Review Article

Giant Cell Tumor of Bone

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J Am Acad Orthop Surg 2013;21: 118-126

http://dx.doi.org/10.5435/JAAOS-21-02-118

Abstract

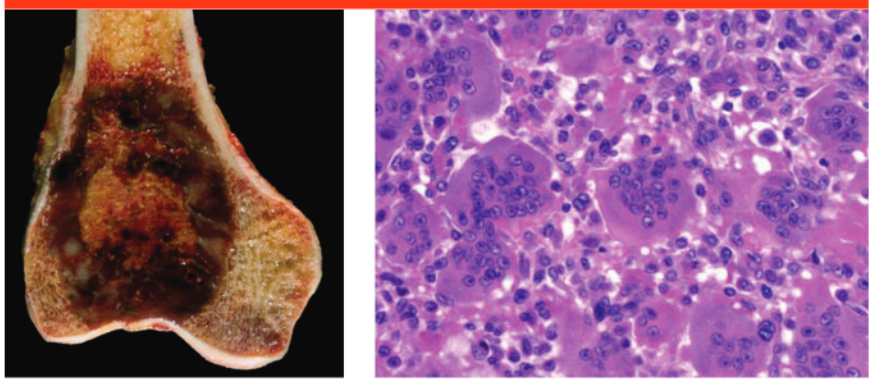
Giant cell tumor (GCT) of bone is one type of giant cell-rich lesion of bone. This benign mesenchymal tumor has characteristic multinuclear giant cells. Mononuclear stromal cells are the physiologically active and diagnostic cell type. Most GCTs are located in the epiphyseal regions of long bones. The axial skeleton—primarily the sacrum—is a secondary site of involvement. Most patients present with pain, swelling, joint effusion, and disability in the third and fourth decades of life. Imaging studies are important for tumor staging and radiographic grading. Typically, these clinically active but slow-growing tumors are confined to bone, with relatively well-defined radiographic borders. Monostotic disease is most common. Metastatic spread to the lungs is rare. Extended intralesional curettage with or without adjuvant therapy is the primary treatment choice. Local recurrence is seen in ≤20% of cases, and a second local intralesional procedure is typically sufficient in cases that are detected early. Medical therapies include diphosphonates and denosumab. Denosumab has been approved for use in osteoporosis as well as breast and prostate cancer metastatic to bone. Medical therapy and radiotherapy can alter the management of GCT of bone, especially in multifocal disease, local recurrences, and bulky central/axial disease.

Giant cell-rich lesions of bone include reactive processes and locally aggressive benign neoplasms that are characterized by the presence of numerous multinucleated osteoclast-type giant cells. These cells are present in a variety of benign and malignant bone lesions, including brown tumor of hyperparathyroidism (Recklinghausen disease), giant cell reparative granuloma, aneurysmal bone cyst (ABC), chondroblastoma, giant cell osteosarcoma, and malignant and benign giant cell tumor (GCT) of bone.[1-3] Brown tumors are reactive and develop secondary to hyperparathyroidism.

In 1953, Jaffe[1] coined the term "giant cell reparative granuloma" to describe a tumor of the jaws that had previously been diagnosed as GCT of bone. GCT of bone may develop adjacent to the blood-filled cystic regions of ABCs. These benign entities (ie, ABCs) are not epiphyseal, and they may occur in any bone. Local recurrence is common.

Chondroblastoma and GCT are also closely associated. At our institution, one case that was originally documented as GCT of bone later transformed into aggressive chondroblastoma. Chondroblastoma and GCT of bone are both epiphyseal, and they have radiographic similarities. However, they are easily distinguished based on their histologic profiles. In giant cell osteosarcoma,

Figure 1



A B

Gross appearance (**A**) and high-power photomicrograph (**B**) of a distal femoral giant cell tumor of bone (hematoxylin-eosin).

malignant spindle cells produce osteoid in a background of giant cells, whereas it is the presence of malignant stromal cells that is indicative of malignant GCT of bone. Clinical history, laboratory results, and physical examination can be helpful in the differential diagnosis.

