Behçet's Disease

Reynold C. Wong, M.D., Charles N. Ellis, M.D., and Luis A. Diaz, M.D.

From the Immunodermatology Unit, University of Michigan School of Medicine, and the Veterans Administration Medical Center, Ann Arbor, Michigan

Behçet's disease is classically described as featuring recurrent aphthous ulcers in the mouth and genital organs and relapsing iritis.[1] Other manifestations involve the skin, joints, cardiovascular and central nervous systems, and gastrointestinal tract.[1]

Hippocrates was the first physician to describe patients with orogenital ulcerations and chronic inflammation of the eyes.[1] Between 1908 and 1931, similar cases were often described in the literature and attributed to syphilis, staphylococcal infection, streptococcal hypersensitivity, or tuberculosis allergy. In a series of publications beginning in 1937, Hulusi Behçet, a Turkish dermatologist, described a clinical entity, which now bears his name, characterized by transient and recurrent ulcerations in the mouth and genitalia and relapsing uveitis.[1] The ocular involvement sometimes was complicated by pus in the anterior chamber of the eye (hypopyon).

During the ensuing 45 years, the broad, multisystem nature of this disease has been recognized; in addition to the characteristic findings, intestinal, articular, vascular, and neurologic involvement has been noted in some patients.[2] Despite intensive study, the etiology of Behçet's disease is unknown.

The diagnosis of Behçet's disease is based on clinical grounds because there are no pathognomonic laboratory features.[3] Unfortunately, neither is there any single sign or symptom that is sufficiently specific to establish the diagnosis. Each is seen alone or in combination with others in a variety of disorders. The fact that the signs and symptoms of Behçet's disease can remit spontaneously and are often separated from one another by years has resulted in diagnostic confusion in more than one patient. Table 1 lists the most common findings in Behçet's disease. A list of differential diagnoses includes Stevens-Johnson syndrome, Reiter's syndrome, systemic lupus erythematosus, recurrent aphthous stomatitis, inflammatory bowel disease, and aphthous stomatitis with vulvitis in girls and young women.[2,4]

The disease has a peculiar distribution: most cases have been reported in patients from the Mediterranean basin, the Middle East, and Japan.[5] The prevalence in Japan is 1 in 10,000, with an estimate in 1979 of 11,000 affected persons in that country alone.[2] In Yorkshire, England, the prevalence is about 1 in 150,000, and in Olmsted County, Minnesota, the prevalence is about 1 in 300,000.[2,5] The disease occurs more often in men than in women in most series, but in North America, Britain, and Australia, women are in the majority.[2,5] The mean age of onset is in the third decade.[4]

Clinical Manifestations

Findings in Behçet's disease have been grouped into major and minor criteria (Table 1). The diagnosis may be made with confidence if all four major symptoms appear in the clinical course of the patient[2]; however, combinations of major and minor criteria have been proposed by various authors as reasonably specific for Behçet's disease.[4,6,7]

Aphthous Stomatitis

Recurrent aphthous stomatitis occurs in nearly all patients diagnosed as having Behçet's disease (Fig. 1).[3] The oral ulcers are the first manifestations of the disease process in 75% of patients.[8] Preferential sites of ulceration are the mucous membranes of the lips, the gingiva, buccal mucosa, and tongue.[8] At an early stage, there is a circular red area.[2] In 1 or 2 days, a shallow round or oval ulcer develops that is 2–10 mm in diameter and has discrete erythematous borders.[2,4,8] A white or yellowish necrotic pseudomembrane usually covers the surface of the ulcer.[2,4] Lesions heal within 10–14 days, usually without scarring.[2,8] The ulcers appear either as single or

Supported by Research Grant IROI AM 21608-03 AI from the National Institute of Health.

Address for reprints: Reynold C. Wong, M.D., Department of Dermatology, University of Michigan, Ann Arbor, MI 48109-0010.

TABLE 1. *Diagnosis of Behçet's Disease*

Major criteria
Recurrent aphthous stomatitis
Recurrent aphthous genital ulcerations
Eye lesions
Recurrent uveitis
Chorioretinitis
Skin lesions
Cutaneous vasculitis (erythema nodosumlike lesions)
Thrombophlebitis
Skin hyperreactivity
Minor criteria
Arthralgia/arthritis synovitis
Intestinal ulcers
Central nervous system involvement
Meningoencephalitis
Brain stem involvement
Psychologic changes
Orchitis/epididymitis

multiple lesions[8] and recur at irregular intervals (several days to several months).[2,4]

Genital Ulcers

Aphthous ulcers similar to the mouth ulcers also occur as genital lesions, usually on the scrotum, glans penis, vulva, vagina, and perianal area.[2,3,9] They usually are small, punched-out, and deeper than the oral ones.[2,3] They tend to be more painful in men and may leave scars in both sexes.[2] In most patients, recurrences of the genital ulcerations are less frequent than recurrences of the oral ones.[5]

