Histopathological and clinical evaluation of papulopustular lesions in Behçet's disease

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ABSTRACT

Objective. *Behçet's disease (BD) is a chronic inflammatory disorder characterised by aphthous stomatitis, genital ulcerations, erythema nodosum-like manifestations and papulopustular lesions. While a neutrophilic vasculitis accompanies most skin lesions it is usually regarded that the papulopustular lesions in BD are similar to acne vulgaris (AV). The aim of our current study was to further assess the clinical and histopathological features of papulopustular lesions in BD and how these features compared to those of AV.*

Methods. *To analyse the histopathological features of BD and AV, 89 punch biopsies were taken from 58 BD (52 male, 6 female) and 31 AV patients (26 male, 5 female). Sections were evaluated in a blind manner by two different pathologists. A dermatologist who was blind to the patients' diagnosis counted the number of papules, pustules, comedones, folliculitis, cysts and nodules on the face, chest, back, upper and lower extremities.*

Results. *The number of papules, pustules and comedones was higher on the face in the AV group, whereas in the BD group, both number of papules and folliculitis on the back and that of folliculitis were higher on the lower extremities in the AV group. With the exception of comedone formation, which was more frequent among the AV patients [20/31 (64.5%) vs. 23/58 (39.6%), p=0.025] the presence of suppurative folliculitis/ perifolliculitis, intrafollicular abscess formation, leukocytoclastic vasculitis or microorganisms were not useful in differentiating BD from AV. However the interobserver agreement for histologic assessment was low. Kappa was 0.17 for suppurative foliculitis / perifolliculitis; 0.39 for intrafollicular abscess formation; 0.51 for leukocytoclastic vasculitis.*

Conclusion. *In the BD group, although the inflammatory lesions located on the face were less than those in the AV group inflammatory lesions such as folliculitis on the legs were only seen, again in the BD group. The papulopustular lesions of BD could not be distinguished from AV by histology. Some of this might be due to high interobsever variation in interpretation. Acne is an inherent manifestation of BD.*

Introduction

Behçet's disease (BD) is a chronic systemic inflammatory disorder characterised by relapsing episodes of recurrent aphthous stomatitis, genital ulcerations, ocular lesions, erythema nodosum-like manifestations and papulopustular lesions (1-5). Papulopustular and acneiform lesions are among the International Study Group Diagnostic Criteria for Behçet's Disease (6-8). Papulopustular lesions in BD are on the face, back and chest just as in acne vulgaris (AV) but also are found on the arms and the legs. Acneiform lesions are comedone based eruptions that are found on the seborrhoeic areas of the body. Acne can manifest as papule, pustule, comedone, cyst and nodule. Papulopustular lesions in BD patients are scattered on the body except palms, soles, and mucous membranes. When associated with hair follicles, pustule containing a hair in the center is designated as a folliculitis. It had been shown that sebum production was increased in BD just as in AV on frontal area of the face (1, 9). It also had been pointed out that papulopustular lesions in BD cases could not be distinguished clinically by experienced dermatologists from those in AV (10).

However controversy still exists about distinguishing histopathologic features and the pathogenesis of papulopustular lesions in BD compared to what is associated with AV. The histopathology of

papulopustular lesions ranges from leukocytoclastic vasculitis, a lesser dense neutrophilic vascular reaction, to follicular involvement similar to that seen in acne vulgaris (11). Both Chun *et al*. (4) and Ergun *et al*. (12) have proposed that vasculitis is not a feature of the papulopustular lesions. However Kienbaum *et al*. (13) and Boyvat *et al*. (14) have observed vasculitis in some instances of non-follicular papulopustular lesions which were not acneiform. Ergun *et al*. (12) had studied punch biopsies from pustules localised on the legs and arms of 17 BD cases and from pustules on the upper arms of 6 AV patients. Histopathologic features were evaluated in that study by a single pathologist. The only study to date that has utilised more than one pathologist has been the report by İlknur *et al*. (15). However in that report, the findings were presented as a consensus opinion. We reasoned that a further assessment was needed among a greater number of patients using two independent, blind observers to evaluate the frequency of vasculitis in BD.