Benign GCT of bone is composed of cytologically benign, oval- or polyhedron-shaped mononuclear cells that are admixed with numerous evenly distributed osteoclast-like giant cells. It arises in the ends of cancellous long bones and typically is destructive locally (Figure 1). First described by Cooper and Travers[4] in 1818, GCT of bone was known to be an aggressive, destructive lesion of the long bones with an unclear relationship to malignant counterparts, such as osteosarcoma. Virchow first described GCT of bone as a tumor that can both recur and degenerate into cancer.[2] Even though GCT of bone is benign, it can metastasize to the lungs.[5] Metachronous and multicentric GCTs of bone are even less common and lack a clear etiology for additional sites of osseous disease.[6]

GCT of bone typically presents in persons aged 20 to 40 years. It is rare in adolescents and children, and <10% of cases are seen in patients aged >65 years.[2] Many series indicate a slightly higher incidence in women than men, with a female-to-male ratio of 1.2:1.[5,7] In most cases, GCT of bone occurs in the metaphyseal and epiphyseal regions of long bones. However, in children with open physes, GCT of bone may be centered in the metaphysis and may abut the physis.

GCT is most commonly found in the distal femur, proximal tibia, and distal radius. In the axial spine, GCT is most often located in the sacrum. GCT is found infrequently in the vertebral body of the mobile spine and rarely in the posterior elements.[8] Other rare locations of involvement are the hands, feet, patella, and talus. There are cases of multicentric GCT of bone in which all these locations are affected.

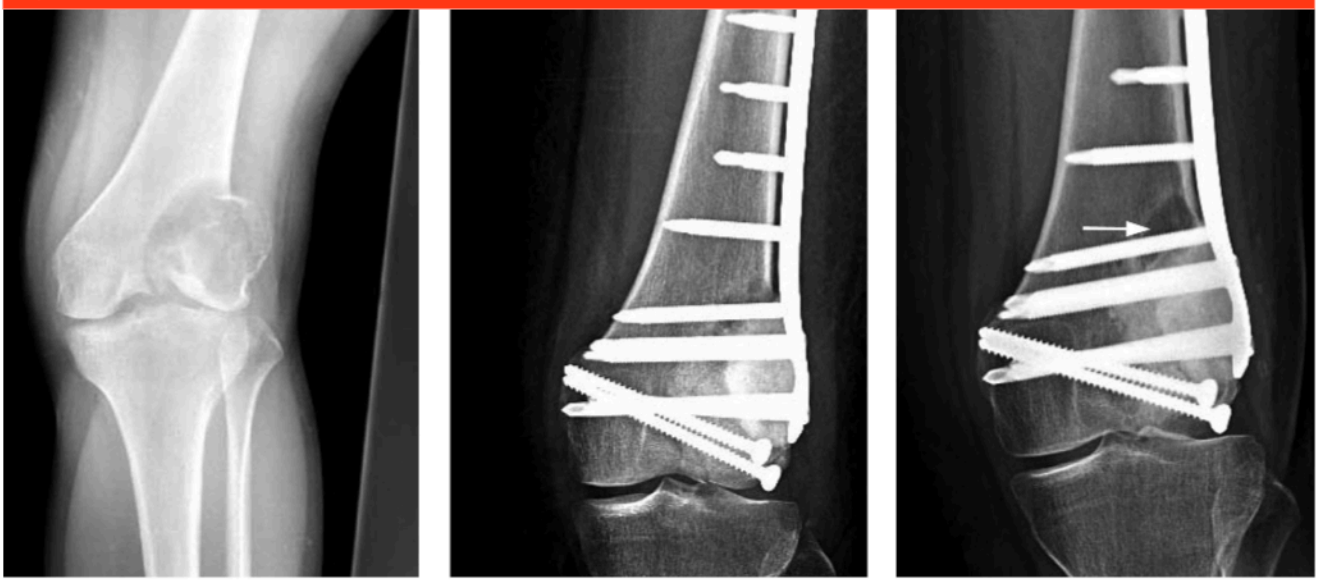
Presentation and Staging

Patients typically present with pain. Pain may be activity-related or experienced at rest or at night. Activity-related pain is caused by the loss of structurally important bone and mechanical failure of bone as the result of the presence of the tumor. Pain at rest or at night is the result of tumor growth, tumor-related expansion of the periosteum, and the response of the periosteum to the threat of the advancing neoplasm. Duration of pain varies, but most patients experience pain for 3 to 6 months, and the initial presumptive differential diagnosis ranges from arthritis to intra-articular derangement. Physical examination usually reveals an area of direct tenderness to palpation, soft-tissue swelling over the affected area, and the presence of either sympathetic or direct joint effusion. Patients often demonstrate an antalgic gait that favors the affected side.