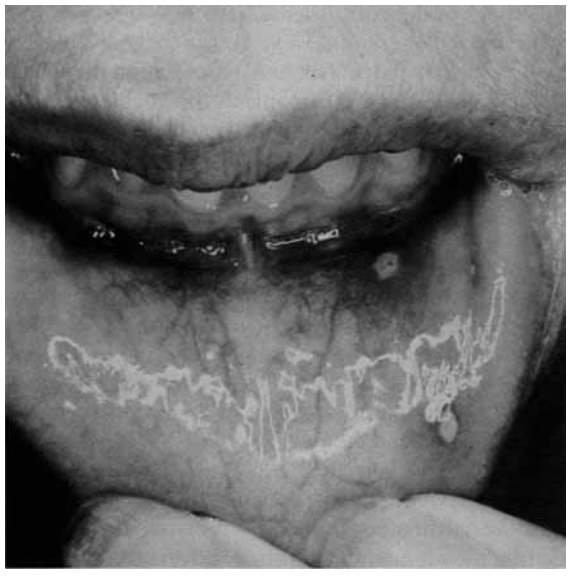

FIG. 1. Aphthous ulcerations on the lower lip.

Other Cutaneous Lesions

Nodular lesions on the lower extremities resembling erythema nodosum are often found in Behçet's disease.[2] The nodules tend to be small, few in number, sometimes grouped and ulcerated, bluish in color, and tender.[4,5] They tend to disappear in 10–14 days, but recurrences are common.[2] Clinically, the lesions in Behçet's disease correspond closely to erythema nodosum; however, the Behçet lesions differ histologically from classic erythema nodosum because they lack histiocytic granulomas.[4]

A characteristic, although not pathognomonic, finding in Behçet's disease is pathergy or skin hyperreactivity, believed to be secondary to increased chemotaxis.[2,10] Twenty-four to 48 hours after a sterile needle prick or an intradermal injection of saline, saliva, or genital ulcer extract, the patient develops a tuberculinlike reaction, with erythema and edema.[2] Aseptic pustules often occur as well. Histologic findings are time-dependent: at 6 hours, an inflammatory exudate composed mainly of polymorphonuclear leukocytes is seen; after 24 hours, there is a dense polymorphonuclear infiltration along with mononuclear cells and large numbers of mast cells.[10] The percentage of Behçet patients with a positive pathergy test varies. Studies in this country show pathergy to be uncommon.[11,12] In the Mediterranean countries, including Israel and Turkey, however, there is a 40–88% prevalence of pathergy in patients with Behçet's disease.[4,10,13,14] A study conducted in Turkey in 1980 revealed a positive pathergy test in 88% of 84 patients with the disease, compared with no reaction in 20 healthy controls and positivity in only 7% of 102 diseased controls (patients with recurrent aphthous stomatitis, iridocyclitis, herpes genitalis, idiopathic erythema nodosum, or rheumatoid arthritis).[10]

Other associated skin lesions include papules, pustules, vesicles, abscesses, folliculitis, pyodermas, and erythema multiforme.[2,5,8,9] An eruption resembling acne vulgaris is sometimes seen (Fig. 2).[2] Thrombophlebitis is not uncommon in patients with Behçet's disease.[2,4]

Ocular System

Commonly, the most serious problem in Behçet's syndrome is ocular involvement.[2] Recurrent attacks of anterior and posterior uveitis can lead to blindness.[2,3,9] Iridocyclitis and hypopyon are common in the anterior chamber and are usually transient with no apparent long-term sequelae (Fig. 3).[5,8] Manifestations in the posterior ocular structures include chorioretinitis, retinal vessel arteritis or phlebitis, optic papillitis, and vitreous hemorrhage.[4,8] Recurrent attacks in the posterior struc-

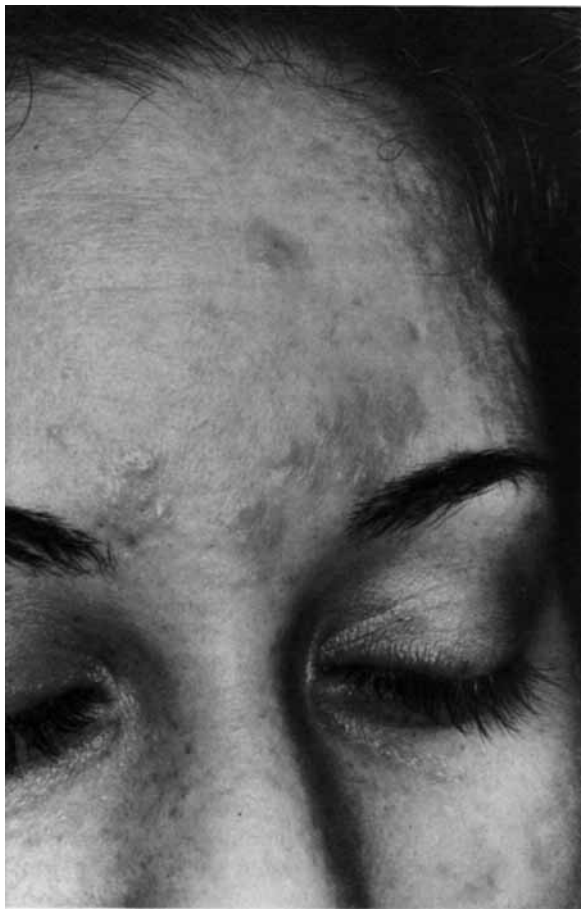

FIG. 2. Acneiform eruption of the face.

