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Central Giant Cell Granuloma: Uncommon Yet Important

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Abstract:*The central giant cell granuloma is an uncommon, benign and proliferative pathological condition accounting for less than 7% of all benign lesions of the jaws whose etiology is not clearly explained. It is characterizedhistologically by cellular fibrous tissue containing multiple foci of haemorrhage, aggregations of multinucleated giant cells, and occasionally, trabeculae of woven bone. Various theories brand it from being a 'reactive' to hamartomatous to a neoplastic lesion. It has an increased predilection for mandible and females, in younger age groups. Some of the lesions are thought to display a markedly 'aggressive' behavior and a clinically 'aggressive' model of CGCG has been proposed. Smaller, `nonaggressive' tumors generally respond very well to conservative enucleation or curettage but recurrence is seen to be common with 'aggressive' lesions. The clinical differential diagnosis for a solitary or multilocular CGCG includes ameloblastoma, odontogenic myxoma, and odontogenic keratocyst. Various medical therapies including injections of intra lesional steroids, subcutaneous calcitonin and interferon have been proposed for the treatment of 'aggressive' lesions. This article will review current concepts in relation to etiology, histopathology, diagnosis, and management of giant cell lesions of the jaws.*

Keywords:*Central Giant Cell Granuloma, Giant-cell reparative granuloma, Granuloma*

I. Introduction

Central Giant Cell Granuloma (CGCG) is rare benign pathology seen in the jaws. CGCG of the jaws reflects a non-neoplastic and localized benign proliferation, which may sometime,shows aggressive osteolytic behavior. Itis typically characterized by destruction of the bone, facial asymmetryand displacement of tooth and tooth germs, especially in younger patients[1]. Neville et al classified this lesion to be a non-neoplastic lesion and the World Health Organization (WHO) considered it as a lesion related to bony structures, not a tumor, even though its clinical behavior and radiographic features are often related to a benign tumor[2].There are two lesions which are closely related to CGCG are Giant cell of tumor (GCT) of long bones and Giant cell reparative granuloma(GCRG) of small bones. Various studies concludes that these lesions are histologically and phylogenetically similar[3].

II. Definition

The World Health Organization has defined it as *"an intraosseous lesion consisting of cellular fibrous tissue that contains multiple foci of hemorrhage, aggregations of multinucleated giant cells and occasionally trabeculae of woven bone[4]".*

Chuong et al stated that aggressive giant cell lesions were defined as lesion exhibiting size greater than 5 cm as and show rapid growth, tooth displacement, root resorption, perforation or thinning of cortical bone, recurrence after curettage, equal to or greater than 5 cm and/or that recurred after curettage[5].

What's in the Name?

Jaffe in 1953, described CGCG as a "Giant-cell reparative granuloma". The designation "reparative" has been deserted since due to the differentiation of central giant cell lesions between aggressive and non-aggressive lesions. Still, the literature does not reach on an agreementthat most correct term used for these lesions[2]. There are various terms for this lesion like central giant cell granuloma, central giant cell 'reparative' granuloma, giant cell lesion,' and 'benign' giant cell tumors by various authors, in the subsequent discussion

about this lesion, we will use the CGCG as it is the most frequently used term; readers can also use the more equivocal term 'giant cell lesion'. The term CGCG has been preferred to be used to explain both for a reactive response to hemorrhage or trauma, and a neoplasm. These days it is designated as 'central giant cell granuloma' or 'central giant cell lesion[3]'.

III. Clinical Features

CGCG is intrabony non-odontogenic pathology and its occurrence is less common than its counterpart peripheral giant cell granuloma (PGCG). Lesions are chiefly reported in children and young adults, with mostly lesions (as high as 75%) representing before 30 years of age. Often females are more affected in comparison to males, in a ratio of 2-11. High estrogen conditions, such as pregnancy, have been connected in CGCL proliferation, lesions, however, rarely express estrogen receptors. CGCG occurs predominantly in the mandible followed by anterior maxilla, although isolated cases in facial bones also have been reported. It tend to involve the jaws anterior to the permanent molar teeth and sometimes extended across the midline. In a very few incidences, the lesions involve the posterior jaws, including the ramus and condyle[3].

