

Up-to Date Review And Case Report

Management of orofacial granulomatosis: a case report

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Abstract – Introduction: Orofacial granulomatosis is characterized by recurrent swelling affecting the lips, cheeks, and tongue. The rarity of this pathology and the lack of consensus in therapeutic management make the reporting of this clinical case relevant. **Observation:** A 48-year-old man consulted for labial and gingival orofacial granulomatosis. The treatment consisted of 40 mg/L injections of triamcinolone acetonide once weekly for 3 weeks. The symptoms improved after 1 week of treatment. **Comments:** The usual treatment for this condition targets the inflammation caused by the lesion. Corticosteroids (clobetasol, triamcinolone acetonide, prednisolone), monoclonal antibodies (infliximab, adalimumab), or TNF- α inhibitors are commonly used. Symptom recurrence is frequently observed after treatment with corticosteroids. Biotherapies are often used as a second-line treatment. **Conclusion:** Orofacial granulomatosis symptoms are rare and difficult to diagnose due to its varying manifestations. Common treatments target one of the steps of the inflammatory response. The detection of specific cellular markers is a way to enable a more precise etiological diagnosis and allows for a more targeted therapy.

Introduction

Orofacial granulomatosis can be defined as recurrent, persistent, edematous lesions of the lips, tongue, inner cheek, or gingiva. They can be caused by any granulomatous inflammation, but are not related to any other systematic pathology, such as Crohn's disease or sarcoidosis [1].

Its etiopathology is still unclear. There are different hypotheses such as a delayed hypersensitivity reaction, a mycobacterial infection, or a genetic predisposition [2].

The term orofacial granulomatosis tends to encompass old nosological entities such as Melkersson and Rosenthal Syndrome (MRS) or Miescher cheilitis. MRS presents as a triad of symptoms: (a) facial paralysis, which occurs in 33% of cases; (b) folding and edema of the lips, which occurs in 75% of cases; (c) facial edema, which is seen in some cases [3]. Miescher cheilitis is a nonresolving labial edema that can be translated as a monosymptomatic MRS [4]. Indeed, the underlying histopathological change in Miescher cheilitis, MRS, and orofacial granulomatosis is a lymphocytic inflammatory infiltrate with giant cell epithelioid granulomas [5]. The sex ratio is 1:1 and

there is no variation in prevalence among ethnicities. Symptoms usually appear the third decade. A prevalence of 0.8% was reported in 1996, but in the absence of valid epidemiological data, this figure could not be confirmed [6].

In this paper, we report our experience with a clinical case of orofacial granulomatosis, and discuss the therapeutic management strategies of these rare conditions.

Observations

A 48-year-old patient consulted for a chronic macrocheilia for a duration of 4 months, which was predominantly in the lower lip (Fig. 1). The patient reported pain, especially when eating and upon touch.

The diagnosis of an isolated case of orofacial granulomatosis was confirmed after lung and gastroenterological examinations. Indeed, the lung examination had ruled out sarcoidosis. Chronic inflammatory diseases of the intestines such as Crohn's disease were also eliminated during the gastroenterological examinations. The biopsy was performed on the mucosal side of the affected lip. In the histopathological examination, a giant cell granulomatous inflammation without central caseous necrosis was observed (Fig. 2).

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Fig. 1. Initial pictures showing the swelling of the lower lip with inflammation and scaling of the skin.

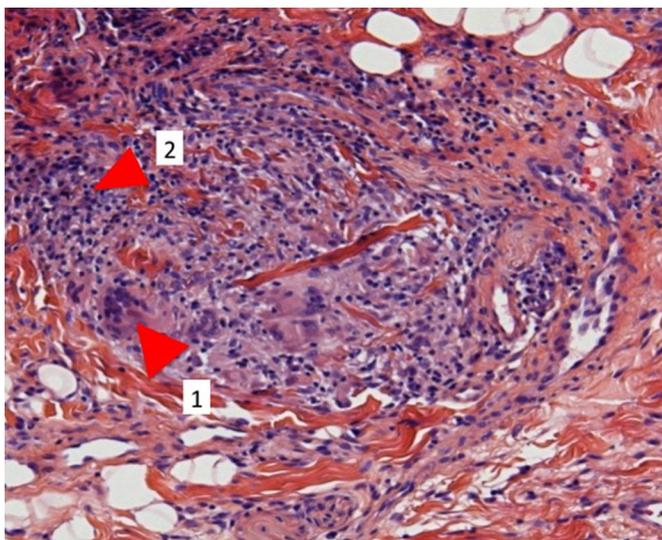


Fig. 2. Histological analysis of the labial biopsy ($\times 10$). 1: Epithelioid giant-cell granulomas, 2: Inflammatory infiltrate.