Materials and methods

Consecutive patients with BD who had papulopustular and/or follicular lesions and control patients with AV, who gave verbal informed consent, were included in the study cohort (Table I). Patients all fulfilled the International Study Group Criteria for the Diagnosis of Behçet's Disease and followed up at the Istanbul University Cerrahpaşa Medical Faculty dedicated, multidisciplinary Behçet's Disease outpatient clinic. In addition, patients included in this study had not been taking drugs such as immunosuppressive agents (corticosteroids, azathioprine, cyclosporine-A etc) or isoniazide for at least three months. The control group consisted of patients with AV who were followed up in the dermatology outpatient clinic. They were also not using drugs such as isoniazide, and systemic corticosteroids etc. which could cause acneiform eruptions on the skin. Biopsies were obtained using a 4-mm punch after local anaesthesia.

We performed biopsies of three types of inflammatory lesions, the papules on the back (16 AV, 21 BD patients), the pustules on the back (15 AV, 18 BD patients; Fig. 1) and the folliculitis in the lower extremities especially thigh region (19 BD patients; Fig. 2). In total, 31 AV patients and 58 BD patients were evaluated.

Table I. Demographic features of the Behçet's disease and acne vulgaris patients examined in this study.

	Male	Female	Mean age	Location/Back	Location/Upper Leg
BD	52	6	29.5 ± 8.58	39	19
AV	26	5	21.9 ± 6.34	31	0

$p<0.001$

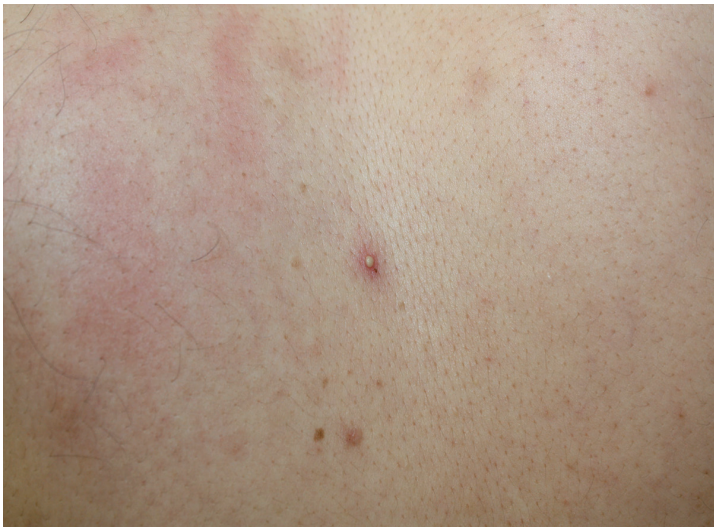

Fig. 1. Pustule formation on the back of a Behçet's disease patient.

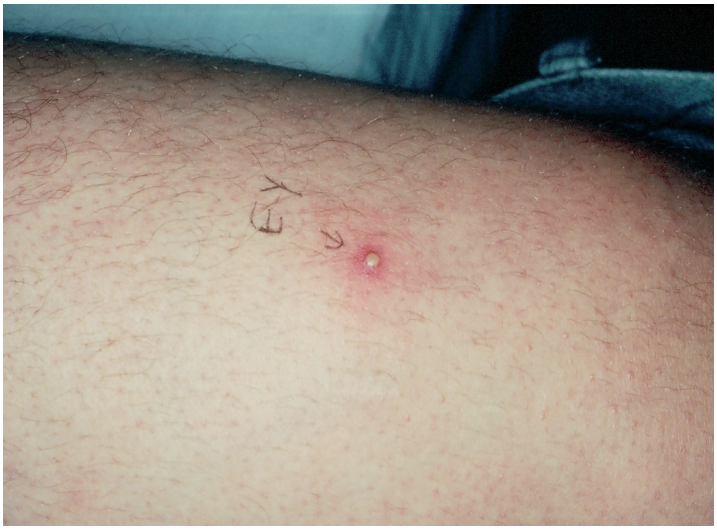

Fig. 2. Folliculitis located on the femoral area of a Behçet's disease patient.

