Antiphospholipid syndrome: a series of surgical emergencies and the current evidence for its management

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ABSTRACT

It is generally accepted that antiphospholipid syndrome remains a major medical problem characterised by hypercoagulability, arterial and venous thrombosis and thrombocytopenia. It is unclear how best to treat these patients should they require emergency surgery. If a lupus anticoagulant is present, hypercoagulability may occur *de novo* but surgical interventions along with sepsis are two important predisposing factors. We describe three patients with primary antiphospholipid syndrome and discuss the implications for surgery.

KEYWORDS

Antiphospholipid syndromes – Surgery – Peri-operative care

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Antiphospholipid syndrome is an autoimmune disorder characterised by recurrent medium-to-large vessel thrombotic events and fetal loss in the presence of circulating antibodies directed against protein epitopes complexed with negatively charged phospholipids.^{1,2} Commonly, the antibodies detected are anticardiolipin or lupus anticoagulant. In the absence of an underlying connective tissue or other rheumatic disorder, antiphospholipid syndrome is considered as primary.

The features of antiphospholipid syndrome are well documented and more recently a catastrophic antiphospholipid variant with a mortality rate of nearly 50% has been described.⁵ In common to all types of antiphospholipid syndrome, in the presence of lupus anticoagulant, thrombosis may occur spontaneously or may be precipitated. Typically, infection, surgical intervention and introduction of oral contraceptive pills are important precipitants.

Antiphospholipid syndrome, especially the catastrophic variant, poses a diagnostic and therapeutic dilemma, as it often leads to a rapidly progressive multi-organ failure. Withdrawal of anticoagulation therapy prior to surgery is often followed by an increase in hypercoagulability and its attendant problems. Even in the absence of hypercoagulability, thrombocytopenia, a common feature of antiphospholipid syndrome may cause life-threatening haemorrhage.

We present three patients with antiphospholipid syndrome and discuss the current peri-operative management.

Case reports

Case 1

A 70-year-old woman was admitted acutely with right upper quadrant pain, vomiting, fever and jaundice. She had no other relevant past medical history and was not on any form of medication. Clinically, she was unwell, febrile (temperature 38.3°C), jaundiced and tachycardic (pulse rate, 106 min⁻¹; blood pressure, 130/88 mmHg; respiratory rate, 18 min⁻¹).

She had marked tenderness in the right upper quadrant with a positive Murphy's sign. Cardiorespiratory examination was unremarkable.

Clotting function (Table 1) was deranged as was the liver function test (Table 2). Lupus anticoagulant screen was performed to investigate persistently prolonged APTT and was found to be strongly positive.

Ultrasound scan of the abdomen showed multiple stones in the gallbladder with ductal dilatation with at least two stones impacted in the distal end of the common bile duct. Following adequate fluid, Enoxaparin and antibiotic therapy (Ciprofloxacin) she underwent ERCP and trawling of the CBD stone. Patient is awaiting laparoscopic cholecystectomy.

Case 2

A 66-year-old Caucasian woman was admitted to the surgical ward with complaints of right upper quadrant pain

Table 1 Coagulation screening tests

Tests	Case 1	Case 2	Case 3
Haemoglobin (g/dl)	12.3	13.2	14.6
White cell count ($\times 10^9/l$)	22.1	5.3	19.1
Platelets ($\times 10^9/l$)	296	202	406
Prothrombin time (s) (normal range = 12.3–16.3)	17.1	14.8	16.1
APTT (s) (normal range = 27.3–38)	58.8	57.2	72.0
Fibrinogen (mg/dl) (normal range = 200–400)	377	244	397
Lupus anticoagulant screen ratio (normal < 1.2)	2.36	1.83	1.76
Lupus anticoagulant confirm ratio	1.09	1.12	1.10
Lupus anticoagulant index (normal < 1.2)	2.17	1.64	1.60
Kaolin clotting time ratio (normal < 1.2)	2.50	2.34	1.08
C-reactive protein (CRP)	206	NA	303

accompanied by nausea and vomiting. She had multiple admissions for similar complaints over the past 8 years and was extensively investigated. Apart from a small insignificant polyp (< 5 mm in size) and sludge in the gallbladder on ultrasound scan, no other abnormality was detected to explain her symptoms. Lupus anticoagulant screen was moderately positive for which she was put on long-term anticoagulation (see Table 1). Liver function test was normal (Table 2).

