Spine

SPINE Volume 40, Number 22, pp E1201–E1204

CASE REPORT

Response of Aneurysmal Bone Cyst to Denosumab

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Study Design. Case report and literature review.

Objective. To describe a unique case of large sacral aneurysmal bone cysts (ABCs) treated with denosumab and review the literature on this rare entity.

Summary and Background Data. ABCs are expansile osteolytic lesions that typically contain blood-filled spaces separated by fibrous septa. Standard treatment includes surgical resection or curettage and packing; however, for some spinal lesions, the standard approach is not optimal. One therapeutic strategy is to treat spinal ABC with an agent that targets a pathway that is dysregulated in a disease with similar pathophysiology. The bone destruction in both giant cell tumors of bone and ABCs is mediated by RANK ligand (RANKL) produced by the tumor cells. Denosumab, a human monoclonal antibody to RANKL, is effective in the treatment of giant cell tumors of bone.

Methods. We report a case of a large sacral ABC that responded to denosumab. A 27-year-old male developed increasing back pain. Imaging revealed a lytic lesion in the sacrum with no clear solid component and regions where the cortex was difficult to identify. ABC was diagnosed on biopsy. Surgery or radiation treatment was expected to be associated with serious morbidity; therefore, denosumab was given using the regimen for giant cell tumors of bone (120 mg monthly with a loading dose).

Results. The patient's pain gradually resolved after 2 months of treatment. New bone formation with a more clearly defined cortex was evident on computed tomographic scan at 16 weeks and continued to show evidence of improvement at 7 and 12 months. Biopsy at 12 months revealed a hypocellular fibrous stroma with new bone formation and no giant cells.

Conclusion. We conclude that denosumab can result in symptomatic and radiological improvement in ABC and may be useful in select cases.

Key words: aneurysmal bone cyst, denosumab, RANKL, spinal lesions.

Level of Evidence: 5

Spine 2015;40:E1201-E1204

Aneurysmal bone cysts (ABCs) are expansile osteolytic lesions that contain blood-filled spaces separated by fibrous septa containing giant cells.[1–4] The usual treatment is curettage and packing or possibly surgical resection in an expendable bone. In some cases, embolization, injection with sclerosing agents, or radiation may be useful. However, these approaches may be associated with severe and long-lasting morbidity in cases with spinal lesions, such as large sacral lesions.[5–7] Recent studies have suggested that the pathophysiology of ABC is similar to that of giant cell tumors of bone (GCTB). In GCTB, the malignant cell secretes receptor activator of nuclear factor κ-B ligand (RANKL).[8–15] Here, we report a case of large sacral ABC that achieved resolution of clinical symptoms and improved radiological findings after treatment with denosumab, a human monoclonal antibody to RANKL that has been effective in the treatment of GCTB.[11–13,15]

CASE REPORT

A 27-year-old male developed low back pain after falling at work. History, family history, and review of systems were unremarkable except for a history of gastroesophageal reflux disease treated with antacids and proton pump inhibitors. Physical examination was unremarkable except for some tenderness to pressure in the right sacral area. Imaging revealed a 5.6 × 4.1 × 3.5 cm lytic lesion in the right sacrum with no clear solid component and regions where the cortex was difficult to visually distinguish (Figure 1, left panel). Biopsy revealed an ABC (Figure 2, panels A and B) with blood-filled cystic spaces separated by cellular fibrous stroma containing mononuclear cells and rare osteoclast-

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Acknowledgment date: March 18, 2015. First revision date: June 16, 2015. Acceptance date: June 16, 2015.

The device(s)/drug(s) that is/are the subject of this manuscript is/are being evaluated as part of an ongoing FDA-approved investigational protocol (IDE) or corresponding national protocol.

No funds were received in support of this work.

Relevant financial activities outside the submitted work: board membership, grants, employment.

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DOI: 10.1097/BRS.0000000000001027

