CASE REPORT

Secondary Antiphospholipid Syndrome with Recurring Acute Coronary Events

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ABSTRACT

A 41-year-old gentleman with a recent history of Hodgkin's lymphoma sustained an acute inferior wall myocardial infarction, managed with percutaneous coronary intervention, thromboaspiration and stenting in a totally occluded right coronary artery. He was placed on triple antithrombotic treatment with dual antiplatelet therapy and oral anticoagulation because of a large thrombotic load in the right coronary artery. Three months later and 5 days after discontinuation of prescribed oral anticoagulant, he had a new acute coronary event due to acute reocclusion in the right coronary artery. Thrombus aspiration and repeat angioplasty restored vessel patency. The patient was put back on triple antithrombotic therapy and was investigated for uncommon causes of blood hypercoagulability. Blood assays revealed elevated anti-β2 glycoprotein I (anti-β2GPI) (IgM) and anticardiolipin antibodies (IgM), consistent with a diagnosis of secondary antiphospholipid syndrome.

ABBREVIATIONS
aCL = anticardiolipin antibodies
anti-β2GPI = anti-β2 glycoprotein I antibodies
APA = antiphospholipid antibodies
APS = antiphospholipid syndrome
ECG = electrocardiogram
MI = myocardial infarction
PCI = percutaneous coronary intervention
RCA = right coronary artery

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Conflict of Interest: none declared

INTRODUCTION

Coronary thrombosis as a manifestation of the antiphospholipid syndrome (APS) is rather uncommon. Patients with APS usually present with recurrent episodes of deep vein thrombosis, pulmonary thromboembolism or thromboembolic stroke. Recurrent coronary events have only been rarely reported. We describe a case of a 41-year-old patient with prior percutaneous coronary intervention (PCI) who had recurrent episode of acute coronary ischemia after discontinuation of oral anticoagulant agent and laboratory testing revealed anti-β2 glycoprotein I (anti-β2GPI) and anticardiolipin (aCL) antibodies.

CASE REPORT

A 41-year-old male patient with no history of coronary artery disease, habitual smoker without any other risk factor for coronary disease, presented to the emergency department complaining of crushing retrosternal chest pain which woke him up. The pain radiated down to his left arm and was accompanied by diaphoresis. The patient had been diagnosed with Hodgkin's lymphoma one year earlier and he had already

completed 13 cycles of chemotherapy with ABVD (adriamycine, bleomycin, vinblastin and dacarbazine). He was also recently started on a new chemotherapeutic regimen with cemcitabine and vinorebline having already completed 2 cycles of it; last cycle was received 10 days prior to this admission.

At presentation, he was pale with a pulse of 70 beats/min and a blood pressure of 125/80 mmHg. Heart sounds were normal without any audible murmurs and lung auscultation was also normal. He had no peripheral edema and all peripheral pulses were present. The 12-lead surface electrocardiogram (ECG) showed ST-segment elevation in the inferior leads II, III, aVF (Fig. 1). Cardiac enzymes were found elevated with high sensitivity troponin T levels at 2150 pg/ml; other blood tests were within normal limits; the platelet count was >120000. Accordingly, a diagnosis of an acute inferior wall myocardial infarction (MI) was established and the patient was submitted to primary percutaneous coronary intervention (PCI).

Coronary angiography revealed total proximal occlusion of the right coronary artery (RCA) and presence of intracoronary thrombus (Fig. 2, panel A); the left coronary artery was patent. A thrombus aspiration catheter (Export®) was used and a large amount of thrombotic material was aspirated from the RCA (Fig. 2, panel C); four Genous® stents were subsequently implanted that restored vessel patency (Fig. 2, panel B). At the same time, intravenous eptifibatide (a platelet glycoprotein IIb/IIIa inhibitor) was started and administered for 24 hours. The patient was discharged home 4 days later with prescriptions that included oral anticoagulation with acenocoumarol instructed to maintain a target INR between 2.0 and 2.5, low-dose aspirin, clopidogrel, beta-blocker, nitrates and a statin.

