International Journal of Medical Science in Clinical Research and Review
Online ISSN: 2581-8945
Available Online at https://ijmscrr.in/ Volume 7|Issue 05 (September-October) |2024 Page: 1025-1031

Original Research Paper

Effects on histomorphology of Giant cell tumor due to advancement in the treatment modalities – An insight from a tertiary care centre

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Article Received: 22-August-2024, Revised: 12-September-2024, Accepted: 02-October-2024

ABSTRACT:

Introduction: Giant cell tumor (GCT) of bone is a neoplasm which is characterized by presence of multinucleated osteoclasts type giant cells embedded in a mononuclear stromal cell. Surgery is the primary treatment for GCT of bone, but recurrence remains the concern. In this article, we discuss the morphological changes in histopathology by different modalities of treatment of GCT. Material and methods: Histologically proven fifteen cases of GCT of bone were studied over a period of one year in 2023 from the Department of Pathology, Bharati Vidyapeeth Medical College, Pune, Maharashtra, India. The data was collected on various relevant clinical aspects and evaluated. **Discussion**: GCT of the bone is a locally aggressive osteolytic neoplasm that involves the epiphysis of long bones. GCT affects individuals in the second or fourth decade. The tumour has an equal sex predilection. It is the outcome of interaction between RANK (Receptor activator of nuclear factor kappa B) and RANKL (Receptor activator of nuclear factor kappa-B ligand) which is expressed on the osteoclastic giant cells and mononuclear cells, respectively. In recent years, development of targeted therapy in GCT has changed the pathway for treatment. Denosumab is a monoclonal antibody that targets RANKL, thus resulting in effects on histomorphology which are deceptive to the pathologist. **Conclusion**: GCT is characterized by a proliferation of mononuclear stromal cells and the presence of many multi-nucleated giant cells with homogenous distribution. Various treatment modalities with recent advances in targeted therapy is now changing the landscape for treatment. It is necessary that the pathologist should be aware of these targeted therapy related changes on morphology to prevent diagnostic pitfalls as it poses therapeutic and prognostic implications.

Keywords: ***1) Giant cell tumor 2) RANKL 3) Denosumab***

INTRODUCTION:

Giant cell tumor (GCT) of bone is a neoplasm which is characterized by presence of multinucleated osteoclastic type giant cells embedded in mononuclear stromal cells (1). The most common sites for GCT includes epiphysis and metaphysis of the long bones such as distal femur, proximal tibia, distal radius, and proximal humerus. Other uncommon sites include sacrum, pelvic bone, vertebrae, small tubular bones of hands and feet (2). Although surgery is the primary treatment for GCT of bone, but recurrence remains a concern. Occurrence of GCT at difficult anatomical sites makes the treatment more challenging. In such cases, targeted therapies have emerged (3). The development of denosumab, a monoclonal antibody for treating both primary and recurrent disease cases of GCT has created a paradigm shift. The aim of the study is analysing the histomorphological changes in GCT with their treatment effects. This will enable appropriate diagnosis after Denosumab treatment hence reducing errors.

MATERIALS AND METHODS:

A total of fifteen histologically proven GCT of bone were studied over a period of one year in 2023 from a tertiary care hospital in, Maharashtra, India. The data was collected for the clinical presentation, location, radiological findings, histo-morphological characteristics, treatment, and its effect with morphological changes. The treatment effect on morphology were studied in detail to avoid pitfalls in the diagnosis. The results are discussed below in detail. Radiology and histopathology images of relevant cases are provided below for better understanding.

RESULTS:

This is a study of fifteen cases of GCT which were confirmed on histopathology over a duration of one-year 2023. The age group for the cases ranged from 17 years to 62 years. The maximum cases (7 cases) were in the age group of 21-40 years which is the similar finding to existing literature. Female were more common than the males. The most common site for GCT in our study was phalanx (6 cases) followed by tibia (4 cases).

Out of 15 cases, we received local resection in 04 cases and in 11 cases curettage was done (Details given in Table 1). On tracing back the treatment history, Denosumab was given in 02 cases after that they underwent local resection.

