INTERNAL MEDICINE

□ CASE REPORT □

Membranous Nephropathy Associated with Chronic Hepatitis B Occurring in a Short Period After Acute Hepatitis B Virus Infection

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Abstract

We herein present a case of membranous nephropathy associated with chronic hepatitis B following acute hepatitis B virus (HBV) infection. A 22-year-old man was admitted to our hospital for evaluation of proteinuria, pitting edema on both legs, and increased body weight in December 2002. At the age of 18, he had suffered from acute hepatitis A and syphilis, and was found to be negative for hepatitis B surface antigen (HBsAg). Furthermore, he suffered from acute hepatitis B (AH-B) at the age of 21; he was found to be positive for HBsAg and anti-IgM antibody to core antigen (IgM HBcAb). However, he discontinued outpatient treatment before confirmation of HBsAg clearance or the appearance of antibody to HBsAg (HBsAb). At the present admission, HBsAg, antibody to hepatitis B e antigen (HBeAg), and HBcAb were positive, while IgM HBcAb was negative. His genotype of HBV was type A (HBV/A). Histopathological findings of the renal biopsy specimen confirmed glomerulonephritis and glomerular deposition of HBsAg. Thus, he was diagnosed as having nephrotic syndrome caused by membranous nephropathy (MN) associated with chronic hepatitis B (CH-B) following AH-B. Although interferon-alpha (IFN-α) administration was started for the treatment and temporary improvement of proteinuria was observed, remission of MN was not achieved.

Key words: hepatitis B virus, genotype A, membranous nephropathy

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Introduction

Hepatitis B virus (HBV) can cause hepatitis, as well as various extrahepatic complications through the formation of immune complexes. These include nephrotic syndrome (1), polyarteritis nodosa (2) and essential mixed cryoglobulinemia (3). Adult patients with HBV-associated nephropathy are known to have different characteristics than childhood patients. Many adult patients with HBV-associated nephropathy have symptoms attributed to nephrotic syndrome (1, 4, 5, 22) and 30% of patients ultimately progress to renal failure (1). Therefore, nephropathy is considered to be an important complication in determining the prognosis.

In Japan, a nationwide program to prevent mother-to-infant infection by HBV was started in 1985, and passive-active immunoprophylaxis in high-risk babies was highly efficacious in preventing perinatal transmission of the HBV carrier state, resulting in marked decreases in the number of patients with hepatitis B surface antigen (HBsAg) (6). However in recent years, the number of patients with acute hepatitis due to HBV/A, which is treated as a sexual transmitted

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Table 1. Laboratory Data on Admission

Peripheral blood			***Biochemistry***			***Viral markers***		
WBC	4700	/μL	TP	4.5	g/dL	HBsAg (RPHA)	256	X
RBC	5.24×10^4	/μL	Alb	2.1	g/dL	HBsAg (CLIA)	>10000	IU/mL
Hb	16.0	g/dL	T.Bil	0.4	mg/dL	HBsAb (CLIA)	<10.0	mIU/mL
Ht	45.3	%	D.Bil	0.1	mg/dL	HBeAg (RIA)	123.5	(+)
Plt	20.3×10^4	/μL	AST	70	IU/L	HBeAb (RIA)	0.0	%
ESR	31	mm/hr	ALT	91	IU/L	HBcAb (RIA)	101.0	%
Coagulation		+	LDH	243	IU/L	HBcAbx200 (RIA)	99.9	%
HPT	109	%	ALP	231	IU/L	HBV-DNA (TMA)	8.6	LGE/mL
PT	92	%	γGTP	64	IU/L	HBV-polymerase	3056	cpm
Fib	233	mg/dL	Ch.E	504	IU/L	HCV-Ab (C.O.I)	0.39	(−)
Urinalysis			T.chol	436	mg/dL	IgM-HA Ab	0.4	(−)
Protein	(4+)11.3g/day		Cr	0.80	mg/dL	EBV-VCA-IgM	<10	X
Sugar	(−)		BUN	9.1	mg/dL	***Serology***		
Occult blood	(+)		TTT	5.4	U	IgG	715	mg/dL
NAG	30.3	U/L	ZTT	5.8	U	IgA	315	mg/dL
24hrCcr	83.5	ml/min	Glu	108	mg/dL	IgM	199	mg/dL
Sediments			NH_3	21	μg/dL	C3	78	mg/dL
Granular cast	1〜2	/vf	CRP	<0.3	mg/dL	C4	32	mg/dL
Cellular cast	1〜2	/vf				CH50	21.4	U/mL
Oval fat body	(+)					ANA	<40	×
						Cryoglobulin	(+)	

disease and imported infectious disease, has been steadily increasing and some of these patients have progressed to chronic hepatitis (7). This trend should therefore be monitored. Here, we present a case of membranous nephropathy (MN) associated with chronic hepatitis B (CH-B) occurring in a short period after acute HBV infection.

