Case 1 – Multidisciplinary treatment of a giant cell tumor of the bone affecting the sacrum of a young woman

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Abstract
Giant cell tumor (GCT) of the bone is a benign but locally aggressive tumor arising in the bones. The sacrum represents the most common involved site of the spine. At this level GCT might cause relevant neurological deficits and/or impair activities of daily living. The mainstay of treatment is still represented by the adequate removal of the tumor limiting at the same time the impact of surgery. However, GCT may relapse or present in "difficult" locations or with very large destructive lesions that may not be operated preserving the function of the involved bone. In this scenario, subcutaneous administration of denosumab, a fully-humanized monoclonal antibody specifically directed against RANK-L, can reduce surgical risks and invasiveness improving outcomes. Here we present the case of a young lady affected by a large GCT of the sacrum that emphasizes the importance of the multidisciplinary management of this disease taking into account patient's preferences.

Key words: denosumab, giant cell tumor of the bone, multidiscipinary management

Introduction

We here present and discuss the case of a young woman presenting with a large giant cell tumor (GCT) of the bone arising in the sacrum and involving the 5th lumbar vertebra, passing the sacrum-iliac line, with a clinical picture characterized by pain and initial neurological impairment of plexus L4-L5 and L5-S1. The case emphasizes the implication of a multidisciplinary treatment strategy thoroughly shared with the patient herself.

Case description

A 24 year-old woman was referred to our center because of pain, initial left lower limb strength deficit and a mass in her left lumbar-gluteus region. Her medical history was unremarkable and she was a university student in Italy. The clinical picture was dominated by pain exacerbated by the sitting position and during descending stairways. She did not complain of sphincteric dysfunction. The patient reported that she had noticed the development of an asymptomatic lump in her lower back almost a year previously. She was under pressure because of her studying and had deliberately ignored the mass. In recent weeks she had started to have back pain, especially after having spent several hours sitting studying until recently, when she would avoid sitting unless on cushions, and then for a short time only. In the previous week, she had begun to complain of pain in the lower limb that radiated along the sciatic nerve.

Clinical examination showed an otherwise healthy young woman with a readily detectable mass occupying her lower back and upper gluteus. On palpation the lump was solid and firmly rooted to her deeper tissues. Sensitivity was preserved but her lower left leg was hyposthenic with a posi-

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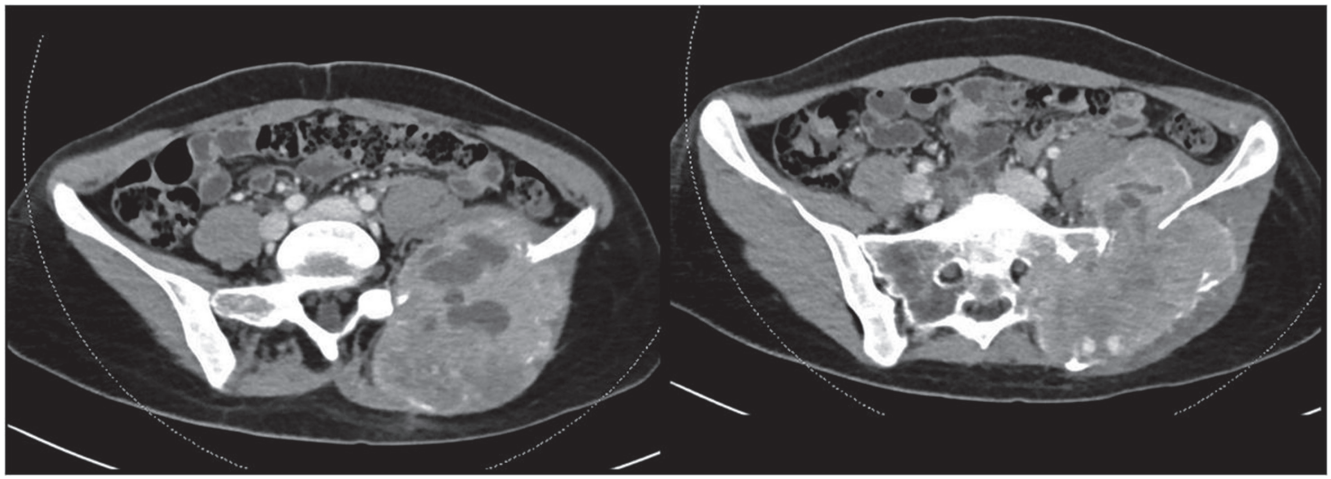

Fig. 1. Baseline computed tomography scan showing a huge bone lesion causing wide lysis of the left ilium and left sacral tuberosity with partial involvement of first sacral foramen and the 5th lumbar vertebra along with infiltration of psoas, gluteus and paravertebral muscles.

