



# Characterization of Venous Involvement in Vasculo-Behçet Disease

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**Background:** Behçet disease is a chronic inflammatory disorder with a varying etiology. Herein, we report the involvement of peripheral veins in Behçet disease and discuss the treatment thereof.

**Methods:** Thirty-four patients with venous involvement in vasculo-Behçet disease were retrospectively analyzed over 15 years. We reviewed the clinical manifestations, treatment choices, and complications of these patients.

**Results:** Deep vein thrombosis (DVT) was observed in 24 patients (70.59%) and varicose veins in 19 (52.94%). Immunosuppressive treatment was administered to all patients due to the pathological feature of vein wall inflammation. In patients with DVT, anticoagulation therapy was also used, but post-thrombotic syndrome was observed in all patients along with chronic luminal changes. Eleven patients with isolated varicose veins underwent surgery; although symptoms and lesions recurred in half of these patients, no cases of secondary DVT occurred.

**Conclusion:** When DVT was diagnosed in patients with Behçet disease, there was no cure for the lesions. Ultrasonographic abnormalities were observed in all patients, and post-thrombotic syndrome remained to varying degrees. In cases of isolated varicose veins in patients with Behçet disease, DVT did not occur after surgical treatment. If the activity of Behçet disease is controlled, surgical correction of varicose veins is preferable.

**Keywords:** Behcet syndrome, Venous thrombosis, Thrombophlebitis

## Introduction

Behçet disease is a rare, chronic inflammatory disorder characterized by the triad of oral ulcers, genital ulcers, and ocular inflammation. In addition to its principal clinical symptoms, Behçet disease can clinically manifest in many other major organ systems, such as the vascular, gastrointestinal, and musculoskeletal systems [1].

Behçet disease is most prevalent in regions ranging from the Mediterranean to East Asia, following the Silk Road, an ancient trade route. Outside of this area, however, the prevalence of this uncommon disease varies enormously. For example, there are between 20 and 420 cases per 100,000 population in Turkey and 0.64 cases per 100,000 population in the United Kingdom [2-5]. In Korea, the

prevalence is 32.8–35.7 per 100,000 population [6]. In Behçet disease, vascular lesions can involve both arteries and veins, as seen in 14%–39% of patients with this condition. However, most lesions occur in veins [7-9]. In some cases, venous insufficiency or DVT is diagnosed as the first symptom of Behçet disease [10].

In this study, we report the outcomes of vasculo-Behçet disease involving peripheral veins from a single center for 15 years. This case series included patients with varicose veins, deep vein thrombosis (DVT), and thrombophlebitis.

## Methods

We retrospectively reviewed 34 patients diagnosed with Behçet disease who were treated at the Peripheral Vascular



**Table 1.** Manifestations of Behçet disease with accompanying venous involvement

Manifestations	No. (%)
Oral ulcers	33 (97.06)
Genital ulcers	15 (44.12)
Uveitis	4 (11.76)
Arterial involvement	6 (17.65)
Gastrointestinal involvement	3 (8.82)
Arthritis	11 (32.35)

Disease Center of Pusan National University Hospital between 2004 and 2019. The time of diagnosis varied, and this group of patients included those who received treatment for venous manifestations. The patients included 17 men and 17 women. The mean age of the patients at the time of the diagnosis of venous lesions was 51.41±12.48 years, and their average follow-up duration was 130.67±68.90 months.

Five patients were first diagnosed with DVT, and Behçet disease was diagnosed during anticoagulation treatment, while 2 patients were diagnosed with Behçet disease following relapse after DVT treatment. The remaining 27 patients had already been diagnosed with Behçet disease by a rheumatologist, and venous manifestations of the disease were observed during treatment.

DVT was diagnosed by computed tomography (CT) venography and/or compression ultrasonography. In addition, CT scans for pulmonary thromboembolism were performed in all cases when DVT was diagnosed.

In the case of venous insufficiency, the superficial vein, deep vein, and perforator vein were evaluated and diagnosed through color flow Doppler ultrasonography. Treatment was determined after consultation with rheumatologists according to the degree of reflux and the severity of the accompanying venous manifestations.

