Case Report

An adolescent with acute renal failure, thrombocytopenia and femoral vein thrombosis

Tobias Petras, Birgit Rudolph, Guido Filler, Miriam Zimmering, Gerhard Ditscherlein, Stefan A. Loening and Jochen H. H. Ehrich

Department of Urology, 
Department of Paediatric Nephrology, 
Institute of Pathology, Charité, Humboldt University, Berlin, Germany

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Introduction

Haemolytic uraemic syndrome (HUS) may be due to a variety of causes and patients without a history of diarrhoea should be carefully investigated for the underlying disease [1]. Extrarenal complications are frequently found in patients with thrombotic microangiopathy, however, thrombosis of large vessels and ureteritis are uncommon findings. We report an adolescent with an unusual cause of HUS complicated by femoral vein thrombosis and ureteritis due to antiphospholipid antibody syndrome.

Case report

A 15-year-old female was admitted to hospital with nausea, macrohaematuria, and fever (38°C) for 2 days. Proteinuria (> 1 g/l), generalized oedema and thrombocytopenia were found. She became oliguric (150 ml/24 h) Her personal history was unremarkable apart from epidemic parotitis in early childhood. She had no allergies. Two months earlier, she had started using an oral contraceptive. She had recurrent non-bacterial tonsillitis 6 months prior to admission. A homeopathic treatment with Luivac (hydrolized Staphylococci and Streptococci) was given 1 month before onset of renal symptoms. The patient was transferred to our unit for further investigation.

On admission, we saw an afibrile female with hepatosplenomegaly, star-shaped rashes on both thorae and hypothenar palms as well as telangectasia on her chest. Laboratory analysis showed thrombocytopenia (33 000/µl). Blood haemoglobin level was initially 14 g/dl and decreased to 7 g/dl. Leukocytes were 16 300/µl. Serum creatinine was 210 µmol/l. C-reactive protein was 106 mg/l. Transaminases were normal. LDH (16.0 µmol/l) was elevated. C3-complement 0.98 g/l, C4-complement 0.25 g/l. D-Dimers (0.70 µg/ml) were elevated. Urinary analysis showed proteinuria (1.28 g/l) and macrohaematuria with dysmorphic erythrocytes. Toxicological screening for drugs was negative. High serum antibody levels were found against phospholipids such as anticardiolipin (aCL)-IgG: 65.2 (×1.35 of maximum normal) and anticardiolipin (aCL)-IgM: 79.1 (×1.8 of maximum normal). Ten days later there was a further increase of aCL-IgG to 92 (×1.9 of maximum normal) and of aCL-IgM to 195 (×4.4 of maximum normal). Antibodies against cryoglobulins and thrombocytes were absent and the C3-nephritis factor, as well as anti-dDNA, anti-ENA, and p-ANCA levels were not elevated. Serology was negative for verotoxin-producing E. coli O157:H7, Hanta-virus, HIV, and Cytomegalovirus.

Abdominal ultrasound showed two kidneys with increased echogenicity of normal size. Duplex Doppler ultrasound showed occlusions of the right superior and the right deep femoral vein. A biopsy taken from the nasal septum did not show evidence of Wegener's granulomatosis.

On kidney biopsy, dilatation of capillary loops and mesangiolysis were found in seven out of 18 glomeruli (Figure 1). The capillary lumina were filled with aggregates of erythrocytes and fibrin (Figure 2). The arterioles revealed swelling of endothelial cells and fibrinoid clots (Figure 3). Peritubular capillaries showed patchy thromboses. There were interstitial haemorrhages. The tubuli showed multiple cell necrosis. Glomerular immunofluorescence for IgG, IgA, IgM, and C3 was negative. Electron microscopy (EM) showed mostly endothelial damage, mesangial deposits of biodegradable material, and flattened foot processes (Figures 4 and 5). Electron-dense immune deposits were absent. The morphological diagnosis was...
ARF, thrombocytopenia and femoral vein thrombosis

compatible with thrombotic microangiopathy and mesangiolysis.

The clinicopathological diagnosis was haemolytic uraemic syndrome (HUS) and femoral vein thrombosis with antiphospholipid antibody syndrome. An effort to recanalyze the femoral vein with a balloon catheter was unsuccessful. Further thrombotic events were prevented with full heparinization followed by warfarin therapy. Daily oral prednisolone (80 mg/day) for 4 weeks and three i.v. cyclophosphamide pulses (0.5 g/m² BSA every 4 weeks) failed to reverse renal failure (creatinine 350 μmol/l) and thrombocytopenia (33 000/mm³). Cutaneous involvement disappeared within 2 weeks. A second renal biopsy 8 weeks after admission showed persistent thrombotic microangiopathy. Following i.v. immunoglobulin (0.4 g/kg body weight every 4 weeks), plasmapheresis (six sessions) and alternate day prednisolone therapy (50 mg/48 h), thrombocyte count increased to 154 000/mm³. Serum creatinine decreased within 4 weeks to 176 μmol/l and proteinuria declined from 1.8 g/l to 0.44 g/l. Consequently, serum albumin was 44 g/l and thrombocytes were 290 000/mm³. Ultrasonography revealed a mild dilatation of the renal pelvis on both sides, 12 weeks after admission. The girl was discharged and seen in the outpatients’ clinic at intervals of 2 weeks. Eight months after onset of the disease there was a sudden increase in creatinine (from 140 to 214 μmol/l). Now renal ultrasonography showed severe bilateral hydronephrosis and suggested postrenal failure. On surgery, the left side revealed a 1-cm long complete stenosis of the upper ureter, which was resected. Histological examination showed ureteritis with fibrosis (Figure 6). An end-to-end anastomosis was performed. On the right side, surgery showed a ureteric stenosis which was opened for a catheter. Catheters were placed into both ureters for 6 weeks. Within 1 week, serum creatinine declined to 100 μmol/l. [⁵¹Cr]EDTA clearance was 56 ml/min per 1.73 m² body surface area, [¹²³I]-hippurane clearance 248 ml/min per 1.73 m² BSA, proteinuria 1.1 g/l, and haematuria 9 erythrocytes/μl. Maintenance immunosuppression consisted of prednisolone 20 mg/48 h, azathioprine 50 mg/day, and i.v. immunoglobulins (0.4 g/m²) every 4 weeks. Antihypertensive treatment included nifedipine, captopril, and furosemide.

