Review Article

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The diagnostic challenge of recurrent oral aphtosis in children: one symptom, many diagnoses

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Abstract

Recurrent oral ulcers (OU) are a common manifestation in infancy affecting up 40% of children. The first step necessary for the diagnosis is the search for associated systemic symptoms. Recurrent aphthous stomatitis (RAS) is the most common diagnosis in patients with isolated OU, being a diagnosis of exclusion. Among patients with associated symptoms, the diagnostic process must distinguish conditions in which other manifestations represent the main and relevant sign (e.g. autoinflammatory diseases, celiac disease, systemic lupus erythematosus, SLE) from other ones characterized by ulcers of such size and number to be particularly disabling (e.g. Behçet disease, BD). We elaborated an algorithm with the aim to provide help in the diagnostic challenge of children with OU.

Keywords: Behçet disease; oral ulcers; recurrent oral stomatitis.

Introduction

Oral ulcerations (OU) are a common condition in childhood representing a frequent reason for seeking medical attention. The discomfort of OU can impact negatively on the quality of life of a child, interfering with eating and speaking [1]. The causes of OU are numerous from minor irritating triggers to systemic diseases, recurrent apthous stomatitis (RAS) is the most common and it is a diagnosis of exclusion. OU can be classified as minor, major or herpetiform on the basis of ulcer size, number and healing time. Minor ulcers are superficial and small in size (<10 mm), occur singularly or in groups and heal within about 7 to 10 days without scarring. They are generally located on the nonkeratinized mucosa of the mouth. Major ulcers are larger, deeper and more painful than minor ulcers, may involve each region of the mouth, heal with scarring and tissue lost and may persist for several weeks. Herpetiform ulcers are numerous (up to 100) and tend to coalescent becoming confluent in large plaques. They may heal with scarring in 7 to 30 days [2]. ROU can be divided in two forms: simple aphthosis and complex aphthosis. The latter is used to describe patients suffering from recurrent oral and genital ulcers or almost constant, multiple (>3) oral aphthae [3].

OU without any associated symptoms

Recurrent aphthous stomatitis (RAS) is the most common cause of OU without associated symptoms, representing a diagnosis of exclusion (**Figure 1**). It is reported to affect up to 30-40% of children [4]. Etiology is unknown and the best defined predisposing factor is the hereditary [5]. At least 40% of the patients have a RAS family history and tend to develop the disease at an earlier age, with more severe symptoms and more frequent attacks. Predisposing factors in children and young people include trauma, stress, hormonal imbalance, and certain foods [6]. Minor aphthae are more common but also major and herpetiform aphthae can be observed. The correct diagnosis of RAS is dependent on a detailed and accurate family history, clinical evaluation (including associated medical conditions, such as genital ulceration (GU), skin lesions, gastrointestinal (GI) symptoms, drugs assumption) and on some blood examinations (**Table 1**).

OU accompanying more relevant symptoms

OU can be associated with other symptoms, which represent the main manifestations of the clinical picture (**Figure 2**); while in other cases, they arise with such size and number as to constitute the main sign despite the presence of a symptomatic corollary **(Figure 3)**. In the differential diagnosis of a patient with recurrent fever and aphtae, cyclic neutropenia should be first considered. Cyclic neutropenia is an autosomal dominantly inherited disorder that presents generally before 5 years of age, characterized by phases of neutropenia every 21±4 days. During neutropenic phase, lasting 3-7 days, fever, malaise, aphthous ulceration, arthralgia, bacterial infections and various other symptoms arise. Diagnosis is established by serial blood examinations (3 times/week for 6-8 weeks) to

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document periodic neutropenia and the evidence of mutation in the gene for neutrophil elastase (ELANE) confirms the diagnosis [7] (**Table 2**).

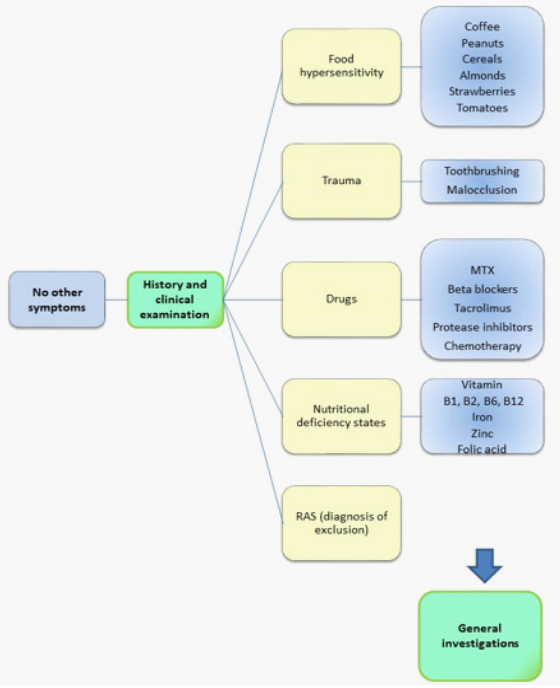

Figure 1: *OU without any associated symptoms.*
MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; RAS, recurrent aphtous stomatitis.

