

Orofacial Granulomatosis – Is Diagnosis Enough?

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Case Report

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Abstract: The descriptive term ‘Orofacial Granulomatosis’ has been used for any granulomatous process of unknown etiology involving the oral cavity, which on lesional biopsy shows lymphodema and non-caseating granulomas. The diagnosis is based on exclusion of possible systemic diseases and conditions that are capable of producing similar histopathologic and clinical features. Orofacial granulomatosis can be a distinct clinical disorder or can be an initial presentation of an underlying systemic disease such as Crohn’s disease or spectrum of related disorders that may go undetected for a long period of time.

Keywords: OFG, Granulomas, Crohn’s disease.

INTRODUCTION

Orofacial Granulomatosis (OFG) may be defined as “a group of related conditions characterized by non-necrotizing granulomatous inflammation of the oral and maxillofacial region that presents clinically as labial enlargement, perioral and/or mucosal swelling, oral ulcerations and gingivitis.” The diagnosis is based on exclusion of possible systemic diseases and conditions that are capable of producing similar histopathologic and clinical features [1]. Though it is strongly associated with Crohn’s disease, other conditions include chronic facial swelling such as Melkersson-Rosenthal syndrome, Meischer’s cheilitis, hypersensitivity reactions, acquired and hereditary C1 INH-related angiodema, sarcoidosis, tuberculosis, leprosy, deep fungal infections, Anderson- Fabry’s disease and Ascher’s syndrome [2].

Etiology

The aetiopathogenesis of OFG remains elusive, although there are minor immunological changes detectable in a number of patients. Patients with OFG may have a history of atopy, intolerance to food additives e.g. Mono-sodium glutamate, food preservatives and chocolate, delayed hypersensitivity to dental materials, infection by *Mycobacterium paratuberculosis* etc. Its precise aetiopathogenesis is yet to be elucidated. There is a slight female predominance [3].

The condition was first described by Hubschmann in 1894 and after various studies, re-introduced by Weisenfeld *et al.*, in 1985. The primary aim of the researchers was to encompass, into a single entity, all those patients whose clinicopathological features resembled Crohn’s disease, but who did not have the characteristic gastrointestinal findings of the inflammatory bowel disease [1, 4].

Nowadays, the term OFG includes a group of disorders showing chronic, non-caseating granulomatous lesions involving the perioral tissues of the face and the oral mucosa [4].

The mechanism of enlargement is granulomatous inflammation that usually does not cause any pain. Persistent or recurrent enlargement of lips causes them to protrude and evert. If recurrent, the interval during which lips are enlarged may be weeks or months.

The pharmacological treatment of OFG is not based on rational protocol, but on an escalation of therapeutic strategies based on clinical findings [5]. We hereby present two cases of gingival and labial swellings in patients of different age groups who reported to the department of Oral Medicine and Radiology to have a better understanding and in depth view of their presentation.

Case History: Case Report 1

A six years old female patient presented with a painless swelling in her upper lip and gingiva since one and a half years. As noticed by parents, the gingival swelling was more during the morning, which gradually decreased through the day. As told by parents, the patient's diet consisted mostly of wafers and chocolates leading to indigestion and passage of hard stools. Upon inspection, an erythematous painless swelling was seen on upper lip and gingiva without bleeding or ulceration. Upper permanent incisors were clinically missing. There were several mucosal tags present on the left buccal mucosa along the line of occlusion with two soft tissue tags present at the right corner of the mouth on precommissural area (Figure-1, 2). The dorsum of the tongue was normal in colour without fissures.

Upon palpation, the gingiva was firm, non-pruritic, non-tender and non-granular (Figure-3). The middle portion of the upper lip showed fissuring suggestive of cheilitis (Figure-4). There was no evidence of cervical lymphadenopathy. The routine blood examination was normal except for the raised neutrophil count. The incisional biopsy from gingiva showed mild acanthosis, papillomatosis and focal suprabasal cleft formation with sub-epithelium showing dense chronic inflammation composed of lymphocytes and plasma cells. Seen amidst were numerous naked epithelioid cell granulomas with foreign body giant cells.

The patient was referred to a gastroenterologist for an endoscopic examination to rule out any gastrointestinal findings. The duodenal biopsy was performed and the microscopic examination revealed fragments of duodenal mucosa with maintained villous pattern. Lamina showed mild inflammation with no increase in the macrophages or surface epithelial lymphocytes. No other pathology was noted. The patient was kept under regular follow up and recall for six months as no invasive treatment was advised due to small age.

