



Antiphospholipid antibody syndrome causing acute myocardial infarction in a young adult

Benjamin Sussman, DO, B. Brent Simmons, MD

From the Department of Family and Community Medicine, Hahnemann University Hospital, Drexel University College of Medicine, Philadelphia, PA

KEYWORDS:

Myocardial infarction;
Antiphospholipid
antibody syndrome;
Factor V Leiden;
Hypercoagulable state;
Anticoagulation;
Young adult

Myocardial infarction (MI) is more frequent in patients older than 45 years of age; however, it can occur in young patients and it is important to include in the differential diagnosis of chest pain. In this case, a 29-year-old male presented to the emergency department with chest pressure. Electrocardiography revealed an acute ST elevation MI. The patient was found to have a mixed hypercoagulability disorder, including antiphospholipid (aPL) antibody syndrome, which led to the infarction. aPL antibody syndrome is a common cause of acquired hypercoagulability in the general population. It is a clinical syndrome characterized by repeated arterial and venous thrombosis, recurrent fetal loss, and positive antibody tests. Asymptomatic patients with low titer aPL antibodies require no treatment. Asymptomatic patients with moderate to high titer aPL antibodies are managed with low-dose aspirin, as are patients with a history of pregnancy-related complications. Patients with more severe manifestations, such as venous or arterial thrombosis, are managed with lifelong administration of warfarin.

© 2010 Elsevier Inc. All rights reserved.

Case report

A 29-year-old male presented to the emergency department with a two-day history of progressively increasing chest pain. He stated the pain was left-sided, substernal, and began while he was sitting. The pain at presentation was a 10 out of 10 on a pain scale and associated with nausea, sweating, shortness of breath, and radiation to his left arm and jaw. He denied fever, chills, abdominal pain, dizziness, blurry vision, or headaches. It was described as dull in nature and felt like “a piano was sitting on my chest.” All other review of systems was negative. He denied any trauma to his chest. He had never experienced chest pain like this. He had a past medical history of ulcerative colitis, which was in remission, and he was supposed to be taking sulfasalazine, but admitted he rarely used it because his “stom-

ach” felt fine. He denied any allergies. He was a nonsmoker, denied any illicit drug use, and was a social drinker. His father developed hypertension in his 60s, and his maternal grandfather had coronary disease diagnosed in his 70s. He denied any family history of premature or sudden death of anyone younger than age 55.

At arrival to the emergency department, he was pale, diaphoretic, and tachycardic at 110 bpm, which then slowed to 83 bpm after a few minutes. His blood pressure was 110/70, respiratory rate was 22 breaths/min, temperature was 98.5°F, and his oxygen saturation was 100% on room air. There was no peripheral edema and all his pulses were normal. Heart auscultation was regular without any murmurs, rubs, or gallops. His lungs were clear without any rhonchi or rales. His abdominal, neurological, and rectal examinations were all normal. A portable chest x-ray was clear. A 12-lead electrocardiogram was performed and showed sinus rhythm with ST-segment elevation in the anterior precordial leads (Fig. 1). He was given aspirin, nitroglycerin sublingual tablets followed by intravenous

Corresponding author: Dr. Benjamin M. Sussman, Department of Family and Community Medicine, Drexel University College of Medicine, 10 Shurs Lane, Suite #203, Philadelphia, PA 19127.

E-mail address: drsuss@gmail.com.

