

UNVEILING THE CURTAIN ON OROFACIAL GRANULOMATOSIS: AN OVERVIEW

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ABSTRACT

Orofacial granulomatosis is a granulomatous disease of orofacial region, which can occur for a variety of reasons. The clinical features are highly variable and sometimes so insidious that signs and symptoms are not frequently severe to cause alarm. The lips are most commonly involved with persistent & recurrent swelling. The medical history is very important as Crohn's disease and sarcoidosis can present oral manifestation. Other causes like mycobacterial infection, foreign body reaction, fungal infection, and allergy should be excluded with further investigation to establish diagnosis.

INTRODUCTION

Orofacial granulomatosis (OFG) and also termed granulomatous cheilitis, cheilitis granulomatosa, cheilitis granulomatosa and oral granulomatosis, is a condition characterized by persistent enlargement of the soft tissues of the mouth, lips and the area around the mouth on the face. The enlargement does not cause any pain but the best treatment and the prognosis are uncertain. The mechanism of the enlargement is granulomatous inflammation. The term orofacial granulomatosis was proposed by Wiesenfield et al. in 1985 [1]. Focal granulomas may occur anywhere in the oral mucosa or in the subcutaneous tissue of the skin where they present as localized firm mass that are occasionally multinodular. When diagnosis of non caseating granuloma is made

microscopically, the patient should be evaluated for several systemic diseases such as crohn's disease, sarcoidosis, tuberculosis, tooth associated infections, food or contact allergies and the local processes that may be responsible for similar oral lesion has to be ruled out. The precise cause of OFG is unknown [2].

The classic presentation of OFG is a nontender recurrent labial swelling that eventually becomes persistent. This swelling may affect one or both lips (Fig 1), causing lip hypertrophy (macrocheilia). The swelling is initially soft but becomes firmer with time as fibrosis ensues. However, the clinical presentation can be highly variable, making the diagnosis difficult to establish. The recurrent facial swelling may affect the chin, cheeks, periorbital region and eyelids, and in rare cases, it may not be associated with lip hypertrophy. Intraoral involvement may take the form of hypertrophy, erythema or nonspecific erosions involving the gingiva, oral mucosa, or tongue. The diagnostic dilemma may be further complicated by the

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fact that OFG may be the oral manifestation of a systemic condition, such as Crohn's disease, sarcoidosis, or more rarely Wegener's granulomatosis [3]. In addition, several conditions, including tuberculosis, leprosy, systemic fungal infections, and foreign body reactions may show granulomatous inflammation on histologic examination. Therefore, these conditions must be distinguished. The diagnosis of OFG is made by histopathologic identification of noncaseating granulomas. Local and systemic conditions characterized by granulomatous inflammation must be excluded by appropriate clinical and laboratory investigations [4]. Melkersen Rosenthal Syndrome (MRS) is the term used when cheilitis occurs with facial palsy and plicated tongue. MRS is occasionally a manifestation of Crohn's disease or OFG [5]. Chelitis Granulomatosa of Miescher is characterized by swelling restricted to the lips. Miescher cheilitis is generally regarded as a monosymptomatic form of the MRS, although the possibility remains that these may be two separate diseases. According to Neville et al [6], these two entities should not be considered distinct diseases and should both be included in the spectrum of OFG.

In granulomatous cheilitis, normal lip architecture is eventually altered by the presence of lymphoedema and noncaseating granulomas in the lamina propria. The frequency is unknown; the condition is rare. Morbidity depends on whether underlying organic disease, such as Crohn's disease or sarcoidosis, is present. No racial predilection is recognized. No sexual predilection is known. Onset usually occurs in young adult life.

Signs and symptoms may include

Persistent or recurrent enlargement of the lips, causing them to protrude. If recurrent, the interval during which the lips are enlarged may be weeks or months. The enlargement can cause midline fissuring of the lip ("median cheilitis") or angular cheilitis (sores at the corner of the mouth). The swelling is non-pitting and feels soft or rubbery on palpation. The mucous membrane of the lip may be erythematous and granular. One or both lips may be affected. Oral ulceration which may be aphthous like, or be more chronic and deep with raised margins. Alternatively, lesions similar to pyostomatitis vegetans may occur in OFG, but this is uncommon.

