MEDICAL GRAND ROUNDS

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Mucocutaneous-Rheumatic Syndromes
Behcet's

by

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BEHCET'S SYNDROME

INTRODUCTION

Description of patients with Behcet's syndrome have been found as far back as the writings of Hippocrates, but it was not until Dr. Hulusi Behcet reported six patients with oral and genital ulcers and ocular lesions in 1937 (1) that this triple-symptom-complex became recognized as a clinical entity and gained the status of a syndrome. Prior to that time, however, patients with similar symptoms had been described by Bluthe (2), Adamantiades (3), Dascalopoulos (4), and Whitwell (5). Subsequently, it has been recognized that Behcet's syndrome is a systemic disorder affecting multiple organ systems and that limitation to, or in fact, requiring the presence of the triple-symptom-complex described by Behcet is too restrictive for proper recognition and diagnosis.

EPIDEMIOLOGY

Behcet's syndrome has a world-wide distribution with cases having been reported from virtually every geographic area. However, a vast majority of reported cases have been concentrated in three regions - the Mediterranean basin, the Middle East, and Japan. Behcet's syndrome occurs more frequently in males than in females with a ratio of 2.3:1 calculated from 683 cases collected from the literature (6) although male:female ratios ranging from 1:1 (7) to 10:1 (8) have been reported. The age of onset has an extremely wide range from 6 (7) to 72 (6) years old, but the mean ages in various large series cluster relatively closely in the third decade with an overall mean of 27 years. Familial occurrence has been reported in only six cases leading to the conclusion that genetic factors are unlikely to play a major role in development of this disorder.

CLINICAL MANIFESTATIONS

Behcet's syndrome is characterized by a series of exacerbations and spontaneous remissions. Since the initial symptoms are usually relatively mild and intermittent, patients usually present themselves to physicians only after a lag period averaging 3 years (reported range: 6 months to 40 years) during which more distressing progression of the initial symptoms or, frequently, development of new symptoms occurs. Table 1 shows the frequency of initial and presenting symptoms of Behcet's syndrome.

Table 1

FREQUENCY OF INITIAL AND PRESENTING SYMPTOMS

OF BEHCET'S SYNDROME

Symptom	Initial Manifestation(%)	Presenting Manifestation(%)
Oral Ulcers	52-76	4-27
Genital Ulcers	2-66	0-2
Ocular Lesions	10-20	28-60
Skin Lesions	2-17	4-20
Arthritis/Arthralgia	0-16	7-52
Thrombophlebitis	0	0-15
Neuropsychiatric	0	0-25

ORAL ULCERS

Oral ulcers are the most frequent clinical manifestation of Behcet's syndrome occurring in 99% of patients (6). As previously shown in Table 1, they represent the most frequent initial symptoms, but less often constitute the reason for seeking medical consultation. These aphthous ulcers are typically shallow, discrete lesions which are exquisitely painful and may interfere with oral intake because of pain. Although scarring may occur, these lesions are usually shallow enough that permanent scar formation does not occur. They appear in crops on the mucous membranes of the lips, cheek, palate, pharynx, tongue, and gums and may extend into the esophagus. Characteristically the ulcer has a whitish-gray base with a red, erythematous border, and may range in size from a few millimeters to greater than 1 centimeter. Non-specific constitutional symptoms such as fever and malaise may be associated with exacerbations of oral ulcers. Initially, aphthous stomatitis may appear alone, but later as the disease progresses to involve other organ systems multiple manifestations may exacerbate simultaneously. There usually is no prodrome to the exacerbations.

GENITAL ULCERS

Second in order of frequency of occurrence of clinical manifestations of Behcet's syndrome is genital ulceration which is present in 87% of patients. In males, genital ulcers (a) are present on the glans penis, scrotum, or shaft of the penis, (b) are usually single in contrast to the crops of oral ulcers, and (c) may be more painful than genital ulcers in females. In women, ulceration (a) may appear on the vulva, labia, vagina, cervix, or perineum, (b) are usually multiple and (c) are frequently less painful than genital lesions in males. In my experience from following several patients with Behcet's syndrome, two observations about genital ulcers in females are noteworthy. First, internal ulcers on the vagina and cervix may be painless and may, in fact, not interfere with intercourse. Therefore, both internal and external pelvic examination should be performed frequently on patients known to have or suspected of having Behcet's syndrome. Second, external ulcerations may be very painful and slow to heal since because of anatomical considerations urine frequently comes in contact with and causes irritation of the ulcers. Additionally, the external ulcers may interfere with intercourse because of pain resulting from physical irritation. The general appearance of the genital ulcers is similar to those of the oral mucosa except that genital lesions are more frequently larger and deeper, and more often result in scar formation.

OCULAR LESIONS

In most large series, ocular lesions occur in a majority of patients at some time during the course of the disease. Frequency in individual reports has varied from 22% (9) to 96% (8) of cases with a mean of 68% in the 683 cases reviewed by Chajek and Fainaru (6). Eye manifestations usually occur from 2 to 12 years after the onset of the disease, a factor highly contributory to the wide range in incidence of ocular symptoms in various reports with shorter duration of disease when the reported frequency is low. The delayed onset but more distressing nature of eye problems is responsible for the differences in their frequency as initial (10 to 20%) and presenting (28 to 60%) manifestations since the duration of this delay coincides closely with the lag between initial symptoms and seeking medical attention.

Typically, one eye is affected first but progressive involvement of both eyes usually develops. Although iritis with hypopyon is considered to be the classic eye lesion, it is interesting to note that none of Behcet's original six cases demonstrated this lesion—only episcleritis and erosions of the cornea were noted.

