

Approach to Orofacial Granulomatosis and Review of Literature

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Abstract

Background and Aim: Orofacial granulomatosis (OFG) comprises a group of diseases characterized by non-caseating granulomatous inflammation affecting the soft tissues of the oral and maxillofacial region.

Wiesefeld 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 establish.

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 associated with a variety of granulomatous diseases, the diagnosis of orofacial granulomatous often presents a dilemma for the clinician. The most common differential diagnosis 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

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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-lactalbumin, 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 le-

sions. 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 light-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 vidualized 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]. Adalimumab 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, antranasal 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.

References

- 1-Wiesenfeld D, Ferguson MM, Mitchell DN, MacDonald DG, Scully C, Cochran K, et al. Oro-facial granulomatosis – A clinical and pathological analysis. *Q J Med.* 1985 Jan;54(213):101-13.
- 2-Challacombe SJ. Oro-facial granulomatosis and oral crohns disease: Are they specific diseases and do they predict systemic Crohns disease? *Oral Dis.* 1997 Sep;3(3):127-9.
- 3-Alioğlu Z, Caylan R, Adanir M, Ozmenoğlu M..Melkersson-Rosenthal syndrome: report of three cases. *Neurol Sci.* 2000 Feb;21(1):57-60.
- 4-Rosenthal C.Klinisch-erbblologischer Beitrag zur Kon- stitutions-Pathologie: Gemeinsames Aif-treten von (rezidivie- render familiärer) Fazialis-lahmung, angingeuotschem Gesichtsoedem und Lingua plicata in Arthrismusfamilien. *Ztschr Neurol Psych* 1931; 131:475–501.
- 5-Kuske H. Macrocheilia granulomatosa with re-current right facial nerve paralysis (Melkersson-Rosenthal synd.); cheilitis granulomatosa; macro-cheilia with chronic recurrent erysipelas of the up-per lip. *Dermatologica.* 1955 Mar-May; 110 (3-5):392-6.
- 6-Shengold MA, Sheingold H.Oral tuberculo-sis.Oral Surg Oral Med Oral Pathol. 1951 Feb;4 (2):239 .50.
- 7-Crohn BB, Ginsburg L, Oppenheimer GD. Regional ileitis 1932: A pathologic and clinical entity. *Mt Sinai J Med.* 2000 May;67(3):263-8.
- 8-Sanderson J, Nunes C, Escudier M,et al. Oro-facial granulomatosis: Crohn's disease or a new inflammatory bowel disease? *Inflamm Bowel Dis.* 2005 Sep;11(9):840-6.
- 9-Mignogna MD, Fedele S, Lo RL, Lo ML. The multiform and variable patterns of onset of orofa-cial granulomatosis *J Oral Pathol Med.* 2003 Apr;32(4):200-5.
- 10-Odukoya O. Orofacial granulomatosis: report of two Nigerian cases. *J Trop Med Hyg.* 1994 Dec; 97(6):362-6.
- 11-Rogers RS III. Melkersson-Rosenthal syndrome and orofacial granulomatosis. *Dermatol Clin.* 1996 Apr;14(2):371-9.
- 12-Sainsbury CP, Dodge JA, Walker DM, Aldred MJ. Orofacial granulomatosis in childhood. *Br Dent J.* 1987 Sep 5; 163(5):154-7.
- 13-Clayden AM, Bleys CM, Jones SF, Savage NW, Aldred MJ. Orofacial granulomatosis: A di-agnostic problem for the unw-ary and a manage-ment dilemma. *Aust Dent J.* 1997 Aug; 42(4):228-32.
- 14-Eveson JW. Granulomatous disorders of the oral mucosa. *Semin Diagn Pathol.* 1996 May; 13 (2):118-27.
- 15-Leão JC, Hodgson T, Scully C, Porter S. Re-view article: orofacial granulomatosis. *Aliment Pharmacol Ther.* 2004 Nov 15;20(10):1019-27
- 16-Daley T, Armstrong J. Oral manifestations of gastrointestinal diseases. *Can J Gastroenterol.* 2007 Apr;21(4):241-4.
- 17-Sciubba JJ, Said-AI-Naief N. Orofacial granu-lomatosis: Presentation, pathology and manage-ment of 13 cases *J Oral Pathol Med.* 2003 Nov; 32(10):576-85.
- 18-Nevil B, Damm D, Allen C, Bouquot J.Oral and Maxillofacial Pathology. 3rd. ed. Philaadelphia: W.B. Saunders; 2009;341-345.
- 19-Mignogna MD, Fedele S, Lo RL, Lo ML. Orofacial granulo-matosis with gingival onset. *J Clin Periodontol.* 2001 Jul;28(7):692-6.
- 20-Gottwald W. Melkersson-Rosenthal syndrome: 2. Diagnosis, differential diagnosis, course, prog-nosis, neuropathology, therapy. *Fortschr Med.* 1981 Mar 12;99(10):326-30.
- 21-James J, Ferguson MM.Orofacial granulomatosis presenting clinically as tuberculosis of cervical lymph nodes. *Br Dent J.* 1986 Jul 5; 161(1):17-9.
- 22-Loftus EV Jr. Clinical epidemiology of in-flammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology.* 2004 May;126(6):1504-17.
- 23-Oliver AJ, Rich AM, Reade PC, Varigos GA, Radden BG. Monosodium glutamate-related orofa-cial granulomatosis. Review and case report. *Oral Surg Oral Med Oral Pathol.* 1991 May; 71 (5):560-4.
- 24-Taibjee SM, Prais L, Foulds IS. Orofacial gra-nulomatosis worsened by chocolate: results of

