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Mucocutaneous Findings in Behçet's Disease

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Abstract

Behçet's disease is a chronic inflammatory disease with an unpredictable course. The disease may affect almost all organ systems resulting with significant organ-threatening morbidity and mortality. Mucocutaneous lesions mostly constitute the initial symptoms of the disease and precede other manifestations. As there is yet no pathognomonic diagnostic test in Behçet's disease, the recognition of cutaneous and mucosal findings let the physician enable an earlier diagnosis and earlier treatment. Therefore, the purpose of this chapter is to emphasize the importance of the mucocutaneous manifestations of Behçet's disease and to review the mucocutaneous lesions in detail. Finally, childhood Behçet's disease, differential diagnosis and treatment of mucocutaneous manifestations will be briefly reviewed.

Keywords: Behçet's disease, mucocutaneous manifestations, oral ulcer, genital ulcer, papulopustular lesions, pathergy test

1. Introduction

Behçet's disease (BD) is a chronic, relapsing inflammatory multi-systemic disease of unknown etiology with a course of exacerbations and remissions [1–4]. Prevalence of BD is higher in countries lying along the ancient Silk Road, extending from eastern Mediterranean to East Asia [5]. Turkey probably has the highest occurrence level of the disease with prevalences of 110–420 cases per 100,000 population [6–8]. Today, due to immigrations, BD is encountered almost all over the world [9, 10].

The disease was first defined in 1937 by the Turkish dermatologist named as 'Hulusi Behçet' with the presence of 'triple symptom complex' of recurrent oral ulcers (OU), genital ulcers

(GU) and uveitis [1]. After the initial description, it now became increasingly evident that BD is a multi-systemic disease with involvement of mucocutaneous, vascular, neurological, musculoskeletal and gastrointestinal systems with significant morbidity and mortality [2, 3, 9, 11, 12]. The main histopathological finding is the vasculitis of the arteries and veins of any size or thrombophilia according to the site of involvement [13].

Although the exact etiopathogenesis of BD is still unknown, it has been hypothesized that in genetically predisposed individuals, a development of an inflammatory reaction against to an infectious, an environmental or an autoantigen and/or the presence of disturbances in molecular mechanisms in regulating immune responses may contribute to the disease [2, 3, 11, 14–17].

Today, most of the authors classify BD as a group of systemic vasculitis (under the title of variable vessel vasculitis) as a result of the consensus; '2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides' [18].

The first symptoms of BD usually occur in the third and fourth decade of life [2, 4, 9, 19]. However, childhood cases have also been reported [20]. Juvenile BD was found in 7.7% and family history was found in 11.6% of the patients in the study reported by Alpsoy et al. [21]. In another study by Gurler et al., the presence of family history in the first degree relatives of patients with BD has been reported as 7.3% [22]. Male patients, a younger onset and HLA-B51 positive patients are found to have more severe kind of the disease [11, 21, 23, 24]. Contrary to these results, Davatchi et al. found no association between severe organ involvement and male gender except vascular involvement [25]. Clinical features of BD include OU, GU, ocular inflammation, cutaneous lesions, as well as articular, vascular, neurological, pulmonary, gastrointestinal, renal and genitourinary manifestations [2–4, 11]. BD may start with just one or two symptoms but other symptoms may gradually appear over the years [19, 22, 24, 26–29].

As there is no pathognomonic test, the diagnosis of BD depends on clinical criteria [3]. In 1990, the International Study Group (ISG) for BD defined new diagnostic criteria by reviewing the data of 914 patients from 12 centres in seven countries around the world. The ISG criteria for BD have a sensitivity of 92% and specificity of 97%, compared with previous sets of criteria. According to these criteria, the diagnosis of BD consists of the presence of recurrent OU in addition to two of the following features: GU, eye involvement, skin lesions and positive skin pathergy test. At minimum three episodes of oral aphthous ulcer in a year should be observed for the diagnosis of BD [30]. In order to increase the sensitivity and specificity, these criteria are re-assessed and revised [31]. Since patients may present with only OU for a long time showing a long prediagnostic duration [19, 22, 32].

Various studies from different countries have documented that mucocutaneous manifestations are the most common, and often the first signs of the disease [2, 3, 9, 11, 21, 22, 24, 26–29, 33–37]. Mucocutaneous findings are the hallmarks of the disease and recognition of them have a great importance in confirming the diagnosis, in the follow up and in preventing both the morbidity and mortality [2, 3, 19, 21, 26, 28].

This chapter aims not only to define the mucocutaneous lesions but also to elaborate the features of the mucosal and cutaneous lesions in detail. Furthermore, mucocutaneous lesions in paediatric BD, differential diagnoses and the management of the mucocutaneous lesions will briefly be reviewed.

