

The Role of Denosumab as an Adjuvant Treatment in the Bone Tumor of Giant Cells: Case Report

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ABSTRACT

The bone tumor of giant cells represents 5% of primary bone tumors and is classified as locally aggressive. For treatment it is important to make the differentiation between resectable or unresectable tumor. Currently, the great role of Denosumab has been established as a post-operative adjuvant treatment. Although at the beginning of its approval for this tumor, its administration was preoperative, with subsequent studies it was observed that this only increased recurrence. We present the case of a female patient of the fifth decade of life, who has had an excellent answer: clinical and of imagen based on the RECIST criteria, with post operation neoadjuvant treatment with denosumab, after partial loaf resection in an unresectable tumor to be in the skeleton axial.

Keywords: Giant-cell tumor of bone, Denosumab, RANK, Bone tumors.

INTRODUCTION

The bone tumor of giant cells is rare, represents 5% of primary bone tumors and is classified as locally aggressive, but rarely metastatizes (2-6%) and when it does it is more frequent to lung.

This tumor shows a maximum incidence between 20-30 years of age and is slightly more frequent in women.

It mainly affects the metaphysis and epiphysis of the long bones with a maximum prevalence in the upper limb by 43%, lower limb by 30%, and decreases to a minimum of 1.45% in the axial skeleton.

Histologically it is composed of giant cells similar to osteoclasts with neoplastic mononuclear stromal cells, which have the hyperactivity of the rank ligand that leads to hyperactivity of multinucleated giant cells and finally to osteolysis.

In immunohistochemical these stromal cells express the mutant protein H3.3G34W.

Clinic is characterized by pain, limitation for movement and sometimes pathological fracture occurs (10%).

Characteristics on imaging studies include an osteolytic lesion that may be expansile, cortical involvement with thinning, bulging and probable rupture, as well as expansion into soft tissue. To stage it we use the Campanacci radiographic grading. (Table 1). The importance of this classification is that according to the patient's stadium, treatment is established.

Within therapeutic conduct, they are first divided into resectable and unresectable. In the former, according to Campanacci radiographic grading, stages I and II are treated based on curettage and subsequent adjuvant treatment followed by mechanical reconstruction of the tumor cavity with autograft or artificial bone. Type III is based on wide resection plus prosthetic reconstruction and subsequent adjuvant treatment. On the contrary for unresectable tumor, all are treated as stadium I and II of Campanacci, including stadium III, because the wide resection is not optional for its location.

Within the adjuvant treatment, the current trend is the use of Denosumab, which was approved by the FDA since 2013, for unresectable tumors or with high morbidity and mortality.

Table 1: Campanacci radiographic grading nacci

Grade	Description
I	Well-defined margins and intact bone cortex
II	Margin relatively well defined, bone cortex thinned and moderately expanded.
III	Bordes indistintivos y destruccion cortical.

CASE REPORT

Female 40 years of age who started in 2017 with low back pain and presence of a tumor in the right sacroiliac region. Diagnosis of giant cell tumor was given by biopsy in 2017. (Illustration 1). In 2018, embolization and partial bone resection of the tumor was performed and in 2021, treatment with denosumab 120 mg subcutaneously per month began.

Before starting denosumab, the axial tomography showed an expansile osteolytic lesion at the level of the sacral bone. 20.9 cm x 15.4 cm in axial section and 13.4 cm high in coronal axis, with a sum of all diameters of 49.7.

