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Update on Giant Cell Tumor of Bone

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Abstract: 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.

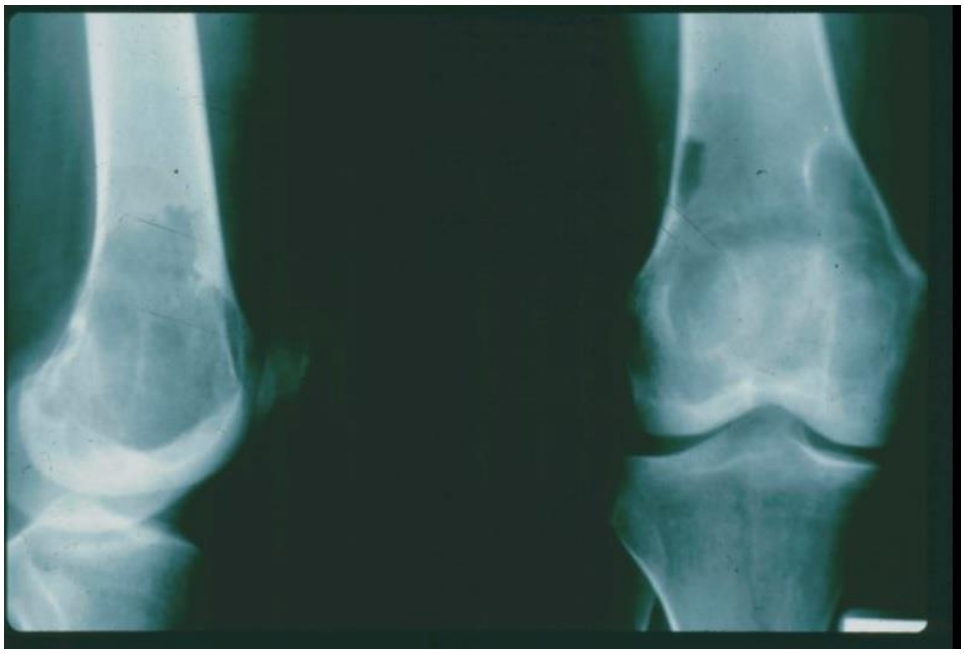
There is no widely held consensus regarding the ideal treatment method selection. There are advocates of varying surgical techniques ranging from intra-lesional curettage to wide resection. As most giant cell tumors are benign and are located near a joint in young adults, several authors favor an intralesional 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: Giant cell, Tumor, Benign.

Introduction:

Giant cell tumors of the bone are benign multi-nucleated cell masses that are commonly found at the epiphyses and sometimes the metaphyses of long bones. [1] Giant cell tumors have a high recurrence rate and a potential for aggressive behavior.[2] The metastatic forms of giant cell tumors are known as malignant sarcomas.[3] Giant cell tumors of the bone are one of the most challenging benign bone tumors due to resulting substantial bone damage, local reoccurrence, lung metastasis, metastasis to lymph nodes, and malignant transformation.[4]

Fig.1. Show the Giant Cell Tumor-distal femur



Giant cell tumor of bone (GCTB) is usually a benign bone tumor with a high rate of recurrence and possibility of "benign" pulmonary metastases or transformation in a malignant blastoma [1-4]. Numerous terms including myeloid sarcoma, tumor of myeloplaxus, osteoblastoclastoma, and osteoclastoma have been used to depict this tumor [5,6]. It accounts for about 5% of all primary bone tumors in adults and predominantly occurs in the third and fourth decade of life with a slight predilection for females [7,8]. GCTB is described as a locally invasive tumor that arises close to a joint in a mature bone [2,9]. It usually affects the meta-epiphyseal region of long bones, preferably the bones around the knee joint, the distal radius, and the proximal humerus [10]. The definitive treatment of GCTB varies from intralesional curettage with or without different adjuvants followed by bone grafting and/or bone cement packing to wide resection which could compromise limb function [11].

