Review Article

Approach to Orofacial Granulomatosis and Review of Literature

A. Javadzadeh [1], A. Pakfetrat [1], F. Falaki [2], S.A. Seyyedi [3]

[1] Associate Professor, Department of Oral Medicine, School of Dentistry, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Assistant Professor, Department of Oral Medicine, School of Dentistry, Mashhad University of Medical Sciences, Mashhad, Iran
[3] Assistant Professor, Department of Oral Medicine, School of Dentistry, Urmia University of Medical Sciences, Urmia, Iran

Abstract

***Background and Aim*:** Orofacial granulomatosis (OFG) comprises a group of diseas es characterized by non-caseating granulomatous inflammation affecting the soft tis sues of the oral and maxillofacial region.
Wiesenfeld introduced the term orofacial granulomatosis in 1985 for the first time.
The precise cause of OFG is unknown; however, some theories have been suggested including allergy, infection and genetic predisposition.
The clinical presentation can be highly variable, making the diagnosis difficult to es tablish.
The aim of this review was to define clinical features, differential diagnosis and treatment protocols of OFG.
***Materials and Methods*:** All English articles from 1950 to 2010 in Pubmed, InterScience, ScienceDirect, Google Scholar databases were searched using the key words**:** orofacial granulomatosis, approach, and treatment. Persian articles were also selected from Iran Medex.
***Results and Conclusion*:** Because of the relatively nonspecific clinical findings asso ciated with a variety of granulomatous diseases, the diagnosis of orofacial granuloma tous often presents a dilemma for the clinician. The most common differential diagno sis includes Crohn's disease, sarcoidosis, and infection. However, a variety of other conditions may be associated with granuloma formation. Often an extensive clinical, microscopic, and laboratory evaluation may be required to reach to definite diagnosis and proper treatment.

***Key Words*:** Orofacial granulomatosis, Approach, Treatment

Corresponding author:
Seyyedi S.A., Associate Professor, Department of Oral Medicine, School of Dentistry, Mashhad University of Medical Sciences, Mashhad, Iran
seyyedia871@mums.ac.ir

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Introduction

Orofacial granulomatosis is an uncommon clinical and pathological condition. This condition is characterized by recurrent and persistent overgrowth of oral and maxillofacial soft tissues specifically lips and the specific characteristic of non-caseous granulomatous inflammation in the absence of detectable systemic diseases such as Crohn's disease or sarcoidosis [1,2]. The etiology of this condition is unclear, therefore its exact treatment and long-term prognosis remains unclear. This article is a comprehensive review of the existing literature about management, clinical manifestations, probable etiological factors, differential diagnoses and treatment steps of orofacial granulomatosis.

History: Orofacial granulomatous lesions unrelated to a certain systemic disease was first reported and described by Melkersson in 1928 as an orofacial swelling accompanied with facial

nerve palsy [3]. Also in 1931, the term–Melkersson- Rosenthal Syndrome was defined by Rosenthal to describe the triad of persistent lip and face swelling, facial nerve palsy and fissured tongue [4]. In 1945, granulomatous lesion of the lip which was characterized by persistent lip swelling (one sign of the Melkersson- Rosenthal Syndrome) was designated by Meischer as Meischer's cheilitis [5]. Oral granulomatoses were described in accordance with some systemic conditions such as tuberculosis in 1951 [6], sarcoidosis in 1985 [1] and Crohn's disease in 2000 [7] But, the term orofacial granulomatosis or oro-facial granulomatosis was first presented as a scientific term by eldWiesenf in 1985 that encompasses Melkersson-Rosenthal Syndrome cheilitis granulomatosis of Meischer.(Fig.1)