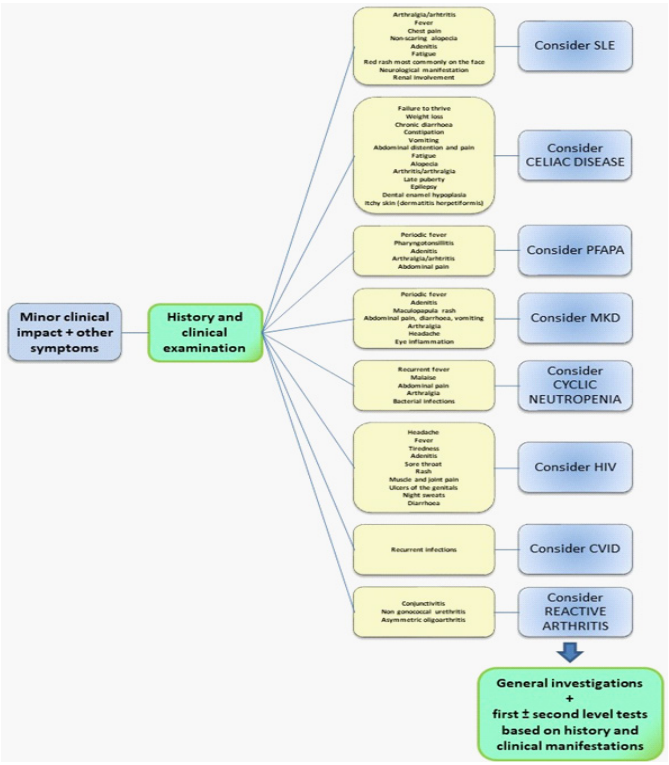

Figure 2: *OU accompanying more relevant symptoms.*
CVID, common variable immunodeficiency syndrome; HIV, Human immunodeficiency virus; MKD, mevalonate kinase deficiency; PFAPA, Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis; SLE, Systemic lupus erytemathosus.

Table 1: *Investigations that should be performed in all patients with recurrent oral aphtosis.*
CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; TGA, transglutaminase.

General investigations
Hemoglobin and full blood count
ESR/CRP
Screening for celiac disease (Total IgA and TGA-IgA)
Serum B12 and folate levels
Ferritin

Table 2: *Examinations that should be performed according to the clinic.*
ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; ASCA, anti-dsDNA, anti-double stranded DNA; anti-Saccharomyces cerevisiae antibodies; anti-SM, anti-Smith; C, complement; CNS, central nervous system; CT, computed tomography; CVID, common variable immunodeficienciency; EGDS, esophagogastroduodenoscopy; ELANE, neutrophil elastase ; EMA, anti-endomysial antibodies; GI, gastrointestinal; HIV, Human immunodeficiency virus; HLA,Human Leukocyte Antigen; Ig, immunoglobulin; MKD, mevalonate kinase deficiency; MRI, Magnetic Resonance Imaging; PFAPA, Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis; SSA, serum amyloid A; SLE, systemic lupus erythematosus; US, ultrasound.

	First level tests to consider in initial testing based on clinical manifestations and history	Second level
Bechet's disease	• All patients: HLA-B51 + ophtalmologic evaluation • GI: Faecal calprotectin + abdominal US • Arthralgia: articular US • CNS: brain MRI • Vascular: Doppler US	• Pathergy test • GI: colonoscopy and/or EGDS • Joint: articular MRI
IBD	• ASCAs - pANCA • Faecal calprotectin • Abdominal US	• Colonoscopy and/or EGDS
Autoinflammatory disease (PFAPA, MKD)	• SAA • Immunoglobulins • Lymphocyte subtypes	• Genetic analysis (CIAS1, TNFRS1, MEFV, MKD)
Cyclic neutropenia	• Repeated blood counts (3 times/week for 6-8 weeks)	• Genetic analysis (ELANE)
Reactive arthritis	• Stool and urogenital tract cultures • Chlamydia serology • HLA B27 • Articular US	• Articular MRI

