Echocardiographic manifestations of Adamantiades-Behcet’s disease

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Received 21 May 2006; received in revised form 24 July 2006; accepted 27 July 2006
Available online 28 September 2006

Abstract Adamantiades-Behcet disease (ABD) is a multisystemic, chronic inflammatory disorder of unknown etiology with diffuse clinical manifestations including those involving the cardiovascular system. While the disease is most prevalent in the Mediterranean region, the Middle East and the Far East, its prevalence is increasing in Western countries due to migration patterns. Cardiovascular involvement in ABD may include myocardial disease, venous disease and disease of the aorta and great vessels. Use of echocardiography in these patients is crucial to assess their pathology and in this article we review the spectrum of echocardiographic findings in patients with ABD.

KEYWORDS
Adamantiades-Behcet disease; Cardiovascular pathology; Echocardiography

Introduction

Initially described by dermatologist Hulusi Behcet and ophthalmologist Benediktos Adamantiades, Adamantiades-Behcet disease (ABD) is a multisystemic, chronic inflammatory disorder of unknown etiology. In addition to the classical clinical triad of oral and genital ulcerations and eye lesions, clinical manifestations in many other locations including the cardiovascular system have been described. Venous and/or arterial vasculitis may occur in up to 40% of patients with mortality of up to 20%. Cardiac involvement, while less recognized clinically, may occur in up to 16% of patients on pathological examination. The clinical presentation of cardiac complications in ABD may include fever, dyspnea, chest pain, hemoptysis and edema and these patients are frequently referred for echocardiography as part of their clinical evaluation. While the disease is most prevalent in the Mediterranean region, the Middle East and the Far East, its prevalence is increasing in Western countries due to migration patterns. It is therefore crucial for cardiologists and

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particularly echocardiographers to have an understanding of the varied cardiovascular pathology present in ABD and in this article we describe and review the spectrum of echocardiographic abnormalities in patients with ABD.

All charts of patients with ABD followed in our institution were systematically reviewed and patients with cardiovascular complications identified. In addition, a search of the published literature was performed using the MEDLINE database using the search terms Behcet’s disease, cardiovascular disease, myocardial disease, pericardial disease and echocardiography. Reference lists from identified studies were also reviewed for potentially relevant studies. All relevant studies were included in the review.

Experience with cardiac manifestations of ABD in our institution is described in Table 1. While the overall incidence of clinically apparent cardiac ABD in our patient population is low, in certain subgroups, such as patients with pulmonary involvement, the incidence of intracardiac thrombus may reach 50%. Other cardiac manifestations included right atrial thrombus and pseudoaneurysm of the ascending aorta. Patients with major venous or peripheral arterial involvement also appear to be at relatively high risk for cardiovascular complications.

We present illustrative cases of the varied clinical and echocardiographic manifestations of ABD.

Arterial disease

A 24 year old man of Arab descent with a diagnosis of ABD presented to the ER with two weeks of gradually increasing chest pain and shortness of breath. The patient was initially diagnosed with ABD at the age of 12 when he presented with carditis, arthritis, fever and oral and genital ulcers and was treated with steroids and colchicine. Three years later he had an exacerbation manifested by diffuse aneurysms of the coronary arteries and thrombus in the right ventricle and coronary vein and was again treated with chronic steroid therapy and institution of methotrexate. The patient was non-compliant with his medical therapy and four years prior to the current admission he was hospitalized with a ruptured intrarenal artery aneurysm. He underwent selective embolization of the affected renal vessel and was again started on steroids and methotrexate but did not return to follow-up and was not compliant with his medical regimen. On the current admission the patient appeared ill, was afibrile with blood pressure of 100/50 in both arms, and a pulse of 80 beats per minute, palpated equally over all 4 extremities. Physical examination was notable for oral aphtae, a decrescendo 3/4 diastolic murmur compatible with aortic regurgitation and crepitations over both lungs. An ECG demonstrated normal sinus rhythm with evidence of left ventricular hypertrophy. Transthoracic echocardiography revealed a large chamber with a narrow neck adjacent to the ascending aorta consistent with pseudoaneurysm of the ascending aorta. Trans esophageal echocardiogram confirmed these findings (Fig. 1) and the patient was referred to the operating room where the diagnosis of acute aortic root pseudoaneurysm was confirmed.

Arterial involvement in ABD is characterized pathologically by neutrophilic vasculitis of the vasa vasorum, which in turn leads to destruction and necrosis of elastic fibers and smooth muscle cells in the media. Arterial disease manifests clinically as occlusive lesions or aneurysm formation which may occur in many different medium and large-sized arteries, generally, although not exclusively, as a late complication of the disease. Both aneurysms and pseudoaneurysms of the sinuses of Valsalva and the ascending aorta have been described in BD. While some studies utilizing echocardiography have documented up to a 48%

Table 1 Institutional experience with cardiovascular manifestations of ABD

<table>
<thead>
<tr>
<th>Cardiac complications</th>
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<tr>
<td># of patients</td>
</tr>
<tr>
<td>M/F</td>
</tr>
<tr>
<td>Arabs/Sephardic Jews</td>
</tr>
<tr>
<td>Pulmonary disease</td>
</tr>
<tr>
<td>SVC syndrome</td>
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<td>Arterial disease</td>
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SVC = superior vena cava.