tures can lead to blindness in 5–6 years.[2,8] Glaucoma and cataracts also can occur.[8] Severe ocular involvement occurs with particular frequency in Japanese victims of Behçet's disease: 50–80% of Japanese patients suffer partial loss of vision.[2] In fact, Behçet's disease is a leading cause of acquired blindness in Japan, accounting for about 12% of all acquired blindness before the age of 50 years.[2]

Joint Manifestations

More than one-half of the patients will develop signs or symptoms of joint involvement during the course of the disease.[2] Usually, these include arthralgias, erythema, and swelling; the knees, wrists, elbows, and ankles are the most frequently involved joints.[2,4,8] The synovial fluid is of the inflammatory type with a predominance of polymorphs, and it forms a poor mucin clot.[4,5] Destruction and atrophy of bone and cartilage can occur occasionally.[2]

FIG. 3. Hypopyon iritis. (Courtesy of Alan Sugar, M.D., Department of Ophthalmology, University of Michigan Hospitals.)

Gastrointestinal Tract

Serious involvement of the digestive tract can occur, with ulcers being observed throughout the alimentary tract, usually involving the terminal ileal, colonic, and rectal mucosa.[2,4] The ulcers are shallow with normal intervening mucosa.[2,4] There is no formation of abscesses or granulomata. In at least 50% of patients, some gastrointestinal symptoms are present, including vomiting, abdominal pain, flatulence, diarrhea, and constipation.[2]

Central Nervous System

Neurologic involvement occurs in 25% of the patients,[4] usually in the 2nd–5th years of the disease.[9] Meningoencephalitis, cerebellar symptoms, pyramidal tract, and extrapyramidal tract signs may appear.[2–4,8]

Other Systems

The cardiovascular system, lungs, kidneys, liver, and testicles occasionally are involved, with arterial occlusions, venous occlusions, aneurysms, pulmonary opacities, glomerulonephritis, hepatomegaly, and epididymitis.[2]

Course and Prognosis

The clinical course of the disease is variable. Typically, oral aphthous ulcers and ocular lesions appear first, followed by genital ulcers, skin lesions, and arthritis.[2,4] Nervous-system or vascular involvement begins later.[2] Frequent attacks early, with a slower rate of attacks after 3–7 years, characterizes the course of the disease in many patients. Eye symptoms tend to become chronic during this later period, with loss of visual acuity and, ultimately, blindness.[2–4] Without central nervous system, bowel perforation, or large artery involvement,

the prognosis for life is good.[8] Generally, young men have the worst prognosis.[2] Some investigators think that the progression of the disease may be altered with therapy, particularly with immunosuppressive agents.[3,15]

Etiology and Pathogenesis

The cause and pathogenesis of Behçet's disease are unknown; some of the theories about the pathogenesis of Behçet's disease are presented below.

Genetic Studies

A genetic predisposition has been postulated because of the three- to fourfold increased frequency of HLA-B5 in Behçet's disease patients in some countries.[1,2,5,8,9] This has been observed in Japan, Turkey, Israel, and Southern France, but not always in England or the United States.[1,2,5,9] HLA-B5 seems to be particularly associated with ocular disease.[8,16] The occurrence of HLA-B12 also is increased in Behçet's disease, especially in association with mucocutaneous involvement.[8,16] In several studies from England, the prevalence of HLA-B27 was increased and was associated with arthritis.[2,9,16]

Immunologic Findings

Allergies reportedly play a part in initiating the onset of Behçet's disease.[2,17] There is evidence that ingestion of certain foods, such as English walnuts, exacerbates oral ulcerations in Behçet's disease.[17] A reduced in vitro T cell reactivity to both walnut extract and candidal antigens in both Behçet patients and controls within 2 days after ingestion of 100 grams of walnuts has been observed, with associated increases in the frequency and severity of typical Behçet lesions in the former[17]; however, it is reasonable to speculate that oral mucosal trauma by nut spicules is the inciting event for the well-documented postwalnut flares.[5]

In 1963, Oshima et al showed antibodies against human mucous membranes in 42% of 40 patients.[18] Several years later, O'Duffy et al demonstrated elevations of serum immunoglobulins A (4 of 9 patients), M (4 of 9 patients), and G (1 of 9 patients).[11] Markedly decreased levels of both free and bound secretory component of IgA in the saliva of four patients with Behçet's disease have been demonstrated. Secretory IgA is important for host defenses at the mucous membrane level, and the secretory component is needed for local IgA binding.[19] This supports the theory that an antigenic substance (ie, virus) exists in the oral cavity and is able to gain transmucosal access because of impaired IgA binding with resultant stimulation of antibody formation and an immune complex disease.[5]

Immune complexes may be important in the pathogenesis of this disease,[20] because many of the clinical manifestations of Behçet's disease, such as erythema nodosum, arthritis, and uveitis, have been attributed to immune complexes.[21] Immunofluorescence confirms the deposition of IgM and IgG in vascular walls, especially in the venules.[2] Elevated levels of circulating immune complexes were shown in one study to be present in up to 60% of patients.[5] In another series, 44% of patients were found to have significantly elevated levels of immune complexes by the Raji-cell assay and 50% by the Clq-binding assay.[20] In both studies, a good correlation was shown between the disease activity and the measured amount of immune complexes.[1] It has also been shown that the levels of immune complexes are higher in the neuroocular and arthritic types of Behçet's disease than in the mucocutaneous variety.[22]

