



CASE REPORT

Aneurysmal bone cyst of the spine treated by concentrated bone marrow: clinical cases and review of the literature

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Received: 27 September 2016 / Revised: 11 December 2016 / Accepted: 24 January 2017
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Abstract

Purpose ABC is a benign lesion with unpredictable behavior. Its treatment is challenging, especially in poorly accessible surgical areas, such as spine and pelvis. Currently, the first-line treatment of ABC is repeated selective arterial embolization (SAE) until healing. Other options have been used with variable success rates. We propose an alternative treatment for spine aneurysmal bone cyst (sABC) based on the injection of concentrated autologous bone marrow.

Methods We retrospectively report and analyze here two cases of patients, a 14-year-old girl and a 16-year-old boy, both affected by ABC in C2 vertebra which were impossible to treat by SAE. They were treated with single or repeated injection of concentrated autologous bone marrow into the lesion. Their follow-up period is 27 months for both patients.

Results In the two cases reported here we observed a progressive ossification of the lesion, which was slow in one case, requiring three subsequent injections of concentrated bone marrow, and fast in the other case, beginning 1 month after the procedure. In both cases, the healing of the lesion was associated with symptom relief and the clinical status of the patients remains stable after 2 years.

Conclusions Although SAE can still be considered the first line in the treatment of ABC in the axial skeleton, new promising therapeutic procedures involving the use of mesenchymal stem cells are developing.

Keywords Aneurysmal bone cyst · Benign spinal tumors · Fluid–fluid levels · Selective arterial embolization · Surgical treatment · En bloc resection · Local recurrence · Intralesional injection · Bone marrow concentration · Mesenchymal stem cells

Introduction

Aneurysmal bone cyst (ABC) is a cystic lytic lesion of bone, consisting of blood lacunae separated by connective septa. In 30% of cases ABC is found inside other bone diseases (giant cell tumor, osteoblastoma, chondroblastoma, telangiectatic osteosarcoma), while in 70% of cases it occurs as a primary lesion.

Primary ABC has been considered for several years a pseudotumoral lesion of uncertain origin, but now it is proven to be a real benign primary tumor. It is described as an expansive and hemorrhagic primary tumor, usually showing a characteristic translocation resulting in the activation of the gene USP6 placed on 17p13. Primary ABC is a rare disease (about 1% of primary bone tumors) [1].

According to Enneking [2, 3], staging of ABC can be classified into latent (grade 1), active (grade 2) and aggressive (grade 3). Although ABCs of the spine are considered benign, they can be locally aggressive, garnering up to an Enneking stage 3 classification for benign musculoskeletal lesions. If local recurrence occurs after the index treatment, the recurrent ABC can be very difficult to manage and can result in significant local neurological and structural impairment [4, 5]. Therefore, selecting and delivering the appropriate index treatment is pivotal for the management of spinal ABCs. Given the variability in ABCs presentation, these lesions can be treated by a

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variety of methods, including intralesional resection, en bloc resection and selective arterial embolization (SAE) [6].

If the surgical treatment is considered, because of the presence of pathological fracture, spinal instability or neurological impairment, en bloc resection with the goal of wide margins is an effective treatment method with an extremely low recurrence risk and is especially advised for more aggressive tumors. However, though en bloc resection is more effective at preventing recurrences, its benefits must be weighed against increased morbidity. If intralesional resection is undertaken, preoperative embolization is strongly recommended to prevent significant intraoperative bleeding. To avoid the risks associated with surgery, another viable treatment option is SAE alone. This treatment is limited by potentially increased morbidity associated with multiple embolization procedures and subsequent radiation exposure. However, this risk must be weighed against the risks associated with surgery, particularly en bloc resection, and SAE should be considered first-line treatment in cases that do not involve extensive neural elements or increased risk of pathological fracture.

Ultimately, decisions concerning treatment must be carefully weighed by considering a patient's unique clinical picture, size and location of the spinal ABC, and the surgeon's familiarity with the different treatment options [4–7].

