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Uncovering Behçet's Syndrome. A Case Report of a Rare Disease in Colombia

Descubriendo el Síndrome de Behçet. Reporte de caso de una enfermedad rara en Colombia

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Abstract

Introduction: Behçet's syndrome is a multisystem disorder of unknown etiology classified as a variable-vessel vasculitis, it is characterized by oral and genital ulcers, skin lesions and ophthalmological, neurological or rheumatic manifestations, with oral and genital aphthae being the most frequent features; the presence of the HLA-B51 antigen is associated with up to 60% of cases. **Clinical case:** 35-year-old female patient, with history of recurrent aphthous stomatitis who presented with one month evolution clinical picture characterized by the appearance of painful ulcers in the oral cavity and genital associated with fever. Most likely infectious and inflammatory causes were ruled out and Behçet's syndrome diagnosis was considered by exclusion and application of international criteria; although the pathergy test was negative, the determination of the HLA-B51 allele was positive. The patient showed improvement after treatment with corticosteroids and colchicine. **Discussion:** Behçet's syndrome is a rare and underdiagnosed disorder in our environment with an approximate prevalence of 1.1 per 100,000 inhabitants. Diagnosis is often difficult and it must be made in an exclusion manner It is recommended to use the international criteria for Behçet's disease and, treatment is aimed at attenuating inflammatory exacerbations and preventing relapses to maintain a good quality of life. **Conclusion:** Behçet's syndrome is a multisystemic disorder that is probably underdiagnosed due to low prevalence, high diversity in clinical presentation and low diagnostic suspicion among healthcare professionals.

Keywords: Behçet's disease, Stomatitis, Vasculitis, HLA-B51 antigen.

Resumen

Introducción: El síndrome de Behçet es un trastorno multisistémico de etiología desconocida clasificado como vasculitis de vaso variable, que se caracteriza por úlceras orales y genitales, lesiones cutáneas y manifestaciones oftalmológicas, neurológicas o reumáticas, siendo las aftas orales y genitales las más frecuentes; la presencia del antígeno HLA-B51 se asocia hasta en el 60% de los casos. **Caso clínico:** Mujer de 35 años, con antecedente de estomatitis aftosa recurrente que presentó cuadro clínico de un mes de evolución caracterizado por aparición de úlceras dolorosas en cavidad oral y genital asociadas a fiebre. Se descartaron causas infecciosas e inflamatorias más probables y se consideró el diagnóstico de síndrome de Behçet por exclusión y aplicación de criterios internacionales; aunque la prueba de patergia fue negativa, la determinación del alelo HLA-B51 fue positiva. La paciente presentó mejoría posterior al tratamiento con corticoides y colchicina. **Discusión:** El síndrome de Behçet es un trastorno poco frecuente e infradiagnosticado en nuestro medio con una prevalencia aproximada de 1,1 por 100.000 habitantes. El diagnóstico es a menudo difícil, debe realizarse de forma excluyente, se recomienda utilizar los criterios internacionales de enfermedad de Behçet y el tratamiento está encaminado a atenuar las exacerbaciones inflamatorias y prevenir las recaídas para mantener una buena calidad de vida. **Conclusión:** El síndrome de Behçet es un trastorno multisistémico probablemente infradiagnosticado debido a la baja prevalencia, alta diversidad en la presentación clínica y baja sospecha diagnóstica por parte de los profesionales sanitarios.

Palabras clave: Síndrome de Behçet, Estomatiis, Vasculitis, HLA-B51.

Introduction

Behçet's syndrome is a multisystem disorder of unknown etiology classified as variable-vessel vasculitis It is characterized by oral and genital ulcers, skin lesions and ophthalmological, neurological or rheumatic manifestations (1). One of the first disease reports was documented in 1937 by the Turkish dermatologist Hulusi Behçet and, thenceforth, the disorder has been recognized as Behçet's syndrome (2).

