The Journal of One-Day Surgery
Vol. 32 No. 4 (2022): JODS November

Multiple Central Giant Cell Granulomas in the mandible - A rare presentation with literature review.

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Central giant cell granulomas (CGCG) are rare, benign destructive osteolytic lesion of osteoclastic origin with variable aggressiveness that occur in the maxilla and mandible. It has a peak prevalence between the ages of 10 to 25 years old with a clear preponderance for the mandible and female population. CGCG typically presents as a solitary lesion, appearing as a multilocular radiolucency with scalloped margins and a honeycomb or soap bubble like appearance. These lesions are histologically characterised by mononuclear and multinuclear giant cells on a mesenchymal stromal background. First reported by Jaffe the lesion was coined giant cell reparative granuloma; a term no longer used as understanding of the pathogenesis develops. Genetic sequencing has shown familial association and a connection with “RAS/MAPK syndromes” as they are linked by overlapping facial features and are caused by mutations at different points along the RAS/MAPK pathway. Thirty percent of CGCG present as aggressive lesions characterised by rapid growth and bone destruction. The most common treatment is surgical curettage. However, increasing knowledge of the underlying pathogenesis has led to development of non-surgical treatments such as intralesional corticosteroid injections, therapy with calcitonin, interferon and monoclonal antibodies. This paper presents the rare case of an asymptomatic 14-year-old boy with bilateral CGCG which were noted as an incidental finding on a panoramic radiographic as part of an orthodontic assessment. It was treated successfully through surgical curettage.

Introduction

Central giant cell granulomas (CGCG) are rare benign lesions of the maxilla and mandible with varied presentation since their first report by Jaffe in 1953 (1). Reports have shown a variable aggressive nature of these destructive osteolytic lesions, which mainly afflict young adults and children between the ages of 10 and 25 years old, with a preponderance for the mandible and female population (62%) (2) (3) (4).

Usually presenting as a solitary lesion, CGCG radiologically appear as a multilocular radiolucency with scalloped margins and a honeycomb or soap bubble-like appearance. It has a prevalence of 0.00011% and accounts for <7% of all benign tumours of the jaws (3). The World Health Organization defines this entity as a "localised benign but sometimes aggressive osteolytic proliferation consisting of fibrous tissue with haemorrhage and hemosiderin deposits and presence of osteoclast-like giant cells with reactive bone formation." (1)

Indicative of its neoplastic nature CGCG often develops spontaneously, although reports have shown trauma as an important etiological factor (5). Pathogenesis theories have included that CGCG may be an inflammatory or reactive lesion, a true tumour, or an endocrine lesion (3). Recent developments in molecular genetics have highlighted several genetic aberrations that help differentiate from giant cell tumours of the bone or other giant cell-rich lesions (5).

Treatment options vary depending on the clinical characteristics of the lesion; however, surgical curettage is the most common treatment (6). More invasive resections with peripheral ostectomy have seen lower recurrence rates, although aesthetics and function are impacted further (7). Non-surgical options have been shown to reduce the size of lesions, although in many cases, surgical intervention was also required (8).

Case

A 14-year-old male presented to the orthodontist with malocclusion of his teeth following a referral from his dentist. His medical status was unremarkable, with no known systemic disorders. No history of trauma was recalled, nor were any systemic or local infections. The prenatal history was unremarkable and delivery was at full term with no complications.

