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Giant Cells Tumour

Abstract

Background: The first line of treatment of Giant Cells Tumor (GCT) consists in the curettage and coverage with bone graft. New treatments as Denosumab have shown great results as adjuvants in its treatment, and is gaining popularity in the treatment, especially because the high rates of local recurrence after surgery and the limitations of the technique in very aggressive tumors, or in those located in complex regions. This monoclonal antibody inhibits Receptor Activator of Nuclear Factor Kappa Beta Ligand (RANKL) and can only be administered in skeletally mature patients, so it is contraindicated during pregnancy. There are other adjuvant therapies to surgery, such as cryotherapy with liquid nitrogen or the phenolization, which can be equally effective.

Methods: We present the case of a pregnant woman of 28 years old diagnosed with an aggressive GCT of proximal tibia during the first trimester of pregnancy. On this occasion, surgical treatment was performed by curettage and high speed milling. Adjuvant treatment was added with liquid nitrogen and the cavity was filled in with demineralized bone matrix and hydroxyapatite. Based on our experience and on a revision of the literature, there are few cases described of the treatment of a GCT in a woman during the pregnancy.

Results: The patient's symptoms disappeared after the intervention. There have not been shown signs of recurrence after 10 months of clinical follow-up and simple radiology controls. The treatment did not produce adverse effects in the fetus during pregnancy neither breastfeeding.

Conclusions: Indications of Denosumab in the treatment of GCT include unresectable tumors or those in which its resection leads to high morbidity, as well as tumors in the spine, sacrum, pelvis and challenging lesions located in the upper and lower extremities. If we cannot opt for this drug for medical or other reasons, cryotherapy with liquid nitrogen may be effective in its treatment.

Authors

Copete I[1],
Ferràs J
Angulo MA.

Hospital Univeristari I Politècnic La Fe, Valencia
Avda Fernando Abril Martorell 106, Valencia, Spain

1. Corresponding Author: ivan.copete01@gmail.com

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Introduction

Giant cell tumor (GCT) is a locally aggressive neoplasm characterized by a richly vascularized tissue with and multinucleated giant cells. It represents between 5% and 8.6% of primary bone tumors [1,3] . It usually appears after achieving skeletal maturity, when the growth plates have already been closed, between the ages of 20 and

40 years, with a predominance in females (2:1) [3] . The 60% of the GCT occur in long bones and it often extends to the articulation [1,2,3] . The most common sites are the distal femur, proximal tibia, distal radius, the proximal humerus and sacrum. Rarely, it can be multifocal and when it happens, it is very often associated with Paget's disease. The metastatic spread is rare [2,3,13] .

Clinical Presentation

The most frequently symptoms are pain and local inflammation. There may be functional limitation or even pathological fractures. The clinical behavior of the CTG cannot be predicted with accuracy with histologic findings, clinical examination neither radiological images. Despite this, there have been numerous attempts to set the aggressiveness of a tumor and it seems that less aggressive tumors have a higher trabeculation and a smaller and softer cortical than more aggressive GCT.

Recurrences after surgical treatment by means of curettage and bone graft are frequent and they range between 12% and 50% [1.2] .

Radiological presentation

GCT is presented in plain radiography as an osteolytic, expansive and located eccentrically lesion, with usually well-defined but not sclerosing edges. It may present trabeculation or internal pseudotrabeculation, which represents the non-uniform growth of the tumor, and it normally doesn't have periosteal reaction. It is important to make the differential diagnosis with a chondroblastoma, especially in those cases with signs of aggressiveness [2] .

The Computed Tomography (CT) allows to delimit the extent of the tumor and a better view of the areas of cortical destruction. Nuclear Magnetic Resonance (NMR) images of the GCT present low signal intensity on T1-weighted image (T1WI), and high signal on T2-weighted sequences (T2WI). NMRI are also effective to demonstrate the involvement of subchondral bone and the extent of the tumor to the joint.

The Positron Emission Tomography (PET) images, do not provide additional information, although they can be useful in the detection of multiple foci if clinically a GCT is suspected.

The malignant GCT does not have additional radiographic characteristics.

Numerous classifications have been developed to establish the better protocol to the management of the TCG, but neither prognosis nor the risk of recurrence are predictable on the basis of the clinical presentation, radiographic or histological.

