A Behçet's Case Presenting with Central Retinal Vein Occlusion: Case Report

Santral Retinal Ven Tıkanıklığı ile Ortaya Çıkan Bir Behçet Olgusu

Mehmet Rami HELVACI, MD,[a]
Fatih ÖZCURA, MD,[b]
Alper HACIOĞLU, MD,[c]
Kısmet ÇİVİ, MD[d]

Department of [a]Internal Medicine, Medical Faculty of the Mustafa Kemal University, Antakya
Departments of [b]Ophthalmology, [c]General Surgery, [d]Pathology, Medical Faculty of the Dumlupinar University, Kütahya

Geliş Tarihi/*Received:* 17.04.2007
Kabul Tarihi/*Accepted:* 07.09.2007

Yazışma Adresi/*Correspondence:*
Mehmet Rami HELVACI, MD
Medical Faculty of the
Mustafa Kemal University
Internal Medicine, Kütahya
TÜRKİYE/TURKEY
mramihelvaci@hotmail.com

ABSTRACT Behçet's disease is a systemic vasculitis, dominated clinically by recurrent oral and genital ulcerations, uveitis, and erythema nodosum-like cutaneous lesions. However, widespread organ involvement is now well recognized, and geo-graphic and ethnic variations of the clinical manifestations are common. The majority of the affected individuals do not have a life-threatening disease, but mortality can be increased with vascular and/or thrombotic complications. Although ocular involvement occurs approximately in 70% of patients, clinically presented retinal vascular events are rare in the disease. We report a Behçet's case, initially diagnosed with a right-sided central retinal vein occlusion in the absence of uveitis as a rare presentation and a short review of the literature.

Key Words: Behçet syndrome; retinal vein occlusion

ÖZET Behçet hastalığı, yaygın klinik bulguları tekrarlayan oral ve genital ülserler, üveit ve eritema nodosum benzeri cilt lezyonları olan sistemik bir vaskülittir. Yaygın organ tutulumu iyi bilinmekle birlikte klinik ortaya çıkışta coğrafik ve etnik farklılıklar sıktır. Hastalıktan etkilenenlerin çoğunda hastalık hayatı tehdit etmez fakat mortalite vasküler ve/veya trombotik komplikasyonların ortaya çıkışıyla artabilir. Hastalıkta göz tutulumu yaklaşık %70 oranında görülmesine rağmen klinik olarak ortaya çıkan retina vasküler hastalıkları nadir görülür. Biz bu makalede üveit yokluğunda nadir bir ortaya çıkış şekli olan sağ gözde santral retinal ven tıkanıklığı teşhisi ve sonrasında Behçet hastalığı tanısı konulan bir olgu ile kısa bir literatür özeti sunacağız.

Anahtar Kelimeler: Behçet hastalığı; retinal ven tıkanıklığı

Turkiye Klinikleri J Med Sci 2008, 28:403-407

Behçet's disease (BD) is a systemic vasculitis, affecting vessels of different type, size, and localizations, and the most common presentations are recurrent oral and genital ulcerations, uveitis, and erythema nodosum-like cutaneous lesions. Widespread organ involvement is now a well-known entity and the clinical course and degree of organ involvement is often similar in relapses for a given patient. The frequency and severity of the unpredictable exacerbations and remissions may diminish over time. Additionally, geographic and ethnic variations of clinical manifestations are common. Although the onset of the BD is most commonly within the third decade, the final diagnosis is usually made in the fourth decade of life, and

both genders can be affected. It has a worldwide distribution, although it is more prevalent in countries of the ancient Silk Route (from the Mediterranean countries to Japan). The etiology of the BD remains unknown, although an autoimmune phenomenon triggered by an unknown agent in a genetically predisposed individual has been suggested.[1]

Although the majority of the affected individuals do not have a life-threatening disease, mortality can be associated with vascular and/or thrombotic complications. Vascular complications develop in about 20 to 40% of patients,[1] and BD associated with lesions in the large vessels is termed "vasculo-BD" and it includes venous and arterial occlusions and aneurysm formations. We report a Behçet's case initially diagnosed with a right-sided central retinal vein occlusion as a rare presentation.