Pathologic fractures can occur through lytic lesions of long bones and may be the reason for initial evaluation and pain, especially in weight-bearing bones. Because the tumor occurs in the epiphyseal region of long bones, the fracture line may extend through the articular surface of the joint. In such cases, management and reconstruction may be particularly difficult because of the shell-like appearance of bone surrounding the tumor. If the joint is congruent, it is sometimes appropriate to wait for the fracture to heal before performing surgery. No data indicate that pathologic fracture increases the chance of local recurrence or development of metastatic disease[9] (Figure 2).

The Enneking[10] staging for benign bone tumors may be used to determine definitive management. Campanacci[5] described a grading system for these lesions based on radiographic imaging (Table 1, Figures 3 and 4). Enneking stage 1 and Campanacci grade 1 lesions are rare. Most GCTs of bone are stage 2 or grade 2. In the most advanced lesions, the soft-tissue mass has formed outside the bone and can be quite large and vascular and can push on surrounding normal anatomic structures. It can even cross to adjacent bones through ligaments (eg, cruciate ligament).

Figure 2



A B C

A, AP radiograph demonstrating giant cell tumor of bone in the distal femur, with pathologic intra-articular fracture. **B,** AP radiograph obtained 1 month following open reduction and internal fixation with curettage, bone grafting, and packing with polymethyl methacrylate cement. **C,** AP radiograph obtained 2 years postoperatively demonstrating local recurrence (arrow).

Radiographic Evaluation

Radiographically, GCT of bone manifests as a large, purely lytic mass that frequently extends from the subchondral bone plate into the metaphysis and epiphysis. Larger tumors may involve the adjacent diaphysis, focally destroy the cortex, and invade neighboring soft tissues[11] (Figure 5). GCT of bone is one of many equally predictable tumors that are frequently found invading the ends of long bones, such as chondroblastoma, intraosseous ganglia, and clear cell chondrosarcoma. GCT lesions arise within the medullary portion of bone, although they are frequently eccentric. They may appear to expand the bone and elevate the periosteum, resulting in a thin periosteal shell. The tumors do not provoke much bone reaction, and the periosteal shell may appear to be focally incomplete. However, the fibrous periosteum is usually intact over the lesion, despite the absence of mineralization. Even when the adjacent soft tissues are invaded, a thin rim of bone is usually seen about the associated soft-tissue mass. The articular cartilage often serves as a good barrier to intra-articular spread of the tumor; however, as these lesions grow and erode the subchondral bone, the articular cartilage may be found to be floating on a bed of tumor. Although the medullary margins are well-defined, they are usually not sclerotic; in some cases, they may appear moth-eaten.

Cystic degeneration is a common secondary finding. Typically, the lesions are extremely hypervascular and dem-

Table 1

Comparison of the Enneking and Campanacci Grading Systems for Bone Tumors

Grade/Stage	Enneking	Campanacci
1	Benign, indolent, or biologically static	Radiographically well-circumscribed lucent lesion with no aggressive features (eg, periosteal reaction, soft-tissue mass, cortical breach). Rare.
2	Progressive growth, limited by natural barriers	Relatively well-defined radiographic borders without a radiopaque rim
3	Locally aggressive with corresponding soft-tissue mass	Indistinct or ill-defined borders with radiographic demonstration of cortical bone destruction, and a soft-tissue mass

Figure 3

Enneking stages 1 through 3 giant cell tumor of bone. **A,** Axial CT scan of a left distal femur demonstrating Enneking stage 1 involvement. Lateral (**B**), oblique (**C**), and AP (**D**) radiographs and a T2-weighted sagittal magnetic resonance image (**E**) of the distal radius demonstrating Enneking stage 2 involvement. AP (**F**) and lateral (**G**) radiographs demonstrating Enneking stage 3 involvement in a knee.

