Central Giant Cell Granuloma Of Maxilla: A Case Report And Literature Review

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Abstract

Central giant cell granuloma (CGCG) is a benign reactive lesion rather than benign neoplastic lesion. In 70% of cases, it is seen in mandible and the remaining 30% occurs in maxilla. Females are affected more than males and commonly seen in children and young adults. The etiology is still completely unknown but thought to be of a reactive process to some unknown stimuli. However, it has radiographic features similar to some neoplastic lesions. The incidence in the general population is very low. Central giant cell granuloma is characterized by the presence of multinucleated giant cells of varying shapes and sizes, fibrous tissue, vascular channels and macrophages. We report a case of central giant cell granuloma in the right anterior maxillary region of a 12 year old boy, who develop a painless swelling on the right side of the face since three months and gave a history of trauma at the same time. The patient was treated surgically and one year follow up did not show any sign of recurrence.

KEYWORDS: Central giant cell granuloma, Maxilla, Multinucleated giant cells.

Introduction

Central giant cell granuloma (CGCG) is an uncommon benign intraosseus lesion that occurs almost exclusively in jaws, introduced for the first time by Jaffé in 1953[1]. The clinical behavior of CGCG is variable. It ranges from slow-growing, asymptomatic swelling to an aggressive lesion which manifests with pain. The etiopathogenesis has not been clearly established but it has been suggested that it is the result of an exacerbated reparative process related to previous trauma and intraosseous haemorrhage that triggers the reactive granulomatous process. The CGCG may occur at any age, but it is most commonly seen in the first three decades. 37.5% of CGCGs are located in the incisor, canine, and premolar regions of the mandible (Kaffe et al, 1996). CGCG of the jaw is usually unifocal and have traditionally been treated surgically; the common therapy being curettage or resection (Kermer et al, 1994; Eisenbud et al, 1988)[2,3,4].

Case report

A 12 year old boy reported to the department of Oral Pathology and Microbiology, Subharti Dental College with a painless swelling on the right side of the face since three months. Patient gave a history of fall from the bed three months back and developed pain and swelling in the right maxillary anterior region. He consulted a local doctor and on whose medications, the pain subsided but the swelling gradually increased. Past medical history was not significant and the patient was moderately built and nourished. Extra oral examination showed diffuse swelling extending from upper lip to ala-tragus line causing obliteration of nasolabial fold and resulting in facial asymmetry (Figure 1). Skin overlying swelling was normal with no raised temperature. Intra oral examination revealed the presence of a painless, firm swelling of 2cm to 2.5cm in size on the right anterior maxillary ridge extending from labial frenum to the right corner of the mouth with well defined borders and it was fixed to

