

# DIAGNOSE THIS

## A 25-year-old female with papulopustular rash, arthritis, and retinal vasculitis

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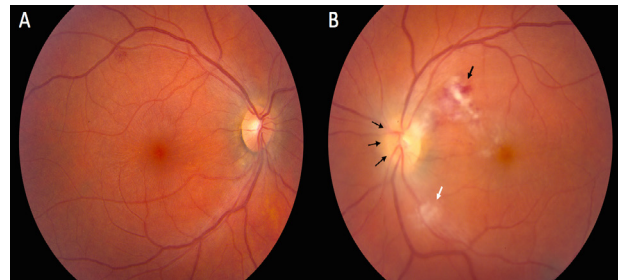
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**C**ase: A 25-year-old Caucasian female was referred to ophthalmology with a three-week history of decreased vision in her left eye. Review of systems by history and physical exam was positive for dyspnea, a widespread papulopustular rash, heart palpitations, oral and genital ulcers, migratory arthralgia (especially in her knees), and fatigue. Her medical history was significant for past intravenous (IV) drug use. She had initially been seen by a community ophthalmologist and subsequently admitted to the internal medicine service for further investigations due to concerns of significant systemic illness. She was afebrile and her vital signs remained normal.

On ophthalmologic exam, her corrected visual acuity (VA) was measured at 6/6 right eye (OD) and 6/60 left eye (OS) and intraocular pressures were 14 mmHg OD and 15 mmHg OS. A subtle relative afferent pupillary defect was noted in the left eye. Slit lamp examination was unremarkable and no vitritis was noted. Extra-ocular movements were full. Fundoscopic examination revealed bilateral intra-retinal hemorrhages and perivascular sheathing (Figure 1). Roth spots (white centered hemorrhages), cotton-wool spots, and optic nerve edema were noted OS.

Systemic investigations were initiated and targeted towards a differential diagnosis including inflammatory (e.g., systemic lupus erythematosus, reactive arthritis, vasculitis, sarcoidosis, inflammatory bowel disease), infectious (e.g., human immunodeficiency virus, syphilis, tuberculosis, Lyme disease, infectious endocarditis, disseminated herpetic disease), and other (e.g., disseminated intravascular coagulation, coagulopathy) possible etiologies.

A chest x-ray demonstrated no evidence of granulomatous inflammation nor hilar adenopathy and a transthoracic echocardiogram was normal. Initial laboratory investigations showed a mild thrombocytosis ( $420 \times 10^9/L$ , normal range  $150\text{--}350 \times 10^9/L$ ) and elevated C-reactive protein (133 mg/L, normal range 0–8 mg/L). Urinalysis showed 8 RBC/HPF (normal range 0–5) and was positive for leukocyte esterase. Studies for anti-neutrophil cytoplasmic antibodies were negative. A knee joint aspiration was completed and noted inflammatory cells without bacterial growth. Dermatology obtained a skin biopsy of the rash and the resulting pathology showed a mixed perivascular infiltrate with leukocytoclasia (Figure 2).



**Figure 1.** View of retina OD (A) and OS (B) with cotton wool spot (white arrow), intraretinal hemorrhage (black arrow), and optic disc edema (3 black arrows) noted OS.

Which of the following is the most likely diagnosis?

