

Denosumab-treated Giant Cell Tumor of Bone Exhibits Morphologic Overlap With Malignant Giant Cell Tumor of Bone

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Abstract: Giant cell tumor (GCT) of bone is a locally aggressive benign neoplasm characterized by an abundance of osteoclastic giant cells that are induced by the neoplastic mononuclear cells; the latter express high levels of receptor activator of nuclear factor κ-B ligand (RANKL). Denosumab, a RANKL inhibitor, which is clinically used to treat GCT, leads to a marked alteration in the histologic appearance of the tumor with giant cell depletion and new bone deposition, leading to substantial histologic overlap with other primary tumors of bone. Most significantly, denosumab-treated GCT (tGCT) with abundant bone deposition may mimic de novo osteosarcoma, or GCT that has undergone malignant transformation. To histologically characterize tGCT, we identified 9 cases of GCT biopsied or resected after denosumab treatment. tGCT cases included 16 specimens from 9 patients including 6 female and 3 male individuals aged 16 to 47 (median 32) years. Duration of treatment varied from 2 to 55 months. We compared these tumors with malignant neoplasms arising in GCTs ($n = 9$). The histology of tGCT was variable but appeared to relate to the length of therapy. All tGCTs showed marked giant cell depletion. Early lesions were highly cellular, and the combination of cellularity, atypia, and haphazard bone deposition caused the lesion to resemble high-grade osteosarcoma. Unlike de novo high-grade osteosarcoma or malignancies arising in GCT, however, tGCT showed less severe atypia, reduced mitotic activity, and lack of infiltrative growth pattern. Tumor in patients on prolonged therapy showed decreased cellularity and abundant new bone, deposited as broad, rounded cords or long, curvilinear arrays. The latter morphology was reminiscent of low-grade central osteosarcoma, but,

unlike low-grade central osteosarcoma, tGCT was negative for MDM2 and again lacked an infiltrative growth pattern. Overall, tGCT may have a wide range of morphologic appearances. Because the treated tumors bear little resemblance to their pretreatment counterparts, careful attention to the history of denosumab administration is crucial to avoid a misdiagnosis with an important impact on therapy. Unlike malignant GCTs, tGCTs lack significant nuclear atypia, mitotic activity, and infiltration of preexisting bone, but instead show a unique pattern of intralesional bone deposition.

Key Words: denosumab, giant cell tumor, malignant giant cell tumor
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Giant cell tumor (GCT) of bone is a locally aggressive but benign neoplasm. It typically occurs in the epiphyseal-metaphyseal region of skeletally mature individuals. It is usually diagnosed during the third to fifth decades of life, with the most common presentation being pain, swelling, and limitation of motion. GCT usually arises in the appendicular skeleton with the most common site being the distal femur, followed by the proximal tibia and distal radius. Within the axial skeleton, the sacrum and pelvis are most often involved.¹ GCT manifests on imaging studies as an eccentric, expansile, lytic lesion surrounded by a peripheral rim of sclerosis.² Histologically, the tumors are characterized by evenly dispersed large osteoclast-type giant cells admixed with round and spindled mononuclear stromal cells.³ Multiple lines of experimental evidence suggest that the eponymous giant cells are not themselves neoplastic; rather, their growth and proliferation is induced by the mononuclear mesenchymal cells with an osteoblast-precursor phenotype, which exhibit mutations in the histone H3 family 3A protein (H3F3A).^{4–7} The mononuclear cells express high levels of receptor activator of nuclear factor κ-B ligand (RANKL), a surface protein involved in bone homeostasis. Membranous RANKL binds to RANK, a receptor expressed on the surface of multinucleate osteoclast-type giant cells and their precursors. This interaction leads to activation and proliferation of these cells, leading to reabsorption of bone in the region of the tumor.⁸

Recently, denosumab, a monoclonal antibody antagonist of RANKL, has shown promise as a mechanism-based therapy for GCT. This offers an alternative to

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traditional management by resection or curettage, particularly for lesions that are either recurrent, as occurs in 8% to 65% of cases,^{9,10} or located at sites not readily amenable to resection. Early clinical studies have demonstrated the efficacy of this approach in 30 of 35 treated patients, who demonstrated either a radiologic or histologic response to therapy.¹¹

The histologic response to denosumab is characterized by giant cell depletion and new bone formation. Consequently, successfully treated tumors bear little resemblance to their pretreatment counterparts. To this point, only a single large series has described the histologic changes associated with denosumab therapy, and it focused on histology as a measure of treatment response.¹² The morphology of denosumab-treated GCT (tGCT) raises a differential diagnosis that includes entities with distinct prognoses and therapeutic options, including benign lesions, such as fibrous dysplasia and non-ossifying fibroma, and, more significantly, malignant bone-forming tumors (ie, various forms of osteosarcoma). Herein, we directly address the resemblance of tGCT to osteosarcoma by evaluating a series of tGCT. We discuss the histologic features of denosumab treatment and compare them with those typically seen in osteosarcoma. We also gathered a series of malignancies arising in GCT of bone, either at primary presentation (pMGCT) or secondarily, after resection or radiation therapy (sMGCT). Although this is a relatively rare occurrence, some of the same features that characterize malignant transformation, including giant cell depletion and increased cellularity, are also seen in a subset of tGCT, making this comparison particularly relevant.^{13–15}

