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CASE REPORT

Acute Renal Failure Associated with Acute Non-fulminant Hepatitis A: A Case Report and Review of Literature

Pei-Chun Fan, Yung-Chang Chen, Ya-Chung Tian, Chih-Hsiang Chang, Ji-Tseng Fang, and Chih-Wei Yang

Kidney Research Center, Department of Nephrology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan

Most of the cases of non-fulminant hepatitis A carry good renal and overall prognosis. Here we present a case of acute renal failure associated with acute non-fulminant hepatitis A, for which kidney biopsy showed interstitial nephritis and tubular necrosis. We also review the literature and possible pathogenesis.

Keywords hepatitis A, acute kidney injury, nephropathy

INTRODUCTION

Renal involvement is well known in association with viral hepatitis B and C infection, but rarely recognized with hepatitis A virus (HAV). In 1978, S. P. Wilkinson first described acute renal failure associated with non-fulminant hepatitis A.[1] Since then, more and more cases of non-fulminant hepatitis A with renal involvement have been reported. Usually identified as a mild, self-limited disease lacking extrahepatic involvement, HAV has recently been shown to have the potential to cause a broad spectrum of systemic complications, ranging from arthritis, vasculitis, and cryoglobulinemia to acute renal failure, fulminant hepatic failure, and death. Described here is a case of acute non-fulminant hepatitis A complicated by acute renal failure.

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Address correspondence to Ji-Tseng Fang, MD, Department of Nephrology, Chang Gung Memorial Hospital, 199 Tung Hwa North Road, Taipei, 105 Taiwan; Tel.: 886-3-3281200 ext 8181; Fax: 886-3-3282173; E-mail: cyc2356@adm.cgmh.org.tw

CASE REPORT

A 36-year-old previously healthy male presented to a local hospital in the Philippines with intermittent fever up to 41°C for four days. The fever subsided after he was admitted to the hospital. For the next four days, he experienced progressive icteric skin, mild right upper quadrant dull pain, anorexia, nausea, vomiting, and general weakness. He denied headache, neck stiffness, sore throat, cough, chest pain, diarrhea, dysuria, gross hematuria, decreased urine output, flank pain, retroorbital pain, myalgia, arthralgia, or skin rash. He is Taiwanese, and has been living in Subic Bay in the Philippines for three to four years. He had eaten local seafood several days prior to admission and denied intravenous drug use, previous blood transfusions, tattooing, homosexual activity, exposure to non-steroidal anti-inflammatory drugs or aminoglycosides or contrast medium, or insect bites. Dengue fever was suspected, and he was then referred to Chang Gung Memorial Hospital.

Upon admission, his temperature was 35.9°C, pulse rate 70 bpm, respiratory rate 15/min, and blood pressure 149/98 mmHg. A physical examination revealed icteric skin and sclera, bilateral lung basal crackles, and bilateral pretibial grade I pitting edema. Other physical findings were unremarkable. The white blood cell count was 6,900/uL, hemoglobin 13.2 g/dL, and platelet count 234,000/uL. Biochemistry tests showed blood urine nitrogen (BUN) 77 mg/dL, creatinine (Cr) 17.98 mg/dL, serum sodium 136 meq/L, serum potassium 4.5 meq/L, total bilirubin 8.3 mg/dL, direct bilirubin 5.6 mg/dL, aspartate aminotransferase (AST) 112 U/L, alanine aminotransferase (ALT) 990 U/L, alkaline phosphatase (ALK-P) 23 U/L, and serum albumin/globulin 2.7/5.0 g/dL. The prothrombin time was mildly prolonged (13.5 s, INR 1.3). Arterial blood gas showed metabolic acidosis with respiratory

