

Up-to Date Review And Case Report

Rare aggressive form of giant-cell granuloma: a three years follow-up case report and discussion about medical therapeutic solutions

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Abstract – Introduction: Central giant cell granuloma (CGCG) is a rare and benign intraosseous lesion that usually occurs in the mandible and the maxilla. It might be aggressive. Nowadays, several treatments exist. **Observation:** This case report, with a three years follow-up, was about an aggressive and recurring form of CGCG exclusively managed by surgical approach. **Comments:** Several pharmacologic approaches are possible (intralesional injections of glucocorticoids, administration of calcitonin, alpha-2a interferon, denosumab) and could be an interesting alternative or complement to the surgical management when CGCG is aggressive, recurring, or non resectable. **Conclusion:** Surgical approach is the gold standard for the treatment of CGCG but sometimes, pharmacologic approaches could be proposed. According to the scientific literature, denosumab appears as a reliable and effective treatment but more prospective studies are needed.

Introduction

Central giant cell granuloma (CGCG) belongs to the family of nonodontogenic giant cell tumors (GCT) along with cherubism, GCT of bone, aneurysmal pseudo-cysts, and the brown tumors found in hyperparathyroidism [1,2].

It is a benign tumor whose incidence is estimated at 1.1/1 000 000. Women are more likely to be affected than men and it is two times more likely to occur in the mandible than in the maxilla [3,4]. It generally appears before the age of 30 years and its etiopathogenesis remains uncertain.

Its clinical course, though usually painless, is very often limited to the development of intraoral swelling. Its diagnosis is difficult and histological analysis is necessary to confirm it.

It exists in two forms: aggressive and non-aggressive. According to the reference study by Chuong *et al.*, key clinical and radiographic features make it possible to differentiate them [5]. A size of >5 cm, rapid growth, the rate of recurrence after surgical treatment, cortical thinning or perforation, and tooth displacements or root resorptions all indicate the aggressive forms. Histological and immunohistochemical

elements such as a significant size index, a large space occupied by giant cells, and high-level factor CD34 expression, also influence the diagnosis of an aggressive form [6,7].

The primary objective of this report is to raise awareness of a rare pathology. The secondary aim is to provide a summary of existing therapeutic modalities.

Observation

A 15-year-old patient was seen in March 2017 when she presented with experiencing pain and discomfort in the left mandibular molar area. Treatment with paracetamol had only partially relieved the pain. She had no health problems and did not smoke.

In April 2015, a germectomy procedure with alveolectomy was performed on four wisdom teeth (Fig. 1). At the 1-month postoperative follow-up, the areas had regained their normal appearance. However, a satellite adenopathy measuring 1 cm was palpable in the left submandibular region. This was caused by prior inflammation to the dental alveolus of tooth 38, which occurred 3 weeks after the operation and was resolved with amoxicillin treatment. In September 2016, the patient consulted for discomfort distal to 37. A minimal,

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non-indurated, distal swelling of this molar was found. It was a bit painful but there was no sign of inflammation. The rest of the intraoral and extraoral clinical examination was normal. The cone-beam computed tomography (CBCT) found a patchy, homogeneous, and well-defined image of the left mandibular angle (Fig. 2).

Curettage of the lesion was performed until bone contact was achieved and up to the level of the distal root of 37. The remnant tumor was very hemorrhagic, raspberry-colored, and discreetly “blowing out” the lingual cortical bone, but remained easily cleavable. Histological analysis confirmed a CGCG. Postoperative clinical checks at 1 and 4 months, revealed that the intraoral appearance was normal without any symptomatology. A fresh CBCT was performed at 4 months, which showed an osteolytic 22 × 16 mm image having irregular contours with thinned lingual and vestibular cortices, near the distal root of 37.

In March 2017, 2 years after the gementomies, the patient consulted again for minimal pain, with respect to 37. Upon inspection, there was only a discreet gingival swelling distal to this tooth (Fig. 3). On a percussion test, teeth 35, 36, and 37 were not tender and the vitality tests responded positively. The rest of the examination was unremarkable. A CGCG recurrence was immediately suggested, but the standard procedure is to first rule out any malignant pathology.

A fresh CBCT was performed, which found a large osteolytic lesion of the left ascending ramus of the mandible. The vestibular and lingual cortices had a “blown-out” appearance and there was displacement of the inferior alveolar nerve toward the basilar edge (Fig. 4). Laboratory tests were performed to rule out hyperparathyroidism (the brown tumors encountered in this pathology having a similar histological appearance to CGCG). A biopsy was performed under local anesthesia to confirm the diagnosis of a CGCG recurrence.

