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# Peripheral ulcerative keratitis: an unusual primary ocular manifestation in Behçet's disease

**Shailesh Mogra, Anuradha Singh**

*Military Hospital Ahmedabad, Ahmedabad Cantonment, Shahibaug, Ahmedabad, India*

## ABSTRACT

Behçet's disease is an idiopathic systemic inflammation with a predilection for skin and mucosal surfaces of the eye. We report a case with Behçet's disease associated with peripheral ulcerative keratitis and corneal perforation in the left eye. The patient was initially managed dconservatively, followed by tectonic sectoral keratoplasty and systemic immunomodulator therapy. Peripheral ulcerative keratitis is an uncommon but severe manifestation of Behçet's disease, which requires early diagnosis and intensive management to preserve globe integrity and achieve a favourable visual outcome.

**KEY WORDS:** Behçet's disease; peripheral ulcerative keratitis; corneal perforation; tectonic graft

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## INTRODUCTION

Bechet's disease (BD) is a multisystem vasculitis of unknown cause, primarily involving mucosal surfaces of the eyes and the skin. It is a disease of young adults, commonly found in the Asian and Middle-East regions and is associated with HLA-B51 positivity [1]. Ocular involvement occurs in 50–70% of the patients, while in about 20% of cases, ocular disease is the primary manifestation of the syndrome [2]. Initial ocular involvement may be unilateral but invariably progresses to bilateral disease [2]. It commonly presents as uveitis, vitrits, retinitis, and retinal vasculitis [3]. Corneal involvement is very rare. Diagnosis is primarily clinical, by the constellation of systemic and ocular symptoms and signs, supported by laboratory investigation [4]. Due to the relapsing and remitting nature of the disease, the diagnosis can be a lengthy and tedious process. There is no cure to date, and the clinical outcome depends on a high index of suspicion and intensive management [4]. We report a rare case of BD with peripheral ulcerative keratitis (PUK) and corneal perforation of the left eye.

## CASE PRESENTATION

### History

A 42-year-old male presented with painless diminution of vision in left eye of one week duration in the Eye Outpatient Department of a part of western India. It was associated with redness and watery discharge from the affected eye. There was no history of trauma, spectacle/contact lens use, or prior ocular surgery. The patient had had a similar episode in the right eye 7 years back, which was treated with oral steroids, and the patient was advised surgery, which he did not undergo at the time.

CORRESPONDING AUTHOR:
Anuradha Singh, Military Hospital Ahmedabad, Ahmedabad Cantonment, Shahibaug, 380003 Ahmedabad, India; e-mail: anuradha9000@gmail.com

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Systemic comorbidities included pulmonary tuberculosis, diagnosed 4 years back, which was managed with 6 months of anti-tubercular therapy. There was a history of recurrent oral ulcers (4 episodes) and genital ulcers (2–3 episodes) over the past 3 years. There was no history of joint pains or diagnosed arthritis.

## Clinical evaluation

At presentation, the patient's unaided visual acuity was 6/9 in the right eye (OD, *oculus dexter*) and 6/24 in the left eye (OS, *oculus sinister*), with no further improvement. Examination of the OD revealed an oval, well-demarcated, vascularised 4 mm x 3 mm maculo-leucomatous corneal opacity at the 9 o'clock position in the corneal periphery, along with multiple nebulomacular peripheral corneal opacities with corneal thinning inferiorly from 4–9 o'clock (Fig. 1).

The OS showed circumcorneal ciliary congestion (CCC) and an iridocorneal scar with fleshy growth of conjunctiva over the scar at 9–10 o'clock position. There was a corneal perforation with iris prolapse from 3–4 o'clock. Multiple nebulomacular opacities in the peripheral cornea with peripheral corneal thinning were also present in the OS. Multiple keratic precipitates (KPs) were scattered all over the corneal endothelium. The anterior chamber was shallow nasally and temporally with 3+ cells [the Standardization of Uveitis Nomenclature (SUN) classification] and a hypopion of 1 mm (Fig. 2) [5].