Laparoscopic cholecystectomy was performed in view of the patient's persistent biliary symptoms. On the advice of the haematologist, warfarin was stopped peri-operatively and she was placed on 40 mg of Enoxaparin (Clexane®) subcutaneously, thrombo-embolic deterrent stocking and pneumatic compression boots.

She made an uneventful recovery and was discharged the following day. Histology revealed mild acalculous cholecystitis but no evidence of gallbladder polyp. On review at 6

weeks, she was well with no recurrence of abdominal pains and has restarted long-term warfarin therapy.

Case 3

A 57-year-old woman was admitted acutely with a history of sudden onset of severe epigastric pain radiating to the back and nausea. She had previously been admitted to the hospital on five occasions with similar complaints. Previous investigations (ultrasound scan of the abdomen, computed axial tomography, colonoscopy, small bowel meal and follow-through) had been normal. Gastroscopy revealed a mild uncomplicated hiatus hernia (< 3 cm) and mild antral gastritis. She was on no regular medication and, in particular, had not taken any non-steroidal anti-inflammatory drugs or steroid therapy.

Physical examination revealed a middle aged Caucasian woman in severe painful distress (pulse rate, 112 min⁻¹; blood pressure, 110/72 mmHg; respiratory rate, 26 min⁻¹; temperature, 37.3°C.). Abdominal examination revealed marked tenderness in the central abdomen with guarding and rebound tenderness. Cardiorespiratory system was normal. Routine blood investigations showed leukocytosis (see Table 1) and abnormal clotting profile. Lupus anticoagulant screen was strongly positive.

Ultrasonography performed during this admission showed gas within the portal vein and moderate ascitis. Arterial Blood gases revealed acidosis (pH 7.29; PO_2 9, PCO_2 27, HCO_3 11). Following administration of analgesia and fluid resuscitation, she proceeded to surgery.

Operation

With the patient lying in supine position and catheterised, she underwent emergency exploratory laparotomy via a midline incision. At operation, she was found to have

Table 2 Results of liver function test

	Normal range	Case 2	Case 3
Bilirubin ($\mu\text{mol/l}$)	3–17	5	22
Alkaline phosphatase (IU/l)	30–135	82	149
ALT (IU/l)	< 65	39	13
AST (IU/l)	< 45	14	28
Total protein (g/l)	64–82	63	57
Albumin (g/l)	34–50	40	26
Globulin (g/l)	28–40	23	31

gangrenous small bowel extending from duodenojejunal flexure to the terminal ileum. Due to the extent of the gangrene, a formal resection was deemed inappropriate. The wound was closed by standard mass closure technique, using loop Polydioxanone suture. The patient died on the second postoperative day.

Discussion

Surgical intervention remains a major risk factor for precipitating serious complications in patients with antiphospholipid syndrome. It is universally accepted that the optimum treatment for these patients in the peri-operative period remains to be determined. High-dose anticoagulation suitable for the long-term management of these patients presents a major problem in the peri-operative period. Bleeding due to thrombocytopenia may occur in up to 20–40% of patients.⁴ Sub-optimal anticoagulation leads to hypercoagulability and its attendant problems as well as the risk of catastrophic antiphospholipid syndrome.

Antiphospholipid syndrome is characterised by heterogeneous antibodies and, therefore, requires several tests for the diagnosis. Enzyme-linked immunosorbent assay (ELISA), activated partial thromboplastin time (APTT), dilute Russell viper venom (RVVT) and activated clotting time are the commonly utilised diagnostic tests. Recently, methods using β_2 -glycoprotein-1 (β_2 -GP-1) in the absence of any phospholipid have been reported. Its exact role in diagnosis and management is yet to be established.⁵

Although thrombosis is the major risk in antiphospholipid syndrome, bleeding can occur because antibodies such as anticardiolipin (ACL) associated with this syndrome interact with phospholipid present on the surface of activated platelets leading to their aggregation and, subsequently, thrombocytopenia.⁶ None of our patients experienced excessive bleeding either due to anticoagulation or thrombocytopenia. In case 1, the patient was not offered sphincterotomy during ERCP due to concern about postoperative bleeding. This patient was particularly at risk because of her jaundice. Vitamin K therapy in her was considered too risky, as this would correct the deficient vitamin K dependent clotting factors and, therefore, put her at risk of further thrombosis.

