Giant Cell Tumor of Bone

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ABSTRACT

Giant cell tumor of bone (GCT) is a benign, locally aggressive bone tumor. Giant cell tumor of bone primarily affects the young adult patient population. The natural history of GCT is progressive bone destruction leading to joint deformity and disability. Surgery is the primary mode of treatment, but GCT has a tendency to recur locally despite a range of adjuvant surgical options. Pulmonary metastasis has been described. However, systemic spread of GCT rarely becomes progressive, leading to death. This review presents the clinicopathologic features of GCT and a historical perspective that highlights the current rationale and contro-

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Almost 200 years ago, Sir Astley Cooper first described osteoclastomas, now called giant cell tumor of bone (GCT). For more than 100 years, scientists debated the histologic origin of the giant cells: neoplasia, infection, or inflammation. Bloodgood coined the term GCT in 1912. In 1940, Jaffe defined GCT as a neoplasia arising from the supporting connective tissue of the marrow, made up of ovoid stromal or spindle-shaped cells interspersed with multinuclear cells. Many tumors can contain giant cells: aneurysmal bone cyst, nonosteoegenic fibroma, giant cell reparative granuloma, pigmented villonodular synovitis, chondroblastoma, histiocytic fibroma, myeloma, undifferentiated sarcoma, and extrasosseous fibroxanthomatous giant cell tumor. Giant cell tumor is distinguished from these other tumors by histology.

Giant cell tumor was originally described as a myeloid sarcoma and considered to be a malignant entity. Clinicians debated the optimal treatment of GCT: surgery, radiation, or nonsurgical management. However, it was not until the benign character of GCT was recognized that amputation was replaced by radiation therapy as the treatment of choice. As time passed, poor local tumor control and sarcomatous change were noted with radiation treatment, and the field turned back to surgical intervention.

**Background**

The most common locations for GCT to arise, in order of occurrence, are around the knee (ie, distal femur and proximal tibia), proximal femur, distal radius, and distal tibia, and eccentrically in the sacrum abutting the sacroiliac joint. Giant cell tumor may also occur in flat bones, the diaphysis of any long bone, and the anterior portions of the axial skeleton. The breakdown between sexes has ranged from even to a predilection toward females (51.5% to 60%).

**Giant cell tumor accounts for approximately 5% of all biopsy-analyzed primary bone tumors in Western populations and 20% of all biopsy-analyzed primary bone tumors in the Chinese population.** Giant cell tumor typically occurs between the ages of 20 and 45 years, but GCT is also documented in skeletally immature patients. Most GCT occurs in the epiphyseal or metaphyseal region and can invade the intrarticular compartment. Giant cell tumor has a higher incidence in people living in urban (73%) rather than rural (27%) areas. Giant cell tumor is also associated with Paget’s disease.

Localized pain and tenderness to palpation are some of the presenting symptoms of GCT. Some patients may have a visible or palpable mass. Patients with GCT presenting near a joint may also have a joint effusion, decreased range of motion, or activity-related pain. Ten percent of patients present with pathological fracture. Giant cell tumor is rarely diagnosed as an incidental radiographic finding.

Giant cell tumor is a benign tumor and rarely metastasizes or causes death. However, GCT can metastasize to other portions of the body, specifically the lungs, kidneys, liver, and brain. These tumors are classified as benign. Pulmonary metastasis occurs in 1.8% to 9.1% of cases in the extremities and in 13.5% of cases in the spine. Pulmonary metastases commonly present 3 to 4 years after the initial diagnosis and are rarely fatal. Pulmonary metastases are 6 times more likely to appear in patients with a recurrent GCT. Unfortunately, if GCT presents with pulmonary metastasis, it deviates from its traditionally benign course and has a mortality rate of 14% to 25%.

There are documented cases of malignant GCT, but these cases are rare. Malignant GCT has 1 of 3 histologic subtypes: malignant fibrous histiocytoma, fibrosarcoma, or osteosarcoma.

Malignant GCT usually occurs after multiple locally recurrent lesions or lesions previously treated with radiation. Patients with Paget’s disease experience multiply locally recurrent GCT; half are benign and half are malignant. In one case series, 95% (18/19) of malignant GCT had radiation therapy prior to recurrence. Survival rates for malignant GCT approaches 30% at 5 years after diagnosis of the malignant tumor. The patients with the best survival after malignant GCT tended to have more radical procedures, including amputation.

