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Original Research

Vascular Involvement in Behcet's Disease: An Evaluation of 147 Cases and Literature Review

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ABSTRACT

Objectives: Behcet's disease (BD) is characterized by systemic vasculitis with inflammation that can affect various body organs. In BD, vasculitis primarily manifests with venous involvement, distinguishing it from other forms of systemic vasculitis.

Methods: We retrospectively analyzed the demographic and clinical characteristics of 147 patients diagnosed with vascular BD in our center.

Results: Vascular BD cases accounted for 25.0% (147 out of 589) of all BD patients. A statistically significant correlation was found between gender and vascular involvement that was seen predominantly in males (76.9%). In 71 patients, a vascular event developed during follow-up for BD, while in 76 patients the disease was diagnosed after the occurrence of a vascular event (51.7%). The most common vascular event was deep vein thrombosis in the lower extremities (69.4%). Arterial involvement was primarily observed in the pulmonary arteries (12.9%). Patients with lower extremity deep vein thrombosis tended to be younger, while those with pulmonary artery involvement were typically older. Overall, veins were affected 4.5 times more frequently than arteries.

Conclusion: The prevalent type of venous involvement was deep vein thrombosis in the lower extremities. Thrombotic events in BD cannot be solely attributed to abnormalities in thrombotic factors. The treatment of thrombotic events in BD remains contentious, with anticoagulant efficacy being debated and immunosuppressive therapy representing the primary treatment approach. Behcet's disease should be considered when a young male patient presents with an arterial or venous vascular event, especially if it is recurrent.

Keywords: Aneurysm, Behcet's disease, deep venous thrombosis

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Behcet's disease (BD) is a systemic vasculitis that manifests with chronic inflammation in various organs. The disease was first described in 1937 by Hulusi Behcet as oral aphthous ulcers, genital ulcers, and hypopyon uveitis.[1] The ailment is believed to result from an autoimmune process triggered by different etiologic factors in genetically predisposed individuals. Dr. Behcet focused on the viral etiology when defining the disease. Beyond its classic presentation, this disease can also manifest with skin lesions, joint involvement, and findings associated with gastrointestinal, pulmonary, cardiovascular, and central nervous system involvement, predominantly being encountered in the geographic regions along the historic Silk Road.[2] Given its implications for morbidity

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and mortality, vascular involvement bears paramount significance.[3]

In this study, we examined the demographic and clinical characteristics of patients followed up for vascular BD diagnosis in our clinic between 2019 and 2021. The diagnosis of BD was made according to the International Criteria for Behcet's Disease.[4]

Patients and Methods

This study received approval from the Local Ethics Committee (decision no: 58, dated: May 26, 2021) and was conducted in accordance with the Declaration of Helsinki. Patients who were followed up for a diagnosis of BD in our clinic between April 2019 and March 2021 were identified. From this cohort, 147 patients with BD exhibiting vascular involvement were included in the study. Thrombophilia assessment was made for patients presenting with vascular events and lacking a prior diagnosis of BD. Individuals diagnosed with thrombophilia were subsequently excluded from the study. In addition, factors that could affect the demographic and clinical data of the patients were investigated.

Statistical Analysis

The data obtained in this study were analyzed using the SPSS Statistics for Windows, v.24.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics and frequency tables were used in the interpretation of the findings. Measurement values conforming to normal distribution were examined using parametric methods. When comparing two independent groups of normally distributed data, the independent samples t-test was applied (t-table value). For measurement values lacking a normal distribution, non-parametric tests were employed. Specifically, the Mann-Whitney U test (Z-table value) was used for comparing two independent groups, and the Wilcoxon test (Z-table value) was utilized in comparing two dependent groups. To assess relationships between two qualitative variables, Pearson chi-square cross-tables were employed.

