Mucocutaneous manifestations of Behçet's disease

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ABSTRACT

Behçet's disease is a relapsing multisystem polysymptomatic disease with exacerbations and remissions defined by the presence of the major symptom, recurrent oral aphthous ulcers, plus two of the following: recurrent genital ulceration, eye lesions, skin lesions or a positive pathergy test. Mucocutaneous manifestations like oral and genital ulcers, and cutaneous lesions (papulopustular lesions, erythema nodosum-like lesions, cutaneous ulcers, superficial thrombophlebitis), are considered the "fingerprint" of the disease, being the most common and often the first signs to appear. Although the exact etiopathogenesis is still not known, genetic predisposition and environmental factors may influence and contribute to the development of this disease. Diagnosis is based on the International Study Group criteria. During the last years, this disease has been largely studied and new immunological data and treatment strategies have been postulated. Despite that, further studies and attention to new data are needed.

Keywords: Behçet's disease; Epidemiology; Etiopathogenesis; Cutaneous manifestations; Diagnostic criteria; Treatment.

INTRODUCTION

Hippocrates was the first describing Behçet's disease (BD) in the fifth century BC[1]. In 1908, Bluthe described the triad of iritis, and mucocutaneous and genital ulcers[2]. Although, in 1937, Hûlusi Behçet, a Turkish dermatologist, described this condition more detailed, suggesting a possible viral etiology[3]. A Greek physician, Adamantiades, was the first to report a patient with inflammatory arthritis, oral and genital ulcers, phlebitis, and iritis, in 1930[4]. According to that, Adamantiades-Behçet's disease is also another name suggested for BD, although by International Associations and Societies of "Behçet", "Behçet's disease" should be preferred.

Behçet's disease is a relapsing multisystem polysymptomatic disease with exacerbations and remissions defined by the presence of the major symptom, recurrent oral aphthous ulcers, plus two of the following: recurrent genital ulceration, eye lesions, skin lesions or a positive pathergy test, based on the International Study Group criteria for BD. Genetic predispose and environmental factors may influence and contribute to the development of the disease[3,4].

Concerning the epidemiology of BD there are important regional differences, the highest prevalence occurs in the Mediterranean, the Middle East and the Far East[5,6]. The higher prevalence is in Turkey, with about 80-370 per 10^5 population. In Portugal about 1.5 per 10^5population have BD[7].

Behçet s disease is distributed according to the "Silk Road", which coincides between lattitudes 30º and 45º north in Asian and Eurasian populations[8]. People, and their descendents, who come from an endemic area and immigrate to areas with low prevalence of BD have an intermediate risk of presenting the disease[8].

The preponderance of BD is higher in men in Middle Eastern countries and in the Mediterranean basin. In Japan and Korea[9], women are the most affected[5].

The first symptoms of BD usually occur in the third and fourth decade of life, and rarely appear in children or in patients with an age over 50. When the onset of the disease appears in children or in old patients, the clinical course of the disease is relatively benign[9-12]. In children, the second major symptom usually occurs 8.8 years after the first one, which was most commonly oral ulcerations[10]. Although less frequent, familial cases of BD have been described[11]. When the patient is male, has a young onset of the disease and is positive to HLA B51, we can predict a more severe disease[9,10]. Concerning pregnancy in BD, 67% of pregnant patients with BD suffered an exacerbation, while 33% experienced an improvement of their clinical status. Exacerba-

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tions occurred more often during the first semester[12].

ETIOLOGY AND PATHOGENESIS

Behçet's disease is a multisystemic inflammatory disease, although the etiopathogenesis is still not known. The different authors agree on the effect of possible environmental triggering factors in genetic predisposed individuals. The pathogenesis of BD invokes vascular injuries and autoimmune responses, and autoimmune or autoinflammatory disorders in BD seems to target primarily small blood vessels, specially endothelial cells, causing either vasculitis and/or thrombosis in many organ systems.

GENETIC FACTORS

The strongest associated known genetic factor to BD is HLA-B51. It accounts for less than 20% of the genetic risk and for familial cases, less than 5%. However, recent data has shown that more than 60% of the patients test positive for HLA-B51[13] and more than 81% of Asian patients have HLA B51 allele[6]. This discrepancy indicates that other genetic factors remain to be discovered and further studies are required. Two studies revealed that the MHC region of chromosome 6 was associated with the disease. Genome-wide association studies variants in the MHC Class I identified IL23R-IL12RB2 and IL-10 as BD susceptibility loci[14,15]. As pro-inflammatory cytokine, IL23, stimulates Th17 proliferation, increases the proliferation of inflammatory cytokines, and leads to overexpression of IL23 p19 mRNA in erythema nodosum-like skin lesions in patients with active BD[13,16]. The up-regulation of $CD4^+$ $CD25^+$ T-regulatory cells in a BD like mouse model ameliorated the inflammatory symptoms via the anti-inflammatory cytokine IL10[17]. IL10 and IL23R-IL12RB2 genes may have important roles in pathogenesis of BD.