2. Mucocutaneous manifestations

Mucocutaneous manifestations that are observed in the course of BD are as follows: OU, GU, erythema nodosum (EN)-like lesions, papulopustular (PPL) lesions, superficial thrombophlebitis (TFB), extragenital ulcers, Sweet's syndrome-like lesions, cutaneous vasculitic lesions, pyoderma gangrenosum (PG)-like lesions, erythema multiforme-like lesions and skin pathergy test (SPT) [2–4, 9, 32].

The above-mentioned mucocutaneous lesions may be the initial findings of BD or may be observed at any time during the course of the disease [21, 22, 24, 28, 29]. Especially, OU is the most commonly detected lesion and mostly emerges as the initial clinical finding of the disease [2, 3, 19, 21, 33–37]. OU and GU are mostly considered as the 'fingerprint lesions'. As there is yet no pathognomonic test for the diagnosis of BD, recognition of these mucocutaneous lesions let the clinician make an earlier diagnosis, which also enables an earlier treatment [2, 3].

2.1. Oral ulcers

Oral ulcers (OUs) manifest in the majority of BD patients with a ratio of 92–100% in all countries [2–4, 6, 10, 21, 22, 27, 28, 33]. The majority of the patients experience OU as the most common presenting clinical manifestation [21, 22, 24, 26, 28, 34, 37]. For the diagnosis of BD, the presence of recurrent OU is obligatory according to criteria of ISG [4, 30].

OUs are recurrent and painful ulcerations of the oral mucosa characterized by a round or oval ulceration with sharp borders surrounded by a red erythematous inflammatory area (**Figure 1**). The base of the OU is necrotic with a yellowish-white colour. The most common sites are the mucous membranes of the lips, buccal mucosae, tongue, uvula and soft palate [2, 3, 22]. Clinically, they look like similar in appearance with conventional aphthae that may be seen in several systemic diseases such as inflammatory bowel disease, Sweet syndrome, systemic lupus erythematosus or recurrent aphthous stomatitis (RAS) [2, 12, 32]. OU in BD tends to recur more frequently and to be more in number [38]. Main and Chamberlain reported that OUs in BD have a more diffuse erythematous surrounding rim, they are localized more often in soft palate and oropharynx and they are more in number when compared with the aphthae of RAS [39]. However, no difference was found in terms of frequency of OU between the two groups [39].

OUs are usually classified into three groups based on the diameter of the ulcer [2, 11]:

1. Minor aphthae are shallow mucosal ulcers with a diameter less than 10 mm. It usually spontaneously regresses in a couple of weeks without formation of scarring.

2. Major aphthae have a deeper morphology with a diameter larger than 10 mm. Healing usually occurs in 3–4 weeks with scarring.
3. Herpetiform aphthae are pinpoint shaped, very small and shallow mucosal ulcers and localized in crops.

The majority of the patients were found to have minor aphthous ulcer (75%) followed by herpetiform (20%) and major aphthae (5%) in the study of Vaiopoulos et al. [36]. Different sizes and types of OU may be seen at the same time in oral mucosa in BD [9]. A study comparing the characteristics of OU between BD and RAS was performed by Oh et al. They reported that major OUs were significantly more common in patients with BD, and initiation of OU in BD was more likely related to menstrual cycle when compared with OU in patients with RAS. In addition, they also concluded that patients with major aphthae who have accompanying articular symptoms as initial symptoms should be strictly followed for the possible development of BD [40].

Ideguchi et al. evaluated 412 BD patients' data including 16 years follow-up. The results revealed that a mean of 7.5 years has been proceeded before a definitive diagnosis of BD. In the same study, 14% of the patients had suffered from OU for more than 20 years before the diagnosis of BD [19].

In two different studies reported by Alpsy et al., the mean duration between the OU and the fulfilment of diagnostic criteria was determined to be 4.3 ± 5.7 and 3.77 ± 4.43 years, respectively,



Figure 1. Aphthous ulcer on the tongue in the patient of Behçet's Disease (Courtesy of MD. Assoc. Prof. Müzeyyen Gönül).

and it has been concluded that the disease is often diagnosed with a delay of several years after the appearance of the first sign [21, 26].

Although OUs are the most common and earliest manifestation of BD, a few studies have been reported indicating a course without the presence of OU at the onset of BD [27, 41–44]. On the basis of this issue, Faezi et al. evaluated the clinical features on 175 patients with BD who do not have oral aphthosis (NOA) and compared them with the patients with OU. The results revealed that the first manifestation was uveitis with a ratio of 70.3% in the NOA group, and a pathergy test was more common in NOA group [41].

