

Oral lesions leading to the diagnosis of Crohn disease: Report on 5 patients

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Crohn disease is a chronic granulomatous inflammatory disease of the gastrointestinal tract of unknown etiology. Oral lesions are significant, as they may occasionally precede intestinal and systemic manifestations. In this retrospective study, clinical and histopathologic data were reviewed from the files of 5 patients with Crohn disease diagnosed at the Department of Oral Medicine and Maxillofacial Pathology School of Dentistry, Aristotle University, Thessaloniki, Greece, and Division of Stomatology and Oral Surgery, Faculty of Medicine, University of Geneva, Switzerland. In the 5 patients, clinical signs included erosions, deep ulcers, cobblestoning of the buccal mucosa, mucosal tags, and lip swelling. Histopathologic examination revealed a granulomatous inflammation with noncaseating granulomas and deep fissuring of the oral mucosa. In all 5 patients, oral lesions were the early signs of the disease. The diagnosis of Crohn disease was confirmed by a colonoscopy and a biopsy of colonic lesions. Oral lesions may be significant and/or initial signs of Crohn disease. Recognition of the lesions may provide an early diagnosis. (*Quintessence Int* 2009;40:581–588)

Key words: chronic inflammatory bowel disease, cobblestoning, Crohn disease, mucosal tags, noncaseating granulomas, oral lesions, oral ulcers

Crohn disease, first described by Crohn et al in 1932,¹ is a chronic inflammatory gastrointestinal disorder that affects mainly the ileum

and less commonly the periphery (from the oral cavity to the rectum).² In addition, other extraintestinal metastatic sites of disease involvement, such as skin, eyes, and joints, have been identified.^{3,4}

The incidence of Crohn disease is estimated at 1 to 4 persons per 100,000.⁵ Oral lesions presenting as a clinical sign were first described in 1969 by Dudeney,⁶ and their overall incidence ranges from 0.5% to 30.0%.^{3,4} Diagnosis of Crohn disease via oral lesions was first reported in 1972 and is attributed to Varley.⁷ From 1972 on, cases of patients diagnosed for Crohn disease by oral lesions have been reported.^{8–12}

Oral manifestations are often present in patients with advanced intestinal disease, but in some cases, they precede intestinal lesions.^{13–15} The purpose of the current article is to describe 5 cases of Crohn disease where the oral signs and symptoms of the disease led to the diagnosis.

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CASE DESCRIPTIONS

In this retrospective study, the files of 5 patients with Crohn disease were reviewed. The patients had been referred to the Division of Stomatology and Oral Surgery, School of Dental Medicine, Geneva, Switzerland, and the Department of Oral Medicine and Maxillofacial Pathology, School of Dentistry, Aristotle University, Thessaloniki, Greece, between 1993 and 2007 for examination, diagnosis, and therapeutic management of oral mucosal lesions.

Patients with oral lesions who had already been diagnosed with Crohn disease were excluded from this study.

Of the 5 patients, 3 were men and 2 were women; their ages ranged from 19 to 38 years. The family, medical, and dental history of each patient was analyzed. The recorded clinical signs and symptoms of each patient, as well as the course of the disease, were studied.

An incisional biopsy from oral lesions was performed in all 5 patients, and because the histopathologic examination was indicative of granulomatous disease, Crohn disease was included in the differential diagnosis. The patients were then referred to a gastroenterologist for investigations that included a radiographic examination of the gastrointestinal tract, a colonoscopy, and a biopsy in presence of macroscopically visible lesions.

Family and medical history

Patients' family history revealed that none of the 5 patients had a history of Crohn disease or any other granulomatous disease.

Four patients complained about oral manifestations about 6 months before referral to the authors' departments. These lesions, according to the patients, were recurrent with an interval of 2 to 3 months. Two of the patients (cases 1 and 2) stated in their medical history that they had been having diarrhea for about 1 month before the referral. One of these patients (case 1), 15 days before the referral, underwent a colonoscopy and was diagnosed with a nonspecific colitis. Another patient (case 5) had been having troubling intestinal symptoms diagnosed and treated as ulcerative colitis.

Two weeks later, he was admitted to the hospital with severe nasal obstruction, rhinorrhea, and oral and intestinal symptoms.

Oral clinical findings

Clinical examination revealed that at the time of examination 4 of the 5 patients (cases 1, 2, 4, and 5) presented with mucosal ulcers. In 2 of them (cases 1 and 2), multiple, small (1 to 3 mm in diameter), painful aphthouslike ulcers (flat-based ulcers with a white or whitish/yellow ulcer bed and an erythematous halo) affected the soft palate. They resembled herpetiform aphthous ulcerations, giving the clinical appearance of herpangina (Fig 1).

