients with p53 germ-line mutations can be useful in determining which patients in an affected family are at risk for developing cancers, but much more work is needed in the area of genetic counseling to determine how best to use this information. One study showed that germ-line mutations were present in approximately 3% to 4% of children with osteosarcoma, and that the detection of these mutations was more accurate than family history in predicting the family's susceptibility to cancer (47).

How is this information useful for treatment? One possibility is that the p53 mutations may be potential biologic markers of prognosis and response to treatment (chemotherapy). There is some preliminary evidence that p53 mutations in the tumor may portend a worse prognosis in osteosarcoma. More recently, the association of p53 with apoptosis has suggested possible strategies for chemotherapy, on the basis of the status of the p53 pathway (33, 34). Gene therapy (replacing the missing or mutated gene by transfection with viral carriers) is often discussed, but there are major technical hurdles to overcome before this technology can be used for treating cancers

in humans. However, it might be possible to make tumor cells more antigenic, or to make them more sensitive to antineoplastic drugs, by gene transfer. Another strategy would be to alter normal cells to make them less sensitive to damage by chemotherapeutic agents. Currently, these techniques pose technical challenges, but they offer realistic promise for the near future.

Another exciting area of research in the molecular biology of sarcomas is multidrug resistance (MDR). MDR probably explains why some patients respond to chemotherapy and others do not. Drug resistance may be intrinsic (present at diagnosis) or acquired (appearing after treatment of a tumor) (48, 49). At least four basic mechanisms of drug resistance are now recognized under the category of the MDR phenotype. They are (a) changes in glutathione metabolism, (b) alterations in topoisomerase II, (c) non-P-glycoprotein (P-gp)–mediated mechanisms, and (d) P-gp–mediated mechanisms (6, 7, 48–50). Recent evidence has suggested that P-gp may be of particular relevance to osteosarcoma. P-gp is a glycoprotein encoded by the *MDR-1* gene on the long arm of chromosome 7 in humans (48, 49). *MDR-1* is one member of the aneurysmal bone cyst (ABC) superfamily of genes that encode membrane transport proteins; these proteins function as unidirectional membrane pumps using adenosine triphosphate hydrolysis to work against a concentration gradient. P-gp is a 170-kDa protein that is located in the cell membrane and functions as an energy (adenosine triphosphate)–requiring pump that excludes certain classes (amphipathic compounds) of drugs from the cell. This physiologic mechanism is believed to be important in certain organ systems, such as the blood–brain barrier, placenta, liver, kidney, and colon, for ridding the cell of unwanted toxins, but it is also responsible for actively excluding chemotherapeutic agents, such as *Vinca* alkaloids, anthracyclines, colchicine, etoposides, and taxol (many of which are active in osteosarcoma protocols) from the cancer cell. Another feature of the P-gp mechanism that may have some relevance to therapeutic strategies is that some classes of drugs can reverse the MDR phenotype by blocking the action of the pump. These drugs include verapamil, cyclosporin A, tamoxifen, and others.

Several studies have demonstrated that some sarcomas (25% to 69%) display the MDR phenotype at diagnosis, and that relapsed sarcomas show higher incidence and intensity of MDR expression (48, 49, 51, 52). Because of the small numbers of patients in these studies, and the variety of the methods by which MDR expression was tested, comparisons of the studies and an accurate determination of the incidence of MDR expression are difficult to accomplish. In addition, the age of the patient and the type of sarcoma appear to be related to the incidence of detectable P-gp at diagnosis. One study showed that osteosarcomas have a higher incidence of MDR than other types of adult sarcomas (51). Serra et al. (53) demonstrated that overexpression of P-gp protein was evident in 23% of primary and 50% of metastatic osteosarcomas.

Baldini et al. (54) reported on 92 patients with nonmetastatic osteosarcoma of an extremity who had been treated with chemotherapy and surgery. The study demonstrated that an immunohistochemically determined expression of P-gp predicted a decreased probability of the patient having an event-free survival, and was more accurate in prediction than histologic response to preoperative chemotherapy. Another study failed to find a relation between MDR-1 mRNA expression and outcome in patients treated for osteosarcoma (55).

Findings such as these are important in planning future protocols in human osteosarcoma. The drug-resistant tumor is becoming better identified as one that has a poor histologic response to preoperative chemotherapy and that expresses P-gp. Undoubtedly, it is more complex than this, and other mechanisms will pertain. Several caveats exist. One is the complexity of defining the resistant tumor. Preoperative chemotherapy requires 10 to 12 weeks to provide an estimate of histologic necrosis, unless ways can be found to accurately predict percentage of necrosis by positron emission tomographic (PET) scans, thallium scans, and/or gadolinium-enhanced magnetic resonance imaging (MRI). Detection of P-gp at diagnosis is difficult, and no one method has proven superior. It is probably not sufficient to demonstrate the presence of P-gp; also important is whether the pump is functioning to exclude cytotoxic agents from the tumor cell. Ideally, one would like to reverse the action of the P-gp mechanism but, just as there are no new agents to rescue patients who show poor histologic response, the agents currently available to reverse MDR are of limited benefit. They are potentially problematic in that they make normal cells less tolerant of chemotherapy, and thereby increase toxicity; and in other tumors they have not proven to be effective. The future probably lies in developing more effective reversing agents and in defining other drug-resistant mechanisms.

EVALUATION

A thorough evaluation is necessary for any child presenting with a bone or soft-tissue mass. Although infection and trauma are much more common than a neoplastic process, the consequences of the mismanagement of a patient with a musculoskeletal tumor can be grave (Fig. 13-1).

Medical History. Most children have no significant past medical history, but inquiries should be made. Has the child had a previous fracture? Has the child had other illnesses? Have radiographs been taken previously? Do not assume that the patient or the family will volunteer significant past medical history. Questions that should be asked include: How long has the mass been present? The longer the mass has been present, the more likelihood of a benign process. Especially worrisome are new masses that arise and grow over a short period of time. Is the mass getting bigger or is it stable in size? Masses that are rapidly growing indicate an active process that could be aggressive. Depending on the location, however, such as axial skeleton, some masses may not be noticed until they reach substantial size. Among younger patients, a parent usually notices the mass first, and although the parent will usually think that the mass has appeared overnight, this is rarely the

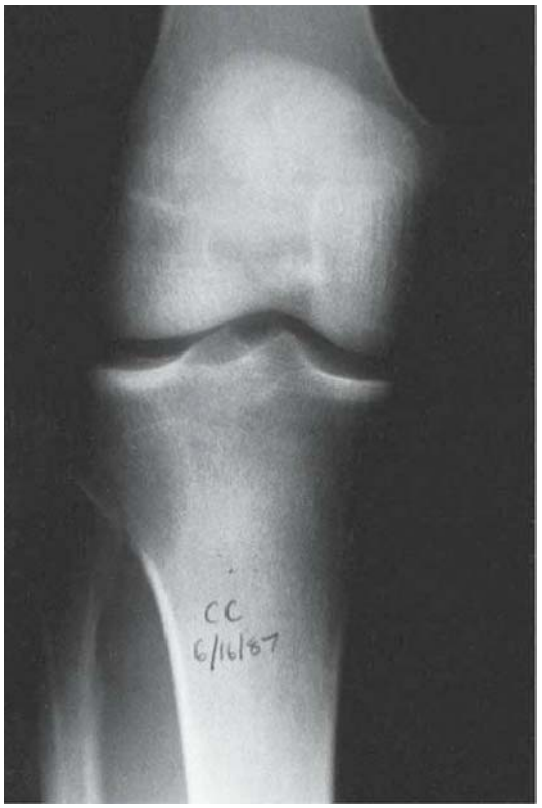


FIGURE 13-1. Anteroposterior radiograph of the knee of a young man who complained of it "giving way." The orthopaedist who saw the patient suspected a derangement, and the patient eventually had arthroscopic surgery. A radiolucent lesion can easily be seen in the lateral aspect of the proximal tibial metaphysis and epiphysis. This giant cell tumor of bone was missed because the physician did not consider this diagnosis when he was examining the patient or the radiograph.

case. Teenagers may report the presence of a mass, but often only after a few weeks or months of waiting for it to resolve spontaneously. Is the mass associated with pain? Pain at the lesional site is a frequent complaint (see below). Active and aggressive tumors will usually present with pain. Painful soft-tissue masses are most often abscesses. Most soft-tissue tumors do not produce significant symptoms until they are large. Although most of the soft-tissue masses seen in children prove to be benign, all soft-tissue masses, even those in children, should be considered to be malignant tumors until proven otherwise. The consequences of mistaking a malignant soft-tissue tumor for a benign tumor can be devastating, whereas the consequences of approaching a benign tumor as if it were a malignancy are minimal. Is there a history of cancer? Depending on the age and the type of tumor, metastatic disease may be the main differential diagnosis.

Chief Complaint. Generally, bone and soft-tissue tumors present in one of four ways:

1. Pain
2. Mass
3. Incidental finding on x-ray
4. Pathologic fracture

Pain is the most common presenting complaint of a child with a musculoskeletal tumor. The characteristics of the pain can help determine the diagnosis. Ask the patient: Where is the pain? How did it begin? Is it sharp, dull, radiating, or constant? Is it associated with activity? Is there a particular activity that makes the pain worse? What makes the pain better? Does it awaken you at night? Is the intensity of the pain increasing, staying the same, or diminishing?

Patients who have active or aggressive benign tumors (e.g., ABC, chondroblastoma, and osteoblastoma) usually have a mild, dull, slowly progressive pain that is worse at night and aggravated by activity. Patients with malignant musculoskeletal tumors complain of a more rapidly progressive symptom complex, not specifically related to activity, which often awakens them at night. Occasionally, the pain pattern is diagnostic. The classic example is the pain of an osteoid osteoma, which is a constant, intense pain that is worse at night, and is almost always relieved by aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). The pain caused by a Brodie abscess (subacute osteomyelitis) is similar to that of an osteoid osteoma, but is rarely relieved by aspirin.

Most children and parents date the onset of symptoms to a traumatic event. The specific nature of the trauma and the relation of the trauma to the current symptoms must be evaluated thoroughly. Trauma without a definitive fracture may be the explanation for an abnormal radiograph, but it should not be assumed to be the explanation, even for a periosteal reaction, unless the history is perfectly consistent. With the increased level of organized sports for children, there has been an increase in the incidence of fatigue or stress fractures, and these can sometimes be confused with neoplasias. Still, one should be cautious about ascribing a lesion to trauma.

The child presenting with a fracture should be questioned about the specifics of the injury that produced the fracture. Most lesions that lead to a pathologic fracture are easily recognized on a plain radiograph, but occasionally they may not be obvious. When the traumatic event seems insignificant, a pathologic fracture should be suspected. Patients should be asked about symptoms, no matter how minimal, that they experienced before the fracture. Most aggressive benign tumors and malignant tumors produce pain before the bone is weakened enough to fracture. Latent benign tumors such as unicameral bone cyst (UBC) and nonossifying fibroma (NOF) are often diagnosed following a trauma, as an incidental finding or a pathologic fracture.

A complete review of systems is mandatory. Ask specifically about fever, decreased appetite, irritability, and decreased activity. Most patients with musculoskeletal tumors do not have systemic symptoms at presentation, and their presence should alert the physician to the possibility of an underlying generalized disorder or osteomyelitis. Rarely, children with a malignant neoplasm, such as EWS, may present with fever, weight loss, and malaise, favoring an infectious etiology. Even

children with large primary malignant musculoskeletal tumors usually appear healthy.

Physical Examination. All patients with musculoskeletal complaints, especially those in the pediatric age group, should have a complete physical examination. Not only can important information be gained about the specific disorder being evaluated, but also other significant abnormalities may be found. For example, café au lait lesions of the skin are a clue that the patient has fibrous dysplasia or neurofibromatosis (Fig. 13-2); numerous hard, nontender, fixed masses near the ends of long bones are suggestive of multiple hereditary exostosis (MHE).

The affected extremity should be examined carefully. The mass should be measured; larger tumors are usually more active and worrisome. Although there isn't a specific number, soft-tissue masses over 5 cm and bone tumors over 8 cm have a higher likelihood of being malignant. The location is an important characteristic. STSs are usually located deep to the deep fascia, while bone sarcomas are usually located around the fastest growth areas (e.g., knee and shoulder). STSs are usually "fixed" to superficial or deep structures (no mobility) and firm to touch; soft, movable, nontender masses, especially those in the subcutaneous tissues, are usually benign. Transilluminate the mass, if light is transmitted more easily through the mass than through the surrounding tissue, the mass is a fluid-filled cyst. The gait pattern should be recorded; muscular atrophy measured, and the range of motion of the adjacent joint should be measured. The presence of erythema, tenderness, or increased temperature should be noted.

Neurovascular exam is essential. Often vascular malformations will be in the differential of soft-tissue tumors; check for pulsations or bruit. Detailed peripheral nerve check will assist in evaluating the proximity to these structures. Check for satellite lesions, the easiest lesion to miss is the second lesion. Examine the abdomen for hepatomegaly, splenomegaly, etc. Examine regional lymph nodes; although most musculoskeletal malignancies metastasize via hematogenous, some will do it via lymphatic. The most common ones are epithelioid sarcoma (16%), synovial sarcoma (15%), RMS (13%), and angiosarcoma (13%) (56).

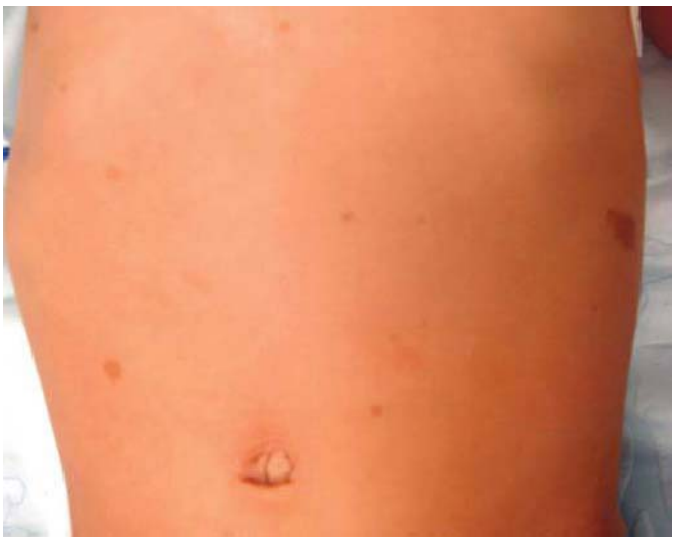


FIGURE 13-2. Appearance of the abdomen of a 4-year-old girl who presented with several café au lait spots and angular deformity of the tibia. Based on physical examination, the diagnosis of neurofibromatosis could be made. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

Plain Radiograph Examination. Plain radiographs are the single most useful image modality to assess a musculoskeletal tumor; all patients should have at least anteroposterior and lateral plain radiographs of the affected area. Often bone tumors are incidentally found after radiographs are taken for other reason. Pathologic fracture is also a common presentation, especially among some benign tumors such as UBC.

The entire lesion must be observed. The radiograph should be reviewed systematically. Look at the bone, all of it, and every bone on the radiograph. Ask yourself these questions: Is there an area of increased or decreased density? Is there endosteal or periosteal reaction, and if there is, what are the characteristics of the reaction? Is there cortical destruction? Is it localized or are there multiple defects? Is the margin in the tumor well defined or poorly defined? Is there a reactive rim of bone surrounding the lesion? Are there densities within a radiolucent lesion? Is the bone of normal, increased, or decreased overall density? Is the joint normal? Is there loss of articular cartilage? Is the subchondral bone normal, thick, or thin? Are there abnormalities in the bone on both sides of the joint? Are there intra-articular densities? Is there a soft-tissue mass? Are there calcifications or ossifications in the soft tissue? If one looks specifically for abnormalities, it is unlikely that an abnormality will be missed.

The pelvis and the scapula are exceptions to this rule. Large tumors involving the pelvis or the scapula, even those with marked destruction of bone, can be extremely difficult or impossible to see on a plain radiograph. If there is a suggestion that the patient has a pelvic or a scapular tumor, computerized axial tomography (CT) scan or magnetic resonance (MRI) is recommended.

Enneking (57) proposes that four sets of questions should be asked when looking at plain radiographs of a possible bone tumor.

1. Where is the tumor? This refers to the lesion's anatomic location: long bone or flat bone; epiphyseal, metaphyseal, or diaphyseal; and medullary canal, intracortical, or surface. Based on the tumor location and the patient's age, one can already formulate a differential list.
2. What is the tumor doing to the bone? Is there erosion of the bone, and if so, what is the pattern? This will determine the lesion aggressiveness.
3. What is the bone doing to the tumor? Is there periosteal or endosteal reaction? Is it continuous? Is it sharply defined? The periosteal reaction will reflect the efforts of the host bone to contain the lesion.

TABLE 13-2 Most Common Pediatric Bone Tumors by Location

Tumor Location	Most Common Tumors
Epiphysis	Chondroblastoma (growth plate open)
	Giant cell tumor (growth plate closed)
	Brodie abscess (subacute osteomyelitis)
	Langerhans cell histiocytosis
Metaphysis	Anything!
	Most benign and malignant bone tumors
Diaphysis	Fibrous dysplasia
	Osteofibrous dysplasia
	Adamantinoma
	Langerhans cell histiocytosis
	Osteoid osteoma
	Bone cyst
	Ewing sarcoma
	Leukemia/lymphoma
	Osteomyelitis
Anterior spine elements	Langerhans cell histiocytosis
	Hemangioma
	Infection
	Giant cell tumor
	Chordoma
	Leukemia
Posterior spine elements	Aneurysmal bone cyst
	Osteoblastoma
	Osteoid osteoma
	Osteochondroma

4. Are there any intrinsic characteristics within the tumor that indicate its histology? Is there bone formation by the tumor? Is there calcification? Is the lesion completely radiolucent?

In addition to this list approach, always consider patient's age and specific location of the tumor within the bone, as these characteristics will limit the differential diagnosis (Table 13-2). Most bone tumors can be diagnosed correctly after obtaining the history, performing a physical examination, and examining the plain radiograph. When the specific diagnosis is made from these examinations, additional studies are requested only if they are necessary for treatment. Often, specific treatment can be planned from only the history, physical examination, and plain radiographs. For example, a 12-year-old boy with a hard, fixed mass in the distal femur that has been present for several years and has not increased in size for more than 1 year complains of pain after direct trauma to this mass. Plain radiographs confirm the clinically suspected diagnosis of osteochondroma (Fig. 13-3). Further evaluation to make the diagnosis is not necessary.

When the specific diagnosis cannot be made, it should be possible to limit the differential to three or four diagnoses, and appropriate additional evaluations can be requested. CT, MRI, and nuclear bone scanning (technetium, gallium, thallium, or indium) may reveal findings that are diagnostic, or that provide the information required for planning a subsequent biopsy.

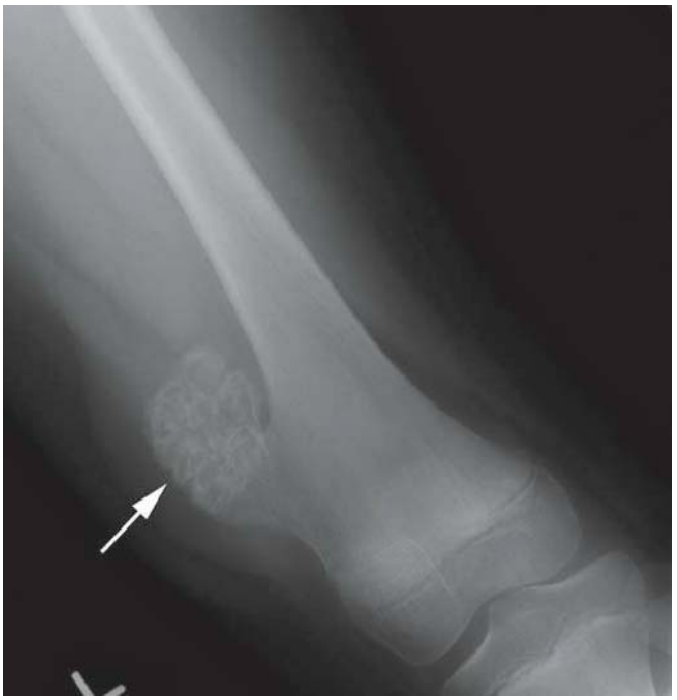


FIGURE 13-3. Anteroposterior radiograph of the distal femur of a 12-year-old boy with a hard, fixed mass that has been present for several years. Note the continuity of the cortex and the outline of the mass, as well as continuity of the intramedullary cavity and the interior of the mass. Also present are calcifications within the mass. The appearance is typical for a pedunculated osteochondroma. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

Additional Diagnostic Studies

Laboratory Examinations. For the most part, serum and urine laboratory values are usually normal in musculoskeletal neoplasia. Nonetheless, a few musculoskeletal tumors are associated with abnormal laboratory values. The erythrocyte sedimentation rate (ESR) is nonspecific but sensitive. Patients with infections or malignant tumors usually have an elevated ESR, but patients with benign disease should have a normal value. A normal ESR value can increase the physician's confidence that a suspected benign, inactive lesion is just that. Patients with active benign or malignant musculoskeletal tumors, particularly those with EWS, often have an elevated ESR, but it is rarely >80 mm/hour. A markedly elevated value (>180 mm/hour) favors a diagnosis of infection and may be just what is needed to justify an early aspiration of a bone or soft-tissue lesion. C-reactive protein (CRP) is another useful serum value that indicates systemic inflammation. Because it increases and returns to normal more quickly than ESR, CRP has been used as the main serum value to follow-up infection.

Serum alkaline phosphatase is present in most tissues in the body, but the bones and the hepatobiliary system are the predominant sources. In the pediatric age group, conventional high-grade osteosarcoma is associated with

elevated levels of serum alkaline phosphatase (58). Not all patients with osteosarcoma have elevated levels of serum alkaline phosphatase, and therefore a normal level does not exclude osteosarcoma from the diagnosis. A minimal elevation can be observed with numerous processes, even a healing fracture. Adults with elevated levels of serum alkaline phosphatase secondary to bone disease are most likely to have Paget disease of bone or diffuse metastatic carcinoma. Patients with a primary liver disorder have elevated levels of serum alkaline phosphatase as well, but they also have elevated levels of serum 5-nucleotidase and leucine aminopeptidase, and glutamyl transpeptidase deficiency. The levels of 5-nucleotidase and leucine aminopeptidase are not elevated in primary bone tumors. Two- to threefold increase in the alkaline phosphatase levels has been associated with worse prognosis in patients with osteosarcoma (58).

Serum and urine calcium and phosphorus levels should be measured, especially if a metabolic bone disorder is suspected. Serum lactate dehydrogenase (LDH) level is elevated in some patients with osteosarcoma. Patients with EWS or osteosarcoma with elevated LDH have a worse prognosis (15, 59, 60). Elevated LDH levels may also indicate relapse in a patient who has been treated for these tumors (59). Patients entering chemotherapy treatment protocols will need to have LDH levels determined in order to stratify them on the protocol. Other laboratory determinations are not helpful and are not recommended.

Radionuclide Scans. Technetium bone scanning is readily available, safe, and an excellent method for evaluating the activity of the primary lesion. In addition, bone scanning is the most practical method of surveying the entire skeleton (Fig. 13-4). Technetium-99 attached to a polyphosphate is injected intravenously, and, after a delay of 2 to 4 hours, the polyphosphate, with its attached technetium, concentrates in the skeleton proportional to the production of new bone. A disorder that is associated with an increase in bone production increases the local concentration of technetium-99 and produces a "hot spot" on the scan. The technetium bone scan can be used to evaluate the activity of a primary lesion, to search for other bone lesions, and to indicate extension of a lesion beyond what is seen on the plain radiograph. The polyphosphate–technetium-99 compound also concentrates in areas of increased blood flow, and soft-tissue tumors usually have increased activity compared with normal soft tissues. The technetium-99 bone scan can be used to evaluate blood flow if images are obtained during the early phases immediately after injection of the technetium-99. The polyphosphate–technetium-99 is cleared and excreted by the kidneys, so the kidneys and the bladder have more activity than other organs. The technetium-99 scan is sensitive but nonspecific, whereas infectious processes will usually present with "hot scans." The principal value of a radionuclide scan is as a means of surveying the entire skeleton for clinically unsuspected lesions. There are exceptions and false negative may occur, in approximately 25% of cases of Langerhans cell histiocytosis (LCH), the bone scan is normal, or there is decreased activity at the site of the lesion (42, 61, 62).

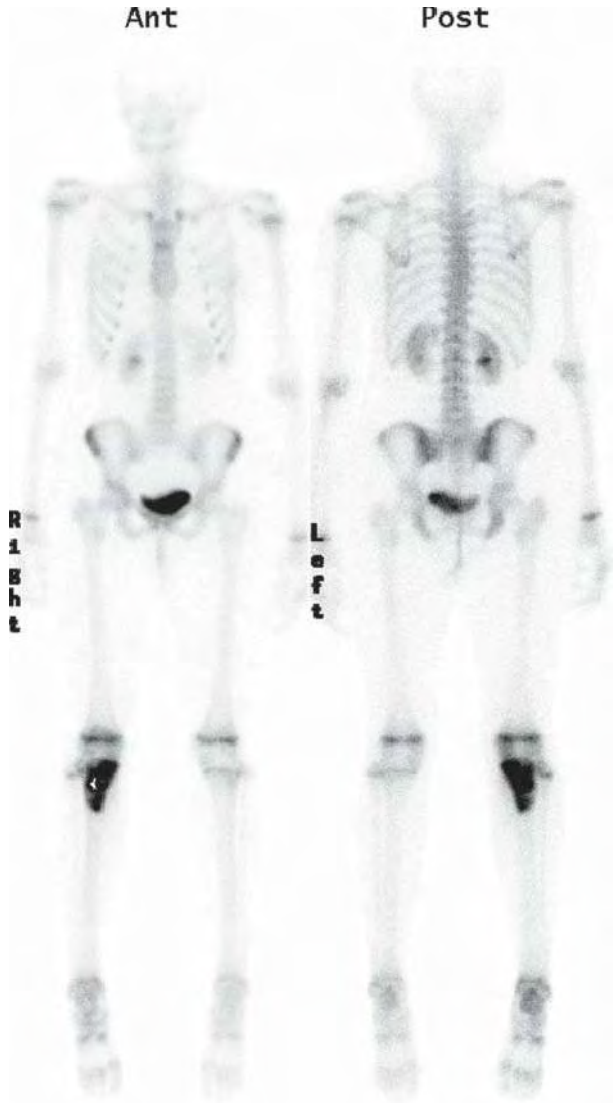


FIGURE 13-4. An anterior and posterior view of a whole-body technetium-99 bone scan. This was a 14-year-old girl with a right proximal tibia osteogenic sarcoma and there is increased activity in the lesional area. There were no other sites of disease based on the bone scan. Technetium-99 bone scanning is an efficient means of evaluating the entire skeleton of a patient with a bone lesion. It is important to have the entire skeleton scanned, rather than limit the scan to a small part of the skeleton. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

PET is being used more frequently in the evaluation of musculoskeletal tumors (42, 63). Fluoro-2-deoxy-D-glucose (FDG) PET is the type of PET used most frequently for the musculoskeletal system. Because there is a differential uptake of FDG between neoplastic tissue and normal tissue (neoplastic tissue has greater uptake), it is possible to identify neoplastic tissue on a PET scan. The role of PET in the evaluation and monitoring of patients with musculoskeletal neoplasia is under

investigation, especially among children. PET with fluorine-18-FDG has proved particularly useful in evaluating patients with lymphoma (64, 65).

Computerized Axial Tomography. When introduced in the late 1970s, CT scan dramatically improved the evaluation of bone and soft-tissue tumors. The anatomic location and extent of the tumor could be determined accurately. The improved accuracy of anatomic localization means that less radical surgery can be performed safely.

The density of a bone or soft-tissue mass on a CT scan is called its "attenuation coefficient" and is measured in Hounsfield units (HU). The density of water is 0 HU; tissues more dense than water have a positive value, and tissues less dense than water have a negative value. The vascularity of a lesion can be evaluated by measuring the increase in the attenuation coefficient of a lesion after intravenous infusion of contrast, and comparing this increase to that in an adjacent muscle. Normal muscle has an attenuation coefficient of approximately 60 HU, and increases 5 to 10 HU with a bolus of intravenous contrast. Fat has an attenuation coefficient of approximately 60 HU, and cortical bone usually has a value of more than 1000 HU.

CT scan can be performed quickly and is less anxiety producing than closed MR, so sedation is less likely to be needed when compared with MRI. The main downside is the amount of radiation delivered in a CT scan, particularly among children (66). CT scan is most useful in the evaluation of small lesions in or immediately adjacent to the cortex (e.g., osteoid osteoma) and lesions with fine mineralization or calcifications (e.g., chondroblastoma). CT is still the gold standard for chest evaluation and to rule out lung nodules (Fig. 13-5). CT has also been used for percutaneous biopsies and treatment of several different lesions.

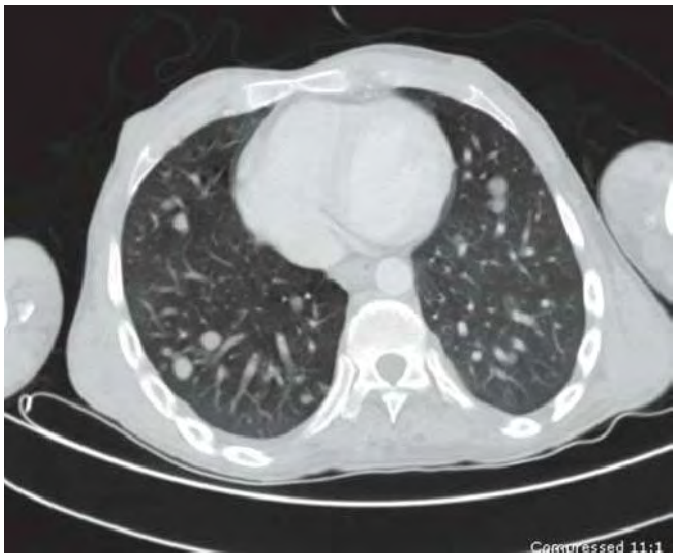


FIGURE 13-5. Axial cut of a CT scan of the chest of an 18-year-old male who had NF-1 and an MPNST of the shoulder girdle with metastatic involvement of the lung at presentation. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

Magnetic Resonance Imaging. MRI does not expose the patient to radiation and has proved to be the most useful tool in the evaluation of soft-tissue lesions. MRI produces images of the body in all three planes (axial, sagittal, and coronal) as easily as in a single plane, and poses no known hazards to the patient.

The images are produced by a computer program that converts the reactions of tissue hydrogen ions in a strong magnetic field excited by radio waves. By adjusting excitation variables, images that are T1- and T2-weighted are obtained. A variety of techniques have been used to produce images of improved quality compared with routine T1- and T2-weighted images. The use of gadolinium as an intravascular contrast agent allows one to judge the vascularity of a lesion, thereby providing even more information about the tumor. Fat-suppression images with gadolinium enhancement are often especially useful in demonstrating a soft-tissue neoplasia. As with CT scan, it is important for the orthopaedist requesting MRI to discuss the case with the radiologist. The radiologist can then determine the optimal MRI settings required for visualizing the lesion.

MRI is the single most important diagnostic test after physical examination and plain radiography for evaluating a musculoskeletal lesion. The ability to view the lesion in three planes, determine its intraosseous extent, see the soft-tissue component clearly, and have an idea of the tissue type from one diagnostic test makes MRI a powerful tool. Unfortunately, variations in technique mean that it is important that the examination be planned carefully if the maximum information possible is to be obtained. T1-weighted (with and without gadolinium), T2-weighted, and fat-suppression techniques are the minimal images needed.

Staging. Patients with neoplasia can be separated into groups on the basis of the extent of their tumor and its potential or presence for metastasis. These groups are called *stages*. Grouping patients by their stage helps the physician predict a patient's risk of local recurrence, metastasis, and outcome. This facilitates making treatment decisions about individual patients and helps in the comparison of treatment protocols. Staging systems are based on the histologic grade of the tumor, its size and location, and the presence of regional or distant metastases. The presence of a metastasis at the time of presentation is a bad prognostic sign and, regardless of other findings, puts the patient in the highest-risk stage. For patients without metastases at presentation, the histologic grade of the tumor is the principal prognostic predictor. Size is next in importance. Higher histologic grade and larger tumors are associated with the worse prognoses (67).

There are two common staging systems in use for musculoskeletal tumors. The task force on malignant bone tumors of the American Joint Commission on Cancer Staging and End Result Studies published a staging system for soft-tissue tumors in 1977, which was most recently revised in 2002 (68). This staging system is based on the histologic grade (G), local extent or size (T), whether the nodes are involved (N), and

metastases (M). The tumors are separated into three histologic grades (G1, low grade; G2, medium grade; G3, high grade) and two sizes (T1 for <8 cm (for bone) or 5 cm (for soft tissue), T2 for equal to or greater than that). Patients with nodal involvement are designated N1, and those without nodal involvement are designated N0. Patients with metastatic disease are designated M1, and those without metastatic disease are designated M0. There are four stages, with subclasses in each stage. Tumors at stage I are associated with the best prognosis, and tumors at stage IV with the worst prognosis.

Enneking et al. (69) also proposed a musculoskeletal staging system. This system is used more often by orthopaedists involved in the management of patients with musculoskeletal tumors. It was designed to be simple, straightforward, and clinically practical. The tumors are separated into only two histologic grades (I, low grade; II, high grade) and two anatomic extents (A, intracompartmental; B, extracompartmental). Patients with metastatic disease in either a regional lymph node or a distant site are grouped together as stage III. Each bone is defined as its own separate anatomic compartment. The soft-tissue anatomic compartments are defined as muscle groups separated by fascial boundaries. There are five stages in this system (Table 13-3).

Enneking et al. (69) also introduced four terms to indicate the surgical margin of a tumor resection. These terms are in common use, and provide a means of describing the relation between the histologic extent of the tumor and the resection margin. The surgical margins are defined as *intralesional*, *marginal*, *wide*, and *radical*. An intralesional margin is the surgical margin achieved when a tumor's pseudocapsule is violated and gross tumor is removed from within the pseudocapsule. An incisional biopsy and curettage are two common examples of an intralesional margin. A marginal surgical margin is achieved when a tumor is removed by dissecting between the normal tissue and the tumor's pseudocapsule. This is a surgical margin obtained when a tumor is "shelled out." A wide surgical margin is achieved when the tumor is removed with a surrounding cuff of normal, uninvolved tissue. This is often referred to as *en bloc* resection and is the most common type of resection used for malignant tumors. A radical surgical margin is achieved when the tumor and the entire compartment (or compartments) are removed together. This usually is accomplished only with an amputation proximal to the joint that is just proximal to the lesion (e.g., an above-knee amputation for a tibial tumor). As a rule, benign lesions can be managed with an intralesional or a marginal surgical margin, but malignant tumors require a wide surgical margin. Radical surgical margins are reserved for recurrent tumors and the most infiltrative malignancies.