Complement components have also been studied in Behçet's disease. The total complement level as well as C9 usually are elevated in patients with this disease; however, there is a significant reduction of C2, C3, and C4 just before an attack of uveitis due to activation of the classical pathway.[21] Biopsy of oral ulcers reveals deposition of C3 and C9 in blood vessel walls and of C9 in the basement membrane.[16] Complement components appear to play a part in the lysis of affected cells in Behçet's disease. Lehner and coworkers found membrane fragments from an unknown source by electron microscopic examination, as well as IgG immune complexes in the blood of patients.[22,23] The results suggest that the immune complexes might activate the C5–C9 sequence, resulting in cell lysis.[23]

Lymphocytes from patients with Behcet's disease show cytotoxicity to homogenates of oral mucosa,[24] and significant lymphocyte transformation is induced by homogenates of fetal oral epithelium in recurrent oral ulceration (which some investigators consider a *forme fruste* of Behçets' disease).[25] Other observations include an enhanced chemotactic activity of polymorphonuclear leukocytes, an elevated erythrocyte sedimentation rate, and a transient elevation in acute phase reactants, such as C-reactive protein, during relapses.[2,4] It is possible that C-reactive protein modulates the immunologic mechanism by inhibiting T-lymphocytes, promoting phagocytosis, and activating complement.[26]

The common antigenic determinants shared among the skin and the mucous membranes of the mouth, gastrointestinal tract, conjunctiva, and external genitalia may play some part in the involvement of different organs in Behçet's disease[1]; however, a coherent basis for autoimmunity is lacking as long as the specific antigen remains unidentified.[5] It should also be noted that most of the immunologic abnormalities lack specificity; for example, many of them occur in uncomplicated recurrent aphthous stomatitis.[5]

Virologic Studies

Many studies throughout the years have lent support to a viral etiology in Behçet's disease. Behçet himself saw viruslike particles in exudate from ulcers and hypopyon fluid.[4,5] Alm and Öberg injected cerebrospinal fluid from patients with Behçet's disease into rabbits by the cisternal route. Four subsequent untreated generations of the injected rabbits developed focal encephalitis, optic neuritis, uveitis, keratitis, and conjunctivitis.[27]

Sezer described the isolation of an agent from the vitreous body and subretinal exudates that he thought was a virus. This agent produced pock lesions on the chorioallantoic membranes of fertile eggs and, sometimes, death of the embryo. It produced signs of encephalitis in mice, and a disease in rabbits similar to the human disease. Antibodies to the agent could be demonstrated by complement-fixation tests at the 1:16 to 1:128 level in the sera of 11 of 12 patients with Behçet's disease and in 3 affected rabbits but not in 16 human and 3 rabbit controls.[28] A further study on 20 patients confirmed his previous observations.[29]

Evans and co-workers reported that they too had recovered a virus by chorioallantoic inoculation with material taken from the anterior chamber and brain of a patient with fatal Behçet's disease. This agent produced pock lesions on the egg membrane and was maintained for 21 consecutive passages.[30] Mortada and Iman reported similar results.[31]

Using the principles that a cell already infected by a virus may be refractory to superinfection by the same or closely related strains of virus and that chromosomal abnormalities are common in viral infections, one recent study indirectly tested the hypothesis that Behçet's disease is caused by a virus. They showed that herpes simplex virus type I had impaired replication on lymphocytes cultured from 37% of the patients with Behçet's disease and that lymphocytes were chromosomally abnormal in 42% of patients.[32] This study provided support for a viral etiology in Behçet's disease.

Studies designed to investigate further the role of viruses, including inoculation of subhuman primates, are in progress.

Nevertheless, numerous other workers have failed to isolate a virus.[7,9,33–36] Arguments against a viral etiology are that infectivity is not a marked feature of Behçet's disease, immunity is absent, the disorder does not occur in epidemics, and only rarely has more than one case in a family been described.[9,37]

Miscellaneous Findings

Heavy metals, such as zinc, and toxic substances, such as organophosphate pesticides, have been implicated in the etiology of Behçet's disease.[2,5] Climatic factors have been claimed to be important, based chiefly on evidence suggesting increased prevalence in colder climates and occurrences of ocular attacks in greater numbers during and immediately after the passage of icy winds across Japan.[2]

Treatment

Many different treatment schedules have been tried with varying success. The treatment of Behçet's disease is difficult to evaluate because of the many spontaneous exacerbations and remissions that mark the course of the disease. The problem is increased further by the rarity of the disease and the limited experiences of most investigators.[38] Most studies are uncontrolled. Side-effects of the treatments are significant in most instances. Topical and systemic corticosteroids are the mainstay of treatment for Behçet's disease.

Topical Therapy

All of the topical therapeutic agents used in recurrent aphthous ulcers have also been used in Behçet's disease with mucocutaneous manifestations.

