Persistent Lip Swelling

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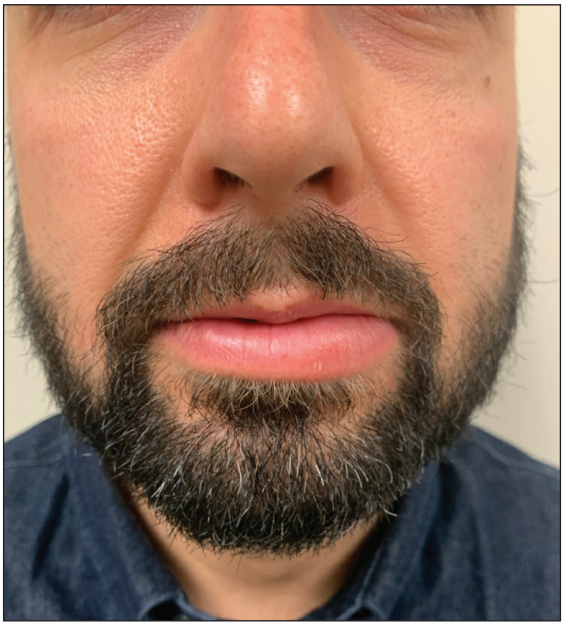

A 36-year-old man with allergic rhinitis presented with lower lip swelling of several months' duration. The swelling was persistent and predominantly on the left side of the lower lip but occasionally spread to the entire lower lip. The episodes of increased swelling would last for several days and were not associated with any apparent triggers. He denied any pain, pruritus, or dryness. He noted more drooling from the affected side but denied any associated breathing difficulty or throat discomfort. Treatment with an oral antihistamine provided no relief. He denied any recent nonsteroidal anti-inflammatory drug or angiotensin-converting enzyme inhibitor use. His family history was notable for lupus in his maternal grandmother and maternal aunt. He denied any personal or family history of inflammatory bowel disease or recent gastrointestinal tract symptoms. Physical examination revealed nontender edema in the left side of the lower lip with no surface changes. No warmth or erythema were noted. The tongue and the rest of the oral cavity were unremarkable.

WHAT'S YOUR **DIAGNOSIS?**

a. angioedema
b. Crohn disease
c. foreign body reaction
d. granulomatous cheilitis
e. sarcoidosis

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The authors report no conflict of interest.
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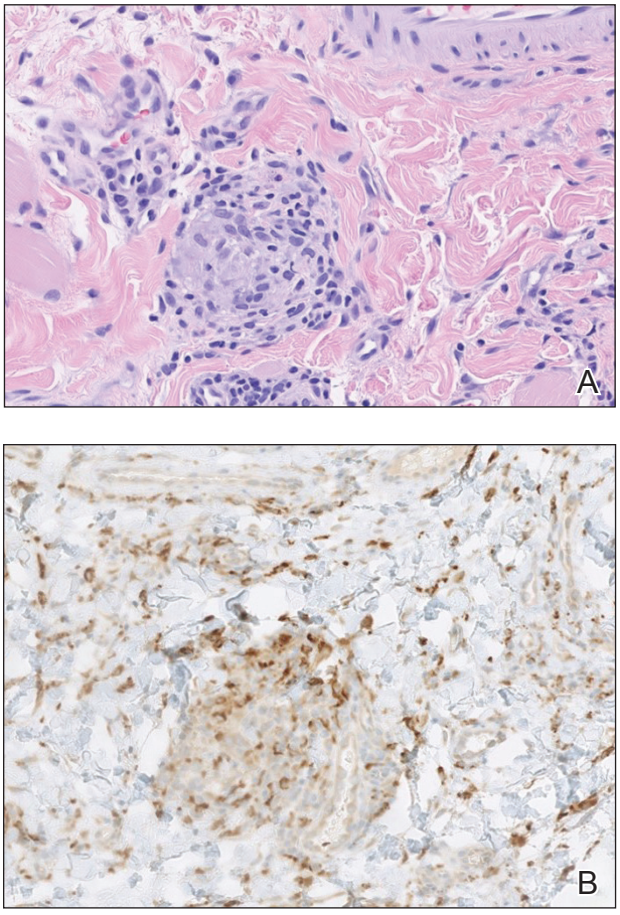
doi:10.12788/cutis.0533

THE **DIAGNOSIS:** Granulomatous Cheilitis

A punch biopsy of the lip revealed a noncaseating microgranuloma in the submucosa with modest submucosal vascular ectasia and perivascular lymphoplasmacytic infiltrates (Figure). Comprehensive metabolic panel, complete blood cell count, angiotensin-converting enzyme (ACE) levels, and inflammatory markers (ie, erythrocyte sedimentation rate, C-reactive protein) all were within reference range. A serum environmental allergen test was negative except for ragweed. Levels of complements—C1 esterase inhibitor (C1-INH) antigen and function, C1q, C3, and C4—and antinuclear antibodies all were normal. Chest radiography was unremarkable. In lieu of a colonoscopy, a fecal calprotectin obtained by gastroenterology was normal. Given the clinical presentation and histopathologic findings, a diagnosis of granulomatous cheilitis (GC) was made.