TABLE 13-3 Staging of Musculoskeletal Tumors

Stage	Grade	Site and Size
IA	Low	Intracompartmental (T1)
IB	Low	Extracompartmental (T2)
IIA	High	Intracompartmental (T1)
IIB	High	Extracompartmental (T2)
III	Any grade; regional or distant metastasis	Any site or size

T1, tumor <5 cm; T2, tumor ≥5 cm.
From Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. *Clin Orthop Relat Res* 1980;153:106, with permission.

Biopsy. Biopsy is an essential part of tumor staging and management decision making for children with a bone or a soft-tissue tumor. Sometimes, a biopsy can be avoided and diagnosis made on basis of history, physical examination, and imaging studies. When a biopsy is required, the prebiopsy evaluation improves the chance that adequate and representative tissue will be obtained, the least amount of normal tissue will be contaminated, and the pathologist will make an accurate diagnosis. It is recommended that the surgeon consult with the radiologist and the pathologist before performing the biopsy to get their suggestions for the best tissue to obtain; furthermore, discussing the case preoperatively with the pathologist will allow the pathologist to be better prepared to make a diagnosis from a frozen section.

The purpose of the biopsy is to confirm the diagnosis suspected by the physician after the evaluation, or to determine which diagnosis, from among a limited differential diagnosis, is correct. In addition to providing confirmation for a specific diagnosis, the tissue obtained must be sufficient for histologic grading. It must be representative of the tumor and, because many musculoskeletal tumors are heterogeneous, the specific site from which the tissue is taken is important. Biopsy is not a simple procedure; the musculoskeletal tumor society has shown that an unplanned or erroneous biopsy can impact negatively the outcome, with higher incidence of unneeded surgery, including amputation and worse outcome (70).

There are two forms of biopsies: percutaneous (needle biopsy) and open (incisional and excisional). Percutaneous biopsy can be done via fine needle aspirate or core. It has the advantage of having low morbidity and sometimes can be done in clinic (older patients). Some of the disadvantages include a small amount of tissue and a higher chance for sampling error that may limit the ability to perform special stains and cytogenetics. The reported accuracy of a needle biopsy is around 85% (71).

Open biopsy has the advantage of obtainment of a larger tumor sample that allows the pathologist to perform all necessary studies and decreases the chance of sampling error. The accuracy of open biopsy is close to 96% (71). Furthermore, most children will require general anesthesia for a biopsy and therefore is important to obtain adequate sampling. Open incisional biopsy is the most commonly used technique. It entails obtaining a sizeable fragment of the tumor without attempting excision of the whole mass. Ideally, the treating surgeon will be the one performing the biopsy. That should avoid several possible complications that could impact in the ability of performing limb salvage and adequate tumor resection. Some of

the principles of open biopsy include drawing definitive limb salvage incision prior to start; avoiding transverse incisions on extremities; avoiding raising flaps or exposure of neurovascular structures; always performing an intraoperative frozen section to ensure acquisition of diagnostic tissue; if a drain is used, it should exit the skin in line with the incision; placing sutures within 5 mm of the incision; sending material for culture and sensitivity; achieving meticulous homeostasis (hematoma from the biopsy may contain tumor cells and will require resection if surgery is the treatment); and avoiding or judicious use of local anesthesia (72).

Occasionally an excisional biopsy, rather than an incisional biopsy, is indicated. Open excisional biopsy differs from incisional biopsy in that the entire tumor is excised and sent for analysis. An excisional biopsy is appropriate when the lesion is small and can be excised with a cuff of normal tissue. It is usually reserved for small (<3 cm) lesions that are likely benign. An excisional biopsy may be appropriate even when a major resection is required. If the preoperative evaluation strongly supports the diagnosis of a malignancy, particularly one for which a frozen section analysis will be difficult to do, an excisional biopsy should be considered. The advantages include single surgical procedure; however, a significant disadvantage is the need for extensive tissue sacrifice if re-excision is necessary (malignant tumor) to obtain appropriate margins (i.e., unplanned excision) (Fig. 13-6). An added advantage of an excisional biopsy is that the pathologist is able to examine the entire lesion, thereby improving the accuracy of the pathologic examination. An incisional biopsy exposes uncontaminated tissues to the tumor, and if the tumor proves to be a malignancy, the definitive resection is more complicated. If the lesion can be treated with curettage or a marginal excision, the incisional biopsy leads to the least functional loss. The final decision is made for each patient on the basis of not only the tumor's characteristics but also the patient's preference. Some patients want to take the fewest chances, and are willing to accept the possibility of slight overtreatment, whereas others choose to take one step at a time. It is the surgeon's responsibility to explain the situation to the patient so that an informed decision can be made.

A final note of caution is offered with regard to the biopsy: osteomyelitis is more common than bone tumors, especially in children, and osteomyelitis often mimics neoplasia. The reverse is also true; therefore, when performing a biopsy, even

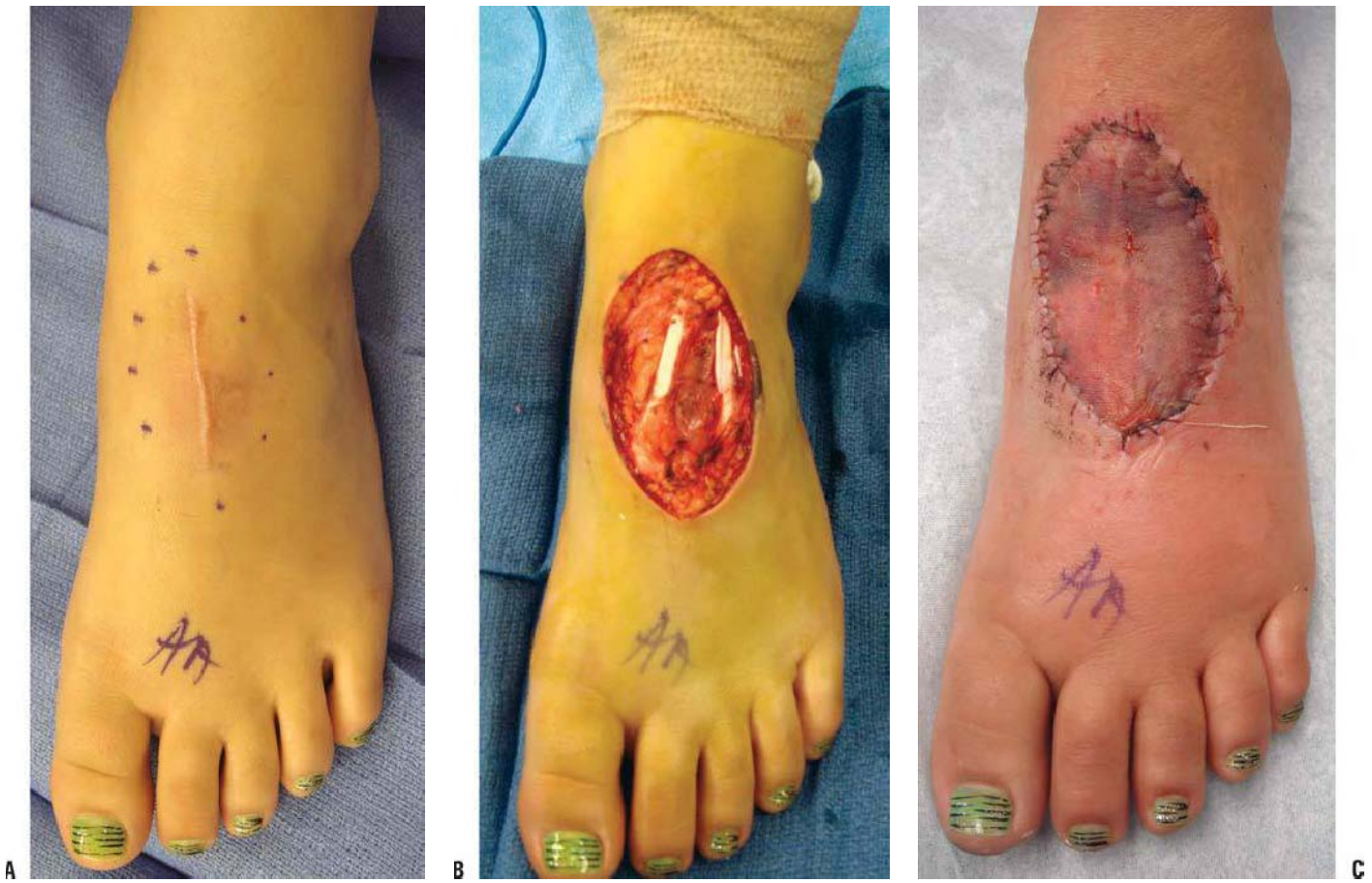


FIGURE 13-6. This 14-year-old girl had an unplanned excision of a "lipoma" of the dorsum of her foot, performed at an outside institution **(A)**. The definitive diagnosis was consistent with a fibrosarcoma. The patient needed re-excision of the lesion with oncologic margins **(B)** and the soft-tissue defect created needed skin grafting **(C)**. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

when the diagnosis seems obvious, culture every biopsy and biopsy every culture.

SPECIFIC BONE TUMORS

This chapter is not designed to be a definitive musculoskeletal pathology text, and only those tumors that are commonly seen in the pediatric orthopaedic practice are discussed. The authors have tried to confine the discussion to pertinent information regarding the tumors, their evaluation, and particularly their treatment.

BENIGN BONE TUMORS

Bone-Forming Tumors

Osteoid Osteoma. Osteoid osteoma is a benign active bone tumor that accounts for 11% of the benign bone tumors in Dahlin series from the Mayo Clinic (73). Osteoid osteoma most commonly affects boys (3:1 girl) between 5 and 24 years of age (80% of all patients). McLeod (74) is credited with the initial description, distinguishing it from a Brodie abscess, and from Garre osteomyelitis.

The classic presentation is pain at lesional site. The pain is not related to activity. Prostaglandins produced by the tumor are suspected to cause the pain, which is sharp, piercing, worse at night, and readily alleviated by aspirin or NSAIDs. If a patient has the typical pain for an osteoid osteoma, but there is no relief by aspirin, the diagnosis should be doubted. Patients with osteoid osteoma show few abnormalities on physical examination, with the exception of scoliosis in patients with osteoid osteoma of the spine. The child may walk with a limp and have atrophy of the extremity involved. If the lesion is superficial, it may be tender on palpation.

Although osteoid osteomas may arise in any bone, around 50% are found in the femur and tibia. The usual radiographic appearance is one of dense reactive bone with new bone periosteal formation, the actual lesion (a.k.a. nidus) is small (<15 mm in diameter), radiolucent, and of difficult visualization especially in the axial skeleton. The nidus may be on the surface of the bone, within the cortex, or on the endosteal surface. Lesions on the endosteal surface have less reaction than lesions within or on the cortex (Fig. 13-7).

Spine is a common location for "occult" osteoid osteoma. Since osteoid osteoma of the spine does not elicit a significant bony reaction, and it is usually located in the posterior elements, it is very difficult to make the diagnosis based on plain radiographs (Fig. 13-8A). When a child presents with painful scoliosis, with or without atypical curve pattern, osteoid osteoma should be considered (75–77).

A technetium-99 bone scan is particularly useful to localize the lesion otherwise missed on the plain radiograph (78). CT is the best imaging modality for visualization of the nidus (79). The distance between the CT scan sections should be small (1 to 2 mm), so that the nidus is not missed (Fig. 13-8B). The window settings of the CT scanner should be adjusted so that the dense reaction around the lesion does not obscure the small, low-density nidus. MRI can be misleading and demonstrate excessive soft-tissue reaction favoring an infectious or a more aggressive diagnosis (79). Serum and urine laboratory values are normal.

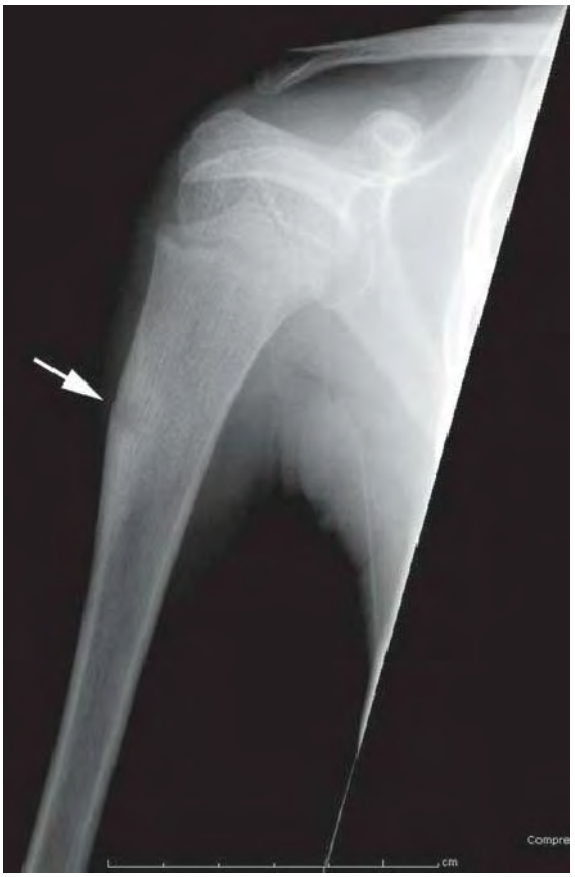


FIGURE 13-7. Anterior–posterior radiograph of the humerus of a 5-year-old girl who presented with night pain that was readily relieved with NSAIDs. Note the intracortical lytic (nidus) lesion, surrounded by new bone formation, no periosteal reaction or soft-tissue mass (*arrow*). The nidus measured <1 cm and the lesion was consistent with an osteoid osteoma. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

On gross inspection, the nidus of an osteoid osteoma is cherry-red and surrounded by dense white bone. The nidus is small, <5 to 10 mm in diameter. A lesion that is identical histologically to the nidus of an osteoid osteoma, but larger than 2 cm, is called an *osteoblastoma*. The nidus is composed of numerous vascular channels, osteoblasts, and thin, lacelike osteoid seams (Fig. 13-9). Multinucleated giant cells may be seen, but are not common (75).

Natural history shows that osteoid osteoma may heal spontaneously although that may take several years (75, 80). Occasionally, a patient may use aspirin or NSAIDs to control the symptoms until the pain disappears, but most often the intensity of pain, the time it takes for the lesion to heal spontaneously, and the amount of medication required are not tolerable, and surgery is indicated.

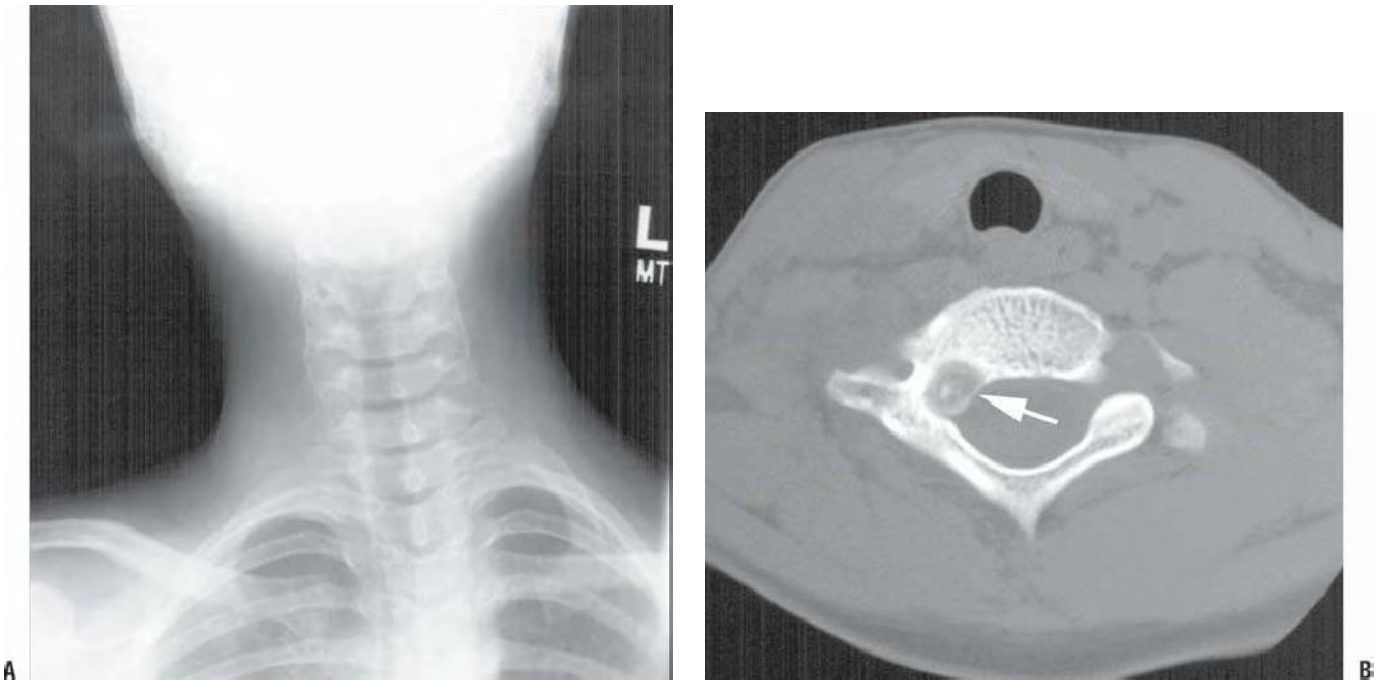


FIGURE 13-8. This is a 13-year-old boy with lower neck pain, worse at night and torticollis; anterior–posterior **(A)** radiographs of the cervical spine is not diagnostic and only shows malalignment due to muscle spasm. Axial CT **(B)** shows the osteoid osteoma nidus located in the pedicle of C5 (*arrow*). (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

Kneisl and Simon (80) treated 24 patients with osteoid osteoma. Thirteen were operated on immediately, and all had complete relief of pain. Nine others were treated with NSAIDs. Of these, three subsequently elected to have surgery, but the six others also eventually became free of pain (an average of 33 months). Complete removal of the nidus relieves the patient's pain. Partial removal may provide temporary relief, but the pain usually returns (80). Only the nidus needs to be excised. The reactive bone around the nidus does not have to be removed.

Minimally invasive CT-guided techniques have become the preferred treatment for osteoid osteoma. The advantages include adequate visualization of the nidus, lower risk of recurrence, fast recovery, and its safety. Radiofrequency ablation is

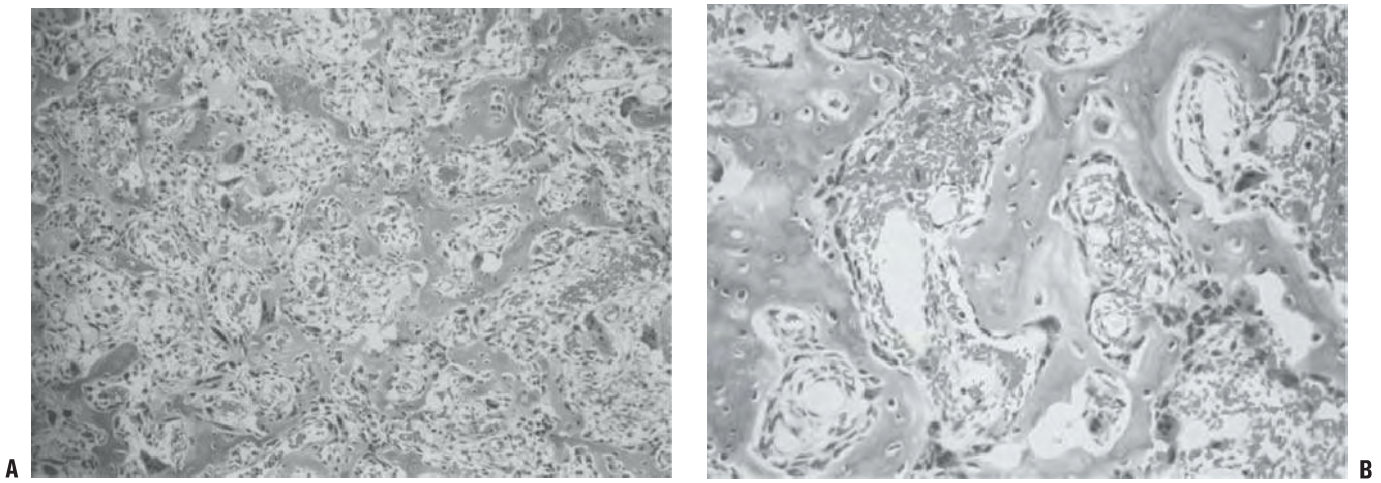


FIGURE 13-9. **A:** Typical histologic appearance of an osteoid osteoma. There is immature (woven) bone lined with osteoblast. Between the woven bone is a vessel-rich fibrous stroma. There is no atypia, and the few mitotic figures are normal (10× magnification). **B:** Higher magnification (40×) of the histology of the osteoid osteoma shown in A. The woven bone lined with osteoblast is easily seen. The red blood cells indicate the intense vascularity that is typical of this lesion.

one of the most common methods used. The procedure is performed under as an outpatient with general anesthesia. A needle biopsy is performed under CT guidance that is followed by placing the radiofrequency electrode with an internal thermistor and ablating the nidus. The success rate is of up to 90% (81).

Sometimes surgery is indicated, especially for recurrent tumors and spine lesions. Once identified, the nidus is curetted. Although this technique usually does not weaken the bone significantly, sometimes bone grafting is required; for spinal lesions, instrumentation may be needed. Failure in removing the entire nidus will cause recurrence of pain (77, 81). Preoperative planning and careful localization of the nidus is the most important means of ensuring that the nidus can be found during the operation. The reactive bone does not need to be removed.

Osteoblastoma. Osteoblastoma is a benign active or aggressive tumor. It is histologically identical to osteoid osteoma, but larger. Osteoblastoma is less common than osteoid osteoma, accounting for <1% of the primary bone tumors in Dahlin series (73). Unlike osteoid osteoma, osteoblastoma is not surrounded by dense reactive bone.

It is most commonly seen in boys in the second decade of life (50% of the patients are between 10 and 20 years of age, although the age range is from 5 to 35 years). Pain at lesional site is the classic presentation; most patients have an average delay of 6 months from start of symptoms and diagnosis (82). The pain of an osteoblastoma is not as severe as the pain of an osteoid osteoma, and aspirin or NSAIDs do not have such a dramatic effect. At least one-third of the lesions are located in the spine, in those cases, scoliosis is present in almost half of the patients (82). Lesions of the extremities are usually diaphyseal; the patient often has a limp and mild atrophy, and complains of pain directly over the lesion, especially on palpation.

The appearance of osteoblastoma on a radiograph is variable. It is usually a mixed radiolucent, radiodense lesion, more lucent than dense. There is usually reactive bone formation but less intense than with osteoid osteoma. When the nidus can be observed, it measures over 2 cm. Lesions in the spine may be difficult or impossible to see when initially examining the plain radiograph, but when located by other studies, the subtle abnormality on the plain radiograph can usually be appreciated. Clues to look for on the plain radiograph to indicate the location of an osteoblastoma are an irregular cortex, loss of pedicle definition, and enlargement of the spinous process (83, 84). As with osteoid osteoma, a technetium-99 bone scan is the best method of localization. On a radionuclide scan an osteoblastoma shows increased uptake, and technetium-99 bone scanning is an excellent method of initially screening a patient suspected of having an osteoblastoma. CT scans are the best method of determining the diagnosis and extent of the lesion (Fig. 13-10A–C). On the CT scan, the lesion usually "expands the bone" and has intralesional stippled ossifications and a high attenuation coefficient (100 HU or more). Laboratory examinations of blood and urine show normal results.

The histology of an osteoblastoma is identical to the nidus of an osteoid osteoma. There should not be abnormal mitoses, although mitotic activity may be observed. There are osteoblasts, multinucleated giant cells, seams of osteoid, and a rich vascular bed. Schajowicz and Lemos (85) suggested that a subset of osteoblastoma be termed *malignant osteoblastoma*. They believe that this subset has histologic features that are worse than those of the usual osteoblastoma, is more aggressive locally, and is more likely to recur after limited surgery. Rarely, an osteoblastoma metastasizes (<1%) but still meets the histologic definitions of a benign tumor, although in those cases it should probably be classified as low-grade osteosarcoma.

Biopsy for diagnostic confirmation is usually indicated. The definitive treatment is surgical, as these lesions will continue to enlarge and damage the bone and adjacent structures. A wide surgical resection is theoretically preferred when practical, to reduce chance of recurrence. A four-step approach (extended curettage, high-speed burring, electrocauterization of cavity wall, and phenol 5% solution) has been shown to be effective with recurrence rates around 5% (82) (Fig. 13-10E,F). Children younger than 6 years tend to recur more frequently (82).

Osteochondroma and Multiple Hereditary Exostoses. Also known as exostosis, osteochondroma is a benign latent or active cartilaginous tumor. Although the pathogenesis of this lesion is not known, an abnormality or injury to the periphery of the growth plate has been suggested as the cause (86). It has been shown in an experimental animal study that the periphery of the growth plate can be traumatized and a typical exostosis can be produced.

The patient with a solitary exostosis is usually brought in by a parent who has just noticed a mass adjacent to a joint. Often, the patient may have been aware of the mass for months or even years, and says that it has been slowly enlarging. Pain at presentation is unusual unless there is a trauma. Occasionally, there is loss of motion in the adjacent joint attributable to the size of the mass. Some patients have pain resulting from irritation of an overlying muscle, bursa formation, repeated trauma, pressure on an adjacent neurovascular bundle, or inflammation in an overlying bursa. Other symptoms may include "catching" or "popping" around the knee due to impingement to tendons and muscles.

On physical examination, the mass is nontender, hard, and fixed to the bone. The rest of the physical examination may show no abnormality. Complete neurovascular examination is important.

Osteochondromas can be diagnosed based on their radiographic appearance alone (Fig. 13-3). The mass is a combination of a radiolucent cartilaginous cap with varying amounts of ossification and calcification. The amount of calcification and bone formation increases with age. The base may be broad (sessile exostosis) or narrow (pedunculated exostosis). In both types, the cortex of the underlying bone opens to join the cortex of the exostosis, so that the medullary canal of the bone is in continuity. This can usually be appreciated on the plain radiograph itself, but if not, CT scan or MRI establishes this finding and confirms the diagnosis.

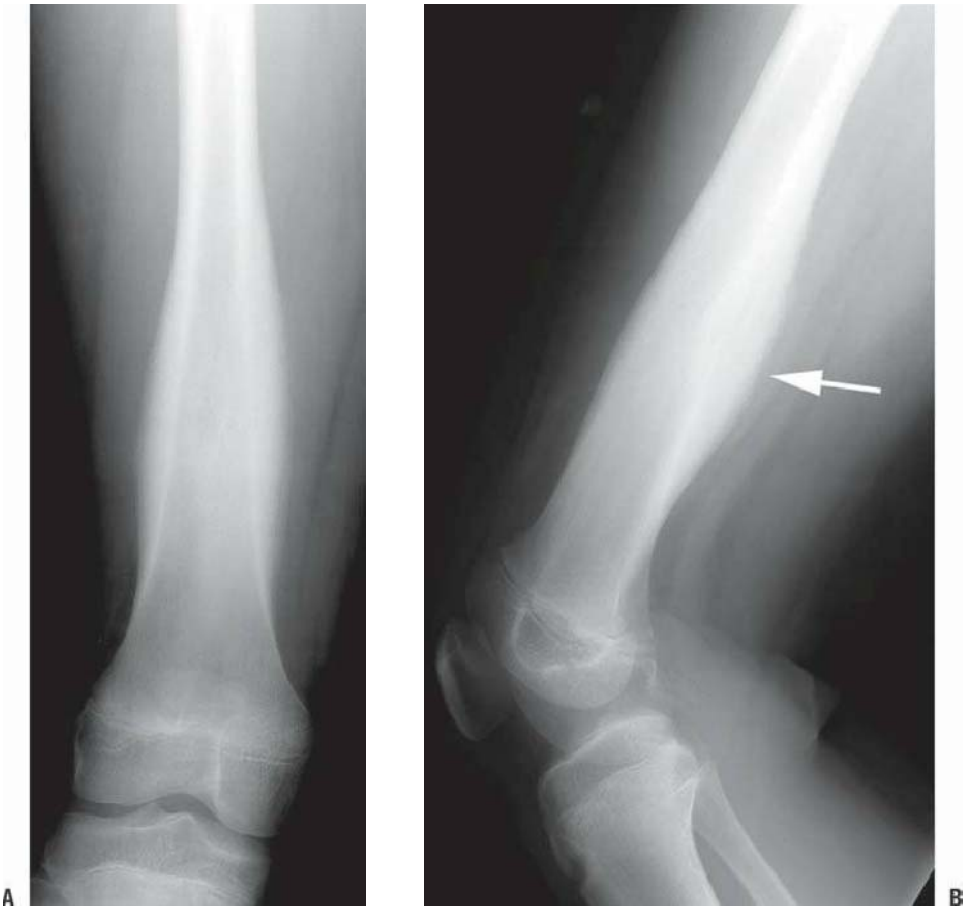
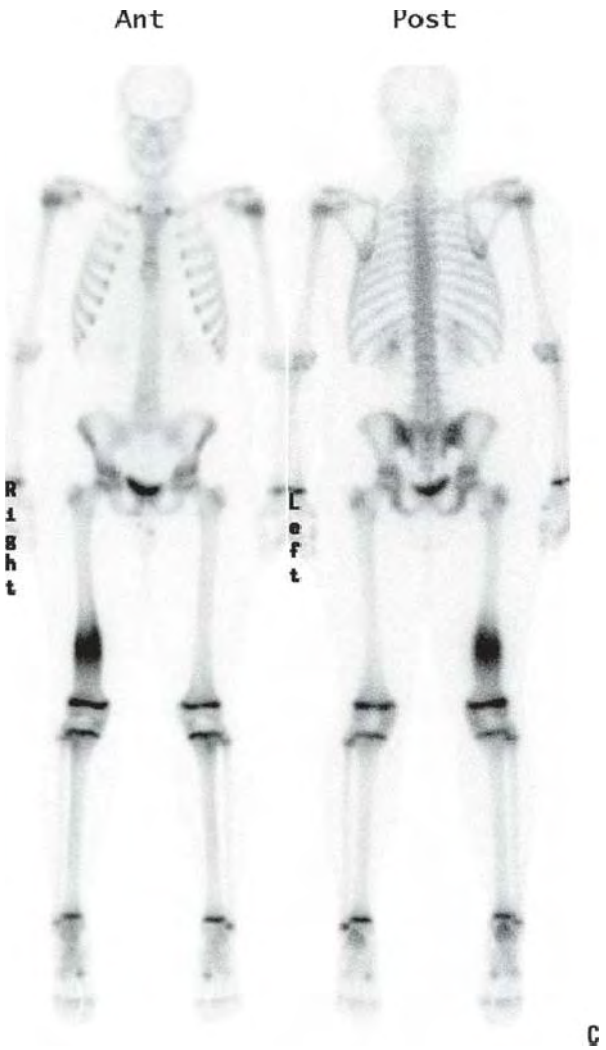


FIGURE 13-10. Osteoblastoma. Anteroposterior **(A)** and lateral **(B)** radiographs of a 13-year-old boy with a 3-month history of increasing thigh pain. There is abundant new bone formation and continuous periosteal reaction. A small lucency is seen in the posterior aspect of the femur (*arrow*). The bone scan **(C)** shows increased uptake in the lesional area, and CT axial cut



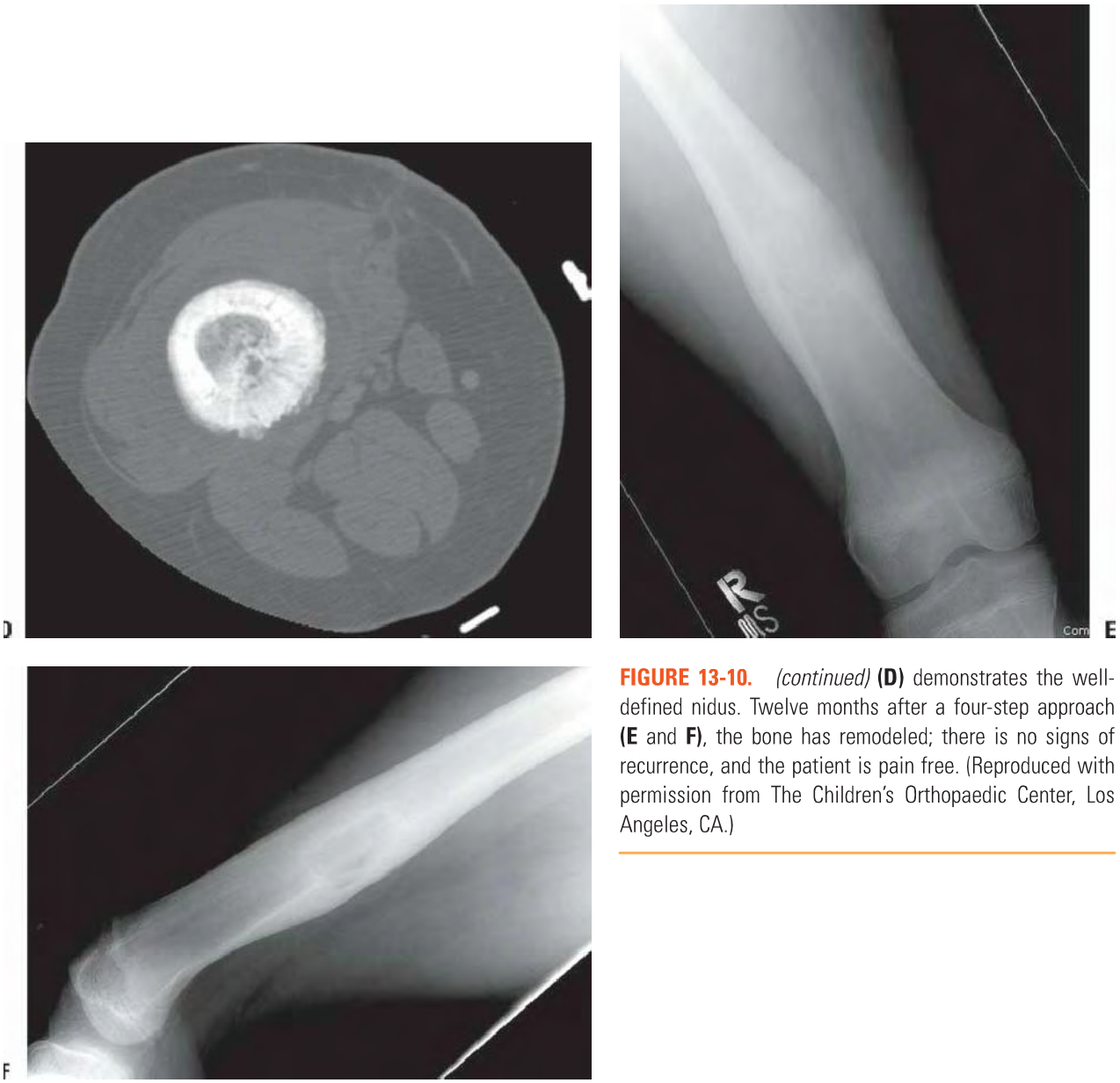


FIGURE 13-10. *(continued)* **(D)** demonstrates the well-defined nidus. Twelve months after a four-step approach **(E** and **F)**, the bone has remodeled; there is no signs of recurrence, and the patient is pain free. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

In the pediatric age group, osteochondromas should be expected to grow. This is not a sign of malignancy. After skeletal maturity, continued growth of an exostosis is usually an indication for removal (87). The growth rate is not steady, and occasionally a lesion grows more rapidly than expected. Removal of the lesion in a child is indicated only for those patients who have symptoms attributable to pressure on a neurovascular bundle or irritation of the overlying muscle. Removal of the lesion in a young child may result in damage to the growth plate and recurrence of the lesion. Degeneration of the lesion into a malignancy is extremely rare in children and uncommon in adults. The definition of malignant degeneration of a solitary exostosis is confusing. Clinically, an exostosis is considered to be malignant in a patient as old as 30 years or older if there is an enlarging cartilage cap and when the cap is more than approximately 2 cm thick. This so-called malignant degeneration is more common in lesions of the scapula, the pelvis, and the proximal femur. The real incidence of malignant degeneration is not known. It is probably <2% (88).

