

Primary Hyperparathyroidism Presented as Central Giant Cell Granuloma of Jaw Bones. A Report of Three Cases

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Abstract: *Three cases of primary hyperparathyroidism presented as central giant cell granuloma of the jaw bones with various clinical manifestations and systemic background of the patients. Generally the mandible affected more by these lesions in this report two of the cases affect the maxilla, while the third case affects both upper and lower jaws. The diagnosis was confirmed by radiographical and laboratory investigation. Multifocal giant granuloma of the jaw bones is indicative of systemic diseases such as hyperparathyroidism or other disorders. Therefore, a careful examination will usually allow adequate differentiation between both lesions and to exclude or confirm hyperparathyroidism.*

Keywords: *Giant cells, Granuloma, Hyperparathyroidism, Brown tumor*

I. Introduction

Central giant cell granuloma (CGCG) is a benign neoplasm, commonly affecting the jaw bones. The lesion has a tendency for female at their second decade of life [1]. The most frequent site for CGCG is reported to be anterior to the mandibular first molars and sometimes crosses the midline [2] followed by maxilla and less frequently attacks other facial bones [3]. Histologically, the lesion mainly composed of fibroblast proliferation together with multinucleated giant cells. Unpredictably CGCG presents a variety of clinical behaviors; nevertheless the lesion is an uncommon, non-neoplastic but locally destructive lesion of the jaws' bone [4-5].

The lesion's etiopathogenesis for site specification as the jaw bones has not been fully recognized yet. Nevertheless, it has been attributed to an unusual aggravated reparative proliferation related to an intra-osseous haemorrhage as a result of a previous trauma that elicits the reactive granulomatous process [6]. The term reparative granuloma was a common nomenclature for some time, as the lesion usually exhibits a destructive clinical behavior which is inconsistent with a reparative process, therefore, the term reparative is not employed to any further extent [7-8]. The presence of multiple central giant cell lesions in the jaws and other facial bones are uncommon and a suggestive or might be an indicative of hyper-parathyroidism, Noonan-like multiple giant cell lesion. Giant cell granulomas are usually unifocal lesions, multifocal lesions should be suspected and inspected for the possibility of hyperparathyroidism. In case of multiple bilateral lesions, cherubism or Noonan syndrome should be kept in mind. Histologically giant cell lesions are exhibiting rich osteoclast fields could not be easily distinguished from cherubism and Noonan syndrome [9].

CGCG and cherubism are different clinical entities but sharing similar histologic finding with different clinical and radiographic features, they should be distinguished from each other. Moreover, cherubism is an autosomal dominant disorder characterized by bilateral expansion of the mandible and/or the maxilla and becomes evident within the first few years of life. It includes multifocal and multilocular cystic lesions of the jaws [10]. Based on clinical and radiographic findings, CGCG lesions are considered either non-aggressive or aggressive types. The non-aggressive lesion, when the lesion is growing slowly, asymptomatic with no cortical bone perforation/ root resorption. The lesion has less chances for recurrent, or the aggressive type that is growing more rapidly, usually seen as larger and painful lesions in younger patients. In this case root resorption and cortical bone resorption might be seen more frequently with higher chances of recurrence [11].

Furthermore, CGCG has two main histological appearances which present a distinctive microscopy for giant cell lesions. Primarily high infiltration of fibroblasts and presence of spindle-shaped cells with high mitotic rate is the most common feature of giant cells and vascular density plus multinucleated giant cells among the fibrous stroma with a wide variation in the number of giant cells size and morphology among individual cases. Both aggressive and non aggressive giant cells display a similar histologic feature as the cells in both types are of unknown origins. [12-13]. Moreover a similar histological feature of CGCG with cherubism and Noonan's syndrome is also reported, however these lesions present different clinical and radiographic features [10].

Careful examination and appropriate diagnosis is required to avoid confusion with other lesions exhibiting very similar clinical and histological features. Some clinically similar lesions usually share the same sites within the jaw bones such as peripheral giant cell granuloma. Nevertheless, central giant cell granuloma reveals more aggressive clinical behavior. [14]. Therefore, the aim of this case series study was to focus on

some important aspects of CGCG and methods of differentiation between various centrally located GCLs which mimic each other clinically and histologically.

