

# Orofacial Granulomatosis: 2 Case Reports and Literature Review

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## ABSTRACT

Orofacial granulomatosis comprises a group of diseases characterized by noncaseating granulomatous inflammation affecting the soft tissues of the oral and maxillofacial region. The most common clinical presentation is persistent swelling of one or both lips. It is important to establish the diagnosis accurately because this condition is sometimes a manifestation of Crohn's disease or sarcoidosis. This article describes 2 cases of orofacial granulomatosis, in one of which the condition was a manifestation of Crohn's disease. The diagnostic approach to and the treatment of orofacial granulomatosis are reviewed.

**MeSH Key Words:** Crohn disease/diagnosis; granulomatosis, orofacial; mouth diseases/diagnosis

© J Can Dent Assoc 2006; 72(4):325-9  
This article has been peer reviewed.

Orofacial granulomatosis (OFG) comprises a group of diseases characterized by noncaseating granulomatous inflammation affecting the soft tissues of the oral and maxillofacial region.<sup>1</sup> This term, introduced by Wiesenfeld in 1985, encompasses Melkersson-Rosenthal syndrome (MRS) and cheilitis granulomatosa (CG) of Miescher.<sup>2</sup> MRS has been described as a triad of persistent lip or facial swelling, recurrent facial paralysis and fissured tongue.<sup>3,4</sup> CG of Miescher is characterized by swelling restricted to the lips.<sup>5</sup> According to Neville and others,<sup>6</sup> these 2 entities should not be considered distinct diseases and should both be included in the spectrum of OFG.

The precise cause of OFG is unknown.<sup>7</sup> Several theories have been suggested, including infection, genetic predisposition and allergy.<sup>8-12</sup> More recently, researchers have identified a monoclonal lymphocytic expansion in OFG lesions and have suggested it could be secondary to chronic antigenic stimulation.<sup>13</sup> It appears that cytokine production by the lymphocytic clone could be responsible for the formation of granulomas in these lesions.<sup>14</sup> However, an immunologic origin

(cell-mediated hypersensitivity reaction) is favoured because of the presence of activated helper T lymphocytes expressing interleukin-2 receptors in these lesions.

The classic presentation of OFG is a non-tender recurrent labial swelling that eventually becomes persistent.<sup>15</sup> This swelling may affect one or both lips, causing lip hypertrophy (macrocheilia).<sup>16</sup> The swelling is initially soft but becomes firmer with time as fibrosis ensues. However, the clinical presentation can be highly variable, making the diagnosis difficult to establish. For example, the recurrent facial swelling may affect the chin, cheeks, periorbital region and eyelids,<sup>17</sup> and, in rare cases, it may not be associated with lip hypertrophy. Intraoral involvement may take the form of hypertrophy, erythema or nonspecific erosions involving the gingiva, oral mucosa or tongue.<sup>16,17</sup> The diagnostic dilemma may be further complicated by the fact that OFG may be the oral manifestation of a systemic condition, such as Crohn's disease, sarcoidosis or, more rarely, Wegener's granulomatosis.<sup>18</sup> In addition, several conditions, including tuberculosis, leprosy, systemic fungal infections and

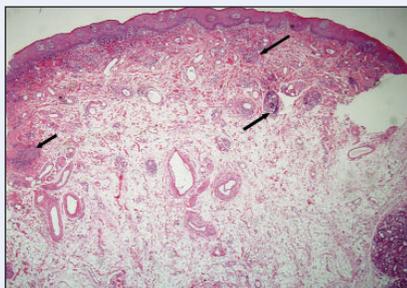
**Case 1**



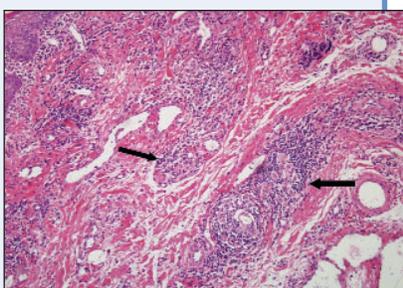
**Figure 1a:** Appearance of the lower lip at the time of presentation. Note the presence of bilateral edema and erythema of the chin.



**Figure 1b:** Intraoral examination revealed diffuse swelling of the lower gingiva. The labial surface of the gingiva has a granular appearance with several petechiae.



**Figure 1c:** Photomicrograph of the lip biopsy sample, showing diffuse edema of the connective tissue and mild fibrosis of the lamina propria. Several granulomas (arrows) are visible at this magnification, along with a perivascular inflammatory infiltrate. (Hematoxylin and eosin; original magnification  $\times 4$ .)



