Total neurological recovery after surgical decompression and treatment with denosumab of large unresectable spinal giant cell tumour expanding to mediastinum

Chirathit Anusitviwat,1 Monchai Ruangchainikom,2 Ekkapoj Korwutthikulrangsri,2 Werasak Sutipornpalangkul2

SUMMARY
There is a controversy over the medical treatment of unresectable spinal giant cell tumour (GCT) regarding dosing and duration. We studied a spinal GCT case that had expanded to the thoracic spinal canal and mediastinum and was successfully treated by surgical decompression and denosumab. A woman in her 30s presented with weakness in both the lower extremities. MRI revealed a large tumour in the posterior mediastinum expanding from the thoracic vertebrae (T3–6), which compressed the spinal cord. The patient underwent urgent spinal decompression with instrumentation and her tissue was sent for a pathology study. Histologically and immunohistochemistry confirmed the diagnosis of GCT. Since it was an unresectable tumour, this patient was treated with denosumab. Her neurological problem resolved after 6 months of treatment. After 4 years of follow-up, the patient displayed no further progression and no side effects from long-term denosumab usage.

BACKGROUND
In giant cell tumour (GCT) of the spine, widely accepted surgical treatments include intrallesional curettage and en bloc resection to increase chances of survival.1 2 However, these treatments can lead to permanent neurological deficits and local recurrence. To reduce the likelihood of unfavourable outcomes, denosumab has been approved to treat patients with unresectable spinal GCT or when resection is likely to result in morbidity.3 4 Even surgical resection of spinal GCT combined with denosumab administration does not guarantee excellent clinical outcomes and radiological findings.4

In general, 120 mg of denosumab injected subcutaneously every 4 weeks with additional loading doses given on day 8 and 15 during the first month of therapy is prescribed for GCT.5 6 This regimen leads to elimination of tumours and consistent suppression of bone resorption. However, there is no standardised denosumab dosage and treatment duration. Previous reports have suggested ranges varying from 4 months to 55 months.7 It can be used to supplement surgery either preoperation or postoperation for spinal GCT as the long-term effects of denosumab use in patients with spinal GCT expanding to the mediastinum has not been reported.8–10

Herein, we report of a rare case of unresectable GCT of the thoracic spine that expanded into the mediastinum and spinal canal, resulting in paraplegia. The patient was treated with surgical decompression without tumour resection and long-term denosumab administration with the final result being full neurologic recovery.

CASE PRESENTATION
A woman in her 30s presented with atraumatic weakness in both her legs for 1 week and had difficulty urinating for 3 days. This patient was referred to our hospital 6 years ago. The patient provided a 10-year history of spinal surgery with instrumentation after a fall from height. The patient was referred to our hospital because of a vertebral compression fracture without neurological deficit. The patient had no other medical problems and her family history was unremarkable. On examination, she presented an old midline surgical scar and mild tenderness on her back. A neurological examination showed signs of near paraplegia (Frankel grade C) in all lower extremity muscles, positive Babinski sign and ankle/knee hyperreflexia.

INVESTIGATIONS
A plain radiographic examination of the thoracic spine showed a large soft tissue mass in the posterior mediastinal region (20.3×18.7 cm) and previous posterior instrumentation from T3–7, which was related to a history of vertebral fracture around 10 years ago (figure 1). The images also revealed right lateral displacement of the heart, mediastinal structure and trachea due to the pressure effect from the mass. Blood for complete blood count, biochemistry and tumour markers were normal except for hyperkalemia and leukocytosis. An MRI of the thoracic spine showed a large heterogeneous enhancing soft tissue mass at the posterior mediastinal region with bilateral paravertebral extension predominately on the left side with a size of about 18.4×18.0×10.4 cm. This mass protruded from the T4 vertebra, leading to a pressure effect of thecal sac at lower T3 to upper T5 vertebrae and total obliteration of the spinal canal, which is suggestive of myelopathy at the T3–5 vertebral level (figure 2). This mass also involved the left lateral chest wall with multiple left posterior ribs erosion. The rest
of her spine MRI showed no other abnormalities. A CT scan also demonstrated a large extrapulmonary mass with internal calcification at the posterior mediastinum extending to the bilateral paravertebral area (figure 3). Last, a whole-body bone scan showed no evidence of bony metastasis.

DIFFERENTIAL DIAGNOSIS
From her clinical condition and imaging studies, we initially considered this tumour to be malignant such as soft tissue or primary bone sarcoma. Due to an incomplete cord compression condition, our surgical plan was urgent decompression via laminectomy. However, we were unable to remove the tumour due to abundant fibrosis from a previous spinal surgery. Therefore, we only carried out partial laminectomy of T3 and T6 with posterior instrumentation T2 to T8 and transpedicular biopsy at T4. A histological examination showed low-grade spindle cells with giant cells, which were unlikely to be malignant. Due to a low tissue sample yield for further investigation, we had to re-do tissue biopsy. Finally, both histological and immunohistochemistry tests (online supplemental file 1) confirmed diagnosis of GCT of the bone with an absence of a mitotic figure (figure 4). Furthermore, the MIB-1 labelling index (Ki-67) was examined and determined to be in the range of 0.5%–1%.

