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Case Report

Minimally Invasive Spinal Stabilization with Denosumab before Total Spondylectomy for a Collapsing Lower Lumbar Spinal Giant Cell Tumor

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A 21-year-old man consulted our hospital for treatment of a spinal giant cell tumor (GCT) of Enneking stage III. Lower lumbar-spine tumors and severe spinal canal stenosis are associated with high risk for surgical morbidity. Stability was temporarily secured with a percutaneous pedicle screw fixation in combination with denosumab, which shrank the tumor. Total en bloc spondylectomy was then performed 6 months after initiation of denosumab, and the patient was followed for 3 years. There was no local recurrence, and bony fusion was obtained. Minimally invasive surgery and denosumab allowed safer and easier treatment of a collapsing lower lumbar extra-compartmental GCT.

Key words: spinal stabilization, denosumab, spondylectomy, giant cell tumor

Bone giant cell tumor (GCT) is a distinct, locally aggressive neoplasm. Although histologically benign, it is associated with a high local recurrence rate and metastatic potential with predilection for the lungs [1,2]. The tumor most frequently involves the ends of long bones in skeletally mature individuals, and accounts for approximately 4% of all primary bone tumors. Spinal GCT is relatively rare, with an estimated prevalence of 2-5% of all GCTs [3].

Denosumab is a new treatment option for locally advanced or unresectable GCTs. Although the effect of this agent on GCT of long bones has been reported, its effect on spinal GCT, especially as a preoperative treatment, remains unclear. We describe a patient with spinal GCT (Enneking stage III), in which denosumab therapy with percutaneous pedicle screw (PPS) stabilization shrank and calcified the tumor, making total en bloc spondylectomy (TES) easier and safer.

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The patient was informed that data from the case would be submitted for publication, and he gave consent.

Case Report

History and examination

A previously healthy 21-year-old man presented with progressive back pain followed by right leg pain. Although he was initially diagnosed as having lumbar disc herniation and had been treated conservatively for 2 months by an orthopedic medical practitioner, his symptoms gradually worsened. He was admitted to a regional hospital because of his severe symptoms, and MRI findings raised the suspicion of a spinal tumor associated with a pathological fracture at the L5 level (he had six lumbar vertebrae). The lesion was diagnosed as a GCT based on needle biopsy results, and he was

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referred to our hospital.

On admission, the patient could neither walk nor sit because of severe low back pain, right sciatica, and numbness in his right leg. Physical examination showed neither muscle weakness nor deep tendon reflex abnormality; however, he experienced dysuria. Laboratory examinations were normal. His dysuria improved several days later after admission and bedrest.

A radiograph revealed a decreased height of the L5 vertebral body, especially on the left side, which was associated with a "winking owl" sign, suggesting a pathological fracture. Computed tomography revealed an osteolytic lesion in the L5 vertebral body, left pedicle, and superior articular process (Fig. 1A, B). MRI revealed L5 vertebral body involvement and tumor extension to the extra-compartmental area, including the spinal canal with severe canal compromise. Gadolinium enhancement showed a strong contrast effect (Fig. 1C, D). The tumor was classified as 2-9/A-D according to the Weinstein-Boriani-Biagini (WBB) classification [4], as type 5 according to the surgical classification of Tomita *et al.* [5], and as Enneking stage III. No evidence of other spinal involvement or lung metastasis was found.

Treatment. Although TES was considered the best treatment choice, two concerns were raised regarding the procedure. One was the potential for neurological deficit induced by the dissection procedure between the ventral side of the dura mater and the tumor, which severely compressed the neural structure. The other was possible tumor dissemination due to rupture of the tumor capsule during isolation of the affected vertebra from the surrounding tissue, including the psoas muscles and segmental vessels, because of the lack of the osseous barrier. Therefore, it was important to shrink the tumor before performing TES, and it was necessary to perform preoperative administration of denosumab and arterial embolization.

Nevertheless, because neurological symptoms had already appeared, it was necessary to obtain stability as early as possible. The effect of denosumab or arterial embolism would take several months to manifest. Therefore, we decided to insert a PPS to achieve temporary stability without any manipulation of the tumor vertebral body (bleeding 10 ml, time 57 min). The screws were inserted one level above and one level below L5. Because we were planning a TES 6 months later based on the recommendations in the report by de Carvalho Cavalcante *et al.* [6] and the patient was young with good bone quality, we considered that the short fixation was sufficient. After surgery, he was put on a rigid brace until TES. As an adjunctive therapy to shrink the tumor, it was necessary to perform arterial embolization as soon as possible. Radiologists embolized the feeding arteries from the bilateral L4 and L5 lumbar segmental arteries on the same day as the PPS.