The patient received 5 more cycles of chemotherapy including cemcitabine and vinorebline without interrupting his triple antithrombotic regimen (dual antiplatelet therapy and anticoagulant agent). Three months later however, he
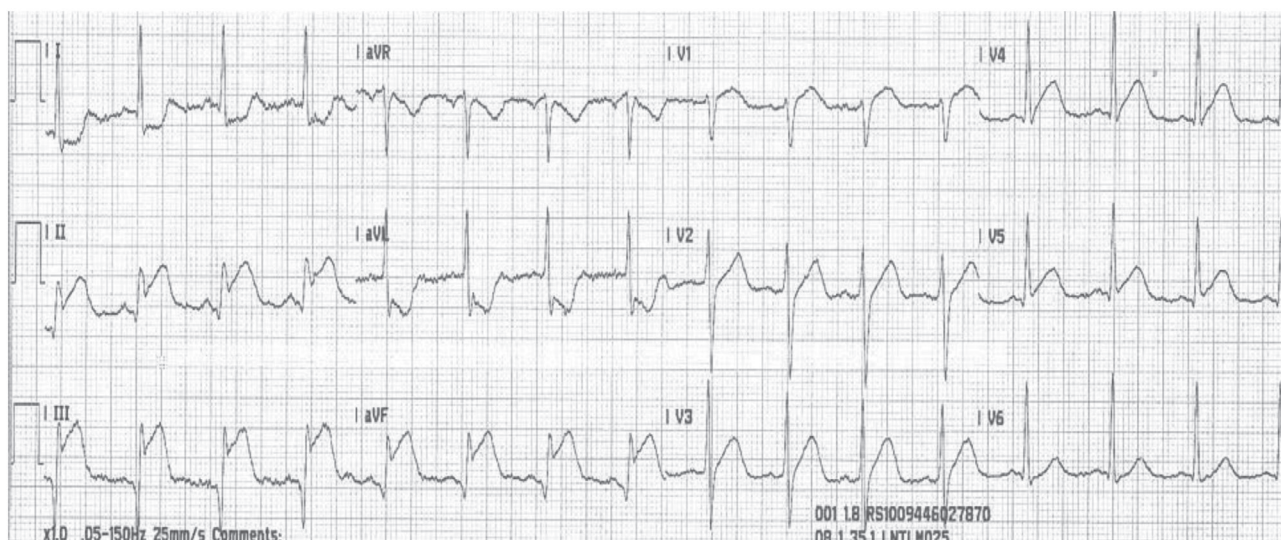

FIGURE 1. 12-lead ECG during chest discomfort with ST-segment elevation in leads II, III, aVF and ST-segment depression in leads I, aVL.
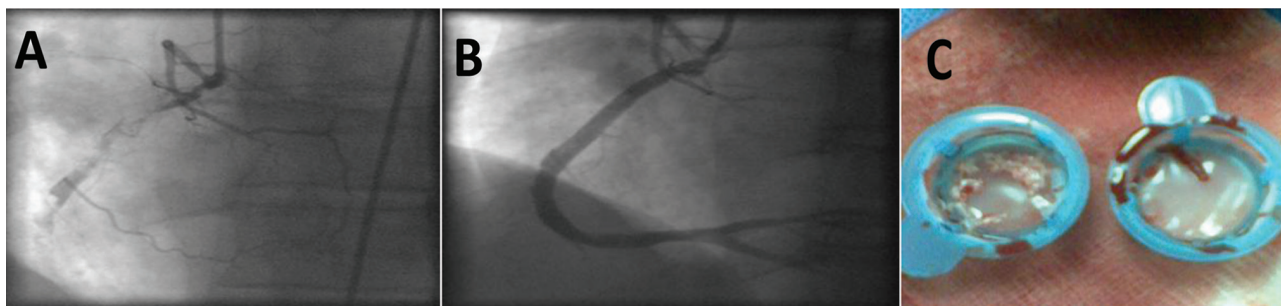

FIGURE 2. Coronary angiogram showed complete occlusion of the proximal right coronary artery , filled with thrombus (**A**), which was fully recanalized after thrombus aspiration and stent implantation (**B**). The aspirated thrombotic material is displayed in panel **C**.

discontinued oral anticoagulation therapy for fear of developing severe pancytopenia as a result of intense chemotherapy (ESHAP scheme: etoposide, methylprednisolone, cytarabine, cisplatin) with a further plan to undergo autologous bone marrow transplantation.