Typically CGCG represented as an asymptomatic pain-less swelling of the affected jaw. Thinning or perforation of cortical plates but rarely involves gross soft tissue as often remains limited to its effects on periosteum.Despitethe lesion have expansive and invasive nature; it does not usually involve perineural sheets so paresthesia is usually not observed in these patients. Even though the nature of this lesion is considered benign, there are still some studies in literature reported metastasis. Osteosarcoma or fibrosarcoma have been reported as malignant transformations in some lesions[3].

Besides the similar features with the Brown Tumour of Hyperparathyroidism and Cherubism, it has also been associated withJaffe-Campanacci Syndrome, Neurofibromatosis-Type I or Neurofibromatosis-Type I with a Noonan-like phenotype[6]."

CLINICAL FEATURES
AGE: < 30 Years, Children & Young adults
Gender: Female > Male
Site & Location: Mandible> Maxilla, Anterior to Molars
Incidence: **Rare benign tumour, 7%of tumors of jaws** **Less common than its peripheral counterpart.**
Associated Condition: **Brown Tumour of Hyperparathyroidism** **Cherubism** **Jaffe-Campanacci Syndrome** **Neurofibromatosis-Type I**

IV. Etiopathogenesis

(Spindle cell induces; giant cell causes CGCG)

Origin: Unknown, but genetic abnormalities may be implicated.The exact reason behind the pathogenesis of CGCG remains unknown. It was thought that there is a reparative response to intrabony haemorrhage and inflammation, CGCG was once considered as a reactive lesion. CGCG is best classified as a benign neoplasm because of its unpredictable nature, occasionally showing aggressive behavior and its possible relationship to the giant cell tumor of long bones. The histogenesis of CGCG of the jawbones remains controversial, as speculations are still debated regarding the possibility that it represents a reactive, an inflammatory, an infective, or a neoplastic process[3].

Vascular hypothesis suggests that CGCG belongs to the spectrum of mesenchymal proliferative vascular primary jaw lesions. Angiogenesis is a phenomenon modulated by several cytokines and growth factors. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are the most potent inducers of angiogenesis and have a synergistic effect. It is produced and released from activated monocytes and macrophages[7].

Perhaps the most widely held view is that the initial CGCG is an endosteal hemorrhage. In 1962,Kramer stated that if the process is concerned with the repair following hemorrhage, then the repair follows a peculiar pattern complicated by repeated new haemorrhages[8].El-Labban (1997) studied CGCG and confirmed Kramer's statement. She observed that majority of vessels showed intravascular fibrin thrombi and endothelial cell damage with gaps in the cell walls.Plasma, erythrocytes and fibrin were seen subendothelially. She also noted that a giant cell had sealed one of the gaps in a vessel. The author suggested that the presence of

the giant cell closed the gap and stopped haemorrhage and the main purpose for the presence of thestromal cells is the repair not only of the hematoma but also of its contributing vessels[9].

The primary tumor cells of CGCGs are fibroblasts. Secondary cells, which are microscopically the most prominent, are multinucleated giant cells. Accessory cells, seen in considerably smaller numbers, include macrophages, factor XIIIa+ dendrocytes, and endothelial cells. The fibroblasts make up the proliferative component of CGCGs, since they express proteins that are indicative of cells in the cell cycle. Tumor fibroblasts are also believed to be responsible for recruitment and retention of monocytes and subsequently for transformation into multinucleated giant cellswhile the giant cell remains to be the most prominent feature of these lesions, it is actually the mononuclear spindle cell, which is the proliferating cell (in cell cycle)[10].
This is indicated by the expression of the cell cycle protein Ki-67 in CGCGs. It is believed by some that this spindle cell (fibroblast or fibroblast-like) recruits monocytes from the vascular system and induces them to differentiate into osteoclastic giant cells through release of cytokines.

