Giant cell tumor of bone: Unusual features of a rare tumor

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Abstract

Giant cell tumor of bone is a benign tumor with an aggressive behavior. Its typical subarticular location and high recurrence risk can be associated with significant morbidity. Although benign, it can rarely metastasize especially to the lungs. Also, it can be multicentric in less than 1% of patients. Late malignant transformation, although rare, can occur with a very poor prognosis. This series reports on these unusual and challenging features and management considerations of giant cell tumor of bone.

This retrospective study included review of the medical records of patients with a confirmed histopathological diagnosis of giant cell tumor of bone.

A total of 25 patients (16 females and 9 males) with a mean age of 34.5 years were included; 22 had primary tumors, while 3 were referred with recurrent tumors. Pain was the most common presenting symptom. Most patients had grade III tumors. Tumors around the knee were the most common. Multicentric tumors were detected in three patients. Twenty-three patients (20 primary giant cell tumor of bone and 3 with recurrence) received treatment. Most patients (15/23) were treated with intralesional curettage with or without adjuvants. Seven patients had wide excision. Recurrence was seen in 45% (9/20) of primary giant cell tumor of bone especially with difficult anatomical locations. Most recurrences occurred more than 4 years after treatment. Pulmonary nodules were detected in four patients; two of them showed resolution during follow-up. One patient developed secondary sarcoma transformation with a fatal outcome.

Giant cell tumor of bone was more common in females. Long bones were more affected, especially around the knee. Intralesional curettage was the most frequently used treatment. Recurrence was associated with inadequate tumor resection (especially in difficult anatomical location), younger age, male gender, and advanced local tumor grade. Denosumab can be used in the treatment of pulmonary metastasis, multicentric and recurrent giant cell tumor of bone. Due to late recurrence and malignant transformation, a prolonged follow-up is warranted.

Keywords

Giant cell tumor of bone, multicentric giant cell tumor of bone, malignant giant cell tumor of bone, denosumab, pulmonary metastasis

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Introduction

Giant cell tumor of bone (GCTB) is a unique benign bone tumor representing about 5% of primary bone tumors. It usually affects the long bones especially around the knee. It is most commonly diagnosed in adults during their third and fourth decades of life, in contrast to most primary
bone tumors that are commonly diagnosed in children and adolescents. Most GCTB series report female predominance.

GCTB has challenging and confusing features. These include the local aggressiveness with high risk of recurrence, in addition to the typical epiphyseal/metaphyseal location with involvement of the adjacent joint. Although rare, it can metastasize, most commonly to the lungs, with the same benign histopathology. Benign GCTB can present as multicentric lesions in less than 1% of patients. With prolonged latency, secondary malignant transformation can occur with a very poor prognosis.

Different treatment modalities are reported with the aim of eradicating the tumor while maintaining function. The most frequently used treatment involves intralesional curettage with or without adjuvants. Different adjuvants are described to reduce the risk of local recurrence. Although wide excision is associated with the lowest risk of recurrence, it can cause significant functional impairment. Other modalities described include serial embolization, bisphosphonates, chemotherapy, and radiation. Recently, denosumab, a human monoclonal antibody against RANKL (receptor activator of nuclear factor-kB ligand), has also been used.

In this article, we are reporting the clinical aspects of a series of GCTB patients with special consideration of the risk of recurrence, multicentric tumors, pulmonary metastasis and malignant transformation.

**Patients & methods**

This is a retrospective study conducted at King Abdullah University Hospital in Northern Jordan between March 2004 and August 2018. Patients with the diagnosis of GCTB confirmed by histopathology were included. The medical records of those patients were reviewed. The following clinical information were obtained: age at diagnosis, sex, presenting complaints, location of the tumor, staging radiological studies, treatment modality, follow-up, recurrence and subsequent treatment.

Tumors local grade was determined according to Campanacci radiological grading system. This system describes three grades of the tumor: Grade I (the cortex is well defined), Grade II (the cortex is expanded and thinned out), and Grade III (the cortex is destructed with soft tissue expansion). This study was approved by the research committee of Jordan University of Science and Technology.

