



## Aggressive central giant cell granuloma of the mandible: A case report and review of literature

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### Abstract

Mandibular aggressive central giant cell granuloma is a rare non-neoplastic giant cell tumour characterised by pain, bone destruction, tooth root resorption, jawbone cortical perforation, and high recurrence rate. This is a case of a 10-year-old boy who presented to the Dental Surgical outpatient clinic of University of Uyo Teaching Hospital with a three-year history of left jaw swelling. The clinical diagnosis was fibrous dysplasia of the left hemi-mandible. Consequently, left hemi-mandibulectomy was performed, and subsequent histopathological diagnosis was aggressive central giant cell granuloma of the mandible. This article presents this rare diagnosis and explores its classification, aetiopathogenesis, clinico-pathological features and management.

Keywords: Aggressive central giant cell granuloma, giant cell reparative granuloma, mandible, jawbone, mass lesion.

### Introduction

Central giant cell granuloma (CGCG) is a rare benign proliferative intra-osseous jaw tumour first described by Jaffe in 1953, which rarely occurs in other (extra-oral) sites and commonly seen in individuals aged below 30 years.<sup>1-8</sup> The World Health Organisation (WHO) defines CGCG as a unicentric benign lesion which may present as an aggressive (destructive) osteolytic growth (mass lesion) composed of fibro-collagenous tissue admixed with foci of haemorrhage, hemosiderin deposits, osteoclast-like giant cells and reactive bone formation.<sup>1</sup> Though the aetio-pathogenetic basis for CGCG is not yet well known, its clinico-pathologic features have been well studied.<sup>1,9,10</sup> Theories on the nature of CGCG variably describe it as a reactive lesion, developmental anomaly, benign

neoplasm or non-neoplastic bone lesion.<sup>2</sup> CGCG, though usually non-aggressive, may become aggressive when it presents with expansion and perforation of jawbone cortex, with the sequelae of mobility and displacement of affected teeth with resorption of the root of these teeth.<sup>1,2,4,6,7,10,11</sup> The aim of this article is to present a rare case of aggressive central giant cell granuloma of the mandible, which can mimic a malignant neoplasm, and to systematically explore its current relevant medical literature, with regards to its classification, aetio-pathogenesis, clinico-pathological features and management in the light of this case. We will also explore the key features of this index case with similar cases reported elsewhere.

### Case Report

This is a case of a 10-year-old boy who presented to the Oral and Maxillofacial surgical outpatient clinic of University of Uyo Teaching Hospital (UUTH) with a three-year history of left jaw (mandibular) swelling. This swelling gradually increased in size and extended from the incisors to the left temporomandibular joint (TMJ) with no associated pain or

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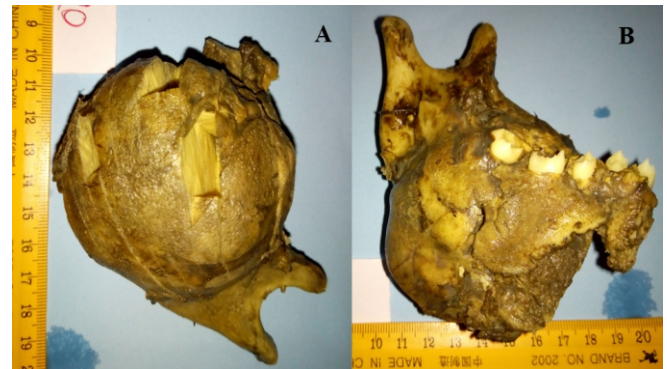
discharge. This swelling was hard to touch and yielded no specimen on fine needle aspiration biopsy (FNAB) for cytopathological evaluation. Radiological evaluation of this swelling showed radiolucency along its expanse. Routine blood investigations results were all unremarkable. A clinical diagnosis of fibrous dysplasia of the mandible was made.

This patient was subsequently booked for jaw surgery. A left-sided hemi-mandibulectomy was performed to completely resect the whole lesion. Intraoperatively, the lesion was seen to have extended to the left temporo-mandibular joint with extensive aggressive loss of cortical bone. The surgical resection specimen was sent to the Department of Histopathology, University of Uyo Teaching Hospital (UUTH) for histopathological evaluation and diagnosis. Currently, though reconstructive surgery could not be performed on this patient because of lack of funds, on follow-up, he is doing well without recurrence of lesion.

