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Case Report

Orofacial Granulomatosis Presenting as Gingival Enlargement – Report of Three Cases

Savithri V*, Janardhanan M, Suresh R and Aravind T

Department of Oral Pathology & Microbiology, Amrita School of Dentistry, Amrita VishwaVidyapeetham, Amrita University, India

***Corresponding author:** Vindhya Savithri, Department of Oral Pathology & Microbiology, Amrita School of Dentistry, Amrita VishwaVidyapeetham, Amrita University, India

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Abstract

Orofacial Granulomatosis (OFG) is an uncommon disease characterized by non-caseating granulomatous inflammation in the oral and maxillofacial region. They present clinically as labial enlargement, perioral and/or mucosal swelling, angular cheilitis, mucosal tags, vertical fissures of lips, lingua plicata, oral ulcerations and gingival enlargement. The term OFG was introduced by Wiesenfeld in 1985. The diagnosis of OFG is done by the clinical presentation and histological picture and this may be further complicated by the fact that OFG may be the oral manifestation of a systemic condition, such as Crohn's disease, sarcoidosis, or, more rarely, Wegener's granulomatosis. In addition, several conditions, including tuberculosis, leprosy, systemic fungal infections, and foreign body reactions may show granulomatous inflammation on histologic examination. They have to be excluded out by appropriate investigations. They have to be excluded out by appropriate investigations. The exact etiology of OFG is not known. Several processes have been suggested including genetic predisposition, food allergy, and allergy to dental materials, infective and immunological. Here, we are highlighting three cases of OFG which presented as gingival enlargement but with different cause.

Keywords: Orofacial granulomatosis; Gingival enlargement; Non-caseating granuloma

Introduction

The occurrence of granulomas restricted to the orofacial region in the absence of any systemic disease is known as Orofacial Granulomatosis (OFG). These are a group of rather uncommon lesions, the etiology of which is still a matter of debate. The clinical presentation may be varied ranging from labial swellings, ulcers, gingival enlargement, facial palsy and fissured tongue. The histopathologic picture is classically that of a noncaseating granuloma. Granulomatous reactions may develop as a reaction to many factors like infectious organisms, foreign bodies or may be idiopathic. Hence the differential diagnosis of any granulomatous reaction should include foreign body reaction, microbial infections, Melkersson Rosenthal syndrome, Sarcoidosis, Crohn's disease and OFG [1]. The term idiopathic OFG is used to encompass all granulomas occurring in the oral mucosa for which no cause can be found. Wiesenfeld et al introduced the term "Orofacial Granulomatosis" in 1985 [2]. Various factors like heredity, genetic, allergy, microbial and immunological agents have been suggested to be responsible for these lesions [3]. Here we present three cases of OFG which presented as gingival enlargement.

Case Presentations

Case 1

A 50 year old female reported to our department with a gingival swelling of three years duration. On examination, the patient was edentulous and a non-tender, firm, painless swelling was observed on the lower alveolar ridge extending from 43 region to 32 region (Figure 1). The patient was also on antihypertensive therapy. A provisional diagnosis of drug induced enlargement was made. An excisional biopsy was done after routine blood investigations and the specimen sent for histopathological examination. Microscopic

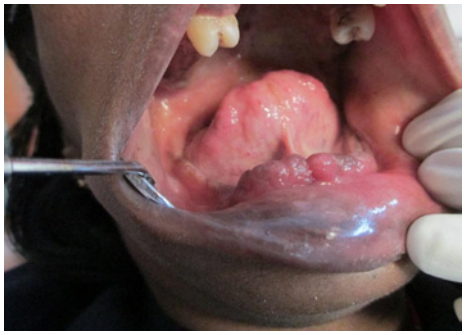

Figure 1: Firm swelling of lower alveolar ridge extending from right canine region to left incisor region.

