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Case Report

Denosumab role in sacral aneurysmal bone cyst: A rare case report

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Abstract

Aneurysmal bone cyst (ABC) is a benign skeletal tumor which is eccentric, expansile and osteolytic lesion. It contains blood-filled spaces separated by fibrous septa. Aneurysmal bone cyst occurs most commonly in long bones and rarely in the sacrum. Because of its proximity to sacral nerve roots standard surgical resection or curettage and bone grafting is not optimal. Recent therapeutic strategy is to treat it with denosumab injections subcutaneously. We report a case of aneurysmal bone cyst involved in entire right half of sacrum in a 13 year old girl and we treated with denosumab injections (60mg/ml) subcutaneously in every month at regular interval for a period of 12 months and followed for a period of 1year, there was symptomatic and radiological improvement present.

Keywords: Aneurysmal bone cyst (ABC), Bone tumor, Sacrum, Denosumab.

Introduction

Aneurysmal bone cysts (ABC) are benign bone tumors[1] with a peak age of incidence in the first 2 decades of life, primarily seen in children and adolescents.[2] They are located eccentrically in the metaphysis of appendicular bones and axial bones, adjacent to growth plate.[3] Most common sites are the long bones (67%), spine (15%), and pelvis (9%), although it can involve any part of the skeleton[4]. They usually present as growing mass, swelling with pain and bone destruction; sometimes they are locally aggressive and associated with pathologic fractures. In case of spinal localization,[6] neurologic deficit may be caused by infiltration and compression of nerve roots. The etiology of the lesion was due to an increase of venous vascular pressure in the bone, resulting in dilation of small vessels that lead to reabsorption of the bone matrix. Recent study reports explain chromosomal rearrangements, such as translocations, resulting in the up regulation of USP6 gene.[7-9]

On radiograph images[10] (x-ray) and CT scan shows expansive osteolytic lesions, magnetic resonance imaging (MRI) shows septate cystic cavities with blood fluid levels. Histopathologically the lesions are blood-filled cavities separated by fibrous septa not lined by endothelial cells and composed of spindle cells, inflammatory cells, and multinucleated giant cells. Biopsy is mandatory to confirm diagnosis. Treatment options are en bloc resection or curettage followed by bone grafting, sclerotherapy, selective arterial embolization, sclerotherapy or radiotherapy. In spinal and large pelvic aneurysmal bone cysts these treatment options were associated with complications. Recent studies show usage of denosumab in the treatment of aneurysmal bone cysts at inoperable sites. Denosumab[5] is a human monoclonal antibody that binds the cytokine receptor activator of nuclear factor kappa B ligand (RANKL). RANKL[14] inhibition blocks osteoclast maturation and function. We report a case of aneurysmal bone cyst involved in the entire right half of sacrum in a 13 year old female child. The patient was treated with denosumab 60mg/ml injections at regular monthly intervals for a period of 12 months, and we observed that there is improvement of clinical symptoms and improved radiological findings after 12 months of treatment.

Case Report

A 13 year old girl presented to us with complaining of low back pain and difficulty while walking since 3 months. Pain increased gradually and aggravated by her daily activities like sitting and sleeping and walking, pain relieved temporarily on taking NSAIDS, there is no history of fever, no history of constitutional symptoms and no history of trauma, family history, and systemic examination were unremarkable. Physical examination was unremarkable except for tenderness over the right sacral area, no motor and sensory deficits, bowel and bladder habits were normal.

Computed tomographic (CT) images revealed a 6.5 x 3.91 x 3.7 cm lytic lesion with thin rim of outer

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cortex in the entire right sacrum (Fig.1a & 1b). Biopsy shows blood-filled cystic spaces separated by cellular fibrous stroma containing mononuclear cells and rare osteoclast like giant cells. Significant hemosiderin deposition was seen. Because of its presence at inoperable site, routine surgical management[4] like intra-lesional curettage and bone grafting was not considered. Surgical treatment was associated with high risk of serious permanent morbidity and disability because of proximity to sacral nerves, and so alternate treatments were sought. Denosumab[5] treatment was started to the patient. Denosumab injection in the dosage of 60mg/ml was administered subcutaneously in every month. Vitamin D 400 IU and calcium (500 mg/day) supplementation was given to the patient to prevent hypocalcemia,[11] a rare but serious complication of denosumab. After 2 weeks of 1st dosage of denosumab pain was subsided in intensity and her gait also improved and she was able to sleep in any position after 3 weeks of starting treatment. By the end of 1 month, the pain was markedly improved and resolved by 2 months after starting denosumab. A computed tomographic scan at 6 months after denosumab injections showed evidence of new bone formation (Fig. 2a & 2b) with a more clearly defined cortex. Treatment was continued for 12 months, at which time imaging revealed new bone formation. Calcium, phosphorus, and alkaline phosphatase levels[12,13] were normal during the treatment, and no major side effects were observed. Biopsy report after treatment revealed new bone formation and hypo-cellular fibrous stroma that contained scattered mononuclear cells and there was no osteoclast like giant cells. Hemosiderin deposition was rare to absent. Treatment was stopped after 1 year and followed annually.