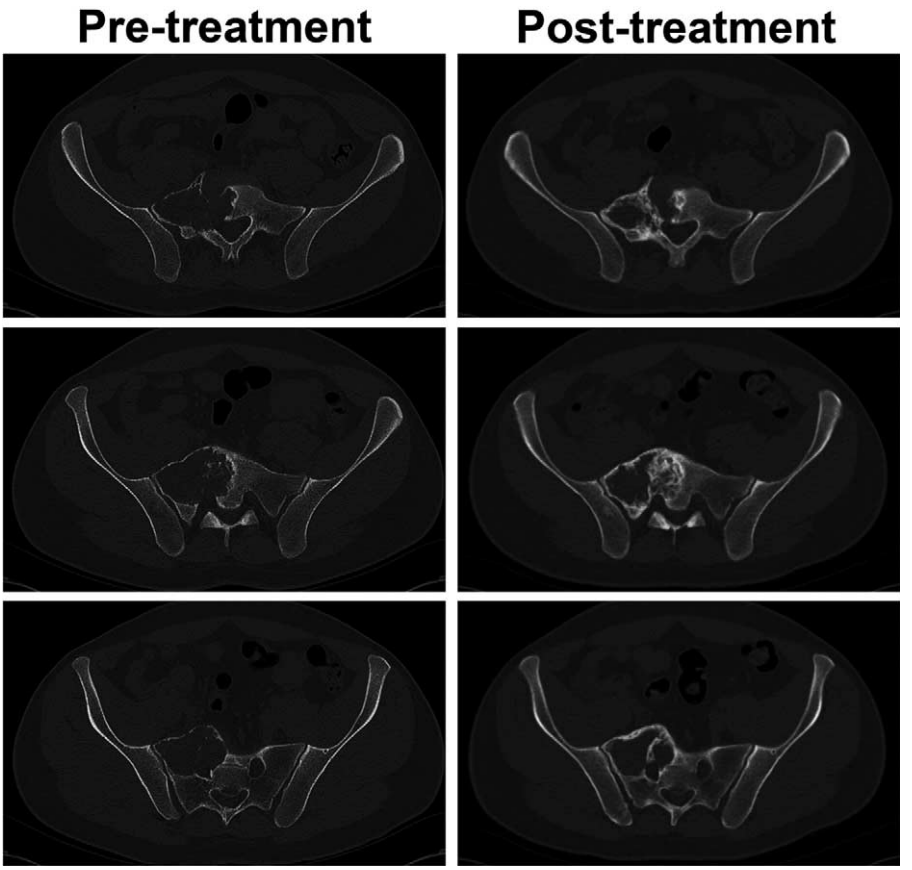

Figure 1. Computed tomographic scans at baseline (left panel) and after 11 months of denosumab treatment (right panel).

like giant cells. Significant hemosiderin deposition was seen. The background contained fragments of lamellar and reactive woven bone (not pictured). Intralesional curettage and bone graft packing was considered to have a high risk of serious permanent morbidity and disability, and alternate treatments were sought. Denosumab treatment, although not Food and Drug Administration approved, was offered to the patient.

The patient received a dental examination by his dentist to ensure good oral health and began vitamin D and calcium supplementation to prevent hypocalcemia, a rare but serious toxicity of denosumab. Treatment was begun using the regimen described for treating GCTB[12–14] (120 mg sc d1, 8, 15, 28 and then monthly). The pain began to improve about 2.5 weeks after starting denosumab, and he was able to sleep in any position 3 weeks after starting treatment. By 1 month, the pain was markedly improved and resolved by 2 months after starting denosumab. A computed tomographic scan 16 weeks after starting denosumab showed evidence of new bone formation with a more clearly defined cortex (not shown). Treatment was continued for 11 months, at which time imaging revealed new bone formation (Figure 1, right panel). A biopsy revealed new bone formation and hypocellular fibrous stroma that contained scattered mononuclear cells. Hemosiderin deposition was rare to absent and no osteoclast-like giant cells were seen (Figure 2, panels C and D). Treatment was stopped after 1 year and follow-up continues.

DISCUSSION

Four other patients have been successfully treated with denosumab in addition to our case [16–18] (Table 1). Denosumab functions by binding RANKL, thus preventing its binding to RANK and subsequent signaling and accumulation of osteoclasts in the tumor. Recruited osteoclasts dissolve bone and may also secrete other factors that have a trophic effect on the monoclonal tumor cells as well. Thus, denosumab treatment decreases bone destruction and by altering the tumor environment may also lead to bone formation as well. Although generally well tolerated, denosumab treatment is not without risk. Denosumab also inhibits normal bone remodeling, and an important toxicity *of bisphosphonates and denosumab* is osteonecrosis of the jaw.[19–21] In addition, use of denosumab in young patients whose growth plates have not yet closed could result in changes similar to osteopetrosis.[22,23] Finally, given the reported lymphoid defects in mice that lack RANKL, other long-term toxicities of denosumab may exist.[24]

In conclusion, denosumab had beneficial effects in the case of ABC described in this report. However, the effects of denosumab in ABC may be complex. Denosumab not only inhibits RANKL, and thus reduces osteoclasts, but also

