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Acneiform Papulopustular Eruptions in Behçet's Disease

Sevgi Akarsu and Işıl Kamberoğlu

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].
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
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

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>BD diagnosis</th>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>Recurrent oral ulceration</td>
<td>Major criteria plus any two of the minor criteria</td>
<td>Recurrent genital ulceration</td>
</tr>
<tr>
<td>Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient recurring at least three times in one 12-month period</td>
<td>Aphthous ulceration or scarring observed by physician or patient</td>
<td></td>
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<tr>
<td>Eye lesions</td>
<td>Anterior uveitis, posterior uveitis, cells in the vitreous on slit-lamp examination; or retinal vasculitis observed by ophthalmologist</td>
<td></td>
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<tr>
<td>Skin lesions</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Pathergy test</td>
<td>Test interpreted as positive by physician at 24-48 hours</td>
<td></td>
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Table 1. International Study Group diagnostic criteria of Behcet’s diseases.
“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-Schönlein 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
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

![Figure 1. (a) Erythematous papulopustular lesions on chest region (upper trunk) and (b) erythematous papulopustular lesions on pectoral region (upper trunk).](http://dx.doi.org/10.5772/65732)
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% leukocytoclasic 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
Acneiform papulopustular eruptions in Behçet’s disease that are referred to as steroid acne. Clinicians must be aware that acneiform papulopustular eruptions in BD may also appear as a result of steroid treatment. It is also important to note that steroid acne and Behçet’s pseudofolliculitis have some similarities and differences between them. Similarly, both of them mostly stay in the trunk and extremities rather than the face. At the same time, PPL in BD may arise as papules, pustules, and comedones at different stages of development. However, steroid acne usually persists 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 resemble 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 one of the strongest medications for BD. Colchicine inhibits the chemotactic activity and decreases the tumor necrosis factor-α, leukotriene-B4, cyclooxygenase-2 activity, and prostaglandin-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-α and etanercept treatment has been reported to decrease PPL frequency. Alternative therapy (dapsone) 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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