However, eye involvement may occur in both the anterior and posterior segments. Mamo and Baghdassarian (8) suggested that the disease may very well begin in the posterior segment and proposed two reasons for detection of iridocyclitis with or without hypopyon as the initial eye manifestation. First, in the past, the diagnosis of Behcet's syndrome was often not made until the disease was well advanced. By that time any possible posterior segment involvement would have been masked by the anterior segment pathology and consequently missed. Since ophthalmologists are more aware of Behcet's syndrome nowadays, the diagnosis is being made earlier, and more posterior segment pathology is being found. Second, in cases seen in the pre-steroid era, eye pathology progressed quite rapidly. Now many patients receive steroids and, in some cases, immunosuppressive drugs even before the diagnosis of Behcet's syndrome is made. Thus, the altered course of the eye lesions and milder degree of uveitis makes the fundus more accessible for examination. Posterior segment lesions are listed in Table 2.

Table 2

CLINICAL MANIFESTATIONS OF BEHCET'S SYNDROME

Ocular Lesions

Posterior segment lesions

a. Perivasculitis or endarteritis

b. Thrombosis of central retinal vein

c. Retinal and vitreous hemorrhages

d. Macular edema

e. Retinitis, choroiditis, or chorioretinitis

f. Neovascularization

g. Optic neuritis and optic atrophy

Anterior segment lesions

a. Iritis, iridocyclitis, hypopyon

b. Corneal ulcer

c. Conjunctivitis

Choroiditis, retinitis, or chorioretinitis, macular hemorrhages, and neovascularization may be among the earliest ocular manifestations with many of those patients eventually developing uveitis with hypopyon. Anterior segment lesions are also presented in Table 2. In addition to the classic abnormality of iridocyclitis with hypopyon, corneal ulcers and conjunctivitis have been reported. Each attack adds additional damage to the eyes and is accompanied by the complications of secondary glaucoma, cataracts, and, in many cases, blindness. Blindness is the most common serious complication of Behcet's syndrome and developed in 33% of cases in one review (10). It often occurs within 3 to 5 years after the onset of uveitis or other ocular lesions and, in another study, was reported in 44% of cases 4 to 8 years after onset of posterior segment involvement (6). Mamo (11) investigated the rate of visual loss in Behcet's syndrome and found that among patients with loss of vision that the average length of time between onset of eye symptoms and blindness was 3.6 years. He also stated that it appeared that steroids may have a mild delaying effect upon the rate of visual loss.

CUTANEOUS LESIONS

In addition to the original triad of symptoms, a variety of other manifestations of Behcet's syndrome have been widely reported. Cutaneous lesions occur in 69% of patients (6) and follow a pattern of exacerbations and remissions like other symptoms. Erythema nodosum-type of skin lesions develop in about one-third of patients (6,8,12). Erythema multiforme is far less common being observed in only 8% of cases in one series (12). A wide variety of papulopustular lesions including pustules, acneiform eruptions, folliculitis, furunculosis, pyoderma, papulopustular dermatitis, and impetigo have been reported in 46 to 60% of patients with Behcet's syndrome (6,8). In addition to the above spontaneously developing skin lesions, patients may also demonstrate an abnormal sensitivity to trauma. This reaction is characterized by the development of an erythematous papule or pustule 24 to 48 hours after a prick with a sterile needle or intradermal injection of distilled water and has been reported in 21 to 42% of cases (6,8,13).

RHEUMATIC MANIFESTATIONS

Joint involvement has been reported in an average of 44% of patients with Behcet's syndrome (6). In a majority of cases, migratory polyarthralgia without frank arthritis has been observed (6,8,12). The incidence and characteristics of the arthropathy

of Behcet's syndrome, however, have been variable.

As early as 1940, Behcet (14) recognized the presence of articular involvement in many cases, and Sezer (15) subsequently stated that "all patients with Behcet's disease had had an illness of the joints similar to polyarticular rheumatism". Both recurrent monoarticular arthritis (16) and non-migratory, subacute or chronic polyarthritis (12) have been described. In 88% of 157 cases recently reviewed by Zizic and Stevens (17), the arthropathy was episodic and in a majority of instances was polyarticular and asymmetric. Despite the recurrent and inflammatory characteristics, clinical and radiologic evidence of articular destruction or deformity are rare (6,8,12,17,18).

Little attention has been given to the characteristics of the synovial fluid in these patients (8,13,17,19). The synovial fluid has usually been inflammatory in type with leukocytosis ranging between 20,000 and 75,000/mm^3 with 75 to 95% polymorphonuclear leukocytes although reports have varied from 250,000/mm^3 (13) to "clear and containing few leukocytes" (6). Typically, mucin clot formation is poor, protein content (4.0 to 5.8 g/dl) and hemolytic complement levels elevated, glucose normal and cultures negative (17). Examination of synovial biopsies has revealed perivascular infiltrates consisting mainly of lymphocytes, increased vascularity and interstitial edema. The frequency of arthritis in various joints is shown in Table 3. The knees and ankles are the most frequently affected joints with relatively infrequent involvement of the small joints of the hands and feet.