2.2. Genital ulcers

Genital ulcers (GUs) are generally the second most frequent disease manifestation [2, 9, 21, 26, 28, 45, 46]. GUs are observed in approximately 60–97% of the patients with BD at any time of the course of the disease [4, 19, 21, 22, 28, 36, 43, 47]. The lowest frequency was reported from Romania with a ratio of 55.5% [43]. As an initial symptom, GU was found in 14.2 and 7.4% of the patients with BD in two different studies from Turkey [21, 22] while in only 4% of the patients with BD in a study from Moscow [34].

GUs are usually localized on the scrotum and on the shaft of the penis in male patients while on the labium major and minor in females (**Figures 2 and 3**). They are rarely seen in the vagina and cervix in females and on the urethral orifice and glans penis in males [2, 3, 9, 11, 22]. They are usually painful or very rarely they can be asymptomatic [2]. They have mostly the same characteristic morphological features of OU. The clinical differences from oral aphthous ulcer include that GUs are larger and deeper, have more irregular borders and a longer healing duration. In addition, GU recurs less often and heal with scarring [3, 32, 48]. Therefore, in the suspicion of diagnosis of BD, scarring of GU on genital region should also be searched.

While some studies have documented higher frequency of GU among one of the genders [21, 24, 35], some did not detect any difference between the two genders [23, 25, 34]. Gender differences (Male>female) at the onset of GU have been observed in the study by Vaiopoulos et al. [36].

GU may cause severe pain, difficulty in micturition, dyspareunia and marked difficulty in physical activity. Deep ulcers located in vagina may be complicated by fistulisation to bladder, urethra or rectum [2–4, 9].

Mat et al. reported a prospective study investigating the frequency of scarring after GU. This study revealed that healing with scarring was observed in 49% of small GU while in 89% of large ulcers. They stated that ulcers on labium minors and vestibule may heal even without scar formation [48].

Faezi et al. reported 64.7% of 6935 cases with BD had GU during the course of the disease. They compared clinical and laboratory features between the patients with GU and patients who never developed GU (non-GU cases). As a result of their study, OU and other cutaneous manifestations such as pseudofolliculitis and erythema nodosum were found to be higher while eye involvement was found to be less common in the GU group [46].



Figure 2. Genital, extragenital ulcers and their scars in male patient with Behçet's Disease (Courtesy of MD. Assoc. Prof. Müzeyyen Gönül).



Figure 3. Genital ulcer in female patient with Behçet's Disease (Courtesy of MD. Assoc. Prof. Müzeyyen Gönül).

2.3. Cutaneous lesions

2.3.1. Papulopustular lesions

Papulopustular lesions (PPLs), which are also called as pseudofolliculitis or Behçet's pustulosis, are dome-shaped papules, which will convert into sterile pustule with an erythematous and edematous base [2–4]. Sometimes it can be localized around a hair follicle [9]. They are commonly seen lesions in BD [2–4]. Various studies have reported an incidence ranging between 25 and 55% [21, 22, 28, 33, 36]. PPLs have also been reported as an onset sign [22].

PPLs are usually localized on the trunk, buttocks and extremities [2, 3, 49]. However, they may be observed on any part of the body and even on palmoplantar regions [9]. In case of face and chest localization, especially in adolescence period, it may be hard to distinguish PPL from an ordinary papul/pustule of acne or folliculitis [2].

PPLs were found to occur more frequently in male patients than females in a study by Tursen et al. [35]. PPLs were found to occur more in patients with positive pathergy test [49].

Since PPLs are non-specific and resemble to ordinary acne pustules and/or folliculitis; some authors suggest that non-follicular lesions located other than face are more valuable for the diagnosis of BD [2, 27, 49] while some suggest that PPL should not be included as a diagnostic criteria [50]. It is suggested to accept PPL as a diagnostic criteria only if leukocytoclastic vasculitis or a neutrophilic reaction histopathologically is detected [2, 50].

A study by Kalkan et al. reported the histopathological evaluation of 42 biopsy specimens of papulopustular lesions of patients with BD. The results revealed leukocytoclastic vasculitis in seven specimens, lymphocytic vasculitis in three, superficial perivascular and/or interstitial infiltration in 15 and folliculitis/perifolliculitis in five. No histopathological finding of vasculitis was observed in the biopsy specimens of pustular lesions of the patients with acne vulgaris in the control group [51].

Another study by Ilknur et al. reported a statistically higher ratio of lymphocytic/leukocytoclastic vasculitis pattern in the histopathological evaluation of pustular lesions of the patients with BD compared with the control group. However, direct immunofluorescence examinations investigating the deposition of IgM, IgG, IgA, C3 or fibrinogen in dermal blood vessels revealed no difference between the two groups [52].

