Clinics in Dermatology (2019) **37**, 227–239

ELSEVIER

Clinics in Dermatology

Behçet syndrome: A great imitator

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Abstract Behçet syndrome is considered to be a multisystemic vasculitis involving the skin, mucosa, eyes, joints, nervous system, cardiovascular system, and gastrointestinal system. The exact pathogenesis of the disease is unknown, but autoimmune factors are thought to play the main role. Vasculitis in Behçet syndrome can involve any kind and size of vessels, and this explains why the disease has the ability of multisystemic involvement. The commonest clinical presentation of Behçet syndrome is recurrent and painful mucocutaneous ulcerations known as aphthosis. The other clinical manifestations vary among patients and populations. The disease tends to be more severe in men. Ocular, vascular, and central nervous system involvements are the major causes of morbidity and mortality. Behçet syndrome is a mimicker of many diseases with its several faces and considered as one of the great imitators in dermatology.

Introduction

Behçet syndrome (BS), also called Behçet disease, was first described as a separate entity by famous Turkish dermatologist Hulusi Behçet in (1889-1948) in 1937. He described the disease in three patients with the classic triad of oral aphthosis, genital aphthosis, and anterior uveitis with hypopyon.[1] Gradually, other clinical manifestations of the syndrome were described. BS is accepted as a multisystemic vasculitis involving skin, mucosa, eyes, joints, nervous system, cardiovascular system, and gastrointestinal system. It is remarkable that vasculitis in BS can involve any kind and size of vessels, and this explains why the disease has the ability of multisystemic involvement[2,3] (Table 1).

BS may mimic many diseases with its several faces and can be considered as one of the great imitators in dermatology (Table 2). This review is mainly focused on the clinical manifestations, diagnosis, and differential diagnosis of BS, especially in the context of its "imitator" aspect.

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https://doi.org/10.1016/j.clindermatol.2019.01.001
0738-081X/

Etiopathogenesis

BS is a multifactorial disease classified as a vasculitis, and many environmental triggers, such as infectious agents, may stimulate inflammatory attacks in genetically susceptible persons. The exact pathogenesis of the disease is unknown, but autoimmune factors play the main role. BS shows many signs of abnormal inflammatory response, and a variety of genetic factors causing this exaggerated response have been studied.[4] Human leukocyte antigen (HLA) B-51 gene expression is the strongest genetic factor affecting disease risk and typical clinical manifestation.[5,6] Endoplasmic reticulum aminopeptidase 1 (ERAP1), interleukin 23 receptor (IL23R), and IL10 variations are the other non-HLA genetic associations.[7,8] The autoinflammatory response driven by all these genetic and

Table 1 Spectrum of the clinical manifestations of Behçet syndrome

Mucocutaneous involvement	Oral aphthosis, genital aphthosis, papulopustular lesions, pathergy phenomenon, erythema-nodosu-like lesions, superficial thrombophlebitis, pyoderma-gangrenosum-like lesions, erythema-multiforme-like lesions, nailfold capillary abnormalities
Ocular involvement	Uveitis, vitritis, retinal infiltrates, sheathing of retinal veins, occlusive vasculitis, neovascularization, secondary cataracts, glaucoma, frosted branch angiitis and macular edema, conjunctivitis, and conjunctival aphthosis, and scleritis being less common
Musculoskeletal involvement	Arthritis, arthralgia, enthesopathy, avascular necrosis, myalgia, and myositis
Vascular involvement	Pulmonary, carotid, aortic, iliac, femoral, and popliteal arterial involvement; pulmonary aneurysm; superficial and deep vein thrombosis; Budd-Chiari syndrome; superior and inferior vena cava occlusion; and dural sinus thrombosis
Cardiac involvement	Pericarditis, myocarditis, endocarditis with valvular regurgitation, coronary arteritis, coronary artery aneurysms, diastolic dysfunction, atrial septal aneurysm, conduction system disturbances, atrial and ventricular arrhythmias, mitral valve prolapse, intracardiac thrombosis, valvular insufficiency, and myocardial infarction
Gastrointestinal involvement	Also known as entero-Behcet disease (any part of the digestive tract from esophagus to the rectum may be involved), acute abdomen, intestinal perforation
Neurologic involvement	Focal or multifocal parenchymal involvement, isolated cerebral venous sinus thrombosis, intracranial hypertension, isolated behavioral syndromes, peripheral nervous system involvement, secondary neurologic involvement
Pulmonary involvement	Pulmonary artery aneurism, pulmonary infection, pulmonary vasculitis, pulmonary fibrosis, pleuritis, and pulmonary emboli

Table 2 Differential diagnosis of the common clinical manifestations of Behçet syndrome

Oral aphthosis	Recurrent aphthous stomatitis, infections (HSV, HIV, and candida-related oral ulcerations), dermatologic diseases (erythema multiforme, Stevens-Johnson syndrome, oral lichen planus, bullous pemphigoid, pemphigus, linear immunoglobulin A dermatosis), rheumatologic diseases (systemic lupus erythematosus, reactive arthritis), gastrointestinal diseases (ulcerative colitis, Crohn disease, celiac disease), autoinflammatory disorders (PFAPA syndrome, hyperimmunoglobulin D syndrome, A20 haploinsufficiency), hematologic disorders (cyclic neutropenia), nutritional deficiencies (iron deficiency, B12 deficiency, folate deficiency), physical factors (trauma, dental prosthetics, irritant oral hygiene products)
Genital aphthosis	Infectious conditions, including syphilitic chancre, chancroid, genital herpes simplex virus, lymphogranuloma venereum, granuloma inguinale, dermatophytosis, secondary bacterial infections, and such noninfectious conditions as fixed drug eruption, trauma, and vasculitides, including Wegener granulomatosis
Papulopustular lesions	Acne vulgaris, infectious folliculitis, and acneiform drug eruption
Uveitis	Crohn disease, ulcerative colitis, rheumatologic disease, and sarcoidosis
Joint involvement	Systemic lupus erythematosus, reactive arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, sarcoidosis, and inflammatory bowel diseases

environmental factors results in systemic vasculitis and associated clinical manifestations.[4]