MATERIALS AND METHODS

Following IRB approval, cases were retrieved from the surgical pathology archives of the authors' institutions or their personal consult files. All available histologic slides were independently reviewed by 3 subspecialty bone and soft tissue pathologists (G.P.N., V.D., A.E.R.). The initial biopsy and posttherapy specimens were reviewed for each case of tGCT. For the cases of sMGCT, both the original and transformed specimens were reviewed, when available (3/6 cases). Slide review included original hematoxylin and eosin-stained slides and immunohistochemical stains for

p63 (Biocare RTU; 1:200 dilution), Ki67 (Leica; 1:200 dilution), and MDM2 (Calbiochem; 1:100 dilution) on selected cases. All available radiology studies were reviewed by a subspecialty bone and soft tissue radiologist (M.A.B.). Clinical history, treatment, and subsequent follow-up were obtained through medical chart review.

RESULTS

Clinical Features

A summary of the clinical findings for the cases of tGCT is provided in Table 1. The patients included 6 female and 3 male individuals aged 16 to 47 (median 32) years. The tumor locations were: sacrum (3), tibia (2), pelvis (1), thoracic vertebral body (1), metacarpal (1), and radius (1). All patients were originally diagnosed with GCT of bone on the basis of biopsy or curettage. The duration of therapy before repeat biopsy/excision ranged from 2 to 55 months. In 2 instances (patients 3 and 5), the patients underwent intermittent therapy. For these patients, the duration of continuous treatment before each histologic sampling is given. All patients presented with a chief complaint of pain at the site of the lesion. None of the patients have developed metastases.

Magnetic resonance imaging studies were available in 6 patients before and after therapy and computed tomography (CT) studies were available in 7 patients before and after therapy. On initial magnetic resonance imaging, GCT typically demonstrated low to intermediate signal intensity on T1-weighted and intermediate to high signal intensity on T2-weighted images. After therapy, a decrease in tumor size with decreased enhancement was seen in 6 cases. Areas of T2 hyperintensity and nonenhancement were noted in 4 cases, suggesting necrosis. On CT, lesions were typically osteolytic with a thin or no margin of surrounding bone. After therapy, new bone formation was observed in all cases with follow-up CT. The new bone was predominately located around periphery of the tumor (Fig. 1).

Gross and Histologic Findings: tGCT

Grossly, the diagnostic biopsy specimens were typical of GCT and consisted of fleshy, red-brown hemorrhagic tissue cores or curretted fragments with a similar appearance, containing variable amounts of interspersed bone. Figures 2 and 3 illustrate the findings typical of resected specimens, which were pale pink (Fig. 3) to yellow-brown in appearance (Fig. 2), with an easily identifiable rim of thick, sclerotic bone. Centrally, the lesions contained were solid, firm, and somewhat chalky in texture. Histologic studies showed that these areas corresponded to solid, cellular areas with extensive new bone formation, as described below.

With respect to histology, the initial diagnostic biopsy was reviewed in each case, and the findings were highly similar and were characteristic for GCT in all cases. They consisted of a cellular specimen with a relatively uniform syncytial proliferation of mononuclear cells admixed with numerous osteoclast-type giant cells, and scattered lymphohistiocytic inflammatory cells. The nuclei of the mononuclear cells were

TABLE 1. Clinical Features of 9 tGCTs of Bone

Case	Age	Sex	Location	Length of Therapy (mo)
1	32	M	Tibia	8
2	30	M	Pelvis	7
3	20	F	Sacrum	2, 19, 39, 13*
4	16	F	Metacarpal	42
5	47	F	Sacrum	14, 14*
6	27	F	Tibia	35
7	42	F	Sacrum	46
8	43	F	T1	55
9	35	M	Radius	6
Median	32			

Length of therapy before excision/biopsy is given in months.

*In cases 3 and 5, denosumab therapy was discontinued and restarted. In these cases, length of therapy is from the most recent reinitiation of treatment.

