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RECOMMENCEMENT OF DENOSUMAB FOR UNRESECTABLE GIANT CELL TUMOUR OF THE CERVICAL SPINE: A CASE REPORT

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ABSTRACT

Study Design

Case report

Objective

To highlight that rapid progression or recurrence of giant cell tumour of the bone (GCTB) can still occur with cessation of Denosumab in the management of unresectable GCTB even in cases with prior demonstration of excellent response to treatment and stable disease over a protracted length of surveillance despite dose reduction. The close proximity of unresectable GCTB to vital structures makes it prudent that we monitor these patients closely given its locally aggressive nature.

Summary of Background Data

Cervical spine GCTB is extremely rare. Unresectable GCTB has historically been a challenge to treat due to the lack of prospective, randomised clinical trials to guide treatment. Radiotherapy has fallen out of favour due to the risk of malignant transformation, especially since most GCTB patients are young.

In recent years, improved understanding of the receptor activator of nuclear factor-κB ligand (RANKL) in the pathophysiology of GCTB has led to the use of Denosumab in patients with recurrent / unresectable / metastatic GCTB and in patients whom surgical resection carries a high morbidity.To date, the optimal dosage and duration of therapy in the treatment of GCTB is unknown.

Methods

We report a case of cervical spine GCTB in a 53-year-old male with positive surgical margins managed with Denosumab.

Results

This is the first reported case of a cervical spine GCTB managed with Denosumab showing excellent response to treatment, recurrence of disease post cessation of Denosumab despite earlier satisfactory disease control and stabilization achieved even with dose reduction and again an excellent response with recommencement of the drug.

Conclusion

Denosumab is an excellent option in patients with unresectable GCTB or when surgery will result in excessive morbidity. However, further studies are required to determine optimal dosing, treatment duration, side effect profile and whether Denosumab is truly able to achieve partial or complete disease remission in the long run.

Key Words

Denosumab; giant cell tumour; cervical spine; recurrence; unresectable; morbidity; disease control; optimal dosing; duration of treatment; side effects

Level of Evidence:4

Introduction

Giant cell tumors of the bone (GCTB) are benign, locally aggressive tumours with a predilection for long bones and are extremely rare in the cervical spine.[1-5] They are typically seen in adults aged 20-50 with a peak incidence between ages 20-30.[6]

Surgery is the treatment of choice for resectable GCTB in view of its high curative rates for localised disease.[7] In cases with positive surgical margins, recurrence, unresectable GCTB or where surgery is contraindicated, various other treatment modalities have been used. While reportedly able to achieve good long-term local control rates, radiotherapy is limited by the risk of malignant transformation and development of secondary malignancies.[8-12]

Denosumab is highly effective in the treatment of GCTB and was approved by the US Food and Drug Administration (FDA) in 2013 for recurrent, unresectable, metastatic GCTB or for patients in whom surgery will result in excessive morbidity.[13-15] The optimal dosage and duration of treatment with Denosumab however, is unknown.

Case Presentation

A 53-year-old Indian male presented with an atraumatic, acute axial neck pain without neurological symptoms to a tertiary hospital in December 2011. On examination, he had midline spinal tenderness over the mid-cervical region with full range of motion of the neck. Neurological examination was normal. Xrays showed a possible C3 pathological fracture (Figure 1). Haematological and biochemical

results together with tumour markers were normal except for a mildly raised erythrocyte sedimentation rate of 16.

Cross sectional imaging (Figures 2-4) showed a C3 vertebral body lytic lesion extending into both pedicles and an associated pathological fracture. Staging CT and whole body bone scan showed no metastases.

Operation

C3 anterior corpectomy with fibular allograft reconstruction, fusion and C2-C4 anterior spine fixation was performed in January 2012.Postoperative Xrays are shown in Figure 5.

Intraoperatively, the tumour was found infiltrating the right vertebral artery with collapse of the C3 vertebral body. Complete resection of the tumour was thus not possible and corpectomy of C3 extending to the lateral body was performed.

