MUSCULOSKELETAL IMAGING

Giant Cell Tumor of Bone: Review, Mimics, and New Developments in Treatment¹

ONLINE-ONLY SA-CME

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LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

Discuss imaging features of GCT of bone and mimic lesions in the differential diagnosis.

• List the complications associated with GCT and common postoperative complications.

Describe traditional treatments for GCT and new developments in treatment.

TEACHING POINTS See last page Corey J. Chakarun, MD • Deborah M. Forrester, MD • Christopher J. Gottsegen, MD • Dakshesh B. Patel, MD • Eric A. White, MD • George R. Matcuk, Jr, MD

Giant cell tumor (GCT) of bone is generally a benign tumor composed of mononuclear stromal cells and characteristic multinucleated giant cells that exhibit osteoclastic activity. It usually develops in long bones but can occur in unusual locations. The typical appearance is a lytic lesion with a well-defined but nonsclerotic margin that is eccentric in location, extends near the articular surface, and occurs in patients with closed physes. However, GCT may have aggressive features, including cortical expansion or destruction with a soft-tissue component. Fluid-fluid levels, consistent with secondary formation of aneurysmal bone cysts, are seen in 14% of cases. GCT can mimic or be mimicked by other benign or malignant lesions at both radiologic evaluation and histologic analysis. Rarely, GCT is associated with histologically benign lung metastases or undergoes malignant degeneration. In the past, the mainstay of treatment was surgical, primarily consisting of curettage with cement placement, with recurrence rates of 15%–25%. Recurrence is suggested by development of progressive lucency at the cement-bone interface. Other complications include pathologic fracture and postoperative infection. Denosumab, a monoclonal antibody that targets the osteoclastic activity of GCT, has produced 90% tumor necrosis in early studies, results indicative of promise as a potential adjuvant therapy.

Introduction

Giant cell tumor (GCT) of bone was described by Cooper and Travers (1) in 1818. The tumor is generally benign and characterized histologically by multinucleated giant cells with a background of mononuclear stromal cells. The multinucleated giant cells appear similar to osteoclasts, which led to the older term *osteoclastoma* (2). Despite being categorized as a benign lesion, GCT may be locally aggressive and recur after surgical resection (3).

GCT usually has a well-defined but nonsclerotic margin, is eccentric in location, extends near the articular surface, and occurs in patients with closed physes (4). However, it may also have aggressive features or fluid-fluid levels and can mimic other lesions at both radiologic evaluation and histologic analysis.

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Abbreviations: ABC = aneurysmal bone cyst, GCT = giant cell tumor, STIR = short τ inversion-recovery

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Figure 1. Typical appearance of GCT of bone. (a) Anteroposterior radiograph of the right knee shows a lytic lesion in the distal femur that is eccentric in location, extends to the subchondral bone, and has a nonsclerotic margin medially (arrowheads). (b) Photomicrograph (hematoxylin-eosin stain) shows a background of monoclonal stromal cells and the presence of multinucleated giant cells (arrows).





b.

In this article, we discuss the epidemiology of GCT of bone, present typical and atypical imaging features, review mimic lesions in the differential diagnosis, and describe its treatment and complications.

Epidemiology

GCT accounts for 5% of all primary bone tumors and 20% of benign skeletal tumors (5–7). There is an unusually high prevalence in southern India and China, where GCT represents 20% of all primary bone tumors (5,6). Although some studies have reported an equal sex distribution, most show an increased prevalence among females (4–8).

The prevalence of GCT peaks during the 3rd decade, with 80% of cases occurring between 20 and 50 years of age. Less than 3% of cases occur before the age of 14 years, and only 13% of cases occur in patients over the age of 50 years (3–8).

Most lesions develop in long bones (75%– 90%), with the majority of cases (50%–65%) occurring about the knee. The three most common locations are the distal femur, proximal tibia, and distal radius, respectively (4–7). GCT may occur in association with Paget disease, most commonly in the skull, facial bones, pelvis, and spine (9).

