Pathomorphological & Radiological Changes Following Denosumab Treatment In Giant cell tumours

Dr Rajesh Rana[1] , Dr Gayatri behera [2], Dr Vinay Pravat [3] ,Dr Sudarsan Behera *[4], ,Dr Sidhartha Panda [1], Dr Sidhartha Sekhar Moharana [1]

1. Department of Orthopedics
SCB Medical College & Hospital Cuttack, Odisha, India
2. Institute of Medical Sciences and SUM Hospital
SOA University, Bhubaneswar Odisha, India
3. Rajendra institute of medical science.
Ranchi, Jharkhand 834009, India
4 All India Institute of Medical sciences Deoghar
Deoghar, Jharkhand, India 814152
Corresponding Author:
Dr Sudarsan Behera

KEYWORDS
Giant cell tumour, Denosumab, Histopathological, neoadjuvant chemotherapy, Campanacci grade

ABSTRACT
Introduction:- The introduction of denosumab has significantly impacted the treatment approach for giant cell tumors (GCTs) of bone, a locally aggressive osteolytic neoplasm. This study aimed to comprehensively investigate the pathomorphological and radiological changes observed in GCT patients following neoadjuvant denosumab therapy. Material methods: - A retrospective analysis of 12 cases was conducted, encompassing primary and recurrent GCT cases treated with denosumab. Clinical, radiological, and histopathological features were thoroughly examined. All cases displayed Campanacci grade 3 lesions with ambiguous borders. Results: - Neoadjuvant denosumab treatment led to distinct clinical benefits, including reduced intraoperative bleeding and increased bone density, facilitating surgical procedures. Histopathologically, denosumab-treated cases exhibited enhanced cellularity, prominent fibroblastic proliferation, spindle cell arrangement, osteoid formation, and fibro-osseous components. The number of osteoclast-type giant cells significantly diminished, sometimes approaching absence. Immunohistochemical analysis using P63 corroborated the diagnosis. Radiologically, denosumab-induced changes included marked osteosclerosis, sclerotic rim formation, and increased intralesional osteosclerosis. Conclusion: - These findings emphasize the significance of recognizing the diverse morphological and radiological alterations in denosumab-treated GCTs.

Introduction

Giant cell tumour is a locally aggressive osteolytic skeletal neoplasm representing 5% neoplasm of bone [1]. Most commonly occurs in young adults from 20 to 40 years of age with a slightly female predominance [2]. Generally, the tumour is considered benign and locally aggressive but rarely in approximately 3% metastasis to lungs [34]. Malignant transformation of Giant cell tumours is extremely rare and occurs in nearly 5% of cases[5]. Generally, treatment for giant cell tumour is surgery. Curettage and high-speed burring are done using chemical adjuvants such as phenol, alcohol, and liquid nitrogen or electrocauterization[6]. Defect filling is done with bone grafts or bone cement. Sometimes giant cell tumour presents with a cortical breach or very thin cortex where curettage & bone grafting or resection is difficult. Denosumab a human monoclonal antibody that explicitly inhibits RANKL, is used before definitive surgical procedure. Denosumab decreases progression & increases calcification resulting in better delineation of the tumour[7]. Denosumab-treated giant cell tumours shows many pathological and radiological changes that are not consistent with a typical giant cell tumour [8]. Consequently, the treated tumours differ significantly from the pretreatment lesion[9]. sometimes it resembles other lesions of soft tissue or bone, leading to confusing situations. There is no consensus about consistent pathomorphological changes following denosumab treatment. Here we discuss the pathomorphological

and clinical findings of 12 giant cell tumour cases who had received denosumab therapy before the operative intervention.

Materials and methods

This study is a retrospective study which was conducted in the institution from Jan 2019 to December 2023. No informed consent was taken because of retrospective nature of study. All the informations were taken from the previous medical records. We included giant cell tumour patients who had received neoadjuvant denosumab therapy before surgery. Cases with Campanacci grade 2 & 3, which were aggressive tumours with ambiguous border were included in the study. We included both primary and recurrent giant cell tumour cases with denosumab treatment. All cases were evaluated with plain radiograph & MRI (magnetic resonance imaging). We confirmed the diagnosis with core needle biopsy in all cases. We excluded cases with any history of chemotherapy, radiotherapy exposure or inconclusive diagnosis. Subcutaneous injections of Denosumab (120mg) were given on days 0, 8,15 and then every four weeks.