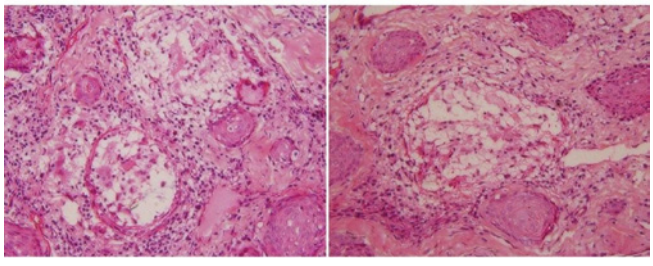

Figure 2: Non-caseating granuloma with multinucleated giant cell and pseudoepitheliomatous islands seen (H&E, 200X).

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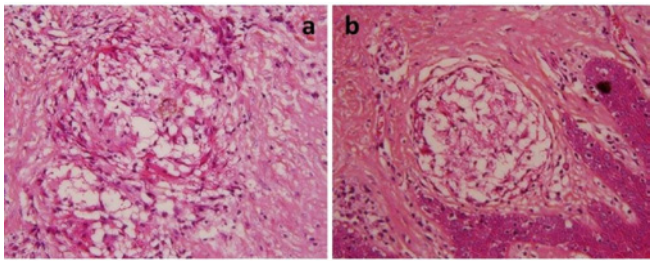

Figure 3: a) Non-caseating granuloma seen (H&E, 200X). **b)** Superficial hyperplastic epithelium with granuloma just beneath (H&E, 100X).

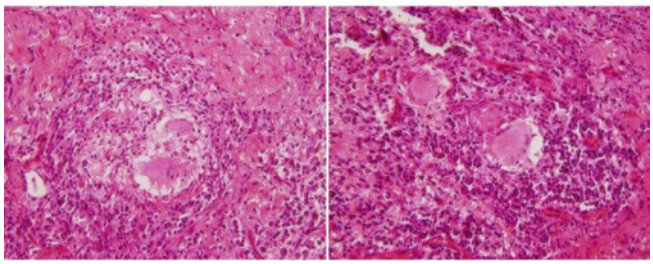

Figure 5: Multiple granulomas with multinucleated giant cells noticed. (H&E, 200X).

examination revealed the presence of non-caseating granulomas with several multinucleated giant cells in the connective tissue stroma with intense inflammatory infiltrate (Figure 2). The surface epithelium was parakeratinized stratified squamous epithelium showing pseudoepitheliomatous hyperplasia at areas. Special stains for the presence of fungal agents and mycobacterium were negative. Serum was tested for ACE enzyme and sarcoidosis was ruled out. Mantoux test for tuberculosis was also negative. Endoscopic examination ruled out the presence of Crohns disease. With the absence of any other systemic disease and any observable cause, we arrived at a diagnosis of idiopathic orofacial granulomatosis.

Case 2

A 24 year old female presented with a complaint of gum swelling in relation to the upper and lower front teeth since six months. Examination showed gingival enlargement involving the attached gingiva extending from 13 to 23 and 43 to 33. The swelling was firm and non-tender. The oral hygiene of the patient was good. The lesion was provisionally diagnosed as idiopathic gingival enlargement and posted for excision. Routine blood examination was done and all values were found to be within normal limits. Microscopic examination of the submitted section showed focal aggregation of chronic inflammatory cells in the connective tissue with the presence of few non-caseating granulomas (Figure 3). Multinucleated giant cells were also observed. Superficial stratified squamous epithelium was hyperplastic and hyperparakeratinized. Special stains like GMS, AFB were done to exclude granulomas due to microbial organisms. Systemic examination and tests were done to rule out Sarcoidosis and Crohn's disease by Lab investigations and endoscopic examination respectively. Mantoux test and chest radiographs did not reveal the presence of any systemic infection. In the absence of any other systemic disease, a diagnosis of orofacial granulomatosis was made. Since the etiopathology of OFG includes allergy to food substances and food additives, a diet chart was prepared to find and eliminate if any food allergens were detected. The patient was found to be allergic to food made with gluten. The patient was advised to go on a gluten free diet.

