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【 CASE REPORT 】

Glucocorticoid in Combination with a TNF-α Inhibitor: Treatment of Deep Vein Thrombosis in a Patient with Behçet's Disease

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Abstract:
A 38-year-old man with deep vein thrombosis associated with Behçet's disease (BD) was admitted to our hospital due to worsening symptoms despite the initiation of direct oral anticoagulants (DOACs). Administration of oral prednisolone and an intravenous anti-tumor necrosis factor-alpha (TNF-α) monoclonal antibody dramatically improved his symptoms. In addition, he was incidentally diagnosed with autosomal dominant polycystic kidney disease, which increases the risk of aortic aneurysms. BD also increases the risk of aortic aneurysms. This case suggests that immunosuppressive treatment is effective in patients with inflammation-related DOAC-refractory venous thrombosis who also suffer from BD.

Key words: Behçet's disease, deep vein thrombosis, anti-tumor necrosis factor-alpha monoclonal antibody, immunosuppressive treatment

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Introduction

Behçet's disease (BD) is a multisystemic inflammatory disorder characterized by recurrent oral aphthae, genital ulcers, ocular manifestations, and skin lesions (1). Vascular involvement is observed in up to 40% of patients (2). Venous involvement, including deep vein thrombosis (DVT), is more common than arterial involvement.

Systemic inflammation resulting in vascular endothelial injury is recognized as the cause of DVT in patients with BD. Therefore, immunosuppressants are key to the successful treatment of inflammation-related thrombosis in patients with BD. However, the use of anticoagulant therapy in such cases, including direct oral anticoagulants (DOACs), remains controversial (3). The efficacy of combination therapy with immunosuppressants and anticoagulants compared to immunosuppressants alone is not proven. In addition, BD increases the risk of an arterial aneurysm as the cause of bleeding.

We herein report a case of DVT with underlying BD that was successfully treated with the administration of prednisolone and an anti-tumor necrosis factor-alpha (TNF-α) monoclonal antibody in addition to anticoagulation therapy.

Case Report

A 38-year-old man presented to our hospital with worsening left leg pain and swelling, typical symptoms of DVT, despite being on oral anticoagulants. According to the Japanese diagnostic criteria, the patient had a 12-year medical history of incomplete-type BD, which was diagnosed based on uveitis, oral aphthae, and genital ulcers. Once colchicine treatment was initiated, the oral aphthae and genital ulcers rapidly improved, without recurrence. Owing to relapsing uveitis, colchicine was replaced with cyclosporine.

Six months before the current presentation, cyclosporine was discontinued due to a worsening renal function. Since

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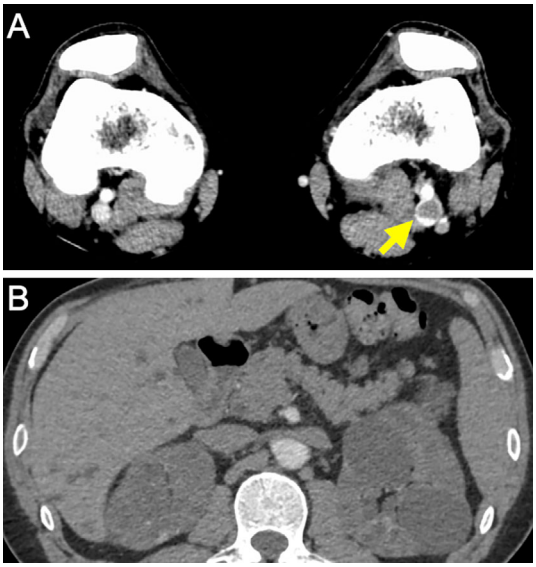

Figure 1. Contrast-enhanced computed tomography on admission revealed a thrombus extending from the left saphenous femoral vein to the popliteal vein (A, arrow) and multiple cysts in the kidney and liver (B).

then, the uveitis had frequently flared up but been managed with the injection of triamcinolone acetonide into the periocular space. Due to this recalcitrant intraocular inflammation, administration of a TNF-α monoclonal antibody was considered a viable treatment modality.

Three weeks prior to admission, he presented with pain and swelling in his left leg. Two weeks before admission, he had been diagnosed with acute proximal DVT in the left leg following venous ultrasonography, and rivaroxaban (30 mg/day) therapy had been initiated at another hospital. However, his symptoms worsened, and subsequently, venous ultrasonography revealed an extended thrombus in his left leg and a new lesion in his right leg. At the same time, he experienced pain, redness, and floaters in his left eye, symptoms similar to those experienced during his past flare-ups of uveitis. He was therefore admitted to our hospital for a further examination and treatment.