On radiological imaging findings were very classic showing lytic expansile lesion at the affected site. On radiological examination, (MRI shows panel A-D) Image D showed a well-defined expansile lytic lesion is noted in the posterior aspect of right 5th rib causing destruction of underlying rib. (Figure 1)

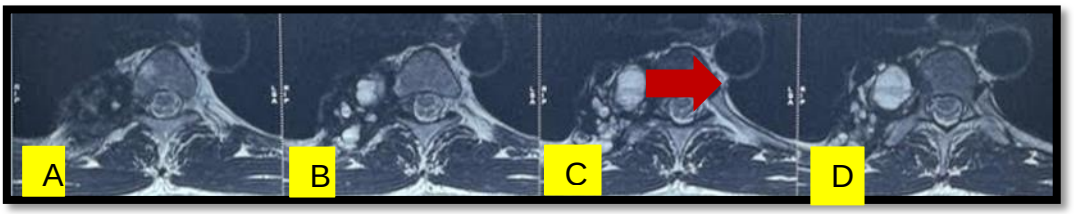

Figure 1: Image D showing radiographic finding of GCT involving rib

Gross findings:

In 11 cases of curettage, we received tumor in the bits with soft tissue and bony bits that were firm to hard consistency. Other 04 cases, local resection was received from rib, mandible and femur and the grossing was done as per standard protocol.

Following gross image shows local resection showing a nodular tumor attached to the rib. External surface was nodular. Cut surface, showed an ill-defined firm to hard variegated areas. (Figure 2)

