



OROFACIAL GRANULOMATOSIS: A SERIES HIGHLIGHTING DIAGNOSTIC AND THERAPEUTIC CHALLENGES

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ABSTRACT

Orofacial Granulomatosis is a rare inflammatory condition characterized by persistent or recurrent swelling of the lips and oral mucosa with histopathological evidence of non-caseating granulomas. It may occur as an isolated disorder or be associated with systemic diseases such as Crohn's Disease and Sarcoidosis. The condition often poses a diagnostic challenge due to its varied clinical presentation. **Objective:** To evaluate the clinical features, histopathological findings, and treatment outcomes of patients diagnosed with orofacial granulomatosis. **Methods:** Patients presenting with persistent or recurrent orofacial swelling were clinically evaluated and investigated to exclude other granulomatous disorders. Histopathological examination was performed to confirm the diagnosis. Relevant laboratory investigations were conducted, and treatment responses were assessed during follow-up. **Results:** Most patients presented with chronic lip swelling and oral mucosal changes. Histopathology revealed non-caseating granulomatous inflammation consistent with orofacial granulomatosis. Systemic associations were excluded in the majority of cases. Treatment with corticosteroids and supportive therapy resulted in symptomatic improvement, although occasional recurrences were observed. **Conclusion:** Early recognition and histopathological confirmation are essential for accurate diagnosis and management of orofacial granulomatosis, and long-term follow-up is recommended due to its chronic and recurrent nature.

KEYWORDS : Orofacial Swelling, Granulomatous Inflammation, Non-Caseating Granuloma

INTRODUCTION

Orofacial Granulomatosis (OFG) is a rare entity characterized by persistent or recurrent soft tissue enlargement, oral ulceration and a variety of other orofacial features. It includes group of diseases characterized by presence of noncaseating granulomatous inflammation affecting the soft tissues of the oral and maxillofacial region [1]. The precise cause of OFG is unknown [2].

OFG may be the oral manifestation of systemic diseases such as inflammatory bowel disease (IBD), sarcoidosis, granulomatosis with polyangiitis (GPA) and Melkersson-Rosenthal syndrome (MRS) [2-4]. The clinical mimicry of OFG with hansen's disease in endemic regions makes its differentiation critical.

Table 1- Case Series

Sr. No.	Age (years)/sex	Site of involvement	Duration	Labial involvement	Buccal mucosa involvement	Treatment given	Duration	Response to the treatment
Case 1	35/Male	Upper lip	6 weeks	Yes	No	ILS, Prednisolone	3 months	Complete resolution (figure 1)
Case 2	68/Female	Lower lip and chin	3 months	Yes	No	ILS, Prednisolone, Metronidazole 400mg three times a day	6 months	Complete resolution (figure 1)
Case 3	29/Female	Left cheek, lower lip and chin	3 months	Yes	Yes	ILS, Prednisolone, Clofazimine (5 mg/kg/day)	6 months	Partial resolution (figure 2)
Case 4	34/Female	Upper lip	4 months	Yes	No	ILS, Prednisolone, Tofacitinib 11mg daily	4 months	Complete resolution
Case 5	58/Male	Right cheek	1 month	No	No	Prednisolone, Clofazimine (5 mg/kg/day)	4 months	Recurrence (figure 2)
Case 6	42/Male	Lower lip	2 months	Yes	No	ILS, Prednisolone	3 months	Partial resolution
Case 7	33/Female	Left cheek and upper lip	3 months	Yes	No	ILS, Prednisolone, Clofazimine (5 mg/kg/day)	3 months	Complete resolution
Case 8	45/Female	Left cheek and lower lip	4 months	Yes	No	ILS, Prednisolone, Thalidomide 200mg daily	3 months	Complete resolution
Case 9	38/female	Right side of chin	3 months	Yes	No	ILS, Prednisolone	3 months	Complete resolution
Case 10	32/male	Right cheek and upper lip	2 months	Yes	No	ILS, Prednisolone	3 months	Complete resolution

The classic presentation of OFG is a nontender, recurrent labial swelling that eventually becomes persistent [5]. This swelling may affect one or both lips, causing lip hypertrophy [6]. Intraoral involvement may take the form of hypertrophy, erythema, or nonspecific erosions involving the gingiva, oral mucosa, or tongue. [4,6]

The diagnosis of OFG is made by presence of non-caseating granuloma on histopathology. Other cutaneous and systemic conditions characterized by granulomatous inflammation must be excluded by clinical and laboratory investigations.