The Enneking staging system for benign bone tumors can be used to determine the definitive treatment. Campanacci described a classification system for these lesions based on x-ray images (Table 1). Grade 1 lesions of Campanacci are rare, and the majority of GCT are defined as grade 2 [2] .

Degree/Stadium	Enneking	Campanacci
I	Benign, indolent and biologically static	A well circumscribed radiolucent lesion, without aggressive features (periosteal reaction, mass of soft parts, disruption of the cortical).
II	Progressive growth, limited by natural barriers	Relatively well-defined edges without a border radiopaque
III	Locally aggressive with soft tissue mass	Affected borders, with destruction of the cortical bone and soft tissue mass

Table 1. Comparison between classification of Enneking and Campanacci

Histological presentation

There is a dual population of cells: mononuclear stromal cells and giant cells, both kind of cells distributed throughout the tumor. These giant cells are morphologically similar to osteoclasts and they have an elevated activity of acid phosphatase. They are round, oval or fusiform and generally have a large core with little chromatin and few nucleoli. The histological study with silver staining reveals a dense network of reticulin fibers surrounding individually the cells. As has already been said, the prediction of the evolution of a TCG based on their histologic appearance is impossible, and the histologic features have not been shown to correlate with the degree of local recurrence neither with the appearance of lung metastases.

The secondary transformation to a malignant GCT histologically diagnosed, is exceptionally uncommon without any previous radiation therapy [13] .

Treatment

The first-line treatment consists on curettage and filling in with bone graft [1,2,4,7,10] , though it is true that its recurrence rate is between 20% and 45%, depending on the serie [2] .

Medical therapies include bisphosphonates and Denosumab [2,3,4,5,6,10,13] . Other treatments that have been used are corticosteroids, interferon and chemotherapy, and new treatments are been developed, as Dasatinib, a new Tyrosine Kinase Inhibitor (TKI). After the approval of Denosumab to the treatment of GCT, the use of chemotherapy or interferon has been relegated to the metastatic malignant tumors [3] .

Phenolization, coagulation with Argon laser, Cryotherapy with liquid nitrogen, hydrogen peroxide, embolization [2,8] and bone cement[2,7] are adjuvant treatments to the surgery.

While as radiation therapy is not used routinely, it has been used as an alternative tool to the GCT located in difficult places such as the sacrum and the vertebral column, because its high risk of local recurrence after curettage. It has

also been used interferon for local and systemic control of the disease, with variable results.

Case report

We present a case of a 28-year-old pregnant woman of 12 weeks with a lesion in the proximal tibia epiphyseal region (Figure 1). Clinically, she referred pain on the medial compartment with the weight load. There was no instability or other symptoms neither signs of interest.

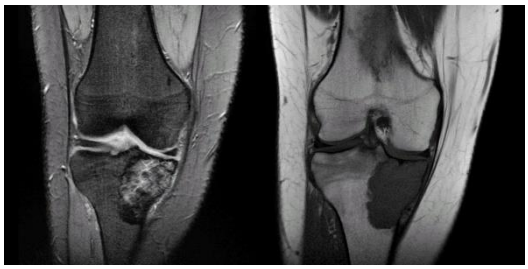

Image 1. Nuclear Magnetic Resonance Images, coronal slices.

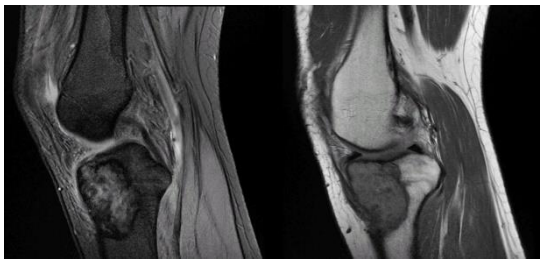

Image 2. . Nuclear Magnetic Resonance Images sagittal slices.

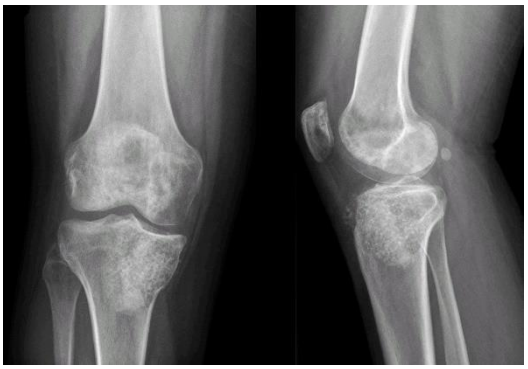

Image 3. Postoperative plain x-ray. AP and lateral projections.

