Case Report

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Intracardiac thrombosis in Behçet's Disease successfully treated with immunosuppressive agents: A case of vascular pathergy phenomenon

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Summary **Behçet's Disease (BD) is a rare multi-systemic inflammatory disorder classified as a systemic vasculitis of unknown aetiology. Vascular involvement occurs in approximately 5-51.6% cases, affecting venous and arterial vessels. Cardiac involvement is rare in BD (6%). There have been published approximately 93 cases of BD associated with intracardiac thrombosis, with different treatments and courses. We present a case of a 35-year-old spanish male that, after a percutaneous pharmacomechanical thrombectomy with venous stent placement, developed high fever and extensive venous thrombosis despite anticoagulation including intracardiac thrombosis (ICT) in the right ventricle and pulmonary embolism that leaded to the diagnosis of BD. The patient was successfully treated with immunosuppressants, achieving the complete resolution of ICT. We hypotesize that the endovenous procedure could have acted as a trigger for the posterior acute attack of the disease, representing a 'vascular pathergy phenomenon'. Vascular BD has to be suspected in cases of thrombosis recurrence despite correct anticoagulation, and intense immunosuppressive treatment should be considered.**

Keywords: Behçet disease, immunosuppressive agents, intracardiac thrombus, thrombectomy, venous thromboembolism

1. Introduction

Behçet's Disease (BD) is a rare multi-systemic inflammatory disorder classified as a systemic vasculitis of unknown aetiology. Onset occurs usually in the third decade and it affects both genders equally. Diagnosis is mainly clinical with no specific laboratory tests (*1*). A correlation with human leukocyte antigen (HLA) class I antigens, notably HLA-B51, but also others like A26 has been observed (*2*). Clinical course is characterized by frequent relapses and remissions. BD may affect almost all vascularized systems. Prevalence of BD worldwide ranges between 0.12-420/100,000 persons with a significant presence in the Silk Road countries (*1-5*).

We present a case of Behçet's disease associated with intracardiac thrombosis (ICT) that developed right after pharmacomechanical thrombectomy of a previous deep venous thrombosis (DVT). Venous manipulation acts as a trigger or a vascular attack of Behçet's disease.

2. Case Report

A 35-year-old spanish male had a history of hypercholesterolemia, active smoking and 2 episodes of pericarditis years ago. A year before he had an episode of

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deep vein thrombosis (DVT) in the left lower extremity that involved the common iliac vein, treated with acenocumarol. Thrombophilia testing was normal. The patient developed a severe post-thrombotic syndrome (PTS) 3 months later. A computarized tomography (CT) showed compression of the left common iliac vein by the right common iliac artery (May-Thurner syndrome). As a severe PTS persisted after one year of anticoagulant treatment, percutaneous rheolytic pharmacomechanical thrombectomy with venous stent placement was performed without complications.

Ten days after the procedure, the patient presented in the emergency department with a 10-day history of high fever, shivers and pain in the left inguinal region. Physical examination revealed: temperature 40ºC, blood pressure 120/55 mmHg, heart rate 110 bpm, edema in the left lower extremity, and the remainder was unremarkable. A stent-related infection was suspected. Anticoagulation with low molecular weight heparin and empirical broad spectrum antibiotic therapy were started. Laboratory tests showed 16.850 leucocytes/mm^3, 78% neutrophils, C-reactive protein 16.2 mg/dL, international normalized ratio (INR) 3.75, erythrocyte sedimentation rate (ESR) 76 mm 1st hour, and the remainder of the laboratory tests was normal. The blood and urine cultures (6 times) were sterile. The peripheral blood smear showed neutrophil granulation. Proteinogram, autoantibodies, lupus anticoagulant, serologies for human immunodeficiency virus, hepatitis C virus, hepatitis B virus, syphilis, *Rickettsia*, *Mycoplasma*, Rose Bengal agglutination, interferon-gamma release assay and PCR for *Thropheryma whipplei*, *Bartonella sp* and *Coxiella burnetii* were normal. A chest X ray and a transesophageal echocardiogram (TEE) were normal. A transthoracic echocardiogram (TTE) showed dilation of the aortic root (38 mm). An abdominopelvic CT showed a subocclusive thrombosis in the iliac stent.