"Full width" gingivitis

Gingival enlargement

Fissured tongue

Enlargement of the mucous membrane of the mouth, which may be associated with cobblestoning and mucosal tags. Enlargement of the perioral and periorbital soft tissues. The facial skin may be dry, exfoliative or erythematous.

Cervical lymphadenopathy

Facial palsy [7].

Etiopathogenesis

The exact cause of orofacial granulomatosis is still unknown, although several theories have been suggested including infection, genetic predisposition and allergy. The etiological agents such as food substances, food additives, dental material microbiological agents have been proposed, but its pathogenesis is uncertain. A delayed type of hypersensitivity reaction appears to play a role, but the antigen inducing immunological reaction varies in individuals. The evidence for role of genetic predisposition to disease is sparse [8]. Tilakaratne et al [9] propose the term idiopathic orofacial granulomatosis as better term for cases restricted to oral region without any identifiable known granulomatous disease and diagnosis should not be changed until patient develops systemic manifestation of specific granulomatous condition. The etiopathogenesis of OFG remains elusive, although minor immunological changes have been reported in a number of patients. Patient with OFG may have a history of atopy occasionally associations with food intolerance, e.g. monosodium glutamate and also allergy to food preservatives and chocolate have been considered. As the removal of amalgam resulted in reduction of swelling of buccal mucosa and lips of OFG in isolated cases, delayed hypersensitivity to dental materials has occasionally been implicated. Microbiological agents and genetic predisposition factors are considered as etiological factors. Furthermore, attempts have been made to analyze the relationship between T cell and cytokines in the pathogenesis [10]

Epidemiology

OFG is uncommon, but the incidence is increasing. The disease usually presents in adolescence or young adulthood. It may occur in either sex, but males are slightly more commonly affected [11].

Histopathological findings

Histologically, the lesion is usually characterized by non-caseating granulomas consisting of lymphocytes and epithelioid histiocytes. In the superficial lamina propria and perivascular aggregation of dilated vessels histiocytes and plasma cells are seen [12].

DISCUSSION

The differential diagnosis of a persistent labial swelling includes angioedema (idiopathic or hereditary), sarcoidosis, Crohn's disease, OFG, chelitis granulomatosa and some specific infections (tuberculosis, leprosy and deep fungal infections) (Fig 2). Amyloidosis, certain soft-tissue tumours, minor salivary gland tumour, and Ascher's syndrome may also be included in the differential diagnosis (Table 1). All of these conditions must be taken into account during the investigation of a patient with persistent lip swelling. The medical history and the results of the clinical examination help to direct the investigation.



The biopsy represents an important step in establishing the correct diagnosis, especially if angioedema is not a favoured possibility [13]. Upon microscopic identification of granulomatous inflammation, special stains are used to rule out deep fungal infections (Periodic acid Schiff (PAS), PAS with diastase, Grocott) or specific bacterial infections (Ziehl-Neelsen, Gram). Polarized light microscopy is used to identify foreign bodies in the tissues. Ancillary tests are ordered to assess whether a systemic disease is responsible for the granulomatous inflammation [14]. Such tests might include chest radiography and assessment of serum levels of angiotensin-converting enzyme for sarcoidosis; complete blood count, erythrocyte sedimentation rate and serum levels of folic acid, iron and vitamin B12 for Crohn's disease; and tuberculin skin test and chest radiography for tuberculosis. Gastrointestinal assessment is essential, especially in the presence of signs of anemia and intestinal malabsorption and symptoms suggestive of Crohn's disease.

If the initial investigation does not confirm the diagnosis, a second assessment should be carried out, especially if the gastrointestinal signs and symptoms persist. The diagnosis of OFG is therefore a diagnosis of exclusion and is based on appropriate clinical and pathologic correlation [15].

