Acute postoperative biventricular failure associated with antiphospholipid antibody syndrome

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Antiphospholipid syndrome (APS) is an autoimmune disorder in which large vessel thrombotic events and/or recurrent fetal loss occurs in the presence of antibodies to negatively charged phospholipids. The antiphospholipid (APL) antibodies most commonly detected are anticardiolipin (ACL) antibodies or lupus anticoagulant (LAC).1 APS may be the most common acquired hypercoagulable state, occurring in up to 2% of the general population.2

Catastrophic APS is a syndrome of multiple non-inflammatory small vessel thromboses. Factors associated with this ‘thrombotic storm’ include surgical trauma, infection, any change in anticoagulation therapy, or introduction of the oral contraceptive pill.3 4 Death occurs in nearly 50% of cases.5

Perioperatively, APS can lead to large vessel thrombosis or thrombotic storm and its treatment may be associated with haemorrhage. The resources to manage major complications are essential. The literature supports widely different estimates of perioperative risk in APS. Those patients with a history of thrombosis are prone to repeat episodes of a similar nature. Immunosuppression does not prevent recurrent thrombosis or fetal loss. Minor alterations in the anticoagulant regime, infection, and surgical insult may trigger widespread thrombosis.

There has been no previous report of the use of extracorporeal membrane oxygenation (ECMO) and plasmapheresis to treat presumed catastrophic APS.

Case report

A 31-yr-old woman required mitral valve replacement for mitral regurgitation secondary to ACL antibody syndrome. A thrombophilia screen had been performed during pregnancy because of a history of deep venous thrombosis when on the oral contraceptive pill. This demonstrated a positive IgG ACL assay of greater than 50 IgG phospholipid units (GPL units, ORG515, Orgentec, Mainz, Germany). Although her activated partial thromboplastin time (aPTT) was normal, her dilute Russell Viper Venom (RVVT) and kaolin clotting times were prolonged. Adding phospholipid to her serum in vitro corrected the abnormal clotting times and confirmed the presence of LAC antibodies. She was treated with clexane and aspirin during pregnancy and postpartum.

Five days postpartum she developed a vasculitic rash, dyspnoea, and renal impairment compatible with systemic lupus erythematosus. Her antinuclear antibody titre was initially positive, but her anti-Smith, anti-double stranded DNA, and anti-ribonucleoprotein antigen and serum complement levels were always normal. Renal biopsy demonstrated microvascular thrombosis without evidence of vasculitis (Fig. 1), suggesting catastrophic APS. A computed tomography pulmonary angiogram indicated multiple small pulmonary emboli. Clexane anticoagulation was maintained at an anti-Xa activity of 0.8 u ml−1 and steroid therapy was started. However, her chest symptoms pro-
gressed and plasmapheresis was started to decrease her antibody load. Her GPL levels when on plasmapheresis fell to the normal range (<10 GPL units, ORG 515, Orgentec, Mainz, Germany). New onset mitral regurgitation was noted. At 30 days, she was discharged on warfarin to a target international normalized ratio (INR) of 3.5. She remained thrombosis-free on this regime despite IgG ACL assays between 95 and 168 IgG GPL units (Autozyme ACL, Cambridge Life Sciences, UK). Two years later she required mitral valve replacement for severe mitral regurgitation. Angiography before surgery showed normal coronary arteries. Preoperative clotting studies included factor assays (Table 1) and an individualised \textit{ex vivo} heparin/kaolin activated clotting time (Haemotech ACT III). To determine her therapeutic kaolin ACT, heparin was added to 2 ml of the patient’s whole blood to obtain heparin concentrations of 1, 2, 3, and 4 u ml$^{-1}$ (Table 2). Based on these results, therapeutic heparinization (heparin concentration >3 u ml$^{-1}$) for cardiopulmonary bypass (CPB) was achieved at kaolin ACT values greater than 600 s.