Finally, the rarest presentation of GCT is multicentric GCT. Multicentric GCT has 2 or more separate GCT lesions confirmed by histopathology. From 1950 to 2002, only 48 cases of multicentric GCT were documented in case reports and small case series. Multicentric GCT is further subdivided into synchronous and metachronous. Synchronous GCT presents with multiple GCT lesions at once or with the second GCT diagnosed within 6 months of the initial GCT. Metachronous GCT is a second GCT diagnosed 6 months after the initial GCT. Multicentric GCT patients tend to present at an earlier age than those with GCT, at approximately 21 years of age. The female to male ratio is 2:1. Synchronous GCT is more common than metachronous. However, rates of local recurrence, pulmonary metastasis, and malignant transformation for multicentric GCT are similar to those of GCT. Multicentric GCT should be a diagnosis of exclusion, and each GCT must be differentiated from other neoplasms that can present in isolation or with multiple lesions (Table).

**Evaluation**

A prebiopsy workup is required for surgical planning. Orthogonal radiograph and computed tomography (CT) scan evaluate the quality of the bone, and magnetic resonance imaging (MRI) of the entire bone evaluates soft tissue extension. A chest CT scan is mandatory in disease
staging to rule out pulmonary metastases. Blood chemistry and metabolic workup are benign. If there is a pathologic fracture or a malignant GCT, the alkaline phosphatase level may be slightly elevated.2

A needle biopsy or incisional biopsy of the expansile, radiolucent, osteolytic lesion clarifies the differential diagnosis via pathology.2,7 At the time of biopsy, fresh-frozen sections should be evaluated with clinical, radiographic, and histologic correlation by the pathologist. After a pathologic diagnosis of GCT, patients require surgical excision because the natural progression of GCT has well-documented morbidity and mortality. Patients treated surgically without the use of adjuvants have rates of local recurrence ranging from 18% to 50%.34 The rate of local recurrence varies with the extent of GCT removal. Patients with incomplete intralesional excision have a guarantee of local recurrence, whereas radical resection has a local recurrence rate approaching 0%.7,21,35 Ninety-seven percent of recurrences will occur within 2 years.2 Most local recurrences occur within 3 years of the index surgery. However, recurrence has been reported as late as 30 years after the initial diagnosis.16

### IMAGING

On radiographs, GCT is an expansile, radiolucent, osteolytic lesion with thinning or fading cortical bone (Figure 1). Giant cell tumor is a well-circumscribed or geographic lesion rarely showing a periosteal reaction.22 It is located in a juxta-articular position eccentric in the epiphysis and contains a sclerotic metaphyseal margin.5-7 Many benign and malignant lesions have the same radiographic appearance (Table).2

Radiographs are used to assess local recurrence after GCT resection. A greater than 5-mm rim around cement used to fill a defect after GCT resection is suggestive of local recurrence.36

Computed tomography has been found to be useful in evaluation of GCT. The density of GCT tissue on CT tends to lie between 20 and 70 Hounsfield units (Figure 2). Radiolucent, osteolytic lesions below 20 Hounsfield units tend to be aneurysmal bone cysts. This information is helpful for the preoperative workup and surgical planning.14

Magnetic resonance imaging of GCT demonstrates a low signal with respect to muscle on T1 imaging and a heterogeneously higher signal with respect to muscle on T2 imaging (Figure 3). More than 60% of GCT lesions contain hemosiderin deposits that create low signal intensity on T2 spin echo sequences. This effect is due to the excessive amount of extravascular erythrocytes in contact with the GCT. However, several other tumors contain hemosiderin, limiting the usefulness of MRI in diagnostic workup of GCT.37

### PATHOLOGY

In 1961, Schajowicz23 provided the pathologic and histological foundation of GCT. Giant cell tumor displays a soft, fleshy appearance on gross examination.
with areas that vary in color from “gray to a light red or dark hemorrhagic hue.” The tumor itself is separated by thin septa of connective tissue or bone, and the complex is surrounded by a thin shell of bone. In advanced GCT, small, bright red or brownish cavities indicative of necrosis can be found within the tumor. Older tumors tend to show more advanced necrosis, with large blood spaces and cystic degeneration. Larger tumors typically extend beyond the cortex into the surrounding soft tissue. At resection, large tumors may be pulsatile.