Treatment for giant cell tumour was given from a range of 5 months to 14 months. Along with Denosumab, we provided daily 1500 mg of calcium carbonate plus 400 IU vitamin D. The number of cycles and the adverse effect was noted. Radiographs were taken monthly to evaluate the mineralization, ossification status in the lesion, septa formation, and corticalization. We did repeat CT scan before the final operation. Tissues were 4% formalin-fixed, 7% nitric acid-decalcified, and paraffin-embedded. Four-micron hematoxylin and eosin-stained sections were obtained.P63 immunohistochemistry was done in all Denosumab treated specimens. Soft tissue pathologists did all the histopathology studies. All clinical and radiological examinations were reviewed and discussed by a multidisciplinary committee.

Results

Clinical & Pathomorphological features

We included 12 giant cell tumour patients who had received neoadjuvant denosumab therapy before surgery. All the patients were between age 18 to 48 years age (mean age 33 years) and out of which five (42%) were male and rest seven (58%) were female. We found five cases were from the proximal tibia (41.6 %), three (25%) from distal femur, two(16%) from the distal tibia and one (8.33%) from distal radius. All cases were grade 3 according to Campanacci classification, which was aggressive tumours with ambiguous border. Out of 12 cases, ten cases (83%) were primary & rest two (17%) cases were recurrent giant cell tumour cases .After denosumab treatment patients went extended curettage & bone grafting or resection . Intraoperative bleeding was less because of the reduction of microvascular density. There was increase bone density which facilitated easy manipulation and reduced intraoperative unintentional breach.

Pretreatment histopathology feature of all the cases was similar to characteristic giant cell tumour. The histological features were the uniform proliferation of mononuclear tumour cells mixed with numerous osteoclast type giant cells and scattered lymphohistiocytic inflammatory cells in pretreatment cases.

In post-treatment cases, there was gross increased cellularity in comparison to typical giant cell tumours. There was a marked decrease in the number of giant cells in the histopathology. In two cases, there was a gross reduction to a near absence of giant cells (Figure 1). There was predominant fibroblastic proliferation. Spindle cells were arranged in a fascicular pattern (Figure 2). There was the presence of osteoid and woven bone formation lined by osteoblasts (Figure 3). There was a proliferation of fibroblasts also with the local storiform pattern. Most of the cases showed fibro-osseous component merging with the peripheral shell of reactive bone (Figure 4). There was the proliferation of mononuclear cells with round to oval nucleus with fine to vesicular chromatin. All fields were showing low mitotic indexes with no necrosis. One case was showing partial resemblance with osteosarcomas with mitotic count 1 to 2 per HPF.

Radiological features

Pretreatment cases showed soap bubble appearance osteolytic lesion in epipysio metaphyseal region in the plain radiograph. Lesions had thinned cortical wall with expansions. Some of the patients had a cortical breach. There was narrow jone of transition with no surrounding sclerosis. One case showed the pathological fracture. There was no matrix calcification or mineralization in all cases.

Post-treatment cases showed marked osteosclerosis & sclerotic rim formation. The osteolytic areas show osteosclerotic changes with opacity in the plain radiograph. Sclerotic changes are more pronounced at the periphery of the tumour. The peripheral mineralized cortical borders were thick & irregular (Figure 5). Intralesional osteosclerosis was of variable consolidation type.
CT scan showed sclerotic changes in tumour matrix and marginal sclerosis.CT delineates better sclerosis & neocortex formation.