SLE	• ANA, anti SM, anti dsDNA, C3 and C4 serum levels • Direct Coombs test • Urine analysis • Antiphospholipid antibodies	• Renal: 24h proteinuria or albumin/creatinine ratio + abdominal US ± renal biopsy • CNS: brain MRI • Chest: US, x-ray, CT scan, MRI • Joint: articular US
CVID	• Serum immunoglobulins • IgG subclasses • Lymphocyte subtypes	• B-lymphocytic phenotype • Immune response to vaccine antigens
HIV	• IgG subclasses • Lymphocyte subtypes	• Screening HIV
Celiac disease	• Total IgA • TGA-IgA	• TGA-IgA < 10x ULN: EGDS with Biopsy • TGA-IgA ≥ 10x ULN: EMA-IgA

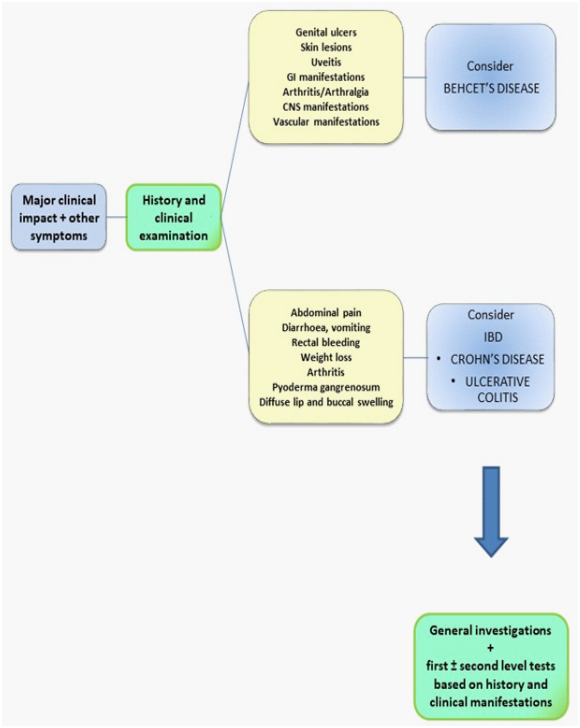

Figure 3 *Disabling OU associated with other symptoms.*
CNS, central nervous system; GI, gastrointestinal; IBD, inflammatory bowel disease.

Among the conditions in which OU represent an accompanying symptom, we include some autoinflammatory syndromes, particularly aphthous stomatitis, pharyngitis, adenopathy (PFAPA) and mevalonate kinase deficiency (MVK). These patients experience recurrent inflammatory attacks featured by fever and a corollary of aspecific symptoms, without any evidence of infections [8, 9]. PFAFA syndrome arises before the age of five years, presenting with pharyngotonsillitis, aphthous stomatitis, cervical lymphadenopathy and sometimes arthritis/arthralgia and slight abdominal pain. The length of febrile episodes is of 3-6 days with an interval of about 21-28 days among the attacks. Blood tests show an increase of inflammatory markers during the critical phase, while no abnormality is found in the wellness intervals [7].

MKD is a periodic fever syndrome characterized by an early onset, in the first 6 months of life, with recurrent episodes of fever lasting from 3 to 7 days. Typical attacks are featured by gastrointestinal manifestations in 98% of patients (abdominal pain (88%), diarrhea (84%) and vomiting (69%)), lymphadenopathy (90%), arthralgia (71%), OA (60%), maculopapular rashes (39%), headache (38%). In this condition, aphthous stomatitis, usually presenting as aphthae major, is more severe than in PFAPA. Diagnosis relies on the clinical phenotype, after the exclusion of cyclic neutropenia and of an immunodeficiency disorder with a first level immune assessment (serum immunoglobulins levels and lymphocyte subsets). In front of a patient with persistently elevated inflammatory markers, particularly serum amyloid A (SAA) in the intercritical phase, and presence of abdominal pain during the febrile attacks, a second level examination including the search for mutations in disease genes (CIAS1, TNFRS1, MEFV, MVK) is recommended, in order to diagnose monogenic autoinflammatory diseases [8,9] (**Table 2**).