Subsequent CT (Figure 6) and MR angiogram 3.5 months post-operatively showed local extension of the residual tumour invading into the right transverse foramen with partial encasement and displacement of the vertebral artery with no compromise to the patency of the artery. Denosumab was chosen over surgical resection in view of the likelihood of injury to the vertebral artery and high risk of a posterior circulation stroke.

Subcutaneous monthly Denosumab 120mg injections were commenced at 4 months post-operatively for 9 months. Regular CT scans at 3-monthly intervals showed good response to treatment (Figure 7).

We then reduced his Denosumab injections from monthly to 2-monthly intervals for 1 year. Repeat CT scans (6-monthly) showed no disease progression despite dose reduction (Figure 7) and Denosumab was ceased (after 21 months).

Interval disease progression was seen at 6 months post cessation of Denosumab, prompting recommencement of the monthly subcutaneous 120mg Denosumab injections. Good response was again seen on subsequent CT scans (Figure 8).

Our patient remained clinically well throughout the 4.5-year follow-up timeframe with complete resolution of neck pain since 3 months post surgery and no associated adverse events.

Discussion

Denosumab is an excellent option in patients with unresectable GCTB or for patients in whom surgery will result in excessive morbidity.[13-15] However, the optimal dose and duration of treatment is unclear and there are no long-term studies to assess whether GCTB can continue to remain sensitive to Denosumab or whether its efficacy decreases over prolonged use.

Denosumab, while able to control the disease to a large extent, could not completely eliminate it. Thus lies the importance of complete clearance of disease at time of surgery. Unfortunately, in cases like ours where the patient may not be willing to accept the risk of morbidity, Denosumab remains an excellent option even if started sometime after surgery. We started treatment at 4 months post-operatively and were able to achieve disease control.

Long term effects of Denosumab in patients with normal density bone is unknown. This is especially relevant in the treatment of GCTB as most of the patients are young.[6] There has been reports of profound osteopetrosis in RANK-deficient mice and osteopetrotic-like bone in a 10-year-old girl with metastatic GCTB after 20 months of Denosumab treatment.[16-17] Our case demonstrated similar efficacy of the drug despite halving the dose after the disease has stabilised. This may be one way to minimise long-term side effects post disease stabilisation.

Further studies are required to determine the optimal dosing, duration of treatment, side effect profile and whether Denosumab is truly able to achieve partial or complete disease remission in the long run.

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Figure Legends:

Figure 1: C-spine Xrays (AP, lateral views) showing a possible C3 pathological fracture

