Pathol. Oncol. Res. (2017) 23:157–164
DOI 10.1007/s12253-016-0123-0

ORIGINAL ARTICLE

Clinicopathological Features of a Series of 27 Cases of Post-Denosumab Treated Giant Cell Tumors of Bones: A Single Institutional Experience at a Tertiary Cancer Referral Centre, India

Bharat Rekhi[1] · Vivek Verma[2] · Ashish Gulia[2] · Nirmala A. Jambhekar[1] · Subhash Desai[3] · Shashikant L. Juvekar[3] · Jyoti Bajpai[4] · Ajay Puri[2]

Received: 20 December 2015 / Accepted: 4 October 2016 / Published online: 8 October 2016

Abstract Giant cell tumor of bone (GCTB) is mostly a benign tumor, but associated with recurrences and metastasis. Lately, denosumab is being utilized in the treatment of certain GCTBs. Twenty-seven tumors, analyzed in the present study, occurred in 16 males and 11 females (M: F = 1.45:1), in the age-range of 16 to 47 years (mean = 29.5, median = 29). Most tumors were identified in the tibia(6) and femur(6), followed by the humerus(3), radius(3), pelvis(3), fibula(3), sacrum(1), metacarpal(1) and metatarsal(1) bones. There were 18(66.6 %) primary and 9(33.3 %) recurrent tumors. Exact tumor size (19 cases) varied from 3.7 to 15 cm (mean = 7.8, median = 6.4). Eight of the 19 tumors (42.1 %) had size more than or equal to 8 cm. On histopathologic examination of post-denosumab treated specimens, more than half cases (15)(55.5 %) revealed complete absence of osteoclast-like giant cells (OCLGs) and 12 cases revealed residual OCLGCs. In addition, there was replacement by fibro-osseous tissue, including reactive woven bone or osteoid in most cases, followed by variable amount of spindle cells, hyalinisation, fibrosis and chronic inflammatory cells, including lymphocytes, macrophages and plasma cells. Post-treatment follow-up (25 cases, 92.5 %), over 7–27 months duration (median = 18), revealed 20 cases continuously disease–free. Five patients developed recurrences at 9, 12, 13, 14 and 18 months, respectively. Out of these, who underwent repeat surgical intervention, 4 patients are alive with no evidence of disease and a single patient, planned for a second surgery, is alive-with-disease. Denosumab was mostly offered to patients with large sized, borderline salvageable tumors, in order to decrease the morbidity of index surgical procedure, that led to disappearance of OCLGCs in most cases. Post-denosumab treated GCT cases appear as low grade osteosarcomas on histopathologic examination, but lack the clinical behaviour of an osteosarcoma, therefore may be considered as pseudo malignant bony lesions.

Keywords Giant cell tumor of bone · Denosumab · Targeted therapy · Bone tumor

Introduction

Giant cell tumor of bone (GCTB) is a benign, but locally aggressive primary bone neoplasm that usually occurs in young adults with majority of patients in their third or fourth decade of life [1]. This tumor comprises 5 % of all primary bone tumors in the United States and is relatively more common in India and China where it constitutes 20 % of all primary bone tumors [2, 3]. GCTB constitutes 6.2 % of bone tumors treated at our centre [4]. Histopathologically, a GCTB comprises proliferating mononuclear, spindly stromal cells (tumor cells), amidst macrophages and several multinucleated osteoclast like giant cells (OCLGs).

✉ Bharat Rekhi
rekhi.bharat@gmail.com

[1] Department of Surgical Pathology, Tata Memorial Hospital, 8th Floor, Annex Building, Dr E.B. Road, Parel, Mumbai 400012, India

[2] Department of Surgical Oncology (Bone and Soft Tissues), Tata Memorial Hospital, Parel, Mumbai 400012, India

[3] Department of Radiodiagnosis, Tata Memorial Hospital, Parel, Mumbai 400012, India

[4] Department of Medical Oncology, Tata Memorial Hospital, Parel, Mumbai 400012, India

Certain tumor necrosis factors (TNF), expressed in varying proportions have been identified in the regulation of osteoclast formation, function and survival have been implicated in the causation of osteoclastogenesis/resorption; eventually leading to tissue destruction in case of a GCTB. Osteoprotegerin ligand (OPGL), mostly expressed by spindly stromal cells and osteoblasts and its receptor RANK (TNF related protein receptor activator of nuclear factor $NF\text{-}_{K}\ \beta_{)}$, expressed by macrophage-like mononuclear cells and OCLGs have been identified as promoters for osteoclastogenesis, while an osteoclastic inhibitory factor, osteoprotegerin (OPG), expressed by all the three cells, is known to inhibit the OPGL/RANKL-RANK combination [5–8]. Isolate studies have shown differential immunohistochemical expression of RANK and OPG in giant cells and stromal cells, respectively of a GCTB and its close diagnostic differential, namely a chondroblastoma [9].

Few years back, a fully human monoclonal antibody inhibitor, named denosumab was identified against RANKL that came as a breakthrough in the treatment of GCTBs [10, 11]. Subsequently, open-label, phase 2 studies have shown efficacy and safety of this drug that was approved by the Food and Drug Administration (FDA) on June 2013 for treatment of unresectable or recurrent GCTBs [12, 13]. Thereafter, very few studies have been published on histopathologic assessment of post-denosumab treated GCTBs, including none from our country [14–16].

