Case report

Peripheral ulcerative keratitis in Behçet's disease: A rare bilateral presentation with subsequent corneal perforation

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Abstract

Peripheral Ulcerative Keratitis (PUK) is marked by stromal inflammation and degradation of the cornea and is a rare ocular presentation of Behçet's Disease (BD). Early diagnosis and treatment are essential to prevent ocular morbidity. A 36-year-old male known to have BD presented with one month duration of bilateral ocular pain, redness, tearing, photophobia and impaired vision. There was previous history of oral and genital ulcers, skin rash, arthritis and subacute deep venous thrombosis of the superior vena cava. Slit lamp revealed a right inferotemporal corneal ulcer (3x1mm) with a vascularized margin and a left inferonasal corneal perforation with lost anterior chamber and iris prolapse; with no evidence of intraocular inflammation. The unaided visual acuity was 0.05 (right) and 0.016 (left). Scleral patch graft was used to repair the left corneal perforation. Autoimmune profile and thrombophilia screen were negative. The patient was treated with pulse methylprednisolone (1g/day) for 3 days followed by cyclophosphamide (1g/month) for 6 months; then he was maintained on oral steroids, azathioprine (150mg/day), oral colchicine (1mg/day) and anticoagulation. After one month, the ocular pain decreased and hyperemia resolved with improved vision. On follow-up, slit-lamp revealed right clear cornea and left healed scleral patch (2x3mm) at 8.30 o'clock. BD may atypically present with bilateral PUK; which might be complicated by corneal perforation. This case contributes to raise the awareness of rheumatologists and ophthalmologists regarding this unusual presentation of BD. Patients with PUK may require evaluation for coexistent rheumatic diseases.

Key words: Peripheral Ulcerative Keratitis (PUK), Corneal perforation, Behçet's Disease (BD), Rheumatic diseases

Introduction

Peripheral Ulcerative Keratitis (PUK) is a potentially sight threatening condition; which is characterized by a juxtalimbal crescent-shaped defect, stromal inflammation, thinning and degradation. It has been attributed to several local and systemic causes; either infectious or non-infectious[1]. PUK is the second most common ocular manifestation in Rheumatic Diseases (RDs) following anterior uveitis[2] and has been reported to be the initial presentation in 50% of cases[3]. Rheumatoid Arthritis (RA) accounts for 34% of the systemic causes of PUK; bacterial and viral aetiologies are the most commonly implicated[1]. Ocular manifestations are the presenting complaint in 10% of Egyptian BD patients with a subsequent high frequency of ocular complications in 22%[4]. However, other systemic aetiologies such as Granulomatosis with Polyangiitis (GPA), inflammatory bowel disease, hepatitis C and Human Immunodeficiency Virus (HIV) have also been associated with PUK[1].

The most common pattern of Non-Infectious Uveitis (NIU) in Egyptian systemic autoimmune diseases patients is panuveitis with Behçet's Disease (BD) as the most frequent aetiology and cataract the most common complication[5]. BD is a chronic systemic inflammatory vasculitis of unknown aetiology, characterized by mucocutaneous manifestations, including oral and genital ulcers, ocular affection, variable vessel vasculitis; as well as gastrointestinal and neurological involvement. Ocular involvement in BD occurs in 50% of patients, being more prevalent among males and usually presenting at early-disease onset[3]. The most common ocular manifestation in BD is bilateral non-granulomatous uveitis (posterior or panuveitis). However, isolated anterior uveitis has been also reported, accounting for 5-10% of BD patients[3]. In Egyptian BD patients an association of macrophage migration

inhibitory factor promoter polymorphism with posterior uveitis was revealed[6]. Corneal pathology is a rare occurrence in BD; in which cases of PUK[7,8] were reported. This work presents a case of BD manifesting atypically with bilateral PUK and complicated by left corneal perforation.