Five days after the discontinuation of acenocoumarol, the patient presented to the emergency department again with a clinical and electrocardiographic picture of a new inferior wall MI. He was initially stabilized and 24 hours later he underwent coronary angiography which revealed reoccluded RCA (Fig. 3, panel A). Thrombus aspiration (Fig. 3, panel C) was again performed using the Export® aspiration system followed by implantation of additional 3 stents which again restored vessel patency (Fig. 3, panel B). The patient received eptifibatide for 24 hours and acenocoumarol was restarted.

Due to the recurrence of myocardial ischemia in a young patient along with the presence of a heavy thrombotic load within the affected coronary artery in the absence of other risk factors except for smoking, the patient underwent a full search for thrombophilia, which revealed abnormally elevated anti-β2 glycoprotein I (anti-β2GPI) IgM and aCL IgM (Table 1). Based on these finding, the diagnosis of secondary APS was established and he was discharged on aspirin, clopidogrel, statin, nitrates, propranolol and acenocoumarol. Echocardiography indicated a mild decrease in left ventricular function. The patient remains asymptomatic one year later.

DISCUSSION

The antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by the presence of persisting antiphospholipid antibodies (APA) along with a thrombotic event (arterial or venous thrombosis) and/or recurrent fetal loss due to placental thrombosis. The syndrome occurs in the absence (primary APS) or in association with another systemic autoimmune disease (secondary APS), mainly systemic lupus erythematosus.[1,2] Approximately half the patients with APS have
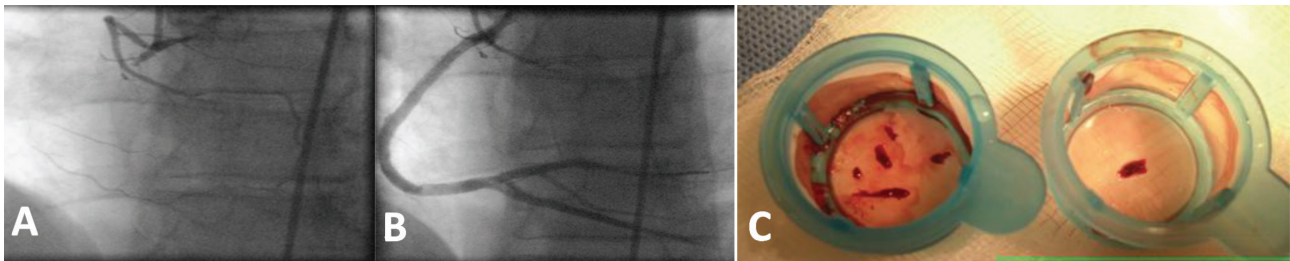

FIGURE 3. Total occlusion of the right coronary artery (**A**) and restoration of flow after percutaneous coronary intervention and thromboaspiration (**B**); aspirated thrombi shown in panel **C**.

TABLE 1. Thrombophilia Testing Results

Antibodies examined			
Test	**Result**	**Reference**	
Anti cardiolipineIgG	4.5	0.1-20	GPL
Anti cardiolipineIgM	63.8*	0.1-20	MPL
Anti β2GPI-IgG	5.2	0.1-8	GPU
Anti β2GPI-IgM	22.7*	0.1-8	MPU
Molecular control (PCR) for mutation			
Factor	**Mutation gene**	**Result**	
Factor V	(Q 506)	negative	
Factor II (prothrombine)	(G20210A)	negative	
Homocysteine	(MTHFR)	negative	

* Abnormal results
anti-β2GPI = anti-β2 glycoprotein I antibodies; PCR = polymerase chain reaction.

