Central Giant Cell Granuloma of the Mandible and Maxilla; A Clinicopathological Study of 21 cases

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Short Report

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Abstract

Central giant cell granuloma (CGCG) presents as an intraosseous, locally invasive, and infrequent non-neoplastic lesion characterized histologically by multinucleated giant cells amid hemorrhage and reactive fibrous tissue. Despite first being described in 1953, its exact etiology remains elusive, though intraosseous hemorrhages or trauma are considered potential triggers. This retrospective study examines 21 cases of CGCG diagnosed at Temple University Hospital from 2015 to 2022. Predominantly affecting children and young adults with a slight female preponderance, CGCG commonly manifests as a unilocular or multilocular radiolucent lesion in the mandible. Clinical presentation varies, with some cases being asymptomatic while others present with pain or fullness in the affected dental region. Differential diagnosis may include conditions like ameloblastoma or brown tumor, necessitating histological evaluation for confirmation. Our findings underscore CGCG’s non-neoplastic nature, its propensity for mandibular involvement, and the importance of distinguishing it from neoplastic conditions for appropriate management.

Introduction

Central giant cell granuloma (CGCG) is a benign, but locally aggressive lesion that occurs in the mandible and maxilla. CGCG was first described by Jaffe in 1953 [1]. Histologically, CGCG is characterized by proliferation of monocytic/spindle mesenchymal cells with aggregates of multinucleated osteoclast-type giant cells, in a background of hemorrhage and reactive fibrous tissue, infiltrating between the eroded bone trabeculae [1, 2]. The exact etiology of CGCG is still unknown, but it is thought to be a reactive lesion to local trauma, infection, or hormonal factors [1, 2, 3, 4]. Radiographically, CGCGs appear as unilocular or multilocular radiolucent lesions, more commonly in the mandible (70%). Children and young adults are more commonly affected, with slight female prevalence [4, 5, 6]. There is a 10% risk or recurrence and some GCCG may have aggressive behavior; therefore enucleation and curettage or osteotomy are indicated for complete removal of the lesion [2, 3, 6, 7]. Other non-surgical treatments with alpha interferon (alpha-IFN), calcitonin and corticosteroids have been described in the literature [8–11]. The purpose of this case series is to review the clinical, radiographic, and histopathological features of CGCG of the mandible and maxilla.

Materials and Methods

A total of 21 CGCG cases were diagnosed by the oral pathology service at our institution over the past 7 years (2015–2022). A retrospective analysis of the clinicopathologic parameters was done including age, gender, symptoms, anatomic site, radiographic findings, clinical presentation, differential diagnosis and histopathologic diagnosis (Table 1).
<table>
<thead>
<tr>
<th>Case Number</th>
<th>AG</th>
<th>SEX</th>
<th>LOCATION</th>
<th>Clinical Presentation</th>
<th>RADIOGRAPHIC FINDINGS</th>
<th>DDX</th>
<th>MICROSCOPIC DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>M</td>
<td>Left anterior mandible</td>
<td>Asymptomatic; Red Raised Lesion</td>
<td>N/A</td>
<td>Central Giant Cell Granuloma</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>F</td>
<td>Right posterior mandible</td>
<td>Asymptomatic</td>
<td>Radiolucent</td>
<td>Central Giant Cell Granuloma</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>F</td>
<td>Left anterior mandible</td>
<td>Numbness</td>
<td>Radiolucent</td>
<td>Hyperparathyroidism</td>
<td>Central Giant Cell Granuloma</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>F</td>
<td>Mandible</td>
<td>Submental fullness with mucocutaneous fistula</td>
<td>N/A</td>
<td>Central Giant Cell Granuloma</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>M</td>
<td>Left posterior mandible</td>
<td>Asymptomatic</td>
<td>Radiolucent</td>
<td>Central Giant Cell Granuloma, and abscess</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>F</td>
<td>Left posterior mandible</td>
<td>Asymptomatic</td>
<td>Radiolucent</td>
<td>Central Giant Cell Granuloma</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>M</td>
<td>Anterior Mandible</td>
<td>Asymptomatic</td>
<td>Radiolucent</td>
<td>Central Giant Cell Granuloma</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>76</td>
<td>M</td>
<td>Left posterior maxilla</td>
<td>Symptomatic</td>
<td>Radiopaque</td>
<td>Central Giant Cell Granuloma, and chronic sinusitis</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>F</td>
<td>Right posterior mandible</td>
<td>Asymptomatic</td>
<td>Radiolucent/Impacted #32</td>
<td>Central Giant Cell Granuloma</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>16</td>
<td>M</td>
<td>Right posterior mandible</td>
<td>Asymptomatic, expandse</td>
<td>Radiolucent expansile</td>
<td>Central Giant Cell Granuloma</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>59</td>
<td>M</td>
<td>Left anterior mandible</td>
<td>Asymptomatic</td>
<td>Radiolucent lesion causing cortical bone resorption</td>
<td>Central Giant Cell Granuloma</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>68</td>
<td>F</td>
<td>Left anterior mandible</td>
<td>symptomatic</td>
<td>Radiolucent, red</td>
<td>Central Giant Cell Granuloma</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>17</td>
<td>F</td>
<td>Right posterior mandible</td>
<td>symptomatic</td>
<td>Radiolucent(#31-#32)</td>
<td>Central Giant Cell Granuloma</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>60</td>
<td>M</td>
<td>Right maxilla</td>
<td>Asymptomatic/Implant</td>
<td>Radiolucent</td>
<td>Central Giant Cell Granuloma</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>57</td>
<td>F</td>
<td>Left anterior maxilla</td>
<td>Symptomatic/ Buccal bony expansion of area of #11</td>
<td>N/A</td>
<td>Central Giant Cell Granuloma</td>
<td></td>
</tr>
</tbody>
</table>
Twenty-one cases of CGCG were retrieved from the pathology archives at Temple University Hospital. The excisional biopsy specimens from the referral hospitals was sent to the oral pathology service at our institution for pathologic diagnosis. The available clinical and radiologic history along with the hematoxylin and eosin (H&E) stained sections were evaluated to reach the final diagnosis (Table 1). No follow-up was available on the selected cases due to limited access to the database.

