Recurrent oral aphthosis as the solitary clinical manifestation of Crohn's disease in children: a case report

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Keywords

Aphthosis; Crohn's disease; intermittent abdominal pain; calprotectin.

Abstract

Crohn's disease is a chronic inflammatory bowel disease that affects the digestive tract, where the clinical presentation highly depends on disease localisation. The majority of patients typically present with (bloody) diarrhoea, abdominal pain, weight loss and growth impairment. We describe an atypical case of a nine-year-old boy with chronic aphthosis for more than one year as sole manifestation of Crohn's disease, without other gastrointestinal symptoms, beside intermittent abdominal pain. Even in the absence of biochemical signs of inflammation and negative calprotectin, further investigations are warrant if oral lesions are persistent, deep with a more atypical

Introduction

Crohn's disease (CD) is a chronic, inflammatory, panenteric gastrointestinal disorder (1). It has a prevalence of 0.3% in Europe, with an expected increase over the next decades (1). CD is primarily diagnosed in young adults, but up to 25% of patients developed symptoms in childhood (1). Patients typically present with gastrointestinal complaints, such as abdominal pain, chronic diarrhoea with or without bloody stools, and weight loss (1). Since CD is a panenteric disease, patients can also present with upper gastrointestinal symptoms including oral lesions (1). Oral manifestations of CD are prevalent (7-40%) and comprise a spectrum of different types of lesions (2, 3). Some oral manifestations have typical clinical and/or histologic characteristics related to CD, such as cobblestoning of the mucosa, granulomatous cheilitis, mucogingivitis, linear ulcerations or mucosal tags (2-4). Whereas aphthous stomatitis (2), the most prevalent oral manifestation of CD in children, is related to a variety of disorders and thus not specific to CD (2, 6). Diagnosing CD can prove challenging when children present with oral lesions without gastrointestinal symptoms, leading to physicians' delay in treating CD and subsequent patient burden.

We present a case of a nine-year-old boy diagnosed with oral lesions as the sole clinical manifestation of CD.

Case

A nine-year-old boy initially presented at a secondary care centre with recurrent oral aphthosis and mucosal swelling resulting in anorexia for several weeks (figure 1,2). Occasionally there were complaints of abdominal pain, nonetheless, this was not a source of significant discomfort. His bowel movement pattern was normal with a tendency to constipation. There were no other gastrointestinal symptoms, nor extraintestinal manifestations (fever, joint pain, uveitis, skin lesion). Clinical examination revealed deep and linear aphthous stomatitis of the tongue, soft palate, and buccal mucosa (figure 1). There were no other clinical abnormalities with a height between the 50-75 percentile (131.5cm) and a weight between the 25-50 percentile (24.5kg). He had no known medical history or recent medical therapy and his familial history for chronic diseases was negative. Biochemical evaluation was performed and revealed no haematological abnormalities or signs of inflammation (normal white blood cell count of 9.0 x103/uL, neutrophil count (58%)), C-reactive protein of 3mg/L [N < 5mg/L]and slightly elevated sedimentation (34mm/h [N <20 mm/h]). There was a low iron status with a ferritin of 50ug/L [N ≥30 - ≤400µg/L] and a transferrin saturation of 14% [N ≥16 - ≤45%] (transferrin 2.3g/L [N ≥2.00 - ≤3.60g/L]), without other signs of nutritional deficiencies (including zinc). Both IgM and IgG for herpes simplex and cytomegalovirus were negative. Antinuclear and anti-neutrophil cytoplasmic antibodies testing were negative. IgA anti-tissue transglutaminase was negative and faecal calprotectin was within the normal range (41 µg/g). There was no occult blood in the faeces sample and stool cultures were negative.

Since the patient had no obvious evidence of underlying infection, gastrointestinal disease, or auto-immune disorder, he was referred for further stomatological evaluation with the advice to continue local therapy and to start iron suppletion. Despite seeking medical treatment in several centra for more than one year the lesions persisted and were even more severe than initial, resulting in weight loss. Eventually, a biopsy of an ulcerative lesion of the tongue was taken. Histology showed severe acute on chronic inflammation with deep granulomatous ulceration. Since histological findings could be associated with oral CD, he was referred to a tertiary centre. At that time, he had continuous severe oral pain which led to anorexia and weight loss, where the weight dropped to the 10th percentile and height to the 50th percentile.

