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Seminars in
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Benign Osseous Tumors and Tumor-Like Conditions

Tamara Miner Haygood, PhD, MD and Behrang Amini, MD, PhD

We will provide an imaging-focused discussion of 3 benign bone tumors that do not fit in the categories of cartilaginous tumors or osteoid tumors. We have chosen giant cell tumor of bone, unicameral bone cyst, and fibrous dysplasia. All 3 of these entities are common enough that one does not have to be a musculoskeletal radiologist in a cancer hospital to encounter them occasionally, but none of them should be seen frequently.
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Introduction

This article discusses 3 benign osseous tumors, giant cell tumor, unicameral bone cyst, and fibrous dysplasia. They were chosen because (1) they are common enough that radiologists in a general practice or in a subspecialty other than musculoskeletal imaging will likely encounter them at least every few years but (2) they are not so common as to be mundane in their familiarity. We hope to provide some helpful information that is not widely known outside of oncologic practices, and we ask your indulgence if this article seems to have turned into a treatise on denosumab. The authors do not hold stock in Amgen, Inc.

Giant Cell Tumor of Bone

Giant cell tumor (GCT) of bone typically occurs in skeletally mature young adults, with the peak age range between 20 and 45 years. It most often occurs in the ends of long bones, with the distal femur, proximal tibia and distal radius being the 3 most common sites, in that order. It is the only tumor that especially prefers the distal radius. It can also occur in the axial skeleton, such as in the spine, sacrum, and pelvis.

Radiographically, GCT is lucent (Fig. 1) with well-defined, nonsclerotic margins. There is no radio-opaque matrix, though there may be some spared trabeculae or ridges of cortex. It starts in the metaphysis, but by the time it is discovered it is almost always within a centimeter of the articular cortex of the nearest joint. Lesions in the proximal femur may approach the cortical surface of the greater trochanter rather than the articular surface of the femoral head, as the greater trochanter is an epiphyseal-equivalent location. GCT is often expansile and results in remodeling and thinning of the overlying cortex. In the long bones, it is usually eccentric.

Although GCT is generally considered to be benign, it is not a no-touch lesion. It presents with pain and swelling and is accompanied by enough bone destruction to place many patients at risk for pathologic fracture, a complication that occurs in up to 20% of patients.[1]

GCT occasionally metastasizes, nearly always to the lungs (Fig. 2). The metastatic rate has ranged from 1% to 9% in various series.[2-4] Lung metastases tend to be slow-growing and to retain their benign histologic appearance. The majority of pulmonary metastases will be discovered within the first 3 years after discovery of the primary tumor, but they have also been reported to occur nearly 12 years after diagnosis.[3]

Development of lung metastases may be more common with primary tumors in the radius (up to 38%) than in any other location,[2] although this finding has not been consistently reported.[3] Between 54% and 71% of patients with lung metastases have local recurrence at the site of the original tumor.[2,3] Outcomes in patients with pulmonary metastases are reasonably favorable, although a minority of patients may succumb to the metastases. Complete resection of the metastases may be curative.[2,3] Lung metastases in GCT tend to be well-defined round or oval masses with a predisposition to the peripheral and basilar parts of the lungs. On pathologic examination of nodules, ossification of nodules can be

Department of Musculoskeletal Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX.
Correspondiing author: Tamara Miner Haygood, PhD, MD, Department of Musculoskeletal Imaging, Unit 1475, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. E-mail: Tamara.Haygood@mdanderson.org

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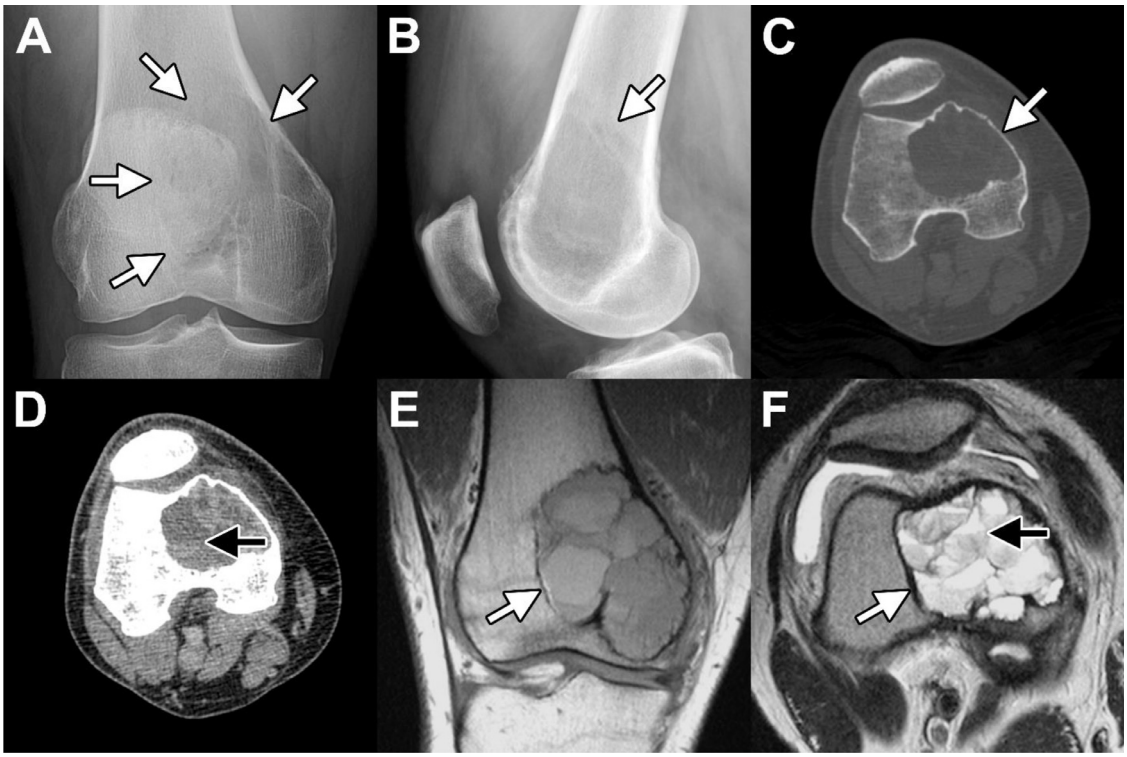

Figure 1 Thirty-year-old man with GCT of the distal femur. Frontal (A) and lateral (B) radiographs show a lucent lesion with well-defined, nonsclerotic margins (white arrows) and no internal matrix mineralization. Axial CT images with contrast using bone (C) and soft tissue (D) windows show thinning of the medial cortex (white arrow) and fluid-fluid levels due to internal hemorrhage (black arrow). Coronal T1-weighted MR imaging (WI), (E) shows a lesion with a low-signal hemosiderin rim (white arrow) and internal high signal related to hemorrhage. Axial T2-WI (F) shows the low-signal hemosiderin rim (white arrow) and fluid-fluid levels (black arrow).

seen in more than half of all cases. Mineralization is typically not apparent on conventional radiographs but may be seen on CT (Fig. 2).[2]

The primary treatment for GCT is curative surgery, either excision or curettage. Curettage (Fig. 3 A and B) can be used with accessory treatments to try to decrease the chance of recurrence. These accessory treatments include high-speed burring, intralesional treatment with phenol, ethanol, or liquid nitrogen, and filling the lesion with polymethylmethacrylate cement. The recurrence rate after surgery (Fig. 3C) can be as high as 15%-50%.[5] Some studies have suggested a higher recurrence rate for curettage than for en bloc resection, though in a meta-analysis of literature on curettage for GCT, Errani et al found that the type of surgery, including the use of any of the adjunctive treatments, was not significantly associated with the recurrence rate.[6] Recurrence tends to be more common with lesions in the distal radius and proximal femur.[5,6]

GCTs contain osteoclast-like multinucleated giant cells, mononuclear cells derived from macrophages, and oval or spindle-shaped stromal cells. The osteoclast-like cells are thought to be responsible for the resorption of normal surrounding bone.[5,6] The stromal cells are considered to be the neoplastic component because they can form tumors in mice and can also be maintained and will proliferate in culture

