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BRIEF REPORT

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Catastrophic antiphospholipid syndrome in a 14-year-old child

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Abstract Antiphospholipid syndrome (APS) is an autoimmune disease. Less than 1% of patients with APS present with life-threatening catastrophic APS (CAPS). We report here a case of CAPS in a young girl with cardiac, gastrointestinal and renal involvement. Although the management was complicated, the outcome was better than expected. We suggest that CAPS be included in the differential diagnosis of acute renal failure in children with multi-organ involvement and prolonged phospholipid-dependent coagulation time and promptly treated with immunomodulating agents and anticoagulants.

Keywords APS · Renal failure · TMA · Myocarditis · Cholecystitis

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by recurrent vascular thrombosis and/or pregnancy loss in the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies). APS may be primary or secondary, associated with connective tissue diseases, particularly systemic lupus erythematosus (SLE) [1]. Less than 1% of patients with APS present with a life-threatening condition resulting from thrombosis in multiple organs and subsequent multiorganic failure, which is defined as catastrophic APS (CAPS) [2, 3]. In classical APS, usually a single arterial or venous medium-to-large blood vessel occlusion dominates the clinical picture, and renal complications are rare [2, 3]. On the other hand, CAPS is characterized by rapid, diffuse small vessel ischemia and thromboses affecting various organs. Renal involvement is common and severe in CAPS [4]. CAPS is rare in children and may be confused with hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) and SLE. The case reported highlights the difficulties in the diagnosis and management of this aggressive form of primary APS in a young child.

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Case report

A 14- year-old white girl was admitted with acute renal failure to the Department of Nephrology of the General Hospital of Athens. Three days earlier, she had had diarrhea, abdominal tenderness and fever. Her past medical history included a total thyroidectomy 3 years earlier. Histopathology revealed benign thyroid hyperplasia. Subsequently, she has been taking thyroid hormone tablets. She was not on any other medications. One month earlier, on a routine checkup, her renal function and urine examination were normal.

On admission, the patient's height was 163 cm and her weight 59 kg. Her blood pressure was 105/70 mmHg, heart rate 90 bpm, respiratory rate 22 breaths per minute and temperature 37.5°C. Examination of the lungs and heart revealed no abnormalities, and there was no peripheral edema. Examination of the abdomen revealed diffuse abdominal tenderness, which was more severe in the umbilical area and in the right hypochondrium. The liver was palpable 2 cm below the right costal margin, and bowel sounds were diminished. The neurological examination revealed no abnormal findings. No skin rash or petechiae were observed. Initial laboratory investigations revealed: hemoglobin 13.4 g/dl, white blood cell count 12.5×10^9/l (neutrophils 84%, lymphocytes 9%, eosinophils 1%), platelets 106×10^9/l; one to two fragmented erythrocytes (schistocytes) per optical field were found on peripheral smear examination, and the reticulocyte count was 0.5%. Urea was 50 mg/dl and serum creatinine 5.6 mg/dl, while random glucose, serum sodium, potassium, total calcium, phosphorus and total bilirubin were normal; aspartate aminotransferase was 216 IU/l (normal, 10–30 IU/l), and alanine aminotransferase was 229 IU/l (normal, 5–40 IU/l),

while gamma-glutamyl-transpeptidase, alkaline phosphatase, total proteins and serum albumin were normal. Lactic dehydrogenase was 1,448 U/l (normal, 390–580 U/l) and creatine kinase 975 U/l (normal, 50–240 U/l). Prothrombin time was 14.7 s (control 11–18 s), the International Normalized Ratio 1.17, activated partial thromboplastin time (aPTT) 138 s (normal, 25–38 s), fibrinogen 419 mg/dl (normal, 150–350 mg/dl), fibrinogen degradation products 6 μg/ml (normal, <5 μg/ml), D-dimers 0.5 μg/ml (normal, <0.5 μg/ml) and C-reactive protein 56.6 mg/l. The urine analysis revealed (++) proteinuria, 15–20 red cells (50% dysmorphic)/optical field. Chest radiograph and electrocardiogram were normal. An ultrasound scan of the abdomen showed that both kidneys were of normal size (10.5 cm in length) without obstruction; the liver was moderately enlarged. The gallbladder appeared to contain granular precipitate (sludge), but there were no gallstones or dilatation of the biliary tree.

On day 1 after admission, the patient remained anuric; dialysis was initiated with fresh-frozen plasma. In the same night, the abdominal tenderness worsened, and bowel sounds were further diminished. A computerized tomography of the abdomen was performed. It showed a small amount of free serous liquid between bowel helices, a moderate diffuse hepatomegaly and a gallbladder with thick walls, giving an image of acalculous cholecystitis. Surgical intervention was deferred.

