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(CASE REPORT)

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Giant cell lesions: A diagnostic mystery, case report and review of literature

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Abstract

Giant cell lesions is a broad term encompassing a wide range of lesions that are biologically and morphologically diverse with an uncertain aetiology, whether it is a benign tumour, reactive lesion, inflammatory lesion or a self-healing lesion is ill understood. Their relation to each other also is not very clearly defined as they differ in their clinical and radiographic characteristics and their only similarity is in the histologic finding of non-neoplastic osteoclast like giant cells of different lineage. Owing to this fact their exact diagnosis continues to be one of the most obscure making them a dilemma, leaving many questions regarding their treatment and prognosis unanswered. Here we present a case of Central Giant Cell Tumor that was misdiagnosed as fibrous dysplasia that lead to an elusive treatment plan.

Keywords: Giant cell lesion; Biopsy; Multinucleated giant cell

1. Introduction

Central giant cell tumor is an uncommon, but well recognized intra osseous benign entity seen in the maxillofacial region, with an unknown aetiology and variable clinical behaviour. It has a spectrum of presentations ranging from quiescent non-aggressive to aggressive lesions. It accounts for 7% of all benign tumours of the jaws (Kramer et al, 1991) [1]. It is commonly seen children and younger adults usually before the age of 30 years.

2. Case Report

An 18 year old female reported to the Department of Oral and Maxillofacial Surgery, Sri Sai College of Dental Surgery, Vikarabad, Telangana, India with the complaint of swelling in the front region of the lower jaw since one and a half years which had gradually enlarged to cause facial disfigurement at the time of presentation. The swelling was asymptomatic and was not associated with any pain or paraesthesia.

No associated history of trauma, systemic or local infections was elicited. Systemic examination revealed moderately built and moderately nourished female with no systemic disorder. On local examination facial asymmetry due to a poorly defined solitary swelling in the anterior region of mandible measuring approximately 3 x 4 cm was noted. It extended supero-inferiorly from the corner of the mouth till inferior border of the mandible and Antero posteriorly from the corner of the mouth till 2 cm anterior to the ear lobe. Overlying skin was normal (Fig.1).

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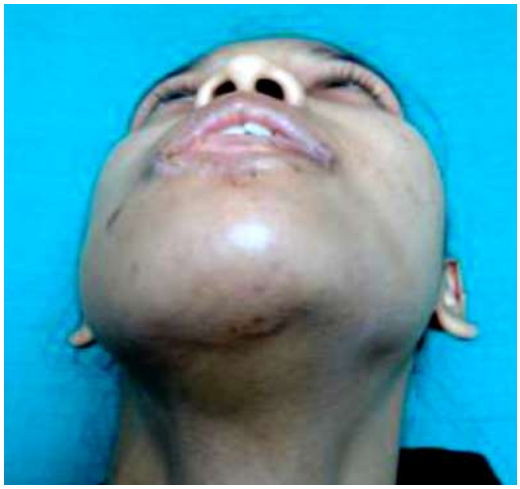

Figure 1 Extraoral presentation

On palpation skin above the swelling was smooth and pinchable, with no localized rise in temperature, bony hard in consistency and non-tender. Intra oral examination revealed a diffuse enlargement in the alveolar portion in relation to left and right mandibular incisors and premolars with obliteration of the vestibule in relation to the same. Overlying mucosa appeared bluish-brown in colour, adjacent oral mucosa and dentition were normal. No tooth displacement or mobility was noted in that quadrant. Mandibular right premolars were root canal treated and a tooth vitality test for the remaining teeth in the quadrant revealed normal pulpal response.

Radiographic examination with an orthopantomogram (Fig. 2) revealed a well-defined unilocular lesion measuring approximately 2 x 4 cm with mixed radiolucent and radio-opaque patches, no resorption of roots of any of the associated teeth was seen.

