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ABSTRACT

Introduction: Orofacial granulomatosis (OFG) is a lesser known disease entity, which presents a confounding spectrum of oral manifestations. It is a non-specific granulomatous inflammation caused by an elusive etiopathogenesis. It usually manifests as persistent and/or recurrent upper and/or lower labial enlargement. The clinical features, both extra-oral and intra-oral, are highly variable and at times, insidious. This disease can be both cosmetically and functionally debilitating.
Case Report: This is a report of an unusual case of orofacial granulomatosis which presented as a persistent severe generalized gingival enlargement in a nine-year-old child. There was no evidence of an underlying allergic or systemic cause. Surgical intervention (i.e., gingivectomy) showed no alleviation of symptoms.
Conclusion: Making a prompt and precise diagnosis of orofacial granulomatosis is often challenging, however complete remission is possible with targeted therapy.

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Dhupar Anita[1], Carvalho Karla M.[2], Spadigam Anita[3], Syed Shaheen[4]

Affiliations: [1]MDS, Professor; Department of Oral and Maxillofacial Pathology, Goa Dental College & Hospital, Bambolim, Goa, India; [2]MDS, Lecturer; Department of Oral and Maxillofacial Pathology, Goa Dental College & Hospital, Bambolim, Goa, India; [3]MDS, Professor and Head; Department of Oral and Maxillofacial Pathology, Goa Dental College & Hospital, Bambolim, Goa, India; [4]MDS, Assistant Professor; Department of Oral and Maxillofacial Pathology, Goa Dental College & Hospital, Bambolim, Goa, India.

Corresponding Author: Dr. Karla Maria Carvalho, Liberty Apartments, Flat No: 202, Feira Alta, Mapusa, Goa, India, 403507; Email: karlamariac@gmail.com

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INTRODUCTION

A granuloma is a distinct histological entity, formed as an immunological response to a chronic non-degradable product of active hypersensitivity [1]. Orofacial granulomatosis (OFG) is a term used to describe granulomatous lesions affecting the orofacial tissues in the absence of provable systemic granulomatous conditions such as sarcoidosis or Crohn's disease [2]. Till date, some authors consider OFG to be a non-specific disease because of several overlapping clinical and histopathological features with other granulomatous conditions, in particular with Crohn's disease [3–6]. The unknown etiology of both orofacial granulomatosis and Crohn's disease further challenges efforts in categorizing the disease entities [2, 7].

The diagnostic dilemma tackles the question: Is OFG an early oral manifestation of Crohn's disease, or is it a distinct disease entity? This is a rare case of OFG in a child which presented solely as persistent gingival enlargement.

CASE REPORT

A nine-year-old girl, presented with a chief complaint of progressive gingival enlargement in both upper and lower jaws which she had noticed since the past 1 year. She was extremely conscious about her smile as she was being teased in school. She underwent two gingivectomy surgeries, at two different occasions, for both, the upper and lower dental arches, in the span of 1 year. A positive history of bleeding on brushing, difficulty in mastication due to impingement of enlarged gingiva was elicited. There was no relevant systemic history noted. Diet history showed that the patient favored cocoa based foods and showed a daily intake of the same.

Detailed oral examination revealed gross enlargement of upper and lower labial gingiva. The marginal, papillary and interdental gingiva of both jaws (i.e. labial and palatal/lingual) appeared erythematous, with a soft consistency and a granular surface texture (Figure 1). She had dental restorations in her lower right and left first permanent molar and lower right second permanent molar, which were a month old (Figure 2). Periodontal pockets were absent. Permanent canines in both arches were seen in the erupting stage (Figure 3). Examination of other oral sites which included lips, tongue and faucial pillars showed no signs of any abnormalities.

The preliminary investigations included a complete hemogram, bleeding time, clotting time, erythrocyte sedimentation rate (ESR), fasting blood sugar levels, tests for tuberculosis (i.e., sputum for acid fast bacilli, chest radiograph and Mantoux test), renal and liver function tests. Except for a mild eosinophilia (10%) observed on the hemogram, all other results were normal.

An incisional biopsy of the enlarged gingiva, revealed granulomas, multinucleated giant cells, dystrophic calcifications, sheets of plasma cells and lymphocytes .The lymphocytes had an atypical morphology (Hematoxylin and Eosin stain, periodic acid Schiff stain and van Gieson stain). No evidence of a deep fungal infection was seen (Figure 4).