Surgical revision under general anesthesia was decided upon. The hemorrhagic tumor had an elastic consistency and was easy to separate from surrounding tissues. Curettage supported by bone drilling was performed. The excised specimen was sent to the anatomic pathology laboratory. Postoperative prescriptions comprised level-I and level-II analgesics, chlorhexidine mouthwashes, and a 7/100th postoperative toothbrush. Histological analysis showed dense tumor proliferation with a multinucleate giant cell component, which was fusiform but rather monomorphic, with no cellular atypia (Fig. 5a and b). Focally, thin bony trabeculae were found, in addition to hemorrhagic cystic reshuffle. No signs of malignancy were observed. A recurrence of CGCG was therefore diagnosed.

At the 3-month and 1-year postoperative follow-ups, the patient reported no symptoms and the intraoral appearance was normal with a vital 37. A fresh CBCT showed reossification at the excision site (Fig. 6).



Fig. 1. Dental panoramic X-ray performed before the gementomies of the wisdom teeth without any osteolytic manifestation (March 2015).



Fig. 3. Intraoral view of the minimal soft-tissue swelling in the left mandibular retromolar region (March, 2017)



Fig. 2. CBCT sections and 3D reconstruction showing an osteolytic tumor “blowing out” the cortices opposite the former site of germ 38 (September 2016).



Fig. 4. Axial, frontal sections and 3D CBCT reconstruction showing a well-defined, unilocular, osteolytic tumor in the retromolar region of the left mandible and on the left ascending ramus. It should also be noted that the lower alveolar nerve is pushed back toward the basilar edge of the mandible (April 2017)

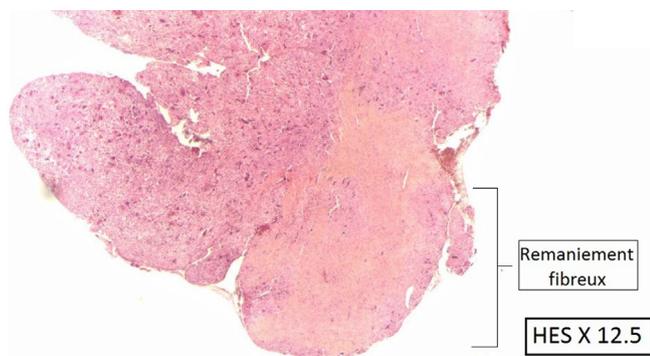


Fig. 5. (a) Tumor with variable cellularity but rich in giant multinucleated cells. In the lower right part of the section, we notice a significant fibrous reorganization. (b) Giant cells completely surrounded by oval and fusiform cells.

Discussion

Although surgical treatment remains the gold standard for the initial management of CGCG, several pharmacological treatments exist. Among these alternatives, there are intralesional corticosteroid injections [8,9], systemic interferon alpha-2a administration [10], intralesional calcitonin administration, or the subcutaneous administration of denosumab [11–14].

In the case of our patient, the tumor was still moderately sized and amenable to nonradical surgical treatment. The pharmacological therapeutic modality was thus preferred.

In a literature review, De Lange presents findings on postoperative recurrence rates, which range from 11 to 49%, the highest percentage rates being found in patients with signs and symptoms that favor the aggressive form [15].

There are no formal recommendations for the management of CGCGs. However, it seems that for larger tumors whose surgical resection would result in tissue loss, pharmacological treatments are often used to decrease their size and thus permit

second-stage surgical intervention. Pharmacological treatments could also be prescribed as part of the treatment plan for a recurrent CGCG notwithstanding previous surgical treatment.

The intralesional administration of corticosteroids may inhibit the process of resorption mediated by the lysosomal proteases produced by the giant cells found in CGCG. This could induce apoptosis of these “osteoclast-like” cells [12]. However, to date, no controlled study has been conducted to evaluate the effectiveness of this therapy.

Calcitonin, a hormonal peptide produced mainly by the thyroid, plays a major role in calcium–phosphorus metabolism and has an inhibitory effect on osteoclasts. Its inhibitory effect on the functioning of giant cells found in CGCG is now widely recognized.

Interferon alpha-2a is a cytokine with immunomodulatory and anti-angiogenic effects, which is important because CGCGs develop a large angiogenic component. De Lange also reports that its use as monotherapy in aggressive CGCGs would decrease the rapid growth of the lesion or even cause it to decrease in size. However, surgery would still be necessary to completely eliminate the lesion [15].

Denosumab is a monoclonal antibody used in the treatment of osteoporosis, bone metastases from solid cancers or multiple myelomas, and GCTs of bone found in the metaphyses of the long bones. It intervenes in the differentiation cascade and inhibits osteoclast activity by blocking the RANK receptors, which are essential elements of this cascade. In this way, denosumab inhibits bone resorption which, in the case of CGCG, is increased by the synthesis of RANK ligand (RANK-L) synthesized by osteoblast-like cells. The effectiveness of denosumab has been reported in several case reports [12–14]. It should be noted, however, that major studies have shown that it may be the cause of osteochemonecrosis of the maxilla, whose frequency is approximately 2% according to the main studies (of cases where denosumab was used in an oncological context rather than in the treatment of CGCG) [16].