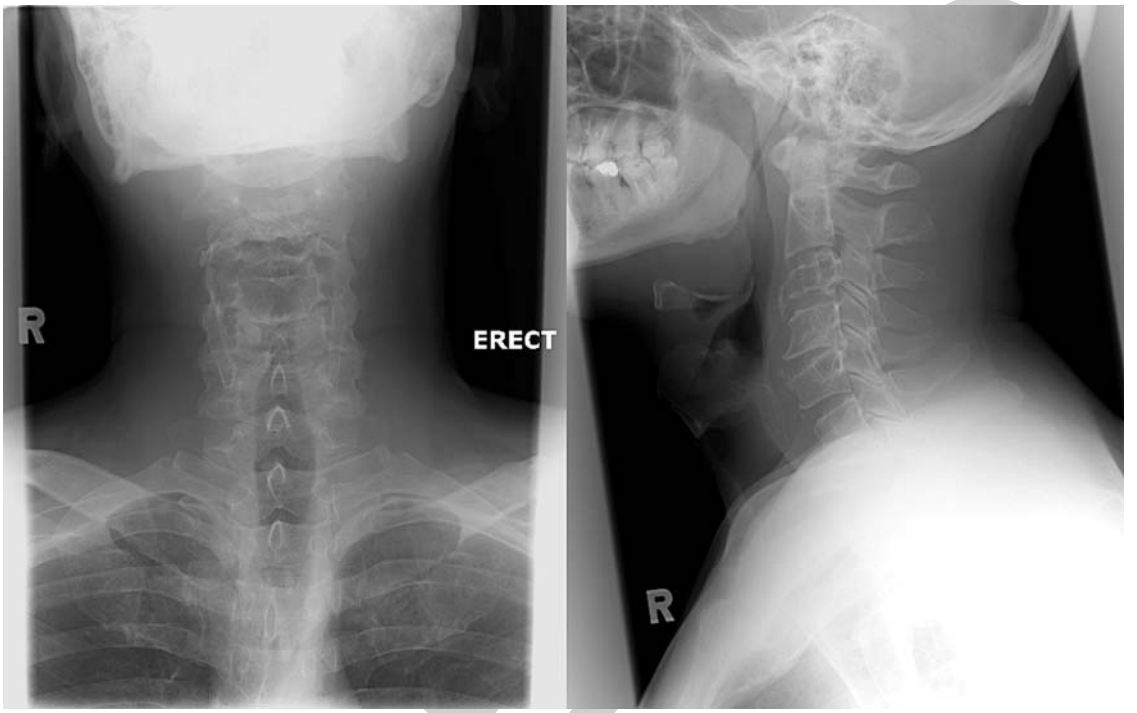

Figure 2: MRI C-spine saggital cuts showing a C3 body pathological fracture with complete loss of fatty marrow signal