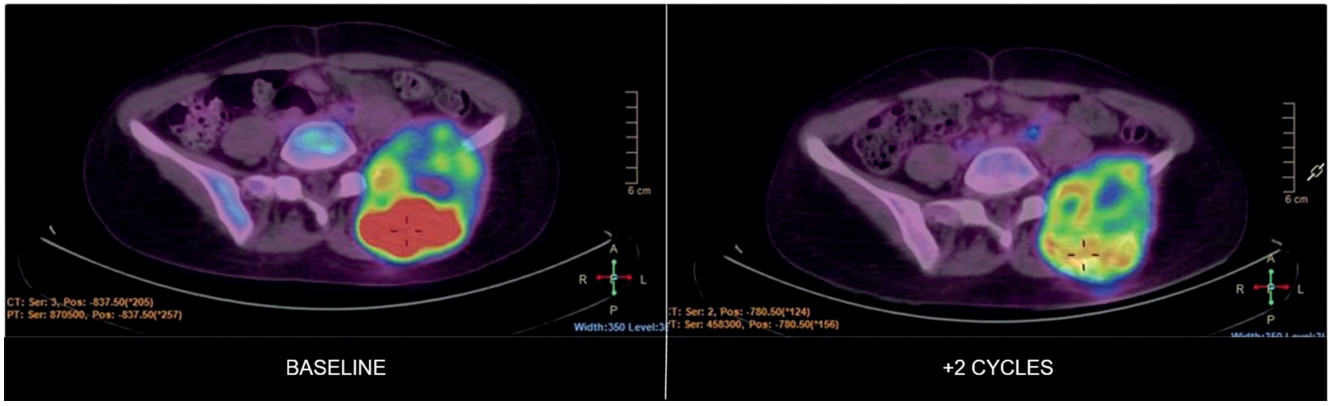

Fig. 2. Positron emission tomography scan revaluation showed significant reduction in fluorodeoxyglucose uptake after 2 cycles.

tive ipsilateral straight-leg-raising test at 30-45°, with an initial muscle atrophy and impaired reflexes.

Baseline computed tomography (CT) scan and magnetic resonance imaging (MRI) showed a solid lesion of 83 ×115 × 132 mm involving left hemipelvis. The lesion caused wide lysis of the left ilium and left sacral tuberosity with partial involvement of the first sacral foramen and the 5th lumbar vertebra along with infiltration of psoas, gluteus and paravertebral muscles (Figure 1). To confirm a suspicion of a high-grade bone tumor, the patient underwent a positron emission tomography (PET) scan that showed a high fluorodeoxyglucose (FDG) avidity of the lesion without other pathological findings (Figure 2). In March 2014 the lesion was biopsied, with a histologic diagnosis of GCT of the bone [1].

Given the extent of the disease, after a thorough discussion of the benefits and toxicities of denosumab and after odontostomatological and organ function evaluation, the patient started treatment with denosumab at the dose of 120 mg on day 1, 8, and 15 for the first cycle and then once a month [2, 3].

The treatment was well tolerated without relevant toxicities. The patient reported a progressive improvement of symptoms starting after the first administrations of denosumab. The left straight-leg-raising test at 30-45° was negative after the second cycle and the pain in lower limb that had radiated along the sciatic nerve improved and completely disappeared after the third cycle. Within a few months the patient showed complete recovery of her correct gait and returned to normal daily activities. The improvement in symptoms was confirmed by FDG-PET performed after two cycles, that showed significant decrease in FDG uptake of the lesion (decrease in maximum standardized uptake value [SUV] from 9.9 to 6.5) (Figure 2).