Gross examination of an exostosis reveals a lesion that looks like a cauliflower. It has an irregular surface covered with cartilage. The cartilage is usually <1 cm thick, except in the young child, in which it may be 2 or 3 cm thick. Deep in the cartilaginous cap, there is a variable amount of calcification, enchondral ossification, and normal bone with a cortex and cancellous marrow cavity. Typically, the microscopic appearance of the cartilaginous cap is that of benign hyaline cartilage, which has the configuration of a slightly disordered growth plate (Fig. 13-11).

Some patients have multiple osteochondromas, a condition called multiple hereditary exostosis (MHE) (89–91). A patient may have 3 or 4 lesions, but more often there are 10 to 15. Usually, the patient has exostoses of all shapes and

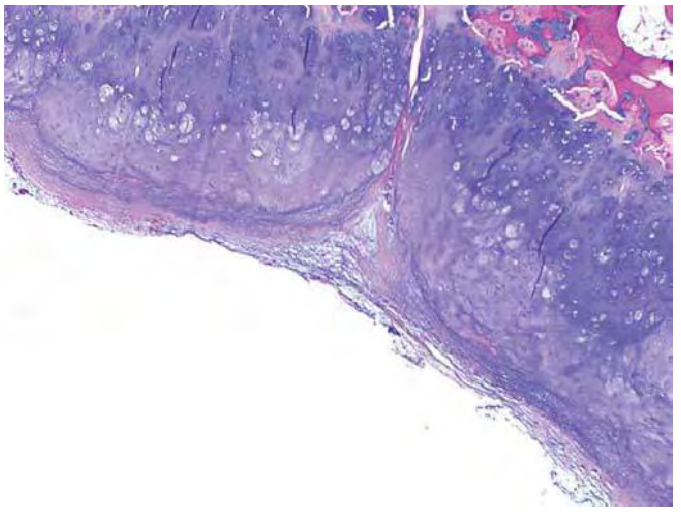


FIGURE 13-11. Low-power view of an osteochondroma cartilage cap, showing the very blend benign hyaline cartilage, low cellularity, no mitoses or pleomorphism. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

sizes. They are concentrated in the metaphysis of the long bones, but may be in the spine, the ribs, the pelvis, and the scapula. On physical examination, they are hard, fixed masses adjacent to joints. Patients with multiple exostoses are usually shorter than average but not shorter than the normal range. The affected joints show loss of range of motion, especially forearm rotation, elbow extension, hip abduction and adduction, and ankle inversion and eversion.

MHE is transmitted by an autosomal dominant gene with a variable penetrance, and there is an approximately 50% chance that a child of a parent with the heritable gene will show clinical manifestations of this condition (88, 89, 92, 93). Up to half of the cases are spontaneous mutation (88). The disease may manifest with extensive involvement in the parent, but with minimal involvement in the child, or vice versa (88). In most patients with MHE, the radiographic appearance of the proximal femur or the knees is diagnostic (Fig. 13-12).

Occasionally, one or more of the exostoses need to be removed in order to relieve the pain related to repeated local trauma, or to improve the motion of the adjacent joint. Lesions in the pelvis and the spine should be observed closely because they have the greatest risk of undergoing malignant degeneration. We do not recommend that these lesions be removed simply because they are present. MHE patients often need surgery for correction of angular deformities. Secondary chondrosarcoma is rare in the pediatric age group (94, 95). After the third decade, patients with MHE are at increased risk of developing secondary chondrosarcoma (96, 97). Among large series on chondrosarcoma in children, around 25% of the cases are secondary to a benign cartilaginous lesion (96, 97). We advise patients with exostosis, in particular MHE, to be examined at least yearly. Patients are told to report symptoms or increasing size immediately.

Enchondroma. The origin of enchondroma is debatable; it may be the result of epiphyseal growth cartilage that does not remodel and persists in the metaphysis, or it may result from persistence of the original cartilaginous anlage of the bone (86). Both possibilities have been suggested as the cause of this common benign latent or active tumor. Most patients with a solitary enchondroma present with either a pathologic fracture through a lesion in the phalanx, which is the most common location (86, 98); or a history of the lesion having been an incidental finding on a radiograph taken for another reason (Fig. 13-13). Enchondromas are common lesions that account for 11% of benign bone tumors (99, 100), and they

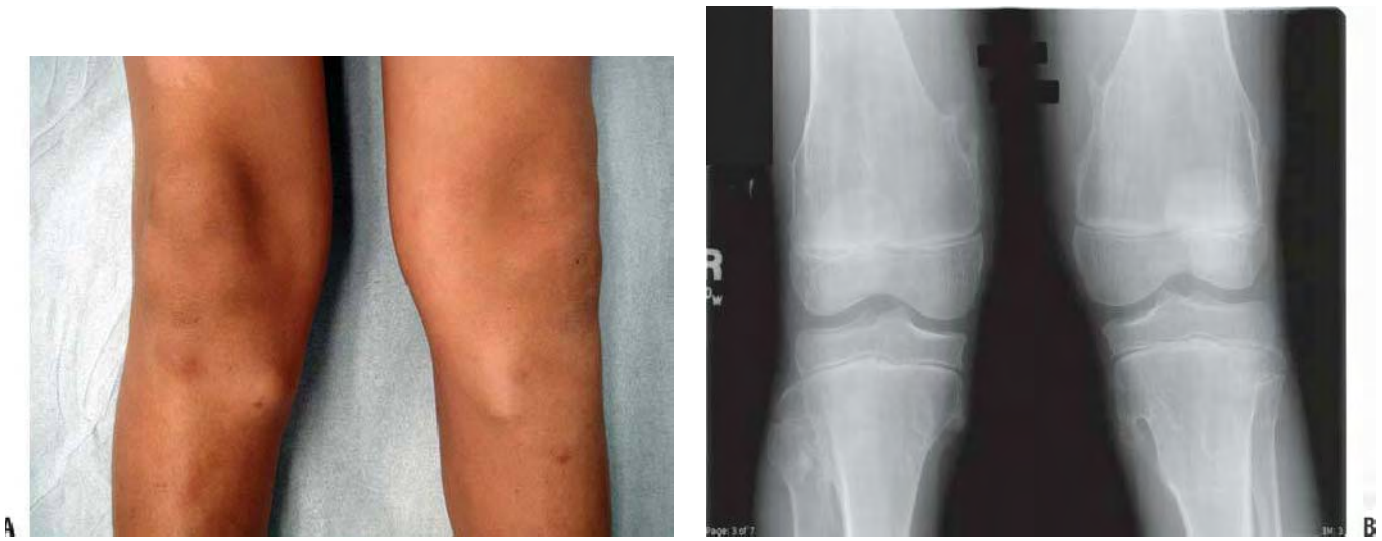


FIGURE 13-12. Clinical appearance **(A)** and anteroposterior radiograph **(B)** of a 12-year-old boy with MHE demonstrates several osteochondromas arising from distal femur and proximal tibia. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

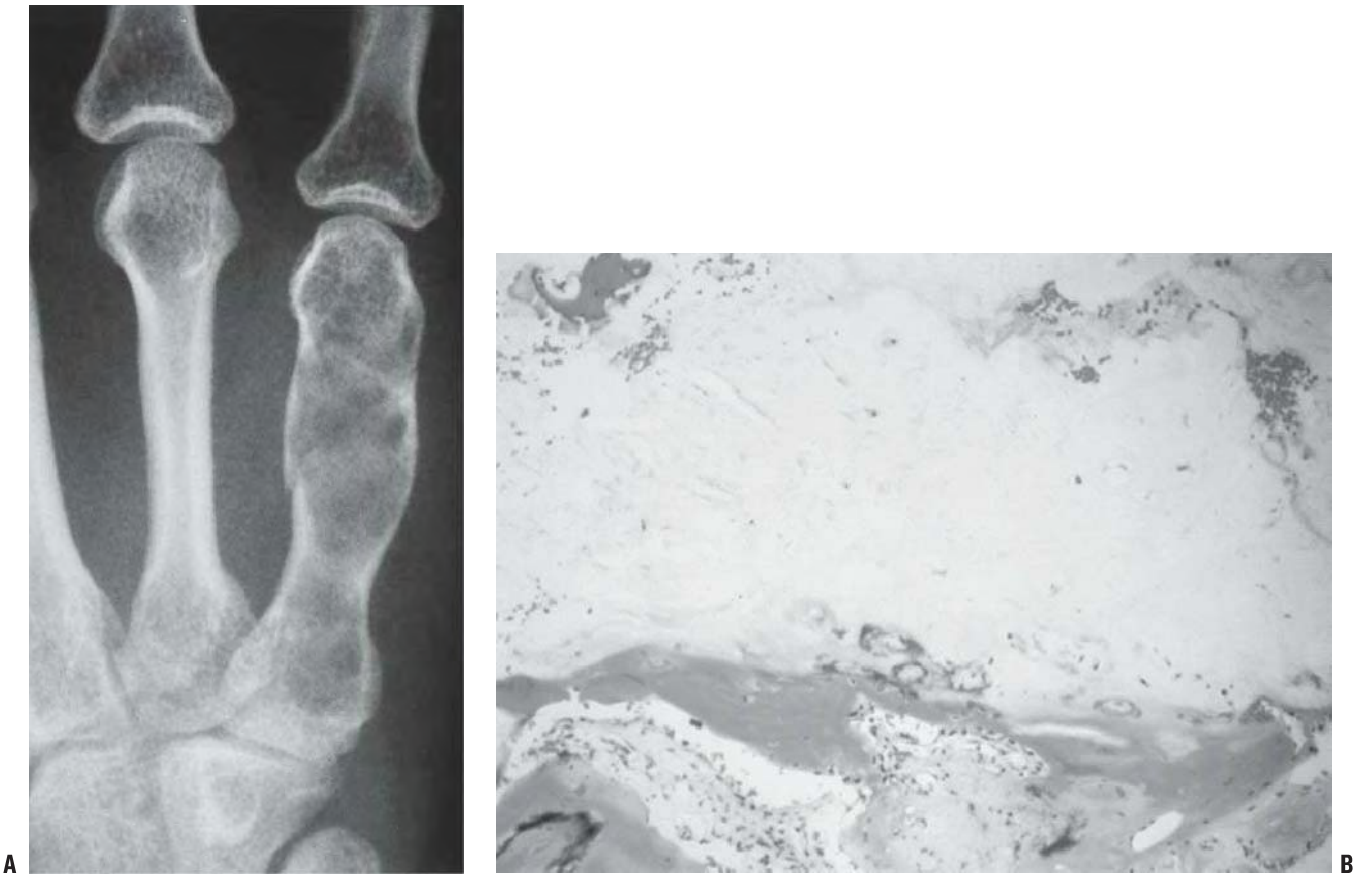


FIGURE 13-13. **A:** This enchondroma of the fifth metacarpal is typical. The shaft is enlarged, and the lesion is radiolucent, with cortical thinning. This patient had been aware of this lesion since she was 10 years of age. She had sustained numerous pathologic fractures and decided to have it curetted. The curettage was done after the fracture had healed. **B:** Enchondroma can have varied histologic appearances with varying cellularity, but generally the cartilage, the amorphous material in the center of the image, has few chondrocytes. Typically, the cartilage is lined by a thin band of bone, and the adjacent marrow is normal. Often there is considerable calcification within the cartilage component of the lesion (10× magnification).

do not necessarily need to be removed. However, they may be difficult to diagnose. Usually, the diagnosis can be made from the clinical setting and the plain radiograph. Forty percent of enchondromas are found in the bones of the hands or feet, usually a phalanx. An enchondroma should not produce symptoms unless there is a pathologic fracture. There are no associated abnormalities of blood or urine. The femur and proximal humerus are the next most common sites.

Enchondromas are located in the metaphysis and are central lesions in the medullary canal. The bone may be wider than normal, but this is caused by the lack of remodeling in the metaphysis rather than by expansion of the bone by the tumor. The cortex may be either thin or normal; the lesion is radiolucent in the pediatric age group, but at later stages it shows intralesional calcifications (101). There is usually no periosteal reaction. The appearance of an enchondroma on MRI is typical. The cartilage matrix has intermediate signal intensity on the T1-weighted image and high signal intensity on the T2-weighted image (102, 103). It has a sharp margin with the adjacent bone, without peripheral edema (102, 103).

When the findings are typical of an enchondroma, no biopsy is necessary. Repeat plain radiography and physical examination should be performed in approximately 6 weeks, then every 3 to 6 months for 2 years. Although there are reports of solitary enchondromas differentiating into chondrosarcomas, usually late in adult life, this does not occur frequently enough to justify the removal of all enchondromas. The patient should be advised that after age 30 years, if the lesion becomes painful or enlarges, it should be considered a low-grade chondrosarcoma and be surgically resected. Bone scan is also used to evaluate the tumor activity level and to help determining preferred treatment (101–103).

Incisional biopsy is usually contraindicated. Pathologists have difficulty distinguishing between active enchondroma (most pediatric patients have active lesions) and low-grade chondrosarcoma. The clinical course is the best measure of the lesion's significance, and an incisional biopsy alters the status of the lesion and makes subsequent evaluation difficult. If the patient or the patient's parents insist on biopsy, it is best that the entire lesion be removed.

Patients with multiple enchondromatosis (Ollier disease) are far fewer than those with solitary enchondromas. Multiple enchondromatosis was originally described in the late 1800s by Ollier (104). Most patients with Ollier disease have bilateral involvement but with unilateral predominance. These patients have growth deformities, both angular and in length (Fig. 13-14). The deformities of the extremities should be managed surgically in order to maintain the function of the limbs, without specific regard to the enchondroma. Patients with Ollier disease have an increased risk of developing secondary chondrosarcoma later in life and should be so advised (105, 106). The incidence of secondary chondrosarcoma and other tumors in patients with Ollier disease is not known but may be as high as 25% (96, 107). The pelvis and the shoulder girdle are the most common locations of secondary chondrosarcoma.

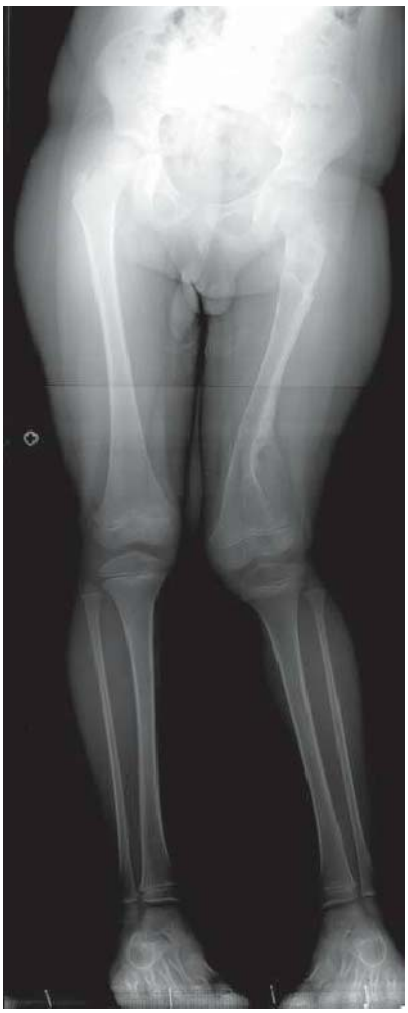


FIGURE 13-14. Hip-to-ankle radiographs of a 5-year-old boy that presented for evaluation of angular deformity. Note the well-defined, mostly radiolucent lesion in the proximal femur and in the distal femur, with cortical thinning, no periosteal reaction, no soft-tissue mass and resultant valgus deformity of the femur. Ollier disease often predominates in one side of the body. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

Maffucci disease consists of multiple enchondromatosis and soft-tissue hemangiomas (108). Patients with this disorder have an even greater risk of developing malignant tumors than do patients with Ollier disease; more importantly, beside the risk of malignant degeneration, they have a great risk of developing carcinoma of an internal organ (96, 107, 109).

Chondroblastoma. Chondroblastoma, or Codman tumor, is a benign active tumor. It was first described by Codman in 1931 as an "epiphyseal chondromatous giant cell tumor" (110); since Codman was particularly interested in the shoulder, he thought this lesion was found mostly in the proximal humerus (Fig. 13-15A). It has since become clear that chondroblastoma is found in many bones, but the proximal humerus is the most common site (approximately 20%) (99).

Chondroblastoma accounts for 1% of bone tumors (111, 112). The patient with a chondroblastoma is usually in the second decade of life, with an open growth plate, but the condition may occur in older patients as well. The initial symptom is pain in the joint adjacent to the lesion. The findings on physical examination also may suggest an intra-articular disorder because most patients have an effusion and diminished motion in the adjacent joint. Frequently, the patient is believed to have chronic synovitis; he or she does not have other symptoms or abnormal physical findings. The patient's laboratory data are normal.

The lesion arises in the secondary ossification center. In children, it is the most common neoplastic lesion of the secondary ossification center (74); in adults, only giant cell tumor of bone involves the secondary ossification center more often. In children, osteomyelitis is the most common condition that can produce a lesion in the secondary ossification center.

On the plain radiograph, the lesion is radiolucent, usually with small foci of calcification (99). The calcification is best seen on a CT scan (Fig. 13-15B). There is usually a reactive rim of bone surrounding the lesion and, sometimes, metaphyseal periosteal reaction. The edema associated with chondroblastoma can be appreciated on MRI (Fig. 13-16). There is increased uptake on a technetium-99 bone scan. Chest radiography or CT scan should be performed because chondroblastoma is one of the benign bone tumors that can have lung implants and still be considered benign (<2% incidence) (113).

Chondroblastoma and osteochondritis dissecans can have similar appearances on plain radiographs, but they should not be confused with each other. Osteochondritis dissecans produces an abnormality in the subchondral bone; in chondroblastoma, on the other hand, the subchondral bone is almost always normal. Patients with chondroblastoma have more of an effusion than patients with osteochondritis dissecans, and their pain is constant and not related to activity as it is in patients with osteochondritis dissecans.

Histologically, the appearance of chondroblastoma is typical and is rarely confused with other diagnoses. It consists of small cuboidal cells (chondroblasts) closely packed together to give the appearance of a cobblestone street (114). In addition,

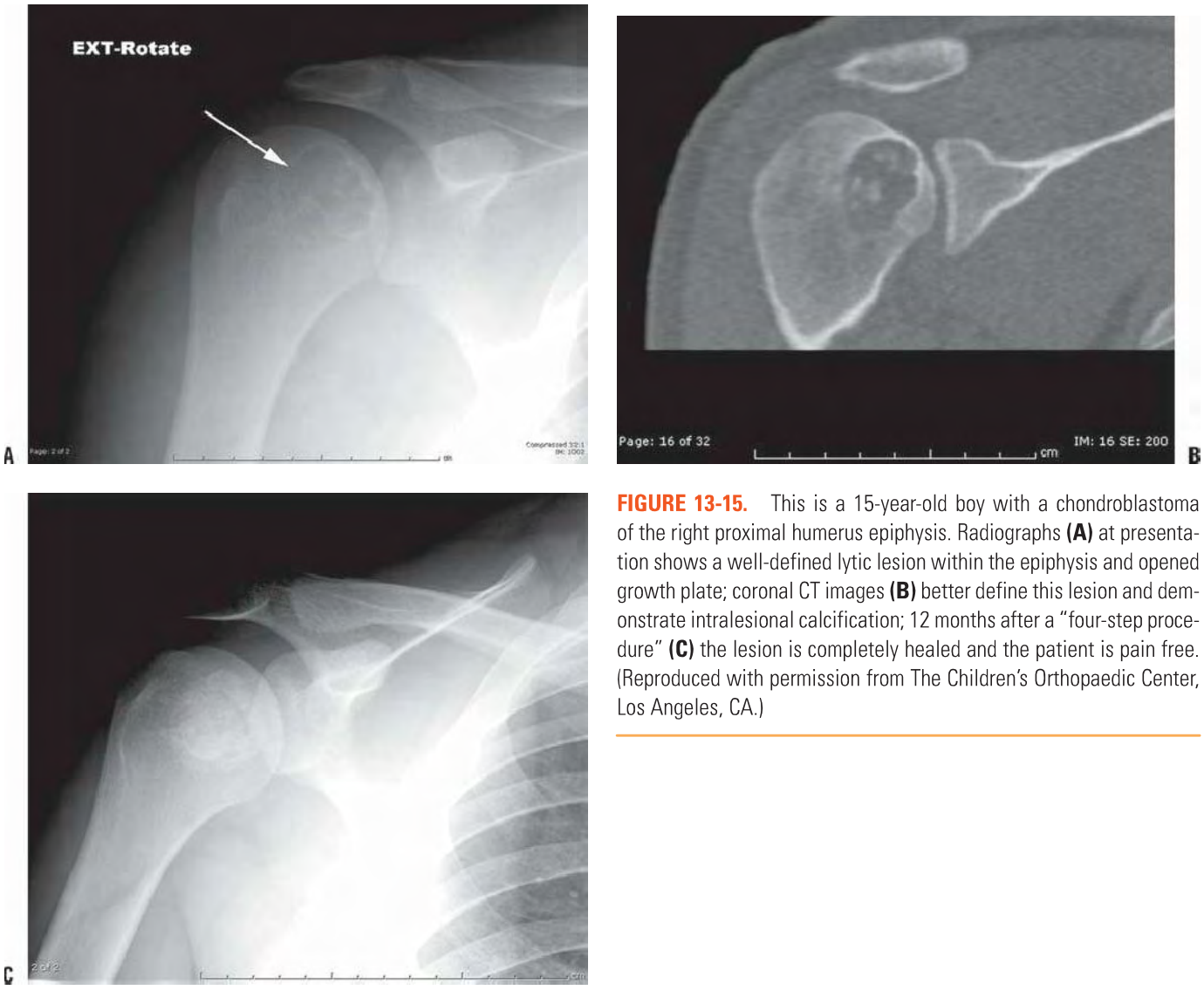


FIGURE 13-15. This is a 15-year-old boy with a chondroblastoma of the right proximal humerus epiphysis. Radiographs **(A)** at presentation shows a well-defined lytic lesion within the epiphysis and opened growth plate; coronal CT images **(B)** better define this lesion and demonstrate intralesional calcification; 12 months after a "four-step procedure" **(C)** the lesion is completely healed and the patient is pain free. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

there are areas with varying amounts of amorphous matrix that often contains streaks of calcification, and usually there are numerous multinucleated giant cells. Chondroblastoma is not as vascular as osteoblastoma; there are few, if any, mitoses, and no abnormal ones (Fig. 13-17).

Chondroblastomas progress and invade the joint. They should be treated when found (111). Following biopsy for diagnostic confirmation, curettage is the treatment of choice, but it should be a thorough curettage and should extend beyond the reactive rim (four-step approach described above) (Fig. 13-15C). The lesion should be seen adequately at the time of the curettage, which usually means that the joint should be opened. Iatrogenic seeding of a joint is not a significant risk, and intra-articular surgical exposure is recommended if this facilitates visualization. Most recurrences are cured with a second curettage, but a rare lesion can be locally aggressive and requires a wide resection (111). Chondroblastoma of the pelvis frequently behaves more aggressively than that in long bones, and an initial wide excision is recommended if it can be done with limited functional loss and morbidity. Most patients are close to skeletal maturity when the diagnosis is made, and the risk of growth disturbance from the tumor or its treatment is usually minimal. When the patient is younger than 10 years old, care should be taken not to damage the growth plate. Intra-articular penetration and articular cartilage damage are real risks that should be avoided.

Chondromyxoid Fibroma. Chondromyxoid fibroma is a rare benign active, rarely aggressive tumor. The patient is usually of the male sex (men are more frequently affected than women, at a ratio of 2:1) in the second or third decade of life (99, 115). The patient complains of a dull, steady pain that is usually worse at night. The only positive physical finding is tenderness over the involved area, and occasionally a deep mass can be detected.

Approximately one-third of chondromyxoid fibromas occur in the tibia, usually proximally. It is a radiolucent lesion that involves the medullary canal but is eccentric and erodes the cortex (100, 116) (Fig. 13-18). It may be covered by only periosteum, and is often mistaken for the more common ABC.

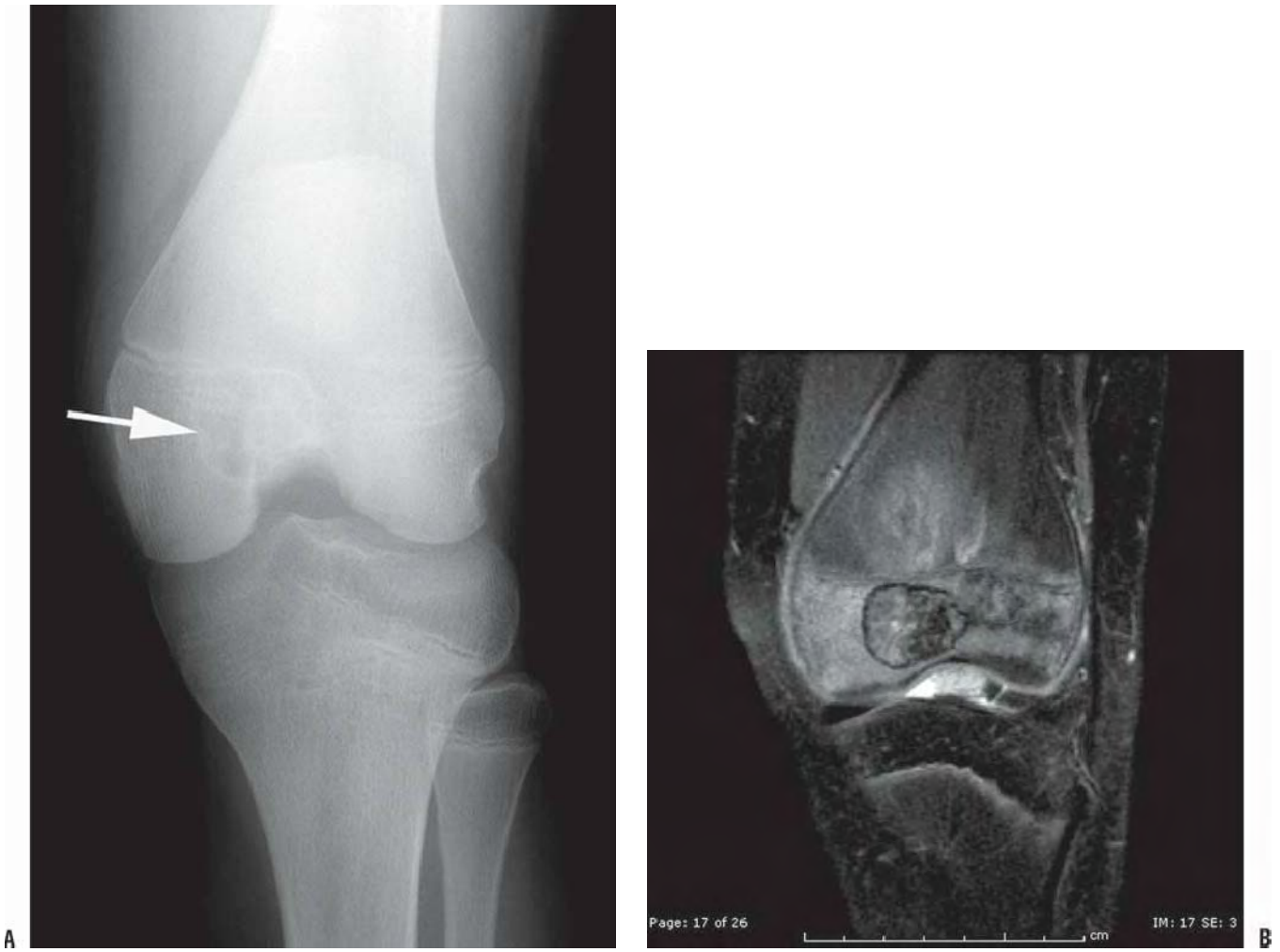
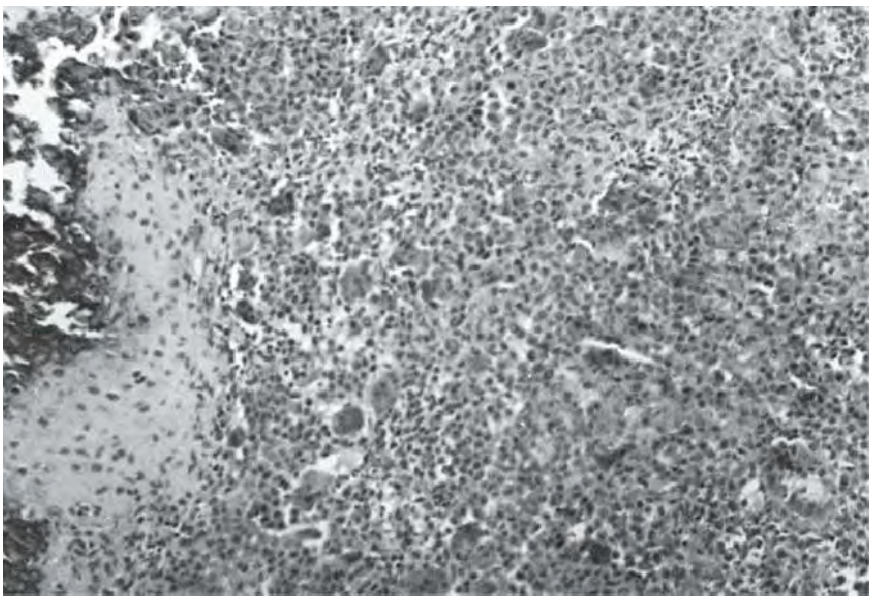


FIGURE 13-16. A 14-year-old boy with a diagnosis of a distal femur chondroblastoma. Plain radiographs **(A)** show a well-defined, lytic lesion within the distal femoral epiphysis; T2-weighted coronal MRI **(B)** demonstrates the lesion better, its relationship to the joint line and the growth plate. Note the abundant surrounding osseous edema. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

FIGURE 13-17. Histologic appearance of a chondroblastoma. The tumor consists of cuboidal cells (i.e., chondroblasts), varying amounts of amorphous matrix (some of which is calcified), and multinucleated giant cells. Calcification is seen (**left**). The cuboidal cells fit together in such a manner that they have the appearance of cobblestones (original magnification ×10).