Results

Of the 589 patients followed up, vascular involvement was detected in 147 (25.0%) with a mean age of 41.47±10.43 years. In 71 patients, a vascular event occurred after the BD diagnosis, whereas in 76 cases (51.7%), the vascular event manifested before any BD diagnosis. Among these 76 patients, 14 (9.5% of all patients with vascular involvement) had experienced multiple vascular events before being diagnosed with BD (Fig. 1). When the etiology of the vascular events was investigated, a BD diagnosis was established, and the events were found to be linked to the disease. When considering the entire cohort, the rate of vascular events preceding BD diagnosis was 12.9% (76/589).

A statistically significant correlation was noted between vascular involvement and gender (χ^2=47.674; p=0.000). Patients without vascular involvement were predominantly in the 30-39 age range, while those with vascular involvement were mostly aged 40-49 (Table 1).

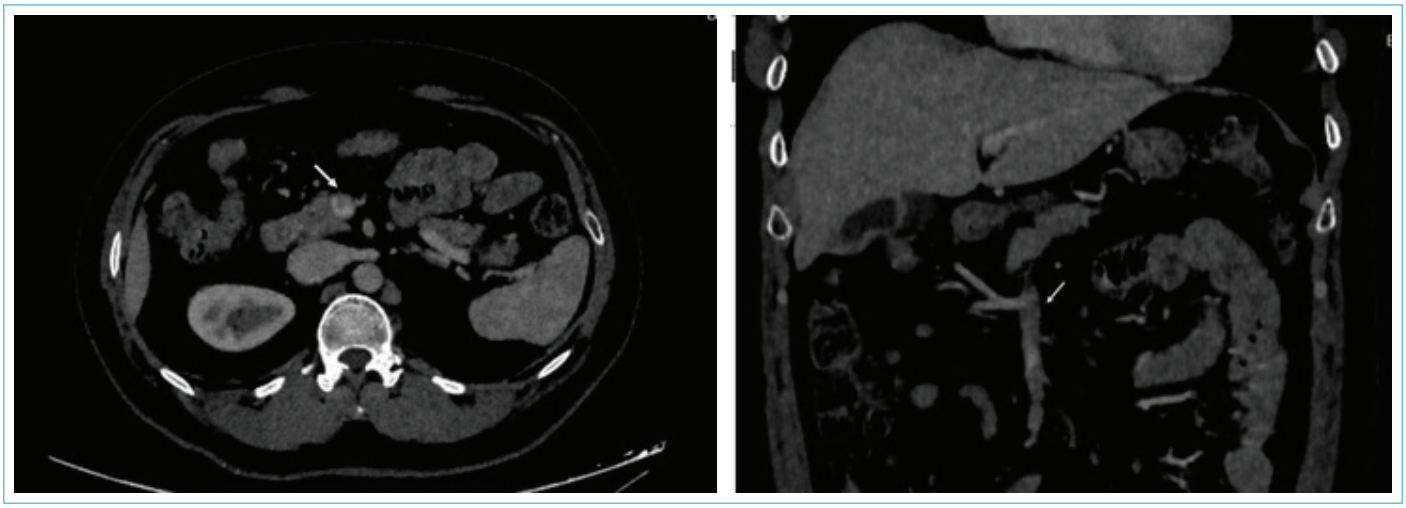

Figure 1. (a) Axial and **(b)** coronal computed tomography images taken in the venous phase show a filling defect consistent with a thrombus in the lumen of the superior mesenteric vein. The patient presented to the emergency department with acute abdominal pain, and the medical history revealed prior instances of pulmonary artery thrombosis and deep vein thrombosis in a lower extremity. Consequently, the patient was under warfarin medication. The international normalized ratio (INR) value of the patient was 2.6 (range: 0.8 to 1.2). Computed tomography angiography (CTA) confirmed the diagnosis of mesenteric vein thrombosis.

