Whether Behçet's patients with large vessel involvement have concurrent small vessel involvement? A Case Control Study

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Research Article

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Abstract

BACKGROUND: Behçet's disease (BD) is a chronic multisystem disorder. The principal pathological finding in BD is vasculitis, which may involve vessels of different sizes. Concurrence of small and large vessel involvement in BD patients is undetermined. The aim of this study is to evaluate small vessel involvement in BD patients with large vessel involvement.

METHODS: 35 BD patients with large vessel involvement (cases) and 35 BD patients without large vessel involvement (controls) were included. For evaluation of small vessel involvement, capillaroscopy was done for all patients. Capillaroscopic findings were compared between two groups.

RESULTS: According to the capillaroscopic findings, all of our BD patients had small vessel involvement

The most abnormality was tortuosity (87.1%), followed by avascular areas (51.4%) and decreased density of capillaries (44.2%). Capillaroscopy findings were not statistically different between the case and the control groups. In the case group, the number of avascular areas was associated with superficial phlebitis (p=0.044) and deep vein thrombosis (p= 0.022). In addition, there was a significant association between micro bleeding and the history of erythema nodosum (p=0.015), tortuosity and the history of skin aphthosis (p= 0.015), architectural derangement and the history of uveitis (p=0.029), the number of avascular areas and active oral aphthosis (p= 0.021), and architectural derangement and increased ESR (p=0.011).

CONCLUSION: There was no difference in nailfold capillary involvement between BD patients with and without large vessel involvement. However, Among BD patients with large vessel involvement, the number of avascular areas was significantly associated with superficial phlebitis and deep vein thrombosis.

Introduction

Behçet's disease (BD) is a chronic disorder characterized by multi-organ involvement ([1]). Vasculitis is the principal pathologic finding in this disorder ([2]). BD is classified as variable vessel vasculitis ([3]) and is characterized by oral and genital aphthosis, cutaneous, ophthalmic, central nervous system, gastrointestinal, articular, and vascular involvement ([1]).

Vascular involvement is one of the most important manifestations of Behçet's disease, which causes severe morbidity and mortality ([4]). The prevalence of large vessel involvement in BD is 25 to 35%, including superficial thrombophlebitis, deep vein thrombosis (DVT), cerebral venous thrombosis, aortic and peripheral artery aneurysms, pulmonary artery occlusion and aneurysm, coronary artery aneurysm, and abdominal veins thrombosis ([5], [6]). On the other hand, small vessel involvement occurs in 48–90% of BD patients ([7], [8], [9], [10], [11]). Moreover, vasculitis and phlebitis, lymphocytic vasculitis, and leukocytoclastic vasculitis have been reported in 48%, 31%, and 17% of skin biopsies in BD patients, respectively ([12]).

There is no data about the concurrence of large and small vessels involvement in BD patients. The aim of this study is to evaluate involvement of small vessels in BD patients who have large vessel involvement.

Materials And Methods

35 BD patients with vascular involvement (cases) and 35 BD patients without vascular involvement (controls), who were referred to Behçet's disease clinic of Shariati Hospital in Tehran from 2017 to 2018, were enrolled in this study. They all fulfilled the International Study Group criteria for BD. Diagnosis of vascular involvement in the case group was based on the previous imaging findings, including the presence of superficial thrombophlebitis or deep vein thrombosis in Duplex ultrasound, pulmonary embolism in CT angiography, cerebral venous thrombosis in MR venography, abdominal vein thrombosis in CT angiography, and arterial aneurysm in CT or MR angiography.

Demographic findings (including age, sex and ethnicity), BD manifestations, BD activity according to Behçet's Disease Dynamic Activity Measurement (IBDDAM) criteria, The Behçet's Disease Current Activity Form (BDCAF) criteria and physician global assessment, Pathergy test, para clinical results (including CBC, ESR, CRP, HLAB5 and, HLAB51), and drug history at the time of capillaroscopy were recorded in all patients.