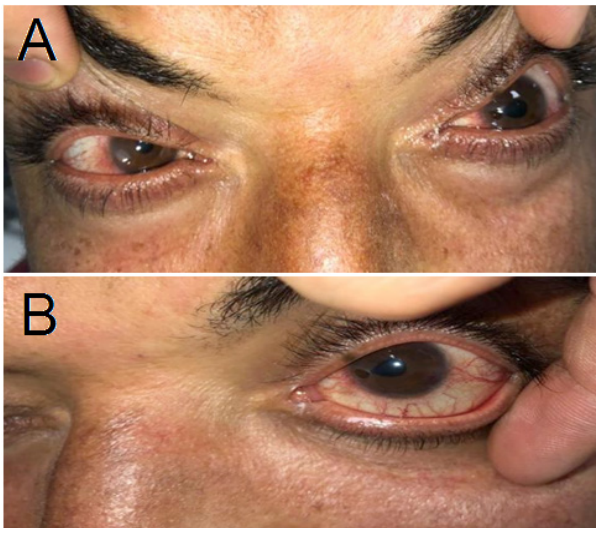
Case report

A 36-year-old male patient presented to the Ophthalmology Department, Cairo University Hospitals with bilateral severe ocular pain, redness, tearing, photophobia and impaired vision for a month. Seven years prior (2016), the patient gave history of monthly recurrent oral and genital ulcers, papulopustular skin rash on forearms and lower limbs, erythema nodosum and arthritis of both ankles and knees; fulfilling the international diagnostic criteria of BD[9]. The patient was born and living in Beni-Suef, married with 3 children, was a chronic smoker 10 cigarettes/day for 15 years and had a body mass index of 24.1 kg/m^2. He was initially diagnosed by a dermatologist and treated with oral colchicine for a year, with improvement of ulcers and skin lesions; then follow-up was lost. In 2021, the patient experienced recurrent attacks of frontal headache, facial puffiness, dyspnea on exertion, orthopnea and plethora, more on lying flat. At that time, vascular duplex of the neck veins and upper extremities revealed bilateral subacute Deep Vein Thrombosis (DVT) of the Superior Vena Cava (SVC), Internal Jugular Veins (IJVs), innominate veins and subclavian veins as well as subacute superficial thrombophlebitis of the right antecubital vein and venous tributaries on the posterior aspect of both forearms, being distended by wall-adherent iso-echoic thrombus exhibiting recanalization. Carotid duplex revealed elevated restrictive indices of bilateral vertebral arteries (vertebrobasilar insufficiency). Therapeutic anticoagulation was started for one month and then stopped due to improvement of the patient's condition. The patient provided an informed consent to present his case and use the pictures. The approach was in accordance to institutional ethical standards of Cairo University Hospitals and in line with the 1964 Helsinki declaration.

Ophthalmological assessment of the patient revealed right inferotemporal corneal ulcer (3x1mm) with a vascularized margin and visual acuity 0.05; and left inferonasal corneal perforation with lost anterior chamber and iris prolapse and visual acuity 0.0167 (Figure 1). There was no evidence of old or recent intraocular inflammation.

The patient had no symptoms suggestive of other systemic connective tissue disorders or chemical or physical exposure. His drug and past medical history were unremarkable. Examination revealed facial puffiness, visible dilated veins over the chest wall, congested neck veins; scars of old healed genital ulcers on the scrotum and intact peripheral pulsations.

Figure 1: A. Right inferotemporal corneal ulcer (3x1mm) with vascularization at the margin. Left inferonasal corneal perforation. B. Left inferior and nasal perforation with evident iris prolapse and shallowing of the anterior chamber



Laboratory investigations revealed normal erythrocyte sedimentation rate (25mm/1st h) and C-reactive protein (5mg/L), haemoglobin (14.4g/dl), total leucocytic count (6.6 x10^3/mm^3), platelets (213 x10^3/mm^3), alanine transaminase (17 IU/L), aspartate transaminase (22 IU/L), urea (32mg/dl) and creatinine (0.8mg/dl) with normal lipid profile: triglycerides (52mg/dl), low-density lipoprotein (107mg/dl) and high-density lipoprotein (51mg/dl). The autoimmune profile including rheumatoid factor, anti-cyclic citrullinated peptide, anti-nuclear antibodies, extractable nuclear antigens, anti-neutrophil cytoplasmic antibodies and the antiphospholipid profile were negative. Thrombophilia screen revealed normal protein C, protein S and anti-thrombin III.