Topical Steroids. Topical corticosteroids are useful in aphthous ulcers if they are applied during the prodromal stage of ulceration. The most useful preparations are triamcinolone cream 0.1% in Orabase, 2.5 mg tablets of hydrocortisone sodium succinate, and 0.1 mg tablets of betamethasone valerate.[21] The steroid tablets can be made into a slurry with water. Topical steroids should be applied three to four times daily.[21] Suppression of ocular inflammation also has been achieved with topical steroids.[11]

Tetracycline. Tetracycline is the drug of choice in the treatment of the oral ulcers.[21] The mode of action is uncertain, but it does have antibacterial, antimycoplasmal, and antiviral properties.[21] The results of a double-blind trial of tetracycline versus placebo in 25 patients with recurrent aphthous oral ulcerations revealed significant reduction in ulcer size, duration, and pain in the tetracycline group.[39] Such treatments are accomplished by dissolving the contents of one 250 mg capsule in about 5 ml of water or flavored syrup. The patient holds the solution in the mouth for about 2 minutes, then swallows it; this is repeated four times daily.[39] This represents a combination of topical and systemic therapy.

Miscellaneous Agents. Patients with severe ulcerations find it difficult to maintain their oral hygiene and may accumulate large deposits of bacterial plaque. Mouthwashes used once or twice daily can be helpful.[21] Chlorhexidine used as a mouthwash once or twice daily has been tried in a small double-blind trial with some resolution of the ulcerations.[40]

Treatment of uveitis with mydriatics has been reported to be partially effective.[41]

Systemic Therapy

Immunosuppressive and Antiinflammatory Agents.

Systemic Corticosteroids. Although it is at best palliative,[2,7] corticosteroid therapy is the mainstay of therapy for all manifestations of Behçet's disease, especially cutaneous, ophthalmic, and neurologic disease and progressive thrombophlebitis.[3,4,7] Corticosteroids exert a beneficial effect on the acute manifestations but seem to have little effect on the chronic and late sequelae, such as blindness and paralysis.[4] Recurrences are common,[4] and the disease may progress even while steroids are being used.[11] Doses as low as 4 mg of prednisone daily have been shown to be useful in suppressing the cutaneous and articular symptoms[11]; however, 60 mg of prednisone orally per day is required during the acute manifestations.[4,7] Some investigators think that a relapse is a signal for combined corticosteroid and azathioprine or chlorambucil therapy.[7,42,43] Corticosteroids also can be injected into affected joints or retrobulbar tissues to reduce inflammation.[4]

Chlorambucil. Chlorambucil is the best studied of the immunosuppressive agents and is probably the least toxic, the best tolerated, and the most effective in comparison with azathioprine and cyclophosphamide.[5,15,43,44] In three separate studies, a total of 36 patients with iridocyclitis and conjunctivitis with decreased visual acuity were treated with chlorambucil. Approximately 80% of the patients showed improvement in visual acuity over a period of observation of 1–5 years, and some had no recurrences during this time.[15,43,44] In addition to the benefits in ocular disease, similar benefits were noted in oral, genital, and cutaneous lesions, arthritis, neurologic involvement, and thrombophlebitis. It appears that chlorambucil is best administered with corticosteroids, with gradual tapering of the latter.[3] No serious toxic side-effects were encountered with patients on 6–8 mg per day of chlorambucil.[15]

Azathioprine. The use of azathioprine therapy for Behçet's disease has been effective in reducing ocular symptoms in some patients, but side-effects have been significant with leukopenia, exanthems, nausea, and epigastric pain, forcing discontinuation in a few patients.[7,43,45] Dosages used were in the range of 1.0–2.0 mg/kg/day.

Other Drugs. One case report demonstrated clearing of mouth ulcers and visual improvement with prednisone and cyclophosphamide therapy but not with prednisone alone.[46] Antiinflammatory agents, such as indomethacin and aspirin, have been used with limited success.[47]

Other Systemic Therapies.

Levamisole. Levamisole, an antihelmintic, is thought to have effects on cellular immunity, probably by influencing T cells.[21,48–50] Because T cell dysfunction is suggested in Behçet's disease,[5] it is hypothesized that levamisole might correct this dysfunction by correcting a deficiency in T suppressor cells, thus potentiating cell-mediated immune responses.[21,50] In a recent study, 9 of 11 patients responded to levamisole with a reduction in the number and severity of buccal and genital lesions, a decrease in ocular inflammation and gastrointestinal symptomatology, and an improvement in neurologic status.[51] James stated that 50 mg of levamisole three times daily for 2 days each week was helpful in overcoming oral or genital ulcers in about one-third of patients.[16]

Colchicine. The chemotactic activity of polymorphonuclear leukocytes is increased in Behçet's disease, and this has provided the rationale for using colchicine, a strong inhibitor of chemotaxis, in the treatment of the disease.[52] Conflicting reports regarding the efficacy of colchicine have been published.[53–57] A controlled double-blind study in 1980 had 14 patients receiving colchicine 0.5 mg per day and 14 patients receiving placebo. There was no effect of colchicine on oral aphthous ulcerations, genital lesions, pyodermas, or eye lesions. In some patients, however, it was useful in controlling erythema nodosum and arthralgias.[53] On the other hand, two uncontrolled studies from Japan seemed to show significant improvement using colchicine.[54,55] One was a retrospective study of 157 patients with typical and frequent ocular attacks treated with colchicine for more than 1 year on a dosage of 0.5 mg orally one to three times per day. Thirty percent of patients were much improved, 37% improved, 27% had no change, and about 7% got worse.[54] The second study presented five patients with oral ulcers, genital erosions, and erythema nodosum, which greatly improved with colchicine therapy after 1 month.[55] One case of Behçet's disease with necrotizing vasculitis, arthritis, and oral and genital ulcers was responsive to colchicine 0.6 mg p.o. twice per day to four times per day.[56] Another case report of Behçet's disease characterized by anterior uveitis, arthritis, and oral, genital, and cutaneous lesions documented remission of cutaneous lesions and no recurrence of ocular or gastrointestinal manifestations with 0.6 mg oral colchicine twice daily for a period of 5 weeks.[57]