Clinical evaluation

Evaluations were made by same dermatologist who did not work in BD and dermatology outpatient clinics. The number of papules, pustules, comedones, folliculitis, cysts and nodules located on face, chest, back, upper and lower extremities were recorded for each region.

Histopathological evaluation

For histopathological evaluations, serial sections were obtained from the formalin fixed paraffin blocks of 89 biopsies and stained with Hematoxylin and Eosin (H&E) and periodic acid-Schiff (PAS). Only one biopsy was performed in each patient. Specimens were evaluated by two different pathologists according to the previously determined

criteria in a blind manner. "PNL infiltration without folliculitis" denoted perivascular or interstitial infiltration, containing neutrophilis, without any evidence of folliculitis or perifolliculitis in serial sections. If the dermal infiltration was devoid of neutrophils, but mainly made up of mononuclear inflammatory cells, "Mononuclear inflammatory cell infilration without folliculitis" was the designation given. "Folliculitis and/or perifolliculitis" pointed out folliculocentric infiltration, invading the follicular epithelium or even destroying it. If leukocytoclastic vasculitis was detected in any of these patterns, it was recorded. The presence of neutrophils and/or nuclear debris and fibrinoid necrosis within the vessel wall were considered as the major criteria for vasculitis. Comedone and intrafollicular abscess formation were the other histologic features evaluated. The presence of microorganisms, mostly fungal agents were searched throughout the serial sections, using PAS stain.

Statistical evaluation

For statistical evaluations, Kendall correlation coefficients, and concordance analyses of Cohen Kappa, Chi-square, and Fisher exact tests were used. Interobserver agreement was evaluated using the Kappa test, and Kappa values >0.40 were considered to be clinically important. According to Landis and Koch classification; values between 0.21 and 0.40 were accepted as "fair", and those between 0.41 and 0.60 as "moderate", and those between 0.61 and 0.80 as "substantial", and those between 0.81–1.00 as "almost perfect" (16). Mann-Whitney U-test was used for clinical evaluation. Statistical analyses were done using SPSS 19.0 software.

Results

The BD patients were older by a mean of 8 years as seen in Table I. AV patients had more papules, pustules and comedones in the faceas compared to the patients with BD (ps <0.001 for each; Table II). On the other hand the frequency of the nodules and cysts were similar on the face between the BD and AV groups. The number of papules and folliculitis was clearly higher, (8.73±7.13, $p<0.05$; 0.58±1.92, $p<0.05$, respectively) in the BD than that of AV patients on the back with no differences in the frequency of pustules, comedones, nodules and cysts (Table II). While there were no differences in the arms; folliculitis on the legs only among the BD patients [12/58 (20.6%), there were no patients (0/31) with folliculitis in AV group. There were however no differences in the frequency of other acne elements.

Table II. Mean and comparison of manifestations on face, back, chest, upper and lower extremities in acne vulgaris and Behçet's disease patients.