**Results**

A total of 25 patients (16 females and 9 males) with histopathological diagnosis of GCTB were included in this series. Their mean age was 34.5 years.

Pain was the most common presenting symptom in 72% (18/25) of patients, while the presence of a mass was the presenting complaint in 16% (4/25) of patients. The remaining patients presented with a combination of both pain and mass.

Local imaging studies including computed tomography (CT) and magnetic resonance imaging (MRI) revealed Campanacci grade II tumors in 8 patients, while 17 patients showed grade III tumors with extension into the surrounding soft tissues. Systemic staging studies included CT of the chest, bone scan, and occasionally positron emission tomography (PET)/CT scan.

Different biopsy techniques were performed to provide the histopathological diagnosis of GCTB. Open biopsy was the most frequently used in 11 of 25 patients. Biopsy under image guidance with either CT or ultrasound (US) was performed in 9 of 25 patients. Frozen section examination provided the initial diagnosis in three patients while the diagnosis was confirmed after excisional biopsy in two patients.

**Anatomical locations**

GCTB affected both the appendicular and the axial skeleton (Figure 1). Long bones represented the most common tumor locations (17/25). Within these bones, both the epiphysis and metaphysis were affected in most cases (10/17). Tumors were confined to either the epiphysis or metaphysis in four and three cases, respectively. Tumors around the
knee including distal femur, proximal tibia, proximal fibula, and patella consist nearly half of the tumors (52%). The distal radius and the vertebral column including the sacrum were equally affected.

Multicentric giant cell tumors, in which the tumor involved more than one location, were detected in three patients (Figure 1). In the first patient, the posterior eighth rib was primarily affected with synchronous involvement of the vertebral bodies and posterior arches of both the eighth and the seventh thoracic vertebrae. In the second patient, the tumor affected the first rib primarily with synchronous involvement of the transverse processes of the seventh cervical and first thoracic vertebrae. The third patient had proximal femur and sacral synchronous lesions.

**Treatment groups**

Among the 25 patients included in this series, 23 patients were treated at our institution, whereas two patients refused further treatment: one patient with a scapular tumor and another one with a multicentric GCTB involving the eighth rib. Treatment methods for these patients included primarily either intralesional curettage or wide resection (Table 1).

### Table 1. Demographic and clinical characteristics of treatment groups.

|                      | Curettage ± (reconstruction) | Adjuvant | Wide resection ± (reconstruction) | Margin | Total |
|----------------------|-----------------------------|----------|-----------------------------------|--------|-------|
| Number               | 15                          | 8        | 7/16                              |        |       |
| Age (average, years) | 30.3                        | 44.1     |                                   |        |       |
| Sex (male/female)    | 4/11                        | 3/5      |                                   |        |       |
| Location             |                             |          |                                   |        |       |
| Distal femur         | 3 (autograft)               |          | 2 (mega-prosthesis)               |        |       |
|                      | 2 (BC, chips)               | BC and phenol |                              |        |       |
| Distal radius        | 1 (autograft)               | LN, BC, H₂O₂ | 1 (st. allograft and plate)      |        |       |
|                      | 1⁺ (BC)                     | Phenol   |                                   |        |       |
| Proximal tibia       | 1 (autograft)               |          | 1⁺ (mega-prosthesis)              |        |       |
|                      |                             |          | 1⁺ (no reconstruction)            |        |       |
| Proximal fibula      | 1 (autograft)               |          |                                   |        |       |
| Acetabulum           | 1 (cemented THA)            | BC       |                                   |        |       |
| Proximal humerus     | 1 (BC)                      | BC       |                                   |        |       |
| First rib            | 1 (none)                    | H₂O₂     |                                   |        |       |
| Patella              | 1 (autograft)               | LN, H₂O₂ |                                   |        |       |
| Mandible             | 1 (none)                    | Dexamethasone |                               |        |       |
| Proximal femur       |                             |          | 1 (HA)                            |        |       |
| Vertebra             | 1 (PLF)                     | H₂O₂     | 1 (PLF and cage)                  |        |       |
| Sacrum               |                             |          | 1 (PLF)                           |        |       |
| Campanacci II        | 6                            |          |                                   |        | 7     |
| Campanacci III       | 8                            |          |                                   |        | 13    |
| Pulmonary nodules    | 3                            |          |                                   |        | 4     |
| Recurrence⁺          | 6/14                        | 3/6      | 9/20                              |        |       |

BC: bone cement; LN: liquid nitrogen; H₂O₂: hydrogen peroxide; THA: total hip arthroplasty; HA: hemiarthroplasty; PLF: posterolateral fusion; chips: cancellous allograft chips; st.: structural.