Preoperatively, warfarin was stopped and i.v. heparin started to maintain the aPTT at twice control. Anaesthesia was induced in theatre with propofol 2 mg kg$^{-1}$, pancuronium 0.1 mg kg$^{-1}$, and fentanyl 10 µg kg$^{-1}$. Her cardiac index post-induction was 3.1 litre m$^{-2}$ min$^{-1}$ (Baxter PA catheter). Pre-bypass, the kaolin ACT was 819 s. Bypass flows were 2.4 litre m$^{-2}$ min$^{-1}$. Anaesthesia was maintained with inhaled/oxygenator isoflurane 0.5%. Mean arterial pressure throughout bypass was greater than 60 mm Hg. Bypass time was 73 min with an ischaemic time of 48 min. A Starr Edwards 28 mm mechanical mitral valve was implanted. Separation from bypass was accomplished without inotropic support. As planned previously, the chest was closed without protamine reversal. The kaolin ACT was 603 s at the time of chest closure.

One hour postoperatively, she became hypotensive with a profoundly ischaemic ECG. At re-opening of the chest, both ventricles were severely hypokinetic. There was palpable pulsatile flow at both coronary artery ostia. Transoesophageal echo (TOE) confirmed globally poor biventricular function and normal valve function. The working diagnosis was either thrombotic microangiopathy (catastrophic APS) of the myocardium or acute fulminant autoimmune cardiomyopathy.

Following 20 000 u of heparin i.v., she was placed on ECMO bypass to support her circulatory collapse, which was unresponsive to inotropes or intra-aortic balloon pump (IABP). Antiplatelet aggregation treatment with prostacyclin was started together with an i.v. heparin infusion to a target kaolin ACT of greater than 800±1000 s, corresponding to a heparin assay of 3±5 u ml$^{-1}$ and an anti-factor Xa level of greater than 2.0 u ml$^{-1}$. Mean arterial pressure was 70 mm Hg and urine output greater than/equal to 0.5 ml kg$^{-1}$ min$^{-1}$ on ECMO support. Plasma exchange of 3 litres (approximately 1 plasma volume) with fresh frozen plasma as the exchange medium was instituted to decrease the antibody load. Following plasma exchange, both the ST changes and repeat TOE showed improvement. Excessive blood loss of nearly 1 litre h$^{-1}$ led to prostacyclin being stopped. On ECMO, the direct heparin assay was 4.6 u ml$^{-1}$ and the anti-factor Xa activity was between 2 and 6.7 u ml$^{-1}$. Separation from ECMO was achieved on the second postoperative day with IABP and epinephrine support. The next day, the target kaolin ACT was reduced to 300 s.

### Table 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference range</th>
</tr>
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<tbody>
<tr>
<td>Prothrombin time (s)</td>
<td>42 s (warfarin)</td>
<td>9 s</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>49 s</td>
<td>32 s</td>
</tr>
<tr>
<td>50:50 mix</td>
<td>32 s</td>
<td></td>
</tr>
<tr>
<td>Thrombin time (s)</td>
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<td>9 s</td>
</tr>
<tr>
<td>Dilute RVVT Ratio</td>
<td>1.86</td>
<td>(ratio)</td>
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<tr>
<td>Dilute RVVT Platelet Neutralization Ratio</td>
<td>1.13</td>
<td>(ratio)</td>
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<tr>
<td>Factor II activity (%)</td>
<td>0.55 u ml$^{-1}$</td>
<td>0.5–1.5 u ml$^{-1}$</td>
</tr>
<tr>
<td>Factor V activity (%)</td>
<td>1.22 u ml$^{-1}$</td>
<td>0.5–1.5 u ml$^{-1}$</td>
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<td>Factor X activity (%)</td>
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<td>0.5–1.5 u ml$^{-1}$</td>
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<td>ACL antibody titre</td>
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<tr>
<td>IgG</td>
<td>29.4 GPL</td>
<td>0–13.3 GPL</td>
</tr>
<tr>
<td>IgM</td>
<td>4.9 MPL</td>
<td>0–9.8 MPL</td>
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### Table 2