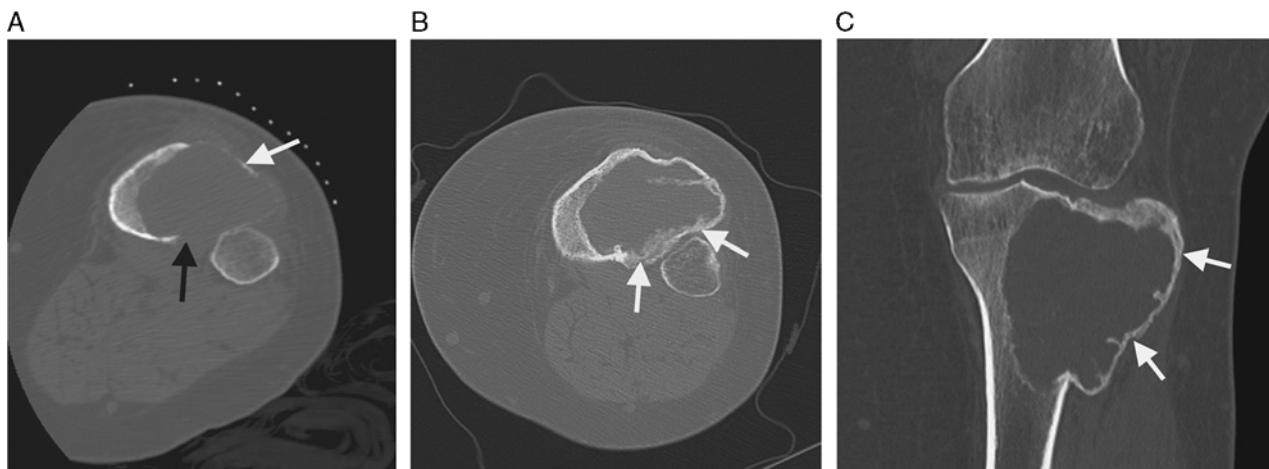


FIGURE 1. Radiologic features. CT of the proximal tibia before (A) and after (B and C) denosumab treatment. A, Axial CT image obtained as part of a biopsy shows a lytic lesion in the proximal tibia with thin sclerotic margin (white arrow) and areas of cortical break (black arrow). B and C, Axial and coronal images after denosumab therapy show interval bone formation (white arrows) involving predominately the peripheral aspects of the tumor.

morphologically similar to those within the giant cells. The giant cells were present in all biopsies and generally evenly distributed throughout, although there were few areas in which giant cells were fewer in number. In these areas, the tumor cells were spindled and arranged in short intersecting fascicles. There were also areas of hemorrhage and fibrin deposition. Immunohistochemistry showed that the mononuclear cells were diffusely and strongly positive for p63. The Ki67 proliferation index was variable ranging from 8% to 15%.

In contrast to the pretreated tumors, the treated specimens were variable, although they shared a marked decrease in the number of giant cells, which were sparse to absent. When present, most commonly in the lesions resected after a shorter duration of treatment, the giant cells

were primarily located at the periphery of the lesion and tended to be smaller and to contain fewer nuclei (5 to 10) than those seen in the pretreatment biopsies.

Four specimens (patients 1, 2, 9, and one of the specimens from patient 3), all resected relatively early in the course of therapy (2 to 8 mo), showed a markedly cellular proliferation with mixed sheet-like and storiform growth pattern, composed of mononuclear cells with vesicular and hyperchromatic nuclei that demonstrated moderate pleomorphism (Fig. 4). These cells were accompanied by variable amounts of lymphocyte-predominant inflammation. In some cases, the inflammation was pronounced. Foamy histiocytes were present in the background to varying degrees, usually scattered throughout the lesion but, in some areas, arranged in clusters. The treated tumors contained a peripheral shell of reactive woven bone, with prominent



FIGURE 2. Gross specimen, case 2. Gross image of the partial hemipelvectomy specimen. The tumor shows a peripheral rim of sclerotic (arrows) cortex surrounding a chalky yellow-brown, solid cut surface. The lesion involves the pubic ramus, acetabulum, and ischium, and forms a solid, focally mineralized mass extending into the posterior soft tissues (*).



FIGURE 3. Gross specimen, case 4. The gross specimen consisted of a central tan pink, firm, mass (*) with a narrow rim of sclerotic cortex (arrowheads) and no soft tissue extension.

osteoblastic rimming, and varying degrees of new bone deposition within the tumor.

The amount of new bone appeared to correlate with the duration of treatment, growing in prominence over time. The bone was more pronounced peripherally, and the pattern of new bone deposition was recognizable in multiple forms, often as a continuum (Fig. 5). The most incipient new bone was present as small, rounded aggregates and short strands resembling sclerotic collagen. Elsewhere, there

were thickened, rounded areas with osteoblast rimming at their periphery. Immunohistochemical staining for p63 highlighted rare cells or was altogether absent. Ki67 proliferation index was low (range, 3% to 8%).

Tumors resected after a greater duration of therapy (19 to 55 mo) showed decreased cellularity. The residual stroma consisted of varying degrees of spindled mononuclear cells and foamy histiocytes. The spindle-cell component was bland and monotonous (Figs. 4C, D).

