Case Report

Novel regimen of combined intralesional triamcinolone and salmon calcitonin nasal spray to treat a large central giant cell granuloma

ABSTRACT

About 10% benign tumors of the jaw are known to be central giant cell granulomas (CGCGs) affecting mandible more than maxilla. They are more commonly seen among young females, mean age range being 10–25 years. The aggressive variants of CGCG require surgical intervention, leaving colossal disfiguring defects. This being the reason for many nonsurgical alternative therapies as calcitonin injections and nasal spray, intralesional steroid injections and subcutaneous interferon injections advocated for its management. Although the exact success rate of using these nonsurgical therapies are not fully known, they provide the advantage of being conservative in nature, as majority of the patients are young adults. This lack of accurate regimen is due to paucity of randomized control trials and systematic reviews addressing the topic. This manuscript attempts to present a novel regimen protocol which was followed for a case of CGCG, right mandible on a 22-year-old female patient, for a period of 1.5 years and trailed by a follow-up of 2 years.

Keywords: Central giant cell granuloma, combination therapy regimen, intralesional corticosteroid, nonsurgical therapy, salmon calcitonin

INTRODUCTION

The World Health Organization defines central giant cell granulomas (CGCGs) as "an intraosseous lesion consisting of cellular fibrous tissue containing multiple foci of hemorrhage, aggregations of multinucleated giant cells (MNGCs), and occasionally, trabeculae of woven bone."[1] Though more common in mandible, CGCGs are also known to originate in extra-gnathic bones, primarily in the craniofacial region, small and long bones of the hands and feet. It occurs more commonly in females than males, in a 2:1 ratio affecting those <30 years of age. It is more dominant in the anterior than posterior jaw, time and again crossing the midline.[2] Jaffe in 1953 separated these pseudo-tumors of the jaw from other lesions when he termed them as "giant cell reparative granulomas." At the time, they were believed to originate exclusively in the jaws and were thought to be linked to the presence of teeth in some manner, though they were not considered to be an odontogenic lesion. Another school of thought projected them as lesion originating from the giant cells which may have derived from the odontoclasts, causing resorption of the primary dentition, explaining why they are seen in a certain age group and involve only the dentate part of the jaws.[3]

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The most common symptom associated with these lesions is the presence of a painless, slowly emerging, growth in the jaw; peripherally, a bluish brown aspect can be observed. Sensory deficits are rarely associated with them. Clinically, malocclusion can be seen due to frequent displacement of the dentition. Radiologically, it is a diverse entity ranging from a trivial unilocular lesion to a huge multilocular lesion with displaced tooth germs also associated with occasional root resorption and cortical perforation. Multiple lesions are rare and are frequently linked with a syndrome like (neurofibromatosis type 1 or Noonan syndrome) or with cherubism.[4]

The management of CGCG predominantly varies between surgery, ranging from simple surgical curettage to radical resection. High recurrence rates have been reported (as great as 72%) after conservative surgeries like simple curettage. Surgical resections have been the mainstay and the go to technique which have resulted in low recurrence rates. Lesion size and area of involvement usually affects the postsurgical outcome and is associated with vast degrees of morbidity and esthetic compromise. Though radical surgeries can be effective, they usually lead to inevitable loss of dentition and jaw structure, leading to functional derangements like difficulty in chewing, swallowing, and presence of paresthesias. Reconstruction of these large composite defects can be a challenging task with not so ideal esthetic outcomes.

Literature search reveals many conservative regimens including administration of systemic calcitonin, injection of subcutaneous interferons, osteoprotegerin, human mononuclear antibody to receptor activator for nuclear factor ligand (AMG 162), imatinib, and systemic and intralesional corticosteroids. Reports of radiotherapy use are sparse and their success in its management have always been frowned upon.[1]

Though many successfully treated cases have been reported in literature previously using conservative options, to the best of our knowledge, none of them ever used a combination therapy of intralesional corticosteroids with simultaneous administration of salmon calcitonin nasal spray. We also propose a successful treatment protocol using this combination with a disease-free follow-up of 2 years. We are also attempting to put forward a brief outline of the various complications which were evident during the course of this regimen.