INFECTIOUS FACTORS

Infectious factors are possible environmental triggers of BD, specially herpes simplex virus (HSV) and *Streptococcus sanguis* (*S. sanguis*). *S. sanguis* levels in oral flora of patients with BD are higher than in healthy or disease controls[18,19]. In studies with skin injection, or oral prick tests, with streptococcal antigens in patients with BD, a response with oral ulcerations and delayed cutaneous hypersensitivity reaction was shown. The serum levels of IgA antibodies against to mycobacterial heat shock protein-65 (HSP-65), which has cross reactivity with some strains of *S. sanguis,* are significantly elevated in BD patients[20,21]. We may consider that HSP--65, which scavenge denature intracellular proteins, has an important role on the pathogenesis of BD. By proteomic techniques, cross-reactivity between anti--human α-enolase antibody (in sera of BD patients) to *Streptococcus sanguis* antigen was described[19]. Concerning HSV type I, its DNA can be detected in oral, intestinal and genital ulcers by polymerase chain reaction in BD patients comparing with healthy controls[22]. HSV DNA sequences were demonstrated in cutaneous ulcers from Behçet's disease-like mouse model developed by inoculation of imprinting control region (ICR) mouse earlobes with HSV. Although treatment with famciclovir in ICR mice seemed to not prevent from the disease after HSV inoculation, an improvement in Behçet's disease-like symptoms has been described in mouse model[23,24]. Elevated levels of IL-6 were found in LCR of patients with Neuro-Behçet.

AUTOIMMUNITY AND AUTOINFLAMMATION

Using proteomics, it was shown that IgM-type anti-endothelial cells antibodies (AECA) in patients with BD have as target α-enolase[19]. Since that, from several authors, different mechanisms trying to explain the action of AECAs in the pathophysiology of BD were described. The binding of AECA to endothelial cells, activating these cells and leading to secretion of chemoattractants and/or cytokines, as well as secretion or inhibition of prostacyclin, is one of the proposed mechanisms. IgM-type anti-endothelial cells antibodies may also be envolved in complement-dependent cytotoxicity and/ /or antibody-dependent cellular toxicity. A lower expression of cytotoxic T-lymphocyte antigen-4 (CTLA-4) has been shown in various autoimmune or autoinflammatory disorders. In patients with BD a reduced expression of CTLA-4 in $CD4^+$T cells was observed, and this may correlate with CTLA-4 polymorphisms and susceptibility[25]. It was also shown that the neutrophils of BD produce an increase amount of superoxide and an excess of lysosome enzymes.

We may consider BD as an autoimmune disease due to the presence of significant levels of high-titer autoantibodies or antigen specific T-cells; and as autoinflammatory disorder considering the involvement in episodes of recurrent inflammatory reactions of the innate immune system, mostly mediated by neutrophils. Infectious agents, such as *S. sanguis* and HSV, may trigger inflammatory reaction via innate immune system

and lately, to sustain this reaction, by the adaptive immune system.

HISTOPATHOLOGY

Systemic perivasculitis accompanied with infiltration of neutrophils, endothelial cell swelling and fibrinoid necrosis may exist in BD. Besides infection, there are other causes of infiltration by neutrophils, such as active lesions like those induced by the pathergy test[26]. These neutrophils are overactive, proved by the increased serum levels of their citokynes such as: Tumor necrosis factor (TNF), IL-1b, IL-8, myeloperoxidase, and the increased production of superoxide, lysosomal enzymes and enhanced chemotaxis[27,28].

Mucocutaneous lesions are characterized by lymphocytic infiltration, immunoglobulin, and complement deposition. Liquefaction-degeneration occurs at the dermal-epidermal junction, leading to formation of ulcers[27].

Leukocytoclastic vasculitis may exist in papulopustular lesions, compatible with an immune complex vasculitis. Pustules are often contaminated by *Staphylococcus aureus* and *Prevotella* species[16]. Results of biopsies shown vasculitis near affected lesions (oral and genital ulcers and lesions of the central nervous system and eyes). The large vessels are affected by a vasculitis of the *vasa vasorum*. It is also proposed that vascular injuries are involved on the hypercoagulability observed in some of the BD patients.

CLINICAL FEATURES

The clinical aspects of BD result from a multisystemic involvement and they are described essentially by mucocutaneous, vascular, ocular and neurological manifestations. Mucocutaneous manifestations (oral and genital ulcers and cutaneous lesions), considered the "fingerprint" of the disease, are the most common, and often the first signs, whereas the other manifestations, although infrequent, probably represent the most serious presenting symptoms of the disease[29,30].

The evolution of BD is characterized by exacerbations alternating with relapse and remission periods[31].

Despite the BD presentation and evolution to be variable and closely related with geographical, ethnic and individual differences, there are some key features that allow us to make disease diagnosis[31].

Identifying the major features correlated with the disease, like recurrent oral ulcers, genital ulcers and ocular disease as well as their association with minor symptoms as gastrointestinal ulcers, arthritis, epididymitis, vascular and neurological lesions, proves to be extremely important, due the lack of a clinically acceptable laboratory screening profile and/or histological characteristics of BD.

A timely diagnosis can change the course of disease and delay the emerge of gastrointestinal, vascular or central nervous systems involvement, which are associated with considerable morbidity. Serious complications confer a rise of mortality, which is mainly due to neurological system involvement, and with lower frequency, arterial occlusion, aneurism rupture and intestinal perforation[5,32].

ORAL ULCERS

Oral ulcers (OU) occur constantly and with high incidence (47-86%), constituting the hallmark of BD. Although the lesions may arise at any time in the history of the disease, they most commonly emerge at the beginning, many years before the other manifestations appearance[30-36].