Fibrinolytic Drugs. Ethylestrenol and phenformin, as well as oral streptokinase and stanozolol, an anabolic steroid, have been used successfully in patients with thrombophlebitis and a decreased blood fibrinolytic activity.[58,59] Phenformin and ethylestrenol also have been used effectively on a patient with thrombophlebitis and a normal blood fibrinolytic activity.[60] These investigators proposed that these drugs might have been acting by decreasing platelet adhesiveness or by modifying fibrinolysis in the tissues without modifying the blood fibrinolytic activity.[60]

Transfer Factor. Effectiveness has been noted in various studies using subcutaneous injections of transfer fac-

tor derived from the lymphocytes of healthy people.[2,61,62] Remission of some recalcitrant lesions and reduction in the number of new lesions and new attacks have been observed.[2] In one study, 5 patients with Behçet's disease were treated with transfer factor for aphthous stomatitis, genital ulcers, and skin lesions. Three patients showed great improvement, one showed moderate improvement, and one was unresponsive.[61] In another study, three patients were treated with weekly injections of transfer factor, with one patient showing clearing of arthritis, conjunctivitis, and mucosal ulcers after 5 months, a second patient having only a slight decrease in the severity of oral ulcerations, and a third patient showing worsening of genital lesions.[62]

Hematotherapy. Transfusions of fresh blood, gamma globulin, or plasma have been shown in three studies to induce temporary remissions in aphthous ulceration, uveitis, and colitis in a few patients.[63–65] Most of these patients were on concomitant oral prednisone and azathioprine. In general, hematotherapy is ineffective in Behçet's disease.

Poliomyelitis Vaccine (Sabin). In Israel, two patients have been treated with the Sabin polio vaccine with encouraging results. One was a 33-year-old woman with a 12-year history of Behçet's disease,[66] and the other was a 22-year-old man with a 5-year history of Behçet's disease.[67] Four to five drops of the vaccine were taken orally every month for 3–5 months. The patient's responded rapidly, and at the end of 2½–3 years, all orogenital ulcerations and skin lesions had disappeared in both patients. The woman was completely well, and the man had only some residual arthritis and stable uveitis. This treatment may deserve further trials.

Chloroquine, Hydroxychloroquine. O'Duffy mentions that chloroquine or hydroxychloroquine used in five patients with Behçet's disease was helpful.[41]

Summary

Behçet's disease is a multisystem disease featuring mucocutaneous, ocular, intestinal, articular, vascular, urogenital, and neurologic involvement. While classically intermittent in its manifestations, the disease can stabilize and become chronic in a given organ system. The diagnosis of Behçet's disease is based on clinical criteria. Recurrent aphthous ulcerations in the mouth, skin lesions, eye lesions, and genital ulcerations must be present during the course of the disease for a diagnosis of Behçet's disease to be made unequivocally. A nonspecific skin hyperreactivity called pathergy is said to be helpful in the diagnosis. There are no pathognomonic laboratory findings, but biopsy usually shows a venulitis.

The pathogenesis of the disease is unknown. No virus has been satisfactorily isolated to date. There is evidence of an increased frequency of HLA-B5 and HLA-B12. Humoral and cellular immunity seem to play a major part in the pathogenesis of the various manifestations of the disease.

The treatment of Behçet's disease is difficult to evaluate because of the many spontaneous exacerbations and remissions during the clinical course of the disease. Topical corticosteroids for orogenital ulcers and ocular inflammation are helpful. Intralesional injections for affected joints and retrobulbar tissues are useful in some cases.

Systemic corticosteroids have appeared to be helpful for all manifestations of the disease. It is customary to use 60 mg of prednisone by mouth daily during acute exacerbations, then to taper as the condition improves. Chlorambucil has been shown to be safe and effective for various manifestations of Behçet's disease; often it is used in combination with corticosteroids. Recently, colchicine has been shown to be effective in some patients and might be used if prednisone and chlorambucil are not effective or poorly tolerated by the patient. For thrombophlebitic complications, fibrinolytic agents may be used.

Predictors of prognosis are not as yet clearly delineated. But in the absence of central nervous system, bowel, or large artery involvement, the prognosis for life is good.

