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Management of giant cell tumor of bone in the era of denosumab: A case series and review of the literature

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ABSTRACT

Giant cell tumor (GCT) of the bone also known as osteoclastoma typically arises from the meta-epiphyseal region of the long bone and comprises 5% of all bone tumors and 20% of benign bone tumors. Understanding pathogenesis is the key to successful systemic therapy with denosumab, a RANK-ligand inhibitor. In this context, we report seven GCT bone-treated denosumab and radiotherapy cases with a diverse clinical presentation from our institute, NRS Medical College, and Hospital Kolkata.

Key words: Giant cell tumor; Bone; Denosumab; Radiotherapy

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INTRODUCTION

Giant cell tumor (GCT) is one type of primary benign bone neoplasm, which can be very aggressive and can metastasize also. It comprises 5% of all bone tumors and 20% of benign bone tumors. Bones around the knee joint, that is, distal femur and proximal tibia are commonly affected, followed by the distal radius and sacrum.[1] Histologically, it is composed of round to oval mononuclear stromal cells and osteoclast-like multinucleated giant cells. These mononuclear stromal cells express RANK receptor and RANK-ligand interaction, macrophage colony-stimulating factor plays a key role in recruiting and differentiating blood-born osteoclastic precursor cells into multinuclear giant cells. This understanding of pathogenesis is the key to successful systemic therapy with denosumab which is a RANK-ligand inhibitor.[2] In this context, we report eight GCT bone-treated denosumab cases with a diverse clinical presentation from our institute, NRS Medical College, and Hospital Kolkata.

The inclusion criteria were (1) histopathologically (HPE)-confirmed GCT and (2) patients willing to give written informed consent voluntarily. The exclusion criteria were (1) patients without HPE reports and (2) not willing to give voluntary consent for this analysis.

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After obtaining ethical clearance, from July 2017 to July 2022, according to inclusion and exclusions criteria, as mentioned earlier, a total of eight HPE proven GCTs were included for this case series. As per the ethical guideline Helsinki, the confidentiality and anonymity of patients were assured.

CASE PRESENTATION

Case No. 1

A 23-year-old college-going student presented with pain and swelling over the lower back and posterior to the sacral region for 4 months and difficulty in walking for 1 month. X-ray pelvis and contrast-enhanced computed tomography scan showed a large expansile lytic lesion in the sacrum causing pressure over both the bladder and rectum. As the patient was an inoperable case, the patient underwent only a biopsy only. At that time, denosumab was not available in our institution, so we started local radiotherapy 50 Gy/25 #/over 5 weeks. One thing we have noticed is that during radiotherapy this patient with an inoperable sacral GCT, who cannot walk before radiotherapy, was able to walk without any support. Four years post-radiotherapy, the disease was a stable condition and the size of the lesion again started increasing and systemic therapy with denosumab was initiated. The disease responded well to denosumab therapy, and presently, she is in stable condition.

Case No. 2 and 3

Twenty-seven- and 15-year-old female patients presented with pain and swelling over the upper end of the left tibia for 1 year and 2 years, respectively. X-ray showed an eccentric lytic lesion in the upper tibia and a contrast-enhanced magnetic resonance imaging scan showed T1-weighted image (WI) showing intermediate signal intensity eccentric lesion and high signal intensity on T2 WI and marked contrast enhancement on post-gadolinium T1 WI (Figure 1). The patients underwent curettage and cementing and due to histology showing GCT (Figure 2), post-operative residual disease, and history of multiple recurrences, systemic therapy with denosumab started. Before starting denosumab therapy, patients underwent contrast-enhanced computed tomography chest and whole abdomen and whole-body bone scans. The whole-body bone scan showed multiple bone metastasis (Figure 3) and the disease responded well to denosumab therapy; presently, both patients were in partial response.

Cases No. 4, 7, and 8

Eighteen and 26-year-old female patients presented with pain and swelling over the lower end of the right and left femur for 6 months and 18 months, respectively. All radiological investigations are suggestive of GCTs of bone. The patients underwent curettage and cementing and due to post-operative residual disease, and history of multiple recurrences systemic therapy with denosumab started. The disease responded well to denosumab therapy, and presently, she was in partial response. As there was no post-operative residual disease, 22-year-old the eighth patient did not receive any adjuvant therapy after surgical intervention.

