ORIGINAL ARTICLE

HISTOPATHOLOGICAL FEATURES OF DENOSUMAB TREATED GIANT CELL TUMOURS OF BONE "A SINGLE INSTITUTIONAL EXPERIENCE" AT A TERTIARY CARE CENTER, KARACHI

Salima Mansoor Ali, Nausheen Yaqoob, Kanwal Aftab, Samar Tauseef, Syed Kamran Ahmed, Syed Ali Anwar Jilani, Saba Jamal

Section of Histopathology, Department of Pathology, The Indus Hospital, Karachi-Pakistan

Background: Giant cell tumour (GCT) is a primary benign, locally aggressive bone tumour. Treatment is surgical however, denosumab has been increasingly used as a treatment in recurrent or unresectable locally advanced GCT because of its effect in reducing tumour size. Denosumab treated GCT can exhibit a wide array of histopathological features resulting in diagnostic problems for pathologists. Our study aimed at identifying these histopathological features to aid pathologists in reaching a correct diagnosis. **Methods:** Our study included 20 patients of biopsy-proven GCT cases treated with denosumab. We received specimens for histopathological examination in our institution from January 2018 to March 2020. The demographic and clinical data of these patients were retrieved from the Health Management Information System (HMIS). The slides were retrieved and studied for histopathological changes. **Results:** The mean age of patients in our study was 29.5 years. There were 11 males and 9 females. Distal radius was most commonly involved bone. On histopathological examination, ovoid to spindle mononuclear stromal cells were seen. Total absence of osteoclast like giant cells was seen in 10 (50%) cases, whereas 3 (15%) cases showed a marked reduction in osteoclast like giant cells. **Conclusion:** Denosumab treated GCT of bone can exhibit a wide spectrum of histopathological features. Pathologists need to be mindful of these features. Correlation of histopathological findings with clinical history and radiological features is important to prevent erroneous diagnosis. Treatment history of patients with denosumab is essential as incorrect diagnosis can be made if the history of denosumab treatment is not provided.

Keywords: Giant cell tumour; Denosumab; Osteoclast like giant cells; Shell formation; Mononuclear cells

Citation: Ali SM, Yaqoob N, Aftab K, Tauseef S, Ahmed SK, Jilani SAA, *et al.* Histopathological features of denosumab treated giant cell tumours of bone "A single institutional experience" at a tertiary care center, Karachi. J Ayub Med Coll Abbottabad 2022;34(1):73–81.

INTRODUCTION

Giant cell tumour (GCT) is a benign locally aggressive bone neoplasm. It represents 4–10% of all primary bone tumours and is usually seen between the ages of 20 and 45 years. About 10% of GCT is seen in the second decade. The most common sites are the distal femur, distal radius, proximal humerus, and proximal tibia but it can involve pelvis, sacrum, and immature skeleton. It rarely involves flat bones however; ilium is frequently affected bone in the pelvis.[1] The involvement of scapula, ribs, or sternum suggests a diagnosis other than GCT such as osteosarcoma and aneurysmal bone cyst.[2] Bones of hands and feet can be involved but occurs at a younger age and tends to be more aggressive. The majority of cases reported as GCT involve the epiphyseal-metaphyseal region of appendicular skeleton.[3] Pain is the primary presenting symptom whereas swelling and deformity are associated with larger lesions. In addition, limitation of motion and extension into the surrounding soft tissue can also occur. In 5–10% of patients, pathological fracture can be seen. Radiographic findings usually show an eccentric lytic lesion involving the end of long bones. A radiologic staging system has been proposed by Campannacci *et al*. according to which grade 1 lesion shows a thin sclerotic rim surrounding a well-defined lesion. Grade 2 lesion shows a well-defined lesion without a sclerotic rim whereas grade 3 lesion shows poor margins with aggressive and permeative patterns.[2,4] Although GCT is a benign lesion, it frequently recurs and has a propensity to metastasize and can also have malignant transformation.[5]

The treatment for GCT is mainly surgical and includes wide margin resection of the tumour or intra-lesional curettage followed by burring of the tumour cavity.[1,5–7] The options for adjuvant therapy include bone cement, cryotherapy, phenol, hydrogen peroxide, argon beam coagulation, and preoperative embolization. Recurrence rate following curettage is 15–50 percent and depends on the extent of curettage and the adjuvant therapy used. Recurrence usually occurs within 2 years.

Local recurrence rate following wide margin excision is low.[1,7]

Histopathological examination of GCT shows uniform proliferation of mononuclear stromal cells along with scattered osteoclast type giant cells. Giant cells are uniformly distributed and usually have 40–60 nuclei. The stromal cells are arranged in sheets of ovoid or spindle-shaped mononuclear cells. These cells show amphophilic to eosinophilic cytoplasm with round to oval nuclei, uniformly distributed chromatin and inconspicuous nucleoli. Mitotic figures can be seen but atypical mitotic figures are never present. The mononuclear cells can exhibit storiform pattern mimicking a fibro-histiocytic neoplasm. Clusters of foam cells, areas of infarct like necrosis and focal or abundant reactive bone formation are frequently seen. Formation of cartilage is uncommon.