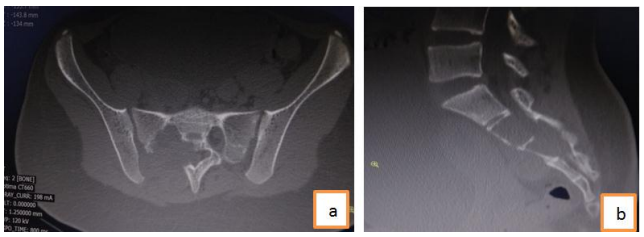

Fig. 1a & b: Pre-treatment CT scan coronal and sagittal cut images shown lytic area in right half of sacrum.

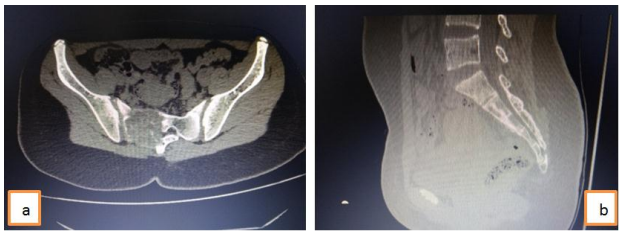

Fig. 2a & b: post denosumab injections (after 6 months) coronal and sagittal images shows tumor regression and new bone formation.

Discussion

Aneurysmal bone cysts (ABC) are benign bone tumors.[1,2] they are locally aggressive and destructive to the bone. They are characterized by blood-filled cavities separated by fibrous septa comprising fibroblasts, inflammatory lympho-histiocytic elements, and multinucleated giant cells[3]. Histopathologically aneurysmal bone cysts contain osteoclast-like mono nuclear giant cells (MNGC) and fibroblast-like cells; this histology picture is similar to giant cell tumors of the bone[11] (GCT). The giant cells that occur in both giant cell tumors and aneurysmal bone cysts have markers of true osteoclasts, so osteolysis is because of these mononuclear giant cells. RANKL[14] is highly expressed in stroma of aneurysmal bone cysts and it activates giant cells, and it binds to RANK present on the surface of monocyte and macrophage lineage precursors. The RANK signalling pathway[14] has vital role in tumor progression. Treatment options available for aneurysmal bone cysts are curettage and bone grafting, embolization, sclerotherapy, and radiotherapy. Surgical management is the gold standard for the treatment of aneurysmal bone cysts (ABC) with a local control rate up to 100%.Other methods has 15–50% failure rates. Traditional treatment options for spinal[6] and pelvic aneurysmal bone cysts (ABC) are associated with severe complications, surgical procedures related complications are neurologic impairment, spinal instability or other vital problems. Sclerotherapy[20] treatment method has response rates up to 85%, after repeated injections. Sclerotherapy[21] associated complications are local inflammation and thromboembolism. Radiotherapy is now limited use due to the risk of radiation induced sarcomas, vertebral body collapse, and growth arrest in young patients. In consideration of these complications, non-invasive innovative therapies are required to treat the bony lesions.

Denosumab[5] is a human monoclonal antibody that binds to RANKL and it causes RANKL inhibition blocks osteoclast maturation and function. Denosumab

is successfully used in the treatment of osteoporosis, skeletal metastases and recently in the treatment of giant cell tumors of bone[11] (GCTB). The immuno-histochemical similarity between giant cell tumor (GCTB) and aneurysmal bone cyst (ABC) justify the hypothesis that denosumab may also have positive effects on aneurysmal bone cyst.

Recent study reports show limited number of patients has been treated by denosumab. Pelle et al[14] reported a case of a 5-year-old boy with sacral ABC treated with denosumab 1.2mg/kg/dose, and reported there was resolution of pain and neurologic improvement occurred after 2 and 6 weeks of treatment respectively, with a significant reduction of tumor volume; no complications were observed. Skubitz et al[15] reported a case of a 27-year-old male with sacral ABC, treated with denosumab 120mg subcutaneously, after 5 months there was resolution of pain and new bone formation on CT scan, decrease in cellularity of fibrous stroma observed. Lange et al[16] reported 2 cases of children (8 and 11 years old) treated with denosumab 60mg/ml for spinal aneurysmal bone cysts at c5 level, where embolization failed, and reported healing of the lesion after 4 months of treatment with improvement of pain, regression of the neurologic deficits and tumor regression. In addition to clinical response, radiological recovery with denosumab treatment was observed in all cases reported in the literature. Palmerini et al[17] reported 9 cases treated with denosumab shows decrease of pain and tumor regression with bone formation. Theoretically denosumab usage may be associated with a dose-dependent risk to develop osteonecrosis of jaw[18] (ONJ) in 1.1%–2.0% of patients, and there is a theoretical risk of retardation in linear growth[19] of children. In all the case reports in the literature showed no such complications were reported. We also observed that there was clinical and radiological improvement in our case after treatment with monthly dosage of 60mg/ml denosumab injections subcutaneously for a period of 1 year, there was decrease in pain drastically after 2 weeks, and associated with bone formation on CT scan. During treatment no complications were observed in our patient. But the long-term outcome is unknown. However some questions remain regarding how long to treat and what happens after discontinuation is still requires research.

Conclusion

We conclude that denosumab treatment in case of aneurysmal bone cysts at inoperable sites can result in symptomatic and radiological improvement and shrinkage of aneurysmal bone cyst size and new bone formation. In view of this, denosumab (60mg/ml) is effective in the treatment of sacral aneurysmal bone cysts.

Source of Funding

None.

Conflict of Interest

None.

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