



CASE REPORT

Giant cell tumor of the thoracic spine completely removed by total spondylectomy after neoadjuvant denosumab therapy

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Abstract

Purpose Denosumab, a novel monoclonal antibody that targets the receptor activator of nuclear factor- κ B (RANK) ligand (RANKL), has recently been used to treat patients with giant cell tumor of bone (GCTB). However, few reports have described the clinical results of denosumab therapy for spinal GCTB and evaluated treatment efficacy with respect to the entirety of the resected vertebra after denosumab therapy.

Methods We present the case of a 51-year-old man with T12 GCTB that was completely removed by a total spondylectomy following 10 courses of neoadjuvant denosumab therapy. Post-therapy radiological findings indicated epidural tumor reduction in the spinal canal and sclerotic rim formation. However, the affected vertebra collapsed despite denosumab therapy and a massive bridging callus formation was present between the spinal GCTB and adjacent vertebra.

Results These morphological changes made the tumor margins unclear and increased the difficulty of dissection of the segmental arteries from the vertebral body and *en bloc* corpectomy by a posterior-approach. Pathological findings indicated increased woven bone at the peripheral lesion of the resected vertebra and RANKL-positive stromal cells remained around the woven bone.

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Conclusions These findings support that GCTB stromal cells survived around the newly formed woven bone after long-term denosumab treatment and total surgical resection of such primary spinal lesions as the gold-standard treatment, even following administration of denosumab. Surgeons should note that prolonged adjuvant denosumab therapy may increase the difficulty of performing a posterior-approach total *en bloc* spondylectomy.

Keywords Giant cell tumor · Denosumab · Total spondylectomy · Spine · RANKL

Introduction

Giant cell tumor of bone (GCTB) that affects the axial skeleton, including the spine, is usually difficult to completely remove. Incomplete removal has resulted in a high-rate of local recurrence [1]. Denosumab, a novel monoclonal antibody that targets the receptor activator of nuclear factor- κ B (RANK) ligand (RANKL) has recently been used to treat patients with GCTB. Denosumab binds to RANKL, which is highly expressed by mononuclear mesenchymal stromal cells in GCTB [2], thereby inhibiting the maturation of osteoclast and osteoclast-like cells from RANK-positive mononuclear preosteoclasts and macrophages [3, 4]. Greater than 90% elimination of multinucleated giant cells or no radiographic progression was achieved in 86% of patients in an open-label phase 2 study [3]. However, to our knowledge, few reports have described the clinical results of denosumab therapy for spinal GCTB and evaluated treatment efficacy with respect to the entirety of the resected vertebra after denosumab therapy. In this case report, we describe the case of a 51-year-old male patient with a T12 GCTB who underwent a posterior-

approach total spondylectomy after 10 courses of neoadjuvant denosumab therapy. We histologically evaluated the entirety of the resected vertebra and assessed the impact of denosumab as a neoadjuvant therapy for spinal GCTB patients.

Case report

A 51-year-old Japanese male with no relevant past or family history presented with 8 months of axial back pain. Initial computed tomography (CT) revealed an osteolytic lesion involving the T12 vertebra with thinned cortical

bone (Fig. 1a). T1-weighted magnetic resonance imaging (MRI) revealed low to intermediate signal intensity and T2-weighted MRI with fat suppression revealed intermediate to high signal intensity (Fig. 1c). A CT-guided percutaneous biopsy was performed and revealed multinucleate giant cells in neoplastic mononuclear mesenchymal stromal cells (Fig. 2). The tumor was diagnosed as GCTB. The primary physician considered that complete surgical removal would be difficult and denosumab treatment was initiated. After 10 courses of denosumab, the patient was referred to our hospital for complete tumor removal by total spondylectomy. On physical examination, he had mild axial back pain, but no neurological deficits.

