Behçet’s disease: clinical features and treatment

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Behçet’s disease which is characterized by a relapsing inflammatory process of unknown etiology presents several clinical manifestations involving many organ systems. Because of the multisystem nature of the disease different treatment modalities have been advocated and many others are still under investigation. In this article, the clinical manifestations, diagnostic criteria and recent advances in the treatment of Behçet’s disease are reviewed. [Journal of Turgut Özal Medical Center 2(1):78-85, 1995]

Key Words: Behçet’s disease, clinical features, treatment.

Behçet hastalığı: klinik bulgular ve tedavi


Anahtar Kelimeler: Behçet hastalığı, klinik bulgular, tedavi.

Although Behçet’s disease (BD) was first recognized by a clinical triad of uveitis, oral ulceration and genital ulceration, it is now well known that many other systems might be involved in the disease. While inflammatory episodes are usually intermittent in the clinical manifestations, the disease can become stable and chronic in a given organ system.

CLINICAL MANIFESTATIONS

Oral ulcerations: Aphthous ulcerations of the oral mucosa develop in 75% to 99% of patients1,2. Although figures as high as 75% have been reported3, approximately in 25% to 30% of patients it occurs as the first manifestation of BD4. Oral ulcers are classified as minor (most common, small, painful ulcers heal without scarring), major (larger, deeper, very painful) and herpetiform (small, numerous, grouped, shallow) aphthous ulcerations5. The lesion may start as an erythematous, circular area evolving into a small, shallow, oval or round ulcer usually within 1 to 2 days. A white or yellow pseudomembrane often covers the surface of the ulcer and it has a sharply demarcated erythematous border. The painful ulcers appear singly or in crops. The lips, gingiva, buccal mucosa and tongue are the preferential sites but on rare occasions the palate, tonsils, pharynx and larynx are involved. Most oral aphthous ulcers heal without scarring within 7 to 10 days, although major ulcers may produce scarring. They tend to recur at irregular intervals, commonly stimulated by certain foods such as black walnuts, chocolate and tomatoes5,6. Oral ulcerations in BD are described as being indistinguishable from recurrent oral ulceration, however, Main and Chamberlain observed some differences in oral ulcerations of BD when compared with conventional recurrent oral ulcerations, such as increased number of ulcers, variation in size, ill-defined erythematous halo and more frequent involvement of soft palate and oropharynx.

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Genital ulcerations: Genital ulcerations similar to the oral lesions in morphology occur in 75% of patients. The vulva and scrotum are the most frequent sites, but penile shaft, glans penis, vagina and perianal area may also be affected. They are usually deeper than the oral ones, hence they leave scars after healing and residual scarring from previous ulcerations are often present in the examination, even if there are no signs of active genital ulcers. The lesions in men seem to be more painful than those in women. In females the ulcers usually appear premenstrually. The genital lesions recur less frequently than oral ulcerations.

Skin involvement: Erythema nodosum-like subcutaneous nodules occur in about one third of patients. Blush to erythematous, painful, recurrent subcutaneous nodules of erythema nodosum appear in crops on the legs but also can be seen on the buttocks, arms, neck and face. The lesions tend to disappear in 10 to 14 days. Clinically, erythema nodosum due to BD had been suggested to differ from the classical erythema nodosum, with the occurrence of less redness, pain and swelling. In addition, histologically these lesions do not exhibit the granuloma formation associated with the classical erythema nodosum, but they are characterized by a perivascular mononuclear infiltrate involving the interlobular septae of the subcutaneous fat. Due to these clinical and histologic characteristics, erythema nodosum lesions in BD have been referred to as "erythema nodosum-like lesions". The dark cell degeneration of the damaged endothelial cells that lead to obliteration in the cutaneous microvasculature in the erythema nodosum-like lesions of BD has also been described in classical erythema nodosum unassociated with BD.

Superficial migratory thrombophlebitis is another common characteristic skin lesion described in BD. The endothelial cell dysfunction caused by primary immunologic mechanisms or direct tissue injury lead to the development of this vascular complication. It is not associated with embolism and occurs both in the lower extremities and in unusual locations, such as the abdominal or chest wall or the upper extremities.

