

Case report

Successful thrombolytic therapy for recurrent right ventricular thrombosis in Behçet's disease

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ABSTRACT

Behçet's disease (BD) is a chronic inflammatory multisystem disorder characterised by recurrent oral and genital aphtosis and ocular involvement. Thrombophlebitis and major vessel thrombosis are common manifestations of vascular involvement in BD patients, whereas intracardiac thrombosis is extremely rare. We describe a 22-year-old woman who presented with deep vein thrombosis and recurrent right ventricular thrombosis complicated by pulmonary embolism. At the time, she complained of fever, recurrent painful oral and genital aphtae and papulo-pustular skin rash so she was diagnosed with BD. She received intravenous streptokinase 50,000 units/hour for three days plus corticosteroids with complete recovery. A review of intracardiac thrombosis in BD is presented and the use of thrombolytic therapy in this rare condition is briefly discussed.

Introduction

Behçet's disease (BD) is a chronic inflammatory multisystem disorder characterised by recurrent oral and genital aphtosis and relapsing uveitis. Other manifestations include cutaneous, articular, neurologic, gastrointestinal and vascular involvement. The latter occurs in 25% of patients and includes deep and superficial thrombophlebitis, venous and arterial thrombosis, arteritis and arterial aneurysms (1). Intracardiac thrombosis (ICT) is considered exceptional among BD patients and its treatment has not been clearly established (2). To our knowledge, we report the first description of deep vein thrombosis (DVT) and recurrent right ventricular thrombosis complicated by pulmonary embolism (PE), occurring in a woman at onset of BD, successfully

treated with intravenous thrombolytic therapy and corticosteroids.

Case report

A 22-year-old woman of mixed ethnicity presented with swelling and pain in her right leg. Ten days before admission, she had a successful pregnancy and delivered a healthy baby. With the exception of recurrent oral aphtae, her medical history was unremarkable. Doppler ultrasonography of the lower extremities showed a right DVT extending into the right external iliac and common iliac veins. Coagulation profile was normal and no common risk factors for thrombophilia such as overweight, smoke or immobilisation were present. Ventilation/Perfusion lung scan (V/Q scan) was normal. Heparin and warfarin were started and a stable INR of 2.0 to 3.0 was rapidly achieved. One month later, the patient suddenly developed chest pain, dyspnea and tachypnea. Chest radiography and electrocardiography showed normal findings. A second lower limb ultrasound scan showed extension of the right leg thrombus to the inferior vena cava. V/Q scan revealed multiple mismatches on both lung fields suggesting PE. Transthoracic Echocardiogram (TTE) was not performed at this time. Pelvic ultrasound and gynecological examination excluded retained products of conception and puerperal sepsis. Repeated blood cultures were negative. Thrombophilia screening was performed whilst on warfarin and revealed increase level of plasma Factor VIII (FVIII). Protein C, protein S, antithrombin III and APC resistance ratio were within normal limits. Lupus anticoagulant, factor V Leiden and prothrombin gene mutation were not detected. Antiphospholipid antibodies, ANA, ANCA and a test for paroxysmal nocturnal haemoglobinuria were negative. Markers of

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acute phase inflammation were elevated (ESR of 66 mm/h; CRP of 58 mg/dl) and haemoglobin was 7.7mg/dl. Subcutaneous enoxaparin 1mg/kg every 12 hours was added to warfarin and an inferior vena cava filter was placed. After a few days of clinical improvement she developed fever, tachycardia and worsening dyspnea. The TTE showed a right ventricular mass. A chest computed tomography (CT) scan confirmed the presence of a large mass in the right ventricle whereas the pulmonary arteries and lung parenchyma were normal. Cardiac surgery was performed to rule out a tumour, and a thrombus tightly adherent to the ventricular wall was removed. Pathologic examination of the mass showed an organising thrombus containing inflammatory cell infiltrate. At the time, our patient complained of painful oral and genital ulcers. Physical examination revealed multiple minor bipolar aphtae and painful papulo-pustular rash on the upper back. Pathergy test was negative and HLA-B51 detection was not performed. According to the International Study Group (ISG) clas-

sification criteria, BD was diagnosed. Despite treatment with enoxaparin and warfarin at therapeutic INR range, there was ultrasound evidence of thrombosis above and below the inferior vena cava filter and TTE showed the presence of a new clot in the right ventricle. After exclusion of pulmonary, cerebral and ophthalmic haemorrhage risk and due to the severe extending thrombosis she received streptokinase, 50,000 units/hour as a continuous intravenous infusion for three days, without a bolus loading dose. On the second day, a TTE showed considerable improvement of the ICT. Intravenous methylprednisolone 500mg/day was administered for three days, followed by oral prednisone 20mg/daily, in addition to subcutaneous fondaparinux 7.5 mg once daily injection, with complete recovery. Six months later, the ESR was 9 mm/h and the haemoglobin 11.1 mg/dl. Her fever, skin rash, oral and genital ulcers were completely resolved and prednisone was tapered to 7.5mg/daily. One year after the onset of symptoms there was no evidence of thrombosis.

Discussion

BD predisposes to venous and arterial thrombosis (10–37% of patients) (1). The main pathological process in BD is vasculitis which may affect all vessel sizes and can partially explain the prothrombotic state typical of this disease. It has been speculated that the thrombotic phenomena is triggered by endothelial cell dysfunction, secondary to inflammation, which leads to platelet activation and inhibition of both fibrinolysis and natural anticoagulant pathways (3, 4). Moreover, thrombosis in BD has been described in association with independent risk factors, such as factor V Leiden, whereas ICT has been reported in association with high levels of plasma FVIII (5, 6).