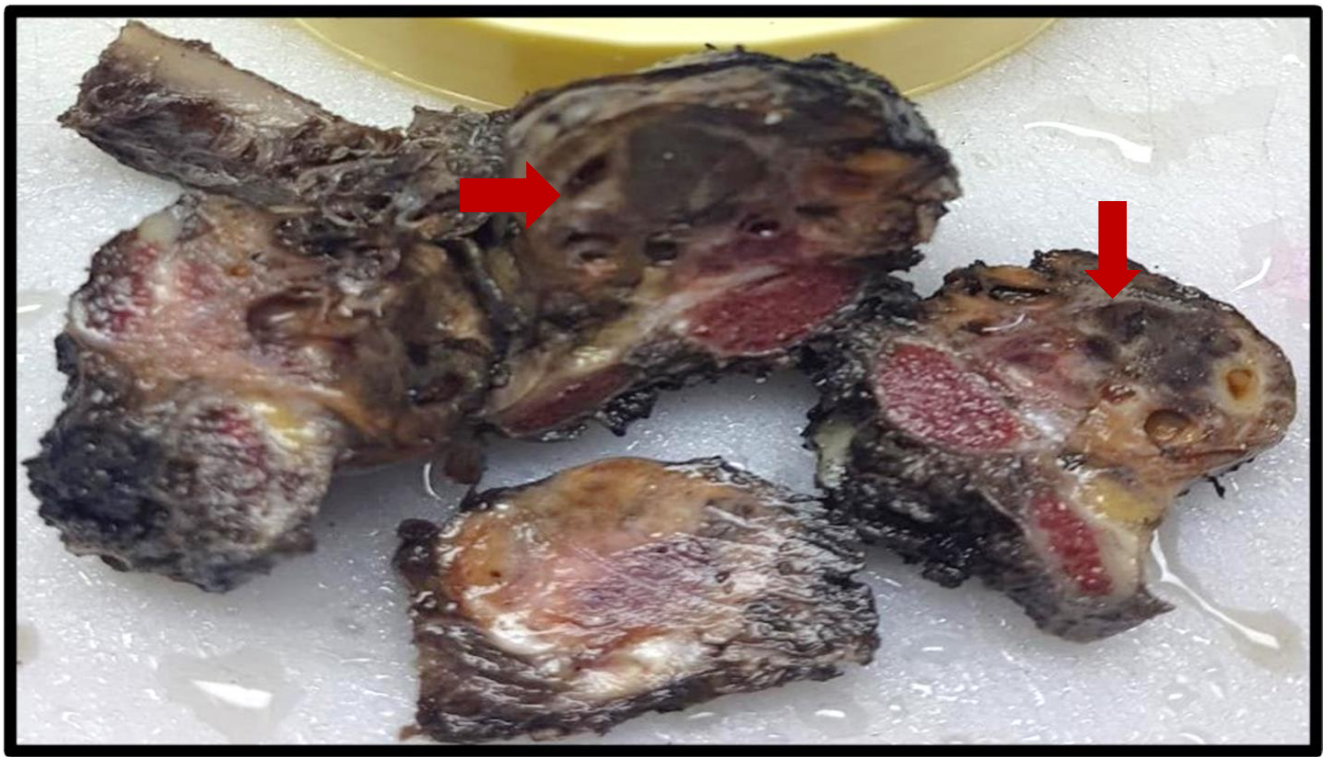

Figure 2: Gross image of local resection of rib (post-Denosumab status).

Microscopy:

Out of 15 cases, 13 cases showed classical histological morphology. Figure 3 shows classical microscopy of giant cell tumor.

