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Review

Behçet's disease: A Narrative Review of Clinical Diagnosis and Treatment

Behçet Hastalığı: Klinik bulgular, Tanı ve Tedavi

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ABSTRACT

Behçet's disease is characterized with recurrent attacks of inflammation that are driven by systemic vasculitis without any clearly demonstrated triggering mechanism. It is more prevalent in the World region so-called "silk road", including Turkey, Iran, Korea, China, Saudi Arabia, and Japan. Involvement of any kind of vessels is possible during the course of the Behçet's disease. Common symptoms of the disease include aphthous oral ulcers, genital ulcers, arthritis, cutaneous lesions, gastrointestinal involvement, and neurologic lesions. In this article, we aimed to present the clinical findings, diagnosis, and treatment options of Behçet's disease and review of the current literature data.

Keywords: Behçet's disease, inflammation, vasculitis

ÖZ

Behçet hastalığı açık bir tetikleyici mekanizmanın gösterilemediği, sistemik bir vaskülitle karakterize, rekürren inflamasyon atakları görülen bir hastalıktır. Tarihi Ipek yolu çevresindeki ülkelerde; Türkiye, İran, Kore, Çin, Suudi Arabistan ve Japonya'da daha yaygındır. Behçet hastalığında hemen her boyut ve tipte damarın tutulması mümkündür. Hastalığın en sık semptom ve bulguları arasında oral aftöz lezyonlar, genital ülserler, artrit, kutanöz lezyonlar, gastrointestinal tutulum ve nörolojik lezyonlar yer almaktadır. Bu makalede, Behçet hastalığının klinik bulgularını, tanı ve tedavi seçeneklerini sunmayı ve güncel literatürü gözden geçirmeyi amaçladık.

Anahtar kelimeler: Behçet hastalığı, inflamasyon, vaskülit

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INTRODUCTION

Behçet's disease (BD) as described by Hulusi Behçet, a Turkish dermatologist, is more prevalent in the World so-called "Silk Road", including Turkey, Iran, Korea, China, Saudi Arabia, and Japan (1). The general prevalence of the disease has been reported between 350 to 6000 per million of the population (2,3). It is more common among men aged 20 to 40 years whose origins are in the Mediterranean region and among women from Northern Europe (1). However, there are also opposing studies in the literature that reported higher prevalence in women compared to men (2-4).

Recurrent acute attacks of inflammation that are characterized by systemic vasculitis with obscure triggering factors are the hallmark of the disease. Since any kind of vessel might be involved, the vasculitis of Behçet's disease may involve almost every part of the body that has a vascular supply (5). The disease is characterized by a chronic course of relapses that include oral aphthous ulcers, genital ulcers, arthritis, cutaneous, gastrointestinal, and neurologic lesions (6). The most common symptoms of BD are genital and oral ulcers, which are usually the initial manifestations (7,8).

In this review, we aimed to review the clinical findings, diagnosis, and treatment options of BD in the light of literature data.

Clinical Findings of BD

Oral ulcer is the most common clinical manifestation of BD, which is seen in almost all patients. It is the initial symptom in most (about 80%) of the cases (9). The ulcers are similar to those seen in common oral aphthous lesions but they are often multiple and extensive. Oral ulcers can be as painful as to cause difficulty in eating. They are round to oval and their size varies from a few to 20 mm. Oral ulcers less than 10 mm are called minor aphthous and those equal to or larger than 1 cm are called major aphthous ulcers. Moreover, according to the arrangement of the lesions, another form of oral ulcer is described and is called herpetiform ulcers (9,10). Oral lesions usually heal within 1 to 2 weeks but major aphthous ulcers may persist longer and may heal with scarring (9). The occurrence rate of oral ulcers tends to decrease after 20 years from disease manifestation (11).

Genital ulcers are seen in 60–90% of subjects with Behçet's disease (12). They are usually painful lesions that look like oral ulcers (13). However, they have a lower recurrence and higher scar formation rate as compared to oral lesions (14). These ulcers are very specific lesions for BD and occur about every three of the four cases. The lesions most commonly involve the scrotum, glans, shaft of the penis and vulvae and may persist as long as 10 days to one month (15). Deep genital lesions may induce the formation of fistulas, especially in women (16). Other than urethritis, genitourinary manifestations include salpingitis, epididymitis, and varicocele (17).

Cutaneous lesions of BD include acneiform lesions, erythema nodosum, papulovesicular or pustular eruptions, and pyoderma gangrenosum like rashes, and thrombophlebitis. Acneiform lesions look like typical acne and are more common in subjects with arthritis (18). Vasculitis is a common finding of up to one-half of the biopsies obtained from patients with erythema nodosum (19). Local sterile skin injury response associated with the erythematous papulopustular lesion is called pathergy positivity. The skin reaction occurs in pathergy-positive patients 48 hours after a sterile needle prick of the skin. Pathergy positivity is more common in the areas where the incidence of BD is high (20).