CASE REPORT

A 22-year-old female, mother of a 2-month-old child, presented to the Department of Oral and Maxillofacial Surgery, Saraswati Dental College, Lucknow, with a complaint of slow growing, asymptomatic swelling present on the right posterior aspect of the lower jaw with obliteration of buccal vestibule extending from distal aspect 44 to mesial aspect of 48 tooth number, extraorally a diffuse swelling of approx. 4 cm × 4 cm size with bony hard consistency was noted involving the submandibular fossa, lower cheek, and extending below the right ear lobule [Figure 1a and b]. Full complement of the teeth was present except missing 47 and 16 tooth. Cortical expansion was present on buccal, lingual, and lower border of the mandible.

Radiographically the lesion was well defined, multilocular and radiolucent involving the right-side body of mandible with buccal and lingual cortical expansion and multiple areas of perforations [Figure 2a and b].

Aspiration was negative, parathormone and alkaline phosphate levels were within normal limit. An incisional biopsy was performed which confirmed the diagnosis to be CGCG.

Initially a consensus for surgical resection was made but owing to the extremely poor economic condition of the family and young age of the patient, it was decided to go ahead with a conservative nonsurgical therapy. A preplanned medical regimen was made after going through the literature.

Our regimen

1. Triamcinolone acetonide injectable suspension (Kenalog®-40) 1 ml diluted with 1.5 ml of (2%) lidocaine with (1:200,000) epinephrine and 1.5 ml normal saline (0.9%) injected within the lesion weekly once for 6 weeks repeated every 3 months and was continued for 3 such cycles over the period of 9 months
2. Salmon calcitonin nasal spray 200 IU per actuation once daily for 18 months (1.5 years) repeated every day in alternate nostrils.

The patient's family was quite compliant and cooperative and reported every week on the same day for the intralesion injection. To ensure that she takes her nasal spray everyday, a compliance chart was made and given to her husband which he ticked everyday once his wife took the nasal spray. To ensure further compliance, the department called her every second day as a reminder.

On follow-up, a computed tomography scan was performed before starting every cycle of intra lesion injections [Figures 3 and 4]. The lesion started to resolve after 3 months and was seen to be fully resolved at the end of 18 months [Figure 5a]. We have followed up the patient for 2 years after that and she remains disease free. The patient is not very concerned about her esthetics therefore no cosmetic shaving of the bone is performed [Figure 6].

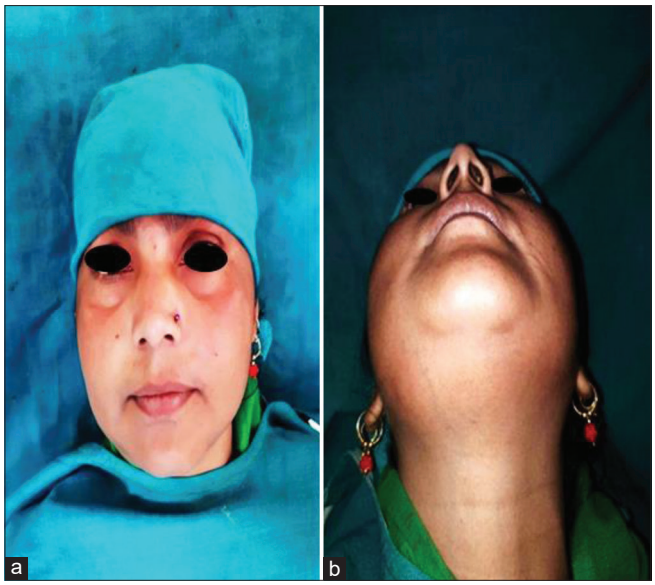

Figure 1: Showing pre-op clinical images. (a) Frontal profile of patient showing facial asymmetry and no pigmentation. (b) Worms eye view showing diffuse swelling on the right submandibular region

