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Total en bloc spondylectomy of the eleventh thoracic vertebra following denosumab therapy for the treatment of a giant cell tumor

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Abstract. Although denosumab has been reported to induce effective clinical results with respect to tumor shrinkage in a short-term follow-up clinical study, total spondylectomy is recognized as the treatment of choice for eradicating giant cell tumors (GCTs) of the spine. The present study reports the case involving a GCT in the 11th thoracic vertebra complicated by idiopathic scoliosis and treated using total en bloc spondylectomy (TES) with preoperative denosumab therapy. A 35-year-old woman received preoperative denosumab therapy for 8 months, followed by surgery using a computed tomography (CT)-based navigation system that optimized accuracy by recognizing the area of the detached parietal pleura, the irregular border of the collapsed vertebra, and the adjacent vertebra. Complete en bloc resection of the vertebra could be performed, suggesting denosumab can be an effective adjuvant therapy which can reduce the complexity of TES and CT-navigation system facilitated the safe use of this surgical method in a patient with idiopathic scoliosis.

Introduction

Giant cell tumors (GCTs) of the bone are aggressive benign primary bone neoplasms, which present mostly at the meta-epiphysis of long bones, causing extensive lytic lesions with an estimated incidence of 1.3 per million per year (1,2). GCTs of the spine reportedly account for 2.7-6.5% of all GCTs in bone (3). Resection at an early stage remains the best strategy for treatment with a low recurrence rate (4,5).

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Key words: giant cell tumor, idiopathic scoliosis, eleventh thoracic vertebra, denosumab, total en bloc spondylectomy, navigation, histology

Although denosumab has been reported to induce effective clinical results with respect to tumor shrinkage in a short-term follow-up clinical study, total spondylectomy is recognized as the treatment of choice for eradicating GCTs of the spine (6). The present study reports a case involving a GCT in the eleventh thoracic vertebra, complicated by idiopathic scoliosis and treated using total en bloc spondylectomy (TES) following preoperative denosumab therapy for 8 months. Surgery was performed using a computed tomography (CT)-based navigation system that optimized accuracy by recognizing the area of the detached parietal pleura, the irregular border of the collapsed vertebra and the adjacent vertebra. Although recent studies have reported that preoperative denosumab treatment induces marked regression of GCTs of the spine, which subsequently permitted surgical resection that may otherwise have been unresectable had it not been for tumor shrinkage (7-10), there are no reports involving GCTs of the thoracic spine in a patient with idiopathic scoliosis treated by a posterior one-stage TES following preoperative denosumab therapy. In this case, analysis of the CT images after 8 months of preoperative denosumab therapy revealed the border between the vertebral body and soft tissue, indicating consolidation of the vertebral cortex. A CT-navigation system facilitated the safe use of the TES that followed.

Case report

A 35-year-old woman was referred to the Outpatient Department of Kitasato University Hospital (Kanagawa, Japan) for the evaluation of severe back pain, which started 4 months prior to her first visit to the hospital on 4th March 2015. The pain had gradually increased and persisted regardless of motion. The patient had been diagnosed with adolescent idiopathic scoliosis at 14 years old and the condition had never been treated. Although a neurological examination was negative, percussion tenderness around the thoracolumbar junction was noted.

Radiographic analysis revealed the collapse of the T11 vertebral body and idiopathic scoliosis with a Cobb angle measurement of 21˚ (Fig. 1). The spinal CT revealed an osteolytic lesion involving the T11 vertebral body and the surrounding soft tissue, which had resulted in collapse of the