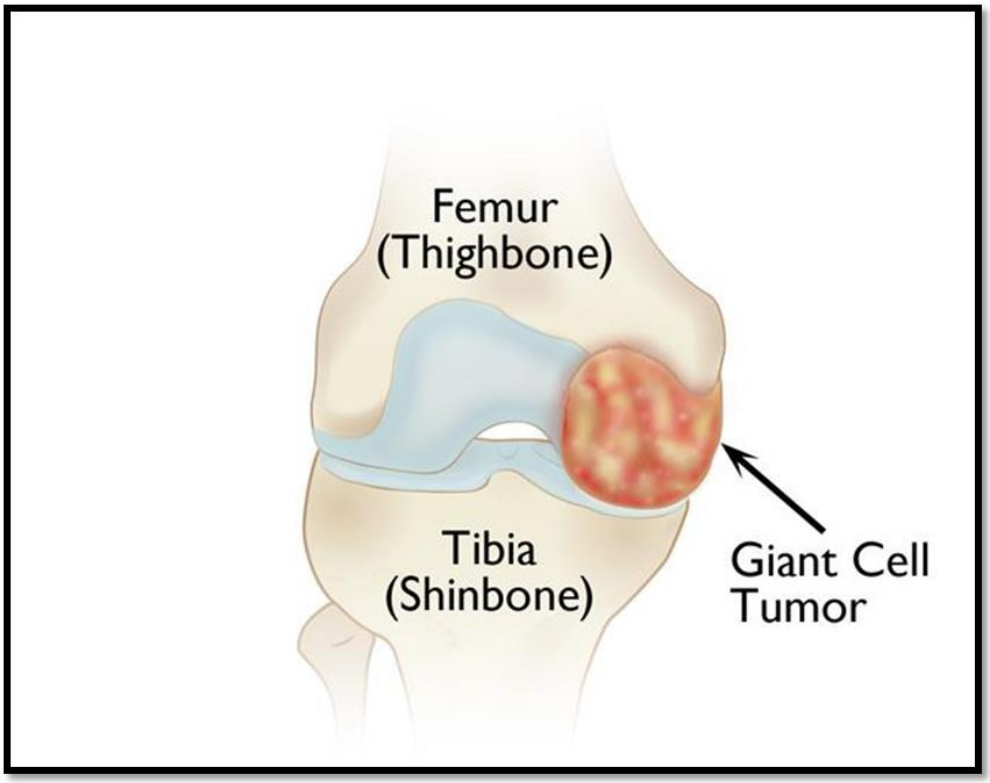
Giant-cell tumor of bone (GCTB) is a benign neoplastic lesion with metastatic potential and high rates of local recurrence [1]. Molecular models supporting the monoclonal neoplastic processes include findings from genomic hybridization, which identified 20q11 amplifications in 55% of GCTB [12]. Other data suggest a role of p53 overexpression in 25% of GCTB [13]. The discovery of receptor activator of nuclear factor kappa B ligand (RANKL) was critical to the pathogenesis of GCTB [12]. Previous studies have identified RANKL as being highly expressed by the stromal cells within GCTB [10].

A giant cell tumor of bone is a type of benign (noncancerous) tumor that has a wide range of behaviors. These tumors typically grow at the ends of the body's long bones. Most often, they appear at the lower end of the femur (thighbone) or upper end of the tibia (shinbone), close to the knee joint.

Giant cell tumors usually occur in young adults, and are slightly more common in females. They are quite rare, occurring in only about one out of every one million people per year.

Although giant cell tumors are not cancerous, they are aggressive and can destroy the surrounding bone. Treatment for a giant cell tumor almost always involves surgery to remove the tumor and prevent damage to the bone near the affected joint. [12].

Fig.2. Shows a giant cell tumor at the lower end of the thighbone. This is a common location for the tumors to occur.