Osteoclast like giant cells have Receptor activator of nuclear factor kappa-B (RANK) receptors whereas mononuclear stromal cells have high RANK ligand (RANKL) expression. The RANK ligand binds to RANK receptor present on osteoclast like giant cells and results in proliferation and activation of osteoclast like giant cells, causing bone resorption. The mononuclear cells are strongly positive for p63 antibody whereas Ki67 proliferation index ranges from 8% to 15%. The mononuclear cells in GCT harbour H3F3A (histone H3 family 3A protein) mutation.[3,8,9]

Denosumab is a monoclonal antibody that functions as RANK ligand inhibitor. It stops monocyte recruitment, proliferation and giant cell production resulting in reduction of osteoclastic activity. This drug has emerged as a possible medical treatment of GCT. Denosumab seems to reduce pain, decrease progression of tumour and increases formation of bone around lesion.[10] Moreover, it seems to decrease bone resorption, increase bone mass and improve trabecular architecture.[11]

Denosumab treated GCT may histologically mimic fibrous dysplasia, osteoblastoma, non-ossifying fibroma, juvenile ossifying fibroma or histological features that overlap with low grade central osteosarcoma. Denosumab treated GCT show abundant woven bone formation along with fibrous tissue and can completely lack giant and mononuclear cells. This finding of lack of giant cells with woven bone formation, fibrosis and minimal cytologic atypia can mimic low grade osteosarcoma.[3,8] Thus, careful attention must be given to the history of denosumab administration as it may be misdiagnosed as osteosarcoma due to pseudo-sarcomatous changes after significant therapeutic effects.

MATERIAL AND METHODS

This observational study includes review of 20 cases of GCT that received treatment with denosumab followed by resection of the tumour at our tertiary care hospital. All post treatment cases received in the histopathology department between January 2018 and March 2020 were included in this study. Before initiating the treatment, the diagnosis of these patients was confirmed on biopsy. The information concerning patient's gender, age, surgical procedure, dose of denosumab, tumour site and size were retrieved using the health management information system (HMIS) and pathology reports.

The indication of giving denosumab at our institution is grade 3 GCT. A dose of 120 mg denosumab was given to these patients at day 0, 7, 15, 28 and then at one-month interval. Most patients received four doses of denosumab (12 patients). Six patients received five doses, one patient received six doses and one patient received seven doses of denosumab.

We studied the slides for the presence of residual GCT and treatment related effects. Following microscopic features were reviewed: presence or absence of osteoclast like giant cells (OLGC), presence of mononuclear stromal cells, pseudosarcomatous changes, necrosis, woven/reactive bone formation, foamy macrophages, inflammatory infiltrates, cystic changes, necrosis, fibrosis, oedematous areas and hyalinization.

RESULTS

This study included 20 patients, 11 males and 9 females were part of the study (male to female ratio: 1.22:1). The age range was 12–50 years (mean: 29.5 years). 17 cases were primary GCT whereas three cases were recurrent GCT. In our study, distal radius (6 cases) was the most common site of tumour, followed by distal femur (5 cases), proximal tibia (3 cases), distal tibia (2 cases) and proximal humerus (2 cases). One case involved 4th metacarpal bone and one case showed involvement of ischial tuberosity and inferior acetabular margin, which are rare sites for GCT. All patients received denosumab following confirmation of GCT diagnosis with biopsy. These patients then underwent surgery. Wide margin excision (WME) was performed in 11 patients, two patients underwent curettage and bone grafting (C/BG) and three patients underwent curettage with bone cementing (C/C). Amputation was performed in four patients. Out of four patients who underwent amputation, two patients had recurrent GCT, one patient had GCT of the metacarpal bone, while one patient was lost to follow up after four cycles of denosumab and returned with an increase in the size of tumour. Tumour size varied from 3.5–20 cm in the greatest dimension.

On gross examination, most tumours were soft to firm in consistency and grey-white to dark brown with areas of haemorrhage.

Radiographic appearance of GCT prior to treatment with denosumab showed expansile lytic lesion, with cortical thinning, narrow zone of transition, and surrounding soft tissue swelling (Figure-1). On histopathological examination, reactive/woven bone formation was seen in all cases. The total absence of osteoclast like giant cells was seen in 10 (50%) cases whereas, three (15%) cases showed marked reduction in osteoclast like giant cells to less than 1%. In seven (35%) cases, substantial amount of residual osteoclast like giant cells were seen. Most tumours showed stromal cells comprising of round to oval spindle-shaped cells. In 3 cases (cases 10, 12 and 14) tumour was completely replaced by fibrous tissue and bone. No osteoclast like giant cells and mononuclear stromal component was identified in these cases. A shell of reactive bone was seen at the periphery in 13 cases. Mitosis was identified in 4 cases, but atypical mitosis was not present in any case. Other features that were seen in denosumab treated GCT included foamy histiocytes, fibrosis, haemorrhage, inflammatory cells, hemosiderin-laden histiocytes, necrosis, storiform collagen, and slit-like vascular spaces. In one case (case 6), tumour showed large cystic spaces filled with blood, focally separated by fibrous septae, comprising of bland fibroblasts and scattered multinucleated osteoclast type giant cells with focal reactive bone formation. These features favoured associated secondary Aneurysmal bone cyst. No pseudo-sarcomatous change was identified in all 20 cases. Moreover, in one case we found formation of cartilage in the tumour. The histopathological findings of each case are summarized in table-1.