This initial surgery improved his low back and leg pain dramatically. He received denosumab (120 mg subcutaneously) monthly and daily supplements of calcium (500 mg) and vitamin D (400 IU) according to the protocol of a phase 2 trial (subcutaneous denosumab was given every 4 weeks with additional doses on days 8 and 15 in cycle 1 only) [7]. The course of the effect of denosumab was followed by radiography and CT. Calcification of the affected vertebra was evident on CT at 6 months (Fig. 2A, B), and we felt that TES would be feasible. An MRI scan obtained before TES revealed marked tumor size reduction, and the tumor was classified as 2-9/B-C according to the WBB classification

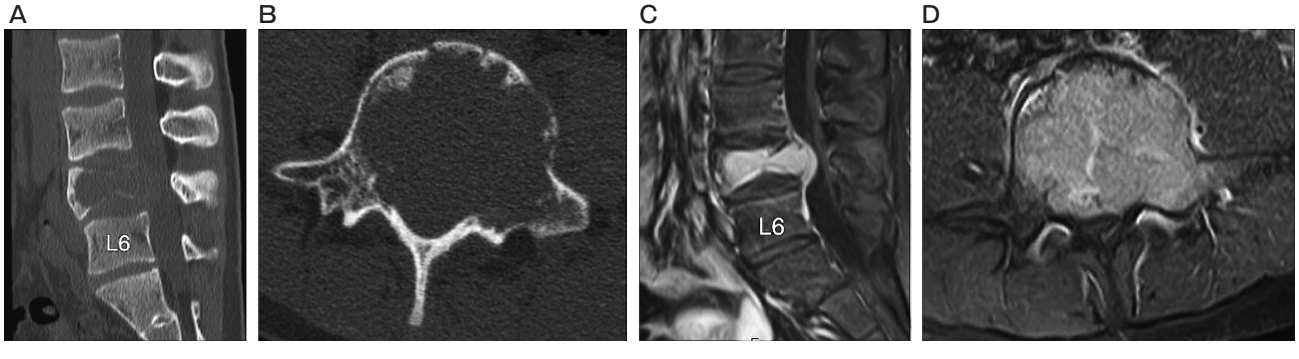

Fig. 1 Preoperative computed tomography scan revealing a pathological compression fracture of the L5 vertebral body and osteolytic lesion (**A**, **B**). Gadolinium-enhanced T1-weighted magnetic resonance image showing marked enhancement and an extra-compartmental extension of the tumor with canal occupation (**C**, **D**).

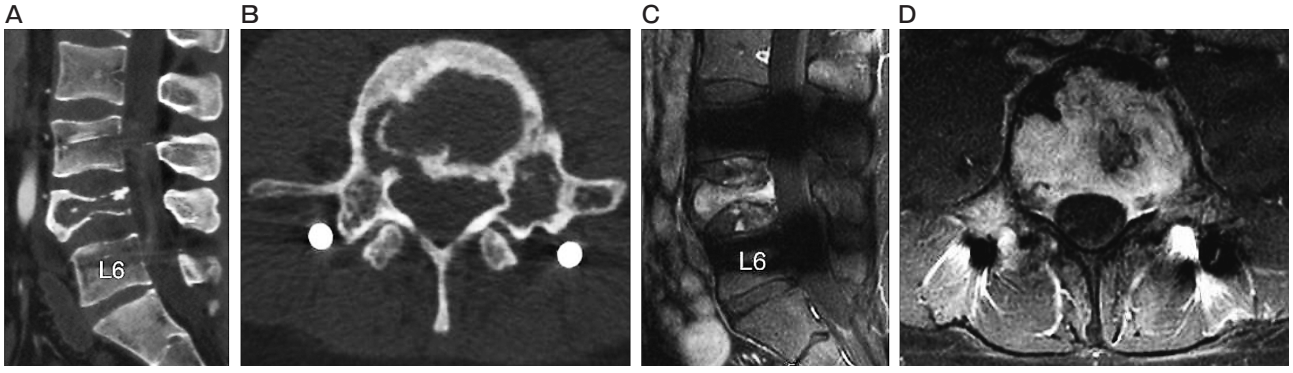

Fig. 2 Computed tomography scan after 6 months of denosumab therapy revealing calcification of the affected vertebra (**A**, **B**). Gadolinium-enhanced T1-weighted magnetic resonance image showing shrinkage of the tumor and no canal occupation (**C**, **D**).

and as type 3 according to the Tomita classification (Fig. 2C, D).

