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## Granulomatous cheilitis of the upper lip in a child

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### **Abstract**

Granulomatous cheilitis is a chronic granulomatous inflammatory condition involving the lips with a multifactorial etiology. The difficulty in treatment of granulomatous cheilitis is reflected in various treatments that have been tried and the lack of consensus regarding the preferred treatment. Combined therapy of intralesional corticosteroid and clofazimine or dapsone is one of the most commonly used treatments for the condition. Other treatment options are prednisone, antibiotics such as metronidazole, tetracycline hydroxychloroquine, sulfasalazine, antihistamines, macrolides, thalidomide and infliximab. However, therapeutic responses of patients with granulomatous cheilitis are often unpredictable and spontaneous recurrences are not uncommon. Therefore, an oral physician must carefully proceed in order to develop an accurate treatment planning. Management considerations for these patients depend upon the results of the investigations, patient's esthetic considerations and severity of the condition. A case of a nine year old child with the granulomatous cheilitis of upper lip who showed an excellent response to intralesional steroids, metronidazole and doxycycline, a combined therapeutic regimen is reported here.

**Keywords:** Granulomatous Cheilitis, intralesional steroids, metronidazole and doxycycline.

### **1. Introduction**

Orofacial granulomatosis is best defined as a group of conditions characterized by granulomatous inflammation in the oral and maxillofacial region [1]. The term Orofacial granulomatosis was introduced by Wiesenfeld in 1985 as a specific clinical entity which may occur in an isolated form or in association with other systemic disease.[2] A subset, granulomatous cheilitis, also called Miescher's cheilitis is a rare, idiopathic, inflammatory disorder which usually affects young adults, clinically manifesting as persistent, diffuse, non-tender, soft-to-firm swelling of one or both lips with the estimated incidence of 0.08 % in the general population.[3] It was described by Miescher in 1945, as an oligosymptomatic form of Melkersson-Rosenthal syndrome [4], which includes facial palsy and a plicated tongue. The exact etiology of granulomatous cheilitis is not known. Different theories have been suggested, involving infection, genetic predisposition and allergy.[5] Suggested underlying mechanisms include lymphocytic infiltration due to the chronic antigenic stimulation, cytokine production resulting in formation of granulomas and cell-mediated hypersensitivity reaction with associated lymphatic blockage caused by granulomas, leading to diffuse swelling by the lymphedema.[6]

Various systemic diseases are related with granulomatous cheilitis including mycobacterial infection, sarcoidosis, Crohn's disease, Wegener's granulomatosis, histoplasmosis and amyloidosis rosacea; medications such as ACE inhibitors and calcium channel blockers; atopic reaction to a wide variety of allergens and hereditary diseases such as C1 esterase deficiency.[7] Histopathologically, it shows granulomas consisting of lymphocytes and epithelioid histocytes with dilated lymphatics in lamina propria and perivascular aggregation of histocytes and plasma cells.[8] Management of granulomatous cheilitis is dependent on its etiology. There is no accepted protocol for treatment of granulomatous cheilitis and available therapeutic options provide only limited and temporary remission. A case of granulomatous cheilitis is reported here which gave excellent response to combined therapeutic regimen of intralesional steroids, metronidazole and doxycycline.

### **2. Case study**

A 9-year-old male reported to the Department of Oral Medicine and Radiology at GDCRI, Bangalore with a chief complaint of persistent asymptomatic swelling of the upper lip since 2 years. The swelling was insidious in onset,

initially small in size gradually growing uniformly to the present size. Patient gave no history of night sweats, persistent productive cough or palsy of facial muscles. There was no history of abdominal cramps, weight loss, dysphagia or chronic fatigue. Patient had received intralesional triamcinolone injection in the past elsewhere with temporary remissions and recurrence of swelling. No family history of similar lip swelling was present. Systemic examination did not reveal any abnormalities with no increase in temperature, pulse or respiratory rate. The extra oral examination revealed no limitation of mouth opening and no lymphadenopathy. Local examination of lip revealed presence of a diffuse erythematous, smooth surfaced firm, nontender, non-pulsatile, non fluctuant swelling of the entire upper lip with no signs of scabs, bleeding, or exudation. Facial skin superior to the vermilion border of upper lip also showed diffuse erythematous extension of the same lip swelling with pigmentation and a granular surface. Intraorally, the upper anterior labial gingiva showed diffuse erythematous enlargement with loss of stippling extending bilaterally from midline upto the maxillary canine. No relevant abnormality was identified in any other site of oral mucosa. The associated upper permanent teeth were intact with no displacement or mobility (Figure 1 and 2). Vitality test in relation to 11-13 and 21-23 regions was performed and the respective teeth were found to be vital.

Accordingly the provisional diagnosis of granulomatous cheilitis with differential diagnosis of angioedema, sarcoidosis, crohn’s disease and tuberculosis involving the lip was considered.



**Figure 1: Front profile of the patient with upper lip swelling.**



**Figure 2: Maxillary arch with gingival enlargement of upper anterior**

Intraoral periapical radiographs in relation to 11-13 and 21- 23 region revealed a mesiodens between 11 and 21. No periapical pathology/other abnormality was present (Figure 3). Maxillary occlusal radiograph (Figure 4), OPG (Figure 5) and Lateral skull radiograph revealed no abnormal radiographic finding.



**Figure 3: IOPA wrt 11, 12 showing mesiodense between 11, 21**



**Figure 4: Maxillary occlusal Radiograph showing mesiodense**



**Figure 5: OPG showing Mesiodense between 11, 21**

Chest radiograph was done, which showed no area of opacity, consolidation or pleural effusion and tuberculin skin test for tuberculosis was negative thereby suggestive of no evidence of tuberculosis.