Imaging Features

The typical appearance of GCT is best demonstrated on conventional radiographs (Fig 1), which show a lytic lesion that has a well-defined but nonsclerotic margin, is eccentric in location, extends to the subchondral bone, and occurs in patients with closed physes (4-6). The magnetic resonance (MR) imaging findings are nonspecific, usually consisting of intermediate or decreased signal intensity on T1-weighted images, increased signal intensity on images obtained with fluid-sensitive sequences, and enhancement after intravenous administration of gadolinium contrast material. Technetium 99m-methylene diphosphonate scintigraphy demonstrates increased radiotracer uptake along the periphery of the lesion. However, central portions of the lesion are often photopenic due to osteolysis or central necrosis.

GCT may also have aggressive features, such as a wide zone of transition, cortical thinning, expansile remodeling, or even cortical bone destruction and an associated soft-tissue mass (Fig 2) (4). These features may be more common in small-caliber long bones, such as the fibula or ulna, and pathologic fracture or periosteal reaction may occasionally complicate the diagnosis (4). GCT may also contain fluid-fluid levels due to secondary aneurysmal bone cyst (ABC) formation (Fig 3), which has been reported in up to 14% of cases (10).

Teaching Point

Teaching Point

Figure 2. Aggressive appearance of GCT. (a) Anteroposterior radiograph of the left knee shows a lytic lesion in the distal femur that is eccentric in location and extends to the subchondral bone with a nonsclerotic margin medially. There is destruction of cortex at the lateral margin (arrowheads). (b) Lateral radiograph shows extension of the lesion into the soft tissues (arrows). The differential diagnosis included GCT and telangiectatic osteosarcoma. (c) Intraoperative photograph shows complete destruction of the lateral margin of the lateral femoral condyle and the presence of a soft-tissue mass (arrows).



Figure 3. GCT with ABC formation. (a) Anteroposterior radiograph of the left knee shows a pathologically proved GCT of the proximal tibia. (b) Axial short τ inversion-recovery (STIR) MR image shows fluid-fluid levels (arrows), a finding that represents secondary ABC formation.





b.







Figure 4. GCT within an apophysis. (a) Anteroposterior radiograph of the right hip shows a lytic lesion with a nonsclerotic margin in the greater trochanter. (b) Frogleg lateral radiograph shows an expansile component with only a thin rim of peripheral cortex remaining. Pathologic analysis demonstrated a GCT. The greater trochanter is an epiphyseal equivalent, and GCT can occur in this location. When GCT affects an apophysis, it does not typically extend to the subchondral bone.

Uncommon Radiologic Manifestations

GCT may also occur in flat bones or an apophysis, which is an epiphyseal equivalent. However, when this occurs the lesion is less likely to demonstrate the classic appearance of a lytic lesion with a well-defined, nonsclerotic margin (11). One such location is the greater trochanter of







Figure 5. GCT involving flat bones. **(a)** Scapular Y radiograph shows an expansile lytic lesion (arrow) in the inferior body of the scapula. Analysis of an excisional biopsy specimen demonstrated a GCT. **(b)** Axial STIR MR image of the pelvis in another patient shows a lesion in the posterior aspect of the right acetabulum that extends to the subchondral bone and contains fluid-fluid levels. Pathologic analysis demonstrated a GCT with ABC formation. Involvement of the flat bones occurs in 15% of cases.

the femur (Fig 4). GCT in this location has only rarely been reported (12,13).

Although GCT most commonly affects the long bones, up to 15% of cases have been reported in flat bones such as the pelvis, sacrum, spine, ribs, and calvaria (Fig 5). Less than 1% of cases have been reported in the scapula (14). GCT may occur in the skull or pelvis secondary to Paget disease (9). The bones of the hands and feet are uncommon locations (Fig 6), with a **Figure 6.** GCT of the calcaneus. (a) Lateral radiograph shows a bubbly lytic lesion with a nonsclerotic margin in the calcaneus. (b) Sagittal STIR MR image shows extension to the subchondral bone at the posterior subtalar joint and fluid-fluid levels. Pathologic analysis demonstrated a GCT with ABC formation. The calcaneus is an uncommon location for GCT.