Embolization of the bilateral L4 and L5 lumbar segmental arteries was also performed 4 days before TES. TES with a combined posterior and anterior approach was performed under spinal cord monitoring using motor-evoked potentials and somatosensory-evoked potentials on the same day. During the first part of the surgery (posterior approach), we inserted pedicle screws 2 levels above (L3, L4) and below (L6, S1) the affected vertebra, and S2 alar iliac screws. Although the screws inserted in the previous surgery did not loosen, they were replaced by new screws with larger diameter. We cut both L5 pedicles with T-saws according to the Tomita technique [8] and removed the lamina and transverse process in an en bloc fashion. The lateral side of the L5 vertebra was separated as anteriorly as possible from the surrounding tissue, including the segmental vessels and psoas muscles. This procedure was less difficult than expected due to the calcification of the lateral wall of the vertebra. Dissection between the ventral side of the dura mater and the posterior longitudinal ligament was relatively easy to perform because of the marked reduction in tumor size. Discectomy was also performed. After we placed the patient in the supine position, we started the anterior approach. A midline incision was made, and a transperitoneal approach was used. Vascular surgeons exposed the aorta and the inferior vena cava and then dissected and isolated these great vessels from the surrounding tissues, which provided easy access to the affected vertebra. The affected vertebral body was isolated from the psoas muscles and removed en bloc after the anterior discectomies of L4/L5 and L5/L6. Anterior reconstruction was performed by inserting an expandable cage within the iliac cancellous bone (Fig. 3A, B). Data of spinal cord monitoring did not change throughout the procedures. The total bleeding was 2,230 ml,

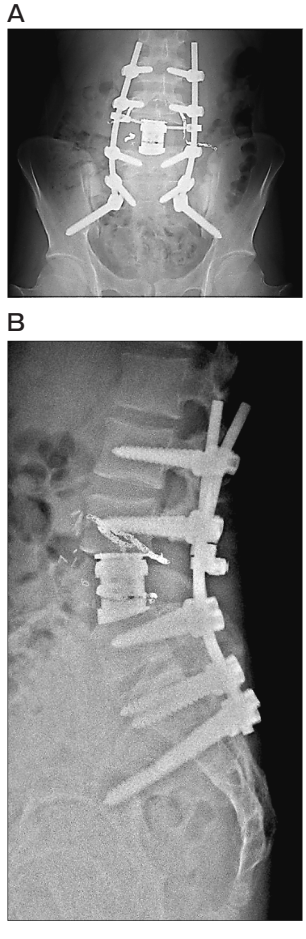

Fig. 3 Postoperative radiograph revealing posterior instrumentation with anterior reconstruction using an expandable cage (**A**, **B**).

and the total operating time was 792 min.

The patient's postoperative course was uneventful, and he was discharged 2 weeks postoperatively with no neurological deficit. Although there was no local recurrence at the 6-month follow-up, chest CT showed a lung nodule suggestive of lung metastasis, which was retrospectively detected as a very small nodule on preoperative CT. This nodule appeared to increase in size after cessation of denosumab following TES. Monthly denosumab was restarted and the size of the lesion decreased after 6 months of use. There was neither local recurrence nor regrowth of the lung lesion at the 3-year follow-up after TES.

Pathological findings. Histopathological examination of biopsy specimens confirmed the typical morphology of bone GCT, with a uniform mixture of mononuclear cells and osteoclast-like giant cells (Fig. 4A). No evidence of aneurysmal bone cyst formation, *i.e.*, so-called malignant osteoid or chondroid matrix, was found. Immunohistochemical analysis, performed according to the same procedure as in a previous report [9], demonstrated typical negative staining for receptor activator of nuclear factor κ-β ligand (RANKL) among the osteoclast-like cells with positive staining among the mononuclear cells (Fig. 4B). The surgical specimen extracted after denosumab therapy was characterized by the absence of osteoclast-like giant cells, while new bone formation was observed, indicating a good response to denosumab (Fig. 5A). Staining with RANKL showed only rare positivity among the mononuclear stromal cells (Fig. 5B).

Discussion

Spinal GCT is relatively rare, and therefore it lacks an established treatment protocol based on strong scientific evidence. According to the literature, surgery remains the preferred treatment method, and the primary goal is complete resection with wide margins in en bloc fashion (if possible), especially for Enneking stage III tumors [10]. However, two conditions, in addition to the anatomical restrictions of the spine, made en bloc resection difficult in our patient. One was extra-compartmental extension, which made it likely that an intralesional procedure would be required due to the lack of a firmer osseous barrier. The other was severe compression of the neural structures, which elevated the risk of neurological deficit [11].