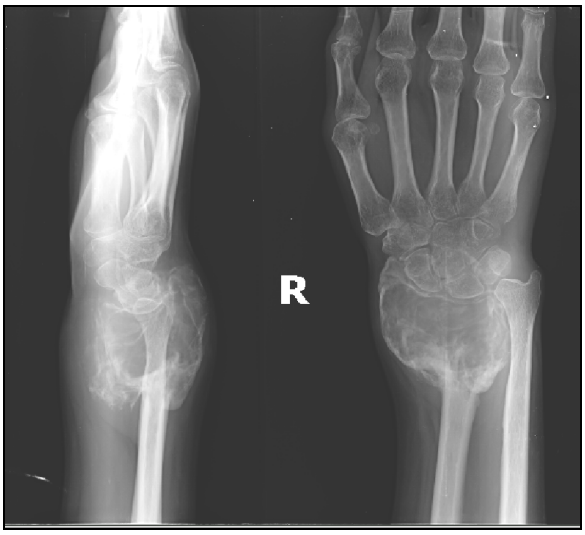

Figure-1: Plain radiograph anteroposterior and lateral view showing lytic lesion at the distal end of radius with significant cortical thinning along medial aspect of distal radius

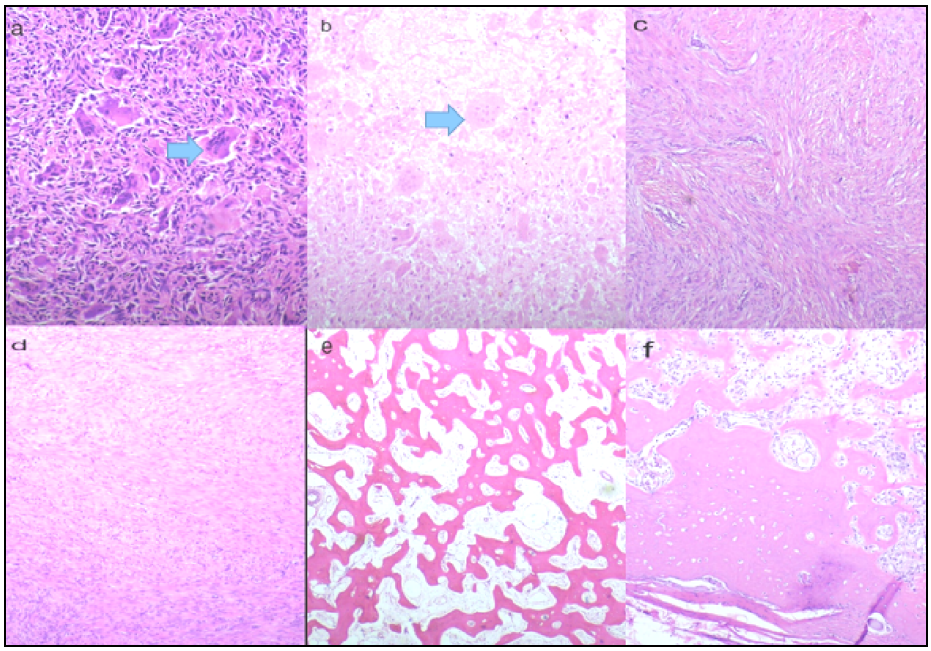

Figure-2: (a) Residual osteoclast like giant cells (arrow), (b) Ghost osteoclast like giant cells (arrow), (c) Storiform arrangement of mononuclear cells, (d) Mononuclear cells arranged in fascicles, (e) Woven bone formation and fibrosis with no residual osteoclast like giant cells and mononuclear cells, (f) Shell of woven bone at periphery.

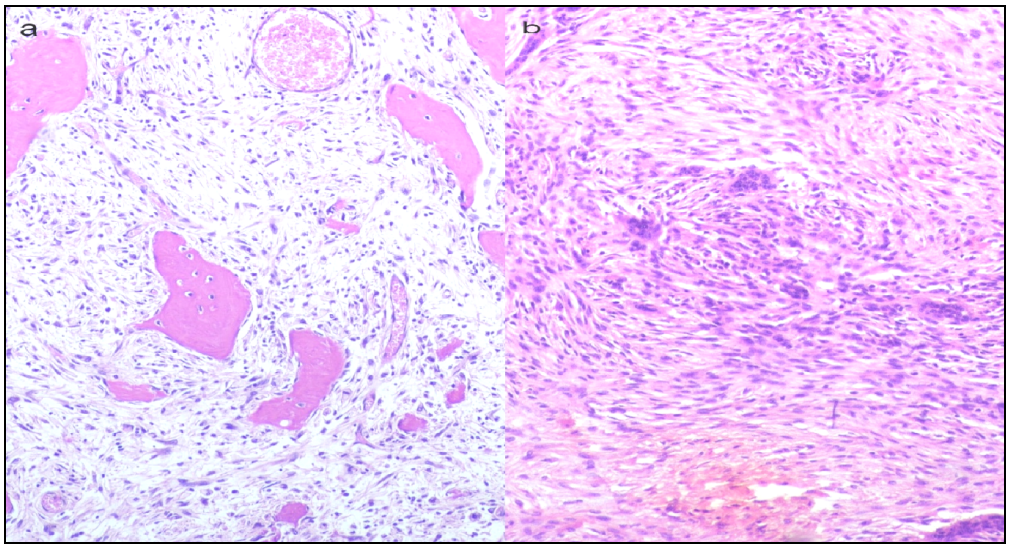

Figure-3: (a) Woven bone in fibrous stroma mimicking fibrous dysplasia, (b) bland spindle cells arranged in storiform pattern with scattered giant cells mimicking non-ossifying fibroma.