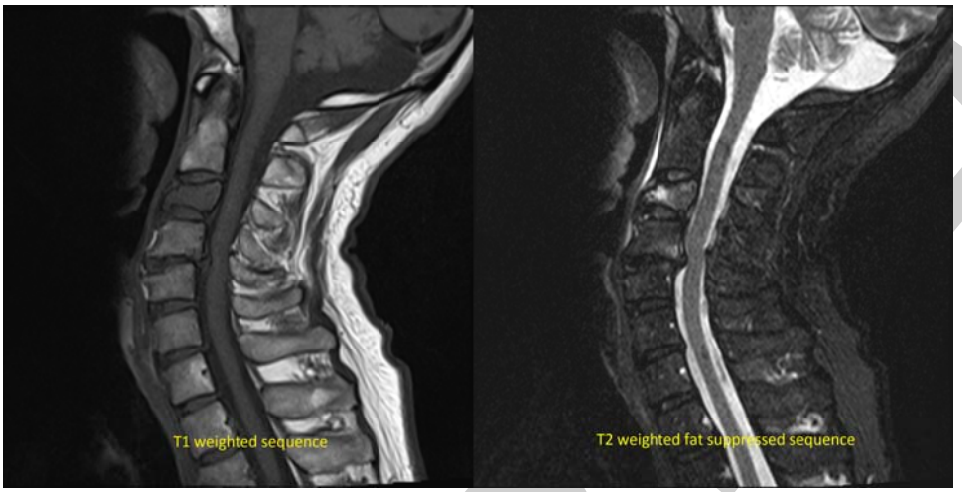

Figure 3: T2 weighted sequence, transverse cuts at level of C3

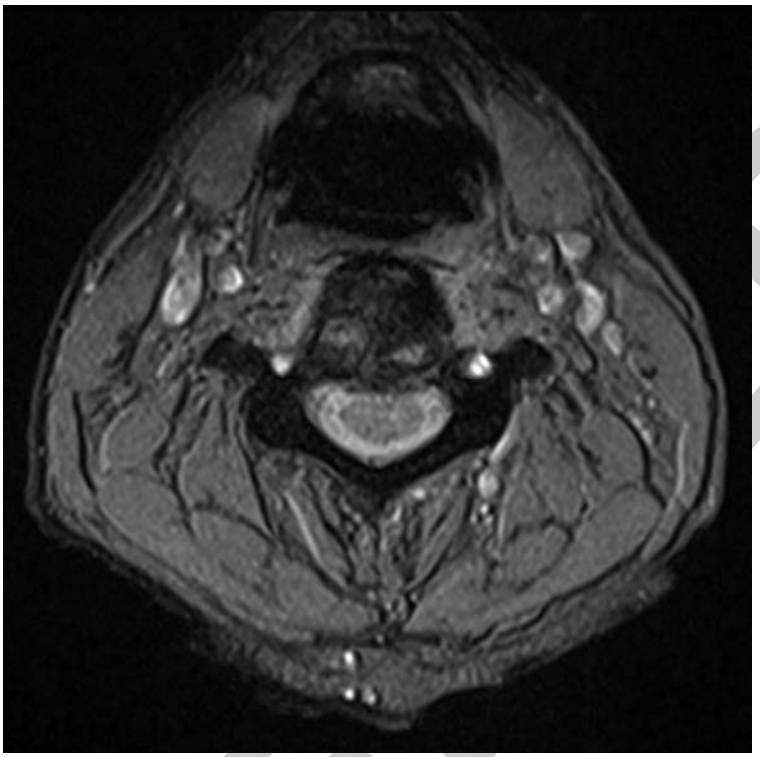

Figure 4: CT C-spine showing a lytic lesion in C3 vertebral body with an associated pathological fracture

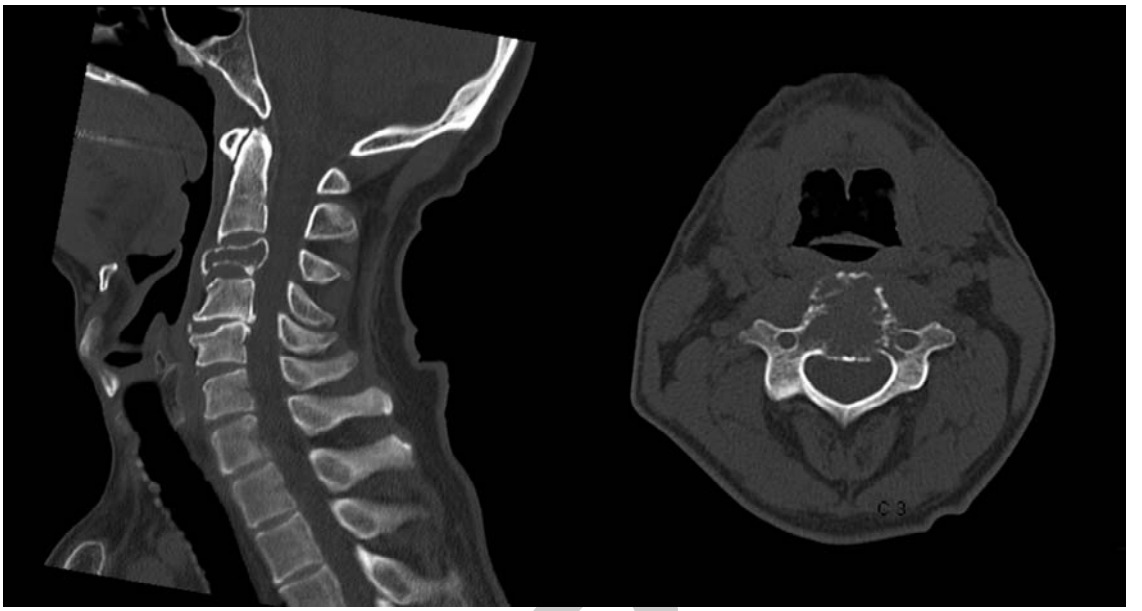

Figure 5: Post-op C-spine Xrays (AP, lateral views)

