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CLINICAL CASE

Experience with Denosumab in central giant-cell granuloma

Experiencia con Denosumab en granuloma central de células gigantes

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What do we know about the subject matter of this study?

Central giant cell granuloma (CGCG) is a rare bone lesion that primarily affects the jaws. It is usually treated surgically, but complete resection of the lesion can cause great morbidity. Denosumab, an anti-RANK-ligand monoclonal antibody, may be a valid treatment alternative.

What does this study contribute to what is already known?

Denosumab may be a valid therapeutic option as the first-line treatment of CGCG in adolescents with lesions that are difficult to resect. Denosumab could reduce tumor size and avoid surgical morbidity. Its use requires monitoring of phosphocalcic metabolism.

Abstract

Central Giant Cell Granuloma is an infrequent bone lesion located mainly in the maxillary bone. The main treatment is surgery with wide margins, so it sometimes causes great morbidity and esthetic alterations. Denosumab, a RANK-ligand inhibitor monoclonal antibody, has been presented as a valid therapeutic alternative in the treatment of these lesions. **Objective:** to describe the clinical and radiological response after treatment with Denosumab in a patient with unresected giant cell granuloma. **Clinical Case:** 12-year-old boy who consulted due to a 24-hour maxillary swelling, without other associated symptoms. Examination revealed a tumor in the upper left maxilla with bulging of the ipsilateral gingiva. A CT scan was performed which showed a large expansive intraosseous lesion in the maxillary alveolar ridge. The biopsy of the lesion was compatible with Central Giant Cell Granuloma. Due to the size and location of the lesion, initial treatment with Denosumab, a human monoclonal antibody with action on RANK-ligand, was indicated. After 10 months of treatment, the patient showed a favorable clinical and radiological response, with a size decrease of the lesion and metabolic activity. As an adverse effect, the boy presented mild hypocalcemia, resolved after supplementation with calcium. **Conclusion**: the use of Denosumab as the first line of treatment in Giant Cell Granuloma may be an adequate therapeutic option in adolescents with lesions that are difficult to resect.

Keywords:
Denosumab;
Giant Cells;
Granuloma;
Pediatrics;
Monoclonal Antibody

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Introduction

Central giant cell granuloma (CGCG) is a benign but locally aggressive intraosseous lesion, mainly located in the mandible or maxilla[1]. Its etiology is unknown; although its appearance has been related to a reparative process after trauma or inflammation, its locally destructive behavior is reminiscent of tumor lesions. On the other hand, cases of CGCG have been described in patients with diseases such as Neurofibromatosis type I (NF-1), Noonan Syndrome, Cherubism, or Ramon Syndrome that present mutations at the level of the RAS/MAPK pathway, and a possible genetic etiology cannot be ruled out[2,3]. Alterations in these signaling pathways may have oncogenic power and may be found in a high percentage of sporadic CGCG[3].

CGCG is an infrequent entity, accounting for approximately 7% of benign mandibular tumors[4]. 75% occur in people under 30 years of age, although more aggressive lesions, with greater resorption, and recurrence, have been described in children. The treatment of choice is surgical resection of the lesion with wide margins but, despite this, the percentage of recurrence after surgery is significant (11-49%)[5]. In large lesions where surgery would be very mutilating, molecules such as Denosumab which act against the proliferative capacity of these lesions have been tested[6].

Denosumab is a human IgG2 monoclonal antibody approved by the Food and Drug Administration in 2013 and by the European Medicines Agency in 2014 for the treatment of giant cell tumors in adults and adolescents when these tumors are unresectable or when their surgical resection involves great morbidity[5]. One of the CGCG cell populations is formed by monocytes expressing the receptor activating nuclear factor-kB (RANK), favoring fusion between them and their differentiation towards osteoclasts by binding to RANKL[3]. Denosumab acts by inhibiting RANK ligand, regulating osteoclast differentiation and bone remodeling. Also, its binding to active RANK on CGCG cells could inhibit their growth[7-9].

Several studies point to the usefulness of this drug as a therapeutic alternative to surgery in unresectable tumors[10-13]. Its adverse effects include alteration of phosphocalcic metabolism as well as the appearance of osteonecrosis or atypical femoral fractures[5,14]. Denosumab is a novel therapeutic option for the treatment of CGCG, with little experience of use in this pathology in the pediatric population, although its effectiveness has recently been described in children for the treatment of unresectable CGCG and recurrent tumors[15,16]. The objective of this work is to describe the clinical experience with the first pediatric patient with CGCG treated with Denosumab in this center.