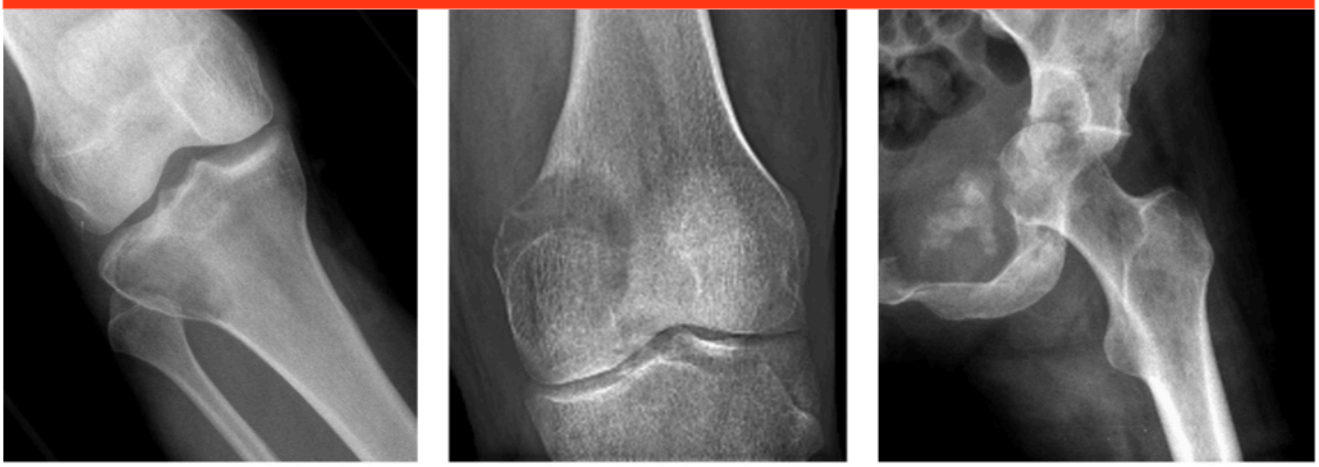
onstrate marked tumor blush on angiography as well as contrast enhancement on MRI and CT. On MRI, the mass appears dark on T1-weighted images, bright on T2-weighted images, and avid on gadolinium-enhanced images. On MRI, GCT of bone bears characteristics similar to those of any aggressive bone tumor, including malignant lesions such as osteosarcoma. Fluid-fluid levels can also be seen because GCT of bone and aneurysmal bone cyst have similar characteristics histologically and on MRI. Telangiectatic osteosarcoma must be ruled out in the presence of fluid-fluid levels. Nuclear medicine bone scanning is usually hot; however, the largely osteoclastic behavior of GCT of bone can render an aggressive, destructive appearance radiographically and a relatively warm or cold region on bone scan.

Initial radiographs typically are classic or typical of benign GCT of bone. In cases in which biopsy is required to confirm the radiographic diagnosis prior to intralesional treatment, the patient should undergo MRI, bone scanning, and chest imaging prior to biopsy. Biopsy performed first will alter the ability to define the local extent of the tumor.

Histology and Pathophysiology

GCT has a soft and often ruddy gross appearance as a result of intra-

Figure 4



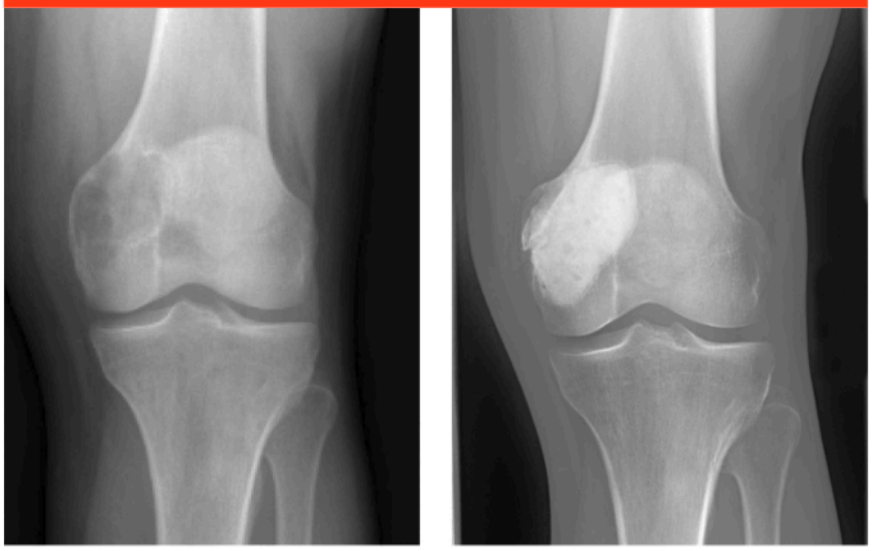
A B C

AP radiographs demonstrating Campanacci grade 1 (**A**) and grade 2 (**B**) giant cell tumor (GCT) of bone of the knee and grade 3 GCT of bone in a left hip (**C**).