We collected data on the manifestations of Behçet disease in these patients, which included the diagnosis of venous lesions, the anatomical location of the lesions, the Clinical-Etiological-Anatomical-Pathological (CEAP) classification [11], the venous clinical severity score (VCSS), treatment progress, any complications, and death.

Adverse outcomes included recurrent symptoms, DVT relapse, post-thrombotic syndrome, and new venous reflux. Diagnosis was made through clinical manifestations, ultrasound examinations, and/or CT examinations in the same way as the initial diagnoses at regular follow-up visits. Venous thrombosis recurrence was defined as progression in the extent of thrombosis or new thrombotic events.

Venous manifestations were classified using the CEAP

**Table 2.** Diagnoses of venous diseases in Behçet disease patients

Diagnosis	No. (%)
VV only	8 (23.53)
DVT only	13 (38.24)
TP only	1 (2.94)
VV+DVT	9 (26.47)
VV+TP	1 (2.94)
DVT+TP	1 (2.94)
VV+DVT+TP	1 (2.94)
Total	34 (100)

VV, varicose veins; DVT, deep vein thrombosis; TP, thrombophlebitis.

system [11]. The severity of venous manifestations was recorded by assigning a score of 0–3 points for each item, depending on the presence of pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, venous ulcer size, number, duration, or whether compression therapy was performed [12].

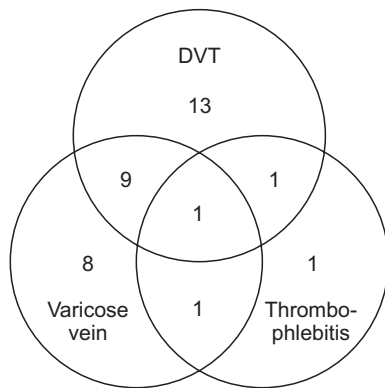
All procedures were performed in accordance with the Declaration of Helsinki and the ethical standards of the Institutional Review Board of Pusan National University Hospital. This study was approved by the Institutional Review Board of Pusan National University Hospital (IRB approval no., H-2004-037-090). The requirement for informed consent from individual patients was omitted because of the retrospective design of this study. MedCalc ver. 18.0 (MedCalc Software bv, Ostend, Belgium) was used for descriptive and statistical analyses, including calculation of the mean, standard deviation, and percentages.

## Results

### Presentation of venous disease and Behçet disease

Table 1 shows the clinical symptoms of Behçet disease accompanied by venous disease. For example, venous disease was observed to be accompanied by oral ulcer(s) in 97.06% of patients and arterial lesions in 17.65% of patients. The diagnoses of venous diseases are reported in Table 2 and Fig. 1. Varicose veins were observed in 19 patients (52.94%), DVT in 24 patients (70.59%), and thrombophlebitis in 1 patient (2.94%). Furthermore, 10 patients (29.41%) had DVT and venous reflux.

Among the 24 patients with DVT, the locations of the lesions and frequency of thrombosis are presented in Table 3. Femoro-popliteal lesions were the most common, as they were experienced by 9 patients (37.5%), and 3 cases (12.5%) were associated with the inferior vena cava.



**Fig. 1.** Venn diagram of venous diseases. DVT, deep vein thrombosis.

**Table 3.** Different locations of deep vein thrombosis in patients with Behçet disease

Locations of the lesions	No. of patients
Popliteal vein	2
Femoral vein	4
Femoro-popliteal vein	9
Ilio-popliteal vein	4
Ilio-femoral vein	1
IVC-femoral vein	2
Renal-IVC-femoral vein	1
Portal vein	1
Total	24

IVC, inferior vena cava.

### Clinical-Etiological-Anatomical-Pathological classification

Table 4 presents the CEAP classification of Behçet patients (n=33, excluding portal vein thrombosis) with involvement of veins of the lower extremities. Of the classic clinical manifestations, C3 (edema) was observed in most patients, and active ulcerative lesions (C6) were also found in 2 cases. In terms of etiological classification, primary varicose veins, DVT, and thrombophlebitis were observed in 31 patients (93.94%). In 11 (33.33%) of the cases we reviewed, both varicose veins and DVT were present. However, these figures only reflect clinical estimates as to which lesions came first. Upon classifying the lesions anatomically, superficial vein lesions were observed in 60.60% of patients, whereas deep vein lesions were observed in 78.79%. In the clinical, etiological, and pathological classification, all lesions observed in the lower extremities were counted. In the pathological classification, reflux alone was observed in 10 patients (30.30%), obstruction in 12 patients

