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Case Series

Non-syndromic multi-focal central giant cell granuloma- Report of 2 rare cases and review of literature

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Abstract

Introduction: Central giant cell granuloma (CGCG) is a rare, benign but potentially aggressive intraosseous lesion affecting the jaws, predominantly amongst females under 30 years. First described by Jaffe in 1953 and later termed by Lichtenstein, CGCG is classified by the World Health Organization as a benign tumor-like lesion. Radiologically, CGCG presents as unilocular or multilocular radiolucencies. Management includes surgical and non-surgical approaches, with high recurrence rates.

Case Report: A 31-year-old female presented with bilateral painless swellings in the lower jaw, progressively increasing over 12 months. Clinical examination revealed bony hard growths in the posterior mandible, confirmed as CGCG through imaging and histopathology. Surgical wide margin excision resulted in uneventful healing and no recurrence over 10 months.

A 32-year-old female reported pain and tooth mobility in the lower jaw. Clinical and radiographic evaluations showed heterogenous radiolucent-radiopaque lesions, confirmed as CGCG histo-pathologically. Wide margin surgical excision and hemi-mandibulectomy with fibula graft led to successful recovery with no recurrence over 13 months. Biochemical tests ruled out hyper-parathyroidism and RASopathy syndromes in both the patients.

Conclusion: This case series highlights two rare cases of multi-focal CGCG, both occurring in the mandible and in female patients without any systemic manifestation.

Keywords: Giant cell tumor, RASopathy, Central lesion, RANKL, Honey-comb, Excision.

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1. Introduction

Central giant cell granuloma (CGCG) is a rare, benign, but occasionally aggressive bone lesion primarily affecting the jawbones. Initially described by Jaffe in 1953 as "giant cell reparative granulomas,".[1] it was later named by Lichtenstein in the same year.[2] The World Health Organization (WHO) classifies CGCG as a benign lesion resembling a tumor, distinguished by unique histological features.[3]

CGCG typically presents as slow-growing, painless masses or fast-growing, painful ones. It most commonly affects females under 30, with the mandible being more frequently involved than the maxilla.[3] Imaging studies show varied patterns, from small single-chambered radiolucencies to larger multi-chambered ones, often reflecting the lesion's behavior.[4] Aggressive forms may cause rapid growth, bone thinning, and root resorption, while non-aggressive types grow slowly with minimal impact on surrounding structures.[5]

Treatment for CGCG includes both surgical and non-surgical methods. Surgery, ranging from curettage to resection, is the primary treatment. Non-surgical options, such as steroid injections, calcitonin therapy, and interferon-α, aim to shrink the lesion.[6] Advances in molecular biology also suggest potential targeted therapies.[3,4] Recurrence rates depend on the lesion's presentation and treatment.[6] Aggressive lesions have higher recurrence rates, requiring more extensive surgery. Non-aggressive lesions treated

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conservatively tend to have lower recurrence rates but require long-term monitoring.[7]

This report discusses two cases of non-syndromic multi-focal CGCG, highlighting the challenges in treatment and recurrence management.

2. Case 1

A 31-year-old female presented with painless swelling in the lower right jaw, gradually increasing over the past 12 months, and a similar swelling in the left jaw for 3 months. She had no history of trauma, medical conditions, or lesions elsewhere but had a dental extraction two years prior.

Extra-oral examination revealed facial asymmetry due to bilateral lesions in the lower third of the face (**Figure 1**). Intra-oral examination showed adequate mouth opening with no lesions on the right buccal mucosa. On the left, a 4x5 cm diffuse growth was noted, extending from the distal aspect of 36 to the ascending ramus. The lesion showed tooth indentations but no ulceration or discharge (**Figure 2**).

Palpation revealed well-defined, bony hard growths on both the right and left posterior mandible. The right lesion measured 3.5x4.5 cm, and the left one was 1.5x2 cm. Both lesions showed buccal cortical plate expansion, with decortication on the right. The right side had paresthesia, while the left showed regional tooth mobility in 36 and 37.

A differential diagnosis of ameloblastoma, kerato-cystic odontogenic tumor, and calcifying epithelial odontogenic tumor (CEOT) was made. Radiographs revealed a multi-locular honeycomb pattern on the right and a well-defined lesion on the left (**Figure 3**). Three-dimensional imaging showed no tooth root resorption. Biopsy confirmed the diagnosis of CGCG, with multinucleated giant cells in a fibrous stroma. (**Figure 4**)

Initial biopsy from both the lesions was done. The H & E stained sections revealed a lesion composed of numerous multi-nucleated osteoclast like giant cells distributed in fibrous stroma. The stromal spindle shaped cells do not show significant nuclear pleomorphism or mitotic activity. The stroma also showed evidence of bony spicules. (**Figure 5**) A final diagnosis of CGCG was given.