In another 2 patients (cases 4 and 5), multiple multifocal and irregular oral ulcers of various sizes were observed. Some of the ulcers resembled minor or major pathos ulcerations (Figs 2 and 3), whereas others presented as deep ulcers with hyperplastic folds (Fig 4). The third patient (case 3) presented with a unilateral, persistent, asymptomatic lip swelling of the right side of the lip (Fig 5).

In 3 patients (cases 1, 2, and 3), clinical examination also revealed a folded and swollen buccal mucosa due to nodular swellings, a clinical sign well-known as "cobblestoning"¹⁶ (Figs 6a and 6b).

Moreover, in case 1, asymptomatic, linear hyperplastic lesions known as "mucosal tags" were detected on the ventral surface of the tongue (Fig 7).

Extraoral clinical findings

Case 5, as previously mentioned, was admitted to the hospital for nasal obstruction and rhinorrhea. An exfoliating erythematous epidermal reaction was detected in case 3 at the perioral area around the lip swelling (Fig 5).

A painful bilateral lymphadenopathy in the regional submandibular and neck lymph nodes was detected in 4 of the patients, whereas in case 1, there was a painless bilateral lymphadenopathy in the regional submandibular and neck lymph nodes.

Fig 1 (left) Multiple, small (1 to 3 mm in diameter), painful, aphthouslike ulcers (flat-based ulcers with a white or whitish/yellow ulcer bed and with an erythematous halo), at the soft palate having the clinical appearance of herpangina or herpetiform aphthae (case 2).



Fig 2 (center) Oral ulcer resembling minor recurrent aphtha at the vermilion border (case 5).



Fig 3 Oral ulcer resembling major recurrent aphtha at the buccal mucosa (case 4).



Fig 4 A deep ulcer with hyperplastic folds at the buccal mucosa (case 5).



Fig 5 A unilateral, persistent, asymptomatic lip swelling at the right side of the lip with an exfoliating erythematous epidermal reaction at the perioral area around the lip swelling (case 3).



Figs 6a and 6b Folded and swollen buccal mucosae known as cobblestoning (cases 3 and 1, respectively).



Fig 7 Mucosal tags characterized by a reticulum of white asymptomatic linear lesions at the ventral surface of the tongue (case 1).

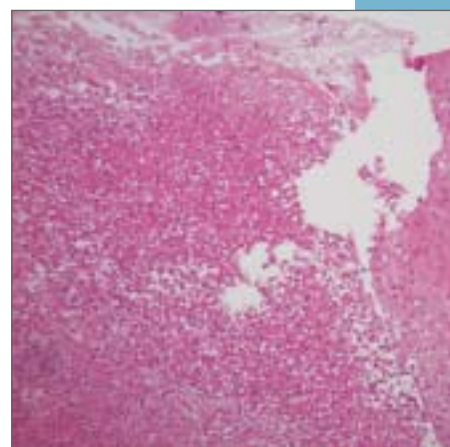
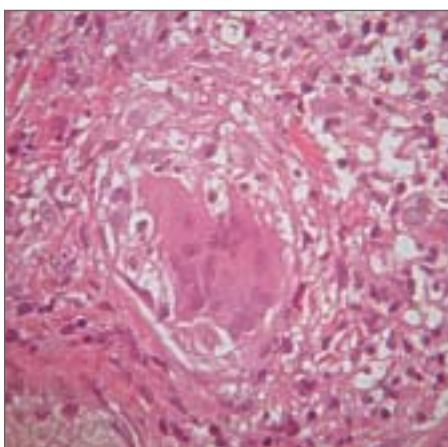
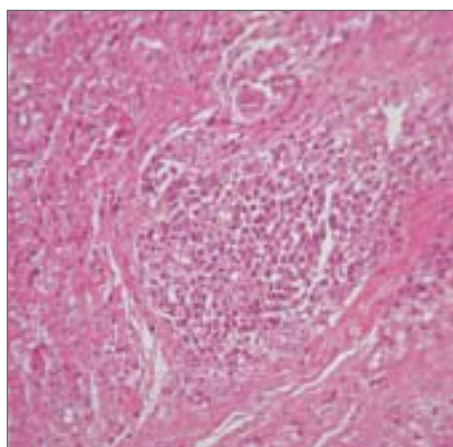


Fig 8 (left) Granulomatous inflammation characterized by the formation of noncaseating granulomas in the histologic examination in Crohn disease.

Fig 9 (center) A giant cell of Langhan type in the histologic examination in Crohn disease.

Fig 10 (right) Granulomatous inflammation and deep fissuring of the oral mucosa in the histologic examination in Crohn disease.



Figs 11a and 11b Ulcers in the colon mucosa revealed by a colonoscopy.

