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Remarkable regression of a giant cell tumor of the cervical spine treated conservatively with denosumab: A case report

Toshiyuki Nakazawa[a], Gen Inoue[a,*], Takayuki Imura[a], Masayuki Miyagi[a], Wataru Saito[a], Takanori Namba[a], Eiki Shirasawa[a], Kentaro Uchida[a], Naonobu Takahira[b], Masashi Takaso[a]

[a] Department of Orthopaedic Surgery, Kitasato University School of Medicine, 1-15-1, Kitazato, Minami-ku, Sagamihara, Kanagawa, 252-0374, Japan
[b] Department of Rehabilitation, Kitasato University School of Allied Health Science, 1-15-1, Kitazato, Minami-ku, Sagamihara, Kanagawa, 252-0373, Japan

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ABSTRACT

INTRODUCTION: Wide resection of giant cell tumors at the cervical spine is sometimes extremely challenging, especially in cases where tumors extend into the nearby tissues, such as vertebral arteries, the spinal cord, or spinal nerve roots. Denosumab, a human monoclonal antibody that binds the receptor activator of nuclear factor κ-β ligand, is reported to be effective for decreasing resorption of giant cell tumor of the bone, but the detailed progress of giant cell tumors in the cervical spine extending into the nearby tissues after such treatment has not been reported.
PRESENTATION OF CASE: A 41-year-old man presented with neck pain. Computed tomography-guided needle biopsy showed numerous giant cells with a large vesicular nucleus, consistent with a giant cell tumor. Because of the extension of the tumor with involvement of the vertebral artery and surrounding tissues, denosumab (120 mg) was administered subcutaneously once per month for 24 months. Six months after denosumab treatment, follow-up computed tomography revealed a dramatic regression and osteosclerosis of the tumor. Two years after starting denosumab treatment, positron emission tomography showed no tumor recurrence.
DISCUSSION: Although the tumor was extended with involvement of the surrounding tissues and surgery following denosumab treatment was not performed, at 24 months since initiation of denosumab treatment we confirmed complete regression radiographically.
CONCLUSIONS: Denosumab may be used as an adjuvant by which to avoid or reduce the risks and morbidity of surgical treatment in patients with spinal giant cell tumors extending into nearby tissues.

1. Introduction

Giant cell tumor (GCT) of the bone is a benign primary bone neoplasm, which presents a locally aggressive behavior causing extensive lytic lesions [1]. GCT occurring in the vertebrae reportedly accounts for 2.7%–6.5% of GCTs of the bone [2]. Although total resection at an early stage remains the best treatment strategy with a low recurrence rate [3,4], the surgical treatment of GCT of the spine is sometimes challenging or unsalvageable because of the complicated surrounding anatomy. Recently, denosumab treatment had been explored. Denosumab is a human monoclonal antibody that binds the receptor activator of nuclear factor kappa-β ligand (RANKL), preventing activation of its receptor (RANK) on the surface of giant cells, osteoclast precursors, and osteoclasts. Prevention of the RANK–RANKL interaction inhibits osteoclast formation, function, and survival, thereby decreasing resorption in GCT of the bone [5]. Herein, we report the case of a patient with GCT of the cervical spine treated with denosumab, which showed remarkable regression without surgery.

2. Case presentation

A 41-year-old Japanese man presented at our hospital with cervical pain for one month. His cervical pain began without any traumatic episode and was continuous regardless of his neck motion. Neurological examination was normal. Plain lateral cervical radiographs showed a collapse of the C5 vertebral body, whose posterior wall protruded into the spinal canal (Fig. 1). Computed tomography (CT) revealed an expansive osteolytic mass lesion on the C5 vertebral body extending into the bilateral transverse foramen (Fig. 2A). ^{18}F-Fluorodeoxyglucose (fludeoxyglucose F 18) positron emission tomography (FDG-PET)/CT showed significant uptake at the C5 vertebral body (Fig. 3A). A CT-guided needle biopsy of the C5 vertebra was performed via the right posterior lamina.

* Corresponding author.
E-mail address: ginoue@kitasato-u.ac.jp (M. Takaso).

