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Chapter 7

Acneiform Papulopustular Eruptions in Behçet's Disease

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/65732

Abstract

Behcet's disease (BD) is a multisystemic inflammatory vasculitic disorder which diagnosed by clinical criteria because of the lack of specific laboratory test and/or pathognomonic histopathological findings. The most frequent diagnostic criteria of this disease are mucocutaneous lesions, appearing at the disease onset or during the course, usually begin before significant organ dysfunction. According to BD International Study Group Criteria, one of the five criteria is dermatologic findings including pseudofolliculitis, acneiform nodules or papulopustular lesions (PPL) diagnosed by clinician in postadolescent patients. In some case reports and clinical studies, the PPL of BD are also denoted as Behcet's pustulosis, folliculitis, acneiform eruptions and pseudofolliculitis. Owing to implementation of follicular lesions in these criteria, there may be difficulties in the distinction between most of the PPL of BD and the other acneiform eruptions/nonspecific follicular lesions (e.g., acne vulgaris, bacterial folliculitis, steroid acne). Certainly, clinicians should distinguish these patterns for accurate diagnosis. Although earlier studies involve numerous quandaries regarding the diagnostic histopathologic pattern of BD (e.g., whether to include vasculitis or nonspecific folliculitis), it was reported recently that the determination of vasculitic changes in histopathological and direct immunofluorescence results might be useful in the differential diagnosis of patients suspected to have BD.

Keywords: Behcet's disease, acneiform eruption, papulopustular lesion, pseudofolliculitis

1. Introduction

Acneiform eruptions have a broad clinical spectrum, where they differ via lesion location and morphology. Certainly, clinicians should distinguish these patterns for accurate diagnosis. One of the differential diagnoses in acneiform papulopustular lesions (PPL) is Behcet's disease (BD), and it should have been firstly recognized, particularly around the Silk Route region [1, 2].

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BD is a multisystemic vasculitic disorder that is characterized by recurrent oral aphthous ulcerations, genital ulcerations, mucocutaneous manifestations, uveitis, and a positive pathergy test. Additionally, later studies showed that the vasculitic pattern has shown articular, gastrointestinal, urogenital, neurological, pulmonary, and cardiac involvement. This disease has a chronic course with unpredictable exacerbations and remissions [1, 3, 4].

In 1937, Prof. Dr. Hulusi Behcet (1889–1948), who was a great scientist and the first professor in Turkey, diagnosed this disease as a trisymptom complex consisting of aphthous ulcerations, genital ulcerations, and ocular involvement. In the ancient literature, some authors named the disease as Adamantiades-Behcet disease. Adamantiades was an ophthalmologist who insisted on "relapsing iritis with hypopyon" in BD. Prof. Dr. Hulusi Behcet insisted on a complex multisystemic synonym, not only ocular involvement. As an honor to Turkish Medical history, the disease was renamed as "Maladie de Behcet," as it is known today [5].

BD is mainly distributed along the Silk Route region, with higher prevalence in the Mediterranean, the Middle East, and the Far East countries. Turkey has the highest prevalence, with about 80–370 cases per 10^5 population. This disease usually begins around the third or fourth decade of life. Globally, female and male distribution rates are equal. Although, if we want to categorize by geographical areas, BD shows male predominance in some Middle Eastern and Mediterranean countries and female predominance in Japan and Korea. Male predominance and young onset usually have worse prognosis [1, 6].

The etiology of BD has not yet been fully elucidated, but the strongest genetic susceptibility is HLAB51 or HLAB5. It has been demonstrated that in some studies, herpes simplex virus and streptococcus sanguinis/pyogenes activate innate and adaptive immunity so that a neutrophilic vasculitic reaction occurs. Additionally, some authors reported that interleukin (IL)-23 and IL-12 share p40 subunits and induce the IL17 pathway. Induced IL-17 and T-helper 17 levels activate oral ulcerations, genital ulcerations, and articular involvements [1, 7].

2. Diagnosis/classification criteria for BD

Due to a lack of distinctive diagnostic laboratory tests, the diagnosis of BD is based on certain clinical criteria. From onset of the disease, diagnosis time has taken approximately 8 years. Based on that, several criteria have been established during the years, all consist of three major criteria, including oral ulceration, genital ulceration, and eye lesions [1, 8, 9].

First of all, in 1969, Mason and Barnes identified major criteria (oral ulceration, genital ulceration, eye lesions, skin lesions) and minor criteria (gastrointestinal lesions, thrombophlebitis, cardiovascular lesions, arthritis, central nervous system lesions, family history), and then suggested that to make the diagnosis of BD, a minimum of three major, or two major and two minor criteria were required [10]. After that, in 1972, the Behcet's Disease Research Committee of Japan answered with a different set of criteria more suitable for their population. In order to get a new point of view, O'Duffy [11] published another criteria in 1974 for Japanese national criteria [12].