Face	Acne vulgaris Mean±SD	Behçet's disease Mean±SD	U	*p*-value
Papule	11.8 ± 13.4	4.41 ± 4.47	281.5	<0.001
Pustule	5.75 ± 5.1	1.55 ± 2.07	198	<0.001
Comedone	42.5 ± 43.7	9.79 ± 14.8	117.5	<0.001
Folliculitis	0	0		
Cyst	0.46 ± 1.21	0.08 ± 0.28	542	>0.05
Nodule	0.12 ± 0.42	0.05 ± 0.23	468.5	>0.05
Back				
Papule	5.62 ± 5.77	8.73 ± 7.13	383.5	<0.05
Pustule	3.7 ± 4.41	7.23 ± 12.7	454	>0.05
Comedone	8.93 ± 13.35	8.73 ± 9.38	454	>0.05
Folliculitis	0	0.58 ± 1.92	480	<0.05
Cyst	0.21 ± 0.79	0.02 ± 0.17	χ: 2.199	>0.05
Nodule	0.03 ± 0.17	0.08 ± 0.28		>0.05
Chest				
Papule	1.34 ± 1.61	1.82 ± 2.99	517.5	>0.05
Pustule	1.65 ± 2.69	1.41 ± 2.82	504	>0.05
Comedone	1.90 ± 5.41	1.32 ± 3.41	515.5	>0.06
Folliculitis	0	0		
Cyst	0	0		
Nodule	0	0		
Upper extremely				
Papule	3.68 ± 4.20	3.52 ± 4.77	793.5	>0.05
Pustule	1.18 ± 1.85	1.44 ± 2.64	593.5	>0.05
Comedone	0.59 ± 1.45	1.70 ± 5.84	542	>0.05
Folliculitis	0	0		
Cyst	0	0		>0.05
Nodule	0	0		>0.05
Lower extremely				
Papule	0.71 ± 1.54	1 ± 2.87	487.5	>0.05
Pustule	0.18 ± 0.89	0.11 ± 0.40	χ:2.29	>0.05
Comedone	0	0		
Folliculitis	0	1.64 ± 3.47	352	<0.001
Cyst	0	0		
Nodule	0	0		

Among the histopathological lesions the only parameter found to be significantly different by both pathologists was the higher comedone formation in AV (23-17, 74%-55% and 27-19, 47%-33% for BD, $p=0.012$-$p=0.043$ for either pathologist, respectively) (Table III; Fig. 3). The first pathologist detected leukocytoclastic vasculitis in 9/58 (16%) BD and 1/31 (3%) AV patients ($p=0.07$), whereas the second pathologist observed vasculitis in 5/58 BD (9%) and 5/31 AV (16%) patients ($p=0.28$) (Fig. 4). Both observers detected vasculitis in the same patients in 4/58 (7%) BD and 1/31 (3%) AV cases. Folliculitis and/or perifolliculitis, pointing out follicle-based pathology was detected in 78/89 (87.6%) and 73/89 (82%) patients in both the BD and AV groups for both pathologists, respectively (Table III; Fig. 5). In contrast, vessel-based pathology was rarely observed; 10/89 (9%) patients in both the BD and AV groups for both pathologists (Table III; Fig. 6).

The interobserver agreement was generally low among the pathologists with better agreement about the presence of perivascular infiltration with PNL ($\kappa=0.43$), leukocytoclastic vasculitis (=0.51) or microorganisms ($\kappa=0.46$) (Table III).

Table III. Interobserver agreement by two pathologists, histopathologic features, and pattern analysis of papulopustular lesions in Behçet's disease and acne vulgaris patients examined in this study. Values above 0.40 are compatible.

Histopathological findings	Acne vulgaris n=31			Behçet's disease n=58			Total Kappa (κ)	χ^2		*p*	
	1st Path	2nd Path	Kappa (κ)	1st Path	2nd Path	Kappa (κ)		1st Path	2nd Path	1st Path	2nd Path
PNL infiltration without folliculitis	1	0	NA	0	2	NA	0.43			0.34*	0.54*
Mononuclear infiltration without folliculitis	0	3	NA	0	1	NA	0.33				0.12*
Folliculitis/perifolliculitis	29	23	0.10	49	50	0.77	0.17			0.31*	0.24*
LCV	1	5	0.29	9	5	0.93	0.51		1.14	0.07*	0.28
Comedone formation	23	17	0.18	27	19	0.29	0.29	6.27	4.08	0.012	0.043
Intrafollicular abscess formation	20	18	0.18	41	31	0.50	0.39	0.35	0.17	0.55	0.67
Presence of microorganisms, etc.	6	3	0.15	12	4	0.22	0.46	0.02		0.88	0.46*

*Assessed using Fisher's exact test. $p<0.05$ was considered to be statistically significant.
PNL: polymorphonuclear leukocyte; LCV: leukocytoclastic vasculitis; done using concordance analysis of Cohen Kappa; NA: not available.

