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Idiopathic recurrent oral ulcerations: A case report

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Abstract

Ulcers are common inflammatory conditions affecting the oral mucosa which typically appear as painful, shallow ulcerations with an overlying pseudomembrane and surrounded by an erythematous halo. The etiology of oral ulcers have been attributed to nutritional deficiencies, inflammatory bowel diseases, infections, autoimmune conditions, drugs as well as dermatological disorders.

We describe a case of a 38-year old Indian female who first attended our clinic in 2009 with a 4-year prior history of recurrent oral ulcerations. Throughout her follow-up spanning a decade, the recurrent ulcerations led to severe scarring of the oral mucosa, causing microstomia and resultant ankylosis of the bilateral temporomandibular joints. The patient also had periodic genital ulcerations, gastrointestinal disturbances, polyarthralgia as well as chronic ulcers over the bilateral Achilles tendon region. Extensive investigations failed to uncover a specific cause of her recurrent oral ulcerations. She was treated empirically for Behçet's disease, Crohn's disease as well as iron and vitamin B12 deficiencies but her ulcers were recalcitrant to long-term steroids, azathioprine, colchicine, methotrexate and pentoxifylline.

Recurrent oral ulcers although seemingly harmless, may have severe long-term incapacitating effects if left undiagnosed. Although relatively common, oral ulcers appear to be poorly understood and hence, may be a challenge to treat.

However, tumour necrosis factor (TNF) inhibitors have been reported to produce promising results in treating recurrent oral ulcers and therefore, have to be further explored as a viable treatment modality.

Keywords

oral ulcers; recurrent; stomatitis; aphtous ulcers

Introduction

Oral ulcers are a common affliction with a myriad of etiological factors that can be arduous to pin-point. Recurrent aphthous stomatitis (RAS) or oral aphthae typically present in childhood or adolescence and appear as painful shallow ulcers covered by a greyish pseudomembranous layer and surrounded by an erythematous halo [1].

Variants of oral aphthae have been described within three clinical forms namely: Minor aphthous ulcers, major apthous ulcers and herpetiform ulcers. Minor aphthous ulcers are the most common subtype, appearing as ulcers measuring 5mm in diameter or less and resolve within 1-2 weeks. Major aphthae consist of large ulcers exceeding 1cm in diameter which persist for weeks or months before healing with scarring [2]. Herpetiform ulcers are an uncommon variety appearing as clusters of pin-point ulcers throughout the oral mucosa and may coalesce to form larger, irregular ulcers.

The term "apthous-like ulceration" (ALU) or pseudo-aphthae has been used to describe recurrent oral ulcerations that are atypical in presentation by virtue of being a manifestation of an underlying systemic disorder [3].

These oral ulcers may be at times, the presenting feature of inflammatory bowel diseases such as Crohn's disease and other orofacial granulomatous disorders [4]. Haematinic deficiencies like iron deficiency anaemia, B12 and folate deficiencies [5] have also been attributed to the aetiology of recurrent aphthous ulcers. More recently, recurrent oral ulcers have been linked to periodic fever syndromes which are a group of auto-inflammatory diseases with multi-system involvement [6].

The following case report highlights the challenges faced in the diagnosis and treatment of recurrent oral ulcers with no discernible aetiology and its sequelae of disease.

Case Report

A 38-year old female of Indian descent presented in 2009 with a preceding 4-year history of recurrent oral ulcerations. The oral ulcers appeared soon after a blood transfusion she received following the birth of her first child. She had no family history of recurrent oral ulceration, no underlying illness, did not smoke nor consumed alcohol. She denied illicit drug use and high-risk sexual behaviour. She reported multiple episodes of painful ulcers with irregular margins, covered by a fibrinous exudate and confined to the non-keratinized oral mucosa; healing over the course of 4-6 weeks with scarring and re-appearing elsewhere in the oral cavity.

The severity of the oral ulcers impeded speech, mastication and caused limitation in mouth opening leading to poor dietary intake. This necessitated multiple hospital admissions as a result of inadequate oral intake and she was hospitalized at least 65 times over the course of 5 years, each stay lasting 4-5 days. Over time, the extensive scarring of the oral mucosa led to circumoral fibrosis, resulting in microstomia (Figure 1) and ankylosis of the bilateral temporomandibular joints.

She had arthralgia, chronic ulcers over the bilateral Achilles tendon region (Figure 2) and right foot leading to deformity of the toes (Figure 3), ulcers and swelling of the metacarpophalangeal joints (MCPJ). She was treated on multiple occasions for cellulitis of the hands, underwent wound debridement of the ulcers on her feet and was diagnosed with joint capsule hypertrophy of the right middle finger MCPJ. Genital ulcerations appeared sporadically lasting several weeks to months and affecting ambulation. There was no history of ocular disease, but she complained of occasional bouts of diarrhoea, vomiting and abdominal

discomfort.