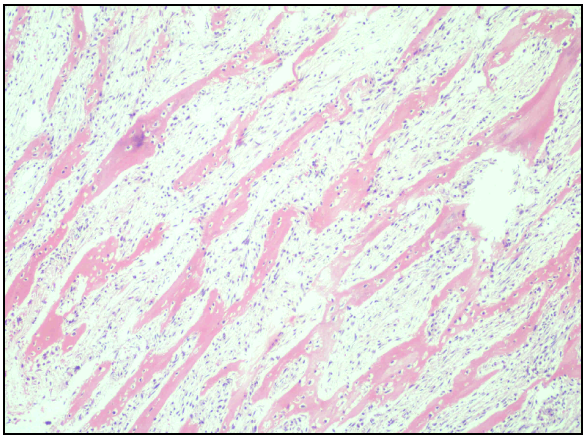

Figure-4: Areas mimicking parosteal osteosarcoma.

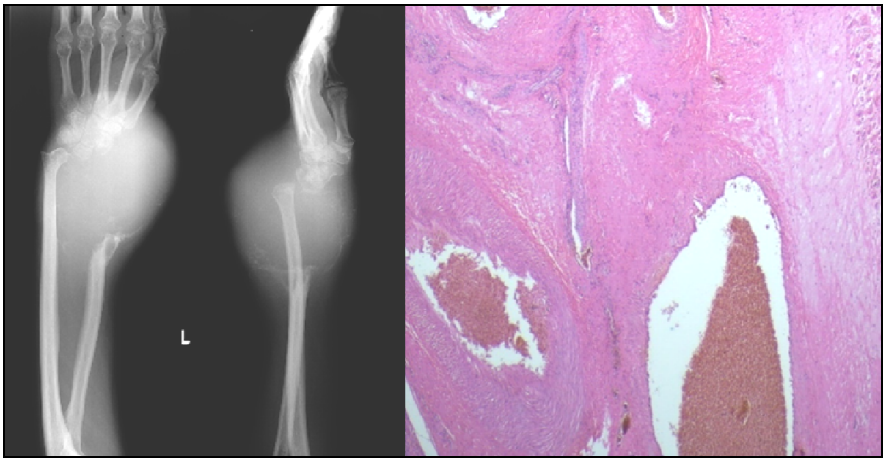

Figure-5: Radiologic and histologic features of GCT with secondary aneurysmal bone cyst (Case 6). (a) Plain X-ray Anteroposterior and lateral view showing large soft tissue area at the distal end of radius with narrow zone of transition and thin septae, (b) Histology showed large blood-filled cyst-like spaces separated by fibrous septa comprising of fibrovascular tissue.