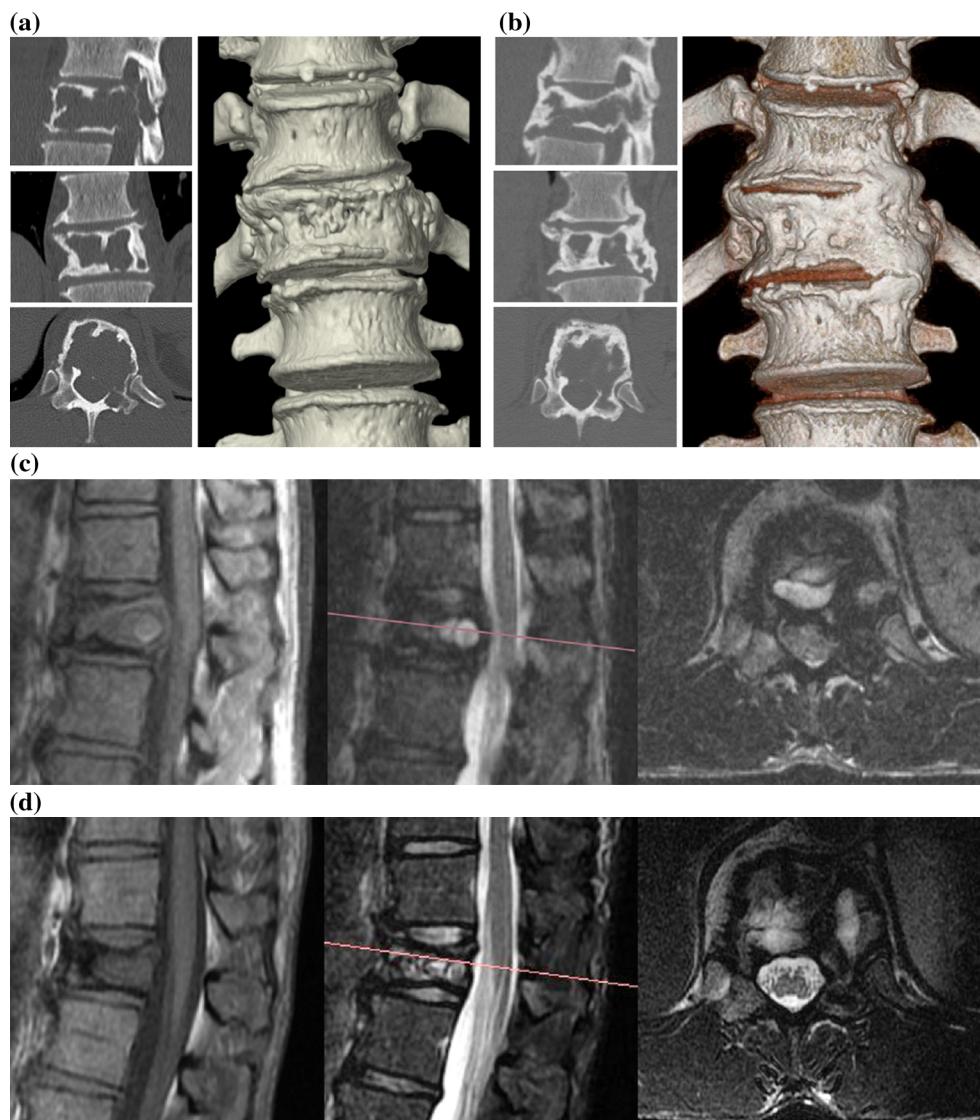


Fig. 1 Preoperative computed tomography (Sagittal, coronal, axial and 3D reconstruction) and magnetic resonance imaging (*left* T1-weighted MRI, *middle and right* T2-weighted MRI with fat suppression). **a, c** Preoperative thoracic magnetic resonance imaging and computed tomography before starting denosumab therapy, showing a

tumor involving T12. **b, d** After 10 months of denosumab therapy, shrinkage of the epidural extraosseous tumor and peripheral rim calcification were observed. Vertebral collapse progressed, with significant callus formation

