European Spine Journal
https://doi.org/10.1007/s00586-018-5528-x

CASE REPORT

Denosumab: a potential treatment option for aneurysmal bone cyst of the atlas

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Received: 5 November 2017 / Revised: 11 February 2018 / Accepted: 14 February 2018

Abstract

Purpose Aneurysmal bone cysts (ABCs) of spine are conventionally treated with en-bloc resection or intralesional excision/curettage and reconstruction or filling of defects with bone cement. For the treatment of upper cervical ABCs, en-bloc resections are often not desirable considering the risk/benefit ratio while the risk of recurrence after intralesional excision is high. Hence, alternative management options are often necessary. We describe our clinical experience with one such treatment alternative-denosumab for the treatment of ABC of Atlas.

Methods and results We present a case of 16-year-old boy who presented with neck pain and restriction of neck movements. A large lytic lesion with multiple fluid–fluid interfaces involving vertebral arch of atlas was identified on further imaging. There was destruction of right lateral mass and the lesion was found encasing the right vertebral artery. Core needle biopsy confirmed the diagnosis of ABC. With no visible CT response after first session of intra-lesional injection of Calcitonin and Methylprednisolone, the patient was treated with denosumab (120 mg SC once-a-month) for a period of 12 months. His symptoms resolved within 7 months of onset of treatment and serial CT scans over 12-month treatment period showed complete ossification of the lesion. Further there was no evidence of recurrence at 12 months after completion of treatment.

Conclusion Our case report contributes to the accruing evidence on the effectiveness of denosumab for the treatment of spinal ABCs. However, long-term safety, risk of recurrence, optimal duration of treatment and consistency of denosumab are yet to be determined.

Keywords Spine · Atlas · Aneurysmal bone cyst · Denosumab · Methylprednisolone and calcitonin injection

Introduction

Aneurysmal bone cysts (ABCs) are rare benign tumours that comprise about 1% of all the primary benign bone tumours. About 10–30% of ABCs are sited in the mobile spine, of these 11–41% are seen in cervical spine [1–4]. ABCs of Atlas are rare and comprise about 10% of cervical ABCs [5]. Radiologically ABCs appear as lytic blood-filled lesions that contain multiple fluid–fluid interfaces separated by multiple fibrous septa. Histologically ABCs are characterized by multinucleated giant cells with hyper cellular stromal cells [2, 3, 6]. The natural history of ABCs is often unpredictable. Some of the ABCs may be slow-growing while others could be rapidly expanding and destructive [2, 4, 7]. Due to their prognostic unpredictability conventional treatment practice is curettage and filling of defects with cement or wide surgical resection with reconstruction [1–3]. This aforesaid approach may not be always feasible in ABCs of spine due to the presence of vital neural and/or vascular structures in their vicinity [1, 2, 5, 8]. From current literature, surgical resections are associated with a complication rate of 15–30% whereas the recurrence following an incomplete excision varies from 10 to 44% [1–3, 5, 9–11].

This case has been presented and discussed at Pesi Chacha Lectureship, National University Hospital, Singapore and Tumour Board Meetings at National University Hospital, Singapore.

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Published online: 22 February 2018

An ideal treatment for spinal ABC must preserve the spinal stability without compromising mobility, prevent recurrence and must be cognizant of the risk to neuro-vascular structures. The risks and complications associated with the surgical intervention led to a growing interest in the use of non-invasive or minimally invasive treatment options for the management of ABCs in upper cervical spine. Even though there is limited evidence to recommend these newer treatment options, they are worth trying in cases when the risks of surgical resections are unusually high [12]. Wide surgical resections, intralesional injection of various substances and serial transarterial embolization (TAE) have been considered for the treatment of atlanto-axial ABCs [13–18]. In this report, we present a case of ABC of the atlas that was surgically unresectable and most of the known alternative therapies were deemed either not suitable or had failed to yield desired results. Subsequently it was successfully and definitively treated with denosumab.

