A RARE GIANT CELL TUMOUR OF THE SACRUM: CASE REPORT

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Abstract: *The current report describes the case a 41 year-old female with a sacral giant cell tumour. The patient presented with low-back pain that radiated to the both lower limbs. Magnetic Resonance Imaging (MRI) revealed a huge tumour mass (110×120 mm in size) involving the sacrococcygeal region between S1 and S5 with invasion of the vertebral bodies at this level, with possible posterior extensions of the spinal canal between S1 and S3. The patient was treated surgically on 10th June 2014. The tumour was subtotal resected. Histopathological examination of removed mass confirmed the diagnosis of giant cell tumor. The patient underwent radiotherapy and an adjuvant treatment with bisphosphonate zoledronic acid from October 2014 until now. After surgery and adjuvant treatment with zolendronic acid, the patient had reduced on intensity back pain, she was able to walk with a cane and had control of the urinary bladder and anal sphincter. Conclusions: Giant cell tumour of the bone is a rare tumour that can be locally aggressive. Radical surgical removal is the optimal treatment. Radiotherapy is preferred for a subtotal resection. Adjuvant treatment with zolendronic acid or denosumab has been reported to be effective and safe.*

INTRODUCTION

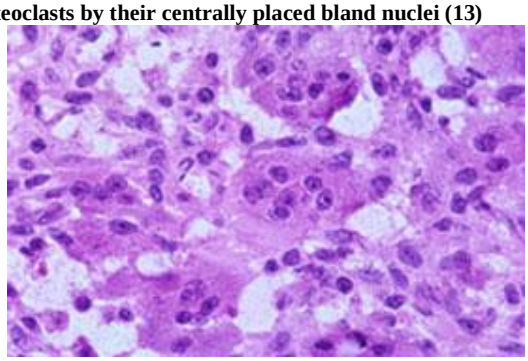
Giant cell tumor (GCT) of bone is an uncommon primary bone neoplasm that usually occurs in the long bones. The giant cell tumors are located in particular within the epiphyses of long bones and frequent extend into the metaphysic of the bones. Only 1,2% of these tumors involved the metaphysis or diaphysis without epiphyseal involvement.(1) They more commonly occur in bones that develop by endochondral ossification and are relatively rare in skull, although when present, they most typically arise in sphenoid and temporal bones.(2,3,4,5) Most commonly, giant cell tumors are solitary lesions; around the knee: distal femur and proximal tibia: 50-65% distal radius: 10-12% sacrum: 4-9% vertebral body: 7% thoracic spine most common, followed by cervical and lumbar spine, fewer than 1% are multicentric.(1,6) GCTs are the second most common type of primary tumor involving bone in the sacrum.(5,7)

It is a benign neoplasm but can be locally aggressive. It has tendency toward local recurrence and late malignant change with metastases especially to the lung has been reported.(5) These tumours contain numerous vascular channels predisposing to areas of haemorrhage and presumably related to the relatively frequent coexistence of bone cysts.(6,7,8,9)

Microscopically they are characterised by prominent and diffuse osteoclastic giant cells (figure no. 1) and mononuclear cells (round, oval, or polygonal and may resemble normal histiocytes).(6)

Radical surgical removal is the preferred modality of treatment. Due to the rarity of the presentation of GCT of the sacral bone, we report this case, which was treated with radical surgery with a good outcome. The frequent symptom that occurs is pain. For larger tumours, there occurs swelling and also deformity, soft-tissue extension and pathologic fracture. The incidence of bone fractures at presentation is 11-37%.(10) Recently, certain authors have claimed that parathyroid hormone-related protein may act locally within GCTs and be significant in the pathogenesis of these tumours.(11) The tumours are locally aggressive despite their benign histology, due to osteolytic expansive lesions. The recurrence rate in the sacrum reported to other skeletal locations is higher. In addition, sacral GCTs have been shown to metastasize.(12) The treatment consists of radiation therapy, surgery (intralesional curettage and complete or partial excision; sacrectomy), adjuvant treatment and arterial embolization.(12)

Figure no. 1. Multinucleated giant cells resembled osteoclasts by their centrally placed bland nuclei (13)



Radiotherapy in modest doses (35 Gy in 15 fractions or equivalent) is a safe and effective option for primary and recurrent giant cell tumors of bone. It should be used if surgery would result in significant functional morbidity.(5) The rate of recurrence is quite high about 40–60%, generally observed within first two years following treatment of the neoplasm.

