

# Denosumab: a potential new and innovative treatment option for aneurysmal bone cysts

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Received: 6 November 2012/Revised: 20 January 2013/Accepted: 5 February 2013/Published online: 1 March 2013  
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## Abstract

**Introduction** Aneurysmal bone cysts (ABCs) are expansive and destructive lesions positive for osteoclast markers, resembling benign giant cell tumors (GCTs). Treatment options include surgical resection, curettage and cavity filling, embolization, injection of fibrosing agents, or radiotherapy. Particularly in children and adolescents with spinal ABCs, these options may be unsatisfactory, and innovative forms of treatment are needed. Denosumab is a human monoclonal antibody that inhibits osteoclast function by blocking the cytokine receptor activator of the nuclear factor-kappa B ligand. Satisfactory results with denosumab in

treating GCTs and immunohistochemical similarities suggest that it may also have positive effects on ABCs.

**Methods and Results** This report is the first description of the therapeutic use of denosumab in two patients with spinal ABCs. Two boys (aged 8 and 11) had recurrent ABCs at C5 after surgery with intralesional tumor resection. Treatment options were discussed by the interdisciplinary tumor board. Arterial embolization was attempted, but failed due to an absence of appropriate afferent arteries. After the families had received extensive information and provided written consent, denosumab therapy was initiated as an individualized treatment, despite the absence as yet of scientific evidence. After the start of denosumab therapy, both patients recovered from pain and neurologic symptoms significantly and are now in a healthy condition with no severe side effects. Magnetic resonance imaging check-ups after 2 or 4 months of denosumab treatment, respectively, showed tumor regression in both patients.

**Discussion** Longer follow-up and clinical studies are warranted to establish the value of denosumab in the treatment of ABCs.

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**Keywords** Aneurysmal bone cyst · Spine · Denosumab · Medical treatment · Giant cell tumor

## Introduction

Aneurysmal bone cysts (ABCs) are a type of benign but expansive and destructive lesion resembling giant cell tumors (GCTs), which are characterized by a stromal cell population thought to originate from a mesenchymal osteoblast precursor and variable numbers of eponymous giant cells. The giant cells that occur in GCTs and also in ABCs are positive for markers of true osteoclasts [16].

Treatment for ABCs involves surgical resection or curettage with filling of the defect with bone cement [1, 13, 20], selective arterial embolization [10], fibrosing agent injection [14], or megavoltage radiotherapy [5]. ABCs located in the spine present the difficulty that these treatment strategies often involve risks of neurological impairment, instability, recurrence, or other vital problems [7]. Treatment for spinal ABCs is still generally unsatisfactory in many cases due to the considerable risk of morbidity, and there is therefore a need for innovative therapies.

Denosumab is a human monoclonal antibody that binds the cytokine receptor activator of nuclear factor-kappa B (NFκB) ligand (RANKL), which essentially initiates bone turnover [16]. RANKL inhibition blocks osteoclast maturation and function [16], and denosumab has been successfully used in the treatment of osteoporosis [15] and skeletal metastases [8], and more recently in GCT therapy as well [18]. The satisfactory results with denosumab in the treatment of GCTs and the clear immunohistochemical similarity and relationship between GCTs and ABCs [19] justify the hypothesis that denosumab may also have positive effects on ABCs. Therapeutic administration of denosumab has already been investigated with a long follow-up period in postmenopausal women, but was found to be associated with an increased risk of severe symptomatic hypocalcemia. Supplementation with calcium and vitamin D is therefore strongly recommended during treatment. Reported rare adverse events include serious infections, dermatologic reactions, and osteonecrosis of the jaw [11]. There is still a lack of data on the use of denosumab in pediatric patients.

## Methods and results

This report describes the cases of an 8-year-old boy (patient no. 1) and an 11-year-old boy (patient no. 2). The first patient presented with left-sided cervicobrachial pain and torticollis that had persisted for a period of 4 months. Radiography and magnetic resonance imaging (MRI) revealed a tumorous lesion at C5, with spinal cord compression and left-sided stenosis of neural foramina C4/5 and C5/6. The vertebral artery was also enclosed inside the tumorous mass. Three days later, he developed acute progressive neurologic paresis of the C5 and C6 nerve roots. An emergency decompression procedure with a left-sided hemilaminectomy of C5 and biopsy was performed. Wide tumor resection was not possible due to the problematic location of the lesion. The biopsy revealed the diagnosis of a typical ABC at C5. The pain and neurologic deficits resolved after the operation. The first MRI check-up 1 month after surgery revealed progression of the tumor

again, with spinal cord and nerve root compression at C5 and C6 on the left side (Fig. 1a–c). The patient had progressive cervicobrachial pain, this time without impaired sensorimotor function.