The corneal thinning noted in both eyes involved the full circumference of the cornea in an irregular fashion, sparing the limbus and adjacent sclera, and was more evident inferiorly. Both eyes showed destructive inflammation of the juxtalimbal corneal stroma with stromal degradation, evident as corneal thinning and multiple vascularised maculoleucomatous corneal opacities. Corneal sensations were decreased, and Schirmer's test was normal in both eyes. There was no evidence of retinal vasculitis or any other posterior segment pathology in either eye. Intraocular pressures (IOP) were 14 mm Hg in OD and 8 mm Hg in OS, measured by gentle Goldmann applanation tonometry (GAT).

The patient was also detected to have multiple hyper-pigmented plaques over the skin of the trunk and upper limbs (Fig. 3), along with a solitary genital ulcer. The rest of the systemic evaluation was unremarkable.

## Investigations

Corneal scraping was done gently from the base and margins of the ulcer and sent for staining and culture to detect an infectious cause, which was reported negative. The patient underwent several investigations to rule out systemic pathology and detect the etiology of his condition. Baseline blood investigations were within normal limits, including complete blood count and hematocrit. The rest of

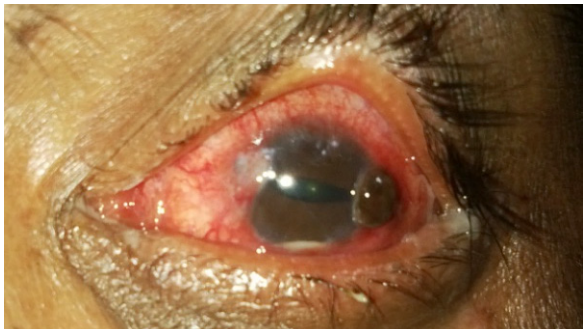

**FIGURE 2.** Left eye showing corneal perforation with uveal prolapse and hypopion. A medial opacity and circumcorneal ciliary congestion are also seen

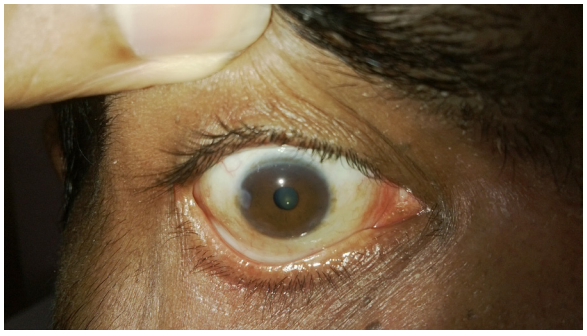

**FIGURE 1.** Right eye showing corneal opacity at 9 o'clock position

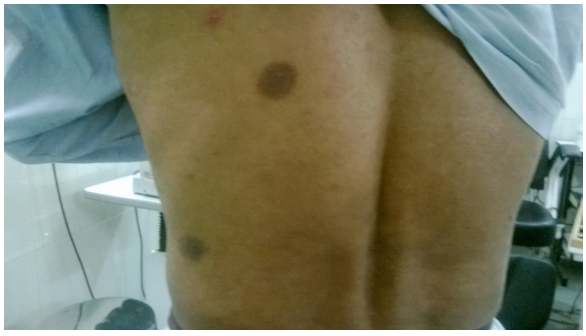

**FIGURE 3.** Hyperpigmented macular lesions over trunk in the same patient

the blood markers, including antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), rheumatoid factor (RF), human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and human leukocyte antigen B27 (HLA B27), were negative. Chest X-ray was normal. The patient tested positive for HLA B51. However, the pathergy test was negative. A conjunctival biopsy of the left eye was done to rule out pemphigoid. Immunofluorescence was negative for immunoglobulins: IgG, IgM, IgA, and complement factor 3.

### Diagnosis

Based on symptomatology, clinical signs, and supportive laboratory investigations, specifically a positive HLA B51, the patient was diagnosed as a case of peripheral ulcerative keratitis with corneal perforation left eye, with Behçet's disease as an associated systemic comorbidity.