The bisphosphonate zoledronic acid (14) and interferon α-2b (5) have been reported to be effective and safe adjuvant treatments in patients with spinal GCT, particularly in those with recurrent and metastatic tumors. Giant cell tumours

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are believed to result from an over-expression in RANK/RANKL signalling pathway with resultant over-proliferation of osteoclasts.(6) Reports indicate that topical or systemic use of pamidronate or zoledronate can be a novel adjuvant therapy for giant cell tumor. Bisphosphonates act by targeting osteoclast like giant cells inducing apoptosis and limiting tumor progression.

Bone is a complex, dynamic structure undergoing constant remodeling throughout life.(15) Due to osteoblasts, the human body removes old bone tissue and replaces it with new bone. Morphologically, the osteoclast was a mono- or multinucleated cell, found almost exclusively at bone surfaces. Multinucleated osteoclasts may contain up to 50 nuclei. Bone resorption is a combination of acidification of the compartment under the osteoclast, and the secretion of a cocktail of proteases. In 1997, it was demonstrated that this common signal was receptor activator of Necrosis Factor κβ ligand (RANKL), identified as a high-affinity ligand for the tumour necrosis factor receptor, RANK. RANKL is a cell surface molecule on osteoblasts. The precursor cells to osteoclasts (pre-osteoclasts), express surface receptors called RANK: receptor activator of nuclear factor-kappa B, a member of the tumour necrosis factor receptor (TNFR). RANK is activated by RANKL. This activation promotes the maturation of pre-osteoclasts into osteoclasts. The RANK and RANKL receptors, also known as Tumor Necrosis Factor-related activation-induced cytokine (TRANCE), osteoprotegerin ligand (OPGL) and osteoclast differentiation factor (ODF). These are essential for the development in vivo of the osteoclast development by targeted disruption.(15)

Denosumab, an RANKL antagonist, that inhibits the maturation of osteoclasts by binding to and inhibiting RANKL is used according clinical trials in osteoporosis, cancer bone metastases and gigant cell tumours.(16) Its activities mimics the natural action of osteoprotegerin which is an endogenous RANKL inhibitor.

It is well-tolerated, denosumab and extremely effective inhibitor of osteoclast differentiation and function in humans. A preliminary study using of denosumab in advanced or unresectable giant cell bone tumours has suggested clinical benefit.(15)

By the way, Denosumab is a targeted therapy also called monoclonal antibody. The drug is administered at the dose: 120 mg subcutaneous every 4 weeks and during first month of therapy with additional dose of 120 mg on days 8 and 15. To prevent hypocalcemia or to treat this must be administered calcium and vitamin D.(7)

CASE REPORT

We present the case of a 41 year–old female with low-back pain that radiate to the both lower limbs. She had vague abdominal discomfort and a change in bladder habits due to neurological symptoms. The symptoms have begun insidious with progressive worsening and without responding to symptomatic treatment. The patient complains of a slowly progressive problem over several months. In June 2014 he addressed the Neurosurgery Clinic in another University Center for diagnosis and treatment. After obtaining a thorough patient history, the neurosurgeon physician had conduct a complete physical examination including abdominal, neurological, spine, and rectal vault assessment. MRI revealed a huge tumour mass (110×120 mm in size) involving the sacrococcygeal region between S1 and S5 with invasion of the vertebral bodies at this level, with possible posterior extensions of the spinal canal between S1 and S3 (figure no. 2). The mass was intensely inhomogeneous with multiple cystic images inside of the tumour, with variable dimensions of 2-4 cm (mixed signal shadows on T12- and T2-weighted images) some cystic lesions with pure liquid content, others with subliminal hematic content (native T1 hypersemnal). Blood biochemistry analysis revealed that the alkaline phosphatase, C-reactive protein concentrations and the erythrocyte sedimentation rate were all within normal ranges. Chest X-ray observations were normal.

The patient was treated surgically on 10th June 2014. The tumour was subtotal resected. Spinal fusion and stabilization was performed with metallic implants (2 titan bars) and fixed with 8 screws inserted trans perpendicular to the level L2,L3,L4,L5 (figure no. 3).

Histopathological examination of removed mass confirmed the diagnosis of giant cell tumour.

Denosumab is the best choice for adjuvant treatment, but the drug is not approved in the oncology list, and its cost is too high to be supported by the patient.

