CASE REPORT

Catastrophic antiphospholipid syndrome complicating orthotopic liver transplantation

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Catastrophic antiphospholipid syndrome (CAPS) is an acutely devastating situation characterized by widespread thrombotic microangiopathy in the presence of elevated titers of antiphospholipid antibodies. We describe a 57-year-old woman who underwent liver transplantation for primary sclerosing cholangitis and developed this malignant variant of the antiphospholipid syndrome. Lupus (2003) 12, 140–143.

Key words: anticoagulation; APS; catastrophic; catastrophic APS; orthotopic liver transplantation

INTRODUCTION

The antiphospholipid syndrome (APS) is characterized by a combination of recurrent arterial and venous thrombosis and usually mild to moderate thrombocytopenia, in the presence of elevated titers of antiphospholipid antibodies (lupus anticoagulant and/or the anticardiolipin antibodies).1,2 It was first recognized in patients with systemic lupus erythematosus (SLE), and later in patients with other autoimmune disorders, or even independently of any underlying disease (primary antiphospholipid syndrome; APS).3

Over the past years a small minority of patients with APS have been described who develop an acutely devastating situation characterized by multiple vascular occlusions, often resulting in death, which is referred to as catastrophic antiphospholipid syndrome.4,5 Several conditions are recognized to trigger this entity, such as infections, major or minor surgery, drugs and anticoagulation withdrawal.6–8

We describe a patient who presented with catastrophic antiphospholipid syndrome following orthotopic liver transplantation (OLT).

CASE REPORT

We report the case of a 57-year-old woman, who underwent OLT for primary sclerosing cholangitis, associated with Crohn’s disease. The patient’s inflammatory bowel disease had remained quiescent during the previous years under medical treatment. She had a history of two transient ischemic attacks six months before transplantation. A brain CT scan was normal and a Doppler ultrasound of the carotid arteries showed 15% occlusion of the left internal carotid artery. The presence of lupus anticoagulant was detected, so she was prescribed acetylsalicylic acid (ASA) (500 mg/day), but anti-cardiolipin antibodies IgG and IgM were negative.

At the time of transplantation the patient was in a stable clinical condition, suffering from intense refractory pruritus, sleep deprivation and severe asthenia.

The transplant procedure was uneventful. Antithrombotic prophylaxis was started intraoperatively with ASA and low molecular weight heparin, and was maintained post-operatively. The immunosuppression regimen consisted of cyclosporin (blood trough level = 220–250 ng/ml), corticosteroids and mycophenolate mofetil (2 g/day).

The patient had a favourable outcome post–OLT until day five, when she started with recurrent, self-limited episodes of profuse sweating, disorientation and disartrhia. Due to a concomitant increase in alkaline phosphatase and transaminases, a liver biopsy was performed, which showed moderate...
acute cellular rejection. She received three daily boluses of 500 mg of methylprednisolone from day 5 – 7.

On day seven, she repeated an episode of disorientation and disartha, with hypotension. Twelve hours later, she developed right hemiparesia. A brain CT scan was normal, and an MRI demonstrated an ischemic lesion in the pons (Figure 1), and evidenced 90% vascular occlusion of the left internal carotid artery. LAC was positive and anti-cardiolipins, protein C and S were negative on retest four weeks after the clinical event.

The patient was started on intravenous anticoagulation with heparin, presenting great difficulty in prolonging the partial thromboplastin time.

On day nine a liver Doppler ultrasound showed a marked hyperflow in the hepatic artery, with complete flow inversion of the left branch of the portal vein without evidence of thrombosis. On day 10, the patient suddenly developed intense dyspnea, tachycardia, right bundle heart block, profuse sweating, abdominal bloating with generalized pain, arterial hypotension, marked acrocyanosis and livedo reticularis of the four extremities, with worsening of her neurologic deficits. An abdominal CT scan showed marked bowel dilatation and a large, uncomplicated subhepatic haematoma. She was started on antibiotic treatment with vancomycin and imipenem.

The patient progressively deteriorated in the following hours, developing encephalopathy, oligoanuria, hyperthermia and hyperdynamic circulation. Lactic acid levels rose to 8.0 mg/dl. A diagnostic laparotomy was performed, which showed extensive, patchy ischemia of both small and large intestine associated to a hemoperitoneum, with no evident bleeding source. During the surgical procedure, the bowel spontaneously repulsed, with stabilization of the hemodynamic parameters. She developed permanent hypertension, requiring nifedipine. All blood urine and abdominal fluid cultures were negative. There was no biochemical evidence of diffuse intravascular coagulation (DIC), and the platelet count remained stable.

Two days later a ‘second look’ laparotomy was performed and no evidence of intestinal ischaemia was found. On day 13 the patient started with copious bleeding through her two abdominal drainages and developed a spontaneous hemothorax, with hemodynamic instability and a seven point fall of the hematocrit. Full anticoagulation was stopped and the patient was maintained with ASA, prophylactic low weight heparin and ticlopidine. Simultaneously, the patient developed sustained hypotension and oligoanuria. The thorax X-ray disclosed a diffuse alveolar infiltrate in the right base. A bronchoalveolar lavage (BAL) was done and the patient remained intubated and was started on mechanical ventilation and hemodynamic support. Blood and BAL specimens were positive for Acinetobacter baumanii, and amoxicillin-sulbactam was started.

The patient presented progressive improvement so she was removed from the ventilator five days later. She was difficult to arouse, even though all sedatives had been withdrawn 48 hours before. A brain MRI showed an extensive ischemic lesion of the left hemisphere, with marked edema and middle line herniation. Antiedema treatment was started.

The patient slowly improved her neurologic status, despite right hemiparesia and severe expressive aphasia. The graft function remained optimal until she developed steroid resistant acute rejection on day 41 post-OLT that was controlled after switching her from cyclosporin to tacrolimus.

