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Is orofacial granulomatosis a distinct clinical disorder?

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Abstract

Orofacial granulomatosis is a rare disorder that is heterogeneously defined in the published literature. Herein, we describe a patient with orofacial granulomatosis with clinical and histologic evidence, discuss differential diagnoses, and offer clinical pearls for diagnosing and assessing this disorder. Our case provides support that orofacial granulomatosis is a distinct disorder as opposed to a sequela of other systemic granulomatous diseases. This information will aid dermatologists in decision making and diagnosing the disorder.

Keywords: granuloma, granulomatous cheilitis, Melkersson-Rosenthal, orofacial granulomatosis

Introduction

Orofacial granulomatosis (OFG) is a rare disorder characterized by painless, chronic facial and/or lip swelling with histopathological evidence of non-necrotizing granulomas. Orofacial granulomatosis is not well defined in the literature; some report it is related to Crohn disease, whereas others define it as a separate diagnosis in the absence of systemic inflammatory diseases. However, the literature does consistently describe OFG as an umbrella term that encompasses the variants granulomatous cheilitis (persistent or recurrent lip swelling) and Melkersson-Rosenthal syndrome (the triad of granulomatous cheilitis, plicated tongue, and recurrent facial palsy). Although OFG is considered to be rare, it is important to define it appropriately to further understand prevalence, etiology, and treatment approaches. We report a case of OFG in a patient with skin of color who did not have evidence of systemic inflammatory disease, thus supporting OFG as a distinct clinical entity.

Case Synopsis

A 58-year-old Black woman with history of essential hypertension successfully managed with lisinopril 10mg daily presented for persistent upper lip swelling ongoing for 10 months, without a diagnosis. The swelling had become more obvious since the onset. There were no associated mucosal lesions or facial swelling (**Figure 1A**). The remainder of the relevant physical examination was unremarkable except stable dermatosis papulosa nigra on the face and neck. The histopathology of a 2mm punch biopsy from the medial superior lip revealed small nodular aggregates of epithelioid histiocytes associated with multinucleated giant cells. No polarizable material was detected in all sections reviewed and the periodic acid-fast stain was negative for fungal organisms. Taken together, the clinicopathologic correlation was consistent with an OFG diagnosis (**Figure 2**). The patient underwent subsequent workup for sarcoidosis (chest X-ray, ocular exam) and inflammatory bowel disease (colonoscopy, upper GI endoscopy, antineutrophil cytoplasmic antibodies panel [ANCA]), which were all negative. To date, the patient has received two rounds of 2mg intralesional corticosteroid injections with improved lip swelling.

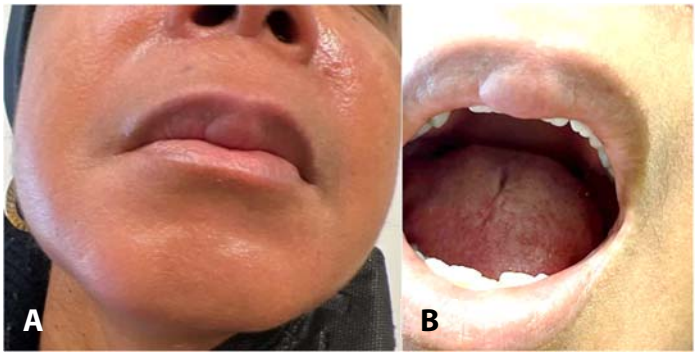

Figure 1. *Clinical photographs of orofacial granulomatosis taken during the initial dermatology visit, prior to therapy.* ***A)*** *Absent facial involvement or swelling.* ***B)*** *Mid upper lip lesion and plicated tongue.*

Case Discussion

Generally, OFG is a diagnosis of exclusion. Common conditions in the differential diagnosis for lip swelling include allergic contact dermatitis, angioedema, and OFG. Although angiotensin-converting enzyme (ACE) inhibitors are the leading cause of drug-induced angioedema, especially in people of African descent, our patient's hypertension was successfully managed with lisinopril for two years without issues and the lip swelling did not follow the typical episodic pattern of drug-induced angioedema. Moreover, the patient had fixed, nodular lip swelling and the biopsy demonstrated non-necrotizing granulomas. Angiotensin-converting enzyme inhibitor-induced angioedema can develop anytime during the treatment course, and therefore cannot be ruled out based on timeline alone [1]. There are published reports describing the imaging, clinical characteristics, and outcome of patients with ACE inhibitor-induced angioedema [1-3], but to our knowledge, no studies examine the histology. Therefore, a granulomatous reaction from the use of lisinopril cannot be completely excluded and this represents a potential limitation of our assessment. We excluded allergic contact dermatitis due to the persistent nature of the lip swelling, confined upper lip distribution, lack of an offending agent, and biopsy results.