Herein, we present clinicopathological features of a series of post-denosumab treated GCTBs from a single Institution in India.

Material and Methods

The study includes analysis of 27 cases of GCTB at our tertiary cancer referral centre from January 2014 to September 2015. All cases were initially confirmed with a histopathologic diagnosis of a GCTB.

Denosumab was administered 120 mg subcutaneously at day 1, 8, 15, 30 and subsequently, at monthly interval. Most patients (16) (59.2 %) received 6 doses of denosumab. Others were given 5 doses (2 cases), 4 doses (4 cases), 3 doses (2 cases), 2 doses (single case) and 7 doses (2 cases).

Post-denosumab treated tumor specimens were grossed similar to post-chemotherapy treated tumor specimens, in order to include entire tumor representation, in all cases [17]. Specimens received as curettage samples were processed in entirety. In cases of resection specimens, for example from long bones, the entire specimen was bisected coronally by an electric bone saw and an *en block* or "slab" representative of the entire tumor was subdivided into smaller tissue blocks and submitted in processing cassettes, along with the various surgical resection margins.

Follow-up was calculated, in months, from the date of surgery (post-denosumab treatment) to the status on the date of last follow-up (30th June 2016).

Results

Twenty-seven tumors occurred in 16 males and 11 females (M: F = 1.45:1), in the age-range of 16 to 47 years (mean = 29.5, median = 29). Most tumors were identified in the tibia (6) and femur (6), followed by the humerus (3), radius (3), pelvis (3), fibula (3), sacrum (1), metacarpal (1) and metatarsal (1) bones.

There were 18(66.6 %) primary and 9(33.3 %) recurrent tumors. Exact tumor size (19 cases) varied from 3.7 to 15 cm (mean = 7.8, median = 6.4). Most tumors (17/19) (89.4 %) had size more than or equal to 5 cm. Post-denosumab curettage, was performed in 15 cases and resection was done in 12 cases, out of which 1 case had microscopically positive resection margin. Gross examination of post denosumab treated resection specimens revealed rather solid, fleshy cut surfaces with cystic changes in few cases.

On histopathologic examination, more than half cases (15)(55.5 %) revealed complete absence of osteoclast-like giant cells (OCLGs); 9 cases revealed scanty residual foci of giant cells, while 3 cases revealed substantial amount of residual OCLGCs. In addition, there was replacement by conspicuous amount of fibro-osseous tissue, including reactive woven bone or osteoid in all cases, followed by variable amount of spindle cells (21 cases), hyalinisation, fibrosis and chronic inflammatory cells including lymphocytes, plasma cells and macrophages in various cases. Spindle cells were arranged in fascicles and whorls in 5 cases. Mineralization was also noted in 6 cases. Infarction necrosis was seen in 4 cases. Twelve cases with residual OCLGCs included 8 cases, who received 6 doses; a single case, each who received 5 doses, 3 doses, 4 doses and 2 doses of denosumab, respectively (Figs. 1, 2, 3, 4, 5 and 6).

Histopathologic and clinical outcome, in the form of response to treatment was available in all cases. Follow-up details regarding local control was available in 25(92.5 %) cases. Post-surgery, follow-up varied from 7 to 27 months (median = 18 months, average = 17.6 months). Twenty patients (80 %) were continuously disease-free (CDF), whereas 5(20 %) patients developed tumor recurrences at 9, 12, 13, 14 and 18 months, respectively. Of these 5 patients, 4 underwent repeat surgery and, presently, have no evidence of surgery (NED). Remaining single patient, planned for a second surgery, was alive-with-disease (AWD), during the last follow up. (Table 1). Only a single patient, who underwent repeat surgical excision, harboured residual OCLGCs in her repeat surgical excision specimen.