Folliculitis and acneiform eruptions have been associated with BD. The pustular lesions in BD are in fact neutrophilic perivascular infiltrates. They appear as numerous papules and sterile pustules on the face, neck, chest and extremities. However, purpura and comedone formation are not found.

More important is the increased reactivity of the skin to needle pricks or intradermal injection of saline (Behçet test). This phenomenon is called "pathergy" and occurs in 40% to 88% of patients, especially during the exacerbation of the disease. However, the higher prevalence of pathergy positivity is observed in patients with BD from the Mediterranean countries and Japan but it is rarely present in patients originating from Britain and the United States. Twenty-four to 48 hours after a needle stick or intradermal injection of an inert substance such as sterile saline, pathergy is manifested clinically by erythematous induration, a papule or an aseptic pustule which may evolve into a sterile ulcer. The intradermal saline method is found to be less sensitive than needle prick and the "simultaneous three needle pricks" gives the most sensitive pathergy reaction. The intensity of this reaction appears to be more prominent with thicker needles and when the disease persists for more than 5 years pathergy positivity seems to decrease.

The histopathologic picture of pathergy lesions is a polymorphonuclear leukocyte infiltration followed by the influx of large numbers of mast cells.

Eye involvement: Ocular involvement is one of the most serious manifestations of BD and occurs in 70% to 85% of patients. The most distinctive features of ocular involvement in BD are the spontaneous remissions and exacerbations of the intraocular inflammatory signs that cause irreversible changes. Loss of vision is a common complication, especially in posterior segment involvement. Chahek and Fainaru showed that blindness occurred in 44% of their patients with posterior segment involvement after 4-8 years. Mamo reported loss of vision in an average of 3.36 years after onset of eye symptoms. Early in the disease, the ocular involvement may be unilateral but eventually both eyes are involved, however intensity of symptoms in both eyes are not the same. The disease can affect both the anterior and posterior segments of the globe. The initial symptom of the most common ocular symptom, anterior uveitis, is generally hazy vision due to inflammatory exudation in the anterior chamber which may lead to hypopyon formation. Posterior uveitis is manifest by vitreal inflammatory response with macular and disc edema and results in blindness if not treated aggressively. The presence of retinal vasculitis and necrotizing retinal inflammation is well known but often obscured by the severity of the anterior reaction. Sanders and Graham have shown diffuse capillary leakage in all of their cases and also reported that the retinal infiltrations and branch vein
occlusions are pathognomonic features of the retinopathy of BD. Secondary fibrous reaction overlying the perivasculitis in the retina may eventually lead to retinal detachment, intraocular disorganization and phthisis bulbi. In the later stages of the ocular disease, the permanent visual loss may be due to retinal atrophy or atrophy of the optic nerve secondary to inflammatory glaucoma. External eye diseases including conjunctivitis, episcleritis and keratitis may also occur.

Central nervous system involvement: Neurologic symptoms occur in 10% to 45% of patients and carry a poor prognosis. Central nervous system involvement usually begins within 5 years after the onset of the disease. Meningoencephalitis is thought to be typical, but brain-stem syndrome and organic-confusion syndrome occur as well. The vascular lesions of BD are arterial and venous occlusions and aneurysms which may cause intracerebral hemorrhage. Symptoms and signs related to neurologic involvement include headache, pyramidal signs, cerebellar signs, sensory symptoms, pseudobulbar signs, intracranial hypertension, meningeval irritation signs, hemianopia, dementia, personality changes, tremor and myoclonic jerks. Papilledema due to intracranial hypertension can be an initial manifestation. Spinal fluid examination reveals a marked pleocytosis with a predominance of neutrophils and lymphocytes and in some, an increase in total protein without elevation in gamma globulin. Increased levels of IL-6, C3, C4, IgM and to a lesser degree IgG, IgA and IgM may also be detected in the spinal fluid. Lymphocyte subset analysis has shown an increased CD8+ (cytotoxic/suppressor) T-cell percentage, which is likely to participate in the development of encephalitis. CT abnormalities commonly occur in these patients with focal deficits and correlate with the activity of parenchymal disease. However, when CT scan is normal despite neurologic symptoms, MRI (magnetic resonance imaging) can reveal abnormal signals which are usually more extensive than clinically expected.

