Severe thrombotic complications secondary to antiphospholipid syndrome and undiagnosed systemic lupus erythematosus

Megan R.W. Barber MD PhD, Ann E. Clarke MD MSc, Corey D. Adams MD MSc, Leslie Skeith MD MHPE

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A 22-year-old man presented to his family physician with intense pain in, dusky discolouration of and reduced sensation to his right foot. He had a history of migraines and 2 years of mild intermittent calf discomfort with exercise, for which he had not sought medical attention. He had a family history of premature coronary artery disease. Peripheral artery duplex ultrasonography showed reduced blood flow in both tibial arteries and a deep vein thrombosis in his right leg. Given the abnormal arterial flow, computed tomography (CT) angiography was ordered, which showed a chronic occlusion in the patient's right superficial femoral artery and an occluded infrarenal abdominal aorta with collateralization (Figure 1). Splenomegaly and axillary adenopathy were noted. He was treated with apixaban and referred to the vascular surgery team.

The vascular surgery team considered performing an aortobifemoral bypass and referred the patient to the internal medicine team for preoperative assessment. Because the patient did not have any clear provoking factors for his unusual arterial and venous thromboses, such as cancer, antiphospholipid antibody testing was ordered and was positive for lupus anticoagulant, and for high levels of immunoglobulin (Ig) G anticardiolipin antibodies and IgG anti-β2 glycoprotein-1 antibodies (aβ2GP1). He was referred to our hematology and rheumatology clinics. Besides apixaban, he was taking no other medications.

The patient recalled 6 months of insidious migratory arthralgia, prolonged morning stiffness and symptoms of Raynaud phenomenon. A few years before initial presentation, he had developed pleuritic chest discomfort, which was attributed to costochondritis, but the pain had never fully resolved. When we examined him, his body mass index was 31, his blood pressure was 140/85 mm Hg and he had dependent rubor and loss of hair on his right leg. Several joints were tender. We did not observe any swollen joints, head or neck adenopathy, or rashes.

Given that the patient's symptoms, thromboses and laboratory results suggested systemic lupus erythematosus (SLE), immune serology was ordered, which showed an antinuclear antibody titre greater than 1:640; antichromatin, anti-Smith and antiribonucleoprotein antibodies; elevated anti-double-stranded DNA; hypocomplementemia; and a positive direct antiglobulin test, without evidence of hemolysis (Table 1).

Key points

- Antiphospholipid syndrome (APS) is an autoimmune condition characterized by the production of autoantibodies and is associated with venous, arterial or small-vessel thrombosis and obstetric complications.
- Testing for antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies and anti-β2 glycoprotein-1 antibodies) should be considered for patients with unexplained, unusual or recurrent thrombotic events, especially those of young age, with an underlying systemic autoimmune disease, or with 3 or more recurrent early pregnancy losses or unexplained late fetal loss.
- Many patients with APS have an underlying systemic autoimmune disorder, most commonly systemic lupus erythematosus.
- Low-dose acetylsalicylic acid and rigorous control of modifiable cardiovascular risk factors and any underlying inflammatory disease may reduce the risk of thrombotic events in patients positive for antiphospholipid antibodies.
- Randomized controlled trials have shown warfarin to be superior to direct oral anticoagulants for patients with APS and thrombosis.

We diagnosed SLE with secondary antiphospholipid syndrome (APS) and started hydroxychloroquine (400 mg/d). We stopped apixaban and started long-term warfarin (target international normalized ratio [INR] 2–3). The patient's leg claudication and hypoesthesia improved without operative intervention. Because of his chronic pleuritic chest discomfort, we ordered CT pulmonary angiography to look for a pulmonary embolism. We did not find any emboli, but observed a large pericardial effusion, which we thought was likely caused by his lupus. We treated him with intravenous steroids followed by a tapering course of prednisone. We added mycophenolate mofetil (1 g, twice daily) as a steroid-sparing agent, and his chest pain and arthralgia rapidly resolved.

