The multiple faces of Behçet’s disease and its aetiological factors

M Önder,* MA Gürer
Gazi University School Medicine, Department of Dermatology, 11. Kat, Besevler, Ankara, Turkey. *Corresponding author; tel. +90 312214 1000/8148; fax +90 312212 9018; E-mail: monder@med.gazi.edu.tr

ABSTRACT

Behçet’s disease (BD) is a chronic, inflammatory multisystemic condition of unknown aetiology. It is clinically characterized by recurrent orogenital ulcerations and skin eruptions; ocular manifestations; arthritis; vasculitis and in some cases neurological and large vessel involvement. Aetiology has not been defined, but genetic, environmental, viral, bacterial and immunological factors have been proposed as causative agents. Treatment includes colchicine, thalidomide, steroids and immunosuppressive agents and it is based on the severity of systemic manifestations, such as central nervous system involvement, arterial aneurysms and thrombosis of the major veins. Mortality is related to major system involvement. In this article the different clinical features, the multiple faces of BD and a list of currently suspected aetiological factors of the disease are discussed, and treatment modalities summarized.

Key words: aetiological factors, Behçet’s disease, clinical features

Professor Hulusi Behçet, a Turkish Dermatologist from Istanbul gave his name to a syndrome in 1937 of ‘recurrent oral ulcers’, ‘genital ulcers’ and ‘hypopyon uveitis’ with an unknown aetiology.1 The disease was probably recognized by Hippocrates who lived in ancient Greece. Many investigators tried to describe patients with these symptoms.2,3 Today Behçet’s disease (BD) is a more complicated entity, with the disease recognized as a chronic multisystem disorder with vasculitis as its underlying pathological process. Variable involvement of many organs and additional features have been added to the disease spectrum.

Epidemiological features

The disease occurs endemically in the eastern Mediterranean and in Middle and Far Eastern countries, the population deriving from the ancient Silk Road. The highest prevalence is reported in Turkey, with familial occurrences reported from endemic areas.4 BD has a higher prevalence in men than in women, with a male/female ratio of 3 : 2.2–10 Usually, the onset occurs in the third decade of life. It is rarely seen in children and has a more aggressive course in young adults (male).11

Criteria for diagnosis

The diagnosis of BD is based on clinical criteria as established by an International Study Group (Table 1).12 These criteria omit the less certain and less common features of the disease. Complex aphthosis, as defined by Ghate and Jorizzo is the presence of almost constant multiple oral or genital aphthae in the absence of systemic manifestations.13 BD is now recognized as an enigmatic vasculitis and multisystem disorder with articular, vascular, intestinal and neurological involvement and pulmonary and renal manifestations.14

Clinical aspects

Mucocutaneous lesions

Oral aphthae

Oral aphtha is considered as one of the most important manifestations of BD and aphthous ulcerations are the keystones to the diagnosis, according to the classification criteria. Often the first symptoms are the ulcers, which occur on the buccal mucosa, tongue, gingiva and the soft palate area (figs 1 and 2). They are classified as minor or major aphthous
ulceration and herpetiform ulceration. Minor ulcers are superficial with a diameter of 2–6 mm and appear as multiple lesions, developing within 1–2 days. They heal without scarring within 7–10 days and recur at various frequencies. Major aphthous ulcers are deeper and painful. They leave scars after healing. Herpetiform aphthous lesions are numerous and grouped as small ulcers.11,12,15–17

Genital aphthae
Located on the vulva, vagina, cervix uteri in women (fig. 3) and the prepuce and scrotum in men (fig. 4). They resemble the oral aphthae, although they tend to be deeper and leave scars. Patients suspected of having BD should be examined for genital scarring (figs 5 and 6).11,13,16,17 It is important to exclude

Table 1: International study group criteria for the diagnosis of Behçet’s disease (used by courtesy of the Lancet)10

<table>
<thead>
<tr>
<th>Recurrent oral ulceration</th>
<th>Minor aphthous, major aphthous or herpetiform ulceration observed by physician or patient, which recurred at least three times in 12-month period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus two of the following criteria:</td>
<td></td>
</tr>
<tr>
<td>Recurrent genital ulceration</td>
<td>Aphthous ulceration or scarring observed by physician or patient</td>
</tr>
<tr>
<td>Eye lesions</td>
<td>Anterior uveitis, posterior uveitis or cells in vitreous on slit-lamp examination or retinal vasculitis observed by ophthalmologist.</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Erythema nodosum observed by physician or patient, pseudofolliculitis or papulosquamous lesions or acneiform nodules observed by physician in postadolescent patients not on corticosteroid treatment</td>
</tr>
<tr>
<td>Positive pathergy test</td>
<td>Read by physician at 24–48 h</td>
</tr>
</tbody>
</table>

Fig. 1: Multiple minor ulcers on the oral mucosa.