Further examinations

A tissue biopsy specimen was obtained from the oral lesions in all 5 cases. Histologic examination in 4 patients revealed a granulomatous inflammation characterized by the formation of noncaseating granulomas. Giant cells, Langhan type, were also evident. In 4 patients, deep fissuring of the oral mucosa was present (Figs 8 to 10). In 1 patient (case 5), the oral biopsy did not reveal any granulomas, but submucosal microabscesses were present. Special staining (Ziehl-

Neelsen, Grocott-Gomori, Gram, periodic acid-Schiff [PAS], and PAS-diastase) was applied to exclude the possibility of specific mycobacterial, bacterial, or deep fungal infections.

The patients were referred to a gastroenterologist for further investigations, including a colonoscopy, which revealed the presence of ulcers in the colonic mucosa in all 5 patients (Figs 11a and 11b).

Table 1 describes the presentation of the 5 cases.

Table 1 Presentation of cases

Case	Gender	Age (y)	Oral clinical findings	Mucosal biopsy	Gastrointestinal findings	Extraintestinal findings
1	Male	22	Aphthouslike ulcers Cobblestoning Mucosal tag	Granulomatous inflammation Noncaseating granulomas Giant cells, Langhan type Deep fissuring of oral mucosa	Aphthouslike ulcers in colon mucosa	Painful bilateral lymphadenopathy in regional submandibular and neck lymph nodes
2	Female	19	Aphthouslike ulcers Cobblestoning	Granulomatous inflammation Noncaseating granulomas Giant cells, Langhan type Deep fissuring of oral mucosa	Aphthouslike ulcers in colon mucosa	Painless bilateral lymphadenopathy in regional submandibular and neck lymph nodes
3	Female	58	Cobblestoning Unilateral, persistent, asymptomatic lip swelling Exfoliating erythematous epidermal reaction at perioral area around the lip swelling	Epithelial noncaseating giant cell granuloma (minor labial salivary gland) Epithelial noncaseating giant cell granuloma (nodule of the buccal mucosa) Deep fissuring of oral mucosa	Aphthouslike ulcers in colon mucosa	Painless polyadenopathy Fatigue Suspicion of hepatomegaly
4	Male	67	Multiple multifocal and multiform oral ulcers, resembling minor or major recurrent aphthae	Granulomatous inflammation Aphthouslike ulceration Deep fissuring of oral mucosa	Chronic granulomatous ileitis with ulcer fissuration Abscesses with crypts situated in ileum and caecum (diarrhea, rectal bleeding)	Painless bilateral lymphadenopathy in regional submandibular and neck lymph nodes Asthenia, fatigue Loss of pounds (perte ponderale)
5	Male	38	Multiple superficial ulcerations on palate, tongue, oral vestibule	Submucosal microabscesses	20-cm inflamed stenosed segment of ascending colon Deep ulcers with hyperplastic folds Red mucosa with deep ulcerations Chronic granulomatous colitis	Painless bilateral lymphadenopathy in regional submandibular and neck lymph nodes Nasal obstruction Rhinorrhea Recurrent epistaxis

DISCUSSION

The signs and symptoms of Crohn disease, although they may present in the pediatric and/or geriatric populations,¹⁷ frequently appear in the second to third decades of life. The etiology of Crohn disease remains unknown, but a multifactorial interplay of the environment and genetics has been suggested.¹⁸

The disease has a familial incidence of 10% to 15%. Among the patients in this report, no family history of Crohn disease was present.

Crohn disease is a relapsing, transmural inflammatory disease of the gastrointestinal mucosa. It may affect the entire gastrointestinal tract from the mouth to the anus. The coexistence of oral mucosal involvement in

Crohn disease and gastrointestinal symptoms ranges from 0.5% to 30.0%.^{3,5} In some cases, oral manifestations of Crohn disease may be the first and/or exclusive¹⁹ symptom and precede other gastrointestinal symptoms by days, months, or even years.^{20,21} Oral and head-neck lesions can occur in many forms and locations, and some cause subjective painful symptoms. These lesions are summarized in Table 2.

Orofacial features of Crohn disease include multiform ulcerations^{16,22} (linear ulcerations of the vestibule; aphthouslike ulceration); erosions; orofacial granulomatosis mainly as granulomatous cheilitis²³; hyperplastic folds known as cobblestoning²⁴; white linear reticular tags known as mucosal tags²⁵; multiple multifocal microabscesses,



Table 2 Lesions in the oral and head and neck area associated with Crohn disease

Specific

- Orofacial granulomatosis (granulomatous cheilitis)
- Focal areas of mucosal inflammatory hyperplasia and fissuring (cobblestoning)
- Indurated polypoid tag lesions on buccal mucosa, retromolar fossa, labial mucosa (mucosal tags)
- Deep, linear ulcers with hyperplastic folds
- Pyostomatitis vegetans
- Midline lip fissuring

Nonspecific

- Persistent lymphadenopathy
- Aphthouslike ulcers
- Angular cheilitis
- Diffuse labial, buccal, or gingival swellings
- Facial edema
- Perioral erythema

ie, pyostomatitis vegetans²⁶; persistent lymphadenopathy; and perioral erythema.²⁷ Although most of these clinical signs are not considered to be disease specific, some authors consider cobblestoning and mucosal tags to be pathognomonic for the disease.²⁸ Not all authors share this view. The lack of a long-term follow-up in this article does not allow definitive conclusions.

