Abstract

Behçet’s disease (BD) is a chronic relapsing systemic vasculitis in which orogenital ulceration is a prominent feature. The disease affects many systems and causes hypercoagulability. We present a 27-year-old male patient who exhibited widespread great vessel thrombosis including right atrial and ventricular thrombi in the setting of right-sided infectious endocarditis and orogenital aphthous ulcerations and erythema nodosum due to BD. We reviewed the enigmatic prothrombotic state of BD, and discuss our prior experiences in this field. (Internal Medicine 40: 68-72, 2001)

Key words: Behçet’s disease, cardiac involvement, vascular involvement, interferon treatment

Introduction

Behçet’s disease (BD) is a multisystemic disorder initially described by orogenital ulceration and ocular inflammation (1). In addition to this classical triad, the disease involves many systems including vascular, cardiac, neurologic or gastrointestinal systems (2, 3). We herein present a young patient who exhibited extensive great vessel thrombosis. The patient also had infectious endocarditis of the right side of the heart with right atrial and ventricular thrombi, which is very rare in BD. In the setting of widespread vascular and cardiac thrombosis, our patient had the history of recurrent oral ulcerations and erythema nodosum. Shortly after admission, genital ulceration also appeared. The patient was diagnosed as having BD according to the published universal criteria (4). Severe, aggressive, life-threatening status of the patient was resolved with therapy directed against BD given as interferon alpha-2b (α-IFN). We describe this unique case and also review the enigmatic prothrombotic state of BD based on our previous experiences in this specific field.

Case Report

A 27-year-old male patient was referred to our tertiary center because of fever and infective endocarditis. He was first admitted to another hospital one year earlier because of fever unknown origin, that was present for 3 months, together with chest pain and hemoptysis. Before that period, he had a history of oral aphthous lesions, which occurred more than three times a year in the previous 2 years, and one bout of erythema nodosum. Echocardiography revealed an intracardiac mass on the right side of the interventricular septum. Due to lack of improvement in his condition and repeated pulmonary thromboembolic events under antibiotic treatment, he underwent the cardiac surgery (thrombectomy) in that center. Although all of the blood and surgical specimen cultures were negative, pathologic examination of the surgical specimen was consistent with infective endocarditis. Fever persisted until the 4th postoperative day. Antibiotic therapy was continued for 21 days after the operation. During that hospitalization period, the patient experienced pain and pallor of the right arm and doppler ultrasonography revealed thrombus in right axillary vein. After intravenous streptokinase therapy, the patient was discharged with warfarin therapy. Two weeks later, he was admitted to another hospital because of dyspnea and swelling of both arms. He was diagnosed as having superior vena cava syndrome (SVC) and was treated with tissue plasminogen activator and intravenous heparin. After being discharged he was free of fever for two months. After this period, he had fever and he was hospitalized again. Abdominal USG revealed splenomegaly and echocardiography revealed a thrombus in the right ventricle. Teikoplanin and amikacin therapy were instituted. For the confirmation of this finding, transesophageal echocardiography (TEE) was performed and a thrombus along the SVC to the right atrium, a vegetation or thrombus on the tricuspid valve and two echogenic masses suggesting thrombosis in the right ventricle were demonstrated. Due to persisting fever he was referred to our medical center. At this time he was taking imipenem, rifampin and warfarin. On physical examination, his blood pressure was 130/70 mmHg, pulse; 100/min., body temperature; 38°C, respiratory rate; 22/min, and the following were noted: aphthous ulcerations in the oral cavity, a 1-2/6
holosystolic murmur at the apex of the heart, slight hepatomegaly and the traube was closed.