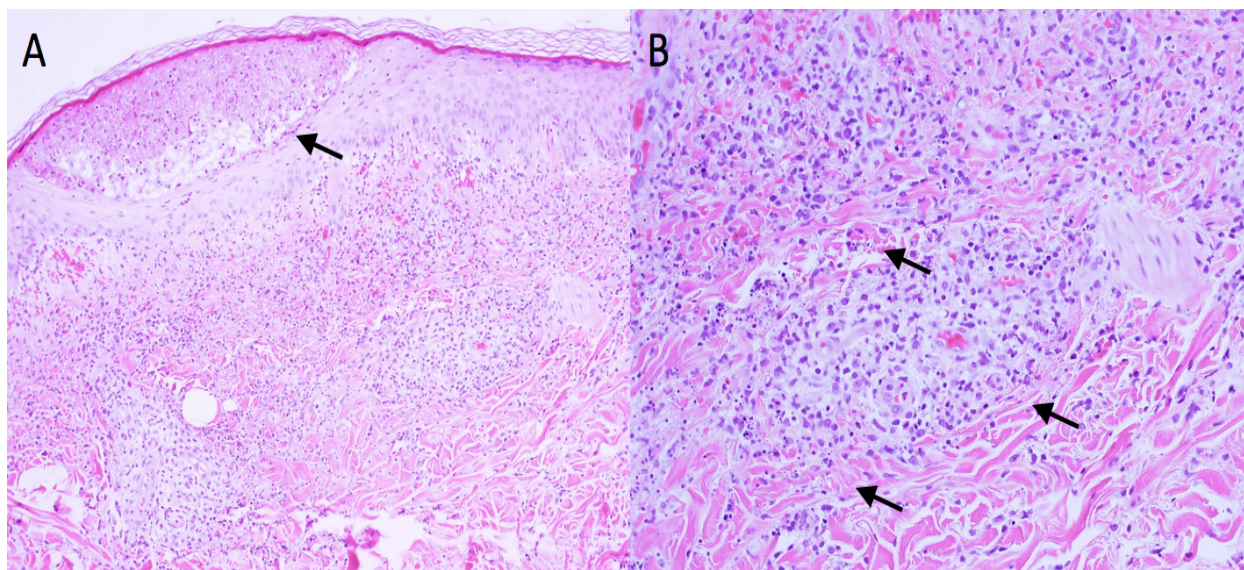
- a) Eosinophilic granulomatosis with polyangiitis
- b) Pustular psoriasis
- c) Disseminated herpes zoster virus with acute retinal necrosis
- d) Systemic lupus erythematosus
- e) Behçet disease

The combination of retinal vasculitis, papulopustular rash, skin ulcerations, migratory arthritis, and supporting laboratory investigations suggest Behçet disease (e) to be at the top of the differential diagnosis. Subsequent genetic studies supported this diagnosis with a human leukocyte antigen (HLA) B51 positive genotype. Work-up for other diagnosis on the differential, including Lyme disease, syphilis, human immunodeficiency virus, systemic lupus, septicemia, and tuberculosis, were negative. Pustular psoriasis may also present with recurrent episodes of widespread, painful erythematous patches accompanied by fever, malaise, arthralgia, and mucosal involvement. However, the presence of retinal vasculitis suggests Behçet disease.

### Background

Behçet disease was first described by Dr. Hulusi Behçet, a Turkish dermatologist in 1937.<sup>1</sup> He presented three cases of patients with uveitis, oral aphthous and genital ulceration, and skin lesions (erythema nodosum).<sup>1,2</sup> Behçet disease is characterized today as a systemic variable vessel vasculitis, with the potential to involve arteries and veins of all sizes.<sup>2</sup>

The prevalence of Behçet disease is greatest in Asian countries stretching from the Mediterranean to Japan. Behçet disease has been coined the “Silk Road disease”;



**Figure 2.** Pathology slides from skin biopsy. (A) Low power view demonstrating pustule. (B) High powered slide demonstrating mixed perivascular infiltrate and leukocytoclastic inflammation.

reflecting its geographic predominance in people with ancestors along the ancient trade route linking the Far East with Europe.<sup>3</sup> In Turkey the estimated prevalence is 80-420/100,000, while in Western countries it is 0.12-0.64/100,000.<sup>4,5</sup> Women are more commonly affected than men. The typical onset is between 30 to 40 years of age, and earlier onset is associated with greater severity of systemic symptoms and eye disease.<sup>2</sup>

### Clinical Features

Behçet disease is not considered a chronic inflammatory disease; rather it is an autoinflammatory disease consisting of recurrent attacks of acute inflammation.<sup>2</sup> Oral ulcerations often represent one of the earliest disease manifestations. Renal involvement is less common and milder in Behçet disease compared to other vasculitides.<sup>6</sup> Table 1 provides an overview of systemic manifestations.<sup>2,7-10</sup>

### Ocular Manifestations

While the most common manifestations of skin lesions and oral and genital ulceration are generally self-limiting, recurrent episodes of uveitis can lead to blindness.<sup>2</sup> Ocular manifestations involving the uvea and retina present in 30-70% of patients and lead to severe bilateral vision loss in about 25% of cases.<sup>11</sup> Signs and symptoms include decreased vision (with or without eye pain), photophobia, periglobal hyperemia, lacrimation, and floaters.<sup>11,12</sup> Cataract formation and glaucoma are additional common ophthalmologic complications.

