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CASE REPORT

Cheilitis Granulomatosa: A Review

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Abstract Cheilitis granulomatosa (CG) is a cosmetically disturbing and persistent idiopathic lip swelling. It is one manifestation of orofacial granulomatosis (OFG), which is a clinical entity describing facial and oral swelling in the setting of non-caseating granulomatous inflammation and in the absence of systemic disease such as Crohn's disease and sarcoidosis. CG can occur by itself or as part of the Melkersson–Rosenthal syndrome, which includes facial palsy and a plicated tongue. Other proposed causes of OFG include dietary allergens such as cinnamon and benzoates. Similar orofacial swelling may be an early manifestation of Crohn's disease or sarcoidosis, and so clinical history is important in diagnosis. The cause of CG has not been wholly elucidated, but a current hypothesis holds that a random influx of inflammatory cells is responsible. Other granulomatous and edematous causes of lip swelling must be investigated prior to diagnosis. Options for treatment include dietary modifications, antibiotics, systemic or intralesional corticosteroids, and surgery, although treatment is not always necessary. CG should be considered in the differential of persistent lip swelling.

Keywords Cheilitis granulomatosa · Granulomatous cheilitis · Melkersson–Rosenthal syndrome · Lip swelling

Patient History

A 68-year-old white male presented for unexplained, unrelenting lip swelling (Fig. 1) of 4 weeks' duration. He had recently been started on diltiazem by his cardiologist and immediately upon taking the first dose noticed lightheadedness, headache, and facial flushing. He stopped the medication and noticed swelling of his left upper lip and left cheek 2 weeks later. On advice from his cardiologist he also stopped lisinopril, but the swelling persisted. He had no history of angioedema or anaphylaxis, although he did report seasonal allergic rhinitis that did not require medication. He had no history of squamous or basal cell carcinoma on his face. There was no family history of angioedema. He had no other complaints.

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Physical Examination and Laboratory Data

Physical exam revealed a healthy appearing white male in no distress with left upper lip and cheek edema but no tenderness. He did notice decreased sensation to light touch on the upper lip. There was no facial asymmetry and facial expression was intact and equal bilaterally. There was no tenderness over the maxillary, ethmoid, or frontal sinuses. Examination of the skin of his head and neck was not worrisome for malignancy. He had good dentition and no concerning lesions were noticed in the oropharynx. The nares were patent but did reveal right nasal septal deviation.

Flexible nasal endoscopy indicated patent ostiomeatal complexes with no obvious swelling or tumor. MRI of the head with contrast was ordered to rule out a maxillary sinus mass causing the edema; the MRI showed diffuse enhancement of the upper lip but was otherwise unrevealing. Chest X-ray was ordered to rule out compression of the left jugular vein and this showed no lesion. ACE level was ordered to rule out sarcoidosis and was normal. An ANA panel including ENA, RNP, SM, PM1, SSA,

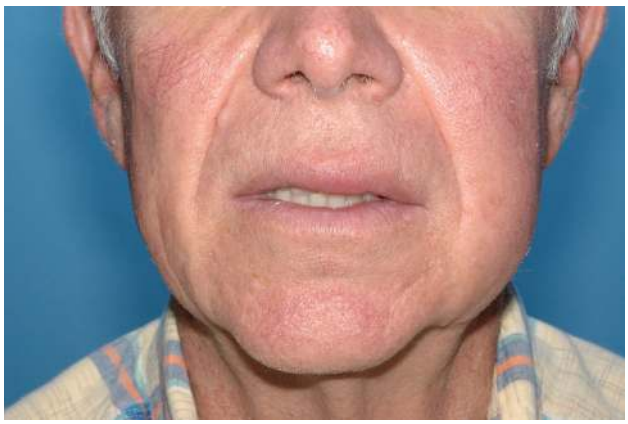

Fig. 1 The gross appearance of the upper lip upon presentation. The *left* upper lip appears swollen

SSB, SCL70, and dsDNA was negative. Allergy testing was not done, although this would have been an important step to rule out other causes of OFG such as cinnamon and benzoate allergy.