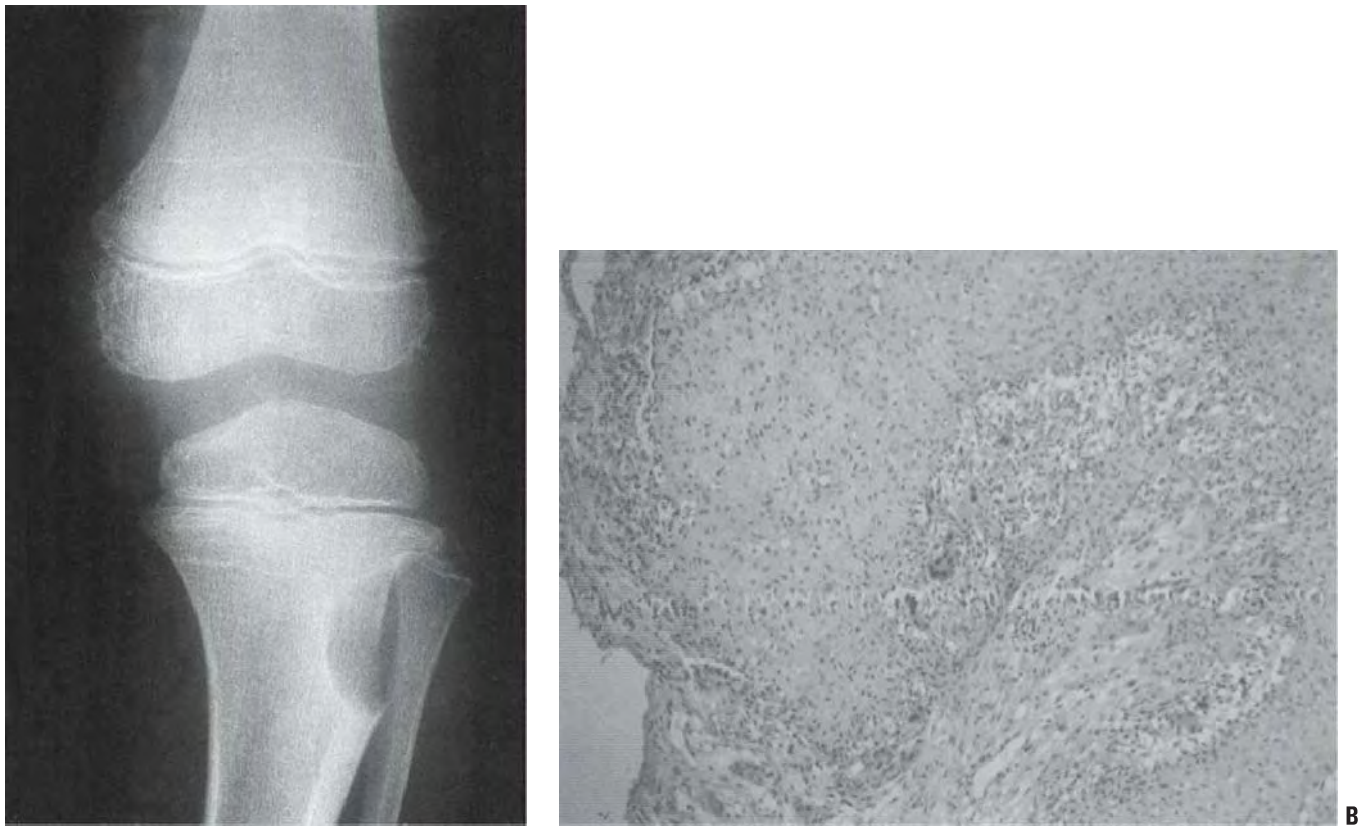


FIGURE 13-18. **A:** Anteroposterior radiograph of a chondromyxoid fibroma of the proximal lateral tibia. The lesion is typically an eccentric, radiolucent abnormality that usually destroys the cortex but is contained by the periosteum. As in this case, the radiographic appearance of chondromyxoid fibroma is often similar to that of an ABC. **B:** Chondromyxoid fibroma does not have typical hyaline cartilage. It is a cellular lesion with areas of chondroid matrix, myxoid matrix, and abundant fibrous tissue. It can be mistaken for a low-grade malignancy if the diagnosis of chondromyxoid fibroma is not considered (4× magnification).

The solid nature of chondromyxoid fibroma versus the cystic nature of an ABC, as seen on MRI, is a means of differentiating between these two lesions. The natural history is not known because the condition itself is infrequent and surgical treatment is nearly universal. Thorough curettage and bone grafting are recommended. Recurrence is a risk, and patients and parents should be so advised.

Juxtacortical Chondroma. This is an uncommon active or latent benign lesion that arises from the surface of the cortex, deep to the periosteum. The patient may present with pain at the site of the lesion or a painless "bump." More than half of such lesions are found in the proximal humerus, and the others are evenly dispersed through the long bones. The lesion can often be palpated. It is a nontender, hard mass that is fixed to the bone. On plain radiographs, it is a scalloped defect on the outer surface of the cortex, occasionally with intralesional calcifications and minimal periosteal reaction. Sometimes, MRI can be used to help in the diagnosis (Fig. 13-19). On microscopic examination, juxtacortical chondroma is a benign cartilage, but it appears more active than enchondroma. It has been mistaken for chondrosarcoma (117). Because local recurrence is a risk, a marginal or wide excision, sometimes including the underlying cortex, is the treatment of choice (117, 118).

Lesions of Fibrous Origin

Nonossifying Fibroma and Fibrous Cortical Defect. Also known as fibroma of bone, nonosteogenic fibroma, and metaphyseal fibrous defect, NOF and fibrous cortical defect are probably the most common lesions of bone (119–121). Fibrous cortical defects are subperiosteal and erode into the outer surface of the cortex, whereas NOFs are medullary lesions that thin the cortex from within. Up to 40% of children have this lesion, which is found most often between the ages of 4 and 8 years (122). Ninety percent of the lesions found are in the distal femur. These are asymptomatic lesions that are usually found when a radiograph is taken for another reason or when the patient has a pathologic fracture. The patient shows no abnormal physical findings, and the serum and urine chemistries are normal.

NOF and fibrous cortical defects should be recognized on the basis of the clinical presentation and plain radiographic findings (123). Biopsy is rarely necessary for diagnosis. Two radiographic appearances are possible. The one that most authors refer to as *fibrous cortical defect* is a

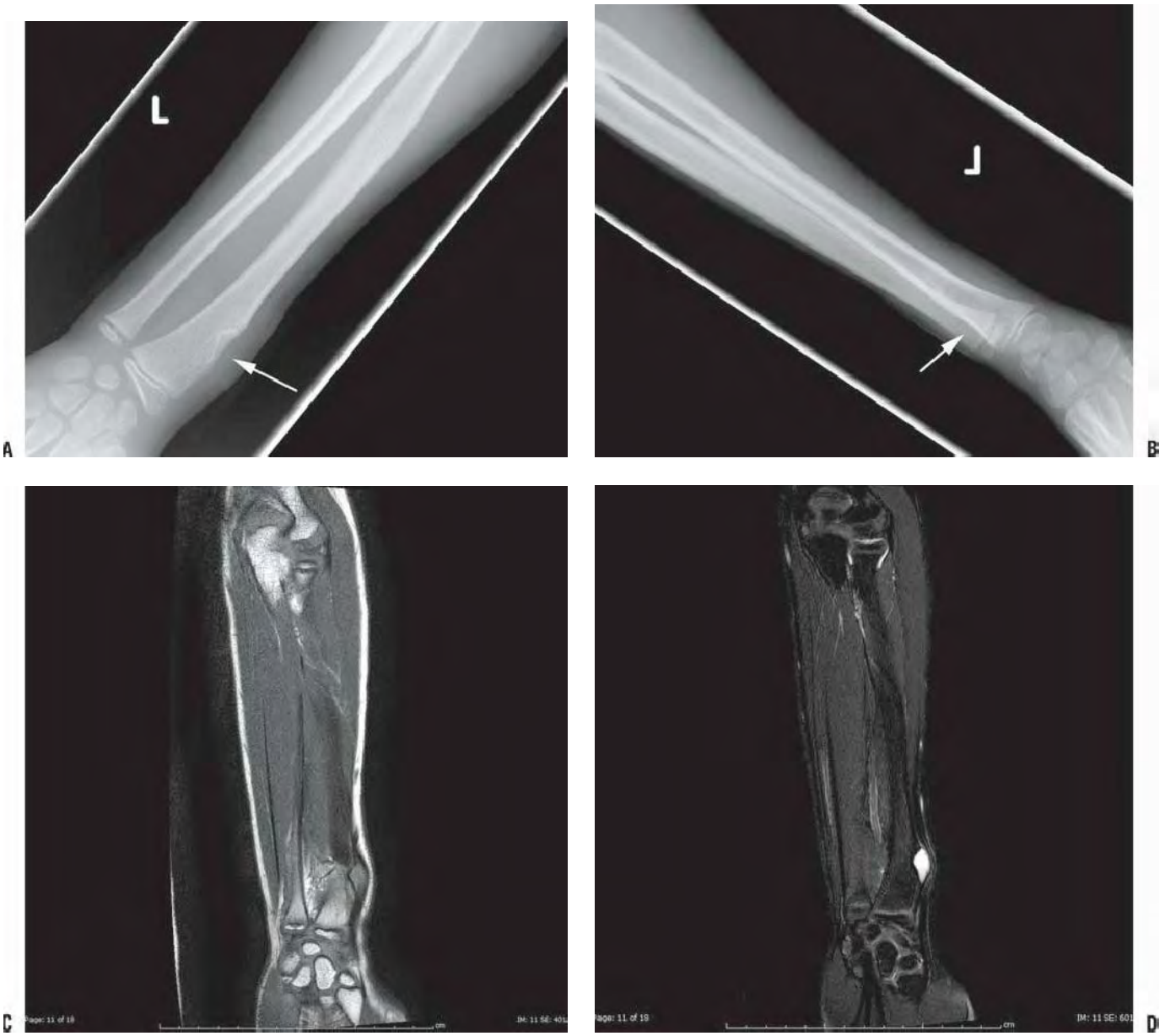


FIGURE 13-19. Juxtacortical chondroma. Plain radiographs of a 10-year-old boy with a history of painless hard mass in the wrist. There are secondary changes in the distal radius metaphysis (*arrow*), but the lesion can be poorly visualized in plain films **(A** and **B)**. T1- **(C)** and T2-weighted **(D)** MRI better shows the cartilage lesion located next to the cortex. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

small (<0.5 cm) radiolucent lesion within the cortex, with a sharply defined border (99). There is little or no increased uptake on the technetium-99 bone scan. A NOF is a metaphyseal lesion eccentrically located (Fig. 13-20). This lesion grows into the medullary canal. It is surrounded by a well-defined, sharp rim of sclerotic reactive bone. There should be no acute periosteal reaction unless there has been a fracture. There may be slightly increased uptake on the technetium-99 bone scan. Multiple NOFs occur in approximately 20% of the patients.

Both lesions consist of benign, spindle, fibroblastic cells arranged in a storiform pattern (123, 124) (Fig. 13-21). Multinucleated giant cells are common, and areas of large, lipid-laden macrophages can often be seen. Hemosiderin is often present within the fibroblastic stromal cells and multinucleated giant cells. There is no bone formation within the lesion, and mitoses are not seen.

The small cortical lesion (fibrous cortical defect) needs no treatment, but should be observed. Radiographs at 3- to 6-month intervals for 1 to 2 years are suggested. These lesions tend to heal spontaneously. NOF may need surgery. The indication for surgery is to reduce the risk of a pathologic fracture. It is however difficult to predict who is at risk of sustaining a pathologic fracture. The less active and

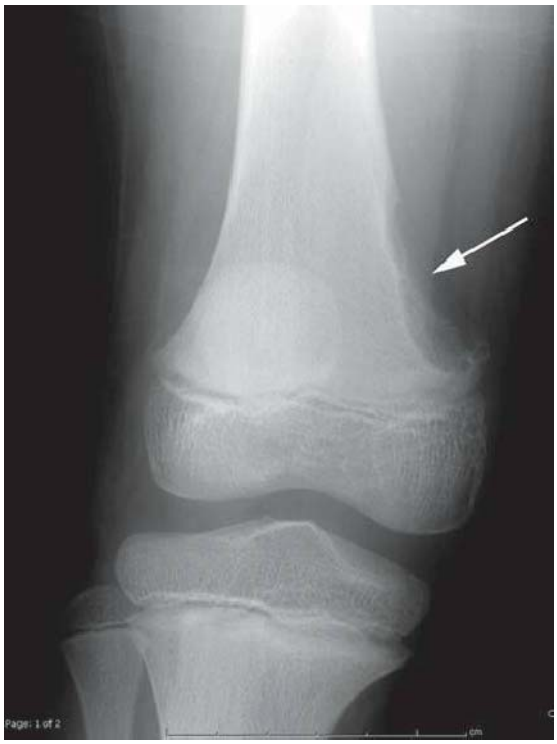


FIGURE 13-20. Anterior–posterior radiograph of the distal femur of a 11-year-old boy that had a minor trauma to the knee and obtained this x-ray. Note this is an eccentric, well-defined, mostly lytic lesion, without periosteal reaction or soft-tissue mass (*arrow*). This appearance is typical for NOF. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

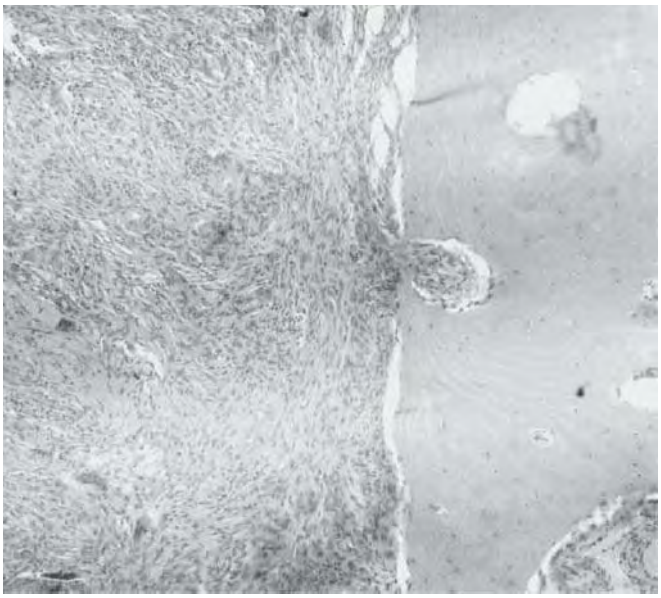


FIGURE 13-21. Low-power histologic view of a typical NOF. The fibroma is composed of benign fibrous tissue and multinucleated giant cells. Hemosiderin is often present. The NOF is invading cortical bone (**right**) (original magnification ×10).

the smaller the child, the less risk there is of the child sustaining a pathologic fracture. NOFs that are <50% of the diameter of the bone can be merely observed because they have little risk of fracture, but curettage and packing with bone graft should be considered if they enlarge (119–121). Patients who present with NOFs that are more than 50% of the diameter of the bone have a risk of fracture with even a minimal injury and should at least be considered for surgery, particularly for lesions in the weight-bearing bones. Recently, an approach using CT analysis and biomechanical modeling has been shown to be of value in more precisely predicting which lesions may be at risk for fracture (115). Many patients with these large NOFs elect not to have surgery and reduce their activity instead. This is an alternative treatment.

Patients who present with pathologic fractures should have the fractures treated nonoperatively if possible. The fracture should heal without difficulty in a normal length of time (Fig. 13-22). There is no evidence that the healing of the fracture increases the chances of spontaneous healing of an NOF. NOF usually heals spontaneously, and this may happen after the fracture; but usually the fracture callus obscures the radiolucent lesion, and the physician is fooled into thinking that the lesion is healing even when it is not. When the callus has remodeled and the cortices become distinct on the radiograph, the lesion can be seen again. Patients with pathologic fractures must be followed until the callus has remodeled sufficiently so that a final determination can be made about the status of the underlying NOF. If it persists after the fracture has healed, curettage and bone grafting may be considered.

Fibrous Dysplasia. Fibrous dysplasia may not be a true neoplasm but a developmental abnormality caused by a somatic mutation leading to a defect in the formation of bone. It is a common disorder that produces a variety of symptoms and physical findings. Most patients (approximately 85%) have a single skeletal lesion (monostotic fibrous dysplasia), whereas the remainder has numerous lesions (polyostotic fibrous dysplasia). The patients with polyostotic fibrous dysplasia may have only two or three small areas of involvement, or may have extensive skeletal abnormalities with grossly deformed bones.

The patient with monostotic fibrous dysplasia usually presents without symptoms, and the lesion is found when a radiograph is taken for unrelated reasons (125–127). Occasionally, the child presents with a pathologic fracture or an angular deformity (Fig. 13-23). The rib is the most common location of monostotic fibrous dysplasia, but any bone can be involved. There are no physical findings that are specifically associated with monostotic fibrous dysplasia, and the café au lait lesions and endocrine abnormalities sometimes found in patients with polyostotic fibrous dysplasia do not occur in patients with the monostotic variant. Serum and urine chemistries are normal in patients with fibrous dysplasia.

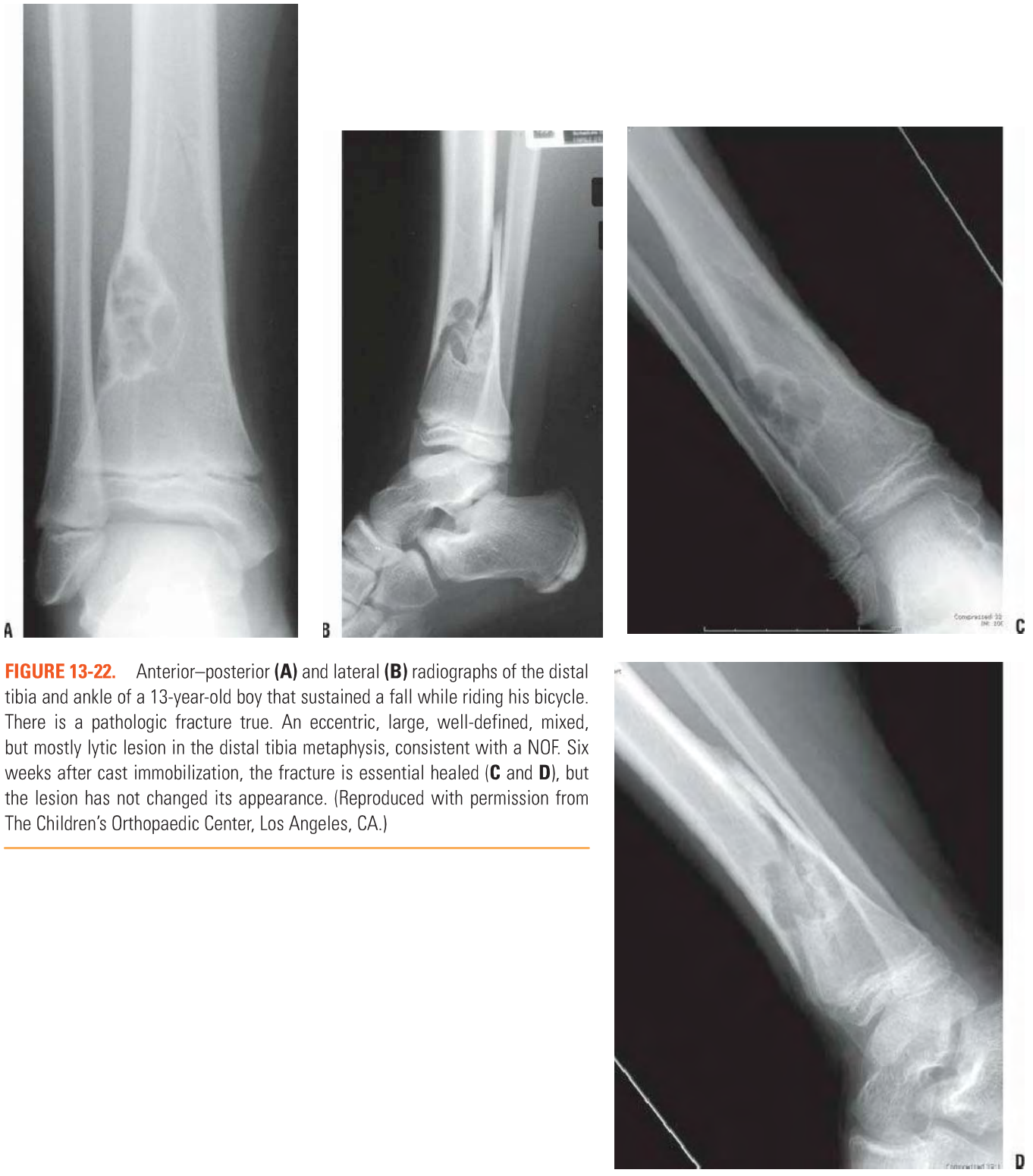


FIGURE 13-22. Anterior–posterior **(A)** and lateral **(B)** radiographs of the distal tibia and ankle of a 13-year-old boy that sustained a fall while riding his bicycle. There is a pathologic fracture true. An eccentric, large, well-defined, mixed, but mostly lytic lesion in the distal tibia metaphysis, consistent with a NOF. Six weeks after cast immobilization, the fracture is essential healed (**C** and **D**), but the lesion has not changed its appearance. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

The plain radiograph is often diagnostic, although the radiographic appearance of fibrous dysplasia is variable (Fig. 13-24A). It is a medullary process that typically produces a ground-glass appearance on the radiograph. The lesion is usually diaphyseal. The diaphysis is larger than normal, and the ground-glass appearance of the medullary canal blends into the thinned cortex so that it is difficult to define the border between the medullary canal and the cortex. When typical-appearing lesions are seen in a single bone or in a single limb, the diagnosis is almost certain. There may be an angular deformity in the bone, especially when the lesion is large. The lesions may mature with age and become radiodense or cystic. Fibrous dysplasia may show excessive uptake on a technetium-99 bone scan, out of proportion to what one might predict from the plain radiographic appearance.

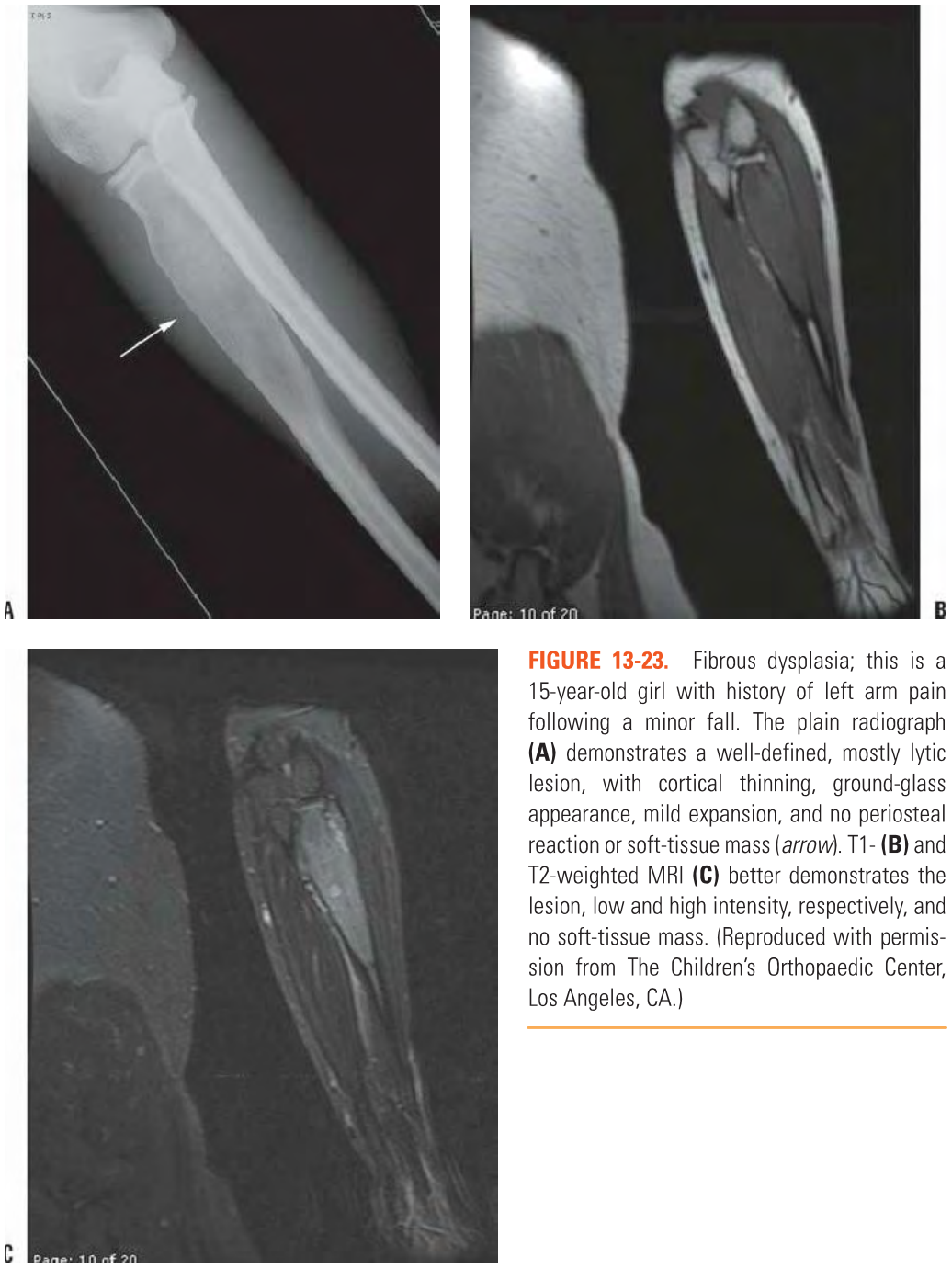


FIGURE 13-23. Fibrous dysplasia; this is a 15-year-old girl with history of left arm pain following a minor fall. The plain radiograph **(A)** demonstrates a well-defined, mostly lytic lesion, with cortical thinning, ground-glass appearance, mild expansion, and no periosteal reaction or soft-tissue mass (*arrow*). T1- **(B)** and T2-weighted MRI **(C)** better demonstrates the lesion, low and high intensity, respectively, and no soft-tissue mass. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

The patient with polyostotic fibrous dysplasia usually presents at about the age of 10 years with an angular deformity of a bone (127, 128). The most common deformity is varus of the proximal femur, or shepherd's crook deformity. The light brown skin lesions with irregular borders are called *coast of Maine* café au lait spots. The lesions that have smooth borders and are associated with neurofibromatosis are called *coast of California* café au lait spots.

Hyperthyroidism and diabetes mellitus have been reported as associated endocrinopathies, and vascular tumors have been seen in association with fibrous dysplasia. McCune-Albright syndrome is a triad of fibrous dysplasia, café au lait spots, and precocious puberty (126). The lesions in polyostotic fibrous dysplasia tend to be unilateral rather than bilateral. The radiographic appearance of the lesion is the same as in patients with monostotic disease. The structural strength of bones with fibrous dysplasia is reduced because of the poorly organized trabecular pattern and the thinned cortex. The weakness of the bones leads to the deformities that are usually present.

On microscopic examination, fibrous dysplasia, both the monostotic and polyostotic forms, is composed of fibrous tissue with normal-appearing nuclei and irregularly shaped strands of osteoid and bone (Fig. 13-24B). There are few, if

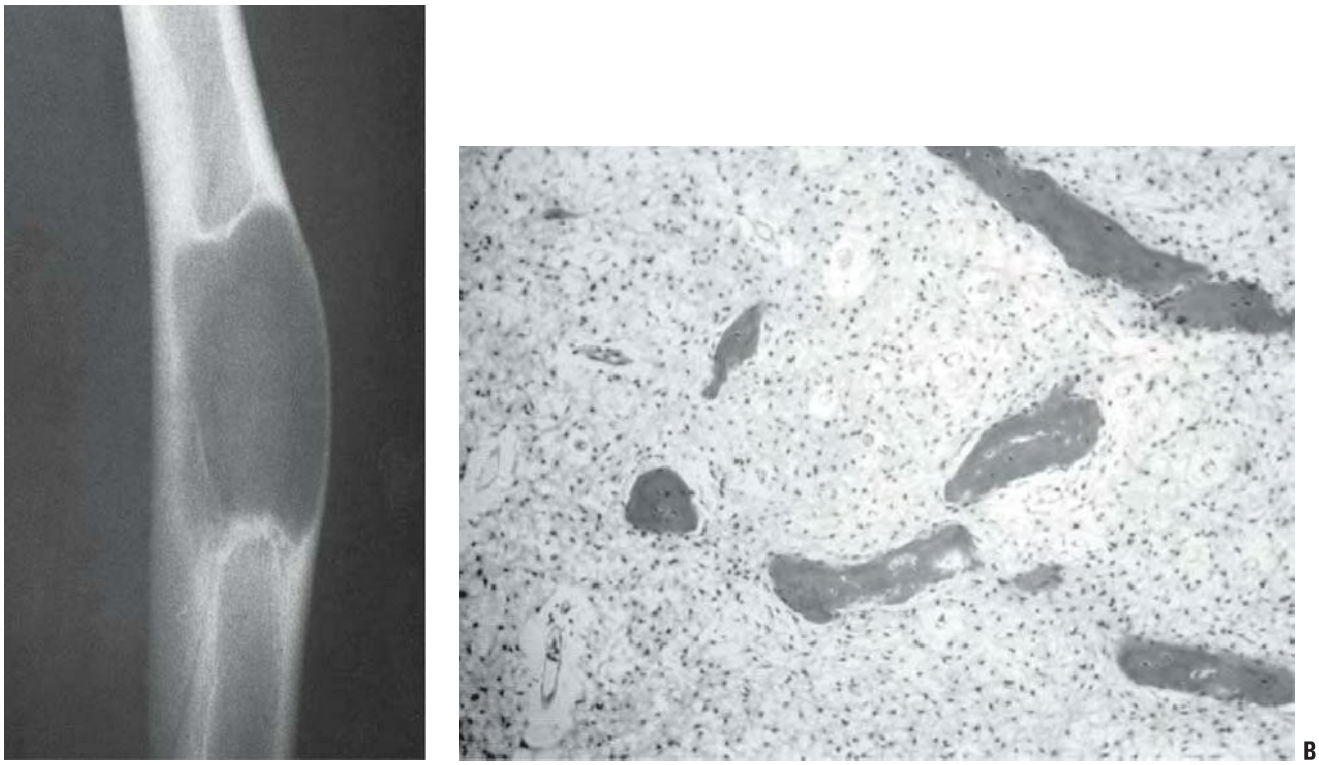


FIGURE 13-24. **A:** Radiograph of a fibrous dysplasia in the diaphysis of a long bone. The ground-glass appearance, the thin cortex, and the angular deformity of the bone are all typical features of fibrous dysplasia. **B:** The tumor is mostly fibrous tissue composed of collagen and fibroblast. Small bits of bone and osteoid, often having a "C" or an "O" shape, seem to have been sprinkled on the fibrous tissue. Osteoblasts are not seen, and the bone seems to be produced by the fibroblastic cells (40× magnification).

any, osteoblasts present, and the osteoid and bone seem to arise directly from the background fibrous stoma. The bone is irregularly organized, and often has a "C" or an "O" shape. Multinucleated giant cells are rare and there are few mitoses, none of which is abnormal. Nodules of cartilage may be present in typical fibrous dysplasia.

Monostotic fibrous dysplasia usually does not need surgical treatment (125, 126). Occasionally, a solitary lesion will be painful and curettage with grafting is required. Small lesions can be packed with cortical cancellous bone graft (autogenous or allogenic), whereas large lesions are probably better treated with cortical bone grafts, and a high incidence of recurrence and/or fibrous dysplasia transformation of the grafted bone is to be expected (129). A special circumstance is a lesion in the femoral neck. These lesions may be associated with a risk of fatigue fractures, and cortical strut bone grafting has been recommended (125, 126). Resorption of the bone graft with recurrence of fibrous dysplasia can occur, and the patient should be followed up for at least 5 years. Occasionally, surgical intervention is needed to prevent or treat fractures or deformity and relieve pain. Progressive bone deformity is unusual in patients with monostotic; however, in the poliostotic disease, bone deformity is frequent. The proximal femur is one of the most common areas of deformity; once a varus deformity develops, curettage and grafting are associated with internal fixation. Recently, coral grafts have been shown to reduce the chance of recurrence. In terms of fixation, intramedullary devices are superior to plates and screws (130, 131). Bisphosphonates have been used with success in polyostotic fibrous dysplasia and McCune-Albright; they prevent fractures, deformities, and most importantly, they seem to decrease pain (132).

Osteofibrous Dysplasia. Osteofibrous dysplasia is a benign active, sometimes locally aggressive bone lesion. The most common presenting symptoms are swelling and painless bowing of the tibia. The lesion is almost always located within the anterior cortex of the tibia and is best seen on the lateral radiograph (Fig. 13-25). Radius and ulna may also be involved (133–135). Sometimes, the diagnosis is made at time of a pathologic fracture. There are often numerous radiolucent lesions with a rim of reactive bone. On the technetium-99 bone scan, there is increased uptake in the area of the lesion.

Osteofibrous dysplasia arises from the cortex and involves the medullary canal late in the disease process. It is usually associated with a bowed tibia and quickly recurs if curetted. There are not many data on patients with osteofibrous dysplasia who have been adequately followed up. The natural history is of gradual growth until around 15 years of age.

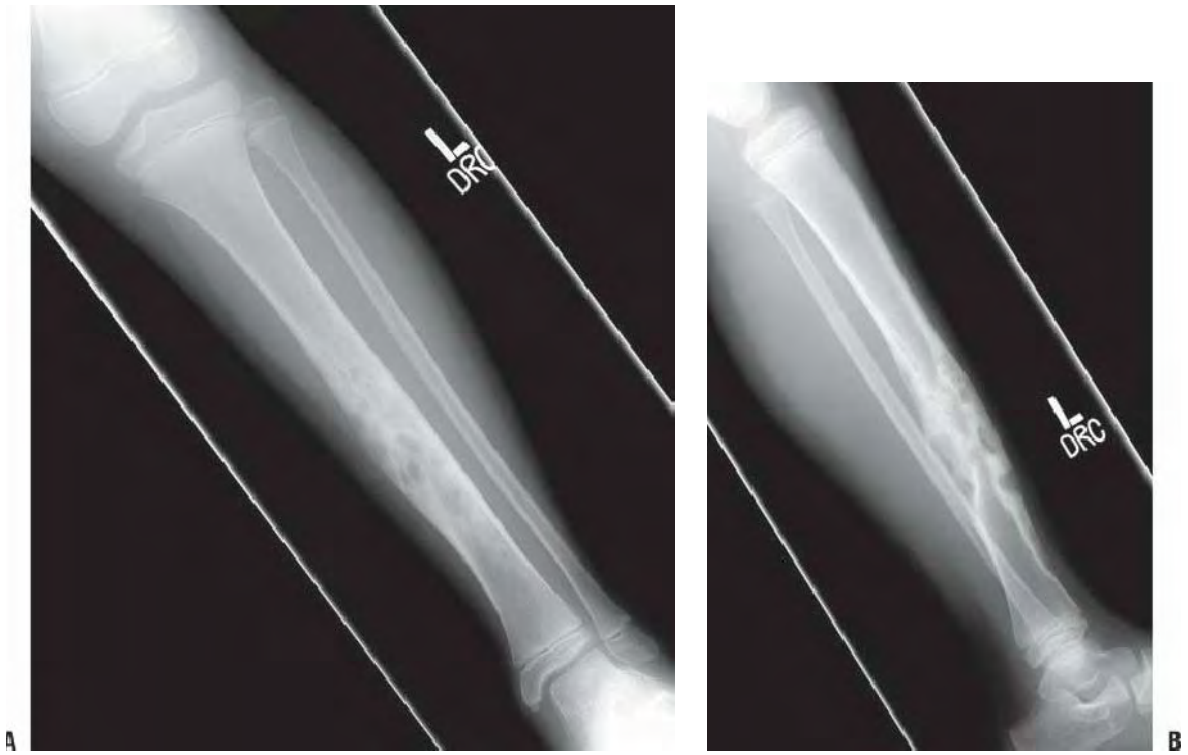


FIGURE 13-25. This is a 6-year-old girl with pain and swelling over the left tibia. Anterior-posterior **(A)** and lateral **(B)** x-rays demonstrate the classic appearance of osteofibrous dysplasia, this is a lytic, loculated lesion, involving the midshaft of the tibia, with mild expansion, angulation, and no soft-tissue mass or periosteal reaction (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

We recommend observation of the lesion when it is found in a patient younger than 10 years of age. Incisional biopsy is not necessary in most cases because the clinical presentation is diagnostic. Also, the biopsy reveals only a small portion of the lesion and does not change the initial management. Bracing can be used to prevent pathologic fracture, pain, and progressive bowing. If the lesion progresses rapidly before closure of the growth plate, biopsy and resection are suggested. If the patient presents after closure of the growth plate, especially if the lesion is large (more than 3 or 4 cm in diameter) or has aggressive features on plain radiographs, a biopsy is suggested. If an adamantinoma is found, a wide resection is recommended. If the biopsy reveals osteofibrous dysplasia, it is best to excise the entire lesion for a complete histologic examination to rule out the possibility of there being a focus of adamantinoma. If the lesion is small (<~3 cm) and the patient has no symptoms, continued observation is suggested.