Methods and results

A 16-year-old boy presented with progressive severe neck pain of 2 months duration, localized to the sub-occipital region. The visual analogue scale (VAS) pain score was 9, Neck Disability Index (NDI) was 45 (scale 0–50) and the neck movements were severely restricted. Past history and family history were unremarkable. There was no focal neurological deficit. Radiographs and CT scan revealed an expansile lytic lesion of the C1 posterior arch and lamina with paper thin cortices (Fig. 1). MRI confirmed the findings revealing an expansile, multiloculated cystic lesion with multiple fluid levels in the C1 vertebrae, involving the posterior arch and right lateral mass (Fig. 2). There was Fielding type 1 rotatory subluxation of C1–C2 (Fig. 1). Percutaneous CT guided core biopsy confirmed the diagnosis of ABC. Digital subtraction angiography revealed the lesion to be hypervascular with multiple small arterial feeders, predominantly arising from the bilateral (right > left) V3 segments of the vertebral artery and some minor supply from branches of right thyro-cervical and deep cervical as well as ascending pharyngeal branches (Fig. 3). There were no dominant hypertrophic tumor feeding arteries suitable for selective embolization.

Under CT guidance a mixture of methylprednisolone (80 mg) and calcitonin (400 IU) was injected percutaneously into the lesion. A small volume of contrast added to the mixture confirmed good distribution of the drugs within the entire lesion. A follow up CT scan at 2-month interval did not show any interval sclerosis of the lesion; neither was any clinical improvement observed. Hence a multidisciplinary team involving a radiologist, oncologist and a spinal oncosurgeon discussed all the possible options with the patient and his family. The final decision to use denosumab for further treatment was reached through consensus.

Skeletal survey was performed to confirm epiphyseal fusion at the hip, pelvis, shoulder and elbow prior to commencing denosumab treatment. Dental examination was normal and calcium, phosphate and vitamin D levels were within normal range. One-hundred and twenty mg

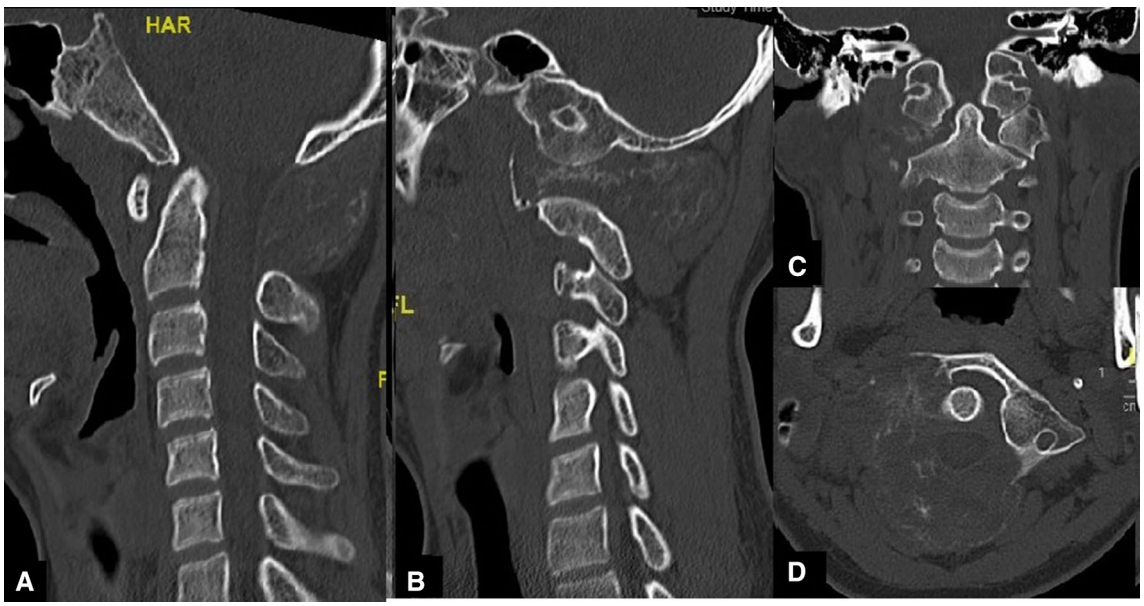

Fig. 1 CT-Scan of 16-year-old male showing lytic lesion involving right lateral mass (**b** and **c**) and posterior arch (**c**). There is Fielding type I rotatory subluxation of C1–C2 (**a**). The cortices have been eroded by the expanding lesion

