A. Sarra*, N.G. Nikitakis** A. Daskalopoulos**,
Giorgos Chouliaras*,
A. Sklavounou-Andrikopoulou**, K. Athanasaki*

* 1st Department of Pediatrics, Medical School, University of Athens, Aghia Sophia Children's Hospital, Athens, Greece
**Department of Oral Pathology and Medicine, Dental School, National and Kapodistrian University of Athens, Greece

e-mail: adaskal@dent.uoa.gr

Orofacial granulomatosis as early manifestation of Crohn's disease: report of a case in a paediatric patient

ABSTRACT

Background *Orofacial granulomatosis (OFG) is a controversial entity mainly characterised by recurrent or permanent soft tissue swelling of sudden onset in the orofacial area with a histologic appearance of granulomatous inflammation. Differential diagnosis includes local diseases and systemic conditions, such as Crohn's disease (CD). A case of OFG in a paediatric patient is reported here, focusing on the clinical features, diagnostic procedures, treatment and long-term outcome.*

Case report *A 7 year-old boy presented with persistent and prominent lip swelling and painful oral mucosa lesions of six months duration. A biopsy of the lower labial mucosa revealed granulomatous inflammation consistent with OFG. The oral manifestations were managed with topical and intralesional corticosteroids. His medical history included gastrointestinal disturbances, perianal skin folds and bloody stools that raised the suspicion of CD. Colonoscopy showed inflammation without clear evidence of CD. One year later, repeated bowel investigation provided evidence suggestive of CD and the patient was placed under systemic treatment. Two years after the initial diagnosis the patient is free of oral or other pathological findings.*

Conclusions *The differential diagnosis in cases of orofacial swellings with histological granulomatous inflammation includes a variety of local and systemic diseases, diagnosis and management of which require full investigation and cooperation by a team of healthcare providers.*

Keywords *Crohn's disease; Lip swelling; Orofacial Granulomatosis.*

Introduction

Orofacial Granulomatosis (OFG) is characterised by the presence of non-specific granulomatous inflammation in the orofacial region causing persistent labial swelling, oral ulcers and a variety of other orofacial manifestations. The typical histopathologic findings include non-caseating granulomas consisting mainly of epithelioid cells; fibrosis and distension of lymphatic vessels that cause lymphoedema are often present. The aetiology and pathogenesis of OFG are not fully clarified [Grave et al., 2009]. Several factors have been implicated, such as certain foods (e.g. chocolate, preservatives), materials used in dentistry, and infections; delayed hypersensitivity has also been suggested to play a significant role in the pathogenesis of OGF [Tilakaratne et al., 2008].

The idiopathic form of OFG is defined by the absence of any systemic granulomatous conditions, such as sarcoidosis, Crohn's disease (CD) or tuberculosis. However, such granulomatous diseases may be associated with orofacial manifestations, which may be clinically or even microscopically indistinguishable from idiopathic OFG. In particular, the association of OFG with CD remains controversial. Since 1985, when Wiesenfeld et al. first introduced the term OFG, it still remains unclear whether this is a distinct clinical disorder or a feature of CD, occurring as an early manifestation or even concurrently with intestinal involvement; moreover, it is difficult to predict if CD will develop in cases originally diagnosed as OGF [Grave et al., 2009].

OFG is an uncommon condition but its incidence seems to increase, particularly in children and young adults [Saalman et al., 2009]. It is particularly important, when diagnosing OFG in children, to evaluate very carefully those symptoms that might indicate the development of full-blown inflammatory bowel disease.

Here we present a case of OFG in a child in order to describe the wide range of its clinical features, the required investigation and the need for multidisciplinary approach and continuous follow-up.

Case report

A 7 years-old boy presented with a 6-month history of lip swelling, burning sensation in the mouth that caused difficulty in feeding and weight loss over the same time

period. A vague history of diarrhoea and blood in the stool was also reported.

On physical examination, generalised swelling of the upper and lower lip with desquamation, crusting and fissures of the vermilion border were present (Fig. 1A). Intraoral examination revealed folds and linear ulcerations in the mucobuccal folds (Fig. 1B); the gingiva especially in the area of upper incisors appeared hypertrophic (Fig. 1C), and geographic tongue was present (Fig. 1D). The perioral skin was dry and exfoliative, and there were hypopigmentation spots on the face. Cervical lymphadenopathy was also noted. In addition, perianal skin tags were present.

A biopsy from the lower labial mucosa revealed granulomatous inflammation compatible with OFG (Fig. 2). Results of blood tests showed mild anaemia and increased Erythrocyte Sedimentation Rate (ESR). In the suspicion of CD, the following investigations were performed: ultrasonography of the abdomen, colonoscopy with bowel biopsies and magnetic resonance enterography, but no evidence of CD was rendered. A final diagnosis of OFG was made. Intralesional corticosteroids (betamethasone) of the lips, repeated every three weeks, along with topical corticosteroids applied on the lips and intraorally, managed to reverse the labial swelling and control the symptoms after the third infusion (Fig. 3A, 3B). The patient was kept under regular follow-up.