Serum level of angiotensin-converting enzyme, was evaluated which was within normal range ruling out sarcoidosis. Further Crohn's disease was ruled out due to absence of occult blood in stool.

Blood investigations (Hb%, BT, CT, ESR, TLC, DLC, HbSAg and HIV), serum folate, iron, and vitamin B12 levels, liver function test were done before performing biopsy. An incisional biopsy of upper lip and upper labial attached gingiva was performed under local anaesthesia.

Biopsy specimen of upper lip showed diffuse, dense inflammatory cell infiltration in subepithelium and numerous epithelioid granulomas with rim of lymphocytes which were suggestive of granulomatous lesion.

Gingival biopsy showed parakeratinized stratified squamous epithelium and subepithelial connective tissue. The superficial connective tissue showed dense infiltration of chronic inflammatory cells. The deeper connective tissue showed few non-caseating granulomas consisting of lymphocytes and epithelioid histocytes in the background of mature collagen bundles and presence of few multinucleated giant cells, suggestive of granulomatous lesion.

The chief complaint, history, clinical examination and subsequent investigations led us to arrive at a final diagnosis of Cheilitis granulomatosa of the upper lip.

The patient was treated with a combination of weekly intralesional injections of triamcinolone acetonide 10 mg/ml in the upper lip for 4 weeks, along with oral metronidazole 200mg three times a day and oral doxycycline 50mg once daily. Subsequently the patient was advised to maintain an alternate day dosing schedule of oral doxycycline 50mg for a month. Post treatment follow-up of the patient at the end of 15 days and one month revealed significant improvement in the colour, texture and size of the gingiva and lip. (Figure 6)



**Figure 6: Follow up of the patient with remission of Lip swelling**

### 3. Discussion

Cheilitis granulomatosa is a rare, persistent, painless, idiopathic non-tender recurrent swelling of the lip.[8] This swelling may affect one or both lips, causing lip hypertrophy (macrocheilia). The swelling is initially soft but becomes firmer with time as fibrosis ensues. Intraoral involvement may show hypertrophy, erythema or nonspecific erosions involving the gingiva, oral mucosa or tongue.[9] Gingival swelling may precede the lip swelling and the gingival changes may appear either as diffuse edematous or as distinct small, irregular, bluish red edematous swelling on the gingival surface especially in the anterior part of the mouth.[10] In the present case gingival enlargement preceded the lip swelling with diffuse enlargements of the gingiva in the maxillary anterior region.

Differential diagnoses considered for the case were Angioedema, Sarcoidosis, Crohn's disease and Tuberculosis. Angioedema usually appears acutely with a history of repeated episodes. However, the lip swelling unlike CG is edematous and nonpitting in angioedema. Sarcoidosis manifests with fever, arthralgia, anorexia and pulmonary symptoms like cough, chest pain, dyspnea on exertion, hemoptysis along with granulomatous cheilitis and shows presence of elevated serum ACE levels. Crohn's disease may also have oral involvement and cause granulomatous cheilitis. The absence of gastrointestinal symptoms, lack of other signs in the oral mucosa and no features of anemia as well ruled out Crohn's disease. Granulomatous cheilitis may be a manifestation of pulmonary tuberculosis. It can be ruled out by negative Mantoux test and chest radiograph.

Management of CG is difficult due to its multifactorial etiology and depends on accurate diagnosis of the condition and identification of any precipitating factors. Unfortunately, no therapy has provided predictable results so far. The goal of therapy is focussed on reducing the swelling to an acceptable state and to improve clinical appearance and comfort for the patient. Although rare, spontaneous remission is possible.

Corticosteroids have been shown to be effective in reducing lip swelling, preventing recurrences and are considered the mainstay of therapy. Patient with mild swelling are commenced on topical steroids. More pronounced swellings of the lip are treated with intralesional triamcinolone acetonide 0.1% injections.[11] Other drugs tried include Antibiotics like sulphamide, tetracycline, minocycline, roxithromycin, metronidazole and isoniazid. Immune modulators such as infliximab and methotrexate. Elimination diets i.e. Cinnamon- and benzoate-free diets have shown benefit in a significant number of patients.[12]

Stein and Mancini treated successfully two children with granulomatous cheilitis, with a combined therapeutic regimen of oral prednisolone and minocycline.[13] Similarly, Coskun *et al* have reported successful results with a combination of intralesional steroids and metronidazole.[14] Combined therapeutic regimen of intralesional triamcinolone, metronidazole and minocycline with weekly intralesional triamcinolone acetonide injections 10 mg/mL in the upper lip (0.25–0.50 mL at three points) for 4 weeks; oral metronidazole tablets 400 mg three times a day and oral minocycline 100 mg daily for one month have yielded excellent response in case studies. A significant decrease in swelling was noticed in these patients after a period of 15 days.[15]

After one month, intralesional steroid and metronidazole were discontinued. Minocycline, however, was continued in a dose of 100 mg on alternate days for the next month. The dose of minocycline was tapered to look out for any relapse and to get sustained results. The patients were followed up regularly for a period of one year without any relapses. The complete remission of the swelling may be attributable to the potent anti-inflammatory action of the drug combination used here and the use of cycline is based on its in vitro ability to inhibit granuloma formation by inhibition of protein kinase C. Hence based on the successful management observed, we decided to give the same therapeutic regimen in the present case and fortunately our patient too responded favourably.

#### 4. Conclusion

Chronic swelling of lips is a clinical challenge to diagnose and manage. It is a socially embarrassing condition. Management depends on the underlying cause. Combination of intralesional triamcinolone injection, along with oral metronidazole and minocycline, seems to be an effective remedy for successful and sustained response in granulomatous cheilitis which is one of the causes of lip swelling.

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