Table 3

CLINICAL MANIFESTATIONS OF BEHCET'S SYNDROME

Frequency of Arthritis in Various Joints

Joint	Frequency (%)
Knee	55-79
Ankle	42-55
Wrist	37-40
Elbow	26-40
Hands	10-37
Feet	5-26
Hips	5-21
Shoulders	3-21

NEUROLOGIC MANIFESTATIONS

The most serious consequence of Behcet's syndrome is central nervous system involvement which has been reported to occur in about 30% of patients (6). Neurologic symptoms become manifest between 3 months and 15 or more years after the onset of disease (6,8,20) as was the case for ocular lesions, and they typically follow a course of exacerbations and spontaneous remissions with residual defects being frequently detectable. Although Pallis and Fudge (21) attempted to classify the neurologic abnormalities of Behcet's syndrome into a brain stem syndrome, a meningomyelitic syndrome, and an organic confusional syndrome, the protean nature of nervous system involvement does not readily lend itself to such a simplified breakdown (6,8,10,20).

The most common neurologic symptom is headache (6,18) which may be severe and may (22,23) or may not (24) have associated papilledema. Papilledema without headache has also been encountered (25,26). Other signs and symptoms which have been reported include intermittent paresthesias and paralysis (6,8,18), brain stem and pyramidal tract signs (6,20,21), a meningomyelitic syndrome (6,20,21), organic confusional states (8,18,20,21), paresis (20), peripheral neuropathy (6) and facial paralysis (19). Studies of the cerebrospinal fluid from patients with neuro-Behcet's syndrome have revealed that leukocytosis with 90-100% lymphocytes and elevated protein were the most consistent abnormalities occurring in 60 to 80% of those affected (18,21).

Development of neurologic involvement holds a serious prognosis for life with 31% to 41% mortality among such patients (20,21). In the report of Schotland et al (20), two-thirds of the deaths occurred within one year from the onset of neurologic abnormalities.

GASTROINTESTINAL ABNORMALITIES

Abnormalities of the gastrointestinal tract have been reported in up to 50% of patients with Behcet's syndrome. By far the largest series studied was that of Oshima et al (18). The symptoms and radiologic abnormalities which they found are listed in Table 4. As shown in this Table, these manifestations sometimes followed a pattern of exacerbation and remission but more frequently were persistent. In addition, the same authors reported impaired fat absorption as determined by the uptake of ^{131}I-olive oil. Blood concentration of ^{131}I was markedly decreased in patients with Behcet's syndrome (4 to 6% in attack, 5 to 10% in remission) when compared to normals (10 to 22%) 8 hours after

Table 4

CLINICAL MANIFESTATIONS OF BEHCET'S SYNDROME

Gastrointestinal Abnormalities[1]

	Frequency (%)	
	In Attack	In Remission
Symptoms		
a. Abdominal distension	43	24
b. Anorexia	31	0
c. Diarrhea	28	21
d. Abdominal pain	28	14
e. Belching	20	0
f. Nausea	16	9
g. Bleeding	--	--
Radiologic Abnormalities		
a. Fluid retention	78	64
b. Dilatation	54	37
c. Segmentation	57	40
d. Flocculation	52	50
e. Gas retention	50	47

[1]Oshima et al (18)

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ingestion. This abnormality also was more pronounced in patients with radiologic abnormalities. In addition to the above problems, ulceration of the esophagus and small intestine (26) and colitis (12,19,27,28,29) have been reported. However, the fact that few cases of colitis have been reported has led to controversy as to whether this problem represents a complication of the underlying disorder or coincident inflammatory bowel disease.

VASCULAR COMPLICATIONS

Venous thrombosis is the most common vascular complication of Behcet's syndrome occurring in 20% of patients. In a majority, the course is one of recurrent, migratory superficial or deep thrombophlebitis of the extremities (6,12,13). However, thrombosis of the inferior vena cava (6,30,31), superior vena cava (6,32), hepatic vein with resultant Budd-Chiari syndrome (33), intracranial venous sinuses (23,24,31) and central retinal vein (34) have been described. Thrombosis at the site of venipuncture is also relatively common (6,31). Arterial involvement with thrombosis (35,36) and aneurysm formation (18,36,37) is relatively rare.

UNCOMMON COMPLICATIONS

A variety of complications have been reported in a few patients with Behcet's syndrome, but relationship to the underlying disease process is unclear. Recurrent orchitis and epididymitis have been detected in 4% to 9% of patients in some studies (6, 10,23), and recurrent urethritis has been recorded in a few cases (6,10,13). Myalgia, at times severe, may occur (8,23) and fleeting pulmonary infiltrates have been observed (6,37,38,39). Pericarditis (12,40), incomplete right bundle branch block (18), pancreatitis (19), and amyloidosis (41,42) have been detected only in single or very few cases.

LABORATORY STUDIES

Laboratory findings pathognomonic for Behcet's syndrome have not been described. Although a few laboratory abnormalities have been reported, a vast majority of tests are normal during both exacerbation and remission. In several large series, patients with active disease commonly had a slight leukocytosis in the 12,000 to 14,000/mm^3 range and elevated erythrocyte sedimentation rate (6,11,18,19,23). These, however, returned to normal levels during remission. Increased plasma fibrinogen (6,43) and hyperglobulinemia, especially α_2 globulins and sometimes polyclonal hypergammaglobulinemia (6,18,19,23), have also been frequently reported. Additionally, C-reactive protein is frequently elevated (18). Most of these abnormalities probably are the result of acute phase reactants during exacerbation.

Extensive coagulation studies have been performed in some patients, especially those with thrombotic vascular disease. Fibrinolysis has been found to be impaired in some cases (6,43,44,45) although normal euglobulin lysis times have been observed (45,46). Factor VIII tended to be elevated in one study (6).