Ocular lesions develop in 1 to 3 of every 4 patients with BD and can be devastating if left untreated. It is more prominent in men, about 3 quarters of men have ocular lesions. A recent study concluded that ocular involvement was associated with HLA B51 expression in BD patients from Middle and Far East Asia (21). These lesions are important in the diagnosis of BD since they are also helpful in establishing diagnosis earlier; before the development of other symptoms (22). A common ocular lesion is uveitis which usually affects both sides and leads a course with relapses. Uveitis is often in the form

of panuveitis that is characterized by the involvement of the whole uvea. Hypopyon is also associated with retinal vasculitis and is characterized by pus in the anterior chamber of the eye (23). The rate of hypopyon in BD is about 1/5. Other ocular manifestations of BD include; neovascularization, occlusion of the ocular vessels, conjunctival ulceration, macular edema, retinal vasculitis, posterior uveitis, and optic neuritis (24,25). The incidence of central nervous system lesions (so-called neuro-Behçet's) is higher in BD patients with optic neuritis compared to those without optic neuritis (26).

Vascular involvement in BD is mainly due to vasculitis or vascular occlusions. It is more common among males compared to female subjects (16). In the course of BD, both venous and arterial vessels of all sizes could be affected, however, venous disease is more common than arterial disease in BD. The rate of vascular involvement in BD was reported as 14%, which consists of arterial occlusion in 4%, superficial venous thrombosis in 53%, and deep venous thrombosis in 30% of the cases (27). The risk of venous disease is fourteen times higher in BD patients compared to the healthy population (28). Venous involvement in BD may include obstruction in both superior and inferior vena cava, hepatic venous thrombosis (Budd-Chiari syndrome), thrombosis of cranial dural sinus, and thrombosis of the deep and superficial veins of the legs. Bayraktar et al reported that about 11% of BD patients had developed hepatic vascular thrombosis, including, vena cava inferior obstruction in 1.6%, both inferior and superior vena cava obstruction in 0.8%, and hepatic venous occlusion in 3% of the cases (29). Post-thrombophlebitis syndrome can accompany BD in cases with relapsing obstruction of leg veins (30). Pulmonary artery aneurysm is not an uncommon finding in BD (31). However, the involvement of the pulmonary artery can also present as thrombosis (32). Vascular disease in BD has great morbidity and mortality, for instance, 23% of mortality rate has been reported for pulmonary artery aneurysm (31). BD usually causes vasculitis in small vessels, however, medium or large vasculatures may also be affected. The rate of vasculitis in large arteries is about 27% (33). Frequently affected arteries in BD include; aorta, pulmonary, carotid, iliac, femoral, and popliteal vessels (23). Renal and cerebral arteries are rarely affected. Unlike other autoimmune diseases, early onset atherosclerosis is not prominent in BD (34).

Intestinal involvement of BD, namely, entero-Behçet's disease, has various signs and symptoms, including, abdominal pain, change in defecation habitus (mostly diarrhea), and lower gastrointestinal bleeding, which are difficult to distinguish from the symptoms of inflammatory bowel diseases. On the other hand, oral ulcer is not a rare presentation in inflammatory bowel disease (IBD), hence, it should be considered before establishing the diagnosis of BD. However, about 3 of every 4 entero-Behçet patients have only mild symptoms and even remission after a few years, some patients may suffer from sustained abdominal symptoms and recurrent attacks. Patients having a high disease activity index, elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), lower age, decreased albumin at onset are more prone to develop recurrent intestinal attacks (35). Mucosal ulceration and even perforation may develop during BD. Ulcerations most likely occur on intestinal segments from ascending colon to terminal ileum (36).

Attacks of BD are associated with arthritis in about 50% of the patients. Arthritis is usually one-sided and non-erosive, so, heal without deformation. However, there are reports in the literature that BD arthritis was associated with deteriorated function (37). Greater joints in the body ie. wrist, knee, and ankle are the most affected joints. Evaluation of synovial fluid reveals inflammatory reaction in arthritis of BD (38). Despite arthritis is monoarticular in about 33% of the patients with BD, more than one joint can be affected in the remaining cases.

Pulmonary involvement in BD is characterized by reduced lung volume in radiologic studies, reticulonodular opacities in the lung parenchyma, as well as vascular pulmonary pathologies.

Pulmonary artery aneurysm, venous and arterial thrombosis, pulmonary infarction, pleurisy and recurrent pneumonia are the major forms of pulmonary involvement (39).