Case Report

The patient was a 22-year-old Japanese man. At the age of 18, he suffered from acute hepatitis A and was found to be negative for HBsAg. At the age of 21, he suffered from general fatigue and appetite loss, and because he was positive for HBsAg and IgM HBcAg, he was diagnosed as having acute HBV infection. At the ages of 18 and 21, It was confirmed more than once that the findings of urinalysis were normal. Although careful observation was recommended, he discontinued hospital visits without confirmation of HBsAg disappearance and HBsAb appearance. Subsequently, he developed proteinuria, pitting edema on both legs, and increased body weight, and was admitted to our hospital for evaluation in December 2002.

On the first day of admission, his height was 173.4 cm and his body weight was 71.0 kg (his previous recorded body weight, 58.0 kg). His blood pressure was 100/50 mmHg. Pitting edema was observed on both legs. Protein, occult blood and sugar in the urine were detected. In the urine, 11.3 g of protein was excreted daily. On biochemical analysis, levels of serum total protein and albumin had decreased to 4.5 g/dL and 2.1 g/dL, respectively, while levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) had increased to 70 IU/L and 91 IU/L, respectively. Creatinine clearance rate was 83.5 ml/min, which was within normal limits, and total cholesterol concentration had increased to 436 mg/dL. On serological and immunological tests, although IgG and CH50 had decreased slightly to 715 mg/dL and 21.4 U/mL, respectively, IgA and IgM remained within normal limits. Cryoglobulin was also detected. No other autoimmune antibodies were detected. Both HBsAg and HBeAg were positive, while anti-HCV antibody was negative (Table 1). HBV genotype was found to be type A.

Renal needle biopsy was carried out for evaluation. On light microscopy, thickening of the glomerular basement membrane and spikes were located in the subepithelial region (Fig. 1a). Immunofluorescence showed granular deposition of C3d and IgG in the subepithelial region (Fig. 1b). Electron microscopy revealed dense deposits in the subepithelial region (Fig. 1c). To verify the relationship with HBV infection, renal biopsy specimens were stained with HBsAg, and HBsAg was confirmed in the subepithelial region (Fig. 1d). Thus, he was diagnosed as having MN stage II associated with CH-B following acute HBV infection.

Although IFN-α administration was started for treatment, and temporary improvement of proteinuria was observed, decreases in HBV-DNA were not observed and proteinuria exacerbated, and remission of CH-B and MN was not obtained (Fig. 2).

Discussion

Since Combes et al (8) reported HBV-associated nephropathy in 1971, mainly pediatric cases have been reported (9-16, 26). These cases have included membranous nephropathy, membranouproliferative glomerulonephritis, IgA nephropathy and minimal change glomerulonephritis (15-18). HBV-associated nephropathy affects both children and adults with different clinical manifestations. Most pediatric patients suffer from transient asymptomatic proteinuria (12, 13, 19) and renal function is preserved in more than 95% of children with HBV-associated nephropathy (14, 16, 19). Thus, the clinical course is generally good in such cases (9, 21).

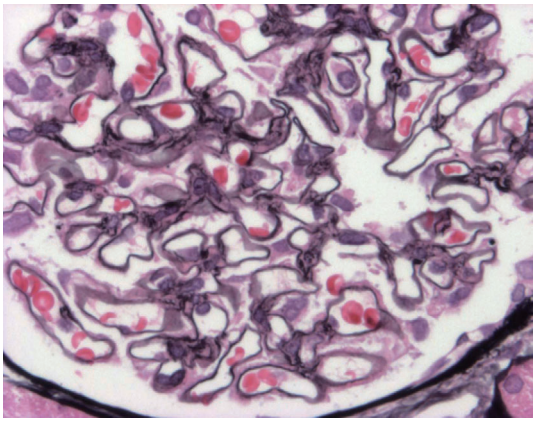


Figure 1a. Light microscopy showing thickening of the glomerular basement membrane. Spikes are located in the subepithelial region (PAM ×400).

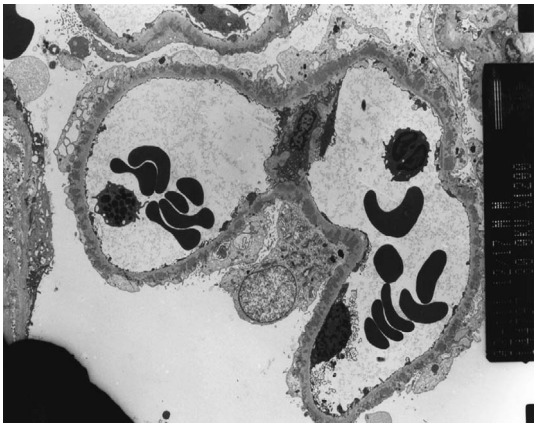


Figure 1c. Electron microscopy showing electron-dense deposits in the subepithelial region.

