



Neoadjuvant denosumab for the treatment of a sacral osteoblastoma

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Abstract

Purpose To present a case of aggressive sacral osteoblastoma (OB) treated with neoadjuvant denosumab therapy and en bloc resection.

Methods Case report of a 14-year-old male with an aggressive OB affecting the superior articular process of the left first sacral segment. The lesion was lytic and metabolically active and involved the left-sided posterior elements of S1–S3 with extension into the spinal canal, affecting the left S1, S2, S3, S4 and S5 nerve roots. He was treated for 1 month with neoadjuvant denosumab followed by en bloc resection.

Results Denosumab therapy caused regression of the tumour and converted the diffuse infiltrative mass into a well-defined solid (osteoma-like) structure, aiding surgical resection and preserving the S1, S4 and S5 nerve roots. Histologically, the treated lesion showed abundant sclerotic woven bone and osteoblasts with absence of osteoclasts.

Conclusions A short course of denosumab caused tumour regression, ossification and conversion of an aggressive OB into a sclerotic, well-defined lesion thus aiding surgical resection and preservation of neural structures. Neoadjuvant therapy reduced osteoclast numbers but PET showed that the lesion remained FDG avid post-therapy.

Keywords Osteoblastoma · Denosumab · RANK · Tumour

Introduction

Osteoblastoma (OB) is a locally aggressive, rare, benign primary bone tumour (1% of all primary bone tumours) that most commonly develops in the second and third decades of life [1–3]. It has a male predominance and often arises in the spine (10–25% of primary osseous spine tumours) with a predilection for the posterior elements [4–6]. OB is a tumour of osteoblast origin that histologically contains plump, epithelioid osteoblasts which form disorganised osteoid and woven bone on the surface of which there are frequent remodelling osteoclasts [3, 7]. OBs can present with variable aggressiveness, from well-defined latent lesions, which are identical to osteoid osteomas in all but size (> 20 mm), to aggressive lesions with infiltrative features that make them

difficult to differentiate from low-grade osteosarcomas [2, 7–13].

A principal aim of spinal OB treatment is local control. Published treatment options include radiofrequency ablation, radiotherapy, chemotherapy, and surgical intervention. Radiofrequency ablation is well described and has a high success rate, particularly in more latent lesions (up to 96% with a single ablation) [14, 15]. However, the lesion needs to be accessible and to have well-defined borders to ensure complete ablation, making it of limited use for diffuse, aggressive lesions [16]. Radiotherapy and chemotherapy have been described as primary treatments for OB or as an adjunct to operative intervention [13, 17–28]; however use of these treatments is controversial as there is no clear evidence that they reduce recurrence [2, 13]; in addition, the potential of malignant change following radiation exposure with radiotherapy and systemic toxicity and poor patient tolerance with chemotherapy militate against these treatments for a benign tumour [25, 28].

Surgical intervention is, therefore, regularly required for OB, particularly if the lesion is not amenable or responsive to radiofrequency ablation. Although the results differ between series and the stage of the lesion, a 29–100%

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recurrence rate is reported with intra-lesional curettage, 10–20% recurrence rate with marginal excision and a 0–20% recurrence rate with en bloc resection [1, 7, 9, 10, 29–36]. Recurrence rates are highest with lesions affecting the spine [33]. Thus, en bloc resection is preferred, provided the benefit exceeds the expected morbidity, including functional nerve root ligation and major structural loss [2, 13, 35].

Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor kappa- β ligand (RANKL). RANKL is expressed by osteoblasts and required for osteoclast formation [37–39]. Denosumab treatment reduces osteoclastic numbers and bone resorption [38, 39] and has been used to treat giant cell tumour of bone, aneurysmal bone cyst, osteoporosis and metastatic bone disease [38, 40–45]. As osteoclasts are known to be present in aggressive OB and tumour growth requires osteoclast resorption, we hypothesised that OB might respond to a denosumab treatment and in this way facilitate surgical resection of a challenging case of sacral OB.