On day 64 post-transplantation the patient was sent to a neurologic center for her rehabilitation.

**DISCUSSION**

Antiphospholipid antibodies have been reported in association with certain entities involving the liver, like primary biliary cirrhosis, autoimmune hepatitis and chronic hepatitis C. Inflammatory bowel disease (ie Crohn’s disease) has also been associated with lupus anticoagulant.

Antiphospholipid syndrome is defined clinically as the occurrence of recurrent venous and arterial
thrombosis, with or without thrombocytopenia or recurrent foetal loss, in the presence of either aCL or lupus anticoagulant repeated 6 months apart, as in this case, and four weeks after the clinical event.\textsuperscript{14} Arterial thrombosis may manifest as bowel infarction, myocardial infarction and even gangrene of the extremities, but most commonly it presents initially as a transient ischemic attack or stroke, as in our patient. As opposed to large vessel venous or arterial occlusions seen in ‘simple’ APS, patients with catastrophic APS present with a devastating occlusive microangiopathy, characterized by multiple organ involvement.

The clinical presentation in this patient was characterized by the rapid succession of multiple occlusive events. Initially she developed an ischemic pontine lesion. In spite of intense immunosuppression, ASA and anticoagulation, two days later she presented with myocardial (sinus tachycardia, right bundle heart block), gastrointestinal and cutaneous involvement. Hepatic microvascular thrombotic compromise was posteriorly suspected, when all Doppler alterations in liver vasculature reversed spontaneously after the patient’s stabilization. Even though the patient developed oligoanuria and hypertension, we had no biochemical evidence in serum or urine suggestive of renal thrombotic microangiopathy.

Asherson first used the term catastrophic antiphospholipid syndrome in 1992 to define a rare, accelerated form of the antiphospholipid syndrome resulting in multiorgan failure.\textsuperscript{5} He reviewed 50 cases and analysed the most frequent clinical presentation. In his series, 78\% of patients had renal involvement. CNS compromise was present in 56\%. The vast majority were initially confused and disoriented and nine patients developed major cerebral infaracts. Cardiac manifestations were seen in half of the patients who were evaluated, and hepatic involvement (microthrombi) in 36\%.\textsuperscript{6}

Considering that all solid organ transplants are critically dependent on the patency of vascular anastomosis, much concern is held on the consequences of a pro-thrombotic condition as APS on transplantation. Vaidya \textit{et al.} evaluated the impact of antiphospholipid antibodies upon renal transplant outcome in 78 patients. Six of these patients had APS and each of them thrombosed their renal allografts within a week of their transplants. All other 72 patients were doing well 1 year after the procedure.\textsuperscript{15} Collier \textit{et al.} has reported two cases of APL following liver transplantation, which resulted in hepatic vessel thrombosis and subsequent graft loss. They analysed the incidence of antiphospholipid antibodies (aPL) in 132 recipients of liver transplants and found an incidence of 6.3\%. While the presence of aPL was not associated with an increased risk of hepatic vessel thrombosis, the presence of APS may result in hepatic artery occlusion and graft loss.\textsuperscript{16} Pascual \textit{et al.} found 100\% presence of IgM and IgG anticardiolipin antibodies in 7 patients with hepatic artery thrombosis (HAT) post-OLT, compared with 54\% in liver recipients without HAT, and in lower titers, suggesting a contributory effect of these antibodies in the pathogenesis of HAT, even in the absence of other clinical conditions suggesting APS.\textsuperscript{17}

In Asherson’s series\textsuperscript{6} precipitating factors were identified in 22\% of patients. This included infection, drugs (i.e., thiazides, captopril, and oral contraceptives), minor and major surgical procedures and anticoagulation withdrawal. Obviously many of these factors can occur in the setting of liver transplantation, and it is clear that there is no way to anticipate which patient with APS can develop a catastrophic form, or how to prevent it. We are concerned about the role of cyclosporin and acute cellular rejection as potentially additional triggering factors. Cyclosporin promotes endothelial damage, leading to the development of microangiopathy, and is associated with constriction of small arteries, which by decreasing blood flow may initiate coagulopathy. The occurrence of endothelial damage has been evaluated by Tienamm \textit{et al.} who demonstrated a dose dependent effect of cyclosporin on the release of endothelial tissue factor pathway inhibitor and Von Willebrand factor antigen on endothelial cell cultures over an incubation period of four days.\textsuperscript{18} Acute rejection results in increased levels of many cytokines, as IL-1, IL-6 and TNF-\textgreek{alpha}, which may contribute through local inflammatory responses to microvascular damage. Although no standard treatment has been established for CAPS, there is an agreement that anticoagulation plus steroids is a first line treatment modality. Alternative options are the use of plasmapheresis (to prompt reduction of antiphospholipid antibodies) or gammaglobulin. Patients with proven clinical APS should be taken into consideration for postoperative anticoagulation as a preventive measure.

Even though neurological manifestations may complicate the clinical course of patients after OLT, Menegaux, in a retrospective study of 391 patients, found only five patients (1\%) who developed cerebral infarct.\textsuperscript{19} Antiphospholipid antibodies have been clearly established as a risk factor for stroke\textsuperscript{20} and Bonster has described two patients who developed this neurologic complication 2 months and 2 years after OLT, respectively, with a favourable outcome after anticoagulation with warfarin.\textsuperscript{21}

\textbf{CONCLUSION}

This is the first report of catastrophic antiphospholipid syndrome complicating liver transplantation.
The association of antiphospholipid antibodies with autoimmune diseases involving the liver, as well as the ever increasing indications for liver transplantation demands a greater awareness of this dramatic complication when other causes of multiorgan failure have been ruled out.

References