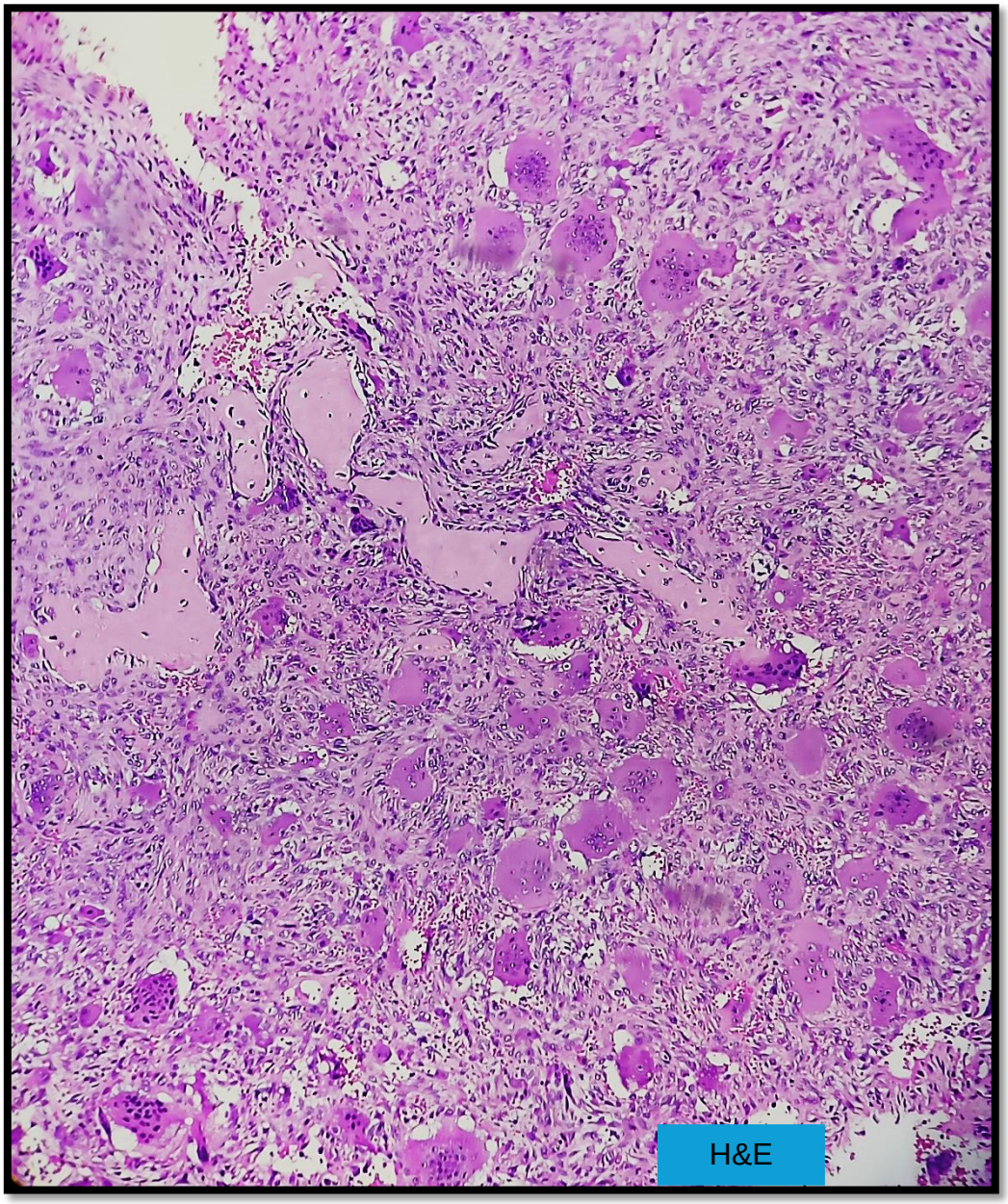

Figure 3: H&E (10x) Microscopy of GCT showing numerous giant cells embedded in mononuclear neoplastic stromal cells.

Histologically, GCTs are characterized by numerous multinucleated giant cells scattered throughout a background of mononuclear stromal cells. The stromal cells exhibit a spindle-shaped or ovoid appearance and can show varying degrees of mitotic activity. The stromal cells are thought to be the neoplastic component responsible for tumor growth, while the multinucleated giant cells are derived from mononuclear cells of the monocyte/macrophage lineage. In 02 cases, there was remarkable difference in morphology pre and post treatment which has been discussed in detail in discussion (Figure 4 and 5, showing pre-treatment and post treatment microscopy of GCT, respectively).

