Behcet's Disease with Absent HLA Serotyping and Pathergy Test

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ABSTRACT

Behcet's disease is a multisystemic vasculitis of unknown etiopathogenesis characterized by recurrent acute inflammation. A 30-year male presented with progressive blurred vision in both eye for one month associated with photophobia, redness and ocular pain. On presentation best corrected visual acuity was 6/9 both eyes. Bilateral ocular examination of anterior segment demonstrated occasional cells. Treatment history of multiple joint pain along with oral aphthous ulcers. Erythematous papulopustular lesion over face, neck, trunk and genital ulcers were being treated. Irrespective of negative human leucocyte antigen B51 and pathergy, patient was diagnosed as Behcet's disease on the basis of clinical criteria and started with topical steroid and cycloplegic. At one-month, ocular symptoms were relieved. Behcet's disease is a rare, autoimmune disease, which lacks universal pathognomonic test and investigations, therefore diagnosis is primarily done with international criteria for Behcet's disease. Multidisciplinary approach certainly helps in early diagnosis and eliminating morbidity.

KEY WORDS

Behcet's disease, HLAB51, Pathergy test, Silk road, Uveitis

INTRODUCTION

Behcet's disease (BD) is a chronic, recurrent, multi-systemic inflammatory disorder initially recognized by Hippocrates, however holds the name of Turkish dermatologist Hulusi Behçet after his intricated description of the illness in 1937.[1] It holds triad of oral ulcers, genital ulcers, and ocular lesions, nevertheless currently multisystemic that is vascular, articular, gastrointestinal, neurologic, urogenital, pulmonary and cardiac involvement are observed.[2-4]

BD has a global distribution however its prevalence has a strong geographic discrepancy. It is often observed with prevalence of 14-20/100,000 population alongside the ancient Silk Road, connecting China with Rome, 30°-40° north of the Equator.[3,5] The association of BD with HLA-B51 was first described by Ohno et al. in 1973.

We report a case of a young male, diagnosed and managed as BD on the basis of international criteria for Behcet's Disease (ICBD), with a point score of 7, in-spite of negative pathergy test and absence of HLAB51.

CASE REPORT

A 30 year male presented to the out-patient department with complaint of blurring of vision both eyes (BE) from one month which was progressive and associated with photophobia, redness and eye-ache. On presentation visual acuity was 6/9 BE with intraocular pressure (IOP) 16 mm of Hg right eye (RE) and 13mm of Hg left eye (LE). Anterior segment examination revealed presence of occasional cells BE (Figure 1). Dilated posterior segment examination showed barrage laser scars in superior peripheral retina BE performed for lattice degeneration (Figure 1). Patient gave history of similar illness BE eight years back for which treatment was done using oral and topical steroids in tapering manner, posterior sub-tenon dexamethasone 4mg along with cycloplegic for one and half month. A period of remission was attained for 2 years. Since then, patient has recurrent episodes of similar illness which is relieved on oral and topical steroids.

Pain in bilateral wrist, elbow joint, neck and left sided hip joint were observed for past 7 years for which treated

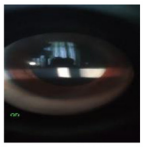
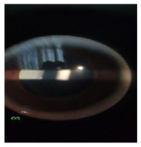
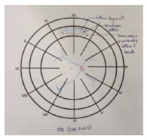
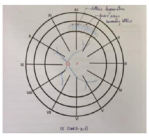
RE	LE	Findings
		Anterior segment showing occasional cells.
		Fundus drawing showing barrage laser surrounding lattice degeneration

Figure 1. **Picture showing ocular examination**

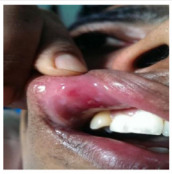
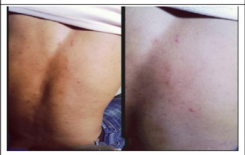
Parameters	Figures	Findings
Oral examination		Oral aphthous ulcer with erosion of oral mucosa.
Cutaneous examinations		Erythematous papulopustular lesions over back

Figure 2. **Oral and cutaneous examination**

with colchicine for multiple episodes. Treatment history of recurrent oral aphthous ulcers 6 times a year from 7 years (Figure 2). Skin lesions suggestive of recurrent erythematous papules over trunk for 5 years and over face and neck for 1year have been treated (Figure 2). Treatment history of genital ulcer since one and half months. HLA-B 51 and pathergy test were documented to be negative. However, ESR and CRP were on higher ends (Table 1).

Table 1. **Blood parameters**

Blood Investigation	
ESR	*49 mm in 1 hour*
CRP	*62.4 mg/l*
HLAB 51	Negative
Pathergy Test	Negative

Patient was advised with Gtt prednisolone acetate 1% QID, Gtt homatropine 2% BD for one week. On follow up visual acuity was recorded to be 6/6 BE with normal IOP, and anterior chamber was free of cells with similar posterior segment finding as that of previous follow up, thus topical steroid was kept in tapering manner, TID for one week, BD for one week and OD for one week. After three weeks, visual acuity was 6/6 BE, IOP was recorded to be within normal range, anterior chamber reactions were absent and patient was symptomatically better. Patient was then asked to follow up on SOS/six monthly.

