Case Report

Acute renal failure in non-fulminant hepatitis A

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Introduction

After Wilkinson et al. [1] described renal failure in uncomplicated acute viral hepatitis in 1978, acute renal failure (ARF) associated with non-fulminant hepatitis A has been infrequently reported. This condition usually has a good prognosis and can be successfully treated with dialysis therapy. Here we add another case and discuss possible mechanisms.

Case report

A previously healthy 30-year-old man was admitted to our hospital on 24 February 1995, because of generalized jaundice skin discoloration and decreasing urine output for 2 days. He had malaise and fever 7 days before admission, which was treated as an upper respiratory infection at a local clinic. There was no history of hepatic and renal disease. At the time of admission, his blood pressure was 130/90 mmHg, pulse rate 90 per min, and body temperature 36.6°C. Physical examination showed icteric skin but no signs of fluid depletion or hepatomegaly. Initial blood biochemistry revealed BUN 74 mg/dl, creatinine 10.4 mg/dl, albumin 3.4 mg/dl, calcium 6.9 mg/dl, phosphorus 5.9 mg/dl, and uric acid 13.5 mg/dl. The serum alanine transferase (SGPT) was 2348 Units, aspartate aminotransferase (SGOT) 3461 Units and total bilirubin 9.8 mg/dl. The haemoglobin was 15.4 g/dl, white blood cell count 9800/mm3 with a normal differential count and coagulation test within normal limits. Hepatitis B surface antigen and hepatitis C antibody were negative, but IgM antibody to hepatitis A virus (HAV) was positive by radioimmunoassay. Serum level of C3 was 157 mg/dl, C4 36 mg/dl. Urinalysis showed a trace amount of protein and the random urine sodium concentration was 65 mEq/l. Because of anuria, haemodialysis was performed beginning on the 2nd day of hospitalization. Urine output was down to 100 ml/day, and serum creatinine up to 15.4 mg/dl. After the 9th hospital day the urine output began to increase and haemodialysis was stopped. Renal function gradually improved and returned to normal 5 weeks after admission. Liver function also improved gradually and returned to normal 4 weeks after admission. (Fig. 1) Renal biopsy on the 5th day showed acute tubular necrosis, presented with tubular dilatation and shortening of epithelial brush border (Fig. 2).

Discussion

Although acute renal failure is not uncommon in patients with fulminant hepatitis, it has been recognized as a rare complication of non-fulminant acute hepatitis A. To our knowledge only 25 cases [2-21] have been reported, 13 of which were found in the Japanese literature [12-21]. The patient in this study is the first Chinese case reported in the literature.

Clinical data available in these cases, are presented in Table 1. These patients were from 7 to 59 years of age, most between 30 and 49 years of age and predominantly male (M 21, F 5). Available urinary sodium concentrations of these patients were high, so hypovolaemia or hepatorenal syndrome can be ruled out. The reported patients had proteinuria ranging from trace to nephrotic range. Serum levels of C3 and C4 were low in four patients (cases 7, 12, 15, 18). Circulating immune complexes were present in case 16. Immune complex may contribute to renal injury in these cases. Most patients were oligouric and recovered after dialysis therapy. Haemodialysis was performed in most patients, except in cases 2, 5 and 10c, who received peritoneal dialysis, and case 9 who received initial haemodiafiltration. Significant haematuria was noted in one-third of patients, raising the possibility of a glomerular or vascular lesion. Transient prolonged prothrombin time was seen in cases 4, 11 and 20. Thrombocytopenia and leukopenia were seen in case 18. Peripheral immune complex-mediated destruction
Fig. 1. Clinical course.

was suspected because of concomitant hypocomplementaemia and normal bone marrow biopsy findings. Drowsiness and general seizures occurred in case 13, despite normal plasma ammonia and fibrinogen levels, and no typical EEG finding of hepatic coma. Acute uraemic encephalopathy and hyponatraemia were suspected and confirmed by the fact that symptoms subsided after haemodialysis. The majority of cases showed a complete recovery in renal and liver function within 2–3 months.

Liver biopsy was performed in five patients, 1–3 months after admission, and revealed mild liver damage, compatible with recovery stage of acute hepatitis. Variable renal biopsy findings have been described in previous reports, including mostly acute tubular necrosis, interstitial nephritis (cases 6, 21), membranoproliferative glomerulonephritis (case 12), mesangial proliferative glomerulonephritis (cases 11, 21), and normal findings (case 8).

So far, the mechanism by which hepatitis A causes renal damage is still obscure. Several possible mechanisms can be put forward. Firstly, prerenal factors, e.g. vomiting or diarrhoea cause circulatory insufficiency, then activate the renin–angiotensin system and impair renal blood flow. This is supported by low urinary sodium concentration and only seen in the cases of Wilkinson et al. [1]. Secondly, hyperbilirubinaemia can decrease effective blood volume by a reduction in total peripheral vascular resistance [22]. In contrast, hyperbilirubinaemia may sensitize renal vasculature to circulating vasoconstricting stimuli and cause vasoconstriction. The combined effect may lead to redistribution of cardiac output away from the kidney. Furthermore, hepatic dysfunction may increase nephrotoxic substances, e.g. bile salts, which may have a toxic effect on the renal tubules by a non-specific detergent effect [23]. The simultaneous improvement in renal and liver function would support the hypothesis of bilirubin toxicity. However, this does not seem to be the situation in cases 6, 11 or 20, since the bilirubin level was very low. Furthermore, renal failure is known to occur during the prodrome of HAV infection [24]. Thirdly, immune complex-mediated nephritis has been postulated for ARF associated with hepatitis B virus and hepatitis C virus infections. Morita et al. [25] produced proliferative glomerulonephritis associated with arteritis in seven of eight marmosets with the intravenous injection of hepatitis A virus isolated from acutely infected patients. The glomerulonephritis was characterized by electron-dense and immunofluorescent deposits, especially marked IgM and C3, and hypercellularity. However, this study failed to demonstrate the presence of an antigenic component of the glomerular immune complex. In a similar experiment, Mathiesen et al. [26] detected hepatitis A antigen in glomeruli in one of two marmosets. The fluorescence in the glomer-
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Fig. 2 a, b. Light-microscopy of renal biopsy showing tubular degeneration with shortening of tubular brush border and dilatation of tubular lumina. Tubular casts are also present (PAS stain x 11200).