Additionally, vascular duplex of the neck revealed distended IJVs; intra-luminal echogenic isoechoic thrombus with no color flow, picture suggestive of subacute DVT. The common, external and internal carotids as well as vertebral arteries were patent with normal color flow and intima media thickness. Computerized Tomography (CT) pulmonary angiography showed non-opacified SVC with prominent collaterals on the right side and dilated azygos and hemiazygos veins highly suggestive of SVC obstruction.

Rheumatology and ophthalmology co-management was considered. The perforation was successfully treated with scleral patch. Pulse methylprednisolone (1g/day) was provided for 3 days, followed by oral prednisolone (0.5mg/kg/day) for a month with subsequent tapering. Pulse cyclophosphamide (1g/month) was started for 6 months; then the patient was maintained on azathioprine (150mg/day) and colchicine (1mg/day). Therapeutic life-long anticoagulation with Low Molecular Weight Heparin (LMWH) (1mg/kg/12h) and warfarin (2mg/day) were commenced for the IJVs DVT and SVC

syndrome; International Normalized Ratio (INR) was maintained on 2.7. The patient reported improvement of dyspnea and facial puffiness. The case was presented and discussed in the Case of the Week meeting of the Rheumatology Department, Cairo University and the ongoing management was approved. After 1 month, ocular pain and hyperemia resolved. The unaided visual acuity improved to 0.8 OD and to 0.6 OS. After 7 months, slit-lamp examination revealed right vascularized corneal leucoma (2x1mm) and left healed scleral patch (2x3mm) at 8.30 o'clock position. After 10 months, right cornea was also clear (Figure 2); fluorescein angiogram revealed right early peripheral vasculitis and normal left retinal vessels (Figure 3).

Figure 2: Post-treatment imaging: slit-lamp examination showing (A) clear cornea of the right eye and (B) healed scleral patch (2x3 mm) at 8.30 o'clock position of the left eye