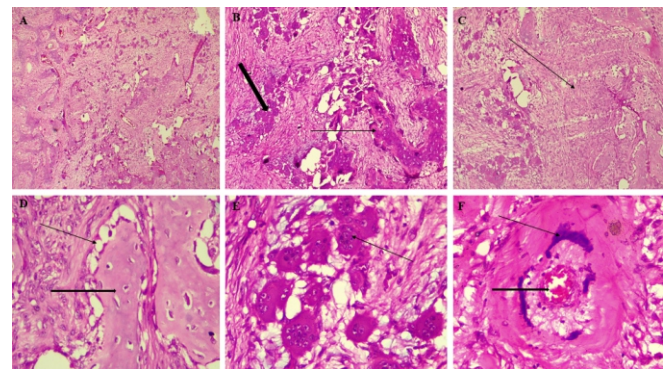
Grossly, at the histopathology department, the surgical resection specimen was, received in 10% formalin fixative labelled with patient's name and hospital number, a left distorted mandibular bony specimen with a bulbous mass protruding from the inferior border of the mandible. This specimen contained five embedded teeth on its medial aspect. This mandibular specimen measures 9.0 x 8.0 x 0.5cm in its widest dimensions and it was covered by a tan-grey capsule-like fibrous tissue. The internal surfaces of this specimen were examined using serial cut sections which were 1cm apart. These serial cut surfaces cut with grittiness and revealed grey-white solid surfaces that were firm to touch (see Figure 1). Representative sections were harvested from this specimen and submitted for tissue processing and microscopic evaluation.

Microscopically, this left mandibular specimen showed a benign fibro-osseous lesion composed of numerous curvilinear and few anastomosing trabeculae of woven and lamellar bone set within a dense to loose fibro-collagenous stromal tissue background. These bony tissues show prominent osteoblastic rimming. Also seen, were numerous diffuse to focal aggregates multinucleated giant cells within the fibro-collagenous stromal tissue background, admixed with the bony tissues (see Figure 2). The specimen was rimmed, in a patchy

pattern, by unremarkable stratified squamous epithelium. Based on these microscopic histopathological diagnostic criteria, a diagnosis of aggressive central giant cell granuloma of the left mandible was made.



**Figure 1[A-B]:** Gross morphological features of the mandibular lesion following surgical cut-up; [A] shows the lateral surface of left hemi-mandible and lesion, the serial cut sections and the areas of harvest of the representative sections can be seen, [B] shows the medial surface of left hemi-mandible and lesion, the five embedded teeth can also be seen.



**Figure 2[A-F]:** Microscopic morphological features of the mandibular lesion; [A] shows numerous multinucleated giant cells dispersed within a dense fibro-collagenous tissue background admixed with trabeculae of lamella bone (*H&E stain, X40*) [B] shows numerous multinucleated giant cells (*thick black arrow*) dispersed within a dense fibro-collagenous tissue background admixed with trabeculae of lamella bone (*thin black arrow*) (*H&E stain, X100*) [C] shows abundance of dense fibro-collagenous tissue background (*thin black arrow*) admixed with woven bone amongst

the other diagnostic features (H&E stain, X100) [D] shows a rim of osteoblasts (thin black arrow) lining the trabecules of lamella bone (thick black arrow) amongst the other diagnostic features (H&E stain, X400) [E] shows a cluster of multinucleated giant cells (thin black arrow) amongst the other diagnostic features (H&E stain, X400) [F] shows a concentric area of dystrophic calcification (thin black arrow) within a dense collagenous tissue surrounding a blood vessel (thick black arrow) (H&E stain, X400).