Fig. 2: Major aphthous ulcer.

Fig. 3: Deep genital ulcer in a 38-year-old woman.

other causes of genital ulcers, such as herpes simplex, syphilis, tropical ulcers and skin infestations. The polymerase chain reaction (PCR) technique offers greater sensitivity and specificity.

Erythema nodosum-like lesions

These usually occur on the lower extremities, but can also be seen on the arms, neck and face. The areas of erythema are slightly elevated with subcutaneous induration and tenderness (fig. 7). Pigmentation may remain after healing.\(^1\)\(^2\)\(^3\) Histopathological features of the erythema nodosum-like lesions include a neutrophilic vascular reaction or vasculitis in the dermis and subcutaneous tissue and perivascular lymphocytic dermal inflammation.\(^1\)\(^3\)

Papulopustular eruptions

Both the International Study Group and the Research Committee of Japan for BD have included follicular lesions as one of the diagnostic cutaneous features of BD\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\) (fig. 8). Papulopustular eruptions are a neutrophil-induced, vessel-based reaction. Pustular lesions in patients with BD may evolve as lesions of small vessel necrotizing vasculitis from a neutrophilic vascular reaction to a lymphocytic perivascular reaction. It has been suggested that they are referred to as ‘pseudofolliculitis’ lesions. Because many young patients especially those receiving corticosteroid therapy have non-specific follicular acneiform lesions, Jorrizzo \textit{et al.} considered that they are not vessel-based histologically.\(^1\)\(^8\) They should not

be considered as a fulfilling a diagnostic criterion for BD. Biopsy confirmation of vessel-based histological findings with exclusion of follicular lesions should be required.18

Pathergy: the pathergy test
This is a diagnostic criterion. It is a non-specific pustule that is an inflammatory reaction to needle pricks. It occurs in approximately 40% of patients, especially during the exacerbation period. After non-specific trauma to the skin with a small needle, sterile pustules develop 24–48 h later at the injection site. This reaction is called positive pathergy (fig. 9). The histopathology of pathergy is polymorphonuclear leucocyte infiltration.11–19

Ocular lesions
Most common manifestations are the hypopyon, posterior uveitis, vitreous deposits, choroiditis and retinitis. Loss of vision is the most serious problem. Posterior uveitis is more common. Patients with anterior ocular problems have better visual prognosis.13 Although mucocutaneous lesions occur early in the course of the disease, eye lesions may be delayed by several years.13,14 The frequency of ocular involvement in patients with BD has been reported to be 70–85%.13 Ocular lesions are characterized by severe vasculitis with arterial and venous occlusions.15,16 Behçet originally described hypopyon as a cause of blindness1 and, therefore, patients with BD should be referred to an ophthalmologist. Fluorescein angiography, colour Doppler imaging and funduscopic examination can detect the retinal features.22

Articular manifestations
Recurrent seronegative arthritis is a common finding in patients. It is a non-specific synovitis, often monoarticular at the knee.14,16 Dilisen et al. found that 10% of their patients had ankylosing spondylitis and 34% had sacroilitis.13 Patients with sacroilitis should be excluded from the diagnosis of BD as these patients are more akin to the Reiter’s spectrum. Obviously, patients with inflammatory bowel disease who are HLA B27 positive would also have aphthae and patients in both groups can have ocular disease.