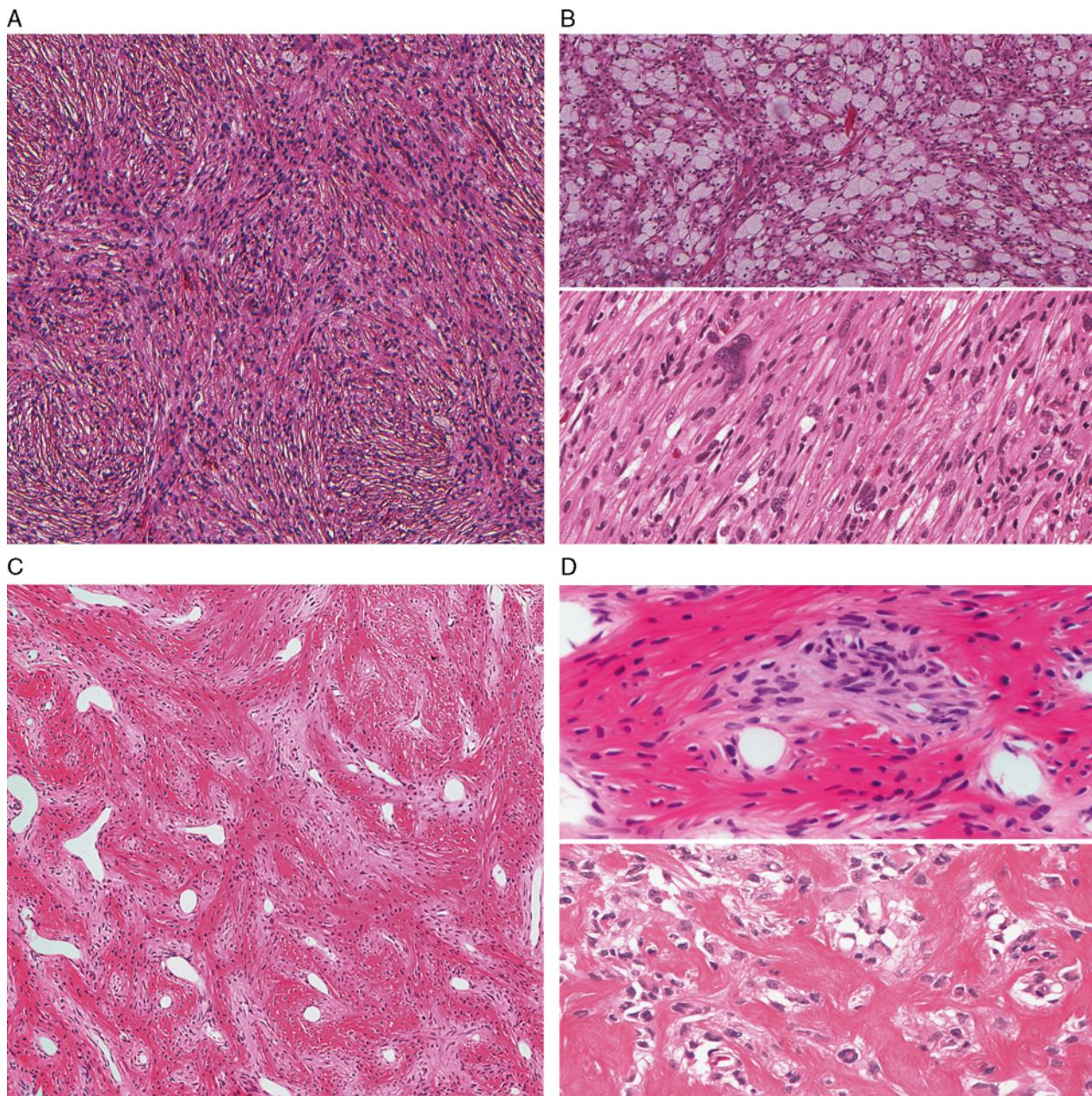


FIGURE 4. Histologic features. A, tGCT, early in the course of therapy. The tumor is cellular, with storiform growth pattern and admixed chronic inflammation. B, Higher-power images of 2 tGCT, illustrating areas of foamy histiocytes (above) and cytologic atypia. C, tGCT, later in the course of therapy. The tumor shows decreased cellularity relative to (A), and is instead dominated by newly formed bone, deposited in long, interconnected strands, emerging from a banal, spindled stroma (D, top). In other cases the strands of bone are thinner, and more irregular, separated by a mildly atypical, but still relatively paucicellular stroma.

In the tumors with the longest duration of treatment, the stroma was a loose, paucicellular fibrovascular network separating trabeculae of the newly formed bone that increasingly dominated the histology. Some of the new bone was similar in appearance to that seen in the earlier lesions but with a greater preponderance of the thick,

rounded cords. In other cases, the bone consisted of long, curvilinear trabeculae that appeared to arise directly from the bland, spindled stroma. Immunohistochemical staining for MDM2 was negative.

Although the overall pattern was of a gradual decrease of stromal cellularity and atypia and an increase in

