

A Case of HLA-B51 Positive Mucocutaneous Variant of Behçet's Disease in a Young Indian Male: A Case Report

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This case was reported from the Department of General Medicine, Calcutta National Medical College and Hospital

doi : <https://doi.org/10.38179/ijcr.v2i1.70>

Received: 2021.03.06
Accepted: 2021.06.19
Published: 2021.06.27

Financial support: None
Conflict of interest: None
Patient Consent:
Patient's written consent for the publication of this case and images was obtained.

Abstract

Background: Behçet's disease is a rare, systemic inflammatory disorder of unknown etiology affecting the mucocutaneous, vascular, skeletal, ophthalmic, gastrointestinal, and neurological systems. While the exact etiopathogenesis of Behçet's disease is yet to be established, numerous studies have supported a strong possibility of underlying genetic factors. It is comparatively more common in Turkey, the Middle East, and Mediterranean regions, and only a few cases have been reported from the Indian subcontinent so far. Although several immunological and genetic associations have been suggested, the diagnosis of Behçet's disease remains primarily clinical and of exclusion.

Case Report: In this report, we describe the case of a 22-year-old Indian male who developed multiple aphthous ulcers over his tonsillar pillars and pharyngeal wall following an episode of acute tonsillopharyngitis. Over the course of the next few days, he reported the presence of a genital ulcer and papulopustular lesions over his chest, back and face, eventually prompting a diagnosis of Behçet's disease. He was treated with oral colchicine and was found to be in remission during a six-week follow-up.

Conclusion: This case emphasizes the importance of awareness regarding Behçet's disease among clinicians in India and warrants further studies on the epidemiology, immunopathogenesis, and management protocols of Behçet's disease, especially in this country for a better understanding of its prevalence, manifestations, and disease course.

Keywords: Behcet's Disease; Behcet Syndrome; Colchicine; Aphthous Ulcer; Diagnosis; HLA-B51; India; Case Report

Background

Behçet's disease (BD) is a rare, chronic, multi-systemic disorder characterized by recurrent mucocutaneous and ocular lesions along with other systemic manifestations [1]. It is a systemic vasculitis involving vessels of all sizes on both arterial and venous sides of the circulation [1]. Although described earlier by Hippocrates in ancient Greece, it is named after Turkish dermatologist Hulusi Behçet, who described the classical triad of oral and genital ulcerations and uveitis, in 1937 [2]. Behçet's disease exists throughout the world, although a significantly higher prevalence is seen in the Mediterranean region, and the Middle East and Far East nations [3]. It is most commonly seen in Turkey (80 to 370 cases per 100,000) and is rarer in North American and North European countries (with prevalence ranging from 1 in 15,000 to 1 in 500,000) [4]. It appears to be rare among Indians, with only five major studies being conducted in the last four decades in the country. One study found the disease to occur in a milder form in the Indian population with primarily mucocutaneous and arthritic involvement [5]. Another study, published in 2008, found ocular involvement to be the most common manifestation in India [6].

While the etiology of Behçet's disease remains unknown, it likely has a strong genetic basis. Several studies have suggested a genetic predisposition with human leukocyte antigen (HLA)-B51 being identified as the most strongly associated immunogenetic risk factor [7]. HLA-B51 is present in up to 60% of Behçet's patients [8]. Additional non-HLA genes have also been suggested to play a role in the underlying immune process [9].

The pathomechanism in Behçet's disease includes systemic autoimmune vasculitis involving small, medium, and large vessels. A role of aberrant pro-inflammatory cells along with an overproduction of cytokines in endothelial injury, with consequent inflammation-related thrombosis, has been reported

[10]. Venous involvement may constitute up to 75% of all vascular complications [11]. Arteries, on the contrary, are less commonly involved, with the most characteristic manifestation being aneurysms [12].

Behçet's disease can be challenging to diagnose since there is no confirmatory diagnostic test. In this report, we describe a young Indian male who was diagnosed with Behçet's disease after an episode of acute tonsillopharyngitis and was successfully treated with colchicine.

This case report emphasizes the importance of increased awareness regarding the disease among clinicians, especially in India.

Case Presentation

A 22-year-old Indian male patient presented to the outpatient department complaining of a sore throat and dysphagia for the last five days. He had swollen tonsils with small white patches of exudates and erythema over tonsils and pharyngeal walls. He had no systemic symptoms. The patient reported no significant medical history or family history and denied any allergy to drugs. A clinical diagnosis of acute tonsillopharyngitis was made and he was started on oral amoxicillin and clavulanic acid (500 mg + 125 mg) every 8 hours for five days. His symptoms, however, worsened. The antibiotic was changed to oral clarithromycin (500 mg) every 12 hours for five days.

