Coincidence of haemolytic uraemic syndrome and c-ANCA-associated rapidly progressive glomerulonephritis

Ioannis Stefanidis\textsuperscript{1}, Udo Helmchen\textsuperscript{2}, Hans Schmitt\textsuperscript{1}, Norbert Maurin\textsuperscript{1}, Heinz-Günter Sieberth\textsuperscript{1}

\textsuperscript{1}Medizinische Klinik II, RWTH Aachen and \textsuperscript{2}Kerninstitut für Pathologie, Universität Hamburg, Hamburg, Germany

**Case Report**

**Key words:** c-ANCA; haemolytic uraemic syndrome; proteinase-3; rapidly progressive glomerulonephritis; secondary haemolytic–uraemic syndrome

**Introduction**

Haemolytic uraemic syndrome (HUS) is a disease characterized by a non-immune haemolytic anaemia, thrombocytopenia, and acute renal failure with platelet thrombi in the microcirculation of the kidney \[1,2\]. Renal biopsies show microthrombotic glomerulopathy as a constant finding which, especially in adults, may be accompanied by preglomerular vascular lesions (i.e. primary malignant nephrosclerosis) \[2,3\]. HUS is basically a disease of children and infants where the majority of cases (90\%) follow intestinal infections with verotoxin-producing \textit{Escherichia coli} (classical HUS) \[4\].

HUS is a rare disease in adults. Adult HUS is occasionally idiopathic or familiar \[5\]. However, in most cases it occurs as a complication of a variety of conditions (secondary HUS), such as pregnancy and the postpartum period, malignant hypertension, drug therapy (oestrogen-containing oral contraceptives, cyclosporin), chemotherapy (bleomycin, cisplatin, mitomycin), malignancy (mucinous adenocarcinoma of the gastrointestinal tract, pancreas, prostate), HIV infection, and with renal disorders complicating systemic collagen diseases (systemic lupus erythematosus, scleroderma) (Table 1) \[6,7\].

Secondary HUS associated with various primary glomerular diseases has rarely been reported. We recently observed a patient with a c-ANCA (anti-proteinase-3)-associated rapidly progressive glomerulonephritis (RPGN) who subsequently exhibited the characteristic clinical/laboratory findings and histologic lesions of HUS. To date, HUS has already been reported in two adult patients and three children with idiopathic RPGN \[8–10\]. To our knowledge anti-proteinase-3-associated RPGN with HUS has never been reported.

**Case**

**History**

A 68-year old female patient was admitted to the renal unit with progressive azotaemia and dyspnoea. The patient had been well until 4 weeks earlier, when she noted weight loss (7 kg in 4 weeks), fatigue, and pretibial oedema. Four days prior to admission she developed nausea, vomiting, progressive exertional dyspnoea, and declining urine production. She had no diarrhea, fever, cough, or skin rash. There was no evidence of diarrhoea in family members or other people she had had contact with. There was no family history of renal disease, hypertension, anaemia, HUS, or thrombotic thrombocytopenic purpura.

**Findings on admission**

**Physical examination.** At the time of admission the patient was pale and in respiratory distress with bilateral crackles on chest auscultation. The blood pressure was 170/80 mmHg and the pulse was 100 beats/min. A grade 2 systolic murmur was audible at the apex. Marked pretibial oedema was present. Spleen and lymph nodes were not palpable. The abdomen was normal, the... 

Correspondence and offprint requests to: Prof. Norbert Maurin MD, Ioannis Stefanidis MD, Medizinische Klinik II, RWTH Aachen, D-52057 Aachen, Germany.
Table 1. Classification of haemolytic uraemic syndrome (HUS)

1. Idiopathic
2. Familial
3. Associated with
   - verotoxin (classical HUS)
   - pregnancy, post-partum, oestrogens
   - systemic disease (collagen diseases)
   - malignant hypertension
   - cyclosporin
   - cancer
   - chemotherapy
   - HIV infection

Modified from [13].

Protein excretion was 6 g/24 h. Microscopic haematuria and leukocyturia were observed.

Serology. This revealed no significant antistreptolysin O and antistaphylolysin titres. Results of direct and indirect Coombs’ tests were negative. Anti-basement-membrane, antinuclear, extractable nuclear antibodies, and rheumatoid factors were negative. E. coli O157:H7 antibody titres were negative. c-ANCA titre was markedly increased (1:1024) and proteinase-3 antibodies were positive (71 U/ml, ref. < 20).

Renal ultrasonography. This revealed kidneys of normal size (left 11 cm and right 12 cm) with increased echogenicity of the parenchyma. Findings from electrocardiography and echocardiography indicated left ventricular hypertrophy. Thoracic roentgenogram showed pleural effusion on the left side.

Clinical evaluation, roentgenogram and CT scanning of the nose and the paranasal sinuses were normal.

Renal biopsy

The patient underwent an ultrasound-guided percutaneous needle renal biopsy.

Light microscopy (5 glomerula) showed focal and segmental tuft necrosis, and cellular or fibrotic extracapillary crescents in all glomerula (Figure 1a, b). In addition preglomerular arterioles showed a marked subendothelial oedema, infiltrated by fragmentocytes and fibroblasts narrowing their lumina (Figure 2a,b). Immunofluorescence microscopy exhibited diffuse granular deposits of immunoglobulin M (IgM) and of fibrin/fibrinogen in the necrotic lesions of the Bowmann’s space. Fibrin deposits were also found within the vascular walls (Figure 2b). Electron microscopy demonstrated thickening and wrinkling of the glomerular basement membrane with several ruptures. Glomerular capillaries showed cell infiltration and fibrin precipitates. The findings were consistent with the diagnosis of remittent intra- and extracapillary RPGN followed by the characteristic lesions of HUS.