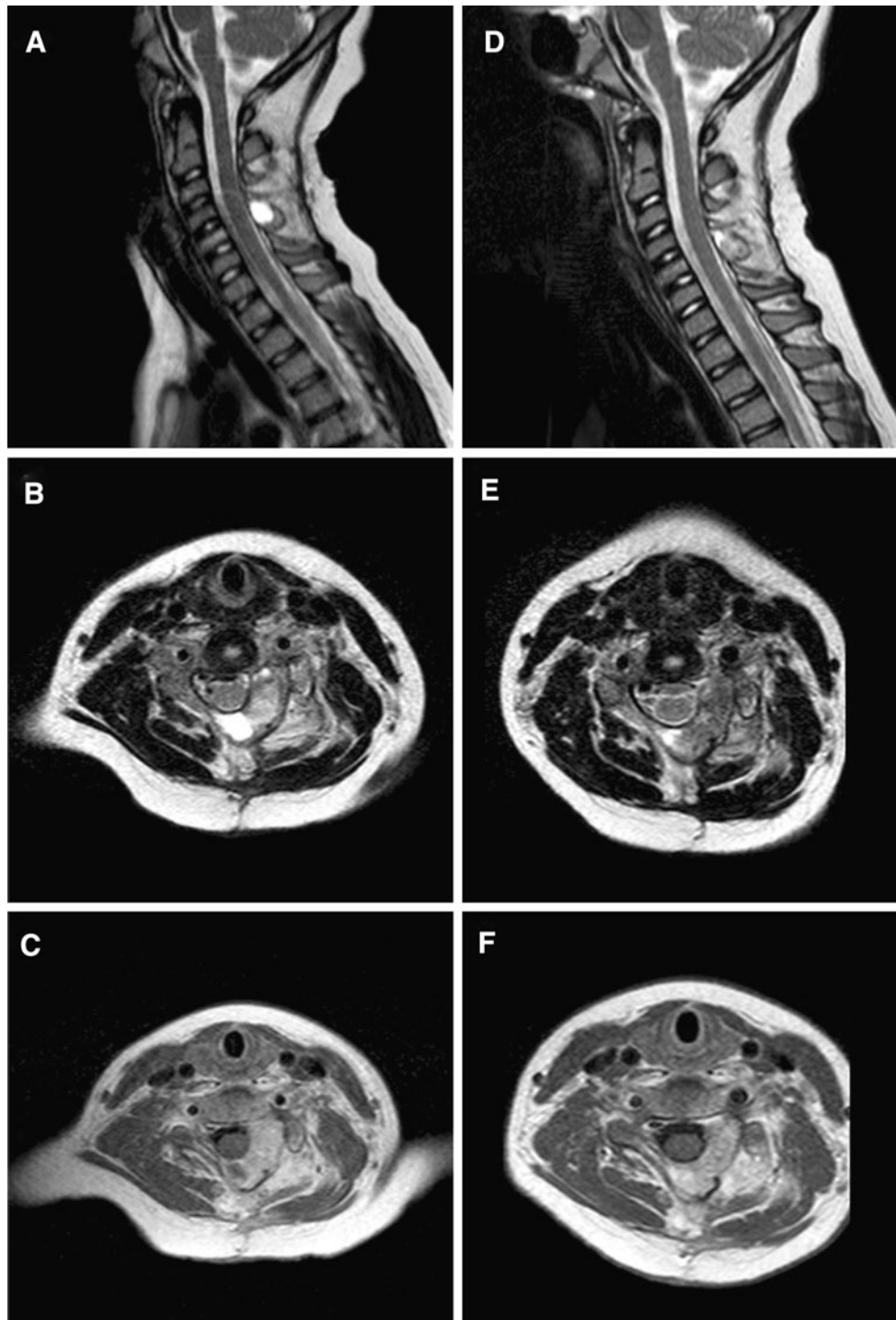
Patient no. 2 initially presented in September 2011 with neck pain and right-sided radiculopathy in the arm, with incomplete paresis of the deltoid and biceps muscles that had persisted for 6 months. MRI revealed an ABC-like tumorous mass at C5. A biopsy was immediately performed, and the diagnosis of an ABC at C5 was confirmed. Intralesional resection of the ABC from anterior, with reconstruction of the spinal column using cage interposition and plate fixation followed by additional posterior tumor resection and instrumentation at C4–C6 using lateral mass screws, was carried out in September 2011. The patient recovered from the initial neurologic deficit and cervico-brachial pain completely. An MRI check-up 8 months later showed a recurrence of the ABC at C5 (Fig. 2a–c). The patient had no neurological impairment, but pain had again developed in the right arm.

