Behçet's Disease

Behçet Hastalığı

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ABSTRACT

Behçet's Disease (BD) was first described by Hulusi Behçet in 1937 as a disease characterized by recurrent aphthous ulceration in the mouth and genital area and hypopyon iridocyclitis. Diagnostic criteria developed by the International Working Group in 1990 were generally accepted among dermatologists. BD usually begins with oral ulcers, and the development of other systemic manifestations last for years. The disease often starts in the second and third decades, but a period of 1-8 years is required for a full clinical picture to be completed. Mucocutaneous findings are the most common manifestations during the course of BD. BD begins with mucocutaneous lesions in 70-95% of the patients. Despite the possibility to affect almost all systems, the disease is often accompanied by mucocutaneous findings. BD is a chronic, multisystemic disease that shows remissions and exacerbations during the course of the disease. In the last two decades, great progress has been made in the treatment of mucocutaneous and ocular involvement of BD. On the other hand, CNS involvement, treatment of thrombosis and arterial aneurysms of major vessels remains a problem. In this article knowledge about etiology and clinical features, has been reviewed.

Key Words: Behçet's Diseaese, therapy, etiopathogenesis, clinical features

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ÖZET

Behçet Hastalığı (BD) ilk kez 1937'de Hulusi Behçet tarafından ağız ve genital bölgede tekrarlayan ülserler ve hipopiyonlu iridosiklit ile karakterize bir hastalık olarak tanımlandı. 1990'da Uluslararası Çalışma Grubu tarafından geliştirilen tanı kriterleri genel olarak dermatologlar arasında yaygın olarak kullanılmaktadır. BH genellikle oral ülserlerle başlar ve diğer sistemik belirtilerin gelişimi yıllarca sürer. Hastalık sıklıkla ikinci ve üçüncü dekatta başlar, ancak tam bir klinik tablonun tamamlanması için 1-8 yıl arası bir süre gerekir. Mukokutanöz bulgular BH seyrinde en sık görülen bulgulardır. BH, hastaların % 70-95'inde mukokutanöz lezyonlarla başlar. Neredeyse tüm sistemleri etkileme ihtimaline rağmen, hastalığa sıklıkla mukokutanöz bulgular eşlik eder. BH, hastalık süresince remisyonları ve alevlenmeleri gösteren kronik multisistemik bir hastalıktır. Son yirmi yılda, BH'nin mukokutanöz ve oküler tutulumunun tedavisinde büyük ilerleme kaydedilmiştir. Öte yandan, santral sinir sistemi tutulumu, tromboz tedavisi ve major damarların arter anevrizmaları bir problem olmaya devam etmektedir. Bu yazıda etiyoloji ve klinik özellikler hakkındaki bilgiler gözden geçirilmiştir

Anahtar Sözcükler: Behçet Hastalığı, tedavi, etyopatogenez, klinik özellikler

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INTRODUCTION

Behçet's Disease (BD) was first described by Hulusi Behçet in 1937 as a disease characterized by recurrent aphthous ulceration in the mouth and genital area and hypopyon iridocyclitis (1).

BD refers to a single clinical entity that has its own clinical findings and can be pre-screened by different clinical indications in different regions of the world. Behçet's Syndrome is the name given to the coexistence of certain findings, which is preferred by those who think that the disease does not express a single disease state and that the etiopathogenesis is unknown (2-5). Besides the impact of the disease on quality of life of the sufferers, the disease causes considerable economic burden for the health care system in countries where the disease occurs endemically (6).

History

It is known that Hippocrates B.C. in the fifth century attempted to identify the possible association between ulceration in the oral mucosa and genital area and inflammation in the eye. Blüthe in 1908, Planner and Remenovsky in 1923, and Shigeta in 1924 reported clinical trials similar to the triple symptoms of BD. However, all suggested that these symptoms may be coincidentally seen or may be related to infections such as tuberculosis, syphilis, and staphylococcal infection (2-3). Hulusi Behçet, after describing the symptoms of three patients whom he had followed up for 21, 7, and 3 years, respectively, decided that all findings were cardinal symptoms of a separate entity and united them under a new disease framework (1-3). He described the issue in a meeting in 1936, published his observations in "Archieves of Dermatology and Veneral Diseases and presented again at a dermatology meeting in Paris in 1937 (1). Oral and genital ulcers were named as "Morbus Behçet" in 1947 upon the request of Prof Mischner of the Zurich Faculty of Medicine at the International Congress of Medicine in Geneva with the approval of the participants (1-6).

Epidemiology

The prevalence of the disease is high in Far East countries, Eastern Mediterranean countries and Japan on the historical Silk road (7). The country with the highest prevalence rate of 80-370 /100.000 is Turkey (8,9). The prevalence in Japan, Korea, China, Iran and Saudi Arabia is 13.5-20/100.000 while it is lower in the western countries, 0.64/100.000 in the UK and 0.12-0.33/100.000 in the United States (7-9).

The disease is mainly seen in adults aged 20-40 years (7,9-12). The age of onset is the same in both sexes (10,13). It is unlikely to be seen in children and in patients over 50 years of age, but there are also cases in the literature beginning in the first months of life and beginning at age 72 (14). Family history is more prominent in early onset cases. In the Middle East, familial occurence rates are 10-15% (9).

The disease is more common in males and the ratio of males to females is generally 3/2 (7,10-12). It is indicated that both sexes are held in equal proportions when all the symptoms of the disease are considered while some symptoms hold more specific genders (15).