Clinical Case

A 12-year-old boy consulted the Pediatric Emergency Department of a tertiary hospital due to a 24-hour history of swelling in the left malar region, with no other associated symptoms. He was initially evaluated by his dentist who, after ruling out infectious pathology at that level, performed an orthopantomography that showed opacity of the left maxillary sinus (figure 1a) and referred him to this center. The examination in the emergency department showed a violaceous tumefaction in the left maxillary region, fluctuating, slightly painful on palpation, at the bottom of the vestibule from tooth 21 to tooth 25 associated with mobility of teeth 11-25 and pain on percussion in teeth 22 and 23.

The patient was evaluated by Maxillofacial Surgery and it was decided to start oral antibiotic therapy (amoxicillin-clavulanic acid) and to extend the study. A craniofacial CT scan showed an expansive lesion of 35 x 39 x 23 mm in the alveolar border of the maxilla, with thinning of the maxillary sinus cortex, partial invasion of the inferior meatus of the left nasal cavity, and slight protrusion into the oral cavity (figure 1, images B, C, and D). A biopsy by hematoxylin-eosin staining of the lesion showed cellular proliferation with abundant multinucleated giant cells of osteoclastic type and, among them, mononuclear and isomorphic cells with nuclei similar to those of giant cells, and negative p63 immunohistochemistry. These findings were compatible with CGCG. He was evaluated by Pediatric Oncology, requesting a ^{18}F-FDG PET-CT which showed hypermetabolism of the lesion (figure 2a).

On the other hand, due to the possible association of CGCG with genetic syndromes, a study of RASopathies was requested by Next-Generation Sequencing, detecting the variants p.Gly464Ala (Chr14:23428971, c.1391 G > C) in exon 14 of the MYH7 gene and p.Gly1815Ser (Chr15:48452664, c.5443G > A) in exon 45 of the FBN1 gene, both classified as probably pathogenic according to the criteria of the American College of Medical Genetics and Genomics (ACMG). In addition, the variant p.Pro637Arg (Chr22:20994994; c.1910C > G) was identified in exon 16 of the LZTR1 gene, classified by the ACMG as a variant of uncertain significance. Given the genetic findings, a cardiological evaluation was performed, ruling out structural cardiomyopathies in the patient. Marfan syndrome was not investigated due to lack of phenotypic correlation with this syndrome. The patient was evaluated by the Clinical Genetics unit, finding no evidence that the variants identified had an associated familial or personal phenotype.

After the diagnosis of CGCG in the patient and considering the size of the maxillary extension and bone disruption, it was decided jointly with Maxillofa-

cial Surgery to initiate treatment with Denosumab before surgical excision and monthly clinical-analytical monitoring and ^{1}□F-FDG PET-CT every 6 months to evaluate changes in the mineralization of the bone matrix and marginal sclerosis as well as to control the metabolism of the lesion. The dose recommended in the datasheet for adult and adolescent patients with Giant Cell Tumor was used, 120 mg subcutaneous weekly for 3 weeks and, subsequently, 120 mg subcutaneous every 4 weeks.

The patient presented a good clinical response to Denosumab, with disappearance of the maxillary swelling in the clinical examination after the administration of the third dose. A PET-CT scan was performed to evaluate the size and metabolic activity of the lesion. In the check-up 8 months after the start of treatment, a partial response was observed after 12 doses with a decrease in the size and metabolic uptake of the lesion (figure 2c). Given the clinical and radiological improvement achieved with Denosumab, it was decided not to perform surgery and to continue with the monoclonal antibody until completing one year of treatment.

Due to the side effects reported for this drug, the phosphocalcic metabolism was closely monitored by analytical tests in parallel to the administration of the antibody (weekly for the first three weeks, then monthly). The patient presented mildly symptomatic hypocalcemia with paresthesia in hands and minimum ionic calcium of 0.98 mmol/L [total serum calcium 7.48mg/dL (laboratory range 8.4 mg/dL -10.2 mg/dL)]. Hypocalcemia normalized after supplementation with calcium and vitamin D chewable tablets at respective maximum doses of 14.7 mg/kg and 11.7 IU/kg after the 4th dose of Denosumab (table 1). Phosphorus and magnesium levels remained within the normal range from the start of treatment. No signs of osteonecrosis were observed after 12 doses of subcutaneous Denosumab.