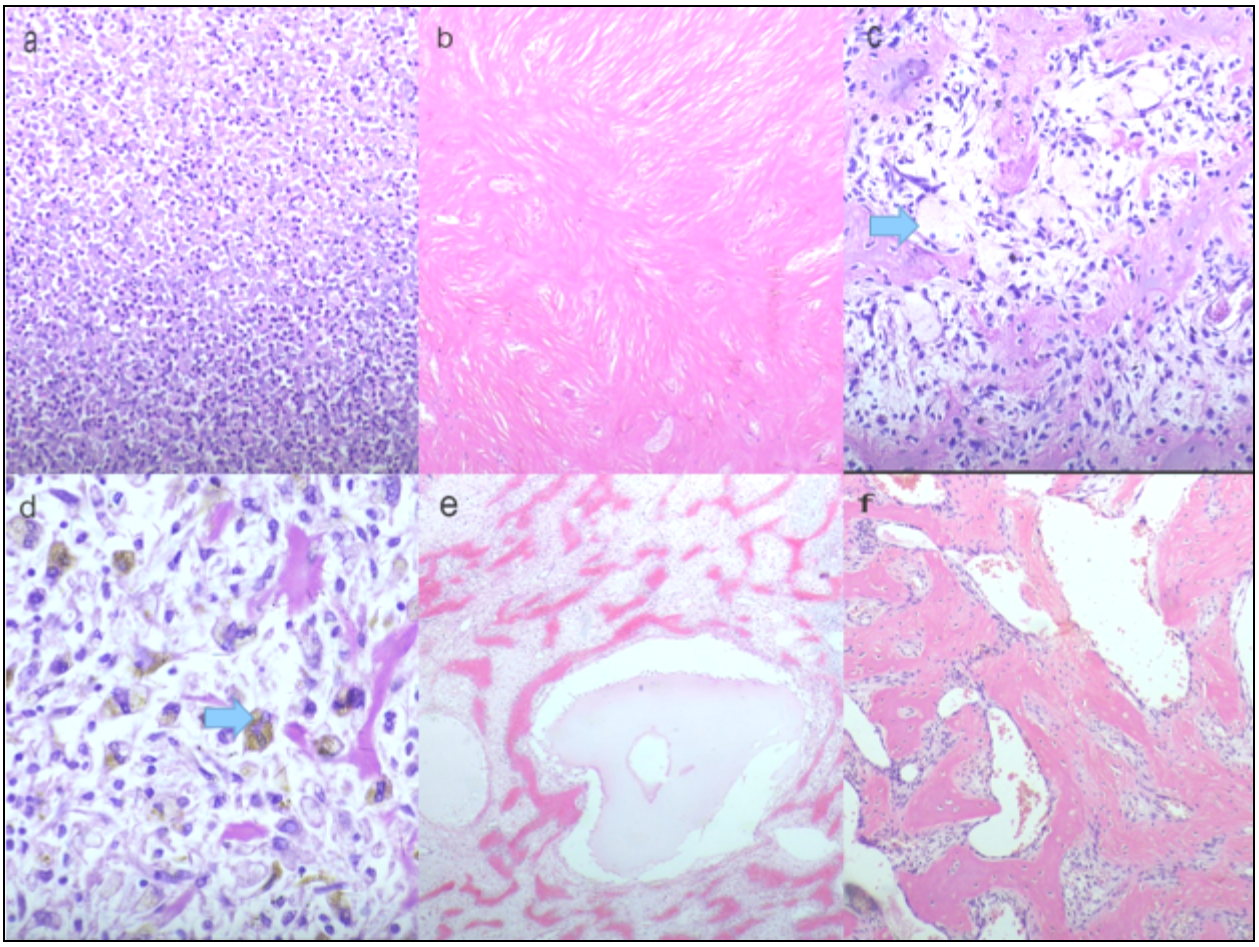

Figure-6: (a) Inflammatory cells, (b) Storiform collagen (c) Foamy histiocytes (arrow), (d) Hemosiderin laden macrophages (arrow), (e) Cystic spaces, (f) Thin-walled blood vessels.

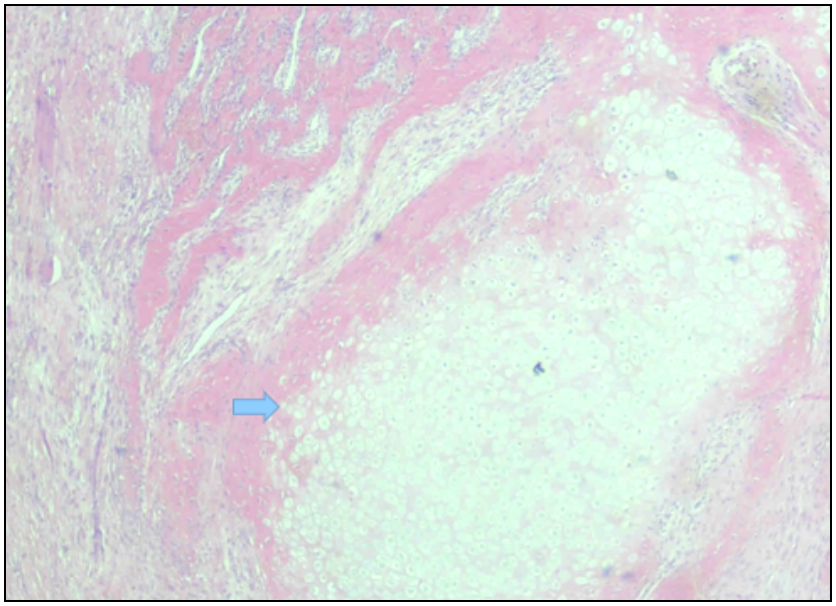

Figure-7: Cartilage formation.

Table-1: Demographic features and histopathological findings in post denosumab treated GCT patients

Case No.	Age	Sex	Tumour site/ laterality	Primary/ recurrent GCTB	Doses of denosumab	Surgical procedure	Microscopic features
1	31	F	R Distal radius	Primary	4	WME	Sheets of stromal cells and osteoclast like giant cells, reactive bone formation, calcification, focal necrosis.
2	25	M	L 4th metacarpal	Primary	4	Amputation	Absent osteoclast like giant cells, fibroblastic proliferation, woven bone formation, oedema, fibrosis.
3	50	M	L Distal radius	Primary	5	WME	Woven bone formation, stromal cells and osteoclast like giant cells, fibrosis, foamy histiocytes.
4	35	M	R Distal radius	Primary	5	WME	Absent osteoclast like giant cells, reactive bone formation, foamy histiocytes, fibrosis, haemorrhage.
5	35	M	R Distal femur	Primary	5	C/C	Absent osteoclast like giant cells, stromal cells, reactive bone formation, fibrosis, haemorrhage, hemosiderin laden macrophages.
6	18	M	L Distal radius	Primary	4	Amputation	Stromal cells, osteoclast like giant cells, reactive bone formation, cystic spaces filled with blood (favouring associated secondary aneurysmal bone cyst), necrosis, scattered mitoses 4-6/10HPF.
7	40	M	R Distal femur	Primary	4	WME	Stromal cells, reduction in osteoclast like giant cells, hemosiderin laden foamy histiocytes, cystic spaces.
8	29	M	L Ischial tuberosity and inferior acetabular margins	Primary	4	C/C	Woven bone, fibroblastic proliferation, stromal cells, absent osteoclast like giant cells.
9	26	F	R Proximal tibia	Primary	4	C/BG	Sheets of stromal cells, absent osteoclast like giant cells.
10	39	M	L Distal femur	Primary	4	C/C	Necrosis, ghost osteoclast like giant cells, mild chronic inflammation, absence of stromal cells.
11	27	M	R Proximal humerus	Primary	7	WME	Reactive bone formation, reduction in osteoclast like giant cells, fibrosis
12	29	F	L Distal radius	Primary	4	WME	Absent osteoclast like giant cells and stromal cells, reactive bone formation, hyalinization.
13	32	F	R Distal tibia	Primary	5	C/BG	Absent osteoclast like giant cells, reactive bone formation, hyalinization, hemosiderin laden histiocytes, fibroblastic proliferation.
14	12	F	R Proximal humerus	Primary	4	WME	Reactive bone formation, absent osteoclast like giant cells and mononuclear stromal cells, haemorrhage, necrosis, storiform collagen.
15	44	M	L Proximal tibia	Primary	5	WME	Fibrosis, foamy histiocytes, reactive bone formation, haemorrhage, osteoclast like giant cells, spindle cells.
16	20	F	L Medial malleolus of distal tibia	Primary	4	WME	Fibrosis, reactive bone formation, reduction in osteoclast like giant cells, cartilaginous rimming, mononuclear cells.
17	25	F	L Distal radius	Recurrent	5	Amputation of forearm	Osteoclast like giant cells, mononuclear stromal cells, necrosis, haemorrhage, 4/10 mitoses, sheets of histiocytes.
18	33	F	L Proximal tibia	Recurrent	6	WME	Absent osteoclast like giant cells, foamy histiocytes, reactive bone formation, haemorrhage.
19	19	F	R Distal femur	Recurrent with metastasis to lung.	4	Amputation	Mononuclear spindle cells, osteoclast like giant cells, haemorrhage, woven bone formation, necrosis, occasional mitoses.
20	22	M	R Distal femur	Primary	4	WME	Mononuclear spindle cells, osteoclast like giant cells, slit like vascular spaces, fibrosis, haemorrhage, woven bone formation.