Definition: Orofacial granulomatosis is used to describe non-caseous granulomatous inflammation of the oral and facial region with recurrent and persistent labial swellings in the absence of any systemic disease. This lesion can be accompanied by manifestations such as oral ulcers, gingival overgrowths, and cobblestone appearance of buccal mucosa [2]. In addition, formation of granuloma results in obliteration of lymphatic vessels, formation of lymphedema, accumulation of interstitial fluid and finally swelling of the lips and other parts of the face. Orofacial granuloma encompasses conditions previously referred to as Melkersson-Rosenthal Syndrome and Meischer's cheilitis. Orofacial granuloma is an uncommon phenomenon, but diagnosis of new cases is currently increasing [1,2]. Controversies have recently been arisen about the point that whether orofacial granuloma is a distinct clinical entity of a clinical manifestation of certain granulomatous diseases such as Crohn's disease or sarcoidosis [8]. In addition, other disorders such as profound fungal infections, tuberculosis, allergic angioedema, leprosy, Wegener's granuloma, etc. also exist with the same clinical features and are later discussed in differential diagnosis.

Clinical features: Orofacial granuloma I variable in its clinical features, with lips being the most common site of involvement. The frequent manifestation of the lesion is indicated as recurrent labial swellings that have the ability to remain persistent [1-9]. The swelling is non-tender in palpation and is initially soft and non-pitting and later becomes rubbery and firm. Other oral manifestations include: oral ulcers, submucoal swellings, mucosal tags, fissured tongue (lingua plica), angular cheilitis, gingival overgrowth, facial swelling and/or erythema, facial nerve palsy, and cervical lymphadenopathy.

Lip overgrowth (labial swelling)

Labial overgrowth can involve lower or upper lip or both [10]. The swelling is often persistent but can also be recurrent, persisting for several weeks or months [11]. The swelling may cause enlargement or clefting of the lip(s) (median cheilitis) and inflammation and clefting of the corners of the mouth. (angular cheilitis) The labial swelling is non-pitting at pressure and non-tender in palpation and can vary from a soft to a rubbery consistency based on its persistence. The labial mucosa can be erythematous and have a granular appearance [9-12].

Oral ulcers: The three principal types of ulcers can be encountered in orofacial granulomatosis with their most common feature of chronicity. In majority of cases, the ulcers are linear and longitudinal at the depth of the labial or buccal vestibule with exophytic margins with often erythematous borders [13-15].

The second less common type of ulcers are superficial symmetrical aphthous-like ulcers with well circumscribed borders that can appear in any part of oral mucosa.

The other type of ulcers which are associated with orofacial granulomatosis are ulcers in the real sense of the word but are described as *pustules* in anterior part of the gingiva, labial vestibular mucosa or soft palate. They have the same appearance as pyostomatitis vegetans and are not clinically purulent. In fact the term *pustule* is used to describe them due to the appearance of intraepithelial leukocytes in their microscopic

evaluation. Therefore, this term is not clinically relevant [16].

Mucosal swellings: Buccal and labial mucosae may be swollen producing plications with a cobblestone appearance that often involves posterior parts of buccal mucosa [17,18]

Mucosal tags: These painless tags of mucosa which are often produced at the depth of labial or buccal vestibule, retromolar area or around chronic ulcerations are orange or red in color [17,18]

Gingival overgrowths: Overgrowths of the free or attached gingiva can occur locally or diffusely. They can precede facial or mucosal manifestations. The gingiva appears granular with normal pink to red in color and rarely ulcerated [19].

Fissured tongue

The dorsal surface of the tongue may be fissured [18]

Facial nerve palsy: Paralysis of the facial motor nerve may occur rarely in orofacial granulomatosis. This condition can also occur as a result of formation of granuloma within the nerve trunk. Facial nerve palsy accompanied with fissured tongue and labial swelling is indicative of Melkersson-Rosenthal Syndrome [11-20]

Facial erythema and swelling: Recurrent facial swelling may occur especially in genial, zygomatic, peri-orbital and palpebral areas of the face and can be unaccompanied with hypertrophy of the lips in rare occasions. These swellings are non-pitting on pressure and usually are firm in palpation with an erythematous surface [17].

Cervical lymphadenopathy: Patients with severe orofacial granulomatosis can have cervical lymphadenopathy that can be localized or generalized, tender or non-tender with variable sizes and usually a rubbery consistency [21].