Vascular manifestations
Thrombophlebitis, both superficial and deep, is a common manifestation. They are the main clinical features of BD. Thrombosis may affect any part of the body. Vascular involvement in BD is peculiar as occurs in young subjects with no vascular risk factors. A few cases of recurrent pericarditis have been reported. Myocardopathy can be the result of inflammation. Arterial involvement is expressed by thrombosis. Aneurysms ‘arterial aphthae’ may be multifocal. Endomyocardial fibrosis is probably associated with an abnormal response to endothelial cells. The dramatic large vessel involvements fortunately occur in only a minority of BD patients. Venous involvement is usually characterized by a superficial thrombophlebitis, seen in approximately one-third of cases. Patients with cardiovascular involvement usually have a poor prognosis. Vasculitis of the coronary arteries may lead to infarction or to aneurysm and usually requires surgical treatment. Arterial lesions carry a poor prognosis because the aneurysms often rupture especially in the pulmonary vessels.24–27

Pulmonary involvement
Pulmonary involvement is uncommon. The manifestations result from pulmonary vessel involvement and they are pleurisy, embolism; pulmonary arterial aneurysms, parenchymal changes and fibrosis.28

Renal involvement
Glomerulonephritis and systemic amyloidosis have very rarely been reported with BD.29

Gastrointestinal involvement
Gastrointestinal involvement in BD can present as ulcerative lesions most frequently occurring in the terminal ileum and caecum and also the stomach and intestine.30 Inflammatory bowel disease must be excluded.

Central nervous system involvement
About 1% of patients with BD develop central nervous system involvement, which manifests itself as a meningonecrophatitis, peripheral nerve involvement with vasculitis, cranial nerve palsies and hemiplegia.31 It is slowly progressive and leads to

paralysis. Cerebral aneurysms can be the cause of mortality. Magnetic resonance imaging may be useful for diagnosing cerebral venous thromboses.32

Hearing and vestibular disturbances can also be found.33 Headaches similar to migraines may occur. Psychological changes and depression may be present in at least 50% of patients during the course of the disease.34

Other skin lesions

Other cutaneous manifestations, such as Sweet-like lesions, pyoderma gangrenosum-like lesions, erythema multiforme-like lesions, palpable purpura, subungual infarctions, haemorrhagic bullae and extragenital ulcerations, may occur in BD.35,36

Laboratory findings

Several laboratory tests have been studied, but none have been shown.13,14,19,20 Histopathological features of early cutaneous lesions are the neutrophilic vascular reaction or leucocytoclastic vasculitis. Histopathological interpretation of late lesions show lymphocytic perivasculitis.38

Aetiology

The aetiology of BD is uncertain. Genetic, environmental, bacterial, viral and immunological factors have been proposed as causative agents. The pathogenesis is probably mediated by a combination of these factors.

Genetic theory

An association with HLA B51 antigen has been reported in certain parts of the world and in some familial clusters. The increased incidence in the Far East and in the eastern Mediterranean and association with HLA B51 suggest that genetic factors are important influences in the aetiology of BD.39–41

Streptococcal theory

BD’s Research Committee of Japan focused on a possible pathogenetic role for streptococcal antigens.42 Lymphocytes from patients with BD incubated with streptococcal antigens released lymphokines that stimulated neutrophil functions. Streptococcus sanguis appears to be the most relevant strain.43

Recent clinical observations suggest that exposure to streptococcal antigens may be a major provoking factor for disease activity. In some patients a skin reaction can be observed when streptococcal antigens are injected intradermally.44 Kaneko et al. reported streptococcal group D antiserum in skin and mucosal lesional biopsies.45 The results of another study from Turkey showed that the combination of benzathine penicillin and colchicine is more effective for controlling the mucocutaneous symptoms of the disease.46

Viral aetiology

A viral aetiology was suggested by Behçet in his original publication, based on observations of inclusion bodies in the ulceration. Viral infection has often been thought to be a provoking factor in the disease; however, no case to case transmission has been described.1 Sezer maintained that a virus was implicated, but many other workers have been unable to substantiate his findings.47 However, some indirect evidence of viral involvement has been found.

The herpes simplex virus type 1 (HSV 1) genome has been found by in situ hybridization in leucocytes from patients with BD, in association with circulating antibodies to HSV-1.48–52 Cytomegalovirus was not isolated in biopsy specimens taken from ulcers.53 There was no difference between Behçet’s
patients and the control group with PCR testing of saliva for herpes simplex virus DNA. They also investigated the sera of patients with BD, but without any positive results.

Heat shock proteins

Significant increases of IgA antibodies against the 65 kDa heat shock proteins characterize BD. Monoclonal antibodies to the heat shock proteins cross-react with selected strains of Streptococcus sanguis. Lehner et al. questioned whether various microbial triggers might act by inducing stress proteins. Rabbit antisera against a 65-kDa heat shock protein of Mycobacterium tuberculosis revealed a corresponding 65 kDa band with all Streptococcus sanguis strains. Direkseneli et al. investigated T-cell responses to 60/65 kDa heat shock protein in Turkish patients and found high T-cell immune responses and also B-cell epitopes.