<table>
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<th>Test</th>
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<td>Kaolin ACT</td>
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<tr>
<td></td>
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<td></td>
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<td>3</td>
<td>469</td>
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<td></td>
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Fig 1 Renal biopsy showing swollen glomerulus and microvascular thrombosis.
for chest closure. Over 36 h and following three further plasma exchanges, the ACL IgG levels fell to normal (Table 3). Her myocardial function improved allowing successful weaning from the IABP on the third post-operative day and from inotropes on day 4. Plasmapheresis continued to a total of six exchanges. Heparin to an anti-factor Xa activity assay greater than 0.7 u ml⁻¹ was maintained until full therapeutic warfarinization was re-established. By the time of discharge 7 weeks postoperatively, her IgG assay was again greater than 100 GPL units.

Her excised valve shows the myxoid degenerative changes seen in anti-phospholipid syndrome (Fig. 2). She has subsequently returned to work with no limitations of her activity. Echocardiography shows nearly normal left ventricular contractility.

**Discussion**

Anti-phospholipid antibodies are a common risk factor for repeated venous and/or arterial thrombosis, recurrent fetal loss, and thrombocytopenia. Anti-phospholipid syndrome is the association of APL antibodies with these clinical events.

**Detection of antibodies**

APL antibodies are a heterogeneous group and thus diagnosis requires more than one test. The two main antibody groups are ACL antibodies and LAC. ACL antibodies are detected by enzyme-linked immunoassay and do not exhibit in vitro anticoagulant activity. Results of ACL assays are expressed as IgG and IgM phospholipid units (GPL or MPL units) based on standard curves. Patients with ACL antibodies are five times more common than those with LAC.

LAC antibodies interfere with the activity of the Xa/Va/Ca²⁺ phospholipid complex. In vitro, this causes prolongation of phospholipid-dependent clotting tests (aPTT, activated clotting time and dilute RVVT). Despite the prolonged in vitro clotting times, LAC is associated with thrombosis in vivo. As with our patient, LAC may not cause a prolonged aPTT on standard laboratory testing. Specialized LAC screening tests (RVVT, dilute activated PTT, or dilute prothrombin time) have low phospholipid concentrations to enhance their sensitivity. Mixing patient and normal pool plasma does not correct the test, verifying the presence of an inhibitor. Correction of the clotting time by adding phospholipid (platelet neutralization and hexagonal phase tests) confirms that the inhibitor is phospholipid dependent. Anticoagulation interferes with testing for LAC antibodies.
In nearly 30% of patients with APS, ACL antibodies react with phospholipid on the surface of activated platelets causing platelet aggregation and thrombocytopenia. As only activated platelets expose phospholipid, it is usually thrombotic APS patients who develop thrombocytopenia. Thrombocytopenia is not protective against thrombosis.

Pathology

The mechanism by which APL antibodies cause or contribute to thrombosis is uncertain. Anti-phospholipid antibody associated thrombosis may require a vascular ‘second-hit’ and a search for local risk factors, for example stasis, surgical trauma, or sepsis, should be made.

Diagnosis

Thrombophilia is suspected in young patients who develop venous thrombosis and in patients of any age with unprovoked or recurrent thrombosis or thrombosis at unusual sites. Thrombosis in association with pregnancy, oral contraceptive, or hormone replacement therapy or an unexplained prolonged PTT also requires investigation. A diagnosis of APS requires at least one clinical criterion (vascular thrombosis or complications of pregnancy) and at least one laboratory criterion (Table 4).