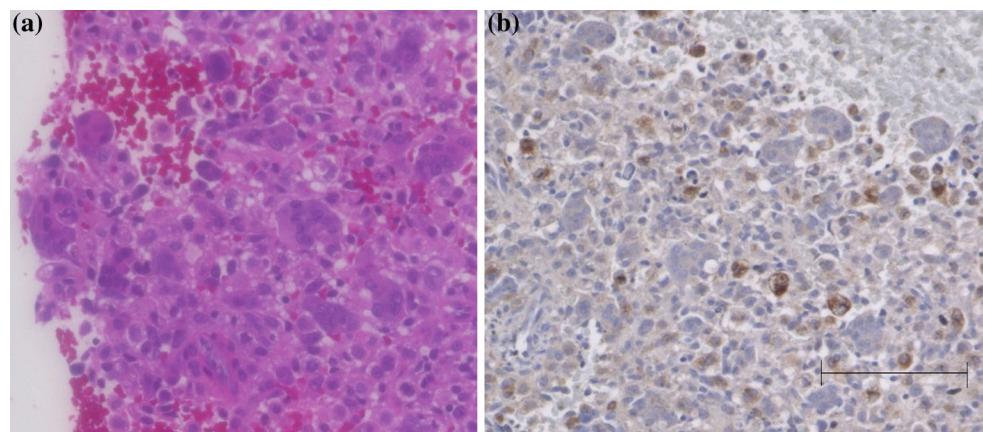


Fig. 2 Histological analysis of CT-guided biopsy specimen before denosumab therapy. Hematoxylin and eosin (**a**) and RANKL staining (**b**). **a** Multinucleate giant cells can be seen surrounded by neoplastic

stromal cells. **b** RANKL expression was detected using immunohistochemistry (IHC) and was found in mononuclear cells around multinucleate giant cells. Scale bar corresponds to 100 μ m

A CT scan and MRI revealed significant sclerotic rim formation at the tumor site and a reduction in epidural tumor size (Fig. 1d). However, the vertebral collapse had progressed and massive bridging callus formation was observed between T12 and its adjacent levels compared with that before denosumab therapy (Fig. 1b).

A posterior-approach total spondylectomy was performed. First, T12 pedicles were cut using a reciprocating motion with a T-saw and the entire posterior element of the spine was removed in one piece (*en bloc* laminectomy). The lateral aspect of the vertebral body was dissected. Thereafter, we attempted to dissect the segmental arteries from the vertebral body; however, it was difficult because of the expanded transverse diameter of the vertebral body owing to vertebral collapse and bridging callus formation between the adjacent vertebrae. Therefore, we performed piecemeal resection of the lateral side of the bridging callus and the sclerotic rim of the vertebra using chisels (Fig. 3). Thereby, a complete manual dissection of the segmental arteries from the vertebral body was achieved. The T11/12 and T12/L1 discs were cut off using L-shaped chisels and the remaining T12 vertebral body was removed *en bloc* posteriorly (Fig. 4). The spine was reconstructed with a cage packed with minced iliac bone graft and posterior instrumentation with iliac unicortical strut bone.

The patient's neurological function remained intact without any perioperative complication. One year after surgery, without postoperative denosumab treatment, activities of daily living were normal with no evidence of local recurrence or distant metastasis. Postoperative radiography and CT demonstrated that the reconstructed spine has been well-maintained with signs of radiographic bony union (Fig. 5).

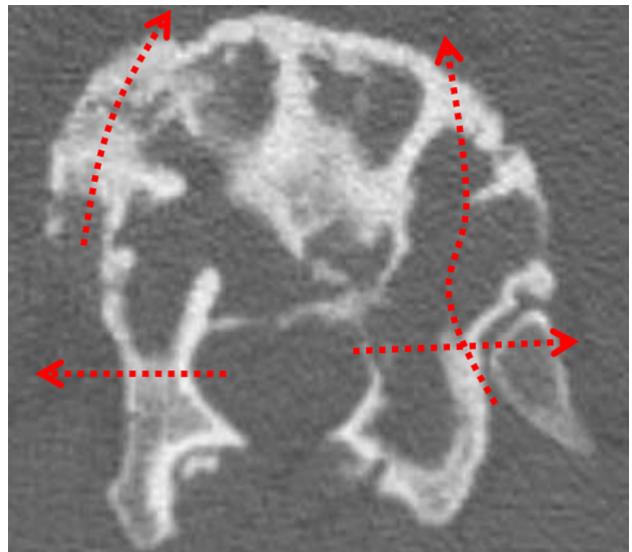


Fig. 3 Diagram illustrating cuts performed through the bilateral pedicle, lateral side of the bridging callus, and the sclerotic rim of the vertebra