In 1990, criteria that were later accepted worldwide were developed by an International Study Group at the fourth International Conference on BD in London. The most specific and sensitive

http://dx.doi.org/10.5772/65732

Major criteria	BD diagnosis	Minor criteria
Recurrent oral ulceration Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient recurring at least three times in one 12-month period	Major criteria plus any two of the minor criteria	**Recurrent genital ulceration** Aphthous ulceration or scarring observed by physician or patient **Eye lesions** Anterior uveitis, posterior uveitis, cells in the vitreous on slit-lamp examination; or retinal vasculitis observed by ophthalmologist **Skin lesions** Erythema nodosum observed by the physician or patient; pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by physician in postadolescent patients not on corticosteroid treatment **Pathergy test** Test interpreted as positive by physician at 24–48 hours

Table 1. International Study Group diagnostic criteria of Behcet's diseasexs.

guide that clinicians have used globally for years is demonstrated in **Table 1**. To make BD diagnosis, the presence of major and two minor criteria is considered to be adequate [13].

Lastly, International Criteria for Behcet's Disease was also renewed in 2010, which is occasionally prevalent in Iran. In this point score system, the criteria (ocular lesions, genital aphthous ulcerations, and oral aphthous ulcerations, each of them 2 points; skin lesions, neurological manifestations, vascular manifestations, and positive pathergy test, each of them 1 point; and scoring ≤4 indicates BD) should not be seen as a part of universal agreement but also have chance to criticize the sensitive ones [8].

Among the many quandaries, the International Study Group criteria and the International Criteria for Behcet's Disease were configured in different cohorts. Davatchi et al. analyzed Iranian BD patients by using the International Study Group criteria versus International Criteria for Behcet's Disease. These authors found that International Criteria for Behcet's Disease sensitivity was 98.2% (78.1% with International Study Group criteria), the specificity was 95.6% (98.8% with International Study Group criteria), and the accuracy was 97.3% (85.5% with International Study Group criteria) [14]. Moreover, Leonardo and McNeil mentioned that the International Criteria for Behcet's disease has higher sensitivity and less specificity due to the fact that they evaluated data from 27 countries. They also said that those studies emphasized that International Criteria for Behcet's Disease can be an easier tool for diagnosis but also may cause overdiagnosis [6].

3. Clinical features of BD

As we mentioned before, the constant diagnostic feature of BD is oral ulcerations. Additionally, other factors occasionally depend on the dermatologist. Thus, mucocutaneous lesions are a

"hallmark of the disease." Oral ulcerations are the most common manifestation, followed by genital ulcerations, mucocutaneous lesions, skin pathergy reaction, and articular and ocular involvement [1, 9].

Recurrent oral aphthous ulcerations are the most common and significant criteria in diagnosis, constituting "fingerprint" of BD. They are characterized by painful ulcerations in non-keratinized mucous membranes such as lips, tongue, gingiva, buccal mucosa or vestibulum. Typically, oral aphthous ulcerations have recurred at least three times over a 1-year period. On the onset of the lesion, slightly elevated erythematous area with a vesiculopustular lesion that changed to an ulceration with well-defined borders and greyish yellow necrotic base in 24–48 hours. Oral ulcerations can be divided into three types: minor, major, and herpetiform. Major and herpetiform types may cause scarring formation [9, 15].

Genital ulcerations are the second most common clinical finding and are similar to oral ulcerations. Mostly, it begins with fragile papule or nodule, after that becomes ulceration area. They are usually located in labia minor, labia major, and vagina for women, and penis and scrotum in men. They are seen as deeper lesions and also heal slowly with scarring. The patients also have fistulas between urethra and bladder that may cause dyspareunia, severe pain, and difficulty of urination [1, 2, 9].

The most common type of mucocutaneous features is PPL. In addition, these lesions may occasionally occur following erythema nodosum-like lesions, superficial thrombophlebitis, skin pathergy test, extragenital ulceration, and Sweet's syndrome-like lesions. Subungual infarctions, hemorrhagic bullae, furuncles, abscesses and acral purpuric papulonodular lesions and also pyoderma gangrenosum-like lesions, erythema multiforme-like lesions, pernio-like cutaneous lesions, Henoch-Schsönlein purpura and bullous necrotizing vasculitis can also be seen in some case reports of BD [1, 9, 15].

4. PPL in BD

In some case reports and clinical studies, the PPL of BD are also denoted as Behcet's pustulosis, folliculitis, acneiform eruptions, and pseudofolliculitis. Clinicians may find papules, pustules, nodules, and also comedones in some BD patients [16–20]. It usually starts as a papule with erythematous base that changes to a pustule in 24–48 hours (**Figure 1**). The PPL of BD mainly stay on the trunk and extremities, except for the palms and soles, where there is a surplus sebum production and hair follicle, but also similar to acne vulgaris they have been occasionally seen on the face. As a point of view, pustules are common in both diseases but microbiological specimens are not similar so that it could be a clue for differential diagnosis [7, 21].