Taking into account all these considerations, we use SAE until healing as first-line treatment for ABC. Bone marrow-derived mononuclear cells injection therapy has been introduced for aneurysmal bone cysts in order to stimulate osteoblastic regeneration with promising results [8, 9]. In this report, we present two cases of ABC localized in C2 vertebra which could not be treated by SAE. Successful management of these lesions was obtained by injection of concentrated autologous bone marrow into the cysts in order to obtain bone regeneration.

Case report 1

History and examination

A 14-year-old girl was referred with an aneurysmal bone cyst in the posterior elements of C2. Diagnosis was based on histopathological examination of tissue samples obtained by open incisional biopsy performed elsewhere. Patient was complaining of gradual onset of neck pain persisting since 1 month, before the biopsy, with no history of trauma. Patient was otherwise healthy and had unremarkable medical history.

Radiological workup with plain radiographs revealed an osteolytic lesion expanding the spinous process of C2 and

the ipsilateral lamina (Fig. 1a–c). MRI showed a hyperintense lesion in the T2 scans with multilobulated pattern and internal septa with multiple fluid–fluid levels expanding the posterior elements of C2, along with the correspondent vertebral body, and destroying the left pedicle (sectors 4–11, layers A to D, according to the Weinstein–Boriani–Biagini classification [10]). The epidural space involvement (layer D) was mild, with no dislocation of the spinal cord (epidural spinal cord compression grade 1-C [11]). Revision of the slides by the pathologist confirmed the diagnosis of aneurysmal bone cyst.

Despite these findings, the major complaint of the patient was pain, otherwise she was neurologically intact. Arteriography showed the necessity to close the left vertebral artery in order to treat the lesion. The closure of left vertebral artery was well tolerated during SAE (Fig. 1d); however, the study of deep cervical artery showed that it was contraindicated to embolize the circle from this artery because of the presence of numerous anastomoses with the cranial stump of the left vertebral artery. Thus, the protocol of serial selective arterial embolizations (SAE) was suspended and percutaneous injection of bone marrow concentrate into the cyst was proposed. As patient and parents accepted, written consent was collected and the procedures were scheduled.

Operative technique

With the patient lying prone on OPT table with Mayfield support for the head and under general anesthesia, correct levels were checked on fluoroscopy. 60 ml of bone marrow was harvested from the posterior iliac crest with a 10-gauge needle. The bone marrow aspirate was placed in a bag for transfusion and MSCs were separated from autogenous bone marrow by Res-QTM 60 BMC concentration system, after centrifugation at 3200 rpm for 12 min. The final product was 6 ml of MSC-enriched buffy coat, as the centrifugation allowed to isolate and concentrate nucleated cells from the other bone marrow elements. Under fluoroscopic control, the lesion was completely filled with the concentrated bone marrow by using a 18G needle (Fig. 2).

Postoperative course

The postoperative recovery was uneventful and patient was discharged the day after surgery.

One month after the procedure, at MRI and CT scan the characteristics of the cyst appeared unchanged and the dimensions appeared slightly increased. The lesion was largely extended in the adjacent soft tissues with a component which invades the vertebral canal. Three subsequent angiographic studies were performed in order to evaluate the possibility of treating the cyst by SAE. However, it was