The interdisciplinary tumor board at our institution extensively discussed the remaining treatment options in these two patients, including revision surgery, selective arterial embolization, fibrosing agent injection, megavoltage radiotherapy and also individualized treatment using denosumab, although the latter is not yet scientifically proven.

In view of the side effects of the various treatment options in these cases, it was decided to carry out angiography and if possible selective arterial embolization in both patients. Unfortunately, the vascularization patterns of both tumors meant that embolization would have involved a very high risk of neurologic complications. Effective embolization was therefore not performed in either patient. In view of their young ages at 8 and 11 years and of the additional risk for myelopathy, megavoltage radiotherapy at this critical location was not considered. The tumor board then suggested individualized treatment with denosumab.

Following extensive discussions with the families regarding this experimental approach and after written informed consent had been obtained, baseline imaging studies were carried out in patient no. 1 (Fig. 1a–c) and patient no. 2 (Fig. 2a–c).

In patient no. 1, denosumab was started at a dose of 70 mg/m<sup>2</sup> body surface area subcutaneously every 4 weeks. The dosage was adapted from the approved adult dosage of 120 mg q 4 weeks. The treatment was supplemented with appropriate daily oral substitution of 500 mg calcium and 1000 IU vitamin D. Even with the supplementation, the first patient developed hypocalcemia, and the dosage was increased to 1000 mg calcium per day.

