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Denosumab: non-surgical treatment option for selective arterial embolization resistant aneurysmal bone cyst of the spine and sacrum. Case report

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Abstract. – OBJECTIVE: Aneurysmal Bone Cyst (ABC) is a cystic lesion of bone, occurring in 70% of cases as a primary lesion. Even if the metaphyseal region of long bones is more frequently involved, vertebral localization is not rare: ABC represents 15% of all primary spine and sacral tumours. Selective arterial embolization (SAE) represents the first treatment option for vertebral ABC. However, in few cases, multiple SAEs are not possible. The aim of this work is to report two cases of vertebral ABC unresponsive to SAE positively treated with Denosumab.

PATIENTS AND METHODS: Two patients affected by ABC of the lumbar spine were treated by SAE without any response. Thus, the patients were submitted to an off-label treatment with Denosumab, following the same protocol already used in case of Giant Cell Tumour (GCT): 120 mg once a week for 4 weeks consecutively, then once every 40 days.

RESULTS: In both cases, patients resulted to be pain-free after 11-13 Denosumab administrations and CT scan showed almost complete ossification of the lesions.

CONCLUSIONS: The two cases reported here are not conclusive but they may support the project of a prospective study to confirm the effectiveness of Denosumab in ABC treatment as an alternative to SAE.

Key Words:
Aneurysmal bone cyst, Spine, Selective arterial embolization (SAE), Denosumab.

Introduction

Aneurysmal bone cyst (ABC) is a cystic lesion of bone, consisting of blood lacunae separated by connective septa; in 30% of cases is found inside other bone diseases (giant cell tumour, osteoblastoma, chondroblastoma, telangiectatic osteosarcoma), while in 70% of cases it occurs as a primary lesion[1].

Primary ABC is a rare disease (about 1% of primary tumours of bone). Considered for several years a pseudotumoral lesion of uncertain origin it is now proven that it is a real benign primary tumor, associated with a specific pattern of genetic alterations that result in the activation of the gene USP6 located on 17p13[2].

Imaging is typical and shows an expansive, osteolytic lesion, which swells and sometimes destroys bone. Aggressive osteolytic area on CT scan and multiple fluid/fluid levels on MRI are characteristics.

Histologically it is composed of large gaps filled with blood, separated by thin fibrous septa of connective tissue, that contain several cellular elements, often including multinucleated giant cells.

According to Enneking, ABC ranges stage 1 to 3[3].

Even if the metaphyseal region of long bones is more frequently involved, vertebral localization is not rare: ABC represents 15% of all primary spine and sacral tumors. Compared to other skeletal locations, vertebral involvement presents clinical and treatment peculiarities.

Enneking stage 3 lesions (benign aggressive) can provoke nerve roots, spinal cord or cauda equina compression with a wide range of symptoms.

Rarely, a pathological fracture may occur and in this case an acute paraplegia or a cauda equine syndrome is possible.

Different surgical (intralesional curettage with or without instrumentation or en bloc resection) and non-surgical (selective arterial embolization (SAE), direct intralesional injection, radiation therapy) options have been proposed for the treatment of primary ABC. The treatment of secondary ABC is that of the primary tumour.

Surgical curettage must be carefully considered due to the high risk of profuse intraoperative bleeding and late local recurrence. En bloc resection, related to high morbidity rate, represents an overtreatment for a benign lesion as ABC. Radia-

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tion therapy is nowadays reserved only for very selected local recurrence cases considering the proven risk of secondary malignancy.

The good results obtained in a previous published study[4] convinced us that selective arterial embolization represents the first treatment option for vertebral ABC.

Despite this, it must be underlined that, in few cases, multiple SAEs are not possible, due to the close connection of tumour vascularity with cord feeding arteries, they do not achieve the expected result or they are contraindicated considering radiation exposure. For this reason, a therapeutic alternative must be found.

Denosumab is a fully human monoclonal antibody that inhibits RANKL (receptor activator of nuclear factor kappa-B ligand), the main osteoclastogenic cytokine; its effect is to drastically reduce bone resorption. FDA approved it for the treatment of osteoporosis and bone metastases. In addition, following the publication of trials that have demonstrated its efficacy, it is spreading for medical treatment of giant cell tumour of bone (GCTB)[5].

Histomorphological characteristics similar in GCTB and ABC is the prerequisite that justifies the use of the antibody in selected ABC cases.

According to the protocol approved by our Institution for non-surgical treatment of GCTB, Denosumab was administered off-label as follow: 120 mg once a week for 4 weeks consecutively, then once every 40 days.

Patients evaluation at follow-up included MRI, CT scan and clinical and radiographical teeth and mouth examination.

The aim of this work is to report two cases of vertebral ABC unresponsive to SAE positively treated with Denosumab.

Case Report

Case 1: 42-year-old healthy man with a 2 years story of lumbar back pain (Figure 1)

At the onset of symptoms an MRI was performed and showed an L5-S1 giant cystic lesion with fluid-fluid levels suspected to be ABC. Treated elsewhere, a biopsy was not performed and the patient underwent selective arterial embolization with partial pain relief. Six months later symptoms recurred, with worsening both lower limbs radicular pain.