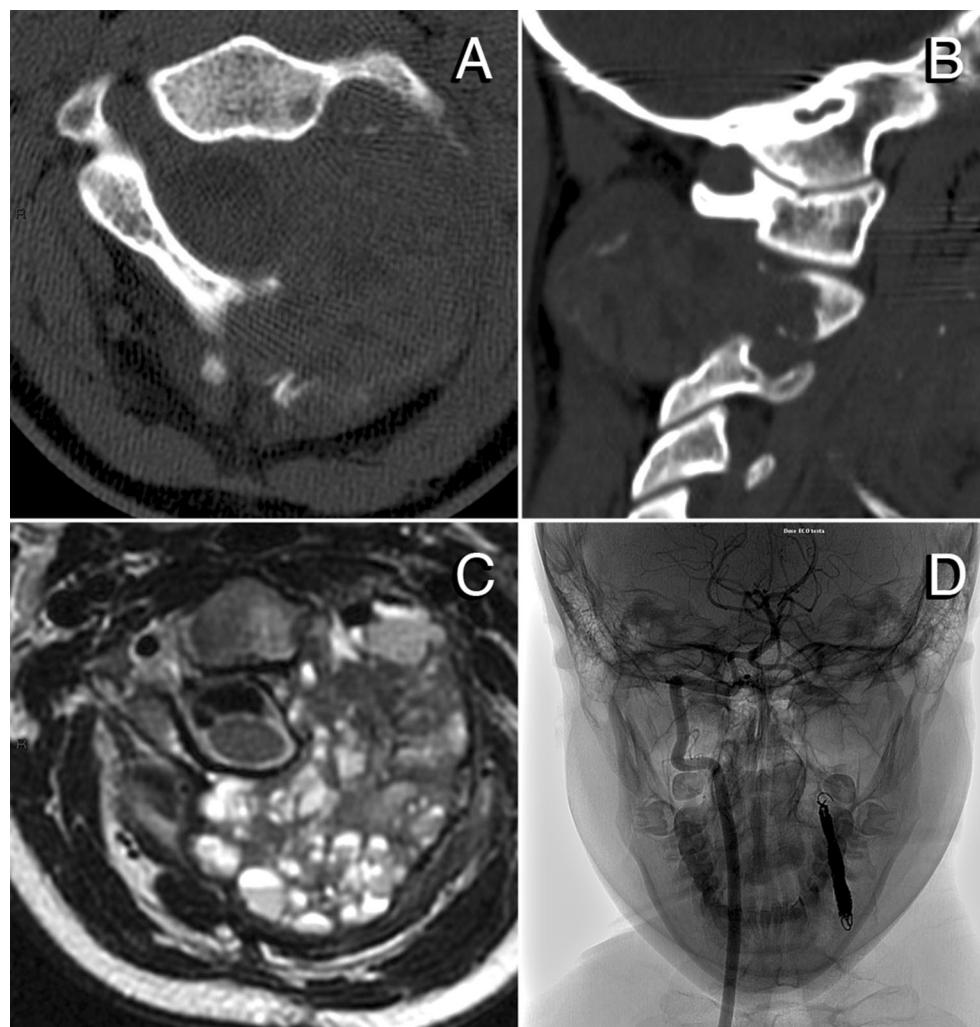


Fig. 1 Imaging concerning case report 1 before the treatment of C2 aneurysmal bone cyst with concentrated bone marrow. Axial (a) and sagittal (b) CT scan views; axial MRI view (c); arteriography for selective arterial embolization (d)

not possible to perform such kind of treatment because the unique pathological circle feeding the lesion was dependent from the left cervical artery.

Four months after the treatment with MSCs, MRI and CT scan analysis showed a slightly increased calcification of the osteolytic component present in the vertebral body and in the left joint of C2 (Fig. 3a).

The procedure of injection of concentrated bone marrow into the cyst was repeated for two more times, at 4 and 8 months after the first treatment.

Two months after the second treatment, MRI and CT scan analysis showed a slight reduction of the cyst dimension and the presence of a sclerotic rim (Fig. 3b). After the third treatment, the process of cyst calcification gradually increased (Fig. 4a, b).

18 months after the first MSCs injection, the patient was asymptomatic. MRI and CT analysis showed a favorable course of the disease, with significant progression of the

cyst calcification (Fig. 4c–e). At the last recent follow-up, 27 months after the first MSCs injection, a further reparative process of the lesion was observed.

Case report 2

History and examination

A 15-year-old boy came to visit with imaging showing a lytic lesion in C2 with net margins and no sign of local aggressiveness, suggestive for aneurysmal bone cyst.

Radiological workup with plain radiographs revealed an osteolytic lesion blowing the spinous process of C2 and expanding the posterior elements (Fig. 5a–d). Subsequent MRI showed the lesion to be hyperintense in the T2-weighted scans with multilobulated pattern and internal septa with multiple fluid–fluid levels. The lesion appeared