The patient was admitted for further evaluation. Clinical examination shows oral aphthosis on the tongue and the lower lip. Further clinical examination was completely normal without abdominal tenderness, peri-anal disease or skin lesions. Ultrasound of the abdomen showed wall thickening in the terminal ileum and proximal third of the colon ascendens. Upper gastrointestinal endoscopy showed haemorrhagic gastritis with small aphthous ulcers without oesophageal or duodenal abnormalities. Colonoscopy revealed inflammation of the caecum

Table 1: Differential diagnosis oral aphthosis.

Differential diagnosis oral aphthosis	
Recurrent aphthous stomatitis	Superficial, small, white aphthosis. Duration +/- 2 weeks (5,6)
Infections	Herpes simplex virus, varicella zoster virus, coxsackie virus human immunodeficiency virus, Treponema pallidum, Mycobacterium tuberculosis, Yersinia enterocolitica, Helicobacter pylori, leishmaniasis (7,8)
Deficiencies	Zinc, iron, folic acid, vitamin deficiency (6)
Drugs	Nonsteroidal anti-inflammatory drugs, beta-blockers, immunosuppressive drugs, or chemotherapy Stevens-Johnson syndrome or toxic epidermal necrolysis (6)
Periodic fever syndromes	Periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome (6,7)
	Cyclic neutropenia (6,7)
	Mouth and genital ulcers with inflamed cartilage syndrome (6,7)
Auto-immune disorders	Systemic lupus erythematosus (hard palate) (6,7)
	Behçet syndrome (6,7)
	Lichen planus (tongue) (6,7)
	Mucous membrane pemphigoid, pemphigus vulgaris, bullous pemphigoid (6,7)
Gastro-intestinal disorders	Inflammatory bowel diseases (2,3)
	Coeliac disease (6)

with deep ulcerations, including the ileocecal valve, confirming the diagnosis of CD. He received induction therapy with corticosteroids, and azathioprine was given as maintenance therapy. Rapid response was seen, however, lesions reoccurred one week after stopping corticosteroid therapy. Step-up therapy with infliximab, an anti-tumour-necrosis-factor-alfa (anti-TNF-α), was associated and the patient again achieved clinical remission. After six months of anti-TNF-α therapy, upper and lower endoscopy showed no macroscopic abnormalities with normal random biopsies of the gastrointestinal tract. Anti-TNF-alfa monotherapy was continued effectively without any flares for four years. This work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent of patient and legal guardians were obtained.

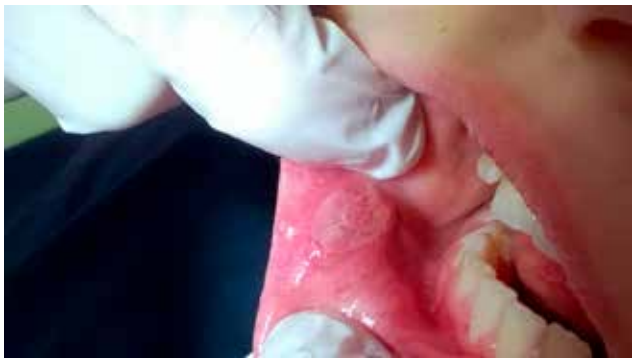
Discussion

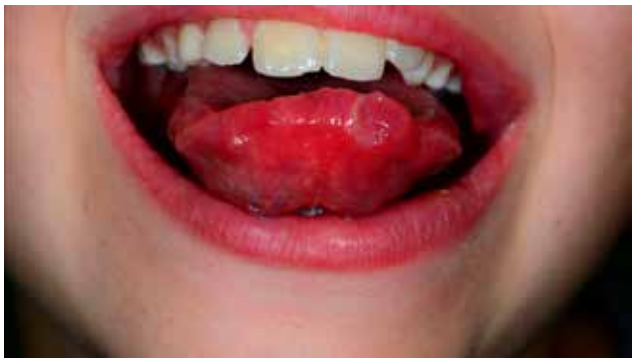
Aphthous stomatitis is a clinically prevalent yet unspecific symptom of multiple diseases, therefore, identifying the potential underlying condition can prove challenging in clinical practice (5). In this report, we presented the case of a nine-year-old boy with recurrent oral aphthous stomatitis with underlying CD without gastrointestinal symptoms or biochemical abnormalities associated with CD.