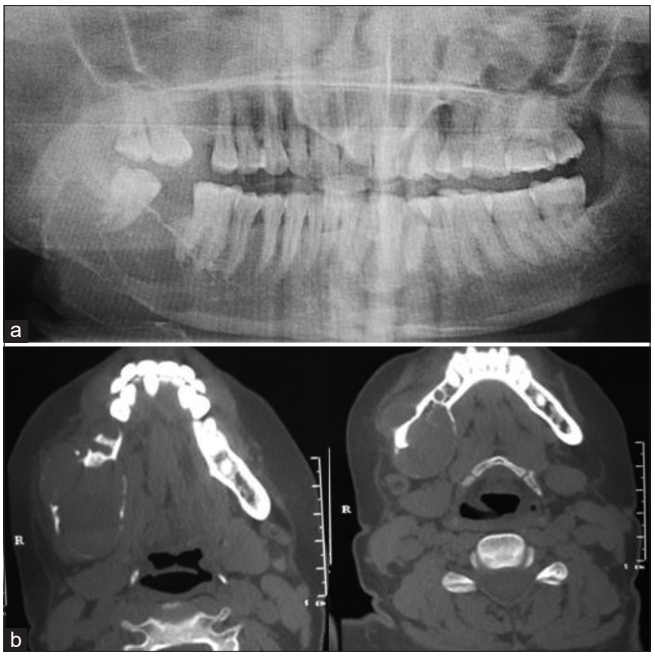

Figure 2: Preoperative radiographic images. (a) Orthopantomograph showing multilocular lesion involving right body and angle region of mandible. (b) Computed tomography images (axial cuts) showing cortical perforations on buccal and lingual side

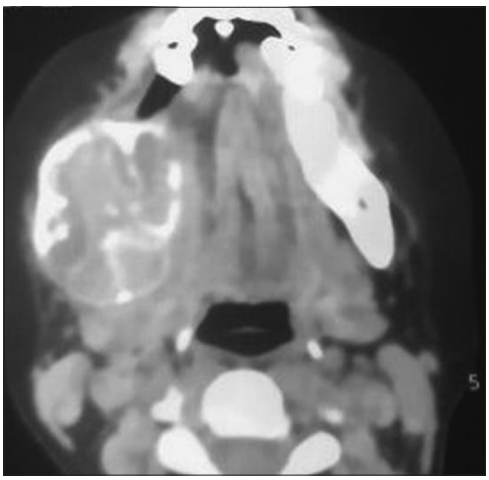

Figure 3: Computed tomography images (axial cut) at the start of 2nd cycle of intralesional injections showing increased peripheral bone formation with flecks of calcifications within the lesion

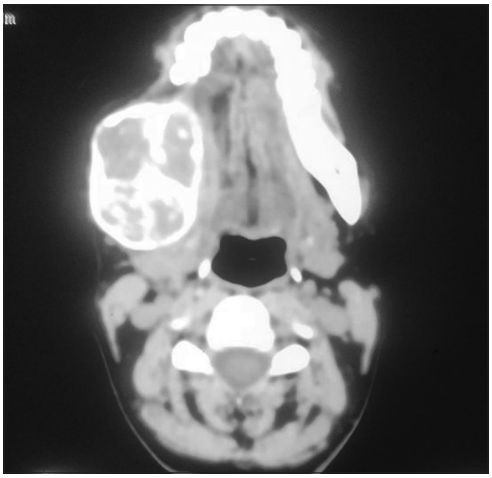

Figure 4: Computed tomography images (axial cut) at the start of 3rd cycle of intralesional injections showing complete peripheral bone formation with thick bony septae within the lesion

Some of the side effects and complications which we noted and complained by the patient during this 1.5-year-long regimen were as follows:

- Increased pain was complained by the patient (after every injection into the lesion) for few days
- Increased hair growth was clearly evident (hirsuitism) [Figure 5b]
- Skin changes were seen (dryness, facial pigmentation) [Figure 5c]
- Visible weight gain and cushinoid appearance
- Nose symptoms such as dryness and crusting and two episodes of nasal bleeding
- Occasional upset stomach
- Nausea, decrease of appetite
- Regular complain of headache, sleep problems (insomnia).

All these complications were managed symptomatically as and when required.

DISCUSSION

Majorly CGCG consists of a cellular fibroblastic stroma with plump spindle-shaped cells and MNGCs where spindle-shaped cells are considered as the main proliferating

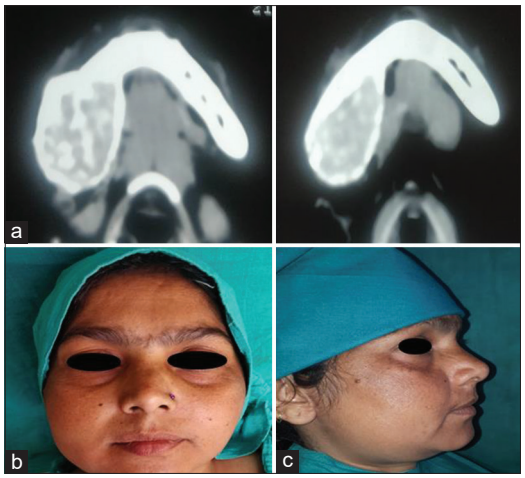

Figure 5: Follow-up after 18 months since the start of therapy. (a) Computed tomography images (axial cuts) showing complete resolution of lesion. (b) Increased facial hair growth as complained by the patient. (c) Visible increase in facial pigmentation