In recent years, there has been an increasing interest in the possible association between histocompatibility antigens and various diseases. In two Japanese studies, HLA-B5 was found to be increased in frequency in Behcet's syndrome patients (47,48). In a group of six patients with Behcet's or partial Behcet's syndrome seen here in Dallas, only one has been HLA-B5. The most common type was A2, B12 detected in 3 of the 6 patients followed by A11, BW35 in 2 of the 6 individuals. However, not enough patients have been tested to allow statistical evaluation of the data. Additionally, the possibility of an association with an immune response gene remains to be evaluated.

With the exception of one study in which rheumatoid factor activity was detected in 20 of 30 patients by agglutination of tanned sheep cells coated with heat aggregated human gamma globulin (49), most studies have failed to find increases in the incidence of rheumatoid factors, antinuclear antibodies, Coombs antierythrocyte antibodies, or syphilis serology (8,19,23). Hemolytic complement levels are also normal (19).

PATHOLOGY

Histopathologic evaluation of tissue from patients with Behcet's syndrome has been reported in several studies (6,8,18,19,20,83). The common underlying lesion in all systems and organs involved was a predominantly lymphomononuclear perivascular infiltrate with some plasma cells present. Most frequently venules and capillaries were involved but arterioles were sometimes affected. Additionally, endothelial cell swelling and proliferation, fibrinoid necrosis, and vascular thrombosis were observed in some cases. This type of non-specific obliterative vasculitis occurs in the dermal submucosal and subcutaneous vessels, the retina, synovium, large veins and arteries, meninges, brain, epididymis, and lung.

DIAGNOSIS

In the absence of pathognomonic or even suggestive laboratory tests, the diagnosis of Behcet's syndrome is, thus, made on the basis of clinical criteria. It should be obvious by now that Behcet's syndrome represents a syndromic spectrum much broader than the original triple-symptom-complex recorded by Behcet. A variety of classification schemes have been proposed, but the criteria presented in Table 5 are frequently used. Generally, the presence of three major criteria or two major and two minor criteria are required for the diagnosis of Behcet's syndrome while two major criteria suffice for a diagnosis of partial Behcet's syndrome. It should be mentioned at this point, however, that the criteria must be applied with some degree of caution in order to prevent confusion with other disorders as will be discussed later in the differential diagnosis.

Table 5

CRITERIA FOR DIAGNOSIS OF BEHCET'S SYNDROME

Major Criteria

1. Oral ulcers
2. Genital ulcers
3. Ocular lesions
4. Skin lesions

Minor Criteria

1. Arthritis or arthralgia
2. Vascular disease
3. Central nervous system disease
4. Gastrointestinal disturbances

CLINICAL COURSE

In summary of the clinical course of Behcet's syndrome which we have discussed above, some salient characteristics are re-emphasized in Table 6.

Table 6

CLINICAL COURSE OF BEHCET'S SYNDROME

1. Characterized by exacerbations and remissions at intervals of several days to several months.

2. Typically begins with recurrent oral ulcers with other manifestations developing later.

3. Six months to 40 years (mean:3 years) between initial and presenting symptoms.

4. Ocular and neurologic lesions may be progressive leading to disability and death in some cases.

TREATMENT

The treatment of Behcet's syndrome is empirical and often unsatisfactory. The natural history of exacerbations and remissions makes evaluation of any form of therapy difficult.

Corticosteroids have been used both topically and systemically and have produced varied results. Topical steroids may alleviate the pain of oral and genital ulcers and hasten healing of these lesions. When used for the treatment of uveitis, on the other hand, they may reduce inflammation, but often do not prevent progression of severe uveitis (6,50). Systemic steroid therapy has similarly been beneficial in many cases (8,19,20,23, 26), but responses have been inconsistent and variable (29,51,52, 53). According to O'Duffy et al (19) cutaneous and articular symptoms were suppressed with lower doses of steroids than oral ulcerations. The more serious systemic manifestations, e.g., neurologic, uveitis and colitis, may respond less well or even exacerbate while patients are receiving steroids. In spite of the variability of response to and potential adverse side effects of corticosteroid therapy, these agents remain the treatment of choice.

Oral fibrinolytic agents have also been used. These were initially administered to patients with recurrent thrombosis since in some such individuals altered fibrinolysis had been detected. The most frequently used regimen employed phenformin 50 mg BID and ethylestrenol 2 mg QID. Although some patients receiving this combination of drugs improved clinically and had a decrease of fibrinolysis time (43,45,54), other cases have been reported in which either no benefit or clinical improvement without change in altered fibrinolysis (45,46) has been observed. This treatment has led to improvement in cutaneous lesions and oral and genital ulcers in addition to thrombotic phenomena. The benefits of phenformin-ethylestrenol therapy may be prolonged and may last for years (43). Also, it has been reported that these drugs may decrease fibrinogen levels (43), increase production of plasminogen activator by the venous endothelium (43), and, possibly decrease platelet adhesiveness (46). Streptokinase was used successfully in two cases (6) but these results were challenged in a subsequent report (55) since in the latter experience a thrombus extended in spite of clinical improvement which was presumed to be due to collateral circulation.

Immunosuppressive drugs have been used in some patients resistant to corticosteroids. Favorable results have been reported using cyclophosphamide (56), chlorambucil (57-59), and azathioprine (60) in all but one case (61). However, results have shown that oral aphthous ulcers persisted, although decreased in size and number, despite chlorambucil in a dose of 0.1 to 0.2 mg/kg/day (59). It

is probable that other unsuccessful therapeutic trials have not been published.

