Clinical Case Report

Renal thrombotic microangiopathy and cerebral venous thrombosis in a young man

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ABSTRACT

We report a patient of primary catastrophic antiphospholipid syndrome who presented with rapidly progressive renal failure and seizures. He was detected to have thrombotic microangiopathy on kidney biopsy and deep cerebral venous thrombosis. The patient was successfully managed with anticoagulants, steroids, plasmapheresis and cyclophosphamide.

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INTRODUCTION

Antiphospholipid syndrome (APS), also known as Hughes syndrome, is a prothrombotic state with an incidence of 2%–5% in the general population. It is characterized by arterial or venous thrombosis, recurrent foetal loss and laboratory evidence of antiphospholipid (anticardiolipin) antibodies (APLA) or lupus anticoagulant (LAC). APS is classified into 'primary' when no underlying cause is identified, and 'secondary' when it is associated with an underlying cause, e.g. systemic lupus erythematosus (SLE), drugs, infections or malignancy.[1]

The descriptive adjective 'catastrophic' was added to APS in 1992 by Asherson[2,3] to highlight an accelerated form of this syndrome that caused multiorgan failure. Patients with catastrophic APS (CAPS) have clinical evidence of multiple organ involvement developing over a very short period of time, histopathological evidence of multiple small vessel occlusions, and laboratory evidence of APLA, usually in a high titre. Renal thrombotic microangiopathy and cerebral venous thrombosis have been rarely reported in APS. We report here a patient of CAPS with thrombotic microangiopathy of the kidneys and cerebral venous thrombosis. To the best of our knowledge, no case with this profile and outcome has been reported in the literature.

THE CASE

A 26-year-old man, non-smoker and with no history of hypertension or diabetes, presented with painless progressive swelling of both lower limbs and dull, throbbing headache for 1 week. He also had breathlessness on exertion and a weight gain of 6 kg during this period. There was no history of fever, decrease in urine output, facial puffiness, sore throat, drug intake, oral ulcers, malar rash or photosensitivity.

On examination, his body mass index was 21.45 kg/m^2 and he was afebrile with a pulse rate of 106 per minute, blood pressure of 200/130 mmHg and respiratory rate of 18 per minute. He had pallor and bilateral pitting pedal oedema. Systemic examination was normal.

Investigations revealed a haemoglobin value of 7.1 g/dl with normal total, differential and platelet counts; peripheral blood smear showed dimorphic anaemia with presence of schistocytes; erythrocyte sedimentation rate was 68 mm after the 1st hour (Westergren) and C-reactive protein was 12 mg/dl. Urine examination revealed 2+ proteinuria, 2–4 white blood cells, 6–8 red blood cells and granular casts. The 24-hour urinary protein was 783 mg. His blood urea nitrogen was 78 mg/dl, serum creatinine 9 mg/dl, serum total protein 4.8 g/dl and serum albumin 2.6 g/dl. Liver function tests, serum electrolytes, coagulation profile, chest X-ray and electrocardiogram were normal. Ultrasound of the abdomen showed bilateral normal-size kidneys (right 9.7 cm and left 10.1 cm) with normal echogenicity.

In view of the normal-size kidneys, progressively rising creatinine and hypertension, a clinical diagnosis of rapidly progressive renal failure (RPRF) was made. Over the next 2 days after hospitalization he became oliguric and on day 3 he developed recurrent generalized tonic–clonic seizures. Neurological examination showed post-ictal stupor with no focal neurological deficit or signs of meningeal irritation. He had a persistently high blood pressure (210/130 mmHg) and required 7 antihypertensive drugs in addition to nitroglycerine infusion. Non-contrast CT scan of the head showed haemorrhages in both occipital lobes and the left parietal lobe. MR venogram of the brain showed multiple haemorrhages in the same areas and central venous thrombosis (CVT) of the deep veins including inferior sagittal sinus and transverse sinus (Fig. 1).