Despite immunosuppression, the patient subsequently developed progressive chest and neck discomfort that was different from his previous chest discomfort, suggesting a non-inflammatory cause. Given his underlying APS and known arterial

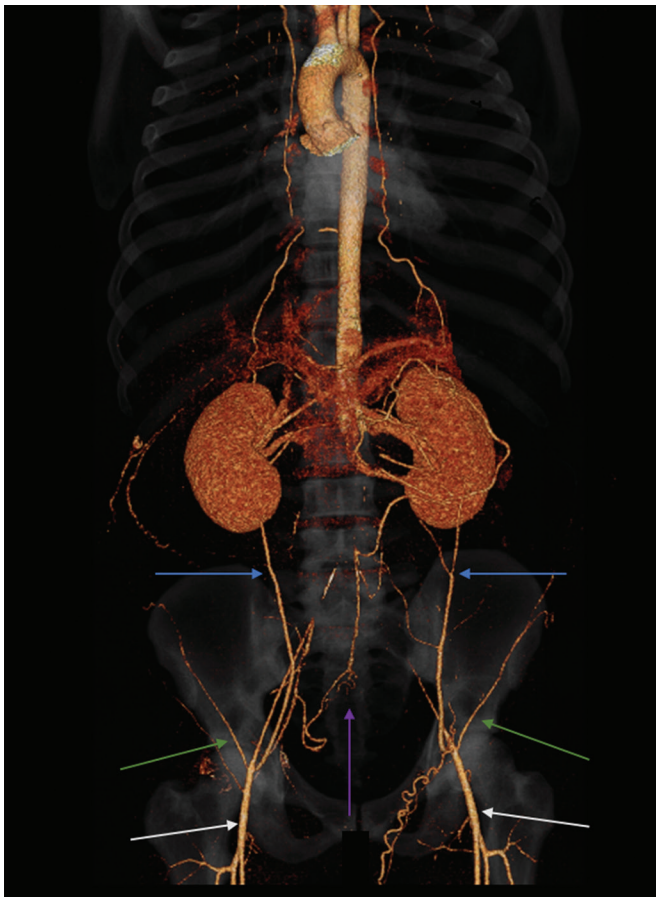

Figure 1: Coronal computed tomography angiogram, maximum intensity projection, of a 22-year-old man with systemic lupus erythematosus and secondary antiphospholipid syndrome, showing complete occlusion of the infrarenal abdominal aorta and common iliac arteries, with reconstitution of bilateral femoral arterial perfusion via numerous collaterals, including the inferior epigastric, intercostal, superior mesenteric and inferior mesenteric artery branches. Blue arrows indicate inferior epigastric artery collaterals, purple arrow indicates superior rectal artery collaterals, green arrows indicate deep circumflex arteries (with collateralization via intercostal arteries, not shown) and white arrows indicate reconstituted flow in the femoral arteries via proximal collaterals.

disease, we were concerned about coronary artery disease and referred him to a cardiologist. A myocardial perfusion scan showed severe ischemia in the left anterior descending artery territory. The cardiologist prescribed clopidogrel (75 mg/d), bisoprolol (2.5 mg/d) and atorvastatin (20 mg/d). He then had coronary angiography, which showed severe triple vessel disease (Figure 2).

The patient underwent triple vessel coronary artery bypass grafting at the age of 24. During the operation, his pericardium was noted to be tethered to the heart, likely owing to earlier episodes of lupus-induced pericarditis.

Discussion

Antiphospholipid syndrome is characterized by the presence of autoantibodies that bind cell membrane phospholipids or phospholipid-binding proteins and by evidence of arterial, venous or small-vessel thrombosis, or obstetrical complications.[1] Thrombotic complications are diverse and may include stroke, myocardial infarction, peripheral thromboembolism or unusual sites for thrombosis, such as splanchnic or cerebral vein thrombosis.[1] Obstetric complications include recurrent early pregnancy loss, late fetal loss, early-onset preeclampsia or preterm delivery from placental insufficiency. Catastrophic APS is an uncommon and life-threatening form of APS that presents as multiple thrombotic complications almost simultaneously.[1]

The incidence of APS is estimated to be 1–2 per 100 000 and the prevalence is about 40–50 cases per 100 000.[2] Antiphospholipid syndrome causes more than 20% of strokes in young patients.[2] Diagnostic criteria for APS include the persistent presence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin or aβ2GP1 antibodies) in association with thrombotic or obstetric complications (see revised Sapporo criteria, Box 1).[3] Antibodies may arise transiently from many factors, including concurrent illness, and therefore must be tested twice, at least 12 weeks apart. Patients can experience other abnormalities such as thrombocytopenia, diffuse alveolar hemorrhage or nephropathy, which are not part of the revised Sapporo criteria.[1]

Antiphospholipid syndrome may be primary, but more than one-third of cases are associated with a systemic autoimmune condition, most often SLE.[4] About 40% of patients with SLE carry these antibodies, and around 20%–50% of those with the antibodies ultimately develop the syndrome.[1,4]

Testing for antiphospholipid antibodies

Antiphospholipid antibodies should be tested in patients with recurrent or unusual venous or arterial thromboses, particularly if the patient is young or has a known or suspected systemic autoimmune disease. Women should be tested for antiphospholipid antibodies if they have unexplained, recurrent early pregnancy loss or fetal demise (Box 1).