Case report

A 14-year-old boy was referred to our tertiary paediatric spinal service with a 2-year history of low back pain and progressive posterior left leg radicular pain. His neurological examination was normal. Initial cross-sectional imaging demonstrated a transitional S1 and a S2 left superior articular process osteolytic lesion ($2.1 \times 0.8 \times 1.3$ cm), with intermediate signal on both T1 and T2 MRI sequences (Fig. 1).

A CT-guided biopsy was performed. Histology showed typical features of an aggressive OB with disorganised, partly mineralised osteoid and trabeculae of woven bone lined by plump epithelioid osteoblasts (Fig. 2a, b). There were numerous scattered osteoclasts on the surface of immature bone. There was no marked nuclear pleomorphism or mitotic activity.

Radiofrequency ablation was attempted, but subsequently significant progression was noted with enlargement of the lesion ($5.2 \times 2.7 \times 3.5$ cm) and infiltration from the left S1 pars through to the posterior elements of S2 and extension into the spinal canal, surrounding the left S1, S2, S3, S4 and S5 nerve roots (Fig. 3).

A PET/CT scan demonstrated isolated, local fluoro-deoxy-glucose (FDG) avidity consistent with a metabolically active tumour without evidence of lymphadenopathy or distant disease (Fig. 4).

A repeat CT-guided biopsy confirmed the lesion to be an aggressive OB; the features were not diagnostic of malignancy. Surgical excision was, therefore, considered; however, as the lesion contained osteoclasts and was largely lytic, a trial of denosumab therapy was undertaken in an attempt to reduce the tumour mass and to solidify the tumour matrix to facilitate surgical excision and potentially preserve nerve roots during surgical resection.

Consent for the experimental use of denosumab was obtained from the patient and parents. Subcutaneous administration of 120 mg denosumab was given on days 1, 8, 15 and 28 in accordance with the published approach to giant cell tumours described by Thomas and colleagues [38]. The

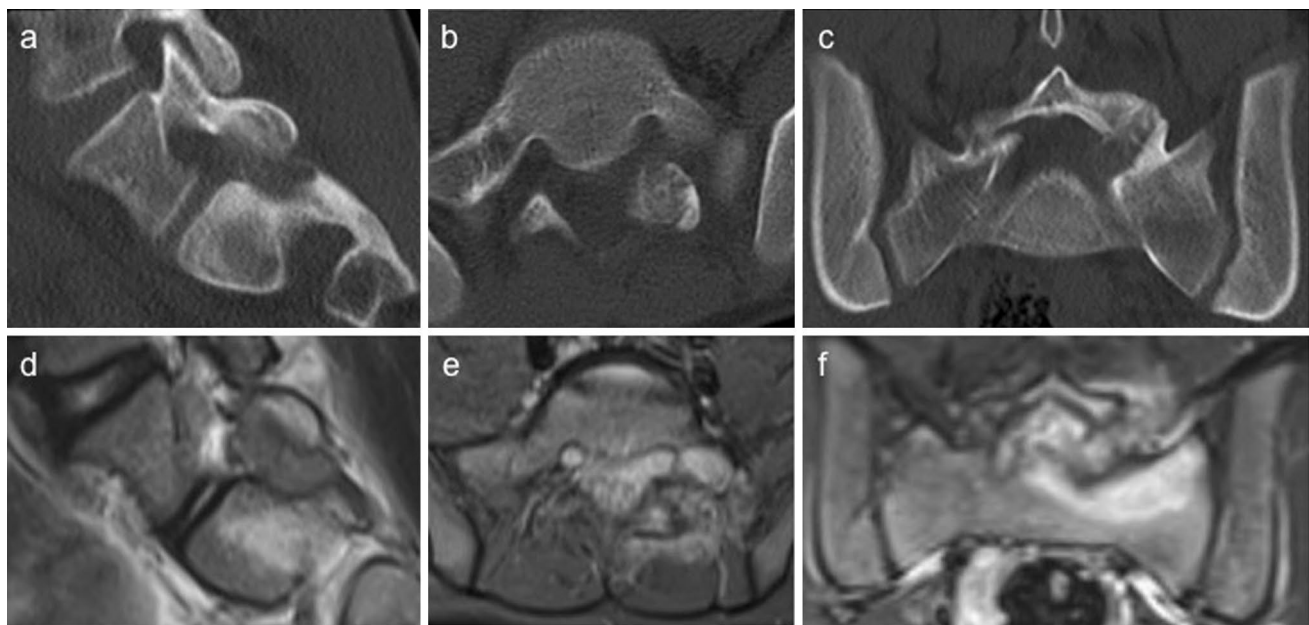


Fig. 1 Sagittal (a), axial (b) and coronal (c) CT scan and reciprocal T1-weighted MRI (d–f) images at presentation