lesional hemorrhage. Masses range in size from a few centimeters to >15 cm. The histologic hallmark of GCTs is the presence of innumerable, multinucleated osteoclast-like giant cells scattered evenly throughout the tumor. The number of nuclei in any individual cell is variable but may be ≥50. This number is larger than for other bone tumors or lesions that contain giant cells. The nuclei are ovoid and vesicular, with central nucleoli, and they tend to be situated in the center of the cell, where they are surrounded by abundant eosinophilic cytoplasm (Figure 1).

GCT of bone is a mesenchymal tumor in which the cell of origin is the fibroblastic-osteoblastic mononuclear cell that produces types I and II collagen. The characteristic and abundant multinucleated giant cell is not the cell of origin; the nuclei of these giant cells are morphologically identical to those of the surrounding stromal cells (Figure 1). The mononuclear stromal cell has an affinity for parathyroid hormone and can produce alkaline phosphatase. The neoplastic legitimacy of the tumor is further supported by demonstrable alterations in the c-*myc*, N-*myc*, and c-*fos* oncogenes. Alterations in p53 have been discovered in the metastatic foci of GCT of bone.[12]

Figure 5



A B

A, AP radiograph demonstrating giant cell tumor (GCT) of bone in a left distal femur. **B,** AP radiograph of the same patient demonstrating GCT of bone after curettage and packing with polymethyl methacrylate.

The mononuclear stromal cells in GCT have ill-defined borders and little eosinophilic cytoplasm. The nuclei are round or ovoid in shape and vesicular, with central nucleoli, and they are morphologically identical to the nuclei of the giant cells. The mononuclear cells may be mitotically active and can show variable degrees of cytologic atypia, which may be prominent in areas admixed with previous hemorrhage and fibrin deposition. Other common findings in-

clude foci of necrosis and vascular invasion. These tumors also have areas that can morphologically resemble benign fibrous histiocytoma or nonossifying fibroma.[5] Ultrastructurally, prominent but nonspecific features in the cytoplasm of the mononuclear cells within GCT of bone include abundant dilated rough endoplasmic reticulum, well-developed Golgi apparatus and mitochondria, and, occasionally, lipid droplets. On electron microscopy, the multinucleated giant cells have features similar to osteoclasts. The mononuclear cells express vimentin and α_1-antitrypsin and do not stain with antibodies to S-100 protein. The giant cells have an immunohistochemical profile similar to that of macrophages. These findings suggest that the mononuclear and multinucleated cells in GCT are of histiocytic derivation; however, this issue has not been resolved. Telomeric fusion, in which different chromosomes are fused, has been noted in GCT of bone.[13] GCTs of bone are associated with significant vascularity, and the expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP) has been implicated in lesions that are known to metastasize and/or hijack the host vasculature for purposes of spread. Kumta et al[14] concluded that expression of VEGF and MMP-9 is directly related to the extent of bone destruction and the potential for recurrence. Further study has indicated that measuring the levels of VEGF and MMP-9 may be useful in determining which patients are at increased risk for recurrence and distant spread.[15]

Management

GCT of bone can be difficult to manage. Decades ago, wide resection was the norm, and the recurrence rate was negligible. However, the subsequent reconstructions were complex and frequently were associated with a high rate of complications. Although surgery remains widely accepted as the mainstay of therapy, medical management using diphosphonates and denosumab has been recently developed.