Epidemiology

BS is known to be an Old Silk Road disease. The incidence and prevalence of the disease is highest along the Old Silk Road, extending from the Middle East to China.[9] The prevalence is the highest in Turkey with 420 cases per 100,000 population. Japan, Korea, China, Iran, and Saudi Arabia have lower prevalence with 13.5 to 22 cases per 100,000 population.[10] This is reported as 0.12 to 0.33 case per 100,000 population in the United States. North America and Europe show lower prevalence with one case per 15,000 to 500,000 population.[10,11]

The mean age of onset is in the third decade of life, but BS can be seen at any age.[12]

The majority of reports showed that men are more involved than women. In 19 out of 33 countries, BS involved men more than women. In six countries, men and women were equally affected. In seven countries, women showed more predisposition to BS than men. Curiously, men are more afflicted in Egypt, Israel, Iran, Greece, Germany, Russia, India, and China, whereas women predominate in Korea, the United States, and Australia. In Turkey and Japan, both sexes are almost equally involved.[12]

Clinical manifestation

The most common clinical feature of BS is recurrent and painful mucocutaneous ulcerations known as aphthosis. The

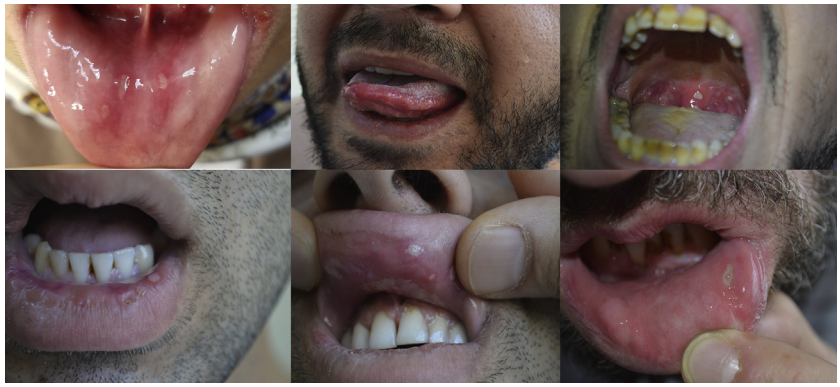

Fig. 1 Aphthous ulcers on different locations of the oral mucosa.

other clinical manifestations vary among patients and populations. The disease tends to be more severe in men. The major causes of morbidity and mortality are ocular, vascular, and central nervous system involvements[13] (Table 1).

Recurrent oral aphthosis

The most frequent manifestation of BS is recurrent oral aphthosis (ROA). The initial manifestation of the disease is also usually ROA. The commonly affected sites are gingiva, buccal mucosa, tongue, lips, soft and hard palate, pharynx, and tonsils (Figure 1). ROA can be described as a painful erosion of the oral mucosa with a round or oval shape in a diameter ranging from few millimeters to centimeters. The ulcer is well-defined and may have a surrounding erythema. The ulcers less than 1 cm in size are defined as minor ulcers. Major ulcers are at least 1 cm in diameter, and they may leave a scar.[12]

Oral ulcers typically heal spontaneously within 1 to 3 weeks, but rarely the healing process can reach 1 month.[12] The recurrence period of ROA ranges from a few weeks to a few months, but shorter or longer periods can also be seen.[14] They may be seem less common after about 20 years of disease and may be a less common manifestation in smokers.[15,16]

OA is a very characteristic feature of BS, but it can also be seen in many conditions. The differential diagnosis involves a wide variety of diseases and can be classified in 10 subheadings.[17,18] Recurrent aphthous stomatitis is the main differential diagnosis that is seen in nearly a quarter of the normal population.

OA is a very characteristic feature of BS, but it can also be seen in many conditions. The differential diagnosis involves a wide variety of diseases and can be classified into 10 subheadings[17,18] (Table 2):

1. Recurrent aphthous stomatitis (RAS): the main differential diagnosis that is seen in nearly a quarter of the normal population.
2. Infections: herpes simplex virus (HSV), human immunodeficiency virus (HIV), and candida-related oral ulcerations.
3. Dermatologic diseases: erythema multiforme, Stevens-Johnson syndrome, oral lichen planus, bullous pemphigoid, pemphigus, and linear immunoglobulin A (IgA) dermatosis.
4. Rheumatologic diseases: systemic lupus erythematosus, reactive arthritis, spondyloarthritis, and rheumatoid arthritis.
5. Gastrointestinal diseases: ulcerative colitis, Crohn disease, and celiac disease.
6. Autoinflammatory disorders: PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy), hyperimmunoglobulinemia D with periodic fever syndrome, and A20 haploinsufficiency.[19]
7. Hematologic disorders: cyclic neutropenia.
8. Nutritional deficiencies: iron deficiency, B12 deficiency, and folate deficiency.
9. Physical factors: trauma, dental prosthetics, and irritant oral hygiene products.
10. Drugs: methotrexate, other chemotherapy, and nicorandil.