High fever and daily shivers persisted for 3 weeks despite anticoagulation and antibiotic therapy. A Positron Emission Tomography - Computed Tomography (PET-CT) was performed showing a thrombus in the right ventricle with hyper-metabolic activity, thrombosis in the infrarenal inferior vena cava (IVC) and in both common iliac veins, thrombosis of the stent in the left iliac vein with two areas of hyper-metabolic activity that suggested infection of the stent (Figure 1A, 1B), and a right pulmonary infarction suggesting pulmonary embolism (PE). A TTE showed a rounded moving 30 mm long image sticked on the right ventricle apex with heterogeneous echogenicity, compatible with moving thrombus (Figure 1C), and a TEE showed no valvular damage. At this point, the patient presented three oral aphthous ulcers and papulopustular lesions in the back. Herpes simplex virus culture isolation of an ulcer was negative. The patient acknowledged oral and genital aphtous ulcers

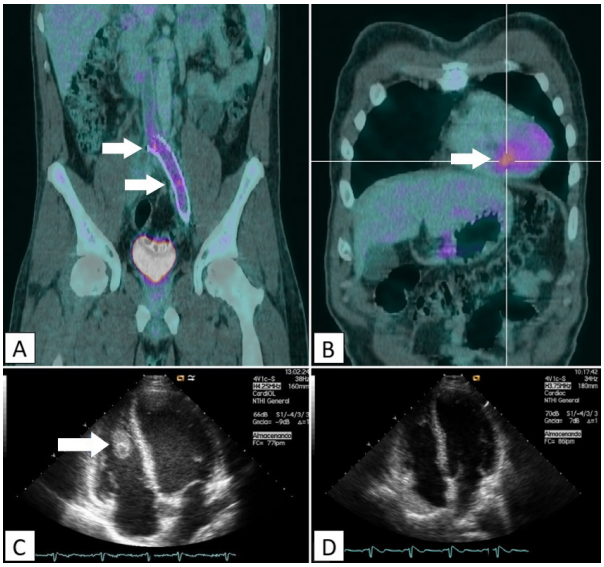

Figure 1. (A), Positron Emission Tomography - Computed Tomography (PET-CT) shows thrombosis of the stent in the left common iliac vein with two areas of hyper-metabolic activity (white arrows); **(B)**, PET-CT reveals a thrombus in the right ventricle with hyper-metabolic activity (white arrow); **(C),** Transthoracic echocardiogram (TTE) discloses a rounded moving 30 mm long image (white arrow) sticked on the right ventricle apex with heterogeneous echogenicity, compatible with moving thrombus; **(D),** TTE performed 2 months later showing total resolution of ICT.

ocasionally in the past few years. A labeled leukocytes scintigraphy was performed and ruled out intracardiac or stent-related infection. He was finally diagnosed as Behçet's disease associated with extensive venous thromboembolism including intracardiac thombus (ICT) in the right ventricle and PE. The pathergy test was negative and the phenotype HLA I was A26-A32/B39-B40(B61)/C02-C12/(Bw4-Bw6). Immunosuppressants were started: methylprednisolone bolus, rituximab and cyclophosphamide. Fever dissapeared within 48 hours. Acute phase reactants normalized after 1 week. A CT performed 2 weeks later showed partial recanalization of IVC and right iliac vein with persistence of thrombus inside the stent. A TTE performed 2 weeks later showed a reduction of the ICT size from 30 to 21 mm. The patient was discharged with prednisone, cyclophosphamide, colchicine, and acenocumarol. A TTE performed 2 months later showed total resolution of ICT (Figure 1D).

3. Discussion

Vascular system is involved in BD in 5-51.6% including venous and arterial beds and it has a relapsing course (*3,4*). BD is unique among other vasculitides as it usually affects veins rather than arteries and it has significant thrombotic tendency associated with vascular inflammation, which cannot be explained by thrombophilic factors (*3*). The most common type of vascular involvement is lower extremity

Table 1. Clinical characteristics and vascular involvement of the previous cases* of Behçet's Disease with intracardiac thrombosis in comparison with our case

Items	Previous cases (*n* = 93)	Our case
Male to female ratio	81:12	Male
Age at diagnosis (years)	27 (mean)	35
Oral involvement (*n*, %)	91 (98%)	+
Genital involvement (*n*, %)	86 (93%)	+
Skin involvement (*n*, %)	45 (57%)	+ (papulopustular lesions)
Pathergy test (*n*, %)	41 (61%)	negative
Ocular involvement (*n*, %)	18 (23%)	-
Pulmonary thromboembolism (*n*, %)	52 (56%)	+
Venous thrombosis (*n*, %)	39 (42%)	+
- Lower extremity Deep veins	31 (33%)	+
- Inferior vena cava thrombosis	6 (6%)	+
- Superior vena cava thrombosis	10 (11%)	-
Arterial involvement (*n*, %)	35 (38%)	+ (dilation of the aortic root)
- Pulmonary artery aneurysm	33 (35%)	-
Thrombosis in the right side of the heart	95%	+
- Thrombosis in the right ventricle	74%	+
- Thrombosis in the right atrium	40 (43%)	-
Sinus thrombosis (*n*, %)	6 (6%)	-
Budd-Chiari (*n*, %)	7 (7%)	-

*Adapted from Aksu *et al*. (*12*).

vein thrombosis, forming 70% of all vascular events (*3,4*). Pulmonary artery involvement (aneurysms and thrombosis) (PAI) is the most common form of arterial involvement (*3,4*). Inferior or superior vena cava, hepatic veins, cerebral venous sinuses, PE, and the right-side heart are other described locations of venous involvement (*3*). PE has been described as a rare complication, and this may be explained because the thrombi in these patients are strongly adherent (*3-5*) and formed in situ because from an anatomical and physiological point of view, the right-side heart and pulmonary arteries seem to be continuum of the vena cava (*3*). Vascular involvement is not included in the International Study Group criteria, but it is included in the revised International Criteria for Behçet's Disease (2010) (*6,7*).