A pediatric consultation followed. Splenomegaly was detected by a positive Castell's sign. A bone marrow aspirate was requested which was negative for malignancy. A normal abdominal ultrasound and no contributory gastrointestinal symptoms ruled out Crohn's disease. Normal C-reactive protein (CRP), angiotensin converting enzyme (ACE) levels and chest radiograph, disproved a diagnosis of sarcoidosis and Wegener's granulomatosis.

Additional tests, such as, LE cell and antinuclear antibody (ANA) proved negative for a frank autoimmune dysfunction. To further support a diagnosis of exclusion, an immunohistochemical panel workup was done. CD 3 and CD 20 (in small lymphocytes), CD 68 (highlighted multiple granulomas) and CD 138 (in plasma cells) markers were found to be positive. A diagnosis of idiopathic orofacial granulomatosis was made (Figure 5).

The patient was advised to strictly eliminate cocoa from her diet. Systemic corticosteroid (i.e., prednisolone) regime with regular follow-up appointments was prescribed which showed immediate positive results

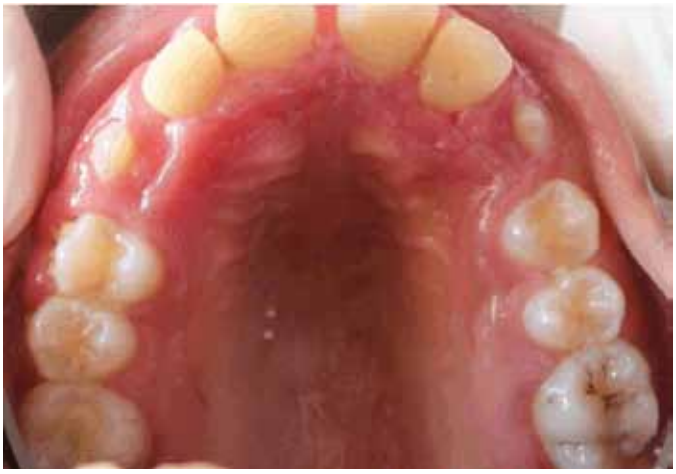

Figure 1: Erythematous enlarged labial gingiva seen in upper and lower dental arches.

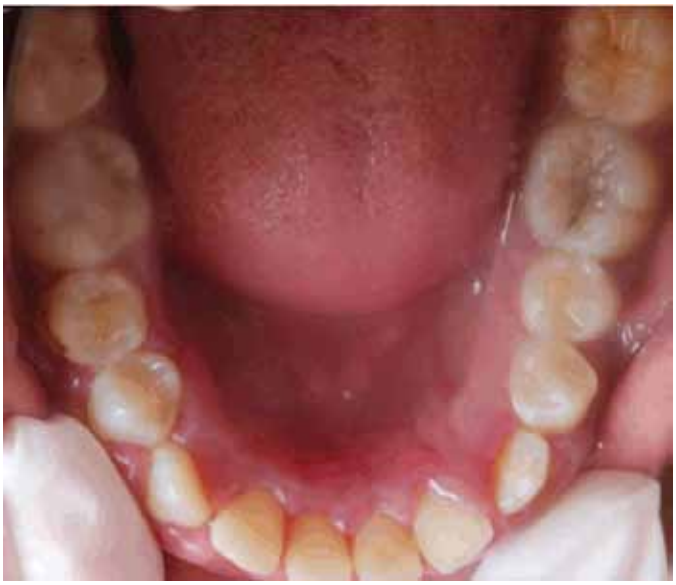

Figure 2: Dental restoration seen in lower right and left permanent molars. Gingiva is enlarged and inflamed in the anterior (incisor) segment of the lingual gingiva.