Histological evaluation

Histological analysis of the T12 vertebral body sections was performed (Fig. 6a). Pathological findings showed significantly increased woven bone at the peripheral lesion in the transverse vertebral sections (Fig. 6b, c). Multinucleate giant cells were not present. RANKL expression in the tumor specimen was examined. A rabbit polyclonal antibody against RANKL (1:500, ab9957, Abcam, Cambridge, UK) was used as the primary antibody. Anti-mouse or rabbit IgG conjugated with peroxidase-labeled polymers (EnVision, Dako, Carpinteria, CA, USA) was used as the secondary antibody. RANKL-positive stromal cells

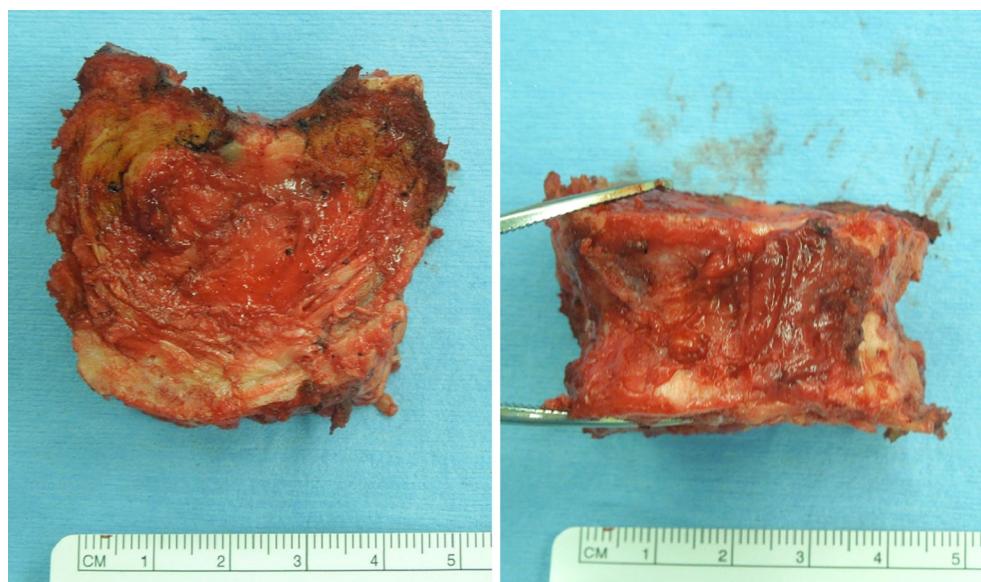


Fig. 4 Photography of the resected specimen. The lateral aspect of the resected vertebral body revealed a *dark reddish-brown mass* owing to piecemeal resection of the lateral side of the bridging callus and the sclerotic rim of the vertebra using chisels