vertebral body (Fig. 2). Magnetic resonance imaging (MRI) of the thoracolumbar spine showed the tumor extended toward the paravertebral soft tissue and into the left pedicle resulting in compression of the spinal cord (Fig. 3A). No additional sites of neoplasm were noted in the whole body. A needle biopsy was immediately performed to collect a sample that could be used to verify the diagnosis. Following fixation with 20% neural buffered formalin for 24 h at room temperature, paraffin-embedded, 4-μm-thick tissue sections from the biopsy specimen were stained with antibodies against vimentin (V9, Dako; Agilent Technologies, Inc., Santa Clara, CA, USA; cat. no. M6725), CD68 (PGM-1, Dako; Agilent Technologies, Inc.; cat. no. M0876), p53 (DO-7, Dako; Agilent Technologies, Inc.; cat. no. M7001) and MIB-1 (Dako; Agilent Technologies, Inc.; cat. no. M7240) antibodies for immunohistological analysis. For vimentin and MIB-1, slides were deparaffinized using PT-Link (Dako; Agilent Technologies, Inc.; cat. no. PT109) at 98˚C for 20 min, and then blocked with peroxidase-blocking reagent included in Envision FLEX Package High PH (Dako; Agilent Technologies, Inc.; cat. no. k8010) for 5 min. Dako AutoStainer plus (cat. no. S3400) was used with secondary antibody and visualization reagent included in Envision FLEX Package High PH (Dako; Agilent Technologies, Inc.; cat. no. k8010). For CD68 and p53, slides were deparaffinized with EZ Prep 10x (Ventana Medical Systems, Inc.; cat. no. 950-102), and then blocked with inhibitor reagent with 3% H_2O_2 included in the i-View DAB Universal kit (Roche Diagnostics, Basel, Switzerland, 760-041). Autostainer Ventana BenchMark XT (Ventana Medical Systems, Inc., Tucson, AZ, USA) was used with the i-View DAB Universal kit. An Olympus BX51 polarizing microscope (Olympus Corporation, Tokyo, Japan) was used to observe the immunohistological staining results at a magnification of x40-400. Pathological and immunohistochemical analyses confirmed a GCT characterized by multinucleate giant cells surrounded by neoplastic stromal cells (Fig. 4).

Based on evidence reported in a phase 2 clinical study, the patient was prescribed denosumab in weekly 120-mg subcutaneous injections for 3 weeks, followed by monthly 120-mg subcutaneous injections for 7 months (11). No adverse effects were observed. At 3 and 7 months after the start of denosumab therapy, thoracolumbar CT scans were performed and the imaging series showed the border of the vertebral body and soft tissue, including the spinal canal, indicating vertebral cortex consolidation (Fig. 5). The MRI showed that the intensity of vertebral body decreased to a level similar to normal vertebrae upon T2-weighted imaging, and compression of the spinal cord decreased owing to tumor shrinkage (Fig. 3B). The patient was scheduled for a TES of the T11 vertebra following 8 months of denosumab treatment. Preoperative angiography and embolization of the segmental artery from T10 to T12 was performed the day prior to surgery to reduce intraoperative bleeding (12). The TES for the resection of the T11 vertebra involved surgery via the posterior approach using transcranial electrical motor-evoked potentials for spinal cord neuromonitoring purposes. Immediately prior to surgery, a three-dimensional CT angiography image revealed that the anterior wall of the GCT had collapsed and the edge of the anterior wall was overlapping the adjacent vertebrae, which made the resection line irregular (Fig. 6). A CT-based navigation system (StealthStation; Medtronic Ltd., Memphis, TN, USA) was used for correct screw placement and to ensure the completion of an en bloc spondylectomy. Release of the border of the T11 vertebra was confirmed using the tip of the navigation probe. The TES was performed without any unexpected perioperative events (Fig. 7). Pathological analysis of the T11 vertebra demonstrated an absence of giant cells and stromal cells (Fig. 8). The patient is followed-up every 3 months and continues on monthly denosumab treatment without any complications or evidence of recurrence (Fig. 9).