Clinical findings are often not sufficient to confirm Crohn disease. When the clinical examination reveals aphthouslike ulcers, the differential diagnosis includes recurrent minor aphthous ulceration, ulcerative colitis,²⁹ Behçet disease,³⁰ and periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome,³¹ etc. On the other hand, when the clinical examination reveals diffuse or nodular swelling in the head and neck region, an orofacial granulomatosis must be suspected, and the differential diagnosis should include Melkersson-Rosenthal syndrome,³² sarcoidosis, foreign body reactions,³³ Wegener granulomatosis,³⁴ and other granulomatous disorders.

It is interesting to note that Scully et al,²⁰ in a study reviewing 19 patients with orofacial granulomatosis, found 7 patients with gastrointestinal Crohn disease. Sciubba and Said-Al-Naief found 6 of 13 patients with orofacial granulomatosis to be affected by gastrointestinal Crohn disease.³⁵

An oral biopsy will often confirm the nature of the lesions in the presence of a granulomatous inflammation. The histopathologic analysis in Crohn disease bears conspicuous resemblance in intestinal and oral lesions. It is characterized by the triad of deep focal fissuring of the mucosa, formation of noncaseating granulomas deep into the superficial mucosa, and the presence of Langhan-type giant cells. Lymphoedema of the upper corium and a diffuse or perilymphatic lymphocytic infiltrate are also often observed.³⁶ Special stains should be performed to rule out the possibility of mycobacterial and deep fungal infections.

Because most of the clinical and histopathologic signs are not disease specific, however, whether their sole presence can be sufficient to confirm diagnosis is questionable. In this regard, Wiesenfeld et al³⁷ originally introduced the term *orofacial granulomatosis* to encompass a group of disorders previously referred to as *cheilitis granulomatosa*, ie, oral manifestations of sarcoidosis and Crohn disease without any evident abnormalities at any other site in the gastrointestinal tract.

In 2003, Sciubba and Said-Al-Naief³⁵ stressed “the similarity and overlap in clinicopathologic and histomorphic features” in Melkersson-Rosenthal syndrome, Miescher cheilitis, Crohn disease, and sarcoidosis. They proposed, therefore, that the term *orofacial granulomatosis* be used to depict a group of conditions almost inseparable in diagnosis and with a wide overlap between Melkersson-Rosenthal syndrome and Crohn disease. They also proposed the notion that patients with oral Crohn disease, with or without intestinal involvement, may be diagnosed as having an oligosymptomatic form of Melkersson-Rosenthal syndrome.

Field and Tyldesley, on the other hand, proposed use of the term *oral Crohn disease*³⁸ when oral granulomatous lesions are detected in the absence of gastrointestinal signs and symptoms, with the advantage that it keeps patients and clinicians alert to the possibility of gastrointestinal signs and symptoms that may arise months or even years later. Their proposal was based on their 10-year follow-up of 10 patients with oral granulomatous lesions, among which 1 patient



developed intestinal signs of Crohn disease 18 months later. Since then, many articles have been published reporting on patients with oral granulomatous lesions that months or even years later developed gastrointestinal signs and symptoms.^{21,22} It is interesting to note that in the current study, at least 3 of the cases were delayed in diagnosis because the first symptoms were in the oral cavity.

In the current study, the authors believe that in the case of oral signs of Crohn disease, the diagnosis shall be made by specific findings from the gastrointestinal tract—colonoscopy and a mucosal biopsy from the colonic mucosa must reveal granulomatous lesions in the colon—besides those of the oral cavity,³⁹ and if this is not the case, the term *orofacial granulomatosis* must be adopted instead.

Diagnosis of the disease by dentists and other clinicians through the evaluation of oral clinical findings is a rare incident. The relative published articles found in the current literature (that is, articles where the intraoral clinical findings led to diagnosis of the disease) are relatively rare and refer to a small number of cases.^{23,25,35,39}

CONCLUSION

The presenting intraoral clinical findings in Crohn disease are numerous and often non-specific. One of the goals of the current article was to remind dentists and other clinicians of this wide spectrum of clinical findings. Oral health care professionals should be aware of the possibility that oral lesions may be the initial signs of Crohn disease (or even be the only manifestations).²⁸ Clinical investigations of the gastrointestinal tract should be performed when typical oral lesions are present (mucosal tags, cobblestoning, linear fissures) or when the patient complains about gastrointestinal symptoms to diagnose the disease early and provide appropriate treatments.

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