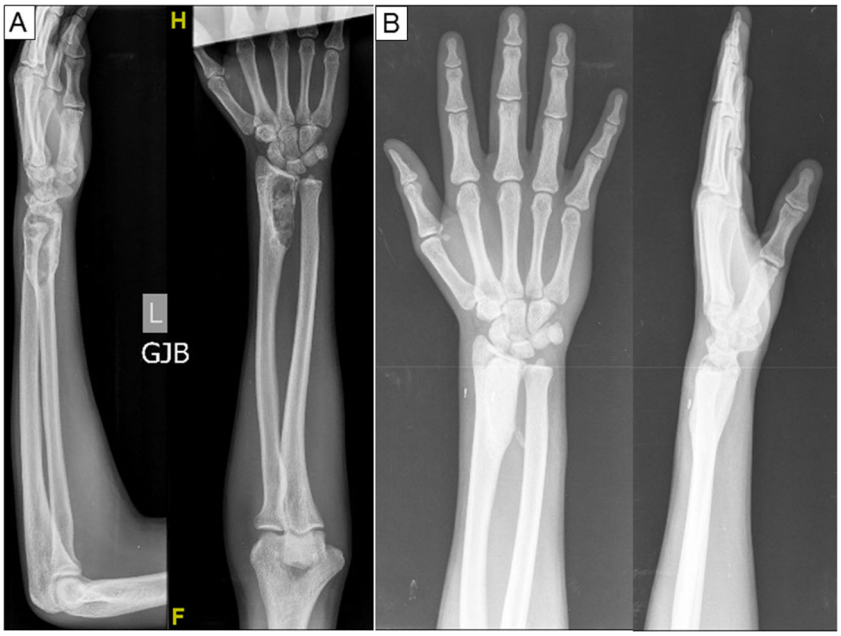

Fig. 1 Case 8. **a** Pre-treatment radiograph showing a large, lytic lesion in the proximal end of radius. **b** Post-denosumab treated radiograph showing treatment response in the form of replacement of initial by dense sclerosis

Discussion

In most cases, giant cell tumors of bone (GCTB) are treated with curettage and/or surgical resection. Following curettage, local recurrence occurs in 15–30 % patients, depending upon thoroughness of the curettage procedure and the nature of adjuvant therapy offered. Recurrence is usually seen within 2 years [1]. In a study of 470 GCTBs from our centre, recurrence rate of 36.1 % and incidence of metastasis with these tumors was found to be 5.1 %, including rare cases with multicentric disease [4]. Denosumab, a monoclonal antibody against RANKL, a tumor necrosis factor, involved in pathogenesis of a GCTB, has been found to be useful in treatment of this tumor in certain cases, especially with large tumor size and recurrent lesions.

Very few studies have been published regarding histopathologic changes in post-denosumab treated tumor specimens, apart from certain case reports, including none with clinical

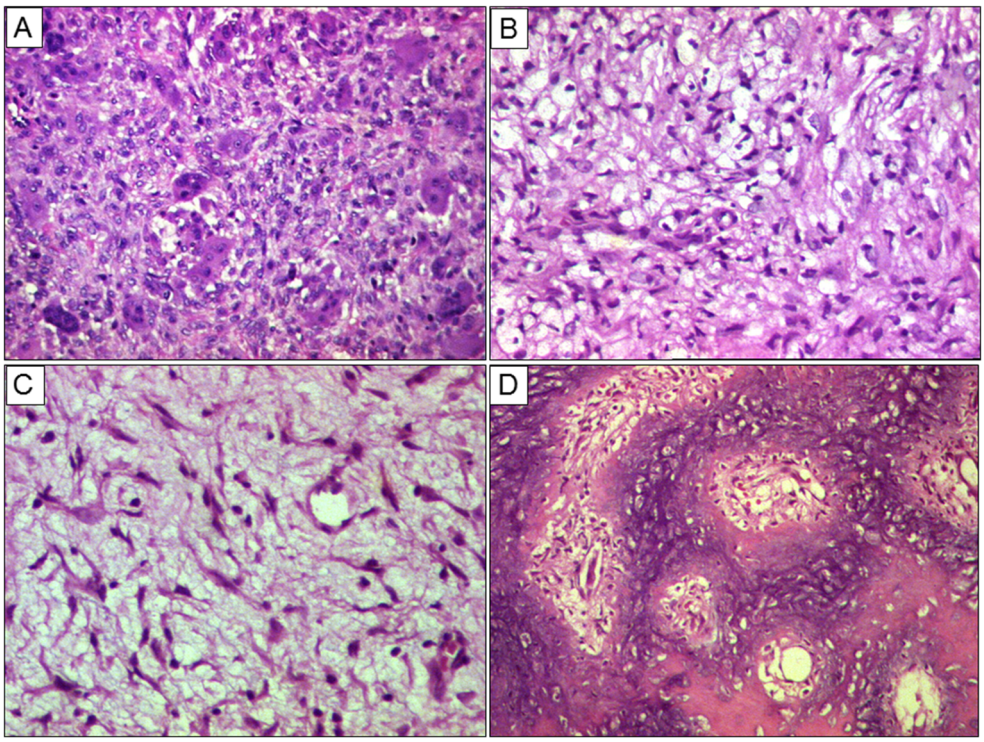

Fig. 2 Case 8. Microscopic findings. **a** Pre-treatment biopsy showing giant cell tumor of bone (GCTB), comprising uniform sprinkling of osteoclast-like giant cells (OCLGCs) with interspersed mononuclear cells. Hematoxylin and Eosin (H and E) × 200. **b**-**d** Sections from post-denosumab treated specimen showing sheets of foamy histiocytes. H and E × 200. **c** Focal myxoid change and interspersed spindle shaped fibroblastic/myofibroblastic cells. H and E × 400. **d** Reactive woven bone with areas of mineralization. H and E × 100