Case Report 2

A forty two year old female patient presented with the chief complaint of swelling on lower lip since twenty years (Figure-5). On anamnesis, patient gave the history of a non-tender swelling with formation of discrete nodules on her lower lip, accompanied by its enlargement, eversion and occasional ulcerations (Figure-6). The condition has persisted for the last twenty years with periods of remission and increase in nodularity. A history of gastritis with intestinal ulcer was given which responded well to medications by her physician. No aggravating factors were associated with the lesion. Her family and personal history were non-contributory. A careful history of allergy/hypersensitivity was recorded to rule out any

allergens responsible for swelling of lower lip. General physical examination and vital signs were within normal limits. On inspection, the lower lip had a dumb-bell shaped swelling with a significant labial-lingual bulge causing an eversion of the lip. A deep fissure with encrustation was present on the middle of lower lip. The borders of the lip were regular and well defined and its surface was smooth and coral pink in color. There were no secondary changes upon the lip and surrounding mucosa was normal. There was no associated lymphadenopathy.

Upon palpation, the swellings were non-fluctuant, non-compressible and non-pulsatile with multiple small non-tender nodules along the labial surface. The nodules were freely mobile and showed no fixity to the underlying structures. The patient was advised for routine blood investigations, Chest X-Ray, Ultrasonography of GI Tract, Fasting and random blood glucose.

Based upon above clinical findings, a working diagnosis of Cheilitis granulomatosa was arrived upon. The differential diagnoses arrived at were, Angioedema, Cheilitis glandularis, Crohn's disease, Pyostomatitis vegetans and sarcoidosis. The incisional biopsy was done on lower lip from the area with maximum nodularity.

The reports of blood test, blood glucose, chest X-Ray and ultrasonography were normal. Histopathology section revealed circumscribed aggregates of non-caseating granulomatous inflammation consisting of lymphocyte and epithelioid histiocytes with multinucleated giant cells. The granuloma consists of central aggregates of histiocytes with peripheral rim of inflammatory cells chiefly lymphocytes. The fibrous connective tissue showed areas of vascularity, multiple granulomas containing lot of giant cells suggestive of granulomatous lesion. Based upon the histopathology report, a final diagnosis of Orofacial granulomatosis was arrived upon (Figure-7).

The treatment of the lesion with Intra-lesional corticosteroid injections was initiated for a period of twelve weeks as treatment with intralesional steroids can heal any non-specific inflammation. The dose was decided according to references in the medical literature for a non-diabetic patient. An injection of 2 ml of triamcinolone (4mg/mL) and half a milliliter of xylocaine 2% was injected weekly into both halves of the lower lip for twelve weeks. The swelling responded successfully to the intralesional corticosteroid therapy with reduction in its size, absence of eversion, absence of nodules and decreased ulcerations (Figure-8, 9). The patients was recalled and followed up for six months.

Table-1:

Specific findings are:	Non-specific findings are:
1. Granulomatous cheilitis with discrete nodules	1. Aphthous ulcers
2. Cobblestoning (feature of ulcerative colitis)	2. Median lip cheilitis
3. Mucosal tags	3. Labial / facial oedema
4. Deep, linear ulcers with hyperplastic folds	4. Gingivitis with Gingival erythema / oedema
5. Pyostomatitis vegetans	