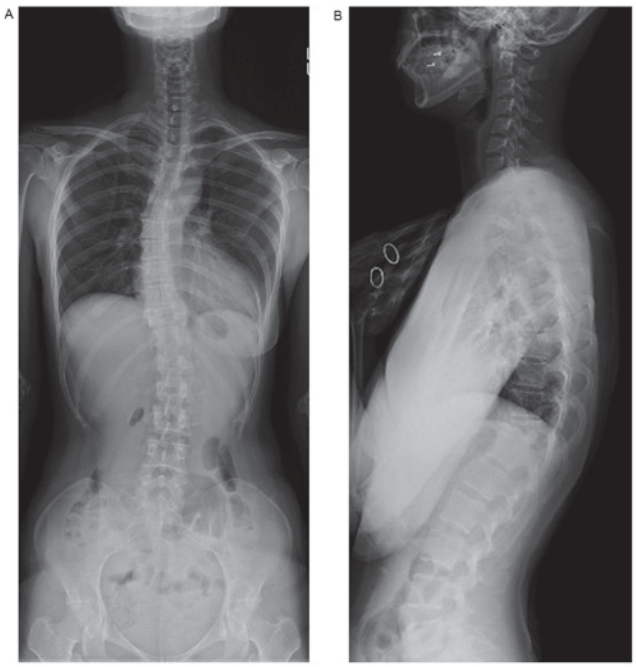

Figure 1. Plain radiographs of the whole spine prior to denosumab treatment. (A) Anteroposterior view. (B) Lateral view. The eleventh thoracic (T11) vertebral body collapsed and the idiopathic scoliosis present measured 21˚ when using Cobb's angle.

Written informed patient consent was obtained for the publication of this study.

Discussion

A GCT of the spine is a rare entity, accounting for 2.7 to 6.5% of all types of GCTs in the bone (3), and its treatment remains a challenge. Currently, there is no consensus regarding the optimal treatment, which can be surgical or conservative (non-invasive) in nature, with or without adjuvant therapy (e.g., radiotherapy, arterial embolization, argon beam coagulation, cryotherapy, bisphosphonates or interferon). A treatment strategy should be decided on by taking into consideration multiple factors, including the age of the patient, lesion location, degree of tumor involvement, neurological status, feasibility of a wide resection and the presence of metastases or fractures (13). A complete surgical resection of the tumor is recognized as the ultimate goal when treating a GCT of the spine, as when it is performed efficiently, it can result in oncological control, a negated risk of local recurrence and the obviation of comorbidities associated with repeat surgery (13-15).

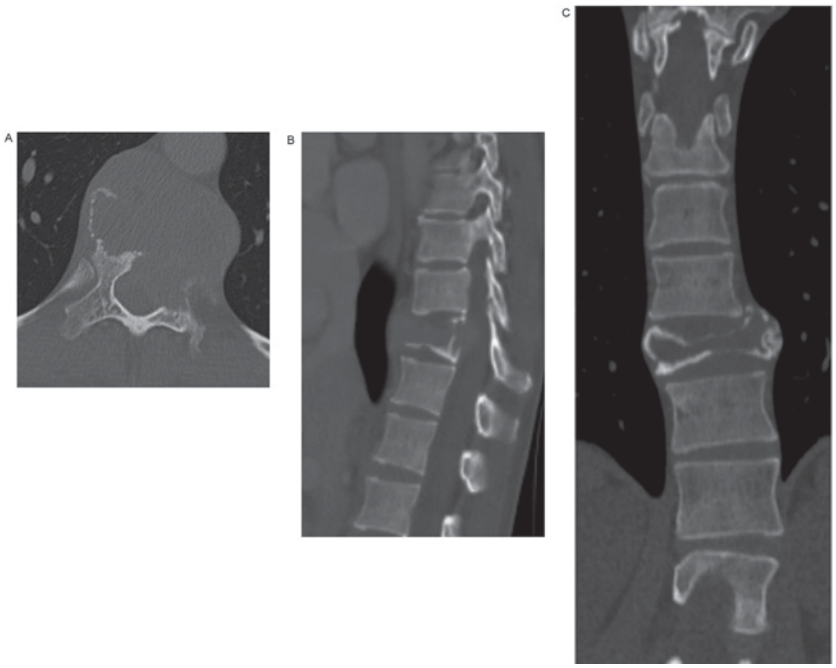

Figure 2. Computed tomography prior to denosumab treatment. (A) Axial view. (B) Sagittal view. (C) Coronal view. An osteolytic lesion involved the T11 vertebral body, which collapsed and expanded into the surrounding soft tissue.