## Discussion

Giant cell granuloma (GCG) is a rare benign mass lesion or tumour primarily characterised by the presence of numerous non-neoplastic multinucleated giant cells.<sup>9,10,12</sup> GCG is a member of a group of lesions called giant cell tumours and pseudotumours.<sup>11</sup> The members of giant cell tumours and pseudotumours are aneurysmal bone cyst (ABC), cherubism, brown tumours and giant cell tumours.<sup>11</sup> Interestingly, some researchers view GCG as a benign neoplasm, however studies have shown that Giant cell lesions are distinct from giant cell tumours (GCT).<sup>12,13</sup> Importantly, GCG can be categorised as central (intra-osseous) and peripheral (extra-osseous) subtypes.<sup>9,12,14</sup> Central giant cell granuloma (CGCG) arises from bone (particularly the mandible and maxilla, anterior to the first molar tooth) while peripheral giant cell granuloma (PGCG) arises from extra-bony tissue such as peri-odontal ligament, gingival soft tissue and mucoperiosteum.<sup>4,9,12,14</sup> CGCG was previously called giant cell reparative granuloma.<sup>9,15,16</sup> Giant cell reparative granuloma of the jawbone was first described by Jaffe in 1953 as a rare non-neoplastic giant cell lesion of the jawbones, that closely mimics the aggressive giant cell tumour of bone found at the end of long bones, occurring secondary to a local reparative granulomatous reaction.<sup>3,16,17</sup> CGCG is hence an intra-osseous non-neoplastic lesion.<sup>9,15</sup> It is important to note that while reparative lesions resolve spontaneously, CGCG do not resolve spontaneously most of the time and are hence generally regarded as an aggressive lesion which require aggressive surgical en bloc resections.<sup>3,12</sup> Notably, CGCG can be further subcategorised into aggressive and non-aggressive subtypes of CGCG

based on their distinctive clinical, radiological, and histopathological features.<sup>1,2,5-7,10-12,18</sup> The aggressive subtype of CGCG is rare and presents as a large painful fast-growing tumour with benign histopathologic features.<sup>1,4-7,12,18,19</sup> Aggressive CGCG is further characterised by expansion of the cortical plate, surrounding bone destruction, tooth root resorption and divergence, and jawbone cortical perforation, as well as high frequency of recurrence (13 to 49%) following surgical enucleation.<sup>1,4-7,12,18,19</sup> The commoner Non-aggressive subtype of CGCG is characterised by tooth root resorption in the absence of jawbone cortical perforation.<sup>1,18</sup> The aetiology of CGCG is not well known and controversial due to its variable reparative, reactive, developmental anomaly, genetic or benign neoplastic aetiologic theories.<sup>4,6,8,10-12,16</sup> Studies show that the aetiology of CGCG is possibly due to recurrent slow minute bleeding into the mandibular parenchyma with or without associated inducing trauma with consequent inflammatory response, hence maybe viewed as a reactive mass lesion.<sup>4,9,12</sup> The higher occurrence of CGCG in younger individuals supports its possible developmental anomaly aetiologic origin.<sup>6</sup> The aetiologic agents can also be categorised into local and systemic agents.<sup>15</sup> The local agents include direct trauma to the site and vascular injuries in the site.<sup>15</sup> The systemic agents are other pre-existing disorders in the patient, CGCG has been found to occur in association with.<sup>2,15</sup> These associated disorders are neurofibromatosis type I, Noonan syndrome, cherubism, and hormonal disorders/imbances such as hyperparathyroidism and hormonal imbalances in pregnancy.<sup>2,15</sup> It is of note that cherubism, neurofibromatosis type 1 and Noonan's syndrome are collectively referred to as giant cell granuloma syndrome.<sup>11</sup> The presence of this syndrome denotes a genetic susceptibility.<sup>11</sup> Importantly, Abdelqader et al reported associated depression (case one) and end-stage renal failure with secondary hyperparathyroidism as well as iron deficiency anaemia (case two) in their study.<sup>11</sup> CGCG may also occur at the onset of menarche or pregnancy and is hence thought to be triggered by normal female hormone levels as evidenced by the female to male ratio of 2:1.<sup>2,6</sup> It is also of note that tooth extraction can precipitate the development of CGCG.<sup>1</sup> This theory is supported by Singh et al's

case report, whose patient had tooth extraction (from the same region that CGCG arose) two weeks prior to presentation.<sup>8</sup> Interestingly, none of these aetiological agents/risk factors were found in our patient.