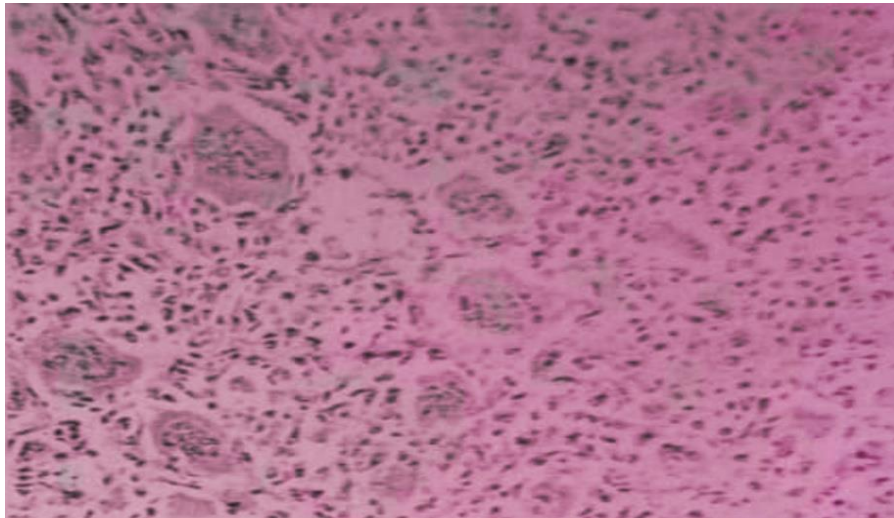
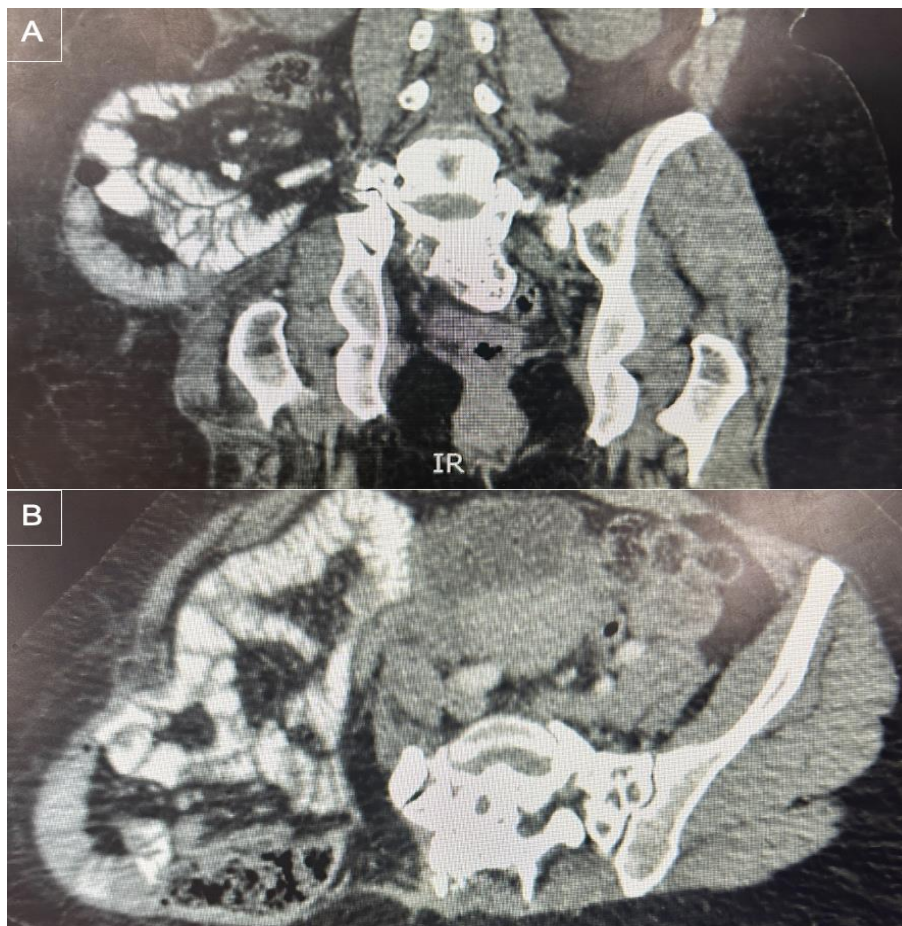


Illustration 1. Giant cells with numerous nuclei. (H & E,40x).



A. Coronal axis. Showing an expansive osteolytic lesion, with cortical disruption and soft tissue involvement. B. Axial cut.

Illustration 2: Simple computed tomography image, pelvis region.

His laboratories after starting denosumab were as follows: urinary calcium 156.2 mg/day, intact parathyroid hormone 78.3 pg/mL, serum calcium 10.3 mg/dL, serum phosphorus 3,725

mg/dL, OH vitamin D 20.9 ng/mL, bone alkaline phosphatase 12.8 IU/L, C telopeptides 0.022 pg/mL, N-polypeptides 17 pg/mL.

In 2022 the lesion showed dimensions of 21 cm X 15.9 cm in axial section and 13.3 cm in coronal axis and in 2023 the measurements were 22 cm x 16.4 cm in axial section and 14.7 cm in coronal axis. (Illustration 2).

Measuring the sum of all diameters, a slight increase in the size of the tumor was found. No extension of the lesion to new bone structures or lung parenchyma was shown.