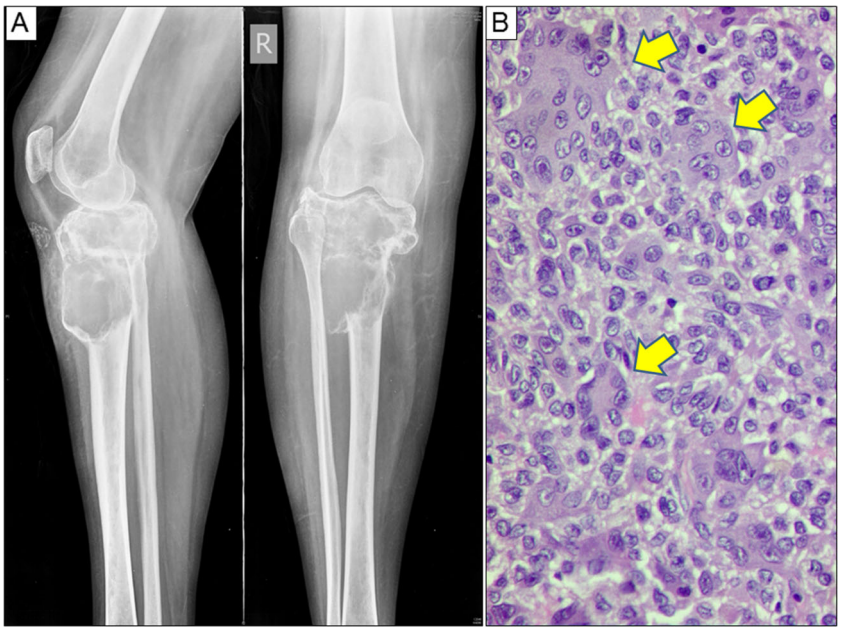

Fig. 3 **a** Case 1. Case of a recurrent GCTB involving upper end of tibia in form of a large, expansile, lytic, destructive tumor with a narrow zone of transition. **b** Biopsy examination showing features of GCTB, including OCLGCs (arrow heads) and intervening mononuclear stromal cells. H and E × 200

outcomes [14–16]. The present study constitutes as the first study of this kind from our country and from the Asian continent. Most cases (89 %) in this study harboured tumors equal to or more than 5 cm and presented as primary tumors (66.6 %). Nine cases presented with recurrent tumors. Indications for denosumab include large, unresectable, recurrent and or metastatic GCTBs, with the intent to reduce morbidity, in such cases [14, 18–20].

In their study, Branstetter et al. [14] observed that in all 20 cases of denosumab-treated GCTBs, there was a decrease of giant cell component equal or more than 90 % and an increased proportion (65 %) of dense fibro-osseous tissue and/or new woven bone. They observed that denosumab treatment of patients with GCTBs significantly reduced or eliminated RANK-positive tumor giant cells. In a recent study on 9 post-denosumab treated cases of GCTB, Wojcik et al. [15] compared histopathologic features of denosumab treated GCTBs with GCTBs undergoing malignant transformation and observed that all denosumab treated GCTBs showed marked giant cell depletion. They also noted that early lesions

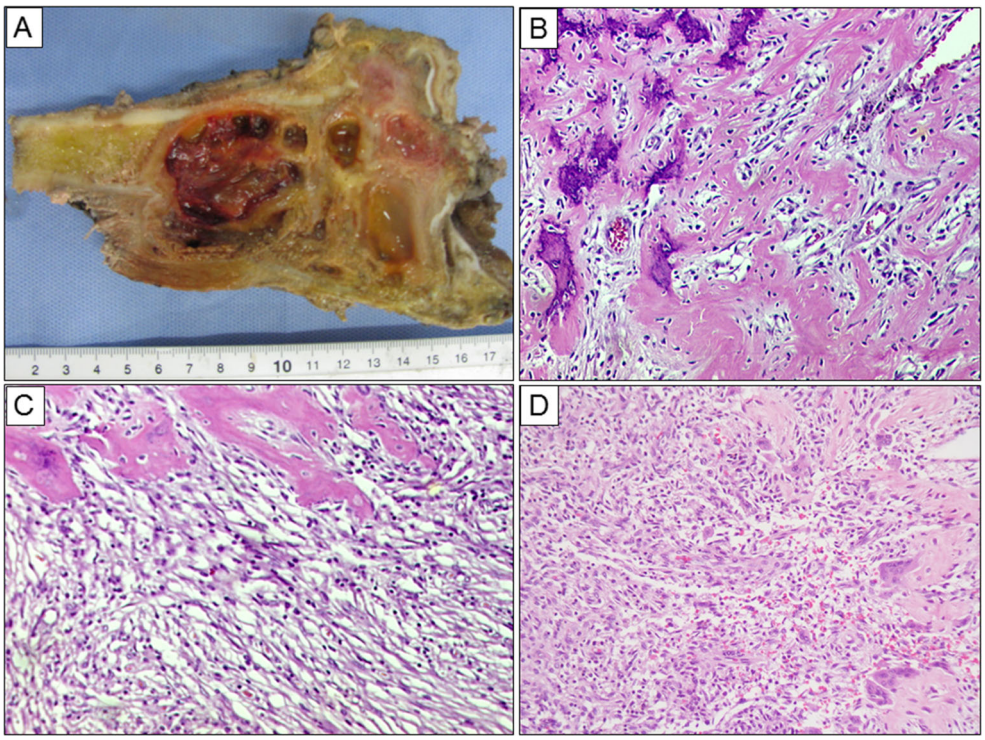

Fig. 4 Same case of GCTB, post 6 doses of denosumab. **a** Resected specimen, bisected with cut surface showing a large, expansile lesion involving epimetaphyseal region of tibia with solid and cystic areas, including few blood-filled spaces. **b** Microscopic examination revealing complete absence of OCLGCs and replacement by interlacing prominent woven bone with mineralization. H and E × 200. **c** Woven bone with areas of with spindle cell proliferation and interspersed chronic inflammatory cells. H and E × 200. **d** Scant focus of residual OCLGs amidst spindle cells, inflammatory cells and reactive woven bone formation. H and E × 200

