Antiphospholipid Antibody Syndrome and Acute Stent Thrombosis

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Antiphospholipid antibody syndrome is an autoimmune disease characterized by the presence of antiphospholipid antibodies and at least 1 clinical manifestation, most commonly vascular thrombosis or fetal loss. Antiphospholipid antibodies are associated with multiple cardiac manifestations, including valve problems, thrombosis within cardiac chambers, and coronary artery thrombosis. We describe the case of a 46-year-old woman with recurrent coronary stent thrombosis who was found to have antiphospholipid antibodies. After successful coronary artery bypass graft surgery, the patient was kept on twice-daily injections of the low-molecular-weight heparin enoxaparin and started on warfarin. Six days after surgery, she was discharged from the hospital in stable condition.

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A 46-year-old woman with a history of hypertension, hypercholesterolemia, and tobacco use was referred for cardiac catheterization after signs of myocardial ischemia were seen on an exercise stress test that had been performed to evaluate exertional chest pain. Cardiac catheterization revealed an ejection fraction of 55% and multiple obstructive coronary artery stenoses, including 90% mid-left anterior descending (LAD), 60% first diagonal (D1), 85% distal circumflex, 70% second obtuse marginal, and total occlusion of the proximal right coronary artery (RCA). Four paclitaxel drug-eluting stents

were placed in the RCA with good results, and it was recommended that the patient return at a later date for percutaneous coronary intervention of the LAD and circumflex stenoses. She was discharged from the hospital the following day and instructed to take clopidogrel 75 mg/d (a 600-mg loading dose had been given before the intervention) and acetylsalicylic acid (ASA) 325 mg/d.

Two months later, the patient returned for the elective coronary intervention. Cardiac catheterization still showed an ejection fraction of 55%, but there was in-stent restenosis of the RCA (total occlusion). Another drug-eluting stent was successfully placed in the RCA, as well as in the mid-LAD and D1. The patient was discharged from the hospital the following day, with instructions to take clopidogrel 75 mg/d and ASA 325 mg/d.

Two days after discharge, the patient developed acute onset of severe substernal chest pressure at rest associated with dyspnea, nausea, and diaphoresis. She was immediately brought to the emergency department, where a 12-lead electrocardiogram showed a 3- to 4-mm ST segment elevation in leads V2 to V5. She received a bolus of intravenous heparin and underwent emergent cardiac catheterization, which revealed an ejection fraction of 35% with anterior wall hypokinesis and total occlusion (with thrombosis) of the LAD, D1, and RCA stents. Successful thrombectomy, drug-eluting stenting of the LAD, and angioplasty of the D1 were performed. During the procedure, the patient developed acute pulmonary edema, which was treated with intravenous nitroglycerine, furosemide, and insertion of an intra-aortic balloon pump. Myocardial infarction was suggested by a peak troponin I level of 167 and a creatine phosphokinase level of 8252 (a creatine kinase, myocardial bound level of 473). The balloon pump was removed after 36 hours, and cardiac catheterization 2 days later showed patent stents. Transthoracic echocardiography showed an ejection fraction of 30%, with moderate dyskinesis of the interventricular septum and the basal inferior wall, and an apical pseudoaneurysm.

Over the next few days, the patient experienced multiple episodes of chest pain at rest associated with transient ST elevation in the precordial leads. Nitroglycerin and morphine relieved the pain. The patient was sent for coronary artery bypass graft (CABG) surgery. She underwent successful CABG x 5 using the left internal mammary artery to LAD, a saphenous vein graft to the posterior descending artery, a composite right mammary artery to D1, and sequential anastomosis of the right internal mammary artery to the ramus intermedius artery and the posterolateral marginal branch.

Given the recurrent episodes of thrombosis described above, and the reported 100% compliance with ASA and clopidogrel, blood work was performed for evaluation of a hypercoagulable disorder. Protein C, protein S, antithrombin III, and homocysteine levels all were within normal limits. Tests for factor V Leiden and prothrombin gene mutations were both negative. Tests for ASA resistance and clopidogrel resistance were negative. Anticardiolipin antibody test results were negative, but test results for lupus anticoagulant were positive.

After CABG, the patient was kept on twice-daily injections of the low-molecular-weight heparin enoxaparin and started on warfarin. The target International Normalized Ratio (INR) was 2.5. Six days after surgery, she was discharged from the hospital in stable condition, with an INR of 2.6.

Discussion

Antiphospholipid antibody syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies (anticardiolipin antibody or lupus anticoagulant) and at least 1 clinical manifestation, most commonly vascular thrombosis or fetal loss. This syndrome can occur in association with other connective tissue diseases (secondary APS) or in isolation (primary APS), as in our patient.[1]

The most common manifestations of APS are deep vein thrombosis, pulmonary thromboembolism, and stroke.[1] The multiple cardiac manifestations include thrombotic and nonbacterial vegetative lesions on cardiac valves, thrombosis within cardiac chambers, and coronary artery thrombosis.[2-9] In this discussion, we will concentrate on the association of APS with coronary artery thrombosis and myocardial infarction.