Table 1. Relationships between vascular involvement in Behcet's disease and age and gender

	Absent (n=442)		Present (n=147)		Statistical analysis*
	n	%	n	%	probability
Age group (years)					
<30	89	20.1	22	15.0	
30-39	126	28.5	37	25.2	χ^2=10.519
40-49	116	26.2	59	40.1	**p=0.015**
≥50	111	25.1	29	19.7	
Gender					
Male	193	43.7	113	76.9	χ^2=47.674
Female	249	56.3	34	23.1	**p=0.000**

*Pearson chi-square cross-tables were used in examining the relationships between two qualitative variables.

Table 2. Comparisons of the patients' ages at the time of Behcet's disease and vascular involvement diagnoses

Variable	Age (years)		Statistical analysis* probability
	$\bar{X}$±SD	Median [Min-Max]	
Age at BD diagnosis	31.52±10.09	30.0 [15.0-74.0]	Z=-6.070
Age at vascular involvement diagnosis	34.10±10.28	33.0 [17.0-74.0]	**p=0.000**

SD: standard deviation; BD: Behcet's disease; *In comparing two dependent groups not showing normal distribution, the Wilcoxon test was used (Z-value); Significant p values are written in bold.

A statistically significant difference was determined between the age of patients at the time of BD diagnosis and at the time of vascular involvement diagnosis (Z=-6.070, p=0.000). The age at which vascular involvement was diagnosed was significantly higher than the BD diagnosis (Table 2).

No statistically significant relationship was determined between gender and the location of the vascular event (p>0.05).

A statistically significant correlation was determined between pulmonary artery involvement and the occurrence of intracardiac thrombus (χ^2=7.859; p=0.005). Likewise, a statistically significant relationship was determined between cerebral vein thrombosis and jugular vein-subclavian vein thrombosis or occlusion (χ^2=8.298; p=0.004).

In addition, a statistically significant relationship was determined between deep vein thrombosis and the age at the time of vascular involvement diagnosis (t=2.654; p=0.009). Furthermore, a statistically significant relationship was established between pulmonary artery involvement and age at the time of vascular involvement diagnosis (Z=-2.115; p=0.034) (Table 3).

Since 76 patients had not been previously diagnosed with BD, they were not receiving treatment. Among them, four patients were receiving anticoagulant treatment due to a history of recurrent thrombosis (Fig. 1). Following the diagnosis of BD with vascular involvement, colchicine and immunosuppressive therapies (azathioprine, cyclophosphamide, or anti-TNF) were started. During the follow-up period, no instances of mortality were recorded among patients diagnosed with vascular BD.

Discussion

Vascular involvement in BD distinguishes itself from that seen in other autoimmune inflammatory conditions, manifesting distinct clinical and histopathological characteristics. Thrombus accompanying vessel wall inflammation, which cannot be explained by thrombophilic factors, is typical for BD. Notably, vascular inflammation of the vessel wall is markedly prevalent. A distinctive histopathological finding is neutrophilic vasculitis encompassing the vasa vasorum, often linked to an elevated neutrophil-to-lymphocyte ratio in BD.[5] At the chronic stage, periadventitial fibrosis is seen. Behçet's disease sets itself apart from other vasculitides with an increased vein wall thickness, as evidenced by Doppler ultrasonography studies.[6,7] The co-occurrence of various arterial and venous events within the same patient, referred to as a vascular cluster, is a recognized phenomenon. The occurrence of venous thrombus in the majority of patients with either vascular cluster or pulmonary involvement sug-

Table 3. Comparisons of the patients' ages at the diagnosis of vascular involvement in Behcet's disease based on selected parameters