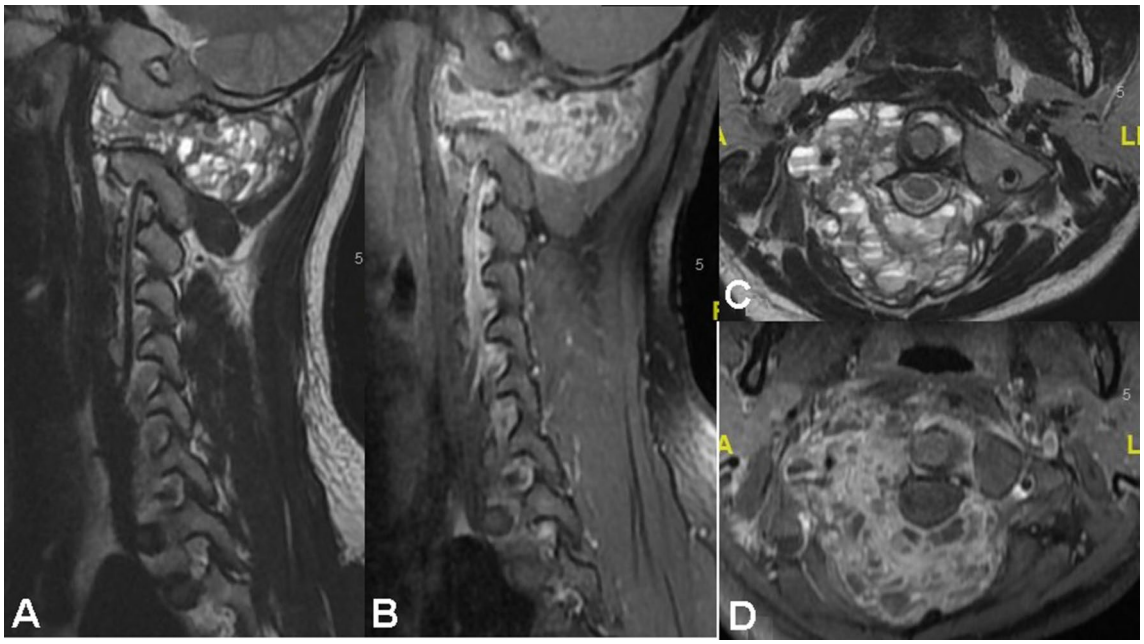

Fig. 2 MRI showing multiple fluid filled lytic lesions that enhances on post-contrast images (**b** and **d**). The lesion can be seen encasing the right vertebral artery (**c** and **d**); **a** T2-weighted parasagittal view, **b** contrast enhanced parasagittal view, **c** T2-weighted axial view, and **d** contrast enhanced axial view

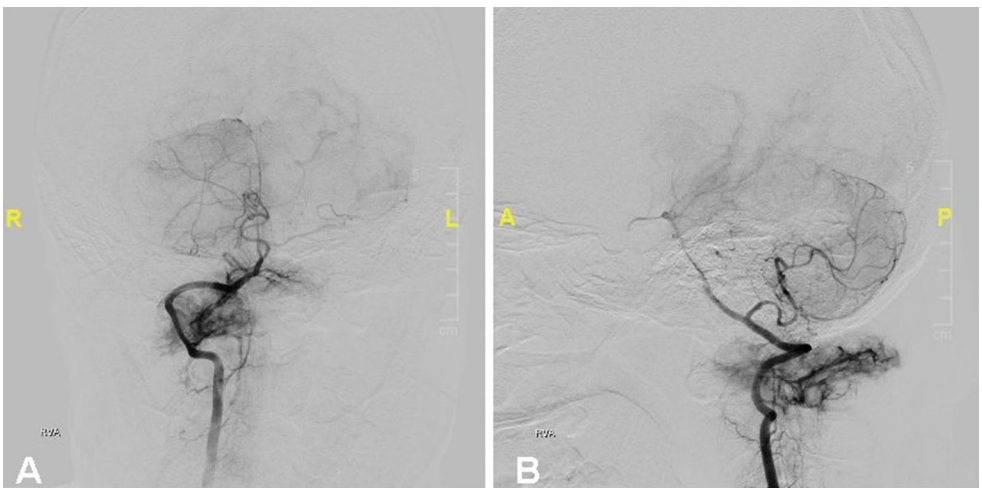

Fig. 3 Digital subtraction angiography showing patent right vertebral artery with multiple small arterial vessels arising from it and supplying the tumour mass; **a** coronal view, **b** sagittal view

of denosumab was injected subcutaneously once a month for 12 months. The patient was provided with a daily oral supplement of 800 mg calcium and 1000 IU vitamin D throughout the treatment and patient was kept on Philadelphia neck collar. The patient's symptoms were noted to improve 6 weeks into the treatment, and at 7 months he had regained pain-free full range of neck movements with a NDI of 5. Notwithstanding the clinical improvement, only patchy areas of ossifications were observed at the end of 6-months of therapy and hence it was decided to continue denosumab for 6 more months (Fig. 4). There was radiological evidence of basilar invagination, but it remained stable on serial scans without any further worsening of rotatory subluxation of C1–C2 (Figs. 4, 5). The lesion showed progressive ossification and no therapeutic side effect of denosumab was noted during this period. After completion of treatment, dynamic radiographs showed no instability (Fig. 6) and CT scan revealed reformation of the C1 lateral mass with