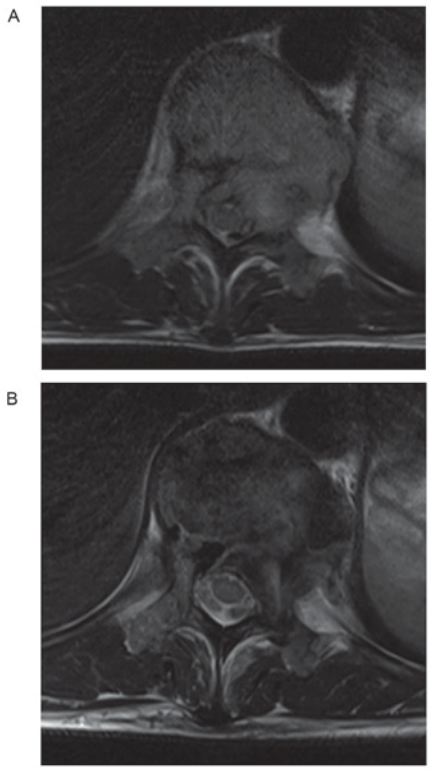

Figure 3. T2-weighted magnetic resonance images showing an axial view. (A) Prior to denosumab therapy. (B) At 8 months after denosumab therapy.

Intralesional curettage with adjuvant treatment is also an option, depending on the status of the patient, as it can provide good functional results. However, as high recurrence rates ranging from 36 to 49% have been reported (15), reoperation and radiotherapy treatment may be necessary if the treatment is not performed meticulously (13).

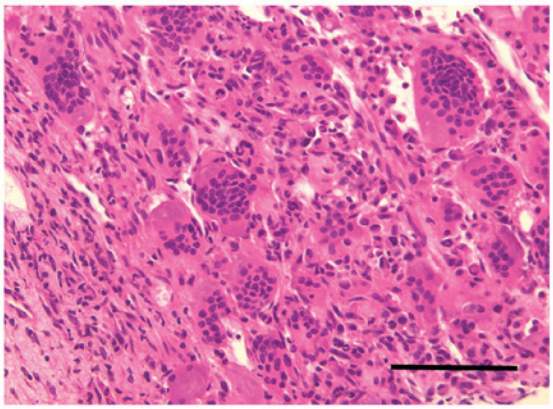

Figure 4. In hematoxylin and eosin staining, multinucleate giant cells were visible, surrounded by neoplastic stromal cells, and the diagnosis of a giant cell tumor was confirmed. Scale bar, 100 μm.

Recently, denosumab has been commonly used for the treatment of GCTs. In an open-label, phase 2 study, 86% of patients treated with denosumab therapy for 6 months were identified with an objective response, defined as >90% elimination of giant cells on histological evaluation or no radiographic progression of the lesion (16). Another phase 2 study reported no disease progression in 96% of patients after a median follow-up time of 13 months (11). Based on these results, the U.S. Food and Drug Administration approved denosumab for the treatment of adults and skeletally mature adolescents with GCTs of the bone. In the present case, the vertebral cortex consolidation that was observed via CT imaging, following treatment for 8 months with denosumab, was marked. Recent studies have reported that preoperative denosumab treatment induced marked regression of GCTs of the spine, which subsequently permitted surgical resection on