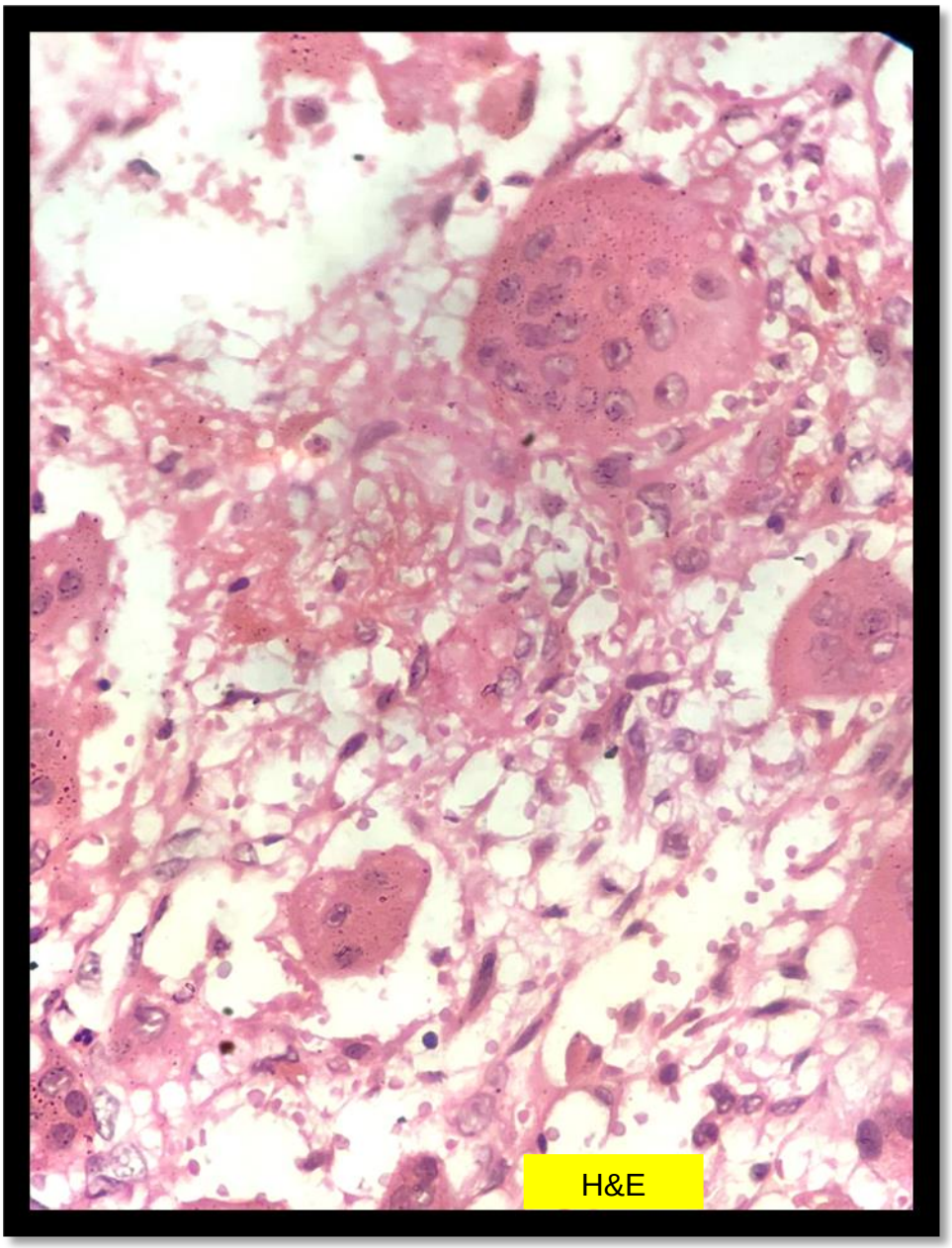

Fig 4: H&E (20X): Histomorphology of GCT (pre-treatment) showed collection of osteoclastic type of giant cells on the background of cellular stroma.