Genital aphthosis

Genital aphthosis (GA) is known to be the most specific lesion for BS and involves about 75% of patients with BS. It can also rarely be the initial manifestation of the disease. GA shows almost the same clinical characteristic of OA, but the size is often larger, ulceration is deeper, and the healing process is longer. GA is also usually painful.[20]

The recurrence frequency of GA is usually less than the ROA. Scar formation is not rare for GA. Larger and deeper genital ulcerations have higher risk of scarring.

In men, the scrotum is the most frequent localization of the GA, followed by penile shaft and rarely the meatus (Figure 2). In women, GA is usually localized to the vulva. The vagina is the second most frequent site, with the cervix rarely involved (Figure 3). Epididymitis, salpingitis, or varicocele formation is also infrequent.[21,22]

Differential diagnosis of GA can mainly be classified into two subheadings[23–26] (Table 2): (1) infectious conditions,

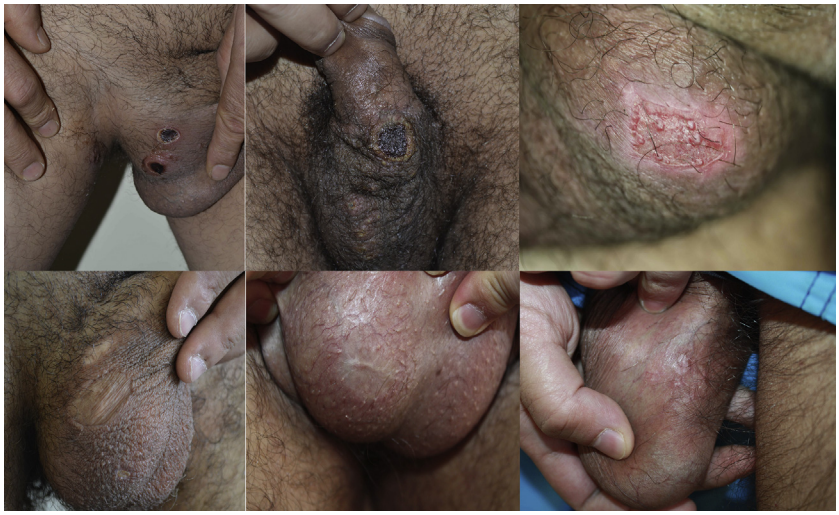

Fig. 2 Genital ulcers and scarring in men.

such as syphilitic chancre, chancroid, genital herpes simplex virus, lymphogranuloma venereum, granuloma inguinale (donovanosis), fungal infection (eg, *Candida*), and secondary bacterial infections; and (2) noninfectious conditions, such as fixed drug eruption, trauma, and vasculitis including granulomatosis with polyangiitis (formerly called Wegener's).

Cutaneous involvement

Cutaneous lesions are a frequent component of BS. In population-based studies, the incidence of skin lesions in BS ranges from 41.1% to 90.5%.[12,27] Many types of skin lesions can be observed in BS. The cutaneous manifestations of the disease can be summarized as follows:

1. Papulopustular lesions are the common form of cutaneous manifestation in BS and also denoted as Behçet pustulosis, folliculitis, acneiform eruptions, or pseudofolliculitis. The localization is usually trunk and extremities (Figure 4). A papulopustular lesion usually starts as a erythematous papule and changes to a pustule in 24 to 48 hours. It may be indistinguishable from ordinary acne.[28,29] The histopathologic sections of papulopustular lesions usually show perifollicular and perivascular mononuclear or neutrophilic infiltrations. Because BS is a multisystemic vasculitis, a vasculitic process can also be seen in the histopathology of papulopustular lesions.[30] Pustular lesions are usually not sterile and may be infected by *Staphylococcus aureus* and *Prevotella* spp.[31]
2. Pathergy phenomenon is a skin reaction to local injury. It is described as a papulopustular lesion appearing 48 hours after skin prick by a 20-gauge needle. The pathergy test is one of the diagnostic criteria of BS. There is no standardization for performing the pathergy test. Different methods, such as intradermal, intravenous, and subcutaneous applications, have been used and there is no a consensus on which form of the test yields a higher positivity rate.[32] The positivity of pathergy phenomenon in patients with BS varies between

Fig. 3 Genital ulcers and scarring in women.

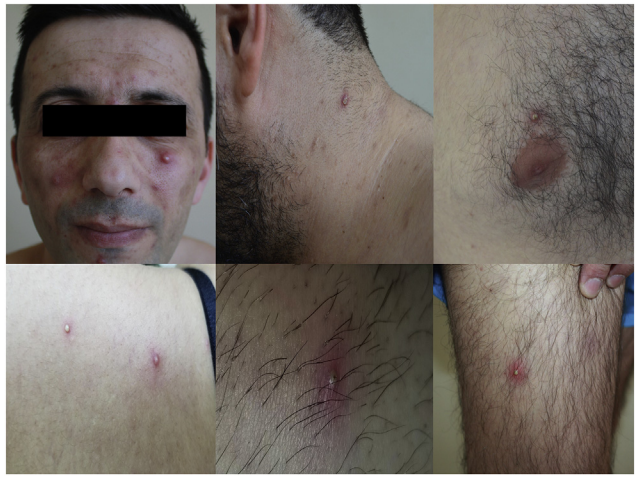

Fig. 4 Papulopustular lesions on different locations.