For nailfold capillaroscopy we used a video capillaroscope (Optilia, model op120021, *200 magnification, Sweden). Before capillaroscopy, all patients rested in the examination room for 15 to 20 minutes with a temperature of 25 C. Patients did not use tea or coffee for 4 to 6 hours before doing capillaroscopy. 8 nails (2d to 4th fingers) were evaluated in each patient, and 4 consecutive pictures were taken from the center of each nailfold except for those with a recent trauma. The nailfold capillaries were evaluated in terms of capillary density, the number of avascular areas, architectural derangement, micro bleeding, enlarged loops, giant capillaries, and tortuosity of capillaries by an expert rheumatologist who was blinded to the patient's condition.

The association between capillaroscopic changes with demographic results, disease manifestation, disease activity, para clinical tests, and drug history were evaluated.

Descriptive statistics were used to determine the frequencies and central tendencies of the cohort. Groups were compared utilizing the student t-test and Mann–Whitney U test for parametric and non-parametric data. Chi-Square test was used to compare categorical data. All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY). A P value of < 0.05 was considered significant.

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (IRB 1398.397, 8/13/2019). All subjects were informed about the study goal and methods. They were enrolled after their written informed consent.

Statistical analysis

Statistical analyses were performed using SPSS (version 21.0). Mean and median (minimum and maximum) values were used for descriptive statistical parameters. The Chi-square test was used to examine the significance of the association between capillary changes in two groups and was corrected using the Fisher's exact test. $P < 0.05$ was considered significant.

Results

70 patients were evaluated (35 cases and 35 controls). The mean age was 41.26 (SD = 14) years in the case group and 46.63 (SD = 9) years in the control group. There was no significant difference in age between cohorts (p = 0.62). 71.4% of patients in the case group and 40% in the control group were men. In the case group, 34.4% were Turk, and 65.6% were Fars. In the control group, the percentage of the Turk and Fars were 22.9% and 77.1%, respectively. 5.7% of the patients in the case group and 2.9% in the control group had hypertension. None of the patients had diabetes in the case or control group. 7% of patients in the case group and 5% in the control group were smokers (Table 1).

69 patients (98.5%) had nonspecific changes in their nailfold capillaroscopy, and one patient had a scleroderma pattern. The most abnormality was tortuosity of capillaries (87.1%), followed by avascular areas (51.4%) and decreased density of capillaries (44.2%) (Table 2). Although these abnormalities were more common in the case group, they did not differ between cohorts (p = 0.279, p = 0.133, and p = 0.86, respectively). Architectural derangement, micro bleeding, enlarged loops, and giant capillaries were observed with the same frequency in the case and control groups. Bushy capillaries were not seen in the capillaroscopy of any of the patients in the case or control groups (Figs. 1 & 2).

The male gender was significantly associated with enlarged capillaries in capillaroscopy (p = 0.043). However, there was no significant association between capillaroscopic changes and age, ethnicity, or duration of illness.

In the case group, vascular involvements included deep vein thrombosis in 38.6%, cerebral venous thrombosis in 5.7%, arterial aneurysm in 4.3%, and superficial thrombophlebitis in 10% of patients. The other large vessel involvements were not presented in these patients. Moreover, the number of avascular areas in capillaroscopy was significantly associated with superficial phlebitis (p = 0.044) and deep vein thrombosis (p = 0.022).

There was a significant association between micro bleeding and the history of erythema nodosum (p = 0.015); tortuosity of capillaries and the history of skin aphthosis (p = 0.015); and architectural derangement of capillaries and the history of uveitis (p = 0.029).

At the time of capillaroscopy, 40% had active mucosal aphthosis, 2.9% had active vessel involvement, and 11.4% had active skin involvement. Active oral aphthosis was associated with the number of avascular areas (p = 0.021). There was no significant association between disease activity and capillaroscopic changes according to IBDDAM, BDCAF, or physician global assessment. Increased ESR directly correlated with architectural derangement (p = 0.011), while there was no statistically significant

association between capillaroscopic changes and other paraclinical results, including CBC, CRP, HLAB5, HLAB51, or pathergy test.