It has been proposed' that this spindle cell takes its origin from the mesenchyme of marrow and an epigenetic event (poorly understood) signals them to release cytokines and finally the osteoclastic giant cell causes bone resorption making the hallmark feature of CGCG. Another hypothesis is that CGCG is a vascular proliferative lesion, which means that angiogenesis under the influence of the tumour cells is required for tumour growth, invasion, and destruction of local tissue. The possible spontaneous involution theory favors this hypothesis[2].

V. Radiological Features

The CGCG may occur initially as a unilocular, cyst-like radiolucency, but as it grows larger, it frequently develops an architecture that causes a soap-bubble type of multilocular radiolucency. This multilocular soap-bubble appearance is associated with a later presentation, and is one of the commoner radiographic patterns seen in patients with CGCG.Different researchers have reported the unilocular lesions to comprise 39-84% of the total number of CGCGs. Generally, if the lesion is located anterior to the permanent molars and possibly crossing midline, with a multilocular radiographic pattern with the patient under 30 years of age, a provisional diagnosis of CGCG can be considered." However, if the biopsy proves it to be a case of CGCG, serum chemistry for hyperparathyroidism has to be done to exclude Brown Tumour[11].

Furthermore, in multiple lesions of CGCG, possibilities of cherubism and Noonan syndrome also have to be considered.The radiological differential diagnosis can include Ameloblastoma, Odontogenic keratocyst, Aneurysmal Bone Cyst and sometimes also odontogenic myxoma and central haemangioma of bone (the latter two often exhibit more of a honey-combed appearance though). For patients in the young age range for CGCG, ameloblastic fibroma, cemento ossifying fibroma (early stages), and adenomatoid odontogenic tumor might be added to this list."The borders of the lesion have been reported as well defined in 56% of cases, poorly defined in 30% of cases, and diffuse in the remaining 14%. They are generally seen to be well delineated, but the margins are generally noncorticated[12].**Whitaker and Waldron** showed that though most of the 142 cases of CGCGs in their study were well delineated, only 19% showed well-corticated borders[13].

VI. Histopathology

CGCG is composed of uniform fibroblasts in a stroma containing various amounts of collagen. Haemosiderin-laden macrophages and extravasated RBCs are usually evident, although capillaries are small and inconspicuous. Multinucleated giant cells are present throughout the connective tissue stroma, and they may be seen in patches or distributed evenly. It has been reported that the multinucleated giant cells exhibit characteristics of the osteoclasts phenotype.Others suggest these cells may be aligned more closely with macrophages. In some cases, the stroma is loosely arranged and oedematous; in others, it may be quite cellular. Foci of osteoid may be present, particularly around the peripheral margins of the lesion. Although red cell extravasation can be extensive in some CGCGs, it does not make these lesions fundamentally vascular, as the proliferating cells are not endothelial cells. The red cell extravasation can probably be explained by vascular permeability caused by cytokine release through mononuclear spindle cells[3].

VII. Aggressive' Vs. Nonaggressive' Lesions

It can be that there is a reactive form (nonaggressive CGCG) and a neoplastic form (aggressive CGCG) and scientists have not been able to devise tools to scientifically separate the two. However, there are no histological differences between the aggressive and non-aggressive varieties what is agreed upon at is their clinical behavior, which marks them as progressive lesions that can be aggressive[14]. Chuong et al suggested that the term ‘nonaggressive’ and ‘aggressive’ should be used with CGCG based on clinical behavior. When CGCG is a slow-growing lesion, it can be asymptomatic and discovered on a routine radiographs, while pain and facial swelling characterize the rapidly expanding aggressive variety[5].

Some authors have suggested that a more 'aggressive' form of CGCG may exist, but efforts to identify such a variant histologically or by immunohistochemistry have not yielded concrete results. It has been shown that 'aggressive giant' cell lesions may have a higher relative size index of giant cells, with an in-creased rate of mitosis and less osteoid formation at the periphery,' but the results have varied and have largely remained inconclusive. However, an 'aggressive model' of CGCG has been proposed on the basis of clinical and radiological findings which characterizes aggressive giant cell lesions on the presence of pain, paresthesia, a size of more than 5 cm, rapid growth, tooth displacement or root resorption and cortical bone thinning or perforation[15].