Adamantinoma is a low-grade malignancy that has a clinical presentation similar to osteofibrous dysplasia. In adamantinoma, however, the patient is usually older (third decade of life), and the lesion appears more aggressive on the radiographs (e.g., soft-tissue extension, acute periosteal reaction, large size, involvement of the medullary canal). It has been suggested that there is a type of adamantinoma that looks very similar to osteofibrous dysplasia, even on histologic examination. Some hypothesize that osteofibrous dysplasia could be a precursor for adamantinoma (136, 137). One must be suspicious of the diagnosis of osteofibrous dysplasia, especially in a progressive lesion in a patient older than 10 years of age (138). If a lesion suspected of being an osteofibrous dysplasia is going to be observed, the patient should undergo radiography at least every 6 months until the lesion stabilizes, heals, or is resected. Typical adamantinoma has a risk of metastasizing, but it is not known whether the adamantinoma that looks like osteofibrous dysplasia can metastasize (133). Nonetheless, osteofibrous dysplasia, osteofibrous dysplasia–like adamantinoma, and classic adamantinoma appear to show a progressive complexity of cytogenetic aberrations, perhaps indicative of a multistep neoplastic transformation (139–141).

Langerhans Cell Histiocytosis. LCH is a rare group of disorders, of unknown etiology, with a wide spectrum of clinical presentation. Solitary osseous lesions are referred as to eosinophilic granuloma; Hand-Schüller-Christian includes the triad of cranial lesions, diabetes insipidus, and exophthalmos; Letterer-Siwe disease is a malignant form of LCH, whereas most patients present before 3 years of age with skin, visceral, and brain lesions, with or without bone lesions, and high incidence of mortality (61, 141–143). This is a disorder of the Langerhans histiocytes, and although eosinophils are a common component of the lesion, they are not necessary for the diagnosis (Fig. 13-26). Theories behind LCH etiology range from an inflammatory process to viral infection (94, 144, 145).

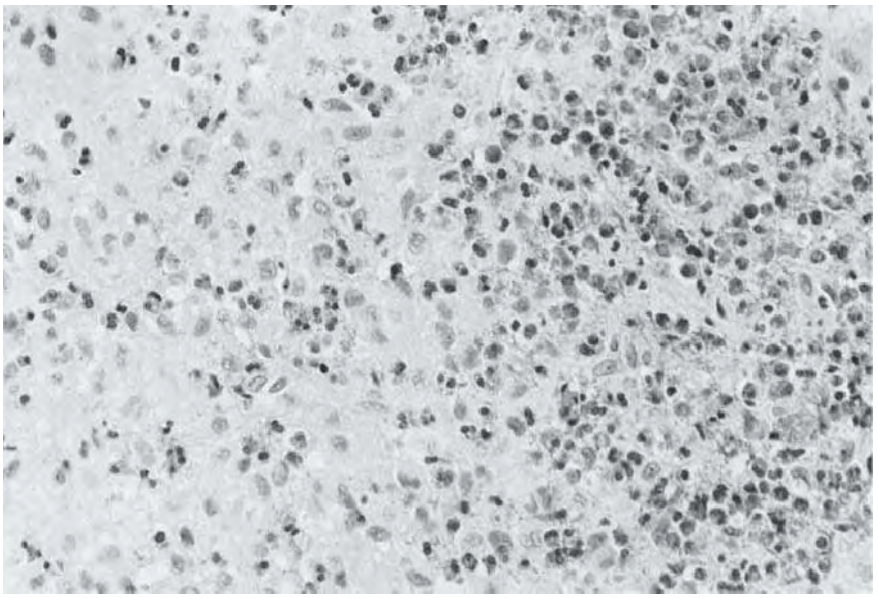


FIGURE 13-26. Low-power view of an eosinophilic granuloma (Langerhans granuloma). The eosinophils are numerous, but it is the presence of histiocytes that defines this tumor. The histiocytes are large cells with a clear, folded nucleus and a prominent nucleolus (original magnification ×10).

LCH is predominantly a disease of childhood, with more than 50% of cases diagnosed between the ages of 5 and 15 years (146). The skull is the most common site of bone involvement (61, 146, 147). Many of the skull lesions are probably not diagnosed because the only abnormality is a painless, small, spontaneously resolving lump in the scalp. The vertebral bodies and the ilium are the next most common sites of involvement (148, 149). When the lesions occur in the long bones, they may weaken the bone to such an extent that the patient presents with activity-related pain suggestive of a fatigue fracture, or with a pathologic fracture.

Due to the highly variable radiographic appearance, LCH has been referred as to the "great imitator." Most lesions are well defined, lytic, with or without sharp sclerotic rim, no periosteal reaction or soft-tissue mass (Fig. 13-27). Although LCH usually presents with increased uptake on a technetium bone scan, as many as 25% of the lesions will not be associated with abnormal bone scans (61), for that reason skeletal survey is often recommended to rule out other lesions (Fig. 13-27E). MRI is sometimes needed, especially for spine lesions, to rule out soft-tissue mass and intraspinal extension.

The clinical course of LCH is quite variable. Isolated osseous LCH is more frequent than the multisystem disease (61). The clinical manifestations depend on the location of the lesion; however, local "bone" pain is the initial symptom in 50% to 90% of the patients with osseous lesion (139, 143, 150, 151). Other reported symptoms in osseous LCH include night pain, soft-tissue swelling, tenderness, pathologic fractures, headaches (skull lesions), diminished hearing and otitis media (mastoid lesions), or loose teeth (mandible lesions) (152–156). Dull, aching neck or back pain is usually the presenting symptom of children with spinal LCH; vertebral collapse may also produce pain and spasm. Torticollis may be seen with cervical spine lesions, and kyphosis might be present with thoracic lesions (157–163).

Patients with eosinophilic granuloma do not progress to Hand-Schüller-Christian disease, but should be evaluated on presentation to exclude the presence of that syndrome. The easiest way to evaluate the patient for diabetes insipidus is to obtain a lateral skull film in order to observe the size of the sella turcica, and test a first voided urine specimen after overnight fluid restriction to determine whether the patient can concentrate his or her urine. Liver enzymes should be determined.

The treatment of LCH remains controversial. Some of the treatment options described include topical steroids, intralesional injections of steroids, NSAIDs, phototherapy, bone marrow allografting, surgical excision, stem cell transplantation, and chemotherapy. The decision should be made based on the severity of osseous involvement, location and size of the lesions, and presence or absence of systemic involvement (61). Biopsy is usually recommended. For isolated bone lesions, the treatment is mainly conservative and aims at controlling the symptoms, maximizing functional recovery, and limiting any long-term disability (141). The clinical course of these patients is generally benign; solitary bone lesions often heal without intervention or after biopsy with curettage of the lesion (61). Multiple bone lesions or systemic involvement is an indication for chemotherapy, and the pediatric oncologist should be consulted (164, 165).

Unicameral Bone Cysts. UBC or simple bone cyst is a common benign active or latent lesion that most often involves the metaphysis of long bones. Most of the lesions involve the proximal femur and proximal humerus (approximately 80% of the lesions) in children around the second decade (166). They are usually painless lesions and approximately 85% of UBCs are diagnosed at time of a pathologic fracture. Their radiographic appearance is so typical that most can be diagnosed without a biopsy (Fig. 13-28). UBCs are a well-defined, central, lytic lesion in the metaphysis. Cortical thinning may

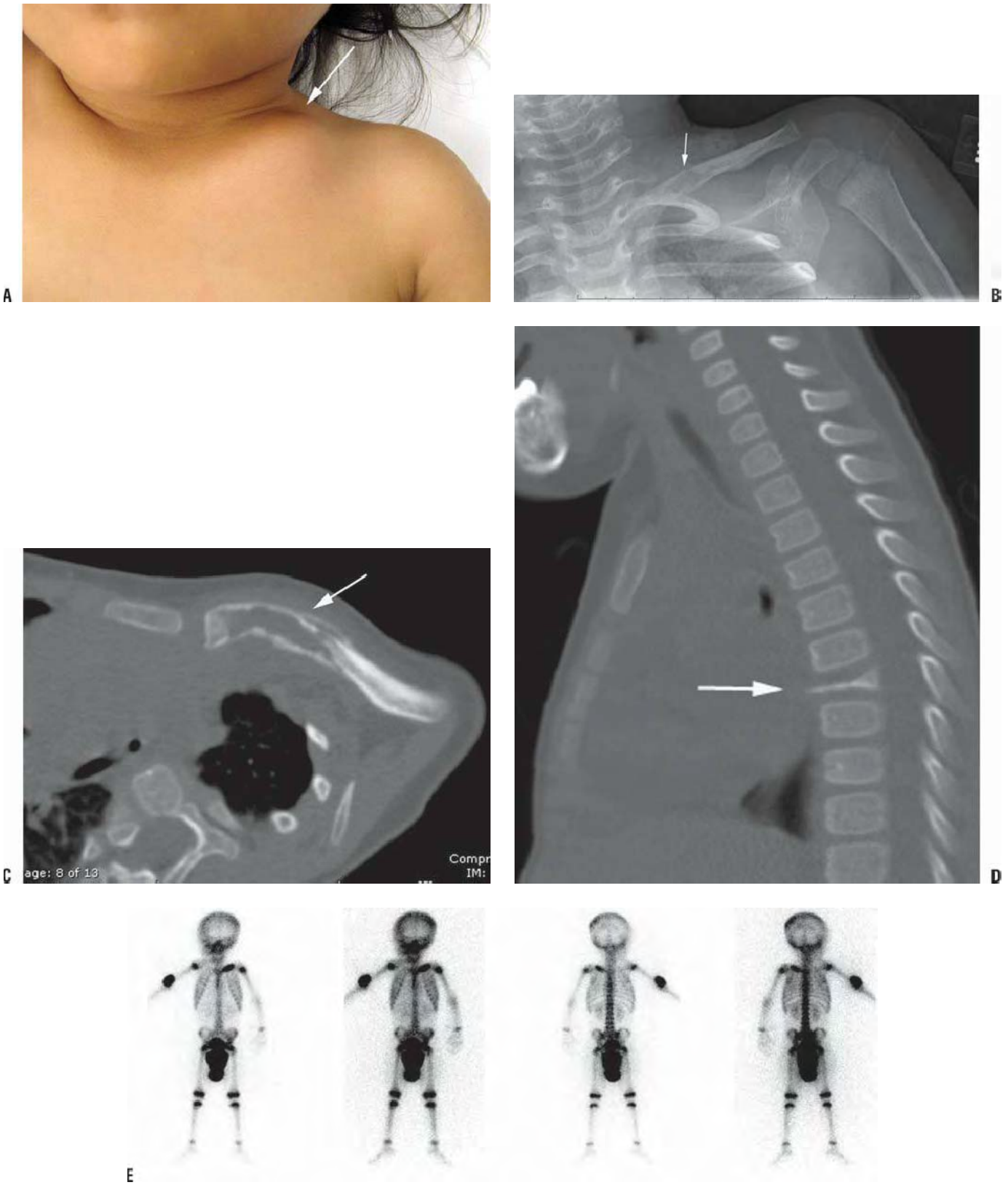


FIGURE 13-27. This is a 4-year-old girl who was being evaluated for a palpable and painful bone mass in the left clavicle **(A)**. Radiograph **(B)** shows a poorly defined lytic lesion within the medial half of the clavicle. CT of the clavicle **(C)** better defines the lesion and shows periosteal reaction with new bone formation and no soft-tissue mass. During the CT of the clavicle, sagittal image of the t-spine **(D)** shows a vertebra plana of T6, favoring the latter confirmed diagnosis of LCH. Bone scan **(E)** didn't show any other bone lesion and failed to demonstrate the T6 lesion. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

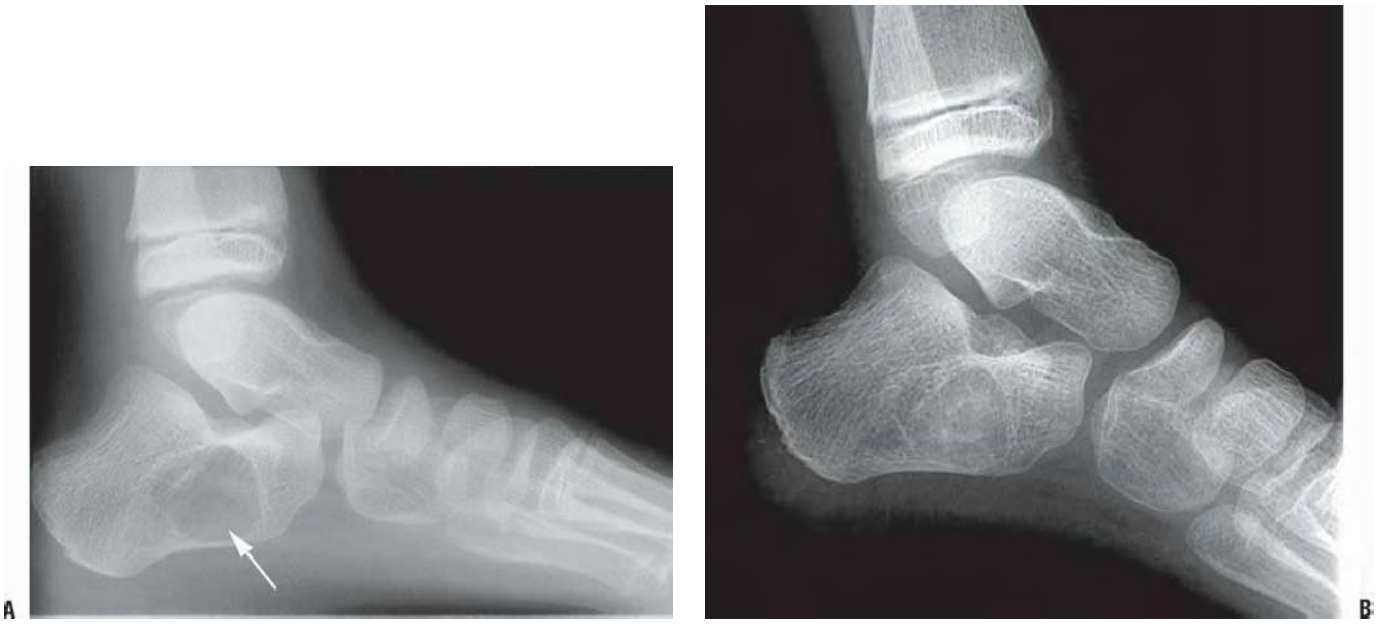


FIGURE 13-28. A 7-year-old boy presents with constant heel pain. Initial lateral radiograph of the calcaneus **(A)** demonstrates a well-defined, lytic lesion, without periosteal reaction or soft-tissue mass. This is a classic location and appearance of UBC. Postoperative image shows complete healing of the cyst, 3 months after a minimally invasive surgical procedure **(B)**. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

occur with larger cysts, but there is no periosteal reaction or soft-tissue mass (166, 167). The metaphyseal bone does not remodel and the metaphysis is broader than normal, but not broader than the width of the epiphyseal plate. When the cyst becomes mature (latent), usually after the patient reaches the age of 10 years, the epiphysis "grows away" from the lesion. The cyst may eventually heal spontaneously and fills in with bone.

The indications for treatment include large cysts in weight-bearing regions, high risk for pathologic fracture, and continued pain. Some UBCs remain small and do not present a significant risk to the patient, while other cysts are large, situated in high-stress anatomic sites (e.g., femoral neck), or persist after the patient has become a young adult, and in these cases treatment is also indicated (168).

For many years, steroid injection was the treatment of choice. The advantages are the low morbidity, low cost, and quick recovery, while the disadvantages include a very high persistence rate and the need to repeat the procedure several times before healing is obtained (169, 170). Before the use of corticosteroid injections became common, curettage and autogenous bone grafting had been the most common treatment. Operative treatment with curettage and autogenous bone grafting is now reserved for those lesions that do not respond to less invasive procedures. Injecting autogenous bone marrow is a technique advocated by some with better results than steroids (171, 172).

Several authors have more recently been advocating cyst decompression as the most efficient way to treat UBCs (173). We described a minimally invasive technique for the treatment of UBCs (174). The procedure is done under general anesthesia with fluoroscopic guidance. The cyst is penetrated with a Jamshidi needle and aspiration follows. Cystogram with Renografin diluted 50% is then performed to evaluate for loculations within the cyst. A 0.5-cm incision is made over the needle site, and the cortex is penetrated with a 6-mm trocar. If there is any question regarding the treatment, an incisional biopsy is done with a pituitary rongeur and specimen is sent for frozen section. The cyst is curetted under fluoroscopy, and any cyst lining or fibrous tissue (following fracture) is excised. The cyst is now decompressed using curved curettes and/or a titanium elastic nail. The last step of the procedure is bone grafting with medical-grade calcium sulfate pellets. In a recent review of intermediate-to-long-term results, the healing rates were around 80% after one procedure and over 90% after repeat procedure (*unpublished data*). Many other substances including demineralized bone matrix gel, bone marrow, allograft or autograft bone chips, and calcium phosphate materials have been proposed as "fillers." Some seem to be better than steroid injections alone, but none of these treatments has been definitively proven to be superior to another. When open excision is performed with intralesional curettage, autogenous bone or allograft cortical cancellous bone can be used for packing the cavity. Freeze-dried cortical cancellous allograft is particularly advantageous because it is associated with an excellent healing rate and little, if any, incidence of complications; also, a secondary incision is not required for obtaining the autogenous bone graft. Calcium sulfate tablets are an alternative material that can be used for filling the cavity. When the cyst is adjacent to the growth plate, care should be taken not to damage the

epiphyseal cartilage during the procedure. If there is doubt about the integrity of the growth plate, it is wise to obtain an MRI to document whether or not it has been violated by the cyst prior to instituting treatment.

Aneurysmal Bone Cysts. ABC is a benign active and sometimes aggressive lesion. ABCs often occur in association with a number of other tumors (e.g., giant cell tumor, chondroblastoma, osteoblastoma, and osteosarcoma). When it is a secondary lesion, the primary lesion is usually obvious, and the ABC component is limited to only a small portion of the tumor. Secondary ABCs are classified by their underlying diagnosis. The presence of a secondary ABC does not change the therapy or prognosis of the underlying primary tumor. The neoplastic basis of primary ABCs has been, at least in part, demonstrated by the chromosomal translocation t(16;17)(q22;p13) that places the ubiquitin protease USP6 gene under the regulatory influence of the highly active osteoblast cadherin 11 gene (CDH11), which is strongly expressed in bones (175, 176).

A primary ABC occurs most commonly in teenagers (80%). More than 50% of these cysts arise in large tubular bones, and almost 30% occur in the spine (175, 176). The patient usually complains of a mild, dull pain, and only rarely is there a clinically apparent pathologic fracture. The physical examination usually shows normal results, and there is no abnormal laboratory finding associated with ABC.

On the plain radiograph, an ABC is a radiolucent lesion arising eccentrically within the medullary canal of the metaphysis (Fig. 13-29). It resorbs the cortex and elevates the periosteum, generally making the bone wider than the epiphyseal plate (characteristic finding). Usually, there is a thin shell of reactive periosteal bone, but occasionally this bone cannot be seen. When ABC arises in a long bone, it is metaphyseal. When it arises in the spine, it originates in the posterior elements but it may extend into the body and, not uncommonly, will extend also to an adjacent vertebral body or rib. The radiograph of an ABC may appear identical to those of giant cell tumor of the bone and telangiectatic osteosarcoma. The periosteal reaction appears to be aggressive, and the lesion may be mistaken for an aggressive or a malignant tumor. ABCs may arise in the cortex and elevate the periosteum with or without involving the medullary canal.

A CT scan is helpful in making the diagnosis of ABC. The lesion should have a density of approximately 20 HU, and this does not increase with intravenous contrast injection. When the patient lies still for 20 to 30 minutes, the cells in the fluid within the cyst cavity settle, and a fluid/fluid level can be seen. Similar findings can be seen on MRI. Fluid/fluid level was originally described in ABC but has subsequently been seen in a number of other lesions, so it cannot be considered to be diagnostic of ABC. An ABC has an increased uptake of technetium on the bone scan, but often the scan has a central area of decreased uptake.

ABCs should undergo a biopsy to establish the diagnosis (175–177). The pathologist should be advised in advance, and the possibility of a telangiectatic osteosarcoma should be discussed. It is uncommon for the histologic appearance of an ABC to be mistaken for that of a telangiectatic osteosarcoma, although the radiographic and the gross appearances can be identical. On gross inspection, an ABC is a cavitary lesion with a villous lining. Microscopic examination reveals the lining to be composed of hemosiderin-laden macrophages, multinucleated giant cells, a fibrous stroma, and usually small amounts of woven bone (Fig. 13-30). The microscopic appearance of the lining of the ABC is similar to that of a giant cell tumor of bone.

Most recommend treatment by curettage and packing of bone graft, but recurrence rates are high (up to 60%) (175–177). Embolization may be used in order to decrease blood loss during surgery and has been associated with fewer recurrences. Whether embolization is necessary or helpful is debatable. Cryosurgery has also been reportedly tried. Cryosurgery may produce complications, and it is not considered necessary in most cases. It may play a role in the treatment of recurrent lesions. Definitive resection (wide or en bloc resection) can be performed when the consequences of the resection are minimal, but it is absolutely necessary only when the lesion has a particularly aggressive clinical growth pattern. We recommend a four-step-approach including extended intralesional curettage, high-speed burring, adjuvant use (such as phenol), and electrocauterization. The recurrence rate in children with this technique is <20% (38).

An ABC of the spine (approximately 30% of cases) can present a particularly challenging problem. The lesion always involves the posterior elements, but can also involve the vertebral body. The patients initially complain of pain at the site of the lesion, but the ABC is often not found until the patient has nerve root or cord compression. Most cases heal with the four-step approach described anteriorly; caution should be taken if adjuvant is used, due to the proximity to the spinal cord and nerve roots (175). Usually the posterior elements are resected, and any involvement of the pedicles or the body is curetted. If complete laminectomy is performed, a short posterior fusion is advised using titanium instrumentation to allow for postoperative MRI or CT scan (178).

MALIGNANT BONE TUMORS

Guidelines for Surgical Treatment of Bone Tumors.

Some benign tumors may not need treatment and can be merely observed. Others are successfully treated with simple intralesional curettage. In general, when curettage is indicated it is best to visualize the cavity thoroughly and carefully remove the entire tumor under direct visualization. The use of a high-speed burr can help assure complete removal of all tumor cells and is especially advised for benign aggressive tumors (179). The use and effectiveness of a local adjuvant such as phenol, argon-beam, and cryosurgery is controversial but common (180–182).

In children, most malignant bone tumors, with the exception of lymphoma, should be surgically resected. The goal of

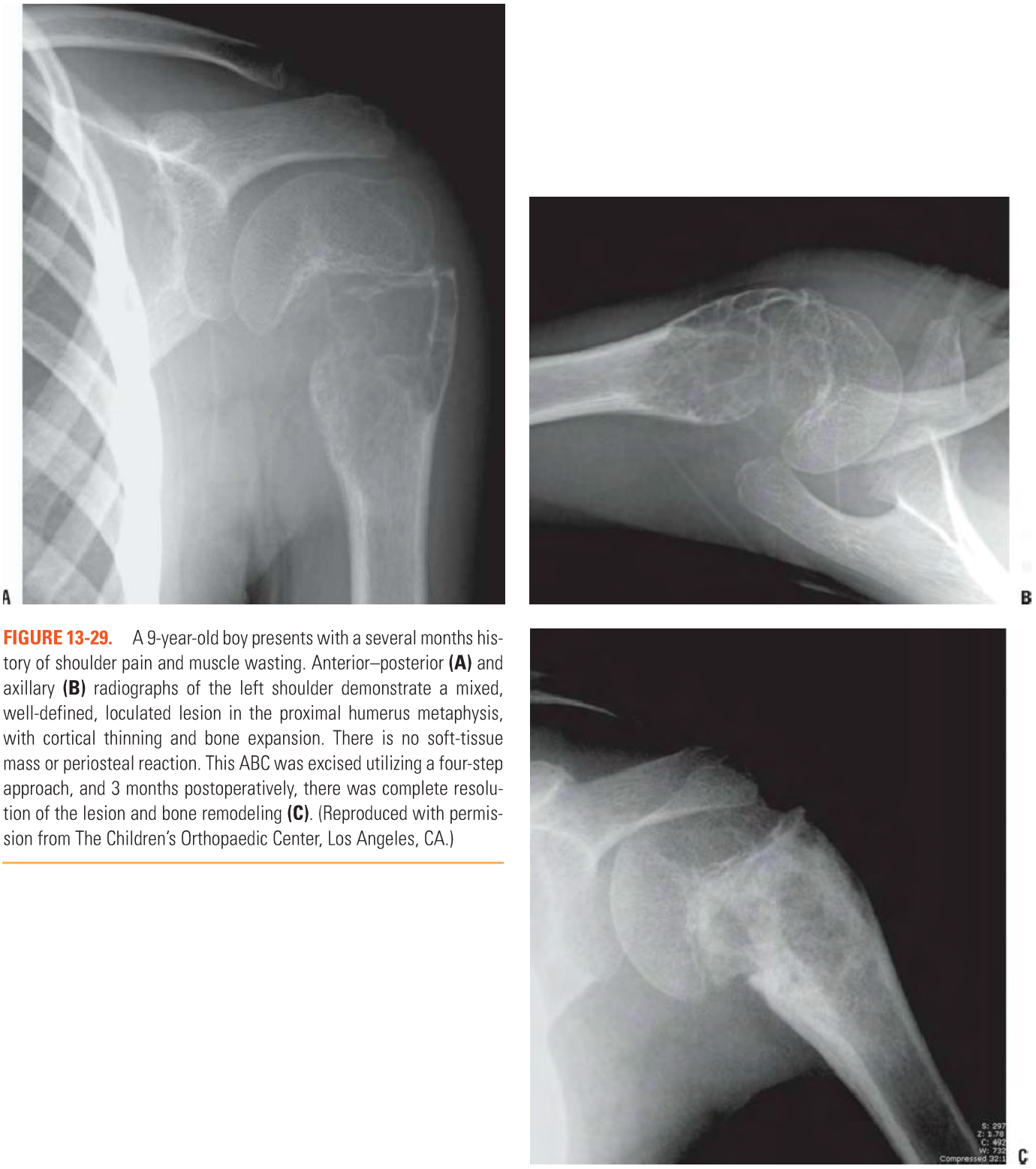


FIGURE 13-29. A 9-year-old boy presents with a several months history of shoulder pain and muscle wasting. Anterior–posterior **(A)** and axillary **(B)** radiographs of the left shoulder demonstrate a mixed, well-defined, loculated lesion in the proximal humerus metaphysis, with cortical thinning and bone expansion. There is no soft-tissue mass or periosteal reaction. This ABC was excised utilizing a four-step approach, and 3 months postoperatively, there was complete resolution of the lesion and bone remodeling **(C)**. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

surgical treatment of these malignant bone tumors is to resect the entire tumor. To accomplish this, some of the adjacent normal tissue must be removed because the tumor infiltrates these tissues. The exact extent of involvement of the normal tissue is impossible to determine preoperatively, although MRI is a reasonably accurate method of determining the extent of the tumor. The greater the amount of adjacent tissue removed, the less likely the patient is to have a local recurrence; therefore, as much adjacent tissue as is practical should be removed (182, 183). Although the goal of treatment is to eliminate local recurrence, it is not practical to try to guarantee that local recurrences never happen, because such an approach would lead to excessive surgery for most patients without a proven benefit in survival.

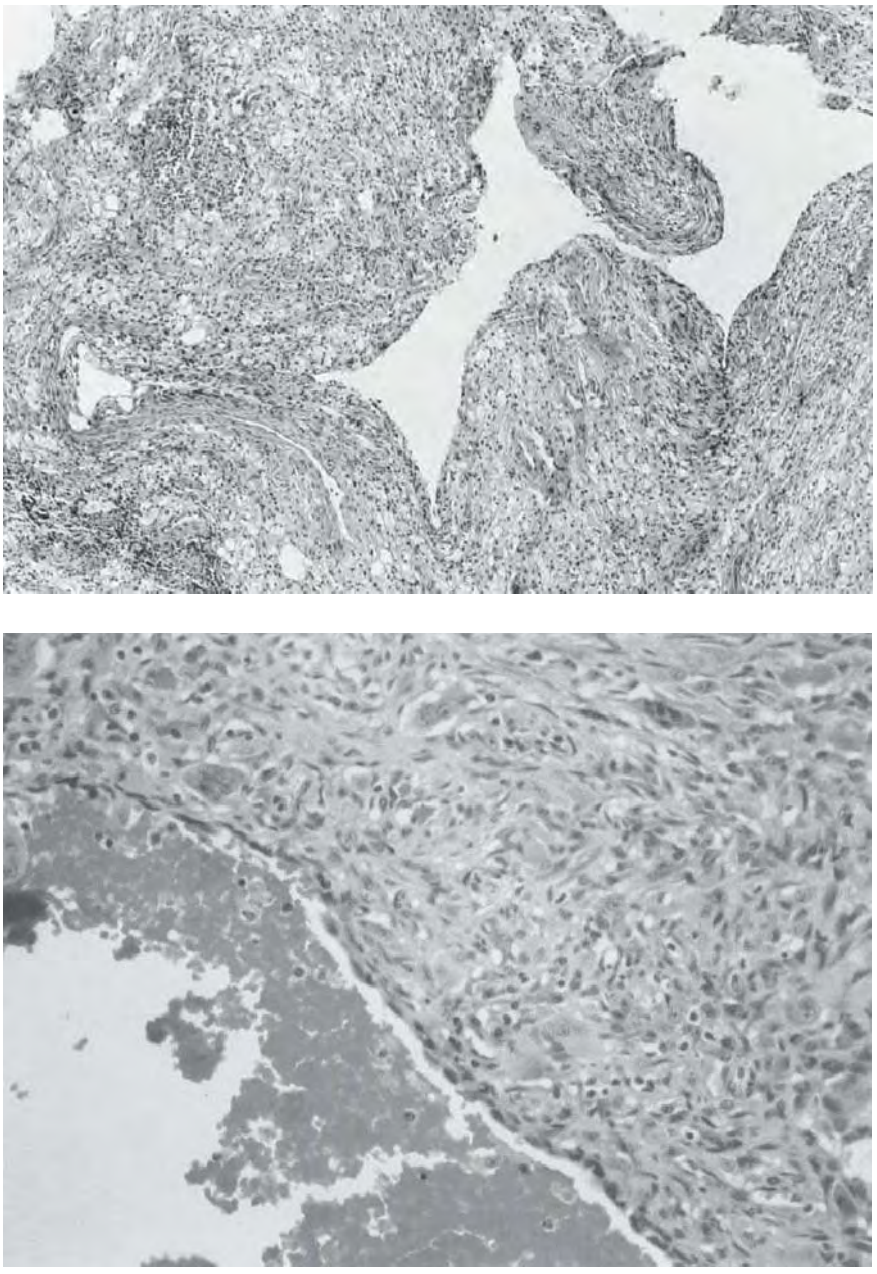


FIGURE 13-30. **A:** Low-power view of the tissue lining an ABC. The lining is composed of fibrous tissue with multinucleated giant cells, foamy histiocytes, hemosiderin and, often, spicules of immature bone (not seen). The fronds and spaces are typical (original magnification × 10). **B:** Higher-power view (40 ×) of ABC. Benign spindle cells, vessels, hemosiderin, and multinucleated giant cells make up the solid component. There is a cystic component filled with blood.

In order to determine how much normal adjacent tissue should be removed, it is useful to first determine what is the minimal amount of tissue that must be removed in order to completely remove the tumor as shown on an MRI. Then add as much additional adjacent tissue to the resection as possible without changing the functional impact of the surgery. For example, if 15 cm of a distal femur must be removed, it is just as functional to replace 25 cm (i.e., a 10-cm bone margin), as it is to replace 17 cm (which would be only a 2-cm margin). If adjacent muscle has been invaded to the extent that what remains is not functional, all of the muscle should be removed. If no additional adjacent tissue can be removed without impacting on the patient's functioning, either an adjuvant is needed, or the patient should undergo the more functionally impacting resection.

Limb-salvage surgery is done for most sarcomas of the extremities, but the decision is often difficult because the surgical margin achieved with an amputation would almost always be much better than the one obtained with a limb-salvage resection (182, 183). In a limb-salvage operation, local recurrence may be higher than with amputation, but no adverse effect on disease outcome (survival) has been shown. The time to recovery is longer, the complexity of the surgery is greater, there are more local complications, the chance of needing additional surgery is increased, and the safe level of physical activity is lower as compared to an amputation, but the patient retains his or her own foot or hand. Since the introduction of adjuvant chemotherapy, especially preoperative (neoadjuvant) chemotherapy, and the availability of CT scanning and MRI, limb-salvage surgery has become more common. The materials used in reconstruction, and the surgeons' experience with these materials and techniques, have improved to such an extent that limb-salvage resections have become commonplace

in most medical centers. Nowadays, a patient rarely needs to undergo an amputation for a sarcoma of the extremity (184).

An amputation may be necessary in those patients in whom surgical resection will remove so much tissue that the remaining limb will be less useful than a prosthesis (184, 185). To make this decision, the patients have to indicate how they want to use the extremity (184, 185). The more sedentary the patient, the greater the amount of tissue that can be removed in limb-salvage surgery without amputation becoming the better option, and vice versa (186). In general, bone, joints, arteries, veins, and muscles can be removed and still leave the extremity functional. Even the need to resect a major nerve is not in itself an indication for an amputation (60, 183, 187–189). It is when a combination of these tissues, including a major nerve, has to be resected that amputation should be seriously considered. Each patient's situation and preferences should be considered individually.