In a patient with OU associated with fever and arthritis, the differential diagnosis include reactive arthritis and SLE. SLE is a chronic autoimmune disease characterized by multisystem inflammation and presence of circulating autoantibodies directed against self-antigens. As any organ may be involved in SLE, the potential clinical manifestations are a myriad; moreover the most commonly organs involved are skin, joints, kidney, blood vessels and the central nervous system (CNS). Fever and fatigue are frequently complained by the patients. OU occur in approximately 21% of patients with SLE [10] and their presence is associated with increased disease activity and worse prognosis [11]. OU are one of the criteria included in the 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for SLE [12]. According to these criteria, ANA positivity is a mandatory criterium to pose the diagnosis of SLE. Other diagnostic laboratory features include the presence of autoantibodies (anti dsDNA, anti Smith, anti phospholipids), hypocomplementemia, direct Coombs test, proteinuria. Second level examinations useful for the conclusive diagnosis are shown in (Table 2). OU can be part of the clinical picture of reactive arthritis,that is characterized by an asymmetric oligoarthritis frequently associated with extra-articular manifestations including: fever, fatigue, conjunctivitis (less frequently uveitis), urethritis, cutaneous manifestations. In the suspicion of reactive arthritis, stool and urogenital tract culture, the search for HLA B27, Chlamydia serology and articular US must be performed (Table 2). Both primary and secondary immunodeficiency can occur with OU. Therefore, in the case of patients with recurrent infections, an immunological evaluation such as immunoglobulins and IgG subclasses dosage, lymphocyte subtypes and HIV test should be performed (Table 2). Interestingly in our clinic, we observed two patients with ROU, without history of significant morbidity but presenting autoimmune manifestations, whose laboratory examinations were indicative for a Common Variable Immunodeficiency Disease (CVID), outlining the need to evaluate humoral and cellular immunity in patients with ROU.

Severe episodes of OU have been reported in patients suffering from human immunodeficiency virus (HIV) infection. It has been described that major ulcers are associated with lower CD4+ cell count and inversion in the CD4+/CD8+ ratio [13].

Vesiculobullous disorders, such as pemphigus vulgaris and mucous membrane pemphigoid, occurring both in childhood and in middle-aged adults, are rare autoimmune conditions causing OU. Diagnosis is confirmed by detection of autoantibodies on the lesions by immunofluorescence [5]. OU can be commonly found in some gastrointestinal diseases as celiac disease, Crohn's disease (CD) and ulcerative colitis (UC). Celiac disease is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals (HLA DQ2 or HLA DQ8 haplotypes), characterized by the presence of enteropathy, gluten dependent clinical manifestations: abdominal distention, diarrhea, vomiting, failure to thrive. It is associated with a wide spectrum of extraintestinal manifestations: iron-deficiency anemia, osteoporosis, aphthous stomatitis, alopecia, arthritis/arthralgia, epilepsy with bilateral occipital calcifications, isolated hypertransaminasemia, dental enamel hypoplasia, late puberty and fatigue. It is important to emphasize that OU may be the first manifestation of celiac disease, that, unlike RAS, heal with the gluten-free diet and are generally less disabling than those occurring in CD and ulcerative colitis (UC). If a celiac disease is suspected, measurement of total serum IgA and IgA-antibodies against transglutaminase 2 (TGA-IgA) should be performed. Celiac disease diagnosis can be established, without duodenal biopsies, if TGA-IgA is ≥10 times the upper limit of normal, the family agrees and endomysial antibodies (EMA-IgA) are positive in a second blood sample. In children with positive TGA-IgA <10xULN biopsy should be performed [14].

Disabling OU associated with other symptoms

In patients with IBD and BD, thought associated with other manifestations, OU can be of such dimension and number to represent a major problem. CD and UC are chronic inflammatory diseases with primary intestinal involvement. Arthritis and OU are the most frequent extraintestinal manifestations of IBD, as confirmed in a cohort of 1649 pediatric patients [15]. The incidence of OU in CD varies from 10 to 80% [16]. Patients with CD may exhibit specific (diffuse lip and buccal swelling, tags, cobblestones) and non-specific oral manifestations (aphthous ulcers, pyostomatitis vegetans, and gingivitis). Cobblestones lesions are granulomatous swelling of the oral cavity; the swelling of the intestinal mucosa has a similar 'cobblestone' appearance in the endoscopic images. Mucosal tags appear as small localized swelling that may surround deep linear ulcerations [16]. Pyostomatitis vegetans, characterized by multiple pustules, erosions, vegetative plaques and mucosal folds [17] can occur in CD, but is more frequently associated with UC. In general, although oral lesions are more common in CD, almost all of the so-called non-specific oral lesions described in CD can also occur in UC [18]. Oral manifestations may precede intestinal inflammation, coincide with it or appear after diagnosis [15].

