

Up-to Date Review And Case Report

Giant-cell granuloma: 2 case reports

Samir Abdelqader¹, Nicolas Roche¹, Laurent Manfredi², Jean-François Papon²,
Louis Maman¹, François Ferré^{1,*}

¹ Dentistry Department, GH Pitié-Salpêtrière-Charles-Foix, Ivry-sur-Seine, France

² ENT Department, GH Kremlin-Bicêtre, Le Kremlin-Bicêtre, France

(Received: 15 February 2018, accepted: 17 April 2018)

Keywords:
giant-cell granuloma
/ brown tumors /
diagnosis

Abstract – Introduction: Giant-cell granuloma (GCG) is a benign tumor occurring almost exclusively in the jaws. These lesions remain rare but can sometime have an aggressive behavior. In this article, we will describe and follow two cases of GCG. **Observations:** The first case is a referred female patient, who presents a mandibular swelling. Its clinical and radiological aspects lead us to do a biopsy, with a histological result of GCG. The second case is a patient with a terminal kidney failure, referred for a buccal swelling in the upper left jaw. The cone-beam computed tomography X-ray shows a compartmentalized lesion with blurry limits. An excisional biopsy is performed and the histological diagnosis is a GCG. **Discussion:** Although the first patient suffers from no systemic disease, the second one presents a terminal kidney failure resulting in a chronic hyperparathyroidism. Hyperparathyroidism can activate osteoclastic resorption and create bone lesions such as brown tumors. **Conclusion:** The slow and asymptomatic growth of these lesions often result in a late diagnosis. It should be kept in mind as a differential diagnosis when dealing with an osteolytic lesion of the jaws with no clear etiology, especially if hyperparathyroidism or kidney failure is associated.

Introduction

Giant-cell granuloma (GCG) belongs to a family of giant-cell tumors and pseudotumors. This group of polymorphic tumors also includes aneurysmal bone cysts, cherubism, giant-cell tumors, and brown tumors caused by hyperparathyroidism [1,2].

GCG is a benign bone lesion that is rarely aggressive. It almost exclusively affects the maxillae and mandibles, and its prevalence is estimated at 7% of all benign maxillary tumors [3]. GCG preferentially affects the mandible as opposed to the maxilla (at a 3:1 ratio). From an epidemiological point of view, 1.15 million inhabitants are affected by this disease but the incidence is slightly higher in females than in males (1.25:1.05). Most of cases occur before age 30 years, with a peak incidence between ages 10 and 19 years [3–5].

GCG was initially described by Jaffe as a reactive lesion caused by inflammation and intraosseous hemorrhage [1]. This notion is currently being questioned because of the disease's unpredictability, variable (sometimes significant) aggressiveness, and potential similarity to giant-cell tumors of long

bones [4]. Although the etiology of isolated GCGs is currently unknown, the presence of GCG syndromes (cherubism, neurofibromatosis type 1, Noonan's syndrome) suggests a genetic predisposition in some cases [6].

In this study, we present two GCG cases along with a discussion regarding management of GCG and a related literature review.

Observations

Case 1

Mrs. G, a 46-year-old woman, was referred for evaluation after being detected with a lower right gingival lesion. She was also suffering from a depressive episode.

On history taking, the patient reported a slowly developing lesion that appeared several months ago. Clinical examination revealed large vestibular swelling that was firm and tender (Fig. 1a), accompanied by a mobile right submandibular lymph node of approximately 2 cm in size. In light of this clinical presentation, the following additional examinations were conducted: panoramic radiograph (Fig. 1b), cone-beam computed tomography (CBCT) (Fig. 1c), and a needle biopsy, which revealed a central GCG. Excision of the lesion and extraction of teeth 44 and 45 were performed under local anesthesia (Fig. 1d). The postoperative management was