Figure 7. Pulmonary metastasis from GCT in a 26-year-old woman. The metastasis was diagnosed after fixation of a fracture of the distal femur at another hospital. The pathologic nature of the fracture was not recognized at that time. (a) Sagittal reformatted computed tomographic (CT) image of the distal femur shows a lytic lesion that extends to the subchondral bone with a soft-tissue component and destruction of the cortex posteriorly (arrowheads). (b) Chest CT image, obtained as part of the staging work-up, shows a benign lung metastasis (arrow).



ally after treatment (22). Most pulmonary lesions are histologically benign, with an appearance similar to that of the primary bone tumor. Although lung lesions are commonly resected, nonresectable lesions often have an indolent course and may not require treatment (22–24).

Rarely, GCT may undergo malignant transformation (Fig 8). This may occur as a result of dedifferentiation of the primary tumor or secondary to prior radiation therapy. The overall prevalence is less than 1% (8,25,26). Usually a high-grade sarcoma is diagnosed, which has a relatively poor prognosis. Bertoni et al (26) found that the average latent period between diagnosis of GCT and diagnosis of a secondary malignancy was 9 years

a.

prevalence of less than 2% (15–17). Multicentric GCT has been reported in less than 1% of cases, with lesions often located in the distal extremities, particularly the hands and feet (18–21).

Lung metastases have been reported in 1%–6% of cases (Fig 7). These lesions are thought to arise from hematogenous seeding of GCT of bone, usu-

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Figure 8. Malignant transformation of a GCT. (a) Lateral radiograph of the right knee in a patient with GCT of the proximal tibia. The GCT was treated with curettage and allograft placement.
(b) Follow-up radiograph 23 years later shows osteolysis and evidence of a soft-tissue mass anteriorly (arrows). (c) Sagittal reformatted CT image shows the bone loss and cortical destruction anteriorly.
(d) Sagittal contrast-enhanced fat-saturated T1-weighted MR image shows the extensive soft-tissue component. Pathologic analysis demonstrated a high-grade sarcoma. (Case courtesy of Kambiz Motamedi, MD, UCLA Medical Center, Los Angeles, Calif.)

in patients treated with radiation and 19 years in cases of spontaneous transformation.

Although GCT is typically included in the differential diagnosis for an epiphyseal lesion, there is evidence that it arises in the metaphysis and extends into the epiphyseal region after physeal closure. For instance, in rare cases affecting pediatric patients, the tumor is centered within the metaphyseal region. In cases of multifocal GCT, lesions may occur in the metaphysis or even the diaphysis. To our knowledge, there are no reported cases in which GCT has extended from the metaphysis into the epiphysis across an unfused physis (1-4,27-30).

Mimic Lesions

Secondary ABC formation occurs in up to 14% of cases of GCT of bone (10). Therefore, these entities can mimic each other at radiologic evaluation and pathologic analysis (Fig 9). One means of differentiation between them is the presence of an enhancing soft-tissue component, which may

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Figure 9. GCT and ABC mimicking each other. (a) Anteroposterior radiograph of the left ankle shows an expansile lytic lesion in the distal fibula with a peripheral thin rim of cortex, a finding that resembles an ABC. Pathologic analysis demonstrated a GCT with secondary ABC formation. (b) Anteroposterior radiograph in another patient shows a pathologically proved ABC of the distal right femur with features closely resembling those of a GCT.