The rate of neurological involvement in BD is about 1 in every 10 cases and more prevalent in male patients (40,41). Neuro-Behçet 's disease is characterized by either parenchymal lesions, non-parenchymal lesions, or both (9). Neuro-Behçet's disease can be classified as acute or chronic depending on the manifestations of its clinical course. Elevated cell count in cerebrospinal fluid analysis and fever suggest acute neuro-Behçet's disease while, cerebral and brainstem changes in radiologic studies, difficulty in sphincter control, mental confusion, and cerebellar ataxia are suggestive of the chronic neuro-Behçet syndrome (42). The neurologic disease usually occurs 5 or 6 years after the establishment of the diagnosis of BD (43). Neurologic involvement can manifest itself as brainstem involvement, myelopathy, paresis, sensory loss, epileptic seizures, cognitive dysfunctions, optic neuropathies, cerebral involvement, difficulty in motor functions (e.g. dysphagia), cerebral venous or arterial thrombosis, peripheral neuropathies, pseudotumor cerebri and vascular dissection and aneurysms. However, it may occur during BD, peripheral neuropathy is a rare entity in neuro-Behçet cases (44). Brainstem involvement in BD may present with pyramidal symptoms, cranial neuropathies, ophthalmoparesis and symptoms of cerebellar dysfunction. Thrombosis in cerebral veins may induce headache, paralysis of nervus abducens, increased pressure of the cerebrospinal fluid and pupil edema (16,45). On the other hand, thrombosis of cerebral arteries may rarely accompany neuro-Behçet's disease (46). Patients with posterior uveitis are more likely to develop parenchymal neurological involvement compared to those without posterior uveitis (47).

Impairment in hearing is reported to be associated with BD. A recent study found that more than 60% of BD patients experience sensorineural hearing loss, which was more prevalent in subjects with arthritis (48).

Renal involvement of BD is characterized by hematuria, proteinuria, and mild to end-stage renal insufficiency. Renal disease in BD is not as serious nor as prevalent as the renal involvement that is seen other types of autoimmune vasculitic syndromes. Advanced kidney disease is extremely rare, such as glomerulonephritis that has an incidence of 0.2%, although about 1 of every 10 cases develop hematuria or proteinuria (49). Other types of renal involvement include renal vascular diseases, secondary amyloidosis, and interstitial nephritis. The mean duration between diagnosis of BD and development of amyloidosis ranges between 3 to 15 years (50).

Establishment of the Diagnosis in BD

The diagnosis of BD is based on clinical manifestations because there are no hallmark tests for BD. Oral aphthous ulcers and together with characteristic clinical findings of BD are required for the diagnosis of the disease. However, oral ulceration is common in the general population. Uveitis with hypopyon, retinal vasculitis, neuro-Behçet findings, vascular involvement; especially aneurysm of pulmonary arteries, thrombosis of hepatic or cerebral veins, and positive pathergy test strongly suggest the diagnosis of BD. Genital lesions have greater specificity but lower sensitivity than oral aphthous ulcers in establishing the diagnosis. Patients from the countries around Silk-Road with above-mentioned signs and symptoms are more likely to have this syndrome (51). According to the criteria of the International Study Group for BD, oral ulcers relapsing at least three times a year, and presence of at least two of the following criteria are required for BD diagnosis: ulcers or scars in genitalia, eye lesions specific to BD, skin involvement (e.g. acneiform lesions, erythema nodosum) and pathergy test positivity (52). Since pathergy positivity is uncommon in Europe and America, neuro-Behçet signs, entero-Behçet findings, joint involvement and arteritis have been suggested to be diagnostic criteria instead of pathergy-positivity (53). Establishing the diagnosis is difficult in patients with other clinical findings of BD that do not meet these diagnostic criteria, however, BD could still a possible diagnosis in such a population, thus these patients should be referred to an experienced rheumatology center.

Diagnostic criteria of the International Study Group for BD have 95% sensitivity and 97% specificity in establishing the diagnosis in BD patients (53).

Since the clinical spectrum of BD is very wide, the differential diagnosis list is also huge and differs according to the patients' clinical findings (54). Oral ulcers are also seen in Crohn's Disease, Reiter Syndrome, Systemic Lupus Erythematosus, gluten-sensitive enteropathy, hyper immunoglobulin-D syndrome, undernutrition, viral infections, dental prosthetic problems, patients receiving chemotherapy, pemphigus, and recurrent oral aphthous stomatitis. Differential diagnosis of Behçet's genital lesions is very wide. For instance, these ulcers are also seen in syphilis, lymphogranuloma venerum, chancroid, and granuloma Inguinale (55). In the differential diagnosis of genital ulcers in BD viral infections; such as Herpes Simplex virus, Human Immunodeficiency Virus (HIV) and Epstein Barr Virus (EBV), drug eruptions, erythema multiforme (56). Uveitis is also seen in inflammatory bowel diseases (IBDs) and spondyloarthropathies; e.g., Ankylosing Spondylitis should be also considered. Non-erosive arthritis of BD can also be seen in systemic lupus erythematosus, inflammatory bowel diseases, sarcoidosis, systemic vasculitis, Reiter's syndrome and psoriatic arthritis.