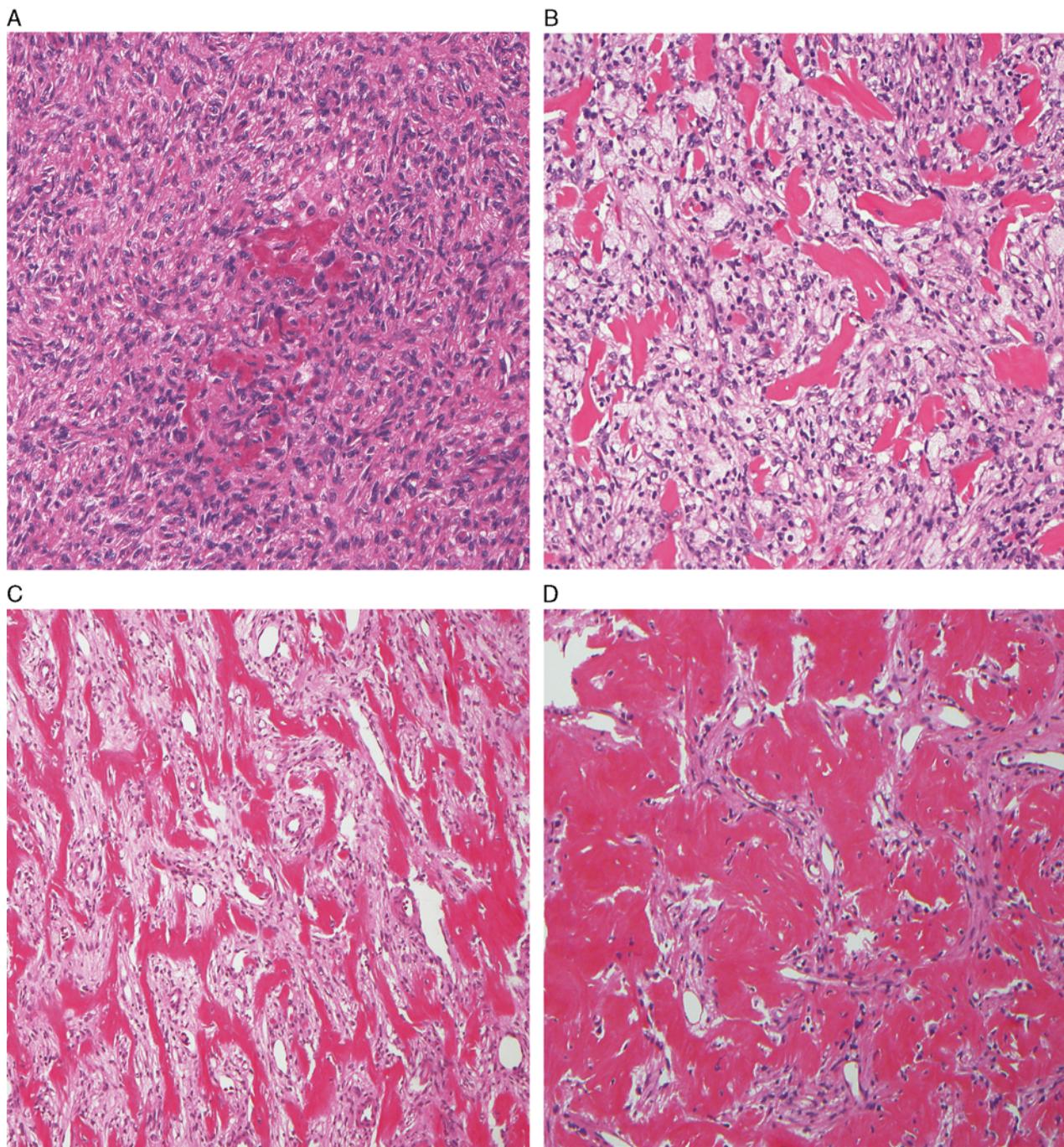


FIGURE 5. Variable morphology of newly formed bone in tGCT. tGCT, particularly early in the course of therapy, may show only focal bone formation in the background of a highly cellular stroma (A), leading to a resemblance of osteosarcoma. Over the course of therapy, the lesions are increasingly dominated by newly deposited bone, in small, haphazard globules (B), as long, thin, interconnected curvilinear strands (C) or as large, rounded cords (D).

bone deposition, a number of findings were confined to individual cases. Two lesions contained distinct areas of remodeled bone and hyaline cartilage with endochondral ossification (Fig. 6A). These findings were interpreted to be consistent with fracture callus (radiologically an intralesional fracture was identified) altered by denosumab therapy. Another lesion contained areas of lace-like mineralization buttressing newly formed bone (Fig. 6B).

Malignancy Arising in GCT of Bone

Malignant transformation is a rare but documented complication of GCT (MGCT).^{15,16} It may be identified either at the time of initial resection, in the case of pMGCT, or secondarily, after excision or radiation