II. Case Reports

Case I: A case of 12-year-old school girl referred to the Service of Maxillofacial Surgery at Teaching Hospital of Sulaimani and reported with the chief complaint of slowly growing, diffuse painless swelling over the premaxilla caused elevation of the frontal part of the face and the nose exposing a facial asymmetry (Figure 1-A). Intraoral examination showed swelling of the anterior maxilla with mainly the buccal and slightly the palatal cortical plate expansion (Figure 1-B). Maxillary central incisors were rigorously displaced causing a large central spacing with distal displacement of the roots of both central incisors.

CT examination with IV contrast for head and neck area showed evidence of a large heterogeneous expansible bone mass lesion measuring (47X40X38 mm) in size involving the upper maxilla mostly at the left side leading to severe bone destruction of the maxilla and involving the left side nasal space and the basal aspect of the left maxillary sinus causing destruction of nasal bone and maxillary sinus wall (Figure 2). Other CT finding in the neck was enlargement of three of parathyroid glands.

Excisional biopsy was performed for the patient which revealed ulcerated squamous mucosa lined by inflamed granulation tissue with features highly suggestive CGCG with no evidence of malignancy. Furthermore the report included a suggestion for further investigations to exclude Brown tumour of hyperparathyroidism. Blood investigation revealed significant elevation of parathyroid hormone above the normal range, thus the case was diagnosed as primary hyperparathyroidism. Another surgical treatment was done for the patient for excision of parathyroid glands with consultation of endocrinologist for further medical treatment and follow up of the patient.



Figure 1-A: Extraoral View showing swelling of the face at right maxilla with slight elevation of the nose.
B: Intraoral view showing expansion of the buccal and palatal plates plus displacement of the central incisors.

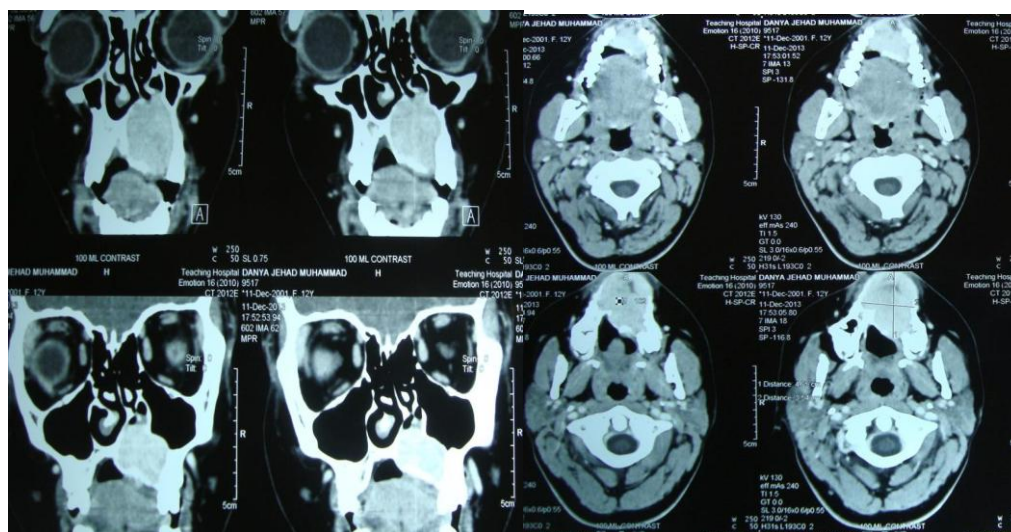


Figure 2: Patient's CT showing bone destructive lesion involved left side of maxillary bone with extension to the nasal bone and maxillary bone.

Case II

A 35-year-old Kurdish female was referred to the Service of Maxillofacial Surgery at Sulaimani Teaching Hospital suffering from long term swelling of the left part of the face. Clinical examination revealed facial asymmetry and deviation of the nose toward the right side (Figure 3-A).

Intraoral examination showed a large swelling of the left maxilla at canine premolars and molars areas with buccal cortical plate expansion. Soft tissue overlying the lesion turned blush red in color. Materia Alba and plaque accumulation was detected in a large amount at the area (Figure 3-B).

CT scan showed boney lesion affected left maxilla at the area of premolars and molars also other lesion was discovered in the right maxillary sinus (Figure 3-C). Excisional biopsy was done for the left maxillary mass and incisional biopsy for the right maxillary lesion by the use of endoscopy. Both biopsies showed giant cell lesions. Laboratory investigation revealed increased blood level for alkaline phosphatase and parathyroid hormone which confirm the diagnosis of brown tumor.