CASE REPORT

A 51-year old female patient attended the Ophthalmology Outpatient Clinic in the Dumlupınar University with sudden onset of blurring of vision of the right eye. Her complaint had a 2-day course. Her best-corrected visual acuities were 20/400 with +0.75 D on the right and 20/20 with -0.50 D on the left eyes. Intraocular pressures were measured via applanation tonometry, and were 10 mmHg in the right and 12 mmHg in the left eyes in the absence of any history of glaucoma. Light reflexes and motility examinations of both eyes were normal. Both eyes were normal on the anterior segment examination performed via biomicroscope. Increased thickness and tortuosity of the retinal veins and disseminated flame-shaped hemorrhages and cotton-wool spots caused by central retinal vein occlusion were seen in the right eye via funduscopic examination, performed after dilation of the pupil (Figure 1). On the other hand, funduscopic examination was normal on the left side and neovascularization was detected neither in the anterior nor in the posterior segment of the right eye. She was consulted to the Internal Medicine Outpatient Clinic of the University for any underlying systemic cause.

A detailed medical history revealed that she had relapsing oral ulcerations for the last 4 years, but never had genital ulcerations. Her physical examination showed oral aphthous lesions and an erythema nodosum-like lesion with sizes of 5 x 4 cm on her right pretibial region present for the last 3 months (Figure 2). A biopsy sample was taken from the cutaneous lesion and histopathology of the lesion revealed small-vessel vasculitis with paniculitis.

Results of a routine check up procedure including routine hematological and biochemical tests, thyroid function tests, markers of hepatitis

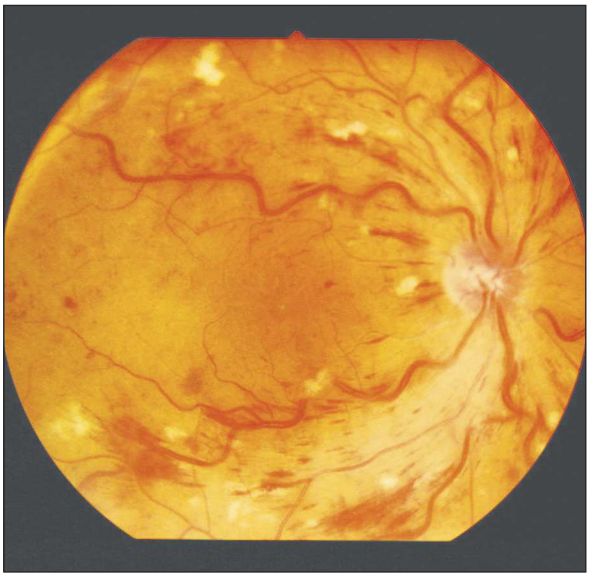

FIGURE 1: Increased thickness and tortuosity of the retinal veins and disseminated flame-shaped hemorrhages and cotton-wool spots in central retinal vein occlusion.

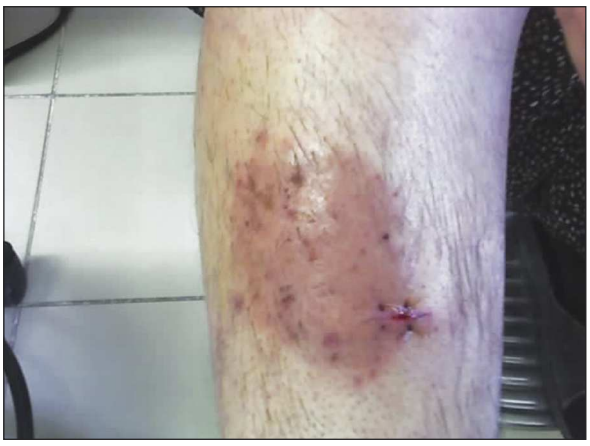

FIGURE 2: Pretibial erythema nodosum-like lesion of the patient.

viruses A, B, and C and human immunodeficiency virus, urinalysis, electrocardiography, and a chest X-ray were normal. A pathergy test, pricking of the skin of the forearm with a sterile needle without injecting anything, was performed and the result was positive (pustule formation was observed 24-48 hours after the needle insertion). BD was diagnosed according to the International Study Group for BD criteria, 1990, in which the agreed diagnostic criteria require presence of recurrent oral ulcerations (3 times in 1 year) plus two of the following in the absence of any other systemic disease:[2]

1) Recurrent genital ulcerations,

2) Eye lesions (uveitis or retinal vasculitis),

3) Skin lesions (erythema nodosum, pseudofolliculitis, papulo-pustular lesions or acneiform nodules),

4) A positive pathergy test (pustule formation 24-48 hours following skin prick).