Anterior uveitis refers to inflammation of the iris

and ciliary body.<sup>13</sup> Episodes of anterior uveitis resolve and relapse spontaneously, but repeated attacks can lead to irreversible structural damage.<sup>14</sup>

Retinal manifestations, including retinal vasculitis, are the most significant ocular complications in Behçet disease.<sup>2,12</sup> Retinal vasculitis, can appear in several ways including perivascular sheathing (a collection of inflammatory cells around the affected blood vessels, Figure 3), cotton wool spots representing arteriolar infarcts (yellow-white, lesions with a cloud-like appearance, Figures 1 and 3), and white centered hemorrhages (Figure 3).<sup>15</sup> The consequences of prolonged retinal vasculitis include optic nerve disease from ischemia, which may present as a relative afferent pupillary defect on pupil exam. Fluorescein angiography is the most informative modality for diagnosing and monitoring retinal vasculitis activity.<sup>2,15</sup>

### Diagnosis

There are no pathognomonic laboratory tests for Behçet disease and several diagnostic criteria have been developed, often for research purposes rather than clinical application.<sup>16</sup> The International Criteria for Behçet disease (ICBD) is the most recently developed clinical criteria which aims to improve on the sensitivity of prior criteria (Table 2).<sup>8</sup> A score of greater than 4 diagnoses Behçet disease with a sensitivity of 93.1% and specificity of 92.1%. A pathology test is positive when a needle stick results in a sterile pustule at the sight of the induced trauma. While it does support the diagnosis, the presence of a positive HLA-B51 genetic marker is not useful as a screening test or as a sole marker of Behçet disease.<sup>2,8</sup>

**Table I.** Summary of key systemic manifestations of Behçet disease.

Feature	Description
Oral ulcerations	These occur in 47-86% of patients. Oral ulcers can involve gingival and buccal mucosa, tongue, and lips but often heal with little scarring.
Genital ulcerations	Deep genital ulcerations occur in 57-93% of patients and can be painful. Unlike oral ulcers, these heal with white or pigmented scars. Perineal and perianal lesions are common.
Cutaneous lesions	Occur in 38-99% of patients. Papulopustular and acne-like lesions may be present on face, limbs, trunk, and buttocks. When biopsied, rashes display leukocytoclastic vasculitis—vascular damage caused by nuclear debris from infiltrating neutrophils. Cutaneous ulcers are rare.
Erythema nodosum-like lesions	Present in 57-93% of patients and more common in females. Typically involve the lower limbs.
Articular	Non-erosive, non-deforming oligoarthritis occurs in 45-60% of patients and can involve the knees, ankles, elbows, and wrists.
Gastrointestinal	Gastrointestinal symptoms affect 3-36% of patients overall and are more common in Japanese individuals. Can involve inflammation and ulceration of the entire gastrointestinal tract, resulting in abdominal pain, diarrhea, and bleeding.
Cardiovascular and respiratory	Thrombophlebitis, deep vein thrombosis, and pulmonary embolism occur in up to 40% of patients. Dilatation of the proximal aorta, interatrial septal aneurysm, and valve disease are findings of cardiac involvement.