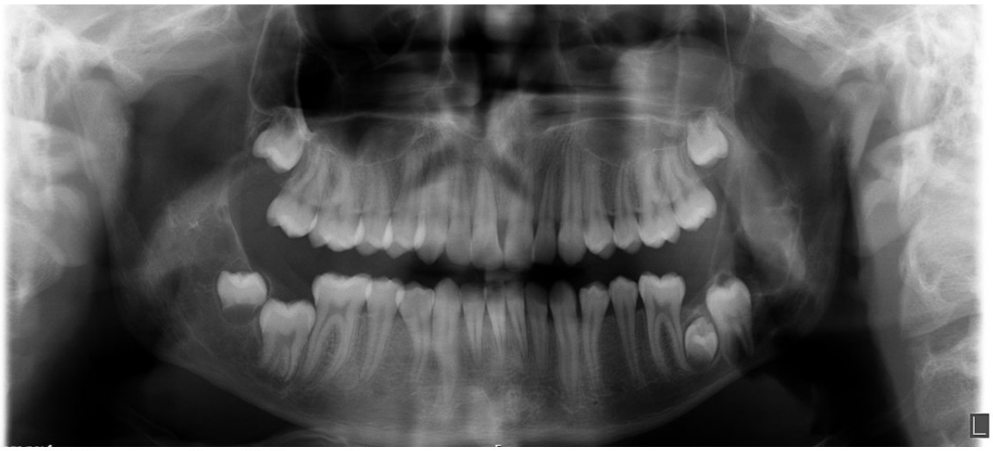

Fig 1. Pre-operative Orthopantogram

An orthopantomogram and cephalogram were taken as part of the primary investigations (Figure 1). The radiograph showed two lesions on either side of the mandible. The left-sided lesion was a well-defined, thinly corticated, multilocular radiolucency on the left anterior ramus within anatomical boundaries. Superiorly the lesion extended to the coronoid process. Posteriorly it contacted the mandibular canal and foramen and its inferior extent was the angle of the mandible. The right side showed a smaller well defined, thinly corticated, multilocular radiolucency immediately distal to un-erupted lower right 8. Clinically the patient had no pain, tooth mobility or swelling. There was no history of similar disease in any of the siblings or the parents of the affected child.

A subsequent cone-beam computed tomography (CBCT) scan was completed to assess the three-dimensional extent of these lesions. The imaging revealed a 30mm x 15mm x 17mm well-defined,

corticated radiolucency of the left anterior ramus, extending to the coronoid process (Figures 2 A and B). It was a single cavity with a multilocular appearance. Anteriorly it was in contact with the follicle of the unerupted most distal molar. Poster-inferiorly it was in contact with the superior wall of the inferior dental canal, with no apparent displacement or loss of its bony wall, and about 2-4mm distance from the mandibular foramen. The lesion extended along the inferior dental canal. There was cortical thinning and mild expansion of ramus laterally, with likely perforations. Lingually the cortex was thinned but intact. The anterior bony margin of the lesion was lost. The internal attenuation was consistent with soft tissue with no internal calcification.

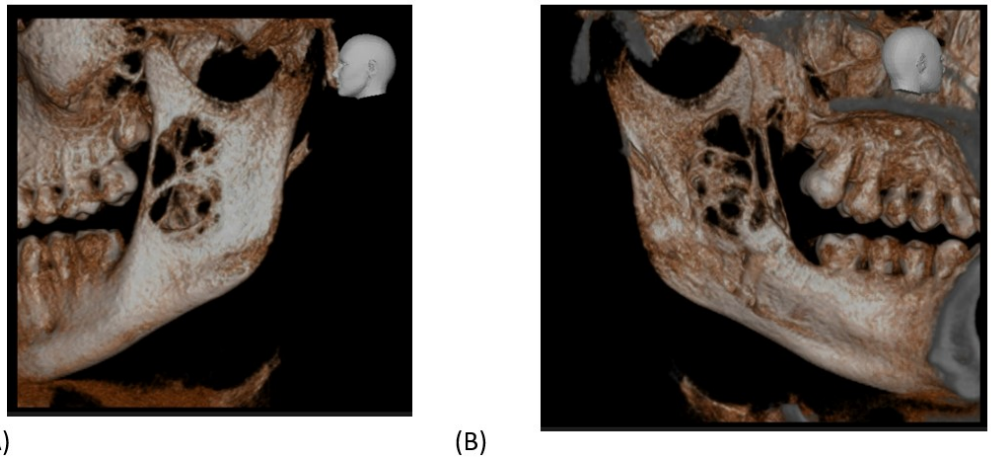

Fig 2. 3D reconstruction of left CGCG from CBCT

Figure 2

The lesion on the right side was a well-defined, partially corticated, irregularly shaped radiolucency distal to the third molar (Figure 3 A, B, C, D). It was multilocular in appearance. Anteriorly it was in contact with the follicle of the unerupted most distal molar, with the maintenance of the bony wall between them. It came close but did not touch the superior wall of the inferior dental canal. There was medial cortical thinning and slight expansion, with possible perforation. In addition, there was some thinning of the lateral cortical plate. Anteriorly there was a small perforation medial to the anterior oblique ridge. Maximum dimensions are 15mm Supero-inferior, 13mm medio-lateral and approximately 14mm antero-posteriorly. Other findings of note show the lower left third and second molar were transposed. Based on the literature, an aggressive giant cell lesion exhibits a size greater than 5cm as well as rapid growth, tooth displacement, root resorption, cortical bone thinning or perforation. They can also cause asymmetry of the face, pain, bleeding, and displaced or loose teeth. None of these are seen in this case; therefore, a diagnosis of non-aggressive bilateral central giant cell granuloma was made.

