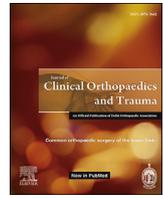




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# Multicentric Giant Cell Tumor (GCT) of bone treated with denosumab alone: A report of two cases

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## 1. Introduction

Giant Cell Tumors (GCT) of bone account for 4–5% of all primary bone neoplasms. They rarely metastasize to the distant organs, most commonly lungs (~5%) and even rarer are the multifocal GCTs. Around 1% of GCTs present as multiple synchronous or metachronous lesions.<sup>1</sup> There is a paucity of published literature for multifocal GCTs, most of it being case reports and small case series. Treating surgically these lesions like primary unifocal GCT of bone with either intralesional Extended curettage or Wide Local Excision results into significant morbidity and always not feasible because of the difficult locations. Surgically approachable lesions are treated with surgery and lesions in the difficult locations and inoperable tumors have been treated with different modalities of treatment like radiotherapy,<sup>1</sup> serial angioembolization and denosumab<sup>2</sup> and some had even tried chemotherapy.<sup>3</sup> There is no consensus and guidelines regarding the management of these multicentric tumors. Denosumab has gained popularity in recent years to reduce surgical morbidity in cases with unresectable, recurrent or metastatic disease.<sup>4,5</sup> We present two cases of multicentric GCTs

managed conservatively with denosumab alone with excellent short-term results.

### 1.1. Case 1

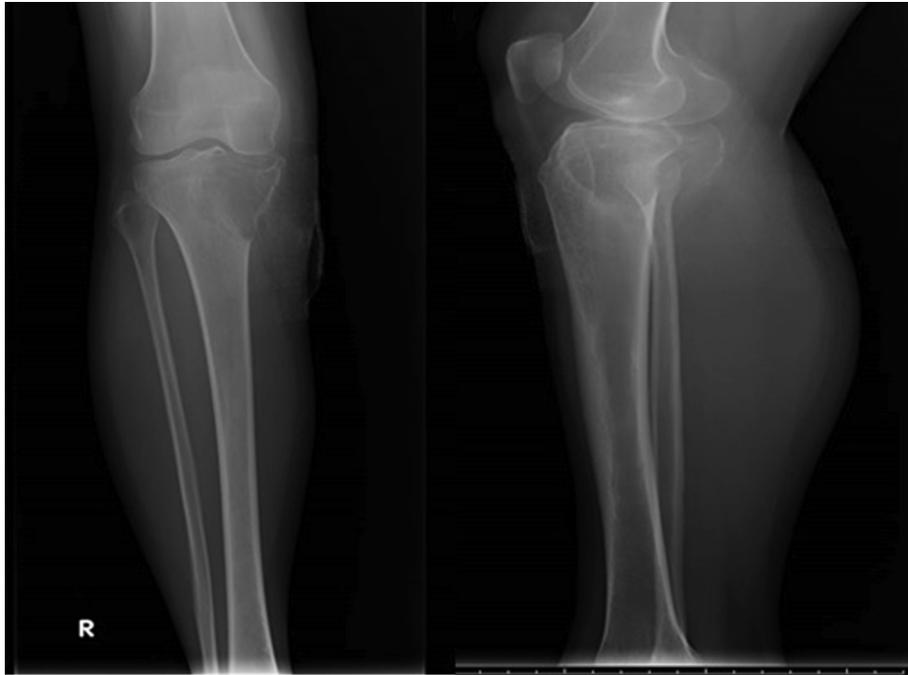
A 22-year-old female presented to us with complaints of pain in the right knee for 8 months and the inability to walk for the past 2 weeks. Plain X-Ray revealed an eccentric epi-metaphyseal lytic lesion with a narrow zone of transition with a cortical break (Fig. 1). Biopsy from the lesion was suggestive of Giant Cell Tumor (GCT) for which she underwent extended curettage + cementation in April 2012. She was doing well and was asymptomatic till 27 months post-operatively, when a small lytic lesion was detected in ipsilateral tibial diaphysis (Fig. 2). 99mTc Tectinium bone scan was done which showed multicentricity of the lesion. Sites of involvement were: tibial diaphysis, ipsilateral scapula, contralateral hemipelvis, cervical spine, and lumbar spine. CT thorax showed no pulmonary metastasis. CT guided core needle biopsy was done from Scapula (right) which confirmed the histological diagnosis the same as the primary lesion. She was started on injection Denosumab 120mg SC on days 1,8,15,29 and monthly after that for 1 year. The lesion healed radiologically with dense sclerosis and the patient remained asymptomatic. Calcium/Phosphate levels were assessed before treatment and at each administration. Pregnancy was ruled out. Dental examination was carried out before treatment and whenever indicated during follow-ups. After a year of starting denosumab, the frequency of administration was reduced to every 3 months for the next 2 years (year 2 and 3) and every 6 months subsequently (year 4 onwards). Currently, she is injection denosumab 6 monthly, clinically asymptomatic without any radiological progression of the disease (Fig. 3).

