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BEHÇET'S DISEASE IN NON-ENDEMIC AREAS: A DELAYED DIAGNOSIS IN A YOUNG MALE WITH RECURRENT BIPOLAR APHTHOSIS

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ABSTRACT

Introduction: Behçet's disease (BD) is a rare chronic multisystem inflammatory disorder characterized by vasculitis of vessels of any caliber. It is classically associated with populations along the ancient Silk Road (from the Mediterranean basin to the Far East), but increasing numbers of cases are now reported in non-endemic regions, where delayed diagnosis is common due to low clinical suspicion and the absence of specific diagnostic biomarkers.

Case description: We report the case of a 28-year-old man from Mexico with an 18-month history of recurrent painful oral ulcers, later associated with genital ulcers, arthralgias, and cutaneous lesions. The patient had been previously evaluated by multiple physicians and received several empirical treatments without improvement. Physical examination revealed multiple oral and genital ulcers, erythematous macular lesions on the palms and soles, and acneiform lesions on the back. Laboratory and immunological studies were unremarkable, and ophthalmological evaluation was normal. After exclusion of infectious and autoimmune diseases, Behçet's disease was suspected. The patient met the International Criteria for Behçet's Disease (ICBD, 2014) with a total of 5 points. Treatment with azathioprine and prednisone led to progressive clinical improvement.

Conclusion: This case highlights the diagnostic challenges of Behçet's disease in non-endemic regions. Awareness of its heterogeneous clinical spectrum and the use of validated clinical criteria are essential to avoid diagnostic delay and prevent irreversible organ damage.

KEYWORDS

Behçet's disease, non-endemic regions, bipolar aphthosis, ICBD, vasculitis

LEARNING POINTS

- Behçet's disease should be suspected in patients with recurrent bipolar aphthosis, even in non-endemic regions.
- The absence of specific biomarkers and histological findings contributes significantly to delayed diagnosis.
- The International Criteria for Behçet's Disease (ICBD, 2014) provide a sensitive and practical clinical tool for recognizing incomplete but clinically relevant forms of the disease.

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INTRODUCTION

Behçet's disease (BD) is a rare, chronic, multisystem inflammatory disorder characterized by arterial and venous vasculitis affecting the endothelium of vessels of any caliber and exhibiting a broad clinical spectrum[1–5].

Behçet's disease has historically been associated regionally along the ancient "Silk Road," (from the Mediterranean basin to the Far East), where its prevalence is considerably higher. Turkey bears the greatest disease burden, with reported prevalence rates ranging from 19.6 to 420 cases per 100,000 inhabitants, which contrasts markedly with figures observed in non-endemic regions[1,2,4].

BD predominantly affects young adults (20–50 years of age) without a clear sex predilection, although disease severity tends to be greater in males[1–5]. Its pathogenesis is not fully elucidated; however, an interaction between genetic predisposition and environmental factors is recognized, with vasculitis, neutrophil hyperreactivity and an aberrant immune response constituting its central pathogenic mechanisms[1,2,4].

The clinical spectrum of the disease is dominated by recurrent mucocutaneous manifestations, particularly oral and genital aphthosis, accompanied by variable systemic involvement that may include ocular, articular, neurologic, vascular, and gastrointestinal manifestations[2–6].

Currently, there are no specific biomarkers or pathognomonic histopathologic findings for BD[1–3,7]. Diagnosis is clinical and by exclusion, based on established criteria such as the International Criteria for Behçet's Disease (ICBD)[1–5,8]. Treatment depends on disease severity and requires a multidisciplinary approach aimed at preventing recurrences and permanent organ damage[1,4,5,9].

In this context, we present the case of a young patient treated at a secondary-level care hospital in Mexico, whose clinical course illustrates the diagnostic challenges in non-endemic regions.

CASE DESCRIPTION

A 28-year-old Latino male born in Guanajuato, Mexico, of entirely Mexican ancestry, with no significant past medical history and no family history of autoimmune, rheumatologic, or other hereditary diseases, presented with an 18-month history of recurrent oral ulcers. Over the previous year, he experienced approximately ten episodes of painful aphthous ulcers associated with odynophagia, dysphagia, and weight loss. Concomitantly, he developed genital ulcers. He denied ocular symptoms.

The patient had previously been evaluated by multiple specialists without a definitive diagnosis. He received several empirical treatments, including nonsteroidal anti-inflammatory drugs, antivirals, antibiotics, and antifungals, with minimal clinical improvement, reflecting the complexity of the case.

On physical examination, multiple oral ulcers were observed *(Fig.1)*.



Figure 1. *Oral ulcers with a whitish-yellow base and regular erythematous borders, of variable size, located in the pharynx, dorsum of the tongue, gingiva, and soft and hard palate.*

Genital examination revealed three ulcers involving the base, shaft, and glans penis. Both knees and the left ankle exhibited arthralgia on active and passive range of motion. Cutaneous examination demonstrated erythematous macular lesions on the palms and soles, as well as acneiform lesions on the dorsal region *(Fig. 2 A-C)*.

A pathergy test was negative, and ophthalmologic evaluation showed no abnormalities. Laboratory and immunological studies were within normal limits.

Given the lack of response to prior treatments and normal laboratory and immunologic findings, a less common diagnosis was considered. Differential diagnoses—including Crohn's disease, systemic lupus erythematosus, rheumatoid arthritis, mpox, and primary immunodeficiency—were excluded. Ultimately, BD was suspected. The ICBD were applied, yielding a score of 5 points (oral aphthosis: 2; genital aphthosis: 2; acneiform lesions: 1), confirming the diagnosis. Treatment with azathioprine (50 mg daily) and prednisone (20 mg daily, tapered down to 5 mg) was initiated, resulting in favorable clinical evolution and progressive improvement of the lesions *(Fig. 3)*.