The osteoclastic giant cells have the ability to enhance bone resorption via a cathepsin K and matrix metalloproteinase [13], supporting the role of RANKL signaling in the pathogenesis of GCTB. The proof of RANKL's role is derived from the critical action of denosumab, a RANKL inhibitor, in the control of the disease [14], However, this did not fully explain the underlying pathogenesis of the disease.

One interesting finding is the activation of bone stromal cells due to local hemorrhage or trauma to the bone with resultant extravasation of these aberrant giant cells of bone into the blood vessels [14]. This is a phenomenon which we observed in our case with pathological evidence of blood vessel invasion and resultant systemic metastasis.

Giant cell tumor of the bone (GCTB) is classified as an intermediate, locally aggressive but rarely metastasizing tumor. It accounts for 4–5 % of primary bone tumor and 20 % of all benign tumors [16]. The mainstay of treatment for the treatment of GCTB had been the surgical removal. To reduce local recurrence, a variety of adjuvant treatments using phenol, liquid nitrogen, high-speed burr, or methylmethacrylate cement have been established [14,17].

The advantage of these adjuvant treatments in the treatment of GCTB has generally been accepted in the field. It has been reported that adjuvant treatment contributes to better prevention of local recurrence (0–34 %) [18] than treatment without adjuvants (12–47 %) [17] GCTB expresses receptor activator of nuclear factor-kappa B (RANK) and stromal cells that express RANK ligands (RANKL) [19].

Therefore, an anti-RANKL antibody denosumab was developed for the treatment of GCTB [20]. The favorable responses and the possibility of surgical downstaging were reported [19]. Although denosumab was predicted to reduce osteolysis and control disease progression in patients with GCTB, the long-term outcome of denosumab has not yet been confirmed. On the other hand, there is little data of the long-term clinical outcome of GCTB after recurrence including the rate of sacrificing adjacent joint due to the additional surgical treatment. The purpose of this study was to evaluate the long-term clinical outcome of recurrent GCTBs of the extremity in the era before molecular target therapy and to determine the factors that influence repetitive recurrence and sacrifice of adjacent joint.

Fig.3. Show the a lytic expansile lesion with multiple septae involving the first metacarpal bone.