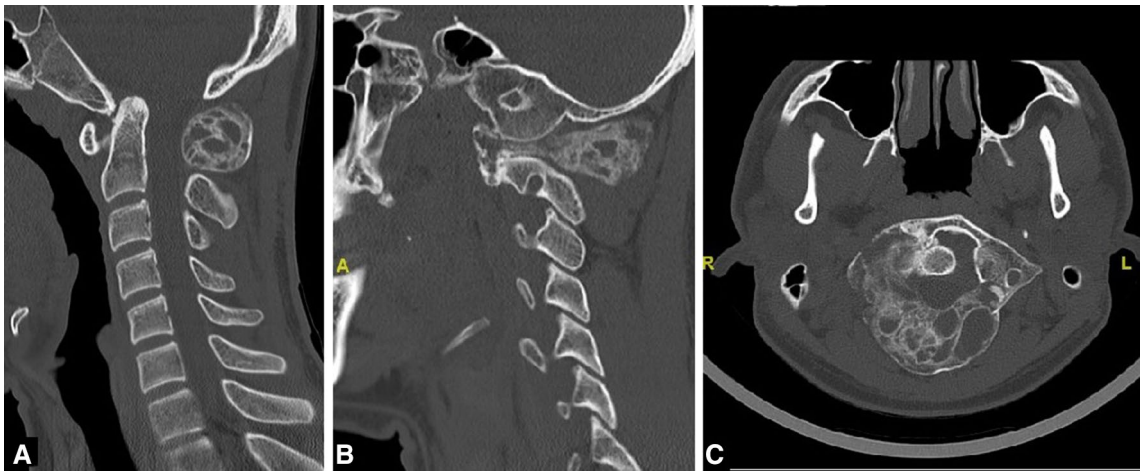

Fig. 4 CT-Scan after 6 months of initiation of denosumab therapy suggestive of sclerosis and ossification of the ABC; there is radiological basilar invagination; **a** sagittal view **b** right parasagittal view, **c** axial view

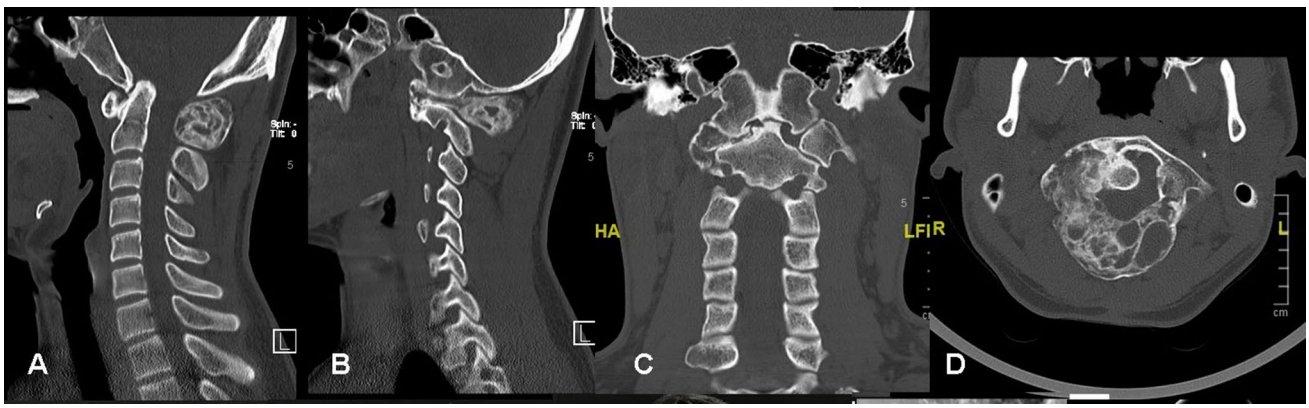

Fig. 5 CT-Scan at 12 months of follow-up after completion of 12-months therapy with denosumab; **a** sagittal view, **b** right parasagittal view, **c** coronal view, **d** axial view