Four days after starting oral clarithromycin, he developed a low-grade fever, and the pain in his throat increased, which led to his inability to swallow liquids, resulting in dehydration. On examination, he was found to be dehydrated, but his vitals remained stable. His oropharynx was found to be grossly congested. Multiple patchy aphthous ulcerations were seen over the anterior tonsillar pillar, the posterior tonsillar pillar, and the posterior pharyngeal wall. Other systemic examinations were found to be within normal.

The patient was admitted to the hospital. Routine laboratory studies were sent revealing neutrophilic leukocytosis (white cell count: 11900 cells/mm³, neutrophils: 90%) and an elevated Erythrocyte Sedimentation Rate (68 mm/1st hr). Peripheral blood smear showed a mild shift to the left in the myeloid series with neutrophils containing toxic granules. Viral serology for Hepatitis B surface antigen, anti-Hepatitis C virus antibody, and Human Immunodeficiency Virus (HIV) I and II were non-reactive. Venereal Disease Research Laboratory (VDRL) test for syphilis came negative as well. A throat swab came negative for pathogens, and in fact, showed suppressed growth of commensal flora, which can be attributed to nearly two weeks of antibiotic administration. A digital X-ray of the neck was done and was found to be normal. Supportive treatment was initiated with intravenous amoxicillin-clavulanic acid 1.2 g every 8 hours (after proper skin testing), analgesics, and intravenous maintenance fluids.



Figure 1:
Papulopustular
lesions on the
back

The following morning, the patient noticed multiple red papular lesions on his face, neck, chest, and back, which developed into pustules within the next 24 hours (Fig. 1). At this point, the skin lesions were in different stages of eruption (Fig. 2A, 2B). We stopped amoxicillin-clavulanic acid and started him on dual oral antibiotic therapy (cefdinir 300 mg every 12 hours and azithromycin 1 g per day), prescribed triamcinolone oral paste for his aphthous ulcers and lignocaine spray for relief as needed. However, he continued to

deteriorate as the pustules started coalescing and he began having intermittent fever which never rose beyond 102.5 Fahrenheit. Blood investigations continued to show a rise in total leukocyte count (22600 cells/mm³ with 78% neutrophils) with a C-Reactive Protein of 94 mg/L (reference range: <10 mg/L). However, the smear and the pus culture from the pustular lesions failed to detect any organism.

With a high clinical suspicion for an underlying resistant bacterial infection, we started him on more potent antibiotics oral linezolid 600 mg every 12 hours and intravenous meropenem infusion at 1 g every 8 hours.



Figure 2: (A) Figure showing coalescing papulopustular lesions on the chest. (B) Figure showing coalescing papulopustular lesions on the face and neck

We repeated a thorough clinical examination and noticed a major aphthous ulcer (1.5 cm x 1 cm) on the posterior aspect of his left scrotum. At this point, the patient mentioned previous episodes of recurrent oral aphthae but claimed to have never received treatment for the same. He reported no previous history of genital

ulcers. These new findings prompted us to consider Behçet's disease as a reasonable diagnosis. A pathergy test was done and it came negative, following which we sent a complete autoimmune panel.

All markers (including antinuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, cytoplasmic anti-neutrophil cytoplasmic antibody, HLA B-27) came negative, except for HLA-B5 and its predominant split antigen, HLA B-51 which returned positive. Skin biopsy from the back lesions revealed inflammatory dermatosis with subcorneal pustules, consistent with the inflammatory process of Behçet's disease.

We stopped meropenem and linezolid, and we started him on oral colchicine 0.5 mg every 12 hours and recommended betamethasone and fusidic acid cream along with sucralfate ointment for local application over his scrotal ulcer. For prognostic value, we ordered nerve conduction velocity (NCV), visual evoked potential (VEP), optical coherence tomography (OCT) tests, all of which were within normal limits. He was discharged after seven days and was found to be in remission in a 6-week follow-up.

Discussion

Behçet's disease is a complex entity that affects multiple systems like the mucocutaneous tissues, eyes, joints, brain, blood vessels, and gastrointestinal tract [1]. BD has a relapsing and remitting course with disease severity and extent of organ damage directly influencing the quality of life. However, the exact immunological phenomenon that results in widespread systemic inflammation remains unclear. Genetic influences, including both HLA and non-HLA genes, have been linked with the underlying pathomechanism [9]. The HLA-B51 is a split antigen of the B5 that is closely associated with BD [8]. In recent years, McGonagle et al. have argued a common underlying immunopathogenesis among BD and several other distinct spondyloarthropathies including

ankylosing spondylosis, all of which are associated with Major Histocompatibility Complex (MHC) class I (MHC-I) alleles [13]. This is in line with the findings of Ahn et al. in their study of Behçet's uveitis patients with HLA-B27 and HLA-B51 double-positive status [14]. HLA-B51 is associated with mucocutaneous manifestations of BD particularly, as was seen in our patient [15]. In addition, recent studies have shed light on the role of environmental and infectious triggers inducing an autoimmune response in genetically susceptible individuals [16].