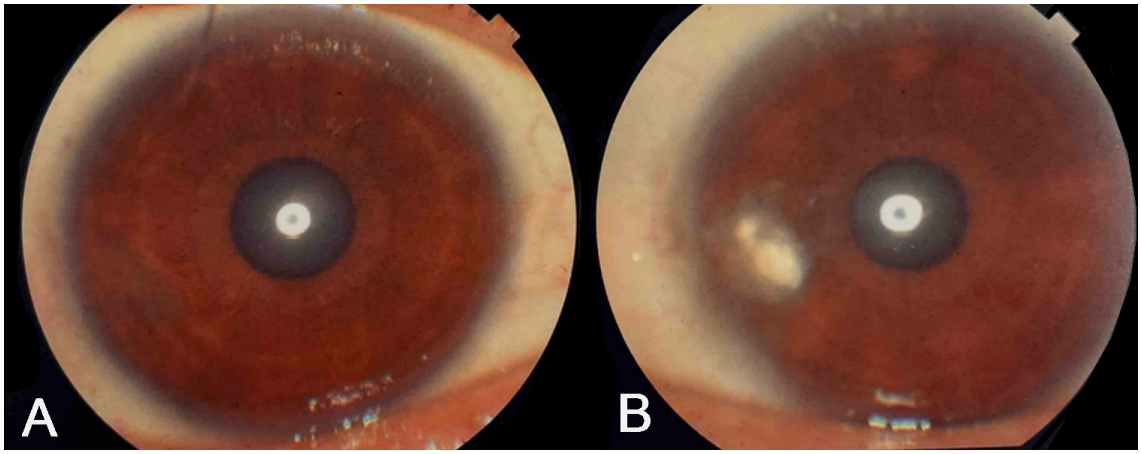
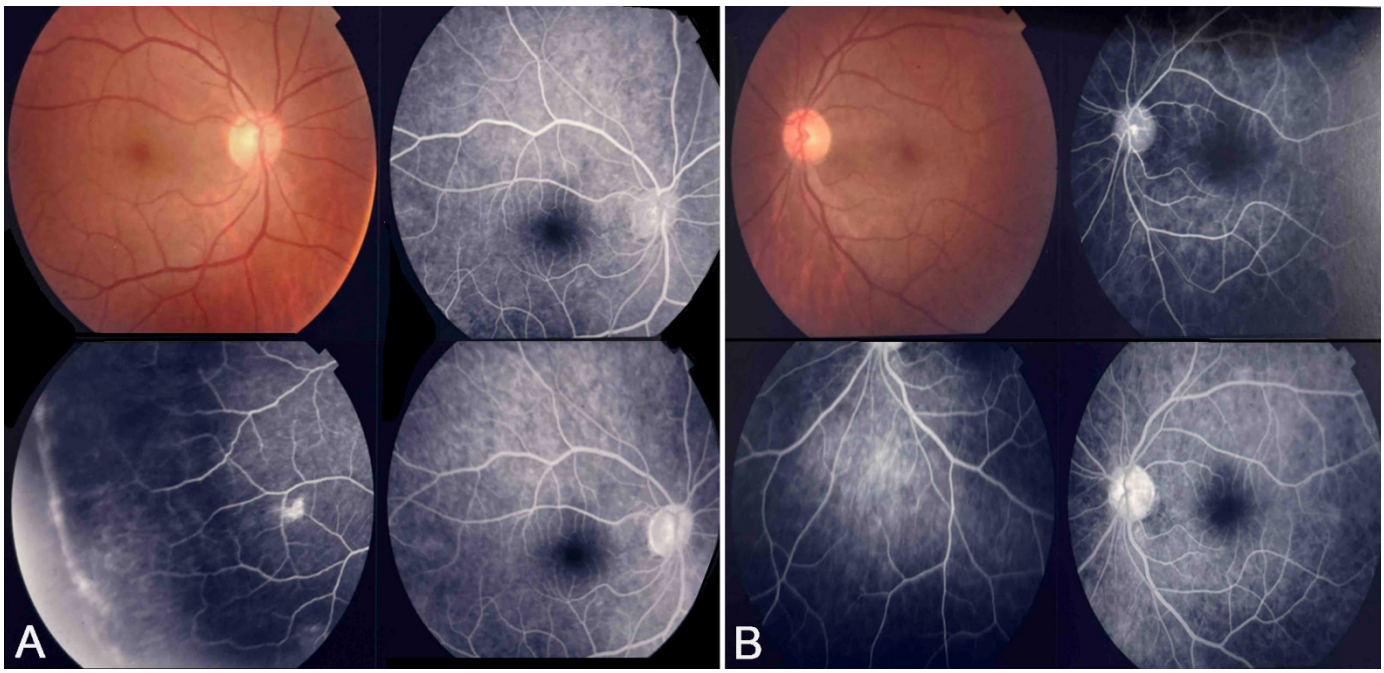


Figure 3: Post-treatment fundus imaging and fluorescein angiogram showing (A) early peripheral vasculitis of the right eye, (B) normal fundus and fluorescein angiogram of the left eye



Discussion

Inflammatory eye presentations with poor visual prognosis were described in 23% of BD patients[10] and macular degeneration and retinal vasculitis are major causes of blindness in 15-25%[11]. Corneal pathologies, including ulceration and perforation, are rarely associated with BD. Eye involvement was comparable between males and females in a nationwide study on Egyptian BD patients[12]. Peripheral Ulcerative Keratitis (PUK) is a vision threatening condition which confers significant morbidity, if it occurs in the context of RDs[2,3]. There are only few case reports with the co-existance of PUK and BD[7,13-17] as presented in Table 1. Altered tear film function and upregulated Matrix Metalloproteinases (MMP) were implicated in the development of PUK in BD[18].