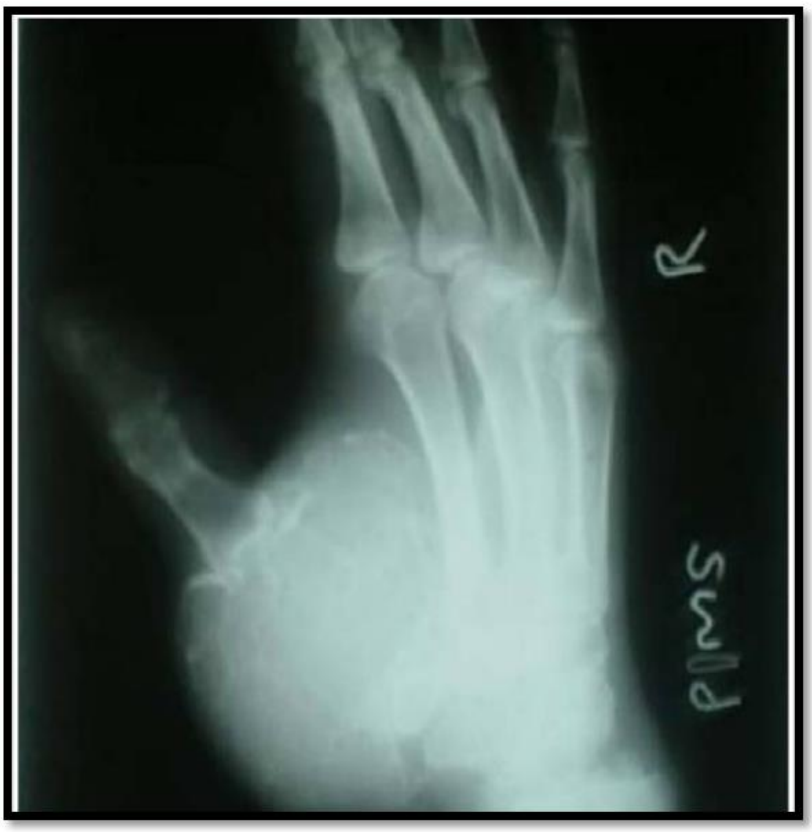
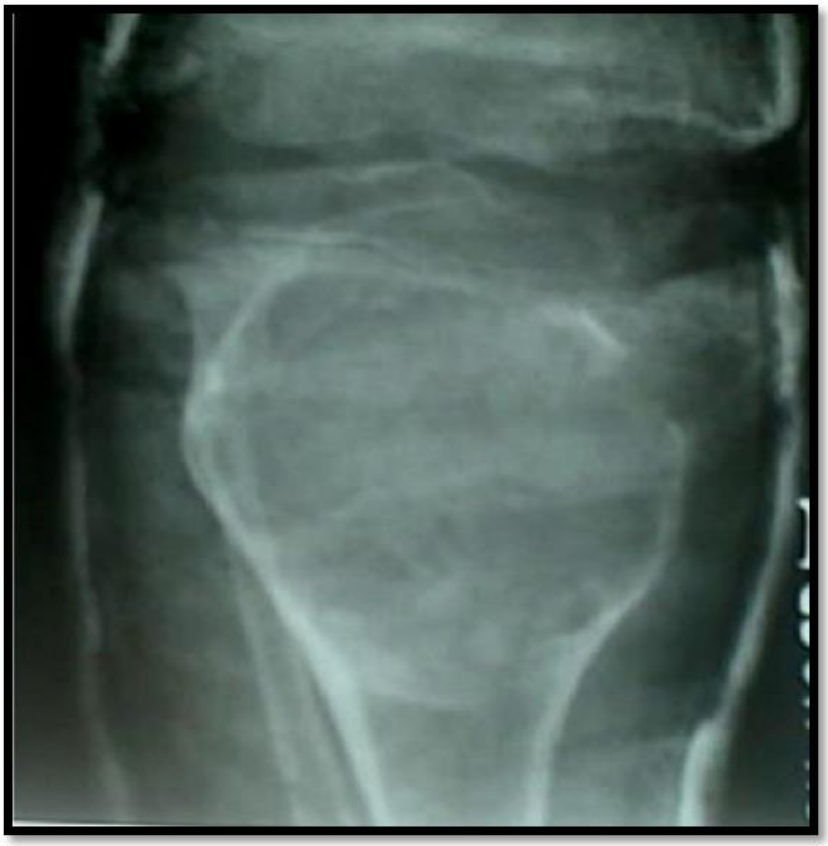


Fig.4.Tibia showing a lytic expansile lesion with septae consistent with aneurysmal bone cyst.



Epidemiology

Giant cell tumors account for 4-10% of all primary bone tumors and represent 15-20% of benign bone tumors. They usually occur in young adults, with 50% occurring in people 20-40 years old. Rare to see in patients older than 50 years.[21]

They have a slightly higher occurrence in females, particularly when located in the spine. Malignant transformation happens in less than 10% of cases, and more often in men.

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[22].

Symptoms

The most common symptom of a giant cell tumor is pain in the area of the tumor. The patient may also have pain with movement of the nearby joint. This pain usually increases with activity and decreases with rest.

The pain is usually mild at first, but gets worse over time as the tumor increases in size. Occasionally, the bone weakened by the tumor breaks and causes the sudden onset of severe pain. [23].

Sometimes, the patient will have no pain at all, but will notice a mass or swollen area instead.

Diagnostic

Giant cell tumors are usually diagnosed by x-rays and verified through histological evaluation with results that are typically found with the specific characteristics of giant cell tumors.[3] Below is a list of diagnostic tests that may be utilized to help identify and distinguish the type of tumor that is present.