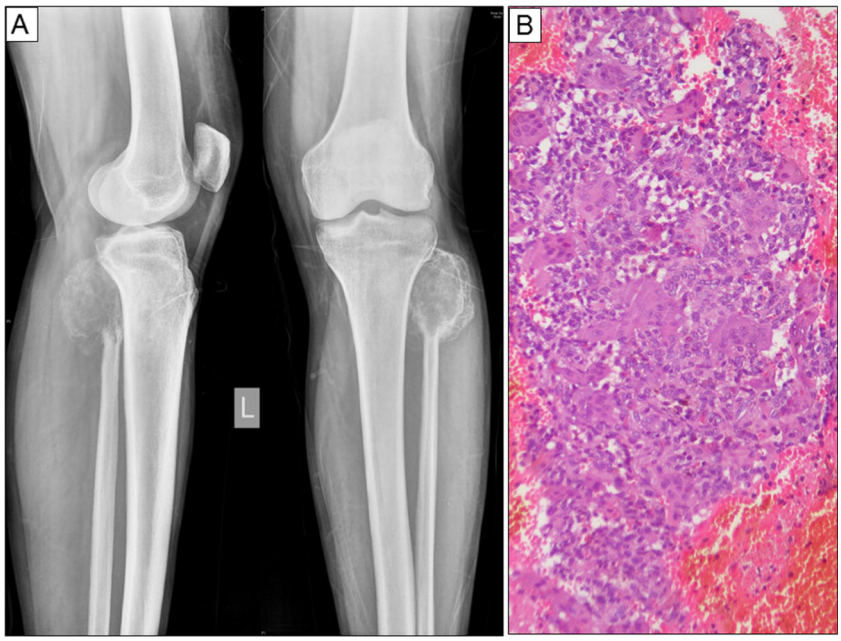

Fig. 5 **a** Case 6 of a primary GCTB involving upper end of fibula in the form of a large, expansile, lytic lesion. **b** Microscopic examination revealing features of GCTB

in such cases were quite cellular, and the combination of cellularity, atypia, albeit mild and haphazard bone deposition caused the lesion to resemble an osteosarcoma in these cases, while tumor in patients with prolonged therapy showed abundant new bone, deposited as broad, rounded cords or linear curvilinear arrays. In the present study, we observed complete absence of giant cells in 15 cases; marked reduction (more than 90 %) of giant cells in 9 cases and substantial number of residual OCLGCs in 3 cases of post denosumab-treated GCTBs. There was no significant association between residual OCLGCs and doses of denosumab that the patients underwent. All 27 post-treatment specimens revealed reactive woven bone, mostly in abundance, simulating a low-grade osteosarcoma. The amount of reactive woven bone formation was significantly higher in post treated cases, as compared to initial biopsy specimens, as noted earlier [14]. There were no atypical cells observed in any of our study specimens, with extensive sampling. Likewise, Wojcik, et al. [15] also noted