Figure 1 Aortic pseudoaneurysm (PS) located posteriorly.
incidence of dilatation of the ascending aorta in ABD patients as compared to controls another, more recent study failed to demonstrate significant differences in aortic diameter between patients with ABD and controls.\textsuperscript{8,12,13} Given the potential for aortic disease assessment of a ABD patient with chest pain should include imaging of the ascending aorta. Asymptomatic patients with aortic dilatation should be followed with regular imaging so as to guide prophylactic surgical intervention. In addition to aortic dilatation, studies using echocardiography have demonstrated reduced aortic distensibility in patients with ABD, a finding which may explain propensity to aneurysm formation in the disease.\textsuperscript{14} Complications due to inflammatory vasculitis without aneurysm formation such as aorta-atrial fistulas have been described as well\textsuperscript{15} so that lack of dilatation of the aorta does not preclude inflammatory involvement.

**Venous disease**

A 45 year old male of Sephardic Jewish descent presented to the emergency room with a two week history of facial and neck swelling. The patient had a history of oral aphthae as well as erythema nodosum. Physical exam was notable for swelling and flushing of the neck and face and fundoscopic examination revealed venous engorgement. A presumptive clinical diagnosis of superior vena cava syndrome was made. Transesophageal echocardiography performed to evaluate this possibility revealed an intraluminal mass consistent with thrombus in the superior vena cava causing turbulence of flow on color Doppler. A second mass was noted adherent to the free wall of the right atrium (Fig. 2). The patient received treatment with anticoagulation and steroids with gradual resolution of the mass in the superior vena cava and dramatic improvement in the clinical findings.

Venous involvement in ABD may include peripheral superficial and deep vein thrombophlebitis, venous occlusion of the upper or lower extremities as well as of the superior or inferior vena cava. Venous involvement in vascular ABD is significantly more common than arterial involvement. Pathologic studies have demonstrated major venous occlusion due to thrombophlebitis in the superior and inferior vena cavae which presents clinically as superior vena cava or Budd-Chiari syndrome.\textsuperscript{14} Interestingly, pulmonary embolism is relatively infrequent, seen in only 2 of 25 cases of major venous occlusion and suggesting relative stability of the in situ thrombus.\textsuperscript{5} As in our patient, venous thrombosis may be associated with right-sided intracardiac thrombus pointing to thrombophlebitis as a common mechanism.\textsuperscript{4,16} Therefore when patients with ABD and signs of ascites or swelling of the upper or lower extremities are referred for echocardiography careful attention should be devoted to imaging of the large venous vessels, particularly if intracardiac thrombi are noted.

**Cardiac disease**

A 34 year old female with a 10 year history of ABD which manifested with oral and genital ulcers, uveitis and pulmonary artery aneurysms presented with hemoptysis and shortness of breath. Chest CT revealed left lower lobe pulmonary artery aneurysm and a suspected filling defect in the right ventricle (RV). Echocardiography revealed a large echodensity (Fig. 3) in the RV apex consistent with thrombus. The patient was treated with steroids, azathioprine and cyclosporine. Anticoagulation was not given due to the pulmonary artery aneurysms and hemoptysis and follow-up echo revealed almost complete resolution of the RV thrombus with anti-inflammatory therapy. A 20 year old male with a history of scrotal ulcers and bilateral lower lobe pneumonectomy for pulmonary artery aneurysms was admitted for evaluation. Review of the lung pathology revealed inflammatory vasculitis in the pulmonary arteries. Chest CT to reassess the pulmonary vasculature revealed a suspected RV thrombus. Echo study confirmed a RV thrombus with suspected attachment to the tricuspid valve. The patient was treated with pulse cyclophosphamide, steroids and anticoagulation with gradual resolution of the RV thrombus.

Clinically-apparent cardiac abnormalities are relatively uncommon in ABD but pathologic

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\caption{Right atrial thrombus described in case 2.}
\end{figure}
evidence is seen in up to 16% of cases.\textsuperscript{7} As in the two cases presented, intracardiac thrombus, primarily but not exclusively right-sided, may occur and frequently coexists with pulmonary vascular disease.\textsuperscript{17–19} Echocardiography should be performed in ABD patients with pulmonary vascular involvement to rule out intracardiac thrombus. Intracardiac thrombus may be a presenting feature of ABD and ABD should be included in the differential diagnosis of patients with intracardiac masses noted on echo. While in most cases of intracardiac thrombi in ABD the thrombi involved the right side of the heart, left ventricular and left atrial involvement have been described as well.\textsuperscript{20,21} Pathologic studies of underlying myocardium in patients undergoing surgical resection of intracardiac thrombi have shown variable results with some reports showing normal myocardium, others with inflammatory infiltrate and others with endomyocardial fibrosis.\textsuperscript{16} Several reports have documented resolution of these thrombi with immunosuppressive therapy alone or in combination with anticoagulation as in our patients and pulmonary or systemic emboli appear to be rare.\textsuperscript{19,22–23} In most cases anti-inflammatory treatment appears to be sufficient particularly given the risks of anticoagulation in patients with pulmonary artery aneurysms and permanent anticoagulation is not supported by the available literature.