Patients with OU and gastrointestinal manifestations, must undergo an extended evaluation including history, physical examination, laboratory exams and endoscopic findings in order to differentiate CD from UC. Patients with CD present a wide combination of signs such as abdominal pain, diarrhea, vomiting, anorexia, weight loss, growth retardation, and extra intestinal manifestations (arthritis, erythema nodosum). Typical presentation of UC is characterized by diarrhea with blood, mucus and pus in the stool. Anorexia, weight loss and growth failure can be present in patients with UC but are more typical of CD. In both diseases blood examination may show anemia, hypoalbuminemia, elevation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); concerning the search for autoantibodies, anti-Saccharomyces cerevisiae (ASCA) can be positive in CD and perinuclear antineutrophil cytoplasmic antibodies (pANCA) in UC. Fecal calprotectin levels are usually elevated. Abdomen-sonography may show in CD a thickened bowel wall. CT and MRI can be used both at the diagnosis and late to assess complications. Endoscopy with histological examinations confirms the diagnosis (Table 2) [19, 20]. Treatment of the inflammatory bowel disease (IBD) will result in resolution of oral lesions in many cases [18].

In the presence of severe OU, BD should be suspected. BD is a multisystem inflammatory condition that usually first arises with OU, which precede other symptoms by years. Almost all children, 92-100%, with BD have OU [5, 21]. The lesions tend to be widespread and multiple, but may also be single. They involve lips, tongue, cheeks and palate; the mean healing time is 10 days but major ulcers may persist for weeks [22, 23]. Increased number of ulcers (more than six at the same time), concurrent variation in size from that of herpetiform to major ulcers and diffuse erythematous surrounds and involvement of soft palate and oropharynx have been suggested to differentiate BD from conventional RAS [23-25]. The diagnosis of BD relies substantially on the clinical features although no specific symptoms and signs are described. Due to the long time interval between first manifestation and the development of a clinical picture compatible with BD diagnostic criteria, the diagnosis in children is particularly challenging. In 2015 the Pediatric Behçet disease (PEDBD) criteria have been published [21]. These criteria include the following six manifestations: ROU, genital ulcers (GU), skin involvement, ocular involvement, neurological sign, vascular signs [21]. Each feature has the same weight and the presence of 3 or more criteria is necessary to define a patient as affected by BD [21]. Examinations such as fecal calprotectin, abdomen sonography, cerebral nervous system (CNS)-brain magnetic resonance imaging (MRI), doppler ultrasound should be performed according to the clinical manifestations [26-28] (**Table 2**).Moreover we strongly support the assumption that, in the evaluation of a child with recurrent oral and genital aphthous ulcers or almost constant multiple oral aphthae, detailed history and a systemic examination must be performed together with the review of BD diagnostic criteria [21]. If BD is suspected, HLAB51 should be investigated and patients should be addressed for an ophthalmologic evaluation for the potential presence of uveitis [27].

The proposal of a algorithm for the diagnostic approach (see Algorithm)

With the aim to simplify the OU diagnostic process, we created an algorithm that include several procedural steps (**Table 1, 2**; **Figure 1-3**). The first diagnostic step is a careful clinical history to search for systemic symptoms, that may be associated with OU. Fever, arthritis, skin lesions, recurrent infections, gastrointestinal symptoms, ocular manifestations should be considered as the main red flags for a systemic condition in patients with OU. The differential diagnosis in patients with-

out associated symptoms include: RAS, nutritional deficiencies (iron, vitamin B1, B2, B6, B12, folic acid, zinc), trauma (malocclusion, tooth brushing), drugs assumption (in particular nonsteroidal anti-inflammatory drugs , methotrexate, chemotherapy, tacrolimus, betablockers, protease inhibitors), food hypersensibility (chocolate, coffee, peanuts, cereals, almonds, strawberries, tomatoes, cheese) (**Figure 1**) [22] . In the case of patients with OU and other associated symptoms, it is first necessary to distinguish the conditions on the basis of the severity of the ulcers. Therefore, number, duration, location, frequency and clinical appearance of OU must be reported. The diseases in which OU generally represent a minor problem compared to other symptoms are: autoinflammatory diseases, cyclic neutropenia, celiac disease, reactive arthritis, SLE, immunodeficiency disorders (**Figure 2**). On the opposite, in other conditions, i.e. Behçet disease (BD) and inflammatory bowel diseases (IBD), OU present with size, such duration and recurrence as to cause serious discomfort and negatively influence the quality of life (**Figure 3**). It is of interest to remark that in BD and IBD, although OU are frequently associated with other manifestations, they may be the first symptom that can last, on its own, long before the disease develops. A detailed history, that focuses on the accompanying symptoms, and the examination of the patient are fundamental in order to direct the diagnostic process towards the choice of selected investigations.

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