Chen et al. reported either lymphocytic or leukocytoclastic vasculitis of the 20 biopsy specimens performed from cutaneous lesions of BD. Eight of the 20 biopsy specimens in which vasculitis detected histopathologically was clinically compatible with PPL [53].

Contrary to these studies, Kutlubay et al. compared the number and histopathological features of PPL between patients with BD and acne vulgaris, as a result, Kutlubay et al. assessed a higher number of PPL on the back and extremities in BD group. However, histopathological interpretation was not found to be useful in differentiating PPL between two entities [54].

2.3.2. *Erythema nodosum-like lesions*

Erythema nodosum (EN)-like lesions are frequently observed skin lesions in patients with BD [9]. The incidences of EN-like lesions have been reported between 15 and 60% in various studies [21, 22, 24, 28, 55, 56]. In 2.8% of the patients with BD, EN-like lesions have been reported as an initial symptom [22]. They are more common in female patients [23, 24, 36, 55]. They are characterized by multiple painful subcutaneous nodules with different sizes. Although they are preferentially located on the lower limbs, they may also be localized on gluteal region, upper extremities and neck [2, 3, 9, 22, 55]. They heal within 10–20 days without secondary ulceration and scar formation. The resolution generally results with residual hyperpigmentation [2, 3]. The clinical features of EN-like lesions resemble conventional EN [2, 3, 9, 11]. However, it has been noted that EN-like lesions have more erythema and oedema around the lesions than the classical EN [57]. Coskun et al. reported that the presence of EN-like lesions precede visceral involvement [55]. Faezi et al. found less common EN-like lesions among the group of BD without OA in their study in which they compared the two groups with OA and without OA [41]. Cebeci et al. compared the clinical features of two groups with and without deep vein thrombosis (DVT) in BD and found more common EN-like lesions in the group with DVT suggesting that patients with EN-like lesions should be followed up for a possible DVT [58].

The evaluation of the histopathological features of biopsy specimens performed from EN-like lesions has been reported in various studies [57, 59, 60]. Chun et al. detected focal lymphocytic vasculitis in 40% of the cases with EN-like lesions of patients with BD and suggested this finding to occur secondary to severe lymphocytic infiltration. On the rest of the cases, the histopathological changes have been found similar to conventional EN [59]. In contrary, two different studies revealed the presence of vasculitis in biopsy specimens performed from EN-like lesions of patients with BD [57, 60].

Misago evaluated the clinicopathological features of EN-like lesions in 26 patients with BD and revealed the presence of vasculitis histopathologically in 73% of the cases. In addition, they suggested that the presence of severe vasculitis, especially phlebitis, was associated with a severe disease course [57].

A study by Demirkesen et al. compared the distinguishing histopathological features of the biopsy specimens taken from EN-like lesions of BD, nodular lesions of nodular vasculitis (NV) and conventional EN. Their results revealed neutrophil-predominating infiltrate in the sub-cutis and vein involvement to be more common in EN-like lesions when compared with NV and EN [60].

2.3.3. *Superficial thrombophlebitis*

BD may affect all types of vessels [3, 11, 61]. The prevalence of vascular involvement in BD has been reported to be between 2.2 and 50% in different patient populations [4, 6, 43, 62–64]. The venous system is the major affected site [9, 11, 61–65]. Superficial thrombophlebitis (TFB) is seen in approximately 4.9–20% of the patients with BD, and it is more frequently seen in

male patients [6, 28, 29]. Sarica-Kucukoglu et al. reported superficial TFB as the most common vascular symptom with a prevalence of 53.3% [62].

Superficial TFB is mostly characterized by linearly arranged erythematous subcutaneous nodules in lower extremities that migrate from day to day. The vein can be palpated as a string-like hardening showing the thrombosis and vessel sclerosis [2, 3]. EN-like lesions and migratory TFB may be thought as the differential diagnosis [2, 3]. Superficial TFB is clinically important since it is frequently associated with other forms of vascular disease in BD [2, 63].

2.3.4. *Extragenital ulcers*

Extragenital ulcer (EGU) is usually a solitary, small, round ulcer with a red rim and yellow base; however, it may have various shapes and sizes [2, 3, 32, 65]. Although observed rarely, it is the most characteristic and specific lesions of BD [2, 65]. EGU may be localized anywhere on the body such as legs, axillae, breast, interdigital skin of the foot, neck and inguinal regions. EGU may persist for a long duration, may be painful and heals usually with scarring [2, 3]. In a report of Azizlerli et al., four cases of EGU were shown to reveal vasculitis histopathologically [65].

A study reported by Ozyurt et al. detected that the patients with family history of BD had more frequent EGU than patients with negative family history of BD [66].