compensation (pH 7.379, PCO2 32.5, PO2 96.6, HCO3 18.7, Sat 97.3%). Urinary analysis showed microscopic hematuria (blood 2+, RBC 24/uL), pyuria (WBC 38/uL), but no proteinuria. The urine sodium was 88 meq/L. Serologic tests were positive for anti-HAV IgM (4.72/1.2/ ABBOTT) and negative for HBsAg, anti-HBs Ab, anti-HBc IgM, and anti-HCV Ab. Serum myoglobin and creatine phosphokinase were within normal limits. Elevated serum n IgG 2150 mL/dL, IgA 437 mL/dL, and IgE 373 IU/mL were found. Serum protein electrophoresis showed a faint band of IgM-kappa. Serum C3 and C4 were within normal limits. Cryoglobulin was positive (IgG 1+, IgA1+, IgM 1+). P-ANCA and C-ANCA, ANA, and RF were within normal ranges, and the blood culture was negative. Abdominal sonography showed one gallstone, without biliary tract dilatation; normal liver texture; and neither ascites nor splenomegaly. Kidney sonography showed bilateral enlarged and swollen kidneys (kidney length left 12.7 cm, right 12.5 cm), increased cortical echogenicity, and prominent papillae, consistent with acute parenchymal disease.

Under the suspicion of leptospirosis or tick borne disease, doxycycline 100 mg BID was given empirically from the first day of admission. In view of progressive azotemia (Cr up to 18.94 mg/dL) with uremic symptoms, hemodialysis was initiated from the third day of admission. Leptospirosis, scrub typhus, and murine typhus antibodies were confirmed negative. Doxycycline was discontinued after a one-week course. The azotemia and hyperbilirubinemia gradually improved. Because there were no further uremic symptoms, hemodialysis was ceased on the seventh day of admission after a total of three sessions. The amount of urine collected during the hospital course was around 1200–2500 ml per day.

He received a kidney biopsy on the tenth day of admission. An H&E stain (see Figures 1A and 1B) showed interstitial nephritis, tubular necrosis with regeneration, glomerulosclerosis and arteriolar sclerosis. An immunofluorescence stain showed eight glomeruli with irregular faint IgM deposition, tubules with 1+ C3 deposition, and arteries with 1-2+ C3 deposition. By the time of discharge on the fourteenth day of admission, Cr had decreased to 3.79 mL/dL, and total bilirubin had decreased to 1.8 mL/dL. One month after initial presentation, Cr further improved to 1.41 mL/dL, and total bilirubin improved to 1.0 mL/dL (see Figure 2).

DISCUSSION

Hepatitis B and C are both known to show extrahepatic involvement, including various nephropathies. The most notable renal manifestation of hepatitis B is membranous nephropathy. Other reported nephropathies associated with hepatitis B included membranoproliferative glomerulonephritis (MPGN), mesangial proliferative glomerulonephritis, IgA nephropathy, serum-sickness-like syndrome, and polyarteritis nodosa.[2] Hepatitis C has been reported to be associated with cryoglobulinemia-related MPGN, immunotactoid glomerulonephritis (GN), fibrillary GN, amyloidosis, non-cryoglobulinemia-related MPGN, mesangial proliferative GN, membranous nephropathy, focal segmental sclerosis, and interstitial nephritis.[3]

Although far less common, since 1978, hepatitis A complicated by nephropathies has drawn clinicians' attention. Some cases merely have mild proteinuria, microscopic hematuria, and mild urinary sediment abnormalities. A review of the literature revealed 36 case reports and two reviews related to hepatitis A and renal failure. In total, forty-seven patients were reported. Table 1 summarizes the data of these forty-seven patients, plus the data for our case, making a total of forty-eight patients.