Etiopathogenesis

Currently, there is no single theory that explains the etiopathogenesis of the disease. In this section, all factors considered to be involved in the etiopathogenesis of the disease are briefly addressed.

Genetic theory

BD is more prevalent in certain ethnic groups and geographies, and the presence of familial cases suggests that the susceptibility to disease is regulated by some genes. Despite the presence of familial cases, the disease does not show a Mendelian type of inheritance (16,17).

The association between BD and Human Leucocyte Antigen (HLA)-B5 was described in 1973 (18). The development of BD is thought to be strongly related to the HLA-B5 group, especially with the HLA-B51 allele (3). The incidence of HLA-B51 positivity varies between 50% and 80%, is high in places with a high prevalence of BD, such as far eastern countries and Eastern Mediterranean countries, and in familial cases (9,10,17,19,20). This ratio is about 20% in healthy individuals. In recent years, the role of genes coding for tumor necrozing factor (TNF) and genes encoding MHC class 1 chain related gene (MICA) genes, transporter associated with antigen processing-2 (TAP-2) IL-1 genes, Factor V gene, ICAM-1 gene, ENOS gene and Killer inhibitor receptor (KIR) gene has been emphasized (17,20-23).

Infectious theory (Viral agents, bacterial agents, heat shock proteins (HSP))

The more frequent occurrence of the disease in crowded communities with low socioeconomic level and the presence of familial cases suggest that microbial agents may play a role in etiopathogenesis of BD (7,23-27).

Many researchers including Hulusi Behçet have suggested that the disease is caused by viruses (1,7,17,20). The detection of HSV-1-specific immune complexes in circulation (17), decreased response to HSV-1 stimulation of CD4 and CD8 cells, decreased sensitivity of HSV-1 antibody to polymorphism(13,17,21), the detection of high levels of HSV-1 DNA by PCR in saliva samples, the occurrence of a BD-like picture by HSV inoculation, the identification of homology between ribonucleic acids and HSV-1 DNA are among the evidence supporting the viral theory (7,17).

In BD patients, the amount of streptococci sangius in oral flora and circulating antibody titers were higher when compared to healthy subjects, and skin hypersensitivity against streptococci sangius was also detected (20,24). In addition, when patient lymphocytes are incubated with these streptococcal antigens, they secrete lymphokines that stimulate neutrophil function (7,9,17). HSP60 peptides were found in skin, in leukocytes and in the oral mucosa of patients with BD. 65 kD HSP are first detected in mycobacteria but also in Gr (-) and Gr (+) bacteria. Peptides of HSP60 in BD show high homology with bacterial HSP60/65 (9,20,21). The possibly to a cross reaction with host tissues also link the etiopathologic theroies such as autoimmunity, cross-linking between microbial and oral mucosal antigens, HSV infection affecting the immune response and the role of certain streptococcal infections in the etiopathogenesis of BD. These peptides also cause impairment in T cell responses (9,16,17,20,21).

Neutrophil functions

Histological evaluation shows that dense polymorphonuclear leucocyte (PMNL) infiltration occurs early in BD lesions. Neutrophil infiltration is also present in active lesions and in the pathergy reaction. Therefore, PMNL and the integrity of endothelial cell function play an important role in disease development. The cellular inflammatory response in BD is thought to be associated with an increase in neutrophil infiltration. BD studies showed that the BD neutrophils are active (7,9,17,27,28).

Endothelial Injury

Vascular changes causing vasculitis and thrombosis are important in the pathogenesis of BD. Small vessel vasculitis plays an important role in pathological mechanisms in BD (9,21). The perivascular infiltration is composed of neutrophils, T and B cells and their secretions such as TNF-α, IL-1 and IL-6 may cause endothelial damage that is observed in BD. Antibodies against endothelial cells have been suggested to interact with these cells and cause vascular damage through the release of various enzymes and cytokines. The endothelin, an endothelial cell-secreted vasoconstrictor peptide, was found to be elevated in BD with vascular involvement. Although the role of endothelial cells in inflammation is unknown, the detection of defects such as 6 keto-prostaglandin F1 production, elevation in thromboxane B2 levels, suggests the disfunctions of endothelial cells in BD (11,15,16,21,25,28).

Vascular inflammation resulting in endothelial injury, increase in plasma lipoproteins, presence of antiphospholipid antibodies, presence of factor 5 leiden mutations and protein S deficiency are involved in the development of thrombosis associated with BD (21,24,25,28).

Immunological Anomalies

The relationship with HLA antigens, the course of BD characterized with attacks, presence of active T lymphocytes in the lesions, the high levels of cytokine and the treatment responses to immunosuppressive agents suggest that immunological factors are involved in the etiopathogenesis of BD. According to this hypothesis, T lymphocytes are first cells that are collected in affected areas in BD, and are followed by neutrophil infiltration. These local changes cause the activation of circulating lymphocytes (7,16,17,20,23,30).

Many inflammatory mediators are found to be increased in BD patients. Both type 1 cytokines (IL-2, IL-12, IFN-γ) and type 2 cytokines (IL-4, IL-5, IL-6 and IL-10) of helper T cells were detected at high levels in BD patients. The cytokine profile shifts towards TH1 in active BD. These cytokines are thought to cause neutrophil infiltration resulting in acute inflammatory tissue damage in lesions. In recent years, the increase in γδ-T cells has been emphasized. HSP or MICA gene products induced by microbial or other stress factors induce γδ-T cells, resulting in the release of different chemokines. The role of these cells in BD is not fully understood, but is thought to potentialize cellular and humoral immune responses (7,16,17,30).