Histopathology

Biopsy was taken of the edematous left lip, which revealed normal keratinizing squamous epithelium overlying changes of solar elastosis accompanied by noncaseating granulomatous inflammation in the deeper subcutaneous and parafollicular tissues (Figs. 2, 3). Ziehl–Neelsen, silver, Periodic acid-Schiff, and Warthin–Starry stains were negative for acid fast (Mycobacteria and Actinomyces, specifically), fungal, and spirochetal organisms. A dermatopathologist was consulted and agreed with this description, noting that the interpretation was consistent with cheilitis

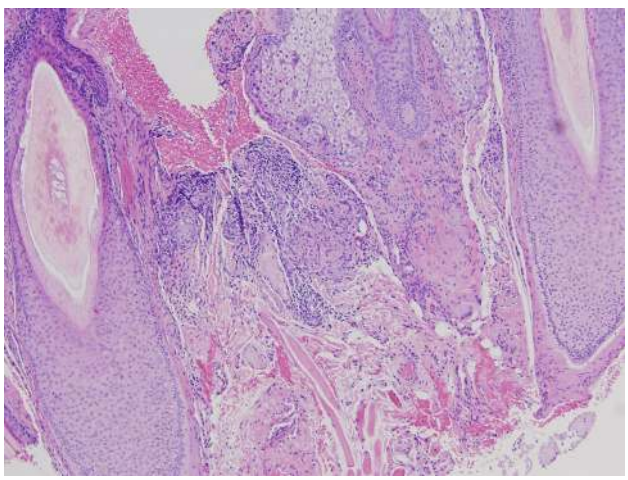

Fig. 2 Medium power magnification of *left* upper lip biopsy showing noncaseating granulomatous inflammation in the deeper subcutaneous and parafollicular tissues

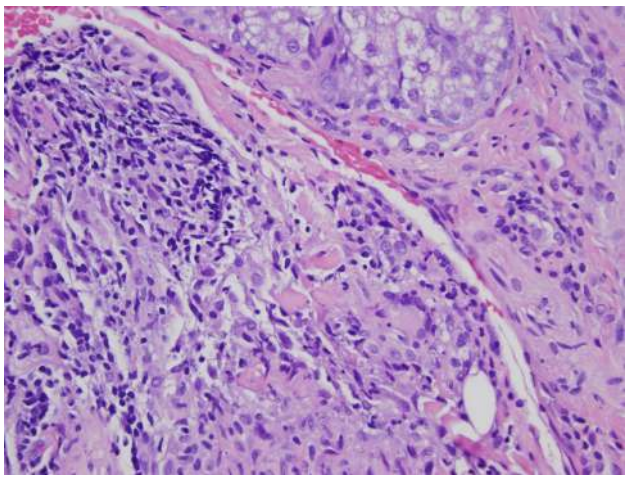

Fig. 3 High power magnification of *left* upper lip biopsy showing noncaseating granulomatous inflammation. No signs of malignancy are seen

granulomatosa, with the primary differential diagnosis of a granulomatous rosacea.

Histologically, 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 T_H1 cells producing IL-12, monocytes producing IL-1, and large, active dendritic B cells [1]. Similar changes may be found in cervical and submandibular lymph nodes. Protease-activated receptor-1 and 2, matrix metalloproteinase-2 and 9, and COX-2 are all over-expressed in immunohistochemical analysis from biopsies [2]. A current hypothesis is that this process is driven by a random influx of inflammatory cells and not a specific, single antigen [1]. Borrelia burgdorferi (a spirochete responsible for Lyme's disease) has been suggested in a pathogenic role, but polymerase chain reaction (PCR) has not been able to identify any Borrelia-specific DNA CG patients [3].

Discussion

Cheilitis granulomatosa is a rare, persistent, painless, idiopathic chronic swelling of the lip. It is considered a manifestation of orofacial granulomatosis (OFG), which is a clinical term describing orofacial swelling caused by noncaseating granulomatous inflammation in the absence of systemic disease [1]. When accompanied by facial palsy and plicated tongue, it is referred to as the Melkersson–Rosenthal syndrome (MRS). CG has no predisposition to race, sex, or age and the incidence has been estimated at 0.08 % in the general population [4]. The first episode typically subsides in hours or days, but both the frequency and duration of the attacks increase until they become

persistent. The upper lip, lower lip, or both lips can be involved.