Since BD is a neutrophilic dermatosis, histopathologic findings of PPL include neutrophilic vasculitis and both of the lymphocytic and leukocytoclastic types in late onset, together. However, some authors found only perifollicular and perivascular mononuclear, or neutrophilic infiltrations in PPL of BD; they could not detect vasculitis [22–27].

BD is an autoinflammatory disease that is qualified by primary dysfunction of the innate and adaptive immune system such as neutrophil hyper-reactivity and T-lymphocytes hypersensitivity to some antigens. In some research studies, increased cytokine and chemokine

http://dx.doi.org/10.5772/65732

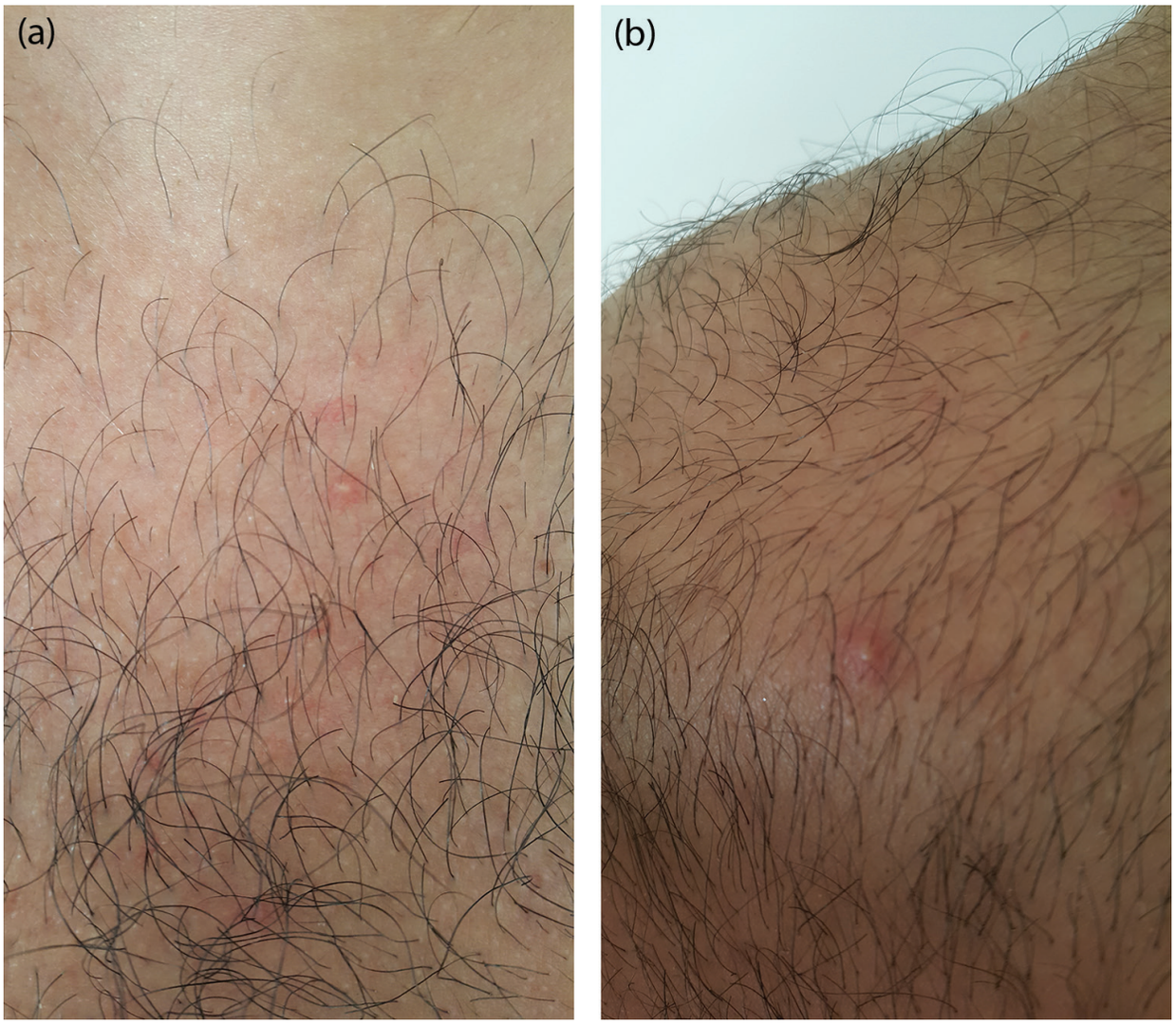


Figure 1. (a) Erythematous papulopustular lesions on chest region (upper trunk) and (b) erythematous papulopustular lesions on pectoral region (upper trunk).