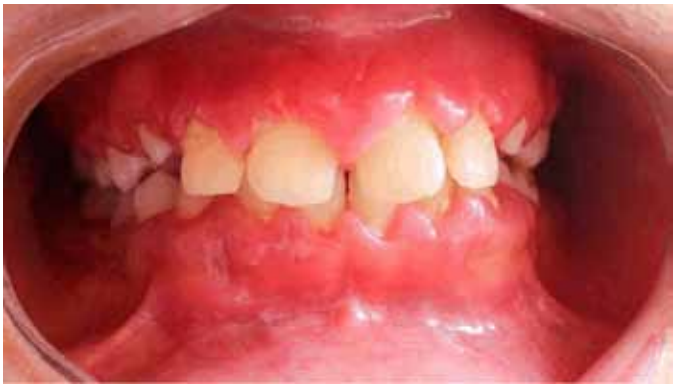

Figure 3: Erupting permanent canines in upper dental arch and mild palatal gingival enlargement seen.

within the first week of treatment. A minimal dose of 1 mg/kg/day for two weeks, followed by gradual taper for four weeks was prescribed. Simultaneous prophylaxis using co-trimoxazole was also initiated. Follow-up after three months showed an almost healthy and well contoured gingiva, in both upper and lower jaw arches (Figure 6A–B).

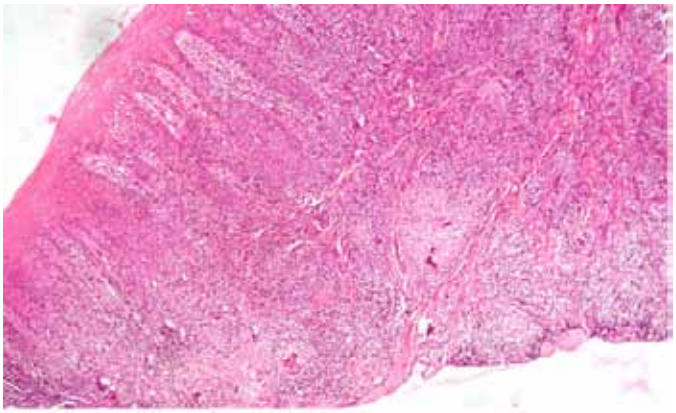

Figure 4: Biopsy section from upper right posterior labial Gingiva showing non-caseating granuloma formation (H&E stain, x100).

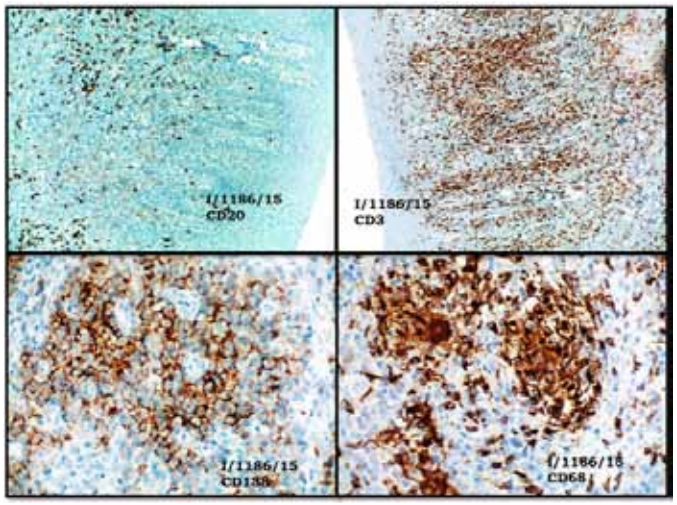

Figure 5: Immunohistochemical panel showing positive CD 3, CD 20, CD 68 and CD 138 markers (Magnifications: x100).

Figure 6: Three month post-treatment follow-up showing complete regression of lesion (A) Labial gingiva, (B) Palatal.

DISCUSSION

An increase incidence of orofacial granulomatosis is seen globally, particularly in the pediatric age group [6]. However, despite advanced diagnostic techniques, it is considered to be a diagnosis of exclusion [3, 5, 8, 9]. Recent evidence has shown OFG to be an immunologically induced granulomatous disorder [1].

The most common clinical symptom is persistent labial enlargement which is non-pitting, and non-tender, involving upper and/ or lower lips [6]. The other oral and facial manifestations include oral ulcers, fissured tongue, mucosal tags, gingival enlargement, facial nerve palsy, facial swelling and cervical lymphadenopathy [2, 8]. Our case mimicked some of the cases studied by Endo et al. and Gale et al., in that; gingival hyperplasia was the sole manifestation [10].