Blood transfusion has been reported to be followed by remission of symptoms lasting up to 8 months in 3 cases (19,62). A similar remission lasting for one week followed leukocyte transfusion in one case (19).

Transfer factor has been used in the treatment of Behcet's syndrome based on (a) the above report of remission following transfusion of leukocytes and (b) the hypothesis that a specific defect of cell mediated immunity similar to those in chronic mucocutaneous candidiasis exists in patients with Behcet's syndrome. Beneficial results have been reported by Wolf et al (62) in 3 of 4 cases, Bernhard and Heim (64) in 2 of 3 cases, Frenkel (65) in one case, Hahn (66) in 2 cases and Fudenberg (67) in several cases.

To date, we have treated six patients with Behcet's or partial Behcet's syndrome with dialyzable transfer factor. Their symptoms are shown in Table 7. Of these patients, two attained remissions, two had marked subjective and objective improvement, and two showed no response. However, one of the two that did not respond received only two single injections one year apart and was concomitantly receiving combined high dose prednisone and immunosuppressive drug therapy. Thus, transfer factor appears to be a beneficial therapeutic agent in at least some cases of Behcet's syndrome. Fudenberg (67) has observed that transfer factor derived from the leukocytes of family members may induce remissions in some patients that were unresponsive to transfer factor from random donors.

Table 7

SYMPTOMS OF BEHCET'S SYNDROME IN SIX PATIENTS

Symptom	No. of Patients
Aphthous stomatitis	6
Genital ulcers	6
Skin lesions	5
Fever	3
Uveitis	2
Conjunctivitis	1
Arthritis or Arthralgia	2
Neurologic Symptoms	1

The clinical course of one of the responsive patients is shown in Table 8.

Table 8

BEHCET'S SYNDROME

B.W. -- 39 yrs., WF

Symptoms at Start of TF

Ulcerations: oropharynx, genitalia
colon, bladder

Arthralgias

Dermal Vasculitis

Fever

Character of Response to TF

At 1 to 3 Days:
Decrease of size of ulcers
Decrease of colon and bladder pain
Decrease of urinary and rectal bleeding
Decrease of fever
Decrease of arthralgias

At 3 to 5 Days:
Asymptomatic

Duration of Remission:
2 to 12 weeks

Summary of Response to TF

Duration of treatment	3 years
Total TF injections	28
Complete remissions	24
Incomplete remissions	2
No response	2
Placebo injections	4
No response	3
Incomplete response	1

Levamisole, an anti-helminthic drug with immuno-stimulatory properties, has been mentioned as showing therapeutic potential in preliminary studies without presentation of data (68).

A large number of other agents have been used to treat Behcet's syndrome including broad spectrum antibiotics (8), smallpox and streptococcal vaccines (8,69), BCG immunization, oral contraceptives, gamma globulin injections (70,71), and penicillamine (72).

ETIOLOGY

Several theories have been proposed regarding the etiology of Behcet's syndrome. Behcet first suggested a viral etiology by describing inclusion bodies in smears of ulcer exudates. Sezer (15) has claimed to have isolated a virus from blood, urine, hypopyon, subretinal exudate, and corpus vitreum from patients with Behcet's syndrome, and neutralizing and complement fixing antibodies were also detected in the serum (15). In some cases, "virus" from Behcet's patients produced disease in mice and rabbits after inoculation (15,73). Evans (74) isolated a virus from brain tissue from a patient dying of Behcet's syndrome and found virus neutralizing antibodies in patients' sera but not in control sera. More recently, the virus theory has been challenged (75) and more recent attempts at virus isolation have been unsuccessful (40). Relationships between Behcet's syndrome and L-forms of α-hemolytic streptococci (76), Chlamydia (77), and cold-agglutinin positive respiratory infections (78) have been suggested or observed but definitive confirmation of an infectious etiology of Behcet's syndrome is lacking.

Several observations led to the proposal of a vascular etiology of Behcet's syndrome. These include (a) prolonged fibrinolysis time in some patients, (b) clinical occurrence of vascular thrombosis, and (c) the pathologic findings of vascular thrombosis and inflammation within and surrounding blood vessels. This theory also lacks definitive support, and it seems more likely that these vascular abnormalities are secondary rather than etiologic in relation to this syndrome.

An allergy or hypersensitivity has also been proposed by some authors as the underlying cause of Behcet's syndrome. This theory has been based on the similarities between the pathologic findings in Behcet's syndrome and delayed type hypersensitivity reactions, and the induction of Behcet's-like disease in rats by injection of Freund's adjuvant (79). Although the rats developed arthritis and, sometimes, cutaneous and genital lesions and iridocyclitis, the histologic detail in this model differed from Behcet's syndrome in man. Additionally, the studies relating to humoral and cellular

immune responses to various infectious agents have been cited as suggesting an etiologic role for allergy.

The last and perhaps most tenable etiologic theory is that of autoimmunity. This hypothesis is supported by the following observations. (a) Antibodies and lymphocyte responses to extracts of oral mucosa have been demonstrated in patients with Behcet's syndrome (7,18,80,81). Although similar antibody and lymphocyte responses have been detected in some patients with aphthous stomatitis (80,81), the lack of a clear delineation between aphthous stomatitis and Behcet's syndrome which may represent different portions of a disease spectrum makes precise evaluation of these observations difficult. (b) Simultaneously decreased *in vitro* lymphocyte responsiveness and clinical exacerbation has been reported in some patients after eating English walnuts (82), and exacerbation of disease in other patients has been observed after eating specific foods (82). These investigators proposed two mechanisms whereby food ingestion might cause exacerbation. They are (a) antigenic cross-reactivity between foods and tissue-antigens and (b) temporary hyporeactivity of suppressor T lymphocytes resulting in autoantibody production.

