Review Article

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Behcet's syndrome: a contemporary narrative review

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Behcet's syndrome (BS) is a chronic inflammatory condition affecting multiple systems, primarily characterized by recurrent aphthous ulcers, genital ulcers, skin lesions, musculoskeletal issues, arthritis, and involvement of the vascular, ocular, gastrointestinal, and nervous systems. A key feature of BS is the unpredictable pattern of relapses and remissions, with oral ulcers being the most common and often the earliest sign of the disease. These painful oral ulcers can significantly impact a patient's daily functioning and quality of life. The development of BS is influenced by a combination of immune processes, environmental factors (such as viral and bacterial infections like herpes simplex virus and streptococci), hormonal changes, and genetic predisposition. Due to its multisystemic nature, a multidisciplinary approach is essential for effective management. The primary treatment goal is to control inflammation and prevent disease progression involving major organs, which can reduce the risk of mortality. Treatment options vary based on severity and organ involvement, ranging from topical therapies to systemic glucocorticoids and immunosuppressive medications.

Keywords: Behcet Syndrome, oral ulcer, ulcer

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Introduction

Behcet's syndrome (BS) is a chronic multi-systemic inflammatory vasculitis characterized by recurrent aphthous ulcers (RAU); genital ulcers; skin lesions; musculoskeletal involvement; arthritis; and vascular, ocular, gastrointestinal, and neurologic disease [1]. Hallmark of BS is a recurrent unpredictable relapsing and remission of clinical manifestations, in which oral ulcers are initially the most common occurrence and begin as the first sign of BS [2]. Painful oral ulceration can affect a patient's function and quality of life [3]. It is well-known that immunological process [2], environmental factors including viral and bacterial infections such as herpes simplex virus infection and streptococci [4], hormonal change [5], and genetic susceptibility [1] play an important role in aetiopathogenesis of BS. According to the multisystemic involvement of BS, multidisciplinary management is rational for optimal treatment. The goal of treatment is to suppress inflammation and prevent exacerbation of disease from major organ involvement and mortality [6]. Treatment options can be varied from topical treatment, systemic glucocorticoids, and immunosuppressive drugs depending on the severity of disease and organ involvement [7]. The aim of this article is to review the current concepts of BS for dental professionals. We searched Pubmed/ Medline from 1990 to present using the term "Behcet disease" "Behcet syndrome". Only relevant published data were selected in this review. Records were limited to those in English.

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Epidemiology

BS has a worldwide distribution which highly prevalent in the Mediterranean region, Middle East countries, Southeast Asia along the Silk Route countries, and particularly in Japan and Turkey. The disease onset is usually in the third to fourth decade of life [1]. The disease is more severe and affects more organs when developed in a very young age patient [8]. Both genders can be affected equally. Males tend to be predominant in Middle East and Mediterranean countries, which is also considered as a risk factor for severe disease and can influence disease prognosis [9].

Pathogenesis of Behcet's syndrome

Genetic factors

The link between HLA-B5 and BS, which is common in Middle Eastern and Mediterranean countries, has been confirmed in multiple studies. HLA-B51, a split antigen of HLA-B5, has been strongly linked to the disease [4]. Furthermore, the presence of HLA-B51 and HLA-A26 increases susceptibility to ocular manifestations. Micro (mi) RNAs, including miR-155, miR-21, and miR-23b may serve as potential biomarkers for BS, whereas miR-146a has been linked to ophthalmic and neurological manifestations in addition to oral ulcers [1].

Immunological markers

During disease activity, there might be an increase in inflammatory indicators including C-reactive protein and erythrocyte sedimentation rate [10]. Anti-endothelial cell antibodies (AECA) are associated with vascular involvement in BS, particularly in cases involving central nervous system (CNS) symptoms. While AECA levels are often elevated in patients with active disease, especially those with severe manifestations like CNS involvement [11].