Fig. 3. Injection of triamcinolone acetonide.

The cosmetic aspect of the lower lip edema prompted us to prescribe the injection of triamcinolone acetonide (*Kénacort Retard*[®]). This synthetic glucocorticoid has a potent anti-inflammatory effect (eight times more potent than prednisone). Moreover, the synthetic characteristics of this molecule induce a metabolic effect and result in less sodium retention than that of hydrocortisone.

Intralesional injections of a 40 mg/mL solution at a frequency of 1 mL per week for 3 weeks [7] were administered, starting at an intraoral location (Fig. 3). This injection was administered under local anesthesia to avoid the pain associated with the increase of tissue pressure of the edematous lip.

The patient reported the amelioration of pain and a consequent decrease in edema from the first week of treatment. The follow-up 6 months after the last injection showed no signs of recurrence (Fig. 4).

Comments

We conducted a literature review for understanding the different modalities of the potential management of these orofacial granulomas. The therapeutic principle is the modulation of intralesional inflammation by corticosteroids, monoclonal antibodies, or TNF- α inhibitors (Table I).

Topical therapies consisting of corticosteroid creams such as clobetasol 0.05% (*Dermoval*[®], *Clarelux*[®]) [8] are moderately effective, but they result in rapid recurrences, especially after they are used alone [9]. Effectiveness has been demonstrated on oral mucosal ulcers associated with orofacial granulomatosis, particularly in precursor syndromes of Crohn's disease [10]. Calcineurin inhibitors such as tacrolimus 0.1% (*Protopic*[®]) are prescribed in cases of painful ulcers resistant to clobetasol [11].

Systemic corticosteroid administration using prednisolone at 1 mg/kg (*Solupred*[®]) is also effective even though relapses upon discontinuation may be common. The frequency of administration is a single injection every 7–14 days depending



Fig. 4. Images taken one month after the start of treatment.

Table I. Table summarizing the main medications used in the management of orofacial granulomatosis (Vidal®).

Molecule	Method of administration	Efficiency	Side effects
Clobetasol 0.05%	Topical	Moderate after local injections, with high risk of recurrence	Very high level of tolerance
Prednisolone 1 mg/kg	Oral	Short-term efficacy for ameliorating edema and ulceration	For long-term treatment: Cushing's syndrome, osteoporosis, diabetes
Triamcinolone acetonide 40 mg/mL	Intralesional injection	Long-term effectiveness	Risk of skin pigmentation
Thalidomide	Oral	Second-line treatment	Teratogenesis and neuropathy
Infliximab/adalimumab	Intravenous	Second-line treatment	Risk of infection, increased risk of cancer

on the severity of the condition. However, long-term corticosteroid treatment may cause significant side effects in the case of recurrences.

Local injection of 40 mg/mL of triamcinolone acetonide shows long-term efficacy in the treatment of orofacial granulomatous lesions. Treatment is intralesional and is administered on a weekly basis for 3 weeks [7]. An older protocol uses 10 mg/mL of triamcinolone acetonide. However, the large volume injected caused severe pain and thus required a nerve block; in addition, a 2-week gap between sessions was necessary [7].

The use of monoclonal antibodies and TNF- α inhibitors is effective in some cases refractory to topical and systemic anti-inflammatory treatments [12]. In France, the prescription of these medications (thalidomide, infliximab, and adalimumab) remains restricted to hospital specialists [12].

A study has shown that low-energy laser treatment has some efficacy in some cases [13]. This treatment method has not reported side effects and could be combined with the abovementioned therapies.

A surgical approach can be employed in cases with intralesional fibrosis (a frequent complication of orofacial granulomatosis) [14]. However, surgical treatment is of interest only if the inflammation is controlled, because recurrence is an issue in cases with uncontrolled inflammation [15].

Some studies have demonstrated an increased prevalence of oral allergic reactions in persons with this pathology; 80% of

patients have a history of allergic reactions compared with 15–20% of the general population [16]. In this context, certain diets have been advocated. Diets “avoiding cinnamon and benzoate (preservatives E211, E212, E213)” seem to show a marked improvement in symptomatology and a decrease in recurrence [17]. The findings of this study seem to be very promising, but these results have not yet reproduced.

Conclusion

Orofacial granulomatosis is difficult to diagnose clinically because of varying clinical manifestations and rarity. Indeed, this pathology can be recurrent and involve the inflammation of not only at the labial level, but also the gingival, lingual, buccal, or suborbital levels. In addition, there are many differential diagnoses (infections, Crohn's disease, sarcoidosis, allergic reactions) [18]. In correlation with clinical symptomatology, a biopsy remains the most definitive way to diagnose the condition.