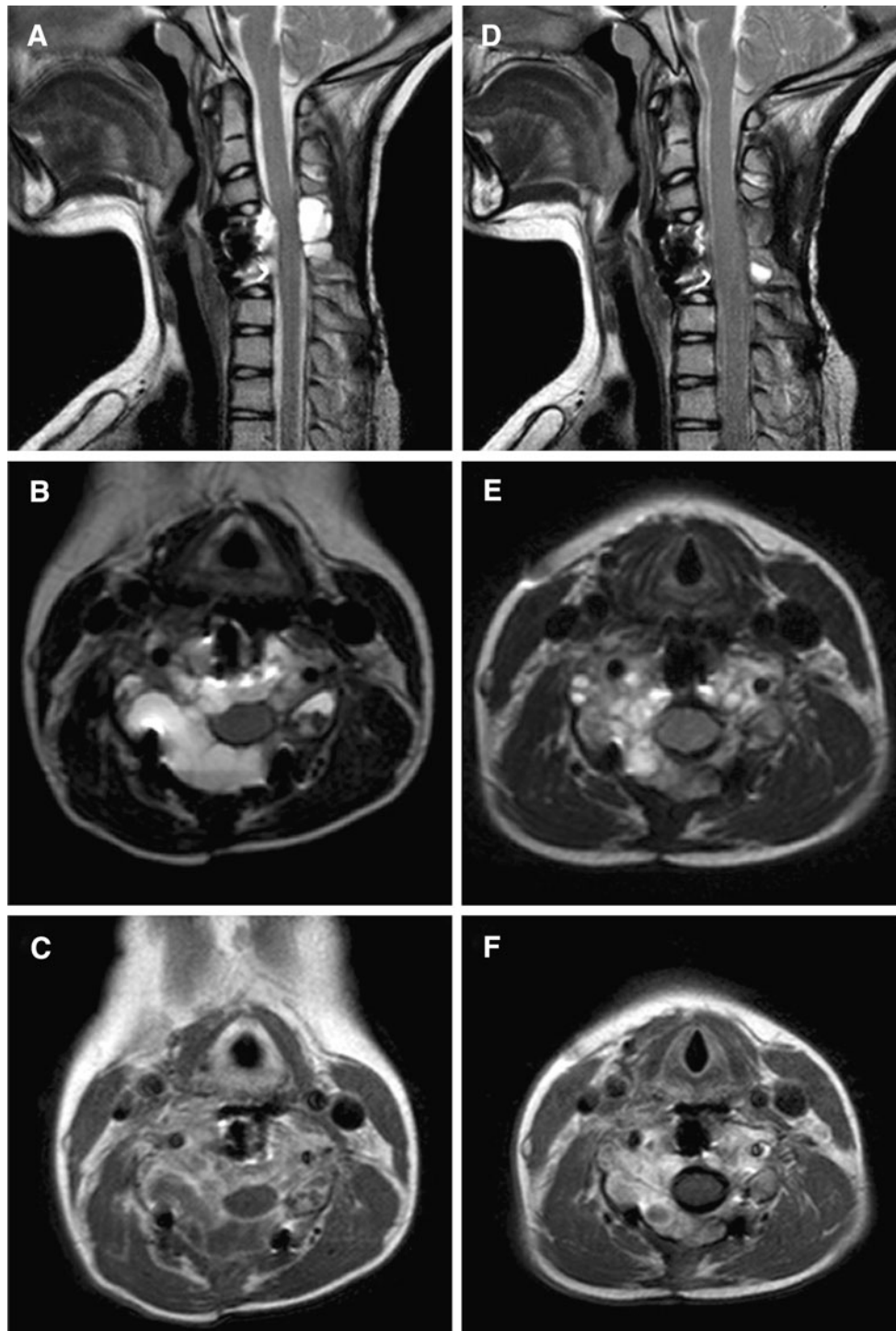


**Fig. 1** Patient no. 1. Images **a** (sagittal T2-TSE), **b** (axial T2-TSE), and **c** (axial T1-TSE with contrast) show the first MRI status with a recurrence of ABC after surgical hemilaminectomy before denosumab

therapy was started. The first MRI check-up examination after denosumab treatment, 2 months later, is shown in images **d** (sagittal T2-TSE), **e** (axial T2-TSE), and **f** (axial T1-TSE with contrast)

Following the initiation of denosumab therapy, patient no. 1 recovered from pain significantly and the neurologic symptoms disappeared. No side effects of therapeutic administration of denosumab were observed in this patient, apart from asymptomatic hypocalcemia.

Regarding the clinically critical situation, patient no. 2 received an intensified denosumab induction treatment phase 4 weeks after the last MRI with four injections of denosumab  $70 \text{ mg/m}^2$  body surface area subcutaneously at weekly intervals, followed by a q 4 weeks treatment schedule as described



**Fig. 2** Patient no. 2. Images **a** (sagittal T2-TSE), **b** (axial T2-TSE), and **c** (axial T1-TSE with contrast) show the first MRI status with a recurrence of ABC after surgical intralaminar tumor resection before denosumab

in patient no. 1. This treatment was supplemented with appropriate daily oral substitution of calcium (600 mg) and vitamin D (400 IU). Notably, even this intensified treatment schedule was well tolerated, since no obvious side effects of denosumab therapy were observed.

therapy was started. The first MRI check-up examination after denosumab treatment, 4 months later, is shown in images **d** (sagittal T2-TSE), **e** (axial T2-TSE), and **f** (axial T1-TSE with contrast)

The first MRI follow-ups were carried out 2 months later in patient no. 1 (Fig. 1d–f) and 4 months later in patient no. 2 (Fig. 2d–f) using identical technical imaging settings. The MRIs showed no further tumor progression in either case, with clear signal alterations in the tumor.

Regression of the cystic formation of the ABC was even observed, in addition to replacement of the previously cystic formations with solid, bone marrow-like tissue. The images for patient no. 1 were acquired at 1.5 T (Gyrosan Intera; Philips Medical Systems, Best, The Netherlands) at two time points. The images for patient no. 2 were acquired at 1.0 T (Panorama HFO; Philips Medical Systems, Best, The Netherlands) at two time points. The imaging protocols consisted of axial and sagittal T2-weighted turbo spin-echo (T2-TSE) sequences and axial and sagittal T1-weighted turbo spin-echo (T1-TSE) sequences, before and after contrast administration.