- patch testing to ingredients of Cadbury's chocolate. *Br J Dermatol.* 2004 Mar;150(3):595.
- 25-Lazarov A, Kidron D, Tulchinsky Z, Minkow B. Contact orofacial granulomatosis caused by delayed hypersensitivity to gold and mercury. *J Am Acad Dermatol.* 2003 Dec;49(6):1117-20.
- 26-Guttman-Yassky E, Weltfriend S, Bergman R. Resolution of orofacial granulomatosis with amalgam removal. *J Eur Acad Dermatol Venereol.* 2003 May;17(3):344-7.
- 27-Riggio MP, Gibson J, Lennon A, Wray D, MacDonald DG. Search for Mycobacterium paratuberculosis DNA in orofacial granulomatosis and oral Crohn's disease tissue by polymerase chain reaction. *Gut.* 1997 Nov; 41(5):646-50.
- 28-Meisel-Stosiek M, Hornstein OP, Stosiek N. Family study on Melkersson-Rosenthal syndrome. Some hereditary aspects of the disease and review of literature. *Acta Derm Venereol.* 1990; 70 (3):221-6.
- 29-Van der Waal RIF, Schulten EAJM, Van de Scheur MR, et al. Cheilitis granulomatosa. *J Eur Acad Dermatol Venereol.* 2001 Nov;15(6):519-23.
- 30-Satsangi J, Jewell DP, Rosenberg WMC, Bell JI. Genetics of inflammatory bowel disease. *Gut.* 1994 May; 35(5):696-700.
- 31-Gibson J, Wray D. Human leucocyte antigen typing in orofacial granulomatosis. *Br J Dermatol.* 2000 Nov; 143(5):1119-21.
- 32-James J, Patton DW, Lews CJ, Kirkwood MM, Ferguson MM. Orofacial granulomatosis and clinical atopy. *J Oral Med.* 1986 Jan-Mar; 41 (1):29-30.
- 33-Armstrong DK, Biagioni P, Lamey PJ, Burrows D. Contact hypersensitivity in patients with orofacial granulomatosis. *Am J Contact Dermat.* 1997 Mar;8(1):35-8.
- 34-Sweatman MC, Tasker R, Warner JO, Ferguson MM, Mitchell DN. Orofacial granulomatosis. Response to elemental diet and provocation by food additives. *Clin Allergy.* 1986 Jul;16(4):331-8.
- 35-Sciubba J, Said - Al - Naief N. Orofacial granulomatosis: Presentation, pathology and management of 13 cases. *J Oral Pathol Med.* 2003 Nov;32(10):576-85.
- 36-Patton DW, Ferguson MM, Forsyth A, James J. Orofacial granulomatosis; a possible allergic bias. *Br J Oral Maxillofac Surg.* 1985 Aug; 23(4): 235-42.
- 37-Levy FS, Bircher AJ, Buchner SA. Delayed-type hypersensitivity to cow's milk protein in Melkersson-Rosenthal syndrome: Coincidence or pathogenic role? *Dermatology* 1996;192(2):99-102.
- 38-Pryce DW, King CM. Orofacial granulomatosis associated with delayed hypersensitivity to cobalt. *Clin Exp Dermatol.* 1990 Sep;15(5):384-6.
- 39-Gibson J, Wray D, Bagg J. Oral staphylococcal mucositis: A new clinical entity in orofacial granulomatosis and Crohn's disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000 Feb;89(2):171-6.
- 40-Apaydin R, Bahadir S, Kakklikkaya N, Bilen N, Bayramguler D. Possible role of Mycobacterium tuberculosis complex in Melkersson Rosenthal syndrome demonstrated with Gen-probe amplified Mycobacterium tuberculosis direct test. *Australas J Dermatol.* 2004 May; 45(2):94-9.
- 41-Ivanyl L, Kirby A, Zakrzewska JM. Antibodies to Mycobacterial stress protein in patients with orofacial granulomatosis. *J Oral Pathol Med.* 1993 Aug;22(7):320-2.
- 42-Savage NW, Barnard K, Shirlaw PJ, Rahman D, Mistry M, Escudier MP, et al. Serum and salivary IgA antibody responses to Saccharomyces cerevisiae, Candida albicans and Streptococcus mutans in orofacial granulomatosis and Crohn's disease. *Clin Exp Immunol.* 2004 Mar;135(3):483-9.
- 43-Muellegger RR, Weger W, Zochling N, et al. Granulomatous cheilitis and Borrelia burgdorferi: polymerase chain reaction and serologic studies in a retrospective case series of 12 patients. *Arch Dermatol.* 2000 Dec; 136(12):1502-6.
- 44-Liu HG. Spirochetes in the cheilitis granulomatosa and sarcoidosis. *Zhonghua Yi Xue Za Zhi.* 1993 Mar;73(3):142-4,189-90.
- 45-Liu HG, Zheng LF, Xiao XZ. Relationship between Melkersson-Rosenthal syndrome and Spiro-