Discussion & Conclusion

A correct diagnosis requires the evaluation of histology and a careful correlation with radiological and clinical findings. It is always a treatment dilemma for a locally advanced disease where getting clear tumour-free margins is difficult. Denosumab has revolutionized the treatment of clinical course[8] and approach to the disease under challenging situations[11]. It inhibits the tumour growth and delineates the borders clearly, facilitating definitive surgery[12]. Denosumab is a monoclonal antibody inhibiting RANKL receptor leading to the downgrading of tumours, but it produces many clinicopathological changes in tumours commonly not seen in giant cell tumour[12]. Pathologist, Radiologist & treating surgeon should be aware of those changes before treating.
Gross morphologically, there is a reduction of microvascular circulation to the tumour & reduction of the tumour's gross size with well-delineated borders. Histopathologically there was a gross reduction of giant cells in the tumour. There was gross increased cellularity with spindle cells arranged in a fascicular pattern[13]. Osteoid formation was found in all cases which were lined by osteoblasts. Proliferated fibroblast had a storiform pattern[9]. There was a very low mitotic index with no necrosis. P63 biomarker was positive in all cases. P63 marker is always valuable adjunct for the diagnosis of giant cell tumour[14]. Radiologically they showed osteosclerosis & sclerotic rim formation. Tumours showed both marginal & intralesional osteosclerosis[15].
There was no clear correlation between length of treatment and specific histopathological changes[13]. Another limitation of our study was the small sample size and the retrospective nature of our research. Some studies show malignant transformation after denosumab treatment[16105], but in our study, we did not get such changes.
In conclusion, denosumab treatment for giant cell tumour patients has increased in recent times. Denosumab treated giant cell tumour of bone shows different degrees and patterns of ossification, reducing osteoclast-type giant cells, fibrosis, and proliferation of mononuclear cells, with bland, oval to spindle nuclei [17]. The changes overlap many other neoplastic conditions like osteosarcoma, osteoblastoma, etc. [5]. A pathologist should always be aware of pathological changes related to Denosumab treated giant cell tumours. A detailed clinical, morphological and radiological evaluation should be done. Malignant transformations should be excluded by assessment of clinical response to denosumab, radiological and histological evaluation. The typical spectrum of histological changes in giant cell tumours after denosumab therapy is marked depletion of osteoclast-type giant cells, atypical

of the mononuclear cells, and an often-dramatic increase in the bone deposition. Chance of sarcomatous transformation is always more in cases of long denosumab-treated patients.

