Orofacial Granulomatosis Treated with Intralesional Triamcinolone

Ivan Alajbeg[1], Ana Andabak Rogulj[1], Zdenka Hutinec[2]

[1]Department of Oral Medicine, School of Dental Medicine, University of Zagreb; [2]Clinical Department of Pathology and Cytology, University Hospital Center Zagreb, Zagreb, Croatia

Corresponding author:

Associate Prof. Ivan Alajbeg, DMD, PhD
Department of Oral Medicine
School of Dental Medicine
University of Zagreb
Gundulićeva 5
Zagreb HR-10000, Croatia
alajbeg@sfzg.hr

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SUMMARY Orofacial granulomatosis (OFG) is an uncommon disease, usually presenting as recurrent or persistent swelling of the soft tissues in the orofacial region, predominantly lips (cheilitis granulomatosa). The cause of this illness is unknown. OFG may also be part of the triad of Melkersson-Rosenthal syndrome (MRS) and some consider it a monosymptomatic form of MRS. We describe a case of a Croatian male patient with recurrent swelling limited to the upper lip for the past 6 years. After establishing the diagnosis, we performed intralesional triamcinolone injections (16 mg, twice on a weekly schedule), resulting in complete remission. OFG differential diagnosis and treatment modalities are discussed.

KEY WORDS: orofacial granulomatosis, therapy, triamcinolone

INTRODUCTION

The term orofacial granulomatosis (OFG) describes a nonspecific granulomatous inflammation of unknown origin, occurring on all parts of oral mucosa, as well as on cheeks, chin and eyelids. Most often, it presents clinically as persistent or recurrent lip swelling, thus the term cheilitis granulomatosa (CG) was previously introduced by Miescher in 1945 (1). It is considered a monosymptomatic form of Melkersson-Rosenthal syndrome (MRS), which, in its fully blown clinical picture, includes CG, facial nerve palsy, and fissured tongue (2,3). All three syndrome components appear rarely, accounting up to only 8% to 25% of cases, the most common component being CG (4,5). Cheilitis granulomatosa usually appears in the second decade of life, more frequently in females (4). Two major diseases may be presented as CG: Crohn's disease (6), and sarcoidosis (7,8). In terms of treatment possibilities and outcome, OFG represents a very challenging and unpredictable condition.

CASE REPORT

A male patient aged 48, with otherwise insignificant medical history, not taking any medications, had intermittent swelling of the upper lip and surrounding intraoral tissues for the past six years (Fig 1). Episodes recurred every 2-3 months and lasted several hours to several days. Palpatory finding included multiple indurated lip nodules. He also had fissured tongue. Angioedema was excluded (total serum IgE was normal, nutritional and environmental allergens were excluded by allergen-specific IgE antibody test). Panel tests for C1-esterase inhibitor levels and complement components C1 through C4 ruled out hereditary

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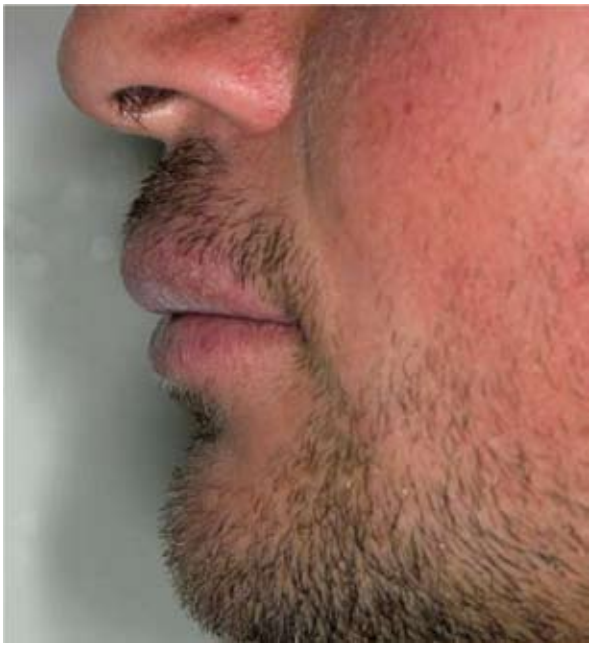