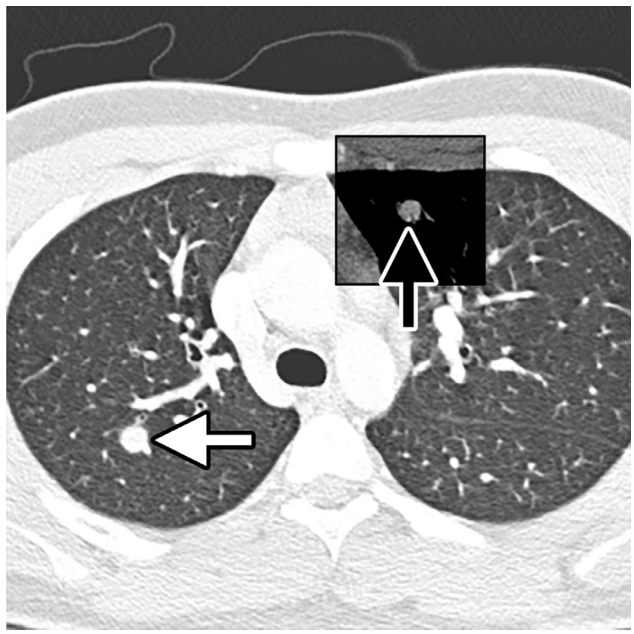

Figure 2 Fifteen-year-old boy with GCT of the pelvis and lung metastases. Axial CT of the chest shows 2 of the patient's pulmonary metastases (arrows). The soft tissue window inset of the left upper lobe nodule shows a small focus of peripheral calcification (black arrow).

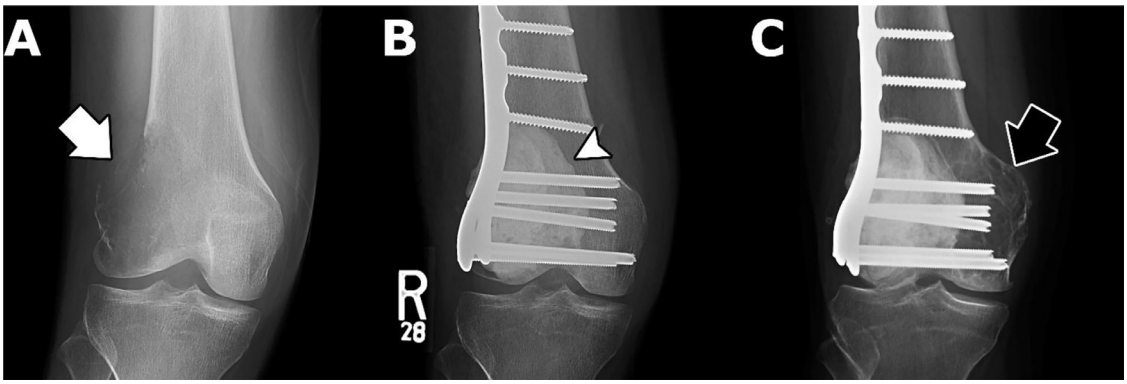

Figure 3 Twenty-year-old man with recurrent GCT of the left distal femur. Initial frontal radiograph (A) shows a lytic lesion with destruction of the lateral cortex of the lateral femoral condyle (white arrow). Postoperative radiography (B) shows that the lesion was treated with curettage, polymethylmethacrylate cement packing (arrowhead), and lateral plate fixation. Frontal radiograph 4 years after surgery (C) shows new lucency with interval cortical expansion in the medial femoral condyle representing recurrent disease (black arrow).

systems.[7,8] The stromal cells are believed to attract monocytes to their location. They also over-produce nuclear factor kappa-B (RANK) ligand. RANK ligand then plays a role in inducing fusion of the monocytes to form the multinucleated giant cells and in activating the giant cells to produce the factors that degrade the surrounding bone and create the lytic lesion that is typical of GCT.[8]

Denosumab is a human monoclonal antibody that was approved by the US Food and Drug Administration in 2013 for use in GCT when the tumor is unresectable or when resection would be accompanied by severe morbidity.[4,8] Denosumab binds to RANK ligand released from the stromal cells. It then prevents the binding of the RANK ligand to receptor sites on the monocytes that function as precursor osteoclasts. This, in turn, inhibits the fusion and maturation of the precursor cells into multinucleated osteoclast-like cells and therefore decreases bone breakdown.[8,9] In this way denosumab inhibits the maturation and action of the osteoclast-like cells in GCTs and prevents enlargement of the area of lytic bone destruction. Denosumab use is also associated with differentiation of the neoplastic stromal cells into non-neoplastic bone components including woven bone, bone matrix, and even mature bone.[10]

Denosumab has been shown to improve the imaging appearance of GCT (Fig. 4). Engellau et al studied the imaging response in 190 patients who had participated in either one of 2 trials of denosumab for GCT. They found that 136 of 190 patients had an objective tumor response by imaging criteria. There was also improvement on positron-emission tomography (PET)/CT in 25 of 26 patients who had PET/CT scans performed.[11] The responses were generally sustained. Over two-thirds of the patients had a response that lasted at least 24 weeks.[11]

Response on imaging includes development of sclerosis around the periphery of the intraosseous portion of the tumor (Fig. 4). This is most easily assessed on CT. It is evident subjectively, but it can also be assessed more quantitatively using histogram analysis of density. This more quantifiable approach to evaluation of sclerosis has potential for use as a response criterion in clinical trials as well as in everyday practice.[12,13]

On 18-F-fluorodeoxyglucose PET/CT there is a reduction in hypermetabolism of lesions with denosumab use (Fig. 4).[11,14] Others have suggested bone mineral density determination using dual-energy X-ray absorptiometry for evaluation of efficacy after denosumab treatment of GCT. A group of 3 patients all experienced a distinct increase in bone mineral density in the area of the tumor following treatment.[15]

A primary use of denosumab is in shrinking inoperable tumors so they can be resected. Zhang reported denosumab use as preoperative adjuvant therapy in 11 patients with unresectable or recurrent GCTs. Denosumab improved symptoms, shrank the tumors, and made surgical resection or curettage possible and/or easier. Three of the 11 patients experienced recurrence during follow-up. The sole recurrence in an extremity lesion was treated by en bloc re-resection. Both patients with sacral recurrences declined further surgery and went back on denosumab with stabilization of their lesions.[16] Denosumab can also improve symptoms. Its use often decreases pain, and several authors have reported improved function and mobility.[10,13,17]

It is not clear whether denosumab use can decrease the likelihood of local recurrence. Jamshidi et al performed a meta-analysis of literature including a total of 714 patients and found a local recurrence rate of 2%, which is below the usual reported rates that typically range up to 50% or even higher. This does suggest some efficacy in preventing recurrence. Unfortunately the follow-up period in the studies ranged from 6 to 30 months. Some of the larger studies were among those with shorter lengths of follow up. As GCT can recur a few years after treatment, one can imagine that there would be additional recurrences in some of these patients. Jamshidi et al were themselves unwilling to ascribe

effectiveness in preventing recurrence to denosumab.[18] Denosumab can also be helpful in shrinking and stabilizing pulmonary metastases from GCT (Fig. 4).[19-21]

There are case reports of denosumab apparently achieving clinical cure of GCTs, although with persistent deformity of the involved bone. Bilgetekin et al reported a 19-year-old patient whose sacral GCT was treated surgically but without complete resection. Repeat resection was expected to be unacceptably morbid, so denosumab treatment was attempted. After 18 months of therapy, active tumor was in remission. Denosumab was continued for 42 months then stopped when the patient needed to undergo an unrelated dental procedure. Eleven months later there was no further recurrence.[9] Complete resolution (except for remaining

