Dilated Cardiomyopathy in a Patient with Antiphospholipid Syndrome

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The antiphospholipid syndrome (APS) is a thrombophilic disorder in which venous or arterial thrombosis, or both, may occur in association with antiphospholipid antibodies. Cardiac manifestations of this syndrome include valvular vegetations and thickening, coronary artery disease, intracardiac thrombi, myocardial dysfunction from cardiomyopathy, or endomyocardial fibrosis. There are rare reports in the literature of myocardial dysfunction from dilated cardiomyopathy without any obvious cause in patients positive for antiphospholipid antibodies. We present the case of a man with APS who was found to have congestive heart failure due to dilated cardiomyopathy without evidence of significant valvular or coronary artery disease. We hypothesize that the APS contributed to the development of dilated cardiomyopathy in the patient.

CASE PRESENTATION

Initial Presentation
A 70-year-old man presented to a tertiary care center complaining of progressive dyspnea and orthopnea with pedal edema of 2 weeks’ duration. He denied chest pain, palpitations, cough, or fever.

Past Medical History
His medical history was significant for APS diagnosed following a hospitalization 2 years ago for bluish discoloration of the left first and second digits. Angiography had revealed thrombotic occlusion of the subclavian, radial, and common interosseous arteries. Routine anticoagulation studies revealed a prolonged activated partial thromboplastin time, and this was followed by a mixing study, which was abnormal. A hypercoagulability work-up was performed and revealed lupus anticoagulant antibodies, high levels of IgG and IgM anticardiolipin antibodies, and antibodies to β2 glycoprotein 1. The patient was treated with warfarin for 6 months following this episode. One year after the thrombotic event, testing for antiphospholipid antibodies again revealed high levels of antibodies and a diagnosis of APS was made based on the International Consensus Statement on Preliminary Classification Criteria for Definite APS.1 Anticoagulation was continued with aspirin and clopidogrel.

His past history was also significant for prostate cancer diagnosed 6 years ago and treated with radical prostatectomy and external-beam radiotherapy with no evidence of recurrence based on annual monitoring of prostate-specific antigen levels and symptoms. He also had a 10-year history of diabetes mellitus, with good glycemic control achieved by an insulin 70/30 regimen of 58 U before breakfast and 28 U before supper. He had a 15-year history of hypertension, which was optimally controlled by metoprolol 50 mg daily and lisinopril 10 mg daily. He had quit smoking 10 years ago after a 30 pack-year history. The patient had no history of angina or coronary artery disease. There was no family history of premature coronary artery disease or clotting disorders.

Physical Examination
On examination, the patient was 5 ft 8 in and he weighed 229 lb. He was tachypneic at 24 breaths/min. His blood pressure was 124/65 mm Hg and his heart rate was 94 bpm. There was no jugular venous distension. Cardiac examination revealed S1 and S2 in regular rhythm with no S3 gallop or murmurs. Auscultation of his lungs was notable for bibasilar crackles. He had significant pitting-type pedal edema without calf tenderness. Homans’ sign (ie, pain on passive dorsiflexion of the foot; a sign of thrombosis of the deep calf veins) was not present.

Laboratory and Diagnostic Studies
The results of the complete blood count and assessment of electrolytes were within normal limits. Cardiac
enzymes were not elevated. The electrocardiogram revealed sinus tachycardia with left bundle branch block, which was unchanged from previous electrocardiograms. The level of brain natriuretic peptide was elevated at 212 pg/mL (normal, 0–100 pg/mL). The D-dimer value was within normal range. Radiography of the chest revealed engorged pulmonary vessel markings and increased pulmonary densities in the lower lung fields, suggestive of heart failure with pulmonary edema.

**Hospital Course and Management**

The patient was admitted to the hospital with a diagnosis of congestive heart failure and was started on oxygen, diuretics, angiotensin-converting enzyme inhibitors, and anticoagulation. Echocardiography revealed a dilated cardiomyopathy with marked left ventricular systolic dysfunction with an estimated ejection fraction of 15% to 20%. There was mild mitral and tricuspid valve regurgitation. There were no intracardiac thrombi. Stress myocardial perfusion imaging using adenosine thallium revealed no evidence of perfusion defects or reversible ischemia suggestive of coronary ischemic disease as the cause for the dilated cardiomyopathy. Other causes of the dilated cardiomyopathy were also excluded. The patient did not have systemic signs or symptoms suggestive of viral, bacterial, rickettsial, fungal, or parasitic infections or use alcohol, cocaine, or other medications known to cause dilated cardiomyopathy. There was no family history suggestive of familial dilated cardiomyopathy, hereditary hemochromatosis, neuromuscular disorders, or hereditary sideroblastic anemias. Since no clear cause of this patient’s dilated cardiomyopathy could be found, we hypothesize that APS contributed to the development of dilated cardiomyopathy in this patient.

The patient improved significantly and his shortness of breath and pedal edema resolved with 2 days of intravenous diuretics. Anticoagulation was initiated with heparin and warfarin, and the patient was discharged home on warfarin to be continued indefinitely given his myocardial dysfunction in the setting of APS and the marked left ventricular systolic dysfunction.