Management

The management of OFG is difficult, particularly in the absence of an etiologic factor. Treatment objectives are to improve the patient's clinical appearance and comfort. Although rare, spontaneous remission is possible.

The elimination of odontogenic infections may reduce the swelling in certain patients. First-line treatment involves the use of local or systemic corticosteroids or both. Intralesional injections of triamcinolone 10 mg/mL is often used in the treatment of OFG. Recently, higher concentrations of the drug (40 mg/mL) have been suggested. The higher concentration offers the advantages of reducing the volume of fluid injected, the administration of a higher dose and the maintenance of remission. The side effects of local treatment are limited to skin atrophy and hypopigmentation. The use of systemic corticosteroid therapy in treating OFG is limited because of the chronic, recurrent nature of the disease and the side effects associated with long-term use of these drugs. Results are often immediate with either local or systemic corticosteroid therapy. However, relapses are common, and long-term treatment may be required [16]. Other therapeutic measures have been reported in the literature, including hydroxychloroquine, methotrexate, clofazimine, metronidazole, minocycline, anti-tumour necrosis factor α antagonists (e.g. infliximab) alone or in combination with oral prednisone, thalidomide, dapsone, and danazol. Cheiloplasty is used by some clinicians, especially in cases complicated by major lip deformation or inadequate response to local corticosteroid therapy.

Surgery may be necessary to manage the complications of the disease and is also used in cases that do not respond to medical treatment. Dietary restriction of a particular suspected or proven antigen may be involved in the management of OFG, such as cinnamon or benzoate-free diets [17].

Table 1. Differential diagnosis of orofacial granulomatosis

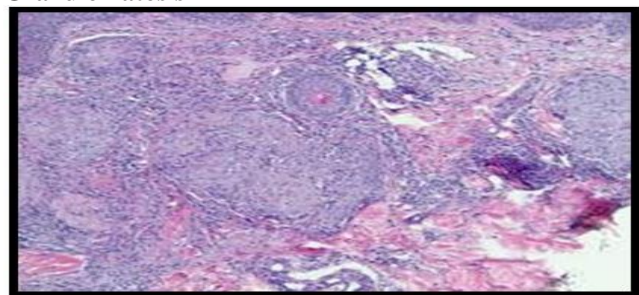
| Disease | Features different to OFG |
|------------------------------|---|
| Crohn's disease | Have illeal and/or rectal disease |
| Sarcoidosis | Pulmonary, cutaneous, lacrimal, salivary, neurological, skeletal features |
| Allergic angioedema | Nonpitting oedema of lips, tongue, pharynx, face. History of atopic disease |
| Miescher's cheilitis | Labial enlargement, similar histopathology to OFG |
| Melkerson-Rosenthal syndrome | Labial enlargement, fissuring of tongue, facial nerve palsy variant of OFG |
| Cheilitis glandularis | Labial enlargement with ulcers. Mild acute and chronic inflammation (without granuloma) within minor salivary glands of lip |
| Tuberculosis | Rarely lips. Usually contain caseating granuloma |

Fig 1. Clinical picture revealing swollen mandibular lip



Courtesy:www.dermopedia.org

Fig 2. Depicting Histopathological feature of Orofacial Granulomatosis



Courtesy:www.dermopedia.org

CONCLUSION

Differential diagnosis of swollen lips and swelling of other orofacial structures includes OFG. The diagnosis is made by excluding numerous other disease entities, e.g., Crohn's disease and sarcoidosis, requiring broad diagnostic workup. Orofacial granulomatosis should be diagnosed early, as later in the course of the disease fibrous tissue

may proliferate, thus narrowing treatment options to surgery. Once OFG is diagnosed, successful and predictable treatment results may be achieved by repeated use of small doses of concentrated slow release corticosteroid intralesional injections, which should be regarded as first-line treatment.

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