Table 1: Behçet disease case reports with associated peripheral ulcerative keratitis (PUK)

Variable	Europe			Asia			North Africa
	France[14]	UK[13]	Spain[16]	S-Korea[7]	China[15]	Japan[17]	Egypt This case
Year	1995	2009	2020	2014	2014	2003	2023
Age (years)	33	22		34	26	31	36
Gender	F	F		F	F	F	M
PUK		Bilateral		Right	Bilateral	Bilateral	Bilateral
Vis Acuity		Reduced		Reduced	Reduced	Reduced	Reduced
IO infl.		No		No	No	Panuveitis	No
Ret.vasculitis		No		No	No	Yes	No
Corneal perf.		No		No	No	Right	Right
RF		Negative		Negative	Negative	-	Negative
ANA		Negative		Negative	Negative	-	Negative
ANCA		Negative		Negative	Negative	-	Negative
Treatment	Steroids	Steroids AZA	Steroids Others	Steroids DMARDs	Steroids Thalidomide Tacrolimus	Steroids Colchicine Cyclosporine SCL	Steroids AZA, CYC Anticoagulants Scleral patch
Outcome	Favorable	Resolved		Ulcer healed VA improved	Ulcer healed VA improved	Iridocyclitis improved Corneal perf. improved	Remarkable improvement and healing

PUK: Peripheral ulcerative keratitis, IO infl.: Intraocular inflammation, Ret. vasculitis: Retinal vasculitis, Corneal Perf.: Corneal perforation, RF: Rheumatoid factor, ANA: Antinuclear, ANCA: Anti-neutrophil cytoplasmic antibodies, AZA: Azathioprine, DMARDs: Disease modifying anti-rheumatic drugs, CYC: Cyclophosphamide, VA: Visual acuity, SCL: Soft contact lens.

In the present case, diagnosis of non-infectious bilateral PUK and corneal perforation was made on clinical grounds after exclusion of other differentials. Autoimmune aetiologies for PUK including RA, GPA, systemic lupus erythematosus, polyarteritis nodosa, Sjögren's syndrome and systemic sclerosis were reported[1]. In this case, the diagnosis of BD was held due to the presence of recurrent oral and genital ulcers, erythema nodosum, papulopustular skin rash and DVT. Corneal scraping for bacterial and fungal causes was not done in this case as an infectious aetiology was unlikely.

This patient was treated with systemic steroids and Disease Modifying Anti-Rheumatic Drugs (DMARDs); with resolution of signs of inflammation and healing of the corneal ulcers. The left corneal perforation was effectively treated with a scleral patch. The early use of systemic steroids is crucial in severe cases of PUK with impending vision loss[19]. DMARDs such as cyclosporine[7] and azathioprine[8] have been used effectively for PUK cases in BD. Also, cyclophosphamide (CYC) has shown promising results in treatment of GPA and RA-related PUK[20,21]. Intravenously methylprednisolone and CYC were drugs of choice in the present patient, owing to the underlying systemic vasculitis and bilateral PUK. For SVC syndrome, anticoagulation with heparin and vitamin K antagonist was started, with regular INR monitoring.

Behçet's Disease (BD) has a wide range of clinical manifestations including sight threatening ocular manifestations. Autoimmune PUK should be addressed promptly by a team of rheumatologists and ophthalmologists using steroids and tailored immunosuppressives. Patients with inflammatory eye diseases including uveitis, scleritis, episcleritis and PUK require multi-disciplinary care for best outcomes, frequently including rheumatologists. Understanding the differentials, diagnostics, and treatment are essential to preserving vision in these patients[22]. Furthermore, in Egyptian BD patients, machine-learning identified top factors for those at higher risk of Vision-Threatening BD (VTBD) including higher disease activity, thrombocytosis, smoking and receiving daily steroid dose[23]. The involvement of the deeper structures of the

eye including posterior uveitis, retinal vessel occlusion, retinal vasculitis and vitritis should alarm rheumatologists to keep in mind that all BD patients should have an eye examination[24].

In conclusion, this case emphasizes that PUK and corneal perforation can occur in association with BD; although co-existence is rarely reported. Early, prompt and timely ophthalmological management of PUK is an important effective conservative therapeutic option and crucial for a favorable outcome to avoid ocular morbidity. Classic DMARDs are effective in controlling the condition. Patients presenting with PUK require extensive systemic evaluation to reveal any underlying RD.

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