Recurrent lesions, regardless of size, would be considered 'aggressive', and may form the strongest indicator of 'aggressiveness'. These 'aggressive' types of CGCGs are seen to be commoner in younger patients with a mean age of 10.7 years compared with an average age of22.5 years for `nonaggressive' lesions[3]. Kruse-Losler et al.have held tumour size to be the most reliable indicator of the 'aggressiveness' and prognosis. Such clinical features should be accounted for to improve the individual planning of the treatment and thence, follow-up. They are thought to comprise of 19.3% of all CGCGs[16]".

So it could be that there is a neoplastic 'aggressive' variant and a reactive `nonaggressive counterpart. However, we think that keeping the general health attitudes and other socioeconomic demographic features in mind, patients with smaller, `nonaggressive', asymptomatic, painless lesions do not seek care early in the course of the disease. Believing the 'reparative' theory, these lesions may 'involute' with time and if some of them 'do not involute', it is often one of the symptomatic feature (such as pain or a grossly enlarged swelling) of the lesion that makes them present to the hospital. 'Aggression' in that scenario, then becomes more duration dependent than the actual clinical behavior of the lesion. It is therefore, pertinent to mention that tooth displacement with or without root resorption is seen invariably in almost all cases seen at our setting. Incidental finding of a brewing small giant cell lesion is, if at all, a remote possibility[3].

VIII. Differential Diagnosis

There are various conditions, which 'mimic' the histological presentation of CGCG. The histopathological differential diagnosis includes PGCG, GCT, Brown Tumour of hyperparathyroidism, Cherubism, Aneurysmal bone cyst and Fibrous dysplasia.PGCG is inseparable histologically from CGCG and it is the clinical manifestation of a peripheral, soft tissue origin in case of PGCG that distinguishes the two.GCT of long bones can sometimes be differentiated from CGCG because of larger giant cells with more nuclei and a homogenous pattern[17].

Malignancy in GCT of the bone was reported by **Bertoni et al.** in 1.8 % of the cases described. These malignancies can be either primary or secondary, including giant cell-rich osteosarcomas, fibrosarcomas, and malignant fibrous histiocytomas[18].Some authors have regarded the GCT and CGCG as a continuum of the same disease process, by reporting some histopathological pictures of 'aggressive' CGCGs which were totally indistinguishable from GCT of long bones.' This led these scientists to believe that CGCGs and GCTs of the extragnathic skeleton are not distinct and separate entities but rather represent a continuum of a single disease process modified by the age of the patient, location, and possibly other factors that are as yet not clearly understood[3].

There have been a few case reports of a reported GCT occurrence in the jaws that metastasized or locally transformed into a malignancy," which fail to clearly report a spontaneous malignant transformation of a previously benign CGCG. What is unclear in most of them that whether it was a primary bone malignancy (osteosarcoma, chondrosarcoma etc.) with a large giant cell population or a radiation-induced sarcomatous change.Brown Tumour of hyperparathyroidism is histologically indistinguishable from CGCG. Termed brown as the haemosiderin-laden tissues give it a brown-coloured appearance, it is imperative to exclude Brown Tumour after every histological diagnosis of CGCG[3].

Serum Chemistry consisting of Calcium, Phosphorus and Parathormone profile along with the classic manifestations of stones (renal stones), bones (bone changes), moans (psychic moans) and groans (abdominal groans), are used to assess bone lesions in hyperparathyroidism[19].Cherubism is an autosomal dominant disorder with bilateral involvement. Though it may be difficult to distinguish Cherubism from CGCG histologically, Cherubism is seen to have a distinct clinical presentation. It includes multifocal and multilocular cystic lesions of the jaws. Early stages of Cherubism may initially present with a single obvious lesion on one side of the jaw and additional lesions, which are quite smaller and rather difficult to detect[20].