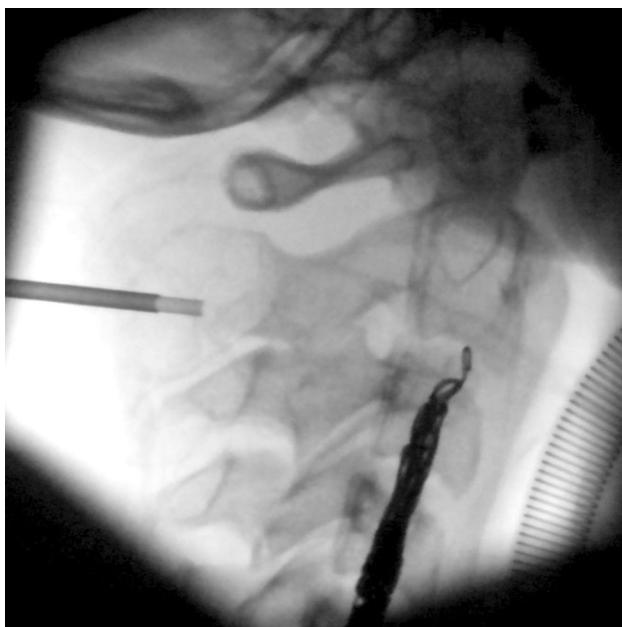


Fig. 2 Radiographic image collected during the injection procedure of concentrated bone marrow into the aneurysmal bone cyst

to be expanding from the posterior elements into the correspondent vertebral body bilaterally, encircling the spinal canal (sectors 1–12, layers A–D, according to the Weinstein–Boriani–Biagini classification [10]). The epidural space involvement (layer D) was mild, with no dislocation of the spinal cord (epidural spinal cord compression grade 1–C [11]).

Despite these findings, the patient was asymptomatic; however, the osteolytic area was increasing over time and the patient was referred for CT-guided biopsy. The histopathological examination of tissue samples obtained by CT-guided biopsy confirmed the suspected diagnosis of aneurysmal bone cyst.

The patient underwent selective arteriography examination, showing the presence of a small pathological circuit feeding the lesion which was dependent on the vertebral and the cervical arteries. Anastomosis between ascendant cervical arteries and vertebral arteries were detected, which did not allow to perform the selective arterial embolization of the lesion with safety margins.

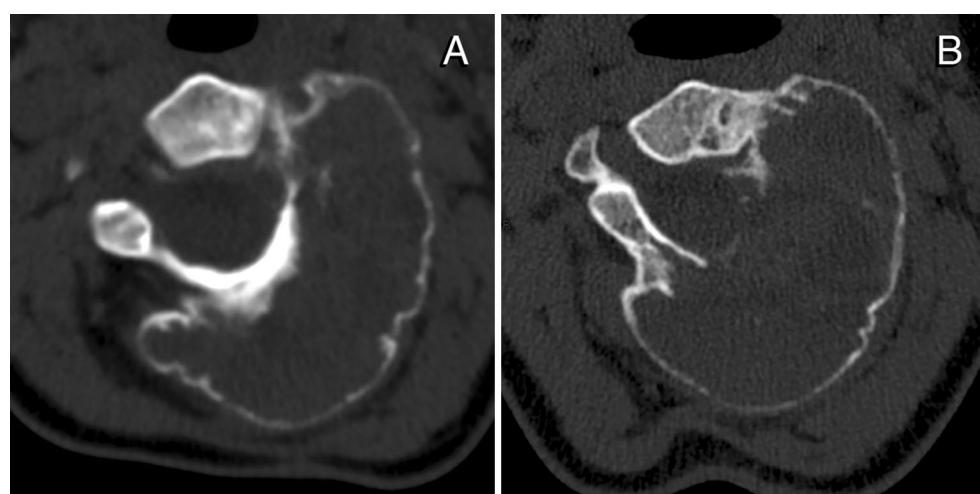


Fig. 3 Case report 1: axial CT scan views of ABC performed 4 months after the first treatment with concentrated bone marrow (**a**) and 2 months after the second treatment (**b**)