Thrombotic complications of pregnancy are well known and our patient developed a DVT shortly after she gave birth. However, no pregnancy-related thrombosis risk factors were detected. Other disorders such as infection, antiphospholipid syndrome and systemic lupus erythematosus, which are complicated by thromboembolism during

Table I. Case reports of intracardiac thrombosis in Behçet's disease treated with thrombolytic therapy.

Report	Sex	Age (yr)	ISG criteria for BD	Vascular involvement	First line treatment	Second line treatment	Third-line treatment	Maintenance treatment
El-Ramahi <i>et al.</i> (13)	M	23	Oral and genital ulcers	RVT, pulmonary vasculitis and PE	Heparin, Prednisone 60mg/d, Azathioprine 100mg/d	SK 250.000U bolus followed by 100.000 U/hr for 48hrs	–	Prednisone 50mg/d, Azathioprine 100mg/d
Ozdemir <i>et al.</i> (14)	M	26	Oral and genital ulcers, relapsing anterior uveitis, thrombophlebitis, papulo-pustular rash	RAT	Two successive infusions of SK 1.500.000 U continuously infused for 24hrs	–	–	Warfarin, Acetyl salicylic acid, Colchicine, Corticosteroids (dose not specified)
Dincer <i>et al.</i> (15)	M	39	Oral and genital ulcers, papulo-pustular rash	RVT and RAT	Surgical removal (recurrence after surgery)	SK 250.000U bolus followed by 100.000 U/hr for 72hrs	–	Cyclosporine 150mg/d; Prednisone 30mg/d; Colchicine 1mg/d; Warfarin
Present case	F	22	Oral and genital ulcers, papulo-pustular rash	DVT and PE with RVT	Warfarin; Enoxaparin 1mg/kg every 12 hrs	Surgical removal (recurrence after surgery)	SK 50.000 U/hr for 72hrs; IV Methylprednisolone 500mg for 3 days	Prednisone 20mg/d; Fondaparinux 7.5mg/d

M: male; F: female; RVT: right ventricular thrombosis; RAT: right atrial thrombosis; DVT: deep vein thrombosis; PE: pulmonary embolism; SK: streptokinase; IV: intravenous; D: day; U: international unit; Hr: hour.

pregnancy and postpartum, were ruled out. Pregnancy does not seem to markedly affect the course of BD, however, several patients have experienced exacerbation of disease during pregnancy or postpartum and some cases of pregnancy in BD complicated by thrombosis/thromboembolism have been reported. Considering the short interval between childbirth and the development of thrombosis, bipolar aphthosis and papulo-pustular rash, it could be supposed that pregnancy triggered the onset of BD or rather their co-occurrence could be purely accidental. This complicated the diagnosis of BD since ISG criteria cannot be used in the presence of other conditions (7). In any case, the diagnosis of BD was suggested by histopathologic examination of the removed thrombus supporting the inflammatory nature of ICT.

ICT in BD is a rare occurrence with lack of guidelines for management and high mortality (8). ICT is extremely uncommon in women with BD, usually it occurs in the right heart in association with PE (67%), DVT (51%), pulmonary artery aneurysm (PAA) (40%) and superior vena cava syndrome (11%) and it is frequently detected before making diagnosis of BD (8, 9). The differential diagnosis of ICT includes cardiac vegetations and tumours, which are often associated with PE, and may lead to diagnostic delay (9). We confirmed the diagnosis of ICT during surgery and, considering the combined findings of chest CT scan and V/Q scan, we assumed that microemboli detached from the right ventricular thrombus led to PE. However, this diagnosis still remains questionable since pulmonary lesions showing mismatch on V/Q scan are frequently seen in BD patients with pulmonary involvement, but are usually considered as related to pulmonary vasculitis rather than PE. Nevertheless, it is not possible to differentiate these clinical pictures through a single perfusion scan, especially if thrombophlebitis is present (10). Pulmonary artery occlusion in BD differs from classic PE

disease since these occlusions mostly represent *in situ* thrombi complicating an underlying vasculitis, which may also result in infarction, haemorrhage, haemoptysis and PAA formation (11). Therefore, pulmonary vascular problems in BD, which are mainly represented by PAA or involvement of small-sized vessels and are concomitant to extrapulmonary thrombosis or peripheral thrombophlebitis in 70–80% of patients, may be erroneously interpreted as PE (11, 12).

It is important to underline that, in the suspect of PE in BD patients, either anticoagulant or thrombolytic treatment should definitely not start before it is confirmed by a CT scan that there are no aneurysms because of the high risk of haemorrhage.

Mogulkoc *et al.* (8) published a review of 25 patients with BD complicated by ICT. With regard to treatment, surgery was performed in 12 patients as first or second line therapy. Four of the patients died and two were lost to follow-up; among the remaining six, five required medical maintenance treatment and one relapsed. In one case complete resolution after surgical excision was achieved. Seven patients were treated with anticoagulant as first line therapy, with or without immunosuppressive drug. They achieved complete resolution of ICT, which recurred in one patient after two years. One patient out of twenty-five achieved almost complete resolution with high dose intravenous streptokinase infusion plus heparin, prednisone and azathioprine (Table I) (13).

The number of reports remains small but several additional cases of ICT in BD have been published in the English literature with some patients successfully treated with high dose intravenous infusions of streptokinase (Table I) (14, 15).

In summary, intravenous thrombolytic therapy must be considered in the treatment of ICT in BD, if associated with corticosteroids and/or immunosuppressants, reducing the need for invasive cardiac surgery.

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