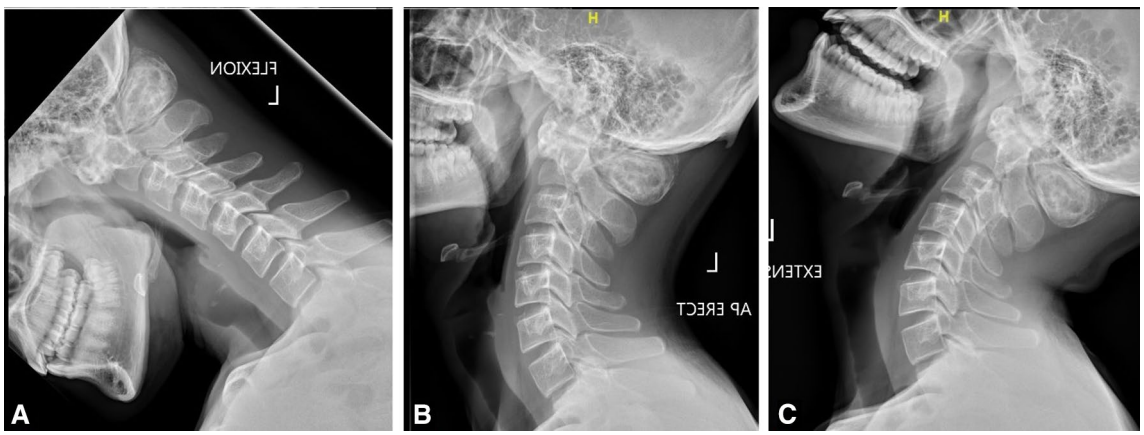

Fig. 6 Dynamic lateral radiographs at 12 months of follow-up after completion of denosumab therapy; **a** flexion view, **b** neutral view, **c** extension view

a hypertrophied C1 posterior arch. There was a 90% reduction in the lucent areas together with extensive intralesional sclerosis and cortical thickening. Follow-up CT scan at the end of 12 months after completion of treatment showed no signs of recurrence (Fig. 5).

Discussion

Treatment of atlanto-axial ABCs is often a therapeutic challenge. En-bloc resections at upper cervical levels are associated with the risk of major adverse events such as massive intraoperative bleeding, cerebral stroke, profound neural deficit and death [8]. The void left by the excision would require extensive reconstruction or filling of defects with cement and occipitocervical fusion [13, 17, 18]. There is a risk of cement seepage and thermal injury of neural structures while fusion would cause severe restriction of neck movements. A combined anterior–posterior or an anterolateral approach would be required and there is a substantial risk of injury to vertebral artery or spinal cord [13]. An overcautious attempt to preserve these structures would lead to an intralesional excision rather than the planned en-bloc or marginal resections, thereby increasing the risk of recurrence to 6-22% [2, 5]. Hence there was a need to explore other treatment alternatives.

Boriani et al. suggested that TAE is the most cost-effective treatment option for treatment of ABC when technically feasible and when there is no pathological fracture or neurological involvement [2]. In a recent study, Terzi et al. found that 17 out of 23 patients (73.9%) responded to serial TAE treated and showed no evidence of recurrence after an average follow-up of 36.3 months [8]. Mohit et al. successfully treated a 10-year-old girl having ABC of Atlas with three serial TAE and there was no recurrence at 18-month follow-up [14]. However, in our case, TAE had a high risk of non-targeted embolization of intracranial vertebral arterial territory and cord-ischemia. Hence was not considered.

Sclerosant therapy was not considered in our patient as the cortices were eroded. Through the eroded cortices there is a risk of seepage of sclerosants in vascular or neural elements leading to catastrophic complications [16]. Megavolt radiotherapy has been described to have good sclerosing effects on ABCs, but was not considered due to the higher radiation risk and its associated morbidities [8].

Multiple injections of intralesional Calcitonin with or without methylprednisolone have been described to suppress osteoclastic activity and promote new bone formation within the fibrous septa of the ABC [15]. Methylprednisolone has antagonistic and fibroblast inhibitory effect and it acts synergistically with calcitonin to cause tumour regression. A trial of intralesional injection of calcitonin and methylprednisolone was made, but there was no clinical or radiological improvement during 2-month follow up. Hence it was decided to commence denosumab therapy.

