

CURRENT CONCEPTS REVIEW**Giant Cell Tumor of Bone - An Overview**

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Giant Cell tumors (GCT) are benign tumors with potential for aggressive behavior and capacity to metastasize. Although rarely lethal, benign bone tumors may be associated with a substantial disturbance of the local bony architecture that can be particularly troublesome in peri-articular locations. Its histogenesis remains unclear. It is characterized by a proliferation of mononuclear stromal cells and the presence of many multi-nucleated giant cells with homogenous distribution.

There is no widely held consensus regarding the ideal treatment method selection. There are advocates of varying surgical techniques ranging from intra-lesional curettage to wide resection. As most giant cell tumors are benign and are located near a joint in young adults, several authors favor an intralesional approach that preserves anatomy of bone in lieu of resection. Although GCT is classified as a benign lesion, few patients develop progressive lung metastases with poor outcomes. Treatment is mainly surgical. Options of chemotherapy and radiotherapy are reserved for selected cases. Recent advances in the understanding of pathogenesis are essential to develop new treatments for this locally destructive primary bone tumor.

Keywords: GCT, GCTB, Giant Cell Tumor of Bone, Review of giant cell tumor

Introduction

Cooper in 1818 first described Giant cell tumors (GCT) of the bone (1). Later Nelaton showed their local aggressiveness, and Virchow revealed their malignant potential. GCT represents approximately 5% of all primary bone tumors (2,3). More than half of these lesions occur in the third and fourth decades of life (3). GCTs are benign tumors with potential for aggressive behavior and capacity to metastasize. Although rarely lethal, benign bone tumors may be associated with a substantial disturbance of the local bony architecture that can be particularly troublesome in peri-articular locations.

Although considered to be benign tumors of bone, GCT has a relatively high recurrence rate. Metastases occur in 1% to 9% of patients with GCT and some earlier studies have correlated the incidence of metastases with aggressive growth and local recurrence (4,5).

There is no widely held consensus regarding the ideal treatment method selection. There are advocates of

varying surgical techniques ranging from intra-lesional curettage to wide resection. The goals of treatment are eradication of the tumor, preservation of limb function, and prevention of local recurrence and distant metastasis. Several adjuvant methods beyond simple curettage have been reported in the orthopaedics literature during the last decade to facilitate better local control and prevent recurrences (1).

The purpose of this narrative review was to comprehensively outline the current concepts of GCT of bone. Although the information is available through textbooks, description of the various treatment regimens and their impact on each other and a literature review has been highlighted here.

Epidemiology

GCT of bone constitutes 20% of biopsy analyzed benign bone tumors. It affects young adults between the ages of 20 and 40 years, several authors have reported a slight predominance of women over men. However, GCT can be

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seen in patients over 50 years old.

Location

Ninety percent of GCT exhibits the typical epiphyseal location. Tumor often extends to the articular subchondral bone or even abuts the cartilage. The joint and or its capsule are rarely invaded. In rare instances in which GCT occurs in a skeletally immature patient, the lesion is likely to be found in the metaphysis (6,7). The most common locations, in decreasing order, are the distal femur, the proximal tibia, the distal radius, and the sacrum (8). Fifty percent of GCTs arise around the knee region. Other frequent sites include the fibular head, the proximal femur, and the proximal humerus. Pelvic GCT is rare (9,10). Multicentricity or the synchronous occurrence of GCT in different sites is known to occur, but is exceedingly rare (2,11-13).

Clinical presentation

Pain is the leading symptom relating to the mechanical insufficiency resulting from the bone destruction. A soft tissue mass or bump can occasionally be seen and results from the cortical destruction and tumor progression outside bone. GCT is often found close to the joint thus limited range of motion is common, joint effusion and synovitis are also possible. At diagnosis, approximately 12% of patients with GCT present with pathologic fracture (13-17). Presentation with a pathologic fracture is thought to indicate more aggressive disease with a higher risk of local recurrence and metastatic spread (1,17,18).