Oral ulcers are described as painful which can be single or multiple (growing in crops), and occur more frequently on the nonkeratinized oral mucosa, with an anterior localization (lips, tongue, gingival, buccal mucosa, oral vestibulum). During a flare, patients have an increased difficulty or are even unable to eat, swallow and speak. Typically, lesions heal spontaneously in one to four weeks presenting a high tendency to recur at least three times a year[30,32,37,38].

Into 48 hours, the elementary lesion which is characterized as well defined, circular, erythematous, slightly elevated with the diameter from 1 to 20 mm, evolves into a round or oval ulcer, covered with a graysh-white pseudo-membrane or central yellowish necrotic base surrounded by a red areola. Similar appearance with common aphthae delays the diagnosis of BD[30,32].

According to some characteristics of the ulcers: as size, number and their evolution; we can classify OU (Table I) as minor (most common), major or herpetiform (uncommon)[31,32].

GENITAL ULCERS

Genital Ulcers (GU) have lower incidence than the oral ulcers, affecting approximately 57-93% of patients[31,32,34,38,39]. Genital ulcers resemble oral lesions,

TABLE I. ORAL ULCERS CLASSIFICATION.

		Minor	Major	Herpetiform
Number		1-5	1-10	>100 (coalescing clusters)
Diameter		< 1cm	>1cm	2-3 mm
Painful		Moderate	High	Variable
Evolution	Scar	Absent	Present	Present/Absent
	Time	4-14 days	10-40 days	Variable

Adapted from Mendes et al.

however they are frequently larger, deeper, heal more slowly (with scarring), generally present a fragile papule or nodule before their development and have higher recurrence rate after resolution[30,32].

Genital ulcers are localized on scrotum and penis in men, on labia minor and major, vulva, vagina and, more rarely, on cervix. Females' GU can be associated with dyspareunia and other complications, as bladder or urethral fistulae, as the consequence of the scarring of a deeper ulcer. The involvement of groin, perianal regions, and perineal by ulcers may appear in both sexes[31,32].

CUTANEOUS LESIONS

Currently, according to the International Study Group for BD, skin lesions are a major criterion for the diagnosis[32,37].

Skin involvement occurs in about 38-99% of BD patients commonly combinated with different forms during the stages of the disease[31,32,34,39]. The most frequent findings include papulopustular lesions (Behçet's pustulosis) which may be mistaken by for acne vulgaris; erythema nodosum like lesions; extragenital ulceration; superficial thrombophlebitis; reaction of the skin to a needle prick or an injection (pathergy reaction), and other cutaneous vasculitic lesions[32].

PAPULOPUSTULAR LESIONS

Papulopustular lesions (PPL) affect 28--96% of the patients. The primary lesion is a papule that evolves into a dome shaped sterile pustule on an erythematous base in 24 to 48 hours. They are mainly located on the trunk, followed by extremities, but they may be seen elsewhere[31,32,39-41].

Because the lesions are clinically nonspecific and resemble ordinary acne lesions, it becomes difficult to make a differential diagnosis, particularly in young patients. Thus the inclusion of papulopustular lesions as a diagnostic criterion is still controversial[32].

In spite of PPL not to be specific, mainly when acneiform or follicle base lesions are also present, the combination between clinical lesions and histopathologic/immunofluorescence studies are the most specific tools to support a correct diagnosis[32,42].

ERYTHEMA NODOSUM-LIKE LESIONS

Erythema nodosum-like lesions are present predominantly in women, with an incidence of 15-78% and they have similar appearance to those of erythema nodosum secondary to other etiologies[32,39].

They are characterized by subcutaneous indurated nodules with different sizes, mostly spread on the anterior part of the legs. However, they have been also located on face, arms and buttocks[30]. Although secondary ulceration is infrequent, residual hyperpigmentation after resolution is common and appears as part of the clinical picture[31,32,39,43,44].

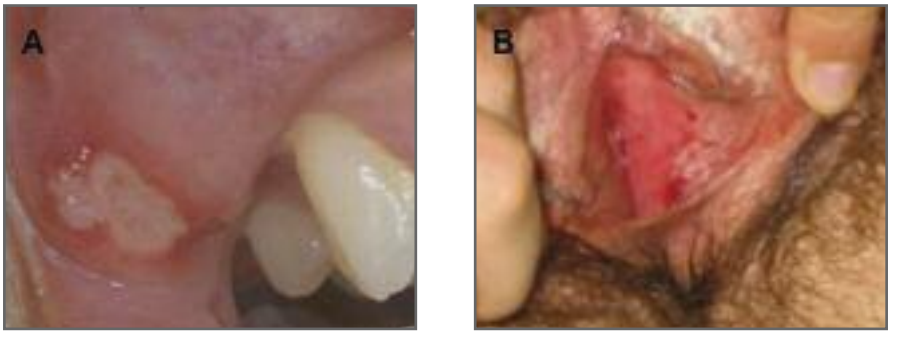

FIGURE 1. (**A**) Oral ulcers. (**B**) Genital ulcers

The healing of the lesions occurs into 2-3 weeks but, unfortunately, they are associated with high recurrence rate[31,32].

