Case report

Unusual cardiovascular events in Behçet's disease

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ABSTRACT

Objectives. *To report on cardiovascular involvement in Behçet's disease (BD).*

Methods. *A retrospective analysis of clinical, EKG, echodoppler, CT-scan, MRI, conventional angiography, treatment and follow-up data was undertaken in 4 patients suffering BD.*

Results. *Cardiac specific complications included coronary artery involvement (n=3), endomyocardial fibrosis (n=1), left ventricle spontaneous rupture with giant wall pseudo-aneurysm (n=1), and massive left ventricle thrombosis (n=1). Follow-up ranged from 1 month to 17 years. Surgery was complicated with vascular patch leakage, recurrent pseudo-aneurysm or upper-limb venous thrombosis in 2 patients who did not receive pre-operative specific treatment because of delayed BD diagnosis. High-dose steroids (n=4), colchicine (n=4), immunosuppressants (n=3) and anticoagulants (n=4) were eventually prescribed and stabilised cardiac disease in all cases.*

Conclusion. *At time of life-threatening cardiac complications, BD was often overlooked. Prompt initiation of steroids and immunosuppressive treatment may prevent post-operative complications, recurrences and death.*

Introduction

Behçet's disease (BD) is a systemic inflammatory disorder that causes non specific vasculitis involving various-sized vessels (1, 2). Heart is involved in less than 10% of patients in clinical series (3) and 17% of autopsy cases (4). We report on 4 BD patients suffering from cardiovascular complications, emphasising the phenotype diversity and severity of cardiac involvement in BD.

Case 1

A 39-year-old Haitian woman was referred for cough, dyspnea, and fatigue. She declined having had any past episode of chest pain. On physical examination, temperature was 38°C and dullness at left pulmonary base was noted. Laboratory tests revealed anaemia (haemoglobin, 9.6g/dl) and raised C-reactive protein level (17.9 mg/dl). Electrocardiogram (EKG) was normal. The transthoracic echocardiography and cardiac computed tomography (CT) scan revealed a huge pseudoaneurysm developing from the inferolateral wall of the left ventricle (Fig. 1A) that communicated with the left ventricle. The coronarography showed a proximal aneurysm of the right coronary (Fig. 1B). The patient underwent surgery with patch closure of the left ventricle perforation and right coronary bypass grafting. No pathologic examination was performed. Three months later, she was hospitalised for right hemiparesis and aphasia. Brain CT scan revealed left temporoparietal and right thalamic stroke. The transthoracic echocardiography confirmed a pseudoaneurysm relapse. Surgical procedure revealed a leakage from the patch with pseudoaneurysm thrombosis. Heart tissue specimen cultures were negative. A new patch was inserted. Four months later, a third relapse occurred and prompted a new cardiac surgery. As this time, more thorough questioning revealed intermittent fever, recurrent oral and genital aphthae, skin disease suggestive of erythema nodosum, and polyarthritis over the past 3 years. BD was diagnosed and prednisone, azathioprine, colchicine and anticoagulants were started. Two years later, the patient was in remission when she was lost to follow-up.

Case 2

A 24-year-old Turkish man had recurrent bipolar aphthae and pseudofolliculitis that were attributed to BD. He was admitted for haemoptysis, headache