Histology of the arterial wall (arteria radialis) was performed in the 30th day after admission during an arteriovenous fistula operation. No histological signs indicating vasculitis or amyloidosis of large arteries could be found in this specimen.

Clinical course

The patient was treated with plasma exchange with fresh frozen plasma (6 sessions with 2.5 litres plasma each over 12 days). In addition she was given 100 mg/day acetylsalicylic acid and a prostacyclin analogue (CG 4203 25 ng/kg/min iv) [11]. On the first 7 days after admission, the patient required transfusion of 5 units packed erythrocytes with the haemoglobin remaining at the same level (80–90 g/dl). Indices of
wool exudates, and papillary swelling were repeatedly looked but were absent. The patient had some central nervous system symptoms. She complained of headache for which no explanation could be found on neurological examination; and which disappeared within 2 days. On the 12th day after admission, the patient was treated with 150 mg/day cyclophosphamide and 100 mg/day prednisolone. Despite this immunosuppressive therapy, the course of the kidney disease finally terminated in end-stage renal failure.

Discussion

The clinical course of the patient reported herein may be summarized as c-ANCA (anti-proteinase-3)-associated RPGN terminating in irreversible loss of kidney function. The outstanding feature of this case is that it primarily presented with laboratory findings compatible with HUS (non-immune haemolytic anaemia, thrombocytopenia, and peripheral red-cell fragmentation). Renal histological findings were consistent with the diagnoses of RPGN accompanied by HUS. The combination of acute (extracapillary proliferation) with chronic (fibrosis) glomerular lesions indicates a longstanding, relapsing course of RPGN. On the contrary, the pronounced intimal oedema of the arterial wall probably reflects early stage primary malignant nephrosclerosis (HUS) [12,13]. According to these findings HUS seems to be the superimposing disorder in this case.

Although most cases of adult HUS are atypical, verotoxin-induced syndrome (classical HUS) has been recognized with increasing frequency in adults (Table 1) [3]. Because no gastrointestinal prodromal symptoms existed there is only a small possibility of a verotoxin-induced HUS in our patient. E. coli O157:H7 antibody was negative [4]. Idiopathic and familial HUS is characterized by a chronic relapsing course and a poor prognosis [3,5,14]. The lack of family history with this disease and complete remission of microangiopathic haemolysis argues against this form of HUS in our patient. Further, there was no evidence of a collagen disease, large-vessel vasculitis, or malignancy.

Malignant hypertension is another cause of secondary HUS [15]. The patient had only moderate hypertension, excluding malignant hypertension as a cause of the observed HUS in this case. However, the possibility of a severe hypertensive period before admission cannot be definitely excluded. The left ventricular hypertrophy (electrocardiogram, echocardiogram) was probably due to chronic undiagnosed hypertension. Funduscopy was normal; specifically, retinal bleeding, cotton-wool exudates and papillary swelling were absent.

Secondary HUS associated with primary glomerular disease, specifically membranous glomerulonephritis, postinfectious glomerulonephritis, focal segmental glomerulosclerosis, and anti-glomerular basement membrane antibody mediated glomerulonephritis, has...
rarely been reported [16–18]. The present observation documents the occurrence of HUS together with another form of glomerulonephritis in adults, c-ANCA-associated RPGN. This further supports the idea that different types of glomerulonephritis may trigger a secondary HUS reaction. HUS has been already reported in three children and in two adult patients with idiopathic RPGN [8–10]. There is one prior report that describes a case with HUS and p-ANCA-associated RPGN [19]. One HUS patient has been reported to have simultaneously positive c-, p-ANCA (anti-proteinase-3, anti-myeloperoxidase), and elastase antibodies; however, without evidence of glomerulonephritis or vasculitis [20]. The coincidence of c-ANCA (anti-proteinase-3)-associated RPGN or Wegener’s granulomatosis with HUS has never been reported.

Endothelial dysfunction appears to be an important factor in the sequence of events leading to the microangiopathic process observed in HUS. Most agents associated with the disease, verotoxins, endotoxins, and certain drugs, are toxic to endothelial cells [3]. In vitro studies using endothelial cells from human umbilical vein showed that proteinase-3 is present in the cytoplasm and the cell membrane. According to these findings of Mayet et al. [21,22] the vascular endothelial cell can be a target of c-ANCA. Immunohistochemistry, however, failed to demonstrate binding of proteinase-3-ANCA to endothelial cells in crescentic glomerulonephritis [23].

A major aetiological role of c-ANCA in the induction of HUS is not probable. HUS does not induce RPGN. Furthermore, classical HUS does not belong to the ANCA-associated diseases. ANCA, retrospectively investigated by indirect immunofluorescence assay in sera of 27 patients with the classic type of HUS, were negative in all patients [24].

We assume a causal relationship between HUS and RPGN in this case because of the histological findings that implicate HUS as the superimposing disorder in this case and since secondary HUS has been described in many other primary glomerular diseases. This and all previous reports on the coincidence of HUS and RPGN support the idea that the presence of a primary glomerular disease needs to be considered early whenever HUS in an adult patient is suspected. Kidney biopsy and start of immunosuppressive treatment immediately at presentation could have improved the course of the renal disease in the case presented here.

References


Received for publication: 16.4.97
Accepted in revised form: 25.2.98