Case 3

A 13 year old female came to our department with a chief complaint of swelling of the upper and lower gums of two years duration with a slow growth. On examination, gingival enlargement extending from 13 to 23 and 33 to 43 was noted (Figure 4). The lesion was erythematous and soft and could be lifted free. The oral hygiene was good. There was no other relevant medical or dental history. The lesion was provisionally diagnosed as idiopathic gingival hyperplasia. Routine blood investigations were carried out and patient posted for excisional biopsy. Histopathologic examination showed a surface hyperplastic parakeratinized stratified squamous epithelium. Dense inflammatory infiltrate chiefly composed of lymphocytes and plasma cells was seen in the underlying connective tissue stroma. Multiple foci of granulomas consisting of epithelioid cells circumscribed by inflammatory cells were observed. Multinucleated giant cells were seen associated with the granuloma (Figure 5) but caseation was absent. A diagnosis of orofacial granulomatosis was given. Relevant investigations were done to exclude Sarcoidosis and Crohn's disease. Special stains like GMS and AFB were done to rule out fungal infections and Mycobacterial infections. A final diagnosis of idiopathic OFG was made. After six months, the patient reported with a recurrence of the lesion. A second excisional biopsy also showed the same histopathological picture of non-caseating granuloma. A diet chart was prepared to rule out allergic reactions to food substances. This did not yield any result. Microbial agents like Mycobacterium tuberculosis, Saccharomyces cerevisiae and Borreliaburgdorferi have been investigated in various studies on OFG [4]. Hence, PCR analysis of the wax block specimen was done for Mycobacterium and yielded a positive result. After consultation with a physician, the patient was started on anti-tubercular therapy even though there was no other

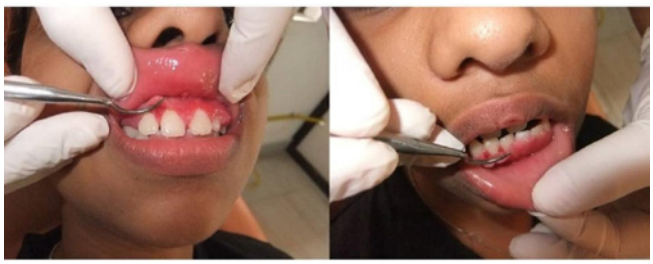

Figure 4: Gingival enlargement in the upper and lower anterior region.

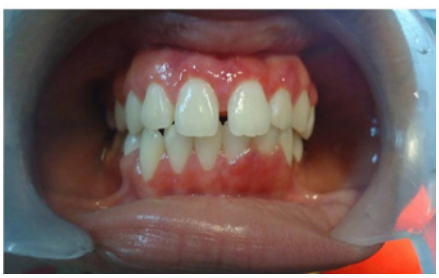

Figure 6: Post anti-tubercular therapy at two months review.

systemic manifestation. The patient showed complete regression of the gingival enlargement after two months of therapy (Figure 6). The course was continued for four more months. The patient has been disease free at the last recall which was three years after the initial visit.

Discussion

Orofacial granulomatosis can occur at any age and has no sex predilection. The clinical presentation is varied and includes labial and mucosal swelling, fissured tongue, lingual plicata, gingival enlargements, frenal tags, ulcers [5,6]. These may be persistent or may be recurrent in nature. Microscopic examination reveals the presence of non-caseating granulomas with or without the presence of multinucleated giant cells. Concomitantly, aggregation of lymphocytes and lymphoedema is seen.