Anticardiolipin and aβ2GP1 antibodies can be tested while a patient is taking anticoagulants. Lupus anticoagulant is tested via phospholipid-dependent coagulation assays, which vary among laboratories. The results cannot be interpreted if the patient is taking a direct oral anticoagulant (DOAC) or heparin, and are hard to interpret in patients taking warfarin, especially if the INR is elevated. International guidance for testing and interpretation of lupus anticoagulant is available.[5]

We suggest that all patients with APS be reviewed for symptoms and signs of an underlying systemic autoimmune disease, such as alopecia, photosensitivity, scarring rashes, inflammatory arthritis, unexplained hematuria or proteinuria, and cytopenias. If patients with APS have features suggestive of a systemic autoimmune disease, referral to a rheumatologist is recommended. Patients with SLE and other connective tissue diseases should be tested for antiphospholipid antibodies, particularly before pregnancy.

Managing thrombotic antiphospholipid syndrome (Box 2)

Low-dose acetylsalicylic acid (ASA) can be considered for primary prevention of thromboses, particularly for patients who

Table 1: Laboratory investigations of a 22-year-old man with severe aortoiliac occlusive disease

Test	Result (reference range)
Hematology and coagulation	
Hemoglobin, g/L	137 (137–180)
Leukocyte count, × 10^9/L	7.1 (4.0–11.0)
Platelet count, × 10^9/L	394 (150–400)
Prothrombin time and international normalized ratio	1.3
Partial thromboplastin time, s	61.4 (28.0–38.0)
Direct antiglobulin test	Positive, IgG and complement components detected
Haptoglobin, g/L	1.01 (0.30–2.00)
Reticulocyte count, × 10^9/L	58.5 (20–100)
Biochemistry	
Creatinine, µmol/L	62 (50–120)
Urinalysis	Bland
Urine protein:creatinine, g/mmol	0.005 (≤ 0.013)
C-reactive protein, mg/L	8.4 (< 5)
Alanine aminotransferase, U/L	23 (< 6)
Albumin, g/L	34 (33–48)
Total bilirubin, µmol/L	9 (< 21)
Lactate dehydrogenase, U/L	195 (135–225)
Low-density lipoprotein, mmol/L	2.71 (0.00–3.40)
Serology and immunology	
Antinuclear antibody	≥ 1:640 speckled (≤ 1:80)
Extractable nuclear antigen panel	
Antichromatin, AI	3.5 (≤ 0.9)
Anti-Smith, AI	4.2 (≤ 0.9)
Anti-U1 small nuclear ribonucleoprotein A, AI	1.8 (≤ 0.9)
Anti-double-stranded DNA, kIU/L	944 (0–9)
C3, g/L	0.91 (0.60–1.60)
C4, g/L	0.05 (0.10–0.40)
Lupus anticoagulant	Present
Anticardiolipin IgG, GPU	High positive, > 160.0 (0.0–19.9)
Anti-β2 glycoprotein-1 IgG, GPU	High positive, > 160.0 (0.0–19.9)

Note: AI = antibody index, GPU = immunoglobulin G phospholipid units, Ig = immunoglobulin.

have autoimmune disease, high-risk antiphospholipid antibody profiles (such as those with triple-positive antiphospholipid antibodies [e.g., positive for lupus anticoagulant, anticardiolipin and aβ2GP1 antibodies]) or other cardiovascular risk factors.[6] The evidence supporting ASA use in other cases is controversial, such as for healthy individuals without autoimmune disease.

Patients with thrombosis are usually treated with a vitamin K antagonist, such as warfarin, indefinitely.[6,7] Direct oral anticoagulants are not recommended because evidence from randomized controlled trials has shown an increased rate of thrombotic events (particularly arterial) in patients treated with DOACs compared with warfarin;[8,9] warfarin's apparent superiority to DOACs is not well understood. For patients with suspected APS (for example, those with 1 positive result for antiphospholipid antibodies, that has not been repeated), it is reasonable for clinicians to prescribe warfarin or refer to a thrombosis expert. Controlling modifiable cardiovascular risk factors (e.g., hypertension, blood glucose, dyslipidemia, underlying inflammatory disease) for those with or without previous thrombosis may further reduce the risk of thrombotic events.

