Oral lesions as first clinical manifestations of Crohn's disease in paediatric patients: a report on 8 cases

G. Favia, L. Limongelli, A. Tempesta, E. Maiorano*, S. Capodiferro

Department of Interdisciplinary Medicine
**Department of Emergency and Organ Transplantation, Aldo Moro University Bari, Italy*

e-mail: capodiferro.saverio@gmail.com

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Abstract

Aim Oro-facial granulomatosis is a descriptive term commonly encompassing a variety of conditions that exhibit similar clinical and microscopic features. It is generally used to describe persistent enlargement of the soft tissues of the oral and maxillofacial region.

Materials and methods We report on the salient clinical features of 8 cases of Crohn's disease in paediatric patients (age range from 9 to 13 years old), with oral lesions as first clinical manifestations.

Results The clinical presentation of oro-facial granulomatosis is highly variable but usually recurrent facial swelling, mainly in the lips with or without intraoral manifestations, is the single most common clinical sign at onset. The association with systemic conditions such as sarcoidosis and Crohn's disease has been widely reported in literature. In paediatric age, oro-facial granulomatosis may frequently represent an extra-intestinal manifestation of Crohn's disease and oral lesions can be the first sign of an unknown intestinal disease. The diagnosis in paediatric patients is challenging as oro-facial granulomatosis may precede Crohn's disease by several years, frequently remaining the only evident active focus of the disease.

Conclusion The detection of specific oral manifestations often preceded by painless gingival enlargement (diffuse lip and buccal mucosal swelling, oral cobblestoning, buccal sulcus ulceration and mucosal tags) and/or unspecific or ancillary ones (cheilitis, scaly perioral erythematous rashes and frank intraoral abscess formation, labial and tongue fissuring, glossitis and aphthous stomatitis) is mandatory for the early diagnosis of intestinal Crohn's disease.

KEYWORDS Crohn's disease, Inflammatory bowel diseases, Oral Crohn's disease, Orofacial granulomatosis

Introduction

The term of orofacial granulomatosis (OFG) describes persistent enlargements of the soft tissues in the orofacial region, mainly occurring in the lips, usually secondary to a granulomatous inflammatory process [Triantafillidis, 2008; Al Johani, 2009] and often associated with systemic conditions such as sarcoidosis and Crohn's disease (CD) [Scully & Eveson, 1991; Sanderson et al., 2005; Jajam, Bozzolo & Niklander, 2017; Scully et al., 1982; Bogenrieder et al., 2003]. The recurrent facial swelling, with or without intraoral manifestations, usually remain the single most common presentation at onset [Al Johani, 2009; Scully & Eveson, 1991; Gagoh et al., 1999; Eveson, 1996; Wiesen, et al., 2007]. The differential diagnosis is usually challenging as OFG may precede gastrointestinal disease, such as CD, and in addiction may remain the only obvious focus of the disease [Al Johani 2009; Wiesen et al., 2007; Halme et al., 1993; Field & Allan 2001; Rowland et al., 2010].Traditionally, CD is described as a disorder affecting 'the mouth to the anus'; oral CD or isolated CD of the upper gastrointestinal tract remain a relatively uncommon findings. Different oral manifestations in patients affected by CD have been reported; many oral lesions are somewhat non specific, as the differential diagnosis includes several forms of nutritional glossitis [Field & Allan, 2001; Reamy et al., 2010]. Specific oral manifestations, often preceded by painless gingival enlargement, classically include diffuse lip and buccal mucosal swelling, oral cobblestoning, buccal sulcus ulceration and mucosal tags [Al Johani, 2009; Jajam et al., 2017; Wiesen et al., 2007; Field & Allan, 2001]. Ancillary oral lesions are angular cheilitis, scaly perioral erythematous rashes and frank intraoral abscess formation, labial and tongue fissuring, glossitis and aphthous stomatitis [Triantafillidis, 2008; Gagoh et al., 1999; Wiesen et al., 2007; Field & Allan, 2001; Sundh & Emilson, 1989]. Before the diagnosis of CD in patient showing one or more of the aforementioned lesions, the biopsy remains mandatory to achieve a diagnosis, and for the differential diagnosis with other OFG, including foreign-body reactions, sarcoidosis, typical and atypical mycobacterial infection and fungal sepsis [Al Johani, 2009; Scully & Eveson, 1991; Eveson, 1996]. Oral lesions may be identified in up to 60% of patients where in 5–10% of cases they may be the first manifestation of disease in adults [Al Johani, 2009;

FIG. 1. Persistent diffuse swelling of the upper and lower lips in children represent the classical clinical appearance of OFG: further investigations are mandatory to exclude other associated systemic diseases such as CD of which this child was affected.