**Figure 1d:** Several noncaseating epithelioid granulomas with giant cells are visible in this photomicrograph (arrows). There is also slight dilatation of the lymphatic channels. (Hematoxylin and eosin; original magnification  $\times 10$ .)

fatigue, weight loss and delayed growth (in children). Other complications may occur because of chronic, recurrent intestinal obstruction, the presence of adhesions or fistula formation. Some patients may have extraintestinal manifestations that require medical attention, such as erythema nodosum, uveitis, arthralgia and migratory polyarthritis. Patients with oral complaints can seek help from their dentist. These patients could suffer from linear and aphthous ulcers, chronic swelling of the lips (macrocheilia) or hypertrophy of the oral mucosa.<sup>20</sup> A “cobblestone” appearance of the oral mucosa is a common presentation.<sup>20</sup> The oral manifestations may appear before, after or at the same time as the intestinal complaints.<sup>21</sup> According to several authors,<sup>6,20,21</sup> a linear ulceration in the buccal vestibule surrounded by hyperplastic mucous folds is highly suggestive of Crohn’s disease.

Microscopic examination of the oral lesions associated with Crohn’s disease reveals epithelioid granulomas with giant cell formation in 67% to 85% of cases.<sup>20,22</sup> In contrast, only 50% of intestinal lesions exhibit similar histological changes. The granulomas are identical with those seen in OFG and sarcoidosis. Therefore, these conditions must be distinguished clinically.

The diagnosis of OFG is made by histopathologic identification of non-caseating granulomas. Local and systemic conditions characterized by granulomatous inflammation must be excluded by appropriate clinical and laboratory investigations.<sup>7,18</sup> This article presents 2 cases of OFG, in one of which the condition proved to be a manifestation of Crohn’s disease. The article outlines the diagnostic approach used to investigate a patient presenting with macrocheilia (lip hypertrophy) and discusses various therapeutic modalities used in treating OFG.

**Case Reports**

**Case 1**

A 63-year-old-woman was referred for investigation of lower lip hypertrophy of unknown cause. She described a recurrent swelling of her lip that had eventually become permanent. The swelling had begun a few months earlier and was not associated with any change in oral hygiene products or cosmetics. The condition had been treated

foreign body reactions, may show granulomatous inflammation on histologic examination.<sup>7</sup>

Crohn’s disease belongs to the group of idiopathic inflammatory bowel conditions. It is characterized by granulomatous inflammation affecting any part of the gastrointestinal tract, from the mouth to the anus. It is especially common in young Ashkenazi or white adults and occurs with equal frequency among men and women. Although the cause of Crohn’s disease is unknown, recent studies have suggested a multifactorial etiology in genetically predisposed individuals.<sup>7</sup> The *Nod2/Card15* gene is the first susceptibility gene to be implicated by several independent research groups in the pathogenesis of this disease.<sup>19</sup>

The initial clinical manifestations of Crohn’s disease are recurrent abdominal cramps and chronic diarrhea. Signs and symptoms secondary to malabsorption appear next and include vitamin deficiencies, pernicious anemia,

with penicillin and an antihistaminic without any appreciable results.

The patient's medical history included temporary facial paralysis following surgical excision of a benign parotid tumour 12 years earlier. The patient suffered from hypertension, which was controlled with diuretics. She reported no intestinal problems that would suggest Crohn's disease, nor did she complain of chronic fatigue. There was no history of tuberculosis.

The extraoral examination revealed no lymphadenopathy, and there was no sign of dysphasia. The lower lip was markedly edematous (Fig. 1a) with erythema of the chin. The lip was firm to palpation and slightly indurated. Intraoral examination revealed a diffuse swelling of the lower anterior vestibule. The gingiva in the area of the lower anterior teeth was erythematous and swollen, with a slightly granular surface (Fig. 1b). There were no appreciable changes on the dorsal surface of the tongue. The rest of the intraoral examination was unremarkable.

The clinical differential diagnosis included OFG, angioedema (idiopathic or hereditary), sarcoidosis, Crohn's disease and an allergic reaction. MRS was ruled out because the reported facial paralysis was presumably related to the parotid surgery and because the tongue appeared clinically normal. Chest radiography and a series of blood tests, including assessment of serum levels of angiotensin-converting enzyme, were requested. An in-depth gastrointestinal investigation did not appear justified in this case, since there were no signs of anemia or symptoms suggestive of Crohn's disease. A biopsy sample of the lower lip was obtained for histopathologic evaluation.