Epidemiology: Orofacial granulomatosis has been defined for 90 years as a chronic persistent swelling of the lip(s) with or without facial swelling and/or with oral and gingival mucosal enlargement without any evidence of involvement in other parts of the body. Occasionally involvement of other organs has led to the diagnosis of Crohn's disease, sarcoidosis, etc. Recently, gastrointestinal involvement in non-endemic regions such as southern Europe, Asia and developing countries is increasing. There is a possibility that the prevalence of orofacial granulomatosis which has a slight predilection to appear in women increases and manifest primarily in children and young adults [9,12,19,22].

Etiology and pathogenesis: The exact cause of the orofacial granulomatosis is currently unknown and has been a matter of debate for long. Five etiologic factors can be attributed to the orofacial granulomatosis [23-27]:

Genetic predisposition

Food allergy

Allergy to dental materials

Infection

Immunologic causes

Genetic predisposition: A comprehensive review of the literature does not show evidence to support genetic causes for orofacial granulomatosis. In a study genetic factors contributed in only 23% of cases and in another study in 6 out of 42 cases [28] Also, it was reported in a study that 10% of normal population could have orofacial granulomatosis, an issue that underscored the role of genetic factors [29]. Association of orofacial granulomatosis with HLA has also been studied, but authors failed to establish a strong correlation between HLA and pathogenesis of orofacial granulomatosis [30,31]. Only one study reported a significant interrelationship with HLA and orofacial granulomatosis [31].

Food allergy: Orofacial granulomatosis can occur because of several nutritional additives and materials. Antigenic stimulants that cause delayed hypersensitivity reactions have been associated with more than 60% of patients with orofacial granulomatosis. It has been declared in several studies that different daily nutrients such as chocolates, carmosine, eggs, peanuts, cinnamon, toothpastes, monosodium glutamate, alpha-lactobumin, benzoic acid, and cocoa were initiators of clinical manifestations in patients with orofacial granulomatosis [23-26,33-27]

Allergic reactions to dental materials: In three independent studies concerning allergic reactions to dental materials, one case was reported to be associated with intraoral use of cobalt [38]. The other two cases were related to amalgam restorations. One of these cases was a 61-year-old woman with a unilateral swelling of soft tissue who had a positive patch test result for mercury and the swelling resolved following removal of the restoration [26]. In biopsy specimens from the swellings of all three patients, non-caseous granuloma was observed and the skin test of the last two cases were positive for mercury and the swellings and inflammation were resolved following removal of amalgam restorations [25].

Infection: The inference of microbiological agents in the etiology of orofacial granulomatosis follows documentation of infective agents associated with chronic granulomatous conditions such as Crohn's disease, sarcoidosis and tuberculosis. These studies have focused on Mycobacterium tuberculosis, M.
paratuberculosis, Saccharomyces cerevisiae and Borrelia burgdorferi [27,39-46] One study from Turkey [40] investigated the possible role of mycobacteria in six patients with biopsy proven orofacial granulomatosis. Using molecular techniques, the authors document the presence of M. tuberculosis complex in labial lesions of three out of six patients. Furthermore, elevated levels of serum antibody to mycobacterial protein were reported in seven out of 10 cases with orofacial granulomatosis [41]. Assessment of the presence of serum anti-S. cerevisiae antibodies showed that this is more common in patients with Crohn's disease compared with normal controls [42]. In some studies, a nonspecific IgA increase was seen in patients with OFG indicating salivary involvement [42].

Immunologic: Recently a monoclonal lymphocyte infiltration was diagnosed in OFG lesions indicating that this could occur secondary to a chronic antigenic stimulation. This shows that cytokines produced by lymphocyte colonies can be a reason for granuloma formation within these lesions. Providing evidence for immunologic etiology of OFG (cell-mediated hypersensitivity reaction) is based upon the presence of activated T-helper lymphocytes that cause presentation of IL-2 receptors in these lesions [47]. It was indicated in a research that diversity of the cell surface markers on lesional lymphocytes, as measured through T-cell receptor (TCR) diversity, was not significantly different from that of lymphocytes present in peripheral blood. This supports that OFG is not a disease with a specific antigenic source [48]. Recently, in diseases influenced by hypersensitivity reactions, a group has been described as self-inflammatory diseases in which the hypersensitivity reactions occur without any significant reason or antigen and without any evidence of high auto-antibody titers or specific T cells for a certain antigen. Diseases such as OFG, Crohn's disease, sarcoidosis, and Wegener's granulomatosis has been categorized in this group.