Figure 1. Swelling involving the entire upper lip.

angioedema. Dental origin was excluded by clinical examination, tooth vitality testing, and x-ray findings. No dental materials were present in the patient's mouth. Medical history was insignificant for any gastrointestinal or digestive problems during the past 6 years, giving not enough indications to suspect the possible Crohn's disease. Sarcoidosis was excluded by the lack of respiratory symptoms, normal chest x-ray and normal serum angiotensin-converting enzyme (ACE) levels.

Upon exclusion of the above mentioned conditions, clinical features and palpatory findings of indurated lip nodules indicated idiopathic OFG. A finding of fissured tongue is consistent with oligosymptomatic Melkersson-Rosenthal syndrome without facial palsy.

Deep biopsy of the affected lip showed histologic features of perivascular and interstitial infiltrates of inflammatory cells composed of lymphocytes, plasma cells and mast cells in subepithelial stroma (HE, 200x; Giemsa, 400x) (Fig. 2). Histologic staining for acid fast bacteria was negative, thus excluding tuberculosis and deep mycoses. Polarizing foreign materials were also excluded histologically. After fulfilling clinical and histopathologic criteria, the diagnosis of OFG was made.

After thorough application of topical xylocaine anesthetic spray, we performed intralesional treatment with corticosteroid injections, according to Mignogna *et al*. (9). We injected 0.1 mL of triamcinolone acetonide (TA) (40 mg/mL) into each of the 4 equidistant points on the border between upper lip vermillion and mucosa. In addition to TA, we added a small amount of epinephrine-free 3% mepivacaine local anesthetic to the injectable solution (0.05 mL of mepivacaine *per* injection point). The needle was inserted vertically towards the top. In order to avoid lip skin ischemia, the needle was directed slightly inwards. The total dose of TA was 16 mg *per* treatment. After one week, the procedure was repeated, resulting in full resolution (Fig. 3.), as assessed 7 days following 2nd treatment.

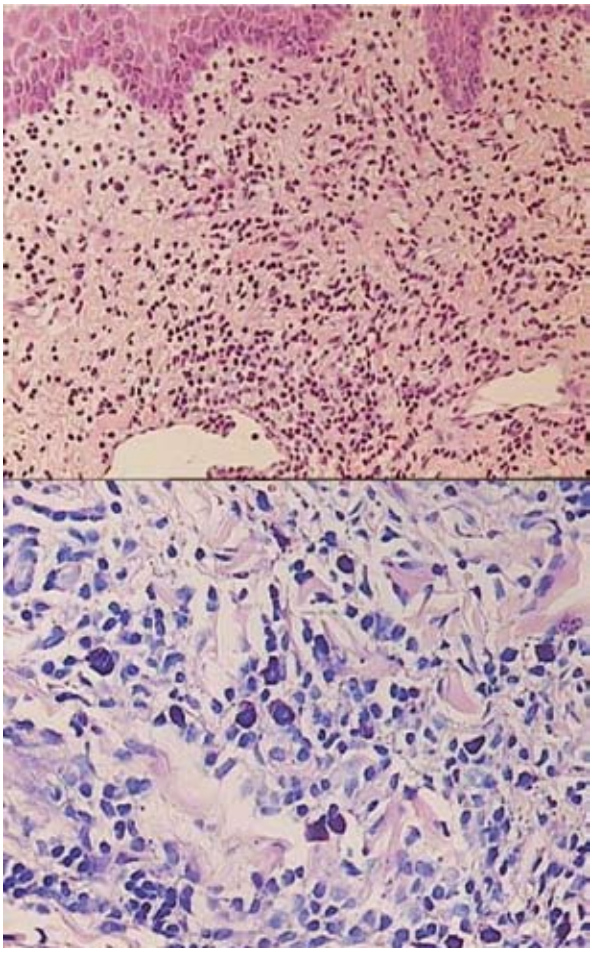

Figure 2. Lip biopsy histologic finding revealing perivascular and interstitial infiltrates of inflammatory cells composed of lymphocytes, plasma cells and mast cells in subepithelial stroma (upper panel: HE, 200x; lower panel: Giemsa, 400x).

