Successful treatment of recurrent intracardiac thrombus in Behçet's disease with immunosuppressive therapy

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ABSTRACT

Behçet's disease (BD) is a chronic multisystem inflammatory disorder characterized by recurrent oral and genital ulcers, skin eruptions and uveitis. Neurological, gastrointestinal, and musculoskeletal systems are also involved. Although venous and arterial vasculitis occur in up to one-third of patients, intracardiac thrombus is a very rare complication. We herein report the case of a 46-year-old man with BD who presented with a large right atrial thrombus. Within a month after surgical removal, the thrombus recurred and was successfully treated with immunosuppressants that included prednisolone and cyclophosphamide.

Introduction

Behçet's disease (BD) is a chronic multisystem inflammatory disease of unknown etiology that is especially prevalent in Turkey, other Mediterranean regions and Japan (1). It is clinically characterized by inflammatory ocular involvement, recurrent oral ulcers, genital ulcers, and skin eruptions. Joints, gastrointestinal, nervous, respiratory, and vascular systems may also be involved, though cardiac involvement is infrequent (1-3). While venous thrombosis reportedly occurs in about 25% of patients, intracardiac thrombosis is extremely rare, but serious (4).

We herein describe a patient with BD who developed a recurrent intracardiac thrombus that responded to immunosuppressive therapy.

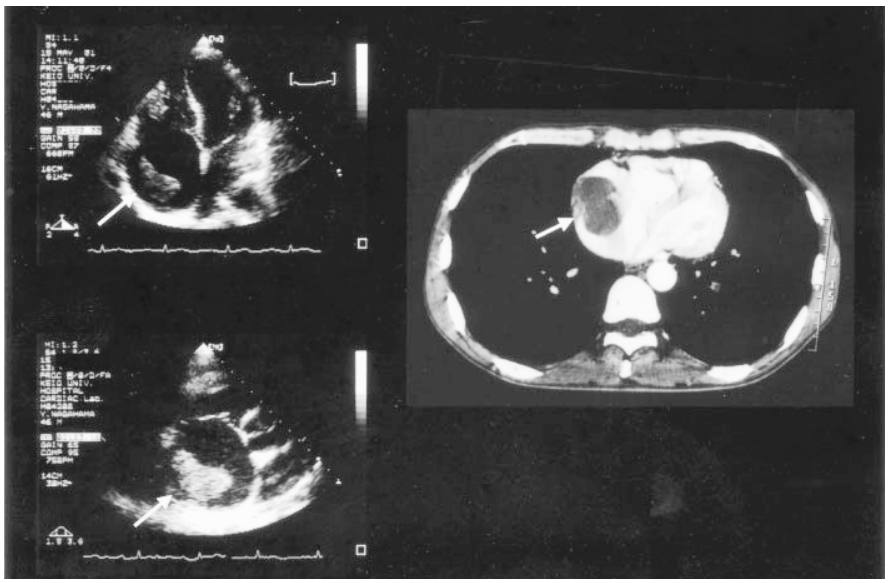
Case report

A 46-year-old Japanese man with BD was admitted to our hospital in August 2001 with recurrence of intracardiac thrombus. A year earlier, he had suffered from recurrent orogenital ulcers and erythema nodosa. In September 2000, bilateral painful swelling in his legs had appeared. He visited another hospital, where he was diagnosed as having deep vein thrombosis and anticoagulant therapy was started. At that time, echocardiography showed no cardiac mass. In January 2001, he was admitted to that hospital because of a high-grade fever over two months and exacerbation of his leg swelling. Echocardiography revealed a large mass in the right atrium, which was thought to be a thrombus because repeated blood cultures, serological examinations and the form of the mass provided no evidence of infectious endocarditis, tuberculosis or malignant disease. In addition, ulcers were detected in the terminal ileum by colonoscopy. Although the fever and the leg swelling due to thrombophlebitis had improved with continuous intravenous heparin, his intracardiac thrombus remained. The patient was admitted to our hospital in May 2001. Echocardiography and chest CT showed the homogeneous, well-defined and mobile mass (70 x 60 mm) on the lateral wall of the right atrium (Fig. 1). The patient was diagnosed as BD based on the criteria of the international study group (3). There were no active symptoms other than thrombus, therefore steroid therapy had not been considered. Because the thrombus was large and failed to respond to anticoagulant therapy, and multiple pulmonary thromboembolisms were found by chest CT with dynamic contrast enhancement, thrombectomy was performed in June. After warfarin therapy was started, he was discharged in July. A month later, he was readmitted for the asymptomatic recurrence of the intracardiac thrombus.

On physical examination, the patient's blood pressure, pulse rate, and body temperature were 94/70 mmHg, 60/minute, and 36.2°C, respectively. He was noted as having oral ulcers and a 3/6 holosystolic murmur at the apex.

Laboratory tests showed erythrocyte sedimentation rate (ESR) of 48 mm/h, no abnormality of urinalysis test and positive stool occult blood test; hemoglobin concentration of 10.2 g/dl, TT-INR of 2.2, FDP of 161 ng/ml (normal < 100), D-D dimer of 1.1μg/ml (normal < 1.0), C-reactive protein of 1.3 mg/dl, and normal level of protein C, protein S, and thrombomodulin. Antinuclear antibody and anti-cardiolipin antibody were negative. HLA-B51 and pathergy test were negative. His ophtamological findings were unremarkable.