The differential diagnosis of persistent upper lip swelling includes other granulomatous diseases such as a foreign body reaction, mycobacterial infection, sarcoidosis, Crohn's disease, Wegener's granulomatosis, and histoplasmosis; 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. There has, in fact, been an association noted between CG and Crohn's disease [5] although CD is more likely to present with oral ulcers and hematological markers of inflammation than simple lip swelling [6].

Treatment

There is no definitive treatment for cheilitis granulomatosa, and this is complicated by the poorly understood mechanism of disease. Corticosteroids are widely used for CG and have been shown to be effective in reducing facial swelling and preventing recurrence [1] but have side effects when used long-term. Bacci et Valente had excellent success in one patient with intralesional injections of 40 mg triamcinolone once a week for a total of three administrations; there was rapid improvement with no recurrence at 1, 3, 6, or 12 months followup [7]. Other treatment options are included in Table 1 [7–12], but it should be noted that these are anecdotal and based on case reports only. An excellent comprehensive review of current medical treatment options for CG was recently published by Banks and Gada in the British Journal of Dermatology [13].

Allergy testing has demonstrated a high rate of sensitivity to cinnamon and benzoates in patients with OFG [14]. A cinnamon- and benzoate-free diet has shown to reduce oral and lip inflammatory scores at 8 weeks and has been proposed by at least one author as first-line therapy for OFG [15]. Therefore, such testing should be included in the workup of patients with suspected OFG.

In the case of our patient, a 2-months trial of dapsone 100 mg p.o. b.i.d. was given. He was seen 1 month later with no improvement in his swelling but no new symptoms. The plan was to try metronidazole after the full 2 months course, but the patient never returned to clinic. It should be noted that without longer follow-up and a demonstrated response to standard treatment the diagnosis of CG remains in doubt. Moreover, other causes of OFG including food allergens were not ruled out through allergy testing.

Approach to Lip Swelling

Lip swelling can be a perplexing presentation, and common etiologies must first be ruled out before more invasive and expensive testing is done. The initial evaluation must include an assessment of stridor or laryngeal swelling, as these can be a medical emergency. A history of atopy or current therapy with an ACE inhibitor or calcium channel blocker should alert the practitioner to the possibility of angioedema, as this is the most likely etiology. A family history of similar orofacial swelling should prompt an investigation into the autosomal dominant C1 esterase inhibitor deficiency, also known as hereditary angioedema. The primary feature that should help diagnose angioedema from other causes is a complete resolution of symptoms between attacks.

The history should include questions about gastrointestinal symptoms, which may alert the clinician to suspect undiagnosed Crohn's disease, as well as inquiring about a chronic chough, which may indicate sarcoidosis, tuberculosis, or histoplasmosis. Current and recently initiated medications should be reviewed and potentially suspended. Physical examination should include a cranial nerve examination to determine facial nerve involvement, a full oropharyngeal examination looking specifically for poor

Table 1 Treatment options for cheilitis granulomatosa

Drug name	Class	Administration
Triamcinolone [7]	Corticosteroid	Intralesional injection 40 mg once per week for 3 weeks
Metronidazole [12]	Nitroimidazole antibiotic	1,000 mg PO daily until clinical response is noted
Clofazimine [8]	Phenelzine dye derivative	100–200 mg PO daily for 3–6 months
Roxithromycin [10]	Macrolide antibiotic	150 mg PO daily until clinical response is noted
Adalimumab [9]	TNF alpha inhibitor	Subcutaneous injection: 80 mg week 1, 40 mg week 2, then 40 mg every other week until clinical response is noted
Combination dapsone and triamcinolone [11]	Folic acid antagonist; corticosteroid	PO dapsone 100 mg daily for 2 weeks followed by 50 mg daily for 25 weeks *plus* intralesional triamcinolone 10 mg every other week for four injections followed by once monthly for three injections