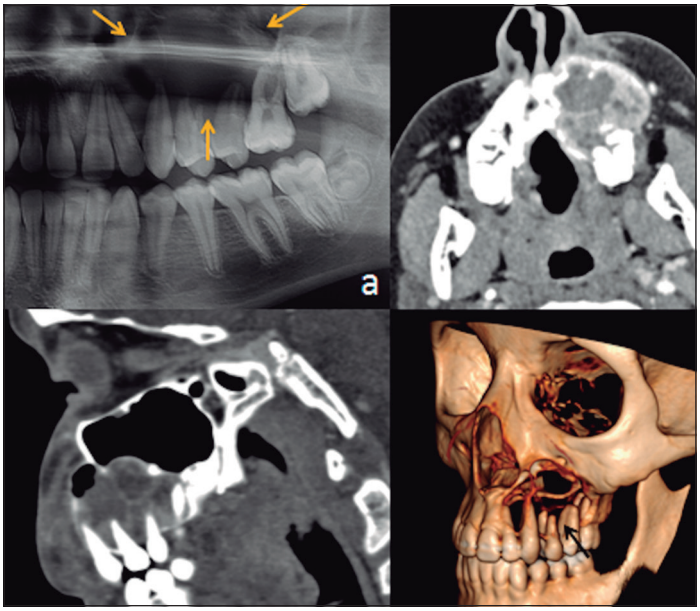

Figure 1. a) Panoramic radiograph showing a large radiolucent and expanding lesion on the left halve of maxillary bone with involvement of 23-24-25 dental roots (arrows). **b)** CT scan with intravenous contrast: in axial reconstruction it can be identified an heterogenous and expansive lesion in the left posterior maxilla which causes bone remodelilng and erosion. **c)** CT with intravenous contrast: in sagittal reconstruction (bone window) it can be identified the affectation of dental roots, significant bone thinning and expansion towards the maxillary sinus. **d)** Volumetric reconstruction showing the lytic lesion that conditions resorption of dental roots (arrows).

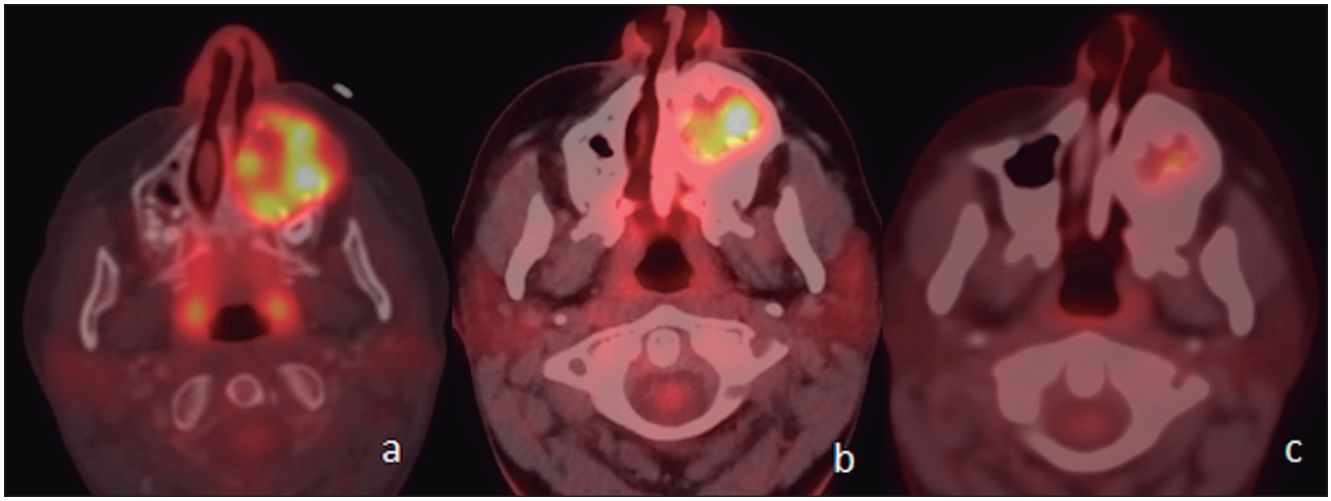

Figure 2. a) 18 F-FDG PET/CT that shows an hypermetabolic lesion in left maxilla. **b) c).** Control PET/CT at 4 and 8 months respectively showing a decrease in size and in metabolic captation, as well as bone remodelation and peripheral bone sclerosis.