Several treatment options other than en bloc resection were available when our patient was admitted. Curettage may offer a less morbid profile in comparison with en bloc resection, but it has been associated with a higher recurrence rate, ranging between 30% and 50% [12, 13]. Several adjuvant therapies have been proposed in addition to curettage or intralesional resection of GCT. Radiation therapy has been reported to be efficient as either an adjuvant or stand-alone treatment. There have been several small case series of successful GCT treatment (83-100% success rate) in the mobile spine with subtotal resection followed by radiation therapy [14]. The main risk of radiation therapy is radiation-induced sarcoma, with an incidence ranging from 11% to 17%, which is not negligible, especially for younger patients [15]. Arterial embolization can lead to the reduction or stabilization in the size of spinal GCT. Although it has been used as a preoperative treatment to reduce intra-

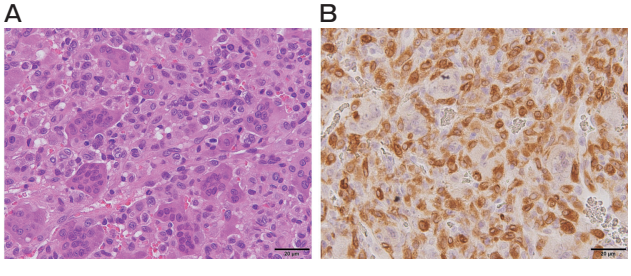

Fig. 4 Histological examination before denosumab treatment. (A) Numerous uniformly spaced, giant cells, consistent with giant cell tumors (hematoxylin-eosin staining; bar = 20 μm). (B) Receptor activator of nuclear factor kappa-β ligand (RANKL)-positive mononuclear stromal cells surrounding osteoclast-like giant cells (RANKL staining; bar = 20 μm).

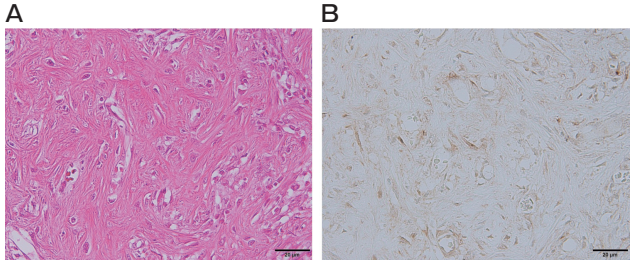

Fig. 5 Histological examination after denosumab treatment. (A) No osteoclast-like giant cells and no diffuse proliferation of short spindle-shaped cells arranged in a storiform pattern are observed. Woven bone formation is apparent (hematoxylin-eosin staining; bar = 20 μm). (B) Rare receptor activator of nuclear factor kappa-β ligand (RANKL)-positive mononuclear cells (RANKL-staining; bar = 20 μm).

operative blood loss and as a stand-alone treatment for inoperable GCT or cases with a high risk of morbidity [16], its efficacy as preoperative adjuvant therapy for Enneking stage III may be insufficient [17, 18]. Over the past decade, some experience with systemic bisphosphonate therapy for GCT was reported [19]. It was used as postoperative adjuvant therapy, especially in patients with inadequate resection, resulting in reduction of the recurrence rate. However, this therapy also has some side effects, especially with long-term use, including osteonecrosis of the jaw, atypical subtrochanteric and diaphyseal femoral fractures, and esophageal cancer [20, 21].

Denosumab is a fully human monoclonal antibody of RANKL. Because neoplastic stromal cells express high concentrations of RANKL, which activate RANK-positive osteoclastic giant cells, denosumab can prevent bone destruction by inhibiting RANK-RANKL interactions [22]. Several lines of evidence suggest the efficacy of denosumab in GCT. Thomas *et al.* reported on 35 patients with unresectable or recurrent GCT of the spine or extremities. Of these, 30 achieved favorable histological or radiological responses within 6 months after beginning denosumab therapy [23]. Chawla *et al.* also demonstrated that denosumab controlled unresectable GCT in 96% (163/169) of patients, including 21 lesions of the mobile spine [7]. In addition, they noted that, among 100 patients with surgically resectable GCT in whom surgery was expected to be associated with severe morbidity, surgery was not performed in 74% of the patients, and 62% of the patients who did undergo surgery experienced less morbidity after the procedure than was expected. The latter observation is extremely important for surgeons who plan invasive and risky surgery, including *en bloc* spondylectomy in the lower lumbar spine with Enneking stage III.