references

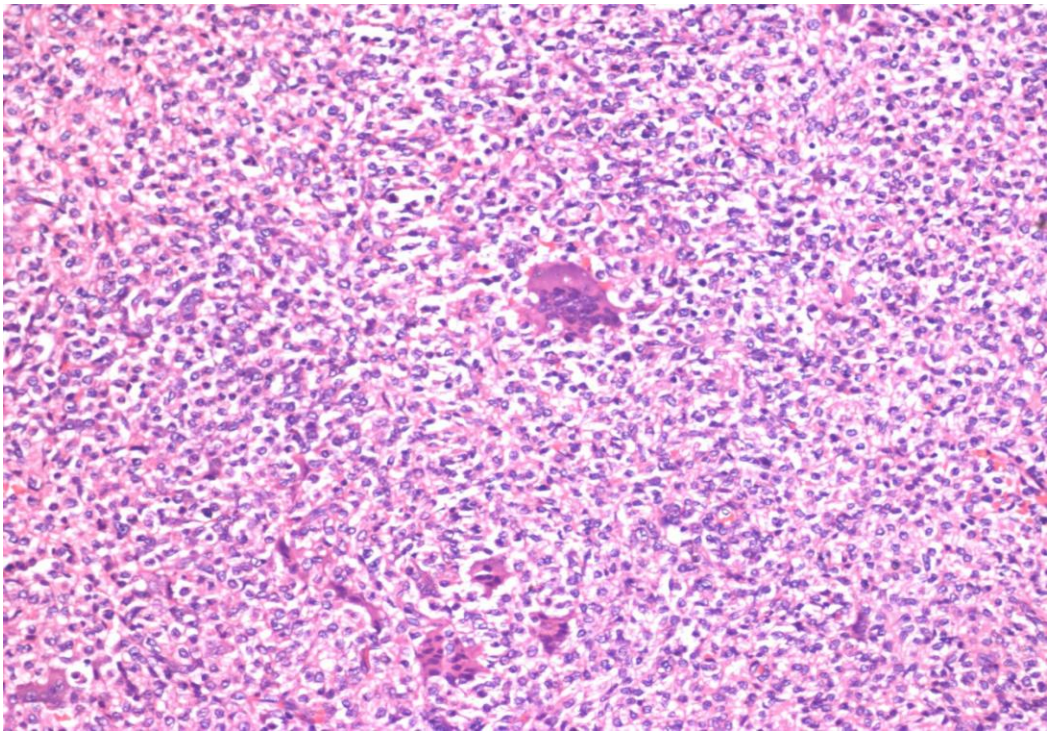
1. Rockberg J, Bach BA, Amelio J, et al. Incidence trends in the diagnosis of giant cell tumor of bone in Sweden since 1958. *J Bone Jt Surg - Am Vol*. 2014;97(21):1756-1766. doi:10.2106/JBJS.O.00156
2. Sobti A, Agrawal P, Agarwala S, Agarwal M. Giant cell tumor of bone - An overview. *Arch Bone Jt Surg*. 2016;4(1):2-9. doi:10.22038/abjs.2016.4701
3. Chan CM, Adler Z, Reith JD, Parker Gibbs C. Risk factors for pulmonary metastases from giant cell tumor of bone. *J Bone Jt Surg - Am Vol*. 2015;97(5):420-428. doi:10.2106/JBJS.N.00678
4. Purohit S, Pardiwala D. Imaging of giant cell tumor of bone. *Indian J Orthop*. 2007;41(2):91-96. doi:10.4103/0019-5413.32037
5. Palmerini E, Picci P, Reichardt P, Downey G. Malignancy in Giant Cell Tumor of Bone: A Review of the Literature. *Technol Cancer Res Treat*. 2019;18. doi:10.1177/1533033819840000
6. Van Der Heijden L, Van Der Geest ICM, Bart Schreuder HW, Van De Sande MAJ, Sander Dijkstra PD. Liquid nitrogen or phenolization for giant cell tumor of bone?: A comparative cohort study of various standard treatments at two tertiary referral centers. *J Bone Jt Surg - Ser A*. 2014;96(5). doi:10.2106/JBJS.M.00516
7. Luengo-Alonso G, Mellado-Romero M, Shemesh S, Ramos-Pascua L, Pretell-Mazzini J. Denosumab treatment for giant-cell tumor of bone: a systematic review of the literature. *Arch Orthop Trauma Surg*. 2019;139(10):1339-1349. doi:10.1007/s00402-019-03167-x
8. Girolami I, Mancini I, Simoni A, et al. Denosumab treated giant cell tumour of bone: A morphological, immunohistochemical and molecular analysis of a series. *J Clin Pathol*. 2016;69(3):240-247. doi:10.1136/jclinpath-2015-203248
9. Deveci MA, Paydaş S, Gönlüşen G, Özkan C, Biçer ÖS, Tekin M. Clinical and pathological results of denosumab treatment for giant cell tumors of bone: Prospective study of 14 cases. *Acta Orthop Traumatol Turc*. 2017;51(1):1-6. doi:10.1016/j.aott.2016.03.004