BD has polyclonal B cell activation which may be caused by excessive secretion of cytokines such as IL-1, IL-6, and IL-10 that cause suppressor T cell dysfunction or B cell activation, additionally, immunocomplexes formed by this activation may cause tissue damage by increasing neutrophil functions (23,30).

Hormonal Factors

In some studies, estrogen has been shown to suppress proinflammatory functions of vascular endothelial cells and neutrophils, may explain the milder course of BD in women (11).

Currently, the hypothesis about the pathogenesis of BD is that, in genetically susceptible individuals, infectious agents stimulate mononuclear cells and endothelial cells through heat shock proteins HSP, mediators released from active mononuclear cells and endothelial cells activate neutrophils and monocytes and cause the multisystemic inflammation of BD. As a result, BD etiopathogenesis is modeled as a systemic vasculitis pattern in which cellular and humoral immune responses change by inducing γδ-T cells induced by microbial or other stress factors HSP or MICA gene products (11,15,16).

Clinical Features

Following the first definition of BD, it has been understood that the disease is a chronic and multisystemic disease that can effect many systems with different findings in different ethnic groups (7,9,10,12,28). Manifestations of GIS are more prevalant in Japan and Europe, while joint findings are more frequently observed in Europe and the United States. Two types of the disease were defined according to clinical findings: mucocutaneous and systemic BD (11,12,16,24,31-36).

BD usually begins with oral ulcers, and the development of other systemic manifestations last for years. The disease often starts in the second and third decades, but a period of 1-8 years is required for a full clinical picture to be completed. Mucocutaneous findings are the most common manifestations during the course of BD. BD begins with mucocutaneous lesions in 70-95% of the patients. Despite the possibility to affect almost all systems, the disease is often accompanied by mucocutaneous findings (9). BD is a chronic, multisystemic disease that shows remissions and exacerbations during the course of the disease. In older ages, the activity of the disease gradually decreases, this is especially true in cases that have not ocular or CNC involvement (10,34). Despite a chronic course with severe organ involvement in varying rates, spontaneous remissions are also seen in the course of BD. Prognosis is often good in cases without neurological, ocular, and vascular involvement (9,15).

Two types of the disease were defined according to clinical findings: mucocutaneous and systemic BD.

A- Mucocutaneous Behçet's Disease

Mucocutaneous findings are the most common manifestations during the course of BD. BD begins with mucocutaneous lesions in 70-95% of the patients.

Oral Ulcers

According to the International Study Group (ISG) diagnostic criteria, oral ulcers are "must" criteria for the diagnosis. It is found in 92-100% of the patients. Recurrent oral ulcers frequently appear as the first sign of the disease. The typical lesion is a round, sharp, narrow, erythematous ulcer covered with a yellowish pseudomembrane. Oral aphtae can be so painful that it is difficult to feed. Local trauma can trigger the development of new mucosal lesions. (8-10,14,25,31,32).

A large number of oral ulcers (6 or more at the same time), a variation in lesion diameters (spectrum ranging from herpetiform ulcers to major ulcers), oropharyngeal and soft palate involvement, presence of an erythematous halo around the lesion, are features that are important in differentiation of BD oral ulcers from RAS. Oral aphthae may be the sole manifestation of the disease. For this reason, especially in the Mediterranean and Far East countries, patients with RAS should be followed up for the possibility of developing BD. In one study, 52% of cases with RAS were reported to develop BD after 7.7 years. (8-10,14,25,31,32).

Three types of oral aphtae present according to their clinical features and diameter (Fig 1): (8-10,13,25,31,32).

Minor aphthae: This is the most common type and the ulcer had a diameter of less than 1cm (often 2-6 mm). Lesions are located mostly on the lip, buccal mucosa, soft palate, ventral surface of the tongue and are located less frequently in the dorsal surface of the tongue, gingiva and hard palate. They recover within 7-10 days without scarring.