no underlying systemic autoimmune disease. Cardiovascular manifestations are observed in approximately 12% of APS patients including thrombotic lesions on cardiac valves or coronary artery thrombosis resulting in myocardial ischemia.[3] Myocardial infarction is diagnosed in 5.5% of patients with APS and is the presenting manifestation in 2.8% of APS patients.[4] In a study of MI patients under the age of 45 years, 21% had persisting APA meeting diagnostic criteria for APS.[5]

Among all malignancies, lymphoma is the fourth malignant tumor most likely to be associated with significant morbidity and mortality related to thrombosis. Pusterla et al[6] supported that APA positive patients suffering from different lymphomas are at high risk for thrombotic complications. Zuckerman et al[7] reported an increased incidence of vascular thrombosis (22%) among APA positive cancer patients. A tendency for thrombo-embolism to occur in APA positive non-Hodgkin lymphomas was correlated with thrombocytopenia at presentation and poor platelet recovery following chemotherapy.[8] Among 86 patients with non-Hodgkin lymphoma, Bairey et al reported that 41% were found with elevated APA levels and such a finding was correlated with shortened survival and has been proposed as an independent prognostic variable.[9]

Antiphospholipid antibodies were first suggested to be in-volved in atherosclerosis in 1993.[10] Antiphospholipid antibodies constitute a heterogenous group of antibodies directed against phospholipid–binding proteins. Current laboratory criteria for APS require two positive tests of anticardiolipin antibodies (aCL), lupus anticoagulant and/or anti-β2-GPI antibodies at least 12 weeks apart. APA are not only diagnostic but also pathogenic auto-antibodies; different mechanisms have been proposed according to which APA cause thrombosis in normal vessels, are associated with accelerated atherosclerosis or even arise at the time of MI as a result to vascular injury and expo-sure to neoantigens.[11] APA exert direct proinflammatory and procoagulant activity on the endothelial surface and may also trigger the inflammatory cascade. Venous thrombotic events are more frequent in lupus anticoagulant positive patients while coronary/carotid/ peripheral arterial thromboses are more frequent in patients with elevated serum levels of aCL or anti-β2-GPI antibodies.[12]

Several studies suggest the involvement of APA in cardio-vascular events; APA is positively associated with the presence of coronary disease and increased risk of ischemic stroke or MI. According to a study on patients with cardiovascular disease, fewer than 2.6% of patients were positive for aCL, whereas 35.6 % were IgA and 1.6% were IgG positive for anti-β2-GPI antibodies[13] which have been found to increase coagulation via the plasminogen pathway and by enhancing platelet adhe-siveness. In a prospective study of 415 patients, Neville et al[14] found that APA predict vascular events independently from other risk factors; apart from prior vascular event, diabetes, gender, age, or activated protein C resistance, it was found that APA positivity predicts imminent arterial or vascular

events. Women aged <50 years with a myocardial infarction or an ischemic stroke were enrolled in the RATIO study.[15] Different APA and genetic prothrombotic risk factors were measured and it was demonstrated that the lupus anticoagu-lant is a major independent risk factor for arterial thrombotic events in young women.[15] Meroni et al[16] also found that IgG/IgM anti-β2-GPI antibodies is a significant risk factor for MI in premenopausal women independently of other risk factors (e.g. degree of coronary artery stenosis) while the significance of IgG aCL is minor. The hypothesis that aCL participate in the pathogenesis of MI has also been reported, due to their inflammatory and procoagulant properties. Zuckerman et al[17] suggested that high levels of aCL are risk factor for subsequent thromboembolic events or myocardial reinfarction after acute MI in relatively young survivors of acute MI. Moreover, in a recent study by Sacre et al,[18] an unexpectedly high prevalence of occult myocardial ischemic disease in APS patients was detected by cardiac magnetic resonance imaging; yet the number of patients was small and further studies are needed to clarify such a finding.