On day 2, the girl had fever (38°C), was anuric with worsening thrombocytopenia (80×10^9/l) and aPTT prolongation (>2 min). Immediately after termination of the second hemodialysis session (and after a weight loss of 0.5 kg), the patient presented signs of congestive heart failure. An M-mode cardiac echo showed global left ventricular hypokinesis with an ejection fraction of 50% (normal, 64–83%); a diagnosis of myocarditis, based on echocardiographic findings, was considered. ECG was normal. Troponin levels were 34 ng/ml (normal, 0–2 ng/ml). An empiric antibiotic treatment was initiated (metronidazole, ciprofloxacin). The serologic investigation revealed: complement (CH50, C3, C4) within normal limits, antinuclear antibody (–), anti-DNA (–), anti-Sm antibody (–), anti-U1-RNP (–), anti-Ro antibody (–), anti-La antibody (–), c-ANCA (–), p-ANCA (–), direct Coombs' test (–) and haptoglobins 1.6 mg/l (normal, 0.5–2.0 mg/l). The microbiologic investigation revealed: negative stool cultures, negative blood cultures, negative urine culture, negative antibodies against hepatitis C, hepatitis B surface antibody (+), hepatitis A antigen (–), human immunodeficiency virus 1 (–), IgM antibodies against CMV, Epstein-Barr, herpes I and II virus, toxoplasma, Coxsackie's B1-B6, rickettsiae and Hantavirus (–).

A serologic test for syphilis (VDRL) was positive; the coagulation times were abnormal as before. A diluted Russel viper venom time ratio was also prolonged (1.7 with normal limits 0.9–1.05). The addition of normal platelet-poor plasma did not correct it. Excess phospholipid addition corrected the inhibited in vitro coagulation (mixing test experiments) [5]. Thus, a lupus anticoagulant (LA)/antiphospholipid antibody (aPL) was identified, and APS was diagnosed. Coagulation factors II, VII, VIII, X, XI, XII and the von-Willebrand factor level were normal, while factors V, IX and X were slightly decreased (63, 41 and 65%, respectively, with normal values between 70–120%). Inhibitors were not investigated. Serologic evidence for SLE was not present. In color Doppler imaging of the renal vessels, there was no venous or arterial thrombosis, but the blood flow resistance index in both renal arteries at the renal hilum was elevated.

Methylprednisolone (750 mg/day, i.v.) was administered followed by prednisolone (50 mg/day, i.v.) for the next 10 days. On day 10, a kidney biopsy was performed. A large subcapsular hematoma was formed in the biopsied left kidney, and the hemoglobin decreased (from 9.5 to 8.0 g/dl) on the day of the renal biopsy. The patient remained anuric for 20 days; hemodialysis was performed as required.

The renal biopsy contained 17 glomeruli, which showed a minimal increase of mesangial cells. Two glomeruli were globally sclerosed, and two were segmentally sclerosed. Glomeruli were retracted and appeared ischemic. There were no crescents. With the Jones stain, there was no evidence of glomerular basement membrane (GBM) duplication. Interlobular arteries and arterioles showed fibrous intimal and/or myointimal proliferation with significant luminal narrowing (Fig. 1). The tubules had extensive

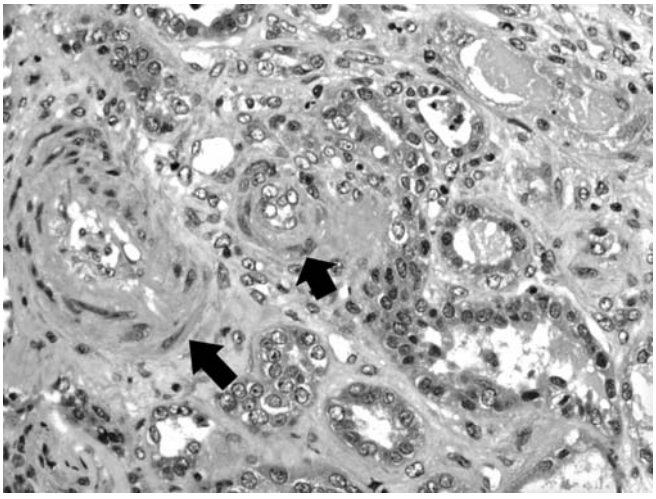

Fig. 1 Interlobular artery and small arteriole show fibrointimal proliferation (*arrows*) (HE ×100)