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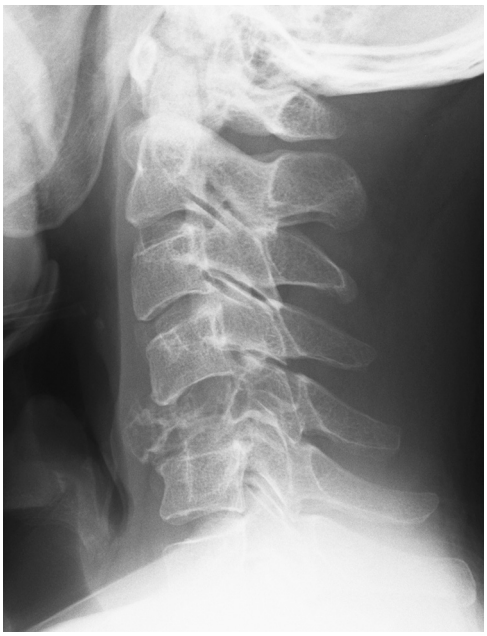

Fig. 1. Plain lateral cervical radiographs before denosumab treatment.
Plain lateral cervical radiographs showing a collapse of the C5 vertebral body, whose posterior wall protruded into the spinal canal.

The tumor was osteolytic and friable, and diagnosed histologically as a GCT of the bone (Fig. 4). Because of the extension of the tumor with involvement of the vertebral artery and surrounding tissues, denosumab treatment was planned. Subcutaneous administration of 120 mg of denosumab (Ranmark, Daiichi Sankyo Co., Tokyo, Japan) was started, and continued once per month. His neck pain disappeared completely within three months after administration, without any adverse events. CT showed dramatic regression and surrounding sclerosis of the tumor six months after denosumab administration (Fig. 2B). We decided to continue the denosumab treatment and to postpone surgical resection. During follow-up, gradual regression and surrounding osteosclerosis were noted on the previously lytic areas every 6 months for 2 years (Fig. 2A–D), without any adverse events. Following FDG-PET/CT showed no obvious uptake (Fig. 3B). Because of the markedly favorable course of this patient, we decided that further surgical resection would not be necessary. The patient is still under clinical surveillance and has remained asymptomatic for 2 years since denosumab treatment started.

3. Discussion

Denosumab is a fully human monoclonal antibody with high affinity for RANKL and therapeutic potential for the treatment of GCT of the bone [6]. In prospective randomized trials, the efficacy of denosumab for GCT has been proven, and it has been registered for treatment of GCT with the United States Food and Drug Admin-