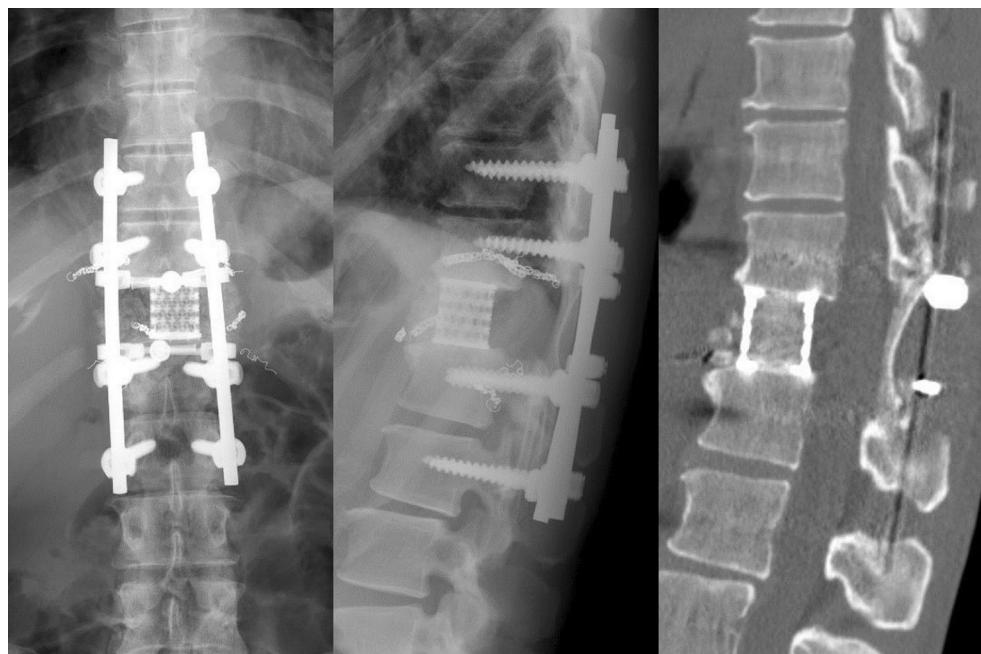


Fig. 5 Postoperative radiological findings 1 year after total spondylectomy. Postoperative radiography and CT demonstrated that the reconstructed spine has been well-maintained with signs of radiographic bony union

remained around the newly formed woven bones of the vertebra (Fig. 6d).

Discussion

Denosumab treatment for patients with GCTB has been shown to significantly reduce or eliminate RANK-positive multinuclear giant cells, replacing them with non-

proliferative, differentiated, densely woven new bone [5]. Denosumab inhibits progressive bone destruction, making it possible to preserve a functional local anatomy. Rutkowski et al. reported that neoadjuvant denosumab therapy in patients with GCTB resulted in beneficial surgical downstaging that either removed the requirement for surgery or permitted the use of a less radical surgical procedure. Surgical down-staging was evaluated in 222 denosumab-treated patients. Almost half of the patients no