WME: wide margin excision; C/C: Curettage and cementing; C/BG: Curettage and Bone Grafting.

Table-2: Follow-up data until the patient last visited hospital.

Case No	Follow up
1	Disease free for 10 months after surgery.
2	Disease free for 8 months after surgery.
3	Disease free for 10 months after surgery.
4	Disease free for 2 months after surgery.
5	Disease free for 6 months after surgery.
6	No follow-up data available.
7	Disease free for 11 months after surgery.
8	Recurrence after 11 months of surgery
9	Disease free for 16 months after surgery.
10	Disease free for 14 months after surgery.
11	Disease free for 11 months after surgery.
12	Disease free for 9 months after surgery.
13	Disease free for 12 months after surgery.
14	No follow-up data available.
15	Disease free for 9 months after surgery.
16	Disease free for 5 months after surgery.
17	Disease free for 6 months after surgery.
18	Disease free for 3 months after surgery.
19	Under treatment with denosumab for lung metastasis. No local recurrence for 7 months after surgery
20	Disease free for 2 months after surgery.

DISCUSSION

The most important finding noted in almost all studies on post denosumab treated GCT is a marked reduction or complete lack of osteoclast like giant cells. A study by Traub *et al.* reported lack of osteoclast like giant cells in almost all but a few cases.[5] Another study by Tariq *et al.* reported a total absence of osteoclast like giant cells in 52.6% cases, whereas residual giant cells were seen in 47.4% cases.[6] A study by Rekhi *et al* reported total absence of osteoclast like giant cells in 15 out of 27 cases. In our study, we found total absence of osteoclast like giant cells in 10 (50%) cases, whereas 3 (15%) cases showed a marked reduction in osteoclast like giant cells. The giant cells tend to be smaller and contain fewer nuclei as compared to pre-treatment specimens [3,6] which was also seen in our study (Figure-2a). Ghost osteoclast like giant cells was also seen in one case (Figure-2b). Proliferation of the stromal cells has been noted in various studies which can exhibit storiform pattern (Figure-2c) or can be arranged in fascicles (Figure-2d).[6,12–15] In our study, eight cases showed only fascicular pattern, whereas both storiform and fascicular pattern of stromal cell arrangement was seen in nine cases. In three cases, tumour was completely replaced by fibrous tissue and bone (Figure-2e). No osteoclast like giant cells and mononuclear stromal component was identified in these three cases, thus the pattern of stromal cell arrangement could not be assessed. Another feature noted was the formation of reactive bone (shell) at the periphery of tumour (figure-2f).

Another important feature in post denosumab treated GCT is formation of woven bone which was seen in all cases in our study. The woven bone is usually seen in the form of anastomosing trabeculae with prominent osteoblastic rimming. Many studies have reported this feature.[5,8,16] The combination of new bone formation with the absence of giant cells and cellular stroma can mimic osteosarcoma or malignant transformation of GCT.[3,8] A study by Wojcik et al summarized the features that could help differentiate post denosumab treatment effects in GCT with osteosarcoma and malignant transformation. According to this study, post-denosumab treated GCT cases show less cytologic atypia, less mitotic figures, low ki67 index and lack an infiltrative growth pattern.[3] Unlike low-grade osteosarcomas, the denosumab treated GCT is negative for MDM2 amplification. Detection of H3F3A mutation is also helpful and supports the diagnosis of GCT.[8]

Malignant transformation has been noted in GCT treated with denosumab.[17] The radiologic features of a giant cell tumour with malignant change shows a large destructive lesion with cortical destruction. Invasion into the surrounding soft tissues is also seen however, these findings can be frequently seen in locally advanced GCT. Histologically, the malignant transformation in GCT can be in the form of malignant fibrous histiocytoma, fibrosarcoma, undifferentiated high-grade sarcoma or osteosarcoma. Features that help to identify malignant transformation include presence of nuclear pleomorphism, brisk mitotic activity and atypical mitosis in spindle cells. These high grade areas can be intermixed or next to conventional GCT areas.[18] In our study, two cases (case 6 & 17) showed radiological findings suggestive of malignant transformation however, on histopathological examination and after extensive sampling, no atypical mitosis or significant nuclear pleomorphism was identified. Thus, a diagnosis of GCT with no evidence of malignant transformation was rendered in both cases.