Recurrent ulcerative aphthous stomatitis is associated with several diseases (see table 1), medication use or trauma / dental appliances. Most common drugs inducing oral aphthosis are nonsteroidal anti-inflammatory drugs, beta-blockers and immunosuppressive drugs (2,3,6-8). Ulcerative lesions can be of infectious origin, wherein herpes simplex, varicella zoster, Epstein-Barr virus, coxsackie virus or cytomegalovirus infection are the most prevalent in children (7, 8). However, in immunocompetent children, they are self-limiting (7). Nutritional deficiencies, being vitamin deficiencies (B1, B2, B6 and B12) or iron, zinc and folic acid deficiencies are associated with oral aphthosis (6). Yet, nutritional deficiencies themselves can also be an expression of underlying diseases related to aphthosis, such as coeliac disease (6). Aphthosis can also present with recurrent fever, such as in cyclic neutropenia, MAGIC (mouth and genital ulcers with inflamed cartilage) or PFAPA (periodic fever with aphthous stomatitis, pharyngitis and adenitis) syndrome or other auto-immune disorders (systemic lupus erythematosus, lichen planus, or Bechet syndrome) (6, 7). However, when patients present with oral aphthosis related to aforementioned conditions, this is frequently accompanied by systemic symptoms (6).

Aphthosis is a relatively common finding in patients with CD, but often clinically underestimated. The prevalence of oral aphthosis varies

Figure 1 & 2: oral aphthosis on buccal mucosa and tongue in our patient





significantly across different cohorts, namely between 3-42% (3). In CD oral ulcerations are often larger, deeper, and more irregularly or linearly shaped than benign aphthous ulcers, which are typically round or oval-shaped (9-11). Oral lesions in CD also appear more often on the gums, lips, tongue, or palate, while benign aphthous ulcers usually occur on the inside of the cheeks or lips. In addition, these lesions tend to persist longer than benign aphthous ulcers, which usually heal within a week or two. Nevertheless, they can be difficult to differentiate clinically with other causes of aphthous stomatitis (10). Histologically aphthous ulcers associated with CD differ primarily from other causes of aphthosis based on the presence of granulomatosis (6). Therefore, a biopsy should be considered in patients with recurrent ulcerative aphthous stomatitis of unknown origin (12). If granulomatous aphthosis is diagnosed, gastrointestinal endoscopy should always be performed, even when patients present without other clinical symptoms or biochemical evidence of CD. Combining topical and systemic treatments is warranted for effectively treating these oral CD lesions.

These oral lesions are part of a broader upper gastrointestinal manifestation of CD. Upper gastrointestinal manifestations are more prevalent in paediatric than in adult CD patients with a male sex predominance (ratio of 1.2:1) and has been described in up to 9% of patients as the sole manifestation of CD (2). Upper gastrointestinal involvement can precede intestinal symptoms, be present at diagnosis or may develop during the disease course (6). Diagnosis could be more difficult as faecal calprotectin can remain strictly negative (1). Nevertheless, the upper gastrointestinal involvement of CD should not be overlooked, as it can result in serious complications such as gastric outlet obstruction depending on the localisation.

Conclusion

To enable early diagnosis and improve the quality of life for patients, paediatricians and dentists must seriously consider that the presence of oral manifestations may precede or follow intestinal symptoms of CD. Persistent aphthous stomatitis should always warrant further investigation, especially if the lesions are deep and atypical. Endoscopy with biopsies should be considered if its cause remains unknown to diagnose or dismiss CD despite negative biochemical evaluation, even in the absence of other gastrointestinal symptoms.

Conflict of interest

Authors declare no conflict of interest.

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