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 aorto-bifemoral 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 (β2GP1). 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).

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...
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 dis-
case (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 epi-

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 complica-
tions.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 pre-
term 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 100 000.7 Anti-
phospholipid syndrome causes more than 20% of strokes in
young patients.2 Diagnostic criteria for APS include the persis-
tent presence of antiphospholipid antibodies (lupus anti-
coagulant, anticardiolipin or αβ2GP1 antibodies) in associa-
tion 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 anti-
bodies ultimately develop the syndrome.1,4

Testing for antiphospholip 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 antiphospho-
lipid antibodies if they have unexplained, recurrent early preg-
nancy loss or fetal demise (Box 1).

Anticardiolipin and αβ2GP1 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 inter-
pretation of lupus anticoagulant is available.5

We suggest that all patients with APS be reviewed for symp-
toms and signs of an underlying systemic autoimmune disease,
such as alopecia, photosensitivity, scarring rashes, inflamma-
tory arthritis, unexplained hematuria or proteinuria, and cytope-
nias. If patients with APS have features suggestive of a systemic
autoimmune disease, referral to a rheumatologist is recom-
mended. 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 pri-
mary prevention of thromboses, particularly for patients who
have autoimmune disease, high-risk antiphospholipid antibody profiles (such as those with triple-positive antiphospholipid anti-

bodies [e.g., positive for lupus anticoagulant, anticardiolipin and αβ2GP1 antibodies]) or other cardiovascular risk factors. 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. 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; 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

| Test                                               | Result (reference range) |
|----------------------------------------------------|--------------------------|
| Hemoglobin, g/L                                    | 137 (137–180)            |
| Leukocyte count, × 10⁹/L                           | 7.1 (4.0–11.0)           |
| Platelet count, × 10⁹/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, × 10⁹/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.
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. Immunosuppressive drugs can be added to anticoagulation in patients with

**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 with permission from John Wiley and Sons.

**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. 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).

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.

References

1. Schreiber K, Sciascia S, de Groot PG, et al. Antiphospholipid syndrome. Nat Rev Dis Primers 2018;4:18005. doi: 10.1038/s41571-018-0002-3.
2. Dabit JY, Valenzuela-Almada MO, Vallejo-Ramos S, et al. Epidemiology of antiphospholipid syndrome in the general population. Curr Rheumatol Rep 2022;24:23.
3. 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.
4. Pons-Estel GJ, Andreoli L, Scanzi F, et al. The antiphospholipid syndrome in patients with systemic lupus erythematosus. J Autoimmun 2017;76:10-20.
5. Devreeze KMJ, Groot PG, Laat B, et al. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis. J Thromb Haemost 2020;18:2828-39.
6. Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 2019;78:1296-304.
7. Skeith L. Anticoagulating patients with high-risk acquired thrombophilias. Hematology (Am Soc Hematol Educ Program) 2018;439-49.
8. Ordi-Ros J, Saez-Comet L, Perez-Conesa M, et al. Rivaroxaban versus vitamin K antagonist in antiphospholipid syndrome: a randomized noninferiority trial. Ann Intern Med 2019;171:685-94.
9. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood 2018;132:1365-71.
10. Ertzon ZB, Erkan D. Treatment advances in antiphospholipid syndrome: 2022 update. Curr Opin Pharmacol 2022;65:102212.

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.

Competing interests: Megan Barber is a co-investigator of Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS-ACTION) and has received moderate fees from GSK, as well as advisory board fees from Janssen, Sanofi-Genzyme, AstraZeneca and Abbvie. Ann Clarke is a member of APS-ACTION and reports honoraria from AstraZeneca, Bristol Myers Squibb and GSK, as well as research funding from GSK. Leslie Skeith is a member of APS-ACTION and the Canadian Venous Thromboembolism Research Network (CanVECTOR), and reports honoraria from Leo Pharma and Sanofi. No other competing interests were declared.

This article has been peer reviewed.

The authors have obtained patient consent.

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.

Contributors: All of the authors contributed to the conception and design of the work. Megan Barber drafted the manuscript. All of the authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Content licence: This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) licence, which permits use, distribution and reproduction in any medium, provided that the original publication is properly cited, the use is noncommercial (i.e., research or educational use), and no modifications or adaptations are made. See: https://creativecommons.org/licenses/by-nc-nd/4.0/

Acknowledgements: The authors gratefully acknowledge the talented contributions of the multidisciplinary team involved in this case, including the patient’s surgeons, perioperative internal medicine physicians, intensivists, cardiologist, anesthesiologist, family medicine physician and allied health staff. They thank Dr. Elizabeth Chan for assistance with interpretation of the cardiac angiogram, Dr. Teresa Kieser for helpful discussion, and Dr. Mathew Li for assistance with interpretation of the computed tomography angiogram and figure acquisition.

Correspondence to: Megan Barber, mrwbarbe@ucalgary.ca