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Single Case

Unsuccessful Treatment of Cheilitis Granulomatosa with Oral Methotrexate

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Keywords
Cheilitis grandularis · Crohn's disease · Facial palsy · Fissured tongue · Granuloma · Melkersson-Rosenthal syndrome

Abstract
Cheilitis granulomatosa (CG) is a rare idiopathic condition with painless lip swelling, characterized by non-necrotizing granulomatous inflammation in the absence of other identifiable causes such as Crohn's disease, sarcoidosis, foreign body reaction, or infection. CG may precede the presentation of Crohn's disease after long-term follow-up. Spontaneous remission of CG rarely occurs. To date, given the rarity of CG, there is no gold standard treatment. Recommended treatments are supported by small studies, case reports/series, and expert opinions. Glucocorticoids are the first-line therapy in the acute stages of the disease; however, recurrence commonly occurs. Previously, methotrexate (MTX) showed a beneficial effect on orofacial swelling in a case of CG accompanied by Crohn's disease. We present a patient with CG without Crohn's disease. He was treated with oral MTX in combination with intralesional corticosteroid injection on one side of the lip. The injected side showed improvement, while lip swelling on the noninjected area remained unchanged after 3 months of treatment. Therefore, CG is refractory to treatment with MTX from our experience. Further studies regarding the optimum dosage of MTX is needed.

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Introduction

Cheilitis granulomatosa (CG) is a rare idiopathic recurrent or persistent painless swelling of one or both lips. Histopathological findings are characterized by non-necrotizing granulomatous inflammation in the absence of other identifiable causes, which must be excluded prior to the diagnosis of CG such as Crohn's disease, sarcoidosis, foreign body reaction, or infection [1, 2]. The main objective for the treatment of GC is to correct the cosmetic outcome for self-concerned individuals. Unfortunately, there is no standard regimen for the treatment of CG. Therefore, the management of CG remains challenging.

Case Presentation

A previously healthy 26-year-old Asian male gradually developed diffuse painless upper-lip swelling for 1 year. Initially, the symptom tended to wax and wane. He noted that the symptom was aggravated by smoking, drinking alcohol, and eating hot and spicy food. The swelling persisted during the past 3 months. He had no fever, facial swelling, facial palsy, intraoral lesion, or genital lesion. He also denied any gastrointestinal symptoms (such as abdominal discomfort, bowel habit change, hematochezia, or melena) or other organ-specific symptoms. He denied local lip procedure, lip injection, or trauma history of angioedema, anaphylaxis, and prior drug allergy was also absent. He was treated with oral prednisolone 15 mg/day for 14 days without clinical improvement.

Physical examination revealed localized upper-lip swelling with a reddish-pink color, smooth surface, and firm consistency (Fig. 1). Other systemic signs were unremarkable. No facial palsy, gingival swelling, ulcer, or fissured tongue were found.

Skin punch biopsy, performed on the upper lip, revealed chronic granulomatous inflammation with multinucleated giant cells in the whole dermis. No foreign material was detected in the section (Fig. 2). Laboratory results on the complete blood count, liver function test, chest X-ray, and fecal examination were within normal limits. Hence, the diagnosis of CG was made based on the clinical and histological findings.

He was treated with intralesional triamcinolone acetonide injection 10 mg/mL on the left side of the upper lip every 2 weeks, together with oral methotrexate (MTX) 10 mg once weekly and folic acid 5 mg once daily. At the 3-month follow-up, the left upper-lip swelling was substantially decreased, while the noninjected right side remained unchanged (Fig. 3). Later, he was given intralesional injections of triamcinolone acetonide 10 mg/mL into the right side of the upper lip every 2 weeks. At 5 months of follow-up, the swelling on both sides of the upper lip was improved (Fig. 4).

Discussion

We report a case diagnosed as CG, a subtype of orofacial granulomatosis. This clinical entity consisted of facial and oral swelling, which was a non-necrotizing granulomatous inflammation in the absence of systemic diseases such as Crohn's disease and sarcoidosis [1]. When a triad of swelling of the lip, facial nerve paralysis, and fissured tongue is complete, it is referred to as Melkersson-Rosenthal syndrome (MRS) [1, 2]