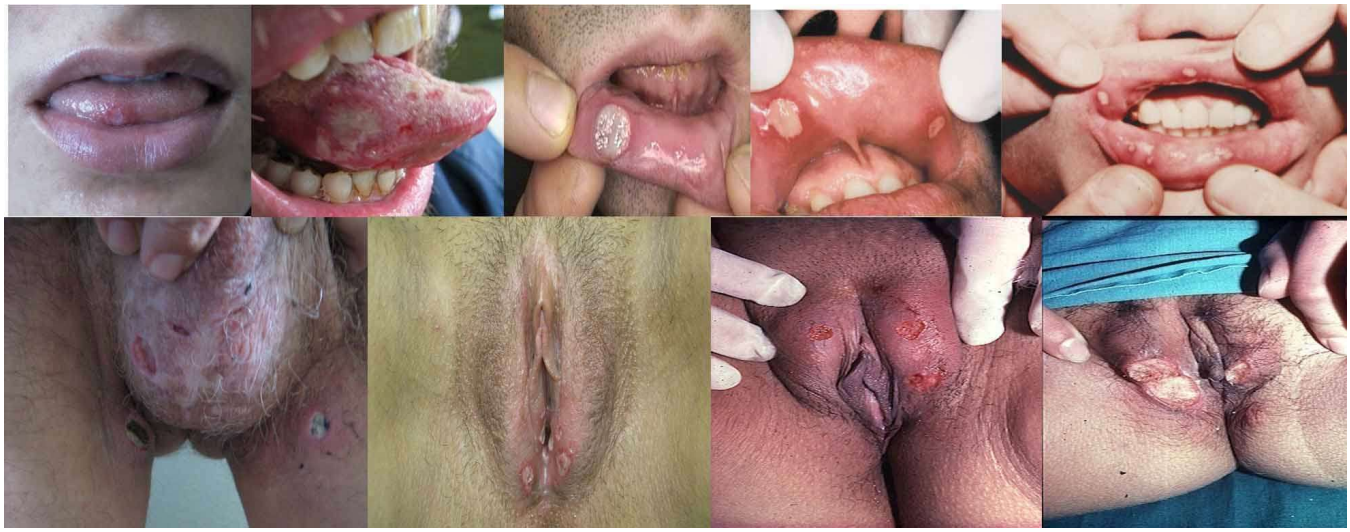

Figure 1: Oral and genital ulcers in BD.

Major aphthae: They look similar to minor ulcers. Their diameter is greater than 1cm and they heal within 10-40 days or longer, up to six weeks. They are deeper and very painful, and heal with scarring. They are usually found in small numbers and can occur anywhere in the oral mucosa.

Herpetiform aphthae: These are numerous and grouped small superficial ulcers that seated on an erythematous base. They heal without scarring.

Genital ulcers

Genital ulcers are associated with BD at 57-93%(Fig 1). They usually begin in the form of papulopustules and rapidly become ulcerated. The appearance and course of genital ulcers is similar to oral aphthae. However, they are usually more painful and less frequently repetitive. These ulcers may be accompanied by fever and regional lymphadenopathy. They may rarely be asymptomatic in women. Deeply located genital ulcers always heal with scarring as a rule. For this reason, they may cause tissue loss (in the vulva) or fistulization in the bladder, urethra and rectum (10,14,15,32)

In males, 95% of the ulcers are located in the scrotum, and less frequently in the glans penis. The most common location in women is the labia, but they may localize in the vulva, vagina, and even the cervix. In vaginal localizations, a bloody purulent discharge can be detected.

The ulcers less frequently develops on the genitocrural folds, anus, perineum and rectum in both sexes. The genital region should be checked for genital ulcer scars in cases that are suspected of BD (8,10,14,15,32).

Skin findings

BD skin specimens are extremely important and highly diverse in the diagnosis of the disease. Skin lesions are accompanied by disease at a rate of 38-99%. The most common lesions are papulopustular lesions and erythema nodosum (EN)-like lesions.

Papulopustular lesions Papulopustular lesions are characterized by folliculitis or acne-like sterile pustules located on the erythema (Fig 2). They start in the form of papules that turn into pustules within 24-48 hours. They are more common in male patients. They are localized on the back, neck, and especially on the face along the hairline. These types of lesions can develop in BD, resulting in local trauma such as shaving. It has been suggested that a biopsy confirmation is necessary for considering papulopustular lesions among the diagnostic features of BD. This is of particular importance in adolescents and in patients using corticosteroids that will also present with the same picture. Histologically, leukocytoclastic vasculitis or neutrophilic vasculitis reaction is observed. (8,15).

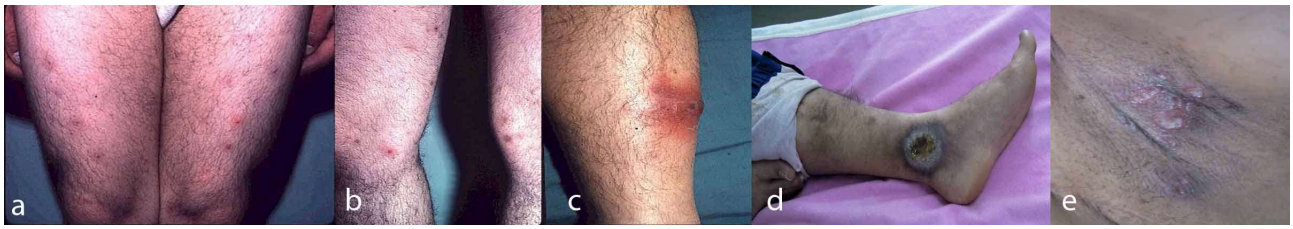

Figure 2: Skin findings in BD**. (a,b)** Papulopustular lesions **(c)** Erythema nodosum-like lesions **(d, e)** Extragenital ulcers

Erythema nodosum-like lesions The only finding that is more common in women is the EN (Fig 2). They are seen in 23-55% of cases. They are subcutaneous, red or purple indurations most commonly located on the anterior aspects of the leg, and less frequently on the arm, neck, and face. When compared with classical EN lesions, EN lesions in BD are smaller, widespread, and have more tendency to recur. They regress spontaneously and heal with postinflammatory hyperpigmentation. Histologically, unlike classical EN, vasculitis or vasculary reaction forming the basic appearance of the disease is observed. (8,15,32).

Superficial thrombophlebitis They are present in 2.2-20% of cases, are common in male patients. They are mainly localized in arms and legs and present with painful, subcutaneous nodule or stiffnesses with a migratory character that are rope-like in shape. Due to its tendecy for irritability, local thrombophlebitis can develop in the course of BD after intravenous injections. (8,15,32).

Extragenital ulcers Extragenital ulcers occur in 3% of cases, they are clinically similar to other ulcers of the disease. They are edematous, erythematous, deep yellow ulcers with sharp edges. They are reccurrent and frequently heal with scarring. They can develop in the legs, axillae, nipples, neck, toe, and inguinal region (Fig 2) (16,32).