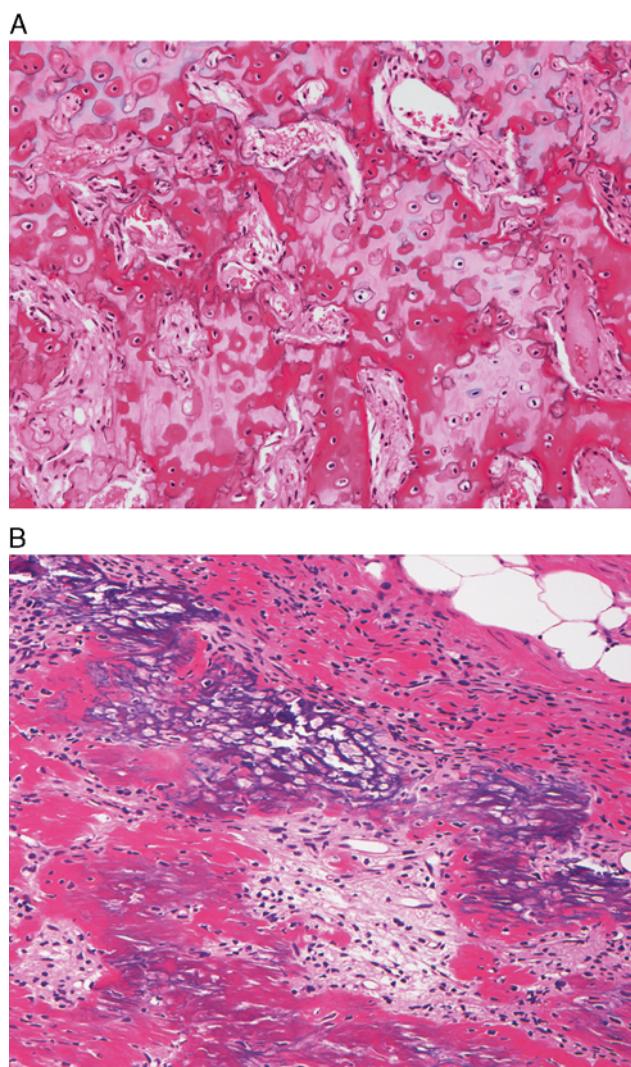


FIGURE 6. Peculiar patterns of mineralization in tGCT. Two cases exhibited peculiar patterns of bone formation and mineralization. In case (A), the patient had intralesional fractures seen on radiology. The absence of osteoclasts gave an osteopetrosis-like morphology to the fracture callus. In (B), the specimen exhibited areas of lacy blue mineralization. These areas were not associated with an atypical cellular proliferation.

therapy (sMGCT). To compare and contrast the histologic features of tGCT with those of MGCT, we conducted a retrospective review of 9 cases of MGCT. MGCT patients included 6 male and 3 female individuals aged 18 to 62 (median 49) years (Table 2). The tumor locations were: femur (4), tibia (3), pelvis (1), and metatarsal (1). Three cases presented with malignancy at the time of initial diagnosis, and 6 patients had a history of prior GCT at the same site, with classic features, which had undergone malignant transformation (sMGCT). Of these cases of sMGCT, 2 patients had a history of radiation therapy to the site.

On histologic sections, all cases showed foci with classic features of GCT juxtaposed with areas of giant cell loss and increased stromal cellularity. Although some foci contained a bland, storiform proliferation, all exhibited at least focal areas of marked pleomorphism, nuclear hyperchromasia, and abundant mitotic activity ($> 10/10 \text{ HPF}$) (Fig. 5). Necrosis was identified in the majority of the tumors (6/9). Six of the tumors contained bone deposition allowing for a diagnosis of osteosarcoma. In these cases, the bone was deposited in a lace-like manner devoid of osteoblastic rimming and, in some instances, encasing individual atypical cells. The pattern of bone deposition noted in tGCTs was not identified in these tumors. In 2 cases, the malignant component consisted of a fascicular spindle-cell sarcoma with hyperchromasia and increased mitotic activity, leading to a diagnosis of high-grade sarcoma with fibroblastic differentiation. The final case, diagnosed as a high-grade spindle-cell sarcoma with rhabdomyoblastic differentiation showed increased stromal cellularity and numerous rhabdoid cells containing dense eosinophilic cytoplasm and eccentrically placed nuclei (Fig. 7C).

DISCUSSION

Here we report on the histologic findings in 9 cases of GCT of bone after denosumab treatment. The impetus behind this study is to highlight the histologic differences between the initial, giant cell-rich lesions present in the diagnostic biopsies and pretreatment curettages to that of the posttreatment specimens and to contrast these changes with MGCTs in order to avoid misdiagnosis and consequent misguided therapy. This comparison is timely, as a recent case report highlighted the resemblance of GCT to osteosarcoma.¹⁷ In a separate case report, a tGCT was seen to undergo malignant transformation.¹⁸ This emphasizes the need for a careful histologic evaluation of all tGCTs and a thorough understanding of the differences between treatment-related histologic changes and malignant transformation.

Posttreatment specimens showed dramatic reduction in the numbers of giant cells and a predominance of spindled and/or plump mononuclear cells with variable amounts of new bone formation. In our series, stromal cellularity was inversely correlated with treatment duration, while new bone deposition was directly correlated with length of therapy. As a consequence of these changes, the combination of cellular stroma with atypia

TABLE 2. Clinical Features of 9 GCTs

Case	Age	Sex	Location	Primary or Secondary	Diagnosis
1	54	M	Metatarsal	Primary	Osteosarcoma
2	49	F	Tibia	Primary	Osteosarcoma
3	37	M	Femur	Primary	Osteosarcoma
4	62	M	Pelvis	Secondary	Fibroblastic sarcoma
5	25	F	Femur	Secondary	High-grade sarcoma with rhabdomyosarcomatous differentiation
6	18	M	Tibia	Secondary*	Osteosarcoma
7	54	M	Femur	Secondary	Osteosarcoma
8	55	M	Tibia	Secondary*	Osteosarcoma
9	33	F	Femur	Secondary	Fibroblastic sarcoma
Median	49				

*Cases 6 and 8 are sMGCT in patients with a history of radiation at the site of the tumor.

in early lesions, as well as the presence of new bone without distinct osteoblastic rimming, produced a resemblance to high-grade osteosarcoma.

We found, however, that, despite this resemblance, there are numerous features that set tGCT apart from osteosarcoma. The pattern of bone deposition was not the lace-like pattern typical of high-grade osteosarcoma but instead took several distinct forms. In the earlier lesions, new bone was predominantly in rounded globules or short, irregular, partially connected seams of variable thickness. Of bone-forming neoplasms, this pattern was distinct from, but reminiscent of, juvenile trabecular ossifying fibroma but lacked distinct osteoblastic rimming. In tumors treated for an intermediate length of time, bone formation was dominated by thick cords with rounded contours. Later lesions contained both of the above forms but also long, curvilinear trabeculae that seemed to arise directly from the spindled stroma. This appearance was more reminiscent of fibrous dysplasia or low-grade central osteosarcoma. Unlike the latter, however, the treated tumors were negative for MDM2.