On admission, a clinical evaluation revealed swelling and tenderness in his left lower limb, accompanied by superficial thrombophlebitis, which was classified as a skin lesion as per the Japanese Behçet's criteria. Oral or genital ulcers were not observed. On an ophthalmologic examination, the eyes presented with panuveitis: inflammatory signs were observed in the anterior chamber, vitreous cavity, and retina. He had no common risk factors for DVT, such as immobility or obesity (body mass index, 21.2 kg/m^2). The laboratory results were as follows: C-reactive protein level, 0.44 mg/dL; erythrocyte sedimentation rate, 14 mm/h; D-dimer, 1.1 μg/mL; and serum creatinine level, 1.2 mg/dL. The levels of antithrombin, protein S, protein C, antiphospholipid antibodies, and lupus anticoagulants were normal. We did not examine his human leukocyte antigen typing.

Contrast-enhanced computed tomography (CT) revealed a thrombus extending from the left saphenous femoral vein to the popliteal vein without defects in the pulmonary arteries (Fig. 1A). In addition, multiple hepatic and renal cysts were observed (Fig. 1B). Venous Doppler ultrasonography of the left femoral vein revealed that the thrombus was attached to the venous wall and partially organized, with a defect in the blood flow signal (Fig. 2).

The patient's father required hemodialysis due to chronic kidney disease, the etiology of which was unknown. In addition, his father's sister and brother suffered from subarachnoid hemorrhaging. Based on the presence of multiple renal and hepatic cysts, his family history, and his mildly elevated serum creatinine level, autosomal dominant polycystic kidney disease (ADPKD) was suspected as a comorbidity. Considering the risk of an aortic aneurysm as a complication of both BD and ADPKD, we performed CT angiography of the arteries and brain magnetic resonance angiography. After excluding aneurysms, especially those in the pulmonary and cerebral arteries, we decided to continue anticoagulation therapy.

We diagnosed him with inflammation-related thrombosis due to vascular involvement owing to BD based on the clinical course of anticoagulant-refractory DVT and exacerbated BD. On the day of admission, oral prednisolone (0.5 mg/kg/day) was added to the ongoing treatment with rivaroxaban (30 mg/day), which dramatically relieved the pain and swelling in his left leg. His levels of D-dimer and inflammatory markers were within the normal range. The uveitis also responded well to local triamcinolone acetonide injection. On the seventh day, venous ultrasonography revealed minimal recanalization of the left saphenous femoral vein. He was discharged after intravenous administration of infliximab, a TNF-α monoclonal antibody, to prevent relapse of uveitis and was prescribed rivaroxaban (15 mg/day) and prednisolone (35 mg/day). The prednisolone dose was gradually tapered and discontinued. Three months later, the superficial thrombophlebitis disappeared without recurrence of pedal edema or uveitis.

Follow-up contrast-enhanced CT revealed reduction in the DVT and no pulmonary embolization. Thus, rivaroxaban treatment was discontinued. Six months later, the DVT improved further, with no episodes suggestive of a relapse of BD under continued treatment with a TNF-α inhibitor.

Discussion

We herein report a favorable response to a glucocorticoid combined with TNF-α inhibitor administration as treatment for DVT in a patient with BD refractory to anticoagulants. Venous thrombosis, particularly DVT in the lower extremities, is the most common vascular complication of BD. However, there are multiple common etiologies of DVT, such as immobility, surgery, obesity, and malignancy (4). DVT associated with inflammation should be distinguished from other conditions because the treatment strategies differ significantly. Inflammation-related DVT due to BD fre-