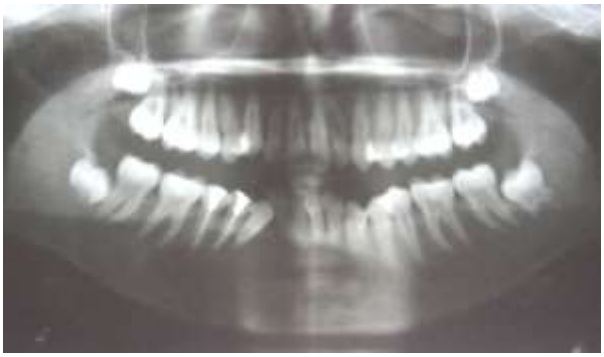

Figure 2 Preoperative orthopantomogram

A mandibular occlusal view (Fig. 3) revealed no expansion of buccal or lingual cortical plates

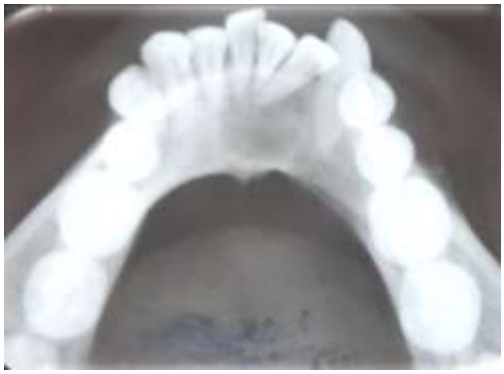

Figure 3 Preoperative mandibular occlusal view

Histopathological report of a chair side incisional biopsy done under local anesthesia showed the presence of predominantly cellular fibrous tissue along with irregularly shaped islands of metaplastic bony areas seen emerging from a fibrous tissue background showing Chinese letter pattern without any osteoblastic rimming. They also showed presence of hematoxylin reversal and resting lines and at the periphery of the bony islands giant cells were observed hence leading to a diagnosis of fibrous dysplasia (Fig. 4).

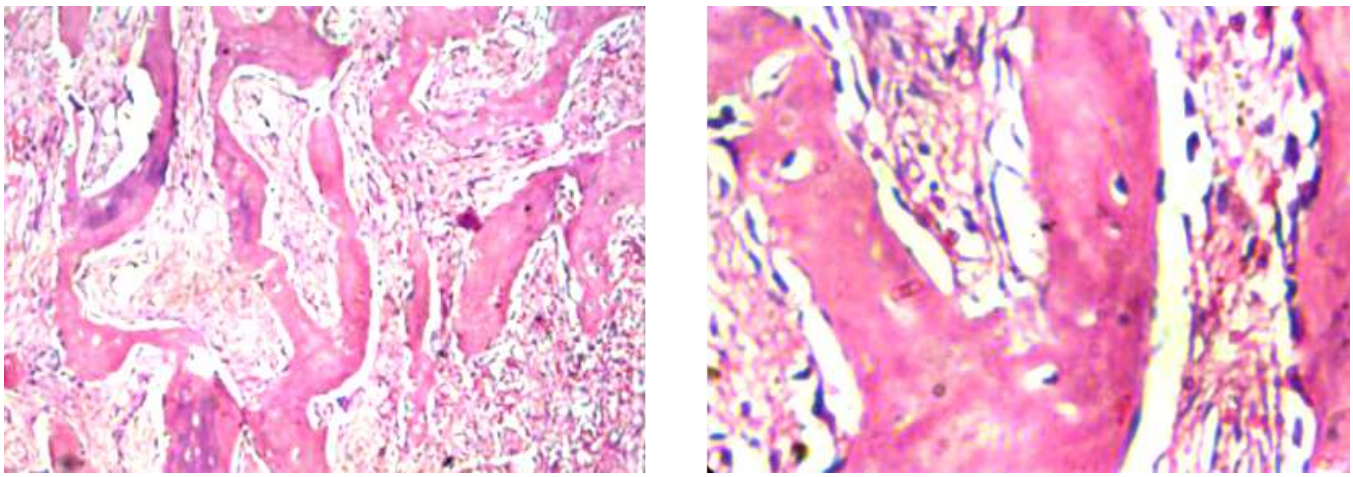

Figure 4 Photomicrograph showing curvilinear pattern of bony trabeculae

The age and sex predilection, fact that the swelling was bony hard, non-tender, asymptomatic and the radiographic findings of mixed radiolucent and radio opaque patches with no perforation of either buccal or lingual cortical plates all co related with the histopathological diagnosis. Since the histopathological diagnosis was conclusive, at the time further investigations were not considered. Owing to the young age of the patient osseous re-contouring was planned under general anesthesia.