Among the forty-eight patients, only one case developed fulminant hepatitis with hepatic coma,[4] and the others had non-fulminant hepatitis. The ages ranged from 7 to 77 (see Table 2) with a male predominance. ALT ranged from 259 to 6629 U/L, total bilirubin from 1.5 to 59.5 mg/dL, and serum creatinine level from 3.99 to

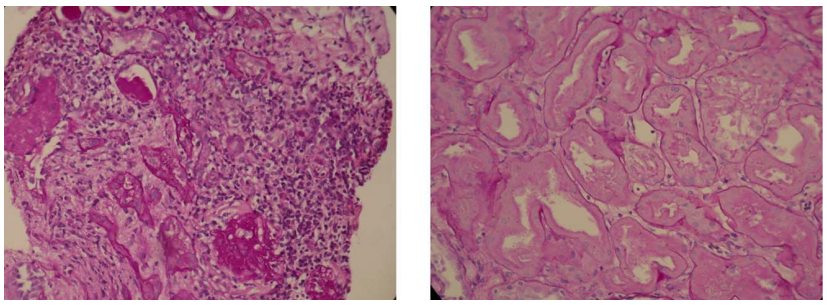

Figure 1. (a) H&E stain of kidney biopsy shows mononuclear cells infiltration of the interstitium, suggesting interstitial nephritis. (b) H&E stain of kidney biopsy shows tubular necrosis.

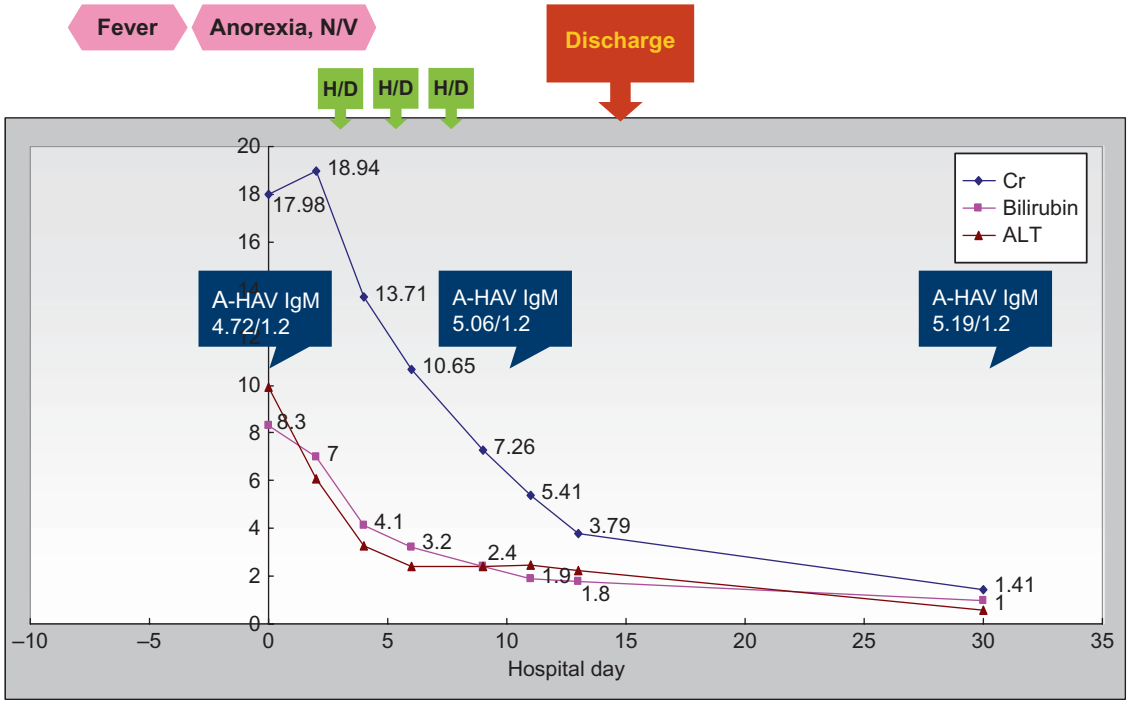

Figure 2. Clinical course of this patient. Abbreviations: H/D = hemodialysis, N/V = nausea/vomiting, Cr = creatinine (mg/dL), ALT = alanine aminotransferase (U/L). A-HAV IgM has a cutoff value of 1.2/ABBOTT. Bilirubin is measured in mg/dL.