The patient underwent wide margin excision with hemi-mandibulectomy on the right and wide margin excision on the left. Healing was uneventful, and no recurrence was noted after 10 months of follow-up.

3. Case 2

A 32-year-old female presented with pain and tooth mobility in the lower right and left back tooth regions for the past 7 months. The pain, dull and continuous, worsened over the last 3 months, causing difficulty in chewing. She had a previous dental extraction two years ago, with no complications.

Extraoral examination revealed mild facial asymmetry on the right side due to swelling in the lower third of the face (**Figure 6**). Intraoral examination showed missing teeth 33, 34, 35, and 38, with grade II mobility in 48 and grade 1 in 47. No swelling, growth, tenderness, or ulcerations were noted. Palpation revealed buccal cortical plate expansion on the right side, particularly in the periapical region of 48, but no changes were noted on the left side. (**Figure 6**)

An orthopantomogram (OPG) was performed, revealing a well-defined radiolucent-radiopaque lesion on the right side of the mandible, measuring 3.5 x 4 cm, extending from the distal root of 46 to the lingula. Root resorption was noted in 47 and 48. On the left side, a diffuse radiolucency was observed, measuring 4.5 x 5 cm, extending from the distal root of 36 to the ramus, with an impacted 38. No bony discontinuity or root resorption was observed. (**Figure 7**)

A provisional diagnosis of ameloblastoma on the right and dentigerous cyst on the left was made. Biopsy from the right side showed a cellular fibro-vascular stroma with multinucleated giant cells, confirming a diagnosis of CGCG.

Biopsy from the right side was stained by H & E that revealed a highly cellular and fibro-vascular connective tissue stroma with actively proliferating plump fibroblasts and endothelial cells, the stroma appeared dispersed with plenty of multi-nucleated giant cells and hemorrhagic areas and haemosiderin pigment-laden areas. Moderately intense inflammatory infiltrates were also noted in the stroma. (**Figure 8**) A final diagnosis of CGCG was given.

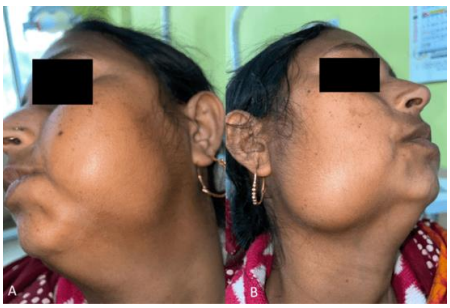

Figure 1: Showing the extra-oral profile of the patient (Case I) from the right side (**A**) and from the left side (**B**).

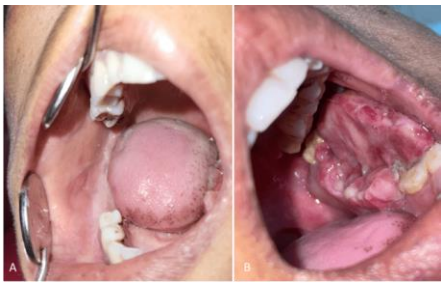

Figure 2: Showing the intra-oral images of the patient (Case II) displaying the right buccal mucosa (**A**) and left buccal mucosa (**B**).

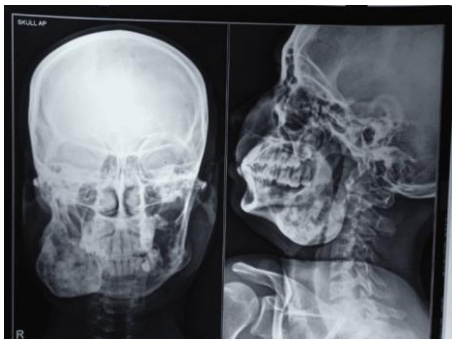

Figure 3: Showing the skull radiograph in antero-posterior view of the patient (case I) that reveals a diffuse multi-locular honey combed pattern mixed radiolucensy-radioopacity involving the right body of the mandible and a well-defined, well corticated heterogenous radiolucent radioopaque lesion was appreciated involving the left mandibular body in relation to 36, 37, 38 region.