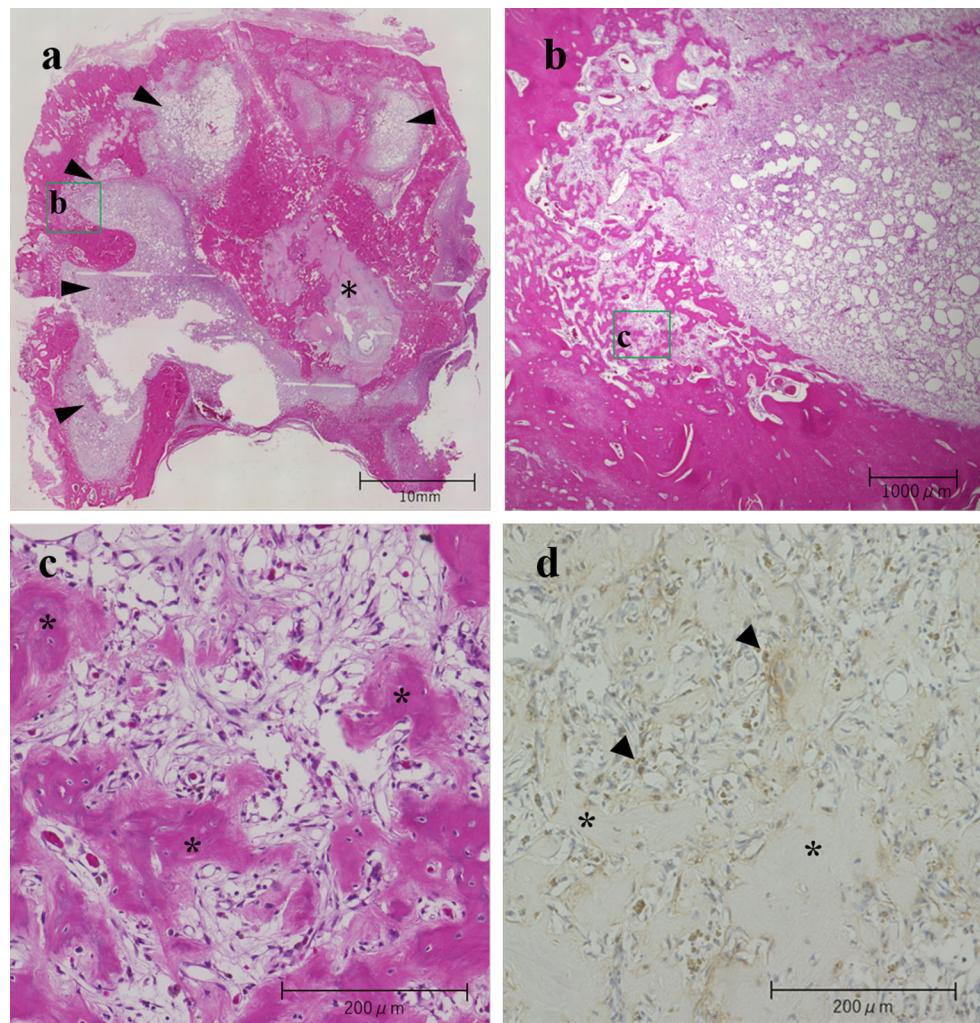


Fig. 6 Histological analysis of the entire resected vertebral body (T12). **a** Transverse section of resected vertebral body (hematoxylin and eosin staining). Significant increased woven bone at the peripheral lesion. The asterisk indicates the disc and the black arrowheads indicate tumor presence around newly formed woven bone. Scale bar corresponds to 10 mm. **b** Significantly increased woven bone at the peripheral lesion. Scale bar corresponds to

1000 μm . **c** Significantly increased woven bone at the peripheral lesion in transverse sections of the vertebra. Multinucleated giant cells were not detected, although mononuclear cells were found. The asterisk indicates newly formed woven bone. Scale bar corresponds to 200 μm . **d** RANKL-positive stromal cells (black arrowhead) remained around newly formed woven bone (asterisk). Scale bar corresponds to 200 μm

longer required surgery ($n = 106$, 48%), but were treated with continuous denosumab therapy, or required a less invasive procedure than originally planned ($n = 84$, 38%). However, this study primarily included patients with GCTB of the extremities and pelvis. There were only eight cases of spinal GCTB, of which, only three underwent surgery [6].

Several reports have detailed the excellent clinical results of denosumab therapy without tumor resection for spinal GCTB patients. Mattei et al. reported a case of C2 GCTB in which there was no recurrence at 16 months without excision while under denosumab therapy [7]. Randhawa et al. reported two cases of cauda equina syndrome (CES) secondary to L5 GCTB in which neurological

recovery was achieved after treatment with denosumab without surgery [8]. Kajiwara et al. reported a case of recurrent C2 GCTB after surgery that was managed using denosumab, in which there was no evidence of tumor recurrence after 18 months [9]. In these patients, total resection was unfeasible owing to anatomical features and local recurrence after tumor resection. Denosumab may be an efficacious option for the treatment of unresectable GCTB of the spine and recurrent GCTB after surgery. However, long-term follow-up is required to monitor local recurrence and malignant transformation.

Recently, four reports have described excellent results for denosumab as a neoadjuvant therapy prior to total spondylectomy for spinal GCTB. Agarwal et al. reported a

case of recurrent T6 GCTB after tumor resection that was previously considered unresectable. After 10 months of denosumab therapy, complete resection was performed. The histological findings of the entire specimen indicated extensive fibrosis and necrosis without any identifiable viable cells [10]; however, the presence of RANKL-positive stromal cells around the lesion or newly formed woven bone was not evaluated. Kumar et al. reported successful surgical resection for a large C7 GCTB after surgical down-staging with denosumab [11]. de Carvalho Cavalcante et al. reported a spondylectomy of L4 GCTB and showed an absence of giant cells and stromal cells inside the L4 vertebral body; however, the entire specimen was not evaluated [12]. Goldschlager et al. reported four patients with GCTB of the spine treated with tumor resection after neoadjuvant denosumab treatment. Imaging after denosumab treatment revealed a reduction in tumor size and calcification of the pseudocapsule, which facilitated preservation of the critical anatomy. However, viable tumor cells were present upon the final histological investigation in one of the four cases. The distribution of stromal cells in the resected vertebra was not described [13].