TREATMENT
In general, the standard treatment for GCT of the bone is wide-margin surgical excision. However, after discussions with the cardiothoracic surgeon about mediastinal mass, our group agreed that this is an unresectable GCT. We provided information on available treatment options for unresectable tumours. The patient voluntarily agreed to receive denosumab, and the consent form was obtained. The patient received a subcutaneous injection of denosumab (120mg) on day 0, 7, 14, 28 and every 4 weeks for 12 months thereafter. This was followed by denosumab administered every 8 weeks for 10 months. After this, the patient received denosumab every 12 weeks for 28 months, and this treatment is still ongoing. The patient is also on an oral daily supplement containing calcium and vitamin D.

OUTCOME AND FOLLOW-UP
In a 2-month follow-up, the patient showed neurological improvement as she was able to ambulate with a walker. Six months later, the patient was able to walk without gait aid and had full neurological recovery. A CT scan done at the 7-month...
follow-up did not show any significant reduction in tumour mass. After 4 years of follow-ups, both CT and MRI imaging showed no significant reduction in tumour size in the mediastinum, but there was a slight decrease in primary tumour mass (Figure 5). Currently, the patient has not developed any further neurological problems and displayed no side effects from long-term denosumab usage.

**DISCUSSION**

In this case, the patient had a large unresectable spinal GCT expanding into the posterior mediastinum that involved the thoracic spinal canal with cord compression, resulting in paraplegia. The patient was treated with standalone denosumab after spinal decompression with posterior instrumentation and without any attempt of tumour resection. The neurological status gradually improved and fully resolved within 6 months of denosumab administration. The interesting point is that this patient had an adequate clinical response but not radiological outcomes. The improved clinical conditions could be the result of urgent decompression and altered loading of the spinal column following posterior instrumentation. Although, repeated biopsy for evaluating histological response was not performed after denosumab administration. The neurological condition of the patient remained stable without any side effects from denosumab usage over 4 years of follow-up.

GCT of the spine is usually located in the vertebral body from where it continues to extend to other parts of the spine, including the lamina, spinous process, and even the paravertebral area. Patients with spinal GCT usually present back pain at the site of tumour or neurological deficit before definite diagnosis. As in this case, the tumour destroyed all spinal columns of thoracic vertebrae and invaded the vital adjacent structures (not only the spinal cord and nerve roots but also the intramedullary organs). The surgical removal of the tumour by total en bloc spondylectomy is an effective method against spinal GCT. This method also leads to improvement in neurological function in patients with complete paralysis before surgery. However, not all patients were suitable to undergo an extensive invasive surgical procedure.

This tumour was defined as an unresectable lesion as it was too large to achieve a wide surgical margin in a difficult anatomical location, leading to potentially severe morbidity and mortality after surgical resection. Therefore, systemic treatment is advised to reduce severity of the disease and stop tumour progression.
One of the effective systemic treatment options is denosumab. A previous study reported that 96% of patients with unresectable lesions showed no signs of further progression after denosumab was given every 4 weeks with a median follow-up of 13 months.13 Denosumab is a fully humanised monoclonal antibody for the receptor activator of nuclear factor kappa-B ligand, which inhibits osteoclastic activity.13 For treatment of GCT of the bone, denosumab causes new bone formation and downgrades a high-grade lesion to a lesser grade by increasing the rim of ossified bone on the periphery.14 15 A formed osseous rim helps decrease the possibility of injury to adjacent neurovascular structures, facilitates ease of surgical resection and prevents tumour contamination.8 Moreover, there have been reports of successful use of denosumab in recurrent, metastatic and unresectable lesions, especially in spinal GCT.5 15 To date, there is still no standard optimal dose and duration of denosumab use in treating spinal GCT. Various doses and durations in previous studies are shown in table 1. The efficacy of long-term treatment and whether GCT remains sensitive with denosumab is still unclear. Interestingly, our case demonstrated disease control after denosumab injection, with a reduced interval from weekly to every 3 months for more than 50 months. However, a previous study reported complications, including osteonecrosis of the jaw, atypical femoral fracture, skin rash and hypophosphatemia following long-term denosumab use with a median time of 54 months for unresectable GCT.16 There were no complications or instances of denosumab toxicity in our patient. This implies that our denosumab regimen is able to control spinal GCT in patients who cannot have the entire tumour removed.

Patient's perspective
I remember that I felt hopeless when I could not move my legs. After the first operation, I still could not move my leg and was afraid that I would be permanently disabled. Surprisingly, 6 months after the operation, the weakness subsided, and I could walk independently. Currently, I am happy with the results even if I have to come to the hospital for drug injections every 3 months.