Denosumab, a human monoclonal antibody, binds to a cytokine receptor activator of nuclear factor-kappa B ligand (RANKL) and prevents the action of agonists acting through RANKL receptors. This prevents the subsequent activation and proliferation of the osteoclasts [19]. Following denosumab treatment, suppression of bone lysis has been reported in conditions including multiple myeloma, osteoporosis and giant cell tumors [20, 21]. Similarly, the malignant giant cells of ABCs secrete receptor activator of nuclear factor k-B ligand (RANKL) which explains a growing interest in the use of RANKL receptor antagonists, such as denosumab, in the treatment of ABCs [12, 22].

To the best of our knowledge, eight cases have been reported in the literature to support the use of denosumab in cervical and lumbosacral ABCs [6, 23]. Lange et al. highlighted the use of denosumab in two young patients (8 and 11 years) with recurrent ABCs of C5 vertebrae, following surgical excision. Tumor regression was observed in both the patients after denosumab and they were followed up for 2–4 months [23]. Pelle et al. reported tumour regression in a 5-year-old boy with a large, aggressive sacral ABC and showed that denosumab is a potential alternative to surgery in select ABC presentations [22]. Dubory et al. reported a sacroiliac ABC in a 27-year-old female that was treated with neoadjuvant denosumab followed by surgical curettage and cement reconstruction [20]. They also reported a cervicothoracic ABC in a 26-year-old female that presented with paraplegia and was treated with surgical decompression and fixation followed by denosumab as an adjuvant. Both these patients were followed for a period of 6 months and there was no recurrence. Skubitz et al. reported symptomatic and radiological improvement in a case of sacral ABC with a follow up of 12 months [6]. Ghermandi et al. reported ossification and no evidence of recurrence at 33-35 months of follow-up in two cases of lumbosacral ABC after 11–13 doses of denosumab [24]. To the best of our knowledge, our case report is the first to demonstrate the effectiveness of denosumab for the treatment of ABC of Atlas. We believe that a follow-up duration of 12 months is sufficient to analyze the tumour regression potential of denosumab as reported previously [20, 22, 23]. Preservation of neck movements and reduced morbidity are added advantages of such a non-invasive therapy. Presently there are no recommendations regarding the duration and frequency of follow-up following denosumab therapy. However the anecdotal experiences of recurrence following denosumab use in giant cell tumour logically dictate that 6-monthly follow-up for duration of 2 years would suffice [25, 26]. Denosumab has been successful in control of the tumour and ossification of the lesion in our report. Hence a local recurrence, if any, can be dealt with a limited surgery in the form of curettage and bone grafting/

cementing rather than an extensive resection and occipitocervical fusion required initially.

Patients on denosumab need monitoring for its potential complications through frequent physical examination, dental examinations and serial blood calcium levels. The disadvantages of denosumab include the risk of asymptomatic hypocalcemia, osteonecrosis of jaw, urinary infections and eczema [23]. Supplementation with vitamin D and calcium is essential for prevention of asymptomatic hypocalcemia. There is also a risk of stunted bone growth and remodelling in patients with open epiphysis [27]. Our case had Fielding type I rotatory subluxation of C1-C2 preoperatively and destruction of the lateral mass raised the concern for formation of stable or unstable craniovertebral junctional (CVJ) deformity during denosumab therapy [28]. The patient was given Philadelphia neck collar and was followed up with serial radiographs and CT scan. There was radiological evidence of basilar invagination during the initial few months of denosumab therapy (Fig. 4), but there was no further progression of basilar invagination or subluxation on serial CT-scans (Fig. 5). The patient was asymptomatic without any restriction of neck movements. Heterotrophic calcification after denosumab therapy can risk the formation of fixed CVJ deformity. Excessive bone formation between odontoid and C1 arch as seen in post-operative radiographs could have restricted neck movements, but due to compensation from the subaxial cervical spine it was not clinically evident. Potential late complications in the form of subjacent segment instability/unintended fusion warrants routine long-term follow-up [29].

The anecdotal experience accrued from our case and previous reports of denosumab in spinal ABCs suggest its potential as a non-invasive modality in the treatment of spinal ABCs. However, the long-term safety, optimal duration of treatment and consistency of denosumab are yet to be determined.

Compliance with ethical standards

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

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