Finally, it should be mentioned that the above theories on the etiology of Behcet's syndrome are not mutually exclusive, for example, a virus infection could lead to autoimmunity as proposed but not proved for many of the connective tissue diseases.

DIFFERENTIAL DIAGNOSIS

Since Behcet's syndrome has been expanded from the original triple-symptom-complex into a multisystem disorder and since the diagnosis has been based on clinical criteria which are relatively ill-defined, the exclusion of other mucocutaneous syndromes is sometimes difficult. Additionally, each of the disorders that are listed in Table 9 consists of a broad spectrum of clinical presentations with multiple possibilities for potential overlap. Laboratory and histopathologic findings, however, may be beneficial in diagnostic classification of some patients.

The differentiation of Reiter's syndrome from Behcet's syndrome is not difficult in the patient who presents with urethritis, arthritis, conjunctivitis, and keratoderma blennhorragica. However, as seen in Table 9, there are many features in common to these two syndromes. The major points of distinction are as follows: (a) Oral ulcers in Reiter's syndrome are usually painless and superficial with limitation to the epithelium. (b) Genital and cutaneous lesions are characterized by hyperkeratotic, scaling plaques and papules rather than the discrete genital ulcers and papulopustular skin lesions of Behcet's syndrome. (c) Conjunctivitis

Table 9

CLINICAL FEATURES IN DIFFERENTIAL DIAGNOSIS OF BEHCET'S SYNDROME

Syndrome	Oral Lesions		Genital Lesions		
	Ulcerative Stomatitis	Vesico-Bullous Stomatitis	Genital Lesions	Balanitis	Non-specific Urethritis
Behcet's Syndrome	X		X		
Reiter's Syndrome	X		X	X	X
Erythema Multiforme	X	X	X	X	X
Pemphigus/ Pemphigoid	X	X	X		

Table 9 (continued)

CLINICAL FEATURES IN DIFFERENTIAL DIAGNOSIS OF BEHCET'S SYNDROME

Syndrome	Ocular Lesions			
	Conjunc-tivitis	Anterior Segment	Corneal Ulcers	Posterior Segment
Behcet's Syndrome	X	X	X	X
Reiter's Syndrome	X	X	X	
Erythema Multiforme	X		X	
Pemphigus/ Pemphigoid	X		X	

Table 9 (continued)

CLINICAL FEATURES IN DIFFERENTIAL DIAGNOSIS OF BEHCET'S SYNDROME

Syndrome	Cutaneous Lesions				Joint Symptoms	
	Erythema Multiforme	Erythema Nodosum	Pustules	Keratoderma Blennorrhagica	Arthralgia	Arthritis
Behcet's Syndrome	X	X	X		X	X
Reiter's Syndrome	X	X	X	X	X	X
Erythema Multiforme	X				X	
Pemphigus/ Pemphigoid	X					

is more common in Reiter's syndrome, but uveitis and corneal ulceration may occur in both. (d) Involvement of the small joints of the feet and sacroiliitis is more common in Reiter's syndrome. (e) Onycholysis with thickening and dystrophy of the nails may occur in Reiter's but not Behcet's syndrome. (f) HLA-B27 is increased in frequency (79%) in Reiter's syndrome.

Erythema multiforme may also be a difficult differential diagnostic exclusion since oral, genital, ocular, cutaneous and joint manifestations may occur. This disorder represents an allergic or hypersensitivity reaction often to Herpes simplex infection. In the absence of bullous lesions, the oral ulcers may resemble those of Behcet's syndrome. However, involvement may be much more extensive in more severe cases of erythema multiforme. The genital mucosa may be similarly affected. Conjunctivitis and corneal ulcers may occur but uveitis has not been reported in this disorder. The clinical appearance and histopathology of the cutaneous lesions in erythema multiforme are major differentiating features. Although diffuse,coalescent erythema and profuse blistering may be observed, the classic finding is that of target lesions with a red margin, pale zone inside that, and a central livid area that my be blistered. Histologically, there is a dermal vasculitis, but subepidermal vesiculation and marked epidermal necrosis may help to differentiate erythema multiforme from an initial attack of Behcet's. Since erythema multiforme may occur in Behcet's syndrome, another important feature is that erythema multiforme has an acute onset with recurrence in only about 25% of patients as opposed to the more indolent, recurrent course of Behcet's syndrome. In fact, since a vast majority of Behcet's patients do not seek medical attention for the initial symptoms, historical evidence of recurrent problems becomes an important differential feature.

Benign mucosal pemphigoid (cicatrical pemphigoid) is the form of the pemphigus-pemphigoid complex most likely to be confused with Behcet's syndrome. In this disorder, pathologic abnormalities occur predominantly along the subepithelial basement membrane of the mucosa and skin producing oral and genital ulceration that is more superficial and less painful than that of Behcet's syndrome. Conjunctivitis with erosions, adhesions and scarring may be detected on eye examination as a result of involvement of the bulbar and palpebral conjunctivae. Cutaneous involvement is usually but not invariably bullous. The major features of benign mucosal pemphigoid distinguishing it from Behcet's syndrome are (a) the superficial, less painful mucosal ulcers, (b) the presence of subepidermal vacuoles or bullae on histologic examination of lesions as well as the absence of prominent dermal vasculitis, and (c) the pathognomonic deposition of immunoglobulin along the subepidermal basement membrane detected by indirect immunofluorescence. The latter finding reflects the binding of antibody to the basement membrane.