Variable	n	Age at vascular involvement diagnosis (years)		Statistical analysis* probability
		$\bar{X}$±SD	Median [Min-Max]	
Deep vein thrombosis in the lower extremities				
Absent	45	47.42±12.04	37.0 [18.0-74.0]	t=2.654
Present	102	32.63±9.09	32.0 [17.0-55.0]	**p=0.009**
Superficial thrombophlebitis in the upper extremities				
Absent	142	34.22±10.36	33.5 [17.0-74.0]	Z=-0.722
Present	5	30.60±7.60	30.0 [21.0-42.0]	p=0.470
Superficial thrombophlebitis in the lower extremities				
Absent	133	34.05±10.51	33.0 [17.0-74.0]	Z=-0.317
Present	14	34.57±8.12	32.5 [24.0-54.0]	p=0.751
Large vein thrombosis occlusion				
Absent	136	34.46±10.24	34.0 [17.0-74.0]	Z=-1.573
Present	11	29.73±10.26	25.0 [18.0-49.0]	p=0.116
Jugular vein, subclavian vein thrombosis				
Absent	141	34.04±10.35	33.0 [17.0-74.0]	Z=-0.524
Present	6	35.50±9.03	39.0 [21.0-44.0]	p=0.600
Pulmonary artery involvement				
Absent	128	33.32±9.82	32.0 [17.0-74.0]	Z=-2.115
Present	19	39.37±11.71	40.0 [20.0-64.0]	**p=0.034**
Cerebral vein thrombosis				
Absent	129	33.85±9.91	33.0 [17.0-64.0]	Z=-0.381
Present	18	35.94±12.84	33.5 [21.0-74.0]	p=0.703
Mesenteric, portal vein thrombosis				
Absent	142	33.84±10.19	32.5 [17.0-74.0]	Z=-1.727
Present	5	41.40±11.28	44.0 [22.0-51.0]	p=0.084
Aorta involvement				
Absent	143	34.00±10.36	33.0 [17.0-74.0]	Z=-0.965
Present	4	37.75±7.14	39.0 [28.0-45.0]	p=0.334
Peripheral artery aneurysm				
Absent	142	34.11±10.32	33.0 [17.0-74.0]	Z=-0.027
Present	5	33.80±9.88	36.0 [23.0-47.0]	p=0.979

SD: standard deviation; BD: Behcet's disease; *In comparing two independent data groups with normal distribution, the independent samples t-test was applied (t-values); In comparing two independent data groups not showing normal distribution, the Mann-Whitney U test was employed (Z-values); Significant p values are written in bold.

gests that there could be a common etiology of vascular events (thrombus, stenosis, aneurysm).[8,9] The prevailing consensus is that coagulation irregularities do not play a role in thrombus formation in BD.[10] Due to the risk of aneurysm development within the procedural area, invasive vascular procedures are not favored for imaging in Behçet's patients.[11]

Doppler ultrasonography, contrast-enhanced CT scans, and MR angiography are the preferred noninvasive imaging methods. However, fluorodeoxyglucose (FDG)-PET-CT has recently been preferred for detecting large vessel vasculitides.[12]

In the current study, the development of a vascular event before having met the BD criteria was at a rate of 12.9%. Patients with deep vein thrombosis in the lower extremities were younger, while those with pulmonary artery involvement were generally older. Notably, nearly 10% of patients experience vascular events before meeting the criteria for a BD diagnosis, and approximately 75% of BD-diagnosed patients encounter a vascular event within the first five years of diagnosis.[13] In the initial years following disease onset, diagnoses of deep vein thrombosis in the lower extremity, pulmonary artery aneurysms, Budd-Chiari syndrome, or dural sinus thrombosis can

emerge. Diagnoses of vena cava thrombosis, abdominal aorta aneurysms, and peripheral artery aneurysms tend to occur at a later stage.[14,15]

The rate of vascular involvement in BD has been reported to range between 10% and 40%.[8, 13, 16] A study conducted in Iran encompassing 6,075 BD patients found a 9.1% prevalence of vascular involvement, distributed as 6.6% deep vein thrombosis, 2.3% superficial phlebitis, 0.2% arterial thrombosis, 0.5% aneurysm, and 1.2% large vein thrombosis.[17] Another study by Taşcilar et al. [13] reported a 14.7% rate of vascular involvement among 5,970 BD patients. Consistent with the literature, the rate of vascular involvement in the current series of BD patients was 25.0%.