21 mg/dL. Most of the urinary analysis showed mild proteinuria and microscopic hematuria, while two patients had proteinuria of nephrotic range.[5,6] The spot urine sodium concentration (UNa) ranged from 24 to 98 meq/L, except for two cases which had initial levels of 2 meq/L.[1] However, both of these cases had subsequently high UNa.

Twenty-three patients received kidney biopsies (see Table 3). The most common pathology was acute tubular necrosis. There were also MPGN, interstitial nephritis, or mixed presentations, although notably two of the biopsies were normal. Thirty-four patients received renal replacement therapy (see Table 4), and ten only received conservative supportive treatment.

Regarding the outcomes (see Table 5), most of the patients had spontaneous and full renal and liver recovery without sequelae, mostly within 2–3 months. However four of the patients died,[1,4,7,8] and one patient with MPGN had permanent renal insufficiency.[6] Other comorbidities included generalized tonic-clonic seizure,[9] disseminated intravascular coagulation or coagulopathy,[6,10–12] type 2 diabetes mellitus,[13] and pneumococcal peritonitis.[14] In the case with generalized tonic-clonic seizure, the electroencephalography did not show the typical findings of hepatic encephalopathy, and the serum ammonia level was normal. The seizures subsided after hemodialysis.

Although there have been plenty of cases reported over the past few decades, the pathogenesis of hepatitis B and C related nephropathies have not been clearly defined. The most accepted mechanism of hepatitis B-related nephropathies is immune complex mediated injury,[2] while that of hepatitis C related nephropathies, cryoglobulinemia, and immune complex mediated injury.[3] Meanwhile, other mechanisms, such as direct cytopathic effects of the virus and indirect effects of virus-induced cytokines, virus-induced immunological effectors (T lymphocytes or antibodies), and virus-induced endothelial injury, have been proposed.[2,3] Actually, the causative role of the hepatitis virus remains controversial, and the diagnosis is mainly supported by clinical time course and by exclusion.

Similarly, whether hepatitis A has a causative effect on nephropathies remains a key question. Currently, we favor hepatitis A as a cause of acute renal failure rather than just a coincidence, based on the following reasons. Acute renal failure usually has an average onset of within ten days after jaundice development, and achieves remission during the convalescent phase of hepatitis A infection. In these cases, there are no historical, clinical, or lab evidence of antecedent renal disease. There is neither systemic disease nor offending agent to explain the acute kidney injury.

Several hypotheses of the pathogenesis of hepatitis A-related nephropathy have been postulated. First, acute hepatitis-related anorexia, vomiting, and diarrhea can cause intravascular volume depletion and activation of the rennin-angiotensin-aldosterone system (RAAS), both of