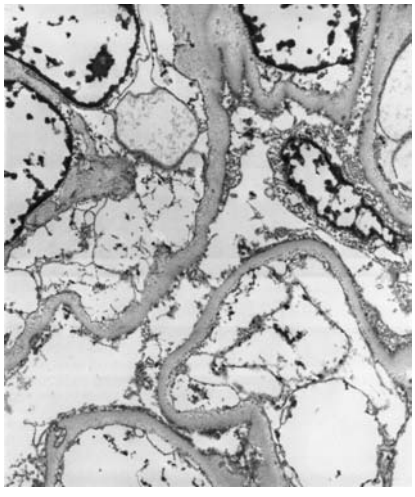

Fig. 2 Ultrastructurally, glomerular endothelial cells were edematous with separation of the cell membrane and occlusion of the capillary lumen (x5,000)

hemorrhagic necrosis with red blood cell casts. Mild focal chronic inflammation was present in the interstitium. There was no evidence of significant fibrosis. Cortical necrosis was absent. Immunofluorescence was negative. On electron microscopy, the most impressive finding was endothelial cell edema and detachment of endothelial cell membranes with luminal occlusion (Fig. 2). There were no fibrin deposits or platelet aggregates. The histopathological findings were consistent with acute thrombotic microangiopathy (TMA) with moderate to severe glomerular ischemia and secondary hemorrhagic tubular necrosis (Fig. 1, upper left corner). A diagnosis of CAPS was made based on the clinical presentation and laboratory and renal biopsy results. Anticoagulation with low-molecular weight heparin was initiated 4 days after the biopsy.

On day 21, 7 days after the initiation of the anti-coagulation therapy, the patient started producing urine. A repeat cardiac echo revealed a normal mobility of the left ventricular walls and a normal ejection fraction. Repeat computerized tomography of the abdomen revealed a normal gallbladder and reduced size of the liver. On day 43, the patient was discharged on oral anticoagulant treatment (warfarin). Serum creatinine was 2.5 mg/dl (creatinine clearance 25 ml/min). The presence of aPL was confirmed upon her discharge from the hospital.

Discussion

In 1992, a new form of APS, termed "catastrophic," was recognized [4]. The definite diagnosis requires four criteria to be fulfilled: (1) evidence of involvement of three or more organs and/or tissues, (2) development of manifestations simultaneously or within 1 week, (3) confirmation by histopathology of small vessel occlusion in at least one organ/tissue and (4) laboratory confirmation of the presence of an aPL (lupus anticoagulant and/or anticardiolipin and/or anti-β2 glycoprotein I) [2]. In the present case, renal, cardiac and hepatic-biliary involvement was present in the 1st week of the disease, acute TMA in the renal tissue was demonstrated, and the presence of aPL was repeatedly documented.

The differential diagnosis of TMA, particularly in the pediatric age, includes sporadic HUS and/or TTP [6]. Heavy thrombocytopenia, the presence of schistocytes on peripheral blood smear, neurological symptoms and renal TMA are classic features of HUS or TTP. In this case, repeatedly negative stool cultures for pathogens like *Escherichia coli* or *Salmonella*, moderate rather than profound thrombocytopenia involvement of multiple organs and particularly the absence of hemolysis with prolonged aPTT made the diagnosis of TTP or HUS less likely [6]. The renal histopathological findings in primary APS include fibrointimal hyperplasia [7, 8, 9]. Interestingly, a child that presented with crescentic glomerulonephritis and another with focal proliferative glomerulonephritis, but not with TMA, have been reported [10, 11]. The absence of "fluffy" deposits or platelet aggregates in glomerular capillary lumens that are characteristic of HUS/TTP support the diagnosis of APS [8, 9]. The constellation of intimal fibroplasia with TMA is considered particularly characteristic of APS [7]. Finally, persistent aPL in an interval of 6 weeks, as well as the negative serologic evidence for systemic lupus erythematosus, made the diagnosis of primary CAPS most likely. The distinction between catastrophic APS and TTP/HUS was of vital importance. Anticoagulant treatment is considered as the first-line therapeutic approach in the former [2] and is contraindicated in the later. Infection is reported to be a contributing precipitating factor in CAPS. Salmonella, upper respiratory infection and others have been well documented to precede CAPS [12]. None was present in this patient. The pathogenesis of CAPS remains unclear, but a role of endothelial cell activation is suggested. Whether aPL antibodies are directly involved is uncertain. Endothelial cell injury is a common denominator in TMA of diverse etiologies, but the inciting factors vary greatly. In TTP, it is secondary to deficient proteolytic enzyme ADAMTS13 in plasma, while in classic HUS, the shiga toxin triggers endothelial injury [6, 12, 13, 14].

In the largest series of catastrophic APS published (80 cases) [4], the mean age of the patients was 37 years; only two were less than 16 years of age. Notably, in both cases abdominal pain was the presenting symptom. Although hepatic and renal involvement is common in the published APS cases, gallbladder involvement is described only in a few [15]. The small number of fragmented red cells in the peripheral blood smear is also rare [4]. Renal histopathology in this case was exclusively vascular, similar to the majority of described cases of APS and in contrast to the two cases described above that had primarily glomerular disease in the form of crescentic and focal proliferative glomerulonephritis.

In conclusion, CAPS has to be included in the differential diagnosis of acute renal failure in children with multi-organ involvement and prolonged phospholipid-dependent coagulation time. Although the diagnosis and management of these cases is complicated, the outcome need not always be fatal.

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