⁺Referred with recurrence.

⁺⁺Malignant transformation.

⁺⁺⁺Primary cases.

Intralesional curettage group. Most patients (15/23) were treated with intralesional curettage with or without adjuvant. Adjuvants used in series (Table 1), either alone or in combination, included bone cement, phenol, liquid nitrogen, hydrogen peroxide, and dexamethasone. Two patients needed no further reconstruction. However, autograft, bone cement, and allograft cancellous chips, either alone or in combination, were used to reconstruct the resulting cavity in the remaining patients (Table 1). Metal implants used include cerclage wire for the patellar tumor, rush rods for one distal radius tumor, pedicle screws for the vertebral tumor, and hip replacement with cemented reconstruction cage for the acetabular tumor. Preoperative embolization to help control bleeding was utilized in two patients: the multifocal first rib and the acetabular tumors.

Wide excision group. Attempted wide excision was performed in six patients. While one patient needed no further reconstruction, tumor mega prosthesis, hemiarthroplasty, structural allograft, interbody spinal cage, and posterolateral fusion were used after tumor excision in the remaining patients (Table 1). Denosumab was used to target the synchronous sacral lesion in the patient with multicentric proximal femur GCTB. Significant decrease in activity and size...
of the sacral lesion was noted on follow-up PET/CT after 1 year. Preoperative embolization was used before resection of vertebral tumor.

**Recurrence**

The 23 treated patients included 20 patients with primary GCTB and 3 patients who were referred with recurrent tumors. The follow-up period after treatment of primary GCTB ranged from 11 months to more than 144 months with an average of 59.3 months. During this follow-up, 9 out of the 20 patients developed recurrence after an average of 65.7 months from their initial treatment (Table 2). Their average age was 26.8 years and females were slightly more affected with female/male ratio of 1.25. Most of the patients (7/9) presented with Campanacci grade III tumors.

While one of the three patients who were referred with recurrent tumors showed malignant transformation, the other two showed no re-recurrence after treatment during their average follow-up period of 79.5 months.

**Pulmonary nodules**

Among the 20 patients with primary GCTB and the two patients with benign recurrent GCTB (Table 1), pulmonary nodules were detected in four patients, two males and two females, with an average age of 32.8 years. Three patients had grade III tumors, while one showed grade II tumor. In two patients, the pulmonary nodules were detected at the initial diagnosis. These two patients had their primary tumor located in the acetabulum and the patella. In the other two patients, the pulmonary nodules were detected at the time of recurrence: one patient with a distal radius tumor and another with multicentric first rib tumor.

During follow-up, the pulmonary nodules in the first two patients did resolve on CT images that were done about 1 year later. The patellar tumor did not recur during 62-month follow-up period. However, the acetabular tumor developed local recurrence about 50 months after surgery with no radiological evidence of recurrent lung nodules.

| Table 2. Clinical and management features of recurrence-free and the recurrent tumors after treatment of the 20 primary GCTB. |
|-----------------------------------|----------------|----------------|
| Recurrence-free group | Recurrence group | Total |
| Number | 11 | 9 | 20 |
| Average age (years) | 37.5 | 26.8 | 35.1 |
| Female/male | 9/2 | 5/4 | 14/6 |
| Campanacci grade | | | |
| Grade II | 4 (20%) | 2 (10%) | 6/20 (30%) |
| Grade III | 7 (35%) | 3 (15%) | 9/20 (45%) |
| Treatment | | | |
| Curettage (– adjuvant) | 2 (10%) | 3 (15%) | 5/20 (25%) |
| Curettage (+ adjuvant) | 6 (30%) | 3 (15%) | 9/20 (45%) |
| Wide resection | 3 (15%) | 3 (15%) | 6/20 (30%) |

GCTB: giant cell tumor of bone.