Although nodular lesions at the lower extremities are common in BD, some reports about their histologic features have been conflicting. On the one hand, some authors indicated these lesions resembled erythema nodosum, while others have reported findings of neutrophilic vasculitis and pointed out that septal or lobular panniculitis, granuloma formation, and necrosis were secondary to vasculitis. According to a study, which evaluates the histologic features of erythema nodosum-like lesions of BD in a blinded manner with control groups, composed of nodular vasculitis and erythema nodosum, mixed panniculitis (both septal and lobular) was the most common type of panniculitis in all three diseases[26].

SUPERFICIAL THROMBOPHLEBITIS

Despite rare, superficial phlebitis is the most frequent type of venous involvement (47,3%), which in turn, has been reported as mainly vascular site affected by BD (88%)[32,45].

This clinical feature is defined as erythematous, with subcutaneous longitudinal nodules in lower extremities that "migrate" from day to day, affecting various vein segments, and involuting in a few days. Due its similar presentation to erythema nodosum and migratory thrombophlebitis is required to make a differential diagnosis[32,46,47].

The differential diagnosis should be made with erythema nodosum and migratory thrombophlebitis. Deep vein thrombosis of the lungs, liver and brain may also occur[31,32,46,47].

CUTANEOUS ULCERS

Cutaneous ulcers (CU), also known as extragenital ulcers or skin aphtosis, are not frequent (3%), but when occur they have a great contribute to diagnosis due to their high specificity[31,32].

Typically, these lesions are recurrent, heal with scarring, and appear in legs, axillae, breast, neck, interdigital skin of the foot and inguinal region[32,48].

PATHERGY TEST

The Pathergy phenomenon is a non-specific hyperreactive reaction of the skin, produced by minor trauma, as a needle prick, characterized by appearance of erythematous small papule or pustule with more than 2 mm in diameter. Seems that papulopustular lesions occur spontaneously in BD patients. To execute a pathergy test a 20-gauge, or a smaller needle 5 mm, is requested in order to perform an intradermal puncture of the skin, obliquely into the patient's flexor aspect of the avascular forearm skin under sterile conditions, and without injecting saline. A positive test occurs when an indurated erythematous small papule or pustule forms, which is generally observed 24-48h after the application of the sterile needle, remaining during 3-4 days[29,30,32,49,50].

The mechanism responsible for this reaction is not clarified but it is thought that an increased neutrophil chemotaxis with an infiltration of PMNLs, first followed by mononuclear and mast cells, can be hypothesized. In addition to this, it is also suggested that some substances, bacterial or skin products, contribute to the reaction, which was shown by the reduced positivity of the test when surgical cleaning of the injection site was performed[30,32].

Although the Pathergy test makes part of the diagnostic criteria applied by some centers its sensitivity has a large geographical variability, presenting particularly high in countries like Japan and the Mediter-

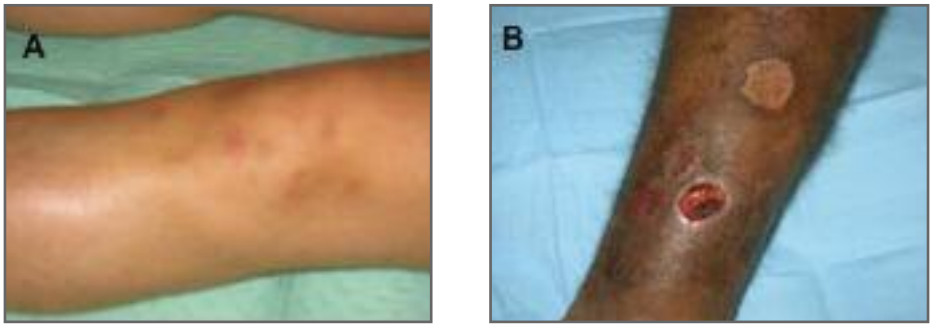

FIGURE 2. **(A)** Erythema nodosum-like lesions. **(B)** Cutaneous ulcers.

ranean countries (60-70%) and low in countries like United Kingdom (5-10%). Therefore the use of skin pathergy reaction as diagnostic criterion is doubtful and questioned[30,32].

OTHER CUTANEOUS VASCULITIC LESIONS

Other skin lesions such as erythema multiforme-like lesions, palpable purpura, Sweet's syndrome-like, pyoderma gangrenosum-like subungual infarctions, furuncles, hemorrhagic bullae and abcesses are less common, but may occur[30,32,51-55].

These features can appear coincidentally, at the same time of manifestations of BD and do not directly related with it, or included in the clinical picture of BD. For this reason, the importance and significance given to them has been questioned[32]

DIAGNOSTIC CRITERIA

Due to the absence of pathognomonic clinical or laboratory findings to the diagnosis of BD, several criteria have been proposed during the last years. Despite that, all have in common three major criteria: oral ulceration, genital ulceration and eye lesions.

Mason and Barnes, in 1969, suggested that to make the diagnosis of BD a minimum of three major, or two major and two minor (from Table II), were required[56].

After Mason and Barnes, the Behçet's Disease Research Committee of Japan, in 1972[57], answered with different criteria, probably more suitable to their population. Following the Japanese, and two years after, O Duffy published another criteria[58] as well as Zhang in 1980[59].