A, A small noncaseating epithelioid granuloma with few lymphocytes (H&E, original magnification ×30). B, CD68 immunostaining showed a cluster of epithelioid histiocytes in the submucosal stroma (original magnification ×30).

Granulomatous cheilitis (also known as Miescher cheilitis) is an idiopathic condition characterized by recurrent or persistent swelling of one or both lips. Granulomatous cheilitis usually is an isolated finding but can occur in the setting of Melkersson-Rosenthal syndrome, which refers to a triad of orofacial swelling, facial paralysis, and fissured tongue. *Orofacial granulomatosis* is a unifying term for any orofacial swelling associated with histologic findings of noncaseating granulomas without evidence of a systemic disease.

Granulomatous cheilitis is a rare disease that most commonly occurs in young adults without any sex predilection.[1] The etiology still is unknown, but genetic predisposition, idiopathic influx of inflammatory cells, sensitivity to food or dental materials, and infections have been implicated.[2] Granulomatous cheilitis initially presents as soft, nonerythematous, nontender swelling affecting one or both lips. The first episode usually resolves in hours or days, but the frequency and duration of the attacks may increase until the swelling becomes persistent and indurated.[3] Granulomatous cheilitis often is a diagnosis of exclusion. A tissue biopsy may show noncaseating epithelioid and multinucleated giant cells with associated lymphedema and fibrosis[4]; however, histologic findings may be nonspecific, especially early in the disease course, and may be indistinguishable from those of other granulomatous diseases such as sarcoidosis and Crohn disease (CD).[5]

Lip swelling may be an oral manifestation of CD. Compared with GC, however, CD more commonly is associated with ulcerations, buccal sulcus involvement, abnormalities in complete blood cell count such as anemia and thrombocytosis, and elevated C-reactive protein and erythrocyte sedimentation rate. Although infrequent, GC may coincide with or precede the onset of CD.[6] Thus, a detailed gastrointestinal history and appropriate laboratory tests are needed to rule out undiagnosed CD. Nevertheless, performing a routine colonoscopy in the absence of gastrointestinal symptoms is debated.[7,8]

Sarcoidosis is a systemic granulomatous disease that can have oral involvement in the form of edema, nodules, or ulcers. Oral sarcoidosis usually occurs in patients with chronic multisystemic sarcoidosis and likely is accompanied by pulmonary manifestations such as hilar adenopathy and infiltrates on chest radiography, which are found in more than 90% of patients with sarcoidosis.[9,10] A diagnosis of sarcoidosis is additionally supported by other organ involvement such as the joints, skin, or eyes, as well as elevated ACE and calcium levels.

Foreign bodies are another source of granulomatous inflammation and may present with nonspecific findings of swelling, masses, erythema, pain, or ulceration

in oral tissues.[11] Foreign body reactions to dental materials, retained sutures, and cosmetic fillers have been reported.[12-14] In many cases, the foreign material is evident on biopsy.

Angioedema may mimic GC and should be excluded before more extensive testing is done, as it can result in life-threatening respiratory compromise. Numerous etiologies of angioedema have been identified including allergens, acquired or hereditary C1-INH deficiency, nonsteroidal anti-inflammatory drugs, ACE inhibitors, autoimmune disorders, and chronic infections.[15] Patients with angioedema may have abnormalities in C4 and C1-INH levels or report certain medication use, allergen exposure, or family history of unexplained recurrent swellings or gastrointestinal symptoms.

There currently is no established treatment of GC due to the unclear etiology and unpredictable clinical course that can lead to spontaneous remissions or frequent recurrences. Corticosteroids administered systemically, intralesionally, or topically have been the mainstay treatment of GC.[2] In particular, intralesional injections have been reported as effective in reducing swelling and preventing recurrences in several studies.[16,17] Numerous other treatments have been reported in the literature with inconsistent outcomes, including antibiotics such as minocycline, metronidazole, and roxithromycin; clofazimine; thalidomide; immunomodulators such as tumor necrosis factor inhibitors and methotrexate; fumaric acid esters; and cheiloplasty in severe cases.[16] Our patient showed near-complete resolution of the lip swelling after a single intralesional injection of 0.5 cc of triamcinolone acetonide 5 mg/mL. The patient has since received 5 additional maintenance injections of 0.1 to 0.2 cc of triamcinolone acetonide 2.5 to 5 mg/mL spaced 2 to 4 months apart with excellent control of the lip swelling, which the patient feels has resolved. We anticipate that repeated injections and monitoring of recurrences may be required for long-term remission.

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