**DISCUSSION**

**Cardiac Manifestations of APS**

Cardiac manifestations of APS include valvular disease, coronary artery disease, intracardiac thrombus, and myocardial dysfunction from cardiomyopathy and endomyocardial fibrosis2,3 (Table). Valvular disease is common in this syndrome, with up to 63% of patients with APS having at least 1 valvular abnormality on echocardiography.4,5 The mitral and aortic valves are commonly involved, with the mitral valves involved more frequently than the aortic valves.6 Vegetations of the mitral or aortic valves are present in approximately 4% of patients with APS.5 Systemic or pulmonary embolism from verrucous endocarditis or nonbacterial vegetations is a significant cause of morbidity and mortality in APS. Insufficiency from leaflet thickening and fibrocalcific changes of the valves has been associated with the syndrome.7 APS is much more common in patients requiring heart valve replacement surgery than in the general population.7 It has been postulated that the antiphospholipid antibodies lead to subendothelial activation, resulting in valvular disease.8 The morphology of the valve lesions in APS may be clinically, echocardiographically, and pathologically indistinguishable from that seen in chronic rheumatic heart disease.9

Coronary artery disease is another important cardiac manifestation of APS. Coronary occlusions account for 23% of the arterial thromboses in APS patients.10 Instances of acute thrombosis after percutaneous transluminal coronary angioplasty and coronary artery bypass graft occlusion have been reported in association with anticardiolipin antibodies.11,12

Antiphospholipid antibodies are also associated with the formation of thrombi within the chambers of the heart, with reports describing thrombus in every chamber of the heart.3,13–15 Intracardiac thrombosis is unusual except in the setting of severe left ventricular dysfunction. The reports of masses within each chamber of the heart in patients with antiphospholipid antibodies possibly implicate these antibodies as pathogenic.

Myocardial dysfunction has also been attributed to APS. The diffuse cardiomyopathy in APS is most likely a result of multiple myocardial microthrombi.16 There are several reports of diffuse cardiomyopathy with

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evidence of microvascular thrombosis without vasculitis. Brown et al reported findings of occlusive thrombosis of intramyocardial arteries with surrounding myocardial necrosis with no evidence of vasculitis in a 22-year-old woman with systemic lupus erythematosus (SLE) and antiphospholipid antibodies who died of heart failure. Murphy and Leach reported extensive platelet thrombi within small intramyocardial arterioles associated with areas of microinfarction in a 40-year-old man with APS who died of heart failure. Greisman et al reported intramyocardial arteries occluded by fibrin thrombi with coronary arteries free of atheromatous changes in a patient with SLE with anticardiolipin antibodies who died of a myocardial infarction. Kaplan et al reported autopsy findings of widespread intramyocardial arteriolar thromboses with no evidence of vasculitis in a young patient with active SLE, antiphospholipid antibodies, and a diffuse cardiomyopathy who died after cardiac arrest. In a study by Leung et al involving 75 patients with SLE and antiphospholipid antibodies, 5 had isolated cardiac dysfunction. Histologic evidence was not available, but occlusive microangiopathy may have been responsible. Al-Kiyumi and Venugopalan reported a case of an 11-year-old boy who presented with acute heart failure due to dilated cardiomyopathy in whom examination revealed the presence of left ventricular thrombi on echocardiography and a marked elevation of anticardiolipin antibodies. Takeda et al reported a case of acute cardiac failure due to dilated cardiomyopathy in a 33-year-old man with SLE and antiphospholipid antibodies.

Finally, endomyocardial fibrosis is a rare cause of myocardial dysfunction in patients with APS. Azeem et al described a case of endomyocardial fibrosis leading to severe right heart failure in a 50-year-old woman with APS.

In our case, the presence of APS provided an interesting differential diagnosis for the possible etiologies for his congestive heart failure, including valvular disease, coronary artery disease, and myocardial dysfunction from diffuse cardiomyopathy or myocardial fibrosis. The patient had no evidence of significant valvular abnormalities or ischemic heart disease. It is likely that the antiphospholipid antibodies contributed to the development of the dilated cardiomyopathy by mechanisms other than valvular and coronary artery disease, likely from thrombotic microangiopathy.

Catastrophic APS

Catastrophic APS is an acute and devastating condition characterized by multiple simultaneous vascular occlusions throughout the body, often resulting in death. There is clinical involvement of at least 3 different organ systems over a period of days or weeks, with histologic evidence of multiple occlusions of large or small vessels. In case reports by Asherson et al, 55% of episodes of catastrophic APS had cardiac involvement, mainly cardiac failure and confirmed myocardial infarction or valve lesions, but occasionally atrial thrombus was seen. Mandal et al described a patient with catastrophic APS who presented with dilated cardiomyopathy and bilateral retinal artery thrombosis. Castro et al described a 33-year-old woman who presented with catastrophic APS associated with acute heart failure due to diffuse cardiomyopathy.

Approach to Management of APS

A consensus has not been reached regarding the management of myocardial dysfunction in APS. In addition to diuretics, angiotensin-converting enzyme inhibitors, and inotropic drugs, these patients need long-term anticoagulation to reduce the risk of thromboembolism of large vessels and thrombotic microangiopathy leading to further cardiac complications. Warfarin is the usual treatment in the absence of contraindications such as pregnancy. The target international normalized ratio is 2.0 to 3.0. The optimal duration and intensity of anticoagulation is uncertain. High-dose glucocorticoids, plasmapheresis, and intravenous immunoglobulins are frequently used in the management of catastrophic APS.

CONCLUSION

Dilated cardiomyopathy should be considered in the differential diagnosis in patients with antiphospholipid antibodies presenting with cardiac failure of no obvious etiology. Management includes long-term anticoagulation in addition to the standard treatment of the congestive heart failure. Early diagnosis and prompt management of this condition may improve the outcomes in these patients. The association between dilated cardiomyopathy and APS may be more prevalent than previously recognized, and further study into this association and the responsible pathogenic mechanism is warranted.

REFERENCES