Figure 10. GCT mimicking and mimicked by metastatic disease. (a) Posteroanterior radiograph of the left wrist in a 48-year-old woman shows an expansile lytic lesion in the distal radius with a nonsclerotic margin, internal septa, and extension to the subchondral bone. Given the patient's age, metastatic disease should be considered, but pathologic analysis demonstrated a GCT. (b) Anteroposterior radiograph of the left knee in another patient shows a pathologically proved metastatic renal cell carcinoma in the proximal left tibia with features mimicking those of a GCT. (c) Digital subtraction angiogram of the left popliteal artery in the same patient as in **b** shows hypervascularity of the tumor, a common finding in metastatic renal cell carcinoma.

be present in GCT with secondary ABC formation but should not be present if the lesion is a primary ABC. The development of hemorrhage within cystic spaces of a GCT leads to the fluidfluid levels identified at cross-sectional imaging. Expansile lytic bone metastases (Fig 10) and plasmacytoma or multiple myeloma (Fig 11) can mimic GCT, particularly when they extend to the RadioGraphics

Figure 11. Multiple myeloma mimicking GCT. (a) Anteroposterior radiograph of the left knee shows a pathologic fracture through a lytic lesion in the distal femur that is eccentric in location, has a nonsclerotic margin, and extends to the subchondral bone. (b) Sagittal contrastenhanced fat-saturated T1-weighted MR image of the lumbar spine shows enhancing lesions in multiple vertebral bodies and spinous processes. Pathologic analysis demonstrated multiple myeloma.





b.

Figure 12. Chondroblastoma mimicking GCT. Posteroanterior radiograph of the left wrist shows a lytic lesion in the distal ulna with a nonsclerotic margin extending to the subchondral bone. A pathologic fracture is noted along the lateral cortex (arrow). The differential diagnosis included GCT, but pathologic analysis demonstrated chondroblastoma with secondary ABC formation. Chondroblastoma usually occurs in the epiphysis and may be included in the differential diagnosis for GCT. If present, prominent adjacent bone marrow edema may be a differentiating feature at MR imaging.

subchondral bone. Metastases and multiple myeloma should be included in the differential diagnosis if there are multiple lesions and in patients over 40 years of age. The most common expansile lytic metastatic lesions include thyroid carcinoma and renal cell carcinoma.

Chondroblastoma is an epiphyseal lesion that classically is included in the differential diagnosis for GCT (Fig 12). Both GCT and chondroblastoma can demonstrate ABC formation at MR imaging. Extensive surrounding soft-tissue and marrow edema at MR imaging may help differentiate chondroblastoma from GCT. Chondroblastoma



may also demonstrate a sclerotic margin and central calcification with a "rings-and-arcs" pattern that represents chondroid matrix.

There are subtypes of osteosarcoma that may mimic GCT. For instance, both telangiectatic osteosarcoma (Fig 13) and giant cell–rich osteosarcoma (Fig 14) are often expansile and typically do not produce the extensive osteoid matrix seen in conventional osteosarcomas. Like GCT,



Figure 13. Telangiectatic osteosarcoma mimicking GCT. Anteroposterior radiograph of the right knee shows a lytic lesion in the proximal tibia that has a nonsclerotic margin and extends to the subchondral bone. Pathologic analysis demonstrated telangiectatic osteosarcoma, which can also demonstrate fluid-fluid levels at MR imaging and should be included in the differential diagnosis for an aggressive GCT.



Figure 14. Giant cell–rich osteosarcoma mistaken for GCT. (a) Anteroposterior radiograph of the left knee shows a lytic lesion in the proximal tibia with a nonsclerotic border laterally and a pathologic fracture medially (arrow). Intraoperative analysis of a frozen section demonstrated multiple giant cells. (b) Radiograph shows the lesion after curettage with cement placement for a presumed GCT. However, further pathologic analysis demonstrated a giant cell–rich variant of osteosarcoma, which may mimic GCT at both radiographic evaluation and histologic analysis. (c) Radiograph shows the appearance after resection of the proximal tibia and placement of a modular endoprosthesis. **Figure 15.** Fibroblastic osteosarcoma simulating GCT. (a) Anteroposterior radiograph of the right knee shows a lytic lesion in the proximal tibia with a nonsclerotic border medially and loss of the majority of the cortex laterally (arrows). (b) Coronal STIR MR image shows areas of low signal intensity within the lesion. Pathologic analysis demonstrated a fibroblastic osteosarcoma.