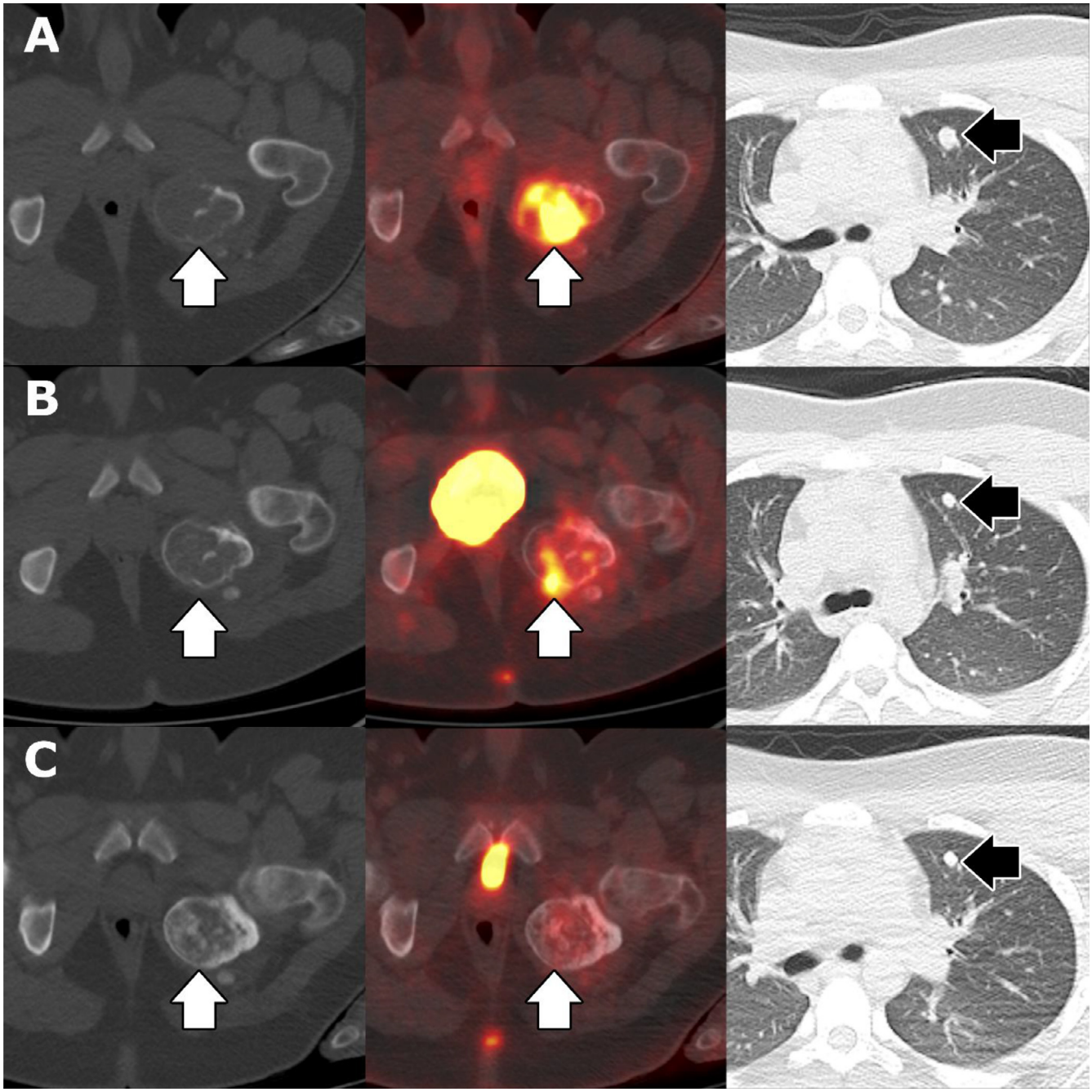

Figure 4 Twenty-year-old man with GCT of the left ischium and pulmonary metastases. FDG PET/CT bone window, fused bone window and chest images at baseline (A) compared with similar images from serial scans at 3 months (B) and 5 months (C) following initiation of denosumab show increasing mineralization and decreasing FDG uptake of the primary lesion (white arrows) and decreasing size of the pulmonary nodule (black arrows).

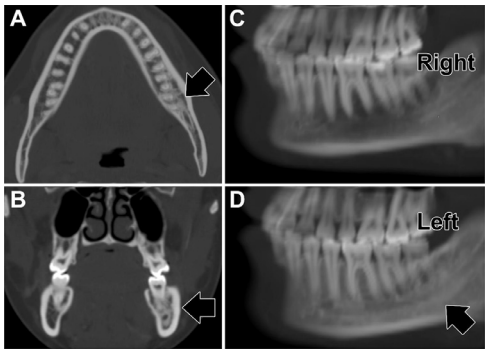

Figure 5 Twenty-five-year-old woman with GCT of the sacrum who developed drug-related osteonecrosis of the jaw 4 years after initiation of denosumab. Axial (A) and coronal (B) CT images show increased sclerosis at the site of osteonecrosis of the left mandible (arrows). Virtual radiographs of the right (C) and left (D) mandible acquired from CT images shows increased sclerosis of the left (arrow) in comparison with the normal right mandible.

osseous deformity) of a GCT in the C2 vertebra of a 22-year-old woman after 16 months of denosumab treatment has also been reported.[22]

Although it is clear that denosumab can be effective against GCT, the main remaining question is, when can the drug be stopped? Palmerini et al conducted a study partly aimed at answering this question with patients in Bologna, Italy, and Santa Monica, California. Patients with GCT that was either unresectable or in whom resection would result in severe morbidity were treated with denosumab according to a typical dosing schedule. Forty-three of 97 patients were eventually able to undergo resection after a median time on denosumab therapy of 12 months and were excluded from the long-term follow-up data.[23] Of the remaining 54 patients, all, even the 14 patients with lung metastases, saw disease improvement. At the time of publication, 34 patients were still on denosumab. The median time on denosumab was 54 months. Although, as mentioned elsewhere in our paper, there are patients who have achieved lasting control after stopping the drug, Palmerini found that, of the 10 patients who had discontinued denosumab treatment for one reason or another and for whom follow-up information was available, 4 had suffered disease progression at a median interval of 8 months following stoppage of the drug. They suggested careful follow-up of at least 2 years for patients who have stopped denosumab.[23]

Many patients tolerate denosumab without complications, but there are exceptions. One serious complication is osteonecrosis of the jaw (Fig. 5). This can also occur with bisphosphonate therapy, and at an approximately equal rate. A combined analysis of 3 trials that compared subcutaneous denosumab with intravenous zoledronic acid (a type of bisphosphonate) for treatment of patients with osseous metastases from solid tumors or with myeloma found that 1.3% of those who received zoledronic acid and 1.8% of those who received denosumab experienced osteonecrosis of the jaw.[24] Atypical femoral fractures, better known as a complication of bisphosphonates, can also be seen with denosumab use (Fig. 6).[25]

In a multicenter trial involving 532 patients at 30 sites, Chawla et al found osteonecrosis of the jaw to occur in 3% of patients. Other adverse side effects of denosumab included pain in the extremities, joints or back, headache, fatigue, and hypophosphatemia. One percent of their patients developed sarcomatous transformation of their GCT, but that proportion was not higher than would be expected without denosumab treatment, because GCT is known occasionally to undergo malignant transformation (Fig. 7).[5] Chawla et al concluded that the risk-to-benefit relationship for denosumab was favorable.[5]

Sampling error in biopsy may cause a giant-cell sarcoma or a giant-cell-rich osteosarcoma to be mistaken for a benign GCT of bone. Denosumab is not an effective therapy for these lesions. So if a lesion that is thought to be a GCT continues to grow while the patient is on denosumab, one should consider the possibility that it is really a giant-cell sarcoma or a giant-cell-rich osteosarcoma.[26]

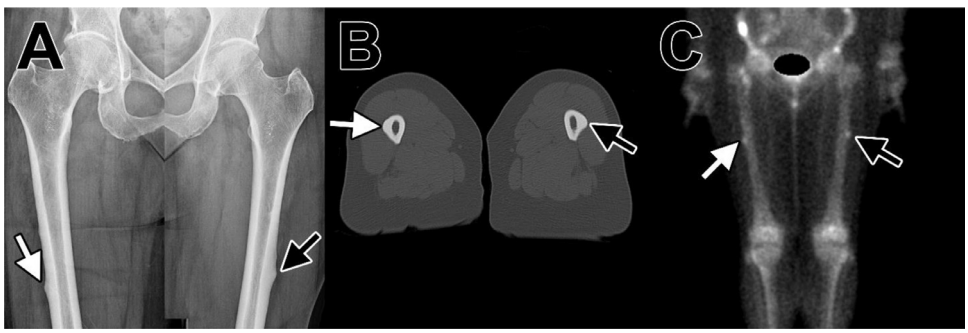

Figure 6 Sixty-five-year-old woman with metastatic breast cancer, receiving denosumab. Composite frontal radiographs of the right and left femora (A) show focal thickening at the lateral cortices of the femora indicating insufficiency response without discrete fracture lines (arrows). If neglected, they may progress to complete fractures. Axial CT images of the thighs (B) show the foci of cortical thickening to better advantage (arrows). Frontal projection of ^{99m}Tc MDP bone scan (C) shows corresponding increased tracer uptake (arrows). There are also scattered sites of uptake related to bone metastases in the pelvis and proximal right femur.