CGCG is suspected to arise from odontoclasts, though it is not seen as a lesion of odontogenic origin.<sup>13</sup> This odontoclasts link to CGCG may explain why it is common in young individuals and why it arises from portions of the jaw with deciduous teeth.<sup>13</sup>

The incidence of CGCG is low, being 0.0001%.<sup>2,10</sup> CGCG is commoner in children and young adults (i.e. individuals aged less than 30 years old) than older individuals, with the peak age incidence between 10 to 19 years old.<sup>2,3,5,6,9-12,15,17</sup> This demographic feature is consistent with our case study and agrees with case studies by Wang et al, Deshpande et al, Kamble et al, Singh et al, Aditya and Aditya whose patients were 6-year-old, 8 year old, 18-year-old, 25-year-old and 27-year-old females respectively.<sup>2,5,8,19,20</sup> However, in contrast, Baskaran et al, Cossio et al, Abdelqader et al (two cases) in their studies reported CGCG in 32-year-old, 48-year-old, 46-year-old, 32-year-old females respectively.<sup>1,11,18</sup> CGCG is commoner in females than in males, with a female to male ratio of 2:1 in some studies or 1.25:1.05 in some other studies.<sup>2,3,9,11-13,15,17</sup> Our case study was a male and this was consistent with Pai et al's case report whose patient was a (2-year-old) male.<sup>21</sup>

CGCG is an uncommon lesion accounting for 7% of all mandibular mass lesions, as well as less than 7% of benign jaw lesions, with a prevalence of 65 to 75% for mandibular mass lesions.<sup>2,6,12,15</sup> Similarly, GCG also accounts for 7% of all benign maxillary tumour prevalence.<sup>11</sup> The non-aggressive subtype of CGCG account for 70% of slow growing bony mass lesions involving anterior mandible and maxilla.<sup>6</sup>

CGCG is characteristically found in the jawbone (mandible), particularly involving the anterior mandible more than posterior mandible, with crossing of the midline.<sup>2,3,8,9,16</sup> CGCG occurs more in the mandible than the maxilla, with 3:1 mandible to maxilla ratio.<sup>2,11,17</sup> Furthermore, CGCG occurs more in tooth bearing portions of the jaw, specifically areas that previously had deciduous teeth, and primarily arise in the mandible anterior to the first molars.<sup>2,3,6</sup> Our case study involved the whole of the

left hemi-mandible, but this contrasts with the case studies by Wang et al, Pai et al, Deshpande et al, and Kamble et al whose patients had right mandibular mass lesions.<sup>2,5,19,21</sup> Also, Abdelqader et al reported lower right gingival (case one) and maxillary vestibular (case two) mass lesions.<sup>11</sup> Similarly, Singh et al reported a right lower back tooth mass lesion (posterior tooth region).<sup>8</sup> While Aditya and Aditya found an upper left posterior jaw/oral nodule, which secondly recurred as a lower right posterior jaw mass, and thirdly recurred as a lower left anterior jaw mass in their case study.<sup>20</sup> Similarly, Baskaran et al found a left lower posterior mandibular mass lesion.<sup>18</sup> Interestingly, Yamaguchi and Dorfman studied 91 cases of Giant cell reparative granuloma diagnosis made from 89 patients and they found that 22 of these mass lesions were sited in jawbones while 69 of them were sited in extragnathic bones (composed most commonly of 17 hand and 16 feet mass lesions).<sup>13</sup> Interestingly also, Patel and Amrutha in their case study found a maxillary mass lesion.<sup>16</sup> Importantly, these features of CGCG contrast with Giant cell tumours (GCT) of bone which rarely arise from craniofacial bones (accounting for 1% of GCT cases) but are quite common in long bones (where they account for 99% of GCT cases).<sup>22</sup>

The pathogenesis of CGCG is suspected to involve an exaggerated reparative process which is secondary to trauma and concomitant bleeding within the jawbone cortex hence eliciting a granulomatous inflammatory response marked by the accumulation of the multinucleated giant cells.<sup>1</sup> Notably, hyperparathyroidism is known to stimulate osteoclastic resorption and eventually give rise to the formation of a mass bone lesion formation such as the Brown tumour, a close differential of CGCG.<sup>11</sup> Grossly, CGCG commonly presents as a cystic bone lesion.<sup>9</sup> Our case was not cystic.