Other skin findings: Skin findings like Sweet syndrome, pyoderma gangrenosum and palpable purpura, erythema multiforme-like lesions, subungual infarcts, hemorrhagic bullae, furuncles and abscesses are also seen in the course of the disease. In the hands and feet, pernio-like and polyarteritis nodosa-like nodules are also included in the literature in case reports. (11,14,16).

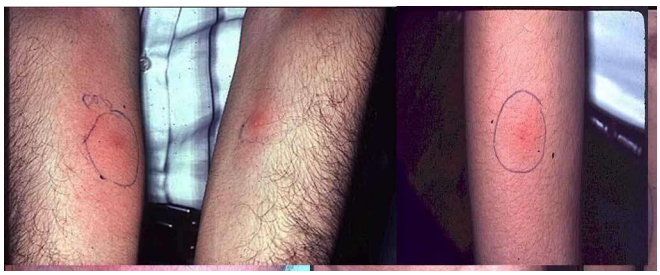

Figure 3: Pathergy test

Joint findings

Most of the patients have arthralgia. BD commonly affects major joints such as knee, elbow, hand and ankle joints and presents with recurrent seronegative arthritis in 16-84% of cases with articular involvement. It is more common in males. Destructive changes rarely develop in BD arthritis (13,34).

Pathergy test

In patients with BD, a skin response to a nonspecific stimulus is obtained and this phenomenon can be demonstrated by a pathergy test. The pathergy test is a nonspecific skin hyperreactivity developed against deep needle penetration. The test, which is among the diagnostic criteria, becomes positive especially during the exacerbation period of BD, and is therefore also used as a criterion to determine the activation periods of BD. Apart from BD, the test is also positive in Sweet's syndrome, pyoderma gangrenosum, and bowel-related dermatitis-arthritis syndrome. (8-10,15, 32).

The pathergy testing is also used to assess skin irritability. In this test, intravenous (IV), subcutaneous (SC) and intradermal (ID) punctures that will penetrate to the dermis is made with a sterile needle on an avascular area on the anterior of the forearm. The formation of erythematous papules or pustules, which starts at 24 hours and is maximum at 48 hours in the field of puncture shows a positive reaction (Fig 3). Histopathologically, in the area of the reaction, there is initial perivascular neutrophil accumulation followed by mononuclear cell infiltration. (8-10,15, 32).

Cellular immunity is thought to play a role in the pathogenesis of pathergy reaction. The positivity rate which is 6-71% in different series, is higher in Japan and Mediterranean countries and lower in western countries. Prior to the test, cleaning of the application site and use of needles with a small diameter will reduce the positivity rate. It is also indicated that gender is among the factors influencing the results of the test. (8-10,15, 32).

Sensitivity and specificity of the pattergy test is quite high. Histologic and immunofluorescence studies have been shown to increase the safety of this test in recent years. (8-10,15, 32).

B- Systemic Behçet Disease

Ocular findings

The incidence of the ocular disease throughout the course of BD is 29-100%, while it is the first manifestation in 10% of the patients. Ocular involvement is the most important cause of morbidity due to BD, is more severe in young men, usually occurs unilaterally, starts in the first years of BD and if untreated, effects the other eye over time. Ocular findings usually show a parallel course to the remissions and exacerbations of BD. (9-11,15,32,34).

First signs of ocular disease are usually periorbital pain and photophobia. The classic and most important ocular finding of BD is retinal vasculitis. Uveitis may be accompanied by conjunctivitis in the early period and hypopyon in the late period. Anterior uveitis, glaucoma, cataracts, chorioretinitis, retinal vessel damage and hemorrhage in the vitreous are among the other ocular symptoms. (9-11,13,15,32,34).

Attacks of uveitis may spontaneously regress in some patients, but reccurence may cause blindness by developing permanent structural changes such as iris deformity and secondary glaucoma. In BD, blindness is seen in 25% of cases. (9-11,13,34).

Central nervous system (CNS) findings

The frequency of CNS disease in BD is reported to be 10-20% in different series. CNS involvement is more common in men who had the disease onset at a younger age. (9-11).

CNS involvement indicates for a poorer prognosis of the disease. Neurological disorders occur in two forms. In the first; thrombosis develops in the dural sinuses and causes headache or causes an increase in the intracranial pressure. The second form is parenchymal involvement that is observed in 75% of BD cases and is characterized by psychosomatic findings such as personality changes and brain- root symptoms such as meningitis, meningoencephalitis and motor disorders. (9-11,13).

Neurological findings usually begin in the first five years of BD, but seldomly occur as early as acute aseptic meningitis or meningoencephalitis as a part of acute inflammation. (9-11,13).

Neurological involvement has a chronic course and is progressive. Neurological manifestations are characterized by attacks and remissions, and become irreversible over time. Dementia develops in about 30% of the severely affected cases. In a 7-year follow-up of patients with a seronegative chronic neurological disease, the death rate was reported as 20% (9-11).

Cardiovascular system (CVS) involvement

Neutrophilic or monocytic vascular inflammation can involve large, medium, and small vessels. Small vessel vasculitis is frequently seen during the course of the disease (9,11,13,15,35,36).

Characteristic CVS findings of BD include venous involvement in the form of superficial thrombophlebitis or deeper venous thrombosis, which is seen in one third of the cases (Fig 3) (6,9,11,13,15,35,36).