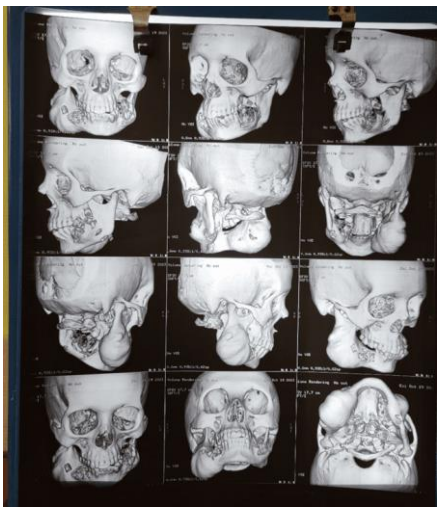

Figure 4: Showing the three dimensionally reconstructed radiographic image(s) from CBCT of the patient (Case I).

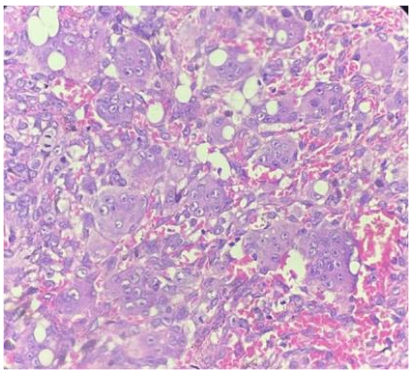

Figure 5: Showing the photo-micrograph of the H & E stained section of Case I that reveals (under 10X) a lesion composed of numerous multi-nucleated osteoclast like giant cells distributed in fibrous stroma. The stromal spindle shaped cells do not show significant nuclear pleomorphism or mitotic activity. The stroma also showed evidence of bony spicules.

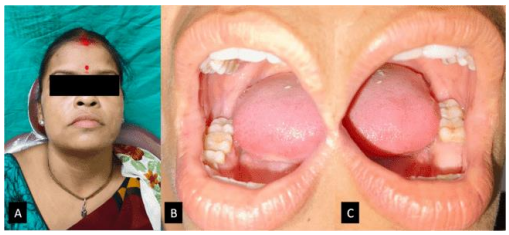

Figure 6: Showing the extra-oral images (**A**) and intra-oral images of the patient (Case II) displaying the right buccal mucosa (**B**) and left buccal mucosa (**C**).

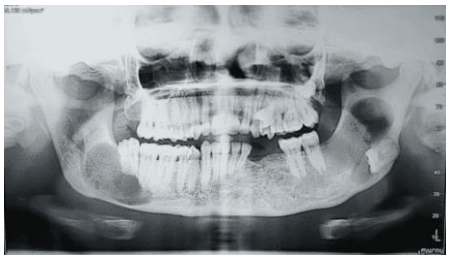

Figure 7: Shows the orthopantomogram (OPG) of the patient (Case II) that reveals a well-defined well corticated heterogenous radiolucent- radiopaque lesion in the right body of the mandible and the left side revealed a diffuse corticated heterogenous radiolucency. Root resorption was appreciated in the distal root of 47, 48.

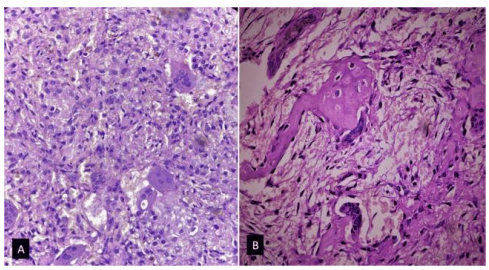

Figure 8: Showing the photo-micrograph of the H & E stained section of Case II under 10X (**A**) and 40X (**B**) that reveals a highly cellular and fibro-vascular connective tissue stroma with actively proliferating plump fibroblasts and endothelial cells, the stroma appeared dispersed with plenty of multi-nucleated giant cells and hemorrhagic areas and haemosiderin pigment-laden areas. Moderately intense inflammatory infiltrates were also noted in the stroma.

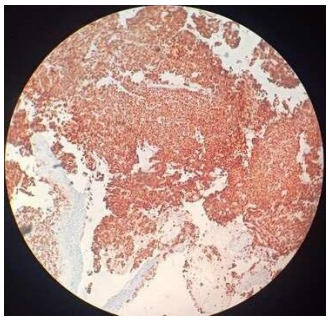

Figure 9: Showing the photo-micrograph under 1OX (A) resolution that reveals strong and diffuse expression of RANK by the mononuclear and multi-nuclear giant cells.