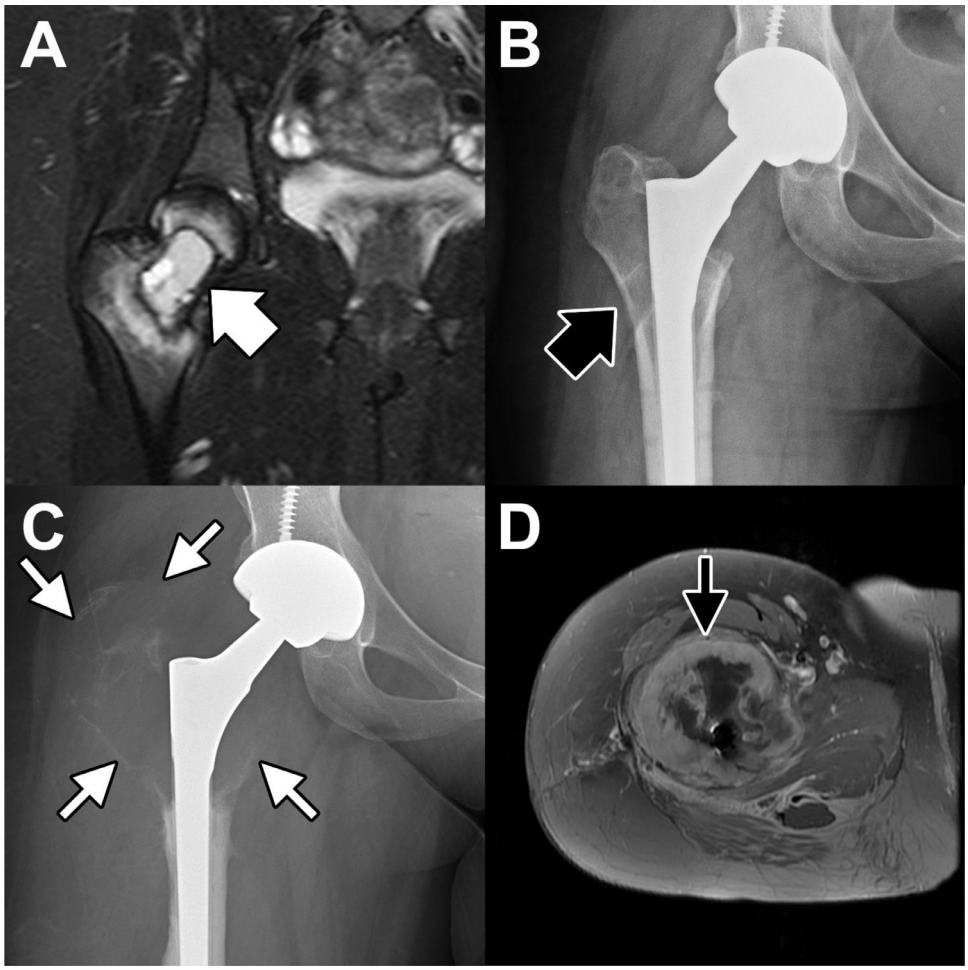

Figure 7 Twenty-five-year-old woman with GCT of the right femoral neck and subsequent malignant transformation into an osteosarcoma. Short tau inversion recovery (STIR) coronal MR image at presentation (A) shows a hyperintense intramedullary lesion with a low-signal hemosiderin rim and adjacent marrow edema (large white arrow). Postoperative radiography (B) shows that the femoral neck was initially stabilized with a dynamic hip screw that was removed (large black arrow points to ghost track) and subsequently replaced by total hip arthroplasty. Radiography 1 year later (C) shows an expansile, destructive lesion arising from the proximal femur (small white arrows). Axial contrast-enhanced T1-WI (D) shows the peripherally enhancing/centrally necrotic osteosarcoma (small black arrow) extending into the soft tissues from the proximal femur.

Denosumab is not the only drug that may be efficacious against GCT. Bisphosphonates also suppress osteoclast activity and inhibit tumor growth in several forms of cancer. Dubey and colleagues tested 3 monthly doses of intravenous zoledronic acid, a type of bisphosphonate, as a preoperative adjunct in 15 patients with GCT. As compared with an equal-sized control group, the patients who received the bisphosphonate experienced a decrease in pain. At surgery their tumors showed an increase in peripheral sclerosis, and an increase in apoptosis. The size of the tumors did not change.[27]

In summary, GCT is a fairly common lesion that should be considered when one encounters either a well-defined metaphyseal lesion extending into the epiphysis or an expansile pelvic lesion in young adults. A variety of therapeutic regimens are available, and careful attention to postoperative imaging is needed to assess for recurrence following definitive therapy.

Unicameral Bone Cyst

A unicameral bone cyst (UBC), also called a simple bone cyst or solitary bone cyst, is a benign lucent lesion that occurs in typical locations that vary depending on the patient's age. Eighty-five percent (85%) occur in children or adolescents, with the typical range being 3-14 years old, and the mean age being 9. They are more common in boys than girls. The proximal femoral lesions tend to occur in older children and the humeral lesions in younger children. Of the lesions occurring in children, 90% are in the proximal humerus or proximal femur. They are the most common benign bone lesion in children and adolescents.[28]

Although they are benign, UBCs can cause problems. They are associated with pathologic fracture and may be painful, even in the absence of fracture. Partly because of the associated fractures, they can lead to limb-length discrepancies or deformity.[28]

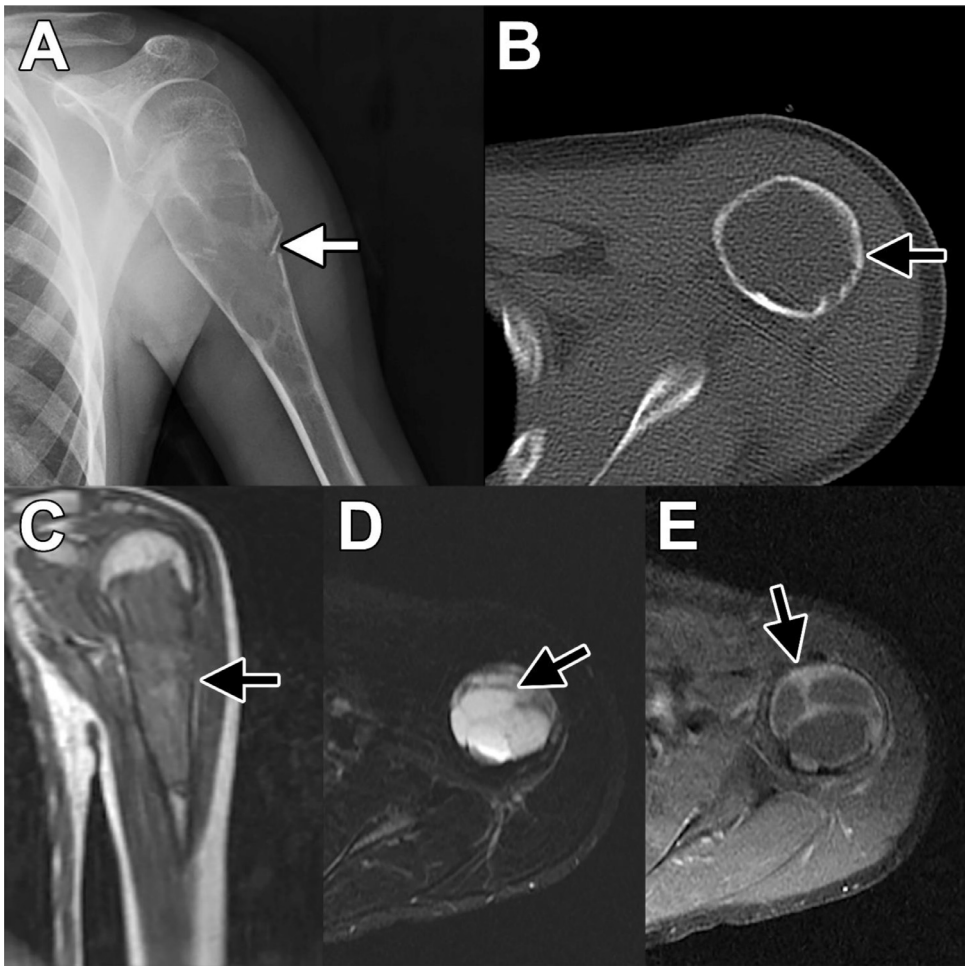

Figure 8 Ten-year-old boy with a UBC of the left proximal humerus. Frontal radiograph (A) shows an expansile lesion with a pathological fracture (white arrow). Noncontrast axial CT image (B) shows a fluid-attenuation lesion with expansion and thinning of the cortex (black arrow). Coronal T1-WI (C) shows an intermediate signal lesion with areas of internal high signal corresponding to hemorrhage due to the pathological fracture (black arrow). Axial T2-WI with fat saturation (FS), (D) shows a hyperintense lesion with internal septations (black arrow). Axial FS T1-WI postcontrast (E) shows a predominantly nonenhancing lesion with peripheral and septal enhancement (black arrow).