We suggest a low threshold to investigate for new venous or arterial thrombotic complications in patients with APS who have suggestive symptoms. Possible treatments for patients with recurrent events while on warfarin include increasing the INR target, adding an antiplatelet agent or switching to low-molecular-weight heparin. Some medications may be added to

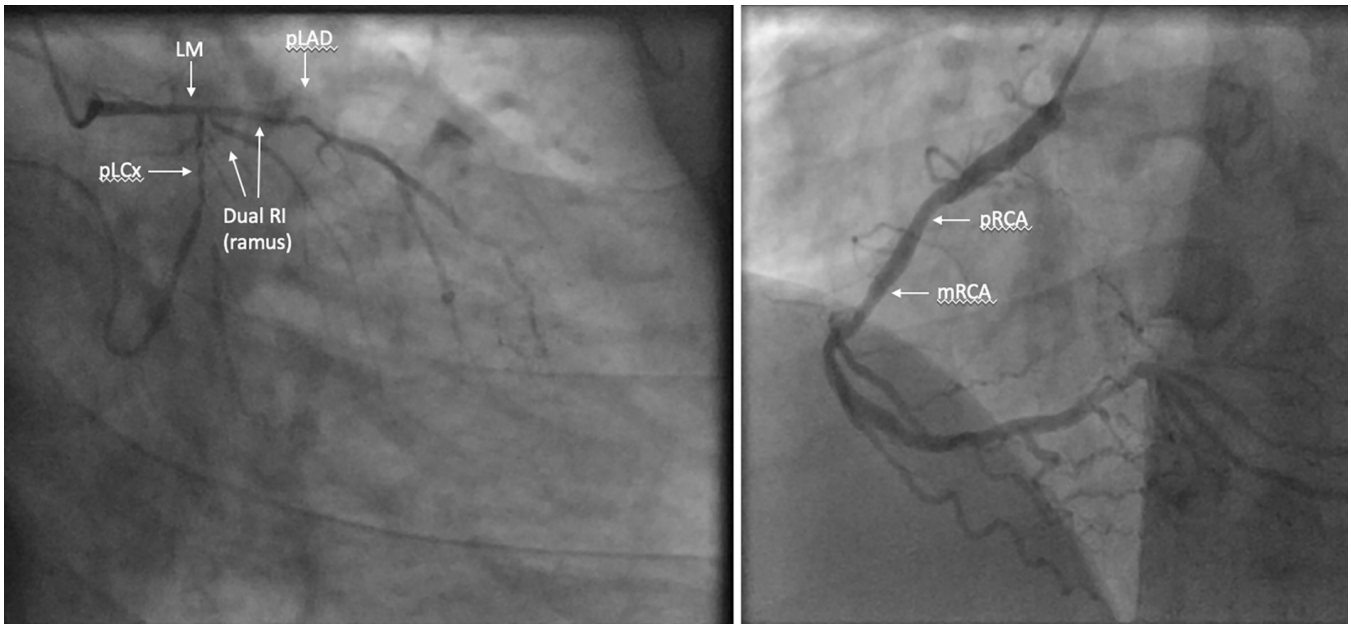

Figure 2: Preoperative left and right coronary artery angiograms from a 22-year-old man with systemic lupus erythematosus and secondary antiphospholipid syndrome, showing diffuse disease throughout the coronary arteries. Arrows indicate a 50% stenosis of the left main (LM) artery, 100% occlusion of the proximal left anterior descending (pLAD) artery, 90% stenosis of the proximal left circumflex artery (pLCx) lesion, 40%–50% stenosis of the proximal and mid right coronary artery (pRCA and mRCA, respectively) and stenosis in the large dual ramus (RI) (60% in the more anterior branch and 80% in the posterior branch). The areas of stenosis were confirmed on multiplanar imaging.

Box 1: Revised Sapporo criteria for the diagnosis of antiphospholipid syndrome

Antiphospholipid syndrome is present if at least 1 of the following clinical criteria and at least 1 of the following laboratory criteria are met:

Clinical criteria

- Vascular thrombosis
  - One or more clinical episodes of arterial, venous or small-vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria.
- Pregnancy morbidity
  - One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation.
  - One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia, or because of recognized features of placental insufficiency.
  - Three or more unexplained, consecutive, spontaneous abortions before the 10th week of gestation, excluding maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes.