Radiology

GCT of bone has characteristic radiolucent, geographic appearance with a narrow zone of transition found at the margin of the lesion. This margin, contrary to that of many other benign lesions, lacks a complete sclerotic rim. Typically, there is no visible mineralization within the tumor matrix. GCTs are eccentric lesions in epiphyseal region with a tendency to extend within centimeter of the subchondral bone. Imaging modalities such as computed tomography and magnetic resonance imaging, may be useful to confirm the typical subchondral location of these lesions within the bone and the extent of a soft tissue mass, either beyond the bone cortex or into the adjacent joint (1,19,20).

Pathology

Grossly, GCT of bone appears brownish in color and is usually solid; however, some tumors may have a hemorrhagic, cystic component. The typical histological appearance is that of abundant giant cells with a benign spindle cell background. The nuclei of the spindle cells are identical to those found in the giant cells. Despite a high degree of suspicion for GCT of bone a planned biopsy to confirm the diagnosis histologically, is needed (1,20).

Differential diagnosis

Various benign and malignant tumors unfortunately may be confused with GCT. They include the brown tumor of hyperparathyroidism, aneurysmal bone cyst,

telangiectatic osteosarcoma, and malignant fibrous histiocytoma (1,20,21).

Basic sciences

Three types of cells are found in benign GCT of bone (1,22). Type I cells look like interstitial fibroblasts, make collagen, and have the capacity to proliferate. This cell is likely the tumor component of GCT. Type I cells share some features of mesenchymal stem cells, they possess features that suggest they could represent an early differentiation into osteoblasts (1,22-25). Type II cells are also interstitial but resemble the monocyte/macrophage family and could be recruited from the peripheral blood stream (26). These cells are thought to be precursors of the multinucleated giant cells. Type III cells are the multinucleated giant cells. They share many characteristics of osteoclasts and have similar morphologies (1,27). They possess enzymes for bone resorption, including tartrate resistant acid phosphatase and type II carbonic anhydrase (1,28). Significant level activity for insulin like growth factor I and II is found in type II and type III cells but absent in type I cells, which suggests that these factors are important in the development and regulation of GCT (29-30). Genetically, 80% of individuals with giant cell tumor of bone exhibit the cytogenetic abnormality of telomeric associations (tas), whereas half of the cells in the tumor show the tas abnormality (1,31). The RANK pathway is often reported to be involved in the pathogenesis of giant cell tumor of bone. This pathway is a key signaling pathway of bone remodeling that plays a critical role in differentiation of precursors into multinucleated osteoclasts, and activation of osteoclasts leading to bone resorption (32).

Classification

GCT were classified by Enneking and later by Campanacci based on radiographic appearance. They described three stages that correlate with tumor local aggressiveness and risk of local recurrence, Stage I – latent, Stage II – active, Stage III – aggressive. Campanacci attempted to grade the lesions based on radiological appearance. All of the tumors, both primary and recurrent, are graded radiographically, using the designations Grade I, Grade II, Grade II with fracture, and Grade III.

- Grade – I tumor has a well-margined border of a thin rim of mature bone, and the cortex is intact or slightly thinned but not deformed.
- Grade – II tumor has relatively well defined margins but no radiopaque rim; the combined cortex and rim of reactive bone is rather thin and moderately expanded but still present. Grade-II lesions with a fracture are graded separately.
- Grade – III designates a tumor with fuzzy borders, suggesting a rapid and possibly permeative growth; the tumor bulges into the soft tissues, but the soft-tissue mass does not follow the contour of the bone and is not limited by an apparent shell of reactive bone.

Treatment

Surgical resection is the universal standard of care for treatment of GCT of bone. As most giant cell tumors are benign and are located near a joint in young adults, several authors favor an intralesional approach that preserves anatomy of bone in lieu of resection (14,33-37). Various studies suggest that wide resection is associated with a decreased risk of local recurrence when compared with intralesional curettage and may increase the recurrence free survival rate from 84% to 100% (1,35,38,39). However, wide resection is associated with higher rates of surgical complications and leads to functional impairment, generally necessitating reconstruction (16,39,40-43).