Scully et al., 1982; Bogenrieder et al., 2003; Eckel et al., 2017; Jajam et al., 2017]. Also in children, the oral manifestations of CD are uncommon and can precede or coincide with intestinal inflammatory lesions, leading frequently to a delayed diagnosis [Bogenrieder et al., 2003; Jajam et al., 2017]. According to the European Crohn's and Colitis Organisation Guideline/Consensus Paper on Extra-intestinal Manifestations in Inflammatory Bowel Disease published in 2016, oral CD includes deep ulcerations, pseudopolyps, and labial or buccal swelling [Harbord et al., 2016; Gomollón et al., 2017].

We report on the clinical and pathological features of 8 cases of oral CD occurring in paediatric patients and preceding intestinal lesions.

Materials and methods

We collected data of 8 paediatric patients sent for observation to our University Clinic as affected by persistent lesions of the mouth of doubtful origin and unresponsive to the medical and instrumental therapies performed by their general dentists.

The age of patients ranges from 9 to 13 years (2 patients were 9 years old, 2 were 10, 2 were 11, one was 12 and the remaining were 13 years). At the clinical examination diffuse lip and buccal mucosal swellings were detected in 5 out of 8 patients (Fig. 1); oral cobblestoning, mucosal tags, chelitis, labial and tongue fissuring, gingivitis were observed in 4 patients (Fig. 2, 3, 4); aphthae or apthous stomatitis in 3 patients, while glossitis and palatal ulceration detected respectively in 1 and

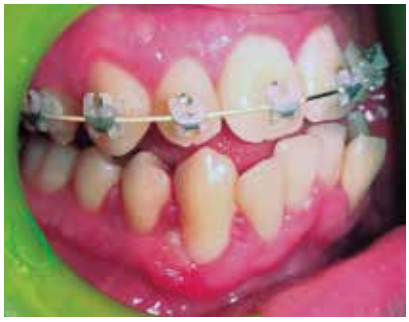

FIG.2 Gingivitis not related to plaque and calculus and unresponsive to periodontal treatments in children affected by CD not yet diagnosed.

FIG. 3 Cobblestoning mucosa of the cheek, often bilateral, both in children and adults, are important clinical signs to detect, as may represent the first clinical evidence of a possible unknown inflammatory intestinal disease.

FIG. 4 Mucosal tags are oral manifestations defined as "specific" of oral CD; their early clinical identification is useful for the early diagnosis of intestinal Crohn's disease.

Oral Crohn's Disease preceding intestinal lesions	CASE 1 9 y.o	CASE 2 11 y.o.	CASE 3 13 y.o	CASE 4 9 y.o	CASE 5 10 y.o	CASE 6 11 y.o.	CASE 7 10 y.o	CASE 8 12 y.o.
Gingivitis/periodontal disease/caries	X	/	X	/	/	X	/	X
Diffuse lip and buccal mucosal swelling	/	X	/	X	X	/	X	X
Aphthae/apthous stomatitis	/	/	X	/	/	X	/	X
Oral cobblestoning	X	X	/	/	X	X	X	/
Buccal sulcus ulceration	X	/	/	X	X	/	X	/
Mucosal tags	X	X	/	X	X	/	X	/
Cheilitis	X	/	/	X	X	/	X	X
Labial and tongue fissuring	X	/	/	X	X	X	X	/
Glossitis	/	/	/	/	/	X	/	/
Palatal ulceration	/	/	X	/	/	/	/	X

TABLE 1 Oral manifestations of CD in 8 patients

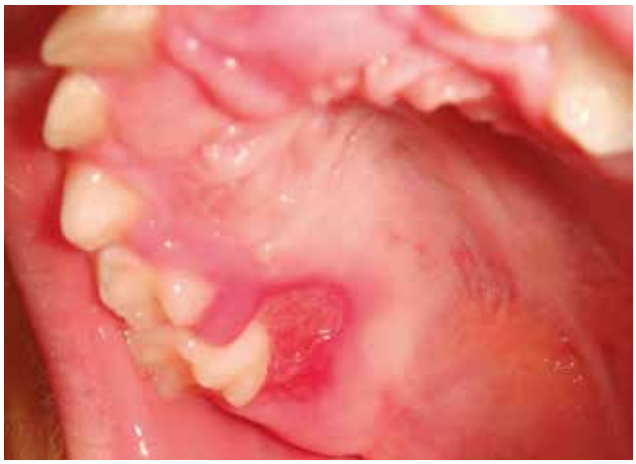

FIG. 5 Palatal ulceration is a rare clinical appearance of oral CD; in this case, the ulcer was located to the palatal adherent gingiva mimicking a periodontal lesion, but showing all the characteristics of a deep ulceration not related to periodontal disease.