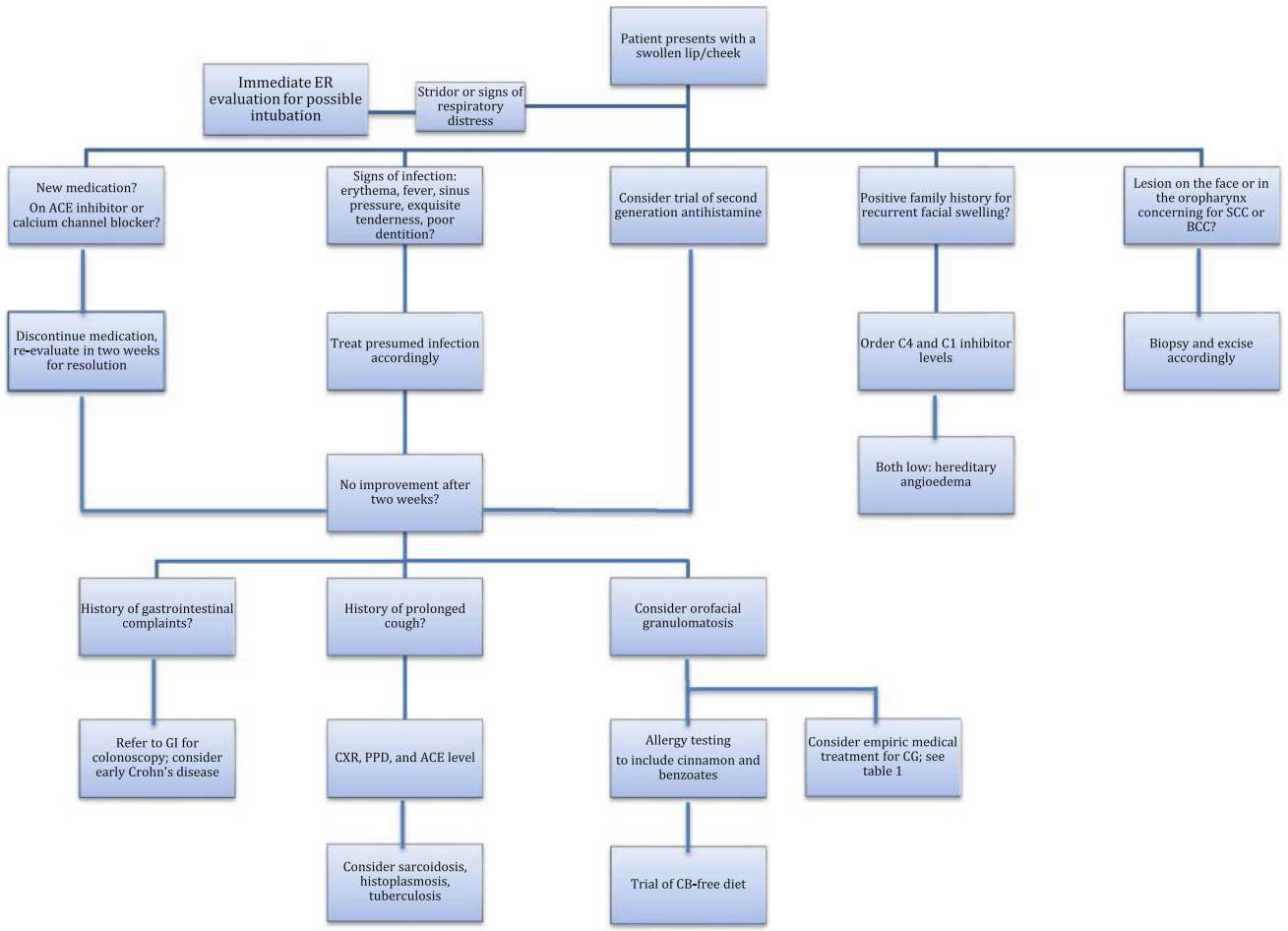

Fig. 4 Proposed approach to lip swelling

dentition or lesions concerning for malignancy, examination of the tongue for plication which make indicate the full MRS, inspection for aphthous ulcers which may suggest early Crohn's disease, inspection for erythematous lesions suggestive of rosacea, and palpation of the affected lip for pain. An algorithm for the approach to lip swelling is proposed in Fig. 4.

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