



Evaluation of Cardiovascular Involvement in Pediatric Behcet's Disease: Case Report and Literature Review with Intracardiac Thrombus

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ABSTRACT

Behcet's Disease (BD) is an inflammatory vasculitis with multisystem involvement. Typical manifestations such as oral-genital ulcerations, joint, skin, and ocular involvement usually occur during the initial period of the disease, whereas cardiac and vascular involvement may be seen in the later stages and in a more severe form of the disease. A 17-year-old male with a history of intracranial thrombosis due to BD was admitted with dyspnea and cough. A CT angiography revealed bilateral consolidation areas that were possibly compatible with pulmonary embolism. Further investigations conducted to find the origin of the embolism revealed one thrombus of 3x2 cm dimensions in the right ventricular apex (by echocardiography) and another one in the superficial branches of the right saphenous vein in the lower extremity. He responded well to early-onset immunosuppressive and steroid therapy. This case-based literature review was presented to emphasize the need for careful and detailed evaluation of thrombosis and vascular involvement in Behcet's Disease.

Keywords: Behcet's disease, intracardiac thrombus, cardiovascular involvement

INTRODUCTION

Behcet's Disease (BD) is an inflammatory vasculitis with multisystem involvement. BD is also known as 'Silk Road Disease', as it is common in regions between the Mediterranean, Middle Eastern, and Far Eastern countries. Pediatric BD occurs before sixteen years of age and constitutes 5.3–7.6% of all BD cases (1). Although the etiology cannot be precisely determined, environmental factors triggering vascular inflammation are responsible in genetically predisposed individuals. Human Leukocyte Antigen (HLA) B51 antigen is the most powerful predisposing factor.

Typical manifestations such as oro-genital ulcerations and joint, skin, and ocular involvement usually occur during the initial period of the disease, whereas organ involvement such as gastrointestinal (GIS), central nervous system (CNS), and cardiovascular system (CVS) may be seen in the later stages and in a more severe form of the disease. Cardiovascular system involvement and younger male patients are more common in Turkey and other Mediterranean countries. In Japan and the other Far Eastern countries, GIS involvement and female cases are more common.

Arteries and veins of any size can be involved in BD. Peripheral venous involvement is the most common vascular involvement. The course of arterial involvement is more severe. Dilatation and aneurysms can be seen in the aorta, coronary arteries, and peripheral arteries in the extremities, and especially in the pulmonary arteries.

Cardiac involvement is very rare in pediatric Behcet's cases. All cardiac components such as coronary arteries, endocardium, myocardium, pericardium, and conduction systems may be involved. Thrombi originating from the venous system (especially from the superficial veins of the lower extremities) can be seen in the atrium and the ventricles. Intracardiac thrombus formation is a rare but serious complication of BD and is usually accompanied by vascular BD. Endothelial dysfunction in BD paves the way for involvement of both clinics (2).

In this report, a 17-year-old male Behcet case with pulmonary embolism secondary to thrombus in the right ventricular cavity was presented.

CASE REPORT

A 17-year-old male suffering from weight loss, fatigue, dyspnea, and cough for 2 months was admitted to our clinic after he had fever for 2 days. He was first referred to our department 2 years ago with recurrent oral and genital ulcers and headache. His aunt had been diagnosed with BD. He had papilledema in the right eye and further radiologic evaluation revealed a thrombus in the transverse sinus and right jugular vein. He was diagnosed with Behcet's disease and was administered colchicine and low molecular weight heparin (LMWH). After 6 months of treatment, LMWH was switched to coumadin when radiological evaluations were normalized and papilledema was resolved. He continued to take colchicine 1 mg daily.

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On the day of admission, he had a fever of 39.58 oC. He had tachypnea and respiratory distress without any pathological sounds in the thoracic and cardiac auscultation. There were painful aphthous lesions in the mouth and ulcerated lesions on the scrotum. The remainder of the physical examination was normal. Eye examination revealed no uveitis and pathergy test was negative.

On laboratory examination, the white blood cell count was 9.300/mm³, absolute neutrophil count was 6.400/mm³, hemoglobin was 12.1 gr/dL, platelet count was 487X 10³/μL, CRP was 101.2 mg/L (normal: 0–5), ESH: 62 mm/hour (Normal: 0–20), Pro-BNP was 12.26 pg/mL (N=0–100 pg/mL), and d-Dimer was 1.6 mg/L FEU (0–0.55). The X-ray of the chest was normal. Cultures of blood, throat, and urine specimens were negative. Protein C and S, antiphospholipid antibody, homocysteine level, Factor V Leiden, methylenetetrahydrofolate reductase (MTHFR), and prothrombin FII 20210 gene mutations for the etiology of thrombophilia were normal. The complement components C3 and C4 were normal. Antinuclear antibody (ANA) and HLA B51 tests were negative and R202Q heterozygote mutation was determined in MEFV gene analysis.