The etiology of CG has not been well established; however, several explanations have been proposed – including genetic predisposition and environmental exposures – that lead to

dermal inflammation [1]. One case report proposed a possible role of UVB-photosensitivity in the pathogenesis of CG [3]. Moreover, the delayed type of hypersensitivity reaction has been implicated as an etiologic mechanism. Allergic reactions to food, food additives, cobalt, and dental materials are speculated causes of CG [1, 4]. However, the exact antigen causing the disease varied in individual patients, and some patients did not mention a possible relevant allergy [1, 5]. Thus, the role of patch testing in the diagnosis of CG remains unclear [1]. CG has been reported to precede full-blown intestinal manifestations of Crohn's disease in several years of follow-up [6]. Some studies proposed that CG might represent extraintestinal Crohn's disease [5]. However, CG is found in only 0.5% of the patients with Crohn's disease [6]. Therefore, whether to perform routine screening gastrointestinal tract investigations or not in patients lacking a history of gastrointestinal symptoms remains controversial [5, 6]. Instead, long-term follow-up is of paramount importance. CG has been noted as a localized form of sarcoidosis in certain patients; even so, focal nodular lesions are more suggestive than diffuse lip swelling [5].

Histopathology of CG characterized by the presence of non-caseating granulomas and perivascular lymphocytic infiltration in the absence of other identifiable causes (e.g., foreign body, sarcoidosis, tuberculosis, atypical mycobacterial infection, cutaneous leishmaniasis, leprosy, etc.) [5]. Histopathological findings are not pathognomonic and may be indistinguishable from Crohn's disease, sarcoidosis, or longstanding Wegener's granulomatosis [1, 5]. Therefore, the diagnosis of CG is made by correlation of the patient history and clinical features and is supported by the histopathologic findings [2, 5].

Spontaneous remission is unlikely [1]. To date, there is no standard regimen for the treatment for CG. Due to the rarity of the disease, randomized clinical trials are therefore lacking. The treatment modality was selected individually according to local settings and concurrent diseases. The most frequently used treatment modality includes locally injected, pulse short-term systemic, or even topical glucocorticoids [2, 7]. In addition, intralesional triamcinolone is suggested by many authors as the first-choice therapy in the acute stages of the disease according to satisfactory short-term results. The dosage ranged from 10–40 mg per injection with intervals of weeks to months between each injection [8, 9]. Nevertheless, recurrences of lip swelling commonly occur. Nonsteroidal systemic modalities, such as MTX, clofazimine, hydroxychloroquine, sulfasalazine, thalidomide, fumaric acid esters, tranilast, or systemic oral antibiotics (e.g., tetracycline, minocycline, doxycycline, roxithromycin, dapsone, metronidazole, etc.) were also reported with moderate responses as alternatives to glucocorticoid regimens [7, 8]. Recent data revealed that anti-TNF antibodies (e.g., infliximab, adalimumab, etc.) led to successful results in cases with refractory to conventional therapies as well [7, 10]. Surgical intervention should be reserved for refractory and severely disfigured lips, showing a moderately effective outcome. However, minor recurrence of lip swelling may occur as well [2, 5].

Low doses of MTX (5–25 mg weekly) have been previously reported to be effective and safe in the induction of remission and maintenance of patients with Crohn's disease [11]. According to Tonkovic-Capin et al. [12], low doses of oral MTX had a beneficial effect on orofacial swelling in a case of CG accompanied by Crohn's disease with recurrence despite systemic glucocorticoids. The study also reported additional reduction on orofacial swelling when the dose of MTX was increased from 5 to 10 mg orally once weekly. Leicht et al. [13] also reported a case of MRS with marked improvement of facial swelling within 3 months oral MTX 7.5 mg once weekly. The therapeutic effect may involve immunomodulation through increased levels of adenosine [11]. In our case, lip swelling in CG without Crohn's disease or MRS showed

clinical response to intralesional triamcinolone acetonide. However, the lesion on the non-injected side was refractory to treatment with oral low-dose MTX through the 3-month follow-up.

Conclusion

We present a case who presented with asymptomatic swelling of the upper lip without gastrointestinal symptoms or other systemic symptoms. The diagnosis of CG was made by clinicopathological correlation. The management of CG remains challenging. Glucocorticoids are still the mainstay in the acute phase of the disease; however, recurrence may occur. Thus, long-term treatment options were discussed with the patient. He was treated with oral low-dose MTX in combination with intralesional steroid injection on one side of the upper lip every 2 weeks. The injected side showed improvement, while the noninjected side remained unchanged after 3 months of treatment. Therefore, from our experience, CG is refractory to treatment with MTX.