Few series documented common EGU in children [67, 68]. However, due to rarity of BD in childhood and few reports concerning the clinical findings in children with BD, the characteristics of the disease in this age group are not completely described [67–69].

2.3.5. *Sweet's syndrome-like lesions*

Few cases of Sweet's syndrome-like lesions have been reported in patients with BD [70–77]. Sweet's syndrome-like lesions are characterized by painful, edematous papules, plaques and nodules localized on face, neck and back [3, 70–75]. Fever and laboratory findings such as leukocytosis, elevated erythrocyte sedimentation rate and C-reactive protein accompany to the cutaneous lesions [73, 74]. Although clinical and histological overlap exists between Sweet's syndrome and BD such as the presence of OU, arthralgia, arthritis, episcleritis, pathergy positivity and neutrophilic infiltrate in the dermis in both of the diseases, there are some distinguishing features. In BD, the development of OU is more frequent, fever is rarely seen, the pattern of articular and ocular involvement is different [3]. In addition, comparing two diseases by human leucocyte antigen (HLA) typing revealed that patients with BD had higher frequencies of HLA-B51 and HLA-Dqw3, while patients with Sweet's syndrome had higher frequencies of HLA-Bw4 [77]. Sweet's syndrome-like lesions have been reported to occur in the acute phase of BD or sometimes have been thought to point a flare in BD [73].

2.3.6. *Pyoderma gangrenosum-like lesions*

Pyoderma gangrenosum (PG) is another rare neutrophilic dermatosis that may be associated with BD [78, 79]. Rare cases of PG-like lesions in patients with BD have been addressed

[78–85]. The lesion is usually characterized by large superficial ulceration localized usually on the buttock or the lower limbs; however, it may reveal vegetative or bullous variants [9, 79, 81]. Both diseases may have clinical and histopathological overlap. The patients with PG may also have OU, GU and pathergy positivity [78, 79]. However, as mentioned above, the frequency of OU and GU is higher in BD. It has been reported that PG is associated with the activation of BD [78, 79, 85]. Also, Hali et al. reported two paediatric cases of BD and PG with a fatal outcome [84].

2.3.7. *Rare cutaneous lesions*

Other rare cutaneous lesions such as palpable purpura, haemorrhagic bullae, necrotizing vasculitic lesions, Henoch Schoenlein purpura, polyarteritis nodosa-like lesions, pernio-like lesions, erythema multiforme-like lesions, acral purpuric papulonodular lesions, furuncles and abscess may also occur in the course of BD [2, 3, 70, 86–97]. It has been suggested that lesions of periarteritis nodosa appear as a marker of the severity of BD [91, 92]. These cutaneous lesions are mostly presented as case reports [86–97]. It is not clear whether these dermatological manifestations are real associations or coincidental. Therefore, it has been postulated that only lesions of 'leukocytoclastic vasculitis' detected in histopathological examination should be evaluated as a cutaneous sign of BD [2, 53, 98, 99].

2.3.8. *Rare mucosal lesions*

Conjunctival ulceration has been reported as a manifestation of BD in a few reports [100–104]. Although it is a rare finding, it has been suggested to be a specific clue for establishing the diagnosis [102, 103].

2.4. Skin pathergy test

Skin pathergy test (SPT) is a non-specific hyperreactive reaction of the skin that occurs as a response to a minor trauma such as a needle prick [2, 3]. SPT was first described by Blobner in 1937 [70, 105]. It is used as an adjunctive test in the diagnosis of BD and according to the ISG criteria for BD, a positive SPT is a criteria needed for the diagnosis of BD [2, 3, 30, 70, 105].

Positive SPT is defined as the development of erythematous, indurated papule which usually evolves into a sterile pustule at the site of the needle puncture after 24–48 hours (**Figure 4**) [70, 105]. Although the exact mechanism of the SPT is still not known, it is thought to occur as a result of enhanced non-specific inflammatory response and aberrant release of cytokines triggered by the cutaneous injury [13]. A number of studies investigating the histopathological examinations of positive SPT reaction (papule/pustule) revealed findings ranging from mononuclear cell infiltration at varying densities in perivascular or periadnexal areas to leukocytoclastic vasculitis [106–110]. Ergun et al. evaluated a chronological histopathological study of sites of SPT and observed intraepidermal pustules and polymorphonuclear infiltrate at the beginning of the inflammation [108]. Androgen receptor levels were found higher in positive SPT sites when compared with normal skin [111].



Figure 4. Pathergy positivity in Behçet's Disease (Courtesy of MD. Assoc. Prof. Müzeyyen Gönül).