BD is at risk of thrombosis and the disease is defined as pre-thrombotic conditions. Thrombotic complications are seen in 12-40% of patients. Involvement of the large vessels such as superior and inferior vena cava and hepatic venous thrombosis, are rarely seen (Fig 3) (6,9,11,15,35,36).

Major arterial disease is reported in 1.5-2.2% of the cases in different series. The main pathology is occlusion or more commonly aneurysms. Pulsatile masses in the femoral and popliteal artery aneurysms, hemoptysis in the pulmonary artery aneurysm, occlusion of the large vessels or aneurysms may result in infarcts and organ failure. Pulmonary vascular involvement usually results in rupture. In these cases, the mortality rate is 50% after 3 years of follow-up after the onset of hemoptysis. (6,9,13,15,35,36).

Cardiac involvement is in the form of endocarditis, myocarditis, coronary arteritis and valve disease. Vascular disease is especially common in young men. Prognosis is poor and mortality is high. Vascular lesions can be detected at an early stage by computerized tomography, angiography and ventilation perfusion scintigraphy in patients with high-risk. (6,9,11,13,15,35,36).

Gastrointestinal system (GIS) findings

GIS manifestations of BD are abdominal pain, diarrhea, melena and sometimes perforation. Ileocecal region is the most frequently affected part of GIS, but lesions may also develop in transverse colon, ascending bowel and esophagus. (9,13,21,31).

Genitourinary system

Renal disease may be mild or asymptomatic. Genitourinary system disease can be seen as focal glomerulonephritis with vasculitis, amyloidosis-related renal disorder or epididymitis (10).

Pulmonary involvement

Pulmonary lesions are detected in 0.7-7% of cases and characterized with various presentations of vasculitis in the thorax. Vena cava superior and mediastinal venous thrombosis, vascular lesions such as pulmonary artery aneurysm and arterio-bronchial fistula, pulmonary infarcts, hemorrhage, pleural effusion, focal or diffuse pulmonary fibrosis may develop during the course of BD. The main pulmonary symptoms are shortness of breath, cough, chest pain, and hemoptysis. (9,13,14).

Histopathology

Histopathologically, the major finding in clinical manifestations of BD is vasculitis of large, medium, and small vessels (7,9,11). Early biopsies of mucocutaneous lesions have neutrophilic vascular reaction, endothelial swelling, erythrocyte extravasation and leukocytoclasia. In some cases, a fully developed leukocytoclastic vasculitis with fibrinoid necrosis accompanying to these findings is described (25). Lymphocytic perivasculitis is seen classically in the late stages of the disease or in autopsies (9). In more severe forms, necrotizing or granulomatous vasculitis develops in mediastinal venules, arteries and capillaries (25).

Laboratory Findings

There is no pathognomonic laboratory finding for BD (9,25). Changes in laboratory findings are basically related to affected organ system (11). In the active phases of the disease, higher levels of the erythrocyte sedimentation rate, serum reactive protein and plasma complement (C) components, C3-C4-C9, was detected. Serum β2 microglobulin and serum amyloid A protein were shown to be clinically active and more sensitive than erythrocyte sedimentation rate and serum reactive protein (10,11). Many researches have been done on the criteria that determine the activation of the BD, which can affect almost all organ systems. These are:

- Turkish Behçet's Disease activity index (37)
- Iran Behçet's Disease dynamic activity evaluation (38)
- Japanese Behçet's Disease research committee disease activity index (39)
- Yosipovitch's Behçet's Disease activity classification (40)
- Chang's Behçet's Disease clinical activity score (41)
- Krause's Behçet's Disease activity assessment (42)
- Behçet Disease instant activity form (43)

Diagnosis

Numerous diagnostic criteria have been defined since the its first description. Behcet's Syndrome Research Committee in Japan, O'Duffy Criteria in the United States, Turkish Criteria of Dilşen, Mason Barnes in England and Zhang Criteria in China (44, 98). Diagnostic criteria developed by the International Working Group in 1990 were generally accepted among dermatologists(44) but also have been criticized for some issues (45-47). These criteria, which are still widely used in BD, are given in Table 1.

Table 1. Behçet's Disease International Working Group (ICG) Diagnostic criteria

Oral aphthae: Minor or major or herpetiform ulcers, defined by the doctor or the patient who develops at least 3 times in 12 months
And two of the following;
Recurrent genital ulceration: An ulcer or scar seen by a doctor or patient,
Eye lesions: Anterior / posterior uveitis, retinal vasculitis or ophthalmologic Cell detection in vitreous with slit lamp examination,
Skin lesions: The eritema nodosum, as defined by the patient or identified by the physician, Papulopustular lesions detected by the physician in adult patients, Pseudofolliculitis or acneiform nodules,
Patergy test positivity: positive at 24th and 48th hours.

Treatment

The treatment of the disease is difficult due to the variable course of the disease and the lack of double-blind studies. A standard treatment scheme that can be applied to all patients or to all manifestations of the disease has not been established, neither is a good treatment for all clinical manifestations of the disease. Treatment is completely symptomatic and treatment options are based on the general condition of the patient, the location and severity of clinical signs (48-76).

The goal in the management of BD is to reduce symptoms associated with mucocutaneous lesions and arthritis, to control inflammation, to correct functional disorders, and to prevent system involvement and recurrences (9,11,12,34-50).

Prognosis

BD is a chronic, multisystemic disease that shows remissions and exacerbations. BD usually begins with oral ulcers, and the development of other systemic manifestations last for years. The disease often starts in the second and third decades, but a period of 1-8 years is required for a full clinical picture to be completed. In older ages, the activity of the disease gradually decreases, this is especially true in cases that have not ocular or CNC involvement (10,11,13,14,16,34).