At the time of each disease revaluation performed every 3 months, the case was discussed within our multidisciplinary team. In the light of the risks of surgery (i.e., incontinence, sciatic nerve deficit) [4-9] and the patient's preference we continued treatment with denosumab. The MRI performed in August 2015 after 17 cycles of denosumab confirmed a slight reduction in tumor dimensions compared with the baseline scan (Figure 3). However, the lesion was less lytic with bone calcification. After a further thorough discussion

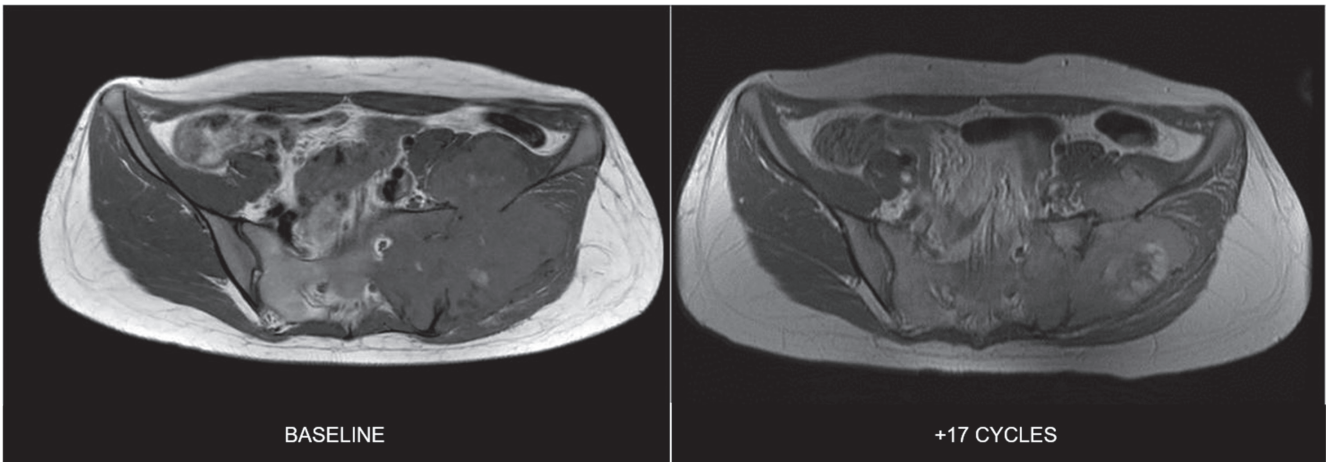

Fig. 3. Magnetic resonance imaging evaluation after 17 cycles showing a substantial dimensional stability with a slight reduction of the intrapelvic component of the lesion.

of the pros and cons the patient decided to undergo surgery. At the time of surgery the lesion appeared as a completely yellowish, friable mass. Marginal osteotomies were performed at the lateral and inferior sides; intralesional osteotomies were performed on the medial and anterior sides, followed by curettage. The margins were treated with local adjuvants (phenol and ethyl alcohol). Neither sciatic nerve deficit nor sphincteric dysfunction were detected at the end of surgery. Two blood transfusions were required due to blood loss during surgery. The post-surgical recovery was fast and without relevant complications. The patient returned to normal everyday life within 1 month. She is now fully active with no signs of disease relapse detected at MRI revaluation performed 3, 6 and 9 months after surgery.

Discussion

Giant cell tumor (GCT) of the bone is a benign but locally aggressive primary tumor arising in the skeleton. In rare cases a high-grade malignant form may be found at diagnosis or, later on, after radiation therapy or surgery [1, 10]. GCT represents 4-5% of all primary tumors of bone with a peak incidence between 20 and 45 years of age and slightly more frequent among female gender. It usually affects the epiphysis at the end of long bones, with distal femur/radius and proximal tibia/humerus the most common involved sites. Flat bones are rarely involved, and in the spine the most common sites are the sacrum followed by the lumbar vertebrae [1].

Patients with GCT may complain of localized pain, tenderness, swelling, and reduced joint motion. In the axial skeleton the tumor may cause neurological deficits. Another less common presentation is related to pathological fracture of the involved bone occurring after minor trauma [1, 10, 11]. Radiologically, GCT appears rather characteristic. It is an eccentric, lytic lesion with a non-sclerotic and sharply defined geographic border, arising in the metaphysis of long bones and extending to the epiphysis in the subarticular region. More aggressive tumors can break through the cortex and extend into surrounding soft tissues. In general there is no sign of calcification [1].