Discussion

This study first confirmed numerically that a. Papulopustular lesions in BD can also be found in the legs (17), a localisation usually not observed in AV; b. the histology of these lesions was indistinguishable from AV apart from the fact that comedones were more frequently observed in AV; c. The papulopustular lesions located on the back of BD patients cannot be distinguished clinically from those of AV (10). Moreover, acneiform lesions of AV have also been noted in BD patients. AV occurs on the face, trunk and extremities and arises in women mostly between the ages of 14-17 years and in men between 16-19 years. It has been shown that the frequency of AV was 35–40% in these age groups. The manifestations of the disease can continue until the age of 35 years. These types of manifestations are seen in 1% of males and 5% of females in their 40s (18). This, obviously is a younger age bracket as compared the age distribution of the BD patients enrolled in this study. In our recent series, we determined pustules in 53%, papules in 70% of BD patients. Similarly in larger series reported by Gurler *et al*. (19) and Tursen *et al*. (20); papulopustular lesions were seen 54.2% out of 2147, and 59.5% out of 2313 BD patients respectively.

In the current study, we studied the distribution of the manifestations of BD and AV in different regions of the skin and also age groups. This study showed us that folliculitis could be seen in the legs of BD patients (12/58, 20.6%,

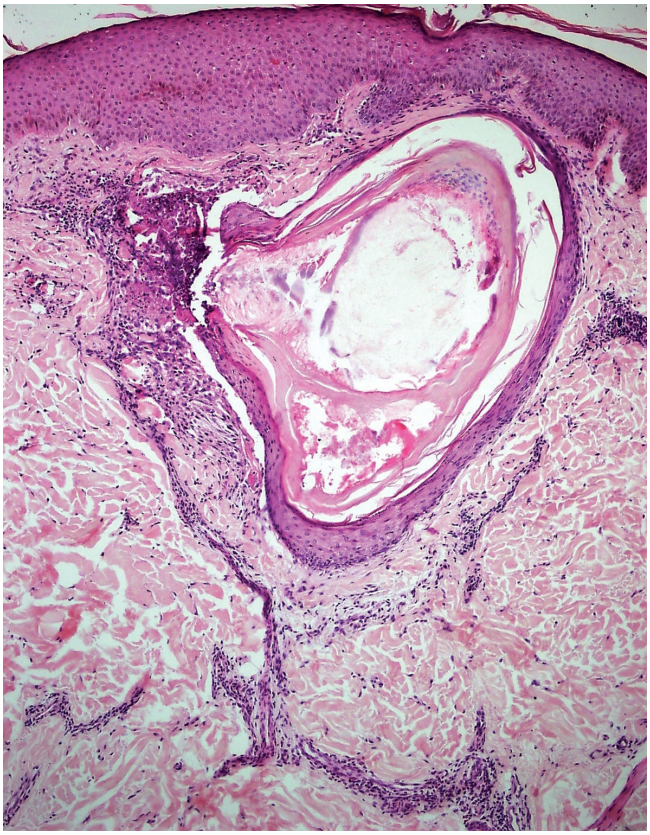

Fig. 3. Comedone formation in a lesion of an acne vulgaris patient (H&E, 100x).