* Correspondence: ferrefrancois@hotmail.com

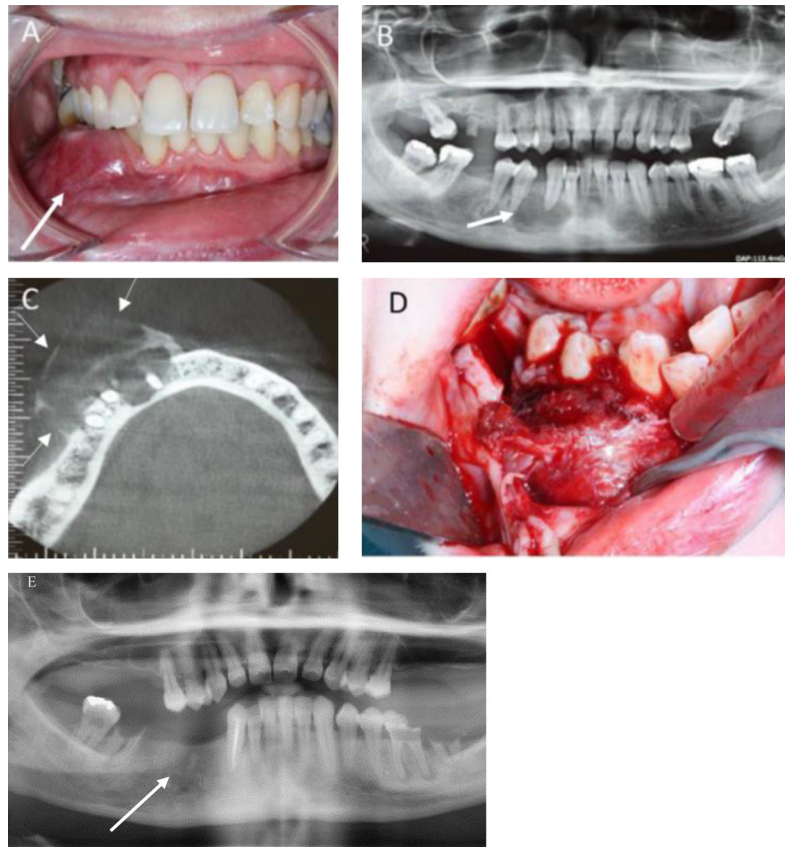


Fig. 1. (A) Intraoral view showing a lower right vestibular swelling. (B) Orthopantomogram showing the lesion at the apex of tooth 43. (C) Axial section of the cone-beam computed tomography showing the vestibular extension with a blister and perforation of the cortex and the partitions of the lesion. (D) Surgical image showing the tumorous nature of the lesion. (E) Orthopantomogram of the patient 8 years after the procedure shows reossification of the site. No recurrence has occurred.

uneventful except for a mild mental nerve paresthesia lasting <2 months. The patients showed no recurrence for 8 years of follow-up.

Case 2

A 32-year-old woman presented with a maxillary vestibular swelling extending from tooth 22 to 25. The patient had end-stage renal failure and was undergoing hemodialysis three times a week, which caused secondary hyperparathyroidism. She also had iron-deficiency anemia.

Similar to the previous case, the slow and asymptomatic progression of the lesion led to the patient's late consultation. On clinical examination, there was a firm, painless swelling (Fig. 2a). Tooth 24 was necrotic. In addition, there was no lymphadenopathy. A radiological assessment including panoramic radiograph and CBCT was performed (Fig. 2b). The panoramic radiograph showed only a slight radiolucency in the periapical areas of teeth 22, 23, and 24. A CBCT examination revealed an extensive lesion invading the cortical bone, with calcified fragments within the lesion. The surgeon decided for complete resection of the lesion by enucleation and complete curettage, followed by a histological examination of the

specimen. The lesion was confirmed to be a GCG through histological diagnosis.

Postoperative management was uneventful except for edema and infraorbital nerve paresthesia lasting for 3 weeks. Clinical and radiological follow-up after 1 year showed good bone healing with no sequelae.

Comments

We presented two cases of GCG in two adult women. In the literature, the typical clinical examination of such lesion reveals an asymptomatic jaw swelling, which can cause facial asymmetry depending on the size of the lesion. Tooth displacement is observed in 18–40% cases and mobility can be identified. Reactive lymphadenopathy can also be associated with GCG [5].