Unlike other forms of vasculitis, various arteries and veins are affected in vascular BD, often presenting as arterial aneurysms and recurring inflammatory venous thrombi.[8] Veins are affected approximately 3-fold more than arteries. [10] In the current series, veins were affected 4.5-fold more than arteries (160 vs. 28), as shown in Table 3.

The most prevalent vascular manifestation is superficial thrombophlebitis, which can be challenging to differentiate from erythema nodosum.[10,17] It manifests with sensitive reddened nodules in regions following the venous pathways, bearing importance as indicators of other vascular lesions.[18] In the current series, the most common vascular involvements were deep vein thrombosis (69.4%) and superficial thrombophlebitis (12.9%). Correspondingly, Davatchi et al. [17] reported a 9.1% rate (n=553) of vascular involvement in 6,075 BD patients, with the most common forms being deep vein thrombosis (n=399, 72.2%) and superficial thrombophlebitis (n=140, 25.3%).Wu et al. [19] reported deep vein thrombosis as the dominant vascular involvement in BD patients at 83.9%, with superficial thrombophlebitis accounting for 4.3%.

Distinguishing between painful erythematous nodular lesions and superficial thrombophlebitis can be complex. Painful nodular swellings extending along a defined line over the vein are indicative of superficial thrombophlebitis. Discrepancies in reported rates of deep and superficial thrombophlebitis exist in the literature, potentially stemming from overlooked cases of superficial thrombophlebitis. Given the retrospective nature of the current study, some cases of superficial thrombophlebitis may have evaded detection.

Hepatic vein thrombosis, also known as Budd-Chiari syndrome, manifests with abdominal pain, ascites, and lower extremity edema. Acute liver failure can develop in these patients, leading to a high mortality rate.[20]

Arterial effects emerge at later stages of the disease. The arterial effect is more in the form of an aneurysm, occasionally presenting as thrombotic arterial occlusion. Notably, the differential diagnosis between Takayasu's arteritis and BD hinges on the distinctive feature of diffuse and homogenous thickening of the artery wall in Takayasu's arteritis. [13] Prognostically, arterial occlusion generally holds a more favorable outlook compared to aneurysms.[14]

Pulmonary involvement

Pulmonary artery involvement in BD occurs in less than 5% of cases, with a higher prevalence among males. Considering the anatomical and physiological attributes of the right atrium, ventricle, and pulmonary arteries, they can be regarded as an extension of the venous system. Pulmonary arteries differ from conventional arteries due to their relatively low pressure, limited elasticity, and thin walls.[13] These characteristics explain the relatively more frequent involvement of pulmonary arteries than other arteries in BD.[16] Patients often present with chest pain, shortness of breath, and hemoptysis, accompanied by radiologically evident bilateral hilar filling.[21] Pulmonary artery aneurysms are a common finding, and in certain cases, pulmonary artery thrombosis may also occur.[21-23] Hughes-Stovin syndrome, characterized by thrombophlebitis and multiple pulmonary aneurysms, carries a risk of fatal pulmonary hemorrhage.[24] With advances in imaging methods, the rate of detection of thrombus in patients with an aneurysm has increased.[21] In the present study, eight patients exhibited thrombi concomitant with aneurysms, while two patients displayed pulmonary artery aneurysms without thrombotic involvement. Approximately 70% of pulmonary artery lesions recover with immunosuppressive treatment, albeit with a mortality rate of approximately 25%.[21] In the current series, the rate of pulmonary artery involvement was 12.9%. Notably, patients undergoing immunosuppressive treatment did not experience any mortality.