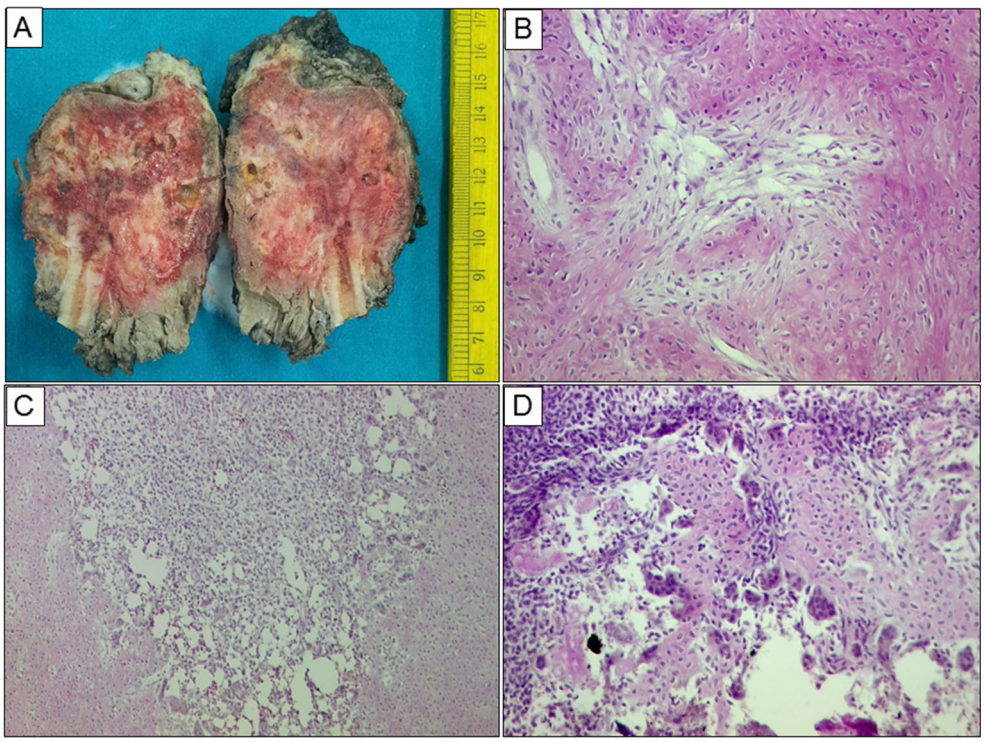

Fig. 6 Same case, post denosumab treated resection specimen. **a** Resected specimen, bisected into two halves showing a rather solid, fleshy cut surface. **b** Microscopic examination revealing fascicles of spindle cells, with woven bone formation. H and E × 100. **c** Distinct residual focus of GCTB. H and E × 100. D. Spindly cells, reactive woven bone formation with interspersed OCLGCs. H and E × 200

Table 1 Clinicopathological features of 27 post denosumab treated giant cell tumors of bone

Age/Sex	Site	Diagnosis	T size (cm)	Histopathological features	Outcomes
29/F	Proximal Tibia	(R) GCTB	10.7	Reactive woven bone, mineralization, cystic change, inflammatory cells. *Residual OCLGCs.*	NA
19/M	Distal Tibia	(R) GCTB	6.4	Reactive woven bone, hyalinisation, inflammatory cells, cystic change, spindle cells. No OCLGCs.	CDF(15 mo)
26/M	Proximal Fibula	(R) GCTB	5.6	Reactive woven bone, spindle cells (storiform pattern). *Residual OCLGCs.*	CDF(27 mo)
23/M	Distal Femur	(P) GCTB	Large	Reactive woven bone, hyalinization, inflammatory cells, fibrosis. No OCLGCs	CDF(24 mo)
37/F	Proximal Humerus	(R) GCTB	8.4	Reactive woven bone, inflammatory cells, fibrosis, spindle cells. *Residual OCLGCs.*	CDF(24 mo)
33/M	Proximal Fibula	(P) GCTB	8	Reactive woven bone, inflammatory cells, fibrosis, spindle cells. *Residual OCLGCs.*	CDF(23 mo)
37/F	Distal Tibia	(P) GCTB	6.4	Reactive woven bone, hyalinization, inflammatory cells, infarction necrosis, fibrosis, spindle cells. No OCLGCs	CDF(23 mo)
16/M	Distal Radius	(P) GCTB	8.8	Reactive woven bone, mineralization, inflammatory cells, fibrosis, spindle cells. No OCLGCs.	LR at 13 mo. NED(21 mo)
40/F	Pelvis	(P) GCTB	13	Reactive woven bone, spindle cells (storiform pattern). *Residual OCLGCs.*	CDF(21 mo)
35/F	Metacarpal	(P) GCTB	3.7	Reactive woven bone, mineralization, spindle cells. No OCLGCs.	CDF(20 mo)
27/M	Femur	(P) GCTB	NK	Reactive woven bone, spindle cells. No OCLGCs.	CD(20 mo)
32/F	Proximal Tibia	(P) GCTB	5.2	Reactive woven bone, spindle cells. No OCLGCs.	LR at 18 mo. AWD(18 mo)
18/F	Proximal Radius	(P) GCTB	NK	Reactive woven bone, fibrosis. No OCLGCs.	LR at 14 mo. NED(14 mo)
23/F	Distal Femur	(P) GCTB	NK	Reactive woven bone, and spindle cells, inflammatory cells. No OCLGCs.	CDF(14 mo)
40/M	Proximal Tibia	(R) GCTB	13.8	Reactive woven bone, spindle cells, infarction necrosis, vascular emboli. *Residual OCLGCs.*	CDF(14 mo)
23/M	Proximal Humerus	(P) GCTB	5	Reactive woven bone, mineralization, spindle cells, inflammatory cells. No OCLGCs.	CDF(13 mo)
22/F	Distal Radius	(R) GCTB	NK	Reactive woven bone, mineralization, fibrosis, spindle cells. No OCLGCs.	LRs at 9 and 10 mo. NED(24 mo)
19/M	Metatarsal	(P) GCTB	4	Reactive woven bone, mineralization, spindle cells. *Residual OCLGCs.*	CDF(19 mo)
40/M	Proximal Fibula	(R) GCTB	5	Reactive woven bone, fibrosis, hyalinisation. *Residual OCLGCs.*	CDF (18 mo)
29/M	Pelvis	(P) GCTB	More than 5	Reactive woven bone, spindle cells (storiform pattern). No OCLGCs.	CDF (18 mo)
22/M	Proximal Femur	(P) GCTB	6.5	Reactive woven bone, fibrosis, spindle cells. *Residual OCLGCs.*	CDF(17 mo)
28/M	Proximal Humerus	(P) GCTB	6.3	Reactive woven bone, spindle cells. *Residual OCLGCs.*	CDF(15 mo)
41/F	Presacral	(P) GCTB	11	Reactive woven bone, infarction necrosis, spindle cells, hyalinisation. *Residual OCLGCs.*	CDF(13 mo)
36/F	Proximal Tibia	(P) GCTB	4.5	Reactive woven bone, spindle cells (storiform pattern). No OCLGCs	LR at 12 mo. NED(12 mo)
47/M	Pelvis	(R) GCTB	15	Reactive woven bone, fibrosis, inflammatory cells. No OCLGCs.	CDF(8 mo)
29/M	Distal Femur	(R) GCTB	NK	Reactive woven bone, spindle cells, infarction necrosis, inflammatory cells, *Residual OCLGCs.*	NA
27/M	Distal Femur	(P) GCTB	Large	Reactive woven bone, inflammatory cells, fibrosis, No OCLGCs.	CDF(7 mo)