In children, unicameral bone cysts usually arise in the metaphysis of long bones. In the femur, they generally occur in the metaphyseal equivalent region next to the greater trochanteric apophysis. As the bone grows, the cyst is left behind and gradually appears to move into the diaphysis.[29] The cyst, of course, does not actually move, rather it stays in the same place while the bone grows (Fig. 9F — the remainder of this figure is introduced later in the article, during a discussion of therapy). Unicameral bone cysts are more likely to be symptomatic when they are closer to the physis. They are considered "active" when they are within a centimeter of the physis and "inactive" when they are farther away. When symptoms occur, they are usually due to a pathologic fracture through the cyst.

The cause of simple bone cysts is uncertain. Of the various explanations that have been proposed, obstruction of venous drainage appears to be the favored etiology.[30]

Conventional radiography is the typical way to diagnose and assess UBCs (Fig. 8). The lesions are centrally located within the marrow cavity. The cortex may be thin and mildly expansile. They usually have well-defined margins.[30] As the cortex remodels and expands, its thickness may be better preserved in some areas than in others, so the cyst may appear to have more than one locule.[30,31] If a fracture has not occurred, these cysts are often found incidentally when imaging for another reason.[29]

If a fracture has occurred, it is possible for a comminuted fragment to fall into the cyst. As the cyst is fluid-filled, the fragment will then fall to the dependent side of the lesion, leading to the fallen fragment (or fallen leaf) sign.[31] In our experience, this appearance is relatively uncommon. It can also be problematic to distinguish a fallen fragment from one that is in place. Using different positions to see if the fragment moves can be helpful, but it will be painful for the child

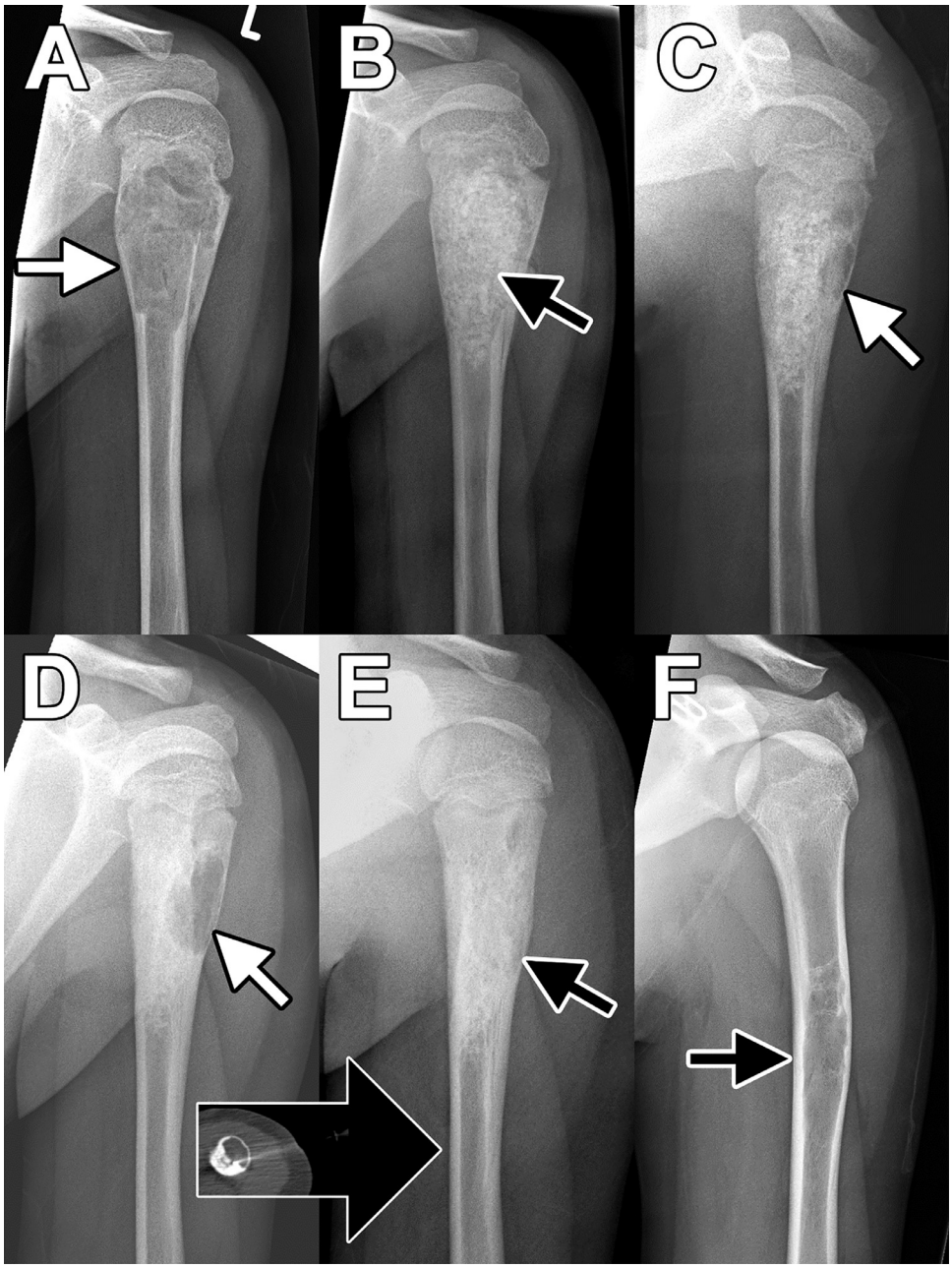

Figure 9 Seven-year-old girl with UBC of the left proximal humerus. Initial radiograph (A) shows an expansile lesion (white arrow) with a healed pathological fracture. Radiography following curettage and bone grafting (B). The morselized bone graft material is indicated by the black arrow. Imaging 2 months after surgery (C) shows a developing lucent area laterally (white arrow) representing recurrent disease. Imaging 4 months after surgery (D) shows enlargement of the recurrent lesion (white arrow). Steroid injection was performed (inset is an image from the CT-guided procedure). Imaging 3 months after steroid injection (E) shows early reconstitution of trabeculae (black arrow). Imaging 5 years after steroid injection (F) shows a healed lesion (black arrow) that is now located in the proximal to mid diaphysis due to bone growth. There is minimal residual deformity of the lateral cortex.

to be moved around, and it will expose the child to additional radiation. Therefore, we do not recommend attempts at identification of a potential fallen fragment. UBCs may resemble fibrous dysplasia or aneurysmal bone cysts on conventional radiographs.[29] Nonethless, the radiographic appearance of the lesion is typically so characteristic that biopsy confirmation is sometimes a formality.