Although the positivity of SPT has been accepted as a criteria in the diagnosis of BD, there is no consensus about performing a standardized method of SPT [105, 112–117]. It is usually performed under sterile conditions with a 20-gauge needle inserted intradermally into the avascular area on the forearm skin of patient with an angle of 45° [105, 112, 113]. Various techniques such as pricking with multiple needles with various applying routes including intradermal, intravenous and subcutaneous methods have been reported [9, 105, 112, 114–116]. Multiple punctures are mostly required [9, 114, 115]. Davatchi et al. suggested three intradermal punctures perpendicular or diagonally one with a 25-gauge needle with intradermal injection of one drop of normal serum saline, one with a 25-gauge needle alone (just a puncture, with no injection) and the last with a 21 gauge needle (puncture, no injection) [115]. A study by Ozdemir et al. suggested that two needle pricks are sufficient for positive SPT [114]. Another study by Ozdemir et al. analysed the changes of SPT positivity in different body areas such as flexor surfaces of the forearms, the lateral aspect of the tibial area, the scapular areas on back, and the lumbar areas of the abdominal region. They concluded that forearm was the most frequent site positive for pathergy reaction whereas abdomen was the least [113]. Akmaz et al. reported higher rate of positivity in SPT by intradermal application compared with intravenous application [117]. Dilsen et al. performed SPT with different needles including sharp and blunt needles in which they confirmed higher frequency of positivity with blunt needles [112]. Sharquie et al. demonstrated an alternative method of which they inserted the needle inside the mucous membrane of the lower lip to the sub-mucosa. However, the sensitivity of the oral pathergy test has been reported lower than of the classical pathergy test [118].

Various prevalence rates of SPT positivity in BD have been reported by several studies [21, 22, 119–123]. The positivity of SPT varies between 40 and 88% with a higher prevalence in Japan and Mediterranean countries, whereas it is lower in countries such as the United Kingdom and the United States [2, 3, 9, 22, 45, 98, 119–123]. Alpsoy et al. reported the positivity of SPT as 37.8% in their study including 661 Turkish patients with BD [21]. A study

comparing the positivity of SPT between Turkish and British patients with BD revealed the positive reaction was only present among Turkish patients [119]. In a German study, SPT revealed positive results in 33.7% of patients with no significant difference between Turkish and German patients with BD [123]. The factors that may affect the rates of positivity of SPT include genetic variables, variations in ethnic origins of the patients, factors related to the method and materials used to perform the SPT and conditions of the patient and the disease [105, 112–114, 124–126].

Contrary results have been reported about the relationship between positive SPT and clinical course of BD [22, 125–128]. Chang et al. found that positive SPT was specific for BD, but not associated with clinical severity [125]. Similarly, Krause et al. found no difference in terms of clinical manifestations and severity in the comparison of pathergy positive and negative patients with BD [126]. Although Yazici et al. have found no correlation between disease severity and positive SPT, they reported that male patients with BD have stronger pathergy reaction [127]. Jorizzo et al. reported a correlation between the histopathological pathergy results and clinical severity [109]. Koç et al. detected higher positive SPT test in patients with vascular involvement compared to patients without vascular involvement [128].

It has been reported that the frequency of SPT positivity has decreased during the last years [115, 125, 129]. One of the best reasons for this issue is the use of disposable needles, which are less traumatic than non-disposable ones [105, 112, 125]. A study by Davatchi et al. investigated the sensitivity and specificity of SPT among 6607 patients followed between the years 1975 and 2010. Their results revealed that the sensitivity of pathergy test has declined, but it still preserves its specificity [115]. Moreover, positivity of SPT in many diseases other than BD has been detected. Neutrophilic dermatoses such as Sweet syndrome, PG, erythema elevatum or other diseases such as RAS, eosinophilic pustular folliculitis, inflammatory bowel diseases and spondyloarthropathies are some in which pathergy reaction positivity has been shown [70]. Despite everything, SPT has still a diagnostic value [115].

3. Childhood Behçet's disease and mucocutaneous manifestations

BD in childhood is rare, has a variable clinical course and less investigated [68, 69, 130–139]. Paediatric onset of BD was found in 5.3 and 7.6% of all the cases [130, 133]. In the study including 661 cases of BD, juvenile BD has been reported in 7.1% [21]. In paediatric cases, a family history of BD has been more frequently observed [21, 68, 130, 131, 136, 137].

The diagnosis of paediatric BD in the reported studies was based on the criteria of ISG and ICD [30, 31]. A recent classification was proposed by Kone-Paut et al., and according to this classification, the presence of any three items among recurrent oral aphthosis, GU, ocular involvement, neurological and vascular signs makes the definitive diagnosis of BD [135, 140].