M Male, *F* Female, (*P*) Primary, (*R*) Recurrent, *GCTB* Giant cell tumor of bone, *T* Tumor, *Large* Word "large" was mentioned in the imaging report, *NA* Not available, *OCLGCs* Osteoclast-like giant cells, *CDF* Continuously disease-free, *LR* Local recurrence (s), *NED* No evidence of disease, *AWD* Alive with disease (post treatment recurrence), *mo* months

that morphological features in some of these cases were reminiscent of low-grade central osteosarcoma, but, unlike low-grade central osteosarcoma, they found that denosumab treated GCTBs were negative for *MDM2* and lacked an infiltrative growth pattern. Other features observed in our study were fibroblastic proliferation,

hyalinisation/fibrosis and chronic inflammatory cells, including lymphocytes and macrophages, as previously observed indicators of tumor response [14–16]. Inhibition of osteoclastogenesis and unopposed osteoblastic activity are reasons for increased new bone formation in post-denosumab treated cases.

In a recent study on phenotypical modifications induced by denosumab treatment in a series of 15 GCTBs, the authors observed that denosumab induced the disappearance of osteoclast-like giant cells, leaving residual spindle neoplastic cells, mostly arranged in a storiform pattern, with deposition of trabecular collagen matrix and osteoid, which showed maturation in the peripheral portions of the lesion [16]. Spindly cells arranged in a storiform pattern were also observed in 4 of our study cases. The same authors [16] observed variability in RANK and RANKL expression, with no significant difference in their expression between pre and post treated tumors. They also observed that there was no significant modification of expression of osteoblastic markers (SATB2 and RUNX2) between pre and post-treated cases, along with a similar histone 3.3 mutation in H3F3A in 2 pre-treatment and posttreatment cases. They concluded that denosumab induces partial maturation towards the osteoblastic phenotype of the neoplastic cells of GCTB, with production of fibrous and osteoid matrix and minor changes in immunophenotypic characteristics [16]. This indicates long term usage of denosumab in cases of GCTB where it is offered. Number of doses of denosumab in the present study was decided on individual case basis. Recurrences in post denosumab treated GCTBs have been reported, as noted in five of our study cases, post-treatment. This was irrespective of the presence of residual OCLGCs in post-treated specimens. Out of the four patients, who developed local recurrences and were treated with repeat surgical resections, only one case harboured residual OCLGCs in her tumor excision specimen. Malignancy is exceedingly rarely reported in post-denosumab treated GCTBs [21]. In the same reported case, denosumab was offered during the third recurrence in a GCTB. Malignant transformation developed after three years of primary disease. The authors could not confirm whether denosumab treatment was causative, or contributive to the development of sarcoma, or was coincidental.

To summarize, denosumab is mostly offered to patients with large sized or borderline salvageable GCTBs, in order to decrease the morbidity of index surgical procedure that leads to disappearance of OCLGCs in most of these cases. Post denosumab treated GCTBs appear as low grade osteosarcomas on histopathologic examination, but lack the clinical behaviour of an osteosarcoma, therefore may be considered as pseudo malignant lesions. Similar studies with longer follow-up will provide newer insights into the clinical course in such cases.

Compliance with Ethical Standards

Conflict of Interest We declare that we have no conflict of interest.