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Statement of Ethics

The authors have no ethical conflicts to disclose. The patient has given written informed consent to publish his case (including publication of images). The study has been done according to the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T.S. collected the data and wrote the initial manuscript draft. K.C. wrote the manuscript and did language editing, and V.V. evaluated and revised the manuscript and acts as the corresponding author. All authors provided critical feedback and contributed to the final version of the manuscript.

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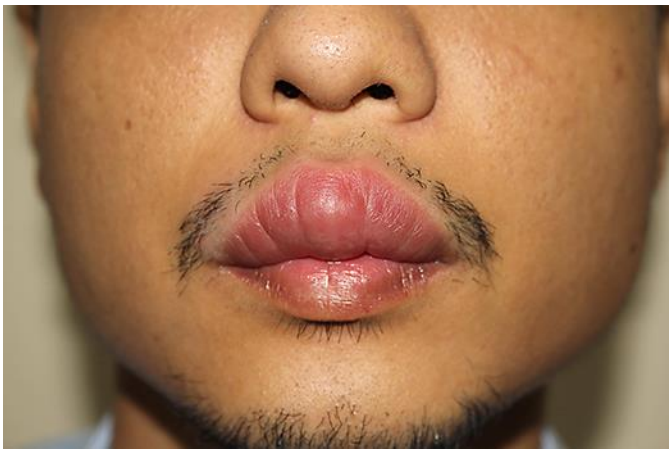

Fig. 1. Localized, nontender upper-lip swelling with a reddish-pink color, smooth surface, and firm consistency.

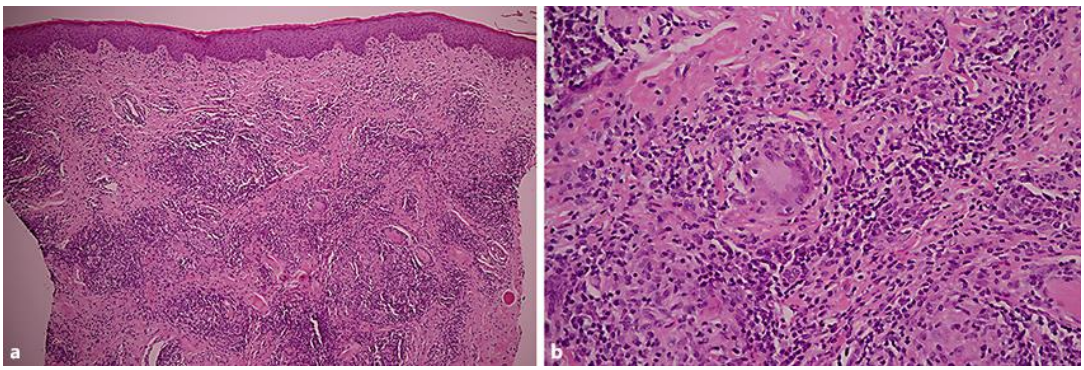

Fig. 2. Histopathological findings. **a** Noncaseating granulomas and superficial and deep perivascular infiltration without epidermal change. HE. ×100. **b** Inflammatory cell infiltration mainly composed of lymphocyte, histiocyte, and multinucleated giant cells. HE. ×400.