Microbiome and BS

1. Oral microbiome

The environmental factors which influence the aetiology of BS include infectious oral foci caused by periodontal and oro-dental disease. The association between the oral microbiome and the pathogen of BS can serve as both a disease prognostic indicator and an aetiological trigger for the aetiology of the disease. This happens when the established microbial population experiences dysbiosis, which causes inflammation and a decline in host pathogen resistance [2]. The aetiology of BS focuses mostly on different streptococci strains. The human cytomegalovirus, Epstein-Barr virus, varicella zoster virus, and herpes simplex virus have been suggested to be aetiologic factors in BS [2]. *S. salivarius* and *S. sanguinis* are highly colonised at the oral ulcer site in patients with BS, according to a United Kingdom oral microbiome study of Seoudi *et al.,* 2015. Additionally, active oral ulcers associated with BS are shown to have substantial S. mutans colonisation [12]. Furthermore, *S. mutans* levels are reported to be higher in male patients who had worse off periodontal indices and a more severe disease course. Serum mannose binding lectin is present at lower level, with increased *S.mutans* colonization in saliva [2]. In comparison to healthy control volunteers, members of the phylum Actinobacteria, particularly those belonging to the genus *Rothia*, were detected on the oral mucosa more often in BS and RAU. *Neisseria* and *Veillonella*, however, were more prevalent in the healthy control oral mucosa [13].

According to Seoudi *et al.,* 2015 study, oral active BS had an imbalanced oral mucosal and salivary microbial ecology. Additionally, it appeared that *Rothia dentocariosa* was less able to develop and multiply at the ulcer sites of orally active BS and RAU [14]. However, Mumcu *et al.,* 2021 found that compared to cases of RAU, ulcer sites in BS are more heavily colonised with S. salivarius. On an active oral ulcer, *S. salivarius* and *S. sanguis* are strongly colonised. From these findings, it can be concluded that altering immunological responses caused by the microbiome profile change contribute to immune dysregulation during the disease development and progression [2].

Gut microbiome

Through a variety of methods, such as by causing intestinal epithelial barrier malfunction, encouraging T helper 1 (Th1) and T helper 17 (Th17) cell activation, and stifling the development of regulatory T cells (Treg), dysbiosis of the gut microbiota may contribute to the pathogenesis of BS [1]. Patients with BS showed abnormal Th1, Th17, and Treg cell activities. Recent research suggested that the gut microbiome may play a crucial role in controlling Th1, Th17, and Treg cells [15]. Butyrate, a metabolite produced by gut microbiota, plays a vital role in maintaining intestinal homeostasis through its support of colonocyte energy metabolism, anti-inflammatory effects, and preservation of intestinal barrier integrity. The decrease in butyrate-producing bacteria in autoimmune patients suggests that increasing butyrate levels could help regulate the immune system and improve gut health [16].

Hatemi *et al.,* 2022 found that individuals with BS had much less alpha diversity and fewer butyrate-producing bacteria in their gut microbiomes than a control group. This appears to be significant since butyrate stimulates Treg cells and inhibits intestinal pro-inflammatory cytokines. Thus, decreased butyrate levels ultimately cause intestinal inflammation [17]. Presently oral and gut microbiome characteristics can alter mucosal immunity, inflammation, and disease progression, which may provide suggestions for new chronic disease treatment options [12].

Immunity

1. Innate immunity

Alarmins are a family of proteins that can activate the innate immune system. Alarmins are crucial for reestablishing homeostasis following tissue injury because they activate pattern recognition receptors (PRR), such as Toll-like receptors (TLR) [15]. TLR and PRRs are able to recognise lipoteichoic acid (LTA) found in the cell walls of gram-positive bacteria. LTA can also increase the production of interleukin-8 in peripheral blood mononuclear cells. It is acknowledged that the oral microbial population could serve as a triggering for TLR2 and TLR4 in BS.