We believe case 3 had catastrophic antiphospholipid syndrome with no obvious precipitating event. She presented several times over many years with unexplained abdominal pain. It was possible that she may have suffered recurrent thrombosis in the arterioles supplying segments of the bowel. Due to good collateral supply, the areas supplied by these vessels re-establish themselves. Erkan *et al.*⁷ reported a similar experience among their patients in which thrombosis within vasa vasorum of the hand led to recurrent thrombosis and necrosis of the muscles of the forearm. Although this patient was given Enoxaparin (20 mg) peri-

operatively, this may not have altered the course of her disease given the extent of the small bowel infarction. Indeed, this finding supports the report by Asherson⁵ who noted a mortality rate of 49% among patients with catastrophic antiphospholipid syndrome.

In the other two cases, antiphospholipid antibodies were incidental findings. This concurs with the observation by Harris and Bos⁸ in which they reported three cohorts of patients with these antibodies. In one group, the patients were asymptomatic and free of thrombosis or associated with one or two episodes of thrombosis usually affecting one artery or vein at a time with long periods free of occlusive events. In the second group, Antiphospholipid syndrome may confer a risk for a disorder characterised by disseminated thrombotic vasculopathy. In the third cohort, the patients presented with acute, catastrophic, disseminated thrombotic vasculopathy associated with high-titre antiphospholipid antibodies.

Antiphospholipid syndrome may be an incidental finding in healthy individuals and the incidence of thrombotic events among such individuals may be low and appears to be related to the serum levels of anticardiolipin.^{9,10} Indeed, moderate-to-high titre anticardiolipin is a predictor for future venous thrombosis.¹⁰ As it is unclear which group of patients is at risk of thrombotic events during surgery, the implications of surgical interventions are complex.

The optimal peri-operative treatment for these patients remains largely unclear. In most patients, these antibodies persist for a life-time and, therefore, put these patients at risk of major thrombotic events. Antiphospholipid-antibody syndrome not only causes serious disease, but also is also difficult to treat.¹⁰ Current evidence suggests that thromboses in antiphospholipid syndrome tend to recur and, therefore, warrant prophylactic therapy.¹⁰ Preventing thrombosis is necessary but there is no universal consensus on what type of anticoagulant therapy to use, its duration and the extent. In a retrospective study of 19 patients with antiphospholipid antibodies and venous thrombosis, Derksen *et al.*¹¹ have shown that the probability of patients on anticoagulant having no further recurrent thrombo-embolic phenomenon over an 8-year period was 100% compared to 22% among patients who discontinued their anticoagulant therapy. In similar studies, Khamashta *et al.*¹⁰ and Roseve and Brewer¹² reported a 70% and 53% recurrent thrombo-embolic events, respectively, among their patients. The difference in the rates between the two-study groups was attributed to the long follow-up in the cohort of Khamashta *et al.*¹⁰

Presently, no single-centre, large series study exist. Treatment is, therefore, given empirically. Currently, prospective data suggest that patients with incidental finding of antiphospholipid syndrome generally have a low risk of thrombosis, although some reports suggest a slightly increased risk.^{5,15} On the basis of this, Madan *et al.*¹⁴ recommended high-dose

thromboprophylaxis in all patients with antiphospholipid syndrome. The recommendation by the British Society for Haematology depends on whether the patient has had any thrombotic event or not. Even among those who have had thrombotic event, treatment depends on whether the patient had venous or arterial thrombosis. The group recommended that patients who are yet to experience thrombotic phenomenon should be offered short-term thromboprophylaxis during the peri-operative period. Long-term anticoagulation therapy is not currently recommended.⁵

The group of patients who have experienced venous thrombosis should be offered initial treatment with intravenous unfractionated heparin or low molecular weight heparin.⁵ Long-term warfarin therapy should be commenced as soon as possible. The ideal target international normalised ratio (INR) is yet to be determined although Khamashta *et al.*¹⁰ have also shown that in order to achieve therapeutic benefit of anticoagulation, the INR should be maintained at a level greater than 3. The group have also shown that low intensity anticoagulation therapy does not appear to prevent thrombosis in this group of patients.