- Biopsy of the Tumor: A sample of the tumor is removed and inspected under a microscope and allows the physician to determine the aggressiveness of the tumor. The cellular structure of the tumor is then examined to rule out other malignant tumors that may resemble a giant cell tumor.[24]
- X-rays: X-rays are diagnostic tests that are used to produce projections of radiographic images of bone tissues and other organ tissues onto film. Giant cell tumors appear as translucent lesions within the bone that are usually near the joint line. The section of the bone that is involved is surrounded by a slim border of white bone; the bone in the region of the tumor is occasionally protracted outward. Chest x-rays should be obtained at the diagnosis of the tumor as well as randomly during the follow-up to view for metastasis to the lung.[25-28]
- Magnetic Resonance Imaging : MRI's are diagnostic tests that use powerful magnetic fields to produce detailed images of internal structures within the body. This imaging procedure will allow for more in depth assessment of the bone that is affected.[29]
- Computerized Tomography scan: A CT or CAT scan is a diagnostic imaging that uses a combination of computer processing and x-rays to generate cross sectional images of the body, they can also generate 3 dimensional images of the internal structure of the body. CT scans are more detailed than x-rays and can show imaging for bones, muscle, fat, and organs. CT scans are often performed in the lungs of patients with giant cell tumors to examine for signs of metastasis to the lung.[30]
- Bone scan: Bone scans are used to help diagnose if a tumor is present and if it has spread to other areas of the body. A bone scan will show up with a "hot spot" in the location of the bone where the tumor is present.[31]
- Complete blood count: Measures the size, number, and maturity of different blood cells in a precise quantity of blood.[29]

Differential Diagnosis

Giant cell tumor sign/symptoms are usually minor in nature and often resemble that of musculoskeletal origin. Sacral tumors are usually not diagnosed early on in their developmental stages due to their similar features to that of low back pain or sciatica. It is not uncommon for physical therapists to receive referrals from physicians before the accurate diagnosis is determined. Therefore it is important for physical therapists to take thorough patient histories and be aware of any red flags that may appear during an evaluation that make you suspicious that the condition is not musculoskeletal in nature.[31] Other tumors of the bone that have to be ruled out at histological analysis are:[32]

- Brown tumors of hyperparathyroidism
- Aneurysmal bone cysts
- Chondroblastoma
- Osteoblastoma
- Osteosarcoma.

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. Campaanacci 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. [33-35].

Grade – I tumor has a well-marginated 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.

Management

Surgical removal has been shown to be the most successful treatment choice for the management of giant cell tumors. The most common form of surgery is called curettage in which the tumor is excavated out of the bone. After this method is performed there is an empty space in the bone that is filled with a bone graft either from other parts of the body or from a cadaver. This method of treatment has a high reoccurrence rate with the tumor returning to that same location up to 45% of the time when only the curettage and bone grafting are performed alone. [36-38].

Therefore, bone cement is also often used instead of the bone grafting and this method is shown to have a lower tumor return rate. “Enhancing the curettage with a high-speed burr or with the use of agents such as liquid nitrogen, hydrogen peroxide, or phenol, followed by placement of bone cement decreases the recurrence rate to 10% to 29%.” If the tumor has resulted in severe destruction or has reappeared in the bone then often more involved tumor removal as well all reconstruction is necessary. [39].

If a tumor is unapproachable or can only be partially removed then radiation therapy may be used as a treatment option, though it is never the primary treatment of choice. The use of radiation therapy is debated and only used for patients who are not surgical candidates since it

has high recurrence rates and a connection has been linked between radiation therapy and malignant transformation of the giant cell tumors[40].

Conclusion:

Giant cell tumor of bone is a benign, primary skeletal neoplasm with an unpredictable pattern of biological aggressiveness. Molecular biological research has increased our understanding of these tumors. This article recent advances in the study of this interesting bone tumor.

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