Mainly in young patients with large lesions in the posterior region, very thorough radiographic examinations (intraoral occlusal radiography, CT with 3-D reconstruction) can be per-formed to rule out the possibility of additional lesions being part of an evolving Cherubism. As a rule of thumb, Cherubism is diagnosed on clinico-pathological grounds. In some lesions, however, the characteristic eosinophilic perivascular cuffing has been noted[21].The diagnosis of Aneurysmal Bone cyst (ABC) is made by the identification of sinusoidal blood spaces within the tumour mass, and sometimes by aspiration of blood

preoperatively[22].Fibrous dysplasia shows only limited foci of giant cells. There are no defined margins radiographically, as it merges imperceptibly with the surrounding bone, atleast in maxilla where it is most commonly encountered. Moreover, growth in fibrous dysplastic lesions normally ceases with maturity[23].

DIFFRENTIAL DIAGNOSIS			
S. NO.	**Lesion**	**Striking Features**	**Other Features**
	CGCG	Distinctive with multinucleated giant cells spread throughout the lesion but often focal in distribution around areas of possible hemorrhage.	
1.	**GCT**	Larger giant cells More nuclei per cell. Multiple mitoses Homogenous pattern.	Unusual in the jaw More aggressive nature and High degree of recurrence
2.	**Brown Tumour of hyperparathyroidism**	Haemosiderin-laden tissue	Calcium, Phosphorus and Parathormone profile Classic manifestations: Stones (renal stones), Bones (bone changes), Moans (psychic moans) and Groans (abdominal groans)
3.	**Cherubism**	Autosomal dominant disorder with Bilateral involvement. Male: female ratio of 2:1 Fewer giant cells Perivascular cuffing.	Gene defect on chromosome 4p 16.3, which encodes the binding protein SH3 BP2
4.	**ABC**	Sinusoidal blood spaces within the tumour mass, Sometimes by aspiration of blood preoperatively	
5.	**Fibrous dysplasia.**	No defined margins radiographically, as it merges imperceptibly with the surrounding boneonly limited foci of giant cells	Presence of Chinese figure like trabeculae of woven & immature bonewith proliferating fibroblastic stroma. Growth normally ceases with maturity

Differences Between PGCL And CGCL[24]

	PGCL	**CGCL**
Etiology	Local irritant factors	Uncertain
Nature	Non-neoplastic	Non-neoplastic
Site	Extraosseous: Gingiva and alveolar ridge	Intraosseous
Clinical behavior	Little aggressive	More aggressive
Recurrence potential	Low	High
Histology	Similar to CGCL	Similar to PGCL
Origin of giant cells	Uncertain	Uncertain
Growth	Exophytic, slow	Endophytic, rapid
Bone resorption	Rare	Present
Dental root resorption	Rare	Present
Treatment	Surgical	Pharmacological and/ or surgical
PGCL: peripheral giant cell lesions; CGCL: central giant cell lesions.		

IX. Immunohistochemistry

Besides the-cell cycle protein Ki-67 which is over-expressed may lead to a dysregulation of the cell cycle, CGCGs have an overexpression of the MDM2 protein/ gene," and it is proposed that it might be the control protein/gene of the proliferating spindle cells. p53 (a protein with antiproliferative and apoptosis-promoting effects) is not known to have an altered expression in cases of CGCGs[16].

X. Genetics

In a simplified overview of osteoclastogenesis, bone marrow-derived osteoclast-precursor cells are committed to osteoclastic differentiation by intranuclear buildup of NFATcI (nuclear factor of activated T cells). NFATcI is amplified both by the presence of SH3BP2 protein and by stimulation of RANK (receptor activator of NF-jB), which is expressed on the osteoclast-precursor cell surface. RANK is stimulated by the RANK ligand (RANKL), which is expressed by osteoblasts. OsteoblasticRANKL expression is in turn stimulated by parathyroid hormone (PTH). Thus, the end result of PTH secretion is osteoclast proliferation, bone resorption, and calcium liberation.Pathologically sustained PTH elevation causes BTOH, which consists of mononuclear osteoclast-precursors and multinucleated differentiated osteoclasts[25].