Despite the possibility to affect almost all systems, the disease is often accompanied by mucocutaneous findings. Despite a chronic course with severe organ involvement in varying rates, spontaneous remissions are also seen in the course of BD. Prognosis is often good in cases without neurological, ocular, and vascular involvement (9,15).

Disease-related mortality in BD is reported to be 2-7% in various series. Causes of death in BD include CNS, respiratory system, major vascular involvement and bowel perforation. The most important factors affecting the mortality rate are delay in diagnosis and treatment. Along with the use of immunosuppressive drugs as new options in the treatment of disease, complications of immunosuppressive drugs among the causes of death in BD have also started to be counted (9,11,14,34).

Poor prognostic factors of BD are HLA-B51 positivity, male sex, and the early onset of systemic findings. Other factors are the onset of the disease at an early age, and delays in diagnosis and treatment. The effects of the pregnancy on the disease are unclear. Along with BD cases that worsened and improved during pregnancy, the disease is generally adversely affected by the first trimester of pregnancy. The group of patients with the worst prognosis of BD in different populations is young male patients (10,12,15,20,25,34).

In the last two decades, great progress has been made in the treatment of mucocutaneous and ocular involvement of BD. On the other hand, CNS involvement, treatment of thrombosis and arterial aneurysms of major venules remains a problem. Biologics have been the preferred therapies with the advantage of not having selective organ toxicities in BD treatment, and especially in treatment-resistant cases. However, treatment protocols related to optimal treatment schemes of anti-TNF drugs and their use with other immunosuppressives should be developed (11,48).