The present case showed that RANKL-positive stromal cells remained around the new woven bone at the rim of the affected vertebral body despite 10 courses of denosumab therapy. This is the first report to evaluate the distribution of RANKL-positive stromal cells in the entire resected vertebra. These leftover neoplastic stromal cells around the newly formed woven bone made it difficult to perform complete curettage, which may have led to a local recurrence. Rutkowski et al. reported that local recurrence after surgery for GCTB (mainly of the extremities) following denosumab therapy occurred in 15% ($n = 17/116$) of patients [6]. This fact suggested the possibility that neoplastic stromal cells remained despite denosumab therapy. These aforementioned clinical data were supported by an in vitro study that showed that denosumab had a minimal inhibitory effect and did not induce apoptosis of GCTB neoplastic stromal cells because it did not regulate the expression of RANKL at either the mRNA or protein level of these cells [14]. Therefore, local adjuvants, such as phenol or liquid nitrogen, are recommended to improve local control during the surgical treatment of GCTB occurring in the extremities [15–17]. However, these agents cannot be used in spinal GCTB owing to the risk of injury to the spinal cord, nerve roots, and great vessels. Therefore, surgical *en bloc* resection of such primary spinal lesions is regarded as the gold-standard treatment, even following denosumab administration.

In the present case, pre-denosumab therapy radiological findings demonstrated that none of the GCTB tumors expanded out of the vertebral body, except for an epidural

lesion. Administration of denosumab resulted in shrinkage of the epidural extraosseous tumor, thereby preserving neurologic functions. However, progression of vertebral collapse and massive callus formation occurred. Although the mechanism of these morphological changes was unclear, these changes might have resulted from overall tumor shrinkage as an early effect of denosumab. This tumor shrinkage might have increased the mechanical stress loading to the remaining locally thinned cortical rim and this increase in mechanical stress might have led to collapse of the affected vertebral body. In addition, this mechanical fragility and instability of the vertebral body owing to the collapse might have stimulated the bridging callus formation as a biological reaction. Accordingly, these morphological changes made the tumor margins unclear. In addition, the difficulty of dissection of the segmental arteries from the vertebral body and *en bloc* corpectomy by a posterior-approach was increased, which could increase the risk of local recurrence owing to intralesional piecemeal resection. As reviewed previously by Boriani et al., Enneking stage III tumors can be adequately controlled by *en bloc* resection. GCTB tumors that expand out of the vertebral body form a pseudocapsule, which allows for *en bloc* resections [18]. In the present case, we assumed that dissection of the segmental arteries from the vertebral body and *en bloc* corpectomy prior to the administration of denosumab would have been easier to perform, as the vertebral collapse and bridging callus formation between adjacent vertebrae would not have been present.

Conclusions

This is the first report to evaluate the histological effect of denosumab and the distribution of RANKL-positive stromal cells using the entire resected vertebral body. Denosumab induced marked formation of new woven bone at the rim of the affected vertebral body; however, neoplastic RANKL-positive stromal cells existed around the woven bone. These findings indicated that GCTB stromal cells survived around the newly formed woven bone after long-term denosumab treatment. The results indicated that total spondylectomy was a more desirable surgery for spinal GCTB compared to intralesional curettage because it reduced the risk of local recurrence, even following administration of denosumab. Denosumab also induced shrinkage of the epidural extraosseous tumor, which may have reduced the risk of neural compression. However, surgeons should note the fact that despite denosumab administration, vertebral collapse could occur and prolonged adjuvant denosumab therapy may stimulate bridging callus formation between the affected and adjacent