In view of RPRF and CVT, the possibility of thrombotic microangiopathy was considered. The collagen profile including anti-streptolysin O (ASO), antinuclear antibody (ANA), dsDNA, cytoplasmic and perinuclear staining antineutrophil cytoplasmic antibody (ANCA) were negative while complement levels were low (C3 0.96 and C4 0.22) and cryoglobulins were detected. LAC and APLA were positive on 2 occasions. Viral markers including

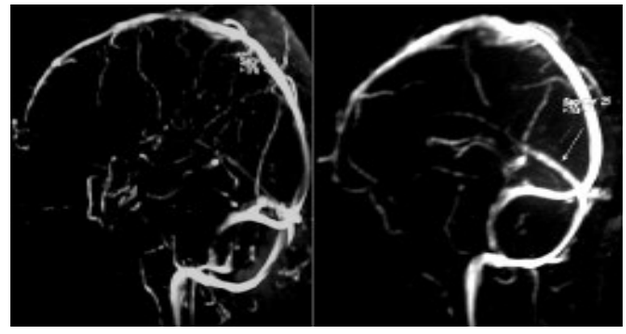

FIG 1. Initial MR venogram of the brain (left) showing absence of inferior sagittal and transverse sinuses, and follow up MR venogram after treatment (right) showing recanalization of the transverse sinus (arrow)

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anti-HCV, HBsAg and HIV were negative. Coagulation parameters revealed deranged prothrombin time of 18 seconds against a control of 12.8 seconds and activated partial thromboplastin time of 52 seconds against a control of 35 seconds. Renal biopsy showed glomeruli with fibrin thrombi and fibrinoid necrosis in the hilar arterioles suggestive of thrombotic microangiopathy (Figs 2 and 3).

Based on the above findings of involvement of 2 organ systems over a short period of time with positive APLA and LAC, a diagnosis of 'probable CAPS' was made. He was treated with 0.5 g of methylprednisolone for 3 days along with low molecular weight heparin (Enoxaparin 40 mg subcutaneously twice a day). Oral anticoagulation with acitrom was started a week later and heparin was discontinued once the target international normalized ratio (INR) of 2.5 was achieved. Oral steroids were continued at a dose of 0.5 mg/kg/day in addition to antihypertensives and anticonvulsants. Since the renal functions showed no improvement over the next 3 weeks, he had daily plasmapheresis for 7 days and was pulsed with intravenous cyclophosphamide. He remained dependent on dialysis for the next 6 weeks during which he was continued on oral steroids, oral anticoagulants and monthly cyclophosphamide pulses. He started showing gradual improvement 10 weeks after onset—his urine output started increasing, blood pressure control became easier, creatinine showed a decline and he became dialysis independent 11 weeks after onset of illness.

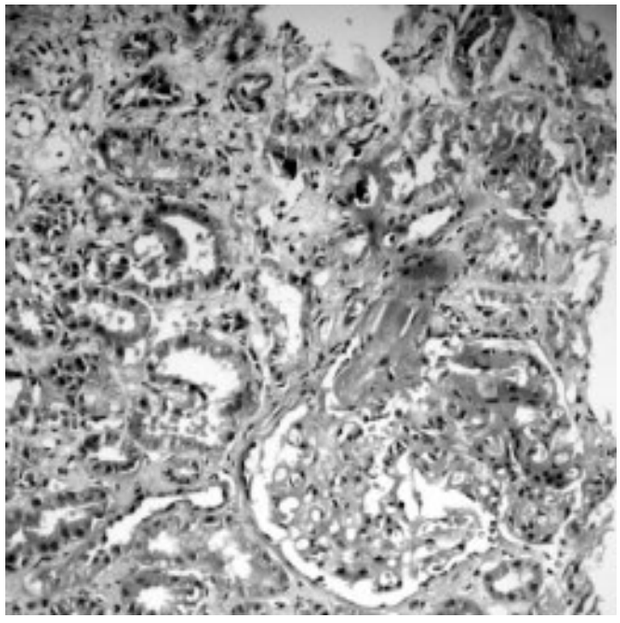

FIG 2. Photomicrograph showing fibrinoid necrosis in the hilar arteriole (H&E ×200)

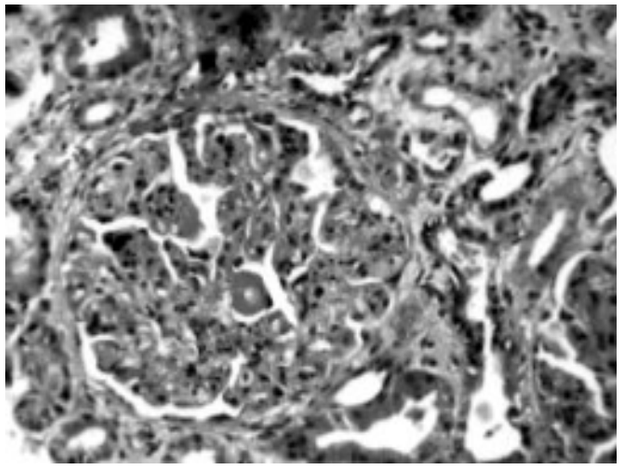

FIG 3. Photomicrograph showing microthrombi in the glomeruli (Massons trichrome stain, ×200)