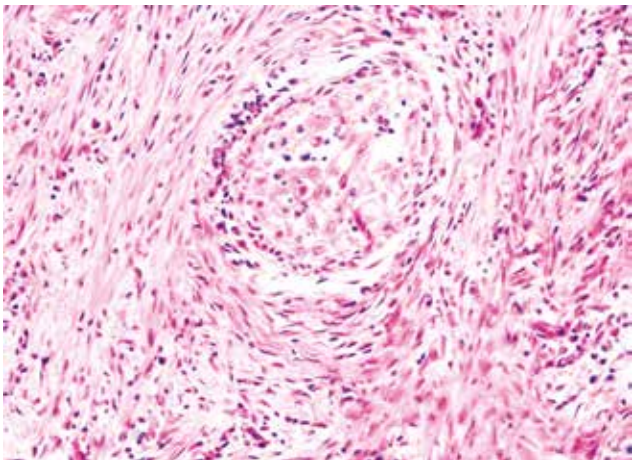

FIG. 6 Histological examination showing the presence of non-caseating granulomas into oral biopsy of oral CD; such finding, along with the clinical ones, leads to the diagnosis of oral CD (Haematoxylin and Eosin stain, original magnification X 20).

2 patients (Fig. 5), as summarized in Table 1. General sign and/or symptoms, referred by patients and confirmed by their parents, were unspecific abdominal pain in 4 cases and sporadic diarrhoea in the remaining 4. All patients showed a skinny appearance.

An oral biopsy of the suspicious lesions was performed in all instances. All the histological examinations showed the presence of non-caseating granulomas in the surgical samples (Fig. 6). On the basis of such findings, a suspicion of granulomatous disease arised in all cases which underwent to a detailed blood examination and colonscopy with bowel biopsy. The latter confirmed the diagnosis of CD without adjunctive extra-intestinal manifestations, and the targeted systemic therapy, with anti-inflammation and immune suppressive drugs, was immediately set on. At the one-year follow up patients showed no more signs of the previous oral lesions, with the exception of cobblestoning mucosa and mucosal tags. Patients were then lost to follow-up.

The study was carried out in accordance to the principles of the Declaration of Helsinki and approved by our internal review board (Study no. 4652, Prot. 66/C.E.); patients signed informed consent for diagnostic and therapeutic procedures and for the possible use of the biologic samples for research purposes.

Discussion

Although the clinical diagnosis of OFG, also in paediatric patients, is almost easy, the nomenclature itself of OFG lacks specificity that, instead, may be useful for differential diagnostic purposes [Al Johani, 2009; Scully & Eveson, 1991; Bogenrieder et al., 2003; Eveson, 1996]. In fact, in the plethora of different definitions proposed, there were many authors who considered OFG a manifestation of a separate and specific inflammatory bowel disease [Sanderson et al., 2005; Jajam et al., 2017], while others suggested that OFG was a generic definition of disease remaining the specific causes of the lesions completely unknown [Scully & Eveson, 1991; Gagoh et al., 1999]. Probably, the description of Bogenrieder et al. [2003] was the most interesting as OFG was considered a generic term for a provisional diagnosis in patients with systemic or local granulomatous disease not yet manifested. The latter is an acceptable definition as OFG may precede gastrointestinal disease also by several years.