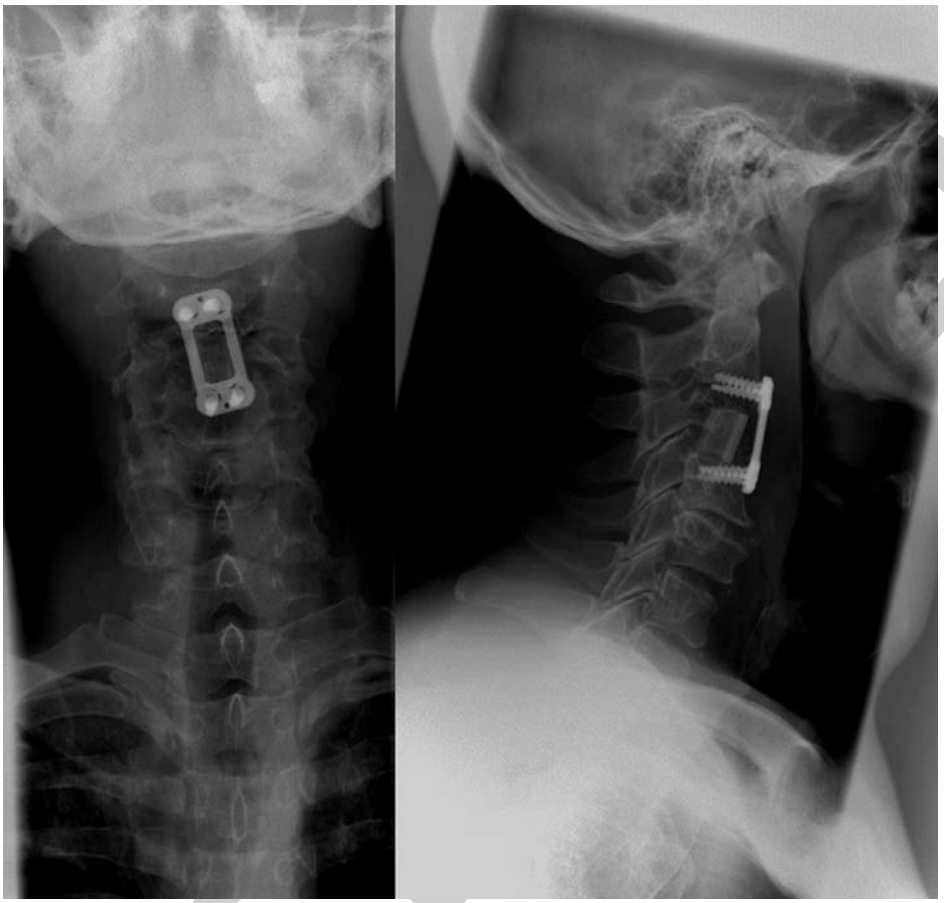

Figure 6: CT scan at 3.5 months postoperatively

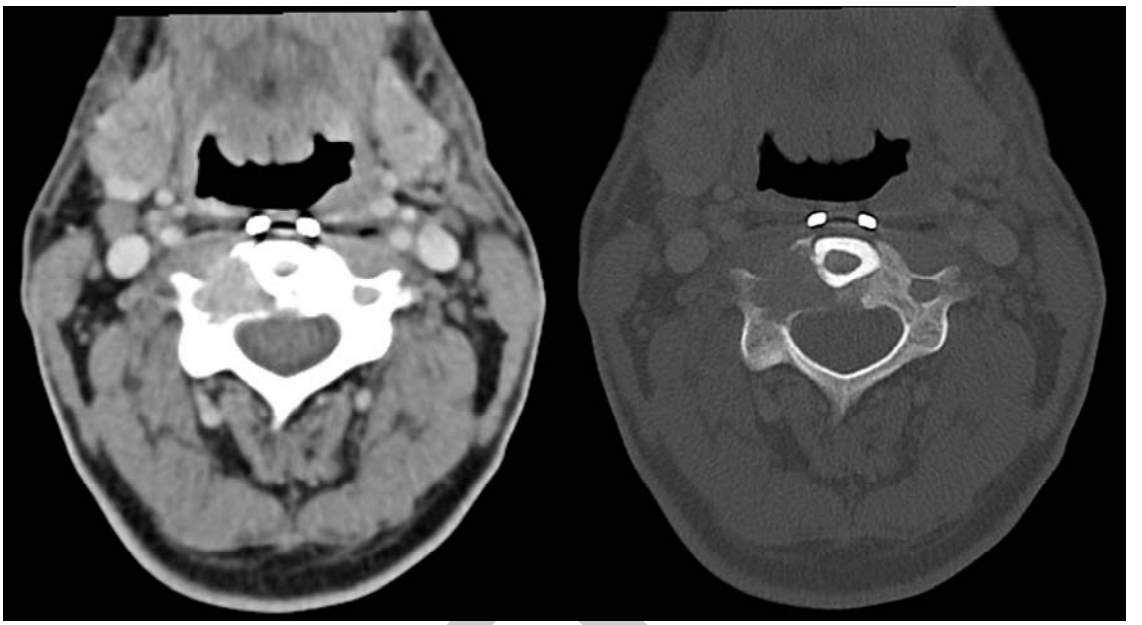

Figure 7: CT scans showing progressive reduction in tumour size in response to Denosumab therapy at 3-monthly intervals