Drug Names

azathioprine: Imuran
betamethasone valerate: Valisone
chlorambucil: Leukeran
chlorhexidine: Hibiclens, Hibistat
chloroquine: Aralen
cyclophosphamide: Cytoxan
hydrocortisone sodium succinate: A-hydroCort, Solu-Cortef
hydroxychloroquine: Plaquenil
indomethacin: Indocin
stanozolol: Winstrol
streptokinase: Kabikinase, Streptase

References

1. Müftüoglu AÜ: Symposium on the hematological and immunological aspects of Behçet's disease: opening remarks. Haematologica 65:374, 1980
2. Shimizu T, Ehrlich GE, Inaba G, et al: Behçet disease (Behçet syndrome). Sem Arthr Rheumatism 8:223, 1979
3. Callen JP: Behçet's syndrome. In: Cutaneous Aspects of Internal Medicine. Edited by Callen JP. Chicago, Year Book Medical Publishers, 1981, p 93
4. Chajek T, Fainaru M: Behçet's disease. In: Clinical Immunology. Edited by Parker CW. Philadelphia, WB Saunders, 1980, p 667
5. O'Duffy JD: Behçet's disease. In: Textbook of Rheumatology. Edited by Kelly WB, et al. Philadelphia, WB Saunders, 1981, p 1197
6. Mason RM, Barnes CG: Behçet's syndrome with arthritis. Ann Rheum Dis 28:95, 1969