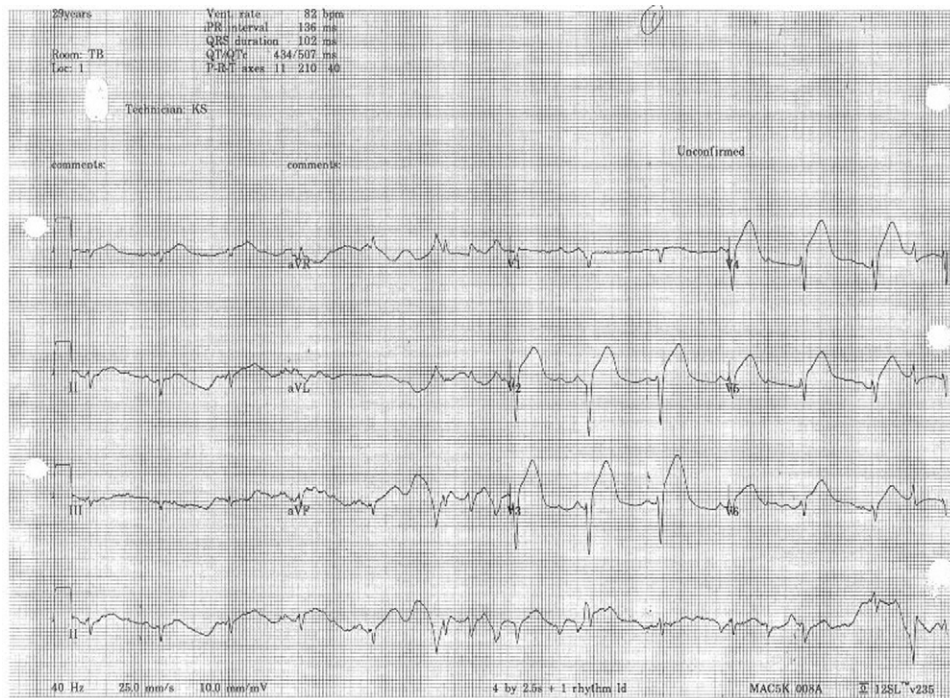


Figure 1 A 12-lead electrocardiogram showing sinus rhythm with ST-segment elevation in the anterior precordial leads.

(IV) nitroglycerin, IV heparin, and eptifibatide. While this was being done, the physician covering the acute myocardial infarction (MI) service was alerted.

The patient's initial troponin I level was 10.27. His initial basic metabolic panel was unremarkable, as was his urine analysis, prothrombin time, partial thromboplastin time, and international normalized ratio (INR). He had a leukocyte count of 16.3 and a hemoglobin and hematocrit of 12.1 and 35.9, respectively. His urine drug screen was negative for phenacyclidine, benzodiazepines, cocaine, amphetamines, tetrahydrocannabinol, opiates, and barbiturates.

The patient was taken to the catheterization lab, where he was found to have a near 100% occluded left anterior descending artery and a 90% occlusion of his right coronary arteries. Cardiac stenting was attempted but was unsuccessful because of the density of the clot. The cardiologist successfully performed a thrombectomy of his left anterior descending artery clot. His IV heparin was continued throughout the hospitalization. An echocardiogram performed later that morning showed a 40% ejection fraction and slight septal wall motion abnormalities. Because of his young age, more laboratory tests were ordered for analysis, which were run from his initial "preheparin" treatment, including lupus anticoagulant, factor V Leiden, prothrombin gene mutation, proteins C and S levels, homocysteine level, and factor VIII levels.

While he was recovering in the intensive care unit (ICU), his hypercoagulable laboratory results returned. His factor V Leiden was heterozygous and he was positive for the lupus anticoagulant. Antithrombin III, proteins C and S, homocysteine level, factor VIII level, and anti-nuclear antibody were normal. His chest pain had been resolved and

two days later he was resting comfortably when he complained again of chest pain. He then suffered a ventricular fibrillation cardiac arrest while in the ICU and was successfully resuscitated. He was intubated during the cardiac arrest and, after recovering, was not able to be extubated. Fourteen weeks after his initial labs, lupus anticoagulant was still positive as was a high titer B2-glycoprotein-I antibody (an antiphospholipid [aPL] antibody). Unfortunately, he continued to have recurrent deep vein thrombosis while in the ICU and he eventually died from a pulmonary embolism. The family declined an autopsy.

Discussion

When approaching a patient such as this, it is vital to understand the differential diagnosis of MI in young adults. The causes of MI in adults younger than 45 years can be divided into four groups: (1) atheromatous coronary artery disease, (2) non atheromatous coronary artery disease, (3) MI related to substance abuse, and (4) hypercoagulable states.¹

Atheromatous coronary disease begins in childhood. In a study of 760 young adults who died of various causes, advanced coronary disease was found in 20% of men and 8% of women between the ages of 30 and 34 years.² The etiology of atheromatous coronary artery disease in young persons is similar to older individuals, with high lipids, diabetes, and smoking being major risk factors.¹ Nonatheromatous coronary artery disease can be caused by congenital abnormalities, such as myocardial bridging (a tunneling

phenomenon that can result in arterial constriction) and coronary artery aneurysm.³ The third major cause—recreational drug use—is common among young patients. Cocaine use was found to be associated in 48% of young adults who presented to the emergency department with nontraumatic chest pain.⁴ Patients with cocaine-related MI cannot be distinguished clinically from other causes. Therefore, patients who lack cardiac risk factors, especially young patients, should have urine cocaine screening routinely performed.