Among patients with arterial thrombosis, there is a high risk of further thrombo-embolism with its attendant risk of permanent disability and death. On this basis, these patients should be offered long-term warfarin therapy with a target INR of 2.5 (range, 2–3). Additional anticoagulation with aspirin does not appear to offer any added benefit; however, the risk of further bleeding is enhanced.¹⁵

In the peri-operative period, Erkan *et al.*⁷ recommended the use of low molecular weight heparin or low-dose unfractionated heparin at least 2 h before the intended general surgical procedure and for an orthopaedic procedure treatment should be commenced 12 h after the completion of the procedure. The use of thrombo-embolic deterrent stockings as well as pneumatic compression boots during surgery is highly recommended. Where possible, early mobilisation of these patients is highly recommended.

Current haemopathological wisdom suggests that catastrophic antiphospholipid syndrome is a thrombophilic disorder in which global microvasculopathy occurs as a direct consequence of production and circulation of mediators. Treatment, therefore, consists of anticoagulation and immunosuppressants. Current evidence about the role of antiplatelet therapy, fibrinolytic agents and intravenous immunoglobulin is less certain.¹⁶ Low-dose aspirin does not appear to prevent thrombosis in antiphospholipid syndrome patients.^{10,12} The role of purified fraction of Malayan snake pit viper venom as well as defibrinide and streptokinase in the management of catastrophic antiphospholipid syndrome remains unproven.^{17,18} Emerging evidence suggest that patients treated with a combination of anticoagulant therapy, steroid and either plasmaphoresis or intravenous gammaglobulin have the highest survival rate (nearly 70%).¹⁹

Summary of current management

- The diagnosis should be suspected in someone with a prolonged activated partial thromboplastin time with other standard coagulation tests normal, along with the presence of an increased antiphospholipid or anticardiolipin antibody titre and elevation of β_2 -glycoprotein-1.
- Thrombosis can also involve both venous and arterial circulations, especially peripheral vessels of the extremities.
- At least one-third of patients with lupus anticoagulants have a history of one or more thrombotic events.
- Eliminate other risk factors, such as oral contraceptives, smoking, hypertension, or hyperlipidaemia.
- In the case of patients who are discovered to have the antiphospholipid antibodies without any known thrombotic problems, the question of preventative treatment is unresolved. Low-dose aspirin is widely used in this setting; however, the effectiveness of low-dose aspirin as a primary preventive tool for antiphospholipid syndrome remains unproven. Clopidogrel has anecdotally been reported to be helpful in persons with antiphospholipid syndrome and may be useful in patients allergic to aspirin.
- Based on the current evidence, perform full anticoagulation with intravenous or subcutaneous heparin followed by warfarin therapy. An international normalised ratio (INR) of 2.6–3.0 is necessary for a minimum of 6 months for a first thrombosis. Patients with recurrent thrombotic events while well maintained on the above regimen may require an INR of 3–4 and generally require life-long anticoagulation.^{12,20}
- For obstetric patients – subcutaneous heparin (unfractionated or low molecular weight heparin) and low-dose aspirin are used. Therapy is held at the time of delivery; it is restarted after delivery and should be continued for as long as 6 weeks postpartum.²¹ Warfarin is avoided during pregnancy as it is teratogenic. Heparin and warfarin may be used while breast feeding.
- Catastrophic antiphospholipid syndrome – treatment with intensive anticoagulation and plasmaphoresis appears beneficial, but no controlled trials have been performed.
- Consider the use hydroxychloroquine in patients with SLE. Additionally, corticosteroids, cyclophosphamide, and intravenous immunoglobulin may be used.
- Surgical care – recurrent DVT may necessitate placement of an inferior vena cava filter.

Conclusions

Antiphospholipid syndrome is associated with recurrent thrombo-embolic episodes. At the present time, it is unclear

what precipitates these events. Currently, treatment is empirical. It is recommended that these patients should be offered prophylactic anticoagulation as well as thromboembolic deterrent stocking and pneumatic compression boots during surgery. Early mobilisation as well as prevention of dehydration with its attendant risk of increased viscosity should be encouraged. Full, continuing anticoagulation may only be needed if there is history of thrombosis. The management of catastrophic antiphospholipid syndrome remains challenging.

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