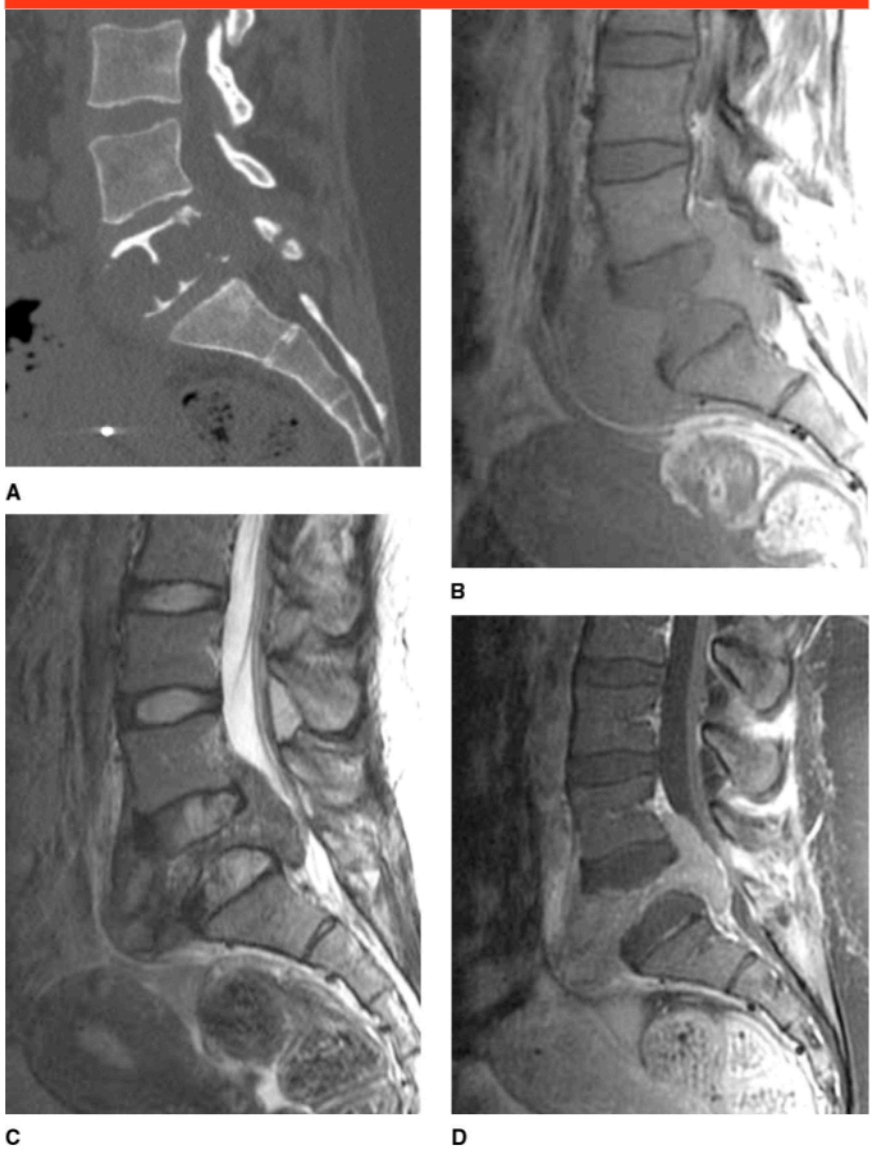
Although radiation therapy is not routinely used, it has been used as an effective treatment for GCTs in difficult locations such as the sacrum and spine, particularly with local recurrences following curettage or other local surgical treatments.[7,16-23] At our institution and others, it has been used successfully in some challenging cases with tumors located in the sacrum.

Intralesional curettage is the mainstay of management for primary GCT of bone (Figure 5), but local recurrence rates approach 20% without local adjuvants.[5] A 45% recurrence rate was reported in a study of 677 patients treated with intralesional curettage and bone grafting alone.[7] The recurrence rate dropped to 17% with the use of adjuvants such as liquid nitrogen, phenol, hydrogen peroxide, and bone cement. In one study, sterile water, 95% ethanol, 5% phenol, 3% hydrogen peroxide, and 50% zinc chloride were determined to be effective on GCT monolayer tumor cultures.[9] Sterile water alone was not as effective as these chemical adjuvants. Other studies have compared ethanol with phenol[24] and coagulation with argon beam laser[25] to improve local control. The local recurrence rates for ethanol and phenol were nearly identical, with no significant difference in Musculoskeletal Tumor Society functional scores. Ethanol is easier to use and safer than phenol. Extension of the cellular "killing zone" of the curettage can also be achieved by argon beam laser.