Arthritis: A recurrent, seronegative arthritis occurs in approximately 40% of patients with BD. It is usually subacute, self-limiting and nondeforming. Most commonly a monoarthritis or oligoarthritis, symmetrically involving the knees, ankles, elbows and wrists are diagnosed. Occasionally the arthritis may be erosive and sacroiliitis may be associated. The arthritic symptoms are related to the activity of the disease.

Vascular involvement: Vascular involvement of BD affects both arteries and veins of all sizes. Koç et al. has reported the prevalence of vascular disease as 27.7% in 137 Turkish patients with BD. The authors have also noted a higher prevalence of pathergy positivity, erythema nodosum lesions and eye involvement in patients with vascular lesions. Venous system is the major affected site among the vascular lesions and the most common type of venous involvement has been subcutaneous thrombophlebitis. However, deep vein thrombosis of the extremities and trunk and intracranial venous sinus thrombosis, often accompanied by superficial thrombophlebitis are detected. Complications may occur in the more proximal veins such as the femoral and iliac veins, or inferior or superior vena cava, in which the venular obstruction may be so serious that death may ensue. Venoocclusive disease in BD may involve hepatic vein and cause Budd-Chiari syndrome. Arterial involvement comprises aneurysm formation, thrombosis and angitis of systemic and pulmonary arteries. The artery most often affected is the aorta, followed by the pulmonary, femoral, popliteal, subclavian and common carotid arteries. Rupture of the large artery aneurysms is the leading cause of death in patients with BD.

Other systems involved in BD: Gastrointestinal system involvement in BD occurs in 5% to 50% of patients with a higher incidence in Scotland and USA. Erosions and ulcers are found usually in the ileocecal region which may give rise to perforation, but also in esophagus, stomach, duodenum, rectal, perianal or colonic regions. Pancreatitis has also been reported as an unusual gastrointestinal complication of the disease. Gastrointestinal symptoms such as abdominal pain, vomiting, diarrhea, constipation, malabsorption and abnormal digestion are present. Serious gastrointestinal involvement in BD results in a poor prognosis. Jankowski et al. have reported that in their study all patients of BD with gastrointestinal involvement have either HLA-DR4 or -DR7 phenotype, suggesting that the expression of DR-related antigens in the gastrointestinal mucosa may modulate the inflammatory response. Intestinal BD may mimic inflammatory bowel diseases particularly Crohn’s disease and may cause considerable diagnostic confusion.

Pulmonary involvement occurs in about 5% of patients in BD. Pulmonary artery aneurysms.
pulmonary embolism, recurrent pneumonia, pleural effusion, pulmonary fibrosis, obstructive lung disease and pulmonary hypertension may occur. The major pulmonary manifestation is hemoptysis which may be so severe that requires blood transfusions or cause fatal pulmonary hemorrhage. Other symptoms are dyspnea, pleuritic chest pain, cough and fever. However, asymptomatic pulmonary infiltrates have been reported in BD.

Cardiac and pericardial involvement are rare and may be due to coincidence. Cardiac findings in BD include congestive cardiomyopathy, myocardial infarction, left ventricular diastolic dysfunction, endocarditis and pericarditis.

Kidneys may be involved rarely by asymptomatic, focal glomerulonephritis. Infrequently diffuse proliferative glomerulonephritis or secondary amyloidosis has been described in BD. Urological manifestations consist mainly of epididymitis and less commonly sterile urethritis.

LABORATORY FINDINGS

During relapses, a high erythrocyte sedimentation rate, acute-phase proteins, particularly alpha2 globulins, mild leukocytosis, high levels of circulating immune complexes and alterations in serum complement levels are detected. Serum concentrations of C9 and complement-reactive protein are increased in all forms of the disease. Serum lysozyme and alpha-1-acid glycoprotein levels are increased in the ocular disease.