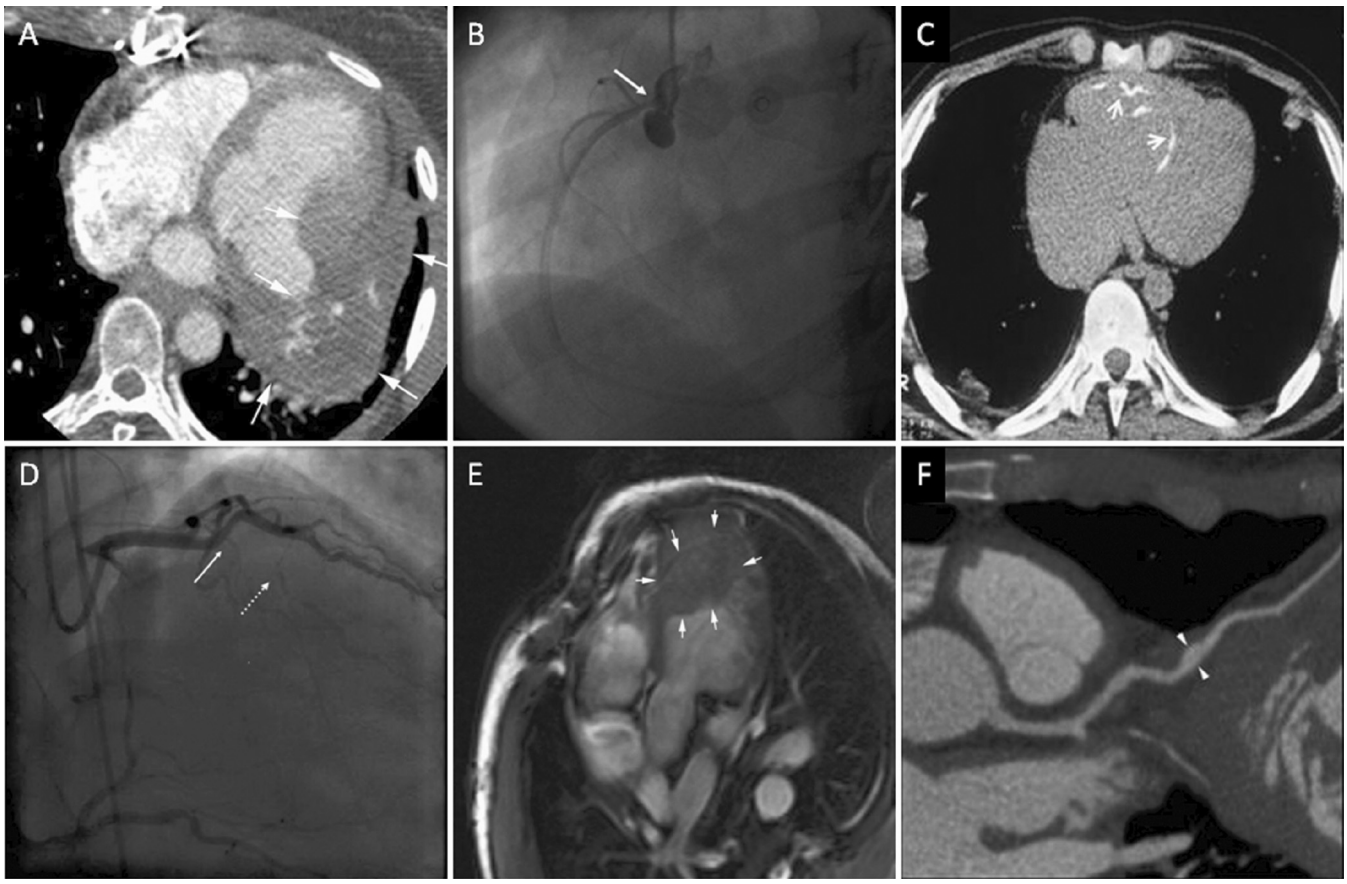

Fig. 1. Heart involvement in BD: Radiological findings.
A: Axial CT image showing a huge dilation of the left ventricle with mural thrombosis (arrows).
B: Coronarography showing an aneurysm located bellow the right coronary artery ostium (arrow).
C: Non enhanced cardiac CT scan showing linear calcifications (arrow) of the right ventricular endocardium typical of endomyocardial fibrosis
D: Coronarography showing chronic total occlusion of mid left anterior descending coronary artery just after the first diagonal branch (arrow) and retrograde collaterality (dotted arrow). **E**: CineMR examination in a 4-chamber view showing a huge marginated thrombus of the apex (arrows).
F: Multiplanar reformations of the left anterior descending coronary showing arterial aneurysms (arrowheads).

and polyarthragias. Physical examination disclosed fever, tricuspid regurgitant murmur, right-sided heart failure, and bilateral papillary oedema. EKG showed right atrial hypertrophy and incomplete right bundle branch block. Chest CT scan and pulmonary artery angiography disclosed bilateral pulmonary aneurysms. Echocardiography displayed a severe tricuspid regurgitation with right ventricular dysfunctions and bright echoes in the right ventricular endocardium. Electron beam cardiac CT showed a 5mm thick low dense area surrounded by linear calcifications involving pulmonary infundibulum (Fig. 1C). Brain magnetic resonance imaging (MRI) showed right lateral sinus thrombosis. Oral cyclophosphamide, prednisone, colchicine and low dose aspirin were started. Ten months later, echocardiography and cardiac CT scan showed increased thickness of right intraventricular mass and heart surgery was decided. A diffuse ulcerated endocarditis was involving the apex, the anterior papillary muscle and extended to the tricuspid valve which appeared both stenotic and incompetent, with fusion of the septal leaflet. Resection of endomyocardial fibrosis and tricuspid valve annuloplasty were performed. Histological examination showed a 50 mm-thick dense fibrous tissue with numerous calcifications, scarce neovessels and inflammatory cells that extended into the myocardium. After 17 years of follow-up, the patient is asymptomatic with low dose prednisone, azathioprine, colchicine and oral anticoagulation.