Neutrophils play a significant part in innate immunity. They are first attracted to the area of higher activity caused by ulcers. In BS, hyperactive neutrophils are a major characteristic of the disease's pathogenesis leading to increase chemotaxis, phagocytosis, and superoxide production [2]. By assessing oxidative burst, phagocytic, and microbicide activity, as well as intracellular signaling pathway activation, one could potentially identify exacerbated neutrophil activity [15]. In addition, Al-Otaibi *et al*., 2005 proposed that the level of superoxide generated from neutrophils may increase and appear to be correlated with the existence of the HLA-B51 [4]. Therefore, innate immune responses triggered by pathogens lead to vasculitis and tissue damage in BS due to the activation of neutrophils and T cells [2].

2. Adaptive immunity

BS is characterized by the involvement of the innate immune system and perpetuated

through the adaptive immune responses of T cells against infectious or autoantigens. The activation of the adaptive immune system constitutes the main cause of the inflammatory processes observed. Notably, Th1 and Th17 cells assume a significant role in the pathogenesis of BS [18].

The involvement of Th1 cells plays a significant role in the development of BS. These cells, identified in lesions like oral and genital ulcers, pseudofolliculitis, pathergy pustules, and bowel ulcers, secrete various factors like Tumor Necrosis Factor-alpha (TNF-α), Interferon-gamma (IFNγ), IL-8, IL-12, and chemokine receptors (CCR5, CXCR3) along with MCP-1, a protein attracting macrophages [15]. IL-12 is synthesized by dendritic cells, macrophages, and B cells, serving as a pivotal inducer of Th1 responses. IFNγ, on the other hand, stimulates macrophages, which play a vital role in cell-mediated immunity against intracellular pathogens and are implicated in various organ-specific autoimmune diseases, including BS. IL-18 functions by promoting IFNγ production through the activation of natural killer (NK) cells, and it also stimulates NK cells' cytotoxic activity. Furthermore, IL-18 stimulates T cells to secrete both IL-12 and IFNγ [18]. In a study conducted by Musabak *et al.* in 2006, it was found that the serum concentrations of IL-18 were notably higher in all subgroups (active or inactive disease, and systemic involvement or mucocutaneous symptoms only) when compared to the healthy individuals. Moreover, these elevated levels of IL-18 correlated with the disease activity score in patients with active BS [19].

Th17 cells play an important role in the progression of autoimmune diseases by governing both inflammation and autoimmunity regulation. Cytokines like IL-6, transforming growth factor-beta (TGF-beta), and IL-23 contribute to the differentiation of Th0 cells into Th17 cells. Once differentiated, Th17 cells generate cytokines including IL-17A, IL-17F, IL-21, IL-22, and IL-23, thereby regulating the modulation of inflammation and autoimmunity. The maintenance of a delicate balance between Treg cells and effector Th17/Th1 cells is significant to ensure effective immune responses while preventing the emergence of pathological autoimmunity. Hence, the balance between Th17 cells and Treg cells holds significant importance in governing inflammation within patients affected by active BS [18].

The intraepithelial Gamma-Delta (γδ) T cell protects the mucosal barrier by generating antimicrobial peptides and triggering mucosal immune responses. Once neutrophils have successfully eliminated the pathogenic microorganisms, γδ T cells detect the bacterial byproducts, subsequently triggering the production of proinflammatory cytokines by monocytes [2]. The γδ T cells play a pivotal role in the modulation of autoimmune responses. TCRVγ9Vδ2^{+} T cells, which constitute the predominant subset of γδ T cells found in the peripheral blood, demonstrate the capacity to generate numerous proinflammatory cytokines. In response to an infection, the population of γδ T cells can rapidly expand within a matter of days, constituting more than 50% of all circulating T cells. The activation of these γδ T cells facilitates the stimulation of IL-17^{+} producing uveitogenic αβ T cells, subsequently expediting the progression of experimental autoimmune uveitis [18].