The geographical distribution of the disease is well characterized with prevalence estimation available for many countries in the world, with the highest prevalence being determined along the formerly called "Silk Road" (3). In a recent systematic review, the prevalence of the disease was determined (expressed in cases per 100,000 inhabitants); documenting prevalence of 10.3 in the general population, 119.8 in Türkiye, 31.8 in the Middle East, 4.5 in Asia, 5.3 in Southern Europe, 2.1 in Northern Europe, and 3.8 in North America/Caribbean Islands (4). The prevalence in the Latin American countries seems to be low, information from 532 patients across 5 Latin American countries determined the mean age at disease diagnosis was 33 years, 58.3% were female and 41.7% male. A study conducted in Brazil reported a prevalence of 0.3/100,000 inhabitants (5). In Colombia, epidemiological information on the disease is scant; however, prevalence of 1.1 per 100,000 inhabitants has been determined, with a predominance in women between the fourth and sixth decade of life (6).

The diverse clinical manifestations and the absence of pathognomonic tests make Behçet's syndrome a diagnostic challenge. The purpose of this article is to present a Behçet's syndrome case and outline the approach that was made, due to the importance of the diagnosis and its low prevalence in our environment.

Clinical case

35-year-old woman, with history of unstudied anemic syndrome since 2015 and limited episodes of aphthous stomatitis in 2016 and 2017, with no history of smoking or drug abuse. She presented with a one-month history of progressively worsening, multiple painful ulcers on the right lateral edge of the tongue, as well as on the mucosa of the lips and cheeks. This was accompanied by an unquantified and intermittent fever, presenting two days before admission, the appearance of a painful ulcer in the genital area. As accompanying symptoms, she reported constitutional manifestations without the presence of ocular symptoms or visual impairment.

Examination

On physical examination, the patient was found to be in acceptable general condition, with chronic disease semblance, generalized paleness, normal vital signs. Findings in oral cavity with multiple rounded, painful, grayish aphthous lesions measuring 1 cm with well-defined

edges, a clean base and erythema, surrounding areas located in the tongue, mucosa of the lips and cheeks, soft palate and gums (Figure 1). Examination of the genitals revealed a hyperchromic macular lesion located in the mucosa of the right outer lip. It was documented as well, multiple pustular lesions on the scalp and anterior and posterior region of the thorax.

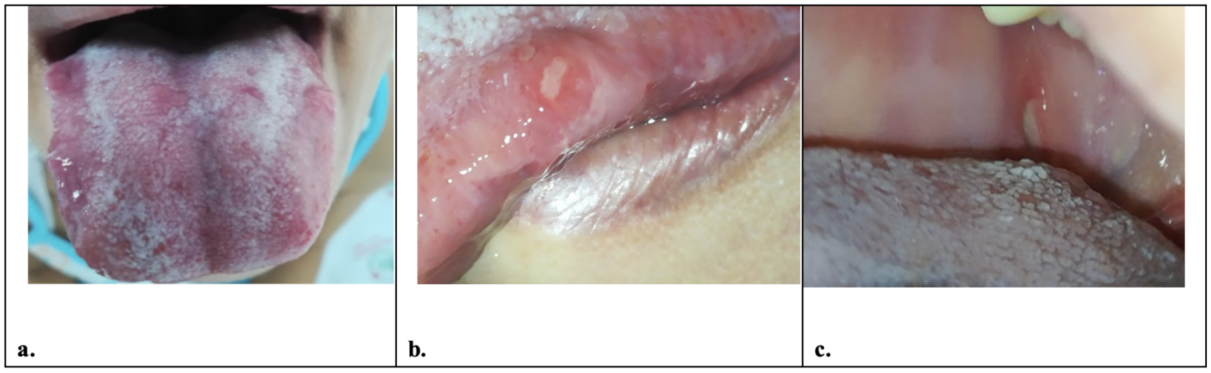

Figure 1. Aphthae on the right lateral edge of the tongue (a and b), Aphthae on the oral muc osa at the level of the right cheek (c).