Microscopic examination of the biopsy sample revealed marked edema of the connective tissue (Fig. 1c). Several noncaseating epithelioid granulomas with multiple giant cells were identified (Fig. 1d). The granulomas were especially concentrated around vessel walls. A perivascular lymphocytic infiltrate with marked dilatation of the lymphatic channels was also noted. Ziehl-Neelsen, Gram, Grocott, periodic acid-Schiff (PAS) and PAS-diastase staining yielded negative results. Polarized light microscopy did not reveal any foreign bodies. The final histopathologic diagnosis was 'cheilitis granulomatosa'.

The results of patch tests, done (with both regular and dental series) to exclude an allergic cause, were negative. The results of the other investigations were also negative. Therefore, a final diagnosis of idiopathic OFG was made.

## Case 2



**Figure 2a:** The lower left lip is affected by diffuse edema; the affected area has a firm consistency. The right side does not appear to be affected.



**Figure 2b:** A deep linear ulcer surrounded by folds of hyperplastic tissue is visible on the left side of the buccal vestibule.

Once the diagnosis was established, systemic corticosteroid therapy (prednisone 50 mg per day for 10 days) was started and was well tolerated. The lip swelling decreased, and there was a net reduction in the vestibular and gingival edema.

The labial edema recurred approximately 2 months after the systemic treatment. Intralesional injection of triamcinolone (40 mg/mL) was recommended. Four sites were infiltrated (0.25 mL or 10 mg per site). A close follow-up, shortly after the injections, showed reduction in lip swelling. Two weeks later, the patient stated that the appearance of her lip had returned to normal.

The patient's condition remained stable for approximately 4 months, after which the swelling reappeared. A new series of injections was carried out, which resulted in complete resolution of the signs and symptoms. At the most recent follow-up, mild swelling of the lower lip was noted, and a third series of injections was initiated. Again, this resulted in complete disappearance of the swelling.

### Case 2

A 19-year-old woman was referred for treatment of multiple oral ulcers involving the buccal sulcus and persistent swelling of the lower left lip. These symptoms had been present for approximately 4 months. The patient suffered from chronic diarrhea and persistent fatigue and complained of occasional pain in multiple joints. She had previously undergone investigation for Crohn's disease (by a gastroenterologist), but the diagnosis had not been confirmed. There was no history of tuberculosis or facial paralysis.

Extraoral examination revealed no lymphadenopathy or signs of dysphasia. A prominent swelling involving the lower left lip was noted (Fig. 2a). Intraoral examination revealed a deep linear ulcer involving the lower left vestibule (Fig. 2b). A second, shallower ulcer was present on the right side. Both ulcers were surrounded by inflamed

and hyperplastic mucosal folds. The dorsal surface of the tongue appeared normal.

The clinical differential diagnosis included Crohn's disease, sarcoidosis and OFG. MRS and CG were considered less likely in this case. Because of the predominance of intestinal symptoms and the history of chronic fatigue, another gastrointestinal examination was recommended. Colonoscopy revealed sharply demarcated hyperemic areas in the terminal ileum with intervening mucosa of normal appearance (skip lesions). Deep, serpiginous linear ulcers imparted a cobblestone appearance to the mucosal surface. Superficial, punched-out aphthous ulcers were also noted. A clinical diagnosis of inflammatory bowel disease was made. Biopsy of the terminal ileum showed transmural inflammation and noncaseating granulomas with multiple giant cells. The final histopathologic diagnosis was Crohn's disease.

Systemic corticosteroid therapy was initiated. A few weeks later, the patient reported significant improvement of her intestinal symptoms. During telephone follow-up, the patient indicated that her oral lesions had reacted positively to the systemic treatment. Unfortunately, long-term follow-up to monitor the patient's condition and response to treatment was not possible.

## Discussion

The differential diagnosis of a persistent labial swelling includes angioedema (idiopathic or hereditary), sarcoidosis, Crohn's disease, OFG, CG and some specific infections (tuberculosis, leprosy and deep fungal infections).<sup>23,24</sup> Amyloidosis, certain soft-tissue tumours, minor salivary gland tumour, and Ascher's syndrome may also be included in the differential diagnosis.<sup>15</sup>

All of these conditions must be taken into account during the investigation of a patient with persistent lip swelling. The medical history and the results of the clinical examination help to direct the investigation. The biopsy represents an important step in establishing the correct diagnosis, especially if angioedema is not a favoured possibility. Upon microscopic identification of granulomatous inflammation, special stains are used to rule out deep fungal infections (PAS, PAS with diastase, Grocott) or specific bacterial infections (Ziehl-Neelsen, Gram). Polarized light microscopy is used to identify foreign bodies in the tissues.