It has also been reported that APA are associated with adverse events and outcomes in angioplasties and coronary artery bypass, especially in young patients.[19] Greco et al[20] found that the presence of APA are not only associated with the presence of coronary disease but also with an increase in adverse cardiac outcomes of patients undergoing proce-dures (angioplasty, stent, bypass) (P=0.045) and extracardiac thrombotic events (P=0.033). At present, only levels of aCL (not levels of anti-β2-GPI) antibodies are proposed as inde-pendent risk factors for recurrent cardiac events regarding postinfarction patients; in fact, patients with elevated levels of IgG aCL and low levels of IgM aCL antibodies have a 3-fold higher risk for recurrent cardiac events.[21] Patients with APS undergoing PCI have worse long-term clinical outcomes and higher levels of revascularization, caused by both restenosis within the stent(s) and accelerated atherosclerosis in vessel areas not covered by stents.[22] Although drug eluting stents are a major breakthrough in the struggle against restenosis, contraindications due to coagulation abnormalities may arise in APS patients and should be taken into account in order to avoid stent thrombosis. To limit potentially life-threatening thrombotic complications by angioplasty procedures which routinely cause vascular damage, prolonged dual antiplatelet therapy combined with anticoagulant treatment should be considered, while thrombophilia screening should be included in the diagnostic workup.[3]

APS should be considered as a potential cause of acute coronary syndrome in younger patients (<55 in men and <65 in women) with structurally normal coronary arteries, no other traditional cardiovascular risk factors, no history of drug abuse or congenital abnormality, who have a history of recurrent thrombotic events and/or abnormal coagulation test results. There is lack of prospective randomized placebo-controlled

trials evaluating specific diagnostic and therapeutic approaches in APS patients with an acute coronary syndrome. Nevertheless there is consensus that APS patients should receive life-long anticoagulation therapy for secondary thromboprophylaxis; patients with prior venous thrombosis should have a target INR of 2.0-3.0 and patients with arterial thrombosis a target INR of >3.0.[2,23] Retrospective and prospective studies have shown the efficacy of warfarin for secondary thrombosis prevention in APS.[24] Based on retrospective studies, 20–70% of patients with APS develop recurrent thrombosis when they stop anticoagulation treatment. Statins have also been proposed in APS drug therapy due to their antithrombotic, anti-inflammatory and pleiotropic effects on vascular endothelium. It remains unknown whether novel orally administered agents, including dabigatran etexilate (direct thrombin inhibitor) and rivaroxaban or apixaban (direct factor Xa inhibitors), have any therapeutic potential in APS patients. Further trials are needed to determine the advantages and risks of these agents.[25]

CONCLUSION

The antiphospholipid syndrome (APS), though uncommon, is an acquired autoimmune hypercoagulable state which should be considered when investigating young patients who have experienced an acute coronary syndrome without other predisposing factors for coronary disease. APS patients with a coronary syndrome and coronary angioplasty have an increased risk for recurrent cardiac event and should receive life-long anticoagulation therapy apart from anti-ischemic and anti-thrombotic treatment.

REFERENCES

1. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; 4:295-306.
2. Gualtierotti R, Biggioggero M, Meroni PL. Cutting-edge issues in coronary disease and the primary antiphospholipid syndrome. *Clinic Rev Allerg Immunol* 2011 Mar 15 [Epub ahead of print]
3. Grzybczak R, Undas A, Rostoff P, et al. Life-threatening cardiac manifestations of primary antiphospholipid syndrome. *Heart Vessels* 2010; 25:267-269.
4. Cervera R, Boffa MC, Khamashta M, Hughes G. The Euro-Phospholipid Project: epidemiology of the antiphospholipid syndrome in Europe. *Lupus* 2009; 18:889-893.
5. Hamsten A, Norberg R, Bjorkholm M, de Faire U, Holm G. Antibodies to cardiolipin in young survivors of myocardial infarction: an association with recurrent cardiovascular events. *Lancet* 1986; 1:113-116.
6. Pusterla S, Previtali S, Marziali S, et al. Antiphospholipid anti-