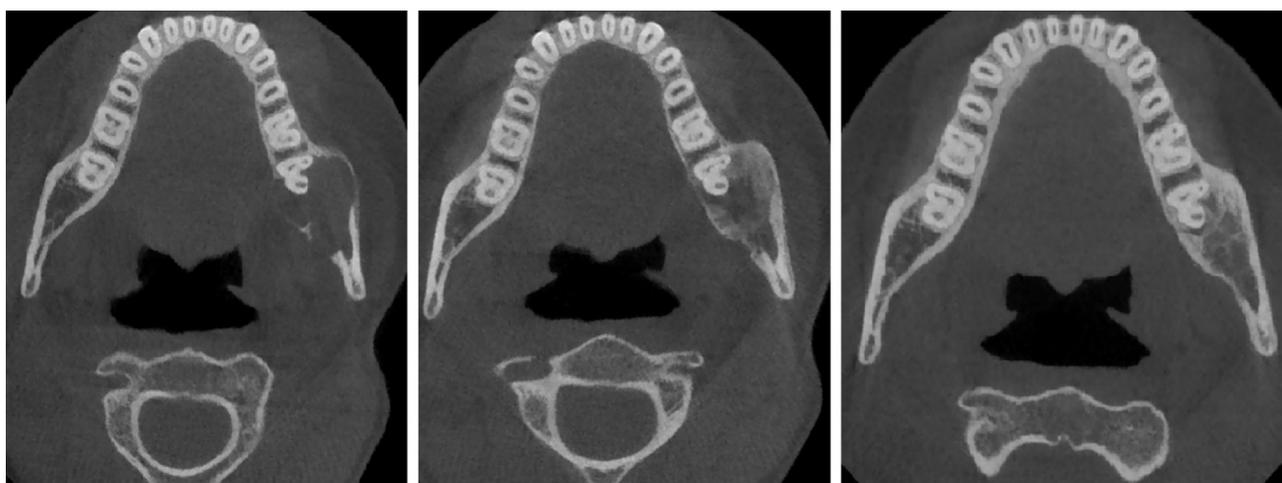
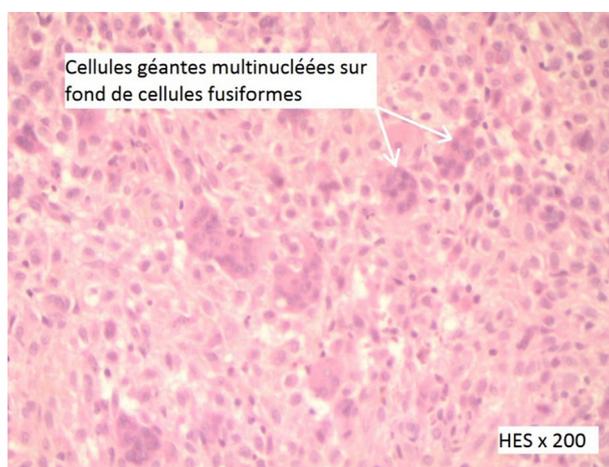


Fig. 6. Axial sections comparing the preoperative situation (April 2017) to the postoperative situations at 3 months (August 2017) and 1-year (end of March 2018). We take note of the reossification occurring at the surgical site in sector 3.

A long-term retrospective cohort follow-up study with five patients and a 25–49-month follow-up recently showed the good curative efficacy of denosumab, associated with the complete disappearance of maxillary or mandibular CGCG metabolic activity in all five patients [17].

Its use in this indication must still be the subject of well-designed, prospective, randomized studies. Some open-label phase-II studies have already been conducted in patients with GCT [18–20]. In one of them, 30 patients (in a cohort of 35) with GCTs of the long, unresectable, or recurrent metaphyseal long-bone lesions showed a positive response to denosumab (defined as the elimination of $\geq 90\%$ giant cells or as the absence of radiographic progression of the lesion) [18]. In the second available study on this topic, 163 of 169 with patients with nonresectable GCT showed no progression of the disease with an average follow-up of only 13 months [19].

CGCGs and GCTs belong to the same family of tumors and have a similar organization with osteoblast-like stromal cells and giant osteoclast-like cells. Denosumab appears to be an effective treatment of these two pathologies.

Conclusion

CGCG is a rare osteolytic tumor that is difficult to diagnose because its symptoms are ill defined. There are several therapeutic possibilities but no real consensual decision tree. In addition to surgery, recent pharmacological treatments such as denosumab are of therapeutic interest despite the need for more well-conducted, randomized, prospective studies to elucidate its long-term benefits in the treatment of CGCG.

Conflicts of interest: The authors declare that they have no conflicts of interest in relation to this article

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