In addition to a distinct pattern of bone deposition, tGCT contained a lesser degree of cytologic atypia than that typically seen in high-grade osteosarcoma. tGCT also contained few mitotic figures (< 1 to 4/10 HPF) and a low Ki67 index. This is consistent with in vitro studies that demonstrate decreased proliferation of the neoplastic cells after denosumab administration.¹⁹ Finally, permeation of preexisting bone was not seen in any of the tGCT cases.

Our study of 9 cases of MGCT revealed that the same features that help distinguish tGCT from de novo osteosarcoma are useful for excluding malignancy arising in GCT. This is important because GCT can be associated with a malignant component at presentation (pMGCT) or, in approximately 1% of cases, undergo malignant transformation, either de novo or, at a higher frequency after radiation therapy.^{16,17,20,21} As in our series, reports in the literature note that the malignant component may vary and include osteosarcoma, fibrosarcoma, and, less frequently, undifferentiated pleomorphic sarcoma. In cases of fibrosarcomatous transformation, lesions contained a gradual transition between GCT and the sarcomatous component characterized by a loss of giant cells

and corresponding increase in the density of the mononuclear component—some of the same features that characterize tGCT.

In both pMGCT and transformed MGCT, however, there are nearly always foci with the aggressive histologic features that define a high-grade sarcoma.²² The tumor infiltrates bone and exhibits marked cytologic atypia, brisk mitotic activity and atypical mitotic forms.^{17,21} Reports in which GCT has given rise to an osteosarcoma with bland cytomorphology are exceptional.¹⁶ Our retrospective review of 9 cases of MGCT is consistent with these reports. They displayed overt high-grade cytologic features, brisk mitotic activity and infiltration of adjacent non-neoplastic bone. High-grade morphology also characterized the sole case report of MGCT arising in the course of denosumab treatment of GCT.²³ In this case, the malignant component exhibited marked atypia, mitotic activity, and necrosis. In our series, tGCT uniformly lacked these features, allowing for a distinction from MGCT.

Although much of our focus has been on the distinction between tGCT and osteosarcoma, it is worthwhile to briefly remark on histologic features that distinguish tGCT from benign mimics. In different tumors and in different areas within a single tumor, certain features could lead to a differential diagnosis of fibrous dysplasia or nonossifying fibroma. Unlike fibrous dysplasia, the newly formed bone in GCTs from patients treated with denosumab was accompanied by significantly less stroma and was present as delicate interconnecting seams of osteoid, rather than the larger islands of randomly distributed curvilinear bone characteristic of fibrous dysplasia. On the basis of purely histologic features the distinction between treated GCT and nonossifying fibroma is more challenging due to the close resemblance, particularly early in the course of treatment when new bone formation is less prominent. A useful feature is that in GCTs from patients treated with denosumab, the osteoclast-type giant cells are virtually absent, or limited to the periphery of the lesion, whereas they are usually scattered throughout the lesion in nonossifying fibroma.

Reports in the literature suggest that immunohistochemical staining for p63 can be a valuable adjunct in distinguishing GCT (p63 positive) from other fibrohistiocytic lesions (p63 negative).^{19,24,25} In our series, however, tGCT