10% and 75% among the countries.[33] Pathergy phenomenon is relatively specific finding for BS but can also be seen in others conditions such as pyoderma gangrenosum and sweet syndrome.[32] It can also rarely be seen in the normal population.[12] The spectrum of histopathologic findings of positive pathergy phenomenon is similar to those of papulopustular lesions of BS.[34]

3. Erythema nodosum (EN)–like lesions are common in BS and are observed in about 45% of patients.[35] EN-like lesions are clinically similar to classical EN and mainly located on the lower limbs but can be rarely seen elsewhere too. Histopathologic features of EN-like lesions are usually different from those of classical EN with the high frequency of vasculitis and the predominance of a lobular or mixed form of panniculitis.[36]
4. Superficial thrombophlebitis (STM) involves large and small veins of the lower extremities and tends to be associated with deep vein thrombosis. STM sometimes may be indistinguishable from erythema nodosum, but string-like appearance following vein tracts on closer examination may be a helpful clinical clue to STM. Doppler dermal ultrasonography can also be a helpful tool to confirm diagnosis.[37]
5. Pyoderma-gangrenosum-like lesions, erythema-multiforme-like lesions, and nailfold capillary abnormalities are the others very rare cutaneous manifestations of BS.[38,39]
6. Extragenital ulcers are rarely found on the axillae, inframammary areas, and feet[12,13] (Figure 5).

Ocular involvement

Ocular manifestation (OM) is one of the diagnostic criteria and the most frequent cause of morbidity in BS.[12] Uveitis is the most common form of ocular involvement in BS. Vitritis, retinal infiltrates, sheathing of retinal veins, occlusive vasculitis, neovascularization, secondary cataracts, glaucoma, frosted branch angiitis, and macular edema are the other possible ocular manifestations. Conjunctivitis, conjunctival aphthosis, and scleritis can also rarely be seen.[40–43]

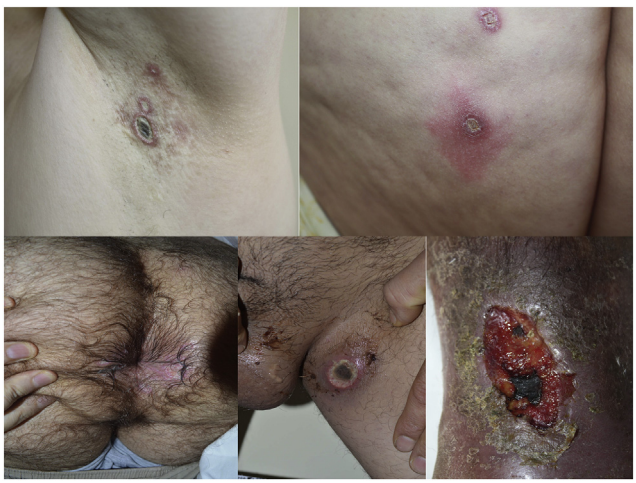

Fig. 5 Extragenital ulcers on different locations.

Ocular involvement occurs in 26.8% to 93% of the patients in population-based studies.[12] It mostly progress to blindness if remains without treatment. Men are more likely to get ocular involvement and have also unsatisfied visual outcomes.[44,45]

Eye involvement also follows the rule of attacks and remissions like other clinical manifestations of BS, but attacks last long and the recovery process is very slow. A new attack occurs before the recovery process completes and this causes an accumulation effect associated with the loss of vision and blindness.[12]

Uveitis is the most common form of ocular involvement of BS as mentioned previously. It is usually bilateral and episodic, often involves the entire uveal tract (pan uveitis), and may not heal totally between the attacks. In a study of BS uveitis, 68% were men and the mean age of onset was 28.5 years for men and 30 years for women. Rate of visual loss for 10 years was 30% for men versus 17% for women.[45]

Uveitis is a major feature of BS but can also be seen in other conditions such as Crohn disease, ulcerative colitis, spondyloarthritis, and sarcoidosis.[46–49] Conjunctivitis, scleritis, and episcleritis are nonspecific findings and may be seen in many conditions.

Musculoskeletal involvement

Arthritis and arthralgia are the most common musculoskeletal findings of BS.[50] The incidence of joint involvement varies between 40% and 70% in different studies.[51–53] Recurrent, self-limited, nonerosive, asymmetric oligo-monoarticular and nondeforming arthritis is the most common presentation. Large joints, such as knees, wrists, ankles, and elbow, are more likely to get affected[51–55] (Figure 6). Arthritis has also episodic course with attacks and remission like the other clinical manifestations of the disease.[12,56,57] Enthesopathy, avascular necrosis, myalgia, and myositis are the other musculoskeletal manifestations of BS.[50]

The pathogenesis of arthritis is not clearly known. Synovial inflammation and hyperemia are thought to be related to the vasculitis, which is the main pathology in BS; however, some authors find no evidence for vasculitis, and no other form of vascular disorder in the synovial pathology is detected.[58,59]

Nonerosive oligo-mono arthritis with presence of typical findings of BS such as oral aphthosis and genital aphthosis is essential for the diagnosis; however, Behçet arthritis is also a diagnosis of exclusion as it is in other findings of BS. Similar involvement of joints can also be seen in systemic lupus erythematosus, reactive arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, sarcoidosis, and inflammatory bowel diseases.[60]

Although arthritis is a common component of BS, it has not been included within the ISG criteria, which are the most used criteria for diagnosis.[20] This exception can be explained by the high incidence of joint complaints in society. The inclusion of

