CASE REPORT

Catastrophic antiphospholipid syndrome in childhood: presentation with an inferior caval vein mass

Abdul Alim Abdul Haium,^{1,2} Mary Sheppard,^{3,4} Michael Rubens,⁵ Piers Daubeney^{1,4}

¹Department of Paediatric Cardiology, Royal Brompton Hospital, London, UK

²Department of Neonatology, K K Women's and Children's Hospital, Singapore

³Department of Pathology, Royal Brompton Hospital, London, UK

⁴National Heart Lung Institute, Imperial College, London, UK

⁵Department of Radiology, Royal Brompton Hospital, London, UK

Correspondence to

Piers Daubeney,
P.Daubeney@rbht.nhs.uk

SUMMARY

Venous thromboembolism remains one of the important causes of pulmonary hypertension in children. The causes of venous thromboembolism are varied and include antiphospholipid antibody syndrome (APS). Catastrophic APS (CAPS) is a severe variant of APS characterised by disseminated thrombosis and microangiopathy resulting in multiorgan failure. CAPS can occur independently (primary APS) but mainly occurs in association with systemic lupus erythematosus including the paediatric population. We report a young girl with primary CAPS who presented with pulmonary hypertension and an inferior vena cava mass masquerading as a tumour.

BACKGROUND

The term antiphospholipid syndrome (APS) was introduced to describe patients with a combination of recurrent arterial and venous thrombosis, recurrent fetal losses, often accompanied by mild-to-moderate thrombocytopenia and elevation of the titres of antiphospholipid antibodies, namely the lupus anticoagulant and the anticardiolipin antibodies.¹ It was originally reported in patients with systemic lupus erythematosus (SLE) and other autoimmune disorders. It is also well known that this syndrome may develop without an underlying disease when it is termed primary APS. 'Catastrophic' APS (CAPS) is a variant of APS characterised by multiple vascular occlusions resulting in multiorgan failure in the setting of APS. We present a case of widespread pulmonary and cerebral venous thromboembolism who initially presented with pulmonary hypertension and an inferior vena cava (IVC) mass, subsequently diagnosed as CAPS based on clinical, laboratory and autopsy findings.

CASE PRESENTATION

A 13-year-old girl, previously fit and well, presented to her local district general hospital with sudden onset of chest pain, cough with fever and shortness of breath. Her chest X-ray showed bilateral small pleural effusions. She was diagnosed as atypical pneumonia and treated with a prolonged course of antibiotics. She only had partial recovery from the illness and continued to have ongoing dyspnoea. She was not taking any other medication (and not the contraceptive pill). There was no family history of rheumatic disorders or thromboembolism.

Four months later she presented to a hospital emergency department with worsening shortness of breath on exertion, tachycardia and low oxygen saturations. When she was assessed urgently in the cardiology clinic she was found to have severe pulmonary hypertension. She was immediately transferred to the paediatric cardiology centre for further investigations and management. On admission she was tall but overweight with a weight of 96.4 kg and a height of 172 cm. She was centrally pink with saturations of 92% in air and had normal pulses. Her jugular venous pressure was not raised. She had a palpable parasternal impulse, normal first heart sound, accentuated pulmonary component of second heart sound and no heart murmur. Her initial echocardiogram showed normal cardiac anatomy, a dilated right heart, abnormal ventricular septal motion, tricuspid regurgitation with a Doppler-derived pressure gradient of 82 mm Hg and dilated pulmonary arteries consistent with significant pulmonary hypertension.

INVESTIGATIONS

Investigation of causes of pulmonary hypertension revealed persistent neutrophil leucocytosis. The renal and liver functions were normal. The coagulation screen showed persistently elevated fibrinogen and factor VIII levels. The D-dimers were positive later in the illness the erythrocyte sedimentation rate and C reactive protein mildly elevated. A sleep study was normal. A CT angiogram (figures 1 and 2) demonstrated a large filling defect in the left

Figure 1 Image showing the filling defect in the left lower lobe pulmonary artery due to thrombus (arrow). Note: uneven attenuation of lung parenchyma (mosaic perfusion) typical of pulmonary arterial hypertension.

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Figure 2 Image showing the filling defect (arrows) in the inferior vena cava due to thrombus.

pulmonary artery consistent with pulmonary embolism. An ultrasound and Doppler imaging showed no evidence of deep vein thrombosis (DVT) in her lower limbs, patent iliac veins and lower IVC. Anticoagulation was started with enoxaparin 1.5 ng/kg once daily.