Table 1: The serum chemistry reports for the patients

S.No.	Serum chemistries	Test results (for Case 1)	Test results (for Case II)	Normal range
1.	Calcium	9.3	9.5	9-11 mg/dl
2.	Phosphorus	2.4	3.1	2.0-4.5 mg/dl
3.	Parathyroid hormone	22.9	25.20	12-75 pg/ml
4.	Alkaline Phosphatase	109	152	108-306 IU/L

The patient underwent wide-margin excision of both lesions, with hemi-mandibulectomy and fibula grafting on the left side due to the lesion's extent. Post-operative healing was uneventful, and no recurrence was noted after 13 months of follow-up.

Immuno-histochemistry was performed for the patients and both stained positive for RANK (receptor activator of nuclear factor-kappa B) confirming the diagnosis of CGCG (**Figure 9**). To rule out Paget's disease and cherubism, serum calcium, phosphorus, alkaline phosphatase, and parathyroid hormone levels were normal (**Table 1**), confirming CGCG. Additionally, radiographic and biochemical tests excluded RASopathy syndromes like Noonan syndrome and neurofibromatosis. The final diagnosis was non-syndromic multi-focal CGCG.

4. Discussion

The classification and understanding of CGCG have evolved significantly over time. Initially, CGCG was not distinguished from giant cell tumors (GCTs) found outside the jaw, but Jaffe in 1953 recognized it as a distinct entity.[8] While some specialists prefer the term "central giant cell lesion," CGCG remains the most commonly used term. CGCG is thought to arise either as a reaction to hemorrhage or trauma or as a neoplasm. Despite earlier confusion, CGCG and GCTs are now regarded as separate conditions.[9]

In non-aggressive cases, CGCG generally does not lead to tooth resorption. A meta-analysis of non-syndromic CGCG revealed tooth resorption in 22.8% of cases, sometimes accompanied by palatal swelling and tooth loosening. Radiographically, CGCG typically appears as a unilocular or multilocular radiolucency with well- or poorly defined borders and varying degrees of bone expansion and cortical destruction. Mineralization is rare, especially in mandible cases, although it is more common in maxillary cases.[8,9,10] Both patients in this series had similar radiographic findings: diffuse, multi-locular radiolucencies with cortical plate expansion.

Clinically, CGCG can be classified into aggressive and non-aggressive types. The aggressive form is larger, grows faster, and may cause bone destruction, tooth displacement, root resorption, and cortical perforation, with a high recurrence risk.[11] CGCGs are most often found in the mandible, especially in the anterior regions, and may cross the midline.[5] However, CGCG can also occur in other facial bones such as the maxillary and ethmoidal sinuses, cranial vault, and even small bones of the hands and feet. Both patients had posterior mandibular CGCGs with regional tooth mobility, impaction, and resorption.[7]

Recent meta-analyses have suggested differences in the pathogenesis of sporadic versus syndrome-associated CGCG cases.[12] Syndromic conditions often involve multiple occurrences of CGCG, while unilocular lesions might still occur in syndromic bone diseases, though this is less common.[13] In presumed syndromic cases, such as those with cherubism or Noonan syndrome, genetic mutations may not always be detectable.[14] Indicators of non-syndromic aggressive CGCG include cortical bone perforation and root resorption, with tooth displacement suggesting a higher risk of recurrence. Interestingly, lesion size does not correlate with recurrence risk.[14] **Table 2** shows all the typical presentation of all the reported cases of non-syndromic multi-focal CGCG reported till now.

Syndromic diseases associated with CGCG include hyperparathyroidism, Noonan-like multiple giant cell lesion syndrome, GCT, cherubism, and Paget's disease.[11] However, synchronous multifocal CGCG without systemic involvement or family history is extremely rare, with only 10 documented cases in the English literature.[13] Microscopically, CGCG resembles the brown tumor of hyperparathyroidism and must be differentiated through serum chemistry. Hyperparathyroidism typically shows elevated calcium, alkaline phosphatase, and parathyroid hormone levels, which are absent in CGCG.[4]

Table 2: Lists the reported cases of non-syndromic multi-focal/ Uni-focal CGCG

S.No.	Author	Year	Age/ Gender	Location	Management	Recurrence
1.	Smith et al[5]	1990	41/F	Right mandibular ramus, left maxillary sinus, nasal bone, orbit, right maxillary sinus.	Surgical curettage, radiation	Yes
2.	Loukota et al[15]	1991	25/F	Maxillary and mandibular body	Surgical curettage	Yes