One year later, there was no evidence of recurrent orofacial lesions (Fig. 3C); however, due to persistent gastrointestinal symptoms (diarrhoea and blood in the stool), the bowel investigation with magnetic resonance enterography was repeated. Evidence suggestive of CD was revealed and oral prednisolone and azathioprine were used as induction therapy. Prednisolone was then gradually tapered until total intermission and azathioprine remained as maintenance therapy. After an acute relapse, azathioprine was replaced by methotrexate with

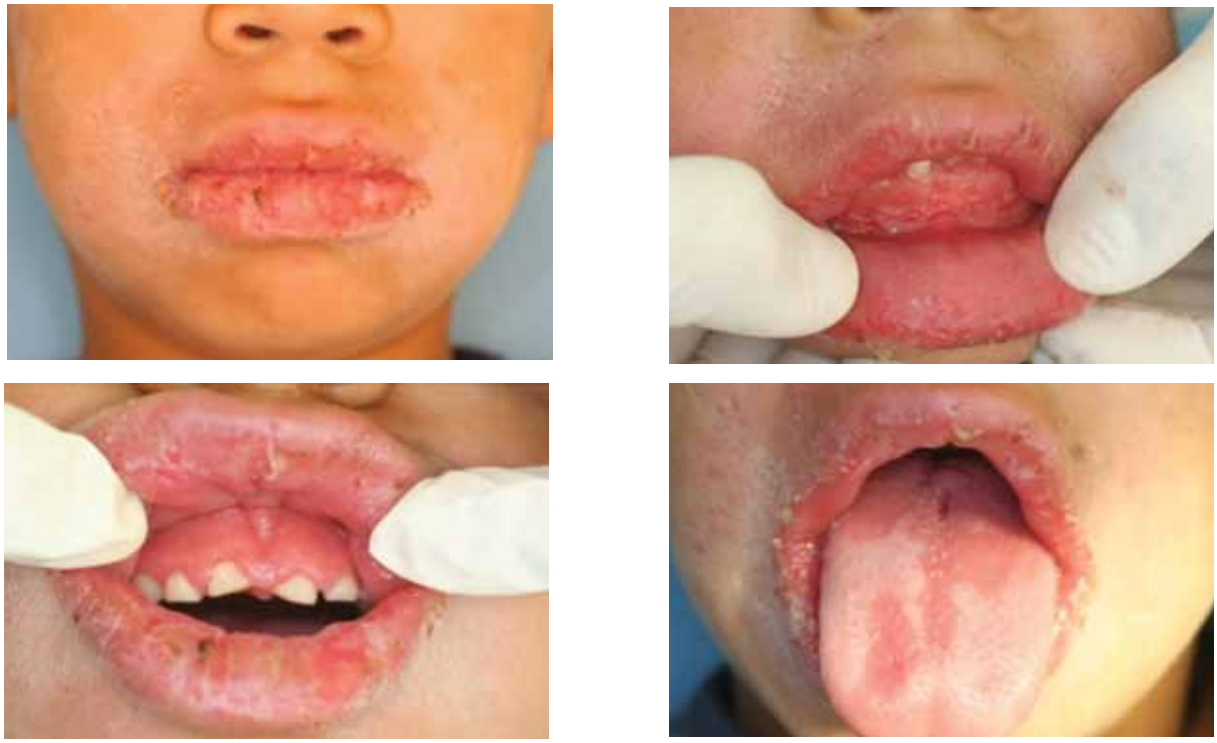

FIG. 1 A) Lip swelling with desquamation, crusting and fissures of the vermilion border; B) Folds and linear ulcerations in the mucobuccal folds; C) Hypertrophic upper anterior gingiva; D) Geographic tongue.

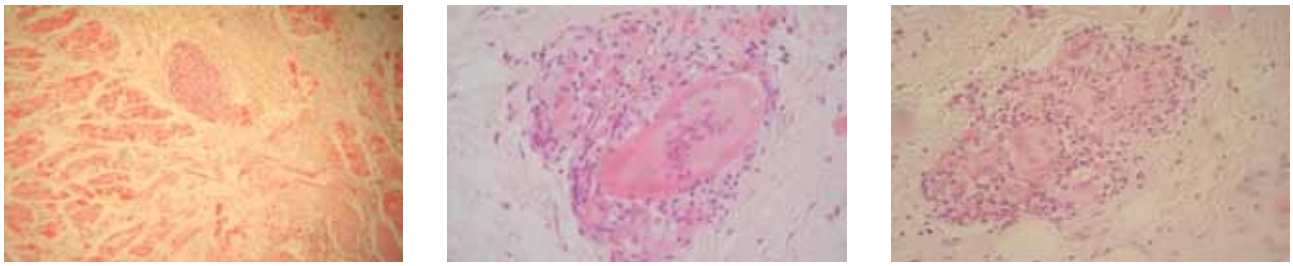

FIG. 2 Photomicrographs of the lower labial biopsy specimen demonstrating well-defined small granulomas containing numerous epithelioid and multinucleated giant cells. Hematoxylin and eosin: A) 100X; B and C) 200X.