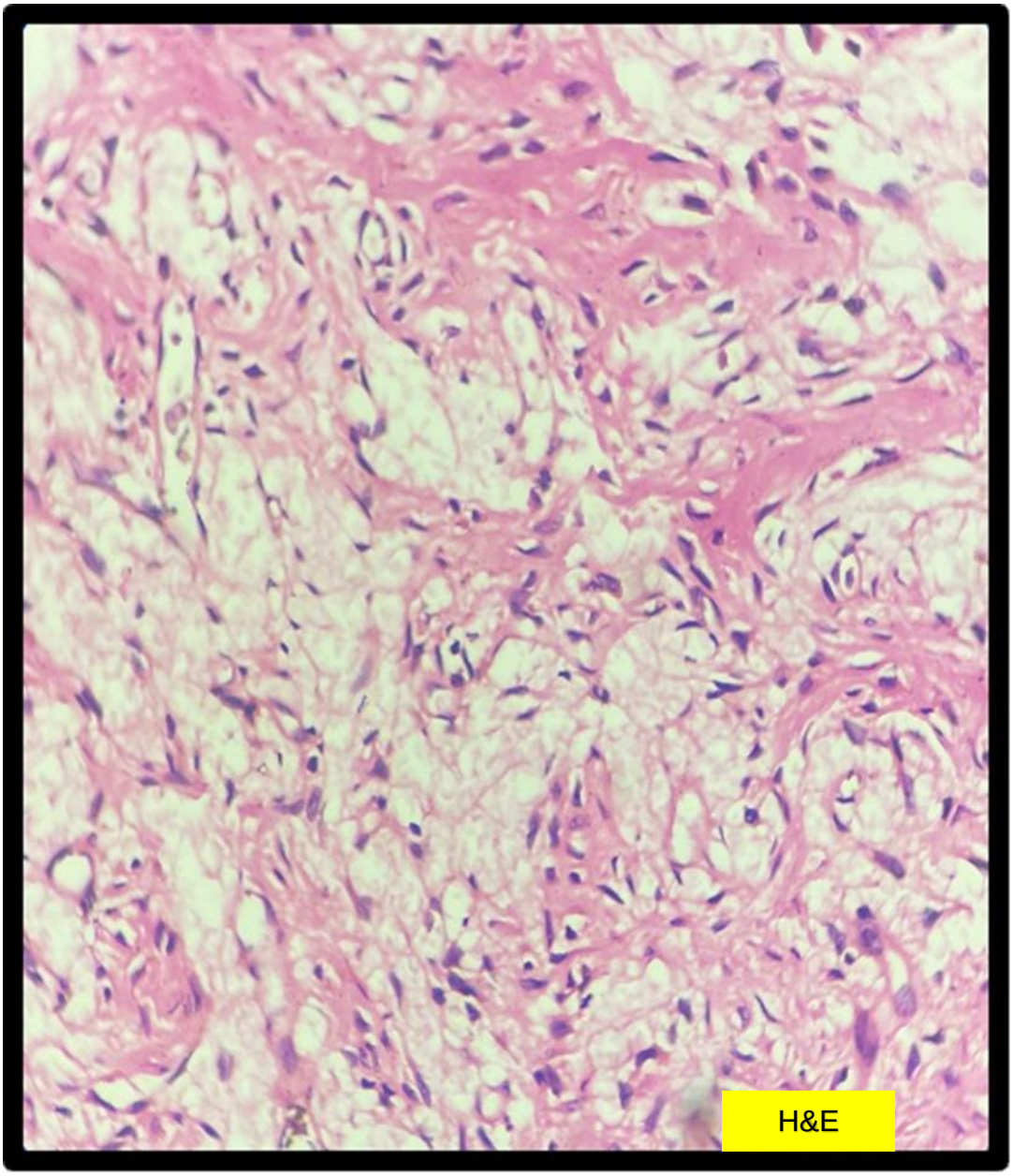

Fig 5: H&E 20x: Post Denosumab treatment resected specimen with marked depletion in the osteoclastic type of giant cells with background showing abundant stroma with few areas showing osteoid formation.

DISCUSSION:

The pathophysiology in the GCT of bone is due to interaction between RANK and RANKL (3). RANK is Receptor Activator of Nuclear Factor Kappa which is present on osteoclastic giant cells. RANKL is Receptor Activator of Nuclear Factor Kappa Ligand present on mononuclear stromal cells. When the interaction between RANK and RANKL is increased, it leads to increased osteoclast activity, proliferation, and survival. Pathophysiology of GCT involves interaction between stromal cells and mononuclear giant cells in GCTs and is partly mediated by the RANK (Receptor Activator of Nuclear Factor κ B) and RANK Ligand (RANKL) signalling pathway. Stromal cells in GCTs express RANKL, which interacts with RANK multinucleated giant cells (MNGCs). This interaction promotes osteoclast-like differentiation of MNGCs and enhances their bone-resorbing activity (2). This mechanism leads to the characteristic bone destruction seen in GCTs, where MNGCs actively resorb bone matrix. Other proposed mechanisms which can lead to GCT are either genetic alteration or tumor microenvironment. Few genetic studies have identified mutations in the H3F3A gene, which encodes histone 3.3, in a subset of cases. These mutations may contribute to altered epigenetic regulation and cellular differentiation within the tumor, potentially enhancing its aggressive behaviour (4). Tumor Microenvironment within GCTs is rich in cytokines, growth factors, and chemokines that support tumor growth and osteoclastogenesis. Factors such as TGF-β (Transforming Growth Factor-beta), IL-6 (Interleukin-6), and M-CSF (Macrophage Colony-Stimulating Factor) are often elevated and play roles in regulating stromal cell proliferation, MNGC recruitment, and osteoclastic activity (5).

Various treatment modalities are now emerging to treat the recurrent cases and cases with difficult anatomical

site. Development of monoclonal targeted therapy against RANKL has been helpful in such difficult cases. Denosumab is targeted therapy against RANKL. Denosumab binds with RANKL, thus reducing osteoclast activity, proliferation, and survival.