The radiographic appearance of GCG may range from a small apical lesion, detected during a routine examination, to large, multilocular, destructive, radiolucent lesions [5]. Root resorptions are observed in 12–43% cases [5]. Radiologically, GCG is difficult to differentiate from other lesions, such as ameloblastoma, odontogenic cyst, aneurysmal bone cyst, myxoma,

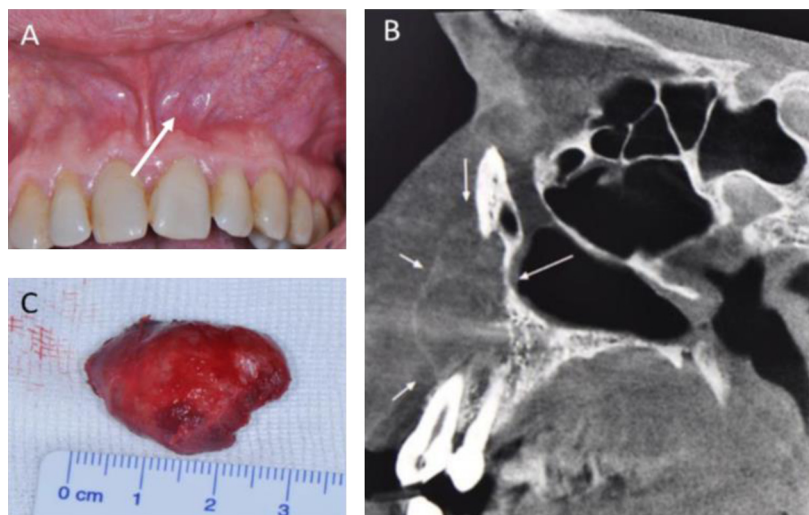


Fig. 2. (A) Intraoral view showing the vestibular arch caused by the lesion. (B) Parasagittal section of the cone-beam computed tomography showing vestibular extension and compartments of the lesion. (C) Image of the operative site.

and odontogenic fibroma [7]. In some cases, these lesions may become aggressive, which is an indication for modifying the clinical management (larger surgical margins, combination drug treatments). Thus, a histological analysis is essential for specifying the nature of the lesion and modifying the treatment. Histological examination demonstrates the presence of a collagenous stroma containing multinucleated giant cells. The latter are concentrated in the perivascular hemorrhagic zones [8].

In the second case, the patient had end-stage renal disease and was undergoing dialysis. However, in these patients, secondary hyperparathyroidism is often observed because of the lack of renal vitamin D production, which leads to hypercalcemia and increased parathormone (PTH) release. During the course of hyperparathyroidism, it is possible to observe bone lesions resulting from severe demineralization and creating fibrous tissue-filled lacunae. The lacunae have a pseudocystic appearance on radiographic examination. When discovered incidentally, these lead to the diagnosis of the previously undetected hyperparathyroidism. On microscopic examination, the fibrous tissue filling the lacunae shows many multinucleated giant cells. Hemosiderin and red blood cell infiltrate can also be observed, giving a brown red color to these lesions, which are thus described as “brown tumors”. Trabecular bone formations are often found. Thus, they are microscopically identical to GCG [9]. Differential diagnosis will be according to blood PTH, alkaline phosphatase, calcium levels, in addition to urea and creatinine levels to assess renal function [9]. In the present case, we noted a lacunar bone lesion and hypocalcemia associated with hyperparathyroidism, in the context of end-stage renal failure. Therefore, in the current case, the lesion is redefined as a brown tumor, as already described in case reports [10,11].

There are two subtypes of GCG, *i.e.*, aggressive or non-aggressive, differentiated on the basis of clinical, radiological, and histological criteria [5] (Fig. 3). Non-aggressive GCGs are

minimally symptomatic or even asymptomatic, and they progress slowly and rarely relapse after surgical removal. This was observed with both cases in presented this report. In fact, there was an absence or near absence of symptoms accompanied by slow growth of the tumor. In cases 1 and 2, no recurrence was observed at 8 and 4 years, respectively, of follow-up. Aggressive GCG includes at least one of these factors: pain, paresthesia, rapid growth, or size >5 cm. According to previous reports, the rate of postoperative recurrence of these lesions is between 37.5 and 72% [3,5,12,13]. In the case of multifocal lesions, it is necessary to consider the possibility of a syndromic disease (Noonan syndrome, neurofibromatosis type 1, cherubism). In the case of cherubism, apart from the characteristic multilocular maxillary lesions, other bones can be affected. The lesions are similar to those in GCG [5]. Noonan’s syndrome, caused by the mutation of the *PTPN11* gene, is characterized by unusual facial features, cardiac malformations, and short stature. Like cherubism, multiple GCGs can be associated with Noonan’s syndrome. In the case of neurofibromatosis type 1, there may be single or multiple lesions [5].