A similar question exists for oral lesions associated to CD, as patients may suffer from intestinal disease, also with detectable endoscopic and histologic abnormalities, but without intestinal symptoms [Al Johani, 2009; Sanderson et al., 2005; Scully et al., 1982; Eckel et al., 2017; Harbord et al., 2016]. The prevalence of oral manifestations of CD is extremely variable, ranging from 10% to 80% [Scully et al., 1982; Rowland, Fleming & Bourke 2010; Jajam et al., 2017]. Clinical signs can be specific, such as diffuse lip and buccal swelling, tags, cobblestones and not-specific, such as aphthous ulcers, pyostomatitis vegetans, and gingivitis [Triantafillidis, 2008; Al Johani, 2009; Jajam et al., 2017; Gagoh et al., 1999; Wiesen et al., 2007; Field & Allan, 2001]. The latter, which remains the most frequent lesion recognised by general dentists, is generally classified as "systemic diseases or conditions affecting the periodontal supporting tissues" after reaching the final diagnosis, when not related to plaque and calculus [Caton et al., 2018; Jepsen et al., 2018]. Also cheilitis, labial fissuring and lip swelling are easily detectable clinical signs that should create a suspicion of CD when persistent, unrelated to other disease/deficiency or recognized in skinny children. Although rare, palatal ulceration remains a doubtful clinical appearance, as the differential diagnosis should be very challenging, thus including both inflammatory lesions and neoplastic ones with ulceration appearance. Diffuse lip and buccal mucosa swellings seem to be among the most frequent clinical appearances, accounting for 5 cases on a total of 8 also in our study. Such clinical signs, although easy to identify by clinicians, may represent the classical onset of several OFGs, including the Melkersson–Rosenthal syndrome; nevertheless, the absence of the classic triad of such disease (swelling, tongue fissuring, facial palsy) does not represent an unequivocal criterion of exclusion. The finding of non-caseating granulomas into oral biopsy of OFG and oral CD, along with adjunctive histopathologic and histomorphologic differences detectable exclusively in oral CD, such as loose macrophage clusters, granulomatous lymphangitis, fibrosis, may help to define the diagnosis, that anyway remains strictly related to the clinical findings. The main problem which can delay the diagnosis is the fact that oral signs of CD might

precede or coincide with intestinal inflammation [Scully & Eveson, 1991; Sanderson et al., 2005; Jajam et al., 2017]. For such reason and in addition for the increasing incidence in the paediatric population, clinicians should always consider CD in the differential diagnosis when one or more oral manifestations are detectable [Al Johani, 2009; Jajam et al., 2017; Wiesen et al. 2007; Rowland et al., 2010; Eckel et al., 2017; Harbord et al., 2016; Jepsen et al., 2018]. In fact, according to the most recent consensus papers of the European Crohn's and Colitis Organisation "The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease" published in 2016, and according to the following suggestions proposed by the "3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management" published in 2017, a single gold standard for the diagnosis of CD is not available for a precise diagnosis and the correct management of CD [Harbord et al., 2016; Gomollón et al., 2017; Jepsen et al., 2018; Caton et al., 2018]. The diagnosis is confirmed firstly by clinical evaluation, but followed by a combination of endoscopic, histological, radiological, and biochemical investigations [Jajam et al., 2017; Eckel et al., 2017; Harbord et al., 2016; Gomollón et al., 2017]. General examination should include also general wellbeing, pulse rate, blood pressure, temperature, abdominal tenderness or distension, palpable masses, perineal and oral inspection, digital rectal examination, and measurement of body mass index [Al Johani, 2009; Jajam et al., 2017; Eckel et al., 2017; Sarra et al., 2016; Crippa et al., 2016; Litsas, 2011].

Recognising oral lesions in paediatric patients, and then requesting a biopsy of the lesions may help clinicians to expedit the diagnosis of CD [Triantafillidis, 2008; Al Johani, 2009; Sanderson et al., 2005; Jajam et al., 2017; Bogenrieder et al., 2003; Wiesen et al., 2007; Eckel et al., 2017; Harbord et al., 2016] considering that approximately up to 50% of CD patients show at least one extra-intestinal manifestation also before the diagnosis of intestinal disease [Harbord et al., 2016]. In the past, it was widely debated if oral CD in patients with intestinal disease should be considered as a true extra-intestinal manifestation or whether it was related to the mucosal disease activity [Sanderson et al., 2005; Rowlandet al., 2010]. Considering that the appearance of one extra-intestinal manifestation increases the risk of development of another, and in addition that oral disease may predate intestinal involvement, the early detection of oral CD is really important in the paediatric population.

Conclusion

Since children and adolescents with CD may often present a more complicated disease course in contrast to adult patients, it is extremely important to achieve an early diagnosis. In addition, the potential impact of CD on growth, pubertal and emotional development of patients underlines the need for a close interaction between all figures involved in observing intestinal and extra-intestinal manifestations (pediatricians, dental practitioners, dermatologists, general surgeon, internists, immunologists).

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