The lesion was accessed through a circumvestibular approach in the lower labial vestibule. However intra operatively the buccal cortical plate appeared thin and fragile and upon further exploration a large soft tissue mass measuring 3 x 4 cms was revealed under it extending up to but not perforating the lingual cortical plate. Hence the treatment plan was altered on table intra operatively and enucleation of the mass in toto and curettage was done. (Fig. 5, 6) There was optimal bleeding that was easily arrested by local measures. We did not require to give fresh blood to the patient either.

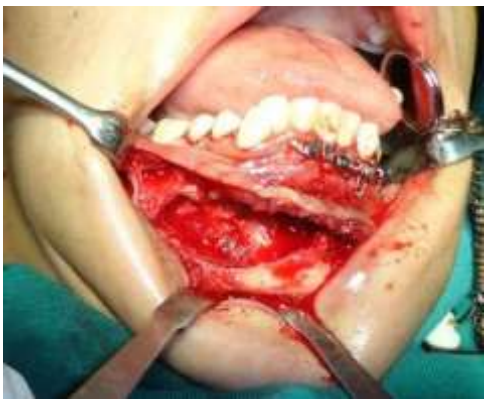

Figure 5 Complete curettage of lesion

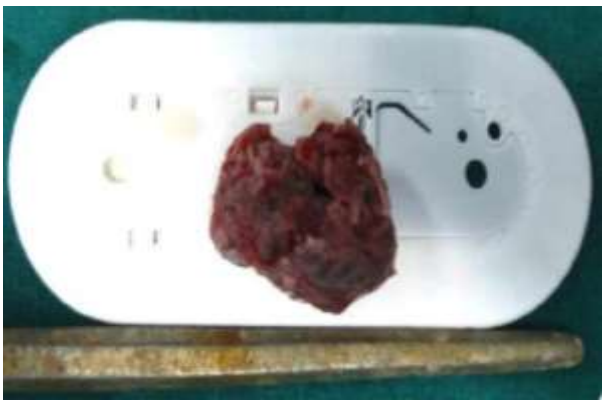

Figure 6 Enucleated soft tissue mass

Histopathological examination of the enucleated mass (Fig. 7) revealed connective tissue stroma with abundant amount of osseous tissue and osseous bony trabeculae interconnected with each other with osteoclastic rimming and osteocytes in lacunae. Intervening connective tissue showed delicate collagen fibres and blood vessels with numerous

multinucleated giant cells containing few to many nuclei especially abundant in areas of haemorrhage, suggestive of Central Giant Cell Tumor.

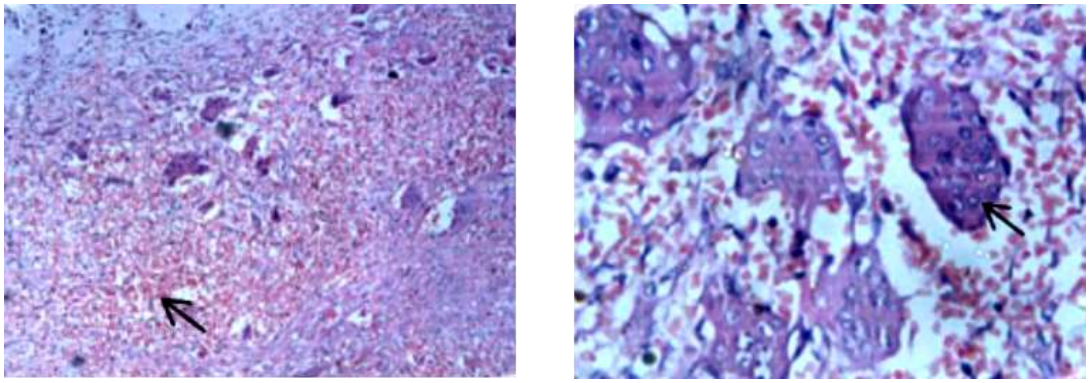

Figure 7 Photomicrograph showing areas of haemorrhage and presence of multinucleated giant cells

3. Discussion

The term giant cell lesions encompasses a wide range of uncommon lesions including Cherubism, Central giant cell tumor, Peripheral giant cell tumor, Aneurysmal bone cyst, Brown's tumor of hyperparathyroidism and Noonan's Syndrome to name a few. Earlier the term Central giant cell reparative granuloma coined by Jaffe in 1953 [2]was used to describe these lesions. It was hypothesized that these lesions were not true neoplasms but merely the result of a local reparative reaction and that they would resolve spontaneously [3,4], which is why they were not found in older patients. However the present opinion is that these are not self-healing lesions and will continue to proliferate without definitive treatment there by making the term reparative obsolete.