There is a fairly wide experience with limb salvage in adults. For children, however, the surgeon encounters problems including growth, small size, and (it is hoped) greater longevity, all of which make reconstruction more challenging (190, 191). The options for limb salvage include osteoarticular and intercalary allograft, metallic prostheses, and vascularized and nonvascularized autograft transplants. All of these are used at various times by the tumor surgeon. Rotationplasty is another option somewhere between limb salvage and amputation; it is occasionally useful in very young patients (187, 192).

In some locations, such as the fibula and clavicle, no bone reconstruction is necessary. Very young children with bone tumors of the foot and ankle are usually best treated by amputation of the ray, or Syme amputation, or below-knee amputation.

The unique issue regarding limb salvage in children is growth of the opposite extremity and the limb-length inequality that follows. For the child who is within 2 or 3 years of completion of growth, this is not a significant issue (187, 193, 194). Fortunately, most malignant bone tumors occur within this age group or in older children. In a patient who is between 10 and 13 years of age, there is sufficient growth potential (particularly in the distal femur, proximal tibia, and proximal humerus, the most common sites for malignant bone tumors) that if limb-salvage surgery is done, special attention is needed to achieve near-equal limb lengths at maturity. Equal or near-equal limb lengths can be achieved with traditional methods initially making the operated leg longer and, if needed, by epiphysiodesis. Usually, for patients whose limb-length inequality will be 2 cm or less, no surgical adjustment is necessary and the patient can use a lift if desired. For limb-length inequality between approximately 2 and 5 cm, an epiphysiodesis is usually the best means of achieving equal limb lengths. For limb-length differences >5 cm, some type of limb lengthening or rotationplasty is advised (195).

For lesions of the proximal humerus, intra-articular or extra-articular resection is performed. If the rotator cuff and part of the deltoid can be preserved, the expected functional outcome is reasonable (195, 196). Reconstruction options include osteoarticular allograft, allograft-prosthetic composite, or endoprosthesis. The advantage of the allograft is better attachment of the rotator cuff and soft tissues; endoprosthesis may prevent late collapse of the joint and fracture (195, 196). For extra-articular resections in which both the deltoid and the rotator cuff are sacrificed, arthrodesis, using allograft, vascularized fibula, or both, may be indicated and tends to be very functional (196). When a formal Tikhoff-Linberg resection including the scapula is necessary, the reconstruction is more difficult; options include custom prosthesis, allograft reconstruction of the scapula associated with humeral reconstruction, or at times flail upper extremity (197).

For tumors around the knee (most common area involved), the resection will almost certainly include an epiphyseal center. One option is to reconstruct with an osteoarticular allograft, and treat the limb-length discrepancy using standard methods of epiphysiodesis, closed femoral shortening, or limb lengthening (185). The results of allograft for limb salvage in osteosarcoma are reasonably good, but the patient should not expect normal limb function. It should be noted that there are no ideal measures of function after limb salvage (although several have been developed), and this remains an area of investigation (197–199). In general, if patients can return to normal walking activities without supports or braces, it is considered to be a good result. Seldom can they return to contact sports or activities involving running. Complications include infection, nonunion, fracture, and joint instability (176, 200). If the patient survives, he or she may need joint arthroplasty at some time in the future, but by then the patient should be old enough that growth is no longer a consideration. Growth equalization can be achieved by contralateral epiphysiodesis, limb shortening, or ipsilateral lengthening (189). The experience with limb lengthening in these patients is limited because limb length is seldom a major issue.

Another option is the use of a metallic prosthesis. Modular prostheses are available and allow the surgeon to construct an implant of suitable length in the operating room (187, 193, 194). Custom implants are seldom necessary. Some prostheses have the ability to be extended or grow as the child grows (201). There are many methods that can be used to lengthen endoprosthetic devices. Some require a major operative procedure, some can be done with limited surgery (Fig. 13-31), and a few endoprostheses can be lengthened without surgery (192–194, 202) (Fig. 13-32). The efficacy and longevity of these "growing" prostheses are the focus of several studies (194). Usually, it is possible to achieve at least 2 cm of length per procedure. In very young patients, this must be repeated every 6 months until maturity, at which point revision to an adult prosthesis may be necessary. There are few data on these prostheses, but at least one report shows that it is possible to gain 2 to 18 cm in length, and to have equal limb lengths at skeletal maturity (187, 192–194). The issues of prosthetic failure, loosening, wear of polyethylene, and infection remain unresolved. The choice between an implant and a reconstructive procedure has to be made by the surgeon and the patient's family. Prostheses are more functional initially, but their longevity is unknown. Extendible prostheses have a high failure rate (187). More than

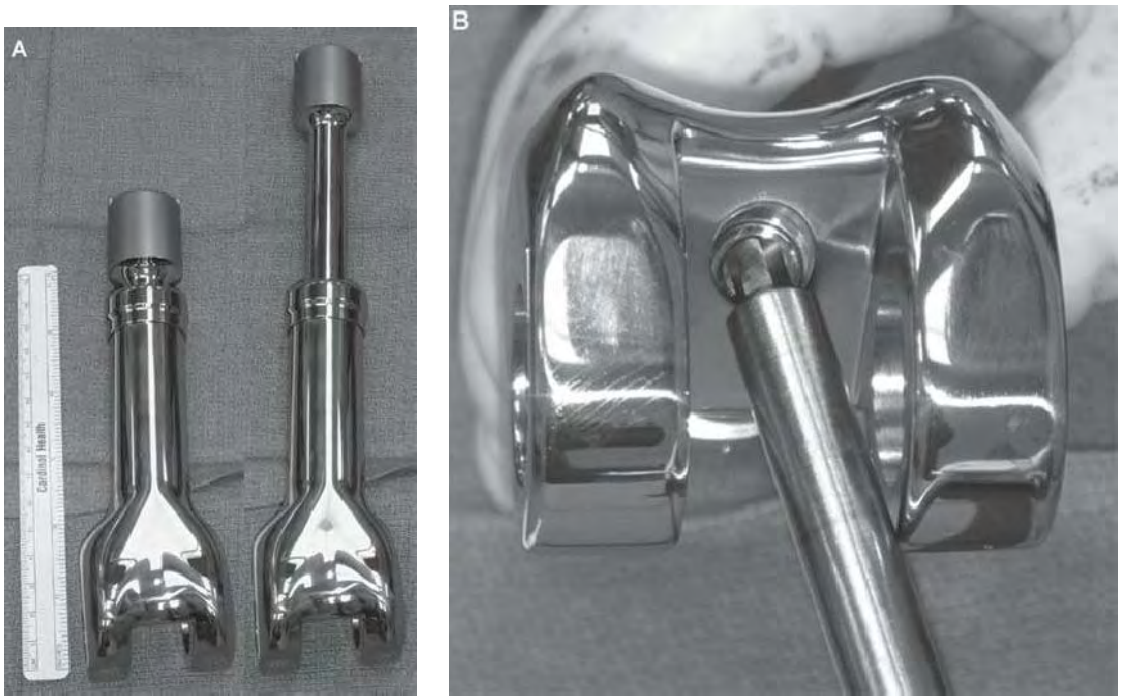


FIGURE 13-31. **A,B:** Example of a coaxial extendible prosthesis that can be lengthened with a minimally invasive procedure, utilizing a screw driver placed into the notch (Reproduced from Arkader A, et al. Coaxial extendible knee equalizes limb length in children with osteogenic sarcoma. *Clin Orthop Relat Res* 2007;459:60–65, with permission.)

80% require revision by 5 years, and the revision rate appears to be higher in uncemented prostheses (183, 189, 192, 194). Many of these patients will have knee stiffness, and the infection rate, especially in the tibia, may be as high as 38%, although this can be improved with the liberal use of gastrocnemius flaps. The modular prosthesis has been reported to have a 5-year revision-free and amputation-free survival rate of 75%, presumably because it is mechanically stronger and less complex (184, 185). Functioning appears to be better in children who are older than 8 years at the time of the reconstruction. Rehabilitation is more difficult with allograft, but they hold the promise of superior longevity. It is very important to tell the patient in either case that the function will not be normal and that neither method of reconstruction will return the patient to sports activities; amputations can still be more functional if the patient is willing to engage in high-level activity (203, 204). Distraction osteogenesis is another means of achieving equal limb length that can be done for patients who have had resections of malignant bone tumors. This should be done only after the patient has completed chemotherapy.

For diaphyseal lesions, an intercalary resection can be performed, sparing the adjacent joints and occasionally the epiphyseal plates. In these patients, reconstruction can be carried out with intercalary allografts and/or vascularized fibula (203, 204). A method of using an allograft to provide initial stability, augmented by a vascularized fibular graft to achieve quicker union and long-term healing potential (205). This technique is especially helpful when only a small segment of the epiphysis remains after the resection (206, 207).

For very young patients with tumors of the distal femur, or older patients who want to be athletically active, rotationplasty is a good option (207). In these patients, above-knee amputation would lead to a very short stump with a poor lever arm with high energy consumption during gait (206). Rotationplasty, by taking advantage of the tibia and foot, provides a longer lever arm and an active "knee" joint. It also avoids resection of the major nerves, so that phantom pain is not an issue. The physical appearance without the prosthesis is disturbing to some patients, but with prosthesis they look similar to other amputees with better function than above-knee amputees (Fig. 13-33). The technical details are well described elsewhere, and the technique has been described for lesions of the proximal tibia and the proximal femur (73). It is very important to have frank discussions with the patient and his or her family about the appearance and the expected outcome of this reconstruction. It can be very helpful to the patient to be able to meet another patient, who has undergone rotationplasty, or at least view a video and meet with an experienced physical therapist and prosthetist. Interestingly, young patients do not view this as an amputation, because the foot is still present, and the long-term psychological outcomes in these patients have been very good.

The more distal the tumor is in the lower extremity, the more likely it is that amputation will be the better treatment choice. A hip disarticulation has so much more functional consequence compared to an ankle disarticulation that limb-salvage surgery for a tumor in the proximal femur is always more valuable compared to limb-salvage surgery for a tumor in the calcaneus.

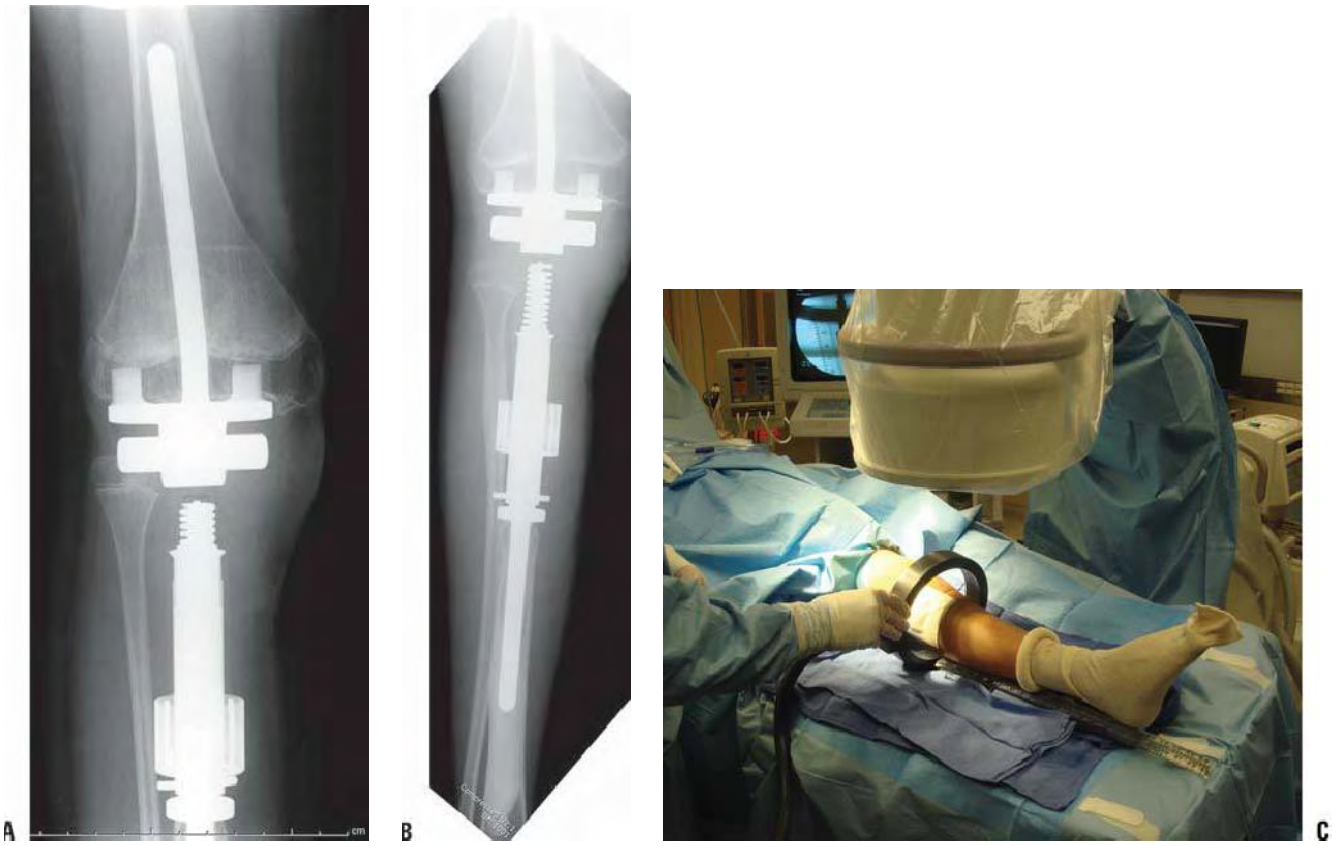


FIGURE 13-32. Radiographs **(A** and **B)** of the knee of a 12-year-old boy that underwent limb salvage surgery with a Repiphysis prosthesis for proximal tibia osteosarcoma. Note the spring-loaded system that expanded following lengthening. The procedure is done under sedation, and the lengthening is obtained by placing the extremity in an electromagnetic field **(C)**. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

Locally recurrent tumor is often indication for an amputation. These patients' tumors have proved that they are more aggressive or more extensive than had been appreciated at the time of their initial treatment and therefore need more aggressive surgery than usual. In these circumstances, limb salvage is less likely to be effective and should be done with caution.

Chemotherapy for Musculoskeletal Tumors. It was not until the 1970s that chemotherapy was believed to be effective in the treatment of malignant tumors of the musculoskeletal system. The extremely high incidence of metastatic disease in patients with osteosarcoma (more than 80%) and EWS (more than 85%), and some promising results in patients with metastatic sarcoma, prompted the use of adjuvant chemotherapy in patients who did not have documented disease but in whom the risk of having subclinical metastases was high. The early results were exciting, and even the use of what was considered minimal amounts of less-than-optimal drugs improved survival. These early studies led to the acceptance of adjuvant chemotherapy for primary bone sarcomas. In the 1980s, preoperative chemotherapy was introduced, and it is now standard for the initial chemotherapy for patients with EWS, osteosarcoma, and RMS. *Neoadjuvant chemotherapy* is a term used to indicate that the patient receives chemotherapy before the definitive treatment of the primary lesion. This was initially used as a means of treating patients with osteosarcoma who were waiting for the production of a custom prosthesis. The effect of chemotherapy on the tumor was considerable and of prognostic significance, and this has led to the routine use of preoperative chemotherapy.

There are numerous chemotherapeutic protocols for the three main skeletal malignancies (EWS, osteosarcoma, and RMS) for which chemotherapy is used. All these protocols use more than one drug, usually three to five. Most protocols are between 9 and 12 months in duration. Approximately one-third of the chemotherapy is given preoperatively, and the remainder is given after surgery.

The drugs used for musculoskeletal tumors include

- Doxorubicin (Adriamycin), a cytotoxic anthracycline antibiotic that passively enters the cell to diffuse into the nucleus, where it binds nucleic acids and disrupts DNA synthesis. It is cardiotoxic, myelosuppressive, and produces alopecia. It is given intravenously in divided doses over 6 months, with 450 mg/m^2 recommended as the maximum dose.
- Methotrexate is an antimetabolite that inhibits dihydrofolic acid reductase. This interferes with DNA synthesis and

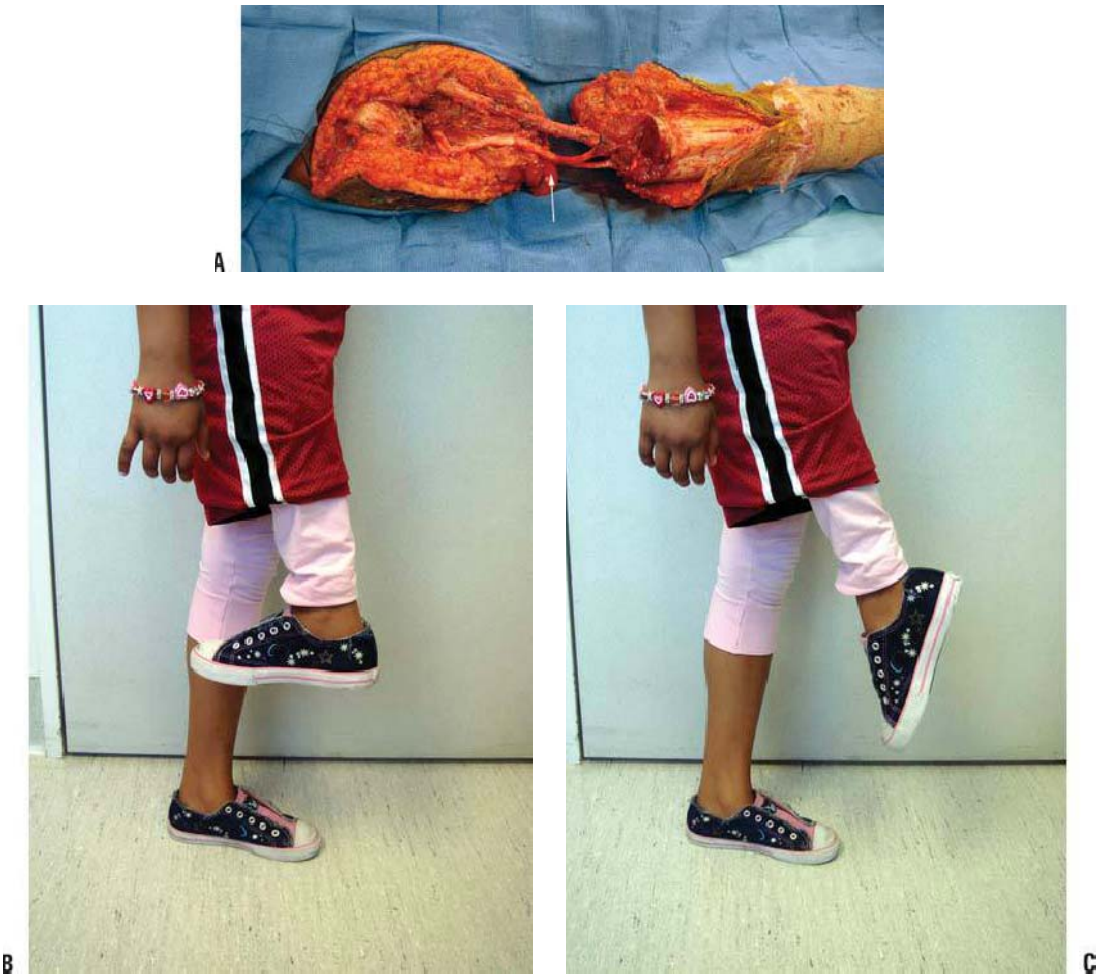


FIGURE 13-33. This 8-year-old girl had an extensive osteogenic sarcoma of the femur, complicated by a pathologic fracture and inappropriate ORIF performed at an outside institution; she underwent a Van Nes rotationplasty with extensive neurovascular dissection **(A)** (*arrow* points to sciatic nerve dividing into tibial and peroneal branches) and retained movement of her ankle (**B** and **C**), that will now be used as a knee. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

repair, and alters cellular replication. When administered in high doses (12 mg/m^2 intravenously), leucovorin or citrovorum factor is given to the patient to rescue the normal cells. Leucovorin is a chemically reduced derivative of folic acid and is used by the cells to complete normal cell functions without the need for dihydrofolic acid reductase. Tumor cells seem less able to use leucovorin than normal cells, and this difference allows methotrexate to be effective against malignant tumors. The primary side effects of methotrexate are gastrointestinal, including nausea, vomiting, and loss of appetite.

- Cisplatin is a heavy metal that is thought to cause intrastrand crosslinks in DNA, and thereby interfere with the DNA. It is given intravenously in doses of 75 to 100 mg/m^2 repeatedly over the course of the treatment. The principal side effect of cisplatin is nephrotoxicity.
- Cyclophosphamide (Cytoxan) is a synthetic drug chemically related to nitrogen mustard. It crosslinks DNA and interferes with DNA functions. It is given intravenously at a dose of 40 to 50 mg/kg in divided doses over 4 to 5 days. The major side effects of cyclophosphamide are gastrointestinal disorders and myelosuppression.
- Ifosfamide is a synthetic analog of cyclophosphamide, with similar actions. It is given intravenously at 1.2 g/m^2/day for 5 days.
- Vincristine is an alkaloid from the periwinkle plant. It is thought to arrest dividing cells in the metaphase state by inhibiting microtubule formation in the mitotic spindle. It is given intravenously at weekly intervals at doses of 1.4 mg/m^2 in adults and 2.0 mg/m^2 in children. The major side effect of vincristine is peripheral neuropathy.
- Bleomycin is a cytotoxic glycopeptide antibiotic from a strain of *Streptomyces verticillus* that inhibits DNA synthesis. It also probably inhibits ribonucleic acid (RNA) and protein synthesis. It is given intravenously at 0.25 to 0.50 U/kg once or twice per week. The most serious side effect of bleomycin is a 10% incidence of severe pulmonary fibrosis.

- Actinomycin D (Dactinomycin) is one of a number of actinomycin antibiotics from *Streptomyces*. It binds to DNA by intercalation with the phenoxazone ring. This inhibits the DNA from being a template for RNA and synthesizing itself. It is given intravenously at 0.5 mg/day for 5 days. Dactinomycin produces nausea and vomiting and is myelosuppressive.

These drugs are given in various combinations and doses, depending on the specific diagnosis, the protocol, the response of the patient, and the aggressiveness of approach of the medical oncologist.

Osteosarcoma. Osteogenic sarcoma or osteosarcoma is defined as a tumor in which malignant spindle cells produce bone. There are two major variants that have significantly different clinical presentations and prognoses. The more common osteosarcoma is called classic high grade, or conventional, and the other is juxtacortical (73). Less common variants of osteosarcoma (e.g., intracortical, soft tissue, radiation-induced, Paget disease) are not discussed in this text.

Conventional Osteosarcoma. The patient is usually a teenager (approximately 50% of the patients present during the second decade of life; more than 75% are between 8 and 25 years of age) with symptoms of pain and a mass around the knee (187, 200, 208). In approximately half of the patients, the lesions are located in the distal femur or the proximal tibia. The proximal humerus, proximal femur, and pelvis are the next most common sites. The pain precedes the appreciation of the mass by a few weeks to 2 or 3 months. Boys and girls are affected with equal frequency. The patient does not have systemic symptoms and usually feels well. The mass is slightly tender, firm to hard, and fixed to the bone but not inflamed. The adjacent joint may have mild restriction of motion.

The remainder of the physical examination is normal, except in the rare (<1%) patient who presents with bone metastases or multiple focal osteosarcoma. One-half of all patients have elevated serum alkaline phosphatase (extremely high serum alkaline phosphatase values indicate a worse prognosis), and approximately one-fourth of all patients have elevated serum LDH level (an elevated LDH level also is associated with a worse prognosis). The rest of the laboratory values for blood and urine are normal.

The plain radiograph of an osteosarcoma is usually diagnostic. The typical lesion is located in the metaphysis, involves the medullary canal, is both lytic (radiolucent) and blastic (radiodense), and has an extraosseous component and a periosteal reaction suggestive of a rapid growth (Codman triangle or sunburst pattern) (Fig. 13-34A). Most osteosarcomas have a soft-tissue component, of a fluffy density suggestive of neoplastic bone, adjacent to the more obvious bone lesion. Those osteosarcomas that consist primarily of cartilage or fibrous tissue are almost purely radiolucent. Telangiectatic osteosarcoma, a histologic variant of classic high-grade osteosarcoma, may be mistaken on a radiograph for an ABC or a giant cell tumor. Usually, this will not be a clinical problem for the pathologist if the surgeon provides adequate clinical information.

MRI is the method of choice for evaluating suspected osteosarcoma. The extent of the lesion, especially the intraosseous component, is more clearly defined by MRI. The lesion can be seen in all three planes, and its soft-tissue extension is easily appreciated. It is critical that the entire bone be included on at least one plane (usually the coronal view). The tumor should be viewed with at least a T1-weighted (with and without gadolinium) image, a T2-weighted image, and a fat-suppressed image (Fig. 13-34B,C).

Osteosarcomas should be resected with at least a wide surgical margin, and the anatomic extent of the tumor is the principal determinant of what operation will be required (209). MRI is the best method of determining the anatomic extent of an osteosarcoma (Fig. 13-34D). The relation of osteosarcoma to the major neurovascular bundle should be determined. The muscles that have been invaded by the soft-tissue component should be identified. Involvement of the adjacent joint must be looked for, the intraosseous extent measured, and the presence of metastasis noted. Talking to the radiologist before MRI is performed helps to ensure that all this information is obtained.

Chest CT scan is performed because of the relatively high percentage (approximately 20%) of patients present with pulmonary metastasis (209). The lung is the most common site for metastatic involvement (osteosarcoma metastasize via hematogenous) (210, 211). The technetium-99 bone scan shows increased uptake in the area of the tumor. Occasionally it is useful in determining the intraosseous extent, although MRI is more accurate. More importantly, technetium-99 bone scanning is an excellent screen of the entire skeleton for occult bone lesions. This screening process is the most important reason for obtaining a bone scan. On rare occasions, a lung metastasis is seen on the bone scan, but usually a hot spot in the chest on the bone scan is secondary to involvement of a rib.

There are five major histologic types of conventional osteosarcoma, and each is graded for the degree of malignancy. The predominant tumor cell type determines the histologic subtype. It is debatable whether the different types have distinct prognoses (210, 211); some believe that if matched for size and histologic grade, all types have the same prognosis. Even telangiectatic osteosarcoma, which was originally described as having a particularly poor prognosis, is thought to have the same prognosis as the other classic high-grade osteosarcomas. The five types are osteoblastic, chondroblastic, fibroblastic, mixed, and telangiectatic (188, 200, 210, 212). These tumors are graded on a scale of either 1 to 3 or 1 to 4; by definition, the higher the grade is, the worse the prognosis. Most osteosarcomas are grade 3 or 4, and of the mixed type. The tumor is composed of a mixture of neoplastic cells, but must contain malignant spindle cells making osteoid. Atypical mitoses are common, and small areas of necrosis are usually seen (Fig. 13-35).

Treatment of classic high-grade osteosarcoma includes adjuvant chemotherapy and surgical resection. The standard protocol consists of chemotherapy (neoadjuvant; usually three

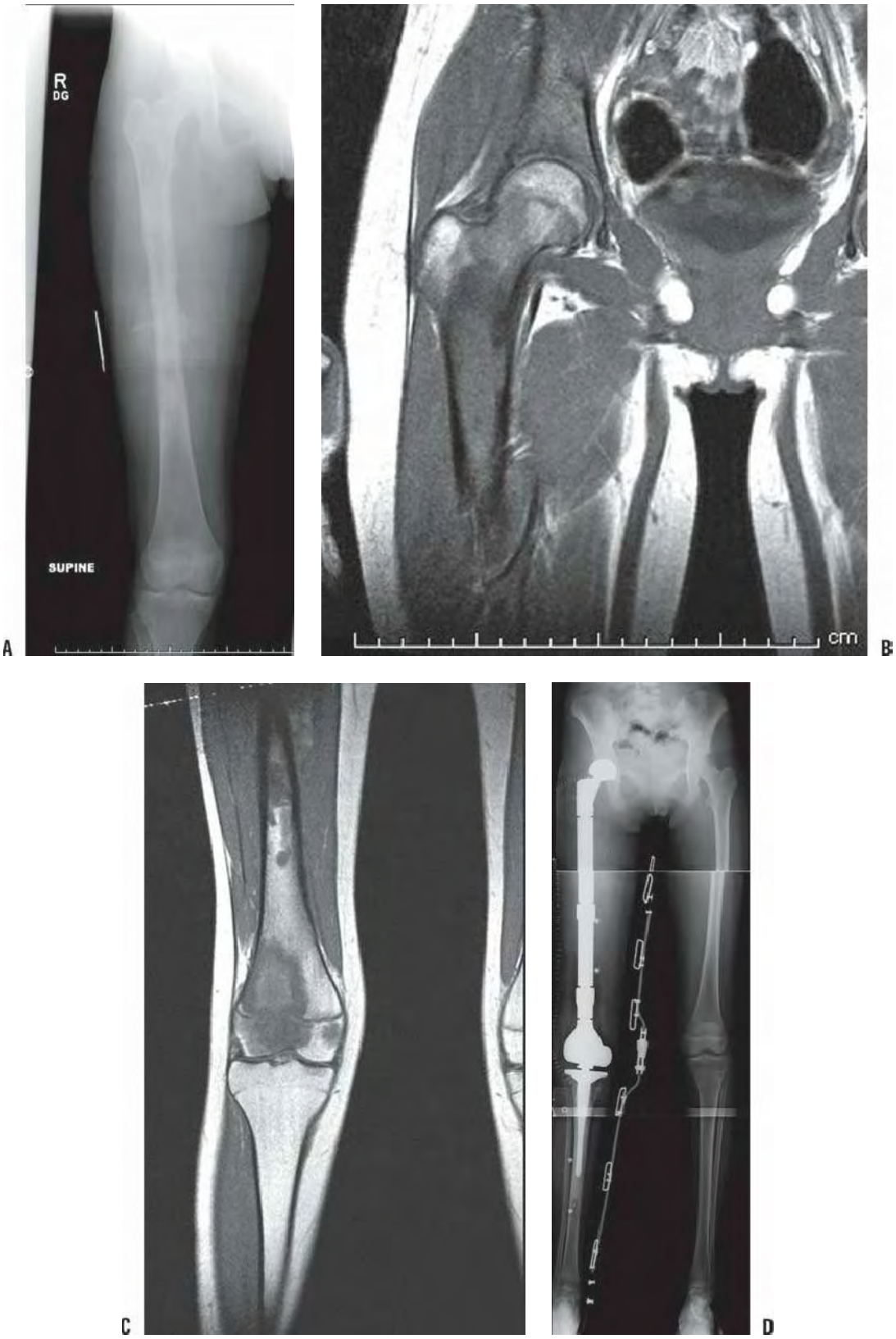


FIGURE 13-34. Hip-to-ankle anterior–posterior radiograph **(A)** of a 14-year-old girl with recently diagnosed osteogenic sarcoma. The image shows an aggressive-looking, permeative, and ill-defined mixed lesion, disorganized periosteal reaction and sunburst appearance, and associated with a soft-tissue mass. Coronal T1-weighted MRI of the proximal femur **(B)** and distal femur **(C)** shows the extension of disease, involving the entire femur. The patient underwent wide resection of the femur with negative margins and reconstruction with a total femur endoprosthesis **(D)**. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

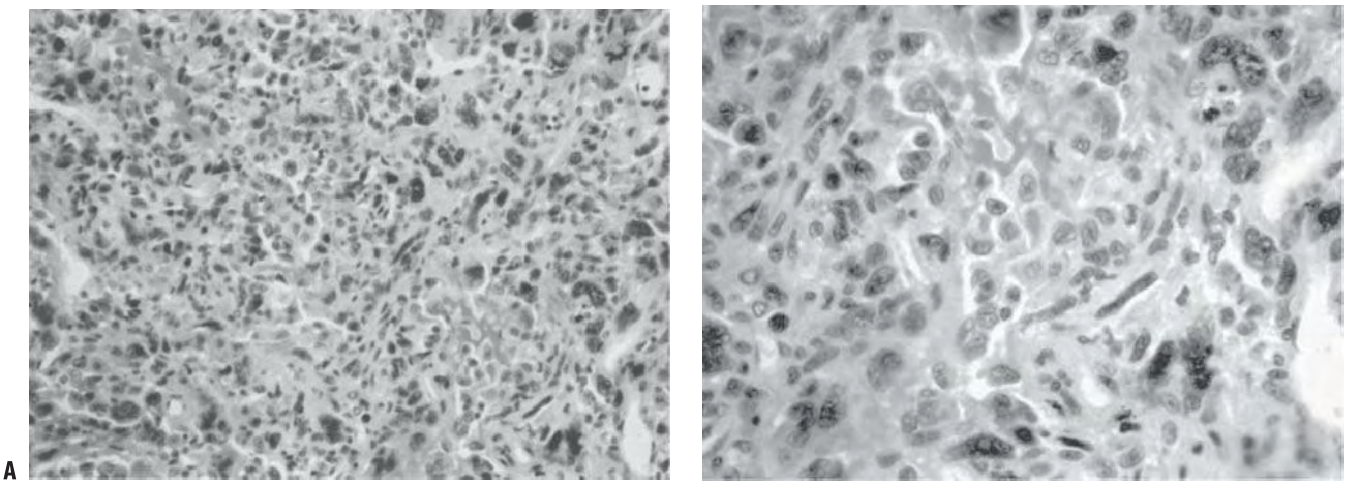


FIGURE 13-35. **A:** Typical histologic appearance of an osteoblastic osteosarcoma. There is immature bone being formed from cells that vary in size, shape, and amount of nuclear material. These findings are typical of malignant cells (10× magnification). **B:** Higher magnification (40×) of the osteosarcoma in (A). The nuclear detail is more clearly seen, and the bone seemingly coming directly from these bizarre cells makes the diagnosis of an osteosarcoma.

or four courses of a multidrug regimen), then surgical resection, and finally additional chemotherapy. The entire treatment takes almost 1 year (188, 200, 210, 212). The surgical resection can almost always be done without an amputation of the extremity, and less radical surgery is being performed now compared with only a few years ago. The use of neoadjuvant chemotherapy has not produced increased survival compared with postoperative adjuvant chemotherapy alone, but it does make surgery easier, and gives the pediatric oncologist a predictor of the patient's chance of survival (Fig. 13-36).