LEGENDS FOR CASE ONE



Fig-1 & 2: Mucosal Tags



Fig-3: Upper Anterior Diffuse Gingival Swelling



Fig-4: Anterior Median Cheilitis

LEGENDS FOR CASE TWO



Fig-5 & 6: Pre Operative View

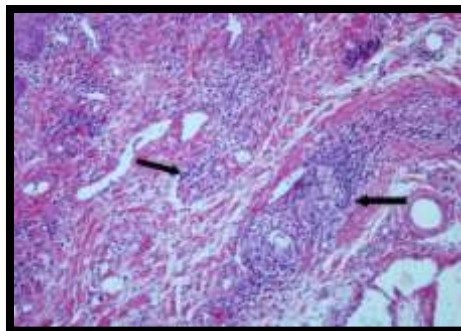


Fig-7: Histopathology Sections Showing Deep Seated Granulomas



Fig-8: Peri-Operative View



Fig-9: Post-Operative View

DISCUSSION

The oral mucosa, in part or whole, is the continuation of the gastro-intestinal mucosa. The oral manifestations of systemic disorders are well represented in literature. The descriptive term 'Orofacial Granulomatosis' (OFG) has been used for any granulomatous process of unknown etiology involving the oral cavity, which, on lesional biopsy shows lymphodema and non-caseating granulomas. Oral involvement may include, localized or diffuse, labial or facial swelling (which may affect one or both lips, on one or both sides, with or without fissuring), angular cheilitis, cobblestoning of the mucosa and mucosal tags, gingival swelling, full-thickness gingivitis, fissured tongue and linear ulcers [5, 6]. It may also manifest as partial Melkersson-Rosenthal syndrome and Crohn's disease. Crohn's disease (CD) is a chronic inflammatory process that may affect any part of the gastrointestinal tract, including the mouth, often in a discontinuous fashion due to an associated malabsorption and subsequent nutritional deficiency. The differential diagnoses for oral / related lesions could be given as sarcoidosis, acute leukaemia, drug or hormone induced gingival hyperplasia, fibromatosis gingivae and allergic angioedema [7].

The precise relationship between OFG and gastrointestinal Crohn's disease remains unclear. It is generally accepted that orofacial Crohn's disease and OFG without proven Crohn's disease share a similar aetiopathogenesis. There are a few studies examining the G.I. tracts of both children and adults with orofacial granulomatosis to ascertain the association between CD and OFG. These studies indicate OFG being an initial presentation of Crohn's disease or may be a feature of patients with concurrent gastro-intestinal Crohn's disease. As the term OFG lacks specificity, its management remains a challenge due to unavailability of a rational pharmacological therapy.

Orofacial granulomatosis is a common manifestation in children with inflammatory bowel disease and is typified by recurrent/ persistent swelling of the lips, cheeks, gingival, or oral mucosa with characteristic non caseating granulomas on histologic examination [8]. Genetic factors appear to influence disease susceptibility and patterns, but environmental factors, possibly dietary factors, and infective agents may also be at play [11].

In case reports presented above, the child showed inflammation of G.I. tract due to unhealthy dietary habits, which might have led to an adverse hypersensitivity reaction of her gastric mucosa leading to mucosal and gingival changes. Crohn's disease being an initial presentation, a careful observation is required in such cases. The adult patient gave the history of gastritis with intestinal ulcers, which may be an underlying cause for lower lip swelling. It was interesting to notice in our case that the patient achieved

complete clinical remission in 10–12 weeks after intralesional injections.

It is imperative to know about the GIT disorders in patients, therefore a detailed GIT history is mandatory [3]. Several recent reports [12, 13] have postulated that some cases of OFG may be an inflammatory bowel disease, distinct from oral Crohn's disease; the latter report has even suggested the possibility of three distinct groups: classical oral Crohn's, the new inflammatory bowel- associated OFG and a form of OFG with no bowel involvement [8].

As a current understanding, a genetic vulnerability (perhaps associated with the NOD2 and ATG16L1 genes) disrupts intestinal microbial antigen identification and presentation to effector T cells (Th1, Th2 and Th17) may lead to concomitant oral changes. Aetiological organisms are unclear, although *Mycobacterium avium* subspecies paratuberculosis has been implicated, and it is possible that others including commensals are a trigger [1].

Biopsy of affected tissues typically shows non-caseating granulomas, with or without multi-nucleate giant cells, and lymphangiectasia and perivascular lymphocytic infiltration [14]. However, a non-specific inflammatory infiltrate may be the only histopathological finding [15, 16, 7, 9, 10].

The lesion was differentiated from the Melkersson–Rosenthal syndrome in our cases due to absence of lower motor neuron facial paralysis and fissured tongue in the patients. Thus, OFG can be clinically diagnosed based upon specific and non-specific findings (Table-1).

CONCLUSION

Orofacial granulomatosis can be a distinct clinical disorder or can be an initial presentation of an underlying systemic disease such as Crohn's disease or spectrum of related disorders that may go undetected for a long period of time. The clinical outcome of OFG patients is generally unpredictable because of the apparent slowly progressing nature of the gingival and labial swellings and occasional spontaneous regression of the swellings. Hence, an early diagnosis can identify the condition and initiate a prompt treatment strategy for the benefit of the patient. A conservative approach in the treatment of the lesions of OFG is recommended by regular follow-up.

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