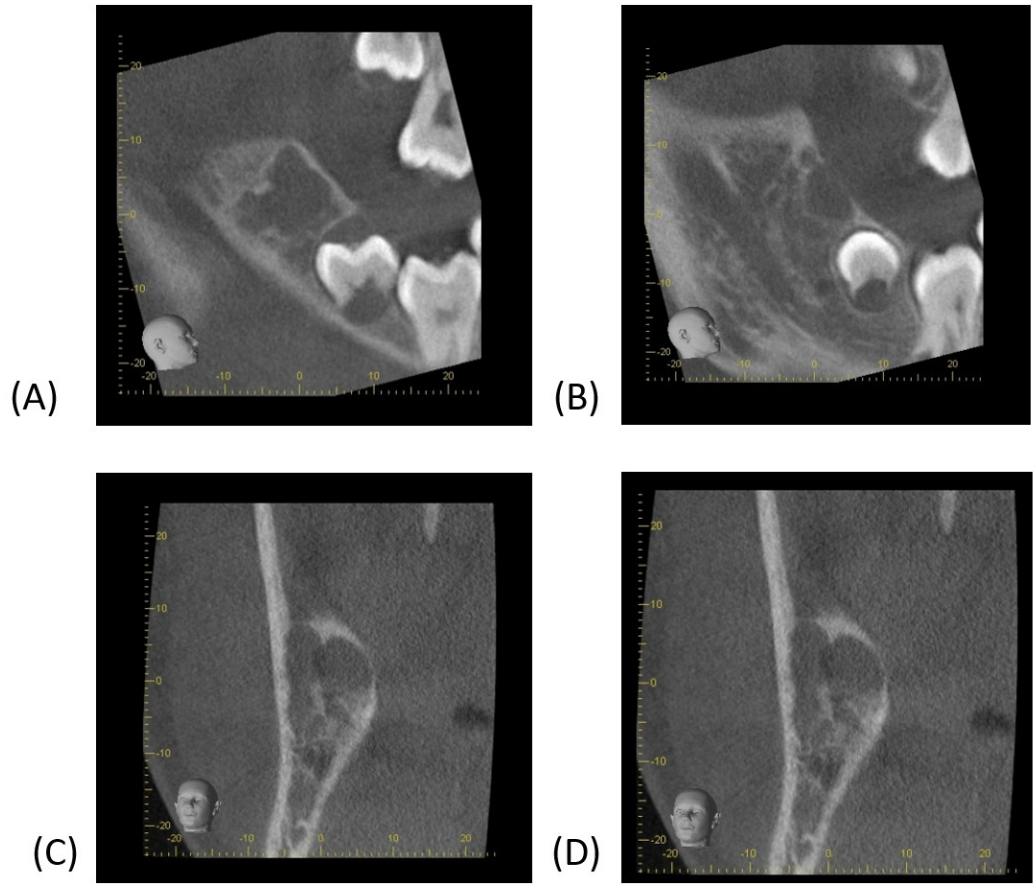

Fig 3. Slices from the CBCT showing the right CGCG

Figure 3

The patient underwent complete enucleation through surgical curettage of both lesions through an intra-oral approach under general anaesthesia. The lower right third molar and transposed lower left third molar were extracted after orthodontic consultation. The wound was then closed primarily. The post-operative course was uneventful. Histology of both specimens showed the characteristic mononuclear and multinuclear giant cells with spindle-shaped mesenchymal stromal cells of CGCG. Preoperative blood investigations were conducted to rule out hyperparathyroidism. The blood results suggested normal calcium metabolism. Re-enquiry of family history did not reveal any syndromic predisposition. We plan to study the tissue to look for activating mutations in the RAS/MAPK pathway.

Discussion

First reported by Jaffe, the lesion was coined giant cell reparative granuloma, a term no longer used as the understanding of the pathogenesis develops (1) (9). The biological behaviour of CGCG