During the subsequent days genital ulcers appeared. The ophthalmologic examination was normal. Urinalysis, renal and liver function test results were normal. The white blood cell count was $8.8 \times 10^6/\mu l$, the hematocrit value was 29.9%, the erythrocyte sedimentation rate was 92 mm/h. C-reactive protein was positive. Antibodies to nuclear antigens and neutrophils were not detected. C3 and C4 levels were 126 mg/dl and 27.5 mg/dl, respectively. Testing for primary causes of hypercoagulability, including antiphospholipid antibodies, protein C and S deficiency, and antithrombin III deficiency, yielded negative results. Factor V Leiden and homocystinuria were not detected. HLA typing assay revealed the presence of A2, B51 (5, W4), B38 (16, W6) antigens. The bone marrow aspiration and biopsy were found to be normal. In one blood culture, methicillin-resistant *Staphylococcus aureus* was isolated. Abdominal ultrasonography revealed splenomegaly.

TEE revealed organised thrombus in the SVC and the right atrium, thickening of the interventricular and the interatrial septa, and an echogenic mass extending from the interventricular septum to the apex in the right ventricle. In addition these thrombi, doppler USG demonstrated thrombus in the superior vena cava, both subclavian veins, the left and right deep femoral and the external iliac veins and at the 2/3 proximal side of the right superficial femoral vein.

The patient was diagnosed as having infectious endocarditis and BD. Cardiovascular surgeons decided to follow the patient with only medical treatment due to the high risk of mortality and morbidity of a surgical procedure. Treatment was teikoplanin and rifampisin for infective endocarditis, and colchicine, interferon, pentoxifylline and warfarin sodium for BD

| Table 1. Clinical Chart of the Patient with Reference to the Diagnosis and Management of the Vascular Events and Behçet’s Disease |
|-----------------|-----------------|-----------------|-----------------|
| **Date** | **Symptoms and signs** | **Ultrasonographic findings** | **Therapeutic approach** |
| **April, 1998** | Fever for three months, Chest Pain, Hemoptysis | Intracardiac mass on the right side of the interventricular septum | Cardiac surgery (thrombectomy), anticoagulation, antibiotics |
| **May, 1998** | Pain and pallor of the right arm | Thrombus in the right axillary vein | Thrombolytic therapy with streptokinase and anticoagulation |
| **July, 1998** | Dyspnea and swelling of both arms (superior vena cava syndrome) | | Thrombolytic therapy with tPA (tissue plasminogen activator) and anticoagulation |
| **November, 1998** | Fever | Splenomegaly and thrombus along the superior vena cava to the right atrium, a vegetation or thrombus on the tricuspid valve and two echogenic masses suggesting thrombosis in the right ventricle | Antibiotics, anticoagulation |
| **February, 1999** | Fever, scrotal and oral aphthous ulcerations | Thromboses in the superior vena cava, both subclavian veins, both deep femoral and external iliac veins, and right superficial femoral vein. Organised thrombus in the right atrium, thickening of the interventricular and the interatrial septa, and an echogenic mass extending from the interventricular septum to the apex in the right ventricle. | Interferon, colchicine pentoxifylline, antibiotics, and anticoagulation |
| **May, 1999** | No symptoms | No thrombus, only organised nodular view on the tricuspid leaflet | Interferon, colchicine pentoxifylline, and anticoagulation |
and its vascular involvement. After 2 weeks, his fever was under control and antibiotic treatment was continued for 6 weeks. After this period the patient was discharged. One month later, at the follow-up visit, he was feeling very well. At control echocardiography there was only organised nodular view on his tricuspid leaflet. No thrombus could be demonstrated. Clinical and important laboratory data of the patient are summarized in Table 1.