cells of the tumor. Though largely the etiology remains unknown, it has been hypothesized that some non-genetic event is responsible for transforming these cells into tumor cells. The cytokines released by them causes the circulating monocytes to become osteoclast like MNGCs.[5] These osteoclasts thus cause resorption of the surrounding bone leading to progression of the lesion. CGCG has always been considered a pseudo-tumor (Nevill *et al.*) whereas Pogrel[6] thought it to be a reparative lesion thus making medical interventions kindle a self-healing process. Jacoway *et al*. were the first to use intralesional corticosteroids for management of CGCG. And put forward a protocol described by Kurtz *et al*.,[7] which used a dosage of 2 ml of solution per 2 cm^2 of radiological size of the lesion, injected weekly at multiple sites within the lesion for at least a period of 6 weeks. Corticosteroids are believed to reduce bone resorption within the lesion by inhibiting the production of lysozomal proteases, and causing apoptosis of the giant cells. Thus, minimizing the progression of the disease.[8] This is in contradiction to the belief that target cells though being the MNGCs are actually not the tumor proliferating cells thus validating the statement made by Pogrel. Previous literature search has revealed that 65% of lesions treated by corticosteroids have completely resolved and 35% recurred or did not respond which was attributed to the fact that certain population osteoclasts lack the cell membrane receptors of corticosteroids.[9]

Calcitonin produced by the C cells of thyroid gland works antagonistically to parathyroid hormone as it causes an increased influx of calcium into the bones. And its use in the management of CGCG is based on an immuno-histochemical study demonstrating the presence of osteoclast like giant cells.[10] These cells express calcitonin receptors[11] and are

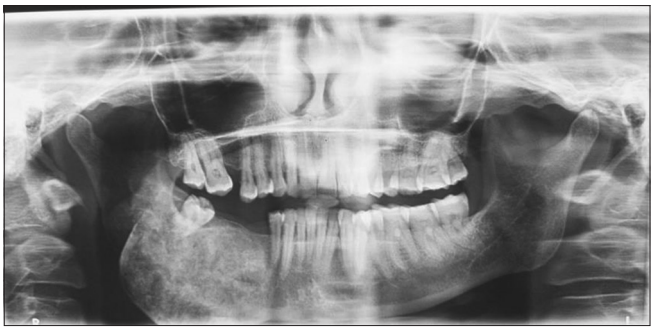

Figure 6: Orthopantomograph at follow-up of 2 years 10 months showing complete resolution of the lesion

expected to be inhibited by the presence of calcitonin hormone. Harris *et al*.[12] were the first to report the use of synthetic human calcitonin in the management of CGCG. Its successful use and complete remission has also been demonstrated by other authors like de Lange *et al*. 1999 in 12–15 months, Pogrel 1999 in 19–21 months, Dominguez *et al*. 2004 in 12–19 months. Hence, after a thorough literature research, we came to a consensus that the minimum time period for which calcitonin should be administered is 18 months and can be increased as per the size and remission status of the lesion. In our case, we saw a complete remission after 18 months of continuous therapy with salmon calcitonin nasal spray with a dosage of 200 IU per actuation. Currently, only salmon calcitonin is available commercially; the effect of salmon calcitonin is stronger than the effect of human synthetic calcitonin.[4]

CGCG has always been considered a controversial entity and its exact nature largely contested. They are known to respond to medical interventions despite not being targeted towards the tumor progression cells. Due to lack of controlled studies in literature, it is difficult to come up with a conclusive regimen and the various interventions used have largely been hit and trial. Also, there are very few reports of combination therapies being used and targeted for its management. Preferring a treatment over the other should be based on the risk of side effects, cost of treatment, and availability.[1]

CONCLUSION

In this report, we are merely putting forward a consensus on the regimen that can be followed when using a combination therapy of intralesional corticosteroids and salmon calcitonin nasal spray. We believe that a minimum of three cycles of injection triamcinolone 40 mg weekly for 6 weeks repeated every 3 months should be used as although the lesion starts to show improvement after the first cycle, multilocular nature (formation of bony septae) [Figure 4] does not allow the solution to reach every aspect of the lesion. Therefore,

follow-up diagnostic radiographs before the start of each cycle helps to identify areas of lesion to be injected and the direction of needle insertion. We also believe that salmon calcitonin though being more potent than human calcitonin, should be used for a minimum of 18 months due to the slow action of the drug.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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