Diagnosis: The diagnosis of OFG is based upon histopathologic evaluation of non-caseating granulomatous inflammation and according to clinical findings of recurrent persistent orofacial swellings irrelevant to microorganisms or foreign objects. Endoscopy, blood chemistry, and radiological evaluations are indicated to differentiate OFG with non-caseating granulomatoses. [1-2-18]

Differential diagnosis: The most common reason for labial swelling is trauma, infection, and angioedema which subside after removing the etiological factors and are transient in nature. A number of diseases can mimic characteristics of OFG specifically persistent lip swelling such as Crohn's disease (fig.4), sarcoidosis, cheilitis granulomatosa, Wegener's granulomatosis, granulomatous infections such as tuberculosis, leprosy and leishmaniasis (fig.2) deep fungal infections, amyloidosis, some soft tissue tumors, minor salivary gland tumors, Sjogren's syndrome, cysts, microcystic adnexal carcinoma and foreign body reactions (fig.3) [18,48-53].

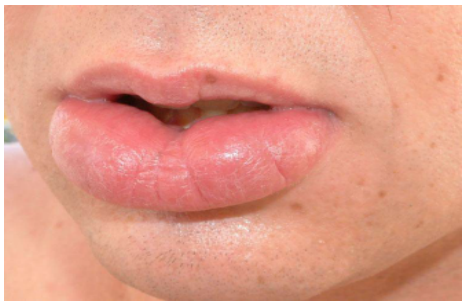

Figure 1: persistent labial swelling in a patient with OFG

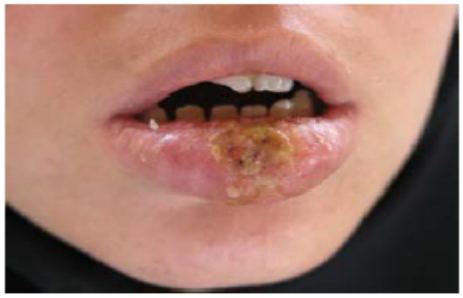

Figure 2: inferior lip swelling with a variable soft and hard consistency and signs of an old ulceration and crust a three-month history in a patient with leishmaniasis.

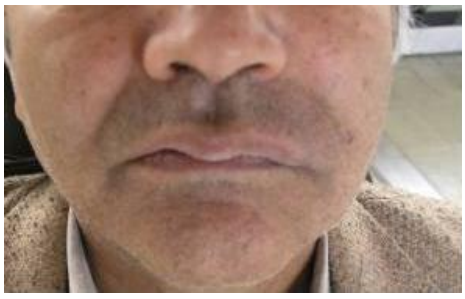

Figure 3: persistent swelling of the lip in a patient with foreign body reaction

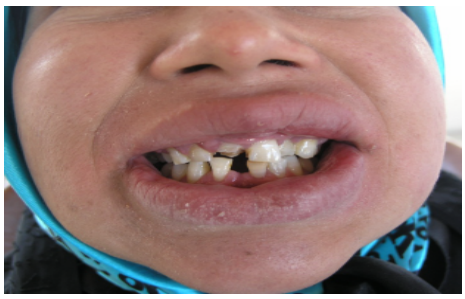

Figure 4: Persistent and diffuse swelling of the lip and gingiva starting four years ago; radiographic evaluation of the chest and serologic evaluation revealed Crohn's disease.

Medical history: Clinical findings as well as laboratory tests, radiographic and endoscopic evaluations are helpful diagnosis of the lesions. Specific staining techniques are used for diagnosis of fungal infections.