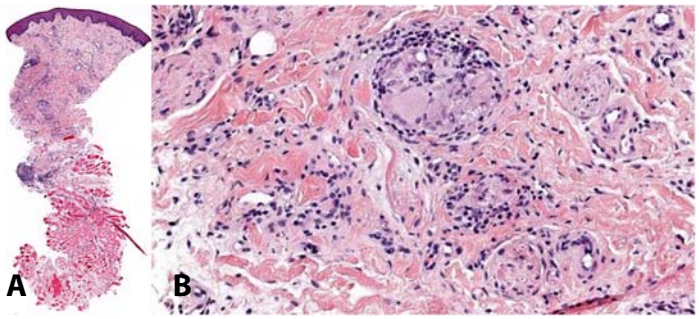

Figure 2. *H&E histopathology demonstrating non-necrotizing granulomas consistent with orofacial granulomatosis.* ***A)*** *View of a punch biopsy taken from the medial superior lip, 1×.* ***B)*** *View demonstrates few small nodular aggregates of epithelioid histiocytes associated with multinucleated giant cells, 10×.*

Once histopathology confirms non-necrotizing granulomas, the differential diagnosis includes the disorders listed in **Table 1**. Systemic inflammatory diseases such as sarcoidosis and Crohn disease necessitate early identification to halt or slow disease progression. Sarcoidosis can affect any organ of the body and accordingly, it usually presents with multiple organ involvement. Oral sarcoidosis is rare and the most common sites include the jawbone, salivary gland, buccal mucosa, and gingiva [4,5]. Even more uncommon, oral sarcoidosis may be the earliest manifestation of systemic disease, though the few reported cases rarely involve the lips [4,5]. Other than the lip lesion, our patient had no other cutaneous manifestations to suggest cutaneous sarcoidosis such as facial papules or plaques or erythema nodosum; together with the negative chest X-ray and ocular examination, we confidently excluded sarcoidosis. Furthermore, it is controversial whether or not patients with isolated skin findings can be diagnosed with sarcoidosis, as strict definitions require involvement of two organ systems or more [6].

The exclusion of Crohn disease in the evaluation of cutaneous granulomatous disease is more straightforward. The gold standard diagnostic tool for Crohn disease is colonoscopy. Since Crohn disease can involve any part of the gastrointestinal (GI) system, upper GI endoscopy is also useful. Although autoantibodies such as ANCA are more often detected in patients with ulcerative colitis, they have been detected in Crohn disease; therefore, presence of ANCA may indicate need for additional workup [7]. Literature suggests buccal sulcus involvement and ulceration of the mucosa are more commonly associated with oral Crohn disease [8-9], thus these findings may serve as key characteristics to differentiate OFG from oral Crohn disease

Table 1. *Differential diagnoses of lip swelling with biopsy-confirmed non-necrotizing granulomas.*

Disease [Reference]	Age of onset	Morphology	Clinical features	Pathology	Lab tests	Treatment
OFG [10]	Usually adults	Lip and/or facial swelling	Umbrella term including MRS and granulomatous cheilitis	NNG	Non-specific	Topical/ intralesional steroids
Granulomatous cheilitis [11]	Usually adults	Lip swelling	Perioral erythema, lip fissuring, angular cheilitis	NNG	Non-specific	Topical/ intralesional steroids
Melkersson-Rosenthal syndrome [12]	Usually adults	Lip swelling	Triad of lip swelling, recurrent facial palsy, and/or plicated tongue	NNG	Non-specific	Topical/ intralesional steroids
Sarcoidosis [6]	Bimodal peaks: third/fourth and sixth decade	Oral mucosa ulcerations and fissures, granulomatous papules on the face	Mediastinal, lung, or liver involvement; other typical skin lesions	NNG	ACE, CBC, CMP, UA, 25-hydroxyvitamin-D and 1,25-dihydroxyvitamin D3, and TSH	Topical/oral steroids, topical calcineurin inhibitors, and oral tetracycline antibiotics
Crohn disease [13]	Bimodal peaks: second/ third and fifth decade	Ulcerated papules and plaques, fissures, and fistulas of the oral mucosa	Other gastrointestinal signs and symptoms	NNG and lymphoid aggregates	Upper endoscopy, colonoscopy, ANCA	Oral steroids, 5-amino salicylates, oral biologics
Granulomatous rosacea [14]	Adults: fourth decade	Red-brown persistent papules favoring the face, periorbital, or perioral skin	With or without other signs of rosacea (e.g., facial flushing, telangiectasias, burning, stinging)	NNG adjacent to follicles	Non-specific	Avoiding triggers, topical/oral antibiotics, azelaic acid, phototherapy
Drug-induced allergic contact dermatitis [15-16]	Any age	Red indurated, scaly plaques; may have vesicles and bulla when severe	History of atopy	Spongiosis, Langerhans cells, may contain foreign body NNG	KOH, patch testing	Allergen avoidance, topical/oral steroids, topical calcineurin inhibitors

ACE, angiotensin converting enzyme; ANCA, anti-neutrophil cytoplasmic antibodies; CBC, complete blood count; CMP, comprehensive metabolic panel; KOH, potassium hydroxide preparation test; MRS, Melkersson-Rosenthal syndrome; NNG, non-necrotizing granulomas; OFG, orofacial granulomatosis; TSH, thyroid stimulating hormone; UA, urinalysis.

preceding systemic disease. Outside of the granulomatous lip lesion, we did not find any clinical evidence of Crohn disease in our patient. The full triad of Melkersson-Rosenthal syndrome is rare [10]. Although this patient did have mild tongue fissures (**Figure 1B**), there was no recurrent facial palsy and fissured tongue is a normal finding in healthy people. This patient did not have clinical evidence or history of granulomatous rosacea. Consequently, we diagnosed our patient with OFG (unspecified variant).

Conclusion

To date, the definition of OFG is not well defined. We hope that our case contributes to the limited

literature by providing diagnostic pearls for OFG, while further suggesting it as a disorder separate from other systemic granulomatous diseases.

Potential conflicts of interest

The authors declare no conflicts of interest.

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