followed by no disease progression despite dose reduction

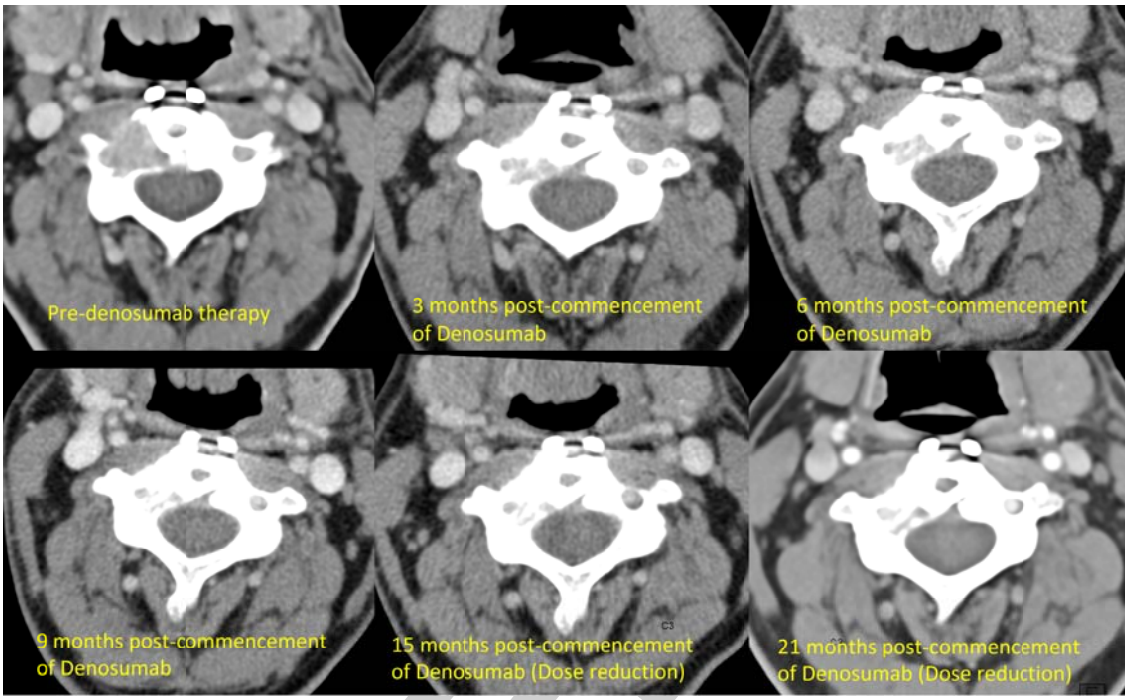

Figure 8: CT scans showing subsequent disease progression post cessation of Denosumab and progressive reduction in tumour size with recommencement of Denosumab