We report 10 cases of oro-facial granulomatosis as described in table 1. It highlights varied presentations of Orofacial Granulomatosis, challenges in diagnosing cases and multiple treatment options.

All cases had insidious onset of diffuse, non-tender, erythematous swelling lasting for weeks to months. Eight patients out of 10 had lip involvement but only one patient had buccal mucosal involvement. Tongue was normal in all cases and none of the patients had lymphadenopathy or facial palsy. No history of preceding trauma or insect bite were noted. None of the patient gave history of food or drug allergy. Systemic examination was within normal limit in all cases. Complete blood count, liver function test, renal function test, erythrocyte sedimentation rate, montoux test, chest x-ray were normal. Absolute eosinophil count was raised in one patient only. Sensations were normal in all cases and nerve involvement was not observed. Hence, leprosy was ruled out clinically.

3-mm punch biopsy was done from the swelling. Histopathological examination showed dense nodular and granulomatous infiltrate distributed throughout the dermis and extending to subcutaneous fat. Granuloma consisted of lymphocytes, histiocytes, plasma cells and foamy macrophages. A few granulomatous nodules showed immature and mature epithelioid cells. These findings were consistent with Oro-facial granulomatosis.

Tuberculosis and leprosy were ruled out by AFB staining.

Patients are treated with various regimen like intralesional steroid, oral prednisolone (1mg/kg/day), clofazimine (5mg/kg/day), metronidazole 400mg three times a day, dapsone 100mg/day, thalidomide 100mg/day, tofacitinib 11mg/day (mentioned in table 1). Treatment was carried out for 3-6 months. Patients were followed up for 6 months after treatment. Out of 10 patients 7 patients had complete resolution and no recurrence. 2 patients had partial resolution and 1 patient had recurrence after 2 months of stopping the treatment.



Figure 1-



Figure 2-

DISCUSSION

The term Orofacial Granulomatosis (OFG) was coined in 1985 by Wiesenfeld [2]. OFG is a rare chronic inflammatory disease of unknown etiology, characteristically presenting with relapsing and remitting lip swelling but also involving the buccal mucosa, gingivae and floor of the mouth [2]. The differential diagnosis of OFG includes many granulomatous diseases hence thorough clinical examination, histopathology and laboratory investigations are required to exclude other conditions.

Clinical Feature

Prominent enlargement of the lips is the most common sign, with little difference in prevalence between the upper and lower lips [2]. The swelling is initially soft, but with time it becomes firmer as fibrosis ensues. Later labial swelling may eventually become persistent [7].

Oral mucosa may be involved presenting as ulcers. Painless enlargement of free and/or attached gingiva arises in the localized or generalized pattern. It varies in color from normal to salmon pink to red [4]. Lateral aspects of the tongue may be fissured. OFG may present with mucosal edema, mucosal tags, nodules and fibrous banding.

Facial swelling affecting the upper half of the face has been described and may rarely be extensive [8]. OFG can involve chin as well. A case series of patients diagnosed with OFG presenting with severe periorbital edema has also been reported [9]. A lower motor neuron palsy of facial nerve may rarely arise in OFG [10]. Persistent or recurrent orofacial edema, relapsing facial paralysis and fissured tongue form a triad of melkersson-rosenthal syndrome.