Discussion

BD has been known since Hulusi Behçet, a Turkish dermatologist, described the triple-symptom complex of recurrent orogenital aphthous ulcerations and relapsing iritis with hypopyon (1). The clinical spectrum of this unique disease has subsequently been expanded. However, the underlying pathophysiological event(s) has not been precisely identified. Immunogenetic predisposition or defect due to some external factors such as environment, climate, viral and bacterial agents has been thought to play role in BD and the therapeutic modalities used in BD have been based on the data obtained from the studies investigating these etiological factors (2, 3, 5–7). The main pathological defect defined in BD is vasculitis, and involvement of the vascular system may explain how BD may affect many systems (5). Five different sets of diagnostic criteria were used until 1990 because of the clinical heterogeneity of BD and lack of diagnostic laboratory or clinical tests. In that year, the International Study Group for BD (ISG) published universal criteria which require the presence of recurrent oral ulceration plus any 2 of the following findings; recurrent genit- al ulceration, eye lesion, skin lesions (erythema nodosum, folliculitis, pustules), or a positive pathergy test (4).

Vascular involvement is very important in BD, since it is one of the major causes influencing the clinical course of the disease, by causing serious complications and death. It is mostly observed as superficial thrombophlebitis and large vein thrombosis (e.g., superior and inferior vena cava, hepatic veins), venous collateralization, arterial aneurysm and occlusion, and its frequency ranges from 8% to 38% (8, 9). In many series, deep venous thrombosis of the lower extremity is the most frequently observed clinical finding in BD, followed by superior and inferior vena cava thrombosis (9). Histological findings in venous and arterial lesions include perivascular lymphocytic and plasma cell infiltrates, swelling and proliferation of endothelial cells, disruption of elastic laminae, degeneration of the tunica media, and vasculitis of small vessels in the vasa vasorum. On the other hand, hyperthrombotic/prethrombotic state of BD is suggested. Although the precise pathogenic mechanisms underlying the thrombotic tendency in BD is not known; vasculitic endothelial cell injury and/or dysfunction with hypofibrinolysis have been argued to play crucial roles (10, 11). We have previously reported an increase in soluble thrombomodulin (TM), which is a cell surface glycoprotein and reflects endothelial injury (12, 13). Arachidonic acid metabolism in the endothelium and platelets is also involved in the process of hemostasis and thrombosis. Stimulation of both cell types results in the formation of eicosanoid derivatives, such as thromboxane B2 (TXB2) and 6-keto prostaglandin Flα (PGF1α). We also reported elevated TXB2 and PGF1α levels in BD, representing activation of both proaggregant and protective antiaggregant pathways, respectively (14). Moreover, we found that in vivo molecular markers of hemostasis (thrombin-antithrombin III complex (TAT), prothrombin fragments 1+2 (PF 1.2) and plasmin-α,-antiplasmin complex) are elevated in BD before any clinically observed thrombosis (15). Finally, we applied a dynamic study to the patients with BD to explore TM, TXB2, PGF1α, fibrinolysis activators and inhibitors and in vivo hemostatic marker concentrations before and after desmopressin acetate (DDAVP) infusion. As a result of this study, we have suggested: a) basal TM concentrations are increased and could not be provoked further by DDAVP infusion, b) both TXB2 and PGF1α increments occur concurrently, c) in vivo coagulation markers, TAT and PF1+2, are elevated and the increased PAP complex levels indicate a subclinical concomitant fibrinolysis, and d) the fibrinolytic process operates in a somewhat complex manner in which plasminogen activator binding kinetics may also be altered (16). Although several studies have indicated hypofibrinolysis in BD, there is no consistent data concerning the status of the fibrinolytic system in BD. Some authors reported normal values of plasminogen activator activity while others documented low levels correlated with disease activity (17–19). Although vascular involvement is highly specific for BD, it is not considered one of the diagnostic criteria for BD by ISGB, due to the lack of sensitivity. However, the prethrombotic/thrombotic state may offer a new diagnostic/distinguishing criterion, as we have suggested (15). Our recent studies on several endothelial markers, hemostatic parameters, and prostanooids in BD are summarized in Table 2.