Examination at the last follow up 6 months after onset of illness showed no pallor or oedema, a blood pressure of 140/80 mmHg and no neurological deficit. His serum creatinine was 3 mg/dl and he was on oral anticoagulants and 3 antihypertensive drugs. Follow up MR venogram of the brain showed a patent deep cerebral venous system (Fig. 1).

DISCUSSION

APS is not an uncommon condition but CAPS develops in <1% of these patients and has a mortality of 50%.[4] Till date, 250 patients of CAPS have been reported, of whom 41% were associated with primary APS. Patients may develop CAPS *de novo*, without any previous history of thrombosis.

Asherson classified CAPS into 'Definite CAPS' when there was evidence of involvement of 3 or more organs, systems or tissues simultaneously or in less than a week and 'Probable CAPS' when only 2 organs, systems or tissues are involved in the presence of APLA and histopathological evidence of small vessel occlusion in at least 1 organ or tissue.[5]

Some of the features of CAPS—thrombotic microangiopathy, haemolytic anaemia, thrombocytopenia, and involvement of the central nervous and renal systems also occur in haemolytic uraemic syndrome—thrombotic cytopaenic purpura (HUS–TTP) syndrome, malignant hypertension, heparin-induced thrombocytopenia and the haemolytic anaemia, elevated liver enzymes and low platelet count (HELLP) syndrome.[6] The histological features common to all these conditions include a gamut of lesions involving the glomeruli and blood vessels. The arteriolar changes are primarily arteriolar narrowing due to swelling of endothelial cells and subendothelial space along with infiltration of the arteriolar wall by fibrin (fibrinoid necrosis). The term fibrinoid necrosis is probably a misnomer as there is no true necrosis but the lesions are related to increased vascular permeability and non-specific trapping of plasma proteins including fibrin in the vascular wall, seen most commonly in the hilum of the glomerulus. As the lesion progresses the microthrombi merge with the arteriolar wall and it is often difficult to distinguish between the microthrombi and fibrinoid necrosis.[7]

Management of CAPS is challenging and an algorithm for treatment has been proposed by Asherson.[5] The proposed first-line therapy is with intravenous heparin followed by oral anticoagulants. Corticosteroids, plasma exchange and intravenous immunoglobulins are second-line measures. Plasma exchange improves the outcome by removing IgG aCL and β2-GPI as well as cytokines such as interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)-α and complement. The third-line therapy comprises cyclophosphamide and newer experimental agents such as rituximab, prostacyclines, ancrod and defibrotide.[8] Cyclophosphamide has been used in the treatment of both primary antiphospholipid antibody syndrome (P-CAPS) as well as SLE-associated CAPS (SLE–CAPS). A meta-analysis by Bayraktar *et al*. suggests that cyclophosphamide leads to a worse outcome in patients with P-CAPS but it is associated with improved survival

in patients with SLE–CAPS.[9] As our patient did not respond to anticoagulants and steroids for 3 weeks, plasmapheresis and cyclophosphamide were added and the response became apparent only after 10 weeks of initiation of treatment. Even in the meta-analysis quoted earlier, 19 patients with P-CAPS had been treated with cyclophosphamide and these patients had a higher mean number of organs involved than those who had not received cyclophosphamide, which could be a factor responsible for a worse outcome in this group of patients.

The description of our patient fits into 'probable CAPS' as there was definite evidence of involvement of 2 systems (kidney and brain) along with other criteria mentioned above. Asherson in a series of 1000 patients with APS reported renal manifestations (glomerular thrombosis, renal infarction, renal artery thrombosis and renal vein thrombosis) in only 27 patients and CVT in only 7 patients.[4] To the best of our knowledge, no case with a combination of these systems is described in the literature.

The peculiar features in our patient were severe hypertension at presentation, which is unusual in CAPS, and the late response to therapy. This case illustrates that addition of second- or third-line therapy should be considered when the response to first-line therapy is not apparent and that the response may be delayed.

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