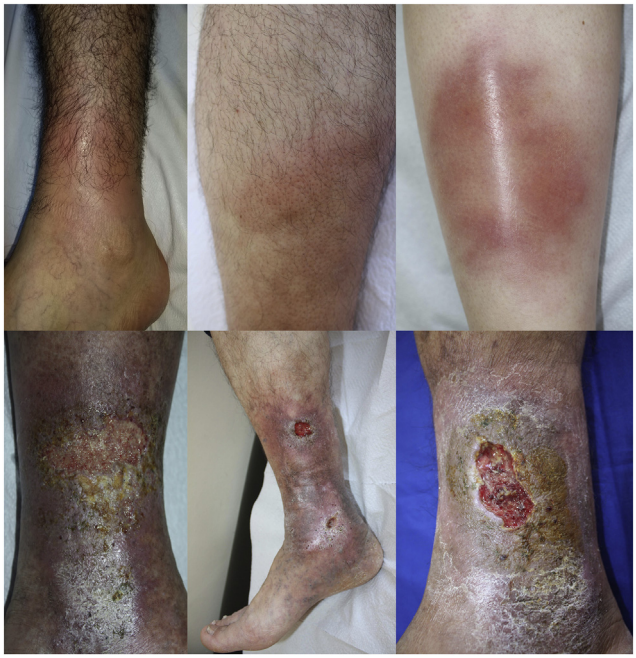

Fig. 6 Arthritis on the hand and knee.

joint involvement in the diagnostic criteria could lead to an increased false-positive diagnosis rate.[50,54]

Despite its nondestructive character nature, it has been revealed that arthritis was associated with overall functional impairment and pain similar to that seen in patients with rheumatoid arthritis in a questionnaire-based study.[61] Behçet disease has also different leg lesions (Figure 7).

Vascular involvement

Vascular involvement is also one of the main features of BS and is associated with a high rate of morbidity and mortality. Vasculitis in BS can involve any kind and size of vessels and this explains why the disease has the ability of arterial and venous circulation[2,3] (Figure 8). The prevalence of vascular involvement varies between 2.2% and 50% in different population-based studies.[12,62–64] Men are more likely to have vascular involvement.[62] The mean period from the diagnosis of BS to the onset of vascular involvement is about 7 years.[65]

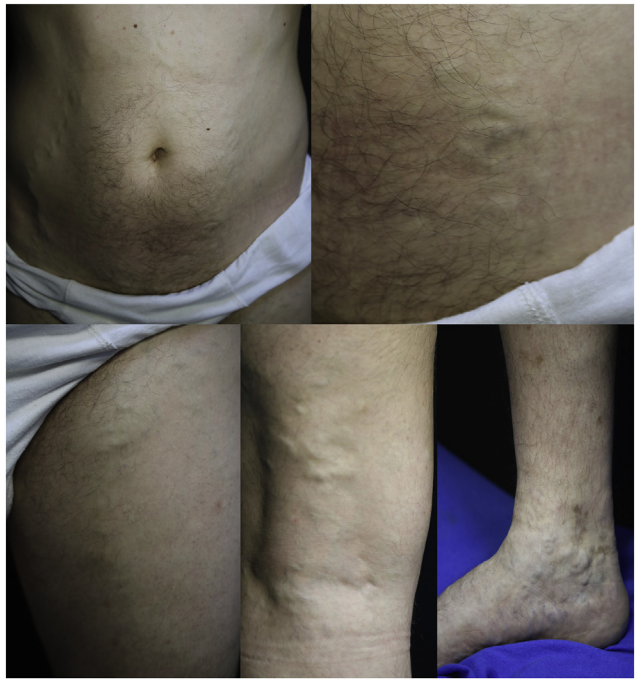

Fig. 8 Cutaneous vasculitis.

Superficial thrombophlebitis is classified in cutaneous involvement. Primary varicose veins in the legs are not categorized as vascular involvement even though they are found in patients with BS.[65]

Vascular involvement of BS can be discussed as arterial involvement or venous involvement.

Arterial involvement

Arterial disease most commonly affects small vessels, but medium-sized and large vessels may also be involved. The most commonly affected arteries are pulmonary, carotid, aortic, iliac, femoral, and popliteal arteries. Perivascular inflammation and endovascular inflammation are the main pathologies and are associated with hemorrhage, stenosis, aneurysm formation, and thrombosis. Pulmonary aneurysm is one of the major causes of mortality in BS. It is usually seen at late stages of the disease. The most common sign of pulmonary aneurism is hemoptysis and is usually associated with

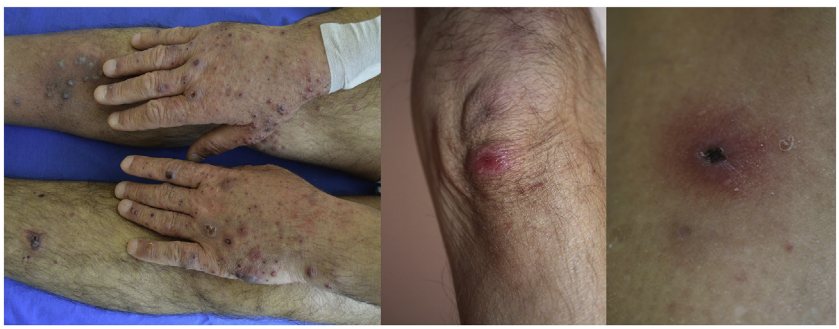

Fig. 7 Different type of lesions on the leg.