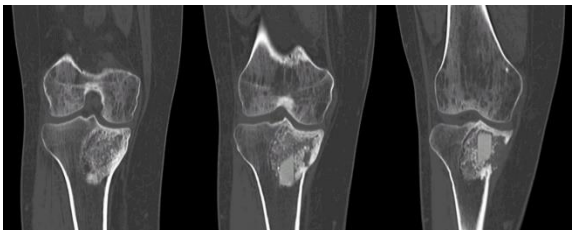

Image 4 . Control CT scan 9 months after surgery. Coronal slices.

A cylindrical piece of tissue was taken using incisional biopsy, and histological diagnosis of giant cell tumor of bone was done.

She didn't present other lesions, such as pulmonary metastases neither symptoms in other places.

The curettage was performed, including high-speed milling, adjuvant treatment with liquid nitrogen and filling in the defect with demineralized bone matrix and hydroxyapatite. After surgery and three days of hospitalization, body weight load was restricted and she was asked for to walk with the help of sticks, protecting the treated leg.

During her hospital stance and the successive follow-up, the patient continued with pregnancy controls, occurring only a cytomegalovirus infection as complication. 10 months after surgery, the patient is asymptomatic and NRMI and Radiographic controls are satisfactory (Figure 6).

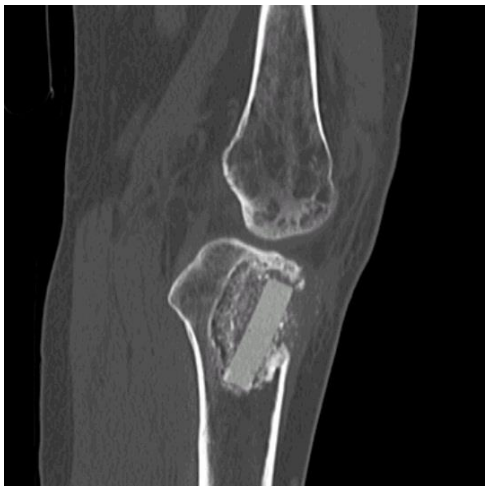

Image 5. control CT scan 9 months after surgery. Sagital slices.

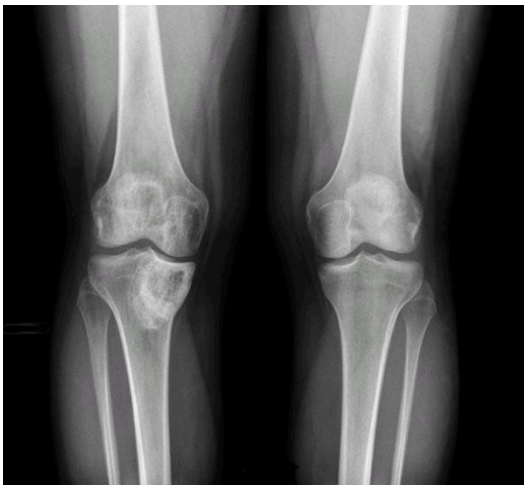

Image 6. X-ray control 10 months after surgery

It is important to bear in mind that, as a pregnant woman, all tests were adjusted to the precise radiation doses, as well as the careful use of fluoroscopy during the procedure.

Surgical Technique

In the first place, an incision medial to the tibial tuberosity is done, deepen until you reach the bone. A resection of the anterior cortex wall is performed and then curettage of the cavity with a little spoon and with high-speed ream is developed. Once this is done, the cavity is filled in partially with bone substitute. On this occasion, 10 ml were used at the level of the articular surface and the, carefully, we added liquid nitrogen. Finally, we filled the remnant cavity with 20ml of bone substitute, a piece of hydroxyapatite of 10x10x40mm and 30cc of hydroxyapatite granules. Finally, all the process was reviewed with fluoroscopy and a drain was also placed.

Discussion

We often come across situations that we cannot deal with the standard procedures and in which we must consider other treatment alternatives. In this cases, it's necessary to know what tools do we have in order to get the better in our specific case.