DISCUSSION

BD, when manifested at a very young age, present with severe forms, with more organs affected Males are believed to be affected 1.5-5:1 times frequently than females with peak age of onset at 20-30 years.[5]

Discrete laboratory investigations have been explored (leukocytosis, increased erythrocyte sedimentation rate, C-reactive protein, elevated IgG, IgA and IgM), none have sensitivity or specificity for the diagnosis. Also, no pathognomonic symptom is used to define the disease.[3,6] Nevertheless, ICBD point score system was developed in 2006 as a replacement to international study group (ISG) developed in 1990 for ensuring comparability of BD entered into epidemiological, clinical and therapeutic studies.[3]

ICBD point score system (Table 2). A patient scoring ≥ 4 points is classified as BD. Pathergy test is optional, but, where pathergy test is performed 1 extra point may be assigned for a positive result.[6] As observed in our patient, ocular, genital, oral and skin were involved with a total of 7 points out of 10 leading the diagnosis toward Behcet's disease despite of negative pathergy and HLAB51.

Table 2. **ICBD point score system.**

Signs/symptoms	Points
Ocular lesions	*2*
Genital aphthosis	*2*
Oral aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathergy test	1

Ocular inflammation in BD is manifested as non-granulomatous anterior uveitis or conjunctivitis; increased risk is observed in young males and lowest is in females.3 BD, frequently has bilateral ocular involvement, most disastrous disease associated morbidity is observed in posterior uveitis with retinal vasculitis.[3,7] Initial two years after the diagnosis of BD is crucial for the therapeutic intervention in order to decrease ocular morbidity. In spite of the treatment, blindness in BD is in 25% of patients.[3,8] In our patient, bilateral non-granulomatous recurrent anterior uveitis was present which relieved on treatment with topical steroid eyedrop.

Genital lesions appear as small red elevated acne-like lesions occurring in scrotum and penis in male and on vulva, vagina and cervix in female. Oral aphthous ulcers are frequently observed in buccal mucosa, gingiva, gums, lip, tongue, soft palate and pharynx which could be associated with pain.[3,9] As observed in our patient, scrotal ulcer and oral aphthous ulcer were present which were treated with topical steroid ointment.

Joint involvement is one of the major complaints, the commonly involved are knees, ankles, wrists and elbows in decreasing order.[9] In our patient multiple join pain was observed which was treated with colchicine. CNS involvement is among the severe complication with

devastating prognosis occurring in 10-20% of BD.[10] However, in our patient no CNS involvement was observed.

Pathergy reaction is the production of a blister/pustule in response to puncture of the forearm skin with a sterile needle. It provokes reactions even in healthy individual as a cutaneous vascular axon reflex, thus promoting the release of inflammatory mediators by the traumatized cells. In BD, these events are abnormal and increased. Sensitivity of the test is variable in equation to the geographic distribution of the population, increasingly positivity has been reported in Israel, Turkey and Japan. As a result, currently there is decline in this trend.[3,7,9] In our case, as patient is not a resident of silk route, we believe, it could be one of the principle cause of negative pathergy test.

Etiopathogenesis of BD remains ill-defined, however inflammatory mediators, TNF-α, chemokines, oxidative stress and lipid peroxidation, genetic factors such as HLA-B51, immune dysregulation (leucocyte and T-cell activation), heat shock protein 65, environmental and microbiological factors(herpes simplex virus, Streptococcus sanguis) and geographic distribution play a vital role.[3,4] The association with HLA-B51 appears to have crucial role in neutrophil activation, however its presence alone is not sufficient to explain the symptoms observed in BD.[5] As observed in our patient, who lacked to have a positive HLAB51 serotyping, however clinical criteria fulfilled to have BD. Numerous studies have been performed including multicentric groups belonging to diverse geographic locations suggesting the involvement of other genes, one of them conducted in Iranian patients by Scherrer et al. demonstrated association with HLA-B35, HLA-B51, HLA-B52, and HLA-Bw4.[5] There exist a strong relationship between geographic distribution thus implicating environmental factors along with genetics of HLAB51 and prevalence of BD as observed by Alpsoy et al., Scherrer et al., Davatchi et al. and Yazici et al.[2,5-7] As, frequency of HLAB51 in the Silk Road area is 50-80% among the patients and 20-25% even in the healthy population.[5]

As HLAB51 has strong geographic distribution, also our patient is not an inhabitant of antient silk road, nonetheless contemplation of multisystemic involvement and imperative examination by multidisciplinary approach concluded diagnosis of BD, fulfillment of ICBD criteria further adds in the diagnosis with a 7-point score out of 10 in-spite of negative pathergy. Dearth of pathognomonic symptoms and precise investigation could lead to detained diagnosis and facilitate morbidities thus, BD ought to be diagnosed early and managed by multisystemic approach.

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