Specifically, for GCT in the mobile spine, Goldschlager *et al.* clearly demonstrated the efficacy of preoperative denosumab therapy (for 145-392 days), followed by piecemeal or *en bloc* resection in 4 patients [24]. They observed a reduction in size (10-40%) and calcification of the tumors induced by denosumab therapy. This made the surgeries safe and more effective. In our case, we initially treated the patient with embolization and stabilization with a percutaneous pedicle screw system to resolve his severe pain and impending paralysis, followed by 6 months of treatment with denosumab for subsequent *en bloc* spondylectomy. As Goldschlager *et al.* described, the tumor shrank significantly and was calcified. De Carvalho Cavalcante *et al.* also reported a patient with L4 GCT who was successfully treated with en bloc spondylectomy after denosumab treatment [6]. Yokogawa *et al.* reported 25 cases of Enneking stage III spinal giant cell tumor, one of which was treated with preoperative denosumab [25]. These reports and ours strongly suggest that preoperative denosumab therapy is effective.

In the histologic report of a phase 2 study of denosumab for bone GCT, all 20 patients showed a decrease in the giant cell concentration by ≥90%, and 65% of samples showed a marked increase in dense fibro-osseous tissue and/or new bone [26]. In our case, the histologic comparison of specimens obtained before and after denosumab treatment revealed that the typical structure of GCT had considerably changed. The GCT, RANKL-positive proliferative densely cellular stromal cells, and osteoclast-like giant cells were changed after denosumab treatment. Variable amounts of collagenous stroma were present between the interweaving fascicles of spindle cells, and the new bone showed only focal RANKL positivity. Osteoclast-like cells were rarely detectable. This indicates that denosumab not only restrains the bone resorption of GCT, but also facilitates new bone remodeling.

Although denosumab may change the treatment paradigm of GCT, surgery will remain the mainstay for resectable GCT. Since the appropriate duration of denosumab as stand-alone therapy is yet to be determined and a rapid recurrence after the cessation of long-term denosumab therapy has been reported, the use of denosumab as stand-alone therapy may tend to be prolonged, and thus may give rise to various complications, including osteonecrosis of the jaw and atypical femoral fracture [27, 28]. These complications have been reported among patients with osteoporosis who used much lower doses of denosumab. Therefore, the current indications of denosumab therapy as conservative treatment are unresectable GCT, such as recurrent GCT and GCT in the upper cervical spine or GCT in which surgery is likely to result in severe morbidity, such as GCT with sacral location.

Although there have been several reports regarding denosumab use as a preoperative treatment, concomitant temporary stabilization using a percutaneous pedicle screw system before TES has not been reported. Temporary stabilization is considered to be important to prevent

malalignment and vertebral collapse, which may disturb the TES procedure due to the expanded transverse diameter of the vertebral body and bridging callus formation, as reported by Yonezawa *et al.* [29]. The area of stabilization may depend on the vertebral level, the patient's bone quality and the area of the osteolytic lesion. Because one level above and below the affected vertebra was sufficient even in our case with lower lumbar level involvement and a severely osteolytic lesion, short stabilization may be adequate irrespective of the vertebral level of the tumor in young patients with good bone quality.

There are 2 issues to be discussed regarding the administration of denosumab. One is how long preoperative use should be. Dubory *et al.* stated that a minimum of 6 months of dosing is required and beyond that the effect of denosumab reaches a plateau [30]. Boriani *et al.* also stated that a minimum of 6 months of preoperative administration is required [31]. In our case as well, bone sclerosis was confirmed by CT evaluation at 6 months, and TES was considered. The second issue is when to terminate postoperative administration in patients with incomplete tumor resection or lung metastasis; this question remains unresolved. Palmerini *et al.* evaluated long-term efficacy and toxicity of denosumab for GCT of bone including spinal GCT [32]. In their study, tumor control and clinical benefits were observed in all patients undergoing denosumab, whereas 40% of patients discontinuing denosumab had tumor progression. On the other hand, relatively mild toxicity including dose-dependent osteonecrosis of the jaw (ONJ) were found in 9% (5/54) of patients with a 5-year ONJ-free survival of 92%. Therefore, they proposed to design of treatment algorithms that take ONJ into account; for example, assessing discontinuation approaches or schedules with inferior dose density (3 monthly and 6 monthly). Despite their proposal, the proper timing of the change in treatment is still unclear and must be decided on a case by case basis.

In conclusion, denosumab can shrink and calcify the spinal GCT, making surgery safer, less invasive, and more radical. The surgical outcome will be improved by preoperative use of denosumab. However, further investigation is necessary, because the reported cases, including ours, have short follow-up periods.

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