- chetes infection. *Zhonghua Yi Xue Za Zhi*. 1994 Feb;74(2):92-3, 127.
- 46-Liu H, Zheng L, Liu H. Spirochetes. The possible etiological factor of the cheilitis granulomatosa. *Chin Med Sci J*. 2001 Mar; 16(1): 52-5.
- 47-Freysdottir J, Zhang S, Tilakaratne WM, Fortune F. Oral biopsies from patients with orofacial granulomatosis with histology resembling Crohn's disease have a prominent Th1 environment. *Inflamm Bowel Dis*. 2007 Apr; 1(4):439-45.
- 48-Facchetti F, Signorini S, Majorana A, Mangannoni MA, Sapelli P, Imberti L. Non-specific influx of T-cell receptor alpha/beta and gamma/delta lymphocytes in mucosal biopsies from a patient with orofacial granulomatosis. *J Oral Pathol Med*. 2000 Nov;29(10):519-22.
- 49-Bishop RP, Brewster AC, Antonioli DA. Crohn's disease of the mouth. *Gastroenterology*. 1972 Feb;62(2):302-6.
- 50-Li MC, Chou G, Chen JT, Wong YK, Ho WL. Amyloidosis of medium-sized arteries presenting as perioral mass: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003 Apr; 95(4): 463-6.
- 51-Fujimura T, Aiba S, Suetake T, Tagami H. Erythematous swelling of the lip associated with Sjogren's syndrome and mimicking cheilitis granulomatosa. *J Dermatol*. 2001 Jan;28(1):47-9.
- 52-Hodgson TA, Haricharan AK, Barrett AW, Porter SR. Microcystic adnexal carcinoma: an unusual cause of swelling and paraesthesia of the lower lip. *Oral Oncol*. 2003 Feb;39(2):195-8.
- 53-High CL, Houston GD. Recurring anterior facial swelling. *Compend Contin Educ Dent*. 2001 Dec;22(12):1066-8, 1070, 1072.
- 54-Takada K, Ina Y, Noda M, Sato T, Yamamoto M, Morishita M. The clinical course and prognosis of patients with severe, moderate or mild sarcoidosis. *J Clin Epidemiol*. 1993 Apr; 46(4): 359-66.
- 55-Krysl J, Korzeniewska-Kosela M, Muller NL, FitzGerald JM. Radiologic features of pulmonary tuberculosis: an assessment of 188 cases. *Can Assoc Radiol J*. 1994 Apr;45(2):101-7.
- 56-Alien R, Mendelsohn FA, Csicsmann J, Weller RF, Hurley TH, Doyle AE. A clinical evaluation of serum angiotensin converting enzyme in sarcoidosis. *Aust N Z J Med*. 1980 Oct; 10(5):496-501.
- 57-Khan K, Schwarzenberg SJ, Sharp H, Greenwood D, Weisdorf-Schindele S. Role of serology and routine laboratory tests in childhood inflammatory bowel disease. *Inflamm Bowel Dis*. 2002 Sep; 8(5):325-9.