On magnetic resonance imaging (MRI) an uncomplicated UBC, one which has not undergone pathologic fracture or previous treatment attempts, should have homogenous fluid-intensity signal within it, approximately isointense to muscle on T1 weighting and bright on T2 weighting. With gadolinium administration there should be enhancement in a thin rim around the periphery of the lesion without frank

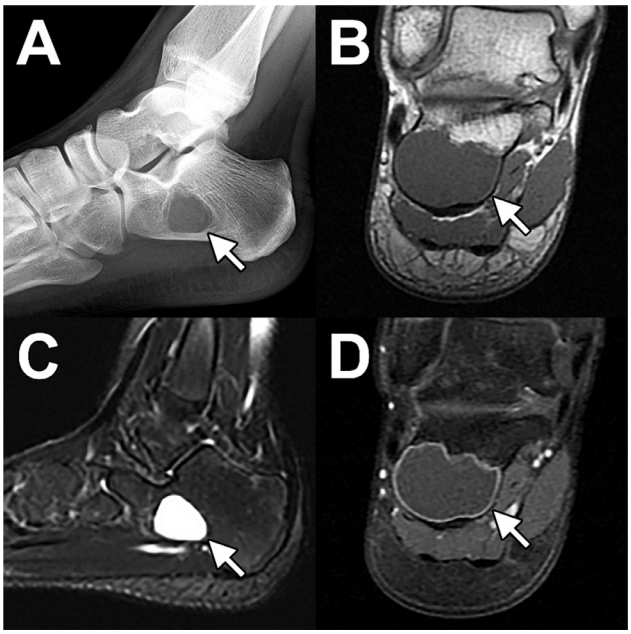

Figure 10 Twelve-year-old girl with a calcaneal UBC (arrows). Radiography (A) shows a well-defined lytic lesion with no internal matrix (arrow). The lesion has uniformly low signal on T1-WI (B, arrow) and uniformly high signal on FS T2-WI (C, arrow). There is a thin rim of peripheral enhancement on postcontrast images (D, arrow).

nodularity. There may be 1 or 2 fluid/fluid levels, and there may occasionally be a septation.[29,31] T1-weighted MRI can be superior to conventional radiography in predicting fracture risk.[32]

Various treatments are possible for UBCs. They include resection, injection of steroids or with bone marrow (Fig. 9), fenestration of the walls of the cyst to reduce internal pressure, and curettage, often with placement of bone graft or calcium sulphate pellets.[29] Surgeons may also inject doxycycline. If there is excessive fracture risk, other methods may be used including placement of cement within the cyst cavity and stabilization with metal fixators. Post-treatment radiographs are used to assess the success of treatment. Their appearance will vary depending on the nature of the treatment as well as its success or failure. In general, however, healing of the cyst creates thickening of the cortex and a generalized increase in the density of the lesion. Over years this will result in remodeling so that the site of the one-time cyst resembles normal bone more closely. If calcium sulphate or bone graft was used, these radio-opaque particles will resorb. Cement will persist for the life of the patient.

UBCs can recur after treatment (Fig. 9). Forty percent is a reasonable estimated recurrence rate although the rate varies from one study to another.[32] When a cyst recurs, a lucent area becomes discernable and grows. Small persistent lucencies may be of little clinical significance if they are stable and if the cortex has thickened to provide adequate strength.[33] When recurrence occurs, growth of the lucent area becomes apparent over the course of serial radiographs. Because of this risk, it is appropriate to obtain follow-up radiographs for a few years after treatment. We are not aware of any generally accepted follow-up protocol.

Once there has been a pathologic fracture or treatment attempts, the MRI appearance of a UBC may become more complex. Internal signal may be altered due to hemorrhage or the presence of extraneous material such as bone graft. Enhancement may become thicker and more nodular in appearance despite lack of recurrence. Internal septations may develop.[31] Otherwise, the appearance of the bone may gradually normalize, as previously mentioned regarding radiographs (Fig. 9).

Calcaneal UBCs have differences other than location as compared to the lesions that occur in the proximal humerus and femur. They have been suggested to have a unique cause, which is collapse of the sinus tarsi artery that provides circulation to the central triangular area of the calcaneus where these cysts form.[34] They occur in the same location where intraosseous lipomas also occur, and it may be that the 2 lesions have a common cause and possibly one can develop from the other.[35]

Calcaneal UBCs are relatively common, placing third in incidence behind the femur and humerus in a series of 352 UBCs.[36] Their typical age range is older than that of the femoral and humeral lesions. The calcaneus is one of the more common sites of UBC in adults.[37] Unlike the femoral and humeral UBCs, they rarely cause pathologic fractures, though they may present with moderate heel pain.[35]

The radiographic appearance of calcaneal UBCs (Fig. 10) is similar to that of UBCs located elsewhere. They cause excessive lucency in the anterior triangle of the calcaneus with a geographic border. On CT and MRI the lesion has fluid characteristics and may have a fluid/fluid level.

In summary, UBCs are common benign lesions that should be considered when a lucent expansile lesion is seen in children and adolescents. The lesions can be complicated by pathological fractures and can lead to limb deformity or length discrepancy.

Fibrous Dysplasia and McCune-Albright Syndrome

Fibrous dysplasia/McCune-Albright syndrome is a developmental disorder that arises from somatic genetic mutations in chromosome 20q13.3. The mutations seem to arise relatively early in development but late enough that they can affect some but not all growing tissues. The mutations lead to mosaic $G\alpha_s$ activation with inappropriate production of intracellular cyclic adenosine monophosphate. These mutations are typical of polyostotic fibrous dysplasia/McCune-Albright syndrome but also are found in most cases of isolated, presumably monostotic fibrous dysplasia. These mutations have been found in over 90% of cases.[38-40] Fibrous dysplasia most often occurs in one bone, with approximately 80% of patients

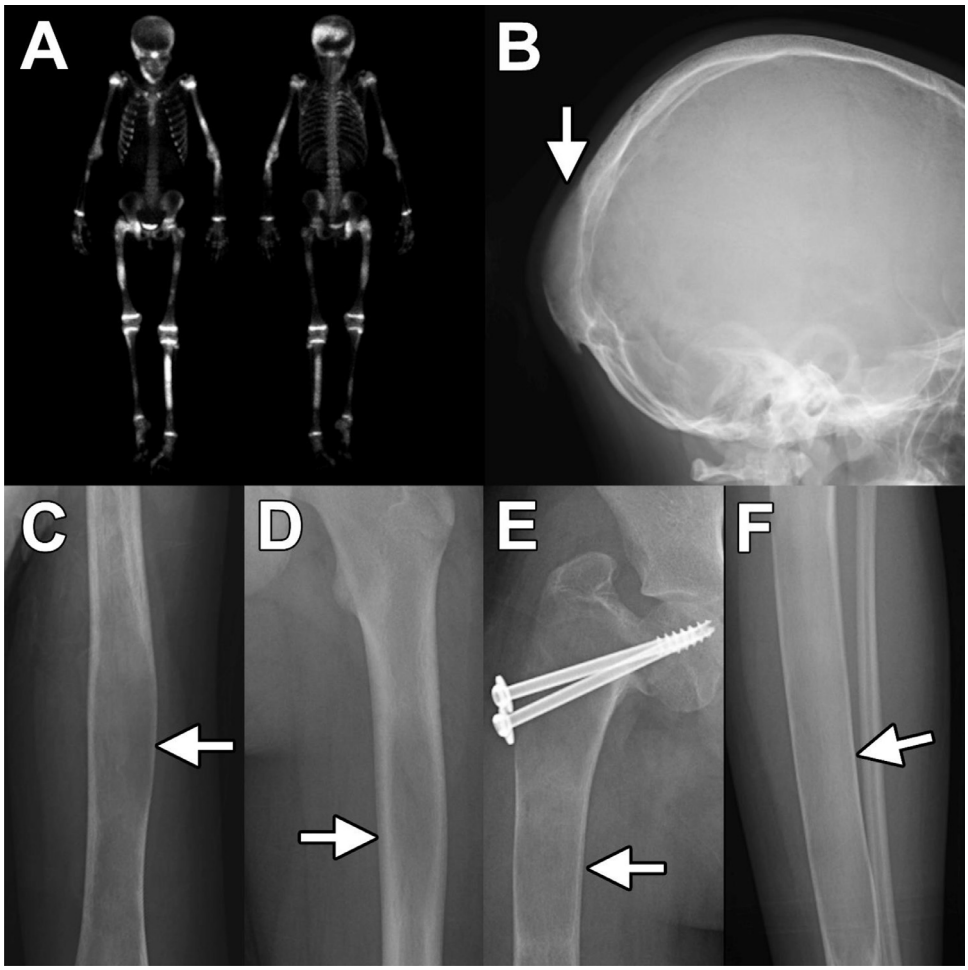

Figure 11 Ten-year-old girl with polyostotic fibrous dysplasia. Bone scan (A) shows multiple areas of uptake in the axial and appendicular skeleton. Radiographs of the skull (B), left humerus (C), left femur (D), right femur (E), and left tibia (F) show typical expansile lesions with ground-glass matrix (arrows). The right femoral neck (E) has been previously stabilized with 2 cannulated screws due to pathological fracture and shows the typical "shepherd's crook" deformity.