Blackley et al[16] reported a 12% recurrence rate in GCT of bone following extended curettage with a high-speed burr only, no adjuvant treatment, and allograft packing. Many surgeons pack the defect with polymethyl methacrylate cement instead of allograft. The physical act of tumor extirpation likely reduces local recurrence more than does the use of adjuvants (Figure 2). Cryosurgery has been shown to reduce the local recurrence rate to <8%.[26] The freeze-thaw cycle kills cells farther from the burred surface, thereby further extending the depth of the curettage. Cryosurgery involves the direct application of liquid nitrogen into the tumor cavity as a freeze-thaw couplet that can be repeated to improve its efficacy.[26] Although cryotherapy has been shown to be an effective adjuvant, it is associated with an appreciable incidence of pathologic fracture and vascular injury. Marcove et al[27] were among the first to study liquid nitrogen as an adjuvant for GCT of bone. Some surgeons consider the complications associated with liquid nitrogen treatment to be unacceptable. Fracture is the most common complication.

En bloc wide resection is an option for recalcitrant or recurrent cases and certain aggressive stage 3 tumors, as well as in cases of GCT in expendable bones.[17] Bulk or structural allografts, endoprosthetic implants, or a combination of the two reconstructive measures can be used in patients with aggressive GCTs of bone and associated extensive bone destruction.[28] The clavicle, distal ulna, and proximal and mid fibula are considered expendable. In most cases, resection of expendable bones has no significant impact on function. The ligaments and soft tissues surrounding some of these expendable bones may benefit from reconstruction to stabilize the remaining portion of the bone. When GCT occurs in these locations, en bloc excision portends excellent functional and oncologic outcomes. Bulk os-

Figure 6



A, CT scan demonstrating giant cell tumor of bone at L5. Sagittal T1-weighted (**B**), sagittal fat-saturated T2-weighted (**C**), and sagittal fat-saturated T1-weighted with gadolinium (**D**) magnetic resonance images.

teoarticular allograft and endoprosthetic reconstruction of massive bone defects are other treatment options in these recalcitrant cases.

The sacrum and axial skeleton pose a unique set of treatment challenges (Figure 6). Three percent to 7% of GCTs of bone involve the spine, and GCTs of bone account for up to 4% of vertebral tumors.[8] The sacrum is the fourth most commonly involved anatomic location; within the sacrum, the sacral arch or wing is the most common site of involvement. Typically, the tumor abuts the sacroiliac joint. In the mobile spine, approximately 60% of cases are discovered in the vertebral body.[8] It may be difficult to distinguish radiographically between ABC and plasmacytoma. Intraoperative hemorrhage is a concern, but adequate preoperative embolization only minimizes this risk. Curettage and bone grafting is more difficult to perform in the axial skeleton than in the appendicular skeleton, and resection with a marginal or microscopically positive margin is not unreasonable. Embolization helps to reduce the gross vascularity of lesions, with the intent of stemming intraoperative bleeding. Lackman et al[29] reported success with repeat embolization of large sacral GCTs of bone. Radiation therapy has been successfully employed for some challenging sacral lesions, particularly those that recur after prior local control measures.[22,23] Diphosphonates may also reduce the osteoclast-like behavior of GCT of bone, dismantling its physiology and thus reducing its vascularity. Wide surgical resection may also be considered to reduce the rate of recurrence, thereby avoiding further surgery for recurrent disease in managing GCT of the axial skeleton.[8]

Medical therapy for GCT of bone is experimental and is based largely on theoretical information about the etiology of the disease. Diphosphonate therapy is currently used because of its antiosteoclastic effects. Tse et al[30] reported on 44 patients with appendicular GCT of bone who underwent intralesional curettage followed by either polymethyl methacrylate cement or allograft packing. Additionally, 24 patients received either oral or intravenous diphosphonate. The local recurrence rate was 4.2% in the patients treated with diphosphonate and 30% in the control group.

Interferon has been used to control local and distant disease, with mixed results.[31] If GCT of bone is a proliferative vascular lesion, it would be expected to respond to antiangiogenic therapy. One promising treatment for the management of aggressive GCTs, which may present in the jaw as giant cell reparative granuloma, consists of enucleation of the

tumor and preservation of vital structures, followed by subcutaneous administration of interferon-α. Combined treatment resulted in a high rate of tumor control and reduced surgical morbidity compared with the historically reported conventional treatment.[31] Yasko[32] reported on variable responses to escalating doses of interferon-α in a series of 12 patients. Patients presented with sacral, spinal, pelvic, and pulmonary metastases. Four patients had tumor progression, but therapeutic effect was noted for up to 6 years.