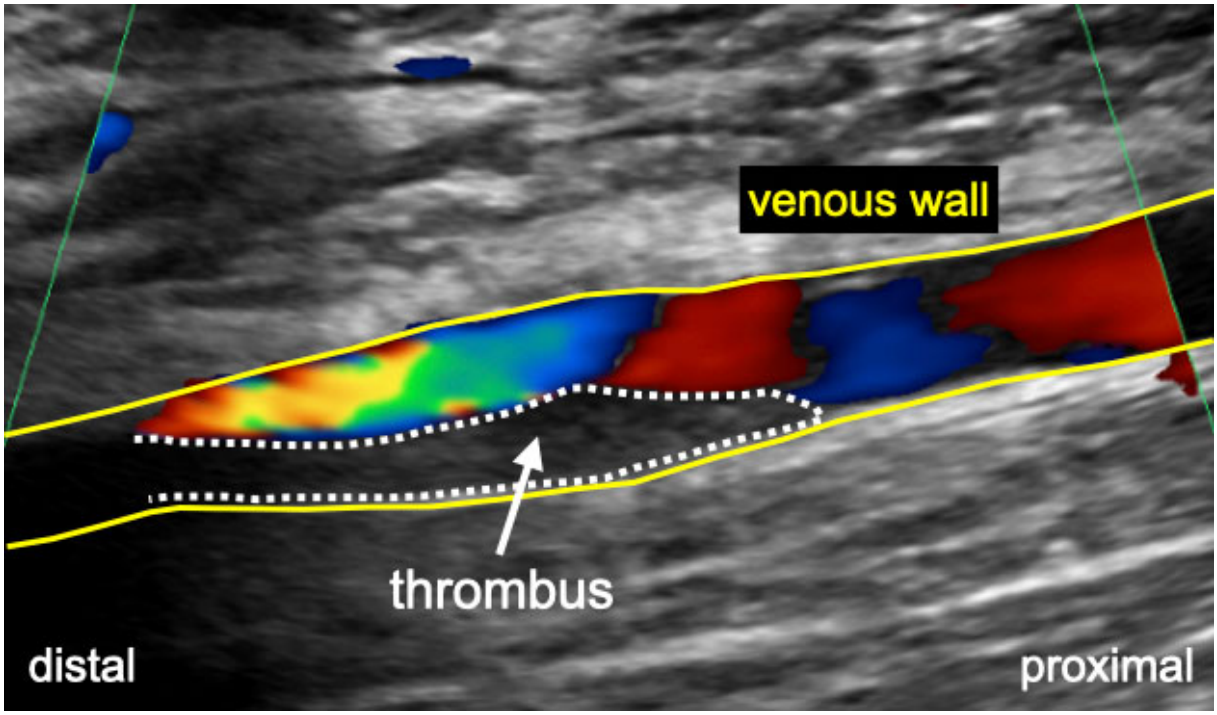

Figure 2. **Venous Doppler ultrasonography of the left femoral vein revealed that the thrombus was attached to the venous wall, with a defect in the blood flow signal.**

quently develops in the popliteal veins during episodes of elevated disease activity and occurs predominantly in men, which matches our findings (5). Venous ultrasonography revealed that the thrombus was adherent to the vessel wall, indicating vascular inflammation (6). Although a previous study showed that venous vessel wall thickness was correlated with the risk of vascular involvement (7), thickening of the venous wall was not detected in this case. In addition, the clinical course of worsening DVT despite the anticoagulant therapy strongly supported the diagnosis of inflammation-related DVT in the background of BD.

The management of DVT in BD mainly consists of immunosuppressive agents since venous thrombosis in BD is believed to result from endothelial inflammation (8, 9). Although glucocorticoids, TNF-α inhibitors, azathioprine, cyclophosphamide, and cyclosporine are recommended for thrombosis in BD, there are no guides on choosing the agents (3). The choice instead depends on patient factors, such as the risk of infection and tolerability. Combination therapy with glucocorticoids and other immunosuppressants is usually chosen for BD cases with systemic and high disease activity that require rapid suppression of inflammation. In the present case, we initiated glucocorticoid therapy combined with a TNF-α inhibitor for acute worsened DVT and attacks of relapsing uveitis. However, no studies have previously reported a beneficial effect due to the use of additional anticoagulants (10-12). Currently, DOACs are being used increasingly frequently in the treatment of DVT. However, previous studies have mainly included patients who received vitamin K antagonists. There are few case reports and clinical studies on the efficacy of DOACs in patients with DVT associated with BD (13). Therefore, the present case of DOAC-refractory DVT in BD is worth reporting.

Furthermore, anticoagulant therapy requires a careful evaluation of bleeding risks and events. In patients with BD, evaluating the presence of a pulmonary artery aneurysm is especially important because of its potentially fatal complications (14). In our case, the patient was incidentally diagnosed with ADPKD, which further increases the risk of aortic aneurysms. To our knowledge, this is the first reported case of BD with ADPKD. However, the underlying mechanism of aneurysms in these pathologies is a matter of debate.

In conclusion, inflammation-related thrombosis should be considered in patients with anticoagulation-refractory DVT. Immunosuppressive therapy is the preferred treatment for venous thrombosis associated with BD. The bleeding risk, including the risk of aneurysms, should be evaluated when administering anticoagulant therapy in such cases.

Written informed consent was obtained from the patient.

The authors state that they have no Conflict of Interest (COI).

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