Source: clinical archive

Differential Diagnosis, Investigations and Treatment

Bearing in mind the clinical picture and documented findings on physical examination, a syndromic diagnostic impression of recurrent complex bipolar aphthosis was established, considering infectious versus rheumatic pathology as a probable etiology. Paraclinical evaluation indicated aim of diagnostic confirmation; labs results were unremarkable except for the presence of anemia (Table 1). All the above led to Behçet's syndrome diagnosis in an exclusion manner apart from application of the international criteria for Behçet's disease (ICBD) (7). Pathergy test was performed which was negative, the HLA-B51 allele was determined with a positive report. Treatment was initiated with prednisone 50 mg daily in a tapering regimen and colchicine 0.5 mg twice a day, showing clinical improvement.

Tabla 1. Clasificación del síndrome de Poland

Parameter	Result	Reference range
	Blood count	
Leukocytes	6900	5000-10000 /mm³
Hemoglobin	10,6	11-16 g/dl
Hematocrit	32	39-50 %

Parameter	Result	Reference range
Mean corpuscular volume	75	80-100 fL
Mean corpuscular hemoglobin	24	28-36 g/dl
Neutrophils	65	50-65%
Lymphocytes	25	25-35%
Eosinophils	3	0-5%
Monocytes	5	0-8%
Platelets	234000	150000-450000 /mm³
Infectious diseases test		
Human Immunodeficiency virus test	Negative	Negative
Venereal disease research laboratory test	Non-reactive	Non-reactive
Hepatitis B virus test	Non-reactive	Non-reactive
Hepatitis C virus test	Non-reactive	Non-reactive
Toxoplasma IgG	Non-reactive	Non-reactive
Toxoplasma IgM	Non-reactive	Non-reactive
Epstein Barr IgG	Negative	Negative
Epstein Barr IgM	Negative	Negative
Herpes Virus 1 IgG	Negative	Negative
Herpes Virus 1 IgM	Negative	Negative
Herpes Virus 2 IgG	Negative	Negative
Herpes Virus 2 IgM	Negative	Negative
Autoimmune tests		
Complement C3	131.8	90-180
Complement C4	21	10-40
Anti-Ro/SSA	1,76	0-20
Anti-La/SSB	1,76	0-20
Anti-RNP	1,59	0-20
Anti-SM	1,82	0-20
Anti-DNA	Negative	Negative

Parameter	Result	Reference range
P-ANCA	Negative	Negative
HLA-B51	Positive	Negative

Source: own elaboration.

Outcome and follow-up

The patient in our case has remained under regular follow-up with the rheumatology service, showing adequate clinical progress. Since the initiation of treatment, there has been no recurrence of the lesions, and the patient has achieved good control of symptoms. Routine laboratories and imaging evaluations have shown stable inflammatory markers and no evidence of disease activity. The implemented therapy has been well tolerated, with no significant adverse effects reported. Ongoing multidisciplinary care and monitoring have been key in maintaining disease remission and ensuring a positive long-term outcome.

Patient perspective

Patient reported *"After being diagnosed with Behçet's syndrome, my life has significantly improved thanks to the proper treatment and ongoing care I've received. Before the diagnosis, I struggled with recurring painful mouth ulcers and fatigue. Now, with a personalized treatment plan and regular follow-ups with my rheumatology team, my symptoms are well controlled, and I feel like I have regained control of my life"*.

Discussion

Behçet's syndrome is a multisystemic autoinflammatory disease characterized by episodes of exacerbation and remission, with unpredictable duration and prognosis (7, 8). It is classified as variable-vessel vasculitis according to the international Chapel Hill Consensus Conference, it can involve both arterial and venous vessels (9). Understanding the disease pathogenesis is still limited. Currently, it is proposed that, as in several autoimmune or autoinflammatory syndromes, diverse infectious agents, immunological and/or environmental factors converge in a genetically predisposed patient to trigger the disease outset (10). The peculiar geographical distribution of Behçet's disease has been considered evidence that supports genetic influence as part of the pathogenesis of the disorder, documenting the finding of the HLA-B51 allele in up to 60% of cases in areas where the disease is endemic (11, 12). However, although HLA-B51 is the most relevant genetic factor, other genes outside of HLA also play a pathophysiological role (13). HLA-B51 accounts for less than 20% of the genetic risk for Behçet's syndrome, with additional susceptibility loci identified in HLA genes (MICA, HLA-C, HLA-B27, HLA-A*26). Genome-wide studies have also revealed loci in non-HLA genes involved in inflammatory and