References

1. Athanasou NA, Bansal M, Forsyth R, Reid RP, Sapi Z (2013) Giant cell tumor of bone. In: Fletcher CD, Bridge JA, Hogendoorn PCW, Mertens F (eds) World Health Organization (WHO) classification of tumors of soft tissue and bone, 4th edn. IARC Press, Lyon pp 321–324
2. Beebe–Dimmer JL, Cetin K, Fryzek JP, Schuetze SM, Schwartz K (2009) The epidemiology of malignant giant cell tumors of bone: an analysis of data from the surveillance, epidemiology and end results program (1975–2004). Rare Tumors 1:e52
3. Szendroi M (2004) Giant-cell tumour of bone. J Bone Joint Surg Br 86:5–12
4. Gupta R, Seethalakshmi V, Jambhekar NA, Prabhudesai S, Merchant N, Puri A, Agarwal M (2008) Clinicopathologic profile of 470 giant cell tumors of bone from a cancer hospital in western India. Ann Diagn Pathol 12:239–248
5. Yasuda H, Shima N, Nakagawa N, Yamaguchi K, Kinosaki M, Mochizuki S, Tomoyasu A, Yano K, Goto M, Murakami A, Tsuda E, Morinaga T, Higashio K, Udagawa N, Takahashi N, Suda T (1998) Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/RANKL. Proc Natl Acad Sci U S A 95:3597–3602
6. Hsu H, Lacey DL, Dunstan CR, Solovyev I, Colombero A, Timms E, Tan HL, Elliott G, Kelley MJ, Sarosi I, Wang L, Xia XZ, Elliott R, Chiu L, Black T, Scully S, Capparelli C, Morony S, Shimamoto G, Bass MB, Boyle WJ (1999) Tumor necrosis factor receptor family member RANK mediates osteoclast differentiation and activation induced by osteoprotegerin ligand. Proc Natl Acad Sci U S A 96:3540–3545
7. Huang L, Xu JK, Wood DJ, Zheng MH (2000) Gene expression of osteoprotegerin ligand, osteoprotegerin, and receptor activator of NF-B in Giant cell tumor of bone possible involvement in tumor cell-induced osteoclast-like cell formation. Am J Pathol 156:761–767
8. Morgan T, Atkins GJ, Trivett MK, Johnson SA, Kansara M, Schlicht SL, Slavin JL, Simmons P, Dickinson I, Powell G, Choong PF, Holloway AJ, Thomas DM (2005) Molecular profiling of giant cell tumor of bone and the osteoclastic localization of ligand for receptor activator of nuclear factor kappa B. Am J Pathol 167:117–128
9. Won KY, Kalil RK, Kim YW, Park YK (2011) RANK signalling in bone lesions with osteoclast-like giant cells. Pathology 43:318–321
10. Balke M, Hardes J (2010) Denosumab: a breakthrough in treatment of giant cell tumour of bone? Lancet Oncol 11:218–219
11. Lipton A, Jacobs I (2011) Denosumab: benefits of RANK ligand inhibition in cancer patients. Curr Opin Support Palliat Care 5:258–264
12. Thomas D, Henshaw R, Skubitz K, Staddon A, Blay JY, Roudier M, Smith J, Ye Z, Sohn W, Dansey R, Jun S (2010) Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. Lancet Oncol 11:275–280
13. Chawla S, Henshaw R, Seeger L, Choy E, Blay JY, Ferrari S, Kroep J, Grimer R, Reichardt P, Rutkowski P, Schuetze S, Skubitz K, Staddon A, Thomas D, Qian Y, Jacobs I (2013) Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. Lancet Oncol 14:901–908

14. Branstetter DG, Nelson SD, Manivel JC, Blay JY, Chawla S, Thomas DM, Jun S, Jacobs I (2012) Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. Clin Cancer Res 18:4415–4424
15. Wojcik J, Rosenberg AE, Bredella MA, Choy E, Hornicek FJ, Nielsen GP, Deshpande V (2016) Denosumab-treated giant cell tumor of bone exhibits morphologic overlap with malignant giant cell tumor of bone. Am J Surg Pathol 40:72–80
16. Girolami I, Mancini I, Simoni A, Baldi GG, Simi L, Campanacci D, Beltrami G, Scoccianti G, D'Arienzo A, Capanna R, Franchi A (2015) Denosumab treated giant cell tumour of bone: a morphological, immunohistochemical and molecular analysis of a series. J Clin Pathol. doi:10.1136/jclinpath-2015-203248
17. Desai S, Rekhi B, Jambhekar NA (2011) Musculoskeletal system. Bone. In: Desai SS, Bal M, Rekhi B, Jambhekar NA (eds). Grossing of surgical oncology specimens: a practical guide towards complete pathology reporting. Tata Memorial Hospital pp. 70–79
18. Stadler N, Fingernagel T, Hofstaetter SG, Trieb K (2015) A recurrent giant cell tumor of bone treated with denosumab. Clin Pract 5:697. doi:10.4081/cp.2015.697. eCollection
19. Demirsoy U, Karadogan M, Selek Ö, Anik Y, Aksu G, Müezzinoglu B, Corapcioglu F (2014) Golden bullet-denosumab: early rapid response of metastatic giant cell tumor of the bone. J Pediatr Hematol Oncol 36:156–158
20. Blay J, Chawla SP, Broto JM, Choy E, Dominkus M, Engellau J, Grimer R, Henshaw RM, Palmerini E, Reichardt P, Rutkowski P, Skubitz KM, Thomas DM, Zhao Y, Qian Y, Jacobs IA (2011) Denosumab safety and efficacy in giant cell tumor of bone (gctb): interim results from a phase ii study [abstract 10034] J Clin Oncol 29. [Available online at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=102&abstractID=82649; cited August 16, 2013]
21. Aponte-Tinao LA, Piuzzi NS, Roitman P, Farfalli GL (2015) A high-grade sarcoma arising in a patient with recurrent benign giant cell tumor of the proximal tibia while receiving treatment with denosumab. Clinl Orthopaed Related Res 473:3050–3055