DISCUSSION

Orofacial granulomatosis is a recurrent disease, episodic, and intermittent, often recalcitrant to treatment. Complete and spontaneous remission is

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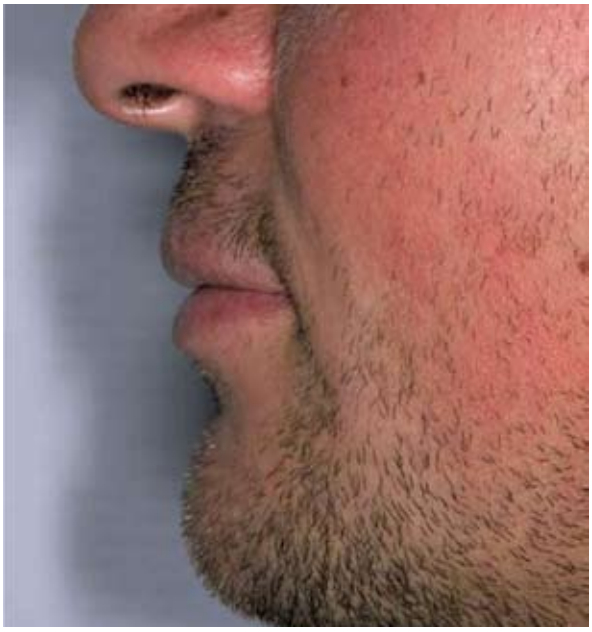

Figure 3. Complete resolution after 2 sessions of intralesional corticosteroid treatment.

unlikely. Some authors consider it the first clinical sign of MRS, or its mono-/oligo-symptomatic form (4,5,9), but there is no consensus on the subject. Apparently, up to 42% of MRS patients present with CG, whereas other signs may appear later in life. Others consider CG and MRS two different entities, as most of CG patients never develop MRS (10).

Histologically, it is characterized by noncaseating granulomatous inflammation (11,12). van der Waal *et al*. (10) state that, although noncaseating granulomas are classically present, the histology may be nonspecific, with edema and perivascular lymphocytic infiltrate. There are 3 major groups of histopathology findings in OFG: 2 include noncaseating granulomas and one includes nonspecific inflammation (13). Thus, it can be concluded that biopsy without granulomas is not inconsistent with the diagnosis of CG. Dilated lymphatics in the superficial lamina propria and perivascular aggregation of histiocytes and plasma cells usually are present, as in our case. Very deep mucosal biopsy should always be performed in order to increase the likelihood of finding granuloma. We obtained a large specimen, roughly 10 mm deep and 10 mm in diameter, but well organized granuloma was not present in that tissue sample. It is consistent with the findings of Perez-Calderon *et al*. (14), and a case presented by Bartell *et al*. (15), depicting "diffuse lymphocytic infiltrate in submucosa, with perivascular, poorly formed granulomas". By thorough literature search, we could not find actual data on the percentage of noncaseating granulomas present in all OFG cases.