Cardiovascular involvement in BD is seen as 0.62–29% and different prevalences have been observed in many trials from different countries (20–22). Cardiac involvement in BD could be classified as follows: a) systolic/diastolic dysfunction of left ventricles, b) painless myocardial ischemia, c) myocardial infarctions, d) decreased parasympatic cardiac innervation, d) pericarditis, endocarditis, myocarditis, e) valvular regurgitation, f) endomyocardial fibrosis (23–25). All of these different disorders are observed due to the high ratio of vascular structures of the heart.

The presented patient can be considered as a demonstrative case for vascular involvement in BD because of the different types of vascular involvement. Although cardiac involvement is rare, two cases reported in the literature were similar to our patient (26, 27). They also had hemoptysis and thrombus in the right ventricles. Their clinical course was very mortal and they had been died following fatal hemoptysis. Before the diagnosis of BD in the presented patient, although warfarin had been properly used, thrombosis had continued. The generally advised treatment for BD with vasculitis is immunosuppressive therapy (28, 29). Because of its immunomodulatory activities, α-IFN therapy has also been used in the treatment of BD, especially with arthritis, and eye and skin involvement (29, 30).
Cardiac and Great Vessel Thrombosis

### Table 2. Recent Studies of Our Group Investigating Several Endothelial Markers, Hemostatic Parameters, and Prostanoids in Behçet’s Disease

<table>
<thead>
<tr>
<th>Finding</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increments in basal plasma soluble TM which could not be provoked further by DDAVP infusion in BD</td>
<td>Endothelial injury due to vasculitis in BD</td>
<td>Haznedaroglu et al 1996 (12) Ᾰ Ozcebe et al 1996 (13) Ᾰ Haznedaroglu et al 1996 (16)</td>
</tr>
<tr>
<td>Increments in plasma TXB&lt;sub&gt;2&lt;/sub&gt; levels before and during DDAVP infusion in BD</td>
<td>Activation of proaggregant eicosanoid pathway in BD</td>
<td>Haznedaroglu et al 1995 (14) Ᾰ Haznedaroglu et al 1996 (16)</td>
</tr>
<tr>
<td>Increments in plasma PGF&lt;sub&gt;1α&lt;/sub&gt; levels before and during DDAVP infusion in BD</td>
<td>Protective compensatory activation of antiaggregant eicosanoid pathway in BD</td>
<td>Haznedaroglu et al 1995 (14) Ᾰ Haznedaroglu et al 1996 (16)</td>
</tr>
<tr>
<td>Increments in plasma TAT and PF 1.2 concentrations in BD</td>
<td>Increased subclinical intravascular thrombin generation suggesting a prethrombotic state in BD</td>
<td>Haznedaroglu et al 1996 (15)</td>
</tr>
<tr>
<td>Increments in plasma PAP concentrations in BD</td>
<td>Protective compensatory activation of concomitant excessive fibrinolysis in BD</td>
<td>Haznedaroglu et al 1996 (15)</td>
</tr>
</tbody>
</table>


Due to infection in our patient, we preferred to use α-IFN therapy. After adding colchicine and α-interferon to the treatment, new thromboses were not seen and thromboses in the heart disappeared. Our patient has benefited from this specific treatment for BD and, to the best of our knowledge, no cases with vascular and cardiac involvement who underwent α-IFN therapy have been reported previously. We have recently published research especially focused on the effects of interferon α-ω treatment on several cytokines and endothelial markers in Behçet’s disease suggesting a mechanism of the observed effects of the drug on the clinical course of BD (31).

In summary, BD should always be considered in the differential diagnosis of thromboses in the young and thrombotic events should be evaluated during the clinical course of BD. Interferon therapy may be an effective alternative treatment for BD presenting with vascular and cardiac events. We think that the current standard anticoagulant approach should be improved with newly developed anti-thrombotic drugs such as direct thrombin inhibitors, pentasaccard and factor Xa inhibitors in the near future. Also, prethrombotic/thrombotic state may offer a new diagnostic criteria for BD.

**References**