The fourth cause—hypercoagulability—is a rare but important cause of MI in young people, as illustrated in this case. The differential diagnosis of the hypercoagulable state can be divided into *congenital* and *acquired*. Congenital causes include antithrombin III deficiency, protein C deficiency, protein S deficiency, homocystinuria, dysfibrinogenemias, hyperlipidemia, and factor V Leiden mutation.⁵ Acquired causes include oral contraceptive use, lupus anticoagulant, myeloproliferative disorders, essential thrombocythemia, polycythemia vera, paroxysmal nocturnal hemoglobinuria, heparin-associated thrombocytopenia, prothrombin complex concentrate infusion, nephrotic syndrome, pregnancy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, malignancy, sickle cell anemia, hyperviscosity syndromes, previous venous thrombosis, and venous trauma (Table 1).⁵

Although it rarely causes MI, aPL antibody syndrome is a common cause of acquired hypercoagulability in the general population. It is a clinical syndrome characterized by repeated arterial and venous thrombosis, recurrent fetal loss, and positive antibody tests.⁶ aPL antibodies are autoantibodies directed against proteins that bind to phospholipids, including cardiolipin and B2-glycoprotein-I.⁷ Patients with aPL antibody syndrome are at increased risk of recurrent arterial or venous thrombosis or pregnancy loss.⁷

aPL antibodies are found among young, otherwise healthy people at a prevalence of 1% to 5% for both anticardiolipin antibodies and lupus anticoagulant antibodies.⁸ Among patients presenting with thrombosis, the prevalence of aPL antibodies is much higher, in the range of 4% to 21%.⁷ Among patients with aPL antibodies, the absolute risk of developing new thrombosis is low (1% per year) in otherwise healthy patients without prior thrombotic events; may be moderately increased (up to 10% per year) in women with recurrent fetal loss without prior thrombosis; and is highest (10% in the first year) in patients with a history of venous thrombosis who have discontinued anticoagulant drugs within 6 months.⁷ Finally, among patients with systemic lupus erythematosus, the prevalence of aPL antibodies can be as much as 30% for anticardiolipin antibodies and as much as 34% for the lupus anticoagulant.⁸

The clinical spectrum of disease for aPL antibody syndrome varies. It can present as vascular events, systemic manifestations (eg, livedo reticularis, thrombocytopenia, hemolytic anemia, nephropathy, cardiac valve disease), catastrophic antiphospholipid syndrome, or asymptomatic aPL positivity.⁹ As far as vascular events, this syndrome can present with arterial or venous thrombosis. Stroke and transient ischemic attack are the most common presentations of arterial thrombosis, whereas deep vein thrombosis is the most common presentation of venous thrombosis.⁹ Catastrophic aPL syndrome is a rare and severe form of aPL syndrome that commonly occurs with thrombotic microangiopathy, thrombocytopenia, widespread thromboses, and microangiopathic hemolytic anemia.

A diagnosis of definite aPL syndrome requires the presence of at least one of the clinical criteria (vascular thrombosis or complications of pregnancy) and at least one of the laboratory criteria.¹⁰ The laboratory criteria required to make the diagnosis are lupus anticoagulant on two or more occasions at least 12 weeks apart, anticardiolipin antibody on two or more occasions at least 12 weeks apart, or anti- β_2 glycoprotein-I antibody on two or more occasions at least 12 weeks apart.¹¹