Neutrophil functions

Neutrophil chemotaxis is increased in cutaneous lesions of BD patients. Lymphocytes may play a major part in generating neutrophil hyperfunctions. Leukocyte adhesion molecules (L-selectin, mac-1 and CD44) are expressed on peripheral leucocytes and may participate in the sequential cascades of leukocyte chemotaxis and adhesions. Chemotaxis is generally accelerated and T lymphocytes may play a part. Histology of cutaneous lesions resembling erythema nodosum and sterile pustules reveal a ‘small vessel vasculitis’ involving particularly the venules with a perivascular lymphocytic and mononuclear cellular infiltration and fibrin deposition in the vessel wall. The punched out ulcers are characterized by a leucocytoclastic vasculitis (neutrophil infiltrate) with fibrinoid necrosis.

Cell lines expressing T-cell receptors have been found to produce large amounts of tumour necrosis factor α (TNF-α) and IL-8, possibly priming neutrophils and causing tissue damage. Neutrophil adhesions are increased on endothelial cells in patients with BD. ICAM-1 and CD11–CD18 molecules are elevated.

Fibrinolytic activities

There is impaired cutaneous fibrinolytic potential. Studies have shown that the plasma fibrinolytic activity was reduced in BD patients. Fibrinolytic abnormalities, prolongation of the euglobulin lysis time and decreased levels of circulating factor XII have been reported. Cutaneous fibrinolytic potential helps in the monitoring endothelial injury and in the prognosis of the disease.

Monocyte function

Monocytes are the principal source for some cytokines and may play a partial part in the pathogenesis of chronic inflammation in this disorder. Expression of adhesion molecules (CD11a, CD11b, CD18) and the role of monocyte supernatants in neutrophil endothelial cell adhesion were investigated. Patient’s monocyte culture supernatants caused significantly increased adhesion of normal neutrophils to endothelial cell monolayers in vitro. This finding suggests that BD patient’s monocytes are active and produce a number of pro-inflammatory cytokines (fig. 10).

Fig. 10 Proposed mechanism for immunopathogenesis of Behçet’s disease. Some infectious agents may trigger mononuclear cells as well as endothelial cells through heat shock peptides in genetically susceptible HLA-B51-positive individuals. At the final step, different mediators released from activated mononuclear cells and endothelium may in turn activate neutrophils and monocytes, resulting in severe inflammation. Used by permission of Sahin et al.
Cytokines and other mediators

Various pro-inflammatory cytokines such as IL-1, IL-8 and TNF-α have been reported to be elevated in the sera of BD patients. BD patients with neurological involvement have elevated levels of IL-6 in the cerebrospinal fluid that correlates with the activity of disease. In another study high autoantibody titres against low-density lipoproteins were found to be important in the pathogenesis. It may be responsible for endothelial dysfunction.

It has been shown that prostacyclin synthesis is impaired in vessel walls, and thromboxane B₂ and prostaglandins are elevated. It indicates the risk of thrombosis during the course of BD.

Zouboulis et al. investigated anticardiolipin antibodies in BD. The results suggest that anticardiolipin antibodies does not play a major pathogenetic role in BD.

Elevation of fibrinopeptide A levels has also been found during active disease suggesting that abnormal fibrinolysis contributes to the pathogenesis of the disease. Protein S deficiency was found in some cases. This observation suggested that when thrombotic manifestations are the first and major symptom, an additional cause of thrombosis has to be investigated.

Plasma endothelin-1 (ET-1) concentrations were determined by radioimmunoassay, ET-1 concentrations were significantly increased in patients with active BD. Elevated ET-1 level is the direct result of its increased synthesis from injured vascular endothelial cells. These results indicate that ET-1 may play an important pathogenetic part in the development or progression of vasculitis. Plasma concentration of ET-1 correlates with the activity of disease.

Thrombomodulin (TM) is a cell surface glycoprotein of vascular endothelium. TM levels were significantly increased in all patients with BD. Increased plasma TM in vasculitis of BD potentially damages to the endothelial cells.

Lipoprotein(a) is newly recognized risk factor in atherogenic and thrombogenic processes. The patients with high Lp(a) levels should be kept under close control especially during the active period of the disease.