rupture of an aneurism. Fever, cough, dyspnea, and pleuritic pain may also be seen. Unfortunately, rupture of the pulmonary aneurism is often fatal. Pulmonary artery thrombosis and aneurysms along with peripheral thrombosis are known as Hughes-Stovin syndrome, and this syndrome is considered to be one of the vascular manifestations of BS.[66,67]

Venous involvement

Superficial thrombosis and deep vein thrombosis are the most common venous involvements in BS (Figure 9). The other manifestations of venous involvement are the Budd-Chiari syndrome, superior and inferior vena cava occlusion, and dural sinus thrombosis.[68–70]

Cardiac involvement

Cardiac involvement is very rare in BS but can have variable manifestations. Pericarditis, myocarditis, endocarditis with valvular regurgitation, coronary arteritis, coronary artery aneurysms, diastolic dysfunction, atrial septal aneurysm, conduction system disturbances, atrial and ventricular arrhythmias, mitral valve prolapse, intracardiac thrombosis, and valvular insufficiency are the possible cardiac manifestations of BS. Myocardial infarction may also rarely be seen.[71–79]

Gastrointestinal involvement

Gastrointestinal involvement of BS is known as intestinal Behçet disease. It is also among rare manifestation of the BS. The prevalence of gastrointestinal involvement varies between 4% and 38% in different population-based studies.[12]

Any part of the digestive tract from esophagus to the rectum may be involved but the most common location of intestinal Behçet disease is the ileocecal area. The characteristic endoscopic finding of intestinal Behçet disease is large, deep ulcerations with discrete borders. Intestinal Behçet disease may share a lot of clinical and endoscopic characteristics with inflammatory bowel diseases, and so it can be very challenging to differentiate gastrointestinal involvement of Behçet disease from inflammatory bowel diseases.[80]

Abdominal pain, diarrhea, and hematochezia are the main clinical presentations of intestinal Behçet disease.[12] Acute abdomen associated with intestinal perforation can also rarely be seen.[80–83]

Neurologic involvement

Neurologic involvement of BS is also known as neuro-Behçet syndrome, and it affects 5% to 10% of all patients with BS.[84] Nervous system involvement is one of the serious manifestations of BS with poor prognosis and occurs usually in men.[85]

Primary neurologic involvement in BS may be considered in two main major forms. The first one shows focal or multifocal parenchymal involvement and mostly presents with a subacute brain stem syndrome and hemiparesis (intra-axial NBS).[84] The majority of patients with neurologic involvement fall into this form. In a study, 94 out of 154 patients with neuro-Behçet disease had parenchymal involvement.[85]

The second one is presented with isolated cerebral venous sinus thrombosis and intracranial hypertension (extra-axial NBS) and has a better prognosis. Rarely, both forms of neurologic involvement can be seen in the same patient. Isolated behavioral syndromes and peripheral nervous system involvement may also rarely be seen.[84]

Neurologic complications associated with systemic involvement of BS and neurologic complications related to treatments are considered secondary neurologic involvement. Vascular-type headache is relatively common in patients with BS and not considered a part of neurologic involvement.[84]

Histopathologic investigation revealed vasculitic involvement in some cases and low-grade chronic nonspecific inflammation in the others.[85] A study investigating 121 patients with neuro-Behçet disease showed a significant lower frequency of HLA-B51 haplotype.[86]

Pulmonary involvement

Pulmonary artery aneurism, which is already mentioned above, is the most common presentation of pulmonary involvement in patients with BS. Seventy-eight percent of patients with aneurysms had concomitant extrapulmonary venous thrombi or thrombophlebitis.[87] The other pulmonary manifestations of the disease are rare and can be summarized

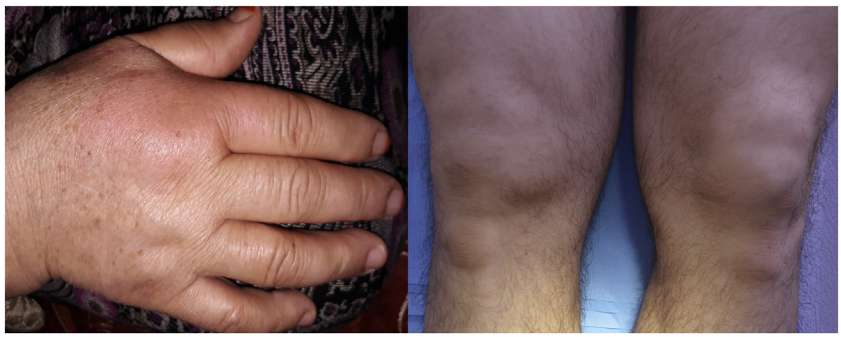

Fig. 9 Venous dilatation and tortuosity.

as follows: pulmonary infection, pulmonary vasculitis, pulmonary fibrosis, pleuritis, and pulmonary emboli.[12]

Diagnosis

There is no diagnostic laboratory test for BS, and the diagnosis is mainly based on clinical interpretation. In all patients with recurrent oral ulcerations, BS should be excluded by obtaining a detailed clinical history. Presence of the other characteristic manifestations along with recurrent aphthous stomatitis should raise suspicion for BS.

Classification and diagnosis criteria

Until now, 17 sets of classification and diagnosis criteria have been suggested for BS. The first one is the Curth criteria (1946), and the latest one is the revised International Criteria for Behçet's Disease (2014).