The onset of BD has been reported at any age between 0 and 16 years [131, 136, 137]. The lowest mean age of 4.8 years old was reported by Nanthapaisal et al. [134]. Similarly to clinical symptoms of adulthood BD, OU was present in most of the children and also constituted the initial symptom in most of the cases [68, 131–139]. The localization and morphology of OU in children were also similar to the characteristics of adulthood OU [136, 137, 140]. GU was detected between 55 and 94% of the paediatric cases [131, 135–138]. Distinctively from adult cases, the presence of GU has been reported significantly lesser than adults [131, 132]. However, Treudler et al. did not reveal any differences in the ratio of GU between childhood and adulthood BD [68], and Nanthapaisal et al. detected recurrent GU more frequently in females [134]. The characteristics of GU were also found similar to the ones seen in adults [136, 137]. Another distinctive feature, perianal aphthosis was to be a specific feature of childhood BD [135].

Skin lesions were reported to occur between 64 and 92% of childhood BD [70, 135, 137, 138]. Kone-Paut et al. reported EN-like lesions in 40% and necrotic folliculitis in 58% [136], while Borlu et al. reported EN-like lesions in 18% and PPL in 47% of the patients [137]. Kone-Paut et al. reported necrotic folliculitis more frequently in male patients [136]. However, no gender differences were detected in terms of skin lesions in the study of Borlu et al. [137]. Erythema multiforme-like lesions and TFB have been less frequently reported [70]. Positive SPT has been reported in 37, 80 and 76% of the patients in three different studies [131, 136, 137].

Nanthapaisal et al. documented skin findings in 11 (23.9%) of 46 patients: These were pustular lesions in three, skin ulceration in two, EN in two, necrotic folliculitis in two, PPL in two and positive SPT in three of the five patients [134].

The duration between the initial symptom and fulfilment of diagnosis of BD has been reported as 3.14 years in the study of Karıncaoglu et al. [131], while a significant diagnostic delay up to 13.5 years has been reported in the study of Nanthapaisal et al. [134]. This may be caused due to rarity and unfamiliarity of the disease in Northern Europe.

Conflicting reports have also been found in the systemic expression of BD in children [130, 132, 133]. BD was usually reported to have a less severe disease [132, 140]. Pivetti-Pezzi et al. reported similar rates of OU, GU, skin lesions in the comparison of adulthood and childhood BD. In addition, no differences were observed in the incidence of arthritis, gastrointestinal and neurological involvement except more severe ocular involvement in childhood. Another study by Sarica et al. compared the patients with mild and severe diseases. An earlier onset and more systemic involvement were found in patients with severe form of the disease [130]. More frequent neurological and gastrointestinal involvements were observed in childhood BD in the study of Karıncaoglu et al. [131].

Generally, it can be interpreted that juvenile BD has a similar clinical spectrum to adulthood BD. The differences in frequency and clinical courses may reflect the geographic, ethnic and genetic variations.

4. Differential diagnosis of mucocutaneous manifestations

The differential diagnosis of mucocutaneous manifestations will not be addressed in detail as this subject does not constitute the main topic of this chapter. Only the essential differential diagnoses of OU, GU, EN-like lesions will be given below.

Oral ulcer [2, 32, 141]:

- Infectious etiology: Herpangina, primary herpetic gingivostomatitis, hand-foot and mouth disease, HIV, syphilis, tuberculosis, etc.
- Systemic diseases: Systemic lupus erythematosus, Reiter's disease, Wegener's granulomatosis, blood disorders (neutropenia, leukaemia), iron deficiency, vitamin B12 deficiency, etc.
- Gastrointestinal diseases: Inflammatory bowel diseases, Celiac Disease
- Primary skin conditions: Sweet's syndrome, RAS, autoimmune bullous disorders (pemphigus vulgaris, pemphigoid, linear IgA disease, etc.)
- Medication induced: Cytotoxic agents, nicorandil, etc.
- Malign neoplasms

Genital ulcer [2, 32, 142, 143]:

- Infectious etiology: Genital herpes simplex, syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, HIV, etc.
- Non-microbial etiology: Erythema multiforme, fixed drug eruption, Lipschütz ulcers, metastatic Crohn's disease, hidradenitis suppurativa, PG, pressure ulcers, sexual trauma, psoriasis and malignancies.