levels are also found in blood samples. Nonetheless, the mechanism underlying these skin lesions remained elusive. Furthermore, investigations have continued during years in order to explain the immunological mechanism. In the beginning in adaptive immune system, cytotoxic T-lymphocytes have been demonstrated as significant effector cells in BD. Cytotoxic T-lymphocytes have been expressed granulysin, which is a cytolytic granule protein. Yamasaki et al. investigated granulysin levels in mucocutaneous lesions of BD by ELISA technique. They found strong expression of granulysin levels in CD4+ and CD8+ T-lymphocytes infiltrating acne-like eruptions. As a result, they suspect that granulysin positive cytotoxic T-lymphocytes may have a significant role in the pathogenetic mechanism for acneiform eruptions [28]. At genetic levels, it is known to have common associations with higher HLA B51 subtypes. Park et al. determined the association of a certain polymorphism (C438T) of the *SUMO4* gene with HLA B51 positive BD patients in Korea. Small ubiquitin-like modifier has been referred as SUMO4 that downregulate the transcription activity of nuclear factor–kappa B. They found that the C438T polymorphism in the *SUMO4* gene is associated with a significantly

increased risk of PPL in HLA-B51-positive BD patients [29]. Moreover, Demirseren et al. configured out the association between the subtypes of HLA-B51. Much interesting data are HLA-B5109 subtype was found to be less frequent in patients with PPL in BD. Thus, the HLA-B5109 subtype could be protective against acneiform eruptions [30]. Finally, Cho et al. detected the immunophenotypes of the common BD-related skin lesions and evaluated the expression of cytokines and composition of the infiltrating cells. In PPL, neutrophils were the most commonly infiltrated type and followed by CD8+ T cells, despite the fact that it was not found as statistically significant. Also, percentage of CD8+ T cells was significantly more than FoxP3.These authors recognized that IL-4 levels were also higher than the interferon (IFN) levels so that the adaptive immune system plays a major role in PPL [31].

4.1. Frequency of PPL in BD

In the diagnosis of BD, the primary aim is to find early diagnostic clues to prevent systemic involvement. For dermatologists, PPL has significant role in these diagnostic criteria. According to International Study Group, data of the chosen patients demonstrated as sensitivity and specificity of these lesions were 70% and 76%, respectively [13]. However, the sensitivity and specificity of PPL were found to be 96% and 11% by Alpsoy et al., so it depends on the experience of the clinician. They suggested that PPL is very sensitive but not specific, so the location of lesions is more important for differentiation from other diseases [22].

Based on a literature review, it may be said that the frequencies of PPL in BD patients range from 12% to 96%, varying greatly from country to country, as demonstrated in **Table 2**. [14, 16–20, 22, 29, 30, 32–46]. There are many studies consisting BD patients in Turkey, which is one of the most common country in terms of BD frequency varying between 39.6% and 75% [22, 30, 34–37, 41, 42]. National-based surveys were evaluated to understand the global pattern of the disease. Some authors analyzed five nationwide surveys of BD in Iran with 5059 patients, Japan with 3316 patients, China with 1996 patients, Korea with 1527 patients, and Germany with 590 patients. It was shown that PPL have varying proportion in terms of incidence in different regions, such as 62% in Germany, 57% in Iran, and 31% in China. These results were interpreted to mean that immigrations have changed the value of the Silk Route Region pattern [47].

The evaluation and differentiation of PPL in 65 patients were considered by Hamdan et al.; they found that 49 patients (55.7%) had PPL, including 25 (28.4%) with acneiform lesions, 17 (19.3%) with pseudofolliculitis, 4 (4.4%) with pustular eruptions, and 3 (3.3%) with nonspecific subcutaneous nodules and rashes. According to this point of view, acneiform lesions are the most common type of PPL so clinicians should take special care to distinguish them from acne vulgaris [16]. According to some previous studies, male patients have more frequent PPL than females and their prognosis was worse [17–20, 29, 35, 36, 39, 41, 43, 46]. Bonitsis et al. [43] has already clarified these results via a meta-analysis study of a German population. Some authors speculated that the main reason of provoking PPL in males may be related with testosterone levels. Durusoy et al. [48] indicated that androgens may play a role at least in the formation of PPL and disease activity in patients with BD.