Microscopically, CGCG has the same features for its aggressive and non-aggressive subtypes, thus typically shows an intra-osseous lesion composed of abundant large osteoclast-like multinucleated giant cells, having about eight to 30 evenly distributed nuclei, (which may surround areas of bleeding as well as blood vessels) with slight pleomorphism, displaying brisk mitosis within a vascularised loose cellular fibro-collagenous or fibro-cellular (connective) tissue background

stroma.<sup>3,6,9,11,14,15,20</sup> These multinucleated giant cells are osteoclasts and the background spindle cells are the active lesional cells.<sup>3</sup> Also, the edge of the lesion shows new bone formation.<sup>9</sup> CGCG does not show areas of necrosis.<sup>9</sup> These microscopic features were found in our case. It is important to note that PGCG has similar microscopic features with CGCG with the exclusion of the bony tissue component.<sup>4</sup>

Clinically, CGCG may present as an asymptomatic mass lesion or as a symptomatic destructive lesion associated with pain, perforation of bone cortex and resorption (loss) of tooth root.<sup>1,6</sup> CGCG typically presents as a progressive slow growing bluish brown jawbone mass lesion which starts off as an asymptomatic lesion but eventually compresses its surrounding structures leading to local discomfort which may or may not be associated with pain.<sup>2,6,8,12,14,15,18</sup>

The sequelae of this typical presentation of CGCG are malocclusion (with development of pain, paraesthesia and teeth displacement), facial asymmetry and difficulty in chewing.<sup>2,6</sup> Furthermore, typically aggressive CGCG will present as a rapid growing painful jaw mass lesion associated with paraesthesia, teeth loosening, teeth displacement with penetration of the cortical bone.<sup>6,18</sup> Our case study was that of a painless jawbone mass lesion similar to that of Deshpande et al but in contrast to Baskaran et al, Kamble et al and Singh et al.<sup>2,8,18,19</sup>

Histopathological evaluation of this mass lesion is the gold standard for arriving at the diagnosis of CGCG.<sup>1-3,5,9,11,12,14,22</sup> A needle biopsy may also precede surgery.<sup>11</sup> However, there are other ancillary diagnostic techniques such as immunohistochemical evaluation and electron microscopy.<sup>9</sup> Immunohistochemically (IHC), CGCG shows CD68 positivity for the lesional multinucleated giant cells.<sup>9</sup> Electron microscopically, CGCG shows presence of numerous fibroblasts, myofibroblasts and histiocytes.<sup>9</sup>

It is also important to carry out the bioassays of serum calcium, phosphorus, alkaline phosphatase, thyroid and parathyroid hormone (PTH) to accurately make a diagnosis of CGCG and rule out its close differentials.<sup>1,15,20</sup>

The radiologic features of CGCG are non-specific and not pathognomonic of it.<sup>3,13,15</sup> However, radiologically, particularly using intraoral

periapical radiograph or panoramic x-ray, CGCG, which commonly affects the mandibles and maxilla, presents as a solitary radiolucent small apical unilocular (uncommonly) or large expansile multilocular/multicystic destructive (commonly) lesion which may also display resorption/displacement of teeth and its roots from its normal position into the cortex of the jawbone, with well delineated (defined) peeled off margins which may have a scalloped appearance as well as patchy internal mineralisation.<sup>1,2,5,6,9,11,12,15,20</sup>

Furthermore, occlusal radiograph may show CGCG as a lesion causing focal expansion of cortical plate around the teeth involved in the lesion.<sup>2</sup> CGCG may also present as a roundish or oval lesion with increased radiolucency that is faintly trabeculated sometimes.<sup>17</sup> CGCG may also present as a single multilocular radiolucency in the mandible which crosses the midline displaying destruction of the overlying crestal bone.<sup>20</sup> It is of note that computerised tomography (CT) scan, particularly Cone-beam computed tomography (CBCT) is ideal for the radiological characterization of CGCG.<sup>1,11,15,20</sup>

Furthermore, CGCG on CT scan maybe characterised as an expansile multiloculated lytic lesion in the mandible, with destruction of both inner and outer mandibular cortices.<sup>20</sup> CGCG has an avid homogenous enhancement with involvement of its surrounding soft tissue, and commonly cross the midline when arising from the mandible.<sup>12,14</sup>

Murphey et al in their study comparing the radiological features of giant cell tumours (GCT) and giant cell reparative granuloma (GCRG) of bone found that their radiologic appearance will often give good pathological correlation and suggest their diagnosis as well.<sup>23</sup> Radiologically, GCT show meta-epiphyseal involvement with extension to the sub-chondral bone whereas GCRG, though has similar features, commonly involves the mandible, maxilla, hands and feet.<sup>23</sup> Furthermore, solid components of cystic GCT show low to intermediate signal intensity at T2-weighted magnetic resonance imaging (MRI).<sup>23</sup> Similarly, Borges et al in their study found that GCT and GCRG appear similar radiologically presenting as a lytic poorly defined lesion.<sup>22</sup>