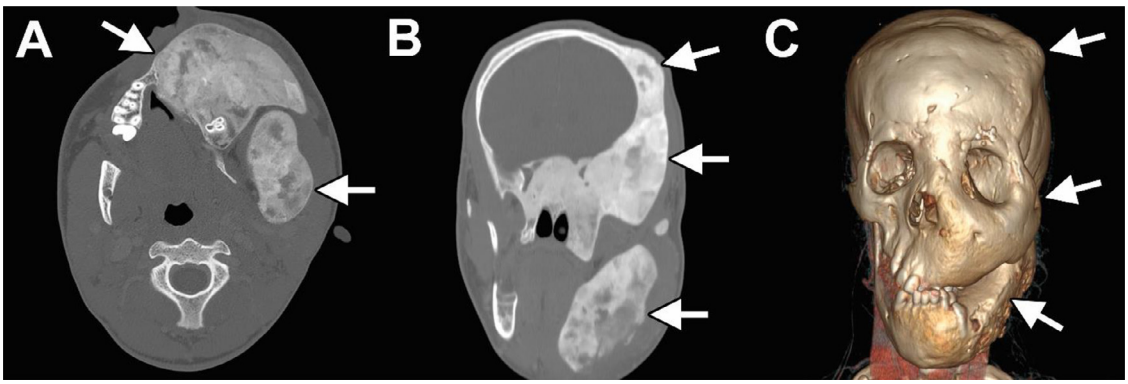

Figure 12 Twenty-five-year-old man with fibrous dysplasia of the face. Axial (A) and coronal (B) CT images show extensive involvement of the bones of the face and skull (arrows). The ground-glass matrix is well-demonstrated in the expanded medullary cavities. Volume-rendered image (C) shows the extensive deformity of the bones (arrows).

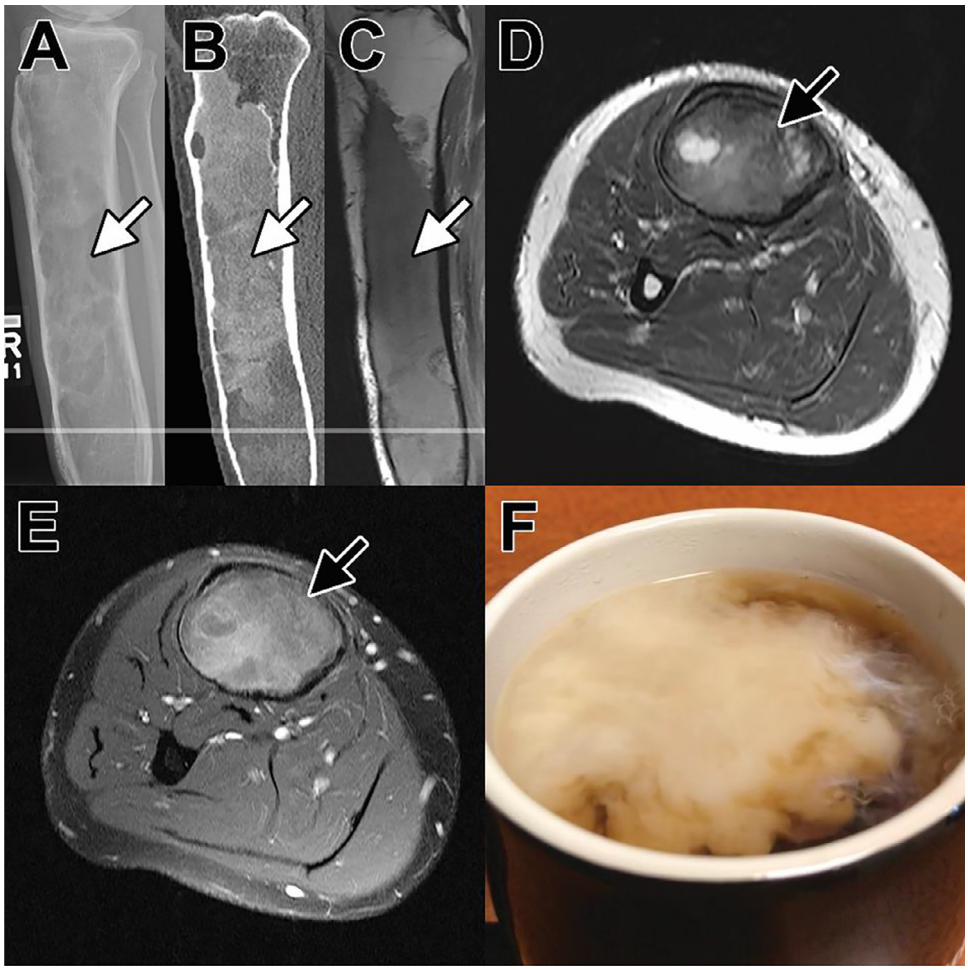

Figure 13 Thirty-five-year-old man with fibrous dysplasia of the right tibia. Lateral radiograph (A) shows an expansile lesion with heterogeneous ground-glass matrix (white arrow). Sagittal CT (B) shows the ground-glass matrix to better advantage with areas of higher attenuation in the proximal aspect of the lesion (white arrow). Sagittal T1-WI (C) shows heterogeneously low-signal with expansion of the cortex (white arrow). The white horizontal line extending across (A-C) indicates the slice location on the axial MRI (D-E) which is through an area of ground glass. Axial T2-WI (D) shows low, intermediate, and high-signal areas within the lesion (black arrow). Axial postcontrast FS T1-WI (E) shows heterogeneous enhancement (black arrow) with a milk-cloud appearance (F).

having monostatic disease. Monostotic lesions typically occur in the femur, calvarium, or a rib.[41]

Polyostotic cases are defined as occurring in more than one bone (Fig. 11). They are likely to involve the skull and femur but also frequently involve the pelvic bones or mandible. When fibrous dysplasia is combined with at least one other typical lesion, including café-au-lait pigmented skin markings with jagged edges that do not tend to cross the midline of the body, or various endocrinopathies, the combined features are called McCune-Albright syndrome.[39,41,42] Fibrous dysplasia accompanied by intramuscular myxomas is termed Mazabraud syndrome.[41,42] Fibrous dysplasia is most often discovered in children, adolescents, and young adults. All or essentially all skeletal lesions are detectable by age 15.[41,42] Once fibrous dysplasia develops, however, it is present for life and therefore may present in later adulthood.[43]

Lesions of fibrous dysplasia may be stable or may grow at variable rates. They tend to grow during childhood and stop after puberty, at approximately the same time that growth ceases in normal bone. They can produce symptoms due to mass effect on nearby structures and may be associated with bone pain. Pain affects about two-thirds of patients, and there is no apparent correlation between the number or size of fibrous dysplasia lesions and the presence, absence, or severity of pain. Other complications include pathologic fracture, osseous deformity, and (uncommonly) malignant transformation. The malignancies that most commonly develop in fibrous dysplasia include osteosarcoma, fibrosarcoma, chondrosarcoma, and pleomorphic sarcoma.[39,41]

In fibrous dysplasia, bone development stops at the stage of woven bone, without development of well-formed trabeculae. This creates the classic ground-glass appearance typical of fibrous dysplasia on conventional radiography, though the