The chest X-ray and ECG were normal. Echocardiography revealed a thrombus (32x17 mm) in the right atrium. A week



(a) **(b)**

Fig. 1. Echocardiography and chest CT before the operation. (**a**) Echocardiography and (**b**) chest CT revealed the presence of a homogeneous, well-defined and mobile mass (70 x 60 mm) on the lateral wall of the right atrium (→).

later after admission, he complained of diplopia with the right oculomotor nerve palsey and brain MRI revealed an enhanced region in the pons, suggesting neurological involvement. He did not have any other neurological findings or sagittal sinus thrombosis.

He was treated with heparin and prednisolone (PSL; 60 mg/day) immediately after admission in August 2001, and his thrombus reduced. But because it enlarged again in October, cyclophosphamide (CPA; 150mg/day) was started. In September the thrombus disappeared and he was free of any neurological manifestations. Because he developed some complications such as an untreatable lung abscess, compression fracture of the lumbar spine, and Pneumocistis jiroveci pneumonitis due to immunosuppressive therapy and high dose use of heparin for a long period, CPA was discontinued, PSL dose was reduced, and warfarinization was started. CPA was restarted in 2003. He has been well over two years without recurrence of the intracardiac thrombus.

Discussion

BD is a multisystem inflammatory disorder of unknown etiology. Cardiac manifestations include pericarditis, myocarditis, endocarditis, conduction-system abnormalities, valvular regurgitaion, and coronary arteritis (1, 2). However, intracardiac thrombosis is extremely rare (4), and the treatment is still controversial (5).

Histopathological examination of biopsy and surgical specimens are helpful in determining the pathological features of cardiac lesions. Mogulkoc *et al*. reviewed 25 BD patients with intracardiac thrombus and reported the presence of endomyocarditis, fibrosis, and inflammatory cell infiltrates in some of specimens (5). We were unable to obtain an endomyocardial specimen because doing so would have increased the risk of endothelial injury and pulmonary thromboembolism.

Thrombus formation in BD probably occurs by endothelial cell ischemia or disruption which leads to an enhanced platelet aggregation, an increase of fibrinolytic inhibitors such as plasminogen activator inhibitor (PAI-1), and a reduction of natural anticoagulants such as thrombomodulin (6, 7). It has also been reported that activated protein C resistance, an inherited coagulation defect, was more frequent in Behçet's patients, especially those with thrombosis (6, 8). The frequency of anti-phospholipid antibody is high in

Table I. Six Japanese cases of Behçet's disease with intracardiac thrombus.

Study	Sex	Age (yr)	HLA B51	Disease duration	Involved cavity	Treatment of intracardiac thrombus	Outcome (time of recurrence)
Fukuzawa *et al*.	F	72	NA	30 yr.	RA	Thrombolytic, PSL, CPA	Died
Nakata *et al.*	M	12	+	None	1st RA	Surgical removal	Recurrence (4 wk)
					2nd RA	Surgical removal	Recurrence (7 wk)
					3rd RA	PSL, LMWH	Disappearance
Yoshimura *et al*.	M	30	+	2 yr.	1st RV	Surgical removal	Recurrence (10 d)
					2nd RV	PSL, heparin, urokinase	Disappearance
Eguchi *et al.*	M	19	NA	None	1st RV	Anticoagulant	Recurrence (NA)
					2nd RV	PSL	Stable
Yasuo *et al.*	M	26	-	None	RV	Surgical removal, CyA	Stable
This case	M	46	-	6 mo.	1st RA	Surgical removal	Recurrence (4 wk)
					2nd RA	PSL, CPA, heparin	Disappearance

d: day; wk: week; mo: month; yr: year; NA: not available; RA: right atrium; RV: right ventricle; PSL: prednisolone; CyA: cyclosporin; CPA: cyclophosphamide; LMWH: low molecular weight heparin.

Behçet's patients, but there may be no correlation with the occurrence of thrombosis (9). It has been reported that the frequency of the prothrombin mutation 20210 gene, which is associated with an increased risk of venous thrombosis, is high in Behçet's patients (6) but, on the other hand, no differences were observed, (10). In this case the intracardiac thrombus did not respond to anticoagulant therapy and disappeared after PSL and CPA. It should be noted that endothelial injury rather than thrombophilic factors might play a pivotal role in pathogenesis.

The clinical and laboratory features of six Japanese patients with BD who developed intracardiac thrombi are summarized in Table I (11-15). The male to female ratio was 5:1 and mean age was 34 years (range, 12 to 72). Two of the four patients tested were positive for HLA B51. Thrombi existed in the right heart in all the patients. Various treatments have been reported, such as surgery, the use of thrombolytic agents, anticoagulants, corticosteroids and immunosuppressive agents independently or together. It should be noted that in all four patients who were not treated with corticosteroids or immunosuppressive agents, the thrombus recurred and then responded well to these medications.

The present case was BD with recurrent intracardiac thrombus. The first approach was thrombectomy, but the thrombus recurred despite the use of warfarin, which was successfully treated with heparin, PSL and CPA. Corticosteroids and immunosuppressive agents might be useful for inhibiting thrombus formation and promoting fibrynolytic effect by suppressing endothelial inflammation and injury.

In conclusion, it is worth considering the administration of PSL and/or immunosuppressive agents against intracardiac thrombus in BD. The mechanism of intracardiac thrombus in BD is still unknown and should be elucidated to establish a more specific therapy.

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