The most widely used, and most accepted criteria, are from 1985, decided during the fourth International Conference on Behçet's Disease, in London, and created by an International Study Group (ISG)[37]. These most specific and sensible criteria are described on Table III.

More recently, in 2010, a group of criteria from Iran, named "The International Criteria for Behçet's Disease (ICBD)" was also accepted. They concluded that there are not an universal criteria, and that each country should adapt better to one specific, taking in account sensibility and specificity[60].

DIFFERENTIAL DIAGNOSIS

Behçet's disease has different forms of onset and clinical aspects, therefore, we may think in a large group of differential diagnosis. It is important a detailed clinical history to make a correct diagnostic and exclude the following hypotheses[31]:

- Reiter's syndrome
- Sarcoidosis
- Stevens-Johnson Syndrome
- Familial Mediterranean fever
- Multiple sclerosis
- Systemic lupus erythematosus
- Mixed connective tissue diseases
- Celiac disease
- Inflammatory bowel disease (Crohn's disease, Ulcerative colitis)
- HSV infection
- Syphilis
- Sweet's syndrome
- Vogt-Koyanagi–Harada syndrome
- Bullous skin disorders
- Erythema multiforme
- Recurrent aphthous stomatitis
- Seronegative arthropathies

TABLE II. MASON AND BARNES CRITERIA FOR BD DIAGNOSIS, 1969

Major	Minor
Oral ulceration	Gastrointestinal lesions
Genital ulceration	Thrombophlebitis
Eye lesions	Cardiovascular lesions
Skin lesions	Arthritis
	Central nervous system lesions
	Family history

Adapted from Mason et al.

TREATMENT

The treatment of mucocutaneous lesions of BD includes a wide spectrum of therapeutic agents, which challenge clinicians[32,61]. Despite the various possibilities to treat the disease, therapeutic agents can only relieve symptoms that occur during the course of disease, as well as, achieve a faster resolution of inflammation, prevent tissue damage, reduce frequency and severity of attacks, and avoid complications[5,31,33].

Although there are no curative measures to BD it is imperative a close and multidisciplinary teamwork, to allow a more effective therapeutic strategy. Advances in

TABLE III. INTERNATIONAL CLASSIFICATION CRITERIA OF BEHCET'S DISEASE.

Major Criteria		Minor Criteria
Recurrent Oral Ulceration		Recurrent genital ulceration
Minor aphthous, major aphthous, or herpetiform ulcers observed by physician or patient, which have recurred at least 3 times over a 12-month period	BD Diagnosis ↓ Major Criteria + 2 Minor Criteria	Aphthous ulceration or scarring observed by the physician or patient
		Eye lesions Anterior uveitis, posterior uveitis, or cells in the vitreous on slit lamp examination; or retinal vasculitis detected by an ophthalmologist
		Skin lesions Erythema nodosum observed by the physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by the physician in a post-adolescent patient who is not receiving corticosteroids
		Positive pathergy test Test interpreted as positive by the physician at 24-48h

Adapted from International Study Group of Behçet's Disease

disease pathogenesis and an increasing availability of therapeutic modalities are a good example that results from a multidisciplinary approach[5,33].

Behçet's disease management depends the site, type and severity of manifestations and the sex and age of the patient[29,31,33]. Therefore, treatment goals should be established according to individual clinical manifestations of each BD patient[32,33].

Corticosteroids, topical, intralesional and systemic, are widely used in the treatment of multiple manifestations of BD due to their capability to decrease acute inflammation[29,31,33,61].

Despite the lack of controlled studies of corticosteroids on BD that prove their efficacy, some authors believe that topical agents of high potency can be an option to treat oral and genital ulcers in prodromal stages[33,61]. On the other hand, in a recent double blind study, in which were compared the results of metilprednisolone acetate (40 mg, intravenous injection, every three weeks) vs placebo, it was demonstrated inexistence of benefits in treatment of oral and genital ulcers, folliculitis and arthritis. The same study showed that low-dose of corticosteroids may play an important role in the control of erythema nodosum lesions, particularly in female BD patients[62].

Although orogenital ulcerations are often self-limited, they may interfere with daily activities, therefore their palliative therapy should be performed: with topical corticosteroid preparations (e.g., triamcinolone) in an ointment base applied to ulcers 4 to 6 times per day; for severe ulcers intralesional corticosteroid (triamcinolone acetonide) may be helpful; moreover, high dosage of oral(prednisolone 30-60 mg/day for at least 4 weeks) or pulse intravenous steroids may be indicated for large and refractory mouth ulcers larger than 10 mm or when the oropharinx is compromised. Besides monotherapy, corticosteroids can be administrated in association with colchicine (1-2 mg sid PO), dapsone (100-150 mg sid PO), interferon-α (3-12 million IU/ 3 times/weekly SC) or azathioprine (initial dose 100 mg sid PO)[63].

Systemic corticosteroids at a dosage of 1mg/Kg/day are also the gold standard to abort and control pyoderma gangrenosum associated with BD[7,85]. The systemic adverse effects of the long-term use of high dose corticosteroids may be attenuated, by combining with immune suppressants, which have a corticoid-sparing action[5,31,33,64].