The three most important drugs used in the treatment of osteosarcoma are doxorubicin (Adriamycin), high-dose methotrexate, and cisplatin (188, 200, 208, 210, 212–214). Most chemotherapy protocols include these three drugs in various dosage schedules, in addition to one or more other drugs. The development of granulocyte-stimulating factor (GSF) to counteract bone marrow suppression has allowed intensification of the treatment with fewer complications; GSF is now used routinely. Overall survival has increased to more than 60%, with even better survival rates being reported for patients with >90% necrosis of the tumor after chemotherapy (182, 183).

Limb-salvage surgery is being performed for all but the largest of osteosarcomas. Amputation is done in fewer than 20% of all cases (183). The accepted incidence of local recurrence with limb-sparing procedure is between 5% and 10% (209, 215). Although the local recurrence does not seem to be directly related to worse survival, this is an area of concern, because it appears that most patients with local recurrence die of osteosarcoma (200, 215, 216). One explanation is that local recurrence is a sign of a more aggressive tumor, not solely the consequence of poor surgery. That being said, however, the insistence on wide (free) margins is paramount (50, 191, 217, 218).

There is currently some controversy about the best method of treatment for patients with pathologic fractures. There is an increased incidence of local recurrence if limb-salvage resection is performed, but this increased incidence of local recurrence does not seem to increase the risk of death (50, 191, 217, 218). The usual treatment of a patient with a pathologic fracture and

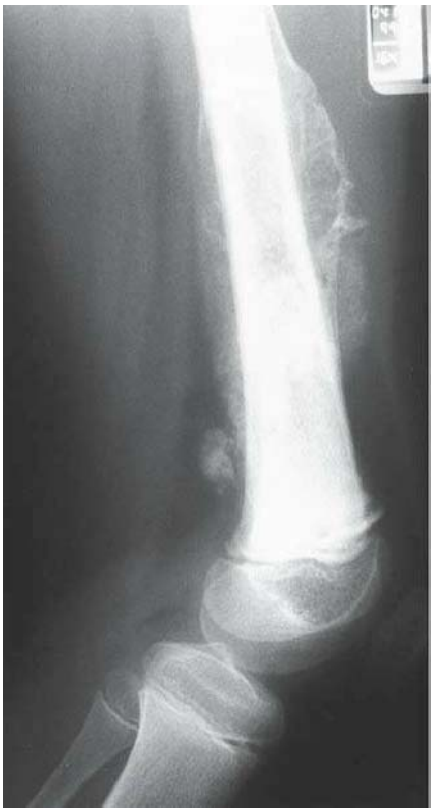


FIGURE 13-36. This plain radiograph is a lateral view of the distal femur of a patient who has had standard preoperative chemotherapy. The original lesion had a large extraosseous component that has been reduced in size, and there has been "maturing" of the periosteal reaction. The patient's pain diminished, and the range of motion in her knee returned to normal.

osteosarcoma is to treat the fracture closed (if amenable) or by minimally invasive technique (avoid further contamination), give neoadjuvant chemotherapy, and perform limb salvage if negative surgical margins can be obtained (73, 219).

Juxtacortical Osteosarcoma. Osteosarcomas that arise from or are adjacent to the external surface of the bone behave differently from those that arise from within the medullary canal (73). They are usually less aggressive locally, have less potential for distant metastasis, and occur less commonly than conventional osteosarcoma. The "old" classification divides these lesions into parosteal and periosteal; neither is common, and how distinct they are from each other remains a topic of debate. Parosteal osteosarcoma is most commonly located in the posterior aspect of the distal femur, and is composed of bone and low-grade malignant fibrous tissue. Periosteal osteosarcoma is more often located in the diaphysis of the tibia, and is composed of bone and cartilage with malignant spindle cells (220). The current nomenclature includes both types under juxtacortical, low or high grade (220).

The patient's age at presentation varies over a greater range (10 to 45 years) than in classic high-grade osteosarcoma, and the median age at presentation tends to be slightly higher (73, 219, 220). The patient usually reports a painless mass that blocks motion in the adjacent joint. This is most often knee flexion because the posterior distal femur is the most common site of a juxtacortical osteosarcoma (73, 219). Occasionally the patient has a mild, dull ache in the area of the tumor, but the symptoms are minimal. The mass is fixed, hard, and nontender. The adjacent joint may have limited passive and active motion because of the mechanical block from the tumor. Inflammation is not observed. The laboratory values of the patient's blood and urine are normal.

The plain radiograph is almost always diagnostic, but the findings may be mistaken for a juxtacortical chondroma or an osteochondroma (Fig. 13-37). The lesion arises from the cortex, which may be normal or thickened. The juxtacortical osteosarcoma often wraps around the bone, with the periosteum between the tumor and the underlying cortex. This growth pattern (wrapping around the bone) produces the "string sign" on

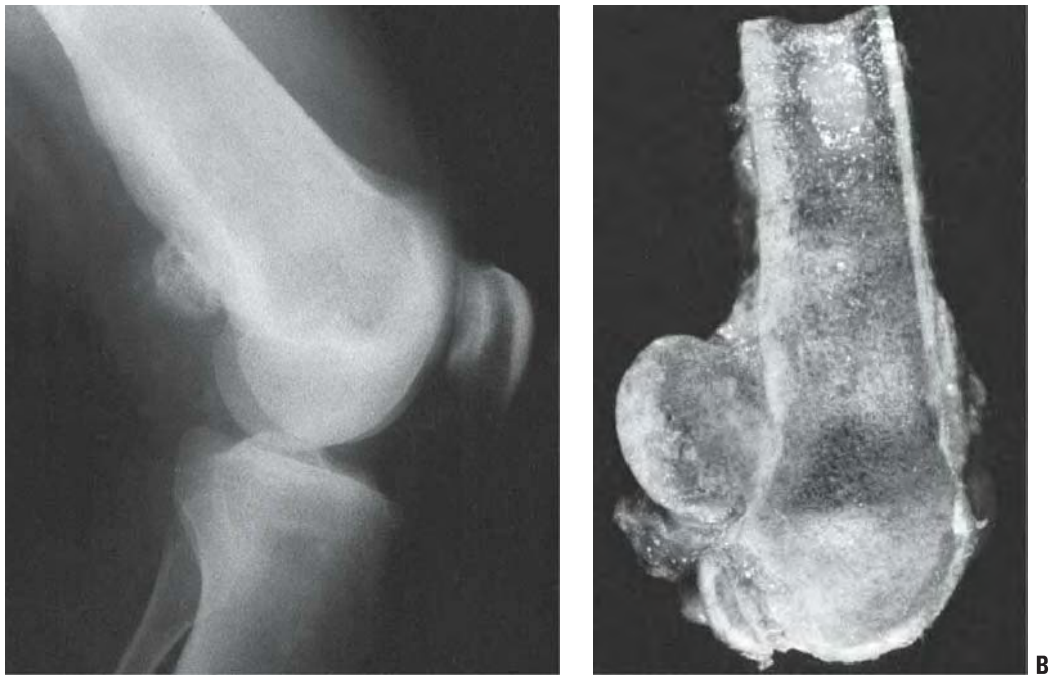


FIGURE 13-37. **A:** Lateral radiograph of the distal femur and knee of a patient with a juxtacortical osteogenic sarcoma. The posterior distal femoral cortex is thickened and slightly irregular. The radiodensity adjacent to the posterior cortex is the central portion of the juxtacortical osteosarcoma. Surrounding this bony mass is a nonossified component of the tumor, composed primarily of fibrous tissue, but with some cartilage. This patient was treated with limb-salvage wide resection of the distal femur and underwent reconstruction with an osteoarticular allograft. No chemotherapy was used since this was a low-grade tumor, and the patient has remained free of disease for 5 years. **B:** The juxtacortical osteogenic sarcoma is larger than it appears on the plain radiograph. The cap of fibrous tissue and cartilage can be seen covering the bony center. The tumor is attached to the cortex, but does not extend through it. This gross relation is similar to that of an exostosis and may lead to a mistaken histologic diagnosis. The gross difference between an exostosis and a juxtacortical osteosarcoma is that the stalk of an exostosis is cortical bone that blends with the cortex of the host bone, and the medullary canal of the stalk and host bone are connected. The juxtacortical osteosarcoma, conversely, is attached to the cortex, but the cortex of host bone is intact, and the medullary canal does not communicate with the parosteal osteosarcoma.

the plain radiograph, with a thin radiolucent line between the lesion and the cortex of the bone. The lesion itself is dense, and has the pattern of bone. There is increased uptake on a technetium-99 bone scan. The appearance of the lesion on a CT scan is characteristic and distinguishes a juxtacortical osteosarcoma from an exostosis. Juxtacortical osteosarcoma is attached to the cortex growing out into the soft tissue and may invade the cortex, but the normal cortex is intact (219, 220). An exostosis arises from the cortex, and the cortex of the normal bone becomes the cortex of the exostosis, with the medullary canal of the bone communicating with the medullary canal of the exostosis. These relations, and also the intraosseous extension of the tumor, are better seen with MRI than with CT scan.

An incisional biopsy of a juxtacortical osteosarcoma can be difficult to interpret and, on the basis of histology alone, the lesion may be mistaken for an exostosis. This is particularly true when juxtacortical osteosarcoma is not suspected by the clinician, or when the pathologist does not examine the radiograph (219, 220). This lesion, more than most other lesions, is diagnosed by its clinical and radiographic presentation and is confirmed by histology. An excisional biopsy is sometimes recommended to avoid local contamination. Higher grade lesions, especially those with medullary involvement, have a greater risk of metastasizing (usually to the lung) than those of lower grade without medullary extension (101, 219, 220).

The cortical margin should be generous and the tumor pseudocapsule should not be disturbed. When a lesion from the posterior distal femur is resected, the neurovascular bundle can usually be freed from the lesion without dissecting the pseudocapsule, but the posterior capsule of the knee and the posterior aspect of the femoral condyle must usually be resected with the tumor. Those lesions that wrap around the bone and show gross invasion of the medullary canal may require a resection that includes the entire end of the bone. The initial resection is the best opportunity to control the lesion without an amputation. Most patients do not need adjuvant chemotherapy (unless the lesion is high grade) because the cure with surgery alone is approximately 80% (221, 222).

Ewing Sarcoma/Peripheral Neuroectodermal Tumor. EWS and PNET are discussed together here because they are basically the same tumor, or are at least closely related. Both have the same chromosomal translocation between chromosomes 11 and 22, similar presentations, identical treatments, and almost identical histologic characteristics (223). PNET is also called Askin tumor and was originally identified from tumors classified as EWS. EWS/PNETs are thought to arise from the neural crest. At least 90% of them have a characteristic chromosomal translocation [t(11:22)(q24:q12)]. This translocation leads to a novel fusion protein called EWS-FLI1 (224).

Before the use of adjuvant chemotherapy, EWS/PNET was associated with a 5-year survival of approximately 15%, being considered the most lethal of all primary bone tumors (225). Before adjuvant chemotherapy came into use, most patients were treated with irradiation alone (224, 226, 227). With improved survival associated with adjuvant chemotherapy the role of surgery has been reevaluated, and there is growing evidence that surgical resection combined with chemotherapy produces improved survival rates, compared with survival after irradiation and chemotherapy (59).

Patients with EWS/PNET initially experience pain. Some have generalized symptoms of fever, weight loss, and malaise, but this is not the usual presentation. Male patients outnumber female patients by a ratio of 3:2, and most patients are between the ages of 5 and 30 years. Any bone may be affected. The femur is the most common site of origin (20%); the pelvis and the humerus are also common sites. There is usually a soft-tissue mass associated with the bone lesion, and this mass can often be palpated during a physical examination. The mass is warm, firm, and tender, and it may be pulsatile. There are no specific abnormal laboratory values that are diagnostic of EWS/PNET, but the sedimentation rate is often increased. Elevated LDH level indicates a poor prognosis (60).

The typical plain radiograph of an EWS/PNET reveals diffuse destruction of the bone, extension of the tumor through the cortex, a soft-tissue component, and a periosteal reaction (Fig. 13-38A). The periosteal reaction may produce a Codman triangle, an "onionskin" appearance, or a sunburst appearance. These suggest an aggressive lesion that has rapidly penetrated the cortex and elevated the periosteum. The extraosseous soft-tissue mass and the medullary canal involvement can be seen on CT scans and MRI scans, and are usually more extensive than what might have been expected from the appearance of the plain radiograph. MRI has proved to be more accurate than CT scan in determining the intramedullary extent of EWS. The inflammation around the tumor is seen more easily with MRI than with other studies, and the extent of inflammation is often more than would be suggested from the findings of other tests. The technetium bone scan is most useful in finding occult bone metastasis. Approximately 20% of these patients present with metastatic disease (lung is the most common site) (60, 225, 226).

The histologic appearance of EWS/PNET is that of a small, round, cell tumor. The EWS/PNET cell has a distinct nucleus with minimal cytoplasm and an indistinct cytoplasmic border. The cells are similar and mitoses are uncommon. Necrotic areas are usually seen (Fig. 13-38B,C). There are glycogen granules in the cytoplasm, and these produce the positive periodic acid Schiff (PAS) stain on routine histologic examination. The intracellular glycogen granules are diastase positive (i.e., exposure to diastase will break the glycogen down, eliminating PAS staining). Under the electron microscope, the glycogen can be seen as dense cytoplasmic granules. Increasingly, genetic analysis is being done in EWS/PNET in order to identify the 11:22 translocation as a means of establish the diagnosis.

The treatment for EWS/PNET is a combination of chemotherapy and local control, either by surgery, radiation therapy, or a combination of both (60, 225, 226) (Fig. 13-39). The drugs commonly used include vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide. Actinomycin D, a drug used earlier, is currently used less often. Most

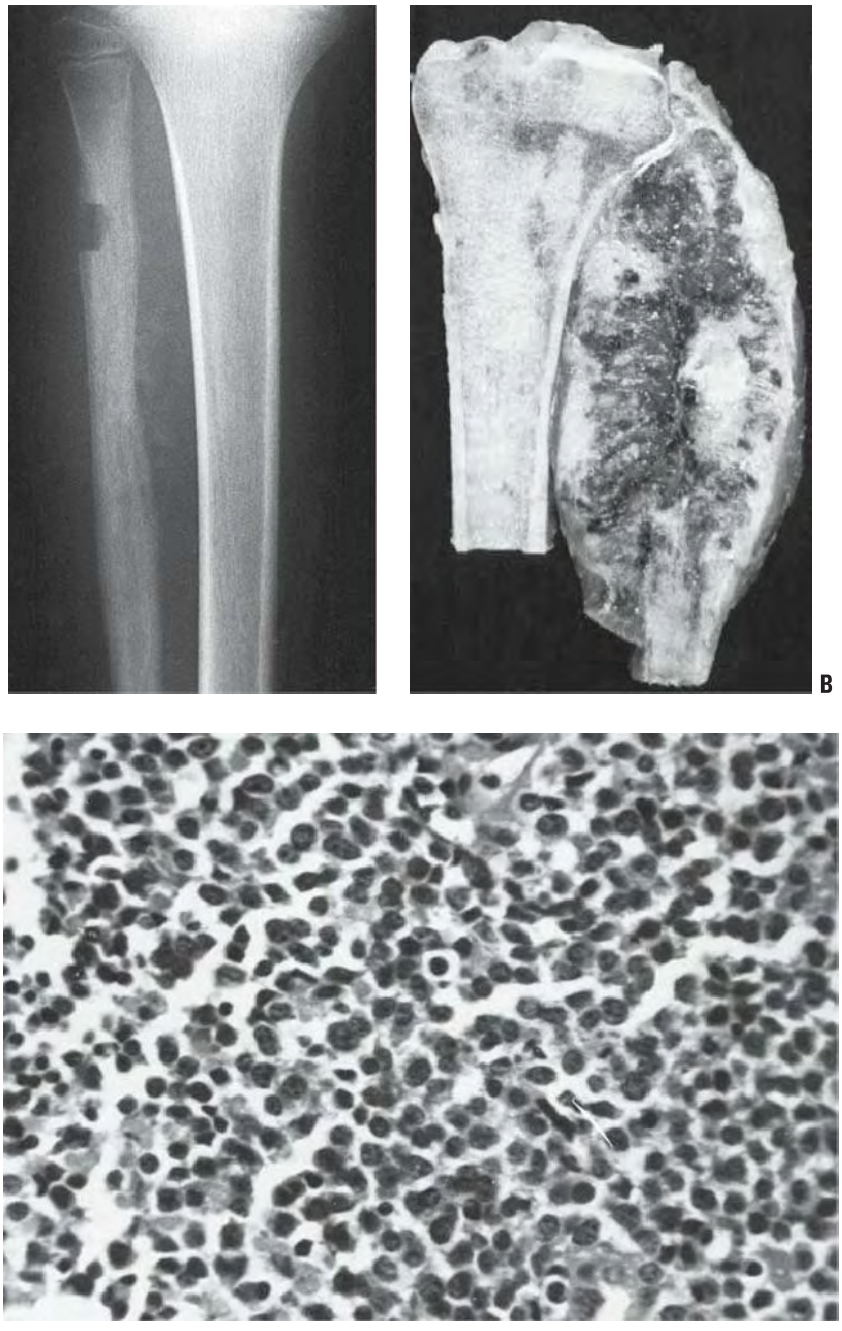


FIGURE 13-38. **A:** Anteroposterior radiograph of the proximal tibia and fibula of a patient with EWS involving the proximal fibula. The fibular cortical detail is lost, and erosion of the medial surface, soft-tissue mass, and periosteal reaction—all typical findings of EWS—are present. The combination of these findings is indicative of an aggressive process. Acute osteomyelitis may have this appearance, but the patient would usually have other signs of infection. The defect in the lateral aspect of the fibula is attributable to an incisional biopsy of the bone. A biopsy of the bone should not be performed if there is sufficient soft-tissue extension. This will lower the risk of pathologic fracture. In addition, the extraosseous tumor is usually easier to cut, and the histologic appearance is better. **B:** Gross specimen of EWS of the proximal fibula, similar to the case in A. The tumor has replaced the proximal fibula, and there is a large soft-tissue mass, with invasion of surrounding muscles and no involvement of the tibia. This patient chose to have an immediate amputation, although this is not standard treatment. **C:** Histologic appearance of EWS. The nuclei are easily seen, and there are nucleoli within each nucleus. The cells are small and round, with very little variation in appearance of the nuclei. Mitoses are rare. The cytoplasm is faint and difficult to see, and the cytoplasmic borders are poorly defined (original magnification × 10).

protocols begin with two to four courses of chemotherapy before a decision is made on how to manage the primary tumor. This usually results in a significant reduction in the size of the primary tumor. Surgical resection is recommended if the consequences of the resection (limitation or loss of function) are acceptable to the patient. If the margins are close and viable tumor is present in the resected specimen, postoperative irradiation is recommended (59, 224, 225, 227). If the primary tumor cannot be resected without undue morbidity, irradiation alone can be used (228). The total dosage should be kept as low as possible, usually around 50 Gy, and certainly <60 Gy, because dosages of more than 60 Gy are associated with an unacceptable incidence of irradiation-associated sarcomas at a later time, as well as other complications in this young age group (59, 224, 227). Current survival statistics for patients presenting without metastasis reveal a 5-year disease-free survival of >5%. Patients who present with metastasis have less chance of being cured, but should be treated aggressively because some will survive (229).

SOFT-TISSUE TUMORS

Soft-tissue tumors are a heterogeneous group of mesenchymal origin lesions that include lesions of different etiology such as congenital, traumatic, benign, and malignant neoplasms. Benign soft-tissue tumors are latent or active lesions and there are as many as 200 different types. Malignant soft-tissue

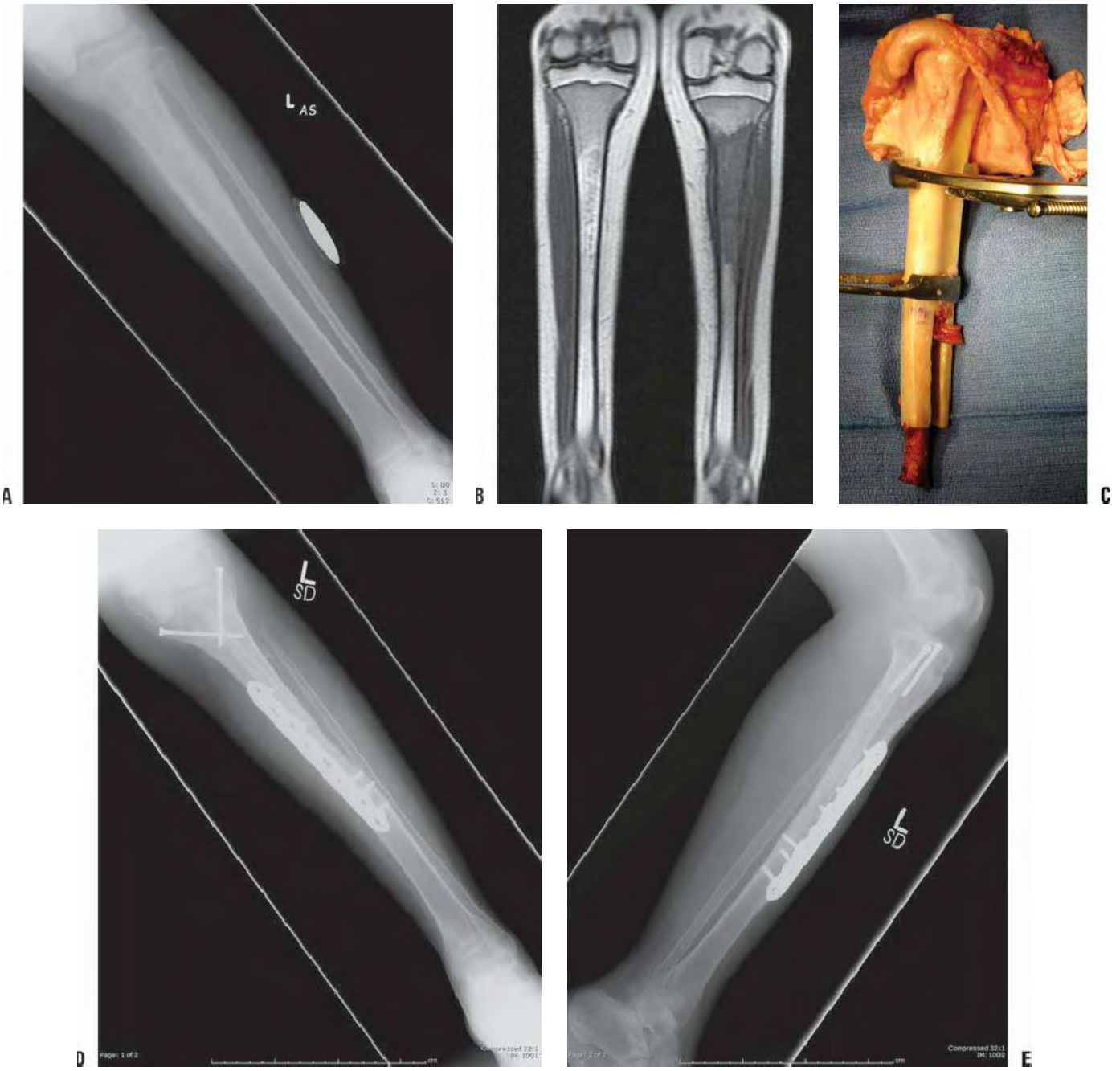


FIGURE 13-39. Ewing Sarcoma; this is the anterior–posterior radiograph **(A)** of the tibia of a 11-year-old girl who presented with a 4-month history of leg pain, demonstrating ill-defined, permeative lytic lesion with "onionskinning" periosteal reaction. After inductive chemotherapy, the tumor shrunk in size as shown in this MRI **(B),** and resection was carried out sparing the proximal tibia epiphysis. An intercalary allograft, combined with a vascularized fibula **(C)**, was performed for reconstruction and the patient is disease free and back to full activity 24 months after surgery **(D,E)**. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

tumors, in particular STSs, are aggressive tumors, capable of distant metastatic spread; there are over 70 types of STS. Most soft-tissue tumors in children are benign (230). Hemangioma, fibromatoses, and nerve tumors are probably the most common. Among malignancies, only RMS in the younger age group and synovial sarcoma in teenagers and older patients occur with any frequency, and still they are both rare tumors (231). In any instance, the physician must be aware of the possibility of malignant soft-tissue tumor in the child and evaluate any lump carefully (232).

Benign Vascular Tumors. Benign vascular tumors are common and most frequently involve the skin. Controversies exist in regards to the tumor classification and the determination between benign vascular lesions, true neoplasms, and vascular malformations. Furthermore, clinicians, radiologists,

and pathologists tend to classify these lesions differently, adding to the confusing differentiation. Understanding the differences and intricacies of vasculogenesis and angiogenesis helps understanding the differentiation between these lesions. A biologic classification, based on cellular kinetics and clinical behavior, has attempted to help resolve the confusion; there are two major categories of vascular anomalies: vascular tumors that arise from endothelial hyperplasia and vascular anomalies that arise from dysmorphogenesis (diffuse or localized errors of embryonic development) and have normal endothelial turnover (233).

Some congenital vascular malformations will not be diagnosed until later in life, suggesting a new appearing vascular tumor. Vascular anomalies can be divided into slow-flow and fast-slow lesions. They can also be divided according to their predominant vessel type (capillary, venous, lymphatic, arterial, or a combination). It is beyond the scope of this chapter to discuss vascular malformations in further detail.

Among true vascular tumors, hemangioma is the most common, particularly in infancy and childhood. Its origin is controversial. A true hemangioma is a benign lesion that often regresses spontaneously. Most are superficial lesions with predilection for the head and neck regions, but sometimes also found in internal organs, especially the liver.

Enzinger and Weiss (232) provide a classification of different forms of hemangioma that includes capillary, cavernous, pyogenic, venous, arteriovenous (racemose hemangioma), epithelioid (angiolymphoid hyperplasia, Kimura disease), diffuse or angiomatosis, and miscellaneous (synovial, intramuscular, neural). We only discuss the most common types in children.

- Capillary hemangioma (including juvenile type): Constitutes the largest group of benign vascular tumors. The juvenile hemangioma variant of capillary hemangioma occurs in 1 out of every 200 live births. They may be cutaneous or deep, and are usually seen within the first few weeks of life, often enlarging for the first 6 months but then regressing and becoming 75% to 95% involute by the age of 7 years. Capillary hemangiomas do not require treatment.
- Cavernous hemangioma: Less common than the capillary variant, but with similar age group and distribution. Cavernous hemangiomas do not spontaneously regress and may require treatment. They most commonly arise within muscle and invade tissue planes extensively. The patient often presents with complaints of swelling, tenderness, and inflammation secondary to thrombophlebitis within the hemangioma. This inflammation resolves within a few days, and can be treated with local heat and oral aspirin. The noninflamed hemangioma is soft and ill defined. The patient may have either no symptoms at all, or the sensation of heaviness or a tight feeling in the extremity. On the plain radiograph, there are often small, smooth, round calcifications called *phleboliths.* The appearance of hemangiomas on MRI is almost completely diagnostic because they are composed of smooth, regular blood vessels and normal fat. Cavernous hemangiomas have an indirect communication with the major vascular tree and do not easily fill with contrast for angiography or venography; they are better visualized with MRI. Occasionally, a tourniquet proximal to the hemangioma permits filling of the tumor veins at the time of venography or angiography. If an intravenous injection does not demonstrate the hemangioma, the dye can be injected directly into the hemangioma. Biopsy may be performed to confirm the diagnosis, but often, the clinical presentation is sufficiently characteristic to render biopsy unnecessary. Resection is not necessary unless the patient has repeated bouts of inflammation or complaints of discomfort (usually a full or tight feeling), or the parents are anxious about the mass.

Surgical excision is usually not required. When surgery is performed, the hemangioma often recurs unless the entire muscle (or muscles) involved is resected. These lesions are probably best considered as congenital abnormalities that involve most of the veins in the extremity. When the grossly involved veins are resected, the surrounding vessels dilate, resulting in clinical recurrence. Hemangiomas do not undergo malignant degeneration, and although they can produce significant abnormalities in the extremity, surgical resection is rarely curative. However, resection may reduce the symptoms. Embolization and sclerotherapy have also been used in patients who have severe pain.

Hemangioma of bone, either solitary or diffuse, is a hamartoma, and not a true neoplasm. The solitary lesions are more frequent, especially in the vertebral bodies where they are most often found (Fig. 13-40). Solitary lesions may occur in any bone, but the skull is the second most common site. These lesions do not produce symptoms and are usually found

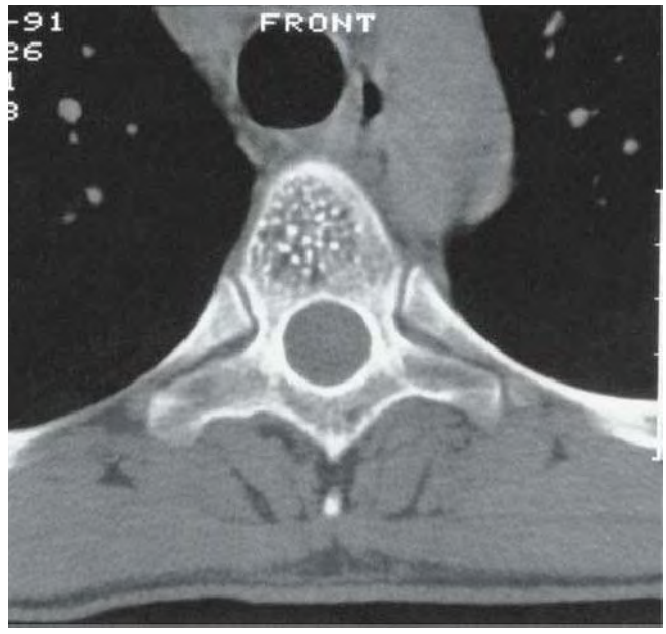


FIGURE 13-40. CT scan of a typical hemangioma of the vertebral body. The small foci of increased density are thickened trabeculae of bone, and the low-density areas are filled with the hemangiomatous tissue.

when a radiograph is taken for another reason. They are most often diagnosed in adults. The radiograph and the CT scan are diagnostic. The bone has a honeycomb appearance, with increased trabecular markings around radiolucencies.

Patients with multiple lesions are more likely to present during the first or the second decade of life, with either mild discomfort or pathologic fracture. The viscera and the skin of these patients may be involved. When multiple sites are involved, they are usually the long bones of the extremities and the short bones of the hands and feet. Treatment should be symptomatic, with curettage and bone grafting for lesions that weaken the bone. Lesions that do not produce symptoms or that are not associated with a risk for fracture should be merely observed. They usually resolve with time.

Fibromatoses. Benign fibrous lesions in children are relatively common and rarely malignant. Extra-abdominal desmoid, or aggressive fibromatosis, is the most common benign fibrous lesion seen in children (234, 235). The less common lesions are not discussed in this text and can be found in detail elsewhere (232, 236).

The patient presents with mild pain and a slowly enlarging mass. The mass is deep, firm, and slightly tender but is not inflamed. The adjacent joint is normal. Approximately 60% of the lesions involve the extremities (234, 237, 238). A soft-tissue mass can be seen on a plain radiograph, but there are no distinguishing features. Calcifications are not expected to be present within the mass.

Technetium bone scan usually shows increased activity in the lesion, but some large masses will not display increased uptake. Often, even when the lesion is immediately adjacent to the bone, there is no increased uptake of technetium. On CT scan, the mass has a density similar to that of muscle, but it is usually more vascular and can be distinguished best from the surrounding tissue by performing the CT scan with an intravenous contrast. On MRI, the classic collagen bundles produce a relative signal void (dark on T1- and T2-weighted images) but, because the cellularity varies, fibromatoses may have an appearance similar to any soft-tissue neoplasia (Fig. 13-41) (235, 239).

Histologically, fibromatosis has the appearance of scar tissue (240). It is composed of dense bundles of collagen with evenly dispersed benign cells. The cell of origin is believed to be the myofibroblast. The histologic appearance and the cell of origin of fibromatosis are identical to those of plantar fibromatosis and Dupuytren contracture, but those lesions are not as clinically aggressive as fibromatosis. Although they too recur, they do not extend proximally from the feet or hands, as they do in aggressive fibromatosis.

Wide excision is the treatment of choice; however, since aggressive fibromatosis is an infiltrative lesion, often the pathologist finds a positive margin during examination under a microscope (236). Fortunately, the presence of a positive margin at the initial resection does not always lead to a local recurrence, and it is recommended that the patient be observed for a local recurrence (234). Approximately half of the patients will develop recurrent disease regardless of the histologic margin. When lesions recur, they must be widely excised if local control is to be achieved. Patients younger than 10 years have a greater risk of developing a local recurrence than older patients. When a wide surgical margin is ensured during the resection of the recurring lesion, local control is usually achieved. When the second surgical margin is also positive on microscopic examination, radiation therapy may be considered (240–243). Most lesions will be controlled with this combination. Chemotherapy is used sometimes, especially for aggressive, nonresectable lesions. There is still debate on whether chemotherapy is efficient (234, 235, 239, 244). Fibromatosis has a variable clinical course, and the treatment needs to be individualized for each patient.