Case 3

A 29-year-old Algerian man was admitted for acute chest pain. He had no history of tobacco abuse, hypertension, hypercholesterolemia or diabetes. Physical examination was unremarkable except for genital scars. EKG registered Q waves in the precordial derivations. Routine laboratory evaluation was normal except for high troponin I blood level (18 μg/l, n<0.15). Echocardiography revealed antero-septo-apical hypokinesia. Coronarography showed occlusion of the left anterior descending (LAD) coronary (Fig. 1D). The other coronary arteries were normal. Coronary angioplasty with stent of the LAD coronary was performed via the right radial artery. Angioplasty was complicated by pseudoaneurysms of both the right radial artery and the LAD coronary, which prompted bypass grafting of the LAD coronary. Twenty days after surgery, the patient complained of a painful right limb oedema ascribed to

Table I. Characteristics of Behçet's disease patients with cardiovascular complications.

Case	Age	Sex	Origin	Clinical signs at presentation	BD diagnosis criteria*	Delayed BD diagnosis	Cardiac involvement	Other vascular involvement	Treatment	Follow-up
1	39	F	Haiti	Cough Dyspnea Fever Cardiac failure	Oral aphthae Genital aphthae Erythema nodosum Polyarthritis	Yes	LV pseudoaneurysm R coronary aneurysm	None	Cardiac surgery Prednisone CYC AZA Colchicine Anticoagulants	2 years then lost to follow-up
2	24	M	Turkey	Haemoptysis Fever Cardiac failure	Oral aphthae Genital aphthae Pseudo-folliculitis Cerebral thrombosis	No	RV endomyocardial fibrosis Tricuspid insufficiency	Pulmonary aneurysms	Cardiac surgery Prednisone AZA Colchicine Anticoagulants	17 years Remission
3	29	M	Algeria	Chest Pain	Oral aphthae Genital aphthae Pseudo-folliculitis Thrombophlebitis	Yes	LAD coronary occlusion LAD coronary pseudoaneurysm	RA pseudonaeurysm Thrombophlebitis Pulmonary embolism	CAB grafting Prednisone Colchicine Anticoagulants	1 month then lost to follow-up
4	49	M	Mali	Dyspnea	Oral aphthae Pseudo-folliculitis Uveitis	Yes	LV intracardiac thrombus LAD and C coronaries aneurysms	Thrombophlebitis	Cardiac surgery Prednisone AZA CYC MMF Colchicine Anticoagulants	4 years Remission

F: female; M: male; BD: Behçet's disease; L: left; RC: right coronary; RV: right ventricle; LAD: left anterior descending; LV: left ventricle; C: circumflex. RA: radial artery, CYC: cyclophosphamide, AZA: azathioprine, CAB: coronary artery bypass, MMF: mycophenolate mofetil.
*According to ISG criteria (2).

superficial femoral vein thrombophlebitis on ultrasonography. Pulmonary scintigraphy showed a perfusion defect in the upper right lobe consistent with pulmonary embolism. As this time, the patient revealed that he had suffered recurrent oral and genital aphthae, pseudo-folliculitis and legs superficial thrombophlebitis for many years. BD was diagnosed. Prednisone, colchicine and anticoagulants were started. The patient returned to Algeria one month later and was lost to follow-up.