Sucralfate suspension (1g/5ml quid 3 months duration) has been used in the treatment of BD mucosal lesions, since it was observed efficacy in placebo randomized controlled trials (RCT). In addition, it diminishes the pain and frequency of oral ulcers and healing time of the oral and genital ulcers. Sucralfate can also be used as prophylaxis against the development of oral ulcers in BD patients[32,62,65,66].

Azathioprine (2,5 mg/kg sid PO), a mercaptopurine derivate, inhibits purine ring synthesis and, conse-

quently DNA and RNA synthesis[31,33,67]. It decreases the frequency of oral and skin lesions of BD and reduces the development of new genital ulcers[61,65,68]. Azathioprine is also beneficial for arthritis, ocular inflammation and probably preventing deep vein thrombosis[29,32,68]. For a beneficial response are necessary at least 3 months of treatment, and patients should be followed due to side effects, such as bone marrow suppression and hepatotoxicity (complete blood count and liver function tests are recommended every 3 months)[29,33].

Methotrexate (7,5-20 mg once a week PO over 4 weeks), a folate analog, has a weak effect in manifestations of BD treatment. Nevertheless, an improvement has been reported of severe mucocutaneous involvement with a low dose methotrexate[31-33,69,70]. The use of Methotrexate requires a tight control due to its organ toxicity side effects (hepatotoxicity, nephrotoxicity, gastrointestinal disturbance and bone marrow suppression)[32,33].

Cyclosporine-A (3 mg/kg sid PO) is an immunomodulator (calcineurin inhibitor), which blocks the synthesis and release of IL-1 and IL-2[33,61].

Several studies have demonstrated improvement of oral and genital ulcers of BD patients as well as efficiency in the treatment of erythema nodosum-like lesions and thrombophlebitis[33,65,71]. While a double-blind trial, which compared results of cyclosporine vs colchicine, concluded that cyclosporine was superior to colchicine in treating oral aphthae and genital ulcers, another study showed that orogenital lesions have a higher improvement with conventional therapy[33,61,72]. Lower dosage, short-term use and close monitoring of cyclosporine-A are recommended, due to side effects such as hirsutism, gingival hypertrophy, hyperglycemia, neurotoxicity, nephrotoxicity, hepatotoxicity and arterial hypertension[29,33,61,73].

Chlorambucil (started with 2mg sid and gradually increased to 5-12 mg sid), is an alkylating agent, which interferes with DNA replication causing a decrease of B and T cells functions[31,33]. Combination therapy with corticosteroids provides, in a number of small reports, an improvement of mucocutaneous lesions[61]. The use of Chlorambucil by physicians is rare due to its complications, such as thrombocytopenia and leukopenia[61,65].

Dapsone (100-150 mg sid PO) is an agent capable of diminishing inflammation, modifying the chemotaxis of neutrophils[31,33,61]. Besides, it decreases the frequency and duration of oral ulcers, number and frequency of genital ulcers. A beneficial effect in erythema nodosum like lesions treatment was also reported[61,65,74].

Colchicine (0,5-2 mg sid PO) has been frequently used in BD, although no definitive evidence has indicated that it is effective on the BD mucocutaneous lesions treatment[61]. Colchicine mechanism of action is based on inhibition of tubuline polymerization, which inhibits migration and phagocytosis, and reduces the inflammatory reaction[31,33,75]. Two RCTs with colchicine demonstrated that when used with the dose of 1,5 mg/day was effective for nodular lesions in some BD patients, and with the dose of 1-2 mg/day an improvement of genital ulcers in women was verified[65,75-77]. In resistant or more severe cases, corticosteroids, azathioprine and methotrexate may be combined to colchicine[33]. Although colchicine is well tolerated, moderate side-effects, like gastrointestinal perturbation, and severe, such as alopecia and marrow supression, may occur[31,33].

Benzathine Penicillin (1,2 MU/ml) combined with colchicine (1 mg/day) appears to produce greater efficacy in the treatment of Behçet disease by reducing the clinical manifestation index, keeping it satisfactory during the first month after ceasing the treatment. The clinical manifestation index is also significantly decreased when colchicine or benzathine penicillin are used isolated; however this reduction is lower than when both drugs are used combined and there is also a fast and earlier relapse[78]. The use of both drugs together allows to a decrease of frequency and duration of OU, erythema nodosum-like lesions and GU. Another study have also demonstrated that the number of arthritis episodes in cochicine-penincillin group is lower when compared with the results obtained in colchicine-alone group[79].

Thalidomide (100-300 mg sid PO; optimal dose 100 mg sid in the evening for 2 months) is an immunomodulatory drug with anti-inflammatory and anti-angiogenic properties, which mechanism of action is based on modulation of the expression of cell surface molecules on leukocytes and on the epithelial cells[32,33,75,80]. Low dosage thalidomide, 100 mg sid, has been reported to be effective in the majority of patients with papulopustular lesions and orogenital ulcers[29,32,33,81]. After thalidomide cessation a high recurrence rate may occur, a maintenance dosage to prevent relapses is recommended[29,32,61]. Thalidomide requires careful use because of its adverse effects, such as teratogenesis and peripheral neuropathy, the most serious

complications. Others such as exacerbation of erythema nodosum, occurrence of papulovesicular transient eruptions, sedation, dizziness, headaches, nausea, xerostomia and weight grain may also appear[31-33,61,75]. Thalidomide is not recommended as a first option therapy, mainly in women, and it should be used with prudence in clinical cases refractory to other treatments, or if there is any contraindication or toxicity with other conventional therapeutic agents[33,61,75,82].

