Case 16
A 53 year-old Thai man from Bangkok

Chief complaint: persistent lower lip swelling for 4 weeks

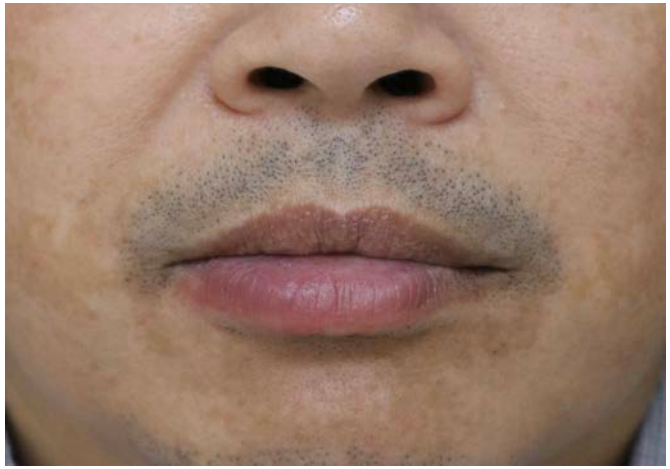

Fig. 16.1

Present illness:
The patient gradually developed diffuse painless lower lip swelling for 4 weeks, the swelling of the lip does not relate to the food which he has consumed nor allergy. Patient consulted a physician 3 weeks prior to his visit for the same problem. He was prescribed prednisolone 15 mg/day for 1 week then tapering to 10 mg/day for 1 week, hydroxyzine 25 mg/day for itching, also topical medication triamcinolone acetate oral paste, but the symptom does not improve. He had no history of angioedema or anaphylaxis.
He had no other complaints.

Past history: Healthy

Dermatologic examination: (Fig. 16.1)

- Mild swelling of lower lip with firm consistency, reddish-pink color, smooth surface
- Intraoral examination shows no gingival swelling, no ulcer, and tongue is normal

Physical examination: Unremarkable

Histopathology: (S17-036950A, skin, lower lip) (Fig. 16.2, 16.3)

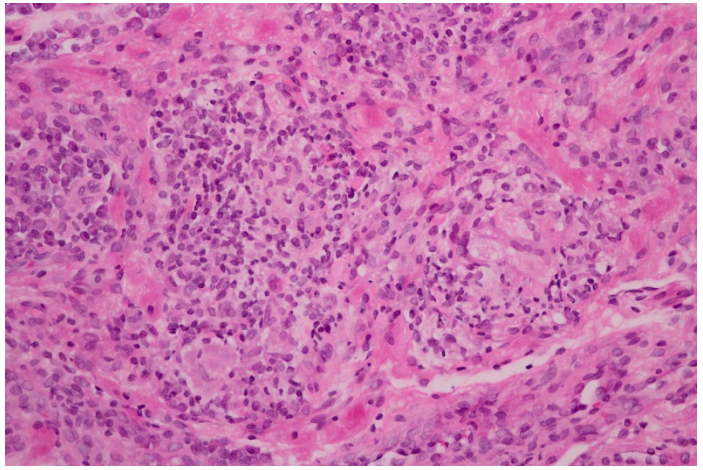

Fig. 16.2

- Dense perivascular and nodular inflammatory cells infiltration, composed of lymphocytes and histiocytes
- Multiple foci of tuberculoid granuloma within the infiltration

Diagnosis: Chelitis Granulomatosa

Treatment:

- Triamcinolone acetonide 10mg/ml 0.2 ml intraleisional

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Discussion:

Cheilitis granulomatosa is characterized by idiopathic recurrent or persistent swelling of one or both lips. It is considered a subtype of orofacial granulomatosis (OFG), when accompanied by facial palsy and plicated tongue, it is referred to as the Melkersson–Rosenthal syndrome (MRS)[1], although the classic triad is not often observed. Additional neurologic disorders are described, particularly in the setting of Melkersson-Rosenthal syndrome, and include facial hyperhidrosis or anhidrosis, epiphora, blepharospasm, hypogeusia, hyperacusia, tinnitus, and migraine-like headache.[14]

The differential diagnosis of persistent lip swelling includes other granulomatous diseases such as a foreign body reaction, mycobacterial infection (tuberculosis, leprosy, atypical mycobacterium), deep fungal infection (histoplasmosis), sarcoidosis, Crohn's disease, and Wegener's granulomatosis, amyloidosis, minor salivary gland tumor, Ascher's syndrome, 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. [1,2,12,15]