Regarding the other two patients, the patient with the recurrent distal radius tumor (Figure 2) was prescribed denosumab after open biopsy confirmed recurrent benign GCTB with no secondary malignancy. The other patient with the multicentric first rib tumor was treated with serial embolization and denosumab medical therapy. Both of the tumor and pulmonary nodules were radiologically stable over 3-year follow-up (Figure 2).

**Secondary malignant transformation**

Among the three patients who were referred with recurrence, one had the recurrent tumor involving the proximal tibia. This patient had a history of multiple surgical treatments for the previously diagnosed GCTB more than 10 years prior to this presentation. The radiological examination revealed heterogeneous mass involving the whole proximal tibia with possible extension into the knee joint (Figure 3). Ultrasound-guided biopsy revealed high-grade dedifferentiated sarcoma. No metastasis was detected on the staging studies. The patient refused above knee amputation. So, attempted wide

![Figure 2.](image-url)
excision and reconstruction were performed. However, final histopathology revealed tumor involvement of the resection margins. Three months postoperatively, the patient developed buccal swelling that showed histopathological features similar to the proximal tibia sarcoma. The patient died of the tumor about 6 months after the diagnosis of the secondary sarcoma.

Patients with no treatment

Two patients refused surgical treatment with no regular follow-up. The first patient with the multifocal eighth rib tumor showed dramatic progression of his tumor over an 8-year period as evidenced by chest X-ray obtained for unrelated condition. The other patient with the scapular GCTB showed a stable disease with unremarkable progression.

Discussion

This series of GCTB reports on the different clinical and management considerations of 25 patients over a period of more than 14 years. All the cases were with proven histopathological diagnosis of GCTB in our referral hospital that covers a population of more than 1 million. This rarity adds to the challenge in the management approach of these tumors. Female predilection in GCTB has been reported by other series,1,2,11,12,37,38 which is similar to this series in which females represented 68% of the patients. Giant cell tumor is commonly diagnosed in patients between 20 and 45 years of age.1–3,7–9,39 Although few patients in this series (3/25) were diagnosed during the second decade of life, most patients (15/25) were diagnosed during their third and fourth decades.

Figure 3. MRI of the recurrent GCTB of the proximal tibia that developed secondary dedifferentiated sarcoma: (a) sagittal and (b) coronal.

Regarding anatomical distribution of GCTB, the ends of long bones were the most common locations in this series with tumors around the knee being the most common. Also, tumors involving both the epiphysis and metaphysis were the most common. This distribution is similar to that reported in the literature.4,5,15,35,40 In the spine, the sacrum has been reported as the most common location.5,41–43 However, in this series, only one tumor involves the sacrum among the three spinal tumors. Other unusually reported locations included the patella44 and the scapula.45

Multicentric GCTB is extremely rare representing less than 1% of GCTB.19–21 In this series, 12% of patients had multicentric tumors in unusual locations reported for multicentric GCTB (Figure 1).21,46 Multicentricity can complicate the diagnosis, treatment, and follow-up of GCTB. The sacral lesion in the patient with the multicentric proximal femur GCTB showed significant improvement on follow-up PET/CT after denosumab treatment. In addition, denosumab was added to control recurrence and pulmonary nodules in the first rib multicentric GCTB with stable disease and pulmonary nodules over 3-year follow-up (Figure 2). Hence, denosumab can be considered in multicentric GCTB management.