Local control without sacrificing joint function has traditionally been achieved by intralesional curettage with autograft reconstruction by packing the cavity of the excised tumor with morsellised iliac corticocancellous bone. Regardless of how thoroughly performed intralesional excision leaves microscopic disease and hence has a reported recurrence rate as high as 60%. The key to ensuring an adequate curettage with complete removal of tumor is obtaining adequate exposure of the lesion (44-46). This is best achieved by making a large cortical window to access the tumor so as to avoid having to curette under overhanging shelves or ridges of bone. Use of a headlamp and dental mirror combined with multiple angled curettes help to identify and access small pockets or residual disease, which may otherwise result in recurrence. A high power burr to break the bony ridges helps extend the curettage (47). A pulsatile jet-lavage system used at the end of the curettage helps to bare raw cancellous bone and physically washout tumor cells (48-50).

Historically, the rate of local recurrence after curettage alone and bone grafting has been reported to range between 25% and 50% (12,33,41,50). This has led surgeons to enhance their surgical procedure with use of chemical or physical adjuvants such as liquid nitrogen, acrylic cement, phenol, hydrogen peroxide, locally delivered chemotherapy, or radiation therapy (1,4,36,51-54). The latter has been linked with malignant transformation in the past but the risk of this complication has been recently challenged and may be different with modern radiotherapy modalities (33,36,55-57). Local adjuvant therapy has been shown to be useful in controlling recurrence rates (58). The literature has shown 6%-25% recurrence rates in GCT treated with curettage and local adjuvant therapy (59-63).

Having described that, recent studies have questioned the role of adjuvants and filling agents in reducing the recurrence rate of GCT, they seem to infer that adequate removal of the tumor seems to be a more important predictive factor for the outcome of surgery than the use of adjuvants. Trieb demonstrated that local recurrence rate of GCT located in long bones treated with or without phenol is similar (50). Prosser recommended primary curettage for intraosseous GCT without adjuvant treatment or filling agents (43).

Reconstructing the defect after curettage can be quite a challenge. If the gap left behind after the curettage is

small and does not jeopardize the structural integrity of bone it can be left alone and the cavities fill up with blood clot, which then gets ossified to form bone. For larger defects the traditional methods of reconstruction have been cementation or use of bone graft with each method having its advantages and disadvantages.

Cementing the defect using polymethylmethacrylate (PMMA) has shown encouraging results (64). It is postulated that the exothermic reaction of PMMA generates local hyperthermia, which induces necrosis of the remaining neoplastic tissue, yet it does not extend to the normal tissues to result in local complications (16). In theory, the possibility that the polymerization, of PMMA may produce a local chemical cytotoxic effect cannot be excluded. Cytotoxic agents like methotrexate and adriamycin have been incorporated in bone cement and other drug delivery systems in an attempt to reduce recurrence.

Rock et al. describe the rates of recurrence after simple curettage range from 10% to 47%, as compared with 10% after curettage and adjuvant treatment with cement (33). The long-term effects of cement replacing the subchondral region of a major weight-bearing joint are unknown. The risk of subchondral cement causing damage to the cartilage and subsequently degenerative arthritis has been cited in the literature, but remains unproven (65,66). Articular degeneration with associated biomechanical changes after treatment with cement has been observed in the weight bearing area in animal studies, whereas other studies have demonstrated the superior ability of subchondral autogenous bone grafts to restore the subchondral osseous anatomy to its normal state (47,65).

To try and forestall this potential problem of late articular degeneration in subarticular lesions where the amount of residual subchondral bone after an extended curettage is less than 1 cm, a multi layer reconstruction technique is recommended (67). A mixture of morsellised auto and allograft (about 1 cm thick) is packed adjacent to the subarticular surface. A layer of gelfoam is layered over this and the remaining cavity is packed with cement. This helps reduce heat damage from the curing cement and the subarticular bone graft. Another perceived advantage is, that should recurrence occur, the danger of damage to articular cartilage during removal of cement is reduced.

Use of steinmann pins has also been described to reinforce the bone cement used to fill the large subchondral defects following intralesional curettage. However, whether this is of real benefit in improving the stability of the defect is controversial. At times it may be necessary to augment the construct with internal fixation (68,69).