At the time of performing capillaroscopy, 40% of the patients in the case group and 17.1% of the patients in the control group were using immunosuppressive drugs, including cyclophosphamide, cyclosporine, and azathioprine. In addition, 68.6% in the case group and 31.4% in the control group consumed corticosteroids. There was no association between immunosuppressive or corticosteroid consumption and capillaroscopic findings. ($p = 0.279$).

There was no significant association between capillaroscopic changes and hypertension or smoking.

Table 1
demographic characteristics, disease manifestation and drug consumption in the case and control groups.

Characteristics		Case group N(%)	Control group N(%)
Female		10 (28.6)	21 (60)
Male		25 (71.4)	14 (40)
Age(years)		41.2	46.6
Hypertension		2 (5.7)	1 (2.9)
Smoking		7 (20)	5 (14.3)
Disease duration(years)		13	17
Oral aphtosis		34 (97.1)	35 (100)
Genital aphtosis		19 (54.3)	16 (45.7)
Erythema nodusom		12 (34.3)	5 (14.3)
Pseudofoliculitis		16 (45.7)	8 (22.9)
Cutaneous aphtosis		3 (8.6)	0
Eye involvement		11 (31.4)	24 (68.6)
CNS involvement		1 (2.9)	0
Artricular involvement		8 (22.9)	8 (22.9)
Gastrointestinal involvement		0	0
Epididimitis		2 (5.7)	0
Disease activity (IBDAAM)		0	0
Disease activity (BDCAF)		0	0
Physician global assessment	mild	14 (40)	14 (40)
	moderate	2 (5.7)	0
	sever	1 (2.9)	0
	inactive	18 (51.4)	21 (60)
Immunosuppressive consumption (cyclophosphamide, cyclosporine, azathioprine)		14 (40)	6 (17.1)
Corticosteroid consumption		24 (68.6)	11 (31.4)

Table 2
capillaroscopic changes in two groups.

Capillaroscopic changes	Case group N (%)	Control group N (%)	Total %	P value
Tortuosity	31 (88.5%)	30 (85.7%)	87.1%	0.860
Enlarged loops	22 (62.8%)	19 (54.2%)	58.5%	0.325
Avascular areas	22 (62.8%)	14 (40%)	51.4%	0.133
Decreased capillary density	19 (54.2%)	12 (34.2%)	44.2%	0.279
Architectural derangement	10 (28.5%)	6 (17.1%)	22.8%	0.350
Ramification	7 (20%)	6 (17.1%)	18.5%	0.690
Micro bleeding	5 (14.2%)	4 (11.4%)	12.8%	0.762
Giant capillaries	3 (8.5%)	2 (5.7%)	7.1%	0.325
Figure1: tortuosity in a patient with BD				

Discussion

Behçet's disease is a multisystemic and chronic condition ([1]). Vasculitis is the main pathologic finding in this disorder ([2]). Nailfold capillaroscopy is a noninvasive and accessible procedure to evaluate microvascular abnormality. These abnormalities have already been described in some rheumatologic conditions ([13]), including lupus, dermatomyositis, polymyositis, rheumatoid arthritis, primary Sjogren's syndrome, and familial Mediterranean fever ([14], [15], [16]). Moreover, nailfold capillary abnormality is shown to be associated with stage, severity, and pulmonary hypertension in scleroderma ([17]). Nailfold changes in capillaroscopy are also valuable for identifying patients in the early phase of connective tissue disorder ([14], [15]).

BD is characterized by variable vessel vasculitis ([3]); as a result, nailfold abnormality can be expected. In this study, All BD patients (cases and controls) had abnormal capillaroscopic findings. Small vessel involvement was not different between cohorts. However, in BD patients with large vessel involvement, the number of avascular areas was significantly associated with superficial phlebitis and deep vein thrombosis. It seems that small vessel involvement is a unique finding in BD with any presentation, but some patterns may be more common in some unique manifestations.