http://dx.doi.org/10.5772/65732

References	Country of study (year)	No. of patients	Frequency of acneiform lesions in BD (%) (different terms used in literature)	Comparisons according to certain variables
Alpsoy et al. [22]	Turkey (–1998)	50	PPL: 96%	–
Zouboulis et al. [32]	Germany (1990–2000)	347	PPL: 53%	–
Shahram et al. [33]	Iran (–2001)	4704	PPL: 62%	–
Azizlerli et al. [34]	Turkey (–2003)	101	PF: 39.6%	Male vs female: 55% vs 45%
Tursen et al. [35]	Turkey (1976–98)	2313	PPL: 54%	Male vs female: 56.1% vs 43.9%*
Hamdan et al. [16]	Lebanon (1977–2005)	90	PPL: 55.7% (28.4% with acneiform lesions, 19.3% with PF, 4.4% with pustular eruptions, 3.3% with nonspecific subcutaneous nodules and rashes)	Male vs female: 59.1% vs 45.5%
Houman et al. [17]	Tunisia (1987–2006)	260	PF: 70.4%	Male vs female: 75.5% vs 58.3%* Ocular lesions (+) vs (–): 69.8% vs 71.6% BD-DVT (+) vs (–): 70.9% vs 70.5% BD Neuro (+) vs (–): 61.9% vs 73.6%
Alpsoy et al. [36]	Turkey (2007)	661	PPL: 55.4%	Male vs female: 62% vs 44.3%*
Alli et al. [37]	Turkey (2001–2004)	213	PPL: 56%	Male vs female: 63.5% vs 49.5%*
Arida et al. [18]	Greece (2000–2008)	142	PF: 44.4%	Male vs female: 61.3% vs 22.6%*
Vaiopoulos et al. [19]	Greece (1991–2007)	202	PF: 1.5% as onset sign, 5.9% as second symptom	Male vs female: 57.1% vs 21.9%*
Davatchi et al. [14]	Iran (1975–2010)	6500	PF: 54.5%	Age groups: <21: 57.0%, 21–40: 54.9%, 41–60: 40.4%, >60: 63.6%
Oliveira et al. [20]	Brazil (2011)	60	PPL: 23.3%, acne-like lesions: 6.7%	Male vs female: 40.7 vs 9.1%*
Park et al. [29]	Korea (2012)	83	PPL: 56.6%	HLA-B51 (+) vs (–):35.7 vs 67.3%*
Singal et al. [38]	India (1997–2011)	29	PPL and acneiform lesions: 31%	
Hamzaoui et al. [39]	Tunisian (1989–2009)	430	PF: 74.4%	Age < 20: 84%, age > 40: 63.2%*
Sula et al. [40]	Southeastern Turkey (2005–2009)	132	PPL: 74.2%	Male vs female: 76.7 vs 72.3%
Balta et al. [41]	Turkey (–2014)	521	PPL: 61.0%	Male vs female: 71.4 vs 52.6%*
Ugurlu et al. [42]	Turkey (2001–2012)	368	PPL: 75.0%	Male vs female: 80.7 vs 68.4%
Bonitsis et al. [43]	Germany (1990–2012)	747	PPL: 46.6%, PF: 47.2%	PPL: Male vs female: 50.6 vs 41.1%*PF: Male vs female: 52.2 vs 40.1% *

References	Country of study (year)	No. of patients	Frequency of acneiform lesions in BD (%) (different terms used in literature)	Comparisons according to certain variables
Ndiaye et al. [44]	Senegal (2015)	50	PF: 30%, acneiform papules:12%	
Fatemi et al. [45]	Iran (2010–2015)	2312	PF: 7.2% (in 430 patients with musculoskeletal manifestations)	Patients with arthritic attacks: 84% * Patients with no arthritic attacks: 16%
Demirseren et al. [30]	Turkey (2014)	51	PPL: 64.7%	
Davatchi et al. [46]	Iran (1975–2014)	6075	PF: 53.2%	Male vs Female: 60 vs 44.4% *

PPL, Papulopustular lesions; PF, Pseudofolliculitis; DVT: Deep vein thrombosis.
*Statistically significant ($p < 0.05$).

Table 2. Frequency of acneiform papulopustular lesions related to Behcet's disease in different ethnic groups.

One study focused on the relationship between age and the frequency of diagnostic criteria. In this study, Hamzaoui et al. separated patients into two groups who were less than 20 years old and more than 40 years old. It was found that cutaneous involvement and pseudofolliculitis were significantly more common in younger age group. However, joint involvements in the older group were more frequent, which is controversial regarding the frequent association between PPL and arthritis [39].

4.2. PPL accompanied by some clinical features in BD

Clinicians should suspect some clinical findings that frequently accompany PPL to facilitate a correct diagnosis. Of these situations, the most known is arthritis. Diri et al. determined acneiform eruptions and relationship of arthritis and BD through evaluating four groups consisting of 44 BD patients with arthritis, 42 BD patients without arthritis, 21 patients with active rheumatoid arthritis and 33 healthy volunteers. They reported that only the BD with arthritis group had significantly higher PPL. As a conclusion, arthritis and acneiform lesions may have same pathogenesis so that they occasionally appear together [49]. Moreover, Karaca et al. argued that PPL and arthritis have an inherited pathogenesis. Likewise, they found BD appears as cluster in familial BD constantly. They also suggested a mechanism that works on the same bacterial pathway responsible for this association [50]. Calgüneri et al. [51] also manifested that prophylactic penicillin treatment alleviated both acneiform eruptions and arthritis attacks. In another study, Fatemi et al. investigated articular involvement in BD. They emphasized that PPL was higher during episodes of arthritis, and in episodic attacks, only the presence of PPL as an extra-articular involvement was statistically meaningful [45].