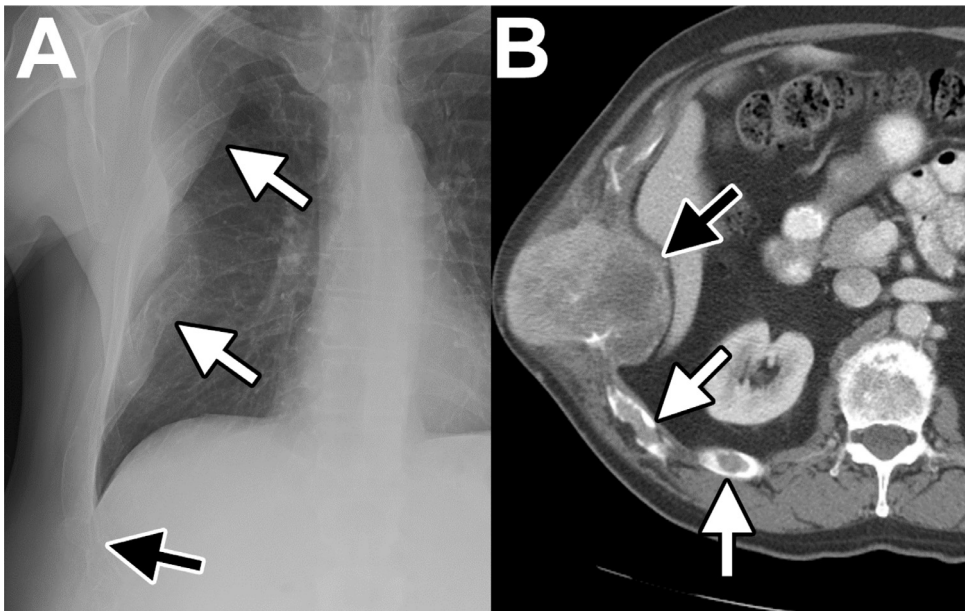

Figure 14 Seventy-year-old man with polyostotic FD with malignant transformation of a lesion in the right anterior 10th rib. Radiography (A) shows multiple expansile rib lesions (white arrows). The malignant lesion of the 10th rib (black arrow) is not well-demonstrated on radiography due to osteolysis of the cortex. Axial contrast-enhanced CT (B) shows cortical breakthrough with soft tissue extension caused by a secondary osteosarcoma of the right anterior 10th rib (black arrow). Benign lesions of FD with a predominance of thick, sclerotic rims and no cortical breakthrough are seen in adjacent ribs (white arrows).

appearance may be more variable, with areas of greater sclerosis or lucency. The lesions usually have a geographic border, although the border may be difficult to discern on conventional radiographs.[42,43] There is often cortical thinning as the intraosseous masses grow larger than the usual size of the medullary cavity and the cortex must remodel to accommodate the mass.

CT can be useful for defining the extent of individual lesions. It is particularly useful for lesions in the skull and face, where the anatomy is too complex for adequate evaluation using conventional radiographs (Fig. 12).[41]

On MRI fibrous dysplasia can have a varied appearance (Fig. 13). It tends to have low to intermediate signal on T1-weighted imaging and higher signal on T2 weighting. There is generally some contrast enhancement with gadolinium administration.[41] On postcontrast T1-weighted images, Franz et al noticed that fibrous dysplasia often contains areas of "cloudy" enhancement within a wider-spread region of low T1 signal. This pattern reminded them of the appearance of milk dissolving into a cup of tea, and they called it the "milk cloud" appearance (Fig. 13F). They reviewed 37 fibrous dysplasia lesions and found a milk cloud appearance in 82% of them. It was more common in lesions located in long bones (91%) than in other locations (67%). Milk clouds tended to occur in the same parts of the lesion that displayed ground-glass attenuation on conventional radiography or CT.[44]

On neither CT nor MRI should there be cortical breakthrough with extension of an enhancing lesion into the soft tissues.[42] If a soft-tissue mass is present, another diagnosis or possibly rare malignant transformation should be entertained (Fig. 14).

On FDG PET fibrous dysplasia can be markedly high in metabolic activity (Fig. 15). Elangovan and Sebro found 26 areas of fibrous dysplasia to have standardized uptake values up to 18.6, though the mean was 1.8 and the median was 2.1.[45]

Treatment of fibrous dysplasia includes selective, carefully planned surgery and physical therapy. There is increased bone turnover in fibrous dysplasia as compared with normal bone, so antiresorptive bisphosphonates have been tried, with mixed results.[39] After denosumab was found to be effective in GCT, it was also tried in fibrous dysplasia because both lesions have abundant expression of RANK ligand. Majoor et al, in a series of 12 patients in whom bisphosphonate treatment had been suboptimal, found that denosumab was well-tolerated and produced sustained reduction in bone turnover and bone pain.[46] Generally denosumab should be used in specialized centers.[42]

If medical therapy of fibrous dysplasia is to be used, it is advantageous to have methods of monitoring other than symptom relief and appearance on conventional radiographs. Sodium fluoride PET/CT may be useful for quantitative evaluation of treatment efficacy in fibrous dysplasia.[47] Serum alkaline phosphatase levels can also be used to evaluate treatment effect because it is correlated with the rate of bone turnover. Return of elevated levels to normal or near normal suggests that the treatment is working.[42,46] As of late 2019, treatment with either bisphosphonates or denosumab remains an off-label use of the medication.

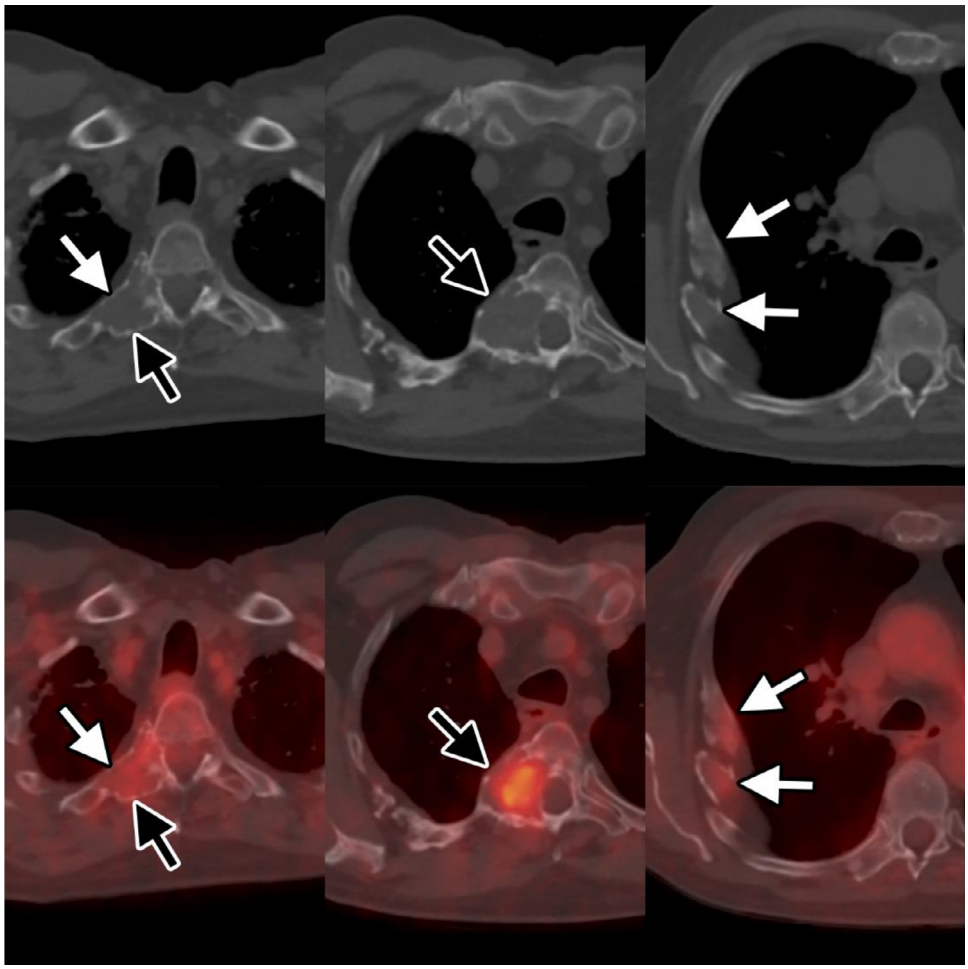

Figure 15 Seventy-year-old man with polyostotic FD (same patient as in Fig. 14) presenting for staging FDG PET/CT after resection of the malignant 10th rib lesion (not shown). Bone window (upper row) and fused bone window (lower row) images show multiple benign foci of FD in ribs (white arrows) and vertebrae (black arrows) with SUV_{max} ranging from 2.5 to 4.6.

Conclusion

This review has focused on classical features of 3 of the more commonly encountered lucent benign primary bone lesions: giant cell tumor, unicameral bone cysts, and fibrous dysplasia. We have focused on imaging features at presentation and on follow-up, as well as novel therapies and their complications.

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