3.	Wise and Bridbord et al[7]	1993	23/M	Left mandibular body, left and right nasomaxillary areas.	Surgical curettage	Yes
4.	Miloro and Quinn et al[11]	1995	37/F	Left posterior maxilla and anterior mandible	Surgical curettage	No
5.	Curtis and Walker et al[12]	2005	62/M	Right maxilla, right body of mandible, left angle of mandible.	Surgical curettage, Interferon therapy	Yes
6.	Martin WD et al[9]	2007	35/F	Left maxilla and right mandible	Surgical curettage	Yes
7.	Bilodeau, Chowdhury et al[14]	2009	42/F	Maxillary and ethmoidal sinus	Surgical curettage, calcitonin nasal spray.	Yes
8.	Kang MS et al[16]	2010	17/M	Bilateral posterior mandible and right maxilla.	Surgical curettage	Yes
9.	Munde A et al[8]	2012	36/F	Left posterior mandible and left posterior maxilla.	Surgical curettage	Yes
10.	Kilinç A et al[3]	2015	61/F	Left maxilla extending to the midline.	Surgical curettage	No
11.	Present Case	2024	31/F	Bilateral posterior mandible	Surgical curettage for both	No
			32/F	Bilateral posterior mandible Extending into the ramus		

CGCG and GCTs share clinical and histological similarities, but they can be distinguished based on certain features. GCTs tend to be larger, more painful, occur in older patients, have poorly defined radiographic borders, and have a higher recurrence rate. GCTs are characterized by multinucleated giant cells with larger, rounded nuclei and less fibrous tissue.[7,8,9] Noonan-like multiple giant cell lesion syndrome presents with features such as short stature, webbed neck, cubitus valgus, pulmonary stenosis, multiple lentigines, and intellectual disabilities, while cherubism leads to symmetrical jaw enlargement in young children and is linked to a genetic mutation on chromosome 4p16:3. Paget's disease affects older adults and presents as "cotton wool" on radiographs with elevated serum alkaline phosphatase levels.[5,11,14]

Treatment of CGCG is determined by clinical and radiographic findings and typically involves surgery, such as curettage or en bloc resection.[15] Medical therapies like steroids, calcitonin, interferon-alpha, and bisphosphonates have also been used with varying success. Recurrence rates range from 11-72%, primarily due to incomplete lesion removal. Long-term follow-up with radiographic monitoring is critical to detect recurrences.[16] Post-surgical excision, both patients in this series was placed under strict follow-up, with no evidence of recurrence to date.

Recent research has explored the molecular mechanisms of giant cell formation, focusing on the role of RANK, its ligand (RANKL) signaling, which is pivotal in the osteoclastogenesis of CGCG. This signaling pathway, primarily involving RANK/RANKL, and the decoy receptor osteoprotegerin (OPG), that promotes osteoclast differentiation and activation.[17] This causes initiation and continued bone destruction, cortical plate expansion, and tooth resorption, resulting in the typical manifestation of CGCG. Immuno-histochemical (IHC) markers such as RANK, OPG, and cathepsin K are commonly used to study these lesions and differentiate CGCG from other giant cell lesions.[18] These markers aid in understanding the patho-physiology and improving diagnostic accuracy.

Recent studies have explored alternative treatments for CGCG, including non-surgical options like intralesional corticosteroid or calcitonin injections. These are typically used for smaller lesions or when surgery is not feasible due to comorbidities or anatomical location of the lesion.[19] Other treatments include radiation therapy, embolization, and pharmacotherapy. Radiation has been effective in controlling aggressive or recurrent lesions, but its long-term impact on dental development remains unclear. Embolization, which blocks blood supply to the lesion, shows potential, though data is limited. Pharmacotherapy with bisphosphonates and denosumab has also shown promise, but further research is needed to confirm their safety and effectiveness.[20,21]

5. Conclusion

The presence of multifocal CGCGs in the maxillofacial area often points to an underlying systemic condition, such as hyperparathyroidism, or a genetic syndrome like Noonan-like multiple giant cell lesion syndrome. However, this paper highlights two rare cases of synchronous, multifocal CGCGs occurring in the right and left posterior mandible, without any indication of a related systemic disease or inherited syndrome.

6. Sources of Funding

None.

7. Conflict of Interest

None.

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