The pathergy test had been researched as another entity. Arida et al. found positive correlation between pathergy test and folliculitis only in male patients [18]. The acronym SAPHO was defined as synovitis, acne, pustulosis, hyperostosis, and osteitis. Due to a lack of research SAPHO overlaps clinically with BD remains to be elucidated. Caravatti et al. published a case

http://dx.doi.org/10.5772/65732

report in which the patient met all diagnostic criteria of both SAPHO and BD. This study shows that similar arthritis mechanism occurs between BD and SAPHO and also both of them consist of acne-like eruptions [52]. Due to necessity of further investigation, Yabe et al. reported two case reports and compared with other studies in literature. They manifested that SAPHO syndrome and BD referred as seronegative arthropathies and also SAPHO could be clinical overlap of BD [53]. However, Alli et al. could not find a statistically significant relationship between arthritis and PPL in SAPHO syndrome [37]. Thus, there is a need for to work harder in order to elucidate similar mechanisms.

4.3. Comparison of the PPL characteristics between BD and acne vulgaris/acneiform disorders

PPL of BD can easily be confused with the acneiform papular and pustular lesions of acne vulgaris. As everyone knows, typical acne vulgaris usually begins around first and second decades and is easily diagnosed. However, both diseases can occur in patients aged 20–40. As how importance is the early diagnosis for BD, clinicians should focus on their main differentiation [54].

The PPL of BD patients are mainly known as sterile pustules, but some authors suggest that they contain a different type of bacteria than acne vulgaris lesions [7, 21]. Hatemi et al. studied 58 BD patients and 37 acne patients, and obtained the culture of pustules. They suggested that *Staphylococcus aureus* and *Prevotella* spp. were significantly more common in pustules from BD patients, and coagulase-negative staphylococci in pustules from acne patients. Prevotella spp. was not cultured from the acne pustules. BD pustules thus have different types of bacteria, which results in a different pathogenesis [21].

BD is a neutrophilic dermatosis that is commonly based on vasculitic disorders, but acne vulgaris is a hyperfunction of sebaceous glands under hormonal control. PPL in BD has been observed mainly in the lower extremities and trunk, but acne vulgaris has been observed mainly in face, chest, and back. Alpsoy et al. researched on 100 patients (50 patients with BD, 79 cases for control group including 21 patients with acne vulgaris) and consequently, it was found that the frequency of PPL in BD patients was 96% and the most common location was the trunk, whereas in the control group the frequency of PPL was 89% and the most common location was the face. The total numbers of PPL on the trunk, upper and lower extremities, and genitalia were higher in patients with BD than in controls [22]. Kutlubay et al. observed that papules and folliculitis on the back and the lower extremities in BD were higher than acne vulgaris group [27]. Prior clinical studies in literature comparing locations, types and numbers of PPL lesions between BD and acne vulgaris are summarized in **Table 3**.

As mentioned before, PPL of BD were evaluated using the International Study Group Criteria due to their 70% sensitivity and 76% specificity [13]. Davatchi et al. [46] determined that BD has dome-shaped pustule, not a sharp pustule like acne vulgaris. However, both of them resembled follicular lesions so that arguments continue about whether or not histopathological differentiation must be necessary via lesional skin biopsy for differential diagnosis. In the literature, there are some histopathological investigation studies of PPL in BD patients. As a result of these studies, there are numerous quandaries about the diagnostic histopathologic patterns

References	No. of patients	Location, type and mean number of PPL
Alpsoy et al. [22]	50 BD/21 AV	Face: 2.6 ± 2.8 in BD/7.5 ± 5.6* in AV; Neck: 1.0 ± 1.4 in BD/2.3 ± 1.9* in AV; Mean total number: 18.8 ± 15.9 in BD/28.3 ± 23.4* in AV
Kutlubay et al. [27]	58 BD/31 AV	Face/papule: 4.41 ± 4.47 in BD/11.8 ± 13.4* in AV; Face/pustule: 1.55 ± 2.07 in BD/5.75 ± 5.1* in AV; Face/comedone: 9.79 ± 14.8 in BD/42.5 ± 43.7* in AV; Back/papule: 8.73 ± 7.13* in BD/5.62 ± 5.77 in AV; Back/folliculitis: 0.58 ± 1.92* only in BD Lower extremity/folliculitis: 1.64 ± 3.47* only in BD

AV, acne vulgaris; BD, Behcet's disease; PPL, papulopustular lesions.
*Statistically significant ($p < 0.05$).

Table 3. Clinical studies comparing locations, types and numbers of papulopustular lesions between Behcet's disease and acne vulgaris.

and regarding whether to include vasculitis or nonspecific folliculitis [23, 27, 55]. Comparison data of the histopathological and direct immunofluorescence findings of PPL between BD and other acneiform lesions consisting of acne vulgaris and folliculitis are summarized in **Table 4**.