Denosumab therapy can lead to following histo-morphological changes in GCT: 1) Reduction in the number of osteoclastic giant cells accompanied by cellular stromal proliferation 2) Irregular new bone formation and osteoid matrix deposition 3) Cellular stroma showed mild atypia in the form of hyperchromatic nuclei 4) High nucleus: cytoplasm ratio, prominent nucleoli in some cells 5) Sparse mitotic activity (5).

Denosumab is recommended for advanced giant cell tumor of bone (GCTB) that is unresectable or resectable with unacceptable morbidity. Few studies also shown that Denosumab is also helpful in cases of myeloma, breast, and prostate cancer as it supresses bone destruction (3).

As Denosumab causes loss of osteoclastic giant cells, prominent woven bone formation with mononuclear cells in stroma showing atypia. These morphological features overlap with low grade central osteosarcoma and in some cases with fibro-osseous lesion (6). It is very important for a pathologist to know treatment history in detail before arriving at a final diagnosis as it can lead to misappropriate diagnosis.

Studies have suggested the utility of immunohistochemistry. H3.3G34W as a helpful marker for arriving at a diagnosis in such Denosumab treated GCT cases which have a close differential diagnosis, as most of the GCTs of bone possess this mutation (6). H3.3G34W shows nuclear positivity in mononuclear stromal cells. It is novel diagnostic marker to be used to rule out other differentials (6,7).

In comparison with other studies, Alothman et al study had a greater number of females which was similar finding to our study (8). Most common site in our study was phalanx (6 cases), while study done by Manglekar P et al had a greater number of cases from distal tibia (4).

Saeed J et al in their study show similar findings histo-morphology of GCT after Denosumab treatment (9). Kamble A et al had similar close differential diagnosis in a treated case with GCT of bone (6). In Huang Y et al study, the most common site of tumor was femur in 57 cases while in our cases it was phalanx in 06 cases (10).

The most important morphologic point to assess after Denusumab treatment and to see treatment response is reduction in number of osteoclastic type of giant cells by 90%, other points include fibrosis, cytologic and nuclear atypia, necrosis and malignant transformation in rare cases (11).

Fewer limitations we found in this study was lost to follow up of the patients, limited number of cases, lack of IHC antibodies and delayed availability of treatment history of patient. With availability of suitable IHC antibody and detailed treatment history of patient, prompt diagnosis could be achievable in difficult cases.

CONCLUSION:

Multiple treatment modalities ranging from curettage to local resection with recent advances in targeted therapy is now changing landscape for the treatment. Clinical details, radiological findings, and treatment history should correlate before arriving at the final diagnosis. Surgery is the primary treatment for GCT of bone, but recurrence remains a concern.

Denosumab therapy showed significant reduction in the number of osteoclastic giant cells accompanied by cellular stromal proliferation, irregular new bone formation and osteoid matrix deposition.

Awareness of post-denosumab related histopathological changes are necessary to avoid misdiagnosis as fibro-osseous lesion and low-grade central osteosarcoma. It is necessary that the pathologist should be aware of these changes to prevent diagnostic pitfalls as it possesses therapeutic implications.

Sources of support in the form of grants: Not applicable

Availability of data: Author elects to not share data

Conflict of Interest: Author declares no conflict of interest

Funding statement: Not applicable

ACKNOWLEGMENT: None

TABLE:

Table 1: Summary of Age, sex, site Distribution with treatment details.

Sr. No.	Age	Gender	Location	Treatment
1	17	M	Right phalanx	Curettage
2	19	F	Neck of femur	Local excision
3	24	M	Right humerus	Curettage
4	28	M	Right thumb	Curettage
5	29	F	Left index finger	Curettage
6	32	F	Mandible	Local resection
7	35	F	Left phalanx	Curettage
8	37	F	Left phalanx	Curettage
9	38	F	Right phalanx	Curettage
10	42	F	Outside block for review from right tibia	Denosumab followed by resection
11	45	M	Left phalanx	Curettage
12	45	M	Rib	Denosumab followed by resection
13	50	F	Left knee	Curettage
14	54	M	Left femur	Curettage
15	62	M	Right phalanx	Curettage

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