Gastrointestinal symptoms and signs of BD can be mimicked by inflammatory bowel diseases.

Treatment of BD

There is a variety of therapeutic approaches according to the clinical manifestations of BD. Targets of BD treatment are remission of the active disease, suppression of exacerbations and permanent disabilities in mucous membranes, skin, eye and joints, and enhancement of life quality (57). Inflammation should be ameliorated and serious clinical signs and symptoms; such as mucocutaneous lesions and arthritis, should be treated with potent anti-inflammatory medications (58).

For oral aphthous ulcers in BD, maintenance of hygiene is advised including daily oral rinsing, decreasing consumption of acidic or salty food, using topical steroids and silver nitrate (59). Moreover, systemic therapy with colchicine with or without corticosteroids, azathioprine may be needed in cases that are resistant to standard treatment.

The most commonly used drug in BD is colchicine, which arrests the chemotaxis of neutrophils (polymorphonuclear leukocytes) (59). It has beneficial effects in the treatment of oral lesions, erythema nodosum and articular involvement in BD. For this purpose, recommended daily dosage schedule of treatment by colchicine is twice or three times of 0,6 to 1 mg (60). It is generally a well-tolerated drug with minimal undesirable effects; such as gastrointestinal discomfort (58).

Topical corticosteroids are useful in the treatment of genital and oral lesions. Similarly, mild ocular disease in anterior segments of the eye can be treated with topical ophthalmic steroids (61). However, life-threatening complications of BD should be treated with high doses of systemic corticosteroids (1g daily for three days followed by 1 mg per bodyweight, daily). These conditions include involvement of posterior segments of the eye, neuro-Behçet, entero-Behçet and serious organ or life-threatening vascular involvement (57).

Since dapsone antagonizes leukotriene-4 (an inflammatory cytokine), it also obviates chemotaxis and adhesion of neutrophils and neutralizes the effects of their oxygen products. It may be beneficial in the salvage of the tissues from auto-inflammatory damage (62,63).

As a potent immune-suppressor agent, cyclosporine A has a limited indication in BD in ocular disease, because of it's side effects (57,64). Azathioprine is also suggested in the treatment of ocular disease in BD (65). Additionally, it ameliorates the arthritis, genital lesions, gastrointestinal involvement and vascular thromboses (58,64,66).

Cyclophosphamide is usually used in neurological complications in Behçet and serious vascular

diseases (57,58,65). Methotrexate, another antimetabolite and antineoplastic agent, is indicated in neurologic involvement and ophthalmic manifestations in BD (67).

Oral ulcers, genital lesions and gastrointestinal involvement benefit from thalidomide treatment (63).

Biologic agents, such as rituximab, gevokizumab, anakinra and canakimumab have been reported in case presentations as drugs to be used in the treatment of BD (57,66,68-71). Adalimumab is suggested in the treatment of uveitis as initial daily doses of 80 mg followed by 40 mg every two weeks (72).

Venous thrombosis in BD may require treatment with anticoagulating agents, however, this is a controversial issue. Since vascular thrombus is strictly adherent to the inflamed endothelial wall in BD, pulmonary thromboembolism usually occurs from local thrombi in pulmonary vessels, rather than embolism from other thrombotic vessels (39). On the other hand, response to anti-inflammatory therapy is better than the response to anticoagulation (73). Patients with BD show deteriorated lysis of fibrin along with increased reactive oxygen species production by neutrophils (74). Serious thrombotic events, such as, dural sinus thrombosis, may require anticoagulation, however, this is controversial since its benefits are not clear and the risk of bleeding may be increased with this treatment especially in subjects with aneurysms (75,76).

There is no consensus regarding the duration of the treatment in Behçet's disease. Individualized treatment according to age and gender of the patient and severity and the type of the organ involvement is recommended. However, 18-24 months of therapy is usually advised in severe cases. Yet, some patients may require sustained immunosuppressive treatment (77).

CONCLUSION

Behçet's disease is a chronic condition characterized with a variable clinical course with exacerbations and remissions. Ocular, vascular and neurologic involvement of BD are responsible of the most of the disease related morbidity and mortality. Mucocutaneous, ocular and articular involvement ameliorate by time in BD. Severity of the disease is variable but is more severe in men patients from Middle East and Far East of Asia. Glucocorticoids and other ımmunsuppressive drugs are the hallmarks of the treatment of BD.

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