Tortuosity of capillaries, avascular areas, and decreased capillary density were the most common nailfold findings in the capillaroscopy of our patients. Various morphological changes such as mega capillaries, microaneurysms, and hemorrhages were reported in the previous studies on BD patients ([7], [8], [9], [10], [11]). Wechsler et al. reported 22 abnormal nailfold capillaroscopy among 30 evaluated patients. Decreased

density of capillaries was not found in their study ([7]). Vaiopoulos et al. reported abnormal capillaroscopic changes in most BD patients ([8]). Movasat et al. reported abnormal capillaroscopy in 40% of patients, with enlarged loops and micro hemorrhage being the most common findings ([9]). Enlarged capillaries were reported as a shared finding in patients with BD in Aytekin et al. study ([10]). Therefore, nailfold capillaroscopic changes seem to be a joint presentation in BD patients.

Although the frequency of avascular areas, decreased capillary density and tortuosity of capillaries were more common in the BD patients with large vessel involvements, it was not statistically significant.

Our results suggest that avascular areas were associated with some other vascular features of the disease, such as superficial phlebitis and deep vein thrombosis (DVT). In confirmation of our study, Movasat et al. found a significant association between enlarged capillaries and superficial thrombophlebitis ([9]).

We revealed a significant association between capillaroscopic changes and some BD manifestations during the disease course, including erythema nodosum, skin aphthosis, uveitis, and active mucosal aphthosis at the time of capillaroscopy. It seems that capillaroscopic changes correlate with some manifestations of Behçet's disease; however, Aytekin et al. did not find any association between capillaroscopic changes and dermatologic expressions ([10]); Whereas Vaiopoulos et al. reported a significant correlation between abnormal capillary changes, skin manifestations, and arthritis/arthralgia ([8]). Movasat et al. found a correlation between micro hemorrhage and articular manifestations ([9]).

Our study showed no association between capillaroscopic abnormality and systemic immunosuppressive drugs or corticosteroid usage. Similar to our findings, Aytekin et al. reported no correlation between capillaroscopic alterations and systemic drug usage ([10]).

This study was the first to compare nailfold capillaroscopic changes in BD patients with vascular involvement and those with no vascular involvement. The first limitation of our study seems to be an inadequate sample size. The drug usage was not matched between the two groups, which may affect the last results.

It seems that unspecific capillaroscopic changes occur in nearly all patients with BD and are associated with some disease manifestations, including skin, ocular, and vascular involvement. Although no specific pattern for capillaroscopic changes in Behçet's disease has been described yet, it may be used for diagnostic and prognostic purposes in future.

Conclusion

All our patients had small vessel involvement, according to capillaroscopic findings. We found no difference in nailfold capillary involvement between BD patients with or without large vessel involvement. Among BD patients with large vessel involvement, the number of avascular areas was significantly associated with superficial phlebitis and deep vein thrombosis.

Abbreviations

BD: Behçet’s disease

DVT: Deep vein thrombosis

IBDDAM: Iranian Behçet’s Disease Dynamic Activity Measurement

BDCAF: The Behçet's Disease Current Activity Form

CBC: Complete blood count

ESR: erythrocyte sedimentation rate

CRP: C-reactive protein

HLA: Human Leukocyte Antigen

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (IRB 1398.397, 8/13/2019). All methods were carried out in accordance with relevant guidelines and regulations. All subjects were informed about the study goal and methods and they were enrolled after their written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

All authors contributed to the conception of the work. Sara Vossoughian, Farhad Shahram, Hoda Kavosi, Mostafa Qorbani, Mohammad Nejadhosseinian, and Hoda Haerian contributed to data collection and statistical analysis. Sara Vossoughian, Seyedeh Tahereh Faezi, Yasaman Ahmadzadeh, and Mohammad Ali Mozaffari contributed to writing the first draft of the manuscript and the revisions. All authors have read and approved the final version of the manuscript and take full responsibility for the accuracy and integrity of the work.