The World Health Organization has defined it as "An intraosseous lesion consisting of cellular fibrous tissue that contains multiple foci of haemorrhage, aggregations of multinucleated giant cells and occasionally trabeculae of woven bone.''

The female to male predilection ratio is 2:1 [5] which could be explained by the recent studies that have suggested that there is a relation between hormone secretion and appearance of CGCT in females [6]. Incidence rate is 1.1 per 106 for the whole population [7]. They are usually seen in children and young adults with more than 60% of the cases occurring before the age of 30 years [8], and occur twice as often in the mandible than in the maxilla [7,9-13]. They are most commonly seen in the anterior portion of the jaws (Regezzi and Scuibba, 1989) [14] crossing the mid line as was seen in our case.

They characteristically present as asymptomatic lesions that come to attention during routine radiographic examination or as a painless but visible swelling of the affected jaw, sometimes intra orally a bluish-brown discolouration of the overlying mucosa can be seen, similar to our case. They enlarge very slowly but do not invade or grow around the nerve trunks hence are not associated with paraesthesia. It also does not invade perineural sheaths or spread through perineural spaces. Perforation of overlying cortical plate, and resorption of roots is also rare. Kaffe et al in 1996 found a radiographic correlation between root resorption and gender, they found that it occurred in 24% of the male patients and only 6% of the female patients [15]. However displacement of the teeth is seen frequently and can lead to malocclusion [16]. With our patient there was no root resorption or tooth displacement. Although considered to be non -neoplastic there are aggressive variants that behave like neoplasms.

These lesions are usually larger in size show more rapid growth and are associated with pain. Paraesthesia, root resorption and perforation of the cortical plates. Our case was diagnosed as a non – aggressive variant as there was no associated pain, paraesthesia, tooth displacement, root resorption or perforation of cortical plates. The radiographic features are not specifically distinctive and change with the size of the lesion. Their presentation can range from well circumscribed small apical lesions that are unilocular and radiolucent and lack internal bone septa to large destructive multilocular radiolucency's with wispy like bony septae involving a large part of the mandible or maxilla [17]. In a study done by Kaffe et al in 1996 on 80 cases they found that 44% of the lesions were unilocular, 51% were multilocular and 68% of the multilocular lesions were seen in the mandible. 5% were not loculated. They also found that the average size of the unilocular lesions was 4.05 cm and that of the multilocular lesions was 7.38 cm hence establishing a correlation

between the size of the lesion and its locularity [15]. In our case we noticed mixed radiolucent and radio-opaque patches indicating it could have been the early stages of fibrous dysplasia.

Histologically they show a uniform appearance with a gathering of multi-nuclear giant cells over a background of ovoid to spindle shaped mesenchymal cells, fibrohistiocytes, big fibroblasts, and extravasated red blood cells [18]. Evidence shows the giant cells may represent osteoclasts/macrophages and may be aggregated focally in the tissue or present diffused throughout the lesion. Even though giant cells are present in abundance, they are not considered to be the proliferating tumor cells, instead it is the spindle cell stroma that may be the proliferating tumor cells since they persist in culture and stain positive for the proliferating marker. They are osteoid like cells that secrete alkaline phosphatase and support osteoid as well as osteoclast formation [18-21]. The giant cells vary in shape, they maybe small and irregular in shape containing only a few nuclei or maybe large and round containing 30 or more nuclei. Areas of erythrocyte extravasation and hemosiderin deposition are often prominent. In our case also multinucleated giant cells containing few to may nuclei were evident in areas of haemorrhage with an intervening connective tissue showing delicate collagen fibres and blood vessels.