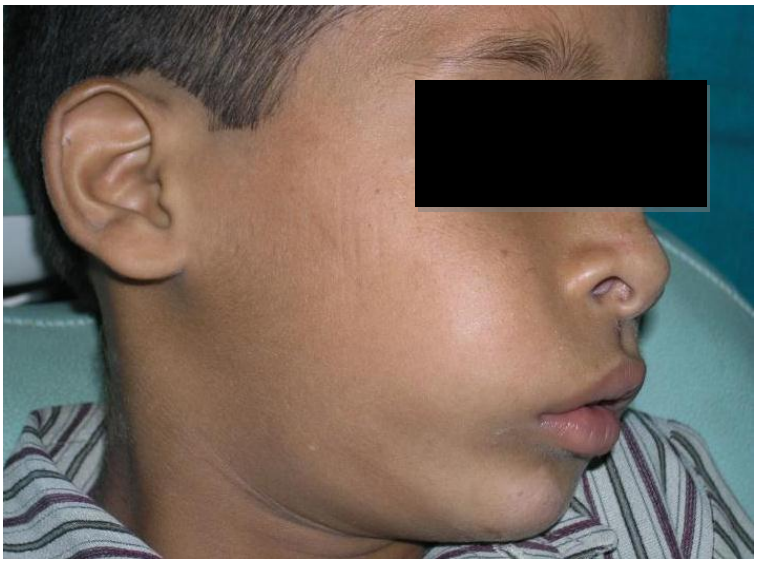

Figure1: Swelling on the right side of the face

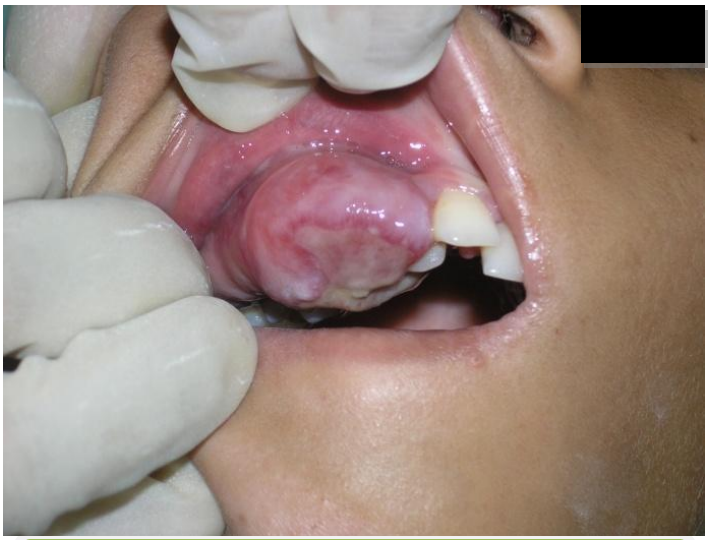

Figure2: Intraoral swelling on the right anterior maxillary ridge

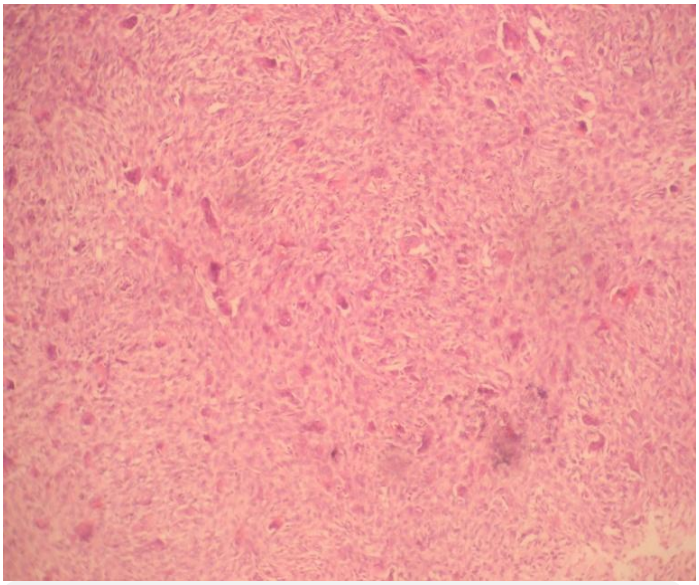

Figure3: H&E(10X) showing multinucleated giant cells

underlying bone. There was no sign of pulsations or fluctuation on palpation (Figure 2). The adjacent dentition and the oral mucosa did not reveal any abnormality. Radiograph showed unilocular radiolucency on the anterior maxillary region. Thus a clinical diagnosis of ossifying fibroma, central giant cell granuloma, ameloblastoma and fibrous dysplasia was made. Histopathological examination revealed a highly cellular fibrous stroma with numerous multinucleated giant cells of varying sizes and shapes and multiple vascular channels (Figure 3). Thus a final diagnosis of central giant cell granuloma was made.

DISCUSSION

A Giant cell granuloma (GCG) is a rare benign lesion. In the head and neck region its incidence is reported to be 0.00011%. It usually affects the mandible in 70% of cases and the maxilla in the remaining 30%. WHO defined GCG histology as intraosseous lesions consisting of cellular fibrous biological tissue, containing multiple hemorrhagic foci, aggregation of multinucleated giant cell, and occasionally trabeculae of woven bone. There are several ways to classify GCG. First, the disease can be classified as central (CGCG) or peripheral (PGCG). CGCG is bone based and usually occurs in the mandible, maxilla, temporal bone and paranasal sinuses. Cases of CGCG of hard palate are rare in the literature. Peripheral is based on biologic tissue and affects frontal alveolar mucosa and gingival mucosa. Even though the histopathogenesis of CGCG, PGCG, and Giant cell tumor (GCT) of the long bones are identical, both CGCG and PGCG have a less aggressive biologic behavior than the GCT of long bone[5,6].

Central giant cell granuloma is a non-neoplastic proliferative lesion of unknown etiology. It occurs most commonly in the mandible than in the maxilla. But our case involved the maxilla. Most mandibular lesions occur anterior to first molars and often cross the midline. It strikingly occurs more commonly on the right side than left side as seen in our case. Central giant cell granuloma also occurs in other bones of the facial skeleton and cranial vault. It rarely occurs outside the craniofacial bones, but it has been described in the short tubular bones of hands and feet[7]. In most of the cases, females have more predilection than males in the ratio of 2:1. It occurs most commonly in children or young adults. Our case was seen in a boy of 12 years of age.