**Table 4.** Clinical-Etiological-Anatomical-Pathological classification

Clinical symptom	No. (%)
C1: Telangiectasias or reticular veins	9 (27.3)
C2: Varicose veins	9 (27.3)
C3: Edema	24 (72.7)
C4a: Pigmentation or eczema	6 (18.2)
C4b: Lipodermatosclerosis or atrophie blanche	2 (6.1)
C5: Healed venous ulcer	2 (6.1)
C6: Active venous ulcer	2 (6.1)

**Table 5.** Drugs used in the treatment of vasculo-Behçet disease

Drug type	No. of patients
Immunosuppressant	10
Immunosuppressant+anticoagulation	23
Immunosuppressant+antiplatelet	1
Total	34

Anticoagulant: warfarin (19), novel oral anticoagulant (4); antiplatelet agent: aspirin (1); and immunosuppressant: prednisolone (27), colchicine (27), cyclophosphamide (3), azathioprine (12), and methotrexate (2).

(36.36%), and both reflux and obstruction in 11 patients (33.33%). Thrombophlebitis was classified as an obstruction. The average VCSS was  $2.69 \pm 2.58$ , on a scale of 0–30.

### Therapeutic interventions

The drugs used for medical treatment are listed in Table 5. The drugs were prednisolone (27), colchicine (27), cyclophosphamide (3), azathioprine (12), and methotrexate (2). All patients received an immunosuppressive agent. Twenty-three were administered anticoagulants, 19 of them received warfarin, and 4 received novel oral anticoagulants (NOAC). Three of the patients who received NOAC were administered rivaroxaban, and 1 received apixaban. One patient with DVT was treated with immunosuppressant and antiplatelet agents without anticoagulants after consultation with a rheumatologist.

Anticoagulants were taken for an average of  $90.92 \pm 87.58$  months (range, 2–64 months) in 24 patients with DVT. Patients who were diagnosed with Behçet disease before being diagnosed with DVT (19 cases) or who were diagnosed with Behçet disease during the first 6 months of anticoagulant therapy (3 cases) continued to take anticoagulants. In 2 patients, anticoagulation treatment was performed for 6 months by extending the basic 3-month anticoagulation therapy [13] and discontinued because they were not diagnosed with Behçet disease at the time of treatment with DVT. Anticoagulant therapy was then resumed later fol-

**Table 6.** Leg symptoms of post-thrombotic syndrome after venous thrombosis (n=23)

Manifestations	No. (%)
Heaviness or fatigue	23 (100)
Pain	21 (91.3)
Swelling	12 (52.1)
Itching	10 (43.5)
Cramps	12 (52.1)
Paresthesia	5 (21.7)
Bursting sensation	8 (34.8)

lowing recurrence and continued. There were no major bleeding events or death associated with anticoagulation treatment.

Surgery was performed to treat varicose veins in 11 patients without clinically significant DVT. The surgical site was determined according to the vein in which regurgitation had been confirmed, and all operations were performed by high ligation and/or stripping and stab avulsion. There were no reports of reoperations. However, in 6 of the 11 patients, deep vein reflux or perforating vein reflux either recurred or persisted, or reflux was newly observed in other superficial veins. In these cases, conservative management using medication and compressive treatment were performed. Notably, none of these 11 patients developed secondary DVT after surgery.

### Adverse outcomes

Follow-up ultrasonography of 24 patients with DVT showed chronic luminal changes, including cord-like changes, partial compression, and increased wall thickness in all patients. No patient showed complete resolution of the lesions. In addition to this, despite persistent medication, post-thrombotic syndrome was observed in all patients to varying degrees. The leg symptoms of post-thrombotic syndrome are described in Table 6. In many cases, multiple symptoms appeared in a single patient. The symptoms worsened when patients were active, walking, and standing, and improved when resting or lying down.

### Death

Three patients died. The cause of death in the first patient was repetitive femoral artery pseudoaneurysm rupture, and the cause of death in the second patient was repetitive supra-renal aortic aneurysm rupture. However, the cause of death in the third patient was unknown.