In order to diagnose the presence of foreign bodies, polarized light-field microscopy is used. Adjunctive tests should be carried out to rule out systemic involvement. For instance, chest X-rays must be taken in sarcoidosis in which pulmonary lymphadenopathy is a major involvement in addition with evaluation of elevated serum levels of angiotensin-converting enzyme and CRP [54]. Also, chest radiography and skin tests are helpful in differentiating tuberculosis and OFG [18,55]. Useful evaluations for differentiation of OFG and Crohn's disease include ESR, CBC, serum folic acid, iron, vitamin B12, as well as gastrointestinal evaluation, endoscopy of empty intestine and biopsy [56,57].

Crohn's disease is an intestinal inflammatory disease characterized by granulomatous inflammation of the gastrointestinal tract. It is more common in whites and young adult individuals. Clinical features of Crohn's disease include recurrent abdominal cramps and chronic diarrhea followed by secondary symptoms of malabsorption and marked weight loss. Symptoms including erythema nodosum, otitis, migratory joint pains, chronic inflammation of the lips, cobblestone mucosal hypertrophy, and linear ulcers may also occur before, after or during occurrence of GI symptoms [58]. (fig.4) Dermatologically, when sterile cutaneous granulomatous lesions occur irrelevant to GI tract the term metastatic Crohn's disease is used which can be applied for oral lesions as well. Dermatologically, when sterile cutaneous granulomatous lesions occur irrelevant to GI tract the term metastatic Crohn's disease is used which can be applied for oral lesions as well. Differential diagnosis and diagnostic methods of OFG are shown in table 1.

Treatment: Spontaneous remission of OFG is rare [17]. Definitive treatment of the disease remains to be elucidated cause of its unknown etiology and the current approach is based upon symptomatic treatments [59] In case mild signs

Table 1: Differential diagnoses and head and neck manifestations of orofacial swellings

Diseases	Head and neck manifestations	Diagnostic remedies
OFG	Recurrent persistent lip swellings, deep linear oral lesions, mucosal swellings with cobblestone appearance, gingival overgrowth, cervical lymphadenopathy, facial nerve palsy, facial swellings, fissured tongue, etc.	Normal blood tests, lack of GI involvement, normal chest x-ray, negative PPD test, negative C1INH, non-caseating inflammation, elevated IgG level, increased serum ACE, increased CRP, negative staining for microorganisms, negative results for polarized lght-field microscopy
Crohn's disease	Aphthous-like lesions, mucosal overgrowth with cobblestone appearance, small mucosal postules, deep linear ulcers	GI symptoms, abdominal radiography, endoscopy, colonoscopy, blood evaluations, decreased vitamin B12, decreased ferritin, increased CRP, anemia,
Sarcoidosis	Solitary or multiple gingival nodules, xerostomia, osseous involvement, salivary glands, facial nerve palsy	Clinical symptoms, chest radiograph, bilateral pulmonary lymphadenopathy, increased serum ACE, increased ESR, elevated CPR, anemia, increased serum and urinary calcium, eosinophilia, negative microbial culture, negative staining, Kveim test
Wegener's granulomatosis	(Strawberry gingivitis Palatal ulcer, facial nerve palsy	Clinical symptoms, vasculitis, necrotizing granulomatosis, chest and sinus radiography, kidney function test, P- ANCA, ESR, C-ANCA
angioedema	Pitting edema of the lips, tongue, pharynx and face, history of hypersensitivity, perioral and periorbital involvement	Increased IgE, normal hematologic tests, normal GI conditions, normal chest X-ray, C1INH evaluation, relatively rapid onset of swelling, lack of granuloma
Tuberculosis	Cervical lymphadenitis, chronic painless oral ulcers, involvement of the tongue and gingiva	Caseous granuloma, Ziel-Neelson staining, PAS-test, positive PPD, chest X-ray
Leprosy	Cutaneous involvement, nasal and palatal cavitation, facial nerve palsy	Granulomatous inflammation, PAS, Acid-Fast staining
Cheilitis glandularis	Labial overgrowth with ulceration, mild chronic or acute inflammation of the minor labial salivary glands	Normal hematologic and serologic tests, normal chest x-ray, lack of GI involvement
Foreign body	Labial and mucosal swellings with foreign bodies, remains chronic	Non-caseating granulomatosis, foreign bodiss can be viualized under polarized light-field microscopy
Deep fungal infections	Painful gingival ulcers, gray-colored diffusely swollen peripheral mucosa, cervical lymphadenopathy, erythema nodosum	Microorganism culture, antibody titer, PAS specific staining