bodies in lymphoma: prevalence and clinical significance. *Hematology J* 2004; 5: 341-346.
7. Zuckerman E, Toubi E, Golan TD, et al. Increased thromboembolic incidence in anti-cardiolipin-positive patients with malignancy. *Br J Cancer* 1995; 72:447-451.
8. Zaidah A, Liza D, Madhavan R, Hassan R, Ganech A. Antiphospholipid antibodies and its clinical association with non-Hodgkin lymphoma. *Haema* 2006; 9:511-518.
9. Bairey O, Blickstein D, Monselise Y, et al. Antiphospholipid antibodies may be a new prognostic parameter in aggressive non-Hodgkin's lymphoma. *Eur J Haematol* 2006; 76:384-391.
10. Vaarala G, Alfthan G, Jauhiainen M, et al. Crossreaction between antibodies to oxidized low-density lipoprotein and to cardiolipin in systemic lupus erythematosus. *Lancet* 1993; 341: 923-925.
11. Davies J, Hunt B. Myocardial infarction in young patients without coronary atherosclerosis: assume primary antiphospholipid syndrome until proved otherwise. *Int J Clin Pract* 2007; 61:379-384.
12. Soltesz P, Szekanecz Z, Kiss E, Shoenfeld Y. Cardiac manifestations in the antiphospholipid syndrome. *Autoimmun Rev* 2007; 6:379-386.
13. Iverson GM, von Muhlen CA, Staub H, et al. Patients with atherosclerotic syndrome, negative in anticardiolipin assays, make IgA autoantibodies that preferentially target domain 4 of β2GPI. *J Autoimmun* 2006; 27:266-271.
14. Neville C, Rauch J, Kassiss J, et al. Antiphospholipid antibodies predict imminent vascular events independently from other risk factors in a prospective cohort. *Thromb Haemost* 2009; 101: 100-107.
15. Urbanus RT, Siegerink B, Roest M, Rosendaal FR, de Groot PG, Algra A. Antiphospholipid andibodies and risk of myocardial infarction and ischaemic stroke in young women in the RATIO study: a case-control study. *Lancet Neurol* 2009; 8:998-1005.
16. Meroni PL, Peyvandi F, Foco L, et al. Anti-β2-glycoprotein I antibodies and the risk of myocardial infarction in young premenopausal women. *J Thromb Haemost* 2007; 5:2421-2428.
17. Zuckerman E, Toubi E, Shiran A, et al. Anticardiolipin antibodies and acute myocardial infarction in non-systemic lupus erythematosus patients: a controlled prospective study. *Am J Med* 1996; 104:381-386.
18. Sacre K, Brihaye B, Hyafil F, et al. Asymptomatic myocardial ischemic disease in antiphospholipid syndrome. *Arthritis Rheum* 2010; 7:2093-2100.
19. Greco TP, Conti-Kelly AM, Greco TJ, et al. Newer antiphospholipid antibodies predict adverse outcomes in patients with acute coronary syndrome. *Am J Clin Pathol* 2009; 132:613-620.
20. Greco TP, Conti-Kelly A, Matsuura E, et al. Antiphospholipid antibodies in patients with coronary artery disease. *Ann N Y Acad Sci* 2007; 1108:466-474.
21. Bili A, Moss AJ, Francis CW, Zareba W, Watelet LF, Sanz I. Anticardiolipin antibodies and recurrent coronary events: a prospective study of 1150 patients. Thrombogenic factors and recurrent coronary events investigators. *Circulation* 2000; 102:

1258-1263.

22. Perl L, Netzer A, Rechavia E, et al. Long-term outcome of patients with antiphospholipid syndrome who undergo percutaneous coronary intervention. *Cardiology* 2012; 122:76-82.

23. Fonseca AG, D'Cruz DP. Controversies in the antiphospholipid syndrome: can we ever stop warfarin? *J Autoimmune Dis* 2008; 11:5:6.

24. Lim W, Crother MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. *JAMA* 2006; 295:1050-1057.

25. Cohen H, Machin SJ. Antithrombotic treatment failures in antiphospholipid syndrome: the new anticoagulants? *Lupus* 2010; 19:486-491.