of the jaws ranges from asymptomatic lesions with slow growth and low recurrence rate to an aggressive pathological process and therefore is best classified as a benign neoplasm. The aggressive lesion is characterised by pain, rapid growth, root resorption, cortical perforation and a high recurrence rate. The Hillerup and Hjørting-Hansen Theory (1978) was widely accepted, and they suggested that CGCG, giant cell tumour and traumatic bone lesions are different manifestations of the same process (10). The theory states that primary bone disease, malformation or minute trauma can lead to intraosseous hematoma; each manifestation is produced by an altered blood supply (10). Trauma has been considered an important aetiological factor in the initiation of this lesion in predisposed subjects (11). Edwards' recent genetic advances have linked multiple CGCG with syndromes such as neurofibromatosis, cardiofaciocutaneous syndromes, Noonans syndrome and LEOPARD syndrome (12) (13). These are categorised as “RAS/MAPK syndromes” which are linked by overlapping facial features and are caused by mutations at different points along the RAS/mitogen-activated protein kinase (RAS/MAPK) pathway. The pathway regulates cell growth, differentiation, senescence, and death (13). Multiple CGCGs are a rare but typical complication of a dysregulated RAS/MAPK pathway and share phenotypic characteristics of cherubism. The underlying genetic mutations and sequelae distinguish the two. Mutations in *SH3BP2* are associated with cherubism, whereas mutations in *PTPN11* and *SOS1* have been reported in people with multiple CGCG (8). Giant cell lesions in cherubism tend to resolve spontaneously, whereas those observed in multiple CGCG can have aggressive signs and symptoms. Left untreated, CGCG of the jaw can continue to expand, causing significant deformity, swallowing changes and speech difficulties.

Aggressive lesions represent up to 30% of all CGCG and are characterised by rapid growth and bone destruction (3). These lesions display no significant histological differences from non-aggressive lesions; however, they have higher recurrence rates. Clinically aggressive lesions are usually greater than 5cm in size and can cause sensory disturbances, bone expansion, cortical perforation, tooth displacement or transposition and root resorption (14).

Surgical curettage is the most common treatment and gives satisfactory results with recurrence rates of 11%-49%. However, treatment plans depend on location, clinical and radiographic features (5). Symptomatic aggressive lesions show a higher rate of recurrence (15). Studies show that more aggressive resections with peripheral ostectomy can have a recurrence rate as low as 6%, although aesthetics and function are consequentially compromised (5). Regular radiological follow-up is necessary to reveal recurrence (16). Non-surgical management is often used for young children to avoid facial deformity in cases where surgery is contraindicated if the lesion has large extensions or a high recurrence rate (17).

Intralesional corticosteroid injections with triamcinolone acetonide have been used since the 1980s. Literature has shown it can decrease the lesion size in 57% of cases, although the complete resolution was reported in only 10% of patients. Further surgical intervention was required in 50% of cases and 7% showed no response (8). Corticosteroids inhibit the extracellular production of lysosomal proteases, induce apoptosis in osteoclast-like cells; inhibit transcription factors for intracellular proliferation; and induce anti-angiogenic effects on endothelial cells (18). These factors lead to inhibition of resorption, thus preventing the growth of CGCG. The discomfort caused by the injections and patient compliance are the main disadvantages with potential systemic effects especially concerning immunocompromised and diabetic patients.

Calcitonin therapy is a viable treatment option and can completely resolve lesions, although treatment usually spans 19 to 21 months. Therefore, this therapy is usually reserved for multiple, recurrent, or particularly aggressive lesions (19). The binding of calcitonin to the receptor causes changes in cell structure, leading to inhibition of DNA synthesis by cells (19).

Monoclonal antibodies prevent the osteolytic process and have shown promising results in the treatment of CGCG, which was trialled on the assumption that the giant cells present in the CGCG are analogous to osteoclasts (5). However, the evidence of its use is scarce. Further randomised

controlled trials are needed to determine its effectiveness in treating CGCG especially when possible side effects such as hypophosphatemia, pain in the extremities, anaemia, and jaw osteonecrosis are considered (18).

CGCG can respond positively to anti-angiogenic therapy after a period of adjuvant interferon-alpha (20). However, the side effects range from flu-like symptoms to complaints such as hypothyroidism and depression (8). Some cases required dose adjustment or cessation of administration. In addition to toxicity, treatment is long. The non-surgical treatment modalities discussed can be effective as an alternative in managing CGCG, although 40% of patients require further surgical treatment (8).

Conclusion

Early detection and treatment aid in successful outcomes for patients. The potential aggressive nature of these lesions prompts justification for surgical management. Left untreated, CGCG can cause significant deformity and symptoms. Progress is being made to understand the pathogenesis of CGCG; however, much remains to be defined. Pharmacological therapies have shown promising results, but well-designed randomised controlled trials remain scarce and are limited by small sample sizes. Most studies are retrospective case reports and case series. For now, surgical therapies remain the mainstay treatment for CGCG, alongside long-term follow-up. We feel that the delineation of aggressive and non-aggressive lesions with more extensive scientific evidence is much needed to aid in making a sound treatment plan and looking after the young population affected by this condition.

Conflict of Interest.

There are no conflicts of interests to disclose.

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