Therapy for antiphospholipid syndrome involves anticoagulation for thrombosis or pregnancy prophylaxis.¹² Treatment is less well-defined for the associated nonthrombotic complications and atypical complications, and for asymptomatic patients. Limited data support anticoagulant therapy in asymptomatic aPL-positive patients.¹² Current recommendations from a recent consensus statement favor low-dose aspirin in asymptomatic patients.¹³ Asymptomatic patients with low titer aPL antibodies require no treatment. Asymptomatic patients with moderate to high titer aPL antibodies are managed with low-dose aspirin, as are patients with a history of pregnancy-related complications. Patients with more severe manifestations, such as venous or arterial thrombosis, are managed with life-long warfarin.¹³ Just as important in these patients is the avoidance of reversible thrombotic risk factors such as smoking or oral contraceptive use.¹² Patients with arterial or venous thrombosis require long-term anticoagulation therapy. Previous

Table 1 Differential diagnosis of hypercoagulable state

Congenital	Acquired
Antithrombin III deficiency	Oral contraceptive use
Protein C deficiency	Venous trauma
Protein S deficiency	Lupus anticoagulant
Homocystinuria	Myeloproliferative disorders
Dysfibrinogenemias	Essential thrombocythemia
Hyperlipidemia	Polycythemia vera
Factor V Leiden	Paroxysmal nocturnal Hemoglobinuria
	Heparin-associated thrombocytopenia
	Prothrombin complex concentrate infusion
	Nephrotic syndrome
	Pregnancy
	Disseminated intravascular coagulation
	Thrombotic thrombocytopenic purpura
	Malignancy
	Sickle cell anemia
	Hyperviscosity syndromes
	Previous venous thrombosis

retrospective studies suggest that long-term, high-intensity (INR 3-4) warfarin was most effective in preventing recurrent thromboembolic events, but the necessity of high-intensity anticoagulation has become controversial.¹⁴ A more recent prospective randomized controlled trial of two intensities of warfarin therapy in 114 aPL antibody-positive patients with previous thrombosis followed for a mean of 2.7 years concluded that moderate (INR 2-3) and high (INR 3-4) intensity anticoagulation were similarly effective.¹⁵ Current American College of Chest Physicians (ACCP) guidelines recommend initial INR range of 2 to 3, but INR range 2.5 to 3.5 for recurrent thrombotic events, or if the patient has any additional thromboembolic risk factors.¹⁶

The patient in this case had a history of ulcerative colitis, which, according to the patient, was in remission. Patients with inflammatory bowel disease (IBD) frequently suffer from macrovascular thrombosis.¹⁷ The incidence of arterial and venous thromboembolism in patients with ulcerative colitis and Crohn's disease is between 1% and 8%, rising to an incidence of 39% in some postmortem studies.¹⁷ The risks for thrombosis in IBD has been attributed to a state of hypercoagulation caused by elevated levels of plasma fibrinogen and factors V, VII, and VIII; as well as thrombocytosis and abnormal platelet aggregation.¹⁷ Interestingly, positive aPL antibodies, in addition to antibodies against β_2 -glycoprotein-I, have been found in patients with IBD.¹⁷ According to some studies, a trend toward an association between anticardiolipin antibodies and worsening thrombotic disease was identified; however, the associations were not strong enough to be statistically significant.¹⁷ In addition, the presence of β_2 -glycoprotein-I antibodies does not seem to be related to thrombotic risk in IBD.¹⁷ Although levels of anticardiolipin antibodies appear to be elevated in patients with IBD, elevated anticardiolipin antibody levels appear to play no role in the pathogenesis of thromboembolic events in patients with IBD.¹⁸

The patient in this case also happened to be heterozygous for the factor V gene mutation. Studies on whether factor V Leiden mutation itself increased the risk of acute MI are ambiguous. A small prospective controlled trial concluded that frequency of factor V Leiden mutation was higher among patients with MI.¹⁹ However, another small study addressed patients presenting with acute MI to assess whether factor V Leiden increases the risk of arterial thrombosis. This particular study showed no evidence of an association between factors V Leiden and acute MI.²⁰ A 1999 study specifically looked at the potential synergy between factor V Leiden and aPL syndrome. This study showed an increased risk of thrombosis in patients with a factor V Leiden mutation and the aPL antibody syndrome.²¹