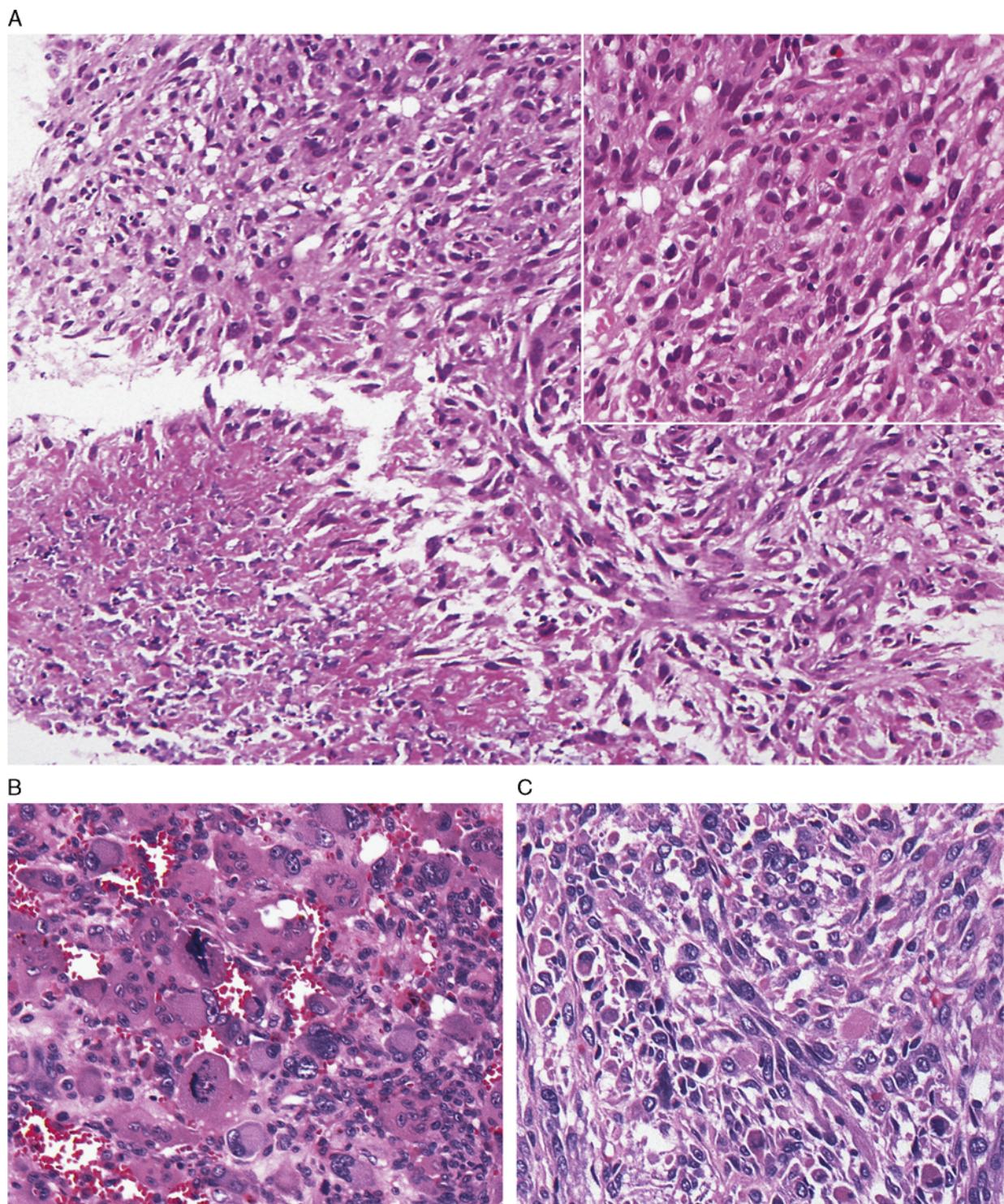


FIGURE 7. MGCT. A, An example of an MGCT, illustrating a highly cellular proliferation with cytologic atypia, brisk mitotic activity (inset, top right), and areas of necrosis (lower left). High-power images from 2 additional cases show marked atypia and mitotic activity (B) and areas of rhabdomyoblastic differentiation seen in 1 case (C).

showed very limited p63 expression, making this marker less helpful in distinguishing GCT from potential mimics, such as nonossifying fibroma. The pattern of p63 staining also changed with time. In all of the untreated specimens, staining

was dark and diffuse in the mononuclear component. After treatment, this staining was retained in the portions of the lesion with continued GCT morphology, but was minimal or absent in the cellular areas that lacked giant cells. In the

lesions resected after a longer course of therapy, p63 staining was limited to osteoblasts surrounding the thickened cords of osteoid.

Therefore, the history of denosumab administration coupled with the knowledge of the histologic features of treated GCT may be critical to arriving at the correct diagnosis. Other clinical information could also be of value, as these entities, that is, osteosarcoma, MGCT, and tGCT, often have distinct presentations with respect to the age of the patient, location of the tumor, and its radiographic appearance.²⁶

What accounts for the altered histomorphology of GCT? Mechanistically, it appears to reflect a shift in the balance of physiological bone formation away from RANK-mediated osteoclastic bone resorption toward osteoprotegerin-induced bone formation. It seems that this shift does not reflect terminal differentiation of the mononuclear neoplastic component of GCT, which has a preosteoblast phenotype, as the morphology reverts to classic GCT upon cessation of denosumab therapy.^{3,8} Rather, denosumab likely temporarily restores or enhances osteoblastic activity through the disruption of osteoclast proliferation and differentiation. Histologically, this shift is evidenced by osteoclast-type giant cell depletion. Indeed, osteoclast depletion, and the attendant decrease in bone turnover, seems to be the mechanism by which denosumab reduces fractures and promotes skeletal integrity in osteoporosis.⁵ The absence of osteoclast-type giant cells may also account for the presence of fracture callus with the morphologic appearance that mimics osteopetrosis (as in case 3), as the mechanism underlying osteopetrosis is a significant diminution of functional osteoclasts.

In conclusion, our findings suggest that there is a spectrum of histologic changes in GCTs after denosumab therapy, characterized by marked depletion of osteoclast-type giant cells, atypia of the mononuclear cells, and an often dramatic increase in bone deposition. Consequently, tGCT may mimic osteosarcoma in histologic appearance or may appear as though it has undergone transformation to MGCT. Unlike MGCT or osteosarcoma, however, tGCT exhibits less atypia, less mitotic activity, and does not grow in a permeative manner. Moreover, treatment-related histologic changes were not associated with aggressive clinical behavior, as none of the patients developed metastatic disease. Thus, therapy-related changes in GCT morphology, in and of themselves, should not be taken as evidence of increased malignant potential, and careful attention to the history of denosumab administration should help to avoid a misdiagnosis with significant therapeutic ramifications.

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