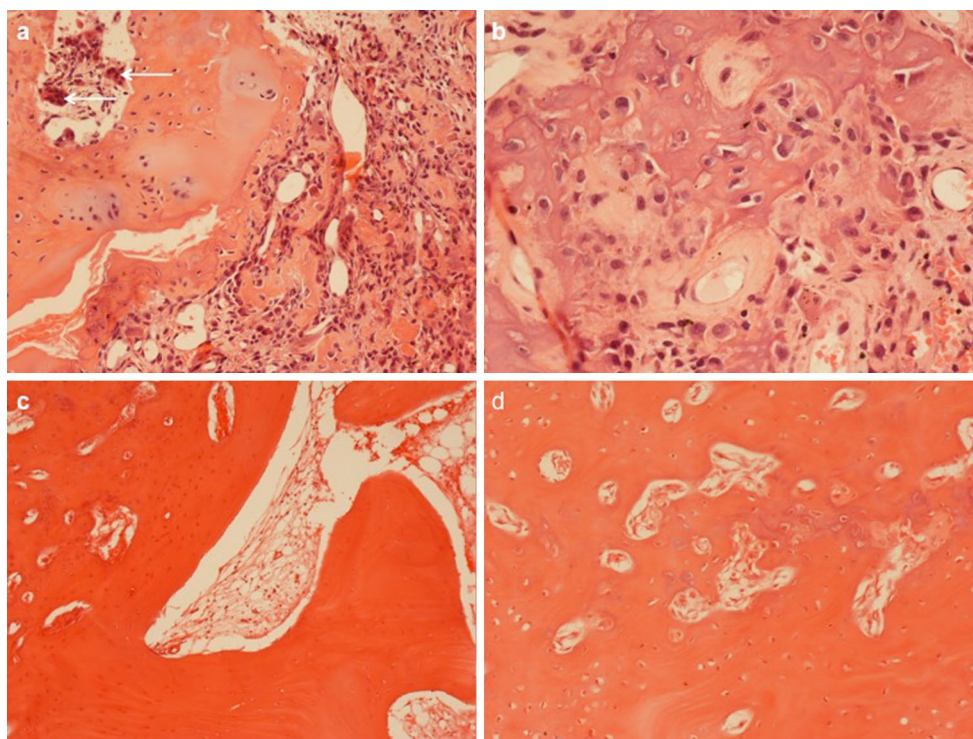


Fig. 2 Low-power (**a**) and high-power (**b**) photomicrographs prior to denosumab therapy showing an aggressive OB with osteoid and woven bone lined by plump epithelioid osteoblasts. Osteoclasts on the surface of remodelling bone are arrowed. Post-denosumab therapy

(**c**), the lesion is markedly sclerotic and has a well-defined edge. It is composed mainly of woven bone with fewer, smaller osteoblasts and there is an absence of osteoclasts (**d**)