Of those patients with APS who present with thrombosis, 30–55% will present with venous thrombosis, especially of the lower limbs. Repeat episodes are often of the same type. Some cerebral arterial events may be secondary to emboli as nearly one-third of patients with APS have non-bacterial (Libman Sacks) valvular vegetations. Where valvular disease requires surgery, Dajee and colleagues recommended the use of bioprosthetic valves to minimize the risk of thrombosis. Our patient received a mechanical valve as she already required life-long warfarin for her thrombotic APS. In one case report, anti-phospholipid syndrome recurred in a bioprosthetic valve. Cardiac risk in patients with APS includes premature coronary artery disease, valvular lesions including bacterial endocarditis, and myocardial infarction with angiographically normal coronary arteries. Acute onset postoperative cardiomyopathy has also been described.

Treatment of APS

The asymptomatic patient with APL antibodies but no history of thrombosis is managed by reducing other risk factors for vascular disease. Aspirin does not protect against thrombosis in asymptomatic men with ACL, although it may provide protection against thrombosis in women with APL and a history of fetal loss.

Patients with primary APS with thrombosis are treated with heparin followed by warfarin in the usual manner. There is controversy over the intensity of anticoagulant therapy, the duration of treatment, and the method for measuring the INR. Recurrent thrombotic events of any type usually signal the need for life-long anticoagulation. Recurrent thrombosis while on standard intensity anticoagulant therapy dictates the use of a higher target INR, but the INR may not correlate well with diagnosis or outcome in APS. Although the risk of thrombosis is reduced with increased anticoagulation, there is an associated increased risk of significant bleeding.

In patients with secondary APS and thrombosis, there is an ongoing endothelial disturbance secondary to the underlying vasculitis and the risk of recurrent thrombotic events is high. Anti-platelet therapy as well as warfarin anticoagulation is indicated. In pregnant women with APL, a history of fetal loss, and no history of thrombosis the most commonly advocated treatment is heparin with aspirin.

Monitoring anticoagulation in APS

Monitoring of anticoagulation in patients with APS is complicated by LAC antibodies’ interference with time-based clotting tests. Anti-factor Xa activity assays are useful, as the aPTT may not reliably measure heparin activity. LMWH is attractive in this setting as it causes a highly predictable anticoagulant effect for a given dose,
During CPB, blood contact with extracorporeal surfaces causes stimulation of the coagulation cascade. To prevent clotting, unfractionated heparin is administered before CPB. Heparin concentrations of greater than/equal to 3 u ml−1 are generally accepted as therapeutic for CPB,19 but individual patient responses to a standardized heparin dose vary. Heparin activity is assessed using the activated clotting time (ACT, Haemotech ACT III). The ACT is a phospholipid-dependent test and may be prolonged by LAC antibodies. Suggested alternative methods for monitoring anticoagulation during bypass in APS include empirically doubling the baseline ACT, obtaining heparin concentrations by protamine titration (Hepcon),20 performing anti-factor Xa assays, or performing heparin/ACT titration curves preoperatively to determine patient specific target ACT levels.

Anti-factor Xa levels of 1.5–2.0 u ml−1 are considered therapeutic for CPB. Postoperatively, levels greater than 1.0 u ml−1 may be associated with excess blood loss.21 However, the turnaround time for anti-factor Xa assays are currently incompatible with the time constraints of CPB. The in vitro heparin/ACT titration curve is a test of an individual patient’s responsiveness to heparin. In the normal patient, a heparin concentration of 3 u ml−1 typically produces a kaolin ACT of more than 450 s. Preoperatively, anti-Xa factor activity assays can be correlated with the patient specific preoperative in vitro heparin ACT titration curve. In this patient, the baseline kaolin ACT was prolonged, possibly secondary to her high intensity warfarin therapy or to the presence of LAC antibodies. However, her kaolin ACT did increase with rising heparin concentration in a predictable and measurable way.

**Perioperative management**

The perioperative management of APS is challenging and close cooperation with the haematology department is essential. Perioperative risks include thrombosis and/ or bleeding secondary to excessive anticoagulation or APL associated clotting factor deficiencies (especially factor II).