10. Wu CC, Hsieh PP. Denosumab-treated giant cell tumor of the bone mimicking low-grade central osteosarcoma. *J Pathol Transl Med*. 2018;52(2):133-135. doi:10.4132/jptm.2016.12.21
11. Agarwal MG, Gundavdad MK, Gupta R, Reddy R. Does denosumab change the giant cell tumor treatment strategy? Lessons learned from early experience. *Clin Orthop Relat Res*. 2018;476(9):1773-1782. doi:10.1007/s11999.0000000000000243
12. Xu SF, Adams B, Yu XC, Xu M. Denosumab and giant cell tumour of bone-a review and future management considerations. *Curr Oncol*. 2013;20(5):e442. doi:10.3747/co.20.1497
13. Roitman PD, Jauk F, Farfalli GL, Albergo JI, Aponte-Tinao LA. Denosumab-treated giant cell tumor of bone. Its histologic spectrum and potential diagnostic pitfalls. *Hum Pathol*. 2017;63:89-97. doi:10.1016/j.humpath.2017.02.008
14. Shooshtarizadeh T, Rahimi M, Movahedinia S. P63 expression as a biomarker discriminating giant cell tumor of bone from other giant cell-rich bone lesions. *Pathol Res Pract*. 2016;212(10):876-879. doi:10.1016/j.prp.2016.07.007
15. Hakozaki M, Tajino T, Yamada H, et al. Radiological and pathological characteristics of giant cell tumor of bone treated with denosumab. *Diagn Pathol*. 2014;9(1):111. doi:10.1186/1746-1596-9-111
16. Alaqaili SI, Abduljabbar AM, Altaho AJ, Khan AA, Alherabi JA. Malignant Sarcomatous Transformation of Benign Giant Cell Tumor of Bone after Treatment with Denosumab Therapy: A Literature Review of Reported Cases. *Cureus*. 2018;10(12). doi:10.7759/cureus.3792
17. Erdogan KE, Deveci MA, Paydas S, Gonlusen G. Morphologic evaluation of the effect of denosumab on giant cell tumors of bone and a new grading scheme. *Polish J Pathol*. 2016;67(4):392-397. doi:10.5114/pjp.2016.65873