The patient reevaluated by ophthalmologists for uveitis following diagnosis, but no sign was detected in the right or the left eye, and ophthalmologic follow-up was planned. Treatment was initiated with oral colchicine 1.5 mg/day and topical corticosteroid for oral aphthous lesions. At one month of colchicine therapy, the patient was reevaluated, and complete disappearance of the erythema nodosum-like lesion and decreased severity of oral lesions was detected, and she was stable ophthalmologically. Now, she is in the second month of therapy and still under follow-up. The patient gave informed consent for the publication of this report.

DISCUSSION

BD has an unknown etiology, but an autoimmune reaction triggered by an infectious or environmental agent (possibly local to a geographic region) in a genetically predisposed individual seems most likely. The higher prevalence of the disease in countries located on the ancient Silk Route may suggest an unknown genetically determined factor, spread via the migration of old nomadic tribes. It is most common in Turkey, where the reported prevalence ranges from 80/100.000 to 370/100.000.[3] The other highest prevalence rates were reported in Iran, Iraq, India, and Japan. Interestingly, these regions lie between latitudes 30° and 45° north, and the disease is rarely encountered in further north, the Americas, and Australasia.[4] A relationship between HLA-B5 and BD was confirmed in several studies from Middle Eastern and Mediterranean countries, but not in patients from the US and UK.[5,6] The frequency of HLA-B51, one of the split antigens of HLA-B5, was also increased in BD patients, for example 54% in cases from Turkey.[7] Unfortunately, we were not able to study the HLA-B51, due to the inadequate laboratory conditions of our hospital. On the other hand, it is still unclear whether HLA-B51 is involved directly in the pathogenesis or is associated with the disease only because of linkage disequilibrium with a nearby gene, a notion supported by the knowledge that BD still arises in the absence of HLA-B51 alleles. In addition, an association between BD and alleles in the tumor necrosis factor (TNF) promotor region was first reported in Japan in 1992 and was confirmed in patients from the Middle East.[8,9] Significant neutrophilic infiltration is present in all early lesions of BD. Additionally, serum levels of neutrophil priming cytokines such as TNF, interleukin-1β (IL-1β) and IL-8 are known to be raised and myeloperoxidase levels, generated by active neutrophils, are also high. Whether the neutrophilic hyperactivity in BD reflects genetic influences or persistent activation by external priming agent(s) remains unresolved, although data from studies on familial Mediterranean fever (FMF), which shares similar features with BD and is encountered in similar geographic regions, suggest that neutrophilic responses are indeed under genetic control. The gene associated with FMF (MEFV) codes for a protein called pyrin, which is thought to be involved in the regulation of neutrophilic functions in the inflammatory responses. Four mutations of the MEFV gene were shown to be more prevalent in patients with BD, suggesting that the MEFV mutations may act as susceptibility factors for BD.[10] Moreover, MEFV mutations present in the Middle East have never been reported in

Japan, which may explain why amyloidosis of BD follows the same geographical pattern.[11]

Since abnormally activated neutrophils were recognized in the pathogenesis of BD, colchicine has been widely used as a basic drug for treatment, based on the claim that colchicine exerts beneficial effects through inhibition of neutrophilic functions. The results of a 2-year randomized, double-blind, placebo-controlled study demonstrated that colchicine significantly reduced arthritis in both female and male patients, whereas it reduced genital ulcers and erythema nodosum only in female patients.[12] Similarly, the erythema nodosum-like lesion of the female patient totally improved with colchicine therapy in a period of 1 month, here. Our case did not have genital ulcerations, and we primarily initiated the colchicine therapy to relieve severity of oral aphthous lesions. However, if a neutrophilic hyperactivity is responsible for the lesions and colchicine shows beneficial effects on inhibition of neutrophilic functions in the BD, it is also possible that colchicine acts on all lesions of the disease at least to some extent.