Others

Hormonal factors

Neutrophils play a role in the development of BS and are activated by testosterone, the primary male sex hormone. Consequently, the male gender is considered a critical prognostic factor in BS [5]. Hormonal changes also occur during different phases of the ovulation cycle and impact various subsets of leukocytes. Menstruation

triggers several conditions, including RAU. Notably, 68% of individuals with BS experience the exacerbation of at least one skin mucosa lesion during menstruation [12].

Vitamin D deficiency

The expression of the Vitamin D receptor gene is diminished in patients with BS [1]. Additionally, Khabbazi *et al.,* 2019 have reported an association between vitamin deficiency and active disease in their study. [20] Interestingly, previous studies have shown a vitamin D deficiency in BS, suggesting that vitamin D supplementation could be beneficial for its prevention and treatment. However, a study by Zhong *et al.,* 2021 found that higher levels of 25-hydroxyvitamin D were associated with an increased risk of developing BS [21].

Clinical manifestations

1. Oral ulcers

Recurrent oral ulcers stand as a distinctive clinical hallmark of BS. The majority of individuals with BS present with multiple ulcers that affect various regions of the oral mucosa. These ulcers are characterized by their painful nature, round or oval shape, well-defined borders, yellowish-white necrotic base, and encircling erythema. Importantly, they typically heal within 1 to 3 weeks without leaving any lasting scars [1]. RAU commonly serves as the initial manifestation of BS up to 86.5% of adults and children [4]. Mumcu *et al*., 2019 documented a reported protective effect of smoking against the development of RAU in individuals with BS. The possible positive influence of smoking on recurrent oral ulcers (ROU) is linked to two factors: the increased growth of epithelial cells in the oral mucosa and the systemic anti-inflammatory properties of nicotine, which affect both endothelial cells and keratinocytes [12]. Oral ulcerations in BS are shown in Figure 1.

2. Cutaneous lesions

Cutaneous lesions hold significant diagnostic value in BS owing to their easily noticeable nature. They represent the earliest and most prevalent indicators of BS [1]. Among the most recurring cutaneous manifestations of BS are papulo-pustular lesions, erythema nodosum, and erythema nodosum-like disease. Papulo-pustular lesions are sterile cutaneous folliculitis or acne-like lesions, emerging on an erythematous base. They begin as papules and progress into pustules within a span of 24 to 48 hours. Typically, these lesions manifest concurrently, primarily affecting the skin on the back, face, and chest. Erythema nodosum-like lesions, a common occurrence in BS, tend to appear on the lower extremities. These lesions are characterized by painful purplish nodules, encompassed by a peripheral halo. Notably, they do not ulcerate and tend to resolve spontaneously [4]. The pathergy test can be conducted during active symptoms of BS by inserting a sterile 20-gauge needle subcutaneously into the forearm without injecting saline. The test is considered positive if, after 24–48 hours, the puncture site develops an aseptic erythematous nodule or pustule larger than 2 mm in diameter [9].