The etiopathogenesis of the CGCG of jawbones has not been clearly established but it has been suggested that it is the result of an exacerbated reparative process related to previous trauma or inflammation and intraosseous haemorrhage that triggers the reactive granulomatous process. Donoff and Rosenberg discussed a case record of an uncomplicated extraction because of pericoronitis in the area of the lesion and claimed the local changes in the blood flow throughout the bone and local bone dysplasia could be probable etiologic factors[8]. Unal et al presented a 12 year-old girl CGCG in the mandible

caused by a molar tooth extraction and explained the pathogenesis by a traumatic aetiology[9].

In our case also there was a clear history of trauma and thereafter the patient developed a swelling. Recent interest in the pathogenesis of the disease is increasing as studies for possible medical therapies are emerging. The target of therapeutic compounds has been to gain control over the proliferation of mononuclear spindle cell. Although prominent on microscopy, giant cells are not the proliferating cells but the mononuclear spindle cells are. These cells also recruit RBC, induce osteoclast activity in giant cells, and express Receptor Activator of Nuclear Factor-kB (RANK). RANK-osteoprotegin antagonist stimulates initiation of resorption. Still untested on human beings. MDM2 protein/gene may be over-expressed in GCTs and CGCGs. This protein, which promotes proliferation through p53 binding, is the only cell cycle associated protein determined to be over-expressed. The p53 gene does not appear to be mutated in these lesions. p63 may be a useful biomarker to differentiate giant cell tumor of bone from central giant cell granuloma and other giant cell-rich tumors, such as giant cell tumor of tendon sheath and pigmented villonodular synovitis. The conspicuous expression of proliferating cell nuclear antigen (PCNA) suggests that the proliferative component of CGCG would be represented by a mesenchymal stromal cell which had the capacity to differentiate along fibroblast/ osteoblast lines[10].

Expression of the c-Src gene has been implicated in the development of CGCG, GCT and cherubism (Wang et al, 2006)[11]. In addition, histologically identical lesions occur in patients with known genetic defects such as cherubism, Noonan syndrome, or neurofibromatosis type 1. Central giant cell granuloma has been shown in a report to be further associated with a reciprocal translocation t (X; 4) (q22; q31.3) (Buresh et al, 1999)[12].

CD68, a transmembrane glycoprotein and a monocyte-macrophage lineage marker has been often used in the investigation of giant cells suggesting the existence of a histiocyte/macrophage origin for some of the cellular components of CGCG and GCT[13]. Accordingly, Liu, et al. (2003) verified the expression of vacuolar H^+-ATPase (V-ATPase), carbonic anhydrase II (CA II), cathepsin K, MMP-9 and tartarate-resistant acid phosphatase (TRAP) in multinucleated giant cell of CGCG, thus confirming the characteristics of an osteoclastic phenotype[14]. Vered, et al. (2006) states that VEGF and bFGF expression could be related to stimulation of osteoclastogenesis in CGCG, suggesting that high levels of VEGF- and bFGF-producing cells in a CGCG, would be related to a more aggressive biological behavior[15].

Giant cells have calcitonin receptors that are inhibited by calcitonin thereby inhibiting osteoclastogenesis. Interferons have anti angiogenic effect and cause inhibition of bone resorption. Intralesional injections of corticosteroids is believed to inhibit the bone resorption and proliferation and differentiation to osteoclasts. Although there is extensive RBC extravasation the proliferating cells are not endothelial cells and so there is little role for antiangiogenic drugs such as VEGF[16].

The clinical behaviour of CGCG varies. Nonaggressive lesion is usually slow growing and asymptomatic, does not show cortical resorption by the lesion or root perforation in teeth affected, and it is significantly less likely to recur than the aggressive type. Aggressive lesions, is usually found in younger patients and is painful, grows rapidly, is larger overall, often causes cortical perforation and root resorption and has a tendency to recur. The radiological appearance of CGCG is variable. Usually the lesion appears as a unilocular or multilocular radiolucency. It may be well-defined or ill-defined and shows variable expansion and destruction of the cortical plate. The radiological appearance of the lesion is not pathognomonic and may be confused with that of many other lesions of jaws. The final diagnosis eventually rests on histopathology because the clinical and radiological features are not specific[4,17].