When admitted to our Institute, clinical examination revealed a scoliotic attitude of the lumbar

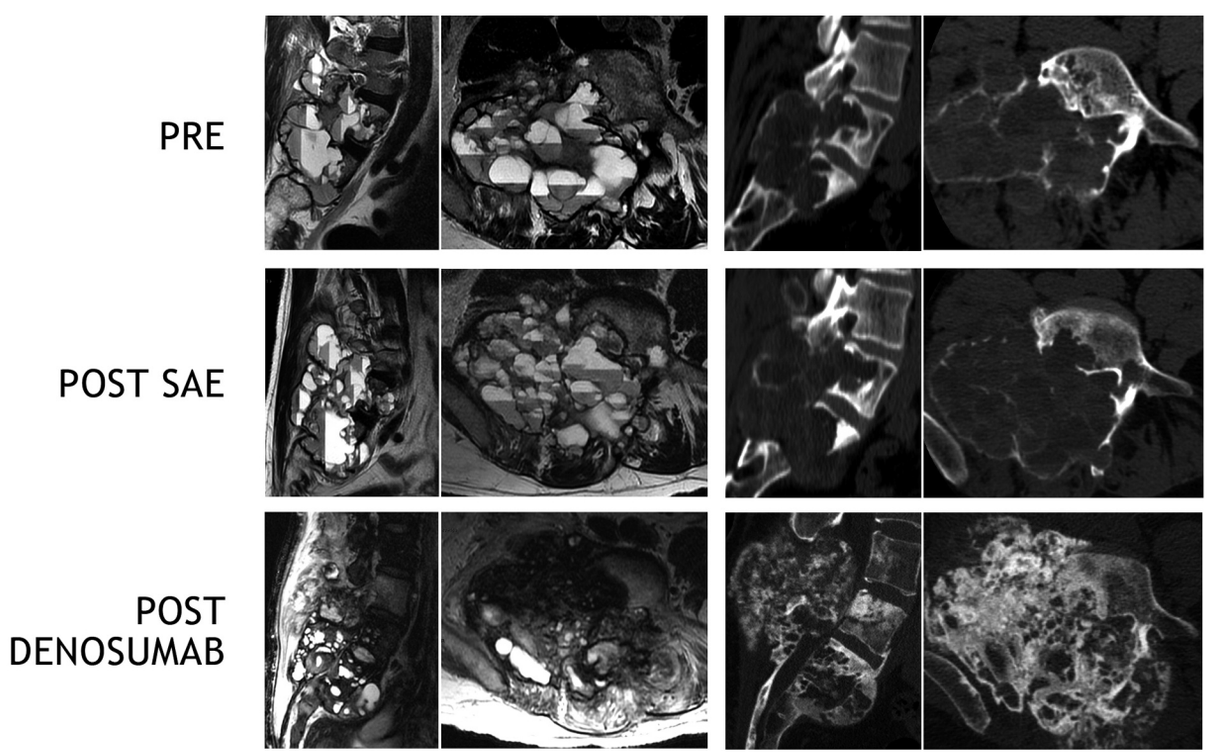

Figure 1. Imaging history of Case 1, reporting CT scan and MRI performed before ABC treatment, after embolization and after treatment with Denosumab.