Zoledronic acid treatment was in line with national regulations (the list of oncological drugs) that the patient started therapy with zolendronic acid on the October 2014 until now. After surgery and adjuvant treatment with zolendronic acid, the patient had reduced on intensity back pain, she was able to walk with a cane and had control of the urinary bladder and anal sphincter. One year later, the patient was able to walk without a cane and had good control of the urinary bladder and anal sphincter. Today, the patient has no pain, she is able to walk without deficiency. Imaging is stationary without local relapse.

Figure no. 2. Magnetic resonance images (MRI) showing the destruction of the sacrococcygeal bones and a huge soft-tissue mass (2014)

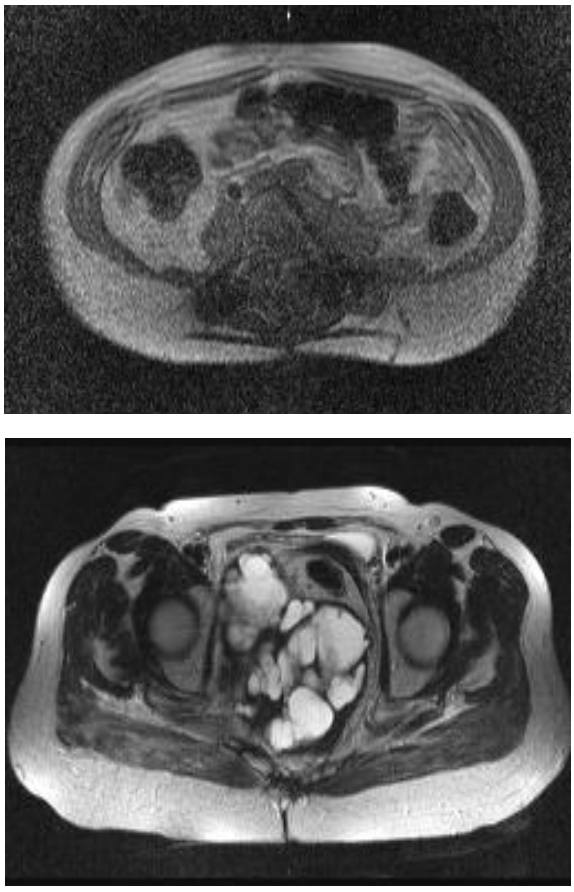
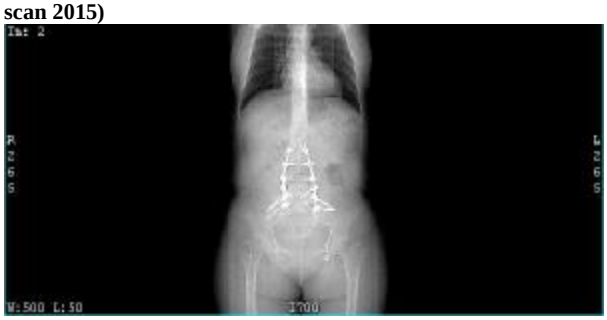


Figure no. 3. Spinal fusion and stabilization was performed with metallic implants (2 titan bars) and fixed with 8 screws inserted trans perpendicular to the level L2,L3,L4,L5 (CT scan 2015)



DISCUSSIONS

Surgery remains the first-line treatment for sacral tumours, but their difficult location and huge size, as well as the possibility of life-threatening intraoperative bleeding, make surgery difficult.(17) In the present case it was performed a subtotal resection. She underwent radiotherapy for local control. The local recurrence rate in the sacrum is higher than recurrence rates at other skeletal locations. Sacral giant cell sacral tumours have been shown to metastasize, especially in the lung.(18)

Systemic adjuvant therapy consists of monoclonal antibody (denosumab) or biphosphonates (zolendronic acid). The bisphosphonate zoledronic acid has been reported to be effective and safe adjuvant treatments in patients with spinal GCT, particularly in those with recurrent and metastatic tumours.(14) Zoledronic acid is a bisphosphonate, the third-generation, that contains nitrogen. It has a high affinity for mineralized bone, especially for those sites with high bone turnover, an antiresorptive agent. The biphosfonate is excreted by the kidney without further metabolism. It induces osteoclast apoptotic cell death, through inhibiting osteoclast proliferation.(10) The drug induce osteoblast differentiation and also increase bone mineralization.(19) The patient undergoes until now therapy with zolendronic acid and she has a good performance status, can walk without deficiency, and has a normal life without pain.

CONCLUSIONS

Giant cell tumour of the bone is a rare tumour that can be locally aggressive.

Radical surgical removal is the optimal treatment.

Radiotherapy is preferred for a subtotal resection.

Adjuvant treatment with zolendronic acid or denosumab has been reported to be effective and safe.

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