Hamstein and colleagues[5] studied 62 patients younger than 45 years who had survived an acute myocardial infarction. Positive titers for anticardiolipin antibodies were found in 21% of the patients, and this group had an increased risk for recurrent cardiovascular events over the next 5 years compared to patients who were not positive for anticardiolipin antibodies. Elevated anticardiolipin levels are not only associated with occlusion of native coronary arteries, they are also correlated to an increased incidence of graft closure in patients who have undergone coronary artery bypass surgery.[6] Although the presence of antiphospholipid antibodies in coronary artery occlusion has been extensively reported, the prevalence is unknown because of the limited number of patients studied.

The association between antiphospholipid antibodies and thrombosis after percutaneous coronary intervention has not been as widely reported. Bick and colleagues[7] examined 40 patients who experienced

early failure of CABG (15 patients), percutaneous transluminal coronary angioplasty (19 patients), or both (6 patients), and found 12 patients (30%) who had positive antiphospholipid antibodies. Half of these patients were positive for lupus anticoagulant and the other half were positive for anticardiolipin antibodies. Only a single case report could be found in the medical literature describing stent thrombosis in a patient with APS. Muir and colleagues[8] described a patient with recurrent stent thrombosis who was later found to have a diagnosis of APS in association with renal cell carcinoma.

The exact mechanisms for thrombosis in patients with APS remain unknown, although several potential pathogenic pathways have been described. Possible mechanisms that may lead to increased procoagulant activity include activation of endothelial cells (with consequent elaboration of cytokines, etc) or injury to the vascular endothelium.[10] Antiphospholipid antibodies may also interfere with the function of the coagulation cascade, leading to a procoagulant state; examples of this process include inhibition of the activated protein C and antithrombin III pathways, inhibition of fibrinolysis, and upregulation of tissue factor activity.[10]

Full anticoagulation with warfarin therapy administered to reach a target INR of 2 to 3, or possibly higher, has reduced the recurrence rate of arterial and venous thrombosis in several retrospective studies.[1,10] It is unlikely that any large, prospective, randomized, placebo-controlled study will be able to directly assess the benefit of warfarin therapy to prevent stent thrombosis in APS patients because of the limited number of events, but empirical anticoagulation therapy should be considered in cases such as the one presented here.

It is reasonable, in the absence of any contraindications, to consider anticoagulation therapy in patients who have stent thrombosis and positive titers for antiphospholipid antibodies.

Conclusion

In this patient, it is reasonable to suspect that the hypercoagulable state associated with APS contributed to the recurrent stent thromboses. In patients who present with acute stent thrombosis, especially when it is recurrent and/or compliance with antiplatelet therapy is certain, the diagnosis of a possible hypercoagulable disorder should be pursued. It is reasonable, in the absence of any contraindications, to consider anticoagulation therapy in patients who have stent thrombosis and positive titers for antiphospholipid antibodies. ■

References

1. Hanly J. Antiphospholipid syndrome: an overview. *CMAJ*. 2003;168:1675-1682.
2. Asherson RA, Cervera R. Antiphospholipid antibodies and the heart. *Circulation*. 1991;84:920-923.
3. Kaplan SD, Chartash EK, Pizzarello RA, et al. Cardiac manifestations of the antiphospholipid syndrome. *Am Heart J*. 1992;124:1331-1338.
4. Sullivan M, DePasquale N, Coplan N. Antiphospholipid antibodies and coronary arterial thrombosis. *Cardiovasc Rev Rep*. 1999;20:315-325.
5. Hamstein A, Norberg R, Bjorkholm M. Antibodies to cardiolipin in young survivors of myocardial infarction: an association with recurrent cardiovascular events. *Lancet*. 1986;1:113-115.
6. Gavaghan TP, Krilis SA, Daggard GE. Anticardiolipin antibodies and occlusion of coronary artery bypass grafts. *Lancet*. 1987;2:977-978.
7. Bick RL, Ismail Y, Baker WF. Coagulation abnormalities in patients with precocious coronary artery thrombosis and patients failing coronary artery bypass grafting and percutaneous transcoronary angioplasty. *Semin Thromb Hemost*. 1993;19:412-417.
8. Muir DF, Stevens A, Napier-Hemy RO, et al. Recurrent stent thrombosis associated with lupus anticoagulant due to renal cell carcinoma. *Int J Cardiovasc Intervent*. 2003;5:44-46.
9. Stoupakis G, Bejjanki R, Arora R. Case report: acute myocardial infarction in a 32-year-old white male found to have antiphospholipid antibody syndrome and MTHFR mutation homozygosity. *Heart Lung*. 2003;32:266-271.
10. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med*. 2002;346:752-763.

Main Points

- The most common manifestations of antiphospholipid antibody syndrome are deep vein thrombosis, pulmonary thromboembolism, and stroke. The multiple cardiac manifestations include thrombotic and nonbacterial vegetative lesions on cardiac valves, thrombosis within cardiac chambers, and coronary artery thrombosis.
- In one study, positive titers for anticardiolipin antibodies were found in 21% of patients younger than 45 years who had survived an acute myocardial infarction; this group had an increased risk for cardiovascular events over the next 5 years.
- The hypercoagulable state associated with antiphospholipid antibody syndrome in this patient contributed to her recurrent stent thromboses.
- Full anticoagulation with warfarin therapy to a target International Normalized Ratio of 2 to 3 or possibly higher reduces the recurrence rate of arterial and venous thrombosis in several retrospective studies.