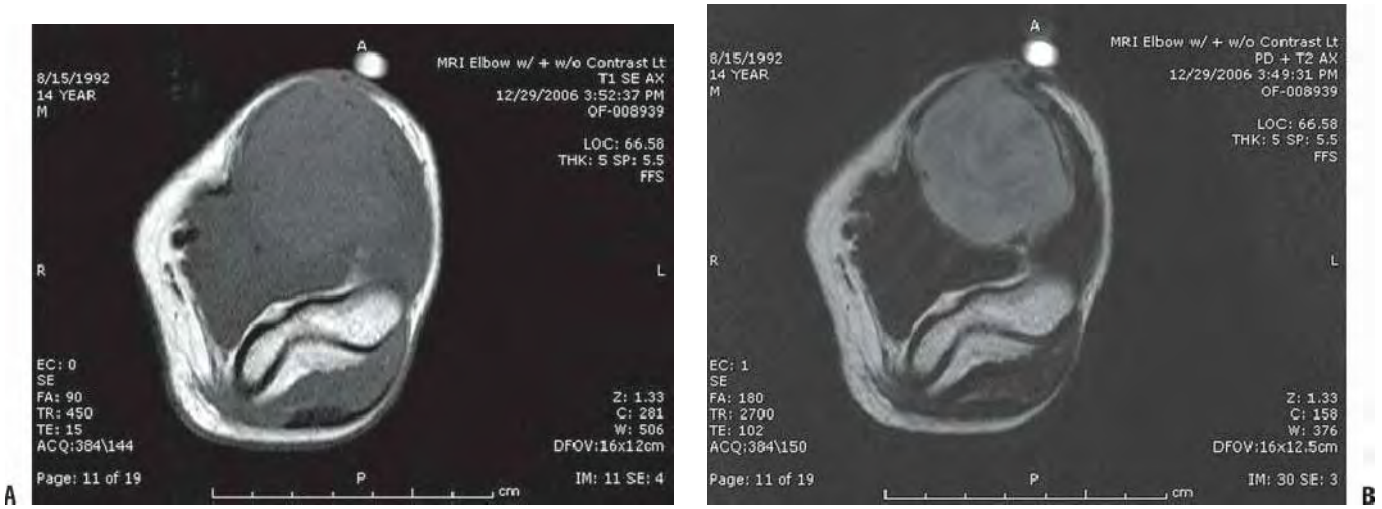


FIGURE 13-41. A 14-year-old boy presented with a slow-growing, painful mass in the anterior aspect of the left elbow. T1- **(A)** and T2-weighted **(B)** axial images demonstrate this well-defined, soft-tissue mass consistent with desmoid tumor. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

Benign Tumors of Nerve Origin. There are two common benign tumors that arise from nerves: schwannomas and neurofibroma (244). Neurilemomas, or schwannomas (now the preferred term), arise from the nerve sheath. They occur most often in early adulthood, and are usually solitary and slow growing. The patient usually presents with a painless mass, and may have a Tinel sign when the mass is tapped. The mass may be from any nerve, but it is often in the superficial tissue arising from a small sensory nerve. When arising from a spinal nerve root, the foramen may be enlarged because of the pressure of the tumor on the bone. Nerve dysfunction is uncommon, and is seen only when the nerve is compressed between the tumor and an adjacent rigid structure. Patients with superficial nerve lesions usually present early with small tumors, but deep-seated lesions may be large before they are discovered (Fig. 13-42).

Schwannomas are nodular masses with a distinct capsule and are easily separated from the nerve of origin. Under the microscope, they appear as a combination of a cellular area (Antoni A) and a myxoid area (Antoni B). The Antoni A area is composed of benign spindle cells that tend to have their nuclei stacked with intervening cytoplasm (Fig. 13-43). This nuclear stacking produces a *palisaded appearance*, and the arrangement of alternating nuclei and cytoplasm is called a *Verocay body.* The Antoni B area is composed of myxomatous tissue that has less cellularity than does the Antoni A area. Schwannomas are treated by observation, or marginal excision without sacrificing the affected nerve (244). Schwannomas do not usually recur.

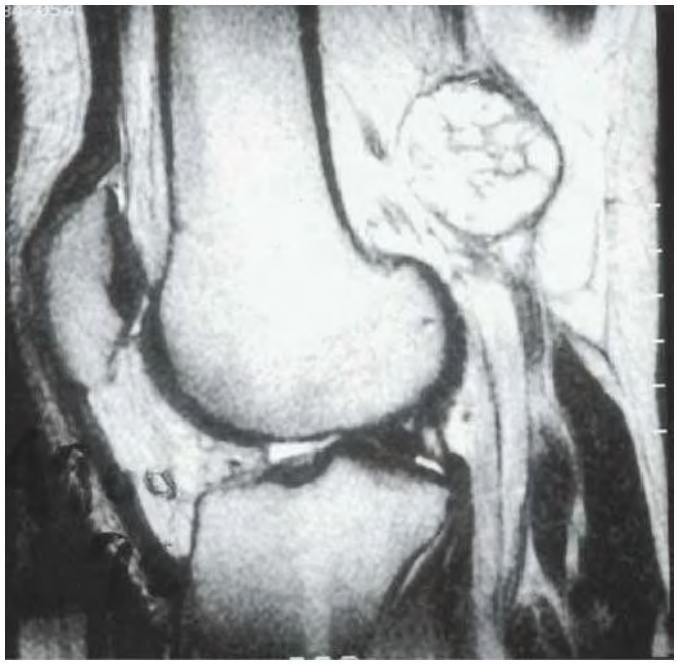


FIGURE 13-42. This is a sagittal view of a T1-weighted magnetic resonance image. The round, well-circumscribed mass posterior to the femur is within the peroneal nerve. It proved to be a schwannoma. Schwannomas have a typical appearance on magnetic resonance images. If they arise from a major nerve, as is the case in this patient, the nerve can usually be traced into the lesion. The schwannoma is smooth, slightly oblong, and has both bright and intermediate signals.

Neurofibroma may arise as a solitary lesion or as multiple lesions. Approximately 90% are solitary and are not characteristic of von Recklinghausen disease, although most patients with neurofibromatosis will have multiple neurofibromas. They may arise in the skin or be associated with a recognizable peripheral nerve. Like schwannomas, they usually present as a painless mass with a Tinel sign. Unlike schwannomas, however, they tend to be intimately associated with the nerve fibers (244). Fortunately, most arise from small cutaneous nerves and can be removed without loss of nerve function. Histologically, neurofibromas are not encapsulated, and they invade the nerve fibers and, rarely, the adjacent soft tissue. The cells are elongated and wavy, and have dark-staining nuclei. There is a collagen matrix composed of stringy-looking fibers. Neurites are usually seen within the lesion. Surgical resection is recommended for those lesions that are solitary and not associated with a major nerve. Lesions arising from a major nerve can be resected, but the nerve fascicles should be split and the neurofibroma should be removed from between them. Careful resection is important as there is an inherited risk for nerve damage and worsening of symptoms following resection (235). Neither solitary schwannoma nor neurofibroma is associated with a significant incidence of malignant degeneration, but patients with neurofibromatosis have a higher risk of developing neurofibrosarcoma.

Benign Synovial Tumors

Synovial Chondromatosis. Synovial chondromatosis is a disorder of the synovial tissues (245). It occurs most often in the knee, but can arise in any joint, tendon sheath, or bursa. Its cause is unknown, and it has no recognized familial pattern of occurrence. Although some authors believe that this is a reactive rather than a neoplastic process, it is mostly a benign metaplastic disease that has malignant potential (245, 246). The subliminal lining of the joint produces small nodules of hyaline-like cartilage that are extruded from the synovial lining to become loose bodies within the joint. If they become large, the cartilage may become necrotic; if they have blood supply, they may undergo enchondral ossification.

The disease is rare in children and presents most commonly between the ages of 20 and 50 years, slightly more common in males (245). The most common joint involved is the knee (approximately 70%), followed by hip and elbow (247). The patient usually presents with mild discomfort, minimal loss of motion, and an effusion in a joint. There may be a history of locking and previous trauma. The knee may appear normal on examination, but usually there is a moderate-to-large effusion, limited motion, and a boggy synovium.

The plain radiographs may be normal, or show only small intra-articular calcified bodies. The arthrogram is usually diagnostic, showing an irregular synovial surface and normal-to-thinned synovial fluid. MRI is most useful imaging for diagnosis of synovial chondromatosis. There are three distinct MR

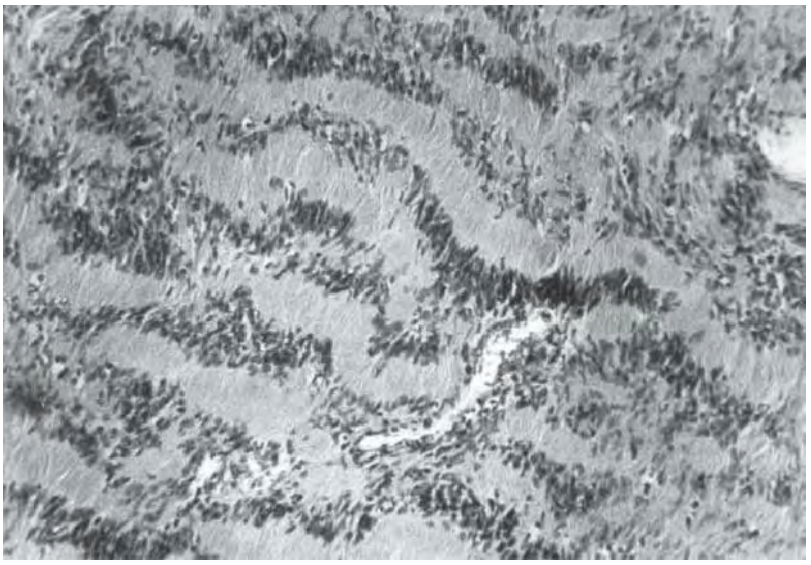


FIGURE 13-43. Histologic appearance of schwannoma (Antoni A area). The nuclei are stacked, giving the lesion a palisaded appearance (original magnification × 10).

patterns: lobulated homogeneous intra-articular signal isointense to slightly hyperintense to muscle on T1-weighted images and hyperintense on T2-weighted images; the previous pattern plus foci of signal void on all pulse sequences (corresponding to areas of calcification); and features of both patterns plus foci of peripheral low signal surrounding central fat-like signal (corresponding to areas of ossification) (245, 248).

Most patients have sufficient symptoms to require removal of the loose bodies. Usually synovectomy is performed, but recurrence is high (approximately 15%) as the synovial lining is regenerated (245). The process seems to have a limited natural course, and the production of new loose bodies ceases after 1 or 2 years. In cases with large amount of lesional tissue, resection is also recommended to avoid secondary joint destruction with degenerative arthritis; the risk of malignant degeneration (approximately <5%) is a relative indication for resection (249–251).

Pigmented Villonodular Synovitis. Pigmented villonodular synovitis (PVNS) is a rare disorder of the synovial tissues, characterized by destructive proliferation of synovial-like mononuclear cells. The synovial lining becomes proliferative and hypertrophic. It can involve a joint (most commonly the knee) or a tendon sheath (referred as to giant-cell tumor of tendon sheath). Most involvement is intra-articular, but extra-articular disease also occurs. When tendon sheaths are involved, PVNS usually occurs in the hand or the foot. Most patients with PVNS are between 20 and 40 years of age (250). The patient presents with a swollen joint that is usually painless. The synovial tissue is boggy on examination. Locking and giving-away sensation may be reported, and symptoms that mimic meniscal tear are common (252). There is a diffuse form of disease that presents with slow clinical course of insidious onset of pain, swelling, and stiffness in the involved joint, often being misdiagnosed as early osteoarthritis, rheumatoid arthritis, meniscal tear, or other ligamentous injury.

The plain radiograph is usually normal except for the soft-tissue swelling, but occasionally, the proliferative synovial tissues invade the bones adjacent to the joint. This happens most frequently when the hip joint is involved. The fluid in the joint has old, dark blood in it, and it is common for the diagnosis to be suspected first when the joint is aspirated just before the injection of contrast material for arthrography. The arthrogram or the MRI scan is diagnostic, with a thickened shaggy lining and demonstration of dark pigment signal on MRI; the high hemosiderin content causes the mass to appear as low signal on T1- and T2-weighted images. (249) (Fig. 13-44). MRI is the best radiographic method to evaluate the extent of the lesion. Bone invasion can be appreciated, as can the extent of enlargement of the synovial cavity. Gradient-echo imaging together with enhanced imaging is the most useful sequence for pediatric patients. The most common areas of involvement are the suprapatellar pouch, Hoffa fat pad, and behind the cruciate ligaments (251, 253).

Treatment varies from surgical synovectomy (arthroscopic, open, or combined) to external-beam radiation. Synovectomy is usually the treatment of choice, but there is a variable incidence of recurrence (from 8 to 50% in some series) (250, 251, 253). Anterior knee lesions, especially for localized disease are best treated with an arthroscopic synovectomy. Posterior knee lesions are difficult to approach via arthroscopic and a combined anterior synovectomy via scope combined with formal open posterior synovectomy is recommended (251). Recurrence may not warrant re-excision (decision is made upon location, size, and symptoms). Some patients have minimal symptoms and will accept the chronic swelling. As long as the bones remain uninvolved, there is no absolute indication for surgical removal (254). Malignant degeneration is exceedingly rare, but it may occur (255, 256).

Rhabdomyosarcoma. RMS is a malignant tumor of skeletal muscle. RMS is the most common STS in children with an approximate annual incidence of approximately 350 new cases in the United States (257–259). RMS is slightly more common in men and in Caucasians. The majority is sporadic; however, some will occur in association with neurofibromatosis,

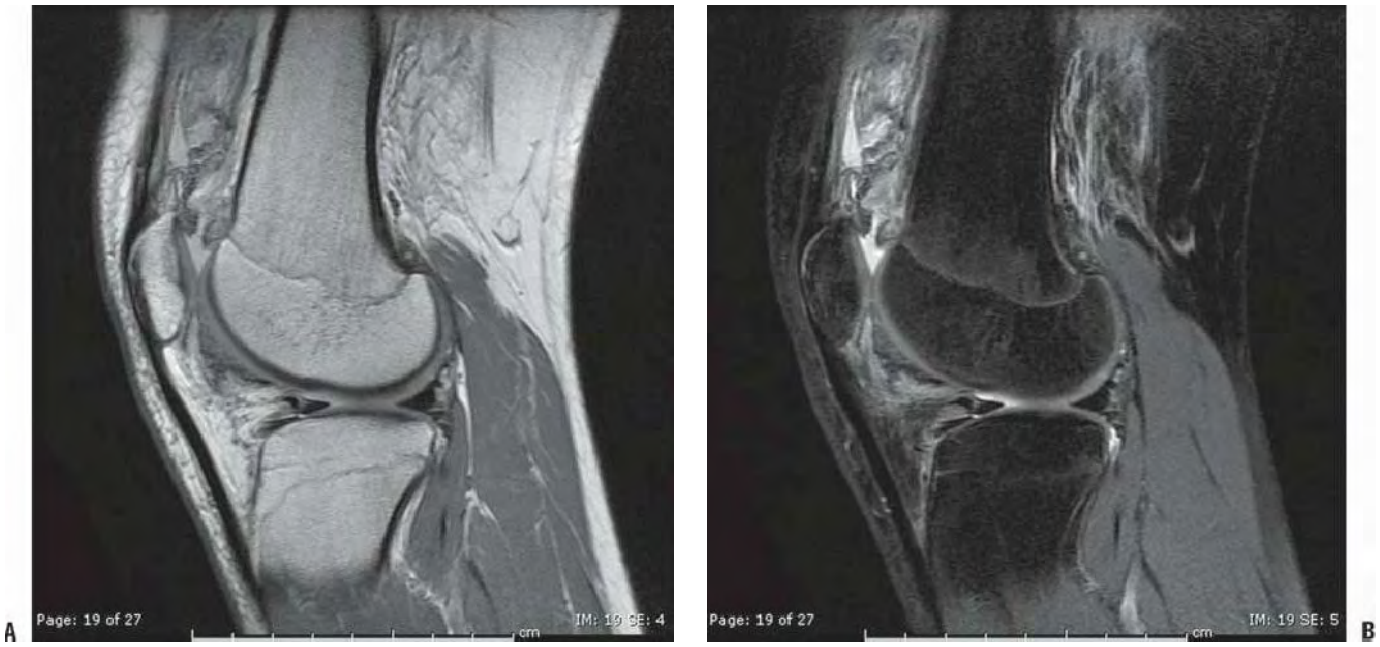


FIGURE 13-44. A 14-year-old boy presenting with knee pain and swelling. Sagittal T1- **(A)** and T2-weighted **(B)** MRI demonstrate the classic appearance of PVNS with dark/ dark intensity. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

Beckwith-Wiedemann syndrome, Li-Fraumeni disease, Costello syndrome, and others. There are four histologic patterns: embryonal, botryoid type, alveolar, and pleomorphic (260, 261).

Embryonal RMS is the most common type, and usually arises in the head, neck, genitourinary tract, and retroperitoneum. It is rare in the extremities. Botryoid-type RMS is histologically identical to the embryonal pattern, but is considered as a separate entity because of its appearance on gross examination. A botryoid RMS is an embryonal cell type that involves a hollow viscus. Botryoid RMS tends to occur in the first decade of life. The histologic appearance of embryonal RMS can vary (262). This lesion consists of poorly differentiated rhabdomyoblasts with limited collagen matrix. The rhabdomyoblasts are small, round-to-oval cells with dark-staining nuclei and limited amounts of eosinophilic cytoplasm. Cross-striations are not seen regularly.

Alveolar RMS is more common in the extremities than in the trunk, and is seen in older children and young adults, usually between 10 and 25 years of age (263). Characteristic chromosomal abnormalities [t(2;13)(q35;q14) and t(1;13)(p36-q14)] have been identified. Approximately 70% of the tumors will have a translocation between chromosomes 13 and 2, whereas another 30% will have the translocation between chromosomes 13 and 1. This occurs with equal frequency in the upper and lower extremities. Alveolar RMS is composed of small, round-to-oval tumor cells loosely arranged together in groups by dense collagen bundles. This arrangement of cells in groups produces an alveolar appearance; hence the name. The patient presents with a rapidly growing deep mass within the muscle (Fig. 13-45).

Pleomorphic RMS is the histologic type seen in adults, and it is the least common. It represents <20% of all cases. It is of difficult differentiation from EWS, neuroblastoma, and melanoma. Pleomorphic RMS has the worst prognosis.

The current treatment is a combination of chemotherapy, surgery, and, if the malignancy is not totally excised, irradiation (235, 254). When chemotherapy is given preoperatively, the surgery required is less radical, and adequate surgical margins are more easily achieved. If the lesion is small, it should be totally resected initially. If an RMS lesion occurs in an extremity, preoperative chemotherapy should be considered. A wide surgical margin is recommended (264). Regional lymph is sometimes indicated. Preoperative irradiation is reserved for lesions that would require an amputation in order to obtain a wide margin. Postoperative irradiation is used when the surgical margins are positive for tumor (265, 266).

The Intergroup Rhabdomyosarcoma Committee, with representation from both the Pediatric Oncology Group and the Children's Cancer Study Group, has been the dominant group treating RMS in the United States. Their coordinated efforts have resulted in major advances in the management of this malignancy (235, 266). Their staging system for patients with RMS is currently in use (267, 268). Prognostic variables include histologic subtype, size of the tumor, site of the tumor, and age of the patient (235, 263, 265, 267). Alveolar subtype, larger tumors, patients older than 10 years, and extremity tumors are associated with a poor prognosis (263, 265, 267, 268). Therefore, the patients that the orthopaedist treats tend to do worse than those treated by the urologist and the otolaryngologist. Better prognosis and improved 5-year overall survival (OS) is seen with younger age (ages 1 to 4 years: ~80% OS) at diagnosis, localized disease (approximately 80% OS),

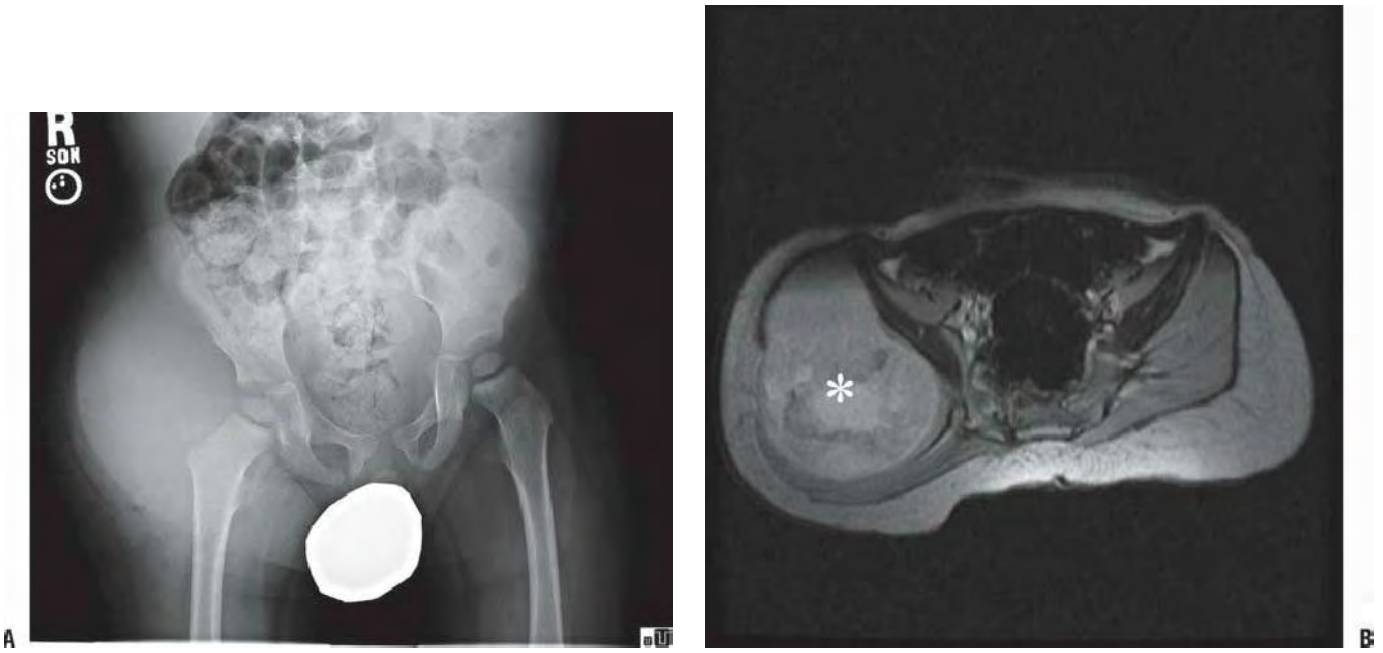


FIGURE 13-45. This is a 5-year-old boy with a large alveolar RMS of the right buttock. Plain radiograph **(A)** shows the soft-tissue shadow, and axial cut MRI **(B)** clearly demonstrates the large, infiltrative mass, located deep within the gluteus musculature (*).

embryonal histology (approximately 70% OS), orbital (approximately 85% OS) and genitourinary (approximately 80% OS) tumors (86, 98, 268–270).

Synovial Sarcoma. Synovial sarcoma is a malignant soft-tissue tumor of cell of unknown origin. It is not related to the synovium, and the term synovial *cell* sarcoma should be avoided. It is the most common non-RMS STS in young adults, it accounts for 10% of all STSs. It has a typical chromosomal translocation, t(x;18)(p11.2;q11.2). Most patients are between 15 and 35 years of age, with male patients being slightly predominant in number. Approximately 75% occur in the extremities with a tendency to develop near large joints (most commonly the knee) (Fig. 13-46). Less than 10% are intra-articular and it is the most common sarcoma of the foot.

Patients often experience pain before they have palpable masses, and many patients give a history of having pain for 2 to 4 years before the lesion was found. Other patients have a palpable mass that has not grown in many years, and suddenly it starts increasing in size. The usual physical finding is a firm, slightly tender mass. Up to 25% of these patients have metastasis to regional lymph nodes, and the lymph nodes should therefore be examined carefully. The patient's blood and urine laboratory values are usually normal.

The lesion may occur in any part of the body. The head, neck, and trunk account for approximately 15% of the lesions, whereas the upper and lower extremities account for more than 50%. Almost 10% of the lesions occur in the hands or feet.

Synovial sarcomas may have calcifications or ossifications within the tumor, and these are often seen on plain radiographs. Neurofibrosarcoma and fibrosarcoma also may have intralesional calcification, but synovial sarcoma is the most common tumor with intralesional densities. The radiodensities are usually very low. Small, irregular calcific foci, or irregular ossification within a soft-tissue tumor, should suggest the diagnosis of synovial cell sarcoma. The CT scan demonstrates a soft-tissue mass, with calcified densities deep within the tumor. Although the small foci of calcification or mineralization are not seen as well with MRI as with CT scan, MRI is preferred to CT scan as the staging test.

The characteristic translocation t(X;18;p11;q11) creates a gene fusion SYT-SSX1 or SSX2. Patients with SSX2 seem to have a better prognosis at least in a small series of patients. At a histologic level, synovial sarcoma can be monophasic with epithelial or spindled cells (more often SSX2); or biphasic with epithelial and glandular-like differentiation (predominately SSX1) (100). Usually, the spindle cell component predominates (Fig. 13-47). Synovial sarcoma is almost always a high-grade STS.

Surgical resection has been and continues to be the principal treatment for synovial sarcoma. Adjuvant chemotherapy is used, but the data regarding its efficacy in synovial sarcoma are equivocal at best. In adults and older children with synovial sarcoma, as in those with other STSs, radiotherapy is considered in conjunction with nonradical surgery in an attempt to salvage the extremities. It used to be thought that the scarring from irradiation precluded its use in the feet and hands but, but with modern techniques, adjuvant irradiation and marginal resection can be performed in most sarcomas of the feet or hands, with preservation of the functioning of the extremity. Radiation may improve local control, but the impact in overall survival is questionable (86, 270, 271).

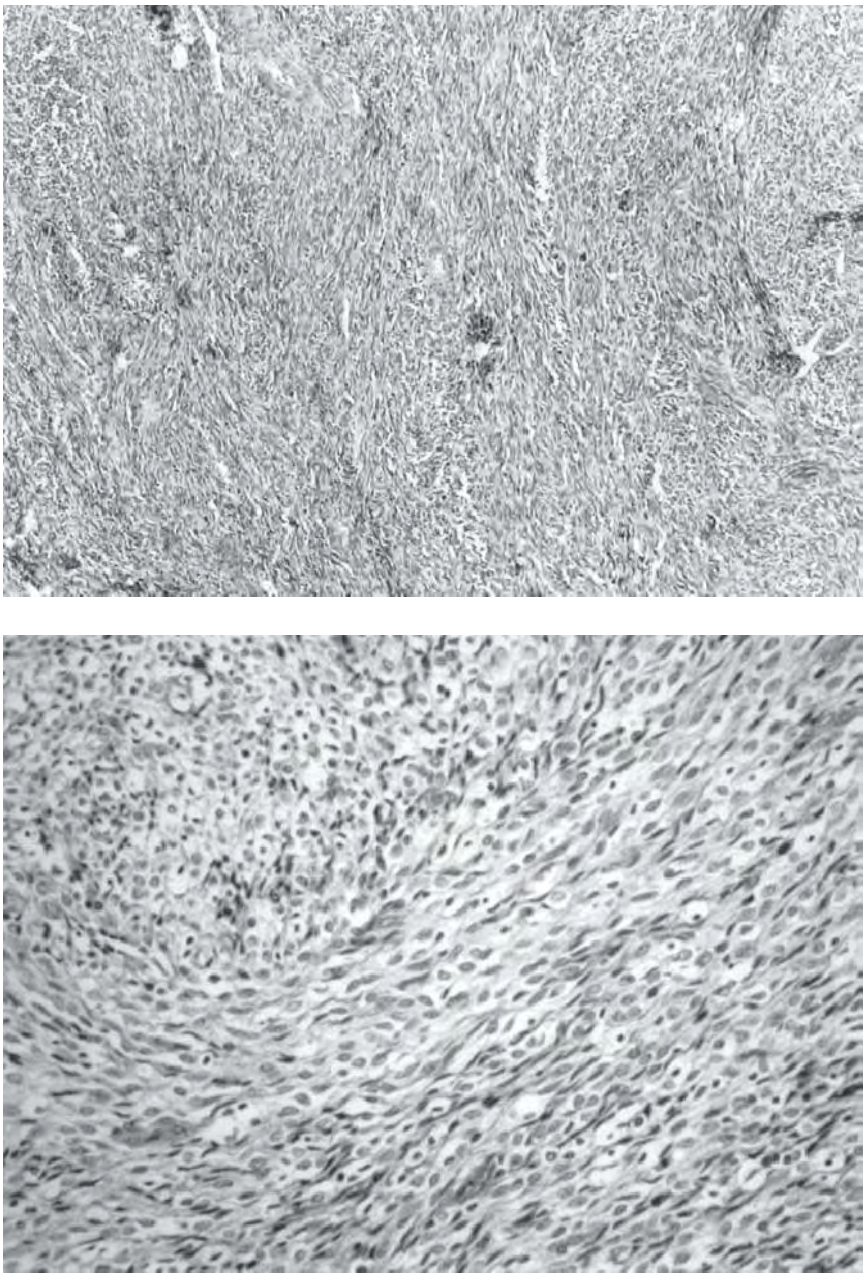


FIGURE 13-46. **A:** Low-power view of the spindle component of a synovial sarcoma. This lesion is composed of malignant spindle cells with a minimal amount of matrix. At a higher power, mitotic figures are seen. Other areas of this tumor have a glandular appearance, which is why synovial sarcoma is a biphasic tumor (original magnification ×10). **B:** Synovial sarcoma does not arise from within joints. It may be monophasic to biphasic. This is a monophasic synovial sarcoma. It is composed of fibrous stroma cells with minimal matrix formation. As can be seen in this image, the direction of the fibers is often at right angles, so that there are areas where the fibers run horizontally (**center**) and other areas where the fibers run vertically (**lower right**) (original magnification ×40).

In a large study including only young patients, the overall survival among 219 patients at 5 years was 80% ± 3% and disease free-survival 72% ± 3%; the incidence of local recurrence 14% at an average 1.3 years, and 42% developed distant recurrence. Among the identified prognostic factors were invasiveness, Intergroup Rhabdomyosarcoma Study (IRS) group, age, metastasis at presentation, margins, and size (272, 273).

Infantile Fibrosarcoma. Congenital or infantile fibrosarcoma (IFS) is the most common STS in children below 1 year of age. It is different than the adult countertype (fibrosarcoma) in that it has a more benign course and very low metastatic potential (approximately 10%) (272–274).

Although wide resection is preferred, due to the relative low risk of metastatic dissemination and the usual young age at presentation, IFS may be treated by a "conservative" surgical management and positive margins may be accepted (95). Late recurrence does not seem to affect survival and there are few reports of spontaneous regression of incompletely excised IFS (95, 272, 273). It is still unclear how effective chemotherapy is; however, it is usually used for large and unresectable lesions (275).

Malignant Peripheral Nerve Sheath Tumor. Malignant peripheral nerve sheath tumor (MPNST) is a malignant nerve tumor that may arise *de novo* or from a neurofibroma; they do not arise from schwannomas. MPNSTs have previously been called neurofibrosarcoma. They represent approximately 5% to 10% of all NRSTS in children, and may occur sporadically (50% to 80%), or in association to neurofibromatosis type 1 (NF-1) (20% to 50%). Interestingly, only 2% to 13% of children with NF-1 will develop MPNST (104).

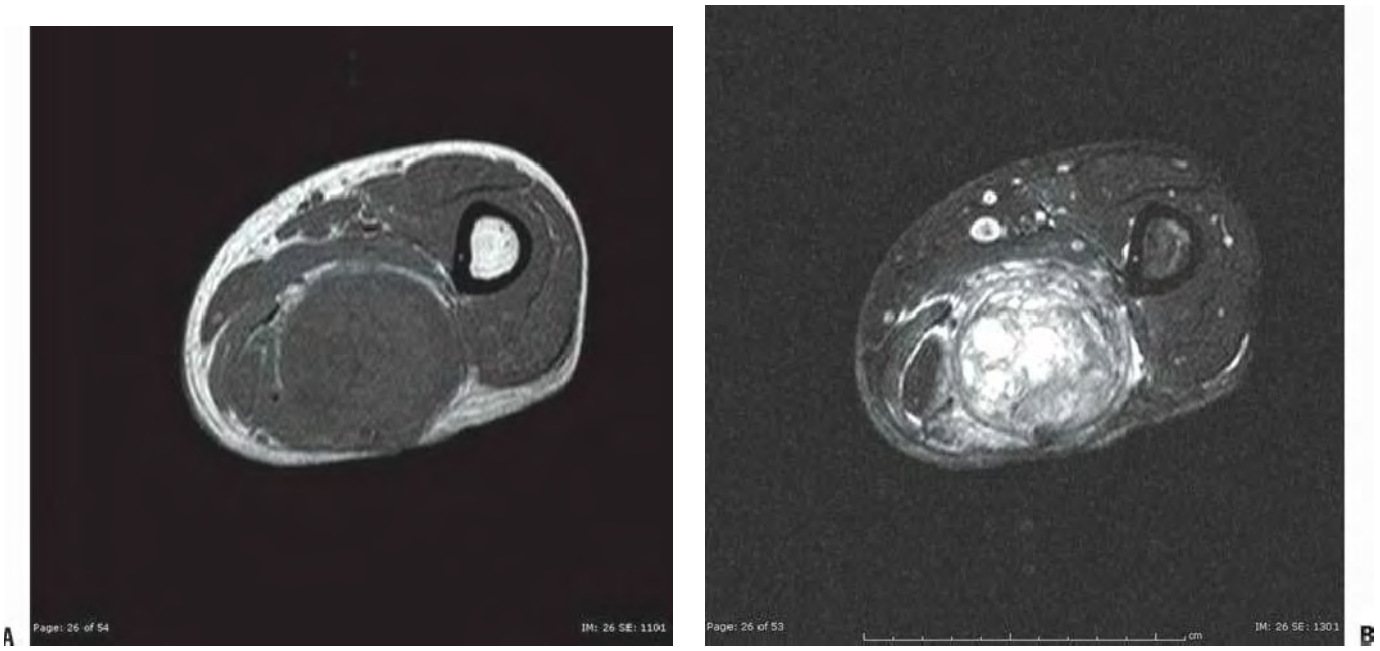


FIGURE 13-47. MPNST; An 18-year-old male with NF-1 and a rapidly growing mass. T1- **(A)** and T2-weighted **(B)** MRI shows the large mass within the sciatic nerve. The gross specimen is shown **(C)**. (Reproduced with permission from The Children's Orthopaedic Center, Los Angeles, CA.)

MPNSTs may also develop at the site of prior radiation. The clinical presentation is one of a slow-growing mass, initially painless but that usually becomes painful as it grows. The tumor usually arises from small peripheral nerves, but at times major nerves can be involved (Fig. 13-47).

Local control of MPNST is best achieved by surgery; chemotherapy is often used for systemic control and radiation can be used both pre- and postoperatively, especially for positive margins. A large study including 167 patients with MPNST showed that NF-1 was present in 17%, there was a good response to chemotherapy in 45%, radiation decreased local recurrence and IRS staging correlated with survival, 82% and 26% at 5 years for IRS I and IRS V, respectively (104, 275, 276). Among the poor prognostic factors are early age at diagnosis, NF-1 positive, large and high-grade tumors.

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