A working hypothesis for the aetio-pathogenesis of BD is proposed by Sahin et al. (fig. 10). Some infectious agents may trigger mononuclear cells as well as endothelial cells through heat shock peptides in genetically susceptible HLA-B51-positive individuals. During the final step different mediators are released and may cause inflammation.

Different mechanisms for the pathophysiology of BD have been proposed. Discussions have centred around whether the process involves immune complex deposition vs. cell-mediated immunity. The expression of major histocompatibility class II antigens suggests there are CD4+ T cells that appear to play a major part in BD via cell-mediated immunity. The relative lack of CD8+ T cells may lead to B-cell stimulation and B-cell activation. This local production of antibodies may lead to immune complex deposition. Consequently, the pathophysiology may be the result of combined humoral and cellular immunological mechanisms.

Additionally, extensive expression of adhesion molecules on vascular endothelial cells were recently reported. This suggests that adhesion molecules may play an important part in the vasculitic process.
Clinical course

BD has a highly variable clinical course with recurrences and remissions. In the absence of neurological and vascular involvement, the disease is generally benign and with a good prognosis. Blindness, which occurs in up to 25% of the patients, is the major cause of permanent disability.

Treatment

The treatment of BD depends on individual clinical manifestations. Topical treatment of oral aphthae, two or three times a day, includes topical antiinfective and anti-inflammatory mouthwash preparations (chlorhexidine 1–2%); topical corticosteroids (triamcinolone ointment), topical anaesthetics (lidocaine 2–5%) or tetracycline mouthwash (250 mg tetracycline + 5 mL glycerine). Topical treatments are beneficial to reduce pain and promote the healing of ulcers. Recently, topical sucralfate suspension was found to be effective for oral and genital ulceration treatment.

In severe forms of the mucocutaneous type of the disease, systemic treatments are required. Drugs that have been used include colchicine, dapsone, non-steroidal anti-inflammatory drugs, corticosteroids, thalidomide, penicillin, acyclovir and IFN-α, azathioprine, methotrexate and cyclosporin are effective in controlling arthritis. Colchicine and dapsone may be used for milder mucocutaneous disease, whereas cyclosporin, tacrolimus and other agents can be reserved for patients with more severe disease, including blindness.

Corticosteroids should only be used in severe ocular and neurological involvement. Azathioprine, 100 mg/d orally, appears to control the ocular manifestations. Methotrexate, 7.5–20 mg/week, can be effective; however, these patients must be monitored for liver and renal insufficiency. Methotrexate, 10 mg/d, produced an improvement in ocular manifestations; however, it has significant long-term adverse effects. Thalidomide (50–300 mg/d orally) is effective for treating the oral and genital ulcers and follicular lesions of BD. In one of the controlled trials doses of 100 mg/d and 300 mg/d appeared to be equally effective. Thalidomide, however, is toxic to the newborn and should be reserved only for patients resistant to other treatment options, because of toxicity such as teratogenicity and polyneuropathy. Colchicine is an alkaloid and has been proven to be an effective agent in BD especially for mucocutaneous lesions and also ocular and articular manifestations of the disease. In our hospital, it gives the best results, increasing the quality of life with the least risk and side-effects. It is administered orally (0.5–2 mg/d) and inhibits the enhanced chemotactic activity of neutrophils. IFN-α has been used in the treatment of BD as antiviral, antiproliferative and immunomodulatory agents. The results of IFN are not standard. Studies with large numbers of patients are needed in order to clarify the optimal dose and duration; however, it can be used as an alternative with the advantage of inducing prolonged remissions. Tacrolimus (FK 506; 0.05–0.2 mg/kg body weight per day orally) has been found to be effective in refractory uveitis; however, it is experimental. Fibrinolytic agents are used in deep vein thrombosis and pulmonary embolism. The prognosis of ocular occlusion is better than arterial aneurysm, which is frequently complicated by fatal rupture. This complication is major cause of death in BD. Arterial punctures for angiography or surgery to bypass aneurysm may lead to the formation of further aneurysms. For these reasons vascular surgeons refrain from operating in these cases. Patients with vascular involvement may benefit from cyclophosphamide alone or in combination with corticosteroids.

Finally, the usual course of BD is of exacerbations and remissions, with a gradual reduction in its severity with the passage of time. This is a problem for therapeutic studies. Experience is very important, and by acting according to previous experience is better than using new therapeutic modalities.

References