Case 4

A 49-year-old Malian man was admitted for dyspnea. He had no cardiovascular risk factors and declined any past episode of chest pain. Physical examination disclosed systodiastolic mitral murmur, oral ulcers, pseudo-folliculitis and mild oedema of the right leg. Routine laboratory tests were unremarkable except for an elevated C-reactive protein blood level (2.9mg/dl). Troponin I and EKG were normal. Ultrasonography of leg veins disclosed sequelae of past right popliteal and superficial femoral thrombophlebitis. Pulmonary scintigraphy was normal. Transthoracic echocardiography and cardiac MRI revealed a massive thrombus in the apical part of the left ventricle (Fig. 1E). The left ventricle was normal in size and contractility. The coronary CT scan showed small aneurysms of the left anterior descending and circumflex arteries (Fig. 1F). Laboratory tests for thrombophilia, including lupus anticoagulant, anti-cardiolipin antibody, anti-β2 glycoprotein 1 antibody, protein S, protein C, antithrombin, activated protein C resistance, factor V Leiden, and prothrombin mutation were negative. The diagnosis of BD complicated with heart thrombosis was highly suspected and prednisone, azathioprine, colchicine and anticoagulants were started. Ten months later, the patient complained from acute blindness of the left eye and genital ulcers. Ophthalmological examination revealed a pan-uveitis with retinal vasculitis of the left eye. Intravenous methylprednisolone and cyclophosphamide were started. The patient's condition improved dramatically and thrombus size in the left ventricle decreased. After 4 years of follow-up, the patient is asymptomatic with low dose prednisone, mycophenolate mofetil, colchicine and anticoagulants.

Discussion

Our 4 patients suffered uncommon and life-threatening cardiovascular BD manifestations including aneurysm, occlusion, and pseudoaneurysm of coronary arteries, left ventricular pseudoaneurysm, endomyocardial fibrosis, and massive intracardiac thrombosis (Table I). According to the criteria proposed by the International Study Group (ISG) in 1990 (2), recurrent oral ulceration is warranted for the diagnosis of BD as well as two of the following: recurrent genital ulcerations, eye lesions, skin lesions and a positive pathergy test. Interestingly, BD was diagnosed after heart complications onset in most cases although all patients had had typical symptoms of BD. It is noteworthy that the main cause of mortality in BD is major vessel disease (5).

Coronary aneurysm is the consequence of perivascular inflammatory cell infiltration, which occludes the vasa vasorum and leads to the destruction of the arterial wall integrity (1, 4, 6). Any vessel superimposed injury – surgical anastomosis, puncture for angiography, trauma – may trigger recurrent false aneurysms (7) as observed in patient 3.

Arterial occlusions occur in less than 5% of BD patients with vascular involvement (6), affect mostly males with a young age at BD onset and are not associated with usual risk factors for atheroma (3). BD coronary involvement typically is monotroncular, proximal and affects the anterior interventricular artery (3), as observed in patient 3. Such arterial occlusions or stenoses are often asymptomatic and rarely cause acute myocardial infarction.

Cardiac pseudo aneurysm is caused by the rupture of the myocardium (8). Although coronarography did not show artery occlusion, specific myocardial small-vessel vasculitis could not be ruled out in patient 1. Cardiac pseudoaneurysms may rupture or cause peripheral emboli as observed here, and should be removed surgically. To avoid BD-related postoperative inflammation (9), such as suture leakage after patching, steroids and immunosuppressive therapy should be started before and continued after procedure.

Endomyocardial fibrosis usually affects the right heart with involvement of the tricuspid valve, and causes intraventricular thrombus (10, 11). Imaging findings mostly consist of a) an intraventricular filling defect with or without calcification, b) bright echo at echocardiography or low CT attenuation along the myocardium, c) displacement of leaflets of tricuspid or mitral valve and d) right atrial enlargement. Endomyocardial biopsy specimen shows dense fibrous tissue, with inflammatory infiltrates and numerous neovessels in the endocardium. In most cases, surgery is required despite steroids, immunosuppressive therapy or anticoagulation.

Intracardiac thrombus formation in BD usually involves the right side of the heart, frequently associated with endocarditis, vein cava phlebitis and pulmonary arteritis (6, 7, 12). In a series of 23 patients, intracardiac thrombus preceded other BD manifestations in 13 cases and seemed overprevalent in men (12). The mechanism of intracardiac thrombosis in BD is unclear. A venous clot may migrate and embolise into the right heart. Heart thrombosis may also be caused by dysrhythmia, myocardial infarction, endocarditis, endomyocardial fibrosis or ventricular aneurysm. In addition, BD clearly is a pro-thrombotic condition which may affect very unusual sites, causing cerebral thrombophlebitis, cava vena thrombosis, or Budd-Chiari syndrome (13, 14). In patient 4, the left ventricular thrombus appeared as a *de novo* phenomenon related to the inflammatory process of BD (15).

In summary, our report emphasises the clinical spectrum of life-threatening cardiovascular involvement of BD. Early diagnosis of BD is mandatory, especially before heart surgery, because prompt initiation of corticosteroids and immunosuppressive treatment may prevent complications and death.

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