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1. Behçet H. Über rezidivierende, aphtöse, durch ein virus verursachte geschwüre am mund, am auge und an den genitalien. Dermatol Wochenschr 1937;105:1152-7.
2. Feigenbaum A. Description of Behçet's syndrome in the Hippocratic third book of endemic diseases. Br J Ophthalmol 1956;40:355-7.
3. Barnes CG. Behçet's syndrome –classification criteria. Ann Med Interne 1999;150:477-82.
4. Saylan T. Life story of Dr. Hulusi Behçet. Yonsei Med J 1997;38:327-32.
5. Tüzün Y. Hulusi Behçet, MD. February 20, 1889 to March 8, 1948. Clin Dermatol 2006; 24:548-50.
6. Sut N, Seyahi E, Yurdakul S, Senocak M, Yazici H. A cost analysis of Behcet's syndrome in Turkey. Rheumatology (Oxford). 2007;46:678-82.
7. Hegab S, Al-Mutawa S. Immunopathogenesis of Behçet's disease. Clin Immunol 200;96:174-86.
8. Tüzün Y, Yurdakul S, Mat C, Özyazgan Y, Hamuryudan V, Tüzün B, Yazıcı H. Epidemiology of Behçet's syndrome in Turkey. Int J Dermatol 1996;35:618-20.
9. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. N Engl J Med 1999;341:1284-91.
10. Önder M, Gürer MA. Behçet's disease: An enigmatic vasculitis. Clin Dermatol 1999;17:571-6.
11. Jorizzo JL, Behçet's Disease: Fitzpatrick's Dermatology in General Medicine. Beşinci baskı. Freedberg IM, Eisen AZ, Wolf K, Austen KF, Goldsmith AL, Katz IS, Fitzpatrick TB (eds), McGraw-Hill Inc, New York 1999, S:2161-5.
12. Kaklamani VG, Kaklamanis PG. Treatment of Behçet's disease-an update. Semin Arthritis Rheum 2001;30:299-312.
13. Yazıcı H, Tüzün Y, Pazarlı H, Yurdakul S, Özyazgan Y, Özdoğan H, Serdaroğlu S, Ersanlı M, Ülkü BY, Müftüoğlu AÜ. Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behçet's syndrome. Ann Rheum Dis 1984;43:783-9.
14. Ghate JV, Jorizzo JL. Behçet's disease and complex aphthosis. J Am Acad Dermatol 1999;40:1-18.
15. Tursen U, Gürler A, Boyvat A. Evaluation of clinical findings according to sex in 2313 Turkish patients with Behçet's disease. Int J Dermatol 2003;42:346-51.
16. Mazzoccoli G, Matarangolo A, Rubino R, Inglese M, De Cata A. Behçet syndrome: from pathogenesis to novel therapies. Clin Exp Med2016;16:1-12.
17. Gül A. Behçet's disease: an update on the pathogenesis. Clin Exp Rheumatol 2001;19(5 Suppl 24):6-12.
18. Azizlerli G, Aksungur VL, Sarıca R, Akyol E, Övül C. The association of HLA-B5 antigen with specific manifestations of Behçet's disease. Dermatology 1994;188:293-5.
19. 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.
20. Direşkeneli H. Behçet's disease: infectous aetiology, new autoantigens and HLA-B51. Ann Rheum Dis 2001;60:996-1002.
21. Lehner T. Immunopathogenesis of Behçet's disease. Ann Med Interne 1999;150:483-7.
22. Kaya Tİ, Dur H, Tursen U, Gürler 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.
23. Schirmer M, Calamia KT, Direskeneli H. Ninth International Conference on Behçet's Disease, Seoul, Korea, May 27-29, 2000. J Rheumatol 2001;28:636-9.
24. Alpsoy E. Behçet's disease: A comprehensive review with a focus on epidemiology, etiology and clinical features, and management of mucocutaneous lesions. J Dermatol 2016;43:620-32.
25. Bang D. Clinical spectrum of Behçet's disease. J Dermatol 2001;28:610-3.
26. Çalgüneri M, Kiraz S, Ertenli I, Benekli M, Karaarslan Y, Çelik I. The effect of prophylactic penicillin treatment on the course of arthritis episodes in patients with Behçet's disease. A randomized clinical trial. Arthritis Rheum 1996;39:2062-5.
27. Mendes D, Correia M, Barbedo M, Vaio T, Mota M, Gonçalves O, Valente J. Behçet's disease-a contemporary review. J Autoimmun 2009;32:178-88.
28. Şahin S, Akoğlu T, Direşkeneli H, Sen LS, Lawrence R. Neutrophil adhesion to endothelial cells and factors affecting adhesion in patients with Behçet's disease. Ann Rheum Dis 1996;55:128-33.
29. Bank I, Duvdevani M, Livneh A. Expansion of gamma delta T-cells in Behçet's disease: Role of disease activity and microbial flora in oral ulcers. J Lab Clin Med 2003;141:33-40.
30. Turan B, Gallati H, Erdi H, Gürler A, Michel BA, Villiger PM. Systemic levels of the T cell regulatory cytokines IL-10 and IL-12 in Behçet's disease; soluble TNFR-75 as a biological marker of disease activity. J Rheumatol 1997;24:128-32.
31. Bayraktar Y, Özaslan E, Van Thiel DH. Gastrointestinal manifestations of Behçet's disease. J Clin Gastroenterol 2000;30:144-54.
32. Michelson JB, Friedlander MH.Behçet's disease. Int J Ophthalmol 1990;30:271-8.
33. Akmaz Ö, Erel A, Gürer MA: Comparison of histopathologic and clinical evaluations of pathergy test in Behçet's disease. Int J Dermatol 2000;39:121-5.
34. Fresko İ, Yurdakul S, Hamuryudan V, Özyazgan Y, Mat C, Tanverdi MM, Yazıcı H. The management of Behçet's syndrome. Ann Med Interne 1999;150:576-81.
35. Koşar A, Öztürk M, Haznedaroğlu İC, Karaaslan Y. Hemostatic parameters in Behçet's disease:a reappraisal . Rheumatol Int 2002;22:9-15.
36. Lee YJ, Kang SW, Yang JI, Choi YM, Sheen D, Lee EB, et al. Coagulation parameters and plasma total homocystein levels in Behçet's disease. Thrombosis Research 2002;106:19-24.
37. Yazici H, Tuzun Y, Pazarli H, Yurdakul S, Ozyazgan Y, Ozdoğan H, Serdaroğlu S, et al. Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behcet's syndrome. Ann Rheum Dis 1984;43:783-9.
38. Kurokawa MS, Suzuki N. Behcet's disease. Clin Exp Med 2004;3:10-20.
39. Chang HK, Cheon KS. The clinical significance of a pathergy reaction in patients with Behcet's disease. J Korean Med Sci 2002;17:371-4.
40. Davatchi F, Akbaran M, Shahram F, Jamshidi A, Gharibdoost F, Chams C. Iran Behcet's Disease Dynamic Activity Measure. Abstracts of the XIIth European Congress of Rheumatology. Hung Rheumatol Suppl 1991;32:10-100.
41. Yosipovitch G, Shohat B, Bshara J, Wysenbeek A, Weinberger A. Elevated serum interleukin 1 receptors and interleukin 1B in patients with Behcet's disease: correlations with disease activity and severity. Isr J Med Sci 1995;31:345-8.
42. Krause I, Rosen Y, Kaplan I, Milo G, Guedj D, Molad Y, et al. Recurrent aphthous stomatitis in Behcet's disease: clinical features and correlation with systemic disease expression and severity. J Oral Pathol Med 1999;28:193-6.
43. http://www.behcet.ws/
44. France B, Davatchi F, Mizushima Y, Hazma M, Dilşen N, Kansu E, et al. Criteria for diagnosis of Behçet's disease. Lancet 1990;335:1078-80.
45. Tunç R, Uluhan A, Melikoğlu M, Özyazgan Y, Özdoğan H, Yazıcı H. A reassessment of the International Study Group criteria for the diagnosis (classification) of Behçet's syndrome. Clin Exp Rheumatol 2001;19 (5 Suppl 24):45-7.
46. Calamia KT, Schirmer M, O'Duffy JD. Reply: Diagnostic criteria for Behçet's disease. J Rheumatol 2000;27:2049-50.
47. Fresko İ. Highlights of the 10th International Congress on Behçet's Disease. Clin Exp Rheumatol 2002;20:59-64.
48. Rotondo C, Lopalco G, Iannone F, Vitale A, Talarico R, Galeazzi M, et al. Mucocutaneous Involvement in Behçet's Disease: How Systemic Treatment Has Changed in the Last Decades and Future Perspectives. Mediators Inflamm 2015;2015:451675.
49. Alpsoy E, Akman A. Behçet's disease: an algorithmic approach to its treatment. Arch Dermatol Res 2009; 301:693-702.
50. Chams-Davatchi C, Barikbin B, Shahram F, Nadji A, Moghaddassi M, Yousefi M, et al. Pimecrolimus versus placebo in genital aphthous ulcers of Behcet's disease: a randomized double-blind controlled trial. Int J Rheum Dis 2010;13:253-8.