The diagnosis of CG is therefore a diagnosis of exclusion. It would include clinical, hematologic and histologic investigations in each patient, in addition to imaging techniques and radioallergosorbent and patch tests if dental materials are present. It is necessary to exclude the possible local (dental) and systemic diseases that can have similar clinical manifestations, including hypersensitivity reactions. Although IgE-mediated allergy was ruled out, our patient was regularly taking antihistamine fexofenadine 180 mg, without improvement in the swollen lip. It is a rather regular scenario, as OFG is generally not suspected. Further workup includes sarcoidosis, Crohn's disease, tuberculosis, deep fungal infections, leprosy, leukemic infiltrate, and foreign body reactions (6,8,11,16-18). Of those mentioned, two are of particular medical interest: sarcoidosis and Crohn's disease. The former is unlikely in the absence of respiratory problems, and if chest x-ray and ACE levels are normal. Biopsy of labial salivary gland can be of help in diagnosing sarcoidosis (18). Regarding the latter, the need for invasive evaluation in a patient with isolated granulomatous cheilitis is not recommended. This is pointed out in a review of 13 patients, in which the authors suggest that no specific diagnostic procedures should be undertaken if gastrointestinal complaints are absent (10).

The treatment of OFG is challenging, with frequent recurrences despite different modalities applied. Medical management includes administration of nonsteroidal anti-inflammatory drugs, broad-spectrum antibiotics, antituberculous drugs, antilepromatous agents (clofazimine), sulfa drugs (sulfasalazine), antimalarials (hydroxycholoroquine), and steroids, be it systemic or intralesional (10,19-21). Surgically, cheiloplasty has shown some results, but would be suggested only for resistant cases, particularly when long-lasting chronic inflammation has caused fibrous tissue proliferation, when it is too late to use medications (22). Thus, early diagnosis and treatment is mandatory for better outcome. Thalidomide has recently been shown to be effective in recalcitrant cases (23).

Among those mentioned above, corticosteroids are first-line treatment, as they are effective in swelling reduction (24,25). As the nature of OFG is relapsing, the use of systemic steroids has limitations because of side effects. Thus, intralesional corticosteroid injections have been suggested (26). Recently, delayed release concentrated TA (40 mg/mL)

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has been pointed as the treatment of choice, used in small quantities of 0.1 mL (4 mg) *per* point of needle insertion (9). Previously, diluted concentration of TA (10 mg/mL) was advocated in OFG treatment, but a significantly higher volume of solution had to be injected (amounting from 3 mL to up to 10 mL) (26). This approach has warranted previous application of local anesthetics, as the procedure would otherwise be painful due to the large amounts of the solution injected. Another problem was the dramatic increase of tissues after injections. We used a small amount of concentrated TA, and a cumulative dosage of 32 mg has proved sufficient for ongoing control of OFG for 7 months to date, as compared to previous relapses occurring every 2-3 months. We did apply topical anesthesia prior to injecting triamcinolone. Adding a small amount of the epinephrine-free mepivacaine local anesthetic to triamcinolone solution (0.05 mL *per* injection point) significantly decreases discomfort during and after application, while only slightly increasing total volume.

Based on the previously published experience and the case presented, we suggest repeating the treatment on a weekly basis until complete response is achieved. This usually requires 2 to 3 applications (9). The potential side effects of corticosteroid such as temporary ischemia, hypopigmentation and soft tissue atrophy may cause cosmetic problems. Thus, the needle insertion line should be inclined orally, and epinephrine-free anesthetic should be used, if any. The expected clinical response is appropriate but not permanent, most probably requiring repeated injections in the future (9,10,26).

CONCLUSION

Differential diagnosis of swollen lips and swelling of other orofacial structures includes OFG. The diagnosis is made by excluding numerous other disease entities, e.g., Crohn's disease and sarcoidosis, requiring broad diagnostic workup. Orofacial granulomatosis (or CG as one of its clinical forms) should be diagnosed early, as later in the course of the disease fibrous tissue may proliferate, thus narrowing treatment options to surgery. Once OFG is diagnosed, successful and predictable treatment results may be achieved by repeated use of small doses of concentrated (40 mg/mL) slow release triamcinolone acetonide intralesional injections, which should be regarded as first-line treatment.

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