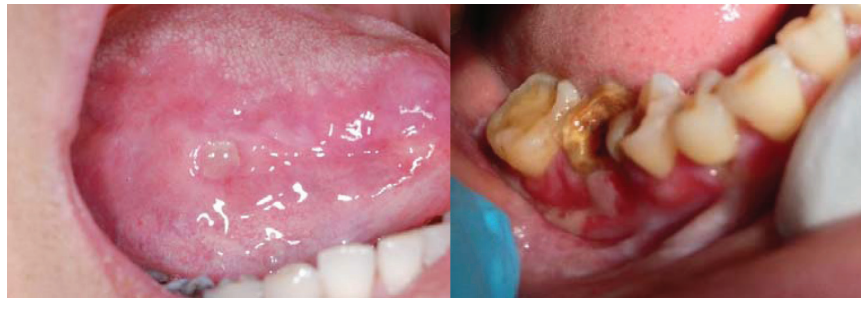

Figure 1 Oral ulceration at the lateral surface of tongue and buccal gingiva

3. Ocular involvement

Ocular symptoms typically do not represent the primary clinical features of BS; however, they can precipitate significant disability. The risk of blindness resulting from macular degeneration is estimated at 15-25% within a 5-year timeframe. Ocular manifestations commonly arise 2-3 years subsequent to the emergence of extraocular signs. Symptoms are observed in 25-75% of patients and encompass a range of issues such as blurred vision, vision loss, ocular congestion, pain, photophobia, tearing, foreign body sensation, and headache [1]. The most common ocular manifestation is relapsing iridocyclitis. Uveitis, uveitis with conjunctivitis (early) and hypopyon (late), retinal vasculitis (posterior uveitis), and optic atrophy can be seen (9). Tong *et al.,* 2019 reported that IL-1, IL-6, and TNF-α serve as prominent proinflammatory cytokines in patients with BS. These cytokines have been detected in the ocular fluid of BS patients for over twenty years and are widely regarded as the primary inflammatory mediators contributing to the pathogenesis of the disease [18].

4. Genital ulcers

Genital ulcers represent a distinct symptom of BS and are present in at least 75% of patients [1]. Genital ulcers share similarities in appearance and progression with oral ulcers. In cases of deeper lesions, there is a potential for complications such as the development of fistulas, particularly among females [8]. Typically, the recurrence rate of these ulcers is lower than that of oral ulcers [22]. These ulcers manifest on areas such as the scrotum, penis, vulva, and vaginal mucosa. Particularly, they are characterized by their depth, intense pain, delayed healing, and propensity to form scars [1].

5. Others

Most of the clinical presentations in BS are attributed to vasculitis, which involves inflammation in small, medium, and large blood vessels. Vein involvement holds a higher predilection, with thrombosis being the prevailing venous presentation. Conversely, arterial involvement can result in aneurysms, constituting the predominant arterial manifestation in BS [1].

Neurological complications within the context of BS are infrequent but primarily affect the CNS. CNS involvement represents a potentially grave complication of BS and can manifest as pseudotumor cerebri, brainstem involvement, neuropsychiatric symptoms, and meningoencephalitis [4]. BS patients with neurological involvement may experience cognitive dysfunction and affective symptoms, such as psychosis, as well as high levels of anxiety and fatigue [23].

The gastrointestinal tract is impacted in 3-26% of patients, with higher incidence rates observed in Japan compared to the Middle East and Mediterranean regions. Mucosal inflammation and ulceration are possible across the entirety of the gastrointestinal tract, with a particular predilection for the ileocecal region [8]. Clinical presentations vary widely, ranging from mild abdominal discomfort to severe abdominal pain, often accompanied by hematochezia or melena. Additionally, manifestations can extend to include complications such as fistula formation and perforation. A distinctive hallmark is the presence of characteristic volcano-shaped ulcers, primarily located within the ileocecum [1].

45-60% of joint involvement is reported in BS patients [8]. Characteristic joint manifestations in BS involve acute, recurrent peripheral mono- or oligo-arthritis, with a predilection for affecting

the knee and ankle joints most frequently. The arthritic episodes are self-limiting, and symptoms typically resolve within a span of 2 to 3 weeks [1] .

Diagnosis

The diagnosis of BS is currently challenging due to the lack of definitive laboratory tests. It is primarily based on clinical symptoms and a process of exclusion to rule out other conditions with similar manifestations. To address this, several diagnostic criteria for BS have been developed over time [1].

In 1974, O'Duffy introduced five key symptoms for the diagnosis of BS, which included oral aphthosis, genital aphthosis, skin manifestations, ophthalmological manifestations, and arthritis/arthralgia. To establish a diagnosis, it was required to have either oral aphthosis or genital aphthosis, along with at least two additional symptoms [24].

The most widely used BS diagnostic criteria in clinical practice are those established by the International Study Group (ISG) and were published in 1990. The ISG criteria are presented in Table 1.