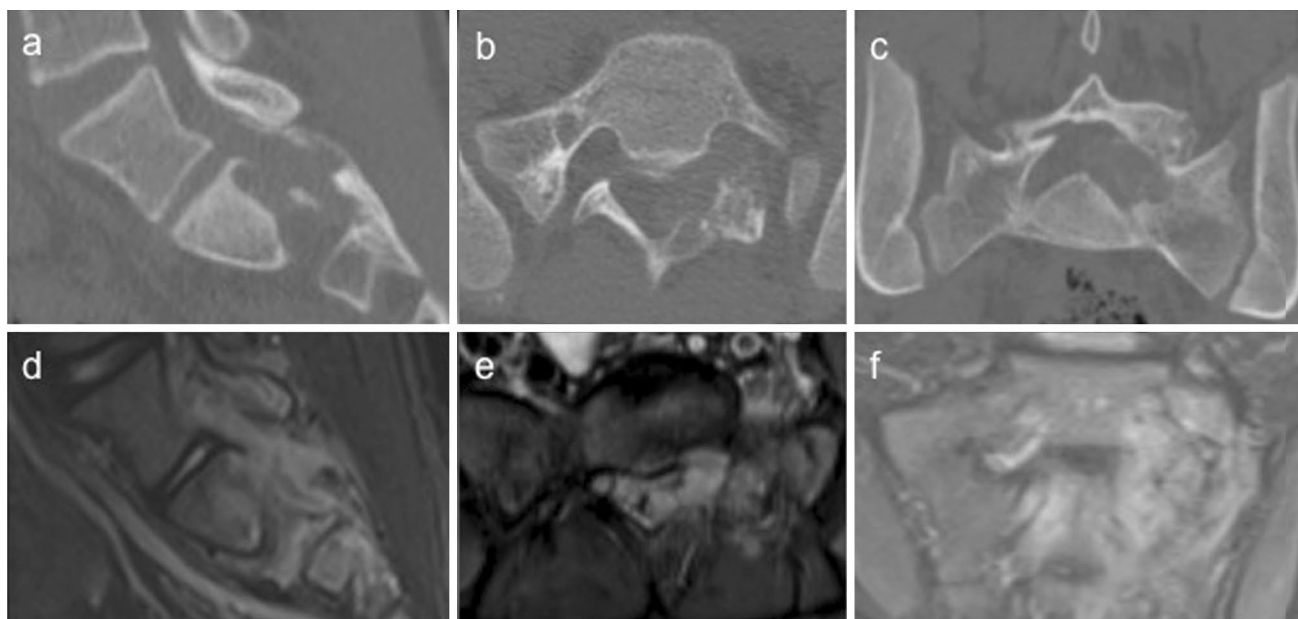


Fig. 3 Sagittal (**a**), axial (**b**) and coronal (**c**) CT scan and reciprocal T1-weighted MRI (**d–f**) images 9 months after presentation

patient developed short-lived jaw pain without evidence of osteonecrosis.

Repeat MRI demonstrated regression of the lesion ($4.5 \times 2.0 \times 3.0$ cm) and a marked change in the signal characteristics from intermediate signal to low signal on both T1

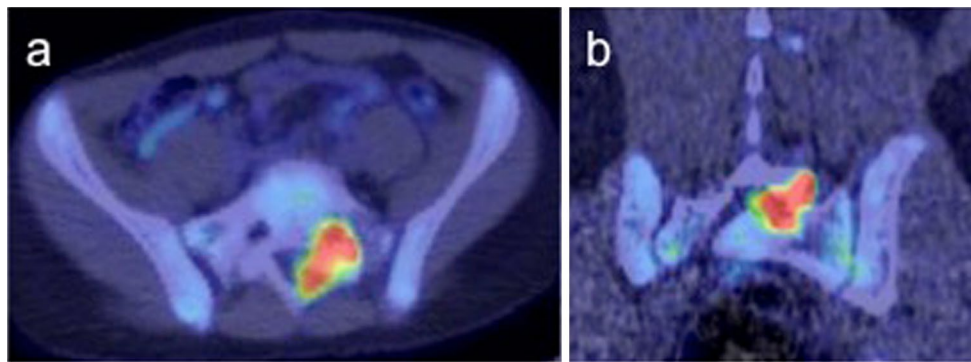


Fig. 4 Representative axial (**a**) and coronal (**b**) FDG PET/CT scan images prior to denosumab therapy

and T2 sequences consistent with osteosclerosis (Fig. 4). A repeat PET/CT scan showed dense sclerosis throughout the previously lytic lesion but persistent high metabolic activity (Figs. 5, 6).

A function sparing en bloc resection of the tumour was undertaken (Fig. 7). This was performed through a midline posterior incision, initially with a right-sided partial caudal S1 laminectomy and S2–S5 hemi-laminectomies, preserving all of the right-sided sacral nerve roots. Then, a left-sided sagittal osteotomy lateral to the tumour margin was performed. The left S2 nerve root was sacrificed while the resected specimen was lifted free. The anterior cortex and much of inferior sacrum were preserved, thus maintaining

pelvic continuity. Supplementary ilio-lumbar stabilisation (L5 to ilium) was inserted.