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Figures

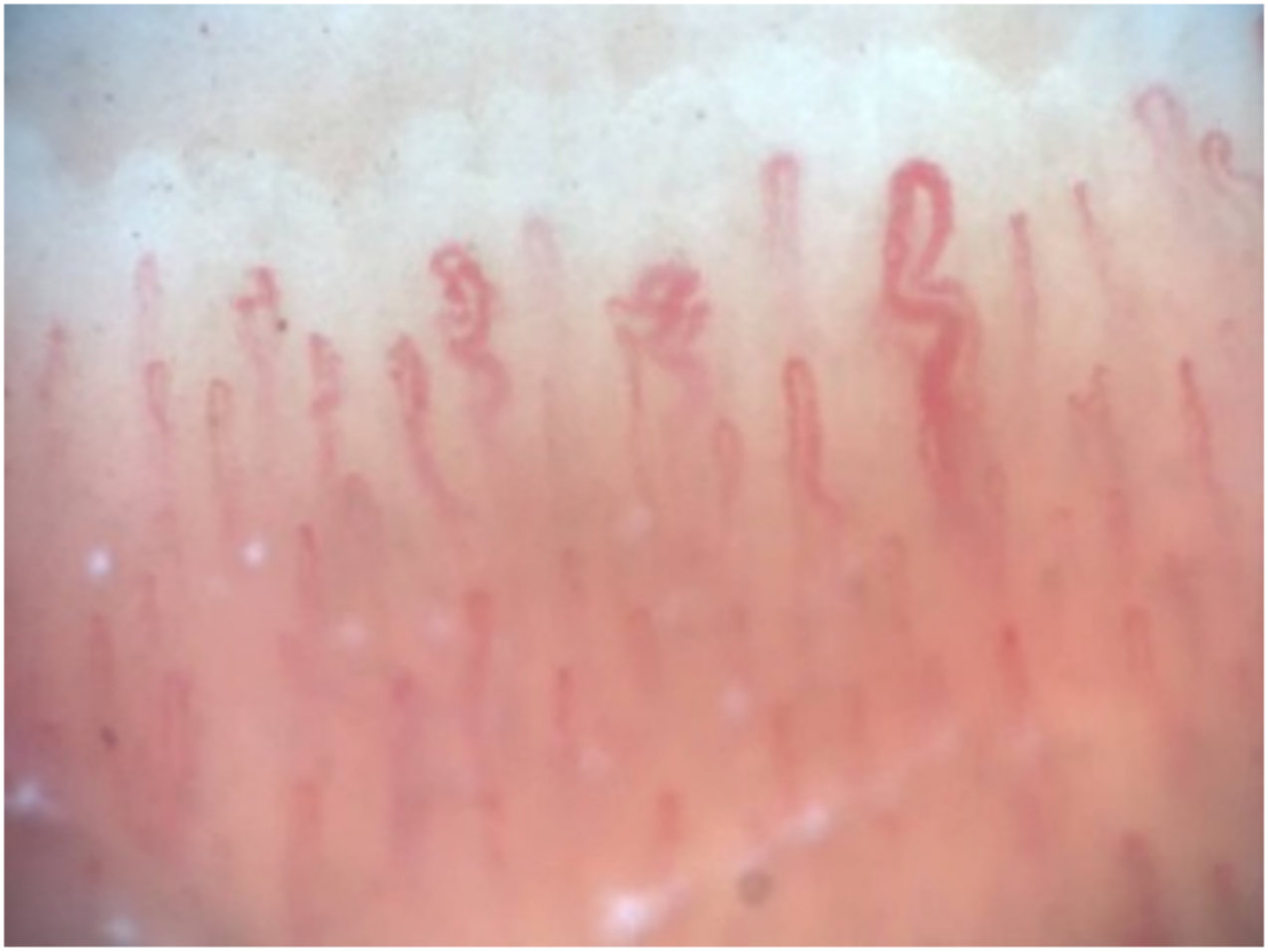

Figure 1

tortuosity in a patient with BD