Ocular involvement is the most significant cause of morbidity in the disease, since it may lead to blindness in about 5 years if not treated. Inflammatory eye diseases occur approximately in 70% of patients, and common ocular manifestations include uveitis, bilateral swelling of the optic nerve head, retinal vasculitis, and bilateral lamellar macular hole. Clinical retinal vascular occlusions are rare and a limited number of cases were reported. On the other hand, venous thrombosis appears to be the major vascular involvement in 7-33% of patients with BD, and represents 85-93% of all vasculo-BD's.[13] Although deep vein thrombosis (DVT) is common, pulmonary embolism is rare, since the thrombi in the inflamed veins of the lower extremities are strongly adherent. Thrombosis of the inferior vena cava and hepatic veins may cause Budd-Chiari syndrome. Thrombosis of the superior vena cava is also common and is often accompanied by thrombosis of other mediastinal veins. Intracardiac thrombosis was also described, which is mostly right sided. Systemic arterial manifestations of the disease are infrequent compared to venous involvement accounting for only 12% of all vascular complications.[14] They include arterial occlusion and aneurysm formation. BD is the most common cause of pulmonary artery aneurysm, in which the underlying process is inflammation of the vasa vasorum of the tunica media, causing destruction of the elastic fibers and dilation of the vessel lumen. It was therefore suggested that arterial involvement in vasculo-BD might be caused by neutrophilic vasculitis targeting the vasa vasorum. Aneurysms of the aortic arch and subclavian and coronary arteries have also been described. In 1994, a point mutation in the factor V gene on chromosome 1 was discovered in Leiden, Holland (the Leiden mutation) and is now recognized as the most common hereditary abnormality of the clotting system. The factor V-Leiden mutation is a well-known cause of activated protein C resistance that results in a propensity for thrombosis. While Lesprit et al found no evidence for this propensity, Gul et al showed that it was present in 38% of Behçet's patients with DVT, compared with 9% of Behçet's patients without DVT.[15,16] Afterwards, the mutation was associated with ocular disease, particularly with vaso-occlusion.[17] However, the vascular thrombosis of BD could not be explained by protein C, protein S, or antithrombin III deficiency or resistance to activated protein C, with or without factor V Leiden mutation, or elevated anticardiolipin antibody levels, and fibrinolysis despite increased thrombin generation, and thrombomodulin.[18] This suggests that the thrombophilia of BD is related to inflammation rather than clotting disorders.

Cutaneous involvements of BD are frequent and show geographic differences. The most frequent involvement types are papulo-pustular and erythema nodosum-like lesions. The papulo-pustular lesions are sterile folliculitis or acne-like lesions on an erythematous base, which initially manifest as papules and evolve into pustules within 24 to 48 hours. They usually arise simultaneously, and most frequently on the skin of the back, face, and chest. They are histopathologically characterized by lymphocytic vasculitis. On the other hand, the erythema nodosum-like lesions are mostly ob-

served on the lower extremities and are characterized by painful purplish nodules. The nodules are surrounded by a peripheral halo and they do not ulcerate and they resolve spontaneously, leaving areas of hyperpigmentation. The histopathology of the erythema nodosum-like lesions, as in our case, shows a focal small-vessel vasculitis and perivascular lymphocytic infiltrate, particularly involving the venules, with panniculitis. Other cutaneous lesions, such as necrotic folliculitis and aphthosis, may also be present in BD, but to a lesser extent.

A non-specific hyperactivity reaction in response to minor cutaneous trauma is observed in the course of the disease and is known as the pathergy phenomenon. Again, there is geographic variation in the frequency of the reaction and it is the highest in regions of the ancient Silk Route and decreases sharply outside these regions. As expected, it was positive in our case. In a positive test, pricking of the skin with a sterile needle with or without injection of a small amount of saline, gives rise to a 1- to 2-mm papule, usually surrounded by an erythematous halo, which transforms into a 1- to 5-mm pustule. The pustule becomes prominent after 24-hours, becomes maximum in size after 48-hours, and disappears within 4-5 days. The phenomenon is usually positive during the active phase and becomes negative or weakly positive when the disease relapses. The variable association of the pathergy test positivity with BD and its occurrence among healthy subjects hinder its use as a screening test.