The post-operative histological findings were markedly different from those in the pre-operative biopsies (Fig. 2c, d). The lesion was very well circumscribed and composed almost entirely of thickened immature woven bone containing prominent cement lines with fibrosis in marrow spaces. The surface of the bone was lined by flattened, smaller osteoblasts which were fewer in number and markedly less epithelioid than in pre-treatment biopsies; there was no mitotic activity or nuclear pleomorphism. Osteoclasts were absent both within the lesion and in bone around the sclerotic lesion, which was representative of an osteoma, although

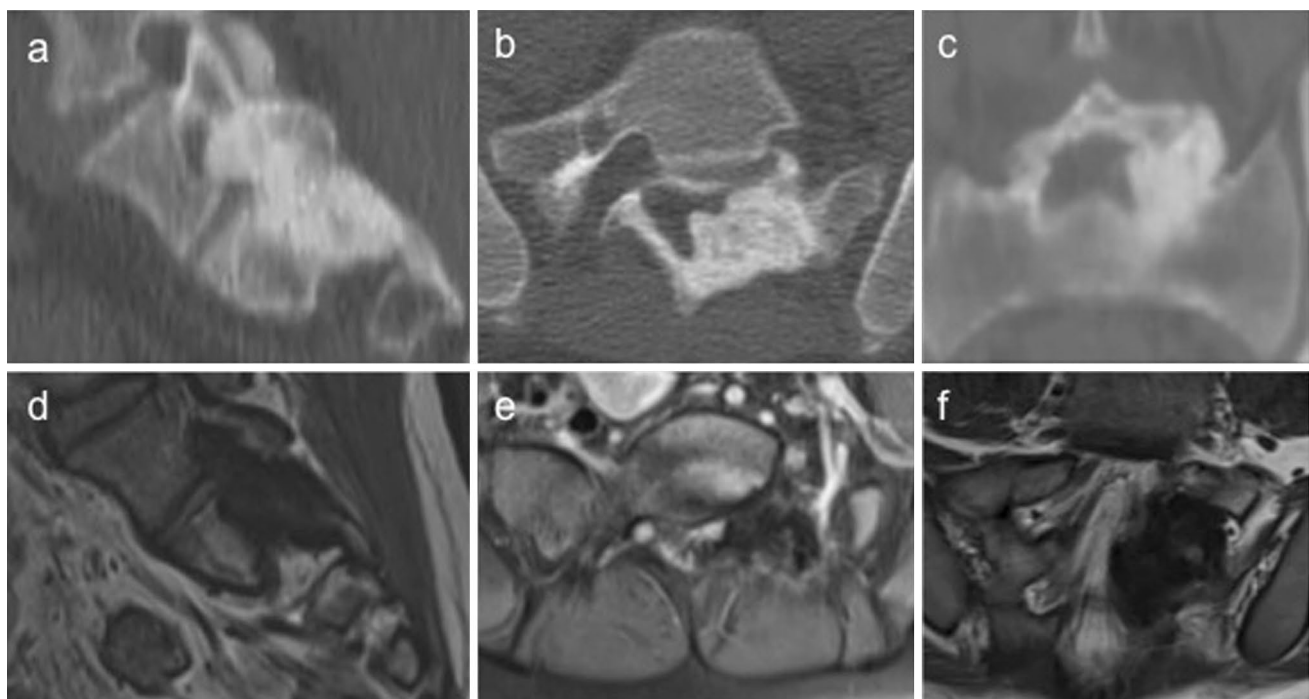


Fig. 5 Sagittal (**a**), axial (**b**) and coronal (**c**) CT scan and reciprocal T1-weighted MRI (**d–f**) images 2 months after denosumab therapy