### 1.2. Case 2

19-year male presented to us with complaints of pain in the right knee and right ankle for 3 months duration in August 2016. Plain radiographs showed mixed sclerotic lesions in the meta-diaphysis of the right distal femur, epi-meta-diaphysis of the right proximal tibia, lytic lesion in epi-metaphysis of the distal right tibia and mixed lytic-sclerotic lesion in right talus (Fig. 4). A skeletal survey done showed no other bony lesions whereas CT thorax was

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**Fig. 1.** 22-year female with eccentric epi-metaphyseal lytic lesion proximal tibia (Right) with a narrow zone of transition AP and Lateral views.



**Fig. 2.** Incidentally detected tibial diaphyseal lytic lesion (arrow).

normal. Biopsy from distal femur lesion was done which was suggestive of Giant Cell Tumor of the bone. He was started on injection denosumab on days 1,8,15, 29 and monthly after that for 1 year. The pain subsided and the patient became asymptomatic after 3

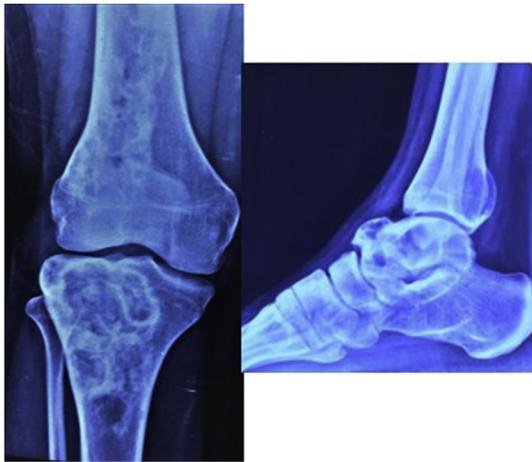


**Fig. 3.** Well-healed scapular and lumbar spine lesions, 5-years on Denosumab treatment.

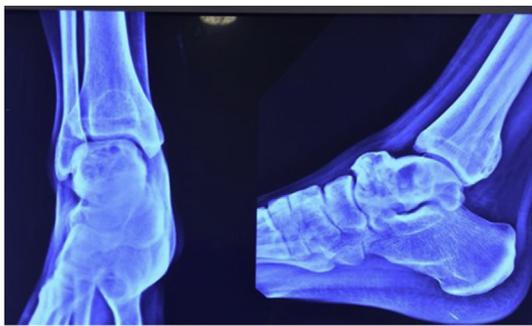
months of treatment initiation. Dental examination was done to rule out dental caries before starting denosumab and serum Calcium/Phosphate levels were checked before each injection. The frequency of administration was reduced to every 3 months after August 2017 and after two years of 3 monthly injections, it was further reduced to every 6 months, August 2019 onwards. Currently, he is asymptomatic, and the disease is radiologically quiescent (Fig. 5).

## 2. Discussion

Multicentric GCTs are rare accounting for less than 1% of GCTs.<sup>6</sup> They are called 'synchronous' if multicentricity is detected at presentation or within 6 months from the detection of the first lesion and 'metachronous' if multicentricity developed after 6 months of detection of the initial lesion.<sup>1,7</sup> Our first case was operated extended curettage + Cementation for GCT right proximal tibia and developed metachronous multicentric lesions 2 years post-surgery.



**Fig. 4.** Multicentric disease with involvement of distal femur, proximal tibia, distal tibia and talus.



**Fig. 5.** Well healed (ossified) distal tibial and talar lesion after 35 months on Denosumab treatment.

Sites of involvement were ipsilateral tibial diaphysis, ipsilateral scapula, contralateral hemipelvis, cervical spine, and lumbar spine. Our second case was a case of synchronous multicentric GCT and sites of involvement were meta-diaphysis of the right distal femur and proximal tibia, ipsilateral distal tibia, and talus.

It has been shown that the multicentric GCTs tend to occur at a younger age with slight female preponderance. Female patients presenting with solitary GCT before the age of 20 have a higher incidence of developing multicentricity and therefore should be followed up carefully.<sup>6</sup> Our first case was a 22-year-old female whereas the second case was a 19-year-old male.