A thrombophilia screen was undertaken. Protein C, free protein S, antithrombin levels, activated protein C resistance ratio and plasminogen activity were all normal. There was no prothrombin mutation detected. Fibrinogen was elevated at 5.6 g/L. Anticardiolipin antibodies (IgG and IgM) were negative on two occasions. The anti- β -2-glycoprotein-1 antibodies were also negative. Rheumatoid factor, antinuclear antibodies, anti-double-stranded DNA and cytoplasmic antineutrophil cytoplasmic antibodies and perinuclear antineutrophil cytoplasmic antibodies were all negative. The Ham's test for paroxysmal nocturnal haemoglobinuria and CD55 and CD59 were normal. The plasma amino acids and homocysteine levels were within normal limits. The only positive test was a positive lupus anticoagulant test, a dilute Russell viper venom ratio of 1.23 (normal 0.8–1.10). She was then started on warfarin to overlap with enoxaparin.

An MRI scan of the heart and IVC showed a mobile wedge-shaped mass at the IVC/right atrial junction protruding into the right atrium. This was anchored by a thin sheath close to the

hepatic vein and measured 1.5–2 cm. It was highly suspicious of an intravascular tumour. Further investigations to rule out malignancy were undertaken. Half-body positron emission tomography–CT fluorodeoxyglucose (FDG) scan confirmed normal tracer uptake and distribution with no definite evidence of malignancy. The tumour marker studies were also negative.

DIFFERENTIAL DIAGNOSIS

After careful consideration in multidisciplinary meetings, it was considered that malignancy as a cause of IVC mass had not been excluded and she was therefore referred for surgery by a combined team of a cardiac and renal oncology surgeon.

TREATMENT

She underwent successful excision of the IVC mass and pulmonary embolectomy. The operative findings were of a multilobulated, friable, necrotic mass with the appearances of a tumour occupying the proximal IVC. This was removed and a piece of IVC containing the sac excised. A large mass in the left lower lobe pulmonary artery of similar morphology was also excised. The histopathology of the mass lesions showed similar features of mainly organising thrombus and necrosis with neutrophilic components. The edge contained spindle cells which were positive for smooth muscle actin and desmin, and negative for MNF116, the immune profile seen in reactive myofibroblasts. It was concluded that there was no viable tumour present in the specimens and the IVC mass was merely a thrombus.

OUTCOME AND FOLLOW-UP

Postoperatively she made an uneventful recovery and maintained on moderate intensity anticoagulation. Unfortunately 11 days after surgery she deteriorated with the recurrence of IVC and left lower pulmonary artery thrombosis, pericardial effusion and subsequently died of bilateral cerebral infarcts with uncal herniation. On autopsy she was found to have extensive and widespread thrombosis of pulmonary arteries (figure 3), superior vena cava, IVC, hepatic veins, cerebral veins and sagittal sinus. The underlying vasculature was histologically normal (figure 4).

DISCUSSION

CAPS, also known as Asherson's syndrome, is an unusual but often life-threatening variant of APS, characterised by the rapid appearance of multiple thrombosis, mainly small vessel, that lead to multiorgan failure. The descriptive adjective 'catastrophic' was added to APS by Asherson² in order to highlight

Figure 3 Image showing the cross section of pulmonary arterial branch distended by layers of pale older thrombus (green arrow) and more recent haemorrhagic thrombus (red arrow).

Figure 4 Image showing the cross section of pulmonary artery with pale older thrombus (green arrow) and red recent thrombus (red arrow). Note: artery wall is normal (H&E stain).

Box 1 Preliminary criteria for the classification of catastrophic antiphospholipid syndrome (APS).³

1. Evidence of involvement of three or more organs, systems and/or tissues*
2. Development of manifestations simultaneously or in less than a week
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue†
4. Laboratory confirmation of the presence of antiphospholipid antibodies (aPL, lupus anticoagulant and/or anticardiolipin antibodies)‡
 - ▶ All four criteria
 - ▶ *Probable catastrophic APS*
 - ▶ All four criteria, except for only two organs, systems and/or tissues involvement
 - ▶ All four criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never previously tested for aPL prior to the catastrophic APS event
 - ▶ Criteria 1, 2 and 4
 - ▶ Criteria 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation

*Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% rise in serum creatine, severe systemic hypertension (>180/100 mm Hg) and/or proteinuria (>500 mg/24 h).

†For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.

‡If the patient had not been previously diagnosed as having APS, the laboratory confirmation requires that the presence of aPL must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS.