Etiopathogenesis

Exact etiology and pathogenesis of OFG and its restriction to the orofacial region remain unclear. It can be linked to food substances, food preservatives, microbiological agents or dental materials. Furthermore, delayed hypersensitivity reaction with the predominant Th1-mediated immune response has been implicated in OFG [11]. A genetic background to explain the occurrence of OFG is not supported [12].

Infection was discussed as a possible cause of OFG, various infective agents were documented by molecular techniques to be present in lip lesions of OFG patients [13], whereas other studies failed to detect mycobacteria in OFG lesions via polymerase-chain-reaction [14].

Allergy in the form of hay fever, atopic eczema or asthma has been reported. [15, 16]. Food substances like cinnamon and benzoates which were positive on patch tests in patients with a variety of oral mucosal diseases including OFG [17]. Some studies have showed improvement in OFG with an elimination diet [16].

Delayed hypersensitivity to dental materials had been implicated in the etiology of OFG. Granulomatous reactions have been found in amalgam tattoos and in subcutaneous deposits of inorganic mercury [18, 19].

Diagnosis

The diagnosis of Orofacial granulomatosis is made by presence of clinical features, non-caseating granulomas on histopathology and the exclusion of systemic disorders having similar manifestations.

Complete hemogram, immunodeficiency work-up, liver function test, renal function test, montoux test, chest X-ray, electrocardiogram should be done for starting long term immunosuppressive therapy.

Endoscopy, radiological evaluation and blood investigations are used to differentiate orofacial granulomatosis from crohn's disease, sarcoidosis, tuberculosis and foreign body reactions.

Orofacial Granulomatosis should be differentiated from other systemic conditions by appropriate investigations.

Table 2- Differential Diagnosis

Disease	Clinical features	Histo-pathology	Additional findings
Sarcoidosis	Facial swelling, may also have pulmonary, cutaneous, lacrimal, salivary, neurological, and/or skeletal features of sarcoidosis	non-caseating granulomas	CRP↑, SACE↑ Chest X-ray-Hilar adenopathy, fibrosis
Crohn's disease	Oro facial swelling, ileal and/or rectal disease	non-caseating granulomas	CRP↑, B12↓, ferritin↓ Gastrointestinal fistulas on endoscopy
Tuberculosis	Facial swelling	caseating granulomas	Montoux test Chest X-ray-Hilar adenopathy, fibrosis, cavitation
Allergic angioedema	Relapsing orofacial edema	Normal	IgE ↑
Cheilitis grandularis	Lip swelling	No granuloma	-
Hansens disease	Erythematous infiltrated plaques/nodules, hypoaesthetic patches, nerve enlargement /neuritis.	Granuloma with foamy macrophages	Slit skin smear positive for lepra bacilli.

Management-

Dietary modification like avoidance of cinnamon, benzoate and following a low phenolic acid diet has been shown to be an effective in the management of OFG [20].

Corticosteroids are considered the mainstay of therapy. Topical, intralesional and/or oral corticosteroids are used in OFG. It reduces facial swelling and prevent recurrences.

Other treatment modalities include dapsone, clofazimine, immunomodulatory agents, e.g. azathioprine (AZA), mycophenolate mofetil, methotrexate and thalidomide, biologics such as infliximab and adalimumab, tumour necrosis factor alpha [20].

Antibiotics such as metronidazole, doxycycline, minocycline can be used where infection is suspected. There is no fixed treatment protocol as the disease etiology is unclear. Surgery may be required for persistent and refractory cases.

CONCLUSION

Orofacial Granulomatosis (OFG) is a rare entity and has wide spectrum of presentation. It requires long treatment and multi-disciplinary approach involving dermatologist, maxillofacial surgeon and gastroenterologist is crucial for optimal outcomes. Through our observations, we stress the importance of considering OFG in chronic orofacial swelling to avoid delayed diagnosis. Prompt diagnosis and

individualized therapy may help reduce disease progression, functional impairment and cosmetic morbidity. This case series adds to the limited literature on OFG, underscoring its diagnostic challenges and the importance of individualized treatment approaches.

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