After establishment of the diagnosis the patient would not attend to the hospital for medical treatment for unknown reasons. Unfortunately she admitted to hospital one year later for renal failure due to multiple stone formations with development of other boney lesion of the right maxilla.

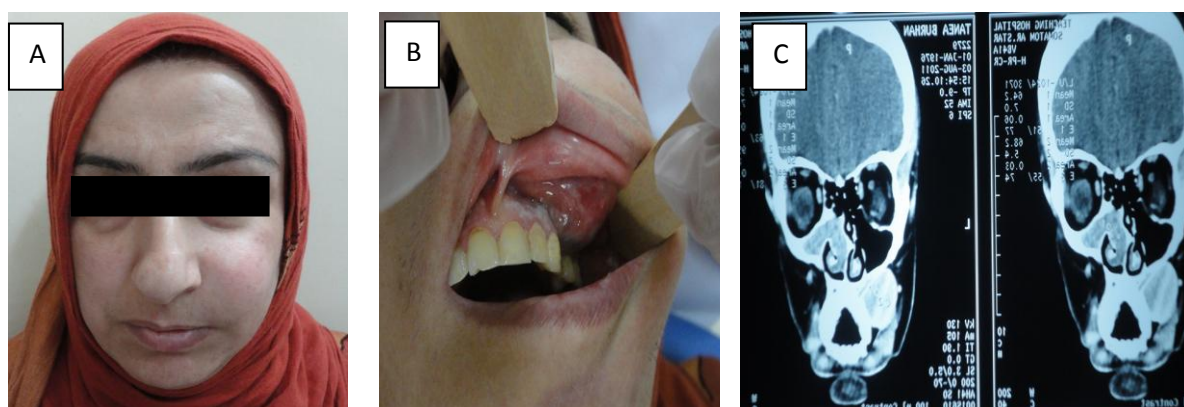


Figure 3-A: Showed facial swelling with asymmetry, B: Intra oral mass in the left side of the maxilla, C: Coronal CT of the affected area

Case III

A 39-year-old female patient presented with swelling of the left premaxilla associated with mobility of upper canine and premolar. Also the patient gave history of extraction of upper incisors due to the same lesion few months ago. Panoramic x-ray showed multiple cystic lesion in mandible both sides in addition to the left premaxillary radiolucency (Figure 4)



Figure 4: X-ray of the patient showed multiple cystic lesions of both jaws.

Excisional biopsy of the maxillary mass indicated a giant cell granuloma, moreover, blood chemistry revealed elevated level of calcium, parathyroid hormones and alkaline phosphatase. Accordingly the patient sent for ultrasonography examination of the neck which showed adenoma of parathyroid glands. Based on the clinical, radiographical and laboratory examination, diagnosis was made as primary hyperparathyroidism. The patient underwent parathyroidectomy and referred to a specialist physician for further care and follow up.

III. Discussion

Central giant cell granuloma (CGCG) is an infrequent benign intraosseous lesion that affects solely the jaw bones with unpredictable clinical expression; however, the lesion in the jaw bones is frequently a non-neoplastic bone lesion [3, 8, 11]

Earlier, central giant cell lesions (GCLs) of the jaws were generally diagnosed as giant cell tumor (GCT) and its diagnosis usually based on its clinical and radiographical appearance which predicts its behavior as being an aggressive or non aggressive lesion [8, 15]. The prevalence of CGCG among populations is very low and patients are generally young with predilection for female. It is difficult to distinguish between Brown tumor of hyperparathyroidism and cherubism to the so-called GCLs exclusively by microscopic examination. GCT of the long bones is virtually identical with CGCG of the jaws on histopathologic examination. Age and local factors are responsible for the clinical presentation of the disease [8].

There is a strong association between multiple lesions of CGCG and disorders such as hyperparathyroidism, Noonan like multiple giant cell lesion syndrome, GCT, cherubism and Paget's disease. The occurrence of synchronous, multi-focal CGCGs without systemic involvement or family history is extremely rare, to date, there are only 10 such cases reported in the English literature [16-17]. The light microscopic appearance of CGCG is identical to that of brown tumor of hyperparathyroidism, and must be differentiated based on serum chemistries. With regard to the giant cell tumor, similar clinical and histopathological pictures may be encountered. A careful examination will usually allow adequate differentiation [18].