Figure 16. GCT mimicking pressure erosions. Anteroposterior radiograph of the right hip shows a lytic lesion of the femoral head and neck that is eccentric in location and extends to the epiphysis, with destruction of cortex medially. The lesion mimics pressure erosions, as are seen in pigmented villonodular synovitis or synovial chondromatosis. However, these processes are unlikely to involve only the medial aspect of the femoral head and neck region. Pathologic analysis demonstrated a GCT with secondary ABC formation.

telangiectatic osteosarcoma often demonstrates fluid-fluid levels at MR imaging. Fibroblastic osteosarcoma also does not typically demonstrate osteoid matrix at imaging; however, central areas of low signal intensity may be seen within the lesion (Fig 15). All three subtypes of osteosarcoma can be included in the differential diagnosis for an aggressive GCT of bone.

When GCT occurs near a joint, it may mimic the pressure erosions seen in a joint-centered process such as pigmented villonodular synovitis or synovial chondromatosis (Fig 16). However, these processes should involve both sides of the joint, whereas GCT is typically eccentric in location and does not cross the joint space.

Clear cell chondrosarcoma of bone is a rare malignant lesion that often occurs in the epimetaphyseal region and can mimic GCT (Fig 17). Chondroid matrix, when present, is a differentiat-



ing feature. However, chondroid matrix is present in less than one-third of cases (31,32).

GCT of the spine and sacrum is rare and is reported in less than 3% of cases (33,34). When they occur in the sacrum, GCT and sacral chordoma may mimic each other at radiologic evaluation. However, chordomas are typically midline in location and may contain areas of calcification or sequestered fragments of bone. When these features are present, they can help in differentiation from GCT (35).



b.

Figure 17. Clear cell chondrosarcoma mimicking GCT. (a) Anteroposterior radiograph of the right knee shows a lytic lesion in the proximal tibia that has a nonsclerotic margin and extends to the subchondral bone. (b) Coronal STIR MR image shows that the lesion is predominantly hyperintense. Pathologic analysis demonstrated clear cell chondrosarcoma, which is a rare tumor that often extends into the epiphysis and may mimic a GCT.

a.



Figure 18. Mechanism of denosumab therapy. The monoclonal antibody denosumab (pink circle) targets the receptor activator of nuclear factor κ -B (*RANK*) ligand (*RANK-L*) (yellow triangle) and stops the osteoclastic activity of cells in GCT of bone.

Treatment

Traditionally, GCT of bone has been treated surgically with curettage and placement of cement (polymethylmethacrylate). However, the recurrence rates have been relatively high, ranging from 15% to 25% (2,3,7,36). The addition of mechanical burr drilling of the wall of the tumor and adjuvant cryoablation with liquid nitrogen have decreased the recurrence rate to as low as 2.3% for primary treatment, although the overall recurrence rate was 7.9% when treatment of recurrent GCTs was included (37). Aggressive GCTs may require wide excision and reconstruction with a modular endoprosthesis (Fig 14). There is debate as to whether recurrent tumor should be treated with wide resection or with curettage and cement placement; however, the recent literature cites a similar rerecurrence rate of 6% (38).

Recently, the new chemotherapeutic drug denosumab has been used to treat GCT of bone. The drug is a monoclonal antibody that targets the receptor activator of nuclear factor κ -B ligand and stops the osteoclastic activity of cells in GCT (Fig 18). This has resulted in a dramatic treatment response, with at least 90% tumor necrosis in cases at our institution (Fig 19) and in phase 2 trials (39). The dramatic sclerosis and reconstitution of cortical bone after denosumab treatment in cases at our institution suggest that preoperative treatment may make subsequent surgical resection

Teaching Point

Figure 19. Denosumab treatment of GCT. (a) Initial anteroposterior radiograph of the left knee shows a lytic lesion in the proximal tibia that is eccentric in location, extends to the subchondral bone, and has a nonsclerotic margin. (b) Anteroposterior radiograph 3 months later shows a marked increase in the size of the lesion with cortical destruction. After GCT was diagnosed at biopsy, chemotherapy treatment with denosumab was initiated. (c) Follow-up anteroposterior radiograph shows a significant treatment response, with sclerosis of the tumor and revisualization of the tibial cortex. (d) Coronal reformatted CT image more clearly shows the sclerosis, which is most pronounced along the periphery of the lesion. (e) Coronal STIR MR image shows the extent of the lesion.