To decrease the risk of recurrence, some researchers propose adjuvant therapies with surgery, such as intralesional corticosteroid injections for several weeks before surgical excision, or the use of interferon alpha (IFN- α) preoperatively [12]. However, the use of corticosteroids presents inconclusive results [14], and the side effects induced by IFN- α (viral infections, leukopenia, lupus erythematosus, etc.) preclude this as a first-line therapy.

Subcutaneous or intranasal calcitonin administration has also been proposed as a treatment with or without surgery [15]. Its usage was studied in a randomized, double-blind, and placebo-controlled trial, in which the researchers reveal a significantly lower recurrence rate when treating GCG by aggressive surgical management followed by intranasal calcitonin [16].

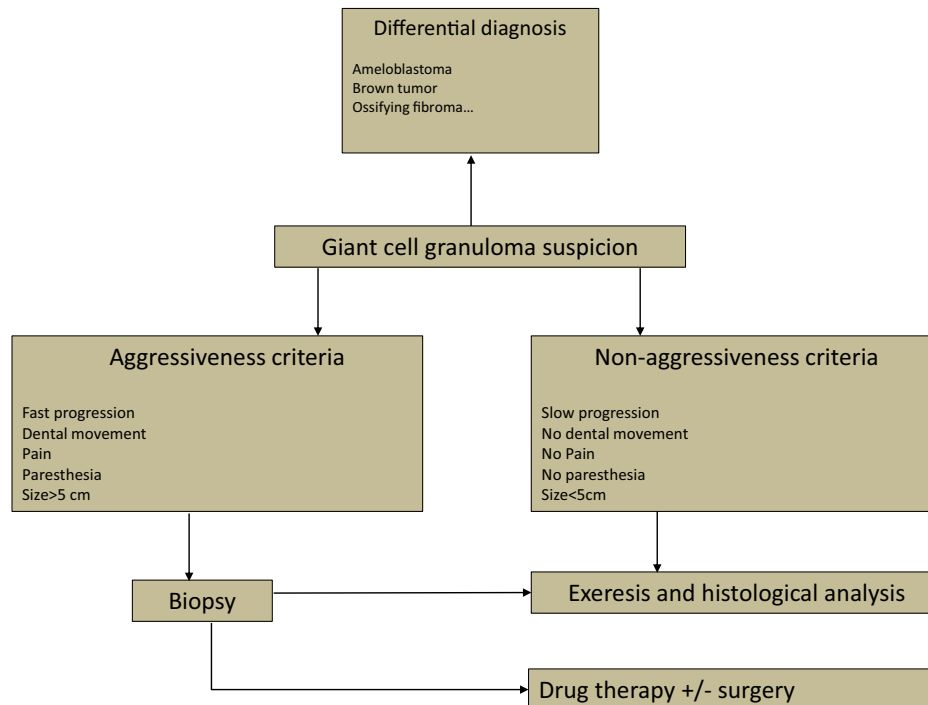


Fig. 3. Decision tree for the diagnosis of giant-cell granuloma (GCG). GCG management will depend on whether or not the lesion meets the criteria for aggressiveness.

A final therapeutic strategy uses denosumab targeted therapy without surgical treatment. It has been documented in the treatment of giant-cell tumors [17–19]. Denosumab is a human monoclonal anti-RANKL antibody (IgG2) and is administered subcutaneously. Denosumab specifically binds to RANKL with high affinity, preventing activation of the RANK receptor on the surface of osteoclasts and their precursors. The first phase-II study describing the use of denosumab in the treatment of GCGs of appendicular skeleton bones dates from 2010 [18]. The researchers report decreased pain and functional improvement in 84% patients. Since then, several other researchers have reported lesion stabilization and/or regression during radiological and histological follow-up [19,20]. However, denosumab causes common side effects such as dyspnea, musculoskeletal pain, maxillary osteonecrosis, hypocalcemia, and hypophosphatemia. Therefore, the evaluation of the risk–benefit ratio should be considered before its use [20].

Conclusion

GCG is a benign osteolytic lesion of the maxillae and mandibles whose diagnosis is primarily histological. Once GCG differential diagnoses, including other giant-cell tumors, have been eliminated, the current standard treatment is surgery. Drug therapy used alone or in addition to successful surgery in several GCG cases described in the literature have not yet been proven effective in randomized clinical trials.