The aggressive variants have a larger surface area occupied by giant cells [22] and this can be used as one of the criteria to ascertain whether the clinical behaviour of the lesion is aggressive or non-aggressive. It is important to be able to distinguish amongst the various lesions containing giant cells such as Brown's tumor of hyperparathyroidism, from which central giant cell tumor is morphologically indistinguishable but could be ruled out in our case as the serum calcium, phosphorous and alkaline phosphatase levels, which are usually elevated in brown's tumor, were normal. Giant cell tumor was also ruled out as these generally occur in 4th and 5th decade of life, are rarely seen in younger age groups [23], erode the cortex and histologically even though they contain giant cells the number of nuclei in them is usually more than 50. Aneurysmal bone cyst is very similar histologically to CGCG but the difference is it shows the presence of blood filled cystic spaces separated by fibrous septa and also a cartilage like matrix called as blue bone, infrequently seen in other giant cell containing lesions [24,25]. Odontogenic myxomas may also present radiographically as poorly defined or well circumscribed radiolucent defects which may be unilocular or multilocular but it shows a tennis racquet appearance which is not seen in case of CGCG.

An array of treatments is available for these lesions. Surgical curettage with or without peripheral ostectomy is the conventional management and continues to be the most frequently applied therapy. Even then a recurrence rate of 15 to 20% is quoted. Margins of the lesion may be thermally sterilized with a laser or cryoprobes and for aggressive lesions radicle surgery and en-bloc resection may be required. Recurrence is higher in patients with aggressive signs and symptoms. Chuong et al reported a recurrence rate of 72% in aggressive lesions [16]. Extensive surgery though indicated for aggressive lesions may cause loss of teeth and tooth germs, paraesthesia of inferior alveolar nerve hence it is questionable if such extensive treatment is required for a benign lesion like CGCG. However as the etiology of the lesion has not been fully understood, several alternative medical treatments that have been promising in delivering successful results have been advocated over the years.

As these lesions histologically resembles those of sarcoid the same treatment as that given for sarcoid may work for giant cell granuloma also. Based on this rationale intralesional steroid injections are given. This was first described by Jackoway et al in 1988 [26]. The protocol suggested is intralesional injection of steroid into the lesion once every week for six weeks. The mechanism is not fully understood but it is hypothesized that corticosteroids on one hand stimulate the proliferation and differentiation of osteoclast precursors but on the other inhibit lacunar resorption by mature osteoclasts isolated from giant cell tumor of the bone [27]. Hence corticosteroids inhibit bone resorption [28]. But the fact that they may cause resorption is also contradictory.

Subcutaneous injections of 100 units of Calcitonin daily, first advocated by Professor Malcom Harris in 1993 [29] have also been used. As giant cell lesions histologically resemble brown tumor of hyperparathyroidism it was thought that parathormone like hormone could be the cause for this lesion. This hormone still has not been identified nevertheless Calcitonin has been used with variable success as it causes an increased influx of calcium into the bones and acts antagonistically to parathyroid hormone. The lesion has to be monitored radiographically, but may not show resolution till six to nine months of treatment, which is continued up to 24 months to achieve maximum resolution. Once this has been reached, further treatment is stopped.

It is also assumed that these lesions may have a vascular origin, although this has not been proved yet, subcutaneous interferon alpha has been used as it has anti angiogenic effects. When used as the sole method of therapy for aggressive lesions it has shown to diminish the rapid growth of the lesion and even reduce the size but it is probably necessary to apply additional surgery to eliminate the lesion. Its use is limited due to side effects such as headaches and flu like illness [30]. Imatinib, a protein tyrosine kinase inhibitor used to treat chronic myeloid leukemia and gastrointestinal stromal

tumours, is shown to act as an effective anti-osteolytic agent and hence could be useful in the treatment of skeletal diseases involving excessive osteoclastic activity such as CGCG [31]

4. Conclusion

The etiology of these lesions remains uncertain and as they differ in their clinical and radiographic presentations, their only similarity being the histologic presence of multinucleated giant cells and to base the diagnosis only on these criteria could be misleading as was seen in our case. We must be able to differentiate between the various sub-types that fall under the term giant cell lesions as the treatment plan would alter significantly with each sub type, hence the surgical plan cannot be based solely on a simple biopsy. Errors that could be encountered with a biopsy could be due to inadequacy of specimen sample or improper sectioning. Also in case of large masses not all the sections taken for staining would show evidence of cells specific to the lesion thereby once again misleading the diagnosis. If we could identify the specific molecular markers for each sub-type it may help to understand the nature of these lesions better, subsequently helping to establish a target pharmacological and surgical approach.

Compliance with ethical standards

Acknowledgments

NA

Disclosure of conflict of interest

None

Statement of informed consent

Informed consent was obtained from all individual participants included in the study

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