In conclusion, physicians should be aware of the BD in vascular occlusions or aneurysms, especially in venous occlusions, particularly in areas in which the BD is frequent.

REFERENCES

1. Koç Y, Güllü I, Akpek G, Akpolat T, Kansu E, Kiraz S, et al. Vascular involvement in Behçet's disease. J Rheumatol 1992;19:402-10.
2. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. Lancet 1990;335:1078-80.
3. Tüzün Y, Yurdakul S, Cem Mat M, Ozyazgan Y, Hamuryudan V, Tüzün B, et al. Epidemiology of Behçet's syndrome in Turkey. Int J Dermatol 1996;35:618-20.
4. Verity DH, Marr JE, Ohno S, Wallace GR, Stanford MR. Behçet's disease, the Silk Road and HLA-B51: historical and geographical perspectives. Tissue Antigens 1999;54:213-20.
5. Davatchi F, Shahram F, Akbarian M. Behcet's disease: analysis of 3443 cases. APLAR J Rheumatol 1997;1:2-5.
6. Bird Stewart JA. Bird Stewart JA. Genetic analysis of families of patients with Behçet's syndrome: data incompatible with autosomal recessive inheritance. Ann Rheum Dis 1986;45:265-8.
7. Kaya Tl, Dur H, Tursen U, Gurler A. Association of class I HLA antigens with the clinical manifestations of Turkish patients with Behçet's disease. Clin Exp Dermatol 2002;27:498-501.
8. Mizuki N, Inoko H, Sugimura K, Nishimura K, Nakamura S, Tanaka H, et al. RFLP analysis in the TNF-beta gene and the susceptibility to alloreactive NK cells in Behçet's disease. Invest Ophthalmol Vis Sci 1992;33: 3084-90.
9. Verity DH, Wallace GR, Vaughan RW, Kondeatis E, Madanat W, Zureikat H, et al. HLA and tumour necrosis factor (TNF) polymorphisms in ocular Behçet's disease. Tissue Antigens 1999;54:264-72.
10. Touitou I, Magne X, Molinari N, Navarro A, Quellec AL, Picco P, et al. MEFV mutations in Behçet's disease. Hum Mutat 2000;16:271-2.
11. Akpolat T, Yilmaz E, Akpolat I, Dilek M, Karagoz F, Balci B, Ozen S. Amyloidosis in Behçet's disease and familial Mediterranean fever. Rheumatology (Oxford) 2002;41:592-3.
12. Yurdakul S, Mat C, Tüzün Y, Ozyazgan Y, Hamuryudan V, Uysal O, et al. A double-blind trial of colchicine in Behçet's syndrome. Arthritis Rheum 2001;44:2686-92.
13. Witowski J, Pawlaczyk K, Breborowicz A, Scheuren A, Kuzlan-Pawlaczyk M, Wisniewska J, et al. IL-17 stimulates intraperitoneal neutrophil infiltration through the release of GRO alpha chemokine from mesothelial cells. J Immunol. 2000;165: 5814-21.
14. Erkan F, Gül A, Tasali E. Pulmonary manifestations of Behçet's disease. Thorax 2001;56:572-8.
15. Lesprit P, Wechsler B, Piette JC, Du-Boutin LT, Godeau P, Alhenc-Gelas M, et al. Activated protein C resistance caused by factor V Arg 506-->Gln mutation has no role in thrombotic manifestations of Behçet's disease. Ann Rheum Dis 1995;54:860.
16. Gül A, Ozbek U, Oztürk C, Inanç M, Koniçe M, Ozçelik T. Coagulation factor V gene mutation increases the risk of venous thrombosis in behçet's disease. Br J Rheumatol 1996;35:1178-80.
17. Verity DH, Vaughan RW, Madanat W, Kondeatis E, Zureikat H, Fayyad F, et al. Factor V Leiden mutation is associated with ocular involvement in Behçet disease. Am J Ophthalmol 1999;128:352-6.
18. Espinosa G, Font J, Tàssies D, Vidaller A, Deulofeu R, López-Soto A, et al. Vascular involvement in Behçet's disease: relation with thrombophilic factors, coagulation activation, and thrombomodulin. Am J Med 2002;112:37-43.