### Management

The patient was managed with topical preservative-free antibiotic (moxifloxacin 0.5%) 2 hourly initially, lubricating eye drops (sodium hyaluronate 0.1%) 4 hourly, and cycloplegic (homatropine 2%) 8 hourly. He was also prescribed oral doxycycline 100 mg twice daily and vitamin C 500 mg once daily. The patient showed improvement in the signs and symptoms of inflammation with conservative treatment in the form of reduced pain and congestion with a reduced reaction in the anterior chamber. Due to its relatively larger size, the corneal perforation was deemed unfit for repair with cyanoacrylate, fibrin glue, or amniotic membrane graft. Therefore, the patient was taken up for a sectoral tectonic keratoplasty in the left eye to maintain corneal integrity and reinforce its strength. A 4 x 4 mm sized full-thickness corneal graft was placed over the perforation site after localised peritomy and prolapsed necrotic uveal tissue excision. It was then sutured with interrupted 10-0 monofilament nylon sutures (Fig. 4). He was also started on oral azathioprine 50 mg once daily in consultation with the Department of Rheumatology.

## RESULT

The patient showed a good response to treatment, improved visual acuity from 6/24 to 6/12 (unaided), and resolved anterior segment inflammation. Subsequent tectonic keratoplasty ensured the preservation of globe integrity and protection from infection. Due to a similar episode in the other eye in the past and clinical evidence of old PUK, along with skin and genital lesions and a positive HLA B51 haplotype, the patient was started on systemic immunomodulatory therapy for BD. He demonstrated remission of inflammation with treatment, with no further flare-up of inflammation over a follow-up period of one year.

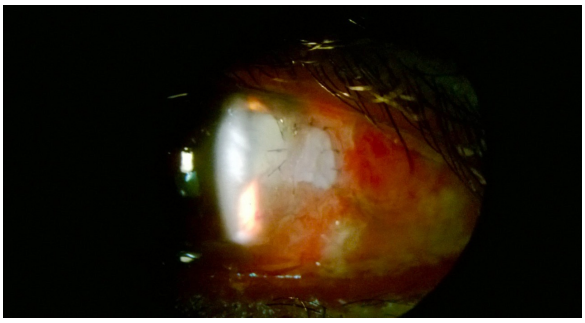

**FIGURE 4.** Post-operative photo of left eye showing tectonic graft with interrupted corneal sutures and conjunctival congestion

## DISCUSSION

BD is an idiopathic vasculitis affecting multiple body organ systems. The disease is common in countries along the "ancient Silk Road", the Middle and Far East countries, and Asia, with a relatively low prevalence in the West [6]. Organ system involvement and gender predilection vary with ethnicity [6]. The disease typically presents with oral, genital, and skin lesions, with a high prevalence of ocular manifestations (50–70%) [2, 7]. Other organ systems affected may include the gastrointestinal (GI), central nervous system (CNS), and cardiopulmonary system, requiring a multidisciplinary approach to the management of the disease [7]. Although the disease is highly associated with HLA B51 positivity, the diagnosis remains primarily clinical [7, 8]. The diagnostic criteria devised for BD, notably the International Study Group for Behçet's Disease (ISGBD) and International Criteria for Behçet's Disease (ICBD), also depend upon clinical features along with a Pathergy test [9, 10].

Ocular manifestations of BD typically include recurrent uveitis, vitiritis, occlusive necrotising vasculitis of the retinal vessels, and cystoid macular edema [3]. Anterior segment features include iridocyclitis (usually as a component with panuveitis), which may be associated with a freely mobile hy-

popion devoid of fibrinous exudate [4]. Conjunctival lesions, scleritis, frosted branch angiitis with or without neuroretinitis, though uncommon, may also be seen [4, 11, 12].

Peripheral ulcerative keratitis (PUK), a destructive inflammatory condition with potentially devastating complications, is an extremely rare manifestation of BD. The peripheral cornea has been deemed vulnerable to inflammation due to the accumulation of immune complexes and products of the complement system pathway in the limbal capillaries and lymphatics [13]. An imbalance between matrix metalloproteinases (MMP) and their tissue inhibitors (TIMPs) has also been attributed to disease progression by the destruction of specific extracellular matrix components [13]. The characteristic presentation is a crescent-shaped lesion involving the peripheral cornea, associated with an epithelial defect, an undermined peripheral edge, and an overhanging central edge, with a tendency to progress centrally [14].