Laboratory criteria

- Lupus anticoagulant on 2 or more occasions, at least 12 weeks apart.
- Anticardiolipin antibody of immunoglobulin (Ig) G or IgM isotype, present in medium or high titre on 2 or more occasions, at least 12 weeks apart.
- Anti-β2 glycoprotein-1 antibody of IgG or IgM isotype, present in medium or high titre on 2 or more occasions, at least 12 weeks apart.

Adapted from Miyakis and colleagues[3] with permission from John Wiley and Sons.

antithrombotic therapy in patients who are refractory to usual anticoagulation, including statins or hydroxychloroquine (even if the patient does not have SLE), but the evidence for these agents is limited and further research is needed.[10] Immunosuppressive drugs can be added to anticoagulation in patients with

Box 2: General principles of management for thrombotic antiphospholipid syndrome (APS)

- Primary prophylaxis with low-dose acetylsalicylic acid may be considered in patients with high-risk antibody profiles, such as those with triple positive antiphospholipid antibodies (i.e., positive lupus anticoagulant, anticardiolipin and anti-β2 glycoprotein-1 antibodies).
- In patients with APS and thrombotic complications, randomized controlled trial evidence supports anticoagulation with vitamin K antagonists (e.g., warfarin) instead of direct oral anticoagulants.
- Tight control of modifiable cardiovascular risk factors (e.g., hypertension, blood glucose, dyslipidemia, underlying inflammatory disease) is needed in patients with APS to further reduce the risk of thrombotic events.
- Immunosuppression is used to treat patients with an underlying inflammatory disease, catastrophic APS and some microvascular and nonthrombotic manifestations of antiphospholipid antibodies (such as diffuse alveolar hemorrhage, nephropathy or cytopenias).
- Perioperative management requires expert involvement to balance thrombotic and bleeding risks, and accurate monitoring of unfractionated heparin in patients with a prolonged baseline partial thromboplastin time owing to the presence of a lupus anticoagulant.

other APS manifestations, such as nephropathy, cytopenias or diffuse alveolar hemorrhage.[10] Patients with catastrophic APS should be managed with heparin, plasmapheresis or intravenous immunoglobulins, corticosteroids and, possibly, rituximab (an anti-CD20 biologic) or eculizumab (a biologic that inhibits the complement pathway).[10]

Exogenous hormones for contraception or hormone replacement therapy should generally not be prescribed to patients with antiphospholipid antibodies or APS because they are prothrombotic. Exceptions include progesterone-only intrauterine devices and progesterone-only oral contraceptives, which do not increase the risk of thrombosis.

Management of patients with thrombotic APS requires multidisciplinary collaboration, particularly during pregnancy and during perioperative periods, when balancing thrombotic and bleeding risks is important. Because having a positive lupus anticoagulant can often falsely elevate the partial thromboplastin time (PTT) at baseline, unfractionated heparin anticoagulation may have to be measured using other tests, such as with anti-Xa levels or a phospholipid-insensitive PTT assay.

Both APS and SLE can present insidiously. Delays in diagnosis and treatment may lead to irreversible organ damage. Clinicians should have a high index of suspicion for APS, especially in young patients presenting with unprovoked or unusual thromboses or unexplained recurrent early or late pregnancy loss. Antiphospholipid syndrome may be the first presentation of an underlying systemic autoimmune disease, often SLE. Management requires multidisciplinary care related to anticoagulation, modification of cardiovascular risk factors and identification and treatment of any underlying inflammatory disease.

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The section Cases presents brief case reports that convey clear, practical lessons. Preference is given to common presentations of important rare conditions, and important unusual presentations of common problems. Articles start with a case presentation (500 words maximum), and a discussion of the underlying condition follows (1000 words maximum). Visual elements (e.g., tables of the differential diagnosis, clinical features or diagnostic approach) are encouraged. Consent from patients for publication of their story is a necessity. See information for authors at www.cmaj.ca.

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Affiliations: Division of Rheumatology, Department of Medicine (Barber, Clarke), Cumming School of Medicine; Libin Cardiovascular Institute (Adams), Cumming School of Medicine; Division of Hematology and Hematologic Malignancies, Department of Medicine (Skeith), Cumming School of Medicine, University of Calgary, Calgary, Alta.

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Correspondence to: Megan Barber, mrwbarbe@ucalgary.ca