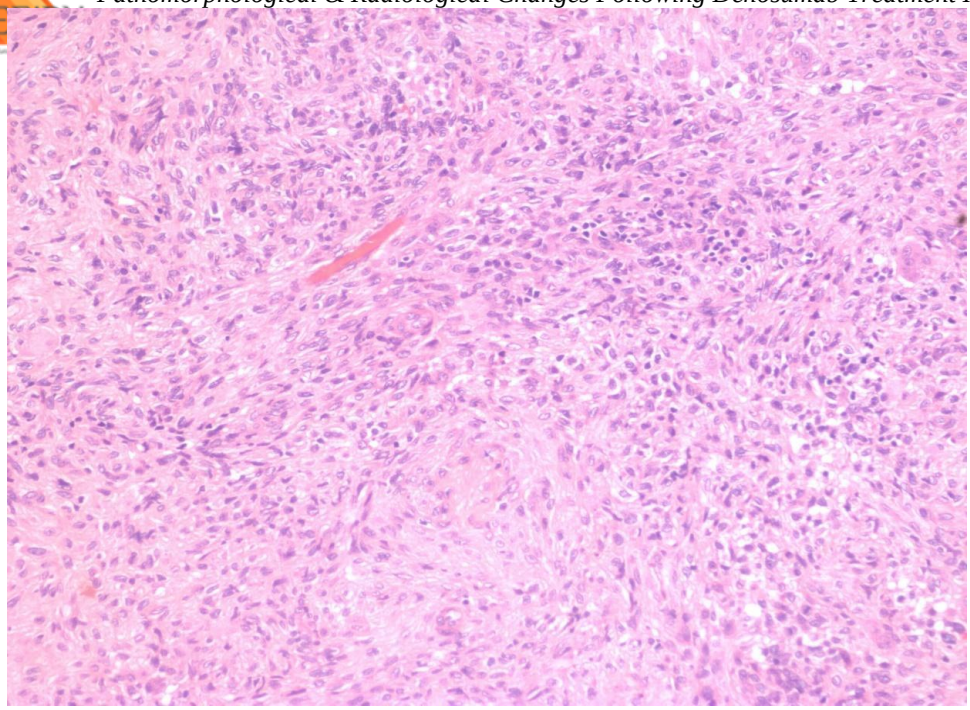
Figure Legends

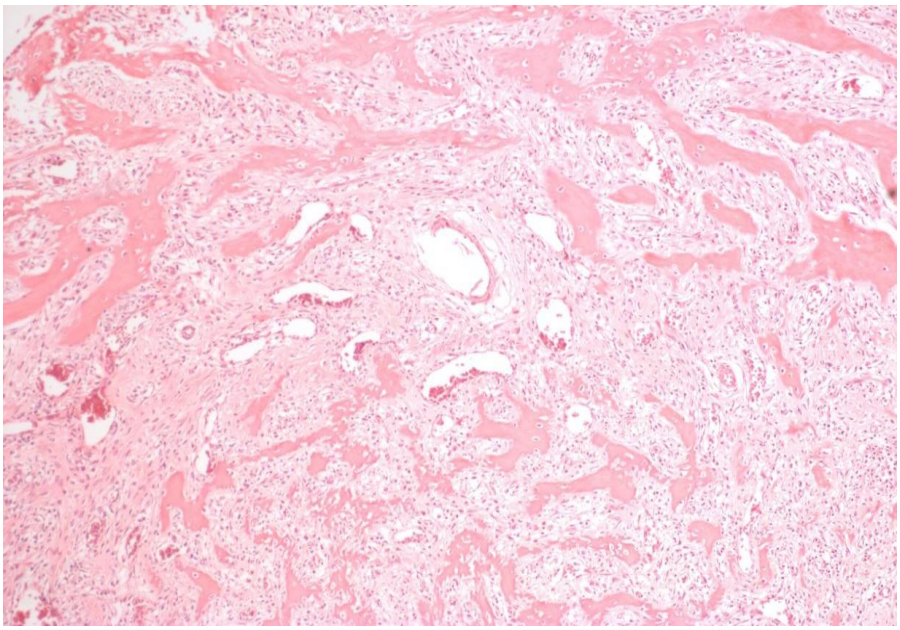
Figure 1: - Predominantly mononuclear cells with round to oval nucleus, fine to vesicular chromatin and moderate cytoplasm with occasional of giant cells. [x 200 H & E].

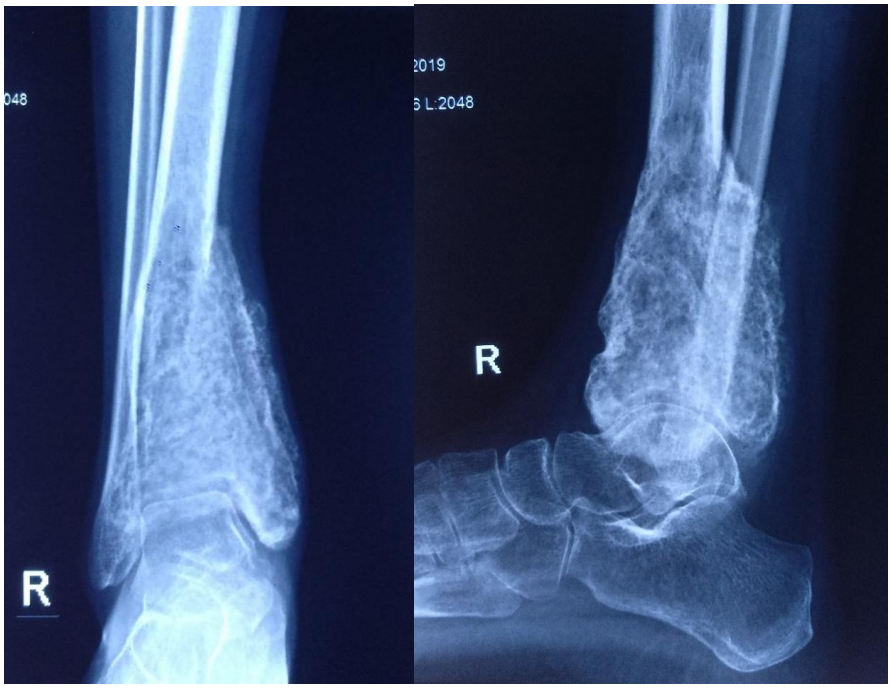
Figure 2: - Short fascicular arrangement of spindle cells [x 400 H & E].

Figure 3: -Woven bone formation [x 400 H & E].
Figure 4: - Post Denosumab treatment radiological view (AP) & Lateral








048
R
2019
L:2048
R