Anaemia workup revealed normal serum iron, B12 and folate levels during an episode of severe oral ulcerations but a deficiency (Iron: 7.19μmol/L; B12: 88pmol/L; Folate: 3.75nmol/L) during a quiescent phase. Haemoglobin remained low throughout, ranging from 6.8g/dL-10.1gdL. Serum haptoglobin, lactate dehydrogenase (LDH) and reticulocyte count were all within normal range. Peripheral blood smear indicated normocytic normochromic anaemia of chronic disease. Anti-parietal cell antibody (APCA) test was negative.

Screening for autoimmune markers were negative for antinuclear antibodies (ANA), anti-nDNA antibodies (nDNA) and rheumatoid factor (RF). Erythrocyte sedimentation rate (ESR) and C-reactive protein were normal. Extractable nuclear antigen (ENA) screening and human leukocyte antigen (HLA) B-51(05) were negative.

Incisional biopsy of oral ulcers were consistent with non-specific inflammation. Tzanck smear was negative, as were direct immunofluorescence for IgG, IgA, IgM, C3 and Fibrinogen. Antibodies to Desmoglein 1 and Desmoglein 3 were also negative. Incisional biopsy of perineal ulcers were nondescript with no viral inclusion, plasmocytosis, dysplasia or evidence of malignancy. Skin Pathergy test to elicit Behçet's disease was negative.

Her oral ulcers were recalcitrant to long-term topical and systemic prednisolone and dexamethasone. Azathioprine, colchicine, methotrexate and pentoxifylline were futile in preventing recurrent episodes. The ulcers failed to respond to intralesional triamcinolone acetonide injections. Consequently, a diagnosis of Behçet's disease was omitted in view of uncharacteristic sites of involvement of ulcers, non-responsiveness to steroid therapy and a negative Pathergy test.

The findings of an initial gastroscopy and random biopsy were highly suggestive of Crohn's disease in view of patchy inflammation proximal to the rectum. However, a successive colonoscopy and terminal ileum biopsy suggested otherwise. Nevertheless, empirical administration of mesalazine was unsuccessful.

The effects of episodic recurrent oral ulceration over an extended duration of time were unprecedented. The resultant fibrosis of the lips led to acquired microstomia. The vermillion of the upper lip was obliterated and permanently deformed causing exposure of the upper incisors. A computed tomography (CT) scan showed total loss of joint space of the bilateral temporomandibular joints.

The lack of a definitive diagnosis compounded by multiple hospital admissions, unsuccessful treatment modalities and permanent disfigurement as a result of her disease manifestation had deleterious repercussions on the patient's mental well-being. As she declined to undergo psychiatric evaluation and treatment due to personal reasons, chairside counselling was carried out. Her improved psychological state resulted in drastic amelioration of her oral ulcers, reduction in frequency of recurrence and increased nutritional intake. She has now been devoid of oral ulcers for almost 1 year but continues to have recurrent genital ulcerations.

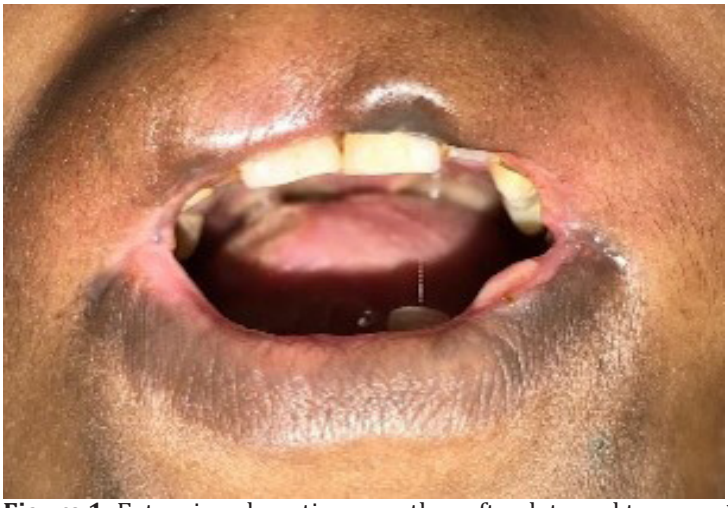

Figure 1: Extensive ulceration over the soft palate and tongue with fibrosis of the upper lip