Conclusions

Hypercoagulability is a rare cause of MI, but should be included in the differential for young patients, along with

coronary disease, anatomical abnormalities, and substance abuse. aPL antibody syndrome is associated with various conditions, including arterial and venous thrombosis and pregnancy-related complications. Diagnosis of aPL syndrome is based on a combination of clinical history and laboratory testing. If a clinical scenario is present, initial testing should include lupus anticoagulant, anticardiolipin antibodies, and β_2 -glycoprotein-I, if available. Laboratory testing should be repeated in 12 weeks. Therapy for aPL syndrome involves anticoagulation for thrombosis or pregnancy prophylaxis. Current recommendations from a recent consensus statement favor low-dose aspirin in asymptomatic patients. Asymptomatic patients with moderate to high titer aPL antibodies are managed with low-dose aspirin, as are patients with a history of pregnancy-related complications. Patients with more severe manifestations, such as venous or arterial thrombosis, are managed with lifelong warfarin. Current ACCP guidelines recommend an initial INR range of 2 to 3, but an INR range 2.5 to 3.5 is suggested for recurrent thrombotic events or if the patient has any additional thromboembolic risk factors. Early recognition and treatment in these patients can be lifesaving.

References

1. Eged M, Viswanathan G, Davis GK: Myocardial infarction in young adults. *Postgrad Med J* 81:741-745, 2005
2. McGill HC Jr, McMahan CA, Zieske AW, et al: Association of coronary heart disease risk factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation* 102:374, 2000
3. Erbel R, Junbo G, Möhlenkamp S: Myocardial bridging: a congenital variant as an anatomic risk factor for myocardial infarction? *Circulation* 120:357-359, 2009
4. Hollander JE, Todd KH, Green G, et al: Chest pain associated with cocaine: an assessment of prevalence in suburban and urban emergency departments. *Ann Emerg Med* 26:671-676, 1995
5. Schafer A: The hypercoagulable states. *Ann Intern Med* 102:814, 1985
6. Osula S, Bell G, Hornung R: Acute myocardial infarction in young adults: causes and management. *Postgrad Med J* 78:27-30, 2002
7. Lim W, Crowther M, Eikenbloom J: Management of antiphospholipid antibody syndrome: a systemic review. *JAMA* 295:1050-1057, 2006
8. Petri M: Epidemiology of the antiphospholipid antibody syndrome. *J Autoimmun* 15:145-151, 2000
9. George D, Erkan D: Antiphospholipid syndrome. *Prog Cardiovasc Dis* 52:115-125, 2009
10. Levine J, Branch D, Rauch J: The antiphospholipid syndrome. *N Engl J Med* 346:752-763, 2002
11. Miyakis S, Lockshin MD, Atsumi T: International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 4:295-306, 2006
12. Sammaritano L: Antiphospholipid syndrome: review. *South Med J* 98:617-625, 2005
13. Alarcon-Secovia D, Boffa MC, Branch W, et al: Prophylaxis of the antiphospholipid syndrome: a consensus report. *Lupus* 12:499-503, 2003
14. Khamashta MA, Cuadro MJ, Mujic F, et al: The management of thrombosis in the antiphospholipid antibody syndrome. *N Engl J Med* 332:993-997, 1995
15. Crowther MA, Ginsberg JS, Julian J, et al: Comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med* 349:1133-1138, 2003

16. Hirsh J, Guyatt G, Albers GW, et al: Executive summary: American College of Chest Physicians evidence based clinical practice guidelines (8th edition). *Chest* 133:71S-105S, 2008
17. Koutroubakis I, Petinaki E, Anagnostopoulou E, et al: Anti-cardiolipin and Anti- β 2-glycoprotein I antibodies in patients with inflammatory bowel disease. *Dig Dis Sci* 43:2507-2512, 1998
18. Aichbichler B, Petritsch W, Reicht G, et al: Anti-cardiolipin antibodies in patients with inflammatory bowel disease. *Dig Dis Sci* 44:852-856, 1999
19. Settin A, Dowaidar M, El-Baz R, et al: Frequency of factor V Leiden mutation in Egyptian cases with myocardial infarction. *Hematology* 13:170-174, 2008
20. Gowda MS, Zucker ML, Vacek JL, et al: Incidence of factor V Leiden in patients with acute myocardial infarction. *J Thromb Thrombolysis* 9:43-45, 2000
21. Pablos JL, Caliz RA, Carreira PE, et al: Risk of thrombosis in patients with antiphospholipid antibodies and factor V Leiden mutation *J Rheumatol* 26:588-589, 1999