REFERENCES

1. Behcet H: Uber rezidivierende, aphthose, durch ein virus verursachte geschwure am mund, am auge und de genitalien. Dermat Wschr 105:1152, 1937

2. Bluthe L: Zur kenntnis des recidiverenden hypopyons. Inaugural Thesis. Heidelberg, 1908

3. Adamantiades B: Sur un cas d'iritis a hypopion recidivant. Ann d' ocul 168:271, 1931

4. Dascalopoulos N: Sur deux cas d'uveite recidivante. Ann d'ocul 169:387, 1932

5. Whitwell GPB: Recurrent buccal and vulval ulcers with associated embolic phenomena in the skin and eye. Brit J Dermat 46:414, 1934

6. Chajek T and Fainaru M: Behcet's disease. Medicine 54:179, 1975

7. Lehner T: Behcet's syndrome and autoimmunity. Brit Med J 1:465, 1967

8. Mamo JG and Baghdassarian A: Behcet's disease. Arch Ophthal 71:38, 1964

9. Haim S: Contribution of ocular symptoms in the diagnosis of Behcet's disease. Arch Derm 98:478, 1968

10. Mavioglu H: Behcet's recurrent disease. Analytical review of the literature. Missouri Med 55:1209, 1958

11. Mamo JG: The rate of visual loss in Behcet's disease. Arch Ophthal 84:451, 1970

12. Mason RM and Barnes CG: Behcet's syndrome with arthritis. Ann Rheum Dis 28:95, 1969

13. France et al: Relapsing iritis with recurrent ulcers of the mouth and genitalia (Behcet's syndrome). Medicine 30:335, 1951

14. Behcet H: Some observations on clinical picture of so-called triple symptom complex. Dermatologica 81:73, 1940

15. Sezer NF: The isolation of a virus as the cause of Behcet's disease. Amer J Ophthal 36:301, 1953

16. Phillips DL and Scott JS: Recurrent genital and oral ulceration with associated eye lesions. Lancet 1:366, 1955

17. Zizic TM and Stevens MB: The arthropathy of Behcet's disease. The Johns Hopkins Med J 136:243, 1975

18. Oshima Y et al: Clinical studies on Behcet's syndrome. Ann Rheum Dis 22:36, 1963

19. O'Duffy JD, Carney JA and Deodhar S: Behcet's disease. Ann Int Med 75:561, 1971

20. Schotland DL et al: Neurologic Aspects of Behcet's disease. Amer J Med 34:544, 1963

21. Pallis CA and Fudge BJ: The neurological complications of Behcet's syndrome. AMA Arch Neurol Psychiat 75:1, 1956

22. Berlin C: Behcet's disease as a multiple symptoms complex. Arch Derm 82:73, 1960

23. Kalbian VV and Challis MT: Behcet's disease. Amer J Med 49:823, 1970

24. Masheter HC: Behcet's syndrome complicated by intracranial thrombophlebitis. Proc Roy Soc Med 52:1039, 1959

25. Wolf SM, Schotland DL, and Phillips LL: Involvement of nervous system in Behcet's syndrome. Arch Neurol 12:315, 1965

26. Wadia N and Williams E: Behcet's syndrome with neurological complications. Brain 80:59, 1957

27. Lehmann H et al: Morbus Behcet und multiple intestionale ulzerationen. Deutsch Med Wschr 100:308, 1975

28. Empey DW and Hale JE: Rectal and colonic ulceration in Behcet's disease. Proc Roy Soc Med 65:163, 1972

29. Smith GE, Kime LR and Pitcher JL: The colitis of Behcet's disease: a separate entity? Amer J Dig Dis 18:987, 1973

30. Thomas EWP: So-called triple-symptom complex of Behcet. Brit Med J 1:14, 1947

31. Mounsey JPD: Behcet's syndrome - a spectrum. Trans St John's Hosp Derm Soc 52:197, 1966

32. Boolukas PJ: Phlebitis and thrombosis of the large veins of the trunk in Behcet's disease. Helv Med Acta 27:264, 1960

33. Valleteau M et al: A propos d'un cas d'association de syndrome de Budd-Chiari et de syndrome de Behcet. Sem Hop Paris 50:2679, 1974

34. Jebejian R and Kalfayan B: Le syndrome oculo-bucco-genital. Ann Oculist 179:481, 1946 (ref. to in 8)

35. Enoch BA et al: Major vascular complications in Behcet's syndrome. Postgrad Med J 44:453, 1968

36. Mowat AG and Hothersall TE: Gangrene in Behcet's disease. Brit Med J 2:636, 1969

37. Hills EA: Behcet's syndrome with aortic aneurysm. Brit Med J 4:152, 1967

38. DeCroix AG: Thoracic manifestations of Behcet's syndrome. Thorax 24:380, 1969

39. Davies JD: Behcet's syndrome with haemoptysis and pulmonary lesions. J Path 109:351, 1973

40. Sigel N and Larson R: Behcet's syndrome: a case with benign pericarditis and recurrent neurologic involvement treated with adrenal steroids. Arch Int Med 115:203, 1965