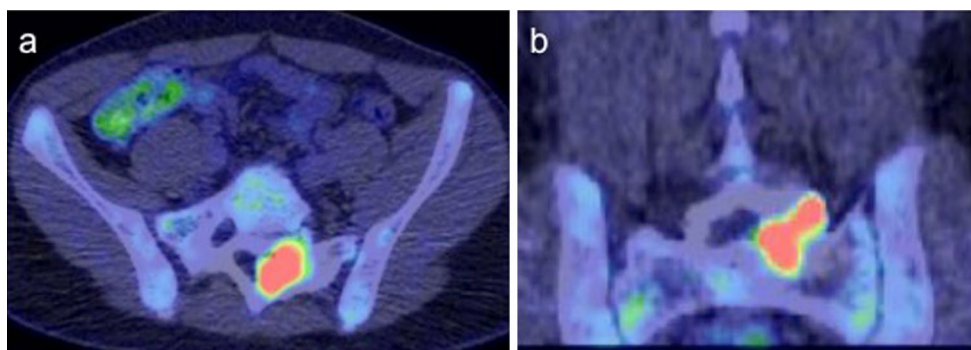


Fig. 6 Axial (a) and coronal (b) FDG PET/CT scan images 2 months after denosumab therapy

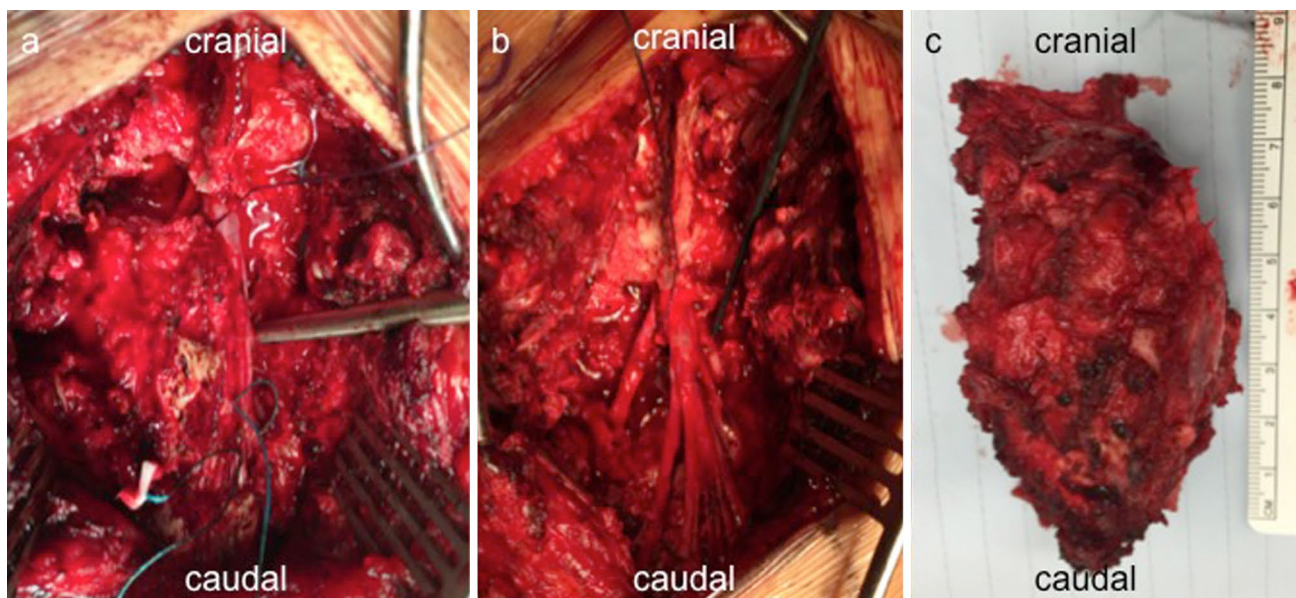


Fig. 7 Representative operative photographs, prior to (a) and after (b) tumour removal. Resected specimen is shown in c

it mainly contained woven rather than lamellar bone. Complete excision of the lesion with clear surgical margins was confirmed histologically.

Post-operative recovery was uneventful with independent full-weight-bearing achieved on day 4. The patient experienced mild left-sided peri-anal numbness but maintained perineal function. The patient has now been followed-up for 18 months after operation and there has been no evidence of recurrence.