Ancillary tests are ordered to assess whether a systemic disease is responsible for the granulomatous inflammation. Such tests might include chest radiography and assessment of serum levels of angiotensin-converting enzyme for sarcoidosis; complete blood count, erythrocyte sedimentation rate and serum levels of folic acid, iron and vitamin B<sub>12</sub> for Crohn's disease; and tuberculin skin test and chest radiography for tuberculosis. Gastrointestinal assessment is essential, especially in the presence of signs of anemia and intestinal malabsorption and symptoms

suggestive of Crohn's disease (as with the case of the second patient described in this report). If the initial investigation does not confirm the diagnosis, a second assessment should be carried out, especially if the gastrointestinal signs and symptoms persist. The diagnosis of OFG is therefore a diagnosis of exclusion and is based on appropriate clinical and pathologic correlation.

The treatment of OFG is difficult, particularly in the absence of an etiologic factor. Treatment objectives are to improve the patient's clinical appearance and comfort. Although rare, spontaneous remission is possible.<sup>1</sup> The elimination of odontogenic infections may reduce the swelling in certain patients.<sup>25</sup> First-line treatment involves the use of local or systemic corticosteroids or both. Intralesional injections of triamcinolone 10 mg/mL is often used in the treatment of OFG.<sup>26</sup> Recently, higher concentrations of the drug (40 mg/mL) have been suggested. The higher concentration offers the advantages of reducing the volume of fluid injected, the administration of a higher dose and the maintenance of remission.<sup>24</sup> The side effects of local treatment are limited to skin atrophy and hypopigmentation.<sup>24</sup>

The use of systemic corticosteroid therapy<sup>1,27</sup> in treating OFG is limited because of the chronic, recurrent nature of the disease and the side effects associated with long-term use of these drugs. Results are often immediate with either local or systemic corticosteroid therapy. However, relapses are common, and long-term treatment may be required.<sup>15</sup> The first case reported here clearly illustrates the natural history of this condition and its response to treatment.

Other therapeutic measures have been reported in the literature, including hydroxychloroquine,<sup>15,27</sup> methotrexate, clofazimine,<sup>27</sup> metronidazole, minocycline<sup>28</sup> alone or in combination with oral prednisone, thalidomide,<sup>29,30</sup> dapsone and danazol. Cheiloplasty is used by some clinicians, especially in cases complicated by major lip deformation or inadequate response to local corticosteroid therapy.

The treatment of Crohn's disease involves the use of sulfasalazine and systemic corticosteroids. The steroids are used in managing acute phases of the disease, and sulfasalazine is used mainly for maintenance between active episodes. Corticosteroid-sparing agents, such as azathioprine, methotrexate and cyclosporine, are also used in certain cases. Metronidazole is sometimes considered. Surgery may be necessary to manage the complications of the disease and is also used in cases that do not respond to medical treatment.

The literature on OFG, MRS and CG shows an important problem in the classification of these entities. This is probably related to a lack of understanding of etiologic and pathogenic mechanisms. For example, some authors consider CG as an oligosymptomatic or monosympto-

matic variant of MRS,<sup>15,16,25</sup> whereas others suggest that these conditions are distinct entities.<sup>5,27</sup> Some claim that CG is a manifestation of sarcoidosis or Crohn's disease. Yet others consider OFG, MRS, CG, Crohn's disease and sarcoidosis to represent different manifestations of the same disease process.<sup>1,31</sup> We, like others,<sup>27</sup> believe that use of the term "OFG" in cases of noncaseating granulomatous inflammation has the advantage of describing a clinicopathologic situation without linking it to a specific disease entity. It is essential then to specify whether the condition is caused by a systemic disease or a local condition or if it is essentially idiopathic. Therefore, terms like "OFG in the context of sarcoidosis or in the context of Crohn's disease" and "OFG secondary to a chronic dental infection or to contact hypersensitivity" are recommended. A diagnosis of idiopathic OFG is made on the basis of negative results of a thorough investigation.

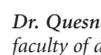
### Conclusions

Two cases of orofacial granulomatosis have been described, one of which occurred in the context of Crohn's disease. The differential diagnosis, investigation and treatment of these cases have been discussed. The authors recommend the use of standardized terminology when reporting such cases to identify epidemiologic, etiologic and therapeutic data. Use of standard terms should eventually lead to improvements in both therapeutic decision-making and patients' prognosis. ♦

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*The authors have no declared financial interests.*

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