regulatory responses (STAT4, IL23R–IL12RB2, IL10, IL1A, IL1B, TNF), antigen presentation (ERAP1), and chemotaxis (CCR1, CCR3). Variants in MEFV and toll-like receptor (TLR) genes have also been linked, with a higher genetic risk observed in males (1).

Among the clinical manifestations, the classic triad that leads to suspicion of this disease includes recurrent oral ulcers, genital ulcers and uveitis (14). Recurrent oral aphthosis is the most distinctive feature of the disease with a prevalence of 97 to 100% and is usually the initial manifestation, as we reported in our patient clinical case (15). Although oral ulcers can resemble canker sores, they must occur on three or more occasions within a 12-month period to meet the diagnostic requirements for this condition (16). Additionally, the ocular, vascular, gastrointestinal and/or neurological involvement occur less frequently, but with potentially serious consequences (17). Figure 2 describes the clinical manifestations associated with the disease. On physical examination, in addition to observing the previously mentioned manifestations, the detection of the pathergy test stands out as a relevant indicator. The test is considered positive when a small red bump or pustule forms, approximately 1 or 2 days after performing a needle puncture in the forearm (18). Although this test is not exclusive to the disease, it does serve as a guiding element for the diagnosis, which is based on well-defined criteria for its definitive confirmation (19).