Available literature shows that underlying pathological process of OFG have not been investigated in detail to arrive at firm conclusions. Several etiologies have been postulated; genetics; food allergy; allergy to dental materials; infection; and immunological process [2], but there are only a few reports providing limited data to support each of these possible causes. Delayed type of hypersensitivity reaction (contact hypersensitivity) appears to play a significant role, although the exact antigen inducing the immunological reaction varies in individual patients.[3]

Cheilitis granulomatosa has been reported to represent extra-intestinal Crohn's disease (CD), with oral manifestations of this disease, however there is no recommendation for routine investigations of the gastrointestinal tract in patients with cheilitis granulomatosa or Melkersson– Rosenthal syndrome who is negative history of gastrointestinal complaints.[5,6,11] CD is more likely to present with oral ulcers and hematological markers of inflammation than simple lip swelling.[1]

Histologically, non-caseating granulomas are seen as well as edema, lymphangiectasia, and perivascular lymphocytic infiltration.[11] Histopathology of Cheilitis granulomatosa (CG) may also be confused with Crohn's disease, sarcoidosis, or Wegener's granulomatosis, especially in longer-standing disease, and clinical history is an important differentiating feature. Submucosal inflammation includes TH1 cells producing IL-12, monocytes producing IL-1, and large, active dendritic B cells.[2] Protease-activated receptor-1 and 2, matrix metalloproteinase-2 and 9, and COX-2 are all overexpressed in immunohistochemical analysis from biopsies.[4] A current hypothesis is that this process is driven by a random influx of inflammatory cells and not a specific, single antigen.[1]

Diagnosis of cheilitis granulomatosa relies on the history, clinical features and presence of non-caseating granuloma on histopathology.

There is no definitive treatment for cheilitis granulomatosa. Most therapeutic regimens include local injection and systemic corticosteroid therapy, intralesional triamcinolone has been suggested by many authors as the first choice therapy. Dosage range from 10-40 mg doses with intervals from weeks to months between injections[8,9], no large studies examine long term efficacy. However some patients do not respond to corticosteroid treatment, so additional therapy is necessary. As shown in table 1, other options have been reported in the literature include clofazimine; antibiotics such as tetracycline, minocycline, doxycycline, roxithromycin, dapsone, and metronidazole; immunomodulators such as infliximab, omalizumab, and adalimumab; tranilast; thalidomide; fumaric acid esters; and methotrexate. These drugs have been used in various combination. Cheiloplasty is reserved for refractory cases or in presence of a major lip deformation.[3]

Nowadays, there are only a few case reports or small case series for therapeutic options and no studies have been performed to evaluate the different treatment modalities. Therefore, more studies need to be done before definitive therapeutic regimens can be made.

Table 1. Medications used in the treatment of granulomatous cheilitis

Drug name	Case study	Administration
Triamcinolone	Coskun et al. Eisenbud et al. Perez-Calderon et al. Bacci et al.[8]	Intraleisional Injection 10-20 mg per dose with weeks to months between doses Intralesional injection 40 mg weekly
Fumaric acid esters (Fumaderm)	Kleine et al. Breuer et al.	120–720 mg daily
Metronidazole	Coskun et al. Miralles et al. Kano et al.	750–1000 mg daily
Roxithromycin	Ishiguro et al. Inui et al.	150–300 mg daily
Methotrexate	Tonkovic-Capin et al. Leicht et al.	5–10 mg weekly
Doxycycline	Oudrhiri Et al.[7]	200 mg daily
Minocycline	Veller Fornasa et al.	100 mg daily
Clofazimine	Podmore and Burrows et al. Fernandez Freire et al. Ridder et al.[10]	100–300 mg daily or every other day 100 mg daily for 30 days , then 100 mg 3 times a week
Tranilast	Chiba et al.	200–400 mg daily
Thalidomide	Thomas et al.	100 mg daily to every other day
Omalizumab	Eustachio Et al.[13]	300 mg every 4 weeks
Adalimumab	Ruiz Et al.[16] Stein et al.[19]	80 mg then 40 mg weekly (subcutaneous)
Infliximab	Ratzinger et al. Barry et al. Peitsch Et al.[17] Badshah Et al.[18] Gaya et al.[20] Kakimoto et al.[21]	3–5 mg /kg per infusion 10 mg/kg every 4 weeks 5 mg/kg (followed by adalimumab)

Adapted from Banks T et al.[9]

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