There are a number of theories, both genetic and immunological, which attempt to explain the course and clinical outcome of this disease [6]. Current research in OFG supports an immunologic or allergen triggering factor as the chief aetiological basis [10].

It is on the basis of the above mentioned research, that the association between Crohn's disease (CD) and OFG is still being debated. It is hypothesized that OFG is a subtype of CD since 20–50% of patients with OFG have concurrent intestinal manifestations and 6.4% have a positive family history of CD. In our case, it is also relevant to note that a known 40.4% of children affected with OFG fall victims to CD during their lifetime [9]. Andrew Zbar et al. in their recent review stated that a frank labial enlargement, exfoliative angular stomatitis and oral ulcerations clinically distinguish OFG from CD. These authors have advocated a complete evaluation for underlying systemic conditions in those OFG cases showing gingival enlargement alone [6]. In our case, suspected leukemia induced gingival hyperplasia was refuted by a normal bone marrow aspirate.

The immunohistochemical evaluation showing a predominance of CD3+ T cells support a diagnosis of OFG without systemic Crohn's disease. It has also been suggested that IgE-expressing B cells (CD20+) in the submucosa of OFG patients play an important role in the pathogenesis and provide a link to type IV hypersensitivity, particularly in cases of OFG without CD in young individuals [10]. This may be reflected by the high expression of CD138+ plasma cells. Since cocoa is a proven triggering factor in a number of OFG cases, the daily intake of cocoa based food by the patient could be contributory to these immunological findings. The multinucleated giant cells of macrophage origin were highlighted by the CD68+ marker. Besides a complete absence of gastrointestinal manifestations, the above mentioned immunological findings do not support a diagnosis of Crohn's disease for this case. Therefore a colonoscopy was not advised [6].

A biopsy showing non-caseating granuloma formation is critical for differentiating OFG from all other

granulomatous disease [6]. The differential diagnosis, include Tuberculosis, Sarcoidosis, allergic reaction, deep fungal infection, Wegener's granulomatosis and a leukemic infiltrate, which were proved negative by the investigative protocol followed [3]. "Idiopathic orofacial granulomatosis" is thus a suitable diagnosis for this case of OFG, given that it satisfies the criteria given by Tilakaratne et al. [6].

The treatment for OFG, given its unknown aetiology is non-specific and subjective [2]. In this case, the elimination of a potential allergen (i.e. cocoa), was advocated before prescribing any medication, however, there was no change in the clinical picture [2, 8]. Corticosteroids with or without the use of an immunosuppressant, is considered to be the first line and the mainstay of the recommended treatment regime [2, 3, 8].

Intra-lesional corticosteroid therapy though ideal in this patient, was not possible as she could not afford it. Systemic corticosteroid therapy in a growing child can result in several adverse effects which include growth retardation [6]. However, the dose given to this patient was minimum and advocated for a short duration of time. A strict follow-up schedule at regular intervals ensures a complete systemic review of the patient during the course of the treatment.

Newer drugs which have proved to be effective are thalidomide, tacrolimus, infliximab and adalimomab (i.e. recombinant monoclonal antibiotic against TNF-K). These drugs can be included in therapy based on the clinical course and severity of the disease [8].

Recurrences and subsequent systemic granulomatous manifestations are relatively common in cases of OFG restricted to the oral cavity. A mandatory regular clinical review for these idiopathic OFG cases is therefore strongly advised. A multidisciplinary approach involving a team made up of a dental surgeon, gastroenterologist and pediatrician (when applicable) is essential to provide timely and targeted care [6]. The clinical, histopathological and immunological findings of this case, separate OFG from Crohn's disease. This case thus supports the hypothesis of these two disease entities being independent sub categories caused by underlying idiopathic immunological dysfunction.

CONCLUSION

It is important to recognize and consider orofacial granulomatosis as a differential diagnosis for idiopathic gingival enlargement cases, with/without other allied oral manifestations. The growing incidence of Crohn's disease, particularly in the pediatric and adolescent age group, warrants an exhaustive investigative analysis for suspected OFG, so as to deliver early targeted treatment.

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Author Contributions

Dhupar Anita – Conception and design, Acquisition of data, Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published
Carvalho Karla M. – Conception and design, drafting the article, Acquisition of data, Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published
Spadigam Anita – Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published
Syed Shaheen – Acquisition of data, Critical revision of the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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