There are only two sets of international criteria for BS: International Study Group on Behçet's disease (ISG criteria, 1990) and International Criteria for Behçet's Disease (ICBD, 2006, revised in 2014). It is shown that ISG criteria have very good specificity but lack good sensitivity and accuracy. ICBD has much better sensitivity with a little less specificity and better accuracy.

ISG criteria

The ISG criteria were described in 1990, with the collaboration of seven countries. The criteria were presented to the Second International Conference on Behçet's Disease.[12,20]

Two minor criteria along with the required criteria are needed to be classified by ISG criteria. Required criteria are recurrent oral ulcerations, such as minor aphthous, major aphthous, or herpetiform ulceration, that are observed by the physician or patient and recurred at least three times in a 12-month period. Minor criteria include (1) recurrent genital ulceration, such as aphthous ulceration or scarring, observed by the physician or patient; (2) an eye lesion (anterior uveitis, posterior uveitis, or cells in vitreous on slit-lamp examination) or retinal vasculitis observed by an ophthalmologist; (3) skin lesions, such as erythema nodosum observed by the physician or patient, pseudofolliculitis or papulopustular lesions, or acneform nodules in postadolescent patients not on corticosteroid treatment observed by a physician; or (4) a positive pathergy test read by a physician 24 to 48 hours.

ICBD criteria

The ICBD was first described in 2006, with the collaboration of 27 countries. It was presented to the 12th International Conference of Behçet's Disease in Lisbon and was revised in 2010 and presented to the 14th International Criteria for Behçet's Disease in London. It was published in 2014.[88]

At least four points from the following list are needed to be classified by ICBD criteria:

- Oral aphthosis (two points)
- Genital aphthosis (two points)
- Ocular manifestations (two points)
- Skin manifestations (pseudofolliculitis, erythema nodosum, skin aphthosis) (one point)
- Vascular manifestations (one point)
- Neurologic manifestations (one point)
- Positive pathergy test (one point)

ISG and ICBD criteria may be helpful for diagnosis, but it should be kept in mind that the criteria were described to categorize patients for study purposes and were not developed to diagnose disease in individuals.

Treatment

The main purpose of treatment in BS is maintaining remission and improving patients' quality of life. Therapeutic management of BS should be based on the clinical presentation and involved systems. Age and sex of the patients, disease severity, involved organs, and comorbid conditions are the main parameters to consider when making a decision for treatment.[89,90] Today there is no curative treatment for BS, but recent investigations that focused on the pathogenetic mechanisms revealed some potential targets.

Topical treatment

It has been shown that the number of oral aphthous ulcerations and the daily frequency of tooth brushing are related to the severity scores of BD[91]; therefore, proper oral care should be the first step to reduce frequency of oral aphthosis.

Topical corticosteroids can be used to relief pain and shorten healing time in oral and genital aphthosis. Cream, ointment, gel, Orabase, and spray formulations are available. Eye drops may be used for ocular involvement.[90,92]

Topical pimecrolimus, one of the topical calcineurin inhibitors, has been reported to be effective in reducing pain and accelerating healing process in genital ulcers.[93,94]

Topical antibiotics and antiseptic agents, such as mouth rinses, triclosan, and chlorhexidine, may be used to reduce pain and shorten healing process with their antimicrobial and antiinflammatory properties in oral aphthous ulcerations.[95] Tetracycline and minocycline mouthwashes have also reported to be effective in oral aphthous lesions.[96]

Topical anti-inflammatory agents, including benzydamine hydrochloride, amlexanox, and topical prostaglandin E2 gel, can be used to reduce pain.[97–99] Amlexanox 5% oral paste has been shown to be effective in reducing ulcer size.[98] In a short-term study, it has been shown that topical prostaglandin E2 gel can prevent formation of new aphthous ulcerations.[99]

Topical anesthetics, including tetracaine, lidocaine, and mepivacaine, are the other agents that reduce pain in aphthous ulcerations.[100] Silver nitrate cautery can be an effective and quick alternative to decrease pain in aphthous stomatitis. It can also shorten the recovery time of ulcers.[101]

Another topical effective agent is sucralfate, which provides a protective barrier on the mucous surfaces. Sucralfate can improve pain and also shorten the healing process in aphthous ulcerations.[102]

In a study that evaluates different treatments for recurrent aphthous stomatitis and patient perceptions, Nd:YAG laser has been shown to be more effective than medications.[103]

Systemic treatment

Colchicine

Colchicine is an alkaloid agent inhibiting leukocyte function and is used frequently for a wide range of manifestations, especially for mucocutaneous and joint involvement, with a dose of 1 to 2 mg/d[92,104]; however, randomized controlled trials of colchicine showed mild effectivity for management of mucocutaneous involvement and arthritis.[105] In a double-blind and controlled study, it has been shown that continuous use of colchicine does not seem to decrease the use of long-term immunosuppressive treatment.[104]

Systemic corticosteroids

Corticosteroids are widely used in BS and may be helpful in short-term; however, long-term use is of major concern due to the side effect profile. There is no a great number of controlled study about corticosteroid use in BS.[89] In a double-blind trial of depot corticosteroids in BS, low-dose depot corticosteroids did not show any beneficial effect on genital and oral aphthosis, folliculitis, or arthritis; however, it was useful in controlling erythema nodosum.[106] European League Against Rheumatism (EULAR) recommends the use of corticosteroids for ocular, vascular, gastrointestinal, and neurologic involvement.[107]