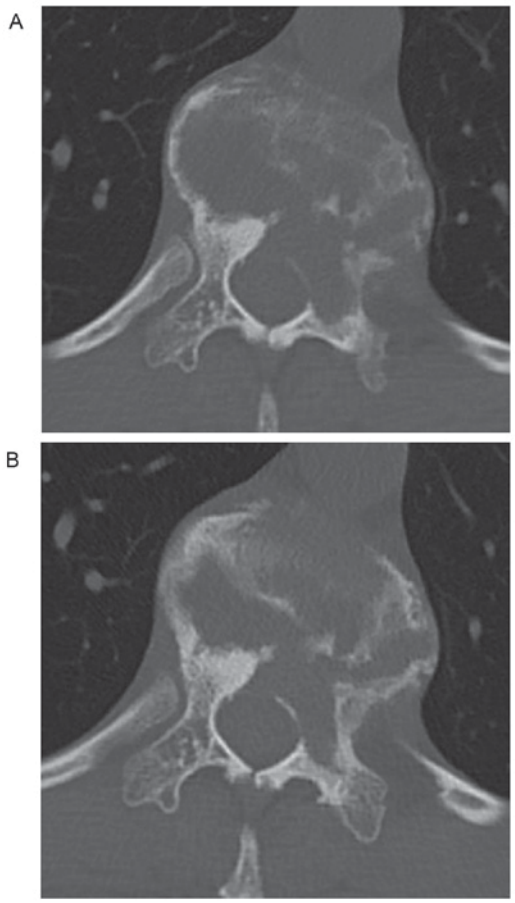

Figure 5. Computed tomography images captured during denosumab treatment. (A) At 3 months after starting denosumab therapy. (B) At 7 months after starting denosumab therapy. Consolidation of the vertebral cortex became increasingly visible as the border of the vertebral body and the soft tissue, including the spinal canal, were more easily distinguished compared with pretreatment images (Fig. 2A).

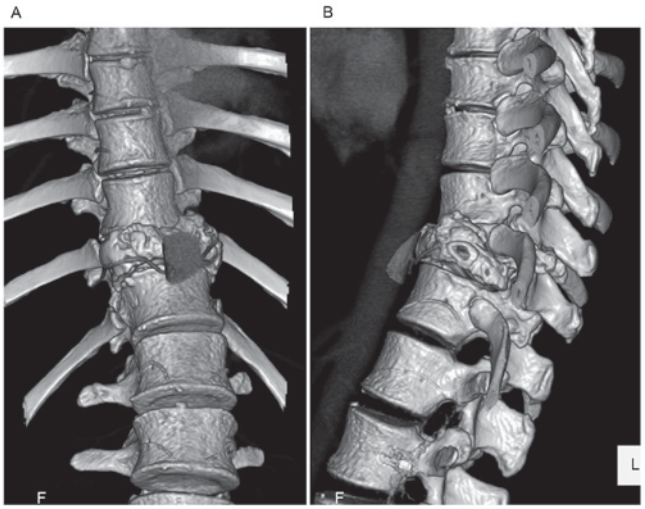

Figure 6. Three-dimensional computed tomography angiography images just prior to surgery. (A) An anterior view. (B) A lateral view. The anterior wall of T11 was collapsed and the edge of the anterior wall overlapped with adjacent vertebrae, which made the resection line irregular.

tumors that may otherwise have been unresectable had it not been for tumor shrinkage (7,8,17). Agarwal *et al* (17) reported

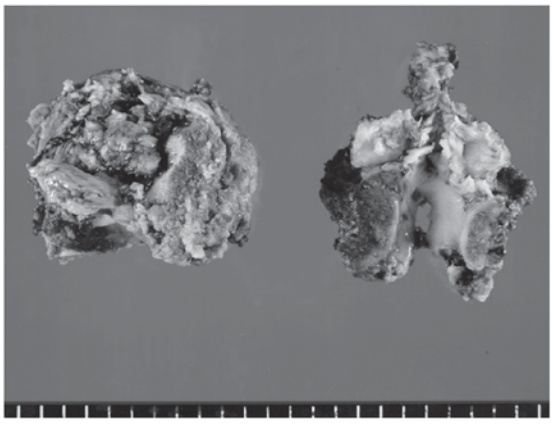

Figure 7. T11 vertebra was completely resected using a posterior approach and was separated into anterior and posterior parts.