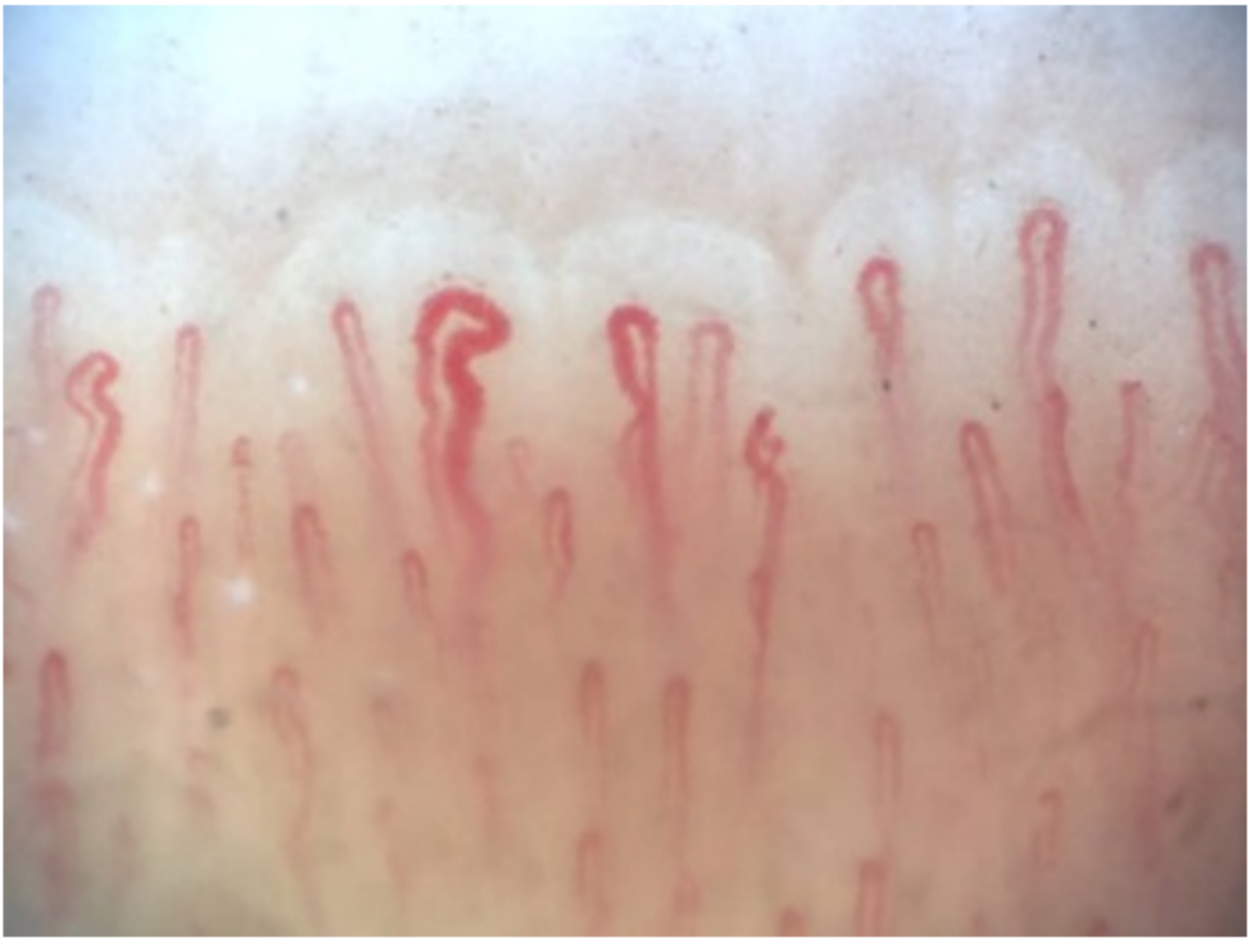

Figure 2

Avascular areas and decreased capillary density in a patient with BD