7. O'Duffy JD, Goldstein NP: Neurologic involvement in seven patients with Behçet's disease. Am J Med 61:170, 1976
8. Cupps TR, Fauci AS: The Vasculitides. Philadelphia, WB Saunders, 1981
9. Wright VA, Chamberlain MA: Behçet's syndrome. Bull Rheum Dis 29:972, 1978-79
10. Tüzün Y, Altaç M, Yazici H, et al: Nonspecific skin hyperreactivity in Behçet's disease. Haematologica 65:395, 1980
11. O'Duffy JD, Carney JA, Deodhar S: Behçet's disease: report of 10 cases, 3 with new manifestations. Ann Int Med 75:561, 1971
12. Kalbian VV, Challis MT: Behçet's disease: report of twelve cases with three manifesting as papilledema. Am J Med, 49:823, 1970
13. Tüzün Y, Yazici H, Pazarli H, et al: The usefulness of the nonspecific skin hyperreactivity (the pathergy test) in Behçet's disease in Turkey. Acta Derm Venereol 59:77, 1979
14. Haim S, Gilham A: Clinical and laboratory criteria for the diagnosis of Behçet's disease. Br J Dermatol 102:361, 1980
15. Mamo JG: Treatment of Behçet disease with chlorambucil. Arch Ophthalmol 94:580, 1976
16. James DG: Behçet's syndrome. N Engl J Med 301:431, 1979
17. Marquardt JL, Synderman R, Oppenheim JJ: Depression of lymphocyte transformation and exacerbation of Behçet's syndrome by ingestion of English walnuts. Cell Imm 9:263, 1973
18. Oshima Y, Shimizu T, Yokohari R, et al: Clinical studies on Behçet's syndrome. Ann Rheum Dis 22:36, 1963
19. Abdou NI, Schumacher HR, Colman RW, et al: Behçet's disease: possible role of secretory component deficiency, synovial inclusions, and fibrinolytic abnormality in the various manifestations of the disease. J Lab Clin Med 91:409, 1978
20. Gupta RC, O'Duffy JD, McDuffie FC, et al: Circulating immune complexes in active Behçet's disease. Clin Exp Immunol 34:213, 1978
21. Lehner T: Progress report: oral ulceration and Behçet's syndrome. Gut 18:491, 1977
22. Levinsky RJ, Lehner T: Circulating soluble immune complexes in recurrent oral ulceration and Behçet's syndrome. Clin Exp Immunol 32:193, 1978
23. Lehner T, Almeida JD, Levinsky RJ: Damaged membrane fragments and immune complexes in the blood of patients with Behçet's syndrome. Clin Exp Immunol 34:206, 1978
24. Rogers RS, Sams WM, Shorter RG: Lymphocytotoxicity in recurrent aphthous stomatitis: lymphocytotoxicity for oral epithelial cells in recurrent aphthous stomatitis and Behçet's syndrome. Arch Dermatol 109:361, 1974
25. Lehner T: Stimulation of lymphocyte transformation by tissue homogenates in recurrent oral ulceration. Immunology 13:159, 1967
26. Lehner T, Adinolfi M: Acute phase proteins, C9, factor B, and lysozyme in recurrent oral ulceration and Behçet's syndrome. J Clin Pathol 33:269, 1980
27. Alm L, Oberg L: Animal experiment in connection with Behçet's syndrome: preliminary report. Nord Med (Hygiea) 25:603, 1945
28. Sezer FN: The isolation of a virus as the cause of Behçet's disease. Am J Ophthalmol 36:301, 1953
29. Sezer FN: Further investigations on the virus of Behçet's disease. Am J Ophthalmol 41:41, 1956
30. Evans AD, Pallis CA, Spillane JD: Involvement of the nervous system in Behçet's syndrome: report of three cases and isolation of virus. Lancet ii:349, 1957
31. Mortada A, Iman ZEI: Virus aetiology of Behçet's syndrome. Br J Ophthal 48:250, 1964
32. Denman AM, Fialkow PJ, Pelton BK, et al: Lymphocyte abnormalities in Behçet's syndrome. Clin Exp Immunol 42:175, 1980
33. Curth HO: Recurrent genito-oral aphthosis and uveitis with hypopyon (Behçet's syndrome): report of two cases. Arch Dermatol Syphilol 54:179, 1946
34. Breslin, HJ: Behçet's disease: report of a case history of seventeen years' duration. Am J Ophthalmol 53:132, 1962
35. France R, Buchanan RN, Wilson MW, et al: Relapsing iritis with recurrent ulcers of the mouth and genitalia (Behçet's syndrome). Medicine 30:335, 1951
36. Katzenellenbogen I: Recurrent aphthous ulceration of oral mucous membrane and genitals associated with recurrent hypopyon iritis (Behçet's syndrome): report of three cases. Br J Dermatol 58:161, 1946
37. Dudgeon JA: Virological aspects of Behçet's disease. Proc R Soc Med 54:104, 1961
38. Chajek T, Fainaru M: Behçet's disease. Report of 41 cases and a review of the literature. Medicine 54:179, 1975
39. Graykowski EA, Kingman A: Double-blind trial of tetracycline in recurrent aphthous ulceration. J Oral Pathol 7:376, 1978
40. Addy M, Tapper-Jones L, Seal M: Trial of astringent and antibacterial mouthwashes in the management of recurrent aphthous ulceration. Br Dent J 136:452, 1974
41. O'Duffy JD: Behçet's syndrome: comments. Bull Rheum Dis 29:977, 1978-79
42. Nethercott J, Lester RS: Azathioprine therapy in incomplete Behçet's syndrome. Arch Dermatol 110:432, 1974
43. Bietti GB, Cerulli L, Pivetti-Pizzi P: Behçet's disease and immunosuppressive treatment. Mod Probl Ophthal 16:314, 1976
44. Mamo JG, Azzam SA: Treatment of Behçet's disease with chlorambucil. Arch Ophthalmol 84:446, 1970
45. Aoki K, Sugiura S: Immunosuppressive treatment of Behçet's disease. Mod Probl Ophthal 16:309, 1976
46. Buckley CE III, Gills JP Jr: Cyclophosphamide therapy of Behçet's disease. J Allergy 43:273, 1969
47. Scarlett JA, Kistner ML, Yang LC: Behçet's syndrome: report of a case associated with pericardial effusion and cryoglobulinemia treated with indomethacin. Am J Med 66:146, 1979
48. Symoens J, Rosenthal M: Levamisole in the modulation of the immune response: the current experimental and clinical state. J Reticuloendothelial Soc 21:175, 1977
49. Bier RE, George B, Wilson T, et al: Evaluation of the therapeutic effect of levamisole in treatment of recurrent aphthous stomatitis. J Oral Pathol 7:405, 1978
50. Drinnan AJ, Fischman SL: Randomized, double-blind study of levamisole in recurrent aphthous stomatitis. J Oral Pathology 7:414, 1978
51. de Merieux P, Spitler LE, Paulus HE: Treatment of Behçet's syndrome with levamisole. Arth Rheumatism 24:64, 1981
52. Matsumura N, Mizushima Y: Leukocyte movement and colchicine treatment in Behçet's disease. Lancet ii:813, 1975
53. Aktulga E, Altaç M, Müftüoglu A, et al: A double blind study of colchicine in Behçet's disease. Haematologica 65:399, 1980
54. Mizushima Y, Matsumura N, Mori M, et al: Colchicine in Behçet's disease. Lancet ii:1037, 1977
55. Miyachi Y, Taniguchi S, Ozaki M, et al: Colchicine in the treatment of the cutaneous manifestations of Behçet's disease. Br J Dermatol 104:67, 1981
56. Hazen PG, Michel B: Management of necrotizing vasculitis with colchicine. Arch Dermatol 115:1303, 1979
57. Raynor A, Askari AD: Behçet's disease and treatment with colchicine. J Am Acad Dermatol 2:396, 1980
58. Cunliffe WJ, Roberts BE, Dodman B: Behçet's syndrome and oral fibrinolytic therapy. Br Med J 2:486, 1973
59. Newland AC, Wood MJ: Behçet's disease. Br Med J 2:1163, 1978
60. Cunliffe WJ, Menon I S: Treatment of Behçet's syndrome with phenformin and ethyloestrenol. Lancet i:1239, 1969
61. Wolf RE, Fudenberg H, Welch TM, et al: Treatment of Behçet's syndrome with transfer factor. JAMA 238:869, 1977
62. Bernhard GC, Heim LR: Transfer factor treatment of Behçet's syndrome, abstracted. J Rheumatol 1:34, 1974
63. Haim S, Sherf K: Behçet's disease: presentation of 11 cases and evaluation of treatment. Israel J Med Sci 2:69, 1966
64. O'Duffy JD, Taswell HF: Blood transfusion therapy in Behçet's disease. Ann Int Med 80:279, 1974
65. Michaud RM, Hathaway DE: Behçet's disease and fresh whole blood transfusion. J Assoc Mil Dermatol 7:30, 1981
66. Tager A: Preliminary report of the treatment of Behçet's syndrome with oral poliomyelitis vaccine (Sabin). Dermatologica 152:372, 1976
67. Fishel B, Tager A, Fishel R, et al: Poliomyelitis vaccine in the treatment of Behçet's syndrome. Arch Dermatol 116:1348, 1980