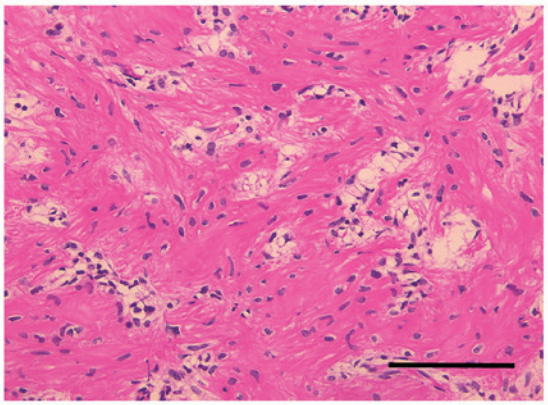

Figure 8. A pathological evaluation of the resected vertebra. Giant cells and stromal cells were not detected in the whole vertebra following 8 months of the denosumab therapy. Scale bar, 100 μm.

that a GCT at T6 had markedly shrunk after 13 months of denosumab therapy followed by a wide resection that included the lower lobe of the lung. Goldschlager *et al* (7) reported a multicenter, prospective series of 5 cases of GCT of the spine treated preoperatively with denosumab; following a mean treatment period of 6 months, denosumab reduced the tumor size by 10-40% compared with the size before treatment (7). de Carvalho Cavalcante *et al* (8) reported a case of TES for L4, following preoperative denosumab treatment for 6 months, which showed tumor regression of ~90% with vertebral body calcification. Therefore, total resection subsequent to preoperative denosumab therapy may be one therapeutic option available for the management of aggressive and locally advanced GCTs of the spine.

The duration of denosumab treatment is not only controversial prior to surgery, but also postoperatively. Following surgery, the present patient continued to receive denosumab, even after a histological evaluation of the removed vertebra, which did not contain any giant cells or stromal cells, similar to the case reported by de Carvalho Cavalcante *et al* (8). The aforementioned case involved the continuation of denosumab once every 3 months after surgery without any evidence of tumor recurrence (17), whereas other studies were of patients who stopped denosumab therapy prior to surgery (7).