Our patient initially presented to the outpatient department with swollen, erythematous tonsils and pharyngeal walls, and was clinically diagnosed with a bacterial infection owing to the presence of exudates on the tonsils and the common incidence of streptococcal infection in the local area. No further investigations were done and he was started on oral amoxicillin-clavulanic acid, according to local hospital protocols. However, the fact that his symptoms were not relieved prompted suspicion of resistance to amoxicillin-clavulanic acid. A culture and sensitivity test would have been ideal at this stage, but waiting for the report would have delayed treatment by several days. Hence, his antibiotic was changed to oral clarithromycin, as per local guidelines.

The diagnosis of BD solely relies on the International Study Group for Behçet's Disease ISGBD clinical criteria, or the newly proposed International Criteria for Behçet's Diseases (ICBD). The latter has a much higher sensitivity, but marginally lower specificity than the former [17]. In order to establish a diagnosis of BD, the ISGBD diagnostic criteria require the presence of recurrent oral aphthous ulcers (at least three times a year) along with any two other features which include recurrent genital aphthous ulcers, eye lesions, skin lesions, and a positive pathergy test [18]. Our patient had recurrent oral ulcers, skin lesions, and a major genital aphthous ulcer for the first time in his life. On the other hand, the more recent ICBD system allots specific points to specific features and requires a minimum of 4 points for the

diagnosis of BD [17]. According to this system, our patient scored 5 points out of 10 (2 for oral aphthae, 2 for genital aphthous ulcer, and 1 for skin lesions).

Our patient presented to us with the mucocutaneous variant of BD. Mucocutaneous lesions are the hallmark of BD and cover a range of features like oral aphthous ulcers, genital ulcers, erythema nodosum, papulopustular lesions, and positive pathergy test [11]. Oral ulcers are recurrent and can be classified as minor aphthae (<10 mm, isolated or multiple shallow ulcers), major aphthae (>10 mm, deeper ulcers), and herpetiform ulcers (numerous, shallow, pin-point ulcers occurring in clusters). Oral ulcers usually involve the mucosa of lips, the floor of the mouth, buccal mucosa, gums, palate, and tongue. Minor ulcers heal without scarring, but major and herpetiform ulcers may leave a scar. Genital ulcers frequently involve the scrotum in males and the labia in females. They are deeper than oral ulcers and have a tendency to scar. Erythema nodosum-like lesions in BD occur mostly on the lower extremities and do not ulcerate. Papulopustular lesions commonly involve the trunk, extremities, and face [19].

The differential diagnoses for oral aphthae cover a range of diseases including systemic lupus erythematosus, reactive arthritis, recurrent aphthous stomatitis, Celiac disease, inflammatory bowel disease, nutritional deficiencies like vitamin B12, iron, and folic acid, and Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome [20]. Moreover, febrile neutrophilia may occur in a variety of infections, neoplastic disorders as well as neutrophilic dermatoses like Sweet's syndrome [21]. A peripheral blood smear, as part of a complete haemogram, and a complete autoimmune panel, were, therefore, ordered to exclude these diseases.

Although several approaches have been proposed for the treatment of BD patients, there is no consensus regarding a single management strategy being superior to

others [22]. In a recent publication, Nakamura *et al.* discussed the currently accepted diagnosis and management protocols for the mucocutaneous variant of BD in the Japanese population and recommended systemic colchicine therapy over systemic steroids for oral and genital ulcers [23]. In a randomized crossover trial, Davatchi *et al.* found that colchicine therapy is of significant benefit compared to placebo [24].

However, treatment continues to vary on a case-by-case basis with options ranging from steroids to immunomodulating agents like infliximab and adalimumab [22]. In the case of our patient with no involvement of vital organs, he showed significant clinical and symptomatic improvement following treatment with oral colchicine.

Conclusion

Although rare, BD must be considered as a diagnosis whenever there is a high index of suspicion. Currently, there is no confirmatory test for BD which makes the diagnosis challenging and may lead to its underreporting, especially in the developing and underdeveloped parts of the world. This case highlights the need for increased awareness among clinicians regarding BD and its manifestations, to promote prompt diagnosis and treatment. Colchicine therapy may be considered for mucocutaneous variants. Its role as an effective and cheaper steroid-sparing agent in the treatment of BD needs to be researched more, especially in the context of developing nations like India.

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