- 58-Dupuy A, Cosnes J, Revuz J, Delchier JC, Gendre JP, Cosnes A. Oral Crohn disease: Clinical characteristics and long-term follow-up of 9 cases. *Arch Dermatol*. 1999 Apr;135(4):439-42.
- 59-Rogers RS III (2000). Granulomatous cheilitis, Melkersson. Rosenthal syndrome, and orofacial granulomatosis. *Arch Dermatol*. 2000 Dec; 136(12):1557-8.
- 60-Reed BE, Barrett AP, Katelaris C, Bilous M. Orofacial sensitivity reactions and the role of dietary components. Case reports. *Aust Dent J*. 1993 Aug;38(4):287-91.
- 61-Van der Waal RL, Schulten EA, Van der Meij EH, Van de Scheur MR, Starink TM, Van der Waal I. Cheilitis granulomatosa: Overview of 13 patients with long-term follow-up-results of management. *Int J Dermatol*. 2002 Apr;41(4):225-9.
- 62-Mignogna MD, Fedele S, Lo Russo L, Adamo D, Satriano RA (2004). Efficacy of small-volume, intralesional, delayed-release triamcinolone injections in orofacial granulomatosis: a pilot study. *Int J Dermatol*. 2002 Apr; 41(4):225-9.
- 63-Sussman GL, Yang WH, Steinberg S. Melkersson-Rosenthal syndrome: clinical, pathologic, and therapeutic considerations. *Ann Allergy*. 1992 Sep;69(3):187-94.
- 64-Hegarty A, Hodgson T, Porter S. Thalidomide for the treatment of recalcitrant oral Crohn's disease and orofacial granulomatosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003 May; 95(5):576-85.
- 65-Casson DH, Eltumi M, Tomlin S, Walker-Smith JA, Murch SH. Topical tacrolimus may be effective in the treatment of oral and perineal Crohn's disease. *Gut*. 2000 Sep;47(3):436-40.
- 66-Mahadevan U, Sandborn WJ. Infliximab for the treatment of orofacial Crohn's disease. *Inflamm Bowel Dis*. 2001 Feb;7(1):38-42.

- 67-Targan SR, Hanauer SB, Van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med*. 1997 Oct 9;337(15):1029-35.
- 68-Gaya DR, Aitken S, Fennell J, Satsangi J, Shand AG. Anti-TNF-alpha therapy for orofacial granulomatosis: Proceed with caution. *Gut*. 2006 Oct;55(10):1524-5.
- 69-Allen CM, Camisa C, Hamzeh S, Stephens L. Cheilitis granulomatosa: Report of six cases and review of the literature. *J Am Acad Dermatol*. 1990 Sep;23(3 Pt 1):444-50.
- 70-Olivier V, Lacour JP, Castanet J, Perrin C, Ortonne JP. Cheilitis granulomatosa in a child. *Arch Pediatr*. 2000 Mar; 7(3):274-7.
- 71-Kauzman A, Quesnel-Mercier A, Lalonde B. Orofacial Granulomatosis: 2 Case Reports and Literature Review. *J Can Dent Assoc*. 2006 May; 72(4):325-9.