Various aetiologies have been outlined for PUK. Mooren's ulcer presents with classical PUK involving one or both eyes in the absence of systemic features. A multitude of systemic inflammatory and autoimmune disorders are associated with PUK, the most common being rheumatoid arthritis (RA), affecting about 30% of all PUK patients [13]. Other systemic causes include ANCA-associated vasculitis, systemic lupus erythematosus (SLE), Sjogren's syndrome, granulomatosis with polyangiitis (GPA), relapsing polychondritis (RP) and polyarteritis nodosa (PAN). It may present with or without necrotizing scleritis, depending on the underlying cause. It can also occur following systemic infections such as tuberculosis (TB) and HIV or following ocular surgery. Local infective causes must be ruled out by gentle corneal scraping for stain and culture in all cases [13].

Very few cases of PUK in association with BD have been reported in the literature. A case of bilateral PUK associated with BD in a 22-year-old Caucasian female was reported in 2009 by Claire Murphy et al. [15]. Similar cases have been reported among middle-aged individuals in 2014 and 2021 [16, 17]. All these patients developed PUK in a setting of previously diagnosed BD. In our case, PUK was the presenting feature that led to a diagnosis of Behçet's on evaluation. A similar case has been reported, also from India, in a 13-year-old girl with PUK as a presenting feature of BD [14]. Our patient did not have any involvement in the posterior segment of the affected eye. This feature was common in all previous case reports [14–17].

PUK has a poor prognosis in most cases. Treatment consists of local treatment along with management of systemic causes where detected. Medical management entails topical antimicrobial while awaiting culture and sensitivity reports and supportive measures such as lubricating agents and cycloplegic. Once an infectious cause is ruled out, the patient can be started on topical steroids, along with oral steroids and collagenase inhibitors such as doxycycline [13]. Topical immunomodulatory agents such as cyclosporine and tacrolimus may also play a role [13]. The surgical approach can include perilimbal conjunctival resection with an amniotic graft to reduce the load of pro-inflammatory mediators. Tissue adhesive and corneal patch graft can be used for small perforations, while a crescentic lamellar keratoplasty can be used to manage extensive peripheral thinning. Though not a routine procedure, a tectonic corneal graft may be required as an emergency solution to preserve globe integrity. It is used in cases with corneal perforation larger than 2mm in size, where closure with amniotic membrane or cyanoacrylate glue may not be sufficient. It has the advantage of providing tectonic support to the globe while an optical keratoplasty is planned later in a quiet eye. However, it may be associated with graft vascularisation and opacification and requires surgical expertise [18]. In all cases, systemic immunosuppression must be administered following corneal graft, as there is a high chance of keratitis recurrence in graft and graft failure [13].

BD treatment is undertaken per guidelines set by the European League Against Rheumatism (EULAR) [19]. The most common initial treatment is with oral azathioprine at a starting dose of 50 mg per day, gradually increasing by 50 mg every four weeks, depending on the response, with a target dose of 2.5 mg/kg/day. The complete blood count (CBC) is undertaken every 2 weeks till the target dose is achieved, and potential renal insufficiency should be ruled out. Other drugs used for treating BD are cyclosporin A, mycophenolate mofetil, and biological agents such as interferon-alpha, infliximab, and adalimumab [19].

BD has been uncommonly associated with PUK. In previous case reports and this case, the patients have been exclusively found to have anterior segment findings in the absence of any posterior segment involvement. Also, the patients experienced a favourable outcome of PUK with timely

diagnosis and treatment. This is an exception to common findings and prognoses associated with BD and PUK. This can be undertaken for further research, though more cases need to be reported to delineate clinical criteria for PUK associated with BD.

## Ethics statement

This manuscript has been prepared after obtaining informed consent from the patient after explaining the process in a language of the patient's understanding. All efforts have been made to keep the identity of the patient confidential.

## Author contributions

S.M.: clinical diagnosis and patient management, collection of data; A.S.: preparation of manuscript, clinical and literature research.

## Conflict of interest

Authors declare no conflict of interest.

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