## Discussion

Aneurysmal bone cysts are generally a rare tumorous lesion in the spine, but can lead to devastating symptoms as they are capable of destructive growth. Common treatment options for ABCs include surgical resection [20], curettage and cavity filling (e.g., with bone or bone cement [13]), selective arterial embolization [10], fibrosing agent injection [14], or megavoltage radiotherapy [5]. For spinal ABCs, however, some of these options entail very considerable risks.

Wide complete resection of a spinal ABC clearly shows the best results in relation to the risk of recurrence, but this is often not possible due to the close proximity of neural structures, especially the spinal cord and nerve roots, and also of essential vessels such as the vertebral artery. An attempt at wide surgical resection may therefore lead only to intralesional curettage, with a risk of recurrence of 10–80 %, most often within the first 6–12 months after initial surgery [12, 21]. Additional cavity filling with bone cement, using the heat to destroy residual cells, may reduce the risk of recurrence, but also carries a risk of causing irritation to neural structures.

Selective arterial embolization of afferent vessels is an alternative in surgery for ABCs; it can slow down tumor progression and possibly even achieve a steady state [10]. Selective arterial embolization has proved successful in cases of ABC located in the extremities, and selective arterial embolization alone is able to heal ABCs located in the spine without further complications [2]. However, care is still required in relation to the individual vascularization of each lesion. Angiography may show that embolization is contraindicated due to a high risk of spinal cord damage caused by ischemia. If feasible, the procedure thus usually serves as an auxiliary preoperative measure to decrease the vascularity of the tumor and reduce intraoperative blood loss [9]. There has also been discussion in the literature of megavoltage radiotherapy as a treatment for ABCs, as it has good effects on tumor regression and recalcification of

the cystic bone lesion. In adolescent patients, however, the risk of secondary malignancies, myelopathy and epiphyseal fusion is substantial, and megavoltage radiotherapy should therefore be considered cautiously [4, 6].

Denosumab has been used with excellent results in the treatment of osteoporosis, skeletal metastases, and GCTs [8, 15, 18]. Concerns about patient safety with denosumab have also been answered by studies evaluating its side effects [17]. An increased risk of urinary infections and eczema, and rare adverse events involving serious infection and osteonecrosis of the jaw, have been reported in patients receiving denosumab therapy for osteoporosis [11, 15]. Beyond that, the therapeutic use of denosumab appears to be safe, but there is clearly a need for further studies to assess potential side effects when denosumab is used to treat pediatric patients and to investigate the appropriate duration of therapy.

In the two cases of recurrent cervical ABC described in the present report, individualized treatment with denosumab led to a good tumor response. MRI check-up examinations showed that the previous cystic formations had been replaced with solid bone marrow-like tissue, a finding that has also been noted in GCT therapy [3]. Radiculopathy and neurologic symptoms also resolved in both patients. Apart from asymptomatic hypocalcemia, no other side effects have yet been observed, but tight clinical check-ups and a longer MRI follow-up period are needed to evaluate the efficacy of denosumab in the treatment of ABCs. On the basis of these first two cases, we have started treating further patients and are considering initiating a clinical study to evaluate this form of treatment specifically in patients with ABC in critical locations and in cases of recurrence after initial surgical treatment.

## Conclusions

- Aneurysmal bone cysts in the spine are a challenge for disease management, due to the substantial risk of recurrence after intralesional resection.
- This report is the first description of the therapeutic administration of denosumab in two patients with an ABC.
- Denosumab is a human monoclonal antibody that blocks osteoclast maturation and function. It has been successfully used in the treatment of GCTs, and due to the immunohistochemical similarity between GCTs and ABCs it may possibly be used to treat ABCs as well.
- In the two cases of ABC reported here, good clinical and radiological short-term responses to denosumab have been observed so far.
- Denosumab represents a new treatment option for a subset of patients with previously untreatable ABCs.

Further research is needed on the potential role of denosumab in curative treatment.

**Acknowledgments** The authors especially thank Sebastian Retzlaff, MD, for contributing the MRI of patient no. 2.

**Conflict of interest** None.

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