## Discussion

This study presents our experiences of treating 34 Behçet disease patients with venous involvement in the setting of vascular surgery. All patients received immunosuppressant medication following consultation with a rheumatologist.

Eleven patients underwent surgical treatment for varicose veins. No reoperations were performed, but recurrence and new lesions were observed in 54.5% of cases. There was no case of DVT after operations for varicose veins.

Among 24 patients with DVT, the most common lesions were femoro-popliteal, including 1 patient with portal vein thrombosis. Most of these patients received continuous anticoagulant therapy, and only 1 patient was administered an antiplatelet drug. All patients with DVT showed post-thrombotic syndrome with chronic luminal changes despite continuing medication. In addition, 11 patients (45.8%) were observed to have DVT and varicose veins simultaneously at the time of diagnosis, but the events preceding this were difficult to ascertain. Clinical progress was poor in patients with mixed lesions, and despite treatment, 3 patients had clinical lesions of C4 or higher.

The form of Behçet disease in which inflammatory cells invade blood vessels of all sizes is called vasculo-Behçet disease [14]. Vasculo-Behçet disease mostly displays venous involvement. Thrombosis of the veins of the lower extremities is the most common manifestation, although all the classic clinical manifestations of the venous disease can be seen [2,3,7].

The main pathogenesis of DVT caused by Behçet disease is inflammation that affects the venous wall, rather than a procoagulant condition of the blood [14,15]. DVT is widely known to occur in the early stages of Behçet disease (usually within a few years), and frequently occurs in the femoral and popliteal veins. Despite treatment, changes due to inflammation, such as shrinkage and cord-like alterations to the venous wall, eventually result in post-thrombotic syndrome and venous ulcers, including repeated leg edema, which is reported in more than 50% of cases [16].

An immunosuppressive agent is the treatment of choice due to the inflammatory pathogenesis of DVT seen in vasculo-Behçet disease [17]. The regulation of DVT is known to be associated with the course of the systemic disease itself [10]. Some investigators have suggested that anticoagulant therapy may be useful in preventing late recurrence of DVT. It has been reported that thrombosis in Behçet disease might be affected by reduced levels of anticoagulants or abnormal procoagulant activities [14,18]. Therefore, we

used additional anticoagulants at our center. However, it is unclear how this affected the course of DVT in comparison to the use of only an immunosuppressive agent.

Behçet disease with isolated varicose veins has been reported in a very small number of patients, and it remains unclear whether varicose veins in such patients are in fact related to Behçet disease. If isolated varicose veins are observed in patients with Behçet disease, the effectiveness of radical surgery is limited due to its pathology. This condition also shows a very high recurrence rate after surgery, so the choice of treatment—conservative management or primary surgery—remains controversial [10]. Furthermore, due to the low prevalence and locally specific characteristics of Behçet disease, there is no standard guideline for treatment. Recently, a study reported high morbidity due to the occurrence of venous thromboembolism when surgery was not performed on isolated varicose veins in patients with Behçet disease [19].

Likewise, no standard guideline for prevention or management exists for varicose veins in patients with Behçet disease. However, it is known that isolated varicose veins without surgical treatment can lead to venous thrombosis [10,19]. Surgery on varicose veins normalizes venous blood flow to some extent, reducing the incidence of venous thrombosis. If the patient's disease activity is controlled following consultations with a rheumatologist, surgery for varicose veins may help to improve the patient's symptoms and to reduce the occurrence of DVT [10,20].

In conclusion, this clinical report of venous involvement observed in Behçet disease was conducted through a retrospective review of cases treated at a single tertiary referral hospital. For Behçet disease patients with DVT, it can be concluded that it is difficult to find a distinct effect on the lesions despite both immunosuppressive therapy and anticoagulation therapy because ultrasonographic abnormalities were observed in all patients and various degrees of post-thrombotic syndrome persisted. Additionally, in Behçet disease patients with varicose veins, DVT did not occur after surgical treatment.

Therefore, in Behçet disease patients with DVT, regular follow-up and close observation along with intensive medical treatment are required. If the activity of Behçet's disease is being regulated, it is preferable to perform surgical correction of the varicose veins without fear of complications to prevent DVT.

## Conflict of interest

No potential conflict of interest relevant to this article

was reported.

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