Pulmonary embolism was suspected. Computerized tomography (CT) scans of the thorax revealed consolidation areas that were possibly compatible with pulmonary embolism in the segmental and subsegmental branches in the lower lobe of the right lung and upper lobes of the left lung (Fig. 1). Further investigations conducted to find the origin of the embolism revealed a thrombus of 3x2 cm dimensions in the right ventricular apex (by echocardiography) (Fig. 2).

Scanning for other thrombi also revealed a thrombus in the superficial branches of the right saphenous vein in the lower extremity. Renal and portal Doppler ultrasonography were normal. Possible pulmonary artery aneurysm was ruled out by CT-angiography. High dose steroid and intravenous (IV) heparin treatments were started. In the following week, the size of the thrombus was remarkably reduced along with the resolution of respiratory symptoms. Intravenous cyclophosphamide pulse treatment was added and IV heparin was switched to low molecular weight heparin. The patient is, at present, in remission with monthly cyclophosphamide pulses and colchicine.

Informed Consent Form: Written informed consent was obtained from the patient's parent.

DISCUSSION

Behcet's Disease is a type of vasculitis involving both arteries and veins with an increased risk for thrombophilia. It is distinguished from other types of vasculitis as it involves all sizes of vessels mainly in the venous system. Previous studies have demonstrated that T-cell mediated mononuclear cells, lymphocytes, and mast cell infiltrations lead to endothelial thickening and fibrinoid degeneration. These inflammatory changes lead to vascular dilatation, aneurysm, and increased risk of thrombosis. Vascular BD has a prevalence of 3–7.6% in children versus 6.3–51.6% in adults (3). Vascular BD was reported to be more common in the male gender and in a younger age and is associated with poor prognosis and increased disease activity. Venous involvement is more common, while arterial involvement is rare but more serious. In an international assessment of 86 pediatric BD cases in 1998 (4), venous involvement was reported in 12% of the cases and arterial involvement in 7%. The most com-



Figure 1. Consolidation marked with red arrows could be compatible with pulmonary embolism in the lower lobe of the right lung

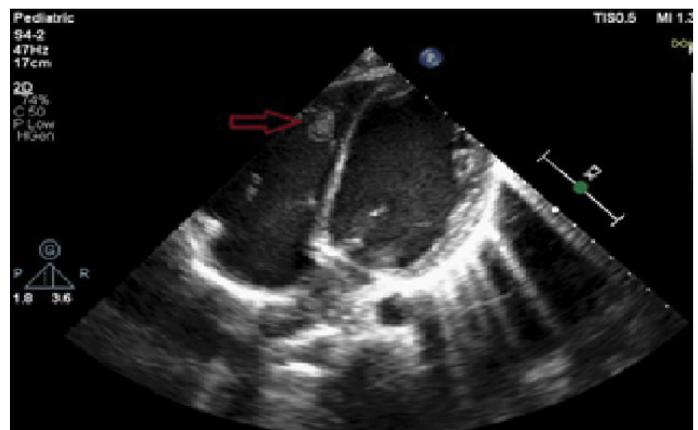


Figure 2. Thrombus marked with red arrow in the right ventricular apex in echocardiographic assessment

mon venous involvement is thrombosis in the superficial or deep veins of the lower extremities; i.e. femoral, popliteal, saphenous, and crural veins. Thrombosis is rarely seen in the superior vena cava and inferior (VCS and VCI). Budd-Chiari Syndrome (BCS) has also been reported in severe cases. Pseudo tumor cerebri is the result of the thrombosis of central veins and requires aggressive treatment. In a study by Tascilar et al. (5), 87.4% of 882 adult vascular BD cases had peripheral venous thrombosis, while 3.9% had CNS involvement. Besides this, serious venous involvement was reported in 8.6% of cases (VCS: 7.8% VCI and 2.4%: BCS). Venous thrombosis might be recurrent in BD. In a recent study by Ozguler et al. (6), recurrences of venous thrombosis were 20% in the first year and 40% in two years after the first attack. Studies over vascular BD reports that deep venous thrombosis is a recurrent vascular event. In our case, two years after thrombosis of the right jugular vein and transverse sinus, additional thrombi in the right saphenous vein and the right ventricle were detected and the patient was admitted to our clinic with findings of pulmonary thromboembolism.