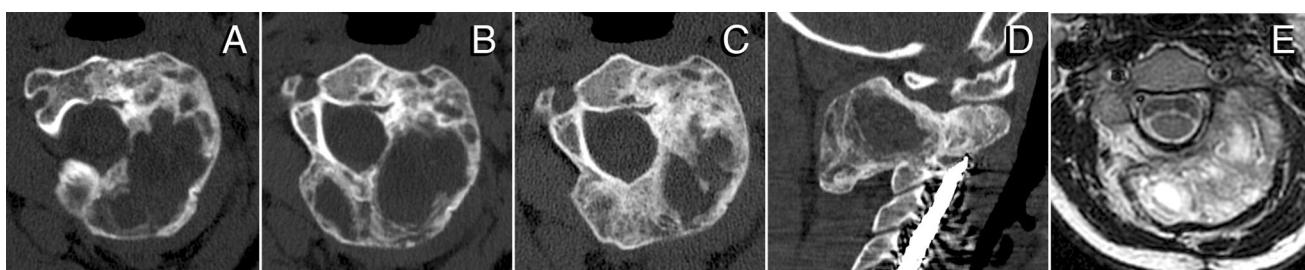


Fig. 4 Case report 1: axial CT scan views of ABC performed 2 (**a**), 5 (**b**) and 10 (**c**) months after the third treatment with concentrated bone marrow, showing the progressive calcification process of ABC. Sagittal CT scan view (**d**) and axial MRI view (**e**) performed at the

same follow-up period (18 months after the beginning of the MSCs treatment), confirming the evolution of ABC with significant ossification of the lesion



Fig. 5 Imaging concerning case report 2 before the treatment of C2 aneurysmal bone cyst with concentrated bone marrow. Sagittal MRI view (a), sagittal CT scan views (b, c), axial CT scan view (d)

Operative technique

At this time, 1 year after the occasional finding of the lesion, CT scan showed a large expanding formation involving most of C2 vertebra, in the body, the lateral masses and the dens, with extension to all the posterior arch that appeared swollen, particularly in the spinous process. The lesion had a multilobulated pattern and internal septa with fluid–fluid levels. It causes an irregular thinning of the cortical bone in several points.

Because of the impossibility of performing SAE treatment, it was decided to treat the ABC lesion by injection of concentrated bone marrow, after obtaining the written consent of the patient and his parents.

The operative procedure was performed as described above.

Postoperative course

The postoperative recovery was uneventful and patient was discharged 2 days after surgery.

MRI and CT analysis, performed at 1 month after the procedure, showed the presence of initial bone remodeling process and increasing of the calcific component of the lesion, particularly in the posterior arch.

The ossification was increased at 3 and 6 months of follow-up and 1 year after the concentrated bone marrow injection, the cyst appeared completely ossified, while the patient was completely asymptomatic (Fig. 6a, b). Clinical and radiographic outcomes remained stable at the last follow-up, 2 years after the first injection.

Discussion

Aneurysmal bone cyst (ABC) is a benign cystic lesion of bone composed of blood-filled spaces separated by connective tissue septa containing fibroblasts, osteoclast-type

giant cells and reactive woven bone. It was first described by Jaffe and Lichtenstein in 1942 as an autonomous pathological entity [12], thus differentiating it from other conditions characterized by giant cells, like giant cell tumors, or by vascular appearance, like hemangiomas or telangiectatic osteosarcomas [13].

ABC is a rare, probably underestimated lesion with an incidence of 0.14 per 10^5 individuals [14], showing a higher prevalence in the first two decades of life and a slight female predilection (ratio 1.16).

Pathogenesis of ABC is unknown and probably inhomogeneous; it may occur de novo (primary ABC) or represent a hemorrhagic–cystic change complicating another benign or malignant lesion (secondary ABC). Even if primary ABC is more frequent than secondary ABC (70 vs. 30%), careful evaluation of the history of the patient and of his imaging must be run out to detect any potentially associate lesion which can either be a primary bone tumor, a metastatic lesion [15] or a tumor-like lesion [16].

ABC is most commonly found in the metaphysis of long tubular bones (femur and tibia); nevertheless, spine is the localization where up to 30% of ABC cases are reported in the English-spoken literature [17, 18], this being one of the most prevalent spinal lesion.

Within spine [4, 19–23], it has been described in cervical, thoracic and lumbar regions as well as in the sacrum, but it was never reported in the coccyx. It most commonly involves asymmetrically the posterior elements of the neural arch.