It is acknowledged that CGCG is strongly related to hyper parathyroidism (HPT) and patients with jaw lesions of CGCG are considered suspected for HPT. Early diagnosis of HPT can be done with assessment of all the radiographic, biochemical, and histopathological parameters. Giant cell lesions like CGCG must be suspected and investigated to rule out HPT. Hyperparathyroidism is a metabolic disorder with excessive secretion of Parathyroid hormone (PTH) extensively above the normal level (12-70 pg/mL) [19-20]. The most common causes of hyperparathyroidism are hyperplasia of the gland or adenoma which is the tumor of the gland. Furthermore, HPT might develops as a result of chronic renal disorder that leads to chronic low level of calcium in the blood and less frequently parathyroid tumors could happen in relevance to an established long lasting HPT which is acknowledged as tertiary HPT [21].

The management of CGCG depends on the clinical and radiological findings. Surgical excision with curettage involving peripheral osteotomy or not is the treatment of choice. Furthermore, steroid and calcitonin can be applied as an adjunctive to surgical therapy with an advantage of inhibiting osteoclastic activity [22]. Interferon alpha found to be affective for the treatment of aggressive central giant cell lesions due to its anti-angiogenic effect [23].

Likelihood of recurrence is high, ranging from 11-72% in published studies which is due to incomplete evacuation of the lesion. Accordingly long term follow up schedule and periodic diagnostic radiography is an important step to determine progression rate of the lesion and to detect any recurrence of the lesion [24].

In this study the presented cases of CGCG were a complication of hyperparathyroidism and one of the cases ended up with renal failure due to incomplete treatment received by the patient. One of the most common complications of HPT is renal troubles due to excessive release of calcium and phosphorous from the bones which demonstrate an increase blood level of these elements which causing an over load on the renal system to release them thus renal complications are started. Furthermore, published articles considered frequency of CGCG is very low in the maxilla compared to mandible [2]. However, the present study reported all the cases as CGCG of the maxillary bone, only one case included the mandible as well.

IV. Conclusion

Multifocal CGCGs of the jaw bones are indicative of systemic diseases such as hyperparathyroidism or Noonan-like multiple giant cell lesion. Therefore, a careful clinical examination in correlation with laboratory investigation and radiographical examination leads to early diagnosis and management of these cases which prevent serious complications.

References

- [1]. Edwards, P.C., et al., Bilateral central giant cell granulomas of the mandible in an 8-year-old girl with Noonan syndrome (Noonan-like multiple giant cell lesion syndrome). *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, 2005. 99(3): p. 334-340.
- [2]. Triantafillidou, K., Venetis, G., Karakinaris, G. & Iordanidis, F. Central giant cell granuloma of the jaws: a clinical study of 17 cases and a review of the literature. *Annals of Otolaryngology, Rhinology & Laryngology*, 2011. 120, 167-174.
- [3]. Kaffe, I Ardekian, L., Taicher, S., Littner, M. M. & Buchner, A.. Radiologic features of central giant cell granuloma of the jaws. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*.1996. 81, 720-726.
- [4]. Hernandez, H.N., Lewiss, R. E., Yousem, D. M., Clerico, D. M. & Weinstein, G. S., Central giant cell granuloma of the hard palate. *Otolaryngology--Head and Neck Surgery*, 1998. 118(6): p. 871-873.