Fig. 2 c. Electron-microscopy showing tubular dilatation and attenuation of microvilli (x 950).

ulii appeared in the basal membrane, and is also suggestive of immune complex deposition. These experimental models show the possibility of an immunologically mediated extrahaepatic disease in human hepatitis A virus infection. Rapid response to plasmapheresis but not to haemodialysis was seen in case 15 with hypocomplementaemia, so immune complex or toxic substances may play a role in development of renal failure. Fourthly, another cause of ARF is endotoxaemia. Systemic hypotension, renal vasoconstriction, release of cytokines and activation of neutrophils, all may contribute to the development of renal injury from endotoxemia [23]. Tanigawa et al. [27] showed hepatitis A virus particles present in hepatic Kupffer cells in acute hepatitis A by electron-microscopy. This may lead to impaired reticuloendothelial function and subsequent endotoxaemia. It is supported by the fact that elevated plasma endotoxin level was seen in case 17. ARF accompanying the acute administration of endotoxin in rats is characterized by progressive reductions in renal blood flow and GFR in the absence of hypotension. Renal histology in such animals is normal, but cortical generation rates of arachidonic acid cyclo-oxygenase metabolites are markedly elevated [28]. There was also evidence implicating some vasoconstrictor mediators in endotoxin-associated renal vasoconstriction in animal and some human studies. These include endothelin-1, thromboxane A2, leukotrienes [29]. Besides, endotoxins can interact with receptors on mononuclear cells to cause the release of numerous host mediators, including tumour necrosis factor-, interleukin-1, interleukin-2 and platelet-activating factor [30]. These mediators have direct renal effects and also activate secondary events that result in amplification of the original response. The fifth possibility is endotoxin-induced disseminated intravascular coagulation (DIC). Endotoxin-induced endothelial injury may predispose patients to intrarenal thrombus formation by diminishing the release of nitric oxide and by promoting platelet aggregation [23]. This may contribute the development of glomerular insufficiency followed by acute tubular necrosis. Elevated fibrin degradation products (FDP) level, prolonged prothrombin time and intraglomerular deposition of fibrinogen were seen in case 20.

The urine sodium excretions were high in the reported patients, acute tubular necrosis accounted for lesion in nine of the 14 cases where biopsies were available. These data suggest that in contrast to immune-mediated glomerulonephritis in hepatitis B and C infection [31,32], acute tubular necrosis is the principal renal lesion in acute renal failure in hepatitis A infection.

However, glomerular lesions were seen in three biopsied patients of acute hepatitis A, and in the report of Winkinson et al. [1] and Montoliu et al. [24], acute tubular necrosis instead of glomerulonephritis was diagnosed as the renal lesion in four patients (HBsAg positive) with acute viral hepatitis because of the absence of proteinuria and high urinary sodium concentration, the mechanism responsible for variable renal lesions up to now among these viral infections remains unclear.

The pattern of recovery in our patient was consistent with the diagnosis of acute tubular necrosis. In this
## Table 1. Clinical and laboratory data of 26 patients with acute renal failure and hepatitis A infection

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>GOT(IU/l)</th>
<th>GPT(IU/l)</th>
<th>Bil(mg/dl)</th>
<th>Cr(mg/dl)</th>
<th>Proteinuria</th>
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<td>358</td>
<td>11.3</td>
<td>12.2</td>
<td>+</td>
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Our case: 30 M 3461 2348 9.8 15.4 Trace NA

FeNa: fractional excretion of sodium; CIC, circulating immune complexes; NA, not available; RBC/HPF, red blood cells per high power field; RF, renal function; HD, haemodialysis; LF, liver function; D, day; M, month; W, week; PT, prothrombin time; ATN, acute tubular necrosis; FDP, fibrin degradation products; PD, peritoneal dialysis; GN, Glomerulonephritis; N, normal; MPGN, diffus mesangial hypercellularity and capillary wall thickening; Note: maximum values are given for renal and liver function.

Patient, the high urinary sodium and no evidence of hypotension argue against the presence of dehydration-induced ischaemic tubular necrosis. The absence of significant proteinuria and relatively high serum complement level suggest that immune complex was an unlikely mechanism for the renal failure. In addition, renal function did not improve concomitantly as the serum bilirubin concentration fell. This suggests hyperbilirubinaemia was not important in the pathogenesis of renal failure in this case. In this patient, endotoxins may have played an important role.

The prognosis of acute renal failure associated with
hepatitis A is good, and the uneventful recovery of our patient is similar to most previously described cases. However, mortality from sepsicaemia following peritonitis was seen in case 9 and the same outcome was also noted in the report of Wilkinson et al. [1]. Partial recovery of renal function was seen in case 11, presented with nephrotic syndrome, acute renal failure and mesangial proliferative glomerulonephritis.

In conclusion, acute renal failure is a rare and still obscure complication of hepatitis A virus infection. The prognosis of acute renal failure following non-fulminant hepatitis A is not absolutely favourable if other complications such as infection, develop. Physicians should be aware of the potential renal involvement of hepatitis A virus infection.

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References


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