Intralesional curettage was performed in most cases (Table 1). The technique and thoroughness of the curettage vary among surgeons which can affect the extent of local control and thus the overall outcome. Due to their controversial role and wide variation,6,7,27,29–31 different adjuvants and filling materials were used following curettage in this series. Given these factors in addition to the small number of patients, it might be difficult to define the role of both the adjuvants and filling materials in the local control of the disease. Recurrence rate among patients with primary GCTB was 43% (6/14). This rate is similar to that reported by several other series.2,12–14,16,32,47

Wide excision has been reported to be associated with the lowest risk of recurrence.2,6,13,14,16,32,48 In this series, half of the six patients with primary GCTB who underwent attempted wide excision showed local recurrence. This might be expected since these three patients had their primary tumor located in anatomically complex locations including the sacrum, third lumbar vertebrae, and the distal radius. Free margin resection can be difficult to achieve in such locations. In addition, these locations are associated with high risk of recurrence as reported by many authors.2,47,49–53

Embolization, alone or in combination with other treatment modalities, has been described in the management of GCTB especially unresectable tumors in anatomically difficult locations.5,7,33,54,55 In this series, serial embolization was used preoperatively to decrease the intraoperative blood loss in addition to help control recurrence.

Denosumab is a recent medical therapy in GCTB. Indications in this series included multicentricity, pulmonary metastasis (Figure 2), and recurrence. In these
situations, the use of denosumab can avoid the possible morbidity and mortality especially when operating in complex anatomical locations.

The overall recurrence rate, in patients with primary GCTB, was 45% (9/20). The range of recurrence rate reported in the literature varies from 0% to 65%. Recurrence has been, commonly, reported to occur during the first 3 years following treatment. However, in this series most patients (6/9) showed recurrence more than 4 years following their initial diagnosis. This can be related to late detection of the recurrence especially with the variable radiological and clinical follow-up approaches. Also, it can suggest that a prolonged follow-up might be warranted.

Although recurrence has been attributed mainly to the extent of tumor resection achieved by different surgical techniques, other risk factors can affect the recurrence rate, which include age, gender, location, Campanacci grade III, and pathological fractures. In this series, the recurrent tumor group were younger and had slightly more grade III tumors in comparison with the group with no recurrence. Males were more likely to develop recurrence compared to females. In this series, three of the four patients had unusual tumor locations for GCTB including the patella, the acetabulum, and the first rib.

Pulmonary nodules were detected with a higher rate of 18% compared to the rate of 3% reported by many series. Some authors suggested atypical locations of GCTB, like the spine and proximal femur, to be associated with increased risk for pulmonary metastasis. In this series, three of the four patients had unusual tumor locations for GCTB including the patella, the acetabulum, and the first rib.

Recurrence and advanced tumor grade had been suggested as risk factors for pulmonary metastasis. However, in this series, only two of nine recurrent patients were detected with pulmonary nodules at the time of recurrence. Also, only 3 of the 16 patients who have Campanacci grade III tumors developed pulmonary nodules.

The course of GCTB pulmonary metastasis is unpredictable. Spontaneous resolution has been reported, as was the case in two patients in this series. Due to the usual benign indolent course and the controversial management of such nodules, histopathological confirmation was not obtained routinely especially with small and inaccessible nodules.

One patient developed late secondary high-grade dedifferentiated sarcoma. Very rare malignant transformation had been reported for GCTB after prolonged latency, with multiple recurrences as a risk factor. In these circumstances, preoperative biopsy is strongly advised before planning further management. Given the decimal prognosis of malignant GCTB, wide excision either with amputation or limb salvage surgery is highly recommended.

The two patients with no treatment in this series shed light on the unpredictable and variable course of GCTB. While one patient showed dormant course over 3 years, remarkable progression was seen for the other patient.

**Conclusion**

GCTB is more common in females. Most common location is the epiphyseal/metaphyseal area around the knee. Multicentric GCTB and pulmonary metastasis were more common. Most patients were treated with intralesional curettage with or without adjuvant. Recurrence rate is 45%. Most patients showed late recurrence. Complex anatomical locations, younger age, male gender, and Campanacci grade III tumors were associated with high risk of recurrence. Some patients showed resolution of pulmonary nodules during follow-up. Denosumab was used for patients with multicentric tumors, pulmonary nodules, and recurrence. Late malignant transformation was detected in one patient with fatal outcome which warrants prolonged follow-up of GCTB.

**Data availability**
The datasets used and analyzed during this study are available from the corresponding author upon request.

**Ethical approval**
Ethical approval to this research was obtained from Jordan University of Science and Technology research committee.

**Informed consent**
No informed consent was required by the University Research Committee for medical chart review in this research.

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