As APS is associated with both thrombocytopenia and clotting factor deficiencies, clotting factor assays should be performed in addition to routine tests. Regional anaesthesia is not contraindicated if the platelet count is normal and there is no evidence of a bleeding diathesis.22

There is no consensus in the literature as to the optimal method for assuring perioperative anticoagulation in APS. Application of antithrombotic regimes recommended for high-risk patients should be standard for patients with APS and periods without anticoagulation should be kept to a minimum. Intraoperatively, physical measures such as anti-embolic stockings, intermittent venous compression devices and adequate hydration are advised.23 Tourniquets should be avoided. Patients can develop recurrent thrombosis despite appropriate prophylaxis. Postoperatively, patients require close monitoring for bleeding secondary to anticoagulation and thrombosis secondary to APS or catastrophic APS.

**APS and cardiopulmonary bypass**

The literature offers widely differing estimates of morbidity and mortality associated with APS and cardiopulmonary bypass. In a retrospective analysis of 19 patients with APS undergoing cardiac or vascular surgical procedures, Ciocca and colleagues reported an 84.2% incidence of postoperative thrombosis or bleeding and a 63.2% mortality.24 Thirteen of the patients in this series underwent cardiac surgery. Individual case reports of cardiac surgical patients frequently describe thrombotic or haemorrhagic complications including early graft occlusion,25 haemothorax,26 pulmonary emboli, and limb ischaemia.27 28 More optimistically, the literature includes several case reports of uneventful cardiac surgery.29 30

**Treatment of thrombosis in APS**

Treatment of thrombosis in APS remains controversial. Long-term anticoagulation is generally recommended, but thrombotic events occur despite heparin or immunosuppressive therapy.31 Antiplatelet therapy may be added but the effectiveness of low-dose aspirin or the newer antiplatelet agents is unproven. In cases where thrombosis continues despite adequate anticoagulation, additional treatment is aimed either at preventing antibody formation or reducing antibody titres and may include corticosteroids, immunosuppressive agents, i.v. immune globulin, or plasmapheresis. Tissue plasminogen activator has been used successfully in one case report of APS with ST changes and normal coronary arteries.32

**Catastrophic APS**

Thrombosis in APS typically affects large vessels. In contrast, catastrophic APS is characterized by small vessel vascular occlusions most frequently in the kidney, lungs, CNS, and heart. Classic precipitating factors for catastrophic APS include surgery and infection, which may be minor or trivial. Treatments with combinations of high-dose steroids, i.v. gammaglobulin, cyclophosphamide, plasmapheresis, and anticoagulation have all failed to prevent death. In Asherson and colleagues33 most recent retrospective case series of catastrophic APS—published after this patient’s surgery—only anticoagulation was associated with statistically significant increased survival. In the 1998 series,34 plasmapheresis did reduce mortality. Plasmapheresis may act by removing cytokines and disrupting the interaction between phospholipid protein complexes and vascular endothelium. As plasmapheresis was effective during this patient’s previous crisis when steroids were not, it was used again. Fresh frozen plasma replace-
ment fluid minimized any decrease in antithrombin III levels. There are case reports of acute biventricular failure in APS with necropsy findings of myocardial microvascular thrombosis.14 23 35–37 In this situation, antithrombotic not anti-inflammatory therapy is likely to be effective.

A diagnosis of fulminant myocarditis could be supported by the global nature of the myocardial dysfunction and its prompt resolution. Fulminant myocarditis is associated with full recovery in over 90% of the patients who survive the event.37 There is one case report of APS associated postoperative fulminant myocarditis managed with immunosuppressive steroids.38

APS is one of the most commonly acquired hypercoagulable states. Minor alterations in the anticoagulant regime, infection, and surgical insult may trigger widespread thrombosis. The resources to manage major complications are essential. A successful outcome requires multidisciplinary management in order to prevent thrombotic or bleeding complications and to manage perioperative anticoagulation.

References