Clinically, ABC might even be asymptomatic but usually presents with pain and swelling. Spinal localizations may present with symptoms of compression on the spinal cord or nerve roots such as numbness, difficulty in walking, sensory disturbances, or motor weakness. These symptoms can even have sudden onset caused by pathological fractures (which are uncommon for ABC in the extremities) [1].

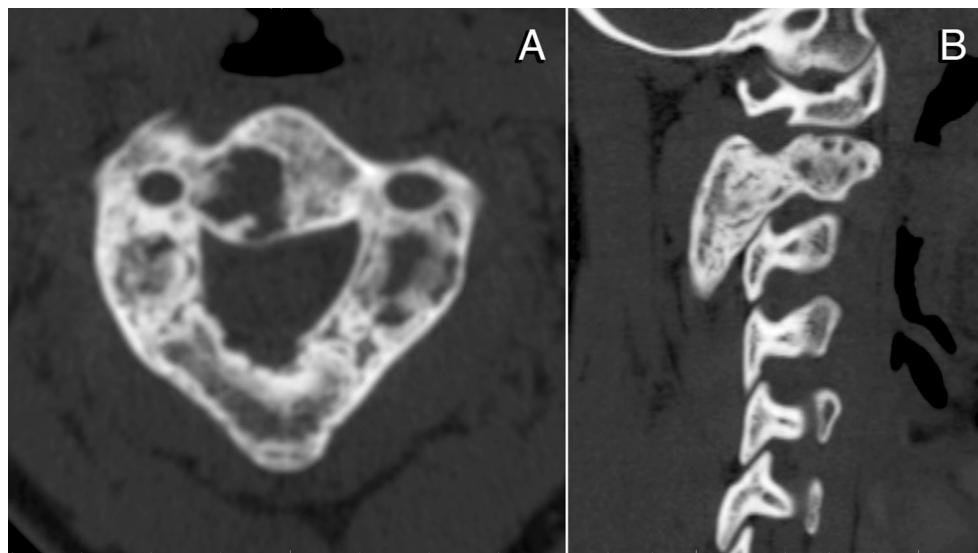


Fig. 6 Case report 2: axial (a) and sagittal (b) CT scan views performed 1 year after the treatment with concentrated bone marrow, showing the complete ossification of ABC

Definitive diagnosis is achieved by biopsy [24] on histological typical pattern, but imaging might be very suggestive showing pathognomonic “fluid–fluid” levels on computerized tomography scan (CT) and magnetic resonance imaging (MRI).

Many treatment strategies have been proposed to manage ABC [6] but, being it a rare lesion, their efficacy is mostly based on the results of retrospective case series [17, 25–32] and only few prospective studies have been run [7].

Surgery has been the treatment of choice for decades, but is burdened by recurrence rates up to 25% [18]. In order to lower recurrence rates, more aggressive surgical protocols have been attempted, up to en bloc resections which in fact did significantly lower recurrence rates. However, such aggressive strategies expose patients to unreasonable risks [5, 33–35] compared to the nature of this lesion, leaving this option suitable just for expendable locations such as proximal fibula or distal ulna. Nevertheless, en bloc resection in spine can still be an option in case of posterior elements only involvement (sectors 9 to 4) in order to decrease intraoperative blood loss. Thus, this technique being not used in an oncological standpoint, achievement of wide or marginal/focally intralesional margin does not significantly affect recurrence rates.

Finally, taking into considerations that the most affected age group is young, aggressive surgery may damage growth plates and result in long-term iatrogenic deformity, despite any reconstructive effort.

For these reasons, treatment for ABC in the axial skeleton focused on less invasive options such as selective arterial embolization (SAE) or cyst injections

(steroids, calcitonin, doxycycline, Ethibloc, osteoinductive agents).

Actually, SAE resulted as effective as surgery, but with lower complications rate and can be considered, when technically feasible and safe, as first option in the treatment of ABC without neurological impairment, pathological fracture nor instability [7, 23]. Despite this, surgery still remains an option in cases not responding to multiple procedures, or when progressive neurologic deterioration or instability occur as complications during repeated SAE therapeutic protocol.

Nevertheless, SAE need to be performed by an experienced interventional radiologist due to the risk of embolization of spinal cord feeding arteries resulting in dramatic neurologic impairment.