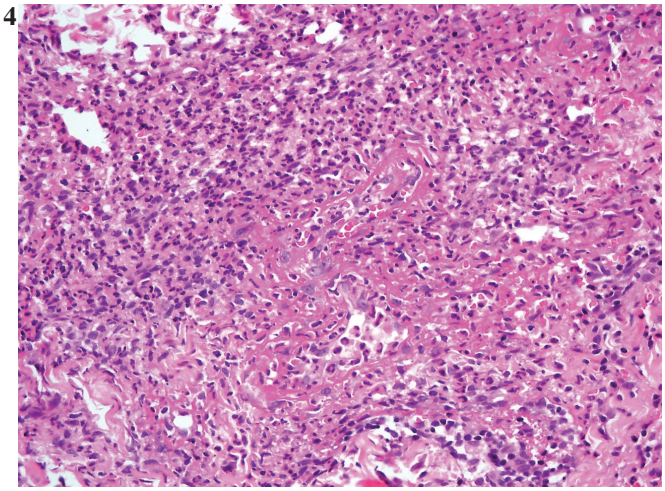

Fig. 4. Necrotising neutrophilic vasculitis in a papular lesion of a Behçet's disease patient (H&E, 400x).

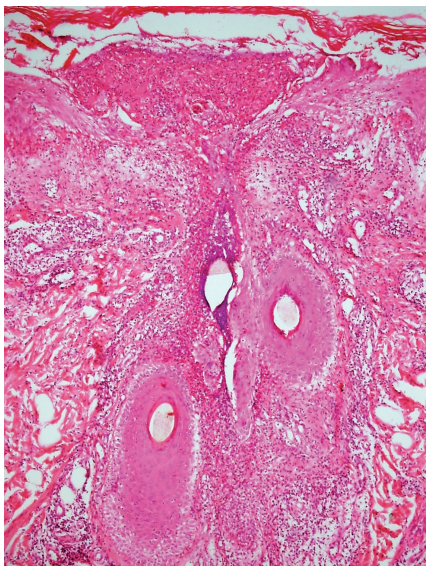

Fig. 5. Follicle based lesion of Behçet's disease with pustule formation in the epidermis (H&E, 100x).

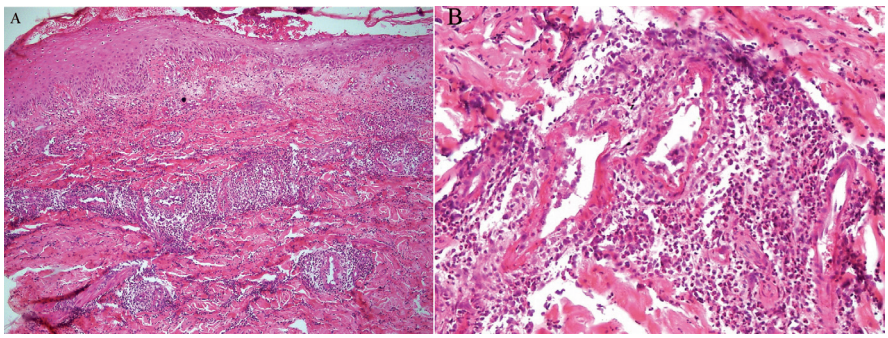

Fig. 6. Vasculitis in a vessel-based lesion of Behçet's disease (**A**: H&E, 100x; **B**: H&E, 400x)

$p<0.001$) but not in any of the AV patients (0/31).

It is to be noted that The International Study Group Criteria for Diagnosis of Behçet's Syndrome does not specifiy the localisation of the skin lesions. As such we propose that the papulopustular lesions in the legs should formally be evaluated as a distinguishing feature of BD in future classification criteria.