The radiological features of individual lesion of multicentric GCT are usually similar to those of a solitary GCT (6). However, in long bones especially in skeletally immature patients, Hoch et al. noted metaphyseal or meta-diaphyseal location with prominent sclerosis and mineralization.<sup>1</sup> Metaphyseal or meta-diaphyseal location for GCT in the immature skeleton is a common feature,<sup>8–10</sup> however, the exhibition of prominent sclerosis and mineralization in multicentric GCTs is an unusual phenomenon not yet explained in the published literature. Proximal tibial and distal femur meta-diaphyseal lesions in our second case showed similar atypical features of excessive sclerosis.

Some authors have used whole body PET-CT<sup>2</sup> while some used whole-body technetium bone scan<sup>11</sup> for detection of multicentricity. We used a technetium bone scan for the first case whereas the skeletal survey for the second case. Biopsy establishes the diagnosis of multicentric GCTs. However, polyostotic conditions such as fibrous dysplasia, brown's tumor of hyperparathyroidism,

Paget's disease, metastasis, multiple myeloma, multifocal osteomyelitis, and multicentric osteosarcoma should be kept as differentials and are to be ruled out.<sup>11</sup> Both of our cases were biopsy-proven multicentric GCTs and serum PTH were normal in both of our cases.

Management of multicentric GCTs is challenging. Complete disease removal in difficult locations such as spine and skull is nearly impossible due to proximity to vital structures<sup>12</sup> whereas multicentric lesions cause significant and at times, unacceptable surgical morbidity if all the sites are operated upon. If the lesions are treated with incomplete removal (debulking) or are deemed inoperable they are usually treated with adjuvants such as embolization,<sup>2,13</sup> radiation therapy,<sup>1,14</sup> bisphosphonates<sup>15,16</sup> and Denosumab.<sup>2,4,17</sup> As surgical morbidity would have been unacceptable if surgeries were planned for all the sites for both of our cases, conservative treatment with injection denosumab was decided for both of them.

Denosumab is a monoclonal antibody to RANK ligand (RANKL) which inhibits RANK-RANKL interaction, a key mediator of osteoclastic activity.<sup>18</sup> It has gained popularity over the recent years in the management of locally advanced, surgically unresectable disease as well as in the metastatic setting.<sup>19</sup> Denosumab alone is not sufficient in bringing the cure for GCT by achieving complete pathological response as it has a very minimal inhibitory effect over the neoplastic stromal cells in GCT.<sup>20</sup> Thus, Denosumab withdrawal is associated with high rates of tumor recurrence. The long-term effects of prolonged denosumab treatment are atypical stress fractures, osteonecrosis of the jaw (ONJ), peripheral neuropathy, skin rash, and hypophosphatemia. ONJ appears to be dose-dependent and more frequently occurs in a patient with dental comorbidities before administration.<sup>4</sup> Both of our patients underwent a dental examination before Denosumab administration and during follow-ups. Also, denosumab is associated with stillbirth and decreased infant growth in animal studies.<sup>21</sup> This will be a major problem for females who wish to have children. Our 1st case was a female patient of reproductive age and she was explained in detail regarding this reproductive toxicity of the drug and was advised to take necessary contraceptive measures.

There are no guidelines regarding the dosing frequency of the drug. We administered Denosumab 120mg subcutaneously on days 1,8,15 and 29 in the first month, monthly after that for 1 year. To minimize the adverse effects of Denosumab in patients requiring long term treatment reducing dose frequency is advised once the steady state (9–12 months on denosumab) has been reached.<sup>19</sup> We followed the same and reduced frequency to every 3 months for the next 2 years [year 2 and 3] and further reduced the frequency of administration to every 6 months year 4 onwards. Our first case was started on Denosumab, July 2014 onwards and she is on 6 monthly injections since July 2016, whereas our second case was started on Denosumab, August 2016 onwards and he is on 3 monthly injections since August 2017. Reducing frequency is essential to reduce long term complications. Both our patients are doing well currently without evidence of disease progression. Recurrence or progression of the disease post-Denosumab cessation usually occurs within 7–9 months. However, denosumab has shown to work effectively on recommencement after secondary progression in a case report by Law et al..<sup>22</sup> We plan to reduce the frequency of administration to yearly injections from year 7 onwards for both the patients. This yearly spacing might help our female patient to conceive and have a child.

Multicentric GCTs are rare and their management is extremely challenging. Surgically amenable sites should undergo surgery aiming at complete disease removal. However, numerous lesions that otherwise would cause significant surgical morbidity and those at difficult locations can be safely treated with injection

denosumab.

### Conflicts of interest

The authors have none to declare.

### CRedit authorship contribution statement

**Rishi Ram Poudel:** Data curation, Formal analysis, Investigation, Methodology, Writing - original draft. **Vivek Verma:** Project administration, Resources, Validation, Writing - review & editing. **Akshay Tiwari:** Conceptualization, Visualization, Supervision.

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