41. Rosenthal T et al: Systemic amyloidosis in Behcet's disease. Ann Int Med 84:220, 1975

42. Beroniade V: Amyloidosis in Behcet's disease. Ann Int Med 84:904, 1975

43. Kirk J and Handley DA: Experiences in the use of fibrinolytic agents in Behcet's syndrome. Aust J Derm 13:5, 1972

44. Cunliffe WJ, Roberts BE and Dodman B: Behcet's syndrome on oral fibrinolytic therapy. Brit Med J 2:480, 1973

45. Sobel JD, Tabori S, and Tatarski I: Fibrinolysis and thrombosis in Behcet's disease. Dermatologica 148:93, 1974

46. Cunliffe WJ and Menon IS: Treatment of Behcet's syndrome with phenformin and ethyloestrenol. Lancet 1:1239, 1969

47. Ohno S et al: HL-A5 and Behcet's disease. Lancet 2:1383, 1973

48. Ohno S et al: Specific histocompatibility antigens associated with Behcet's disease. Amer J Ophthal 80:636, 1975

49. Shimizu T, Katsuta Y and Oshima Y: Immunological studies on Behcet's syndrome. Ann Rheum Dis 24:494, 1965

50. Haim S: Behcet's disease: Etiology and treatment. Dermatologica 150:163, 1975

51. Scott D: Mucocutaneous-ocular syndrome (Behcet's syndrome) with meningoencephalitis; report of a case with autopsy. Acta Med Scandinav 161:397, 1958

52. Fishof FE: Behcet's syndrome. J Int Coll Surg 34:213, 1960

53. Witty CW: Neurologic implications of Behcet's syndrome. Neurology 8:369, 1958

54. Cunliffe WJ: An association between cutaneous vasculitis and decreased blood-fibrinolytic activity. Lancet 1:1226, 1968

55. Tibbutt DA et al: Behcet's syndrome and venous thrombosis. Brit Med J 3:236, 1973

56. Buckley CE III and Gills JP Jr: Cyclophosphamide therapy of Behcet's disease. J Allerg 43:273, 1969

57. Ibrahim M et al: Long-lasting remission of Behcet's disease after chlorambucil therapy. Brit J Ophthal 57:706, 1973

58. Godfrey WA et al: The use of chlorambucil in intractable idiopathic uveitis. Amer J Ophthal 78:415, 1974

59. Mamo JG and Azzam SA: Treatment of Behcet's disease with chlorambucil. Arch Ophthal 84:446, 1970

60. Rosselet E, Sudan Y, and Zenklusen G: Les effects de l'azathioprine (Imuran) dans la maladie de Behcet. Ophthalmologica 156:218, 1968

61. Wong VG: Immunosuppressive therapy of ocular-inflammatory diseases. Arch Ophthal 81:628, 1969

62. Haim S and Sherf K: Behcet's disease. Isr J Med Sci 2:69, 1966

63. Wolf RE et al: Treatment of Behcet's syndrome with transfer factor (TF). Arthritis Rheum 18:432, 1975

64. Bernhard GC and Heim LR: Transfer factor treatment of Behcet's syndrome. J Rheum 1:34, 1974

65. Frenkel LD: personal communication

66. Hahn BH: personal communication

67. Fudenberg HH: personal communication

68. Synderman R: Original triple-symptom complex held "too strict" for diagnosis of Behcet's syndrome. Clinical Trends in Rheumatology 7/1:1, 1976

69. Shore RN and Shelley WB: Treatment of aphthous stomatitis by suppression of intralesional streptococci. Arch Derm 109:400, 1974

70. Breslin HJ: Behcet's disease. Amer J Ophthal 53:132, 1962

71. Curth HO: Aphthosis. AMA Arch Derm 74:439, 1956

72. Machtey I: Adverse reaction to penicillamine in a patient with Behcet's syndrome and ulcer of the leg. J Clin Pharmacol 11:204, 1971

73. Noyan B, Gursky G and Aktiu E: Inoculation of cerebrospinal fluid of a neuro-Behcet patient into mice. Acta Neuropathol 12:195, 1969

74. Evans AD, Pallis CA, and Spillane JD: Involvement of the nervous system in Behcet's syndrome: Report of three cases and isolation of virus. Lancet 2:349, 1957

75. Dowling DW and Hale JE: Rectal and colonic ulceration in Behcet's disease. Proc Roy Soc Med 65:163, 1972

76. Graykowski EA et al: Recurrent aphthous stomatitis. J Amer Med Assoc 196:129, 1966

77. Sugiura S et al: Serum antibodies to various pathologic agents and lymphocytic transformation in Behcet's disease. Acta Soc Ophthal Jpn 76:635, 1972

78. Ström J: Ectodermosis erosiva pluriorificialis, Stevens-Johnson's syndrome and other febrile mucocutaneous reactions and Behcet's syndrome in cold-agglutinin-positive infections. Lancet 1:457, 1965

79. Pearson CM, Waksman BH, and Sharp JT: Studies of arthritis and other lesions induced in rats by injection of mycobacterial adjuvant. J Exper Med 113:485, 1961

80. Lehner T: Stimulation of lymphocyte transformation by tissue homogenates in recurrent oral ulceration. Immunol 13:159, 1967

81. Rogers RS et al: Lymphocytotoxicity in recurrent aphthous stomatitis. Arch Dermatol 109:361, 1974

82. Marquardt JL, Synderman R and Oppenheim JJ: Depression of lymphocyte transformation and exacerbation of Behcet's syndrome by ingestion of English walnuts. Cell Immunol 9:263, 1973

83. Lehner T: Pathology of recurrent oral ulceration and oral ulceration in Behcet's syndrome: light, electron and fluorescence microscopy. J Path 97:481, 1968