The updated Japanese diagnostic criteria for Behcet's disease (BD) were released in 2004, categorizing clinical manifestations into two groups: main and additional symptoms. Complete BD was defined for patients presenting with four main symptoms. Incomplete BD encompassed those with three main symptoms, two main symptoms, and two additional symptoms, as well as those exhibiting typical ocular lesions with one main symptom or typical ocular lesions with two additional symptoms as shown in Table 2.

Table 1 International Study Group (ISG) diagnosis criteria for BS [25]

Criterion	Required features
Recurrent oral ulceration	Minor/major aphthous or herpetiform ulceration observed by the physician or patient at least 3 times in a 12-month period
Plus any 2 of the following:	
Recurrent genital ulceration	Aphthous ulceration or scarring observed by the physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, cells in the vitreous in a slit-lamp examination, or retinal vasculitis observed by an ophthalmologist
Skin lesions	Erythema nodosum observed by the physician or patient; pseudofolliculitis, papulopustular lesions, or acneiform nodules observed by the physician in post-adolescent patients not on corticosteroids
Positive pathergy reaction	Read by physician at 24-48 hrs, performed by piercing a sterile 20-gauge needle subcutaneously into the forearm. It is considered as positive when the puncture leaves an aseptic erythematous nodule or pustule larger than 2 mm.

Table 2 Revised diagnostic criteria proposed by the Behcet's Disease (BD) Research Committee of Japan [26]

Main symptoms

Recurrent aphthous ulcers on oral mucosa

Skin lesions

a. Skin lesions with erythema nodosum
b. Subcutaneous thrombophlebitis
c. Follicular papules, acnetiform papules, skin hypersensitivity

Ocular lesions

a. Iridocyclitis
b. Posterior uveitis (retinochoroditis)
c. If the patients have the following eye symptoms after (a) and (b), diagnose as BD lesions in accordance with (a) and (b).

• Posterior adhesion of iris, pigmentation on lens, retinochoroid atrophy, atrophy of optic nerve, complicated cataract, secondary c. glaucoma, leakage of bulbus oculi

Additional symptoms

Arthritis without deformity or sclerosis

Epididymitis

Gastrointestinal lesion represented by ileocecal ulceration

Vascular lesions

Central nervous system lesions, moderate or severe

Criteria for diagnosis of disease types

Complete type:

The four main symptoms appeared during the clinical course

Incomplete types:

Three of the main four symptoms, or two main symptoms and two additional symptoms, appeared during the clinical course

Typical ocular lesion and another main symptom, or two additional symptoms appeared during the clinical course

BD suspected:

Although some main symptoms appear, the case does not meet the criteria for the incomplete type

Typical additional symptom is recurrent or becomes more severe

Special lesions:

Gastrointestinal lesions-presence of abdominal pain and occult blood should be confirmed

Vascular lesions-vasculitis of aorta, artery, large veins, or small veins should be differentially diagnosed

Neuronal lesions-presence of headache, paresis, lesion of brain and spinal cord, mental symptoms, and other symptoms should be confirmed

1. The International Criteria for Behcet's Disease (ICBD) was developed in 2014 by incorporating five existing criteria, which yielded estimates of both sensitivity and specificity exceeding 90%. Notably, ICBD demonstrates higher sensitivity than the ISG criteria; however, its specificity remains lower than that of the ISG criteria. The diagnostic criteria are presented in Table 3, where each sign or symptom is assigned a point score. A diagnosis of BS requires a minimum of 4 points. In accordance with the scoring system, 4 points indicate a probable diagnosis of BS, 5 points suggest a highly likely BS, and 6 points imply an almost certainly of BS.