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easier in cases of aggressive tumors or may even be considered as a stand-alone treatment in patients who are poor surgical candidates or in cases in which the tumor is in a difficult location to treat surgically. However, further research is needed.

Complications

Tumor recurrence is best identified by comparing follow-up images with the initial baseline postoperative images. When GCT has been treated with curettage and cement placement, follow-up radiographs should be closely inspected for any new lucency at the cement-bone interfaces (Fig 20). Cross-sectional imaging



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Figure 20. Recurrence of GCT. (a) Anteroposterior radiograph of the left knee shows a lytic lesion with a nonsclerotic margin that extends to the epiphysis. Pathologic analysis demonstrated a GCT. (b) Baseline postoperative radiograph shows the lesion after interval curettage and cement placement, as well as placement of a laterally applied plate and screw fixation. (c) Follow-up anteroposterior radiograph 8 months later shows increased lucency at the bone-cement interface (arrows). CT-guided biopsy was performed, and pathologic analysis demonstrated recurrence of GCT.



a.



Figure 21. Pathologic fracture associated with GCT. (a) Anteroposterior radiograph of the left femur shows a fracture through a lytic lesion in the distal femur that has a nonsclerotic margin and extends to the subchondral bone. (b) Anteroposterior radiograph after surgery shows the appearance after interval placement of a plate and screw fixation. The lytic lesion was not initially recognized, and the patient was later referred to our institution for distal femoral resection and placement of a modular endoprosthesis.

a.

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with CT or MR imaging allows better evaluation of osteolysis and the presence of a soft-tissue mass. If there is concern for tumor recurrence at imaging, the case should be discussed with the

orthopedic surgeon to determine an appropriate approach for CT-guided biopsy.

Pathologic fracture may occur in the setting of GCT (Fig 21). There is an increased rate of



Figure 22. Postoperative infection of a GCT. (a) Lateral radiograph of the right foot and ankle shows the appearance of a GCT in the calcaneus after treatment with curettage and cement placement. (b) Lateral radiograph 18 months later shows increased lucency due to osteomyelitis and interval placement of antibiotic-impregnated cement beads (arrows) within the calcaneus.

recurrence and a poorer functional outcome when this occurs (40). It is important to notify the referring physician that a fracture is pathologic to ensure appropriate treatment.

Postoperative infection occurs in 2%-25% of patients treated with curettage and cement placement (Fig 22) (41,42). The prevalence of infection is probably increased with more extensive surgery involving en bloc resection and placement of an endoprosthesis; however, the data on this point are currently limited (42–44).

Conclusions

GCT of bone is typically benign but may demonstrate aggressive imaging features or fluid-fluid levels and can mimic or be mimicked by a variety of other bone lesions. In the past, the mainstay of treatment was surgical, with recurrence rates of 15%–25%. Use of denosumab, a monoclonal antibody that targets the osteoclastic activity in GCT, has resulted in dramatic treatment responses in early studies.

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Teaching Points

Giant Cell Tumor of Bone: Review, Mimics, and New Developments in Treatment

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The typical appearance of GCT is best demonstrated on conventional radiographs, which show a lytic lesion that has a well-defined but nonsclerotic margin, is eccentric in location, extends to the subchondral bone, and occurs in patients with closed physes.

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GCT may also have aggressive features, such as a wide zone of transition, cortical thinning, expansile remodeling, or even cortical bone destruction and an associated soft-tissue mass.

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Most pulmonary lesions are histologically benign, with an appearance similar to that of the primary bone tumor.

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Recently, the new chemotherapeutic drug denosumab has been used to treat GCT of bone.

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When GCT has been treated with curettage and cement placement, follow-up radiographs should be closely inspected for any new lucency at the cement-bone interfaces.