The other giant cell lesions may also represent pathologic variations of osteoclastogenesis, though their mechanisms are less well understood. CGCL and PGCG are composed of mononuclear stromal cells that mimic osteoclast- precursors and MGCs that mimic differentiated osteoclasts. NFATcI expression is also increased in both of these lesions. They differ, however, in that CGCL arises centrally within bone, while PGCG is a gingival soft tissue lesion. The bilateral CGCLs of Cherubism are caused by an activating germline mutation of the SH3BP2 gene (chromosome 4p16.3). Sporadic SH3BP2 mutations have been identified in CGCL, but not in PGCG[25].

By using DNA microarrays containing 19,200 genes, **Carinci et al.** identified several genes who expression were significantly up- or down-regulated, and thus presented a genetic profile of CGCG. These expressed genes cover a broad range of functional activities: cell cycle regulation, signal transduction, and vesicular transport. Those among upregulated genes include AKAP 12 (A-Kinase Anchor Protein 12), STMN1, CNTFR, ELK1 and HSPG (Heparan Sulphate Proteoglycan). Down-regulated genes include TM4SF2 (Transmembrane 4 Superfamily 2), DDA3 and MPP3. It is hoped that this genetic portrait can be used to distinguish between 'aggressive' and `nonaggressive' lesions by monitoring the relative expression in each of them[26].

XI. Treatment & Prognosis:

Conventional management is by curettage or resection, which may be associated with loss of teeth, or in the younger patient, developing tooth germs. Non-surgical treatment includes systemic calcitonin therapy and intralesional injections with corticosteroids[27].

XII. Recurrence

A somewhat higher rate of recurrence has been reported in lesions arising in children and young teens. Lesions with aggressive clinical features also exhibit a tendency to recur[10].

XIII. Conclusion

CGCG though a rare disease of head and neck sometimes shows an aggressive behavior and hence correct diagnosis is established by correlating clinical and histological features. Surgery is the traditional and accepted treatment but may be combined with local injection of steroids and calcitonin to avoid recurrence.