**Discussion**

On admission, systemic lupus erythematosus (SLE) was considered in the differential diagnosis of acute renal failure with haemolytic anaemia, thrombocytopenia, hepatosplenomegaly, the rash, and the femoral thrombosis. SLE associated anti-doublestranded DNA antibodies and complement activation were absent. High titres of anticardiolipin-antibodies led to the diagnosis of antiphospholipid antibody syndrome with atypical HUS.

Antiphospholipid antibodies are not specific for a single disease but can be found in a variety of immuno-

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**Fig. 1.** Glomerulus (×236, Trichrome SFOG) with mesangiolysis and capillary loops filled with aggregates of erythrocytes and fibrin in a patient with thrombotic microangiopathy due to antiphospholipid antibody induced haemolytic uraemic syndrome.

**Fig. 2.** Glomerulus (×252 and ×126) with mesangiolysis.

**Fig. 3.** Kidney (×113) of a patient with antiphospholipid antibody induced thrombotic microangiopathy showing an arteriole with swelling of endothelial cells and fibrinoid clots (arrow).
Fig. 4. Electron micrograph of a glomerulus (× 2000) showing endothelial damage and flattened foot processes (E = erythrocytes, M = mesangium, P = podocytes).

Fig. 5. Electron micrograph of the kidney (× 4800) with endothelial damage and mesangial load with biodegradable material.

logical entities such as autoimmune hepatitis, haemolytic anemia and AIDS. Alarcon-Segovial et al. [2] described a primary antiphospholipid antibody syndrome (aPL-AB) with venous and arterial thrombosis, ulcerations of the legs, livedo reticularis, haemolytic anemia, thrombocytopenia, and focal arterial inflammation. The aPL-AB syndrome was characterized by high concentrations of antiphospholipid antibodies (for
We observed a positive effect of plasmapheresis and intravenous immunoglobulin therapy on the course of HUS and the aPL-AB syndrome. No further thrombotic event was observed during the 8 months course of warfarin therapy and 6 months after withdrawal of warfarin. Maintenance immunosuppression consisted of prednisolone, azathioprine, and i.v. immunoglobulin pulses. During follow-up, antiphospholipid antibodies remained in the normal range.

In summary, antiphospholipid antibody syndrome must be added to the list of causes leading to atypical haemolytic uremic syndrome. We suggest that patients with HUS without diarrhoea should be screened for autoimmunological disorders including antiphospholipid antibodies.

Fig. 6. Left ureter (×23) with obstructed lumen due to surrounding inflammatory infiltrates and fibrosis.

References

1. Filler G, Bredow MA von, Grüne HJ, Ehrich JHH. A child with IgG or IgM > 5 SD of mean normal value) and two of the clinical manifestations mentioned above [1]. The thrombotic mechanism in aPL-AB syndrome is not clear. Reduced synthesis of prostacyclin [3] or aPL-AB binding to freeze-thawed platelets [4] have been offered as an explanation. Renal involvement in aPL-AB syndrome has been described by Appel et al. [5]. The noninflammatory necrotizing vasculopathy appears identical to the vascular changes seen in SLE patients with HUS and other thrombotic microangiopathies. The role of aPL-AB in the pathogenesis of glomerular damage is equally unclear. Endothelial injury and glomerular cell necrosis were found in SLE patients with and without aPL-AB [6]. Baqui et al. [7] reported a 16-year-old girl with elevated antinuclear antibodies and low C3/C4 complement levels. A renal biopsy showed afferent arteriolar thrombogenic with extensive deposition of C3, IgG, and fibrin. This HUS-like syndrome, associated with SLE was described to be a special type of the aPL-AB syndrome. Tsuzuki et al. [8] reported an 18-year-old female with an acute nephrotic syndrome caused by haemangioendothelial injury with mesangiolysis due to aPL-AB syndrome. Bilateral ureteral obstruction was reported to occur in Schoenlein-Henoch purpura through ureteritis or retroperitoneal fibrosis [9], suggesting vasculitis as the pathogenetic mechanism. Similar processes may have been involved in our patient, however, she did clearly not have Schoenlein-Henoch nephritis.

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