When considering the histopathological findings of PPL in BD, Ergun et al. took samples, which were chosen as only fresh pustules from the legs and arms of 17 patients with BD and 6 patients with acne vulgaris. Only 12% patients with BD revealed perivascular involvement without leucocytoclastic vasculitis and results stated that there was no differentiation between acne vulgaris and BD by histopathological evidence. They argued that there is no need to con-

References	Benchmarking acne vulgaris with PPL in BD	No. of patients	Histopathological findings	Direct immunofluorescence findings
Alpsoy et al. [55]	PPL vs normal-appearing skin	17 BD	LV: 64.7% lesional/ 11.8% nonlesional; Pustule: 17.6% lesional; LympV: 5.9% lesional/ 11.8% non-lesional; Mixed: 5.9% lesional/ 17.6% non-lesional; MNC: 5.9% lesional/ 17.6% non-lesional; PMN: 5.9% lesional/ 5.9% non-lesional;	IR on vessels: 70.9% lesional/ 23.5% non-lesional; IgM: 52.9% lesional/ 17.6% non-lesional; IgG: 35.3% lesional; 11.8% non-lesional; C3: 41.2% lesional; 17.6% non-lesional Fibrin: 47.1% lesional; 17.6 non-lesional
Ergun et al. [23]	PPL of BD vs AV	17 BD, 6 AV	**In epidermis** (intraepidermal pustule: 47.1% BD; spongiosis: 35.3% BD/16.7% AV; exocytosis: 11.8% BD; necrotic keratinocytes: 5.9% BD) **In follicle epithelium** (plugging: 58.9% BD/ 100% AV; rupture: 23.5% BD/16.7% AV; necrotic keratinocytes or epithelial necrosis: 11.8% BD/33.3% AV) **In dermis** (endothelial swelling: 23.5% BD/33.3% AV; nuclear dust: 17.6% BD/16.7% AV) **Eccrine** glands (41.2% BD/33.3% AV)	–

References	Benchmarking acne vulgaris with PPL in BD	No. of patients	Histopathological findings	Direct immunofluorescence findings
Boyvat et al. [24]	Specific vessel-based PPL vs nonspecific follicular lesions	20 (23 PPL)	LV: 13.04%; Perivascular infiltration: 21.7%; Perivascular and interstitial infiltration: 8.7%; Perifollicular and perivascular infiltration: 39.1%; Perifollicular inflammation only: 17.4%	–
İlknur et al. [25]	PPL of BD vs folliculitis/AV	18 BD 16 control PPL (11 folliculitis, 5 AV)	Pattern I: vasculitis (lymphocytic or leucocytoclastic) 27.8% BD/ 0% control group; Pattern II: folliculitis and/or perifolliculitis 16.7% BD/ 50% control group; Pattern III: superficial and/or deep perivascular and/or interstitial dermatitis 22.2% BD/ 18.8% control group	IR depositions on vessels; In 22.2% of BD patients (16.7% in pattern I, 5.6% in pattern II; in pattern I; 5.6% IgG, IgM, C3 and fibrinogen as quadruple conjugate, 5.6% C3 and fibrinogen as double conjugate, 5.6% only C3)/In 18.7% of control groups (6.2% in pattern I, 12.4% in pattern II)
Kalkan et al. [26]	PPL of BD vs AV	42 BD, 21 AV	LV: 6.7% in BD*; LympV: 7.1% BD; Superficial perivascular and/ or interstitial infiltration: 35.7% BD/38.1% AV; superficial and deep perivascular and/or interstitial infiltration: 28.6% BD/19.0% AV; Folliculitis or perifolliculitis: 11.9%, BD/42.9% AV*	–
Kutlubay et al. [27]	PPL of BD vs AV	58 BD, 31 AV	PNL infiltration without folliculitis: 1.7% BD/1.6% AV; Mononuclear infiltration without folliculitis: 0.8% BD/4.8% AV; Folliculitis/perifolliculitis: 85.3% BD,83.9% AV; LV:12.1% BD/9.7% AV; Comedone formation: 39.6% BD/64.5% AV; Intrafollicular abscess formation: 62.1% BD/61.3% AV; Presence of microorganisms, etc: 13.8% BD/14.5% AV	–

AV, acne vulgaris; BD, Behcet's disease; PPL, papulopustular lesions; LV, leucocytoclastic vasculitis; LympV, lymphocytic vasculitis; MNC, mononuclear cells; PMN, polymorphonuclear cells; Mixed, mixed cell infiltration; IR, Immunoreactant.
*statistically significant ($p < 0.05$).

Table 4. Histopathological and direct immunofluorescence findings for papulopustular lesions in Behcet's disease.

firm PPL of BD with biopsies [23]. Moreover, Chun et al. [55] also agreed on this hypothesis based on their research. More recently, Kutlubay et al. analyzed punch biopsy samples from 58 BD and 31 acne vulgaris patients by two blinded pathologist. Both of them found vasculitis in the same patients in 7% of BD and 3% of acne vulgaris patients. Follicle-based pathology was detected in totally 87.6% (78/89 patients) and 82% (73/89 patients) in both the BD and AV

groups by both pathologists; controversially vessel-based pathology was rarely observed, 9% (10/89 patients) in both the BD and AV groups [27]. Therefore, they also claimed that there is no pathological difference between BD and acne vulgaris such as vasculitis.