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

References

1. Jaffe HL. Giant-cell reparative granuloma, traumatic bone cyst, and fibrous (fibro-oseous) dysplasia of the jawbones. *Oral Surg Oral Med Oral Pathol* 1953;6:159–175.
2. Auclair PL, Cuenin P, Kratochvil FJ, Slater LJ, Ellis GL. A clinical and histomorphologic comparison of the central giant cell granuloma and the giant cell tumor. *Oral Surg Oral Med Oral Pathol* 1988;66:197–208.
3. De Lange J, van den Akker HP, Klip H. Incidence and disease-free survival after surgical therapy of central giant cell granulomas of the jaw in the Netherlands: 1990–1995. *Head Neck* 2004;26:792–795.
4. Chuong R, Kaban LB, Kozakewich H, Perez-Atayde A. Central giant cell lesions of the jaws: a clinicopathologic study. *J Oral Maxillofac Surg* 1986;44:708–713.
5. De Lange J, Van den Akker HP. Clinical and radiological features of central giant-cell lesions of the jaw. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;99:464–470.
6. Krammer U, Wimmer K, Wiesbauer P, Rasse M, Lang S, Mullner-Eidenböck A, Frisch H. Neurofibromatosis 1: a novel NF1 mutation in an 11-year-old girl with a giant cell granuloma. *J Child Neurol* 2003;18:371–373.
7. Harmon M, Arrigan M, Toner M, O’Keeffe SA. A radiological approach to benign and malignant lesions of the mandible. *Clin Radiol* 2015;70:335–350.
8. Marx R, Stern D. *Oral and maxillofacial pathology*, Chicago: Quintessence Publishing Co Ltd, 2002: 783–789.

9. Raubenheimer EJ, Noffke CE, Mohamed A. Expansive jaw lesions in chronic kidney disease: review of the literature and a report of two cases. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015;119:340–345.
10. Chami LB, El Omri N, El Qatni M, El Wady W, El Mohtarim B. Brown tumor of the palate as first manifestation of primary hyperparathyroidism: a case report. *Med Buccale Chir Buccale* 2011;17:287–291.
11. Mohammed Farouk SH, Ihsane Ben Yahya La tumeur brune due à une hyperparathyroïdie secondaire: à propos d'un cas clinique et revue de la littérature. *Med Buccale Chir Buccale* 2017;23:61–64.
12. Gupta B, Stanton N, Coleman H, White C, Singh J. A novel approach to the management of a central giant cell granuloma with denosumab: a case report and review of current treatments. *J Craniomaxillofac Surg* 2015;43:1127–1132.
13. O'Connell JE, Bowe C, Murphy C, Toner M, Kearns GJ. Aggressive giant cell lesion of the jaws: a review of management options and report of a mandibular lesion treated with denosumab. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015;120:e191–e198.
14. Yanik S, Aras MH. Management of central giant cell granuloma of mandible using intralesional corticosteroids: case report and review of literature. *J Oral Maxillofac Surg* 2013;71:721–722.
15. Schreuder WH, van den Berg H, Westermann AM, Peacock ZS, de Lange J. Pharmacological and surgical therapy for the central giant cell granuloma: a long-term retrospective cohort study. *J Craniomaxillofac Surg* 2017;45:232–243.
16. Tabrizi R, Fardisi S, Zamiri B, Amanpour S, Karagah T. Can calcitonin nasal spray reduce the risk of recurrence of central giant cell granuloma of the jaws? A double-blind clinical trial. *Int J Oral Maxillofac Surg* 2016;45:756–759.
17. Xu SF, Adams B, Yu XC, Xu M. Denosumab and giant cell tumour of bone—a review and future management considerations. *Curr Oncol* 2013;20:e442–e447.
18. Thomas D, Henshaw R, Skubitz K, Chawla S, Staddon A, Blay JY, Roudier M, Smith J, Ye Z, Sohn W, Dansey R, Jun S. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol* 2010;11:275–280.
19. Thomas DM. RANKL, denosumab, and giant cell tumor of bone. *Curr Opin Oncol* 2012;24:397–403.
20. Schreuder WH, Coumou AW, Kessler PA, de Lange J. Alternative pharmacologic therapy for aggressive central giant cell granuloma: denosumab. *J Oral Maxillofac Surg* 2014;72:1301–1309.