During her medical check-up appointments, the patient reported clinical improvement with absence of pain in the joint and improvement in mobility, leading her to be able to perform all her daily activities without impediment.

Adjuvant treatment with Denosumab for 3 years showed adequate clinical response, remaining asymptomatic. Based on modified Response Evaluation Criteria in Solid Tumors (RECIST), the patient remained with stable disease. (Illustration 3).

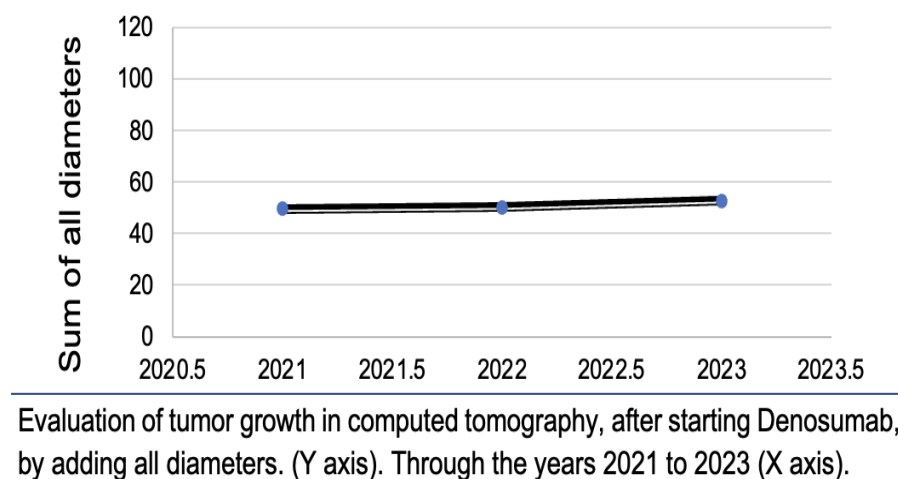


Illustration 3. Response by CT scan to the use of Denosumab.

DISCUSSION

Giant cell tumor is characterized by giant cells expressing receptor activator of nuclear factor kappa B (RANK) and stromal cells expressing RANK ligand.

The importance of neoadjuvant treatment lies in the observation that up to 65% of patients who are not administered after surgical treatment, recurrence.

Denosumab is an IGG2 human monoclonal antibody that is directed against the Ligand Rank preventing the activation of the Rank receptor. Resulting in the inhibition of the formation and survival of osteoclasts, leading to the decrease in the resorption in the trabecular and cortical bone. This has proven useful as an adjuvant treatment in unresectable tumors.

At the beginning of its approval for this type of tumors, Denosumab was used during the pre-surgical time, but in subsequent studies it was observed that contrary to a benefit, there was an increase in post-surgical recurrence, this was explained by the generation of the new matrix bone and thickened cortical bone, which interfered with surgical treatment at the time of tumor delimitation, generating inappropriate resection. In addition, this scheme only included Denosumab prior to surgery and not posterior, which generated subsequent proliferation within the residual oncogenic stromal cells.

It is currently known that Denosumab eliminates the giant cells, but not the neoplasms, which are the stromal. These remain inactive due to the effect of Denosumab, but without the continuous application of the same, they reactivate again and proliferate, leading to a state of recurrence.

Denosumab is the preferred neoadjuvant treatment, for application after the partial or complete resection of the tumor.

An inconvenience to its use is the need for the constant application of the drug and its uncertainty about its long-term use with monthly dose, which is 120 mg subcutaneous.

Studies show that up to 40% of patients with Denosumab fall after 8 months of their suspension.

The long-term adverse effects that have been observed is 5% hypophosphatemia, jaw osteonecrosis by 3%, hypercalcemia and atypical femur fractures in 1% each.

With the use of denosumab up to 84% of patients have control of the disease and 98% of patients can achieve some clinical benefit. When the patient presented lung metastases, the use of denosumab showed their regression by 45%.

CONCLUSION

Denosumab is a widely used treatment for osteoporosis, where its safety profile is already known, however in the bone tumor of giant cells, the long-term security profile is unknown, and the importance is that here the dose is twice as the administered for osteoporosis and is monthly, also must be given without interruption, as already mentioned, due to the high recurrence rate after its suspension.

Since the prevalence of this tumor is low, the case reports and their follow ups after the start of Denosumab, are important to assess whether it can be permanently administered.

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