FIG. 3 A) and B), Remission of labial swelling and improvement of intraoral lesions after treatment with intralesional and topical corticosteroids (two months after the initial presentation); C) Lack of signs of recurrence one year later.

folic acid supplementation, which effectively controlled patient's symptoms.

Two years after the initial diagnosis, the patient remains free of orofacial pathological findings, while his gastrointestinal manifestations are under remission continuing maintenance therapy with methotrexate and folic acid.

Discussion

OFG is a rare clinical entity with unknown aetiology and a wide variety of manifestations that include labial swelling, oral ulcers, mucosal tags, gingival enlargement, fissured tongue, facial swelling and erythema, facial nerve palsy and cervical lymphadenopathy [Grave et al., 2009]. Systemic diseases, such as CD, sarcoidosis, tuberculosis, chronic granulomatous disease, and local processes, such as chronic oral infection, foreign material reaction, and allergy may cause similar orofacial lesions [Tilakaratne et al., 2008]. After initial diagnosis of OFG, the patient should be carefully evaluated in order to exclude any underlying systemic or local cause. If such disorder is identified, then the diagnosis of OFG is revised accordingly.

We present this case to highlight the natural variability of the disease and to emphasize the association between OFG and CD in paediatric patients; in our patient, the original diagnosis was revised to CD based on the development of bowel symptoms and appropriate diagnostic tests. Although it is well established in the literature that OFG and CD have common clinical and histological findings, their exact relationship has not yet been clarified. Studies report that up to 50% of the children with OFG were diagnosed with CD [Rowland et al., 2010], while in 5-10% of cases with CD, oral lesions may be the first manifestation [Zbar et al., 2012]. It has been also proposed that OFG with bowel inflammation may be a completely separate entity from CD with oral manifestations, based on studies on paediatric patients with no intestinal symptoms but histological evidence of chronic inflammation of the intestine [Smith and Murphy, 2013]. It is also important to mention that the time between the appearance of the oral and gastrointestinal manifestations may vary from a period of a few months to several years. There have been reported cases of patients whose gastrointestinal symptoms developed even 9 years after the onset of OFG [Saalman et al., 2009]. Therefore, patients with OFG without GI symptoms can be managed as solitary OFG cases, but should be kept under close follow up and surveillance for the possibility to develop GI manifestations of CD in the future.

Spontaneous remission of OFG is rare and there are several treatment options with variable results, including various pharmacological agents and/or diet modifications [Grave et al., 2009; Kolho et al., 2011]. Elimination diets involving various dietary substances have been used, but their efficacy has not been thoroughly proven [Grave et al., 2009]. Management of oral lesion mainly centers on the use of corticosteroids. In mild cases, topical steroids, in the form of gels or mouthwashes, can be effective. Similar to our case, intralesional steroids may be used with satisfactory results, especially when prominent labial swelling is present; nonetheless, multiple injections may not be easily tolerated in children. In cases resistant to topical or intralesional steroids, as well as in patients with severe painful ulcers or pronounced labial and/or cervical involvement, systemic steroids are used; however, their side effects including the potential risk of growth retardation in children, should be kept in mind. Alternative treatments include other immunosuppressive/immunomodulatory agents, such

as tacrolimus, clofazimine, low dose thalidomide, methotrexate, and infliximab [Zbar et al., 2012]. In our case, combination of topical and intralesional steroids resulted in complete remission of the labial and oral OFG lesions.

Corticosteroids remain the mainstay of therapy in CD, too. Systemic steroids suppress inflammation and are considered the first line treatment for induction therapy and acute exacerbations; however, their use as maintenance therapy is limited by their potential side effects. Instead, immunomodulators, like azathioprine and methotrexate, are recommended for maintenance therapy. In more severe or unresponsive to previous treatments cases, biological agents (e.g. infliximab and adalimumab) are viable options [Ruemmele et al., 2014]. For our patient, following the establishment of CD diagnosis, oral prednisolone and azathioprine were used as induction therapy; maintenance therapy consisted initially of azathioprine and, subsequently, of methotrexate with folic acid supplementation, which controlled effectively the patient's GI symptoms. Interestingly, following their initial treatment, the orofacial lesions of OFG have not shown evidence of recurrence, despite the fluctuation in the GI manifestations.

Because of the variability of the clinical features of OFG (with or without evidence of CD) and the natural history of the disease with possible recurrences, any intervention should be individualized. Most patients suffer from their symptoms for a long time and the outcome is highly uncertain despite therapeutic attempts. Follow-up studies in adults showed that less than 10% of patients had complete resolution of their problem, while in paediatric population more research needs to be conducted [Al Johani et al., 2010].

Conclusions

It is of high importance to perform a thorough clinical and laboratory investigation for any systemic disorder and especially for inflammatory bowel disease of all children diagnosed with OFG as part of their routine management, even in the absence of GI symptoms. Regular follow-up is necessary as CD may develop many years later and multidisciplinary approach by a team of health care providers is also preferable.

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