and symptoms occur, treatment may not be always necessary. The patient's diet should be evaluated to remove allergens [33,60]. Corticosteroids are effective in reducing facial swelling and preventing recurrence. Dose and route of administration is related to the symptoms and swelling. Patients with mild swelling are treated locally [61]. Local swellings of the lips are often treated with intralesional injection of triamcinolone. Such injection can be carried out several times but should be limited in children [62].

Increased concentrations of the drug have been proposed with the advantage of diminished volume of injection and producing maintenance for

the healing process. Side effects of local treatments are limited to skin atrophy and hypopigmentation. Use of systemic corticosteroids are limited due to chronicity and recurrence of the disease and long-term nature of complications. [18,62]. Clofazimine is indicated to be effective in treating OFG. In a survey, treatment with 100mg clofazimine four times weekly for 3-11 months resulted in complete healing in the majority of patients. This was also effective in patients with severe cheilitis granulomatosis. [61,63]. Low dose thalidomide has been shown to be effective, but is not administered for pregnant women and requires regular checkup. However, such administration showed favorable results in patients who failed to respond favorably to previous treatments [64]. Topical tacrolimus ointment is effective in treating oral lesions of Crohn's disease in children whose intralesional injection are problematic [65]. Infliximab is an anti-TNF-α antibiotic which is highly effective in patients with colitis and Crohn's disease. [66,67]. Adalimomab is a recombinant monoclonal antibiotic against TNF-α with effects similar to Infliximab and is influential in treatment of Crohn's disease [68]. Other treatments presented in literature include hydroxychloroquine, methotrexate, azathioprine, metronidazole, minocycline, dapsone, and danazol [18,61, 69,70]. Esthetic lip surgery are suggested by some clinicians when lips are quite enlarged and malformed and the disease do not respond well to local corticosteroids [71].

Discussion

OFG is an uncommon disease with unknown etiology and pathogenesis. Etiologic factors such as nutrients, dental materials, microbiologic and genetic factors are suggested by some authors. Contrary to the abundance of diseases presenting manifestations similar to those of OFG such as persistent swelling of the lip(s) and other parts of the face, some features such as swelling characteristics, systemic involvement, antronasal involvement, and neurologic features can lead to the diagnosis of OFG. A swelling with verrucous, popular, plaque-like, or ulcerative skin accompanied by inflammation of salivary gland orifices differentiates OFG with cheilitis glandularis, Wegener's granulomatosis, sarcoidosis and some deep fungal infections. Lack of systemic involvement such as fever, weight loss, fatigue, malaise involvement of other parts of the body such as GI and respiratory system can rule out the possibility of sarcoidosis, Crohn's disease and Wegener's granulomatosis. In addition, lack of evidence related to antral and nasal involvement (such as obstruction, discharge, hemorrhage, and depression of nasal bridge) will suffice to rule out Wegener's granulomatosis and leprosy. Swelling of the lip(s) occur secondary to the swelling and involvement of the nose and its surrounding skin due to the spread of infiltrative lesions. This finding is not in favor of diagnosing mucocutaneous leishmaniasis, leprosy and deep fungal infections. In case manifestations are accompanied by facial nerve palsy the term Melkersson-Rosenthal syndrome is used. Although it can occur in Wegener's granulomatosis, sarcoidosis, tuberculosis and leishmaniasis, lack of naso-antral symptoms or involvement of other body parts can help in diagnosis of OFG. It cannot be overemphasized that diagnosing OFG is not an end. OFG patients should be monitored for their systemic gastrointestinal and respiratory symptoms which sometimes necessitates changes in treatment planning. It should be taken into consideration that lack of additional symptoms strengthens the likelihood of OFG.

Conclusion

According to the fact that clinical features of OFG are nonspecific in nature, correct diagnosis and treatment planning requires a comprehensive clinical, laboratory and microscopic evaluation in most cases.

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