The histopathological differential diagnosis of CGCG include Peripheral giant cell granuloma (giant cell epulis), odontogenic keratocyst,

unicystic ameloblastoma, ameloblastoma, aneurysmal bone cyst (abc), giant cell tumours, giant cell tumours involving Paget disease, brown tumour or brown hyperparathyroidism tumour, cherubism, Noonan syndrome, neurofibromatosis type I, and fibrous dysplasia.<sup>2,3,6,9,10,12,14,15,20</sup>

Interestingly, Pai et al reported the concomitant occurrence of CGCG and ABC in their patient.<sup>21</sup>

The radiological differential diagnosis of CGCG include Ewing sarcoma, telangiectatic osteosarcoma, cherubism, fibrous dysplasia, odontogenic cysts, odontogenic myxoma, odontogenic fibroma, brown tumour of hyperparathyroidism, cysts, ABC, periapical granulomas, ameloblastomas, keratocysts, myxomas, and sarcomas.<sup>11,12,14,15</sup>

The choice of treatment modality depends on several factors such as age of the patient, clinical features of the lesion, and the size and aggressive nature of the lesion.<sup>12,15</sup> The major (and best) treatment modality for CGCG are surgical options, namely Simple curettage, Curettage with peripheral osteotomy, enucleation and en-bloc resection.<sup>1-3,8-10,12,14,15,22</sup>

The surgical excision maybe accompanied by teeth extractions.<sup>11</sup> The aggressive subtype of CGCG (15 to 20% of cases) are destructive and frequently recurs, hence it is best treated with surgical (en bloc) resection and reconstruction (using bone grafting or implants or prosthesis or microvascular bone free flap transfer) to prevent its recurrence.<sup>1,3,5-7,10,12,15,16,22</sup>

The bone chips used for this bone grafting are harvested from the patient's iliac crest.<sup>1</sup> Local surgical curettage is used in treating the non-aggressive subtype of CGCG.<sup>1,10,12</sup> Our patient was treated with en bloc resection (left hemi-mandibulectomy) and this was consistent with the case study by Wang et al who performed en bloc right hemi-mandibular resection with insertion of a reconstructive titanium plate and condylar prosthesis.<sup>5</sup>

The minor treatment modalities are non-surgical options.<sup>10</sup> These non-surgical treatment modalities, which are derived from the controversy over CGCG's aetiologic origin, include drug treatments with intralesional corticosteroids injections, systemic calcitonin, subcutaneous or intranasal calcitonin, subcutaneous denosumab (a human monoclonal anti-rankl antibody [IgG2]) targeted therapy, immunomodulatory drugs, bisphosphonate

or interferon alpha (IFN- $\alpha$ ) injections.<sup>1-3,6,10-12,23</sup> The intralesional steroid injection is compounded as a 50/50 mixture of 2% lidocaine, 1:100,000 epinephrine and triamcinolone; given as 2ml/1cm intralesional injections which are repeated weekly for 6 weeks.<sup>3</sup> The calcitonin injections are given (to antagonise PTH) subcutaneously in 100 units doses daily, with radiographic monitoring, for six to nine months or up to 24 months depending on response.<sup>3</sup> The IFN- $\alpha$  injection is given subcutaneously for its anti-angiogenic effects.<sup>3</sup> These drug treatments are deployed particularly as adjuvant therapy for aggressive lesions to prevent the adverse effects of the surgical treatment as well as recurrence.<sup>6,7,10,11</sup> However, typical small slow growing (non-aggressive) CGCG maybe solely treated with these non-surgical modalities.<sup>12</sup>

Radiotherapy is contraindicated as a treatment modality for CGCG because of the risk of malignant transformation, though Machnowska, Pauranik and Shah advocated for its use in small slow-growing CGCG.<sup>12,15</sup> Our patient neither received drug treatment nor radiotherapy.

Prognostically, early treatment of CGCG ensures better outcome.<sup>6</sup> Notably, surgical curettage with removal of peripheral bone margins provides optimal treatment for non-aggressive CGCG.<sup>6</sup> Notably also, as an alternative to aggressive surgical treatment options, surgical enucleation with adjuvant subcutaneous injection of IFN- $\alpha$ -2 $\alpha$  provides optimal outcome for aggressive CGCG, in terms of recurrence prevention.<sup>6,7</sup>

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