Papulopustular lesions [2, 54, 144, 145]:

- Infectious etiology: Gram-positive folliculitis, Gram-negative folliculitis, Pityrosporum folliculitis, Demodicidosis, viral plane warts
- Eosinophilic pustular folliculitis
- Acne vulgaris

Erythema nodosum-like lesions [2, 70]:

- Classical EN
- Nodular vasculitis
- Panniculitis
- Cellulitis

Extragenital ulcers [146]:

- Infectious etiology: Necrotizing fasciitis (*Streptococcus haemolyticus*), botryomycosis (commonly *Staphylococcus aureus*), ecthyma gangrenosum (*Pseudomonas aeruginosa*, anthrax (*Bacillus anthracis*), sexually transmitted diseases (syphilis, granuloma inguinale), herpes simplex, leishmaniasis, etc.
- Autoimmune diseases: Scleroderma, rheumatoid arthritis, cutaneous lupus erythematosus, vasculitis, etc.
- Systemic disorders: Blood diseases (Polycythemia vera, sickle cell anaemia, thrombotic thrombocytopenic purpura, paraproteinemia, etc.)
- Medication-induced: Hydroxyurea, methotrexate, chemotherapeutics and immunosuppressives
- Primary skin conditions: Necrobiosis lipoidica, sarcoidosis, pyoderma gangrenosum, panniculitis, etc.
- Factitial: Dermatitis artefacta, Munchausen by proxy, etc.

5. Treatment of mucocutaneous manifestations

Oral and genital ulcers can be treated with topical and systemic treatments [3, 147–152]. In recurrent OU with or without GU, systemic colchicine (1–2 mg/day) must be started as a first choice of treatment [147–149]. Topical steroids, topical sucralfate, local anaesthetics, and tetracycline oral mouth washes are usually combined with oral colchicine treatment [147]. In case of more severe and painful OU and/or GU, a short duration of systemic steroids may be added with colchicine. Corticosteroids combined with systemic antibiotics can be used to decrease the severity of GU attacks [147–149]. In patients with severe mucocutaneous manifestations, immunosuppressive drugs such as azathioprine (AZA), methotrexate (Mtx), cyclosporine A may be used [149]. AZA has been found effective in preventing the recurrences of thrombophlebitis [147]. Thalidomide is another choice of therapy in recalcitrant OU and/or GU. However, it is not preferred due its high toxic effects [147, 149, 150]. Pentoxifylline, dapsone, zinc sulphate, IFN- α and rebamipide are other alternative treatments worth for trying in OU. However, larger and well organized studies are needed in order to clarify their efficacies. In case of EN-like lesions, bed rest is usually required. Especially in female cases with GU and EN-like lesions, the combination of colchicine and benzathine penicillin is recommended [148]. This treatment combination has also been reported to decrease the frequency and duration of both OU and EN-like lesions [150]. IFN- α has been reported to decrease not only the frequency of GU and EN-like lesions but also the number of PPL [151]. Anti-TNF drugs are being used with success in patients with refractory mucocutaneous manifestations [151, 152]. Recent studies of interleukin-1 (IL-1) inhibitors (anakinra, canakinumab) have demonstrated efficacy in OU and GU resistant to conventional therapy [150]. Finally, apremilast, phosphodiesterase 4 inhibitor, has been reported to be effective in treating OU and GU [150, 152]. The treatment options can be seen more detailed in **Table 1**.

Mucocutaneous manifestation	Topical	Systemic
Oral ulcer	Topical steroids Topical sucralfate Local anaesthetics Topical amlexanox Local silver nitrate 5%	Colchicine Tetracycline Azithromycin Systemic steroids (short term) Rebamipide Dapson Immunosuppressive drugs (AZA, Mtx) Thalidomide Anti-TNF drugs IFN- α Pentoxifylline Cyclosporine A (Cyc A) Tacrolimus Apremilast Anakinra Canakinumab
Genital ulcer	Topical antibiotics Topical steroids Local anaesthetics	Colchicine Tetracycline AZA, Mtx CycA IFN- α Anti-TNF Apremilast Anakinra Canakinumab
Papulopustular lesion		Colchicine Azithromycin CycA IFN- α Thalidomide
Erythema nodosum-like lesions	Bed rest Wet dressings (aluminium acetat3 3–5%)	Colchicine NSAII Systemic steroids (short term) Colchicine+benzathine penicillin Dapson Anti-TNF

Table 1. Treatment options for mucocutaneous manifestations.

6. Conclusion

Mucocutaneous lesions are the most important criteria in establishing the diagnosis of BD. In case of recurrent OU, GU and other cutaneous findings mentioned above, it is important to remind the possibility of BD in the diagnosis, which will permit an earlier diagnosis and enable a decrease in mortality and morbidity.

Abbreviations

AZA	Azathiopurine
BD	Behçet's disease
DVT	Deep vein thromboses
EGU	Extragenital ulcer
EN	Erythema nodosum
GU	Genital ulcers
HLA	Human leucocyte antigen
IFN- α	Interferon-alpha
ISG	International study group
Mtx	Methotrexate
NV	Nodular vasculitis
PG	Pyoderma gangrenosum
PPL	Papulopustular lesions
RAS	Recurrent aphthous stomatitis
SPT	Skin pahergy test
TFB	Thrombophlebitis
OU	Oral ulcer

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