GCT is composed of mononuclear cells with scattered macrophages and large osteoclast-like giant cells that are the most distinctive microscopic feature of this tumor. Osteoclast-like giant cells are now acknowledged as non-neoplastic but reactive elements [1]. The truly neoplastic cells are the mononuclear cells that produce the ligand for the receptor activator for the nuclear factor K β (RANK-L) [12, 13]. The abnormal production of RANK-L alters the normally well-balanced RANK-L-to-osteoprotegerin ratio that physiologically regulates bone resorption and formation. Indeed, macrophages and osteoclast-like giant cells are attracted into the tumor wherein RANK-L activates the inflammatory response and proliferation of macrophages that eventually may transform into osteoclast-like cells [14].

Surgery is the mainstay of therapy of GCT [10, 15, 16]. As most benign GCT tumors are located near important joints, an issue is what can be considered adequate tumor removal that is both effective while being able to preserve optimal function in patients in their early adulthood. Wide surgical resection is associated with a lower risk of local relapse, but several authors consider an intralesional approach that may preserve limb function to be an appropriate approach [16, 17]. The key element is to reach a complete tumor removal with a minimally invasive surgery. Therefore, surgery may be integrated with local therapies to destroy residual tumor tissue, such as phenol or cryosurgery [16, 17]. Larger tumors may require more extensive surgery and reconstruction with cementation and/or bone graft. The use of polymethylmethacrylate (PMMA) is attractive because of local hyperthermia and a supposed local chemical cytotoxic effect caused

by the polymerization of this product. Moreover, GCT usually presents with diffuse vascularization that often requires preoperative embolization to control pain and/or bleeding during surgery [1, 17]. In general, referral centers will treat these tumors with several different techniques according to individual clinical presentation [17].

Unfortunately, and despite the fact that several technical advances have been achieved in orthopedics in recent years, GCT may relapse or present in "difficult" locations such as the spine or with very large destructive lesions that may not be operable while preserving the function of the bone involved. Standard therapies were either radiotherapy or chemotherapy [1, 10, 11, 16, 17]. Both of these approaches displayed modest activity and had the potential to increase tumor malignant transformation [1, 10, 11, 17, 18]. In this scenario, an understanding of the complex interplay among the different cells making up the tumor tissue allows the hypothesis that the inhibition of the interaction between the receptor of RANK-L (on monocytes/macrophages) and its ligand displayed by tumor cells might contribute to halting the proliferation and potentially the prominent bone destruction [19, 20].

Denosumab is a fully-humanized monoclonal antibody specifically directed against RANK-L and was originally developed to stop bone reabsorption observed in both osteoporosis and bone metastases [21, 22]. Subcutaneous administration of denosumab provides rapid and sustained suppression of bone turnover in patients with several oncologic osteolytic diseases (such as multiple myeloma, breast cancer and prostate cancer) [21, 22].

The first experience with denosumab in GCT was led by Thomas et al. [2]. The authors showed extraordinary activity of this drug in the series; 86% of patients met the tumor response criteria at 25 weeks. All 20 patients assessed by histology showed a tumor response defined as a 90% or greater elimination of giant cells. Moreover, the spindle-shaped cell-dense stroma was replaced by a less cellular stroma, with new osteoid formation. Radiologic assessment was challenging and showed no major tumor shrinkage. However, FDG-PET displayed significant uptake reduction, confirming reduced metabolism within the tumor tissue, a finding consistent with clinical improvement. A second experience in a large number of patients was consistent with this first report [3]. In response to denosumab treatment, sclerosis and reconstitution of cortical bone was seen on conventional radiographs and CT and led to a less morbid procedure than originally planned in almost two thirds of the patients who underwent surgery. Toxicity was relatively mild, with arthralgia, headache, nausea, fatigue, back pain, or pain in the extremities as the most frequent adverse events. Hypophosphatemia and hypocalcemia were reported in 5% of the patients. A relatively discomforting adverse event was osteonecrosis of the jaw in 1% of the patients. It occurred 13-20 months after treatment start and required oral antibiotics and dental procedures, in some cases up to the extent of jaw surgery with bone reconstruction [3, 21, 22].