Interferon-α (INF-α) (6 Mill. I.U./3 times a week SC, for 3 months) is a natural occurring cytokine with immunoregulatory, antiproliferative and antineoplastic proprieties[31,75]. INF-α, well known for viral diseases such as herpetic and hepatic infections, increases the activity of T lymphocytes, NK cells, which are impaired in BD, and also inhibits the production of IL-8[33,75,82]. Several studies have reported significant reduction of pain and duration of oral ulcers, as well as the frequency of genital ulcers and papulopustular lesions[33,61,65,83,84]. It was also found an improvement of erythema nodosum-like lesions and thrombophlebitis, but the results were not as evident as those obtained in the treatment of other mucocutaneous manifestations[33,61,84].

In addition to the risk of acquiring an autoimmune disease due the production of antibodies secondary the use of INF-α, there are other side effects like flu-like syndrome, leukopenia, thrombocytopenia, alopecia, pruritus and depression[33,61,75,83].

Pentoxifylline (300 mg sid-tid PO) inhibits the production and function of various proinflammatory cytokines, mainly TNF-alpha[31,32,61], and has antioxidative effects[85,86]. It is effective in the improvement of oral and genital ulcers and can be used in monotherapy or in combination with colchicine (presenting better results in treatment of oral ulcers)[61,87].

TNF-inhibitors (infliximab, adalimumab, etanercept) may represent a therapeutic off-label alternative for BD patients who are intolerant or have manifestations of the disease resistant to conventional systemic drugs[5,29,31,75,78]. Successfully treatments with late response using adalimumab and infliximab have been reported in patients with refractory mucocutaneous lesions of BD[89]. TNF-α is a cytokine derived from T-helper cells that mediates inflammatory response in BD.

The elevation of TNF serum levels in BD patients, suggests that this cytokine may play an important role in its pathogenesis[31,61,75,90]. Although the biological agents constitute a new and promising step for BD treatment, some drawbacks as adverse effects (auto-immune reactions, infections, lymphoproliferative disorders), high cost, way of administration and limited evidence to date published, do not allow the use of TNF-inhibitors as a first line treatment[5].

Infliximab, a human chimeric monoclonal anti-TNF-α antibody, has been a therapeutic option in several case reports that present refractory mucocutaneous lesions, and it was observed a significant improvement or complete resolution of the orogenital ulcers, and thrombophlebitis shortly after the first administration[33,61,65,91]. Infliximab should be administered at dosages either 5 or 10 mg/kg by intravenous drip infusion at weeks 0, 2, 6, 10 and subsequently every 6-8 week intervals[31,92-94]. Etanercept, a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human p75 tumor necrosis factor receptor linked to the Fc portion of human IgG1, is administered subcutaneously in a dose of 25 mg twice weekly or 50 mg weekly[31,33,95]. Etanercept diminishes moderately the occurrence of oral ulcers and papulopustular lesions and slightly the frequency of genital

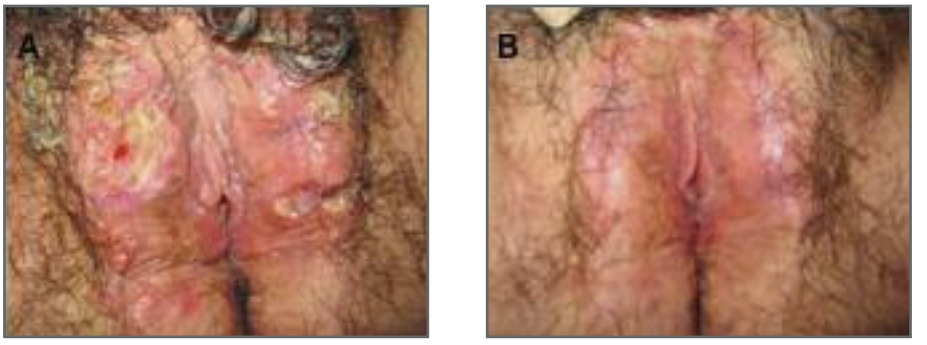

FIGURE 3. **(A)** Genital Ulcers Pre-Infliximab **(B)** Genital ulcers 2 weeks after the first infusion of Infliximab

ulcers and nodular lesions but does not suppress the pathergy reaction[61,65,95]. A double-blind RCT, using 25 mg subcutaneously twice a week during 4 weeks vs placebo, revealed a decrease of mucocutaneous features. However, Arida et al. demonstrated in a randomized, double-blind, placebo-controlled trial that Etanercept was successful in sustaining remission for oral ulcers and nodular lesions[88]. Adalimumab, a fully human monoclonal anti TNF-α antibody, appears to be a useful treatment for oral ulcers (in a dose of 40 mg every other week) although further studies are needed to demonstrate efficacy and tolerability of this biologic agent[97]. Recently, the knowledge gained regarding the pathogenesis of the disease allows the search of new therapeutic strategies with a specific target such as peptides of Hsp-65/60, which may open a new strategy for BD patients[98].

PROGNOSIS

The prognosis assessment of BD is difficult, because, despite the disease tends to die out progressively with age, its chronic and cyclic course is characterized by periods of remissions and recurrences[33,99,100].