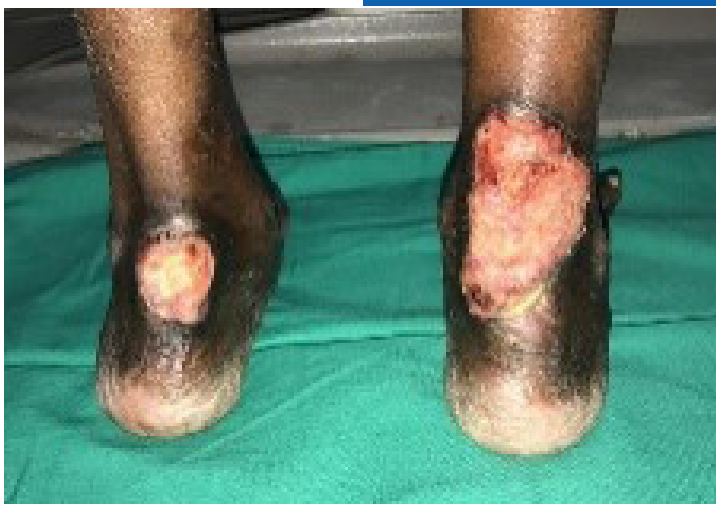

Figure 2: Chronic ulcers over bilateral Achilles tendon region

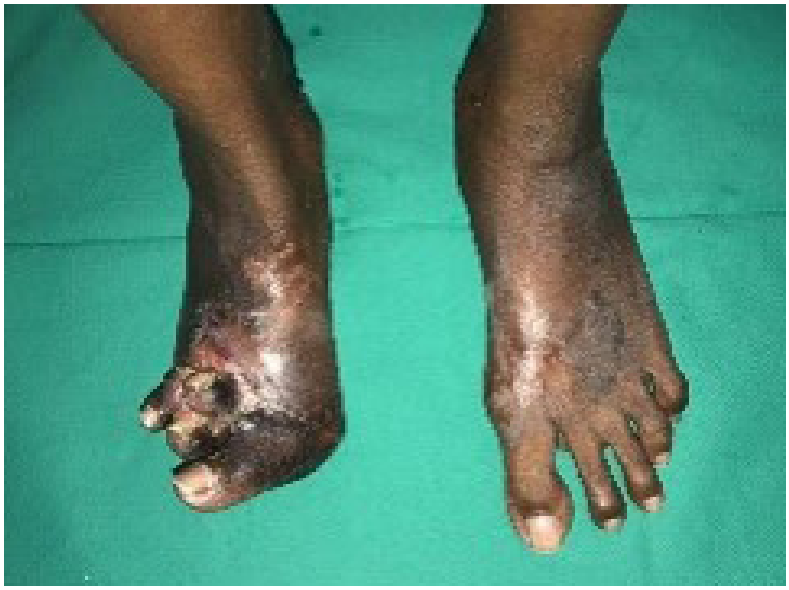

Figure 3: Deformity of the toes

Discussion

In addition to recurrent oral ulceration, this patient had recurrent ulcers on the skin, swelling of the joints, genital ulcerations and abdominal discomfort which further augmented the challenge in obtaining an accurate diagnosis. The differential diagnoses included:

i) Anemia

Studies have reported a direct causal relationship between recurrent oral ulceration and iron, vitamin B12 and folic acid deficiencies [7]. Moreover, a significant number of patients were relieved of their symptoms with replacement therapy once the cause of the deficiency was identified. The haemoglobin and red blood indices of this patient showed unremarkable improvement despite prolonged administration of oral hematinics and parenteral vitamin B12 injections. Frequency and severity of oral ulcerations remained unchanged with haematinic replacement therapy.

ii) Behçet's disease

Behçet's disease is a rare multisystem inflammatory disease with a characteristic triad of recurrent oral ulcers, genital ulcers and uveitis. The disease is diagnosed clinically based on an established set of criteria [8]. HLA B-51 has been found to be the primary risk factor for development of Behçet's disease. Treatment is based on anecdotal evidence; with corticosteroids, azathioprine, methotrexate, colchicine and cyclosporine resulting in improvement of symptoms. Recent studies report promising results with tumour necrosis factor (TNF) inhibitors [9].

iii) Inflammatory bowel disease

Inflammatory bowel diseases (IBDs) are a group of diseases including Crohn's disease and ulcerative colitis characterized by chronic intestinal inflammation. Many patients with IBD may exhibit non-intestinal manifestations such as recurrent aphthous stomatitis in the absence of primary intestinal symptoms [10].

Conclusion

Despite being a relatively common occurrence, the aetiology of RAS is poorly understood and appears to be multifactorial. It is prudent to leave no stone unturned in the investigation of oral ulcers with concurrent systemic manifestations as its long-term effects may be devastating if left untreated.

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