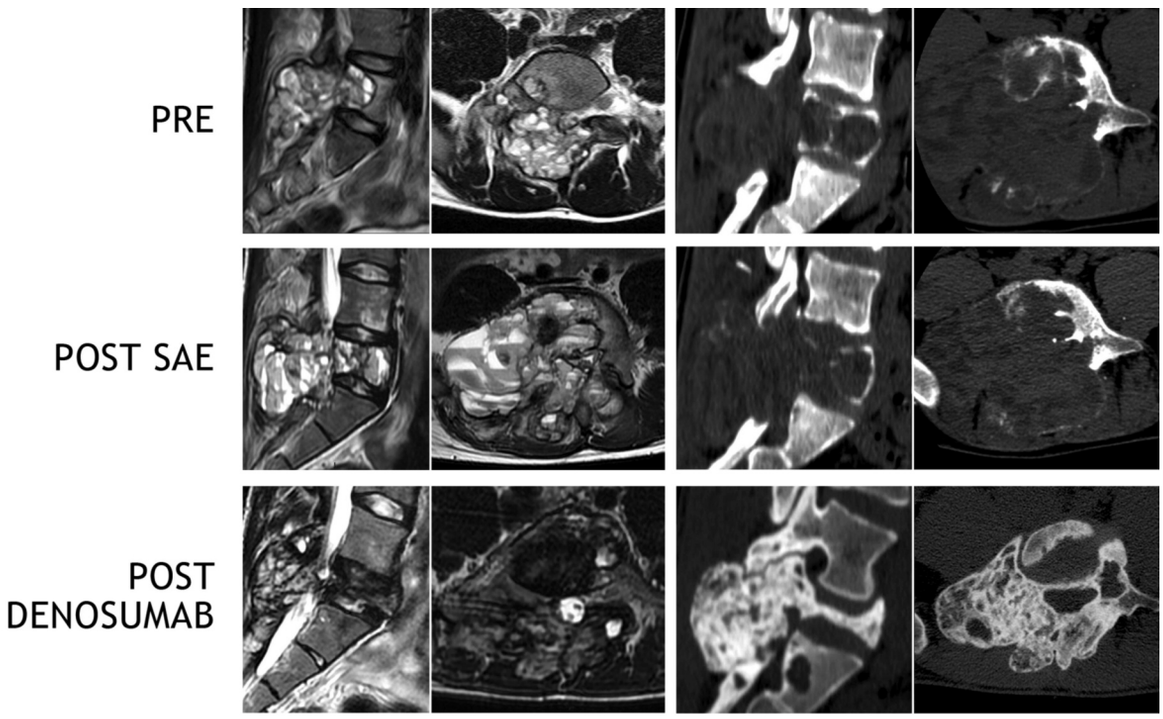

Figure 2. Imaging history of Case 2, reporting CT scan and MRI performed before ABC treatment, after embolization and after treatment with Denosumab.

spine, stretched back muscles, and right L5 and S1 nerve root paresis; hypoesthesia was present too. CT scan confirmed the hypothesis of a wide aggressive L5-S1 ABC showing a ballooning, multilocular lytic lesion with a blown-out thin layer of cortical bone with significant extraosseous extension. MRI showed a large "soap-bubble" lesion with right posterolateral extension causing L5-S1 nerve roots compression.

A consecutive SAEs treatment program was started and performed monthly 6 times. Despite this, a slowly progressive worsening of the lesion was observed: MRI showed mild growth of the mass and increase of typical levels; the patient reported an aggravation of back and leg pain with unchanged paresis. The treatment was stopped and a CT guided trocar biopsy was performed; final histological report confirmed the previous hypothesis of aggressive ABC, in this case unresponsive to SAE.

Avoiding surgery, related to high risk of severe neurological consequences and intraoperative bleeding, and considering literature[6], the patient was submitted to an off-label treatment with Denosumab. The same protocol already used in case of giant cell tumour (GCT) was followed: weekly 120 mg injections of Denosumab were performed first for 1 month, then monthly.

At each admission, CT and MRI were performed and showed progressive ossification of the lesion. Patient was symptoms free after 6 administration of Denosumab (2 months follow-up).

After a total number of 13 Denosumab administrations, at the final follow-up (35 months after diagnosis), the patient was pain-free and CT scan shows almost complete ossification of the lesion.

Case 2: 16-year-old healthy boy with four months back pain and sciatic right leg pain (Figure 2)

When admitted to our Institute, 3/5 strength weakness at right quadriceps and right L5 nerve roots hypoesthesia were recorded.

X-Rays and CT-scan revealed a L5 osteolytic lesion involving pedicle, lamina and spinous process with extraosseous extension. MRI imaging showed a multicystic mass with fluid-fluid levels with an intermediate signal on T1-weighted images and increased signal uptake on T2 images, consistent with blood or fluid. A biopsy was performed first and final histological report confirmed the hypothesis of ABC.

A consecutive SAEs treatment program was started and performed monthly 5 times but without any evidence of efficacy due to pathologic vascularity every time developing after embolization.

After 6 months of treatment, an untreatable right sciatalgia required a hospitalization. CT trocar biopsy was performed again, and the histological result confirmed the diagnosis of ABC, unresponsive to SAE.

The patient was submitted to an off-label treatment with Denosumab following the same protocol already used in case of giant cell tumor (GCT).

Progressive neurological and clinical improvement occurred since the 1st month of treatment; CT and MRI imaging have showed a gradual mass reduction and progressive ossification since the 3rd month of administration.

A total number of 11 Denosumab administrations were performed; at the final follow-up (33 months after diagnosis) the patient is completely pain-free, back to normal daily activities and sport practice.

Discussion

Treatment of spinal and sacrum ABC resistant to SAE is challenging.

Surgical treatment is not recommended considering the danger of intraoperative bleeding, neurological post-operative deficit and late local recurrence in case of intralesional curettage and the high rate of possible complications in case of en bloc resection.

Moreover, radiation therapy is related to the risk of malignant evolution of the tumor.

Denosumab binds and inhibits RANK-L, the most important osteoclastogenic cytokine; it was initially used for the treatment of osteoporosis and bone metastases.

Its use was then extended to the treatment of GCT once discovered that RANK-L role is the key to understand giant cell tumor growth.

Clinical trials have shown that Denosumab is effective in reducing tumor mass dimension in the case of refractory, recurrent or inoperable GCT[7].

Even if different from a clinical, histological and radiological point of view, GCT and ABC share histomorphological characteristics; Pelle et al[8] demonstrated that RANK-L, following the same pattern as in GCT, is basic for primary ABC growth too and, for this reason, the non-surgical treatment with the use of Denosumab is justified in case of ABC.

Literature in this field is still poor and small, and non-homogenous patients' series are not indicated to evaluate efficacy and safety of the use of Denosumab for the treatment of ABC.

Conclusions

Two cases are not conclusive but they may support the project of a prospective study to confirm the effectiveness of Denosumab also in ABC and standardize the treatment protocol.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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