Denosumab is a monoclonal antibody that binds with high affinity and specificity to RANKL [3,4,6 WCSD POLICY] by deleting the osteolytic activity. The GCT is characterized by stromal cells expressing RANKL and osteoclast-like giant cells that express RANK [3] . That's the reason because Denosumab delays the progression of this disease [3] Nonetheless, as other antiresorptive treatments do, it

can lead to hypocalcemia and osteonecrosis of the jaw.

Actually, Denosumab has been approved along with surgery to the treatment of GCT in skeletally mature adults and adolescents on which, because its location, they are considered unresectable tumors or when its resection involves a high morbidity: spinal column, sacrum or the pelvis and challenging lesions in the upper and lower extremities [3,4,5,10,13] With Denosumab, it's possible to reduce the size of GCT preoperatively, providing relief of symptoms before surgery and facilitating the resection of the tumor [12] .Even so, when used for TCG bone, the long-term effects of Denosumab are unknown [10] .

Bisphosphonates are used on the basis of their ability to induce apoptosis in stromal cells and osteoclasts in vitro. The clinical evidence of bisphosphonates in GCT is limited to retrospective series and case reports, and more studies are needed to use it securely[2].

It has been shown that cryosurgery reduces the rate of local recurrence up to 8% [2] . The freeze-thaw cycle kills cells away from the surface, which further extends the depth of the curettage. Cryosurgery involves the direct application of liquid nitrogen in the cavity of the tumor and has been shown to be an effective adjuvant therapy to tumor resection [2] . In spite of this, it has been associated with a significant incidence of pathologic fracture and vascular injury, the first being the most frequent complication [2] .

External beam radiation with argon laser has been used to complement the surgical treatment in patients who are medically inoperable or in those who have tumors that are technically difficult to remove or unresectable, due to its location [2] .

Although radiation therapy is not used routinely, it has been used a great tool to treat the GCT in difficult places, such as the sacrum and the vertebral column. It has also been used interferon for local and systemic control and, with diverse results depending on the series [2] .

Other adjuvant treatments that have been used traditionally are the fenolization , hydrogen peroxide and the embolization and the bone cement .

The use of chemotherapy or interferon has been relegated to the metastatic malignant GCTs [3] .

References

1. Greenspan (311-322)

2. Raskin K, Schwab J, Mankin H, Springfield D, Hornicek F. Giant cell tumor of bone. J Am Acad Orthop Surg. 2013;21: 118-126.

3.Hemetsberger Brodowicz T, M, WINDHAGER R. denosumab for the treatment of giant cell tumor of the bone. Future Oncol. 2015; 11(13): 1811-1894.

4.Thornley P, Habib, Bozzo, Ghert Evaniew N, M. The role of denosumab in the treatment of giant cell tumor of bone. JBJS REVIEWS. 2017;5(4).

5. Law GW et al. Unresectable Recommencement of denosumab for giant cell tumor of the cervical spine: a case report. Spine. 2017.

6. Girolami I, et al. Denosumab treated giant cell tumor of bone: morphological, immunohistochemical and molecular analysis of a series. J Clin Pathol. 2015;0: 1-8.

7. Dreinhofer, K. E.; Rydholm, A.; Bauer, H. C. F.; Kreicbergs, A. Giant-Cell Tumors with Fracture at Diagnosis: Curettage and Acrylic Cementing

In Ten Cases. JBJS. 1995; 77(2): 189-193.

8. Ji T et al. Combining of serial embolization sacropelvic denosumab for large and giant cell tumor. Medicine. 2017; 96: 33.

9. Weintraub B. Trials defined anti-tumor effects of anti-resorptive agents: Denosumab ahead of Zoledronate 2 to 1. Biodrugs. 2011; 25(2): 135-138.

10. Park, Cyprian C, Kyriakos M, McDonald D. malignant transformation of a giant cell tumor of bone treated with denosumab. JBJS Case Connect. 2016;6: e78.

11. Rockberg J et al. Incidence trends in the diagnosis of giant cell tumor of bone in Sweden since 1958. J Bone Joint Surg Am. 2015;97: 1756-1766.

12. Kumar R et al. Gian cell tumor of the cervical spine presenting as acute asphyxia. Spine. 2017; 42(10): 629-632.

13. Piuzzi Aponte-Tinao L, N, P, Farfalli Roitman G. A high-grade sarcoma arising in a patient with recurrent benign giant cell tumor of the proximal tibia while receiving treatment with denosumab. Clin Orthop Relat Res. 2015