In 2016, an international expert consensus group established the Pediatric Behçet's Disease (PEDBD) classification criteria for diagnosing pediatric BS patients. This set encompasses six categories, including oral, genital, skin, ocular, neurological, and vascular involvement. To establish a diagnosis of pediatric BS, a minimum of three findings, each from a different category, is required. It is noteworthy that the PEDBD criteria exhibit higher sensitivity (91.7%) but lower specificity (42.9%) in comparison to the ISG criteria when applied to the pediatric population [26].

Differential diagnosis

BS should be considered in the differential diagnosis when evaluating patients with oculomucocutaneous symptoms, as outlined below [9].

Table 3 The International Criteria for Behcet's Disease (ICBD) – point score system [27]

Sign/symptoms	Points
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestation	1
Positive pathergy test*	1*

*The pathergy test is considered optional, and the primary scoring system for diagnosis does not include pathergy testing. However, in cases where pathergy testing is performed and yields a positive result, an additional point may be assigned [26].

Diseases	Typical features
Sweet's syndrome.	Oral ulcers, conjunctivitis, episcleritis, inflamed tender skin papules or nodules.
Erythema multiforme.	Target-like skin lesions. Oral lesions are presented as painful oral ulcers, typically affecting the anterior non-keratinized mucosa. Hemorrhagic crusts on the lips are common.
Pemphigus.	Oral involvement is often the first sign, with painful flaccid blisters and irregular erosions that affect the mucous membranes.
Pemphigoid.	Blisters, erosions, and ulcerations primarily affecting the gingiva, palate, and also found in another mucosa such as conjunctiva. The lesions are typically tense and less fragile than those seen in pemphigus
Inflammatory bowel disease.	Chronic gastrointestinal inflammation with oral ulcers and mucosal inflammation
Syphilis	Primary syphilis: chancre Secondary syphilis: Condyloma latum, mucous patch, maculopapular rash Tertiary syphilis: gumma

Treatment

The management of BS requires a multidisciplinary approach owing to its involvement across multiple systems. The primary objectives of management are to promptly suppress exacerbations, mitigating potential damage, and to proactively avert further inflammatory attacks [28]. Treatment regimens for BS are based on the patient's sex, age, and the severity of the disease. More severe cases, often associated with male sex, a younger age of onset, and a higher number of affected organs at the time of diagnosis, typically necessitate more aggressive treatment approaches [1].

Mucocutaneous manifestations

The European Alliance of Associations for Rheumatology (EULAR) management recommendations on 2018 for BS propose utilizing topical corticosteroids should be used for the treatment of oral and genital ulcers. The initial approach for preventing the recurrence of mucocutaneous lesions, particularly when the predominant manifestation is erythema nodosum or genital ulcer, involves considering colchicine as the primary therapeutic option [29]. In addition to topical glucocorticoids, isolated oral and genital ulcers in BS can be addressed with calcineurin inhibitors, interferon (IFN)-α gel, and lidocaine gel. Paying attention to oral health practices may contribute to reducing the incidence of oral ulcers [1]. A study by Mumcu *et al*. (2021) found that elevated microbial plaque accumulation is linked to oral ulcer activity and a more severe disease course. Dental and periodontal treatments can help eliminate infection foci, controlling both oral ulcers and systemic symptoms. Regular oral hygiene and topical treatments are key to reducing dysbiosis, promoting ulcer healing, and lowering disease activity [2].

Azathioprine is considered as an effective second-line treatment for oral and genital ulcers, as well as for arthritis, typically administered at a dosage of 2.5 mg per kilogram of body weight per day [30]. Colchicine and azathioprine are effective medications for the treatment of oral ulcers as they aid in regulating neutrophil elastase activity [2].

In the case of patients inadequately controlled with, or intolerant to synthetic immunosuppressive regimens, the consideration of biologic strategies, such as TNF-α inhibitors, can be considered [30]. Etanercept is the only TNF-α inhibitor that has been studied and demonstrated to significantly reduce the number of oral ulcers and erythema nodosum-like lesions when compared to a placebo [31].