Reproduced with permission from Asherson *et al.*³

this accelerated form of APS. CAPS occurs in less than 1% of patients with APS.¹ Preliminary criteria (box 1) for classification and diagnosis of CAPS have been developed.³

In view of the rarity of this condition an international registry of patients with CAPS, the 'CAPS Registry', was created in 2000 by the European Forum on Antiphospholipid Antibodies. It can be freely consulted at <http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM>. A descriptive analysis of 280 patients from this registry and several other reviews on this condition have been published.^{4–10}

Patients with CAPS can be broadly categorised into those with SLE, lupus-like illness, primary APS and secondary to another autoimmune or connective tissue disease.¹¹ The clinical presentation of CAPS is complex as there is multiple organ involvement occurring concurrently over a short period of time. There is a sudden and explosive onset of multiple vascular occlusions affecting multiple organs, such as the lungs, heart, brain, kidney, liver, adrenal gland and gastrointestinal tract, in various combinations.¹¹ 'Triggering' factors may be present in 60% of patients. These are infections, trauma, anticoagulation withdrawal, neoplasia, obstetric related, lupus 'flares' and others, for example, drugs (captopril, oral contraceptives, danazol and thiazide diuretics), ovulation induction and postimmunisation. Malignancy may be an important risk factor for CAPS and in one review, 9% of patients with CAPS presented with an underlying malignancy.¹² CAPS patients with malignancies are generally older than those without malignancies; they generally have the worst prognosis of the entire CAPS cohort.¹³

The clinical manifestations of CAPS depend on the organs affected by thrombosis and extension of thrombosis and presence of systemic inflammatory response. Peripheral thrombosis affecting large veins or arteries, DVT and intra-abdominal thrombosis presenting as abdominal pain are common. Renal dysfunction and pulmonary complications such as acute respiratory distress syndrome (ARDS) and pulmonary embolism are frequently reported. Skin complications such as livedo reticularis, purpura, skin necrosis and cerebral manifestations (infarcts, encephalopathy, seizures or cerebral venous occlusions) have also been reported frequently.

Laboratory abnormalities include thrombocytopenia, evidence of haemolysis and features of disseminated intravascular coagulation. IgG anticardiolipin (aCL) antibodies are usually positive with IgM elevations being less frequent.⁸

Management of CAPS is challenging; early diagnosis and treatment is essential to rescue patients from a potentially fatal condition. Treatment guidelines for CAPS had been proposed.³ Treatment strategies may be divided into prophylactic, specific and non-specific therapies.

Patients known to have APS need careful monitoring for evolution into CAPS. Infections in such patients should be treated aggressively and they should be adequately anticoagulated parenterally during surgical procedures. The puerperium should be adequately covered for a minimum of 6 weeks with parenteral anticoagulants such as subcutaneous heparin. SLE 'flares', although uncommonly associated with CAPS, should also be treated with parenteral anticoagulation.¹⁰

Specific therapies include intravenous heparin followed by high-intensity oral anticoagulants, corticosteroids during acute illness to minimise systemic inflammatory response. Second-line therapy in the form of intravenous immunoglobulin in combination with plasma exchange may be effective. Plasma exchange primarily acts by removal of pathogenic IgG aCL and β -2-glycoprotein-1, as well as cytokines, such as interleukin 1 (IL-1), IL-6, tumour necrosis factor- α and complement. Third-line therapies such as cyclophosphamide have been shown to improve the outcome. Drugs such as rituximab, procyclin, anicord and defibrotide had also been reported to be of some benefit.¹⁰

Supportive therapy such as haemodialysis in the presence of renal failure and ventilatory support for ARDS is important. Patients presenting with hypertension will require antihypertensive therapy. Hypotension could be due to myocardial dysfunction, coronary microangiopathy or haemorrhagic infarction of adrenal glands and may require inotropic support and corticosteroids.¹⁰

Despite these therapies aggressive CAPS carries high mortality (about 50%). Cerebral involvement (stroke), cardiac involvement and infections are considered the main causes of death in

patients with CAPS. The presence of SLE is also associated with a higher mortality rate.¹⁴

In conclusion, CAPS is a rare, potentially life-threatening condition with high morbidity and mortality. Diagnosis needs a high index of suspicion. When adults or children present with unusual widespread thrombotic manifestations, the possibility of CAPS should be considered and early treatment should be initiated.

Learning points

- ▶ Thrombus in the inferior vena cava can mimic the appearance of a tumour or malignancy.
- ▶ Pulmonary thromboembolism is a rare but important cause of pulmonary hypertension in children.
- ▶ When children present with unusual, widespread thrombotic illness, the possibility of antiphospholipid syndrome should be considered and they should be investigated and anticoagulated appropriately.

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