DISCUSSION

This case illustrates the inherent diagnostic challenges of rare diseases such as BD, particularly in non-endemic regions, where a low index of clinical suspicion contributes to delayed diagnosis and recognition of only the most severe cases, which negatively impacts prognosis[5].

In the Americas, BD is significantly less prevalent than in Asia or Europe[1–4]. However, in recent decades, an increase in reported cases has been observed in non-endemic countries, a phenomenon attributed to migration, improved epidemiologic understanding of the disease, and greater diagnostic accuracy[2]. Notably, our patient had entirely Mexican ancestry, with no known ancestral or familial ties to populations historically associated with the Silk Road. This epidemiological context adds particular relevance to the present case, as the absence

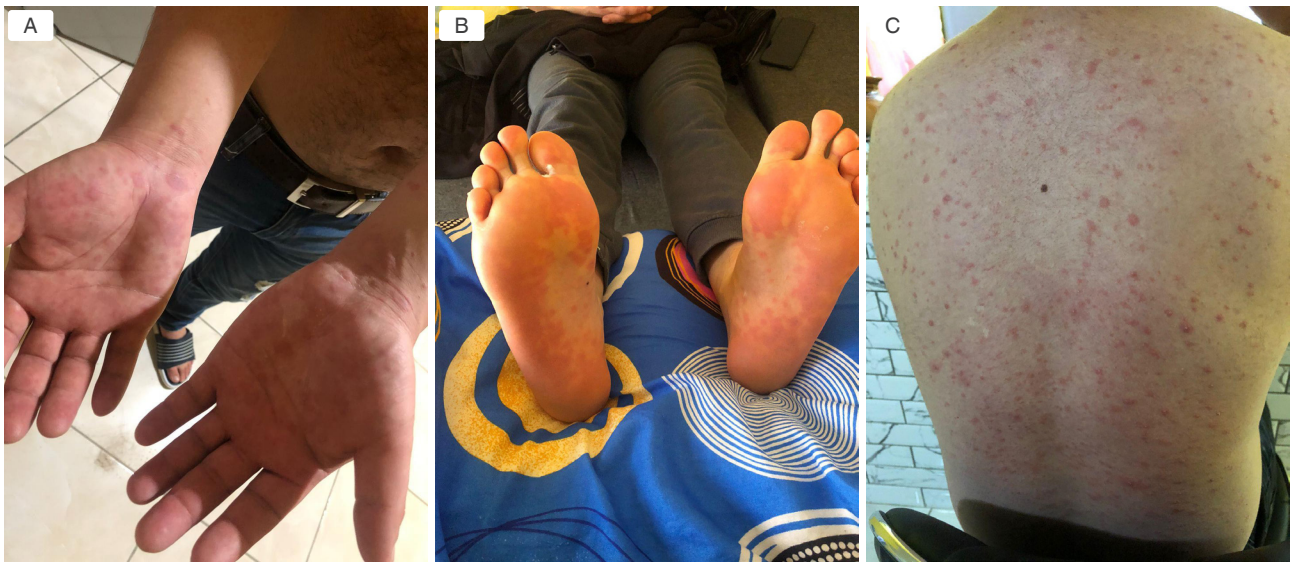


Figure 2. Cutaneous lesions. A) Erythematous macular lesions on the palms; B) soles, non-blanching on pressure and without excoriation marks; C) acneiform lesions on the dorsal region.

of a recognized geographic or ancestral association may further reduce clinical suspicion of BD and contribute to diagnostic delay in non-endemic regions.

The clinical manifestations of BD are heterogeneous and vary according to geographic region. In this case, no ophthalmologic involvement was documented, despite such manifestations occurring in up to 60% of cases[1]. In contrast, the patient developed typical mucocutaneous lesions. The patient did not develop gastrointestinal involvement, consistent with Western case series, unlike reports from East Asian populations, particularly in Japan and China, where gastrointestinal involvement represents a predominant clinical phenotype[6]. Articular involvement was present and has been described in up to 50% of patients[4]; however, it is not included in the 2014 ICBD, underscoring the need to reassess and update these criteria to incorporate incomplete clinical forms and avoid diagnostic delays.

The 2014 ICBD are the most widely used criteria, having demonstrated greater sensitivity (97.6%) and specificity (90.8%) compared with previous criteria sets with important limitations, thereby facilitating recognition of incomplete but potentially severe presentations[1–4,8]. In this case, their application enabled diagnosis after exclusion of other entities.

The pathergy test was negative. Although previously considered a fundamental diagnostic criterion, its current utility is controversial due to lack of standardization and geographic variability[1,5]. Positivity rates have progressively declined, ranging from 20–60% in the Middle East but only 1–2% in Europe[2]. Therefore, its use is currently recommended as optional[3].



Figure 3. Marked clinical improvement with complete resolution of the oral ulcers after treatment initiation.

CONCLUSION

BD should be considered in any patient with recurrent bipolar aphthosis, particularly in non-endemic regions where a low index of suspicion may lead to delayed diagnosis. Its clinical heterogeneity necessitates comprehensive evaluation, with emphasis on the exclusion of differential diagnoses and identification of potentially severe complications.

Use of the 2014 ICBD, which demonstrates the highest sensitivity and specificity, allows recognition of incomplete clinical forms and facilitates more timely diagnosis, directly impacting prognosis. The absence of validated biomarkers and the still limited understanding of its pathophysiology highlight the need for continued research in this field, including the development of biomarkers and targeted therapies to optimize patient management and improve quality of life.

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