Cardiac involvement is a rare (6%) and life-threatening complication. It may be present as pericarditis, myocarditis, endocarditis with valvular regurgitation, endomyocardial fibrosis, coronary arteritis, Valsalva sinus aneurysms and as intracardiac thrombus (ICT) (*8-10*). ICT are strongly associated with pulmonary artery involvement and are mostly located on the right side of the heart probably because of the vena cava extension (*3,8,11,12*). These thrombi contain inflammatory cell infiltrates and are tightly bound to the underlying endocardium or myocardium (*3*). Relapses are infrequent. Cardiac surgery is not recommended unless there are severe complications such as valve failure or pulmonary hypertension (*3*). There have been published approximately 93 cases of BD associated with ICT, most of them are case reports and case series, which have been recently reviewed by Aksu and Tufekcioglu (*12*) with a male to female ratio of 23:2 and a mean age of 27 years. At the time of detection of ICT, fever, hemoptysis, dyspnea, and cough were the predominant symptoms (*11,12*). In 40-56% of patients with ICT PAI was detected, 42-56% of them had venous thrombosis, and 52-55% had PE (*5,11,12*). ICT is uniformly associated with an elevated ESR but it is a poor indicator of disease activity (*11,13*). Cardiac involvement was the first clinical manifestation of BD in 40-50% of cases (*8,10,11*). The similarity and difference of the research findings between our case report and that published by other studies are summarized in Table 1.

Immunosuppressants, with or without glucocorticoids, are essential in the management of vascular involvement in BD. It has been shown to reduce the relapse rate and to prolong survival in several retrospective studies (*3*). Life-threatening conditions such as pulmonary artery involvement, Budd-Chiari syndrome, and peripheral arterial aneurysms/occlusions are managed with aggressive medical treatment, including cyclophosphamide and glucocorticoid pulses. Corticosteroids, azathioprine, cyclosporine A, and cyclophosphamide are recommended in the management of acute DVT (*4*). In resistant cases, anti-tumor necrosis factor (TNF) agents could be also effective (*14*). Whether to add anticoagulants to prevent relapses has been an issue of debate. Several retrospective studies showed the inefficacy of anticoagulation alone or added to immunosuppressants in preventing recurrences (*3,15*). Anticoagulation could increase the risk of aneurysmal rupture (*15*). Nevertheless, the tolerance of anticoagulation therapy was satisfactory in patients with low-risk of bleeding after ruling out pulmonary artery aneurysms and it could be used in refractory venous thrombosis along with monoclonal TNF-alpha antagonists (*16*). Rituximab and methotrexate

were found to be more effective than traditional drugs (cyclophosphamide, azathioprine, and prednisone) in improving all the most dreadful ocular manifestations in a single-blind randomized controlled trial (*17*). When indicated, surgical treatment is not advised in the active phase of the disease. Invasive arterial techniques may cause pseudoaneurysms, especially in the presence of active inflammation (*5,18*). Unfortunately, there are no randomised controlled trials (RCT) (*13*).

In our case, ICT developed shortly after venous manipulation with pharmacomechanical thrombectomy and venous stent placement. Quite similar to pathergy phenomenon, this vascular insult could have triggered the acute attack of BD. In a retrospective study, 32.6% of surgeries in patients with BD were complicated by wound dehiscence, infection, or graft failure and they found that glucocorticoids used in conjunction with immunosuppressive agents significantly reduced the risk of postoperative complications (*18*). There is significant thrombotic tendency that could be triggered even by intravenous needle or cannula insertion (*3*).

BD can cause substantial morbidity (blindness, physical disability, cognitive impairment) and increased mortality. Vascular manifestations like pulmonary arterial lesions (with a 50% mortality within 3 years) and Budd-Chiari syndrome are the leading causes of mortality in BD patients (*3,5,16*). In a 25 cases series, the presence of ICT conferred a poor prognosis (44% were treated with surgery, and 28% died from different causes) (*11*), but in more recent series immunosuppressive agents improved prognosis achieving ICT remission (*3,10*).

In conclusion, we present a case of ICT associated with BD clinically manifested by prolonged high fever of unknown origin, successfully treated with immunosuppresants. We hypothesize that the endovascular procedure could have acted as a trigger of the acute attack of BD, representing a ‘vascular pathergy phenomenon'. Vascular BD has to be considered in cases of thrombosis recurrence despite correct anticoagulation. Different treatment options for ICT in BD have been used including steroids, immunosuppressants, anticoagulation and surgery, with different outcomes. Surgical treatment of ICT is ussually not recommended. Further studies are needed to guide the management of vascular involvement and other life-threatening complications of BD.

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