On the other hand, Ilknur et al. evaluated the follicular and nonfollicular lesions from 18 patients with BD and from 16 patients (11 with bacterial folliculitis, 5 with acne vulgaris) as a control group. They manifested that only the useful pattern for BD diagnosis was vasculitic changes which were not found in control group. The strength of this research is histopathological specimens were analyzed by two different pathologists for the first time, so the results were made with a consensus [25]. According to the study of Boyvat et al., the clinical features cannot be distinguishable for a BD diagnosis, but biopsy specimens must include vessel-based neutrophilic reactions [24]. In another study, Kalkan et al. [26] found that 16.7% leukocytoclastic vasculitis and 7.1% lymphocytic vasculitis were present in BD patients although any vasculitic finding was not found in acne vulgaris patients. Furthermore, arguments still continue to clarify the exact pattern of PPL in BD. More assessments are needed to investigate.

If histopathological findings cannot provide any benefit for BD diagnosis, we may use immuno his to chemical techniques as an additional diagnostic test. In 2003, Alpsoy et al. evaluated 17 patients whose biopsies had taken from lesional and non lesional skin parts to study via immunological tools. The polyclonal antibodies including IgA, IgG, IgM, C3, and fibrin were measured, IgM deposition of thelesional skin was significantly higher than non lesional skin (52.9% and 17.6%, respectively); despite of that, there were no statistically significant differences in terms of IgG, C3, and fibrin deposits on the vessels [55]. Subsequently, Ilknur et al. investigated the direct immunofluorescence results of 18 patients with BD and 16 control patients in order to evaluate any deposition of immunoreactants on dermal blood vessels. They found no significant difference between the groups [25].

4.4. Management of PPL in BD

BD has now become a treatable disease, although it is not yet curable. The choice of treatment is based on clinical features and the severity of the disease. Main treatment approach should be prevention of the severe organ damage. Recent guidelines could not establish a standard therapy for mucocutaneous lesions. A wide spectrum of agents can be used successfully to heal and prevent the formation of new lesions. As our study specifies the PPL management, first-line treatment is topical ones such as corticosteroid or combination with corticosteroid and antibiotics. To support antibiotic use, it is reported that like *Prevotella* spp. and *Staphylococcus aureus* have been cultured in PPL. Although benzathin penicillin is the most commonly used one, minocycline is more effective than benzathin penicillin in reducing of lesions. The systemic approach to BD treatment consists mainly of corticosteroids and colchicine. Corticosteroids are effective choices in almost all mucocutaneous lesions. They can be combined with other drugs such as colchicine, IFN-a or azathioprine. Guidelines recommend that corticosteroid administration begins with 40–60 mg/d for 1–2 weeks and tapers the dosage over 4 weeks. However, this therapy has limitations due to its long-term side effects [57–59]. Corticosteroid treatment has been also a potent trigger for

http://dx.doi.org/10.5772/65732

acne and referred as steroid acne. Clinicians have to keep in mind that acneiform papulopustular eruptions in BD may also appear as a result of steroid treatment. It is also important to know that steroid acne have some similarities and differences between Behcet's pseudofolliculitis. Similarly, both of them mostly stay in trunk and extremities rather than face. At the same time, PPL in BD may arise as papules, pustules, and comedones at different stages of development. However, steroid acne usually stays as small folliculitis at the same stage in the proper area where the corticoid therapy is applied and it usually appears 2 weeks after the therapy has begun. Both of them resembled in neutrophilic involvement in the lesions but BD also has the vasculitic pattern. If the distinction can be made between true PPL and steroid acne in BD, management of the acneiform eruptions in these patients would be different and reasonable [60].

Colchicine is the one of the strongest medications for BD. Colchicine inhibits the chemotactic activity and decreases the tumor necrosis factor-α, leukotrien-B4, cyclooxygenase-2 activity, and prostoglandin-E2 levels. Mainly, it is approached in erythema nodosum and arthritis treatment for female patients. Colchicine combined with benzathine penicillin increases the potency of the therapy. The lack of evidence in the efficacy of colchicine for treatment of mucocutaneous lesions could be related to relative lack of inappropriate researches. Moreover, IFN-a and etanercept treatment has been reported to decrease PPL frequency. Alternative therapy (dapson) has shown a significant capacity to diminish PPL. For severe lesions, azathioprine, pentoxifylline and thalidomide have demonstrated beneficial effects [57–59].

5. Conclusion

According to the International Study Group criteria for BD diagnosis, skin lesions are restricted to erythema nodosum-like lesions, pseudofolliculitis, papulopustular lesions, and acneiform nodules. These lesions excepting erythema nodosum-like lesions are nonspecific and clinically confused with other acneiform papulopustular eruptions (e.g., acne vulgaris, bacterial folliculitis, steroid acne). Although earlier studies involve numerous quandaries regarding the diagnostic histopathologic pattern of BD (e.g., whether to include vasculitis or nonspecific folliculitis), it was reported recently that the determination of vasculitic changes in histopathological and direct immunofluorescence results might be useful in the differential diagnosis of patients suspected to have BD.

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