Table 1
Demographic and clinco-pathological features

Case (reference)	Age	Sex	ALT	Bil	Cr	Proteinuria	Urine RBC/HPF	Dialysis	RF recovery	LF recovery	Renal biopsy	Urine Na	Complication
1a (1)	34	F	AST960	3.15	>1	NA	NA	HD	NA	NA	NA	2; 34	NA
1b (1)	49	M	AST860	5.06	8.22	NA	NA	HD	NA	NA	ATN	2; 98	Died
1c (1)	35	F	AST1100	3.8	8.25	NA	NA	HD	NA	NA	NA	30	NA
2 (9)	38	M	>2000	9.1	16.8	++	Numerous	HD	1M	10M	NA	NA	General convulsions
3 (28)	36	M	2827	3.4	14.3	++	NA	–	7W	5W	ATN	NA	NA
4 (27)	30	M	2590	5.8	11.9	++	2–3	HD	46D	17D	Mild MPGN	NA	NA
5 (26)	21	F	NA	NA	NA	NA		PP	NA	NA	NA	NA	NA
6 (4)	34	M	5780	12.7	10.9	NA	NA	HD	NA	NA	ATN	NA	Fulminant hepatitis, hepatic coma; died of subendocardial infarction
7 (29)	30	M	1480	6.78	11.2	++	8–10	PD	3M	3M	NA	38	NA
8a (30)	8	F	NA	NA	NA	NA	NA	NA	NA	NA	MPGN	NA	NA
8b (30)	10	F	NA	NA	NA	NA	NA	NA	NA	NA	ATN, MPGN, interstitial nephritis	NA	NA
9 (24)	43	F	1077	11.8	12	+/–	0–1	HD then PP	42D	50D	NA	NA	NA
10a (12)	32	M	833	8.8	13.9	++	Numerous	HD	2M	1M	NA	NA	DIC
10b (12)	30–40	M	5370	10.3	14.3	NA	NA	HD	<3M	Once case 9M	NA	NA	NA
10c (12)	30–40	M	4700	4.9	9.7	NA	NA	HD	<3M	Two cases<3M	NA	NA	NA
10d (12)	30–40	M	739	13.1	16.9	NA	NA	HD	<3M	Two cases<3M	ATN	NA	NA
11 (31)	43	M	6914	7.8	9.7	NA	NA	–	2M	2M	ATN	24	NA
12 (10)	51	M	341	13.2	8.2	9.54g/l	Numerous	HD	1M	1M	NA	83	Prolonged PT
13 (32)	39	M	932	10.4	12.2	+	0–5	HD	>14D	NA	NA	NA	Elevated endotoxin level
14 (33)	22	F	NA	2.6	6.7	NA	NA	–	NA	NA	NA	NA	NA
15 (23)	39	F	1486	2.45	5.6	+	6–10	HD	7D	1M	ATN with intraglomerular deposit of IgG	NA	Thrombocytopenia and leukopenia
16 (34)	7	M	634	13.6	8.4	+	6	PD	4W	4W	NA	NA	NA
17 (35)	28	M	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
18 (36)	52	M	259	3.9	20	NA	A few	HD	6W	2W	Interstitial nephritis	NA	NA
19 (5)	21	M	4780	10.9	12.5	4g/day	2–4	HD	1M	NA	NA	104	NA
20 (14)	42	M	NA	20.4	14.39	++	NA	HD	7W	7W	Normal	NA	Recovery from primary pneumococcal peritonitis

(*Continued*)

Table 1
(*Continued*)

Case (reference)	Age	Sex	ALT	Bil	Cr	Proteinuria	Urine RBC/HPF	Dialysis	RF recovery	LF recovery	Renal biopsy	Urine Na	Complication
21 (37)	42	F	4650	8.2	8.5	++++	1+	HD	7M	NA	ATN and acute glomerular ischemia	NA	NA
22 (11)	42	M	3228	3.0	+	+	NA	HD	NA	NA	ATN with intraglomerular deposition of fibrinogen	55	Elevated FDP level and prolonged PT
23 (25)	38	M	NA	NA	NA	NA	NA	PP	NA	NA	NA	NA	NA
24 (21)	42	M	358	11.3	12.2	+	0–1	HD	1M	1M	MPGN with granular deposit of IgA and C1q and interstitial nephritis	NA	NA
25 (7)	59	M	2432	33.4	7.37	NA	NA	HDF then HD	NA	NA	Degenerative changes of tubular epithelium	NA	Died of *E. coli* peritonitis
26a (38)	16	F	504	12.65	8.4	–	–	HD	2W	4D	NA	FeNA>3	NA
26b (38)	41	F	4720	10.1	6.9	500mg/day	–	–	10D	3D	NA	FeNA>3	NA
26c (38)	30	M	5134	7.5	13.2	560mg/day	–	PD	3W	6D	Mild interstitial nephritis and mild tubular necrosis	FeNA>3	NA
27 (6)	33	M	4070	1.5	5.2	25g/day	Trace	–	NA	8D	MPGN with IgM C3 deposits	NA	Prolonged PT, persistent renal insufficiency
28 (22)	35	F	>4000	2.9	8.2	++	2–3	–	NA	NA	Mesangial proliferation, IgA, IgM, IgG and C1q deposition, interstitial nephritis	34	NA
29 (18)	35	M	NA	NA	NA	NA	NA	HD	NA	NA	Normal	NA	NA
30 (39)	37	F	2100	5.6	11	30mg/dl	1, granular casts; 3+, RBC cast	–	2W	5W	ATN	NA	NA
31 (17)	30	M	2348	9.8	15.4	Trace	NA	HD	5W	4W	ATN	65	NA
32 (40)	36	M	1049	59.5	12.3	Trace	5–8	HD	4M	40D	NA	50	NA
33 (41)	26	M	1870	10.5	4.8	Mild	–	–	2W	2W	NA	54	NA
34 (13)	38	M	6629	10.7	21	NA	NA	HD	3M	3M	NA	NA	Type 2 DM