It is difficult to highlight a reference treatment of orofacial granulomatosis because there is a lack of evidence in the literature. On the other hand, therapeutic problems can arise because of a probably multifactorial etiology, involving allergic processes, mycobacterial infection, or an immunological reaction, similar to sarcoidosis or Crohn's disease [18]. The assumption also depends on the extent of the lesions and their locations.

The detection of specific cellular markers is a method for a more precise diagnosis [19]. This allows for the detection of the underlying pathology, and thus allow a more targeted therapy.

The triamcinolone acetonide injection procedure appears to be the most suitable for labial and buccal cases along with a change of diet to prevent recurrences.

Conflicts of interest: The authors declare that they have no conflicts of interest in relation to this article.

References

1. Scuibba JJ, Said-Al-Naief N. Orofacial granulomatosis: presentation, pathology and management of 13 cases. *J Oral Pathol Med* 2003;32:576–585.
2. Tilakaratne WM, Freysdottir J, Fortune F. Orofacial granulomatosis: review on aetiology and pathogenesis. *J Oral Pathol Med* 2008;37:191–195.
3. Zimmer WM, Rogers RS, Reeve CM, Sheridan PJ. Orofacial manifestations of Melkersson-Rosenthal syndrome. A study of 42 patients and review of 220 cases from the literature. *Oral Surg Oral Med Oral Pathol* 1992;74:610–619.
4. Wiesenfeld D, Ferguson MM, Mitchell DN, MacDonald DG, Scully C, Cochran K, Russel RI. Oro-facial granulomatosis—a clinical and pathological analysis. *Q J Med* 1985;54:101–113.
5. Campana F, Ordioni U, Fricain J-C. Chéilite granulomateuse de Miescher: difficulté du diagnostic. *Méd Buc Chir Buc* 2014;20:99–101.
6. McCartan BE, Healy CM, McCreary CE, Flint SR, Rogers S, Toner ME. Characteristics of patients with orofacial granulomatosis. *Oral Dis* 2011;17:696–704.
7. Fedele S, Fung P, Bamashmous N, Petrie A, Porter S. Long-term effectiveness of intralesional triamcinolone acetonide therapy in orofacial granulomatosis: an observational cohort study. *Br J Dermatol* 2014;170:794–801.
8. Mignogna MD, Fedele S, Lo Russo L, Lo Muzio L. The multiform and variable patterns of onset of orofacial granulomatosis. *J Oral Pathol Med* 2003;32:200–205.
9. Leão JC, Hodgson T, Scully C, Porter S. Review article: orofacial granulomatosis. *Aliment Pharm Ther* 2004;20:1019–1027.
10. Troiano G, Dioguardi M, Giannatempo G, Laino L, Testa NF, Cocchi R, De Lillo A, Lo Muzio L. Orofacial granulomatosis: clinical signs of different pathologies. *Med Princ Pract* 2015;24:117–122.
11. AlJohani KA, Moles DR, Hodgson TA, Porter SR, Fedele S. Orofacial granulomatosis: clinical features and long-term outcome of therapy. *J Am Acad Dermatol* 2010;62:611–620.
12. Hegarty A, Hodgson T, Porter S. Thalidomide for the treatment of recalcitrant oral Crohn's disease and orofacial granulomatosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003;95:576–585.
13. Merigo E, Fornaini C, Manfredi M, Meleti M, Alberici F, Corcione L, Buzio C, Rocca JP, Ferri T, Vescovi P. Orofacial granulomatosis treated with low-level laser therapy: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;113:e25–e29.
14. Van der Waal RIF, Schulten EAJM, van der Meij EH, van de Scheur MR, Starink TM, van der Waal I. Cheilitis granulomatosa: overview of 13 patients with long-term follow-up—results of management. *Int J Dermatol* 2002;41:225–229.
15. Tan O, Atik B, Calka O. Plastic surgical solutions for melkersson-rosenthal syndrome: facial liposuction and cheiloplasty procedures. *Ann Plast Surg* 2006;56:268–273.
16. Armstrong DK, Biagioni P, Lamey PJ, Burrows D. Contact hypersensitivity in patients with orofacial granulomatosis. *Am J Contact Dermat* 1997;8:35–38.
17. White A, Nunes C, Escudier M, Lomer MCE, Barnard K, Shirlaw P, Challacombe SJ, Sanderson JD. Improvement in orofacial granulomatosis on a cinnamon- and benzoate-free diet. *Inflamm Bowel Dis* 2006;12:508–514.
18. Al-Hamad A, Porter S, Fedele S. Orofacial granulomatosis. *Dermatol Clin* 2015;33:433–446.
19. Gale G, Ostman S, Saalman R, Telemo E, Jontell M, Hasséus B. Immunophenotype in orofacial granulomatosis with and without Crohn's disease. *Med Oral Patol Oral Cir Buc* 2014;19:e584–e591.