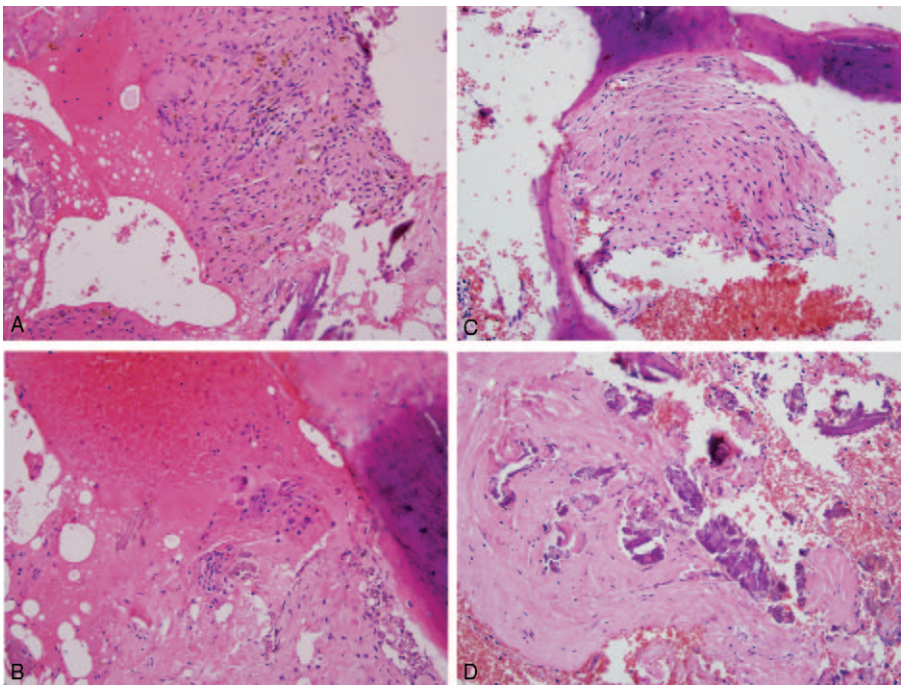

Figure 2. Histopathology at 200× of tumor before (Panels A and B) and after (Panels C and D) 11 months of denosumab treatment. Panels A and B: Blood-filled cystic spaces separated by cellular fibrous stroma containing mononuclear cells and rare osteoclast-like giant cells. Significant hemosiderin deposition was seen. The background contained fragments of lamellar and reactive woven bone (not pictured). Panels C and D: New bone formation and hypocellular fibrous stroma containing scattered mononuclear cells. Hemosiderin deposition was rare to absent and no osteoclast-like giant cells were seen.

TABLE 1. Published and Current Cases of Denosumab Treatment of ABC

	Case 1	Case 2	Case 3	Case 4	Current Case
Age/sex	8-yr-old boy	11-yr-old boy	21-yr-old female	5-yr-old boy	27-yr-old male
Diagnosis	Typical ABC	Typical ABC	Solid ABC	Typical ABC	Typical ABC
Location	C5	C5	Forearm	Sacrum	Sacrum
Initial (pre-denosumab) treatment	Surgery	Surgery	Surgery	None	None
Outcome of initial (pre-denosumab) treatment	Recurrence at 1 mo	Recurrence at 8 mo	Recurred	NA	NA
Denosumab treatment	Denosumab 70 mg/m^2 sc monthly	Denosumab 70 mg/m^2 sc d1, 8, 15, 21, 28, and then monthly	Denosumab 120 mg sc monthly, followed by function conserving surgery	Denosumab 1.2 mg/kg/dose sc d1, 8, 15, 21, 28, and then monthly	Denosumab 120 mg sc d1, 8, 15, 28, and then monthly for 1 yr, followed by observation
Response to denosumab	Recovery from neurological symptoms, and no progression of ABC, with evidence of bone formation on MRI at 2 mo	Recovery from neurological symptoms, and no progression of ABC, with evidence of bone formation on MRI at 4 mo	Initially diagnosed as GCTB and treated with denosumab and surgical excision, but the diagnosis was revised to ABC on the basis of pathology of resected tissue, showing an intracortical lesion and USP6 rearrangement	Resolution of pain and new bone formation with healing of pathologic fracture on MRI	Resolution of pain and new bone formation on CT scan, decrease in giant cells, and decrease in cellularity of fibrous stroma
References	Lange *et al*[17]	Lange *et al*[17]	Pauli *et al*[16]	Pelle *et al*[18]	Skubitz

ABC indicates aneurysmal bone cyst; NA, not applicable; GCTB, giant cell tumors of bone; CT, computed tomographic; MRI, magnetic resonance image; USP6, Ubiquitin-Specific Peptidase 6.

increases serum sclerostin, which leads to depressed bone formation, and inhibits DKK1, which inhibits the sclerostin effect, thus increasing osteoblastogenesis.[25,26] Many questions remain regarding the use of denosumab in ABC, including how long to treat and what happens after denosumab is discontinued. We conclude that denosumab can result in symptomatic and radiological improvement in ABC and may be useful in cases not amenable to surgical interventions, although the long-term outcome is unknown.

➢ Key Points

- ❑ Standard treatment with surgical resection/curettage and packing for some spinal aneurysmal bone cysts (ABCs) is not optimal.
- ❑ Denosumab is a monoclonal antibody to RANKL, which mediates bone destruction in ABC.
- ❑ Denosumab may be useful for the treatment of select ABC cases.

Acknowledgments

The authors thank Michael Franklin for editorial review of the manuscript and assisting with preparing the manuscript for submission.

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