Case No. 5 and 6

Nineteen and 29-year-old female patients presented with pain and swelling over the upper end of the right tibia for 9 months and 1, respectively. All radiological investigations are suggestive of GCTs of bone. The patients underwent curettage and cementing and due to post-operative residual disease, and history of multiple recurrences systemic

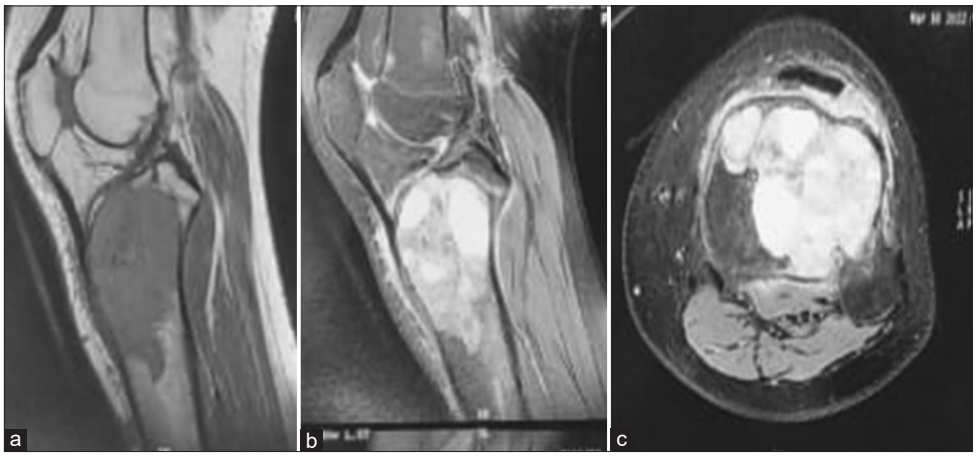

Figure 1: Magnetic resonance imaging appearance of giant cell tumor of bone (upper tibia). (a) T1-weighted image showing intermediate signal intensity eccentric lesion. (b) High signal intensity on T2-weighted image. (c) Marked contrast enhancement on post-gadolinium T1-weighted image

therapy with denosumab started. The disease responded well to denosumab therapy, and presently, she was in partial response. The findings of all eight cases are summarized in Table 1.

DISCUSSION

GCT of the bone also known as osteoclastoma typically arises from the meta-epiphyseal region of the long bone and may be extended to adjacent joint space. Although in the reported literature, the majority of the patients were 4th to 5th decades and more commonly female than male.[1] In contrast, all eight patients were female and under 30 years of age. As previously stated, GCTs can metastasize and the most common site is the lung and commonly seen in the situation of multiple recurrences.[1,2] In our series, one patient who had a history of multiple recurrences and presented with multiple bone metastasis on whole body bone scan (Figure 3).

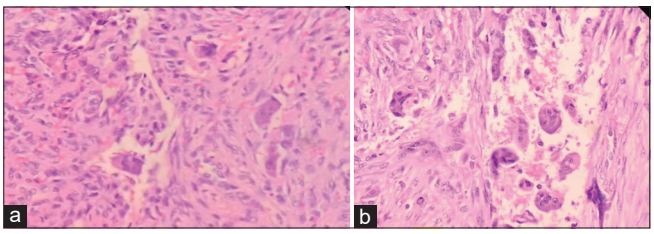

Figure 2: Photomicrograph of giant cell tumor of bone. (a) Low-powered view showing malignant stromal cells and multinucleated giant cells. (b) High-power magnification view-malignant stromal cells and multinucleated giant cells are better appreciated

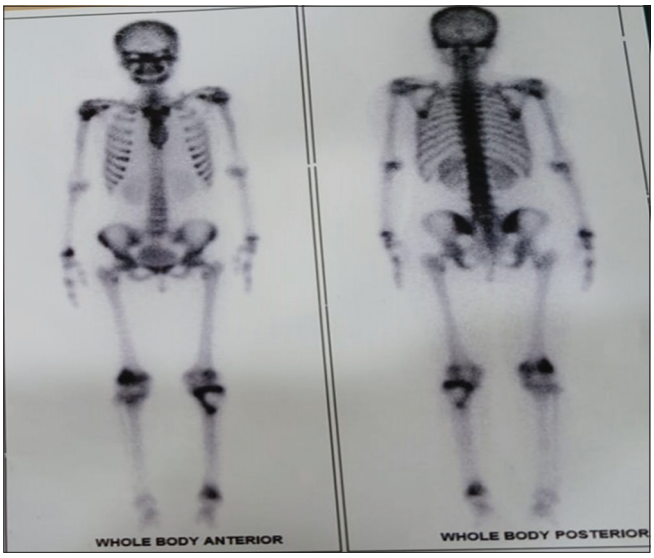

Figure 3: Whole body bone scan showing increased activity in the left upper-end tibia (primary site) and multiple metastatic sites: right upper-end humerus, right lower-end radius; right lower femur, left lower tibia

Surgery

Surgical resection is the standard initial treatment and resection is possible in the majority of cases except in a few situations.[2,3] Although intralesional resection preserves the normal anatomy of the bone, this procedure is associated with a high rate of local recurrence.[4,5] Compared to intralesional resection, curettage followed by adjuvant treatment with bone cementing is associated with a lower rate of recurrence.[6,7] In the scenario, when surgical resection is associated with unacceptable morbidity or unresectable axial location neoadjuvant denosumab and/or serial embolization is preferred.[3] Patients with metastatic disease, local tumor excision along with excision of the metastatic site may be attempted, and if unresectable systemic therapy with denosumab and local treatment with radiotherapy may be attempted. In our series, all except one underwent surgical excision and one patient because the sacral location remains unresectable.