Discussion

This case illustrates the benefit of neoadjuvant denosumab therapy in the management of a case of an aggressive sacral OB. Denosumab resulted in tumour regression and ossification with conversion of the lesion from a largely uncontained

mass into a solid, sclerotic lesion with well-defined margins; this neoadjuvant therapy facilitated surgical resection, permitting preservation of left S1, S3, S4 and S5 nerve roots which otherwise would have required sacrifice to ensure tumour clearance.

Denosumab is a human monoclonal antibody that targets and binds with high affinity and specificity to RANKL; it competitively inhibits RANK–RANKL binding, resulting in a decrease in the formation, activity and survival of osteoclasts. Neoadjuvant denosumab has principally been used in the treatment of osteoclast-rich lesions, particularly giant cell tumour of bone (GCTB). In GCTB, there is a proliferation of mononuclear stromal cells that strongly express RANKL and there are numerous macrophages that express RANK [46]; in the presence of macrophage colony-stimulating factor, RANK+ macrophages interact with RANKL+ mononuclear stromal cells to differentiate into osteoclastic

giant cells. Osteoblasts are known to highly express RANKL [37] and OB is a tumour of osteoblast origin. As is evident in our case, OB contains not only numerous epithelioid osteoblasts but also osteoclasts on the surface of remodelling bone. It is likely that the epithelioid osteoblasts in OB express RANKL and in this way promote osteoclast formation. In GCTB, denosumab treatment results in the disappearance of osteoclasts with a consequent reduction in tumour size and an increase in intra-lesional ossification. A similar effect was noted in our case of OB. Radiologically, prior to denosumab administration, the lesion was principally lytic whereas, after denosumab therapy, it was sclerotic. Histologically, osteoclasts had disappeared from the lesion and there was an increase in woven bone formation. Osteoblasts were still present on the bone surface but they were smaller, more flattened and less epithelioid. Post-denosumab therapy, the lesion remained FDG avid on PET/CT, indicating that metabolic activity in the OB was maintained by osteoblasts and not osteoclasts. It is likely that, as in GCTB, stopping denosumab treatment would be followed by proliferation of metabolically active RANKL+ osteoblasts with consequent osteoclast formation and regrowth of the tumour. Thus, even with neoadjuvant denosumab therapy, surgical excision of the lesion is still required for definitive treatment of aggressive OB.

A role for resorption inhibitors, such as bisphosphonates, in the management of benign bone tumours and tumour-like lesions has been shown in previous studies [47]; Cornelis and colleagues noted a partial response to bisphosphonates in one case of OB [48]. RANKL is known to be expressed by stromal cells in several non-giant cell containing bone tumours including osteosarcoma, chondrosarcoma and fibrous dysplasia [49]. Denosumab treatment has been employed in one case of fibrous dysplasia and one of refractory unresectable (OB-like) osteosarcoma [38, 50]. Aggressive OB does not metastasise, but has some overlap in terms of local invasion with low-grade central osteosarcomas; these tumours frequently show woven bone formation and have a fibrous dysplasia-like or OB-like histology [51]; it is possible that neoadjuvant denosumab treatment could also be useful to control tumour growth and facilitate resection of low-grade malignant bone-forming tumours.

It should be noted that there are a number of adverse effects associated with denosumab treatment. These include osteonecrosis of the jaw [52], joint and muscle pain, electrolyte imbalance, increased risk of skin infections, atypical fractures and allergies [53, 54]. Our patient had jaw (and shoulder) pain that resolved after therapy was stopped, but experienced no other adverse effects. Although encouraging, longer term followup is clearly required in our case to assess fully the effects of denosumab treatment. However, our findings suggest that resorption inhibitors are likely to be

useful in facilitating the surgical treatment of OB and other bone-forming lesions.

Conclusion

A short course of denosumab therapy caused tumour regression, ossification and conversion of an uncontained, aggressive OB into a sclerotic, well-defined tumour with distinct margins; this facilitated surgical resection and preservation of neurological structures. Denosumab therapy resulted in the disappearance of osteoclasts and rapidly converted a lytic OB into a sclerotic OB. Clinicians, however, should be aware that this treatment did not abrogate metabolic activity in the lesion on functional imaging, indicating that surgical excision is still required for definitive treatment.

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Compliance with ethical standards

Conflict of interest None of the authors has any potential conflict of interest.

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