### Pathophysiology

The etiology of Behçet disease is thought to be multifactorial, including genetic (HLA and other genes), infectious, and immunologic factors.<sup>2</sup> While our understanding of Behçet disease etiology is evolving, the features of the disease suggest that it is an autoinflammatory disease associated with over-activation of the immune system resulting in vascular injuries and hyper-function of neutrophils.<sup>17</sup> Unlike autoimmune diseases in which the host adaptive immune system mistakenly attacks self-antigens, autoinflammatory diseases are characterised by an abnormally increased inflammatory response of the innate immune system.<sup>18</sup>

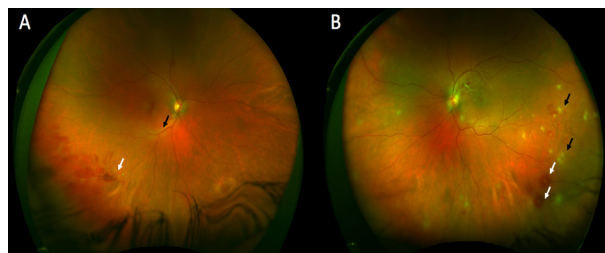
The presence of several HLAs are associated with an increased risk of developing Behçet syndrome. Various HLA-B5 alleles are thought to promote defective antigen presentation leading to activation of adaptive and innate immune responses.<sup>19-21</sup> Particular attention has been placed on HLA-B51, with carriers of this allele estimated to have 5.8 times the odds of developing Behçet disease compared to non-carriers.<sup>22</sup> The prevalence of the HLA-B51 allele is high among patients who live along the silk road (up to 81%) but not among Caucasian patients residing in Western countries (13%).<sup>2</sup> The allele also affects disease severity, since it is more common among patients with posterior uveitis or progressive central nervous system disease, compared to those with milder disease.

The trigger hypothesis of Behçet disease suggests that infection might promote recognition of host antigens via molecular mimicry.<sup>19</sup> Viral infections

implicated include herpes simplex virus, hepatitis C, and parovirus B19. Bacterial infections with *Streptococcus sanguis* have also been suggested as a causative agent, because the bacteria and antibodies are frequently found in the oral flora and serum, respectively, of patients with Behçet disease.<sup>19,23</sup>

### Management

The mainstay of treatment of Behçet disease is immunosuppressive therapy and is targeted towards body systems affected. Corticosteroids are the first line treatment, including both local (topical, periocular, and intravitreal) or systemic (IV or oral) therapy.<sup>2,24</sup> Adjunctive immunosuppressive therapies studied include azathioprine, methotrexate, cyclosporine, mycophenolate mofetil, cyclophosphamide, tumor necrosis factor (TNF) antagonists, colchicine, thalidomide, and interferon-alpha.<sup>25</sup>



**Figure 3.** View of retina OD and OS. Intraretinal hemorrhage (white arrow) and perivascular sheathing (black arrow) are appreciated OD. Intraretinal hemorrhage (white centered hemorrhages, white arrows) and micro-infarcts (cotton wool spots, black arrows) are noted OS.



**Table 2.** International Criteria for Behçet's Disease point score system; total score  $\geq 4$  indicates Behçet's diagnosis.<sup>8</sup>

Sign/Symptom	Points
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathology test	1

Systemic corticosteroids effectively decrease the acute inflammation in eye disease, but do not prevent the recurrence of symptoms and can themselves lead to cataracts and glaucoma.<sup>2</sup> Therefore, for ocular disease affecting the posterior segment, treatment involves systemic corticosteroids in addition to azathioprine.<sup>25</sup> If eye disease is refractory, cyclosporine A, interferon-alpha, or infliximab may be added. Despite therapy, about 25% of patients with ocular symptoms eventually become legally blind (VA < 20/200) in their better seeing eye.<sup>12,13</sup>

#### Case Revisited

Behçet disease is a rare systemic vasculitis with severe ocular manifestations, requiring prompt treatment with systemic steroids and adjunct immunosuppression. In this case, the presenting patient scored 7 on the ICBD diagnostic criteria for Behçet disease. Treatment was initiated with methylprednisolone 1000 mg IV for 3 days, followed by oral prednisone 60 mg daily with a taper. Azathioprine 50 mg daily was added. At follow-up 15 days after initial presentation, corrected VA was measured at 6/6 OD and 6/30 OS. Ocular pressures were 8 mmHg OD, and 15 mmHg OS. A relative afferent pupillary defect persisted OS and anterior slit lamp examination remained normal.

Disclosure: The authors have no proprietary or commercial interest in any materials discussed in this article.

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