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs are useful to manage joint pain in patients with BS.[89] In an open-label study, oral indomethacin 25 mg four times daily for 3 months has been shown to be effective in skin lesions, joint involvement, and oral and genital ulcerations.[108]

Azathioprine

Azathioprine, along with corticosteroids, is recommended as the initial therapy for all patients with BS showing inflammation of the posterior segment of the eye.[107] Azathioprine has also been shown to be effective for vascular, intestinal, and neurologic involvement.[108,109] Up to 3 months may be needed to gain a significant response with azathioprine.[110]

Cyclosporine A

There are many randomized controlled trials showing effectivity of cyclosporine A in patients with BS with ocular involvement.[111–113] It may also be beneficial for the treatment of acute deep vein thrombosis.[114] It should be noted that several case-control studies reported an increased incidence of neurologic involvement among patients with BD under cyclosporine A therapy.[115–117] The drug is not recommended in neuro-Behçet disease. Hypertension and renal failure are the other well-known side effects of the cyclosporine A.[117] Oral and genital aphthosis and skin manifestations may also be reduced in the patients with BS with cyclosporine A.[112]

Tacrolimus is another calcineurin inhibitor like cyclosporine A and may have similar efficacy.[89]

Mycophenolate mofetil

There are no large controlled studies investigating efficacy of mycophenolate mofetil in BS, but in a prospective study, it has been shown that the drug is not effective on mucocutaneous involvement of BS.[118] In a case series, mycophenolate mofetil showed a remarkable efficacy on parenchymal neuro-Behçet disease.[119]

Cyclophosphamide

Vascular involvement and parenchymal neurologic involvement are the main indications for cyclophosphamide in BS.[89] Cyclophosphamide may be a treatment of choice for superior vena cava thrombosis and Budd-Chiari syndrome.[107] In a retrospective study including 40 patients with neuro-Behçet disease showed clinical improvement with cyclophosphamide treatment.[120]

Thalidomide

In a randomized controlled trial, thalidomide was found to be effective on oral and genital aphthosis.[121] Three other open-label studies with thalidomide also showed efficacy on oral and genital ulcerations.[122–124] Thalidomide has also been reported to be effective on intestinal involvement.[125]

Methotrexate

Methotrexate was found to be effective in reducing ocular inflammation in patients with BS in an observational study.[126] It also showed efficacy on neurologic involvement in another study.[127]

Dapsone

A double-blind controlled study showed that dapsone significantly decreased the frequency and duration of oral and genital aphthosis.[128]

Interferon α

Interferon α is another agent showing some beneficial effects on mucocutaneous, articular, and ocular manifestations of BD.[89,129]

Biologics and monoclonal agents

Anti-TNF-α agents

Infliximab

Several studies showed that intravenous infliximab (anti-TNF-α chimeric monoclonal antibody) is found to be effective in reducing ocular inflammation and decreasing the frequency of uveitis attacks.[130,131] Infliximab may also be used for resistant gastrointestinal, neurologic, vascular, joint, and mucocutaneous involvement.[132–136]

Etanercept

In a randomized double-blind, controlled study, etanercept (TNF-α receptor p75 fusion protein) has been found to be effective in decreasing the frequency of oral and genital aphthosis, acneiform lesions, erythema nodosum, and arthritis.[137] Etanercept may also have beneficial effects on ocular involvement.[138]

Adalimumab

A number of case reports showed that adalimumab, an anti-TNF-α monoclonal antibody, may be beneficial for uveitis, recalcitrant genital ulcerations, cerebral vasculitis, and pulmonary artery aneurism in patients with BS.[139–142]

Rituximab

In a randomized controlled study, rituximab (anti-CD20 antibody) has been shown to be effective on recalcitrant ocular involvement of BS.[143]

Other biologic agents

Mainly based on case reports, gevokizumab (recombinant humanized anti-IL-1β antibody),[144] canakinumab (human anti-IL-1β antibody),[145] anakinra (IL-1 inhibitor),[146] tocilizumab (IL-6 inhibitor),[147] alentuzumab (anti-CD52 antibody),[148] and daclizumab (anti-CD25 antibody)[149] are the other biologics that may have beneficial effects in different involvements of BS.

Conclusions

In conclusion, the clues to avoid misdiagnosis and over diagnosis of BS which is a great imitator can be summarized as follows: any oral ulcer is not an aphthous ulcer, even if it is an aphthous ulcer, it may not be associated with BS. It should be remembered that recurrent aphthous stomatitis is frequent in the normal population (12). In BS, oral ulcerations is tend to be more frequent and severe than recurrent aphthous stomatitis (91,92). The commonest finding of the BS is recurrent oral ulcers, but they may not always be the initial symptom of the disease. It should be noted that the puzzle can be completed later. Non specific symptoms like fever and malaise are more likely to accompany oral ulcerations associated with BS (93). Presence of recurrent genital ulcerations are more specific for BS (20). BS has a strong genetic background and it can be seen at any age (12). So, a detailed history of family may be helpful (94). The suspicion threshold should be lower for individuals who live along ancient silk road. Since BS is a multi systemic disease, it should be kept in mind that the syndrome can mimic many rheumatologic, neurologic, cardiovascular and gastrointestinal diseases. Diagnosis of BS should be based on exclusion of the other diseases which can have similar clinical manifestations.

Acknowledgments

The staff and resident physicians of the Istanbul Medeniyet University, Göztepe Training, and Research Hospital provided assistance in the preparation of this contribution, and their photographic archives were used for many of the illustrations.

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