Osteoclastic giant cells express receptor activator of nuclear factor-κB ligand (RANKL), and the antibody denosumab has been used to manage such tumors. In a study by Thomas et al,[33] 37 patients with recurrent or unresectable GCTs were treated with denosumab, a human monoclonal antibody to RANKL. The mononuclear cells express RANKL, and the osteoclast-type cells express receptor activator of nuclear factor-κB. Eighty-six percent of patients had a tumor response. Tumor response was measured by either histologic elimination of 90% of giant cells or no radiologic progression of the target lesion up to week 25. The adverse effects, the most common of which was pain in the affected extremity, remain a challenge to delivering the drug. This use was deemed to be safe, and initial results are promising. In our practice, the use of denosumab has resulted in stabilization of disease and ossification, with lack of osteoclasts noted on histologic evaluation.

External beam radiation has been used to supplement surgical treatment in patients who are medically inoperable or who have tumors that are technically difficult to resect or that cannot be removed because of their locations.[22] Malignant transformation has been reported to occur in as many as 15% of cases, but this appears to be associated with treatment with older orthovoltage techniques in which the radiation dose absorbed in bone was substantially higher than that in soft tissue. The 1999 report by Chakravarti et al[22] described 20 patients with GCT of bone, none of whom manifested radiation-induced malignancy. In this survey of pooled data, which included 136 patients treated with megavoltage irradiation, only 1 patient developed malignant transformation (<1%). The authors noted the possibility of malignant transformation in the absence of radiotherapy. The actuarial 10-year rate for lack of disease progression was 85%. Three patients failed radiation and required surgical treatment. Nevertheless, the risk of radiation-associated malignancy, however small, would suggest the use of external beam radiation for only the most recalcitrant or surgically difficult tumors.

Metastatic and Multicentric GCT and Malignant Transformation

GCT of bone has been reported to metastasize in 2% of cases. Lesions in the wrist and the distal radius have the highest rate of metastasis.[34] The metastases are considered to be benign and bear the same histologic characteristics of the original tumor. Metastatic GCT to the lung shows an increase in *c-myc* oncogene, which is already overexpressed in primary tissues. Surgical resection of the metastatic lesions is recommended, with a 76% disease-free survival rate and a 17.4% death rate. Interferon has also been used to treat patients with metastases.[31,35]

Frequently, metastatic deposits are cured with resection. Sarcoma rarely develops within a GCT, whether de novo, as a local recurrence, or following radiation.

Thirty cases of multicentric GCT of bone were treated at Massachusetts General Hospital and Mayo Clinic from 1950 through 2002.[6] All patients had two or more lesions, and the GCTs were confirmed on histologic examination. The average age of presentation in this series was 21 years. Most of the synchronous lesions noted in this study were found about the knee. Local recurrence was dependent on the type of surgery performed. The risk of pulmonary metastasis in this study was approximately 10%. The authors combined their results with those of several other studies and reported an overall 4% risk of pulmonary metastasis.

Summary

GCT of bone is one of a variety of giant cell-rich lesions of bone. This mesenchymal tumor has characteristic abundant multinucleated giant cells, and the mononuclear stromal cells are the neoplastic cell type. These cells are found in tumors that are located predominately in the metaphyseal-epiphyseal regions of long bones. Secondary sites include the axial skeleton, primarily the sacrum. Most patients present in the third and fourth decades of life with pain, swelling, joint effusion, and disability. Imaging studies are important for staging and radiographic grading of the tumor. Typically, these tumors are clinically active but relatively slow-growing and confined to bone, with fairly well-defined radiographic borders. Monostotic disease is most common. Despite the increased vascularity associated with GCT of bone, metastatic spread to the lungs is rare. Surgery is the mainstay of management, and extended intralesional curettage with or without adjuvant therapy is the primary treatment. Local recurrence occurs in

up to 20% of cases; when detected early, it usually can be managed with an additional local intralesional procedure. Medical therapies have been used more often for advanced disease. Radiation therapy is used only in special clinical circumstances.

Acknowledgment

The authors wish to thank Daniel Rosenthal, MD, G. Petur Nielsen, MD, Thomas F. DeLaney, MD, and Edwin Choy, MD, for their assistance with this manuscript.

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