REFERENCES

[1]. Vered M, Buchner A, Dayan D. Central giant cell granuloma of the jawbones-new insights into molecular biology with clinical implications on treatment approaches. Histol Histopathol. 2008 Sep;23(9):1151-60.
[2]. Jadu, F. M., et al. "Central giant cell granuloma of the mandibular condyle: a case report and review of the literature. Dentomaxillofac Radiol. 2011;40(1):60–4.
[3]. Chattha MR et al. Current concepts in central giant cell granuloma. Pakistan Oral Dent J 2006;26(1)71-8.
[4]. Yadav S, Singh A, Kumar P, Tyagi S. Recurrent case of central giant cell granuloma with multiple soft tissue involvement. National journal of maxillofacial surgery. 2014 Jan;5(1):60.
[5]. Chuong R, Kaban LB, Kozakewich H, Perez-Atayde A. Central giant cell lesions of the jaws: a clinicopathologic study. Journal of oral and maxillofacial surgery. 1986 Sep 30;44(9):708-13.
[6]. Trindade MC, Elias FM, Migliolo RC, Nogueira NC, Ferraz FW. Association between Neurofibromatosis Type I and Central Giant Cell Lesion: Case Report. Pigmentary Disorders. 2015;2(161):2376-0427.
[7]. Mohan RP, Verma S, Agarwal N, Singh U. Central giant cell granuloma: a case report. BMJ case reports. 2013 Jul 22;2013:bcr2013009903.
[8]. Philipsen HP, Reichart PA. Classification of odontogenic tumours. A historical review. Journal of oral pathology & medicine. 2006 Oct 1;35(9):525-9.
[9]. Shrivastava S, Samadi FM, Priya S, Singh A. Central gaint cell granuloma of the jaw bones: a review. J Dentofac Sci. 2012;2013:11-5.
[10]. Regezi JA, Sciubba JJ, Jordan RC. Oral pathology: clinical pathologic correlations. Elsevier Health Sciences; 2012 Apr 15.
[11]. Wood NK, Goaz PW, Kallal RH. Multilocular radiolucencies. In: Wood NK, Goaz PW, eds. Differential diagnosis of oral and maxillofacial lesions. 5th ed. St. Louis: Mosby. 1997; 333- 55.
[12]. Katz JO, Underhill TE. Multilocular radiolucencies. Dental Clinics of North America. 1994 Jan;38(1):63-81.
[13]. Whitaker SB, Waldron CA. Central giant cell lesions of the jaws: a clinical, radiologic, and histopathologic study. Oral surgery, oral medicine, oral pathology. 1993 Feb 1;75(2):199-208.
[14]. Kaur S, Ahluwalia SS, Singh P. Case report of aggressive Central Giant Cell Granuloma-A diagnostician's approach. International Journal of Medical Research & Health Sciences. 2014;3(3):743-7.
[15]. Ficarra G, Kaban LB, Hansen LS. Central giant cell lesions of the mandible and maxilla: a clinicopathologic and cytometric study. Oral surgery, oral medicine, oral pathology. 1987 Jul 1;64(1):44-9.
[16]. Kruse-Lösler B, Diallo R, Gaertner C, Mischke KL, Joos U, Kleinheinz J. Central giant cell granuloma of the jaws: a clinical, radiologic, and histopathologic study of 26 cases. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2006 Mar 31;101(3):346-54.
[17]. Gupta MK, Naidu SG, Maheshwari VJ. Giant cell lesion of the jaw: a case report in a child. People's J Sci Res. 2011 Jan;2013:63-7.
[18]. Bertoni F, Bacchini P, Staals EL. Malignancy in giant cell tumor of bone. Cancer. 2003 May 15;97(10):2520-9.
[19]. Shah VN, Bhadada SK, Bhansali A, Behera A, Mittal BR. Changes in clinical & biochemical presentations of primary hyperparathyroidism in India over a period of 20 years. The Indian journal of medical research. 2014 May;139(5):694.

[20]. Jiao Y, Zhou M, Yang Y, Zhou J, Duan X. Cherubism misdiagnosed as giant cell tumor: a case report and review of literature. International journal of clinical and experimental medicine. 2015;8(3):4656.
[21]. Avril L, Lombardi T, Ailianou A, Burkhardt K, Varoquaux A, Scolozzi P, Becker M. Radiolucent lesions of the mandible: a pattern-based approach to diagnosis. Insights into imaging. 2014 Feb 1;5(1):85-101.
[22]. Rai KK, Kumar HS. Aneurysmal bone cyst, a lesion of the mandibular condyle. Journal of maxillofacial and oral surgery. 2012 Jun 1;11(2):238-42.
[23]. Cawson RA, Odell EW. Cawson's essentials of oral pathology and oral medicine. Elsevier Health Sciences; 2008 Feb 15.
[24]. Vasconcelos RG, Vasconcelos MG, Queiroz LM. Peripheral and central giant cell lesions: etiology, origin of giant cells, diagnosis and treatment. Jornal Brasileiro de Patologia e Medicina Laboratorial. 2013 Dec;49(6):446-52.
[25]. Valentine JC, Nelson BL. Central giant cell lesion. Head and neck pathology. 2011 Dec 1;5(4):385-8.
[26]. Carinci F, Piattelli A, Stabellini G, Palmieri A, Scapoli L, Laino G, Caputi S, Pezzetti F. Calcium sulfate: Analysis of MG63 osteoblast- like cell response by means of a microarray technology. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2004 Nov 15;71(2):260-7.
[27]. Sezer B, Koyuncu B, Gomel M, Gunbay T. Intralesional corticosteroid injection for central giant cell granuloma: a case report and review of the literature. Turk J Pediatr. 2005 Jan 1;47(1):75-81.