Another finding noted by many studies on denosumab treated GCT is the formation of reactive bone at the periphery of the tumour, i.e., shell formation.[3,6,14,19] This finding was also noted in our study in 13 cases. No shell formation was seen in the remaining 7 cases. A study by Xiaohui Niu *et al* reported that denosumab treated GCT tumours showed thickening of the cortical bone (shell formation) along with new bone formation within the lesion. These changes may lead to increased difficulty with intra-lesional curettage because of ossification of tumour and formation of septae but facilitate resection of the tumour because of clear margins. [19] Treatment with denosumab helps in tumour resection by forming a rim of sclerotic bone surrounding the lesion. It also decreases the vascularity of the tumour thereby reducing blood loss.[20]

Some histological features in denosumab treated GCT tumours may mimic other lesions, for instance, the presence of woven bone in fibrous stroma may mimic fibrous dysplasia. The woven bone in this case lacks osteoblastic rimming. Giant cell reaction can also be seen in these cases due to stromal haemorrhage (Figure-3a).[21] Whereas, areas exhibiting bland spindle cells arranged in storiform pattern with scattered giant cells may mimic non-ossifying fibroma/benign fibrous histiocytoma (Figure-3b). Collection of foamy histiocytes and hemosiderin-laden macrophages can also be seen. These histological features were also present in some cases in our study. This may pose a diagnostic challenge.

Mononuclear cells exhibiting atypia is also reported in post-treatment GCT in some studies.[6] Nuclear enlargement with irregular nuclear

membranes along with few mitoses is reported. This can impose a diagnostic challenge in cases in which nuclear atypia is seen along with increased mitoses and osteoid deposition mimicking osteosarcoma. Wojcik *et al* has seen nuclear atypia in patients who have received denosumab for a shorter duration. No significant nuclear pleomorphism was noted in any of our cases. Figure 4 shows areas mimicking parosteal osteosarcoma.

The radiological and clinical findings can be of great help in establishing the correct diagnosis. Features that favour a diagnosis of giant cell lesions other than GCT include the radiographic presence of a lesion in metaphysis or diaphysis of bone rather than epiphysis; lesion in a child; the presence of lesion in jaw, vertebrae or involvement of bones of hand and feet. Non-ossifying fibroma occurs in skeletally immature patients[22] whereas GCT is usually seen in skeletally mature patients.[21] An immunohistochemical stain like p63 can help in differentiating giant cell lesions in pretreatment cases but are of no use in denosumab treated GCT since these tumours do not show positive staining with p63.[14]

In one case (case 6), we found aneurysmal bone cyst (ABC) formation which likely represent a secondary aneurysmal cyst (Figure-5a &b). ABC is characterized by blood-filled cyst-like spaces separated by fibrous septa which comprise of giant cells and fibrovascular tissue. Osteoclast like giant cells may be seen lining these spaces.[21] They can occur as primary or secondary lesions. About two-third of ABCs are primary (70% cases) whereas about one-third ABCs are secondary (30% cases) and are associated with various bone lesions like GCT, Chondroblastoma, Osteosarcoma, and Osteoblastoma.[23]

Other histological features noted in our study were the presence of inflammatory cells, storiform collagen, foamy histiocytes, hemosiderin-laden macrophages, cystic spaces, thin-walled blood vessels, fibrosis, and necrosis (Figure-6 a-f). In one case we found cartilage formation in the tumour (Figure-7).

In our study, we found GCT in a 12-year child which is rare as only 3% of cases occur before fourteen years of age. One patient had involvement of metacarpal which is also rare since GCT of bones of hands and feet is reported to occur in less than 2% cases.[24] Local recurrence of GCT was seen in one patient after 11 months of surgery. Table 2 shows the patient follow-up data until the patient last visited hospital.

Awareness of the histological spectrum of treatment-induced changes is mandatory to know for every pathologist as without this knowledge incorrect diagnosis of many benign lesions and erroneous diagnosis of malignancy can be made.

CONCLUSION

Reduction in the number of osteoclasts like giant cells, proliferation of stromal cells, fibrosis and woven bone formation are the noticeable features in denosumab treated GCT. These cases can often pose a diagnostic challenge for pathologists because of various histopathological findings that can mimic other benign and malignant lesions of bone and soft tissue. For this reason, the correlation of the microscopic features with the clinical history of patient and radiological features is often required to reach a correct diagnosis.

Declaration of conflicting interests:

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval:

Exemption from ethical approval was received from Interactive Research and Development (IRB) as this study was a retrospective study and did not involve human participants (IRB No: IRD_IRB_2020_04_010).

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article

AUTHORS' CONTRIBUTION

SMA, NY, KA, and ST: Reviewed the histopathology slides and took part in writing the manuscript. SAAJ, SKA, and SJ: Reviewed the final manuscript.