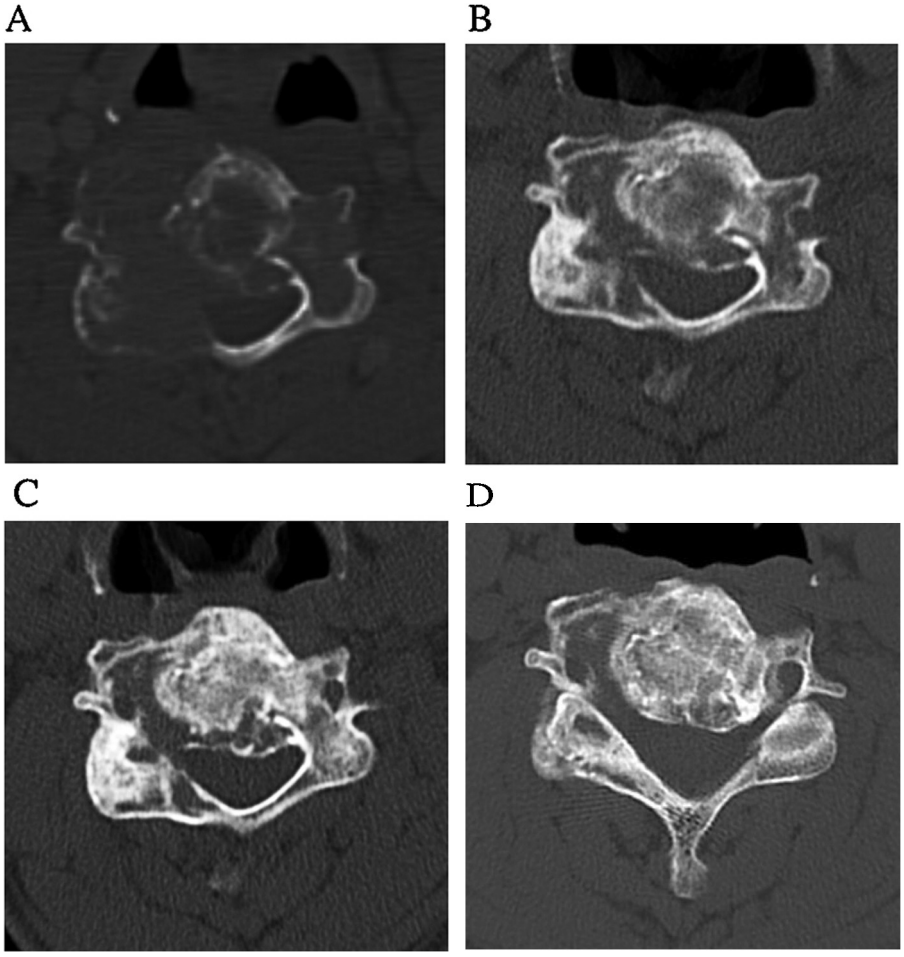

Fig. 2. Axial CT during denosumab treatment.
Axial CT of the C5 vertebra. A. Before denosumab treatment; B, 6 months; C, 12 months; D, 24 months after treatment with denosumab. Gradual regression and surrounding osteosclerosis were noted on the lytic areas, which were seen before denosumab treatment.

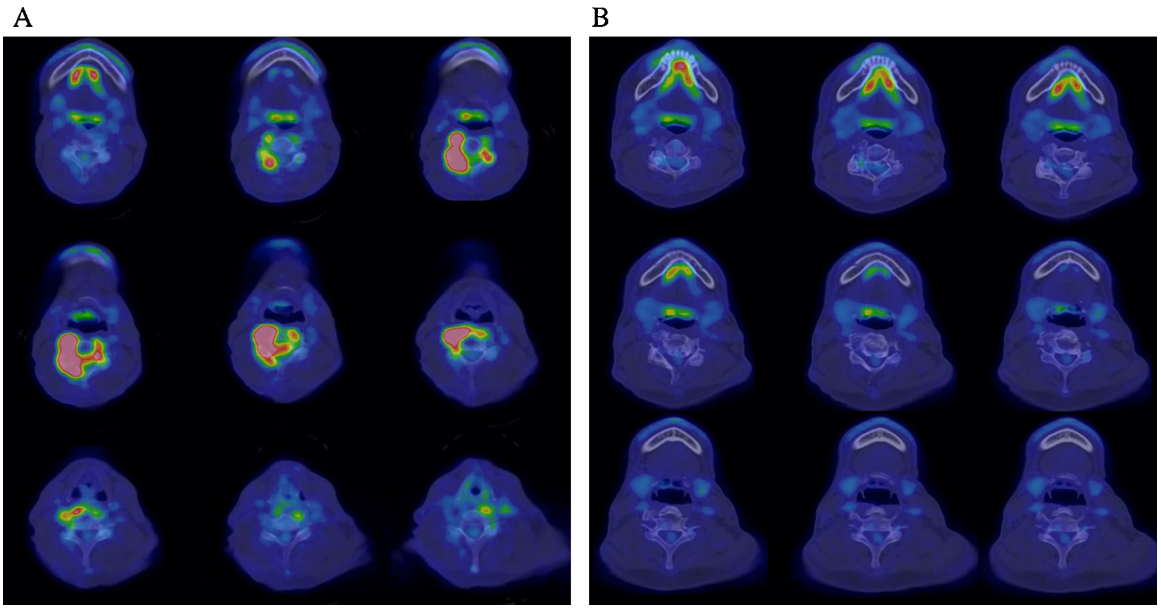

Fig. 3. Axial 18F-FDG PET/CT of the C5 vertebra.
A. Before denosumab treatment, an obviously lobulated FDG uptake was noted; B, 2 years after denosumab treatment, no uptake was seen.