Arterial involvement might often occur as aneurysms and pseudoaneurysms and occlusions are rarely seen. While large central arteries such as pulmonary, renal, iliac arteries, and the carotid and aorta may be involved, the arteries of the upper and lower extremities may also be affected. Pulmonary artery aneurysm (PAA) or pulmonary thromboendarterectomy (PTE) are rare and can show high rates of mortality based on massive pulmonary bleeding and hemoptysis. The most frequent origin of PTE is from a thrombosis in peripheral

veins and the right atrium/ventricle. In a study where 47 BD cases had PTE and PAA, peripheral venous thrombosis coexisted with 77% of the patients and intracardiac thrombus with 33% patients (7). In our case, we determined the thrombus in the right ventricular apex and right saphenous vein to be a source for PTE.

Studies reported a relationship between vascular BD and systemic symptoms such as fever attacks, high acute phase responses, and constitutional symptoms. Our patient presented with constitutional symptoms like weight loss, fatigue, and fever. Several studies on BD demonstrated the association of vascular endothelial inflammation with Protein C and S deficiencies, hyperhomocysteinemia, antiphospholipid antibodies, and Factor 5 Leiden mutations. A pediatric vascular BD study by Ozen et al. (8) reported anticardiolipin antibody positivity in 4 out of 21 cases and protein C deficiency in 2 cases. In our case, the procoagulation factors were negative.

Cardiac involvement in BD is named as cardiac BD. Prevalence of cardiac involvement in adult BD is 1–6% and is lesser in pediatric BD. Cardiac BD cases may manifest with pericarditis, myocarditis, conduction disorders, endocarditis causing valve insufficiency, aneurysm of the coronary artery and sinus valsalva, and intracardiac thrombosis. Pericarditis is the most frequent manifestation and tends to recuperate and recur quickly. Geri et al. (9) reported that while male gender and vascular involvement have higher rates of occurrence, HLA B51 and European origin are lower in cases with cardiac involvement. In the same study, pericarditis was reported in 38.5%, endocarditis in 26.9%, intracardiac thrombosis in 19.2%, endomyocardial fibrosis in 9%, and cardiomyopathy and arterial aneurysms in 6.4% of 52 cases with CBD.

Intracardiac thrombus (ICT) is one of the most serious cardiac complications of thrombosis. It is usually seen in right cardiac species and pulmonary embolism may be the referral clinic. In a recent study by Ghorbel et al. (10), cardiac involvement was 6% and ICT was 1.54% in 518 BD cases. Vascular involvement and ICT usually exist together. Endothelial dysfunction, platelet activation, and increased von-Willebrand factor release due to increased cytokinetic reaction play roles in the etiology of both clinical conditions. Wang et al. (11) reported the ICT incidence as 1.9% of 626 cases with BD, and risk factors were defined as Mediterranean origin, men under 40 years of age, and those not receiving intensive immunosuppressive treatment during the first 10 years after diagnosis. In our case, multiple thrombosis incidences were detected in the segmental and subsegmental branches of the right and left lungs and in the right saphenous vein with an additional thrombus in the right ventricle.

The echocardiographic appearances of the intracardiac thrombus might be confused either with the large vegetations seen in endocarditis or with an intracardiac tumor such as a myxoma. In our patient, we could exclude myxoma and endocarditis due to the negative blood cultures and other radiologic evaluations, revealing the lower limb thrombosis.

Intensive immunosuppressive and steroid treatments are indicated in cardiovascular BD due to increased disease activity and inflammation. Aggressive medical treatments such as cyclophosphamide and pulse steroids are indicated in life-threatening clinical conditions, especially in PAA, ICT, BCS, and arterial aneurysms. Immunosuppressive therapies such as azathioprine, cyclosporine-A, and steroids are preferred in extremity venous thrombosis. Anti-TNF agents are effective in treatment-resistant cases. Thrombi associated with BD are strongly adherent because they develop secondary to inflammation in the vascular wall. Therefore, the

risk of embolism is low and the use of anticoagulant is controversial. Anticoagulation is considered to be contraindicated since the aneurysm may rupture and bleed, especially if it is a pulmonary artery aneurysm. While methylprednisolone and pulse cyclophosphamide were administered for ICT, anticoagulant treatment could be initiated after the thorax CT angiography ruled out PAA.

This case report and literature review was presented to emphasize the need for careful and detailed evaluation of the tendency of thrombosis and cardiovascular involvement in patients with BD. The studies and case series in the literature mostly cover adult cases and there is a need for studies on the pediatric population affected by Behçet's disease.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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