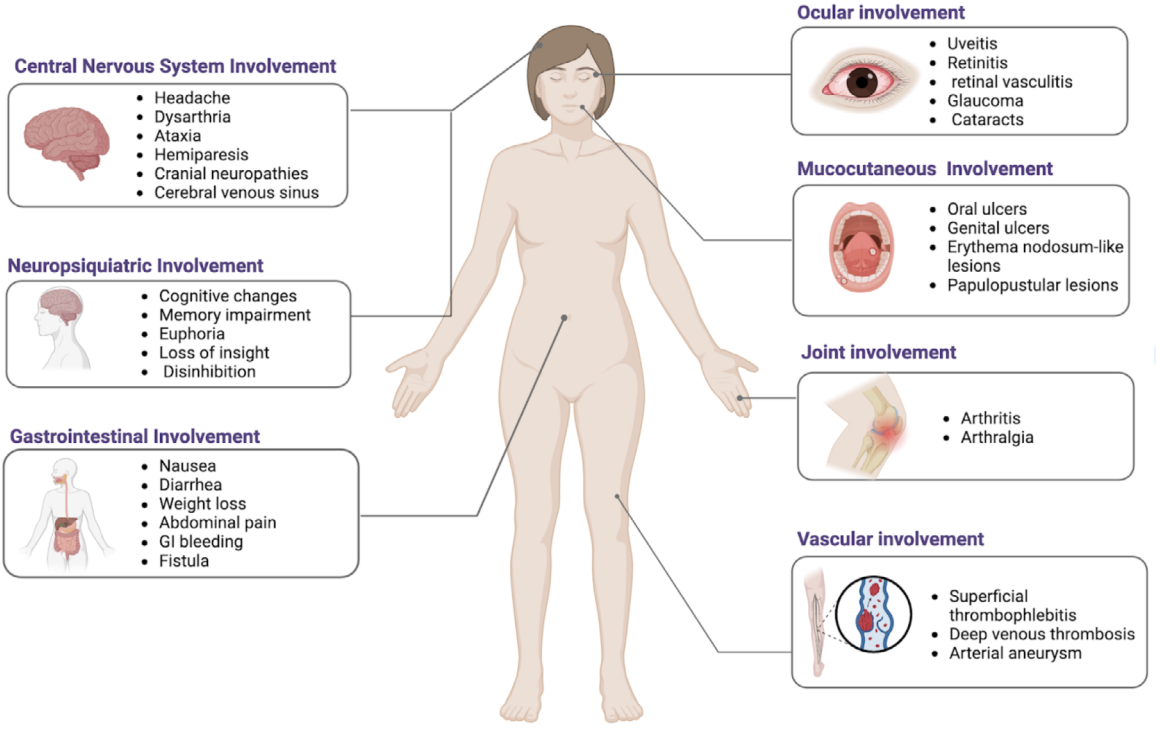

Figura 2. Clinical manifestations of Behçet's Disease.

Source: prepared by the authors with assistance from Biorender.

There are no unique histological or laboratory findings that make the diagnosis of Behçet's syndrome, so clinical characteristics are used to define the entity (20, 21). An association has been demonstrated between the human leukocyte antigen HLA-B51 with an increased prevalence of genital ulcers, ocular and skin involvement, as well as a decrease in the prevalence of gastrointestinal manifestations (22).

Diagnosis of Behçet's syndrome can be challenging due to the diversity in its clinical presentation and the absence of pathognomonic tests, especially in low-prevalence areas such as Colombia where diagnostic suspicion among healthcare professionals tends to be low. In our setting, the difficulty in performing genetic tests like HLA-B51 may pose a barrier to diagnosis. To achieve early recognition, it is recommended to use the international criteria for Behçet's syndrome, in addition to ruling out other causes of oral and genital ulcers (Table 2) (7). In the case reported, the patient presented a score of 5 based on the criteria, with which a diagnosis was made once alternative etiologies were excluded, also associated with a positive molecular test for the HLA-B51 allele.

Tabla 2. International Criteria for Behcet's Disease – point score system: scoring >/ 4 indicates Behcet's diagnosis.

Sign/symptom	Points
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Pathergy test†	1

Source: International Team for the Revision of International Criteria for Behçet's Disease: The International Criteria for Behc"et's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. JEADV 2014, 28, 338–347.

† The pathergy test is not mandatory, and the primary scoring system doesn't incorporate pathergy testing. Nevertheless, if pathergy testing is performed, an additional point may be given for a positive result.

The goals of treatment of Behçet's syndrome are to attenuate inflammatory exacerbations and prevent relapses to maintain good quality of life and preserve organic function; treatment is oriented according to the main organic involvement and must be individualized depending on the patient's prognosis based on the EULAR 2018 recommendations (11, 23).

Colchicine is the first-line therapy in mucocutaneous and joint involvement (24). Patients with more serious clinical manifestations require systemic immunomodulatory treatment to avoid complications and health risks that may arise if the disease does not receive treatment (16). Systemic corticosteroids, immunosuppressants and biologic drugs (anti-TNFα) are used more frequently, depending on the indication (25). In our case, since these were only mucocutaneous manifestations, the treatment was aimed at impacting quality of life, since these lesions do not represent a threat to organic damage or life.

This disease can be associated with great disability and mortality depending on the severity and the organs affected (15). The main related mortality causes are infections (25.1%), underlying organ dysfunction (21.6%) and arterial events (15.2%) (28). It has been observed that the first year of diagnosis constitutes the window of highest death risk among patients (20, 26). Moreover, quality of life of people with Behçet's syndrome is impaired due to adverse impacts on biopsychosocial aspects, fatigue, poor sleep quality, alexithymia and other parameters (27).

Conclusions

Behçet's syndrome constitutes a multisystemic disorder that is underdiagnosed in our environment, probably due to the diversity in clinical presentation and low diagnostic suspicion on the part of health professionals. The disease should always be suspected in patients who present with recurrent bipolar aphthosis, and the diagnostic criteria should be applied once other etiologies have been excluded. Timely diagnosis and the establishment of adequate treatment are key to preventing irreversible consequences secondary to the disease.

Right to privacy and informed consent

The authors have obtained informed consent from the referred patient.

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Conflict of interests

The authors declare that they have no conflict of interest.

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