Histopathology shows proliferation of round to oval, polygonal, or elongated mononuclear cells mixed with numerous large osteoclast-like giant cells that have 50 to 100 nuclei. The giant cells display a round “fried-egg” appearance with centrally located nuclei and a wide, thin peripheral rim of acidophilic cytoplasm. Two mononuclear types are routinely seen during the histologic evaluation of giant cell tumor: round cells and spindle cells. The nuclei of the round cells (solid arrows) are similar to those of giant cells. The spindle cells (hollow arrows) are the neoplastic component of a giant cell tumor. Mitosis may be present; however, atypical mitotic figures suggest transformation to malignant giant cell–rich sarcoma. The tumor may be more aggressive and extend to soft tissue or metastasize to lungs; however, histologic features are always similar to the primary GCT. Areas of fibrosis or aneurysmal change may be seen. Necrosis may be present, especially in larger tumors, and may have suspicious nuclear atypia. Approximately 35% of GCT lesions show histologic evidence of osteoid, although GCT typically does not have osteogenetic capacity. Small foci of bone formation may be found, especially after pathological fractures.

The staging system for benign bone lesions by Bertoni et al uses clinical, dehydrogenase, tartrate-resistant acid phosphatase, and alpha-naphthyl esterase enzymes. Giant cells are believed to arise from stromal cells of mononuclear phagocyte lineage and are not neoplastic. Mitosis may be present; however, atypical mitotic figures suggest transformation to malignant, giant cell–rich sarcoma.

Two mononuclear types of cells are routinely seen during the histologic evaluation of GCT: round and spindle (Figure 4). The nonneoplastic round cells are CD13+ and CD68+. The nuclei of the round cells (solid arrows) are similar to those of giant cells. The spindle cells (hollow arrows) are the neoplastic component of a giant cell tumor. Mitosis may be present; however, atypical mitotic figures suggest transformation to malignant giant cell–rich sarcoma.
pathological, and radiographic findings to stage GCT lesions into 3 categories. Stage 1 classifies the tumor as latent with static growth and without evidence of local aggression. Stage 2 classifies the tumor as active with expansile growth and evidence of local aggression (ie, a radiolucent lesion changing the contour of the cortical bone). Stage 3 classifies the tumor as fast growing with evidence of local aggression (ie, pathologic fracture and extension into the surrounding soft tissues).26 Giant cell tumor typically presents as a stage 2 or 3 lesion depending on extraneous extent. No histopathologic grading system to date is able to predict local recurrence, metastasis, or prognosis.7

Molecular Biology

Giant cell tumor is poorly understood on the molecular level. Several authors have explored the potential molecular signals involved in GCT differentiation and maturation. The ratio of osteoprotegrin ligand to the decoy receptor osteoprotegrin expression was much greater in GCT than in regular bone, identifying a possible reason why this tumor exhibits a higher degree of osteoclastogenesis.40,41 Another factor of interest is the receptor activator of nuclear factor kappa-β ligand (RANKL) pathway involved in osteoclastogenesis. The giant cells resemble osteoclasts in function and phenotype but overexpress RANKL typically expressed by osteoblasts.42 Osteoprotegrin, a decoy inhibitor of RANKL, was expressed at low levels compared with normal serum.40 Spindle cells also express RANKL mRNA and protein.40 The expression of RANKL in GCT explains the high bone resorption characteristic of GCT. Receptor activator of nuclear factor kappa-β ligand is the target of denosumab, a RANKL monoclonal antibody. All (20/20 patients) GCT lesions treated with denosumab demonstrated a greater than 90% decrease in giant cells.43

Giant cell tumor osteolysis is not completely understood. Cathepsin K is a potent collagenase expressed by osteoclasts. It is responsible for degrading the collagen matrix after bone resorption. It has been documented as the most abundant and active protease expressed by GCT.44 In addition, matrix metalloproteinase-9 and cathepsin L are expressed in GCT. However, these proteases are found in their inactive form. The vacuolar-type H+ ATPase is also highly expressed in GCT. These are proton pumps that facilitate and optimize cathepsin K activity. Cathepsin K requires an acidic environment for protease function. Future therapeutic options could target the factors creating an acidic environment that allow for osteolysis.