A severe decrease in visual accuracy, as well as central nervous system and vascular involvement, are poor prognostic signs and are related with an increased morbidity and mortality[31,99,101].

Several studies have reported that young males and Mediterranean and Eastern populations seem to constitute markers of lesser favorable prognosis[31,99].

Overall, the mortality rate in adults is variable. However an outcome study of 387 Turkish patients revealed the highest rate in Turkey (9.8%), probably related to large vessel vasculitis causing sudden death by aneurysm rupture or thrombosis[31,102].

New treatment approaches like the immunosuppressant agents have allowed an improvement of prognosis in the last decade[103,104].

DISCUSSION

Mucocutaneous lesions are the most common manifestations in BD and their high frequency, at any time in the disease course, confirms the importance for early diagnosis and consequently for an effective management, which is also dependent to the clinical intervention and continuous follow-up[105,106].

Although the etiopathogenesis of BD is not completely clarified and does not seem to be homogenous, it seems to be related with multifactorial factors, which include a complex genetic component. Environmental agents as certain microorganisms may trigger an enhanced and unregulated immune response in genetically susceptible individuals[98,107].

Due to the absence of pathognomonic clinical and laboratory findings or histological characteristics the disease is frequently diagnosed with a delay of several years after initial symptoms. Moreover, it has been noted that the duration between the time point of fulfillment of diagnostic criteria and the diagnosis itself tended to be longer in patients that had only mucocutaneous manifestations than in patients that had severe internal organ involvement[37,108-110].

In our own practice with the management of mucocutaneous manifestations of Behçet s disease thalidomide, colchicine, pentoxifylline and systemic corticosteroids are the main therapeutic choices.

We feel they are useful for the management of mucocutaneous lesions with excellent results in patients with severe forms and requiring a rapid control of bipolar aphthosis.

Although literature shows insufficient results, colchicine and/or systemic corticosteroids are still being empirically the treatments of choice for outbreaks of oral aphthosis in most of our patients. Side effects of colchicines like nausea, vomits, diarrhea and abdominal pain are common but usually disappear with treatment reduction or interruption.

In mild cases of oral aphthosis, pentoxifylline is being adopted in our department since many years with good outcomes. Depending on intensity and number of relapses, pentoxifylline or thalidomide are usedas maintenance treatment for oral or bipolar aphthosis. We limit thalidomide use to male patients or nonfertile women, in which, in our experience, 50-200mg daily is more effective then low dose methotrexate 7,5-15mg per week for severe disease treatment. Dapsone 100mg daily is also an alternative drug option which we consider in oral ulcers.

In erythema nodosum lesions colchicine 1-2mg/day is our preferential treatment as monotherapy. We suggest as a second line treatment indomethacin 75mg twice daily or oral corticosteroids 30-60 mg/day or for 3 weeks.

Apart of the mucocutaneous lesions many patients present ocular and/or neurologic involvement. After discussion in a multidisciplinary basis, we have had

several treatment experiences with chlorambucil, cyclophosphamide, azathioprine, cyclosporine-A, anticoagulant agents, plasmapheresis and hemodilution. We have treated a few patients with mucocutaneous involvement plus uveitis with chlorambucil (6-8mg/day for 3 months) with a beneficial effect in both manifestations. When cutaneous vasculitis occurs in association with oral and genital lesions we usually choose pulse cyclophosphamide (intravenous, 1g/m^2 of body surface monthly) in combination with systemic steroid therapy.

Azathioprine (50-150mg/day) was generally used when patients presented mucosal lesions associated with eye disease mainly before the advent of cyclosporine. Cyclosporine-A (5-10mg/kg/day) is now the treatment of choice in patients with refractory cutaneous and genital lesions associated with uveitis. In isolated cases, anticoagulation treatment using enoxaparine has been used for the treatment of superficial thrombophlebitis or venous thrombosis in the acute phase, followed by a maintenance period of warfarin (INR 2,5-3,5). We have had also experience with plasmapheresis which was tried in refractory mucocutaneous lesions associated with mild ocular disease in emergency prevention of organ damage in the active phase of the disease. A total of eight sessions were performed in two patients. There was a rapid improvement of clinical manifestations, which were particularly evident after the 3rd session. Isovolemic hemodilution was also used in a severe case of uveitis and mucocutaneous lesions as an adjuvant rescue therapy with high dose systemic corticosteroid. There was only a partial improvement in this particular case.

More recently, we have had the opportunity to employ infliximab infusions (5 mg/kg) at weeks 0, 2, 6, and every 8 weeks thereafter in a few patients with resistant mucocutaneous compromise and a high life quality impact of the disease, in which it was difficult to control the inflammation with other therapies and for preventing irreversible lesions.The results were good and rapid in these patients but evidently further studies are needed to find optimal doses and long term adverse effects of infliximab in BD[111].

In conclusion, a wide spectrum of novel therapeutic agents has recently emerged. However, no safe, curative, conclusive and standard treatment exists yet, mainly due the unknowns on the BD pathogenesis. Thus, it is imperative to encourage investigation of the pathogenic factors, including the roles of the innate and acquired immune systems and genetics in further detail, and probable differences in the pathogenesis of various BD subgroups to allow the development of more specific therapeutic approaches in the future, including the newly developed biologic drugs[107].

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