Intralesional injections of calcitonin [36], steroids [37, 38] or doxycycline [39] are safe procedures with no major side effects but still high recurrence rates [40]. On the contrary, alcoholic zein solution (Ethibloc) injection is not recommended in the axial skeleton, due to severe potential complications such as meningitis, pulmonary emboli, nerve damage and even death [41].

Radiation therapy has been a popular option in the past decades as an adjuvant to surgery and even used alone, but it has been progressively abandoned. The exposure of a young patient to a high amount of radiation is the limit of this treatment, which can be responsible for the development of radio-induced sarcoma and, for spinal locations, of iatrogenic damaging of neurostructures.

Recently, treatment with Denosumab, a human monoclonal antibody to RANK ligand, has been used for ABC, as well as for giant cell tumor of bone (GCT) [42–46]. This

choice is due to the similar pathophysiology of ABC and GCT, because malignant cells secrete receptor activator of nuclear factor k-B ligand (RANKL) which is involved in bone destruction. We recently used Denosumab in two cases of ABC of the spine, reporting interesting results [47].

Another attractive option is to stimulate the intrinsic healing potential of ABC using a mesenchymal stem cell-based therapy. The goal of this treatment is to interrupt the destructive osteoclastic process and promote spontaneous bone regeneration. Mesenchymal stem cells can be isolated from different tissues, from blood to bone marrow, but v-MSCs showed greater potential for osteoblastic differentiation [48]. Furthermore, v-MSCs can be mixed with several biomaterials which act as osteoconductive scaffolds, such as demineralized bone matrix (DBM). This mixture can be used to fill bone defects during the same single-step procedure, preventing complications associated with in vitro culture of MSCs and reducing discomfort to the patient. To date, some authors [9, 49, 50] performed mesenchymal stem cells therapy for the treatment of ABC in long bones and sacrum reversing expansion and promoting the intrinsic healing potential of ABC. We recently used this kind of treatment for an aneurysmal bone cyst in a thoracic vertebra refractory to multiple embolizations, reporting successful results.

We report here two cases of young patients (14 and 16 years old, respectively) affected by ABC localized in C2 vertebra. Recently, a similar case, reported in a 9-year-old child, was treated by an invasive surgical technique: C2 corporectomy with complete ABC resection, multilevel posterior decompression, C2–C4 anterior corporectomy, discectomy, and fusion, and posterior occipital–cervical fusion. Postoperative CT scan showed no residual tumor, solid incorporation of bone graft and absence of mechanical complications. The patient had a successful postoperative course, reported no complications and remained free of tumor at 1-year follow-up [51].

In our cases arteriography studies revealed the impossibility to proceed safely with SAE treatment, because the pathological lesions appeared to be fed by a pathological circle depending on cervical and vertebral arteries. Thus, in both cases we decided to avoid invasive surgical treatments and we treated the lesions by injection of a mixture of concentrated autogenous bone marrow and demineralized bone allograft to fill the bone loss and enhance a biological response which led to new bone formation and healing.

This treatment provided very rapid and significant improvement in one case, with complete ossification of the lesion within 1 year from the treatment. In the other case, a favorable outcome became evident only after two subsequent treatments with MSCs.

We recently treated some other patients with injection of concentrated autologous bone marrow. However, they still have a short follow-up period (1–6 months); they are repeating the procedure and their results have to be analyzed in order to publish more accurate and significant data.

Conclusion

ABC is a benign lesion with unpredictable behavior. This makes its treatment challenging especially in poorly accessible surgical areas, such as spine and pelvis. Serial SAE were proved to be effective as first-line treatment for ABC. Nevertheless, such protocol is limited by the possibility to perform embolization in safe conditions without the risk to block feeding arteries, causing a significant impairment.

MSCs therapy appears to be a valid alternative for spinal ABC management when SAE treatment is not indicated or ineffective. Moreover, being able to obtain bone marrow with the same surgical incision during spine surgery is of great advantage, since vMSCs showed a promising potential for osteoblastic differentiation.

Acknowledgements The authors thank Mr. Carlo Piovani for his helpful collaboration in patients' images storage and editing and Dr. Cristiana Griffoni for collaboration in the manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Considering this is a retrospective study, formal consent is not required.

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