Cardiac Involvement

Cardiac implications typically manifest as intracardiac thrombi, and it is crucial to consider the potential of accompanying pulmonary artery involvement.[25] Young males with pulmonary artery involvement are at risk of intracardiac thrombus.[26] The current study also identified a link between pulmonary artery involvement and the risk of intracardiac thrombosis. In addition, other cardiac manifestations may include endocarditis, myocarditis, pericarditis, coronary artery aneurysm, and valve failure.[16] In a series of 476 patients, coronary artery involvement was reported at approximately 4%.[27] Risk factors for affected coronary artery have been reported as male gender, skin lesions, positive pathergy test, and elevated sedimentation and CRP values.

Cerebral Sinus Thrombosis

Cerebral sinus thrombosis is usually seen in males and has a better prognosis compared to patients where the brain parenchyma is affected.[28] It is important to note that cerebral venous sinus thrombosis can be seen together with other vascular involvements and is seen in the relatively early stages of the disease. In the current series, there was an increased risk of thrombus in the jugular and subclavian veins in patients with cerebral sinus thrombosis.

Treatment Approach

The formation of a thrombus adhering to the vessel wall accompanying the inflammation is typical. When thrombosis occurs in BD, the primary treatment modality revolves around immunosuppressive therapy, while the effectiveness of anticoagulant medications has been demonstrated to be lacking.[29] Furthermore, anticoagulant therapy does not exhibit efficacy in preventing recurrence.[16,29] However, in cases of resistant thrombus, anticoagulants can be given in addition to immunosuppressive drugs,[30] although the presence of pulmonary artery aneurysm must be discounted as there is a risk of fatal hemorrhage in this method.[31]

For nonsurgical treatment of acute deep vein thrombosis, options include immunosuppressive drugs such as glucocorticoids, azathioprine, or cyclosporine A. In resistant cases and cases with large vein thrombosis, cyclophosphamide and tumor necrosis factor alpha inhibitors, such as infliximab, are selected.[32,33]

In pulmonary artery aneurysms, Budd-Chiari syndrome, or vena cava thrombosis, high-dose methylprednisolone pulses are administered, followed by oral glucocorticoids, cyclophosphamide, or anti-TNF drugs. Surgical endovascular interventions may be considered in Budd-Chiari syndrome or vena cava thrombosis. For pulmonary artery aneurysms with bleeding risk, embolization can be performed. Giant aneurysms might be addressed through lobectomy or segmentectomy. In cases of cerebral sinus thrombosis, lumboperitoneal shunts can be considered an alternative to medical treatment. For aortic aneurysms and peripheral artery aneurysms, medical treatment is the primary approach. If there is a life-threatening condition, endovascular or surgical treatment is applied in aortic aneurysms. Symptomatic patients with peripheral artery aneurysms undergo surgical or endovascular grafting.[34] For both aortic and peripheral artery aneurysms, either graft placement, ligation, or bypass surgery may be preferred. Since the risk of thrombosis is higher in venous grafts in patients with Behçet's syndrome, synthetic grafts are preferred.[35]

To reduce potential risks such as anastomotic leakage, occlusion, or pseudoaneurysm due to surgical interventions, immunosuppressive therapy should be continued in the postoperative period.[36]

Among the current series of patients, six individuals underwent aneurysm repair without encountering any complications during the follow-up periods.

Limitations of this study encompass its retrospective design and the potential for confusion with skin lesions, which impeded the comprehensive determination of superficial thrombophlebitis.

Conclusion

In conclusion, vascular involvement in BD is a significant cause of morbidity and mortality. In approximately half of BD patients with vascular involvement, the diagnosis of BD is made following a vascular event. It is imperative to consider a BD diagnosis, particularly when young male patients present with venous or arterial vascular events. Since the efficacy of anticoagulant treatment for thrombus in BD is controversial, the primary therapeutic approach remains centered on immunosuppressive medications.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Ankara Yıldırım Beyazıt University (No: 58, dated 26.05.2021).

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Conflict of Interest: None declared.

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