### Results

Twenty cases were evaluated with an established histopathologic diagnosis of CGCG. The demographics included 9 males and 11 females; a single case was of unknown gender, revealing slightly increased prevalence in female population. The age of the patients in our cohort ranged from 15–76 years, with a mean of 49.5 years (standard deviation 21.35). For the anatomic site, majority of our cases demonstrated mandibular involvement (n = 17; 81%); while the remaining (n = 4, 19%) showed the maxillary involvement. Most of our cases were asymptomatic (n = 13; 62%), with few cases (n = 8; 38%) showing symptoms due to expansile lesion and cortical bone resorption (n = 2). The radiographic findings whenever available were reviewed. Radiographically, most cases showed well-defined, radiolucent lesion (n = 16) or mixed radiolucent and radiopaque pattern (n = 1). In our study, 4 cases diagnosed with CGCG showed impacted tooth/teeth whereas expansile lesion and cortical bone resorption were others radiologic features that were also noted (Table 1).

The clinical and radiologic differentials varied from benign conditions such as chronic granulomatous inflammation, acute inflammatory process/abscess formation, brown tumor (hyperparathyroidism), rarely non-ossifying fibroma to neoplastic conditions like odontogenic neoplasms including ameloblastoma, giant cell tumor (GCT) of bone, osteoblastoma, chondrosarcoma (12–16). Histopathologic features on examination of H&E-stained slide material showed the presence of numerous multinucleated giant cells, fibroblasts, and reactive bone formation with extensive red blood cell extravasation and droplets of hemosiderin pigmentation (Fig. 1 and Fig. 2). The giant cells are usually located in the center of the lesion or may be present diffusely, and have few to more than 20 nuclei [12–15]. The fibroblasts are spindle-shaped cells that are arranged in a haphazard pattern and produce collagen fibers. The reactive bone formation may be seen at the periphery of the lesion or within the lesion. Histopathology was confirmatory in all the cases, especially where the differential diagnosis included other benign and neoplastic conditions.