Occasionally, even in benign tumors resection may be the preferred option when bone salvagability by intralesional methods would result in severe mechanical compromise in ultimate function. In so-called expendable bones like the lower end ulna, upper end fibula etc. excision may be attempted as the treatment of choice. If marginal/wide local excision is

ected as the treatment of the lesion, either primarily or in recurrence, then reconstruction necessarily implies reconstruction of the joint surface, since GCT invariably involves the end of a long bone and causes significant dysfunction of the joint surface. The options includes: 1) Megaprosthesis joint replacement, 2) Biologic reconstruction with autograft arthrodesis with internal/ external fixation, microvascular fibula reconstructions, Ilizarov method of bone regeneration, osteo-articular allografts (70).

Local recurrence

In the literature, a recurrence after three years has been considered exceptional (35). Historically local recurrence rate ranged from 20% to 50% averaging 33% (2,12). Reports suggests an improvement in the local control rate of these tumors with modern curettage techniques. Recently it has been suggested that total serum acid phosphatase (TACP) could be used as a tumor marker for monitoring response to treatment of GCT. Even though the increasing grade from I to III is not a reflection of the biologic aggressiveness of the tumor, various authors have documented an increased rate of recurrence in Grade III lesions. This may be due to the difficulty in achieving complete clearance. The principles of management remain the same even in recurrent tumors.

Chemotherapy and Radiotherapy

GCT of bone demonstrates profound responses to chemotherapy but these cases are anecdotal and its incidence is disappointing. At the present time there are no recognized effective chemotherapeutic agents available for the management of these tumors. Literature documents a close association of secondary sarcomatous transformation in the region of giant cell tumors treated by radiation therapy (55). Radiotherapy is recommended when complete excision or curettage is impractical for medical or functional reasons (generally for lesions of the spine and sacrum) or for aggressive tumors.

Embolisation

Unresectable GCTs (e.g. certain sacral and pelvic tumors) can be managed with transcatheter embolisation of their blood supply. Since flow reconstitution invariably occurs, embolisation is performed at monthly intervals until significant pain palliation is achieved. Tumors in these areas amenable to surgical resection also benefit by preoperative embolisation in an attempt to reduce the amount of intra operative blood loss (1).

Bisphosphonates

Reports indicate that topical or systemic use of pamidronate or zoledronate can be a novel adjuvant therapy for giant cell tumor. Bisphosphonates act by targeting osteoclast like giant cells inducing apoptosis and limiting tumor progression (71-75).

Metastasis in Giant Cell Tumors

Although GCT is classified as a benign lesion, few

patients develop progressive lung metastases with poor outcomes (25,76,77). Metastases after GCT of bone are rare, occurring in only 3% of patients the behavior of pulmonary metastases is unpredictable (5,12,38,78-81). There is an increased risk of pulmonary metastasis of GCT of bone in patients who are younger, present with Enneking stage-III disease, develop local recurrence, and/or present with axial disease (82).

The metastatic lesions are histologically identical to the primary lesions. The mean interval between the onset of the tumor and the detection of lung metastases is about 18 to 24 months (82). The natural history of metastatic lesions is unpredictable. Complete excision of metastases has been very successful with good long-term survival, but those with inoperable disease may die from metastases. Hence, metastatic lesions should be resected if possible. Radiation and chemotherapy have enjoyed limited success. Steroids have been successfully used in the control of unrespectable metastases. Metastatic disease in giant cell tumor does not carry the same poor prognosis as malignant tumors. Therapy should be direct at achieving adequate local control and if possible complete excision of the metastatic lesions.

Anti-RANKL therapy

The giant cells over express a key mediator in osteoclastogenesis: the RANK receptor, which is stimulated in turn by the cytokine RANKL, which is secreted by the stromal cells. The RANK/RANKL interaction is predominantly responsible for the extensive bone resorption by the tumour. Studies with denosumab, a monoclonal antibody that specifically binds to RANKL, resulted in dramatic treatment responses, which led to its approval by the United States Food and Drugs Administration (US FDA). Recent advances in the understanding of GCTB pathogenesis are essential to develop new treatments for this locally destructive primary bone tumour (83-86).

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