REFERENCES

1. Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F. WHO Classification of Tumours of Soft Tissue and Bone, ed 4. Geneva, World Health Organization, 2013.
2. Unni KK, Inwards CY, Bridge JA, Kindblom LG, Wold LE. Tumours of the bones and joints. AFIP Atlas of Tumour Pathology. Fourth series, Fascicle 2. Washington, DC: AFIP; 2005.
3. Wojcik J, Rosenberg AE, Bredella MA, Choy E, Hornicek FJ, Nielsen GP *et al*. Denosumab-treated giant cell tumour of bone exhibits morphologic overlap with malignant giant cell tumour of bone. Am J Surg Pathol 2016;40:72–80.
4. Sobti A, Agrawal P, Agarwala S, Agarwal M. Giant cell tumour of bone-an overview. Arch Bone Jt Surg 2016;4(1):2–9.
5. Traub F, Singh J, Dickson BC, Leung S, Mohankumar R, Blackstein ME, *et al*. Efficacy of denosumab in joint preservation for patients with giant cell tumour of the bone. Eur J Cancer 2016;59:1–12.
6. Tariq MU, Umer M, Khan Z, Saeed J, Siddiqui MA, Din NU. Spectrum of histological features of Denosumab treated Giant Cell Tumour of Bone; potential pitfalls and diagnostic challenges for pathologists. Ann Diagn Pathol 2020;45:151479.
7. Errani C, Tsukamoto S, Mavrogenis AF. How safe and effective is denosumab for bone giant cell tumour? Int Orthop 2017;41(11):2397–400.

8. Wu CC, Hsieh PP. Denosumab-treated giant cell tumour of the bone mimicking low-grade central osteosarcoma. J Pathol Transl Med 2018;52(2):133–5.
9. Gaston CL, Grimer RJ, Parry M, Stacchiotti S, Dei Tos AP, Gelderblom H, *et al*. Current status and unanswered questions on the use of Denosumab in giant cell tumour of bone. Clin Sarcoma Res 2016;6(1):15.
10. Agarwal MG, Gundavda MK, Gupta R, Reddy R. Does denosumab change the giant cell tumour treatment strategy? lessons learned from early experience. Clin Orthop Relat Res 2018;476(9):1773–82.
11. Kostenuik PJ, Nguyen HQ, McCabe J, Warmington KS, Kurahara C, Sun N, *et al*. Denosumab, a fully human monoclonal antibody to RANKL inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL. J Bone Miner Res 2009;24(2):182–95.
12. Müller DA, Beltrami G, Scoccianti G, Campanacci DA, Franchi A, Capanna R. Risks and benefits of combining denosumab and surgery in giant cell tumour of bone-a case series. World J Surg Oncol 2016;14(1):281.
13. Hakozaki M, Tajino T, Yamada H, Hasegawa O, Tasaki K, Watanabe K, *et al*. Radiological and pathological characteristics of giant cell tumour of bone treated with denosumab. Diagn Pathol 2014;9(1):111.
14. Roitman PD, Jauk F, Farfalli GL, Albergo JI, Aponte-Tinao LA. Denosumab-treated giant cell tumour of bone. Its histologic spectrum and potential diagnostic pitfalls. Hum Pathol 2017;63:89–97.
15. Rekhi B, Verma V, Gulia A, Jambhekar NA, Desai S, Juvekar SL, *et al*. Clinicopathological features of a series of 27 cases of post-denosumab treated giant cell tumours of bones: a single institutional experience at a tertiary cancer referral Centre, India. Pathol Oncol Res 2017;23(1):157–64.
16. Branstetter DG, Nelson SD, Manivel JC, Blay JY, Chawla S, Thomas DM, *et al*. Denosumab induces tumour reduction and bone formation in patients with giant-cell tumour of bone. Clin Cancer Res 2012;18(16):4415–24.
17. Alaqaili SI, Abduljabbar AM, Altaho AJ, Khan AA, Alherabi JA. Malignant sarcomatous transformation of benign giant cell tumour of bone after treatment with denosumab therapy: a literature review and reported cases. Cureus 2018;10(12):e3792.
18. Czerniak B. Dorfman and Czerniak's bone tumours. 2nd edition, Elsevier; 2016.
19. Niu X, Yang Y, Wong KC, Huang Z, Ding Y, Zhang W. Giant cell tumour of the bone treated with denosumab: How has the blood supply and oncological prognosis of the tumour changed? J Orthop Translat 2018;18:100–8.
20. Lipplaa A, Dijkstra S, Gelderblom H. Challenges of denosumab in giant cell tumour of bone, and other giant cell-rich tumours of bone. Curr Opin Oncol 2019;31(4):329.
21. Rosai, J. Rosai and Ackerman's Surgical Pathology. 11 ed. Elsevier, Lyon, France; 2011.
22. Rosenberg AE, Nielsen GP. Giant cell containing lesions of bone and their differential diagnosis. Curr Diagn Pathol 2001;7(4):235–46.
23. Alhumaid I, Abu-Zaid A. Denosumab therapy in the management of aneurysmal bone cysts: a comprehensive literature review. Cureus 2019;11(1):e3989.
24. Chakarun CJ, Forrester DM, Gottsegen CJ, Patel DB, White EA, Matcuk GR Jr. Giant cell tumour of bone: Review, mimics, and new developments in treatment. Radiographics 2013;33(1):197–211.

Submitted: January 18, 2021	*Revised: January 30, 2021*	*Accepted: April 17, 2021*

Address for Correspondence:

Salima Mansoor Ali, Section of Histopathology, Department of Pathology, The Indus Hospital, Karachi-Pakistan
Email: salima.mansoor@tih.org.pk