Denosumab

RANK-ligand secreted by the malignant stromal cells of GCT which enhances recruitment and differentiation of precursor cells to osteoclast, thereby causing bone destruction, that is, osteolytic lesion (Mechanism of action of denosumab depicted in Figure 4). The use the Denosumab, an anti-RANK-ligand monoclonal antibody showed clinical benefit in clinical trials and is presently used in inoperable, post-operative residual disease, and metastatic disease.[3] In our case series, we have used denosumab in seven patients, and all the patients except

Table 1: Clinical findings and treatment

S. No.	Age/sex	Clinical features	Location	Histology	Treatment
1	23/F	Pain swelling difficulty in walking×4 m	Sacrum	GCT	Biopsy, Local RT, and denosumab
2	27/F	Pain, swelling×1-year	Upper tibia	GCT	Excision twice, denosumab
3	15/F	Pain, swelling×2 years	Upper tibia	GCT	Excision 3 times, and denosumab
4	18/F	Pain, swelling for 6 months	Lower femur	GCT	Excision and denosumab
5	19/F	Pain, swelling for 9 months	Upper tibia	GCT	Excision, and denosumab
6	29/F	Pain, swelling For 1 year	Upper tibia	GCT	Excision twice, and denosumab
7	26/F	Pain, swelling denosumab for 18 months limping gait	Lower femur	GCT	Excision, and local RT
8	22/F	Pain, swelling for 11 months	Lower femur	GCT	Excision only

GCT: Giant cell tumor

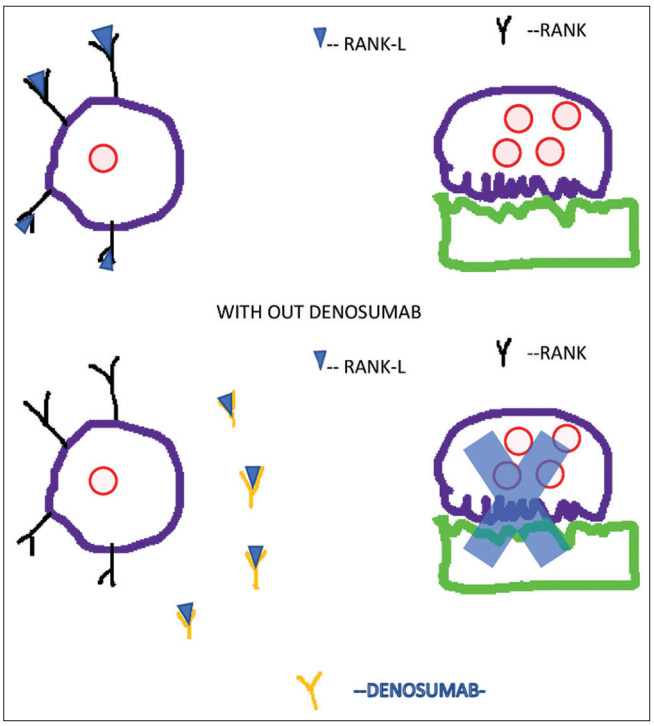

Figure 4: Mechanism of action of denosumab

one are either in partial response or stable disease, whose disease progressed despite denosumab therapy. We encountered hypocalcemia as an adverse event in all patients during denosumab therapy, so once in every 4 weekly cycles gets delayed by 1–2 weeks. We have detected low serum vitamin D3 level in two patients and we believe that this hypocalcemia may get aggravated by low serum vitamin D3 level, and hence, forth at the time of diagnosis of GCT of bone, we are estimating serum vitamin D3 level in each patient. The duration of denosumab therapy is yet to be defined but as in the case of other monoclonal antibodies, it may be continued until disease progression in responding disease or toxicity develops whichever is earlier.

Radiotherapy

At present, the indications of radiotherapy are unresectable, residual, and multiple recurrent diseases, disease which is resistant or refractory to denosumab therapy and to avoid mutilating surgery.[8] The moderate dose of 40–55 Gy has been used in the majority of the published literature with 80% 5 years of local control, but, presently, the recommended dose ranges from 50 to 60 Gy.[3,9] Because the majority of the patients are younger and also live longer, the radiotherapy-induced malignant transformation and second primary are a concern. The risk of malignant transformation varies from 0% to 5%.[3,10] In our series, two patients received radiotherapy either due to unresectable disease or post-operative residual disease that has not responded to denosumab. The dose of radiotherapy was 50 gy/25# over 5 weeks in our series and the patients tolerated radiotherapy very well.

CONCLUSION

GCT of bone is benign but can rarely metastasize. For resectable tumors with acceptable morbidly, surgical excision is the initial treatment of choice, and patients with inoperable, post-operative residual disease, and metastatic disease can be best treated with systemic therapy with denosumab and/or local radiotherapy.

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AB- Conceptualization, methodology, data collection, data interpretation, writing of the manuscript, and reviewing of the final manuscript; **SD, AS, SG, DB, SM,** and **DM:** conceptualization, methodology, data collection, data interpretation, and reviewing the final manuscript.

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