While sporadic cases of myocarditis in ABD have been reported, systolic dysfunction does not appear to be a prominent finding in cardiac ABD.\textsuperscript{24} Several studies have examined diastolic function in ABD. Kumsuoglu et al. examined 22 subjects with ABD and 20 controls and demonstrated filling abnormalities by Doppler consistent with early diastolic dysfunction including prolonged isovolumic relaxation time, prolonged deceleration slope, reversed E:A ratio and increased atrial filling fraction in cases with ABD.\textsuperscript{25} These diastolic abnormalities were confirmed in a study of 82 ABD patients by Ikonomidis et al who also noted reduced flow propagation velocity (FPV) on color m-mode as well as a higher E/FPV ratio in cases.\textsuperscript{14} The authors noted a correlation between prolonged deceleration time and vascular complications after correction by logistic regression suggesting a common pathophysiologic pathway. Several more recent studies failed to demonstrate significant impairment of diastolic function in ABD using the more sophisticated diastolic parameter of Doppler tissue imaging at rest or with exercise.\textsuperscript{12,26}

Several small case-control studies which have systematically examined ABD patients without clinical evidence of cardiac involvement using echocardiography have suggested an increased incidence of valvular disease in ABD. Gurgun et al. examined 35 ABD patients and 30 matched controls with transthoracic and transesophageal echocardiography performed by blinded operators.\textsuperscript{9} The authors noted significantly higher incidences of interatrial septal aneurysm (31% vs 6%), mitral valve prolapse (MVP) (25% vs 3%) and mitral regurgitation (40% vs 6%) in the ABD patients as compared to controls. These findings suggest that systemic vasculitis may cause weakening of endocardial or myocardial tissue. The findings of an increased incidence of MVP in ABD are supported by a study of Morelli et al who noted a 50% incidence of MVP in ABD patients.\textsuperscript{13} Other studies have shown a relatively low prevalence of MVP (1.8%) and mitral regurgitation (3.7%) in ABD patients.\textsuperscript{12} Disease of the aortic valve in the study of Gurgun et al. was noted in 5% of patients and no controls a finding that due to the small numbers did not reach statistical significance. Chikamori et al. described a patient with severe aortic regurgitation due to aortic valve prolapse.\textsuperscript{27} Their review of the literature revealed 20 cases of aortic regurgitation, which was caused in most cases by valvular pathology and not secondary to sinus of valsalva dilatation so echocardiographic evaluation of a ABD patient with aortic regurgitation should include careful assessment of the aortic valve as well as the ascending aorta.

Pericardial disease in ABD appears to be relatively uncommon and case-control studies using echocardiography have not demonstrated an increased incidence of pericardial disease.\textsuperscript{28} Several case reports have described symptomatic and asymptomatic pericarditis and pericardial effusions in patients with ABD which generally resolved with anti-inflammatory therapy.\textsuperscript{29,30} One report

\begin{figure}[h]
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\caption{Right ventricular thrombus noted incidentally in a patient with pulmonary artery aneurysms.}
\end{figure}
References


Table 2 Summary

1. Vasculitis may occur in up to 40% of patients with ABD with cardiac involvement in up to 16%.
2. Arterial disease may include aortic aneurysms or pseudoaneurysms.
3. Venous involvement is more common than arterial and may include venous occlusion of the superior and/or inferior vena cava. Pulmonary embolism is very infrequent.
4. Intracardiac thrombus is not uncommon in ABD and is associated with pulmonary vascular disease. These thrombi in most cases resolve with anti-inflammatory therapy and long-term anticoagulation appears unnecessary.
5. Valvular, myocardial and pericardial disease in ABD are uncommon but have been reported.
6. Echocardiographers studying ABD patients should be aware of the varying cardiovascular pathology that may be present in these patients.

described constrictive pericarditis in an ABD patient with ABD and intracardiac masses. Histology of the pericardium in a patient with ABD and pericarditis revealed infiltration of lymphocytes and granulomas consistent with acute vasculitis. Therefore, although unusual, pericardial disease should also be excluded in ABD patients referred for echocardiography.

In summary, patients with ABD may present with a wide spectrum of cardiovascular pathology which may be the first vascular manifestation of the disease and echocardiographic imaging in these patients should comprehensively examine the great vessels as well as myocardial and valvular performance (Table 2). ABD should be added to the differential diagnosis of the various findings described especially in young patients with ethnic origins from countries around the “Silk Route”.

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