Apremilast is a small-molecule inhibitor of phosphodiesterase 4, an enzyme found in immune and inflammatory cells. By inhibiting this enzyme, apremilast helps decrease proinflammatory mediators while simultaneously increasing anti-inflammatory responses [32]. Apremilast has demonstrated effectiveness in suppressing oral ulcers, leading to a reduction in both pain and the number of oral ulcers in BS. However, common side effects such as diarrhea, nausea, and headache have been reported with Apremilast, and these may sometimes lead patients to discontinue the treatment [31].

Ocular involvement

The primary objectives in the management of Behcet's uveitis include the suppression of intraocular inflammation, preservation of vision, and prevention of recurrence. Early diagnosis and collaboration with ophthalmologists are essential for effective care [1]. Azathioprine and cyclosporine A are traditionally considered first-line treatment options for ocular involvement. IFN-α is a widely used alternative due to its immunomodulatory effects, which include suppressing Th17 cells, increasing IL-10 expression, and restoring T-reg function [31].

Gastrointestinal involvement

In the acute stage, a combination of glucocorticoids with 5-aminosalicylic acid (5-ASA) or azathioprine should be used due to its effectiveness in inducing clinical remission and maintaining a response in patients with mild to moderate intestinal symptoms. Severe or refractory symptoms should be addressed with a TNF-α inhibitor either alone or in combination with thalidomide [1]. However, Thalidomide is not utilized in daily medical practice due to its adverse effects, particularly the risk of irreversible neurotoxicity even at low doses [31].

Vascular involvement

Venous thrombosis: While the primary treatment for an acute episode of deep-vein thrombosis involves moderate-to-high-dose glucocorticoids, immunosuppressives are necessary to prevent relapses [28]. Immunosuppressants that can be utilized include azathioprine, cyclophosphamide, or cyclosporin A. Anticoagulants can be added to the regimen after assessing and mitigating the risk of bleeding and pulmonary aneurysm [1].

Arterial involvement: The typical approach involves treating such patients with a monthly dose of 1 gram of cyclophosphamide for 6-12 months, coupled with pulse methylprednisolone (1 gram/day) for 3 days. Patients who achieve remission are transitioned to azathioprine for maintenance therapy (28). A TNF-α inhibitor could be employed as a second-line drug treatment. For patients at a high risk of massive haemorrhage from pulmonary aneurysms, embolization therapy is preferred over open surgery [1].

Neurological involvement

As per the EULAR 2018 recommendations, azathioprine and daily intravenous glucocorticoid pulses (up to 7 days) are typically prescribed as the first-line treatment for an acute attack of brain parenchymal involvement. TNF-α inhibitors should be considered for patients experiencing relapses, refractory cases, or those with chronic progressive neurological involvement [31]. High-dose glucocorticoids with a gradual tapering regimen are also recommended as the first-line therapy for nonparenchymal Neuro-Behcet's syndrome [1].

Joint involvement

Arthritis in BS typically presents as monoarticular, non-erosive, and self-limiting, with attacks that usually last for a few weeks [28]. The first-line treatment for acute arthritis is recommended to be colchicine [1]. In addition to colchicine, sulfasalazine or methotrexate have shown responsiveness in the majority of BS patients with arthritis. Intra-articular glucocorticoids may be beneficial in cases of acute monoarticular disease [31].

Conclusion

BS is a systemic inflammatory disorder primarily affecting mucocutaneous tissues. Key symptoms include recurrent oral and genital ulcerations, ocular involvement, and systemic vasculitis affecting both arteries and veins of various sizes. The etiology of BS is multifaceted, involving genetic, immunological, microbiological, and other factors. Diagnosis is typically based on clinical criteria, ISG, and ICBD criteria. Management of BS is complex and requires a multidisciplinary approach, tailored to the specific organs affected and disease severity in each individual. Future research aims to identify reliable biomarkers for accurate diagnosis and develop more effective treatments for BS is of great interest.

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