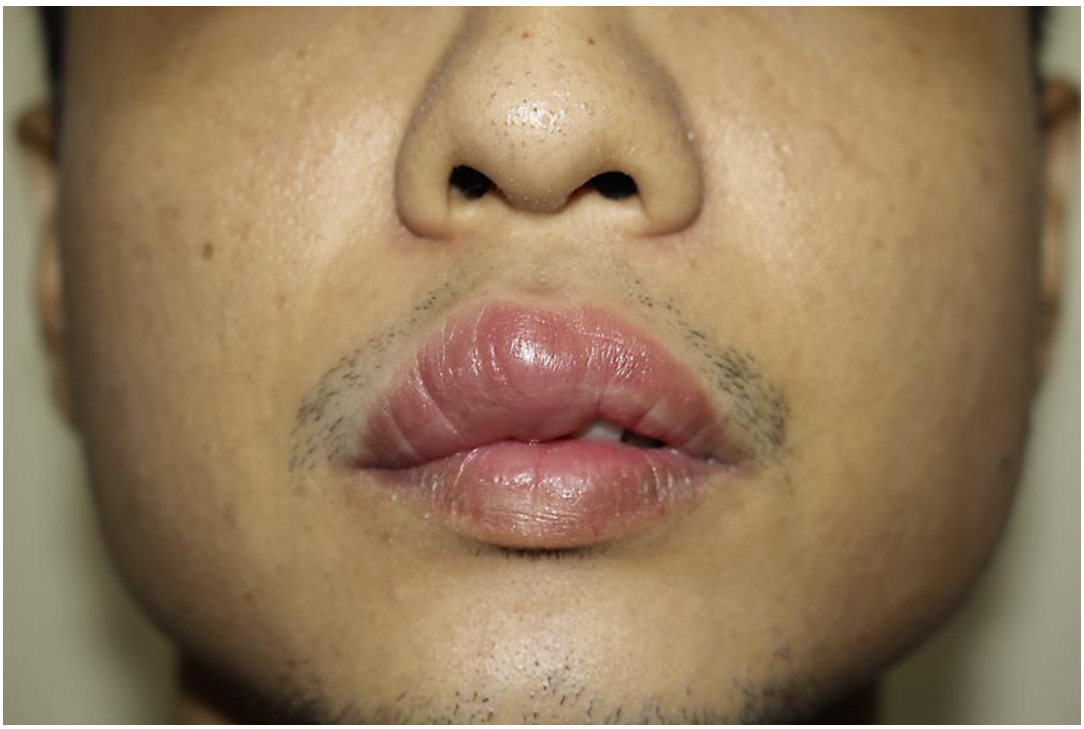

Fig. 3. At 3 months of follow-up, the resolution of the left upper-lip swelling was observed after the 2-week interval intralesional injection with triamcinolone acetonide (10 mg/mL) for 6 sessions in combination with oral MTX 10 mg once weekly for 12 weeks. Note that the right, noninjected side was unchanged.

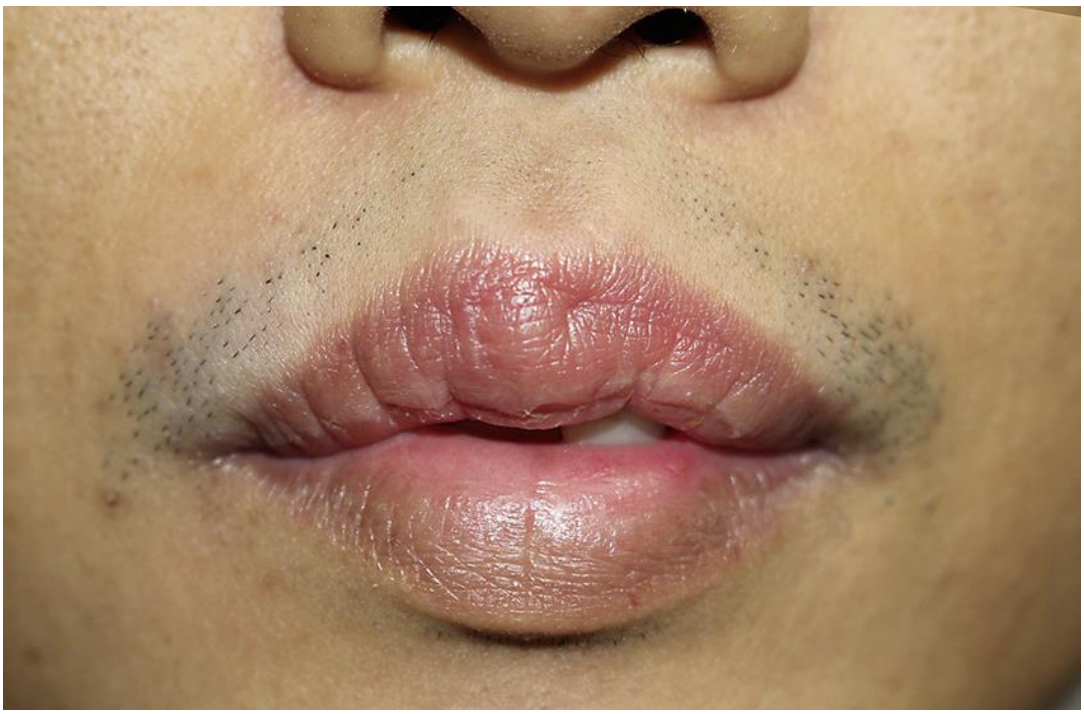

Fig. 4. At 5 months of follow-up, the improvement of the right upper-lip swelling was noted after intralesional injection with triamcinolone acetonide injection (10 mg/mL) in a 2-week interval for 4 sessions.