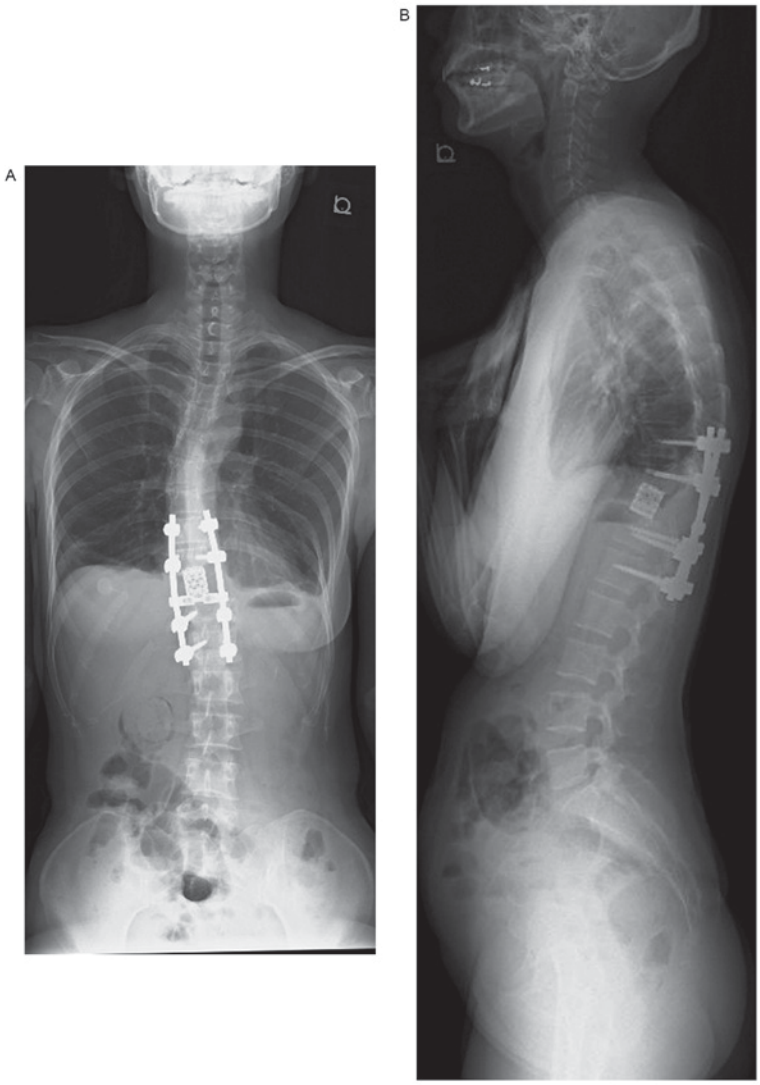

Figure 9. Plain radiographs of the whole spine 3 months after a total en bloc spondylectomy. (A) An anteroposterior view. (B) A lateral view.

Xu *et al* (6) reviewed 102 patients who underwent TES and reported that long-term postoperative bisphosphonate treatment significantly reduced tumor recurrence rate, as assessed by multivariate analysis (6). After TES, and in the absence of postoperative bisphosphonate treatment, >50% of patients experienced tumoral relapse within a mean follow-up period of 39.9 months, suggesting that spinal GCTs can indeed recur after TES. By contrast, Müller *et al* (9) reported 18 cases of GCTs in the extremities or sacrum of patients who were treated postoperatively with monthly denosumab for 6 months and who remained free of recurrent disease after a mean follow-up period of 22 months (9). Based on this evidence, and with the informed consent of all patients, the authors now use denosumab prophylactically after TES. Furthermore, the treatment plan involves discontinuing denosumab 6 months after surgery, and follow-up spinal radiographs and CT are performed every 3 months and 1 year after surgery, respectively, to evaluate for potential disease recurrence. However, a longer follow-up period is necessary.

Recently, 3 cases of high-grade sarcoma arising in GCTs of the bone in patients treated with denosumab have been reported (18,19). The potential association between sarcomatous transformations of GCT and osteosarcoma in patients receiving denosumab therapy is unclear, owing at least in part to the limited published data for this population. Long-term follow-up is therefore necessary. The clinical outcome, following completion of an adequate duration of denosumab treatment, remains uncertain. Further evidence to support how to use denosumab after the resection of spinal GCT is definitely required.

In terms of the present case, a CT-based navigation system was used as the patient presented with idiopathic scoliosis, the affected vertebra was rotated and collapsed, and the edge of the tumor had overlapped the adjacent vertebrae. Recently, clinical studies have demonstrated that CT-based navigation systems are useful as an assistance device to optimize the accuracy of pedicle screw placement during surgery in patients with scoliosis (20-22). Muscloskeletal oncologists also use CT-based navigation systems for pelvic and sacral tumor resection, suggesting its potential to increase the accuracy of tumor resections of anatomical and/or surgical complexity (23,24). For malignant bone tumors of the metaphyses of the long bones, or in iliac bones, CT-based navigation is reported to

facilitate precise planning and execution of joint-preserving tumor resections and reconstructions, resulting in good functional and oncological outcomes (25-27). Tian *et al* (28) used CT-based navigation in posterior decompression surgery for thoracic ossification of the posterior longitudinal ligament (OPLL) in order to identify the border of the vertebrae and part of the OPLL (28). In the present case, by positioning the tip of the navigation probe at the surface of the vertebra or osteotomy line, the surgeons were able to recognize the area of detached parietal pleura, the irregular border of the collapsed T11 vertebra and the adjacent vertebrae, making it possible to insert the chisel at an angle and in the necessary direction for optimizing accuracy. As a result, the TES was performed in a safe manner, particularly considering the collapsed and expanded GCT, and the accuracy of screw insertion was optimized.

In conclusion, the present study reports a case of a GCT in the spine of a patient with idiopathic scoliosis who was treated using a TES with the aid of CT-based navigation following 8 months of denosumab treatment. Denosumab can be an effective adjuvant therapy and it can reduce the complexity of TES, a major surgical procedure used for the effective treatment of GCTs of the spine.

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