Some authors have described folliculitis or perifolliculitis in BD cases, similar to AV (Table IV) (21). Boyvat *et al*. (14) previously examined 23 papulopustular lesions in 20 patients with BD. They observed leukocytoclastic vasculitis in 10 out of 23 (43.5%) papulopustular lesions of BD. Ilknur *et al*. (15) examined 18 patients with BD and 16 control subjects; in the BD patients, vasculitis was detected in 27.8%, and folliculitis and/or perifolliculitis in 16.7% of the cases. Vasculitis was not encountered in the control group. These authors reported that only vasculitic changes may be suggestive of BD in case of histopathological examination of papulopustular lesions. In our present study, however, folliculitis and/or perifolliculitis were observed in 50/58 (86%) of the BD patients.

In an earlier study by Kalkan *et al*. (2) of 42 patients with BD and 21 control patients with AV, leukocytoclastic vasculitis was detected in 7 patients (16.7%) and lymphocytic vasculitis in 3 cases (7.1%) with BD. There was no vasculitis in the AV group. In addition, the rest of BD patients mostly revealed perivascular and/or interstitial infiltration (27 patients, 64%), rather than follicle-based lesions (2). In our AV cases however, vasculitis was found in 1/31 (3%) and 5/31 (16%) patients by the pathologists, respectively (conducted in a blind manner). These findings could be interpreted as secondary to inflammation. Secondary vasculitis represents small vessel thickening and deposition of fibrinoid material in the vessel wall, and is more likely to be secondary to acute inflammation rather than a true neutrophilic vascular reaction (11). Whereas vasculitis was detected in 9/58 (16%) and 5/58 (9%) in BD patients respectively by both pathologists. These data suggest that a histopathological evaluation of the manifestations of BD is open to different interpretations or is non-specific and is thus not helpful in making a diagnosis. In another report by Alpsoy *et al*. (22) of 17 Behçet's patients, vasculitic changes (11 leukocytoclastic vasculitis cases and 1 lymphocytic vasculitis patient) were found in 12 patients (70.5%).

Similar studies from Jorizzo *et al*. (23) and Chen *et al*. (24) have revealed perivascular inflammation and cutaneous vasculitis, both of the lymphocytic and leukocytoclastic types. Jorizzo *et al*. (23) suggested in their study that only pustular lesions with vessel-based (not follicle-based) histopathological changes should be employed as a diagnostic criterion for BD. Kienbaum *et al*. (13) pointed out that neutrophilic aggregations within the vascular structure of the folliculitis-like manifestations in BD patients denoted the vascular nature of this disorder.

Some authors claim that only perifollicular and perivascular mononuclear or neutrophilic infiltrations may be seen in BD but not vasculitis. In a series by Ergun *et al*. (12) papulopustular lesions of 17 BD and 6 AV patients had both perifolliculitis or suppurative folliculitis. Eighty eight percent of the specimens from these patients revealed perifollicular or follicular involvement and 12% revealed perivascular involvement without leukocytoclastic vasculitis.

As was also recently highlighted there are differences in the frequency of skin mucosa manifestations in BD (25) and a drawback of our study was that the males in this study greatly outnumbered the females. The main reason for this was that the females refused punch bi-

Table IV. Comparative analysis of similar studies reported in the literature.

	Vasculitis in BD	Vasculitis in AV
Kalkan *et al*.[2]	10/42 (24%)	0/21
İlknur *et al*.[15]	5/18 (28%)	0/16
Alpsoy *et al*.[22]	12/17 (71%)	–
Boyvat *et al*.[14]	10/23 (43%)	–
Ergun *et al*.[12]	2/17 (12%)	0/6
Jorizzo *et al*.[23]	3/22 (14%)	-
Chen *et al*.[24]	20/42 (48%)	

opsies due to cosmetic concerns. Meanwhile the number of cases in this study was more than many other studies with 58 BD and 31 AV control patients.

Conclusion

The findings of our present study confirm previous observations that the papulopustular lesions of BD, whether they are present at usual or unusual acne sites, are not distinguishable from AV lesions in most aspects apart from the fact that they can appear in the legs among the BD patients. The histopathology of the vascular changes in such lesions, however, deserves further study.

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