35 (42)	32	F	NA	NA	NA	NA	NA	–	1M	1M	NA	NA	NA(History of Cushing's disease)
36 (43)	NA	NA	NA	NA	3.99	NA	NA	HD	NA	NA	Interstitial nephritis and ATN	NA	NA
37 (8)	77	M	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Pericarditis, died of septic shock
38a (44)	NA	NA	NA	NA	NA	NA	NA	HD	NA	NA	ATN	NA	NA
38b (44)	NA	NA	NA	NA	NA	NA	NA	–	NA	NA	NA	NA	NA
39*	36	M	990	8.3	18.94	–	2+, 24	HD			Tubular necrosis with regeneration; Interstitial nephritis; Glomerulosclerosis and arteriolar sclerosis; IgM, C3+	88	NA

*Our case.

Abbreviations: RBC/HPF=red blood cells per high-power field, RF recovery=renal function recovery, LF recovery=liver function recovery, NA=not available, HD=hemodialysis, HDF=hemodiafiltration, PD=peritoneal dialysis, PP=plasmapheresis, D=days, W=weeks, M=months, FeNA=fraction excretion of sodium, ATN=acute tubular necrosis, MPGN=membranoproliferative glomerulonephritis, GTC=generalized tonic-clonic seizure, DIC=disseminated intravascular coagulation, PT=prothrombin time, FDP=fibrin degradation product, DM=diabetes mellitus.

Table 2
Clinical characteristics

Age	7–77 years
Male:female	31:14 (3 not mentioned)
ALT (U/L)	259–6629
Total bilirubin (mg/dl)	1.5–59.5
Creatinine (mg/dl)	3.99–21
UNa (meq/L)	24–98 (2→34, 2→98)*

*Two cases with initial UNa 2, then increased up to 34 and 98, respectively.

Abbreviation: UNa = spot urine sodium concentration.

Table 3
Kidney biopsy (23 out of 48)

ATN	11
MPGN	3
Interstitial nephritis	2
Interstitial nephritis + ATN	3
Interstitial nephritis + MPGN	1
ATN + MPGN + interstitial nephritis	1
Normal	2

Abbreviations: ATN = acute tubular necrosis, MPGN = membranoproliferative glomerulonephritis.

Table 4
Renal replacement therapy

HD	27
PP	2
HD then PP	1
HDF then HD	1
PD	3
No renal replacement therapy	10
Not mentioned	4

Abbreviations: HD = hemodialysis, HDF = hemodiafiltration, PD = peritoneal dialysis, PP = plasmapheresis.

Table 5
Outcome

Death*	4
Permanent renal insufficiency	1 (MPGN)
GTC	1
DIC or prolonged PT	4
Type 2 DM	1
Pneumococcal peritonitis	1

*Four cases died of (1) *E.coli* peritonitis, (2) pericarditis with septic shock, (3) fulminant hepatitis, hepatic coma, subendocardial infarction, and (4) unknown, respectively.

