To the Editor:
Granulomatous cheilitis (GC), also known as Miescher cheilitis, belongs to a larger class of diseases known as orofacial granulomatoses (OFGs), a set of diseases distinguished by their clinical and pathologic features of facial edema and granulomatous inflammation.1-3 Granulomatous cheilitis, a monosymptomatic variant of a more extensive disease known as Melkersson-Rosenthal syndrome (MRS), presents with labial swelling mimicking angioedema. Timely diagnosis of GC and MRS reduces the number of unnecessary tests, health care costs, and unnecessary patient burden. We present a case of idiopathic persistent swelling of the upper lip that was originally misdiagnosed as angioedema.

A 13-year-old white adolescent boy was referred to the allergy-immunology clinic for an alternate opinion regarding a presumed diagnosis of angioedema. He presented with prominent persistent swelling of the upper lip of 1 year’s duration associated with fissuring and discomfort while eating, which led to weight loss of more than 4.5 kg. The patient denied any history of facial asymmetry, paralysis, dental infections, or gastrointestinal tract symptoms. Additionally, he was not on any medications. His parents reported variable symptomatic worsening associated with egg ingestion, but avoiding egg did not provide any symptomatic relief. The swelling was unresponsive to multiple and prolonged courses of antihistamines and oral glucocorticoids. The patient’s medical history revealed no similar episodes of unexplained swelling, and family history was negative for angioedema. On examination, the upper lip was tender with a firm rubbery consistency. No other areas of swelling were noted. Angular cheilosis and minor labial mucosal ulcerations also were observed (Figure).

The persistent nature of the lip swelling and findings of fissures were not consistent with angioedema. Furthermore, prior laboratory studies did not reveal evidence of hereditary or acquired angioedema, and a complete blood cell count with differential was within reference range. Although the clinical suspicion for egg allergy was low, a blood test for serum-specific IgE showed a mild reactivity to egg allergen. The patient was referred to an oral surgeon for biopsy, which revealed dermal foci of noncaseating granulomas consistent with the preliminary diagnosis of GC.

Intralesional triamcinolone injections were initiated with marked improvement. Shortly after

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Granulomatous cheilitis presenting with persistent upper lip swelling with healing midline fissure and bilateral cheilosis.

The initial improvement, however, the symptoms recurred, which necessitated several additional intralesional triamcinolone injections, again with remarkable improvement. Approximately 1.5 years later, the patient presented with recurrence of the lip swelling and admitted to having episodic diarrhea and abdominal cramps. He was referred to a pediatric gastroenterologist and a colonoscopy with biopsy confirmed Crohn disease. He was started on azathioprine followed by infliximab. A few months after this treatment was initiated, both his lip swelling and gastrointestinal tract symptoms remarkably improved. He has been maintained on this regimen and in the most recent follow-up had no recurrence of GC. He is scheduled to have another colonoscopy.

Granulomatous cheilitis is a rare chronic inflammatory condition characterized clinically by persistent lip swelling and histologically by granulomatous inflammation in the absence of systemic granulomatous disorders.1 Granulomatous cheilitis falls under the umbrella of OFGs. When it is paired with facial paralysis and fissuring of the tongue, it is specifically referred to as MRS. The prevalence of GC has historically been difficult to ascertain. In a review, an estimated incidence of 0.08% in the general population was reported with no predilection for race, sex, or age.4,5 Initially, the swelling of GC can be misdiagnosed as angioedema; therefore, it is imperative to include OFG and GC in the differential diagnosis of facial angioedema.3 Other possible diagnoses to consider include contact dermatitis, foreign-body reactions, infection, and reactions to medications such as angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs.5 Chronic lymphedema and other granulomatous diseases also should be considered in the differential diagnosis. Isolated lymphedema of the head and neck, though rare, typically is seen following surgical or radiological interventions for cancer. Lymphatic fibrosis also can occur in the setting of chronic inflammatory skin conditions but is not typically the first presenting symptom, as was seen in our patient.6 Although granulomatous diseases such as sarcoidosis may be difficult to clinically and histologically differentiate from GC, isolated orofacial swelling in sarcoidosis is rare. If clinical suspicion for sarcoidosis does exist, however, a negative chest radiograph as well as serum calcium and angiotensin-converting enzyme levels within reference range may help differentiate GC from sarcoidosis. In our patient, the clinical suspicion for sarcoidosis was low given his clinical history, young age, and race.

The etiology of MRS and GC currently is unknown. Genetic factors, food allergies, infectious processes, and aberrant immunologic functions all have been proposed as possible mechanisms.1,3,7,8 Genetic factors, such as HLA antigen subtypes, have been investigated but have not shown a definitive correlation.8 Numerous food allergens have been suggested as causative factors in OFG via a type of delayed hypersensitivity reaction,7 with cinnamon and benzoate reported as 2 of the most cited entities.9,10 Currently, it is believed that both of these mechanisms may play an exacerbating role to an otherwise unknown disease process.7,8 The infectious process most often associated with GC is Mycobacterium tuberculosis; however, similar to genetics and food allergens, causality has not been determined.4,7 At the present time, the best evidence points to an immunologic basis of GC with the inciting event being a random influx of inflammatory cells.7,11

There is a known association between GC and Crohn disease, especially when oral lesions are present.1,9 Granulomatous cheilitis can be considered an extraintestinal manifestation of Crohn disease. Up to 20% of OFG patients eventually go on to develop Crohn disease, with some reports being even higher when OFG presents in childhood.1,9

One study proposed that both GC and Crohn disease patients shared similar histopathologic and immunopathologic features including a helper T cell (T\textsubscript{H}1)–predominant inflammatory reaction.11

The treatment of GC is challenging, with most evidence coming from sporadic case reports. Given the relatively high rate of cinnamon and benzoate hypersensitivity seen in GC patients, it has been postulated that a diet lacking in them will improve the disease. At least one study has reported positive clinical outcomes from diets lacking in cinnamon and benzoate and in fact recommended it as...
a potential first-line treatment. The mainstay of treatment, however, is corticosteroids, but continued use is discouraged due to their large side-effect profile. Currently, the most agreed upon treatment for patients with isolated GC is intralesional triamcinolone injections. Despite the robust initial response often seen with triamcinolone injections, it is not uncommon for the benefit to be short-lived, requiring additional treatments. Newer medical therapies that have shown promise largely are centered on anti–tumor necrosis factor α medications such as infliximab and adalimumab. It is postulated that due to the potential overlapping pathophysiology between Crohn disease and GC, there may be utility in using the same treatments. In situations where medical therapy fails or in extremely disfiguring cases of GC and MRS, surgical cheiloplasty is performed to reduce lip size and improve cosmetic appearance. In a small study, reduction cheiloplasty gave satisfactory functional and cosmetic outcomes in all 7 patients reviewed at a median follow-up of 6.5 years.

This case emphasizes the importance of paying close attention to history and physical examination features in developing any differential diagnosis. In this patient, persistent orofacial swelling with associated mucosal ulcerations were sufficient to exclude drug-induced, idiopathic, hereditary, and acquired angioedema. The clinical history coupled with the biopsy results yielded a confident diagnosis of GC. Furthermore, similar presentations should raise concern for a subclinical inflammatory bowel disease such as Crohn disease.

REFERENCES