Table 1. Monitoring of ionic calcium during Denosumab treatment, associated symptoms and treatment given

	Diagnosis	Denosumab 1º dose	Denosumab 4º dose	Denosumab 5º dose	Denosumab 10º dose
Ionic calcium (mmol/L)	1.23	0.98	1.03	1.15	1.19
Hypocalcemia related symptoms	No	Paresthesias in both hands	Paresthesias in both hands	No	No
Calcium carbonate/vitamin D (dose mg/UI)	0	500 mg/400 UI	1000 mg/800 UI	1000 mg/800 UI	1000 mg/800 UI

Discussion

GCGC is a rare entity in pediatrics and its proper management requires a multidisciplinary approach. Surgery has a fundamental role in the treatment of these lesions. However, sometimes, extensive and mutilating resections are necessary to achieve disease-free margins, which leads to high surgical morbidity in large lesions located in the facial skeleton[5].

The recurrence rate of CGCG after treatment with surgery, local corticosteroids, or other treatments, such as calcitonin, is very high[13]. The response of intralesional treatment with corticosteroids, either as a first option or neoadjuvant treatment, may be limited to extensive lesions. As for treatment with calcitonin, intranasal or subcutaneous, the response will depend on the expression of calcitonin receptors in the tumor[15]. For this reason, alternative therapeutic options have been evaluated, such as Denosumab, a monoclonal antibody that by inhibiting RANKL could reduce tumor size.

Currently, it has been proven that Denosumab can be an effective drug to reduce the overall size of the lesion in tumors that are unresectable[6,14,15]. This statement is consistent with the results obtained in this patient, the first adolescent with CGCG treated with Denosumab in this center.

The dose of Denosumab in children is not well established, although in adolescents between 12 and 17 years of age with mature bone skeleton, the same dose as in adults is recommended (120 mg subcutaneously every 4 weeks, with additional doses of 120 mg on days 8 and 15 of the first month of treatment). According to this recommendation, in the case presented, this therapeutic guideline was followed, achieving an adequate clinical and radiological response with good tolerance to the monoclonal antibody.

Treatment with Denosumab can cause alterations in phosphocalcic metabolism and osteonecrosis[5,14]. Therefore, in this patient, clinical surveillance for signs of osteonecrosis and analytical monitoring of phosphocalcic metabolism was performed, identifying mild hypocalcemia as the only adverse effect which resolved after calcium supplementation.

The appearance of CGCG can be related to certain genetic syndromes (NF-1, Noonan Syndrome, Cherubism, or Ramon Syndrome)[2,6], so genetic study may be recommended. Variants of the MYH7 gene are mainly associated with structural cardiomyopathies, which were ruled out in this patient. Variants of the FBNI gene have been associated with Marfan syndrome, whose clinical phenotype is not present in the patient. Therefore, it was considered that this information should be treated with caution and an evaluation by Clinical Genetics was requested to determine the pathogenicity of these mutations. In this unit, after the clinical evaluation of the patient and with the data from the genetic studies performed, there was no evidence that the variants found had a phenotypic correlation in this patient.

As limitations of this work, we should point out that it is the experience in a single child with a short follow-up time. Further studies in a pediatric population with a larger number of patients and a prolonged follow-up would be necessary to assess the long-term clinical response.

Conclusions

Treatment with Denosumab achieved in this patient a reduction in lesion size and metabolic activity without significant adverse effects in the short term and avoiding initial surgical morbidity. The initial response was promising, but the recurrence rate with Denosumab is still unknown. Larger studies in the pediatric population would be necessary to obtain more reliable data on the effectiveness of Denosumab in this type of tumor, to assess the presence or absence of local recurrence and the occurrence of long-term side effects.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World

Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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