Learning points
► Patients with aggressive spinal giant cell tumours (GCTs) may exhibit neurological deficit or mediastinal mass.
► Neurological deficits resulting from unresectable spinal GCT can be improved with use of our denosumab regimen.
► Long-term denosumab usage ceases GCT progression and seems to be safe.
► A definite conclusion about our denosumab regimen as standard treatment for unresectable spinal GCT cannot be made.

Acknowledgements The authors are sincerely thankful to Dr. Soranart Muangsomboon, Instructor and Anatomical Pathologist, Department of Pathology, Faculty of Medicine, Siriraj Hospital, for assistance in histological findings review, and Aditya Rana, from the Faculty of Medicine, Siriraj Hospital, Mahidol University, for assistance in proofreading the English of this report.

Contributors CA: conception, manuscript writing and review. EK and MR: editing the manuscript. WS: design the study, data acquisition, manuscript writing and review. All authors read and approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iD Chirathit Anusitisriwat http://orcid.org/0000-0001-6730-7486

REFERENCES
1 Yin H, Cheng M, Li B, et al. Treatment and outcome of malignant giant cell tumor in the spine. J Neurooncol 2019;124:275–81.
2 Lin F, Lin N, Teng W, et al. Recurrence of giant cell tumor of the spine after resection: a report of 10 cases. Orthop Surg 2018;10:107–14.
3 Biermann JS, Chow W, Reed DR, et al. NCCN guidelines insights: bone cancer, version 2.2017. J Natl Compr Canc Netw 2017;15:155–67.
4 Goldschlager T, Dea N, Boyd M, et al. Giant cell tumors of the spine: has denosumab changed the treatment paradigm? J Neurosurg Spine 2015;22:526–33.
5 Thomas D, Henshaw R, Skibutis K, et al. Denosumab in patients with giant-cell-tumor of bone: an open-label, phase 2 study. Lancet Oncol 2010;11:275–80.
6 Hindskoke E, Errani C, Doddarangappa S, et al. Is a short-course of preoperative denosumab as effective as prolonged therapy for giant cell tumor of bone? Clin Orthop Relat Res 2020;478:2522–33.
7 Luengo-Alonso G, Mellado-Romero M, Shenae S, et al. Denosumab treatment for giant-cell-tumor of bone: a systematic review of the literature. Arch Orthop Trauma Surg 2019;139:1339–49.
8 Singh VA, Puri A. The current standing on the use of denosumab in giant cell tumour of the bone. J Orthop Surg 2020;28:239849902097957.
9 Duan P-G, Sheng Y-H, Deng C-H, et al. Recurrent giant cell tumour of the thoracic spine managed by total en bloc spondylectomy and denosumab therapy: a case report. BMC Musculoskelet Disord 2020;21:105.
10 Zhang R-Z, Ma T-X, Qi D-W, Zhao M, et al. Short-term preoperative denosumab with surgery in unresectable or recurrent giant cell tumor of bone. Orthop Surg 2019;11:1101–8.
11 Martin C, McCarthy EF. Giant cell tumor of the sacrum and spine: series of 23 cases and a review of the literature. Iowa Ortho J 2010;30:69–75.
12 Pahlapak P, Sangsin A, Sirichatchavee W, et al. Total en bloc spondylectomy is worth doing in complete paralysis spinal giant cell tumor, a minimum 1-year follow-up. J Orthop Surg 2021;29:239849902110059.
13 Chawla S, Henshaw R, Steeger L, et al. Safety and efficacy of denosumab for adults and skeletal mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. Lancet Oncol 2013;14:301–8.
14 Hakozaki M, Tajo A, Yamada H, et al. Radiological and pathological characteristics of giant cell tumor of bone treated with denosumab. Diagn Pathol 2014;9:111.
15 Branstetter DG, Nelson SD, Manivel JC, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. Clin Cancer Res 2012;18:4415–24.
16 Palmieri E, Chawla NS, Ferrari S, et al. Denosumab in advanced/unresectable giant-cell tumour of bone (GCTB): for how long? Eur J Cancer 2017;76:118–24.
17 Law GW, Yeo NEM, Howe TS, et al. Recommenement of denosumab for unresectable giant cell tumor of the cervical spine: a case report. Spine 2018;43:E551–6.
18 Nakazawa T, Inoue G, Imura T, et al. Remarkable regression of a giant cell tumor of the cervical spine treated conservatively with denosumab: a case report. Int J Surg Case Rep 2016;24:22–5.
19 Mattei TA, Ramos E, Rehman AA, et al. Sustained long-term complete regression of a giant cell tumor of the spine after treatment with denosumab. Spine J 2014;14:e15–21.
Case report

20 Bukata SV, Blay J-Y, Rutkowski P, et al. Denosumab treatment for giant cell tumor of the spine including the sacrum. Spine 2021;46:277–84.

Copyright 2022 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit https://www.bmj.com/company/products-services/rights-and-licensing/permissions/
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:
▶ Submit as many cases as you like
▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
▶ Access all the published articles
▶ Re-use any of the published material for personal use and teaching without further permission

Customer Service
If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow.