Case Report

Nonbacterial Vegetations in a Young Patient with Primary Antiphospholipid Syndrome

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The classical clinical picture of the antiphospholipid syndrome (APS) is characterized by venous and/or arterial thromboses, fetal losses and thrombocytopenia, in the presence of antiphospholipid antibodies (aPL). We present the case of a young male patient who suffered a transient ischemic cerebrovascular attack and whose cardiac investigation revealed a cardiac source of embolus, namely non-bacterial vegetations of the mitral valve. Laboratory testing confirmed the diagnosis of primary APS.

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The term "antiphospholipid syndrome" (APS) was first coined to denote the clinical association between antiphospholipid antibodies (aPL) and a syndrome of hypercoagulability.[1] Its classical clinical picture is characterized by venous and/or arterial thromboses, fetal losses and thrombocytopenia, in the presence of aPL. The clinical spectrum of APS is extremely wide; virtually any organ can be damaged.[2, 12] The brain is the most common site of arterial thrombosis.[3] Cerebral events may also be caused by emboli originating from nonbacterial vegetations of the mitral or aortic valve. These valve lesions are rare findings, presenting in only 4 percent of patients with primary or secondary APS.[4]

Case description

A 26-year-old male patient was referred to our outpatient department for evaluation of a systolic murmur. Two months earlier he had experienced a transient ischemic cerebrovascular attack (TIA), which was manifested as dysarthria and numbness of his left arm. His symptoms disappeared spontaneously within three hours. A brain-MRI and a carotid-ultrasound were performed at that time, but none of them revealed any abnormality. After that episode he remained asymptomatic.

Regarding his previous medical history the patient mentioned an intermittent asymptomatic macroscopic hematuria since childhood, attributed to nephrolithiasis. He was treated for arterial hypertension for two years but he had never been investigated for secondary hypertension.

On physical examination the patient was obese, with a mild (2/6) early systolic murmur, mainly audible at the apex. No other abnormal clinical findings were detected.

Laboratory testing showed significant thrombocytopenia (platelets: 40,000/ml^3) and spontaneous increase of activated partial thromboplastin time, which was 60.6 seconds, while his prothrombin time and international normalized ratio were normal. Significant proteinuria was also detected (1 gram of urine protein/24 hours), although his serum creatinine was not elevated (0.9 mg/dl).

A transthoracic echocardiogram was performed but due to the patient's obesity the acoustic window was poor (Figure 1). The dimensions of the heart cavities were normal and the mitral valve leaflets appear-

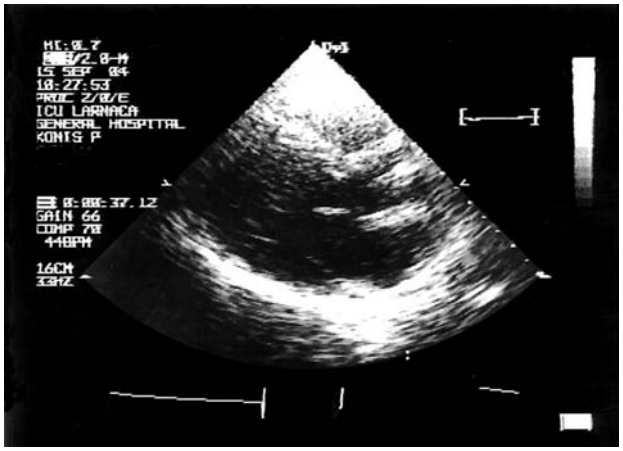

Figure 1. Transthoracic echocardiogram (parasternal long axis view) showing slight thickening of the anterior mitral valve leaflet with no significant pathology.

ed thickened, but without significant pathology. Having in mind the fact that in young patients with stroke or TIA cardiac sources of emboli are common, we proceeded to a transesophageal echocardiogram (Figure 2). This revealed the presence of non-pedunculated apposing vegetations on the atrial surface of both the anterior and posterior leaflets of the mitral valve (Figure 3). Color flow Doppler demonstrated a central jet of a mild mitral regurgitation (1+/4). Since the patient was afebrile, in a very good overall condition and his blood cultures were persistently negative for microorganisms, we concluded that it was a case of nonbacterial thrombotic endocarditis. This was the most probable source of the patient's TIA, even though cerebral artery thrombosis, a well known manifestation of APS could not be excluded.

A more detailed laboratory investigation showed very high titers of anticardiolipin- and β2-glycoprotein antibodies (anticardiolipin total IgG/M/A: 236 u/ml, β2-glycoprotein I total IgG/M/A: 140 u/ml, normal range for both 0-15 u/ml).[5] Antinuclear antibodies and anti-ds DNA were negative, and there were no other clinical or laboratory findings to meet the criteria of systemic lupus erythematosus or other autoimmune diseases.[6] Therefore, the diagnosis of primary APS was established.

Given the patient's proteinuria and hematuria our hospital's nephrologists performed a computed tomography guided renal biopsy. Its most important findings were the occlusive luminar thrombi of interlobular arterioles, with only a minimal perivascular mononuclear cell infiltration, changes known as thrombotic microangiopathy.[7] This histological picture reinforced the diagnosis of primary APS.

Our patient was treated with warfarin (INR 2.5-3.0).[8,9] Until the present time he has remained free of any thromboembolic events.

Discussion

"Primary" APS occurs in patients without clinical evidence of another autoimmune disease, whereas "secondary" APS occurs in association with autoimmune or other diseases, mainly with systemic lupus erythematosus.[4] A recent consensus statement provides simplified criteria for the diagnosis of APS.[11] A patient with APS must meet at least one of two clinical criteria (vascular thrombosis or complications of pregnancy) and at least one of two laboratory criteria (anti-

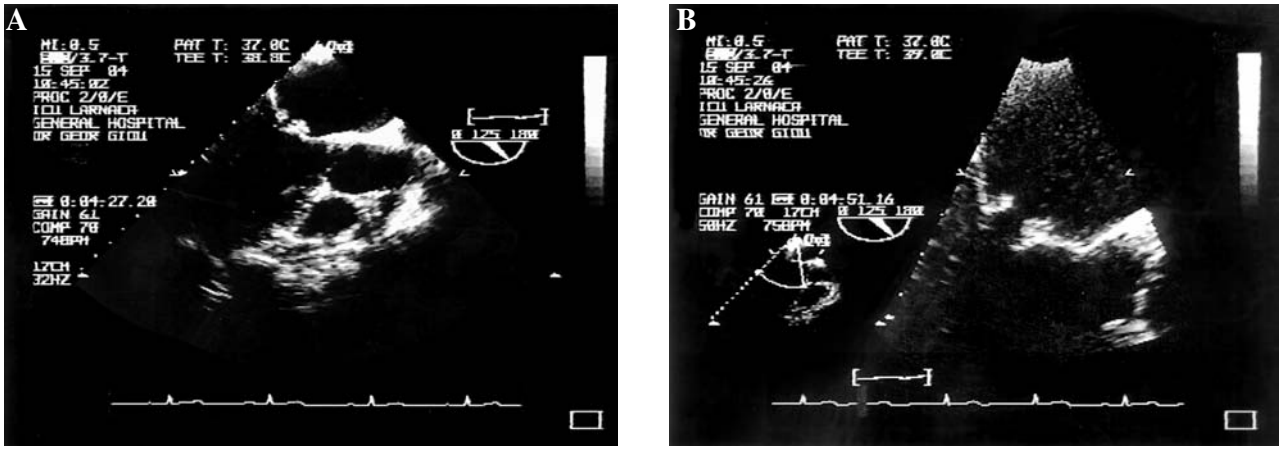

Figure 2. A: Transesophageal echocardiogram (long axis view, 120°) showing large vegetations on both mitral valve leaflets. B: Shows a magnification.

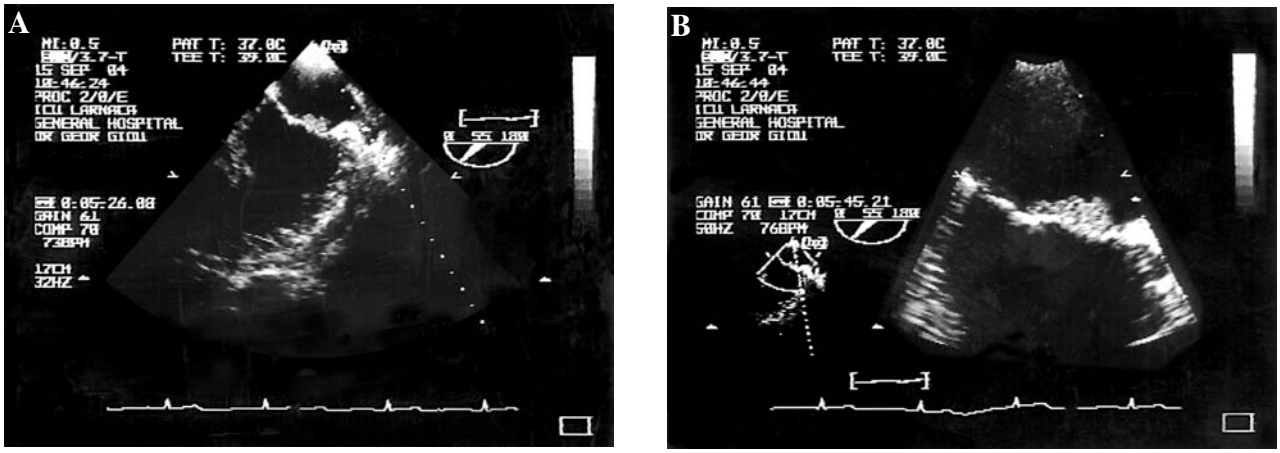

Figure 3. A: Transesophageal echocardiogram (mid-esophageal two-chamber view, 55˚) revealing non-pedunculated apposing vegetations on the atrial surface of the anterior mitral valve leaflet. B: Shows a magnification.

cardiolipin antibodies present at moderate or high levels or lupus anticoagulant antibodies, demonstrated by prolongation of phospholipid-dependent coagulation tests). No limits are placed on the interval between the clinical event and the positive laboratory findings.

The histopathological features of APS reflect a combination of several major pathophysiological processes: ischemia secondary to upstream arterial thromboses or emboli, peripheral embolization from venous, arterial, or intracardiac sources, and thrombotic microangiopathy.

There are no major differences in the clinical consequences between patients with primary APS and those with secondary APS.[12] Virtually any organ can be involved and the range of disorders observed within any organ system spans a diverse spectrum, depending on two key features: the nature and size of the vessels involved and the acuteness or chronicity of the thrombotic process.

Deep venous thrombosis is the most common manifestation of APS,[12] occurring in 29 to 55 percent of patients with the syndrome during an average follow-up of less than six years. Up to half these patients have pulmonary emboli. Arterial thromboses are less common, with strokes and TIA accounting for almost 50 percent of arterial occlusions and coronary occlusions accounting for an additional 23 percent.

The frequency of cardiac valvular abnormalities appears to be quite high, with up to 63 percent of patients with APS revealing at least one valvular abnormality on echocardiography. Many of these abnormalities are of little clinical consequence, such as valve thickening; vegetations of the mitral or aortic valves are present in approximately 4 percent of patients with primary or secondary APS.[13, 14]

Other prominent manifestations of this syndrome include thrombocytopenia (in 40-50% of patients), hemolytic anemia (14-23%), and livedo reticularis (11-22%). Among patients who have APS with renal involvement, hypertension is almost invariably present.

A beneficial role for anticoagulation in decreasing the rate of recurrent thrombosis has been shown in retrospective studies.[8,9] Therefore, the primary therapy of APS is anticoagulation, generally to a level similar to that used for patients with prosthetic valves. There are no long-term controlled studies of the effect of chronic anticoagulation and valve disease. The indications for valve surgery are the same as in other patients.

In conclusion, we describe the case of a young patient who had a transient cerebrovascular attack and whose transesophageal echocardiogram showed nonbacterial lesions of the mitral valve. The presence of anticardiolipin antibodies in high titers confirmed the diagnosis of primary APS. This syndrome is a rare, but real reason for sterile vegetations of the valves, which can be the source of embolic events.

References

1. Hughes GR, Harris NN, Gharavi AE: The anticardiolipin syndrome. J Rheumatol 1986; 13: 486-489.
2. Asherson RA, Cervera R: Unusual manifestations of the antiphospholipid syndrome. Clin Rev Allergy Immunol 2003; 25: 61-78.

3. Asherson RA, Khamashta MA, Ordi-Ros J: The "primary" antiphospholipid syndrome: major clinical and serological features. Medicine 1989; 68: 366-374.
4. Viana JL, Khamashta MA, Ordi-Ros J, et al: Comparison of the primary and secondary antiphospholipid syndrome: a European multicenter study of 114 patients. Am J Med 1994; 96: 3-9.
5. Galli M, Comfurius P, Maassen C: Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. Lancet 1990; 335: 1544-1547.
6. Tan EN, Cohen AS, Fries JF: The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25: 1271-1277.
7. Nochy D, Daugas E, Droz D, et al: The intrarenal vascular lesions associated with primary antiphospholipid syndrome. J Am Soc Nephrol 1999; 10: 507-518.
8. Khamashta MA, Cuadrado MJ, Mujic F, et al: The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995; 332: 993-997.
9. Crowther M, Ginsberg J, Math J, et al: A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med 2003; 349: 1133-1138.
10. Levine J, Branch DW, Rauch J: The antiphospholipid syndrome. N Engl J Med 2002; 346: 752-763.
11. Wilson W, Gharavi A, Koike T, et al: International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome-report of an international workshop. Arthritis Rheum 1999; 42: 1309-1311.
12. Cervera R, Piette JC, Font J, et al: Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002; 46: 1019.
13. Espinola-Zavaleta N, Vargas-Barron J, Colmenares-Galvis T, et al: Echocardiographic evaluation of patients with primary antiphospholipid syndrome. Am Heart J 1999; 137: 973.
14. Hojnik M, George J, Ziporen L, et al: Heart valve involvement (Libman-Sacks Endocarditis) in the antiphospholipid syndrome. Circulation 1996; 93: 1579.