In the light of these results, GCT clinical management is now increasingly multidisciplinary [16, 23]. Surgery remains the final objective, but in any presentation deemed potentially risky for either bone/articular function or adequacy of a sparing surgery, denosumab should be considered as part of the strategy. In particular, in sites like the pelvis or spine [4-9], pre-operative denosumab might reduce surgical risks while improving outcomes and reducing the invasiveness of surgery [2, 3].

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Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

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Commentary

Giant cell tumor of bone (GCTB) is relatively infrequent, locally aggressive, osteolytic tumor that mainly affects the young adults [1-3]. The bone destruction in GCTB is mediated by RANKL (receptor activator of nuclear factor kappa Beta ligand). RANKL is highly expressed by neoplastic mononuclear stromal cells, which play important role in osteoclastogenesis by recruitment osteoclast precursor cells that differentiate into multinucleated osteoclast-like giant cells, whereas RANK is expressed on osteoclast-like cells, which are recruited secondarily in the tumor, but responsive for the aggressive osteolytic activity [3, 4]. The primary treatment for GCTB is surgery, however the local recurrence or metastasis may occur. Nevertheless, up to 20% of GCTB have tumors not amenable to radical surgical resection or surgery may cause substantial morbidity (as hemipelvectomy). In the past moderate-dose radiotherapy (40-55 Gy) been shown as effective primary treatment in unresectable GCTB or in cases of residual or recurrent disease when surgery would result in unacceptable morbidity, but in the era of RANKL inhibitor it needs to be redefined and limited to individualized cases, especially not suggested in young adults. Moreover, it has been reported malignant transformation after use of radiotherapy with the risk up to 5% [3, 5].

In recent years the anti-RANKL antibody denosumab has become a standard treatment option for locally advanced or metastatic GCTB [6-8]. The high efficiency of GCTB denosumab treatment was confirmed in two phase II studies [7, 8]. The analysis of second and larger study shows that 96% of surgically unsalvageable patients had no disease progression during treatment (median follow-up time 13 months) with acceptable drug toxicity. Moreover, 222 patients were assessed for possible downstaging with denosumab for planned surgery [9]. Denosumab therapy resulted in significant number of no surgery or less morbid surgical procedures.

Denosumab treatment should be continued till radical resection of the tumor, progression or unacceptable toxicity. According to ESMO 2014 [10] recommendations for bone sarcomas, denosumab may be used in GCTB to achieve cytoreduction allowing potentially curative surgery, or also in

unresectable and rare metastatic disease, where treatment needs to be maintained to avoid progression.

The case report by D'Ambrosio is an excellent example of preoperative modality treatment combined with radical local surgery and multidisciplinary collaboration of difficult GCTB, what should be the current standard of care. Several data suggest that neoadjuvant therapy with denosumab may become the option for treatment of initially locally advanced tumors (with extensive soft tissue extension, grade 3 according to Campanacci) [11], to facilitate complete surgical resection or avoid mutilating surgery. Preoperative denosumab treatment is suggested to potentially make subsequent surgical resection easier in patients with aggressive GCTB who are poor surgical candidates or in whom the tumor is in a location difficult to treat surgically, due to the formation of a calcified boundary around the tumor [12]. Denosumab has been studied specifically in GCTB of the spine [13]. The results demonstrate a clinically beneficial radiological response and an impressive histological response in most but not all patients. Denosumab has the potential to change the treatment paradigm for spinal GCT [12, 13]. Denosumab can lead to clearly dramatic responses, leading to e.g. decompression of spinal canal [12]. We have similar personal observations. However, even after neoadjuvant treatment, extensive soft tissue involvement and axial localization (e.g. sacral lesions) can offer challenges for a satisfactory surgical approach, so I would like to congratulate Italian colleagues the final results of patient's therapy.

Further studies with denosumab in GCTB are necessary on possible delay or avoidance of recurrent disease with adjuvant therapy, the optimal duration and dose (if lifelong) of denosumab as a therapy for unresectable disease, the long-term safety, the best timing, type of procedure and indications for secondary surgery after denosumab therapy. We do not know also what is the risk of relapse following interruption of therapy and if denosumab be still efficient when reintroduced after a break.

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