The diagnosis of OFG requires the elimination of Melkersson Rosenthal syndrome, Sarcoidosis, Crohn's disease, tuberculosis, fungal infections and presence of foreign bodies [5]. Routine blood investigations should be done in patients with OFG and does not show any abnormal values. In Melkersson Rosenthal syndrome, a triad of labial swelling, lingual fissuring and facial palsy is seen [7]. Examination of serum angiotensin converting enzyme levels can help to eliminate Sarcoidosis. Endoscopic examination should be done to rule out Crohn's disease especially in patients with gastric complaints. Here, the oral lesions may be a manifestation of a systemic ailment. The use of special stains like Periodic acid Schiff and Grocott's methanamine silver can show the presence of fungal organisms. Chest radiographs, Ziehl-Neelsen staining and Mantoux test should be done to differentiate tuberculosis from OFG. In cases where it is indicated, polarizing microscopic examination of the slides to identify birefrigent material can detect the presence of foreign body material. So essentially, the diagnosis of OFG lies in the elimination of these lesions.

The exact cause of OFG is unknown. Various mechanisms which have been postulated are heredity, allergic reaction, microbial agents and immunological reaction. The substances which have been reported are various food substances and food additives like wheat, dairy products, chocolates, egg, cinnamon, peanut, carnosine, glutamate [3,4]. Hypersensitivity reactions to dental materials like amalgam have also been documented [8,9]. Patch tests for these materials have proved the association between them. Heredity and genetic predisposition though implicated has not been conclusively proved to result in OFG. Few studies have tried to find a link between HLA antigens and OFG [10]. One such study has reported a significant increase in HLA alleles A3, B7 and DR2 in patients with OFG. Studies involving microorganisms have mainly focused on *Mycobacterium tuberculosis*, *M paratuberculosis, Saccharomyces cerevisae* and *Borrelia burgdorferi* [3,11]. Raised levels of serum antibody to *mycobacterial* stress protein have been reported [12]. Also, molecular methods have detected the presence of bacterial RNA. Hence, it suggested that the immune response in OFG patients may be triggered by the presence of these microbial agents or their products.

The histopathological features of OFG suggest that it is a type of delayed hypersensitivity reaction. Clonal expansion of T cells have been demonstrated in one study and it was proposed that chronic antigenic stimulation was responsible for this or alternatively increased secretion of cytokines by these lymphocytes may lead to the granulomatous reaction [13]. The nature of T lymphocytes in OFG has also been studied and restricted use of TCRVβ gene by lesional T cells has been observed [14]. Another study showed the raised levels of IFN-γ which indicates that the immune mechanism is Th1 mediated. This is indicative of cell mediated response which is very much similar to what is observed in Crohn's disease [15].

Clearly all the available data suggests that OFG is a delayed hypersensitivity reaction mediated by some antigen. The stimuli may be food substances, food additives, dental restorative materials or microbial material. All the patients reported here presented with gingival enlargement. The age ranged from 13 to 50 years and they were all females. The microscopic picture was very much similar, exhibiting non-caseating granulomas. The antigenic stimuli in one case appeared to be food substance while in another, microbial in nature. In the third case, the etiology could not be discerned. The importance of diagnosing and thereafter eliminating the etiologic agent if possible is an essential prerequisite to the successful management of OFG.

Conclusion

OFG can present with wide variation in clinical presentation. The cause for OFG is also different in each case highlighting the need for a thorough evaluation. The need to rule out Crohn's disease is also important as their clinical and microscopic picture is similar. The oral manifestations of Crohn's disease may at times precede the intestinal presentation. Hence, when young individuals present with OFG, a regular follow-up after a thorough endoscopic evaluation is recommended. The treatment of OFG depends upon its etiology and maybe at times long term [5]. In cases where the cause remains unknown, intra-lesional steroid injections have proved beneficial. Anti-TNF-α therapy is also an emerging option as treatment especially in cases where the conventional modalities have failed and long term studies on their clinical efficacy is required. Studies have shown that treatment with TNF antagonists like infliximab and adalimumab in refractory cases of OFG have shown good short term response [16].

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