DIAGNOSIS

Because of variable involvement of many organ systems and the lack of pathognomonic laboratory tests, the diagnosis of BD has relied on the identification of the more typical clinical findings. Several authors have proposed different criteria, however, none have been universally accepted. The Behçet’s Disease Research Committee of Japan, established by the Ministry of Health and Welfare in 1972, developed a diagnostic criteria which was revised twice, in 1982 and 1987 with the addition of few minor findings. In Table I the diagnostic criteria of BD described by the Behçet’s Disease Research Committee of Japan in 1987 are shown. In this diagnostic criteria major and minor symptoms are classified according to the frequency of occurrence, not to the severity, and only the typical findings of minor symptoms are used. More recently, International Study Group for Behçet’s Disease (ISG) has proposed a single set of diagnostic criteria, which exclude rarer manifestations and are simpler to use. The ISG criteria are shown in Table II.

<table>
<thead>
<tr>
<th>Table I. Revised Japanese criteria for Behçet’s disease (1987)</th>
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<tbody>
<tr>
<td><strong>1. Major criteria</strong></td>
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<tr>
<td>(i) Recurrent aphthous ulcerations of the oral mucous membrane</td>
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<td>(ii) Skin lesions (any of the four)</td>
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<tr>
<td>(a) Erythema nodosum</td>
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<td>(b) Subcutaneous thrombophlebitis</td>
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<td>(c) Folliculitis, acne-like lesions</td>
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<td>(d) Cutaneous hypersensitivity</td>
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<td>(iii) Ocular symptoms (any of the three)</td>
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<td>(a) Iridocyclitis</td>
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<td>(b) Chorioretinitis, retino-uveitis</td>
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<td>(c) Definite history of (a) and/or (b)</td>
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<td>(iv) Genital ulcers</td>
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<td><strong>2. Minor criteria</strong></td>
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<td>(i) Arthritis without deformity and ankylosis</td>
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<td>(ii) Epileptidymatis</td>
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<tr>
<td>(iii) Gastro-intestinal lesions characterized by ileoceleal ulcers</td>
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<tr>
<td>(iv) Vascular lesions compatible with Behçet’s disease</td>
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<tr>
<td>(v) CNS symptoms compatible with Behçet’s disease</td>
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<td><strong>3. Diagnosis</strong></td>
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<tr>
<td>(i) Complete type</td>
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<tr>
<td>Four major symptoms apparent during the clinical course</td>
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<tr>
<td>(ii) Incomplete type</td>
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<tr>
<td>(a) Three major symptoms or two major and two minor symptoms apparent during the clinical course</td>
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<tr>
<td>(b) Typical ocular symptoms and another major symptom or two minor symptoms apparent during the clinical course</td>
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<tr>
<td>(iii) Suspected type</td>
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<tr>
<td>Some major symptoms apparent but not fulfilling the above two, or typical minor symptoms occurred</td>
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<tr>
<td>(iv) Subtypes</td>
</tr>
<tr>
<td>(a) Intestinal Behçet’s disease</td>
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<tr>
<td>(b) Vascular Behçet’s disease</td>
</tr>
<tr>
<td>(c) Neuro-Behçet’s disease</td>
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<td><strong>4. Findings useful in diagnosis</strong></td>
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<tr>
<td>(i) Cutaneous needle reaction</td>
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<td>(ii) Inflammatory reactions: rise in ESR, positive CPR, and increase in number of peripheral WBC</td>
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<td>(iii) HLA B51 (B5)</td>
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</table>

Differential diagnosis of BD includes Reiter’s syndrome, Stevens-Johnson syndrome, systemic lupus erythematosus, Crohn’s disease, ulcerative colitis, ankylosing spondylitis and herpes simplex infection with aseptic meningitis.

COURSE AND PROGNOSIS

BD presents a highly variable clinical course, with recurrences and remissions. The initial manifestations are usually oral or genital ulcers and ocular lesions. As the disease progresses, diffuse vascular and neurologic findings occur. The relapsing attacks are more frequent early in the
course of the disease and may be fatal. Death can also result from treatment of the disease. Eye involvement, in the last stage may cause blindness and comprises one of the major causes of morbidity. The involvement of neurologic, gastrointestinal and vascular system appear to have poor prognosis. The worst prognosis is seen in young, adult males.