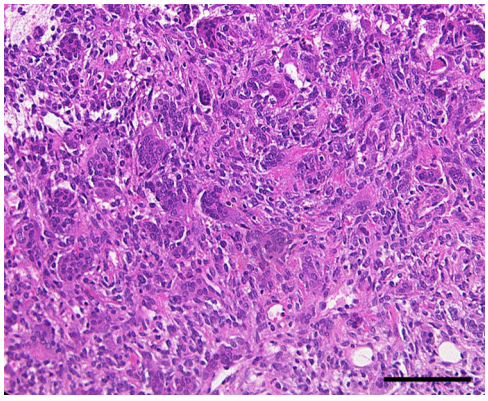

Fig. 4. Histology of the biopsy specimen before denosumab treatment.
Numerous giant cells with a large vesicular nucleus exist, which is consistent with GCT. Scale bar = 100 μm.

istration (U.S. FDA), the European Medicines Agency (EMA), and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. A previous study evaluated the efficacy of denosumab in 282 patients with GCT of the bone, and found 96% of surgically unsalvageable patients had no progression after a median follow-up of 13 months [7]. Tse et al. classified the extent of GCT of the bone into 3 stages based on plain radiographs: stage I, tumors remain confined to a small area within the bone; stage II, tumors expand to the cortex; and stage III, tumors breach the cortex and may extend into the nearby tissues [8]. They reported 7 cases with a recurrence of GCT in 44 patients with surgical resection, and all 7 cases with recurrence were in stage III, indicating that if the tumor extends into the nearby tissues it is easily recurrent. Although the present case was in stage III, its remarkable regression was sustained without local recurrence for at least 2 years. In the present case, we did not use subsequent adjuvant therapy or radiotherapy. van der Heijden et al. reported that additional radiotherapy should be limited to unresectable, residual, or recurrent cases in which treatment with denosumab is not indicated [9]. Whether additional adjuvant therapy or radiotherapy is meaningful for the patients treated conservatively with denosumab warrants further evaluation. Goldschlager et al. reported 4 cases of GCT of the spine with preoperative denosumab treatment followed by surgical resection, and reported an average 6 months' treatment with denosumab reduced tumor size from 10% to 40% before surgery [10]. There are a few cases of spinal GCT with almost complete regression with denosumab after arthrodesis without resection [11]. However, to our knowledge, this is the first report of a case with surgically unsalvageable GCT at the cervical spine treated with denosumab alone for up to two years, thus avoiding the risks and morbidity of the surgery. A complete surgical resection of the tumor is recognized as the ultimate goal when treating a GCT of the spine because when resection is done properly, it can result in oncological control, the risk of local recurrence is mitigated, and it can obviate comorbidities associated with reoperation [12–14]. Although, there reported that no giant cell or stromal cell was detected pathologically in resected vertebra after preoperative denosumab treatment for 6 months [15]. Nevertheless, the duration of denosumab treatment of these cases without resection remains controversial. Recently, a high-grade sarcoma was reported as developing in a case of tibial GCT during denosumab treatment [16]. It is still unclear whether malignant transformation is caused by denosumab treatment itself. Additionally, the clinical course after completion of denosumab treatment with adequate duration is uncertain. Further study of spinal GCT with denosumab treatment with larger numbers of patients and a longer follow up is warranted.

4. Conclusion

Denosumab can be used as an adjuvant therapy, by which to avoid or reduce the risks and morbidity of surgical treatment in patients with spinal GCTs extending into the nearby tissues, considering the adequate duration, safety, and lack of adverse events of this treatment, even though further evidence with more patients and a longer follow-up is warranted.

Conflicts of interest

None.

Funding

None.

Ethical approval

Kitasato University Medical Ethics Organization approved this case report to be published.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Author contribution

Treatment was performed by ToN, GI, TI, WS and MM. GI was a major contributor in writing the manuscript. TaN and ES participated sufficiently in the intellectual content, the analysis of data and the writing of the manuscript to take public responsibility for it. NT and MT have reviewed the manuscript, believe it represents valid work, and approved it for submission. All authors read and approved the final version of the manuscript.

Guarantor

Gen Inoue.

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