### Discussion

CGCG typically presents as a painless swelling or mass that gradually increases in size (non-aggressive lesions). The lesion may be associated with pain, root resorption, paresthesia, and tooth mobility, depending on the location and size of the lesion (aggressive lesions). The age of onset of CGCG is usually between 10 to 30 years, and females are affected more frequently than males. In our study, radiographically, most cases presented as a well-defined, radiolucent lesion with variable borders. It may exhibit unilocular or multilocular patterns and can cause root resorption or displacement of teeth [2–7]. Radiographic finding of multilocular pattern should raise other differential diagnoses including odontogenic keratocyst (OKC), ameloblastoma, hemangioma/arteriovenous malformation (AVM), odontogenic myxoma and botryoid odontogenic cyst [4].
Occasionally, it may appear as a mixed radiolucent-radiopaque lesion due to the presence of calcifications or ossifications within the lesion.

The histopathological features of CGCG include the presence of osteoclast-like multinucleated giant cells, spindle-shaped fibroblast-like stromal cells, and round mononuclear cells. The giant cells are usually located in the central part of the lesion and contain numerous nuclei with prominent nucleoli. The spindle-shaped fibroblasts are distributed throughout the lesion and are responsible for the production of collagen fibers. Reactive bone formation may be seen at the periphery of the lesion or within the lesion. Hemosiderin laden macrophages and extravasated red blood are typically seen in CGCG and they raise the differential diagnosis of giant cell tumor of bone, aneurysmal bone cyst and brown tumors of hyperparathyroidism. Correlation of both radiographic features and histologic features can be helpful in analyzing the clinicopathologic behavior of the lesion as aggressive and non-aggressive lesion. [2]

The pathogenesis of Central giant cell granuloma (CGCG) is not fully understood, but it is thought to be a reactive process triggered by local factors such as trauma, infection, or hormonal factors. Some studies suggest that CGCG is a result of an abnormal immune response, with the multinucleated giant cells representing activated macrophages and osteoclast-like cells. Studies have shown that CGCG expresses markers of osteoclastogenesis such as CD68, RANK, RANKL, and OPG. These markers are involved in the regulation of osteoclastic differentiation and activation, and their expression suggests that CGCG may be associated with osteoclastic activity. [14–16]

Giant cell lesions of the jaws may rarely occur in the setting of RASopathy syndromes such as Noonan syndrome or neurofibromatosis. Recently, central giant cell granulomas (CGCG), have been recognized as benign neoplasms characterized by Ras/MAPK signaling pathway mutations [18].

Gomes and colleagues demonstrated that sporadic CGCL of the jaws do not share the H3F3A pGly34Trp or p.Gly34Leu mutations reported in GCT of long bones. These findings appear to add to the body of evidence that the CGCL of the gnathic bone is distinct and separate from the extragnathic GCT [19].

The treatment of CGCG depends on the size, location, and aggressiveness of the lesion. Small lesions may be observed, while larger lesions require surgical intervention. The surgical approach may include curettage, enucleation, or resection, depending on the size and location of the lesion. Recurrence rates are higher for lesions that are more aggressive, multilocular, or located in the mandible.

Conclusion

Central giant cell granuloma (CGCG) is a rare intraosseous, locally invasive, non-neoplastic, locally aggressive lesion that presents as a painless swelling or mass in the mandible and maxilla. It is a rare benign lesion of the jaws that is characterized by the presence of multinucleated giant cells, fibroblasts, and reactive bone formation. CGCGs are distinct from long bone giant cell tumors (GCT). GCCG is of unknown histogenesis and etiology, although it is still considered reactive. The radiographic and histopathological features of CGCG are characteristic, and treatment is based on the size, location, and aggressiveness of the lesion. Recent studies have identified genetic alterations in CGCG, which may contribute to the dysregulation of osteoclastogenesis and clinical behavior. The treatment of CGCG depends on the size, location, and aggressiveness of the lesion, and long-term follow-up is essential to monitor for recurrence. Further research is needed to better understand the etiology and pathogenesis of CGCG and to develop more effective treatments.

References


Declarations

The work was done at Department of Pathology, Temple University, Philadelphia, PA

Data availability statement

- funding statement: there was no funding for this project

- conflict of interest disclosure: there is no conflict of interest for any of the authors of the manuscript

- ethics approval statement: The IRB approved the protocol 28418.
The study was approved under Exempt review. The IRB determined that the research does not require a continuing review, consequently there is not an IRB approval period.

- patient consent statement: As this research was approved as Exempt, the IRB does not require consent forms

- permission to reproduce material from other sources: NA

- clinical trial registration: NA

**Figures**

Figure 1

CGCG HE 100x
Figure 2

CGCG HE 200x