### Table II. International criteria for classification of Behçet's disease (1992)

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
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<tr>
<td><strong>Recurrent oral ulceration</strong></td>
<td>Minor aphthous, major aphthous or herpetiform ulceration observed by a physician or reported reliably by patient. Reocurrence at least three times in one 12-month period.</td>
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<tr>
<td><strong>Plus 2 of</strong></td>
<td></td>
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<tr>
<td><strong>Recurrent genital ulceration</strong></td>
<td>Recurrent genital aphthous ulceration or scarring, especially males, observed by physician or reliably reported by patient.</td>
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<tr>
<td><strong>Eye lesions</strong></td>
<td>Anterior uveitis. Posterior uveitis. Cells in vitreous on slit lamp examination. Retinal vasculitis observed by qualified physician (ophthalmologist).</td>
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<tr>
<td><strong>Skin lesions</strong></td>
<td>Erythema nodosum-like lesions observed by physician or reliably reported by patient. Pseudofolliculitis. Papulopustular lesions. Or Aneiform nodules consistent with Behçet's disease - observed by a physician and in post-adolescent patients not receiving corticosteroids.</td>
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<tr>
<td><strong>Positive pathergy test</strong></td>
<td>To be read by a physician at 24-48 h, performed with oblique insertion of a 20-gauge or smaller needle under sterile conditions.</td>
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Note: Findings are applicable if no other clinical explanation is present.

### TREATMENT

**Topical therapy**: Topical therapy is mainly used for the treatment of oral, genital and eye lesions. Besides general measures of oral hygiene by using standard mouthwashes or chlorhexidine, topical preparations of local anesthetics (2% lidocaine gel) and topical potent steroid preparations (0.1% triamcinolone acetonide in Orabase) applied three or four times daily provide symptomatic relief. The topical use of tetracyclines which has antiviral, antibacterial and antichemotactic activities has been recommended for oral ulcers. The content of a 250 mg capsule is dissolved in 5 ml of water and the solution is kept in the mouth for 2 minutes before swallowing. In an open, preliminary report, recombinant interferon - alpha has been found to reduce the number of oral ulcers when applied topically, but later with a lower dose, its moderately beneficial effect was not confirmed in a double blind placebo controlled study.

Local application of corticosteroids in genital ulcerations and the use of mydriatics and corticosteroids in the ocular inflammation have therapeutic effects. Topical agents that coat oral ulcers, like sulcrate and tannic acid in alcohol have limited effects.

**Systemic therapy**: Although colchicine is still the first-choice in Japan, Aktulga et al. in a controlled study have shown colchicine to be ineffective in most manifestations of BD. It exerts its therapeutic effect by inhibiting polymorphism nuclear chemotaxis and has been found beneficial in cutaneous and ocular manifestations with 1mg daily dose for 2 months to 2 years. Raynor and Askari have reported that they have achieved remarkable improvement of cutaneous, ocular and gastrointestinal manifestations in a patient with 0.6 mg oral colchicine twice daily for 5 weeks. The purpose of its use, however, is to prevent recurrences rather than to treat the active disease.

Corticosteroids (prednisone or prednisolone) have been advocated in the treatment of acute inflammatory manifestations of BD and especially indicated in patients with severe central nervous system and eye involvement. It is more effective in early active disease than the chronic stage and generally the meningencephalitis has a better response to steroid treatment than other types of neurologic involvement. The recommended dose of oral prednisone is 60 to 100 mg daily for ocular and neurologic manifestations, whereas 4 to 6 mg/day is usually enough to control mucocutaneous and articular symptoms. However, there is debate as to whether corticosteroids improve or may even aggravate isolated macular edema and particularly during tapering the steroid, in order to avoid the exacerbations, additive effect of another immuno-suppressive agent such as cyclophosphamide, chlorambucil or azathioprine is usually required.