- [5]. Dimitakopoulos, I., Lazaridis, N., Sakellariou, P. & Asimaki, A., Giant-cell granuloma in the temporal bone: a case report and review of the literature. *Journal of oral and maxillofacial surgery*, 2006. 64(3): p. 531-536.
- [6]. Infante Cossío, P., Martínez De Fuentes, R., Carranza Carranza, A., Torres Lagares, D. & Gutierrez Perez, J. L., Recurrent central giant cell granuloma in the mandible: Surgical treatment and dental implant restoration. *Medicina Oral, Patología Oral y Cirugía Bucal (Internet)*, 2007. 12(3): p. 229-232.
- [7]. Ebrahimi, H., Yazdani, J., Pourshahidi, S., Esmaeli, F., Zenouz, A. T. & Mehdipour, M., Central giant cell granuloma of the posterior maxilla: A case report. *Journal of dental research, dental clinics, dental prospects*, 2008. 2(2): p. 71.
- [8]. Hongal, B.P., Joshi, P., Kulkarni, V. & Baldawa, P., Central giant cell granulomas of the jaws: A review of the literature with its emphasis on differential diagnosis on related lesions. *International Journal of Contemporary Dental and Medical Reviews*, 2015.
- [9]. Idowu, B.D., Thomas, G., Frow, R., Diss, T. C. & Flanagan, A. M., Mutations in SH3BP2, the cherubism gene, were not detected in central or peripheral giant cell tumours of the jaw. *British Journal of Oral and Maxillofacial Surgery*, 2008. 46(3): p. 229-230.
- [10]. Kaugars, G.E., J. Niamtu, and J.A. Svirsky, Cherubism: diagnosis, treatment, and comparison with central giant cell granulomas and giant cell tumors. *Oral Surgery, Oral Medicine, Oral Pathology*, 1992. 73(3): p. 369-374.
- [11]. Whitaker, S.B. and C.A. Waldron, Central giant cell lesions of the jaws: a clinical, radiologic, and histopathologic study. *Oral Surgery, Oral Medicine, Oral Pathology*, 1993. 75(2): p. 199-208.
- [12]. Chuong, R., Kaban, L. B., Kozakewich, H. & Perez-Atayde, A., Central giant cell lesions of the jaws: a clinicopathologic study. *Journal of oral and maxillofacial surgery*, 1986. 44(9): p. 708-713.
- [13]. Eckardt, A., Pogrel, M. A., Kaban, L. B., Chew, K. & Mayall, B. H., Central giant cell granulomas of the jaws: nuclear DNA analysis using image cytometry. *International journal of oral and maxillofacial surgery*, 1989. 18(1): p. 3-6.
- [14]. Karl R, U.M., Bahadır B, Gul A, Uzun L., Giant cell reparative granuloma a case report. . *KBB Forum*, 2009. 8: p. 39-43.
- [15]. El Hadidi, Y.N., A.A. Ghanem, and I. Helmy, Injection of steroids intralesional in central giant cell granuloma cases (giant cell tumor): Is it free of systemic complications or not? A case report. *International journal of surgery case reports*, 2015. 8: p. 166-170.
- [16]. Miloro, M. and P.D. Quinn, Synchronous central giant cell lesions of the jaws: report of a case and review of the literature. *Journal of oral and maxillofacial surgery*, 1995. 53(11): p. 1350-1355.
- [17]. Kang, M.S. and H.J. Kim, Multiple synchronous central gaint cell granuloma of the maxillofacial region: a case report. *J Korean Soc Radiol*, 2010. 62: p. 11-15.
- [18]. Auclair, P.L., Cuenin, P., Kratochvil, F. J., Slater, L. J. & Ellis, G. L. A clinical and histomorphologic comparison of the central giant cell granuloma and the giant cell tumor. *Oral Surgery, Oral Medicine, Oral Pathology*, 1988. 66(2): p. 197-208.
- [19]. Gulati, D., Bansal, V., Dubey, P., Pandey, S. & Agrawal, A., Central Giant Cell Granuloma of Posterior Maxilla: First Expression of Primary Hyperparathyroidism. *Case reports in endocrinology*, 2015. 2015.
- [20]. Martínez-Gavidía, E., Bagan, J., Milián-Masanet, M., Lloria De Miguel, E. & Perez-Valles, A., Highly aggressive brown tumour of the maxilla as first manifestation of primary hyperparathyroidism. *International Journal of Oral & Maxillofacial Surgery*, 2000. 29(6): p. 447-449.
- [21]. Daniels, J.S.M., Primary hyperparathyroidism presenting as a palatal brown tumor. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, 2004. 98(4): p. 409-413.
- [22]. Allon, D.M., Y. Anavi, and S. Calderon, Central giant cell lesion of the jaw: nonsurgical treatment with calcitonin nasal spray. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, 2009. 107(6): p. 811-818.
- [23]. Eisenbud, L., Stern, M., Rothberg, M. & Sachs, S. A., Central giant cell granuloma of the jaws: experiences in the management of thirty-seven cases. *Journal of oral and maxillofacial surgery*, 1988. 46(5): p. 376-384.
- [24]. Munde, A.D., Modi, P., Karle, R. R., Wankhede, P. & Shoeb, S., Nonsyndromic Synchronous Multifocal Central Giant Cell Granulomas of the Maxillofacial Region: Report of a Case. *Journal of Dentistry of Tehran University of Medical Sciences*, 2015. 12(2): p. 157-162.