Histologically, CGCG contain focal arrangements of giant cells within a vascular stroma with thin-walled capillaries adjacent to the giant cells as seen in our case. There is a spindle cell stroma which may well be the cell of origin. The absence of perivascular cuffing, as seen in our case can help differentiate CGCG from cherubism. Presence of foreign body type giant cell and absence of stromal tumour cells differentiate CGCG from a GCT. 'Solid'aneurysmal bone cysts (ABC) are true benign neoplasms containing giant cells while trauma causing intramedullary hemorrhage has been implicated in the past as the etiology. Normal serum calcium, parathyroid hormone, alkaline phosphatase and phosphorous levels distinguish CGCG from other conditions like Brown tumour of hyperparathyroidism.

Cherubism is a self limiting condition, but giant cell granulomas can be aggressive with a tendency to recur and hence require treatment[17]. Our differential list should also include ameloblastoma and odontogenic myxoma. In contrast, ameloblastoma tends to occur in older age group, posterior in the mandible, and have well-defined, curved septa; whereas,CGCG has wispy ill-defined trabeculation.

Odontogenic myxoma does not cause much expansion, occurs in older age group, and has well-defined septa.

The rate of recurrence varies between 13-49%. Whitaker and Waldron reported a mean interval between diagnosis and initial treatment and treatment of a recurrence was 21 months, and stated that very few recurrences were manifested after 2 years of initial treatment. The most reliable factors related to an increased risk of recurrence include clinical activity of lesions (72% of recurrence in the aggressive forms, 3% of recurrence in the nonaggressive forms), younger patients, demonstrated perforation of cortical bone and tumour size[18]. In the case presented, the patient was a young boy and one year follow up did not show any sign of recurrences. There have been studies suggesting that the greater functional surface area occupied by giant cells and larger relative size of giant cells may identify tumours with aggressive behavior. Recently, Kruse-Loser

et al also proved that the aggressive variant of CGCG presented a high number of giant cells, an increased mitotic activity, and a high fractional surface area. Clinical course of CGCGs from known histological or immunohistochemical features is not predicted[5,19].

An unusual case of idiopathic bilateral case of central giant cell reparative granuloma of the angulus mandible, has also been reported in a12 year old girl[20].

CGGC is considered a non reparative lesion that destroys and grows if it is not treated. Traditionally management has been surgical by means of excision by curettage, which has been associated with a low recurrence rate in the well- located lesions. Curettage with peripheral ostectomy and bone resection is reserved for recurrences. Eisebund et al used the technique of curettage or curettage plus peripheral ostectomy[4]. Unal et al recommended microdrill with diamond burr to obtain margins of security after removing the lesion and filled the cavity with iliac crest chips[9]. The most aggressive or recurrent lesions can require en bloc bone resection and reconstruction, since it can determine a bone defect and teeth loss.

Becelli et al described a case treated by means of excision of a mandibular CGCG, reconstruction using autogenous iliac crest graft, dental implants and overdenture prosthesis. Surgical curettage was the treatment performed in our case. Non surgical approaches include intralesional corticoids or systemic calcitonins that inhibit the osteoclastic activity. Other non surgical treatments include interferon-alpha or bifosphonates. Paediatric patients necessitate conservative management to prevent long term developmental defects. An equal part of triamcinolone acetonide (10mg/ ml) and 0.5% bupivacaine injected into the lesion for a period of 11 weeks has been shown to be effective in a child patient.

Calcitonin nasal spray 200 U/spray once or twice daily was reported to be safe and effective for the treatment of CGCG. These can be used for a long term to achieve healing [21,22].

Conservative treatments have shown varying degrees of success and, when successful, have reduced the necessity for reconstructive surgery.

CONCLUSION

Central giant-cell granuloma (CGCG) is a benign condition of the jaws. It is twice as likely to affect women and is more likely to occur in 20–40 year old people. Central giant-cell granulomas are more common in the mandible and often cross the midline. Histologically identical lesions occur in patients with known genetic defects such as cherubism, Noonan syndrome, or neurofibromatosis type 1. Surgical curettage or, in aggressive lesions, resection, is the most common therapy. However, when using surgical curettage, undesirable damage to the jaw or teeth and tooth germs is often unavoidable and recurrences are frequent. Therefore, alternative therapies such as injection of corticosteroids in the lesion or subcutaneous administration of calcitonin or interferon alpha are described in several case reports with variable success. The long term prognosis of giant-cell granulomas is good and metastases do not develop. Nevertheless, recurrences of CGCG are not uncommon and can be seen in upto 46% of cases[23].

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