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

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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 intralesional 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 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 caused 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



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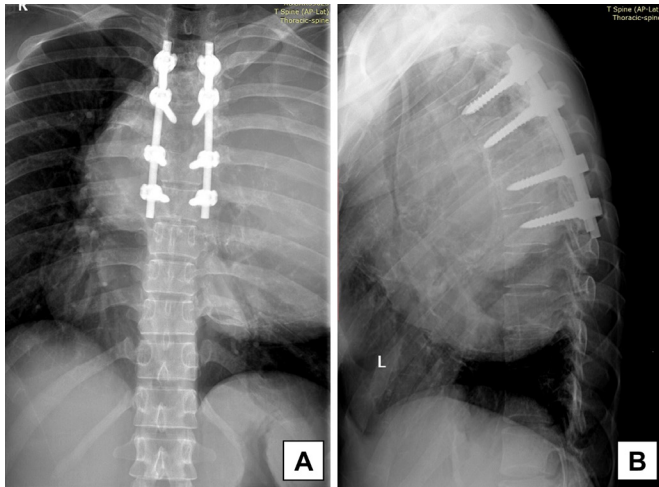


Figure 1 Plain radiography of the thoracic spine showed a large soft tissue mass at posterior mediastinal region. (A) Anteroposterior view and (B) lateral view.

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

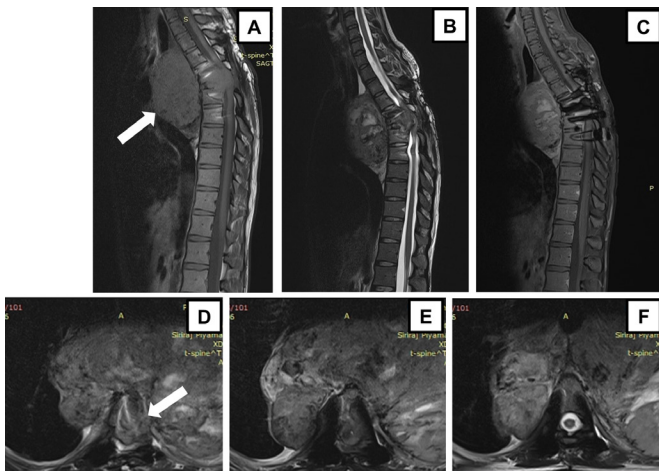


Figure 2 MRI of the thoracic spine demonstrated large heterogeneous enhancing soft tissue mass (white arrow) epicentre at the posterior mediastinal region, which directed invasion to T4 pressure effect to thecal sac at lower T3 to upper T5 vertebral level with total obliteration of spinal canal. (A) The T1-weighted image showed hyposignal intensity. (B) The T2-weighted image showed inhomogeneous signal intensity. (C) MRI T1-weighted with contrast showed inhomogeneous enhancement. (D) Axial T2-weighted image at T4 showed a mass (white arrow) with an occupied spinal canal resulting in spinal cord compression. (E) Axial T2-weighted image at T5 also showed a mass with an occupied spinal canal. (F) Axial T2-weighted image at T6 showed a mass in the mediastinum without occupying the spinal canal.

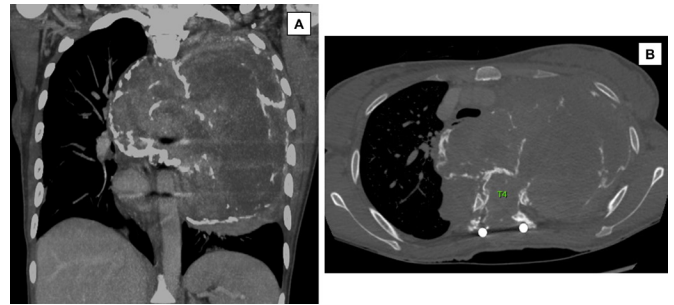


Figure 3 (A) Coronal and (B) axial CT images demonstrated a large extrapulmonary mass with internal calcification involving the mediastinum and thoracic spine extending to the bilateral paravertebral area.

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 (120 mg) 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

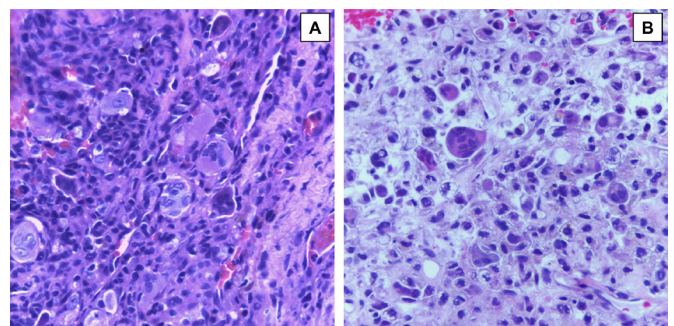


Figure 4 Histological examination (H&E, 400x) of (A) first-time tissue biopsy and (B) second-time tissue biopsy.

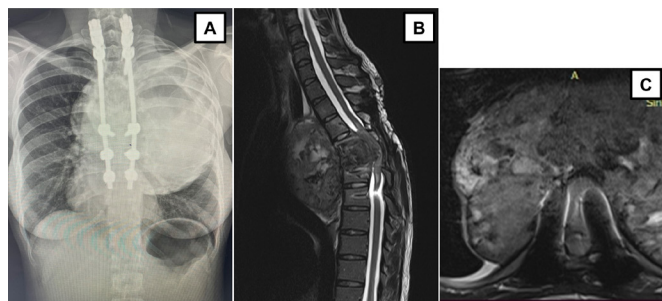


Figure 5 The thoracic spine anteroposterior (AP) view images (A) after a 4 year follow-up showed a large mass in the chest wall without significant reduction in tumour size. However, in MRI of the thoracic spine demonstrated slightly decreased tumour mass in the spinal canal. (B) MRI T2-weighted showed mass without significant reduction in size in the mediastinum. (C) Axial T2-weighted image at T4 also showed a mass with a less occupied spinal canal.

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.⁴ 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.⁹ Patients with spinal GCT usually present back pain at the site of tumour or neurological deficit before definite diagnosis.¹¹ 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.¹² 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.

Table 1 Dose and duration of denosumab for treating spinal GCT

First author	Location	Dose	Duration (months)	Results	Side effects
Duan P-G <i>et al</i> ⁶	T11 and T12 vertebra	Not reported	12	No progression with calcification and regression of tumour	Not reported
Law GW <i>et al</i> ¹⁷	C3 vertebra	120 mg monthly for 9 months and every 2 months for 1 year	21	No progression during treatment, Disease progression at 6 months after stop denosumab	Not reported
Goldschlager T <i>et al</i> ⁴	C, T and L vertebra	120 mg monthly with initial loading dose on days 8 and 15	6	No progression with calcification and regression of tumour	None
Nakazawa T <i>et al</i> ¹⁸	C5 vertebra	120 mg monthly	24	Surrounding sclerosis and regression of tumour	None
Mattei TA <i>et al</i> ⁹	C2 vertebra	120 mg weekly for 3 weeks then 120 mg monthly	16	Newly formed cortical bone with regression of tumour	None
Bukata SV <i>et al</i> ²⁰	C, T, and L vertebra	120 mg monthly with initial loading dose on days 8 and 15	34–74	Complete response 12.6%, partial response 35.9%, and progression 1%	None

AFF, atypical femoral fracture; C, cervical; GCT, giant cell tumour; L, lumbar; ONJ, osteonecrosis of the jaw; T, thoracic.

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.

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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.

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