Transforming growth factor-β1 (TGF-β1) has been consistently found in the mononuclear round cells and giant cells. By using in situ hybridization and Northern blot analysis, the TGF-β1 gene transcript was detected in tumor cells and reactive components.38 When TGF-β1 was added to the medium, it showed a chemotactic effect on osteoclast cells. When TGF-β1 antibodies were added to the medium, there was a significantly reduced chemotaxis. It is currently believed that TGF-β1 acts as a chemotactic agent recruiting mononuclear precursors to form the reactive osteoclast-like multinuclear giant cells.

Tumor Markers

Several studies have investigated the role of serum acid phosphatase as a tumor marker in GCT. One study noted that nearly half of its cases (15/32) had elevated acid phosphatase, whereas the other half had normal levels.45 Patients with larger GCT lesions had higher levels of acid phosphatase. However, postoperatively both populations saw a significant decrease in serum acid phosphatase levels. Despite these results, acid phosphatase is not an effective screening marker for adequate resection or local recurrence.

Creatine kinase isoenzyme BB (CK-BB) is another tumor marker investigated in GCT. This is an enzyme that catalyzes the reversible transfer of phosphate from phosphocreatine to adenosine phosphate to regenerate adenosine triphosphate. It is rarely found in the serum of healthy individuals. It has been most commonly observed in patients with brain injuries, gastric cancer, prostate cancer, and certain types of osteoporosis.46 It is not elevated in patients with osteosarcoma, aneurysmal bone cyst, malignant fibrous histiocytoma, or common osteolytic entities. Patients with GCT present with an elevated level of CK-BB, and, after excision, their CK-BB level returns to normal within 2 weeks. Despite these results, CK-BB is not an effective screening marker for adequate resection or local recurrence.

Prognosis

Telomerase is an enzyme that maintains the ends of chromosomes, which degrade or shorten with each cellular division. Altered telomerase activity is frequently seen in high-malignancy tumors. The telomerase activity measured in 16 GCT lesions demonstrated an increase in telomerase activity in GCT.47 More specifically, the highest telomerase activity and shortest telomere length was found in patients with recurrent GCT. Patients with rapidly growing, recurrent, or pulmonary metastasis all displayed higher levels of Ki67 positive cells as compared with patients with a more benign presentation of GCT.48 Identifying this genetic subtype of GCT may provide an indication for more aggressive surgical and medical interventions.

Research is ongoing to discover markers that have prognostic value in GCT. A study of 92 patients with GCT (72 patients had no recurrence, 11 had local recurrence, and 9 had distant metastasis) used immunochemistry and quantitative polymerase chain reaction to analyze the interleukin-6 (IL-6), urokinase type plasminogen activator (u-PA), urokinase type plasminogen activator receptor (u-PAR),
and urokinase type plasminogen activator inhibitor (PAI-1) genes of the respective GCT lesions. Interleukin-6 is a cytokine released by GCT that stimulates resorption, and the urokinase pathway is implicated in the degradation of extracellular matrix. These genes have abnormal levels in other malignancies and have been implicated in the metastasis and invasion.

Genes were considered amplified if they were 3 times the β-actin control gene. All 4 genes were found to be elevated compared with their control gene in the metastatic group. None of the genes were found to be elevated in the local recurrence group. This likely indicates that the local recurrence is due to inadequate resection and the metastatic component is a more aggressive tumor.

Giant cell tumor has a strong association with major histocompatibility complex (MHC) class II antigen (HLA-DRB1*080). Human leukocyte antigens (HLA) are cell surface glycoproteins that help compose the immune system. The MHC class II antigen is found in many immune cells (B-cells, activated T-cells, dendritic cells, macrophages, and thymic epithelial cells). These cells present an antigen to CD4+ T-cells and activate an immune response. Defects in this portion of the immune system can allow tumor growth to go uninhibited.

Five (62.5%) of 8 patients with documented HLA-DR–negative GCT were positive for the HLA-DRB1*080 haplotype as compared with the healthy control population (2%). People with this genotype are at a high risk for developing GCT.

The expression of several cell cycle regulation genes, oncogenes, angiogenes, and genes involved in the degradation of extracellular matrix had no correlation with GCT prognosis.

These include TP53, CDKN1B, CCND1, MYC, TGFB2, VEGF, MMP9, and PLAU. However, recurrent tumors and malignant tumors demonstrated higher rates of aneuploidy as compared with the diploidic nature of the benign GCT lesions.

**Surgical Technique**

Giant cell tumor is implantable. It can seed surrounding soft tissues and operative scars. Meticulous surgical technique should be used when removing GCT. Ultimately, the more complete the GCT removal, the lower the rate of local recurrence.

Thorough GCT removal is intimately dependent on the extent of curettage, either manual or via high-speed burr, or extension of the curettage beyond the surgical margin via adjuvant therapy.

Meyerding presented an outline for the treatment of GCT that has led to the current standard of care today: (1) complete primary tumor removal (eg, intralesional curettage or wide resection) to prevent recurrence and (2) filling of the bone void (eg, autograft bone, allograft, bone, or bone substitute) for reconstruction.

Prior to 1949, patients with distal femoral GCT that extended into the joint primarily underwent resection and arthrodesis. Kraft and Levinthal documented the first case of joint preservation surgery for GCT when they created an exact replica of a patient’s distal femur, hand carved from acrylic, and replaced the distal femur of a patient who presented with GCT and pathologic fracture. Several years later, Gold performed the same procedure in the distal radius of a patient with recurrent GCT.

In 1959, Johnson and Dahlin presented one of the earliest articles outlining varying degrees of surgical treatment of GCT, including curettage, excision, irradiation, and amputation. They found irradiation alone to be ineffective at treating GCT and that it predisposed patients to sarcomatous tumors at the primary site. They recommended that excision was the preferred treatment with the least amount of secondary intervention because these patients tended to have less local recurrence and better long-term functional results than those undergoing curettage, irradiation, and amputation.

Interestingly, when radiation therapy was the primary treatment regimen due to surgically inaccessible tumors, GCT lesions appeared to increase in size and activity. The tumor would then heal by fibrosis and ossification within the tumor mass, and the cortex showed little to no change.

Patients who underwent wide resection had a higher complication rate and lower functional outcomes than patients with intralesional manual curettage and adjuvant therapy (eg, polymethylmethacrylate [PMMA], phenol). Some studies reported no difference with adjuvant therapy. The recurrence rate was 14% (19/137 patients) when treated with intralesional manual curettage and PMMA. The recurrence rate was 12% (7/59 patients) when treated with intralesional extended curettage with a high-speed burr and bone graft. Polymethylmethacrylate has been widely used due to the understanding that free radicals and the thermal effects of the polymerization reaction may cause up to 3 mm of necrosis in cancellous bone. However, adding PMMA or allograft bone after thorough intralesional extended curettage has been shown to prevent recurrence, suggesting the extent of tumor removal is paramount regardless of the chemical or thermal properties of PMMA. Polymethylmethacrylate has advantages over bone graft because it is inexpensive and allows immediate postoperative weight bearing.

Phenol is another commonly used adjuvant therapy. It causes protein coagulation, DNA damage, and cellular necrosis. It is most commonly used in addition to PMMA after intralesional curettage. Phenol and curettage alone has a reported local recurrence rate between 15% and 26%. Phenol and PMMA have a reported local recurrence rate of approximately 12%.

Care must be taken when using phenol because it can induce chemical burns. It is rapidly absorbed by skin and open wounds and is toxic to the liver, heart, kidneys, and nervous system.
Another chemical adjuvant therapy is aqueous zinc chloride. Zhen et al.\textsuperscript{62} used intralesional curettage, zinc chloride, and bone grafting in 92 patients, and 12 (13\%) had a local recurrence.

Liquid nitrogen cryotherapy is another adjuvant therapy that has been used with success. In a 17-year review of 100 GCT lesions treated by liquid nitrogen cryotherapy, only 2\% (2/100 patients) had a recurrence.\textsuperscript{63} Another study documented 4\% (1/25 patients) had a recurrence after liquid nitrogen cryotherapy.\textsuperscript{64} However, the degree and control of bone necrosis and risk of skin necrosis has prevented widespread use of liquid nitrogen cryotherapy. Fractures are a common complication following liquid nitrogen cryotherapy. One study reported a 42\% (5/12 patients) fracture risk after intralesional extended curettage with a high-speed burr and liquid nitrogen cryotherapy.\textsuperscript{64}

Argon beam coagulation is an adjuvant therapy that has been gaining traction in the orthopedic community. Argon beam coagulation causes a high-frequency electrical energy that coagulates and shrinks tissue at a temperature of 205°C.\textsuperscript{65} In a case series of 37 patients treated with intralesional curettage, argon beam coagulation, and cementation, 3 (8\%) had a bony recurrence and 1 (3\%) had a soft tissue recurrence over a mean 74-month follow-up period.\textsuperscript{19} Advantages of argon beam coagulation over other adjuvant therapies like liquid nitrogen cryotherapy and chemical agents (eg, phenol, zinc chloride) include precise local control of the device and no risk of chemical toxicity.\textsuperscript{19,65}

Reconstruction of GCT around the knee (ie, distal femur or proximal tibia) with allograft bone after wide excision provided good to excellent long-term results in 76\% (42/55) of patients.\textsuperscript{66} Intralesional curettage with bone void filling has a lower complication rate and higher functional outcomes when compared with wide resection.\textsuperscript{59} A cadaveric study found superior biomechanical results with the addition of cross-screw augmentation of PMMA.\textsuperscript{67} The strength and stiffness of this procedure may provide earlier return to rehabilitation and activity.

Reconstruction of GCT around the wrist with a free vascularized fibula after wide excision has allowed surgeons to perform larger excisions without loss of function or cosmesis of the distal forearm.\textsuperscript{68} However, reconstruction with allograft bone avoids donor morbidity but has a higher complication rate.\textsuperscript{69}

Reconstruction of GCT around the pelvis is best approached on a case-by-case basis because pelvic lesions tend to go undiagnosed for much longer periods of time. It is difficult to discern lytic lesions from gas in the bowels on pelvic radiographs.\textsuperscript{70} Pelvic lesions have a larger volume in which to expand before a mass is detected. Pelvic lesions occupy non-weight-bearing portions of the axial skeleton, limiting pain. Hence, it is difficult to create a standard treatment algorithm for these lesions. The patients with the best results were those treated with wide excision and spinal arthrodesis.\textsuperscript{70,71} Irradiation of these lesions is debated. Some reports show sarcomatous changes or failure to contain the disease,\textsuperscript{9,10} whereas a recent study on megavoltage radiation therapy greater than 40 Gy delivered over multiple sessions demonstrated no disease progression when used in the axial skeleton.\textsuperscript{72}

In recurrent GCT after initial intralesional curettage and cementing, it was found that recurretting and cementing the lesions did not increase further recurrence or metastasis vs en bloc resection. In one retrospective study, 14\% (19/137) of patients initially treated with intralesional curettage and PMMA cementation had a local recurrence.\textsuperscript{65} Fifteen of the 19 patients with a recurrent GCT were treated with repeat intralesional curettage and PMMA cementation, and 13\% (2/15 patients) had a second recurrent GCT. Repeat intralesional curettage and PMMA cementation allowed patients to maintain higher functional scores when compared with wide excision and allograft reconstruction.\textsuperscript{21,61}

**CONCLUSION**

Giant cell tumor is a rare benign bone tumor primarily affecting the young adult patient population. Giant cell tumor is an osteolytic lesion leading to progressive bone destruction, fracture, and disability. Surgery is the primary mode of treatment, but GCT has a tendency to recur. Fortunately, surgical and adjuvant treatment has been exhaustively documented over time, allowing the orthopedic community to come to a consensus on the most appropriate treatment. Complete GCT resection via extended intralesional curettage with a high-speed burr using adjuvant treatments to prevent recurrence is the first-line treatment. Recurrent GCT or GCT with inadequate remaining host bone to support intralesional reconstruction may be more appropriate candidates for primary wide excision and reconstruction. Pulmonary metastasis has been described. However, systemic spread of GCT rarely becomes progressive, leading to death. Radiation therapy should be avoided because it provides little if any therapeutic advantage and may increase the rate of sarcomatous change.

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