Cyclophosphamide, chlorambucil, azathioprine and cyclosporine are the cytotoxic agents that are used in BD. Cyclophosphamide, at a dose of 2 to 3 mg/kg/day orally or preferably as intravenous bolus treatment has beneficial effect in mucocutaneous, articular and ocular manifestations. The daily dose should be reduced when leukopenia occurs.

Although the administration of cyclophosphamide in a dose of 1 to 1.5 g intravenously per month is also...
recommended, there is a recent suggestion that it should be given in lower doses more frequently, such as 500 mg per week. Chlorambucil is a low-toxicity drug and is relatively well tolerated. It is administered in doses of 6 to 8 mg daily and useful especially for ocular lesions as well as for mucocutaneous, arthritic, vascular and neurologic manifestations. Prolonged treatment, with doses of 2 to 4 mg daily may be necessary to maintain remission. However, the risks of long-term chlorambucil therapy including myelotoxicity and irreversible azoospermia, outweigh its benefits in BD. Azathioprine, in a 2.5 mg/kg daily dose has been useful in controlling the evolution of the disease, particularly the progression of ocular disease may be prevented if initiated early. It is not effective as a single agent and its serious side effects include myelotoxicity, sterility, opportunistic infections and hepatotoxicity.

Cyclosporin, an immunomodulating agent, has been demonstrated to be effective in acute inflammatory eye disease as well as mucocutaneous and arthritic symptoms. It appears to be superior to colchicine in the ocular involvement. The recommended dose of cyclosporin in BD is 5 to 10 mg/kg/day. Ben Ezra et al. compared 5 to 10 mg/kg/day of cyclosporin with either corticosteroid or chlorambucil. They found that although cyclosporin was superior in its ability to alleviate ocular disease, conventional therapy permitted better control of the extracellular manifestations. Ozyazgan et al. have reported that low dose cyclosporin (5 mg/kg/day) is significantly more effective in the ocular involvement than monthly intravenous bolus injections of 1000 mg of cyclophosphamide for the initial 6 months of treatment. However exacerbations of the symptoms are common after withdrawal of the drug. Side effects such as gingivitis, renal toxicity, hypertension, hirsutism, nausea have been known and may limit its use. Cyclosporin induced renal toxicity can be reduced with the use of bromocriptine (2.5 mg 3 to 4 times daily) in combination.

FK506 is a novel immunosuppressive agent which has a similar action to that of cyclosporin, has been reported to be effective in severe and refractory ocular involvement in BD as well as pulmonary infiltrates and skin lesions of a patient with BD showed improvement.

Other therapeutic approaches: Levamisole, an anthelmintic, in doses of 50 mg three times daily for 2 days each week, has been found to be useful especially in oral and genital ulcerations, possibly due to its immunomodulatory effect. Transfer factor prepared from leukocytes of healthy persons and injected subcutaneously, may be used in reducing the cutaneous and articular manifestations. Plasmapheresis which remove immune complexes from circulation, can be useful adjunct in emergency situations but is not practical for chronic use. Dapsone, a drug of similar action to colchicine has been found effective at a dose of 100 mg daily in patients with skin and genital lesions. Aspirin and nonsteroidal anti-inflammatory agents have been helpful in arthritic symptoms and pericardial effusion. Şimşek et al. have reported that 88% of skin lesions and 80% of joint manifestations of BD responded to indomethacin treatment in an open study. Sulphasalazine, 2 to 4 g daily, is reported to be beneficial in gastrointestinal involvement. Thalidomide, in a dose of 200 to 400 mg/day has been used in mucocutaneous lesions of BD, however, it is highly teratogenic and not available in most countries. The efficacy of the antiviral agent acyclovir in BD is controversial; although it has been found promising in BD. Davies et al. have reported negative results with acyclovir in a double-blind trial. For inflammatory ocular disease methotrexate seems to be a possibility. Durand et al. have suggested that interferon-alpha2b may be a beneficial alternative in BD with severe ocular involvement resistant to standard treatment.

Anticoagulants appear to have no place in the treatment of the vascular complications of BD. Ethylestrenol and phenformin, streptokinase and stanozolol and low-dose aspirin have been recommended to treat thromboembolitis.

REFERENCES

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