Abbreviations: GTC = generalized tonic-clonic seizure, DIC = disseminated intravascular coagulation, PT = prothrombin time, DM = diabetes mellitus.

which can compromise effective renal perfusion. However, except for Wilkinson's cases with low UNa, most patients have high UNa without hypotension or other signs of volume depletion.[1] Therefore, pre-renal factors do not seem to be a good explanation. Second, hyperbilirubinemia secondary to hepatic dysfunction is believed to cause systemic vascular resistance reduction, predisposing renal vasoconstriction, and left ventricular contractility impairment, all of which in turn can compromise effective renal blood flow.[15] On the other hand, elevated bile salt levels secondary to hepatic dysfunction cause direct renal tubular injury by non-specific detergent effects.[16] To support the hypothesis of hyperbilirubinemia and bile salts inducing acute renal failure, most cases have a parallel relationship between elevated bilirubin and creatinine, except for Lin's case.[17] In addition, some cases have low levels of bilirubin. Therefore, hyperbilirubinemia may not fully explain the mechanism. Third, kidney biopsies in two cases showed normal findings, implicating the possibility of hepatorenal syndrome.[14,18] However, except for one case,[4] almost all cases have non-fulminant hepatitis without hepatic failure, and most cases have high UNa. Therefore, the hypothesis of hepatorenal syndrome is not favored. It is possible that the normal kidney biopsy results may be false-negative due to there being un-sampled focal lesions or technical limitations. Fourth, immune complex mediated renal injury has been postulated. In 1978, Mathiesen et al. injected hepatitis A antigen isolated from acutely infected patients into marmosets intravenously, and the deposition of hepatitis A antigens at glomeruli basement membranes was detected in one of the eight marmosets.[19] In 1981, Morita et al. produced proliferative glomerulonephritis and renal vasculitis in seven of eight marmosets by intravenous inoculation of hepatitis A virus from acutely infected patients.[20] Immunofluorescence microscopy revealed mesangial deposits of IgG and IgM and capillary loop deposits of IgA and C3, although there was no antigen identified. In some of the reported cases, kidney biopsies have revealed various immune complex deposition, including IgG, IgA, IgM, C3, and Clq.[6,21–23] This evidence suggests an important role of immune complexes. Fifth, endotoxinemia secondary to hepatic Kupffer cell dysfunction has been proposed to cause systemic vasodilatation, renal vasoconstriction, and release of cytokines, including some vasoactive mediators, which in turn compromise effective renal perfusion.[16] On the other hand, endotoxinemia also induces platelet aggregation and release of nitrite oxide, with resultant intrarenal thrombosis and disseminated intravascular coagulation.[16] In some cases, the endotoxin levels and anti-endotoxin antibody titers were elevated. Elevated FDP levels, prolonged PT, and intraglomerular deposition of fibrinogen were observed in Kamura's case.[11] In Watanabe's case, renal function did not

respond to hemodialysis, but improved dramatically after plasmapheresis.[24] In Suga and Corpechot's cases, the renal function also recovered after plasmapheresis. These cases implicate the possible role of immune complexes or endotoxinemia.[25,26] Sixth, like hepatitis B and C, a direct cytopathic effect of hepatitis A virus has been postulated.[27]

In our case, the high UNa and lack of clinical evidence of dehydration precluded pre-renal azotemia. The high UNa and non-fulminant course also excluded hepatorenal syndrome. Because renal function improved parallel to liver function, the role of hyperbilirubinemia cannot be excluded. The presence of serum circulating IgG, IgM, and IgA and renal deposition of IgM and C3 strongly implicates the role of immune complexes. Unfortunately, we did not have the clinical tools to detect the presence of hepatitis A antigen in the kidneys.

The pathogenesis of hepatitis A related acute renal failure needs further studies, and may be multifactorial. The variability of nephropathies may be associated with host immune response differences and host genetic factors.

CONCLUSION

In conclusion, as is already known with hepatitis B and C, hepatitis A is potentially associated with various extrahepatic renal manifestations. A high suspicion of viral hepatitis, including acute hepatitis A, should arise when a patient presents with concomitant acute hepatitis and renal failure. The prognosis is mostly favorable, though not absolutely so. Further studies are needed to clarify the pathogenesis.

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