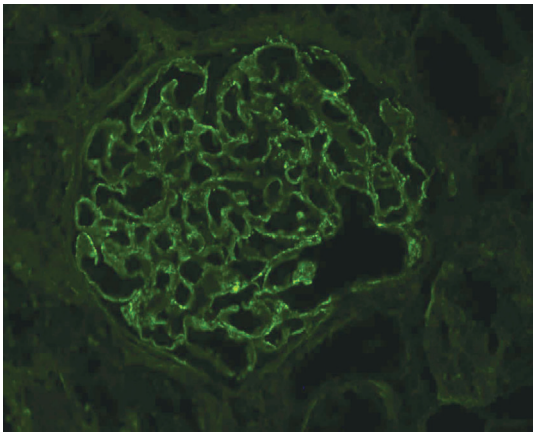


Figure 1b. Immunofluorescence of fine granular deposition of IgG in the subepithelial region.

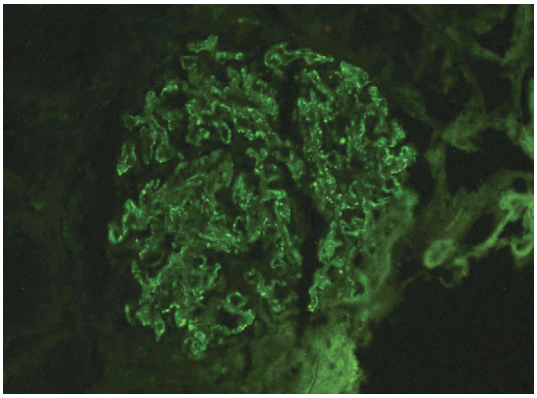


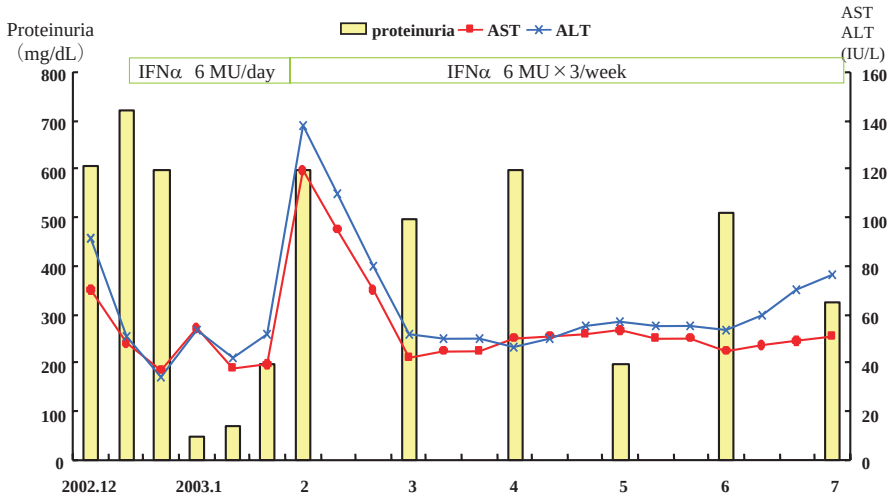
Figure 1d. HBsAg detected in the subepithelial region.

On the other hand, adults with HBV-associated nephropathy can exhibit nephrotic syndrome (1, 4, 5, 22) and 30% of patients ultimately progress to renal failure (5). Therefore, in adult patients, nephropathy is an important complication in the determining prognosis. It has been reported that glomerular deposition of HBsAg (23, 24), HBcAg (12, 25, 27) and HBeAg (5, 9, 10, 14, 27-29) are detected in renal histopathology. Because in the present patient immunopathological findings showed HBsAg in the subepithelial region, we diagnosed him the present patient as having HBV-associated nephropathy.

In pediatric patients, it is thought that the onset age of HBV-associated nephropathy is about two years in patients with horizontal transmission and from 5 to 7 years in patients with vertical transmission. In contrast, adult patients have the potential to develop HBV-associated nephropathy across all age groups (28). The sources of HBV infection in adulthood include cases of HBV carriers since childhood, as well as acute infection after drug abuse or sexual contact (28), and some of the latter group subsequently develop HBV-associated nephropathy. However, viral factors and periods between infection and onset have yet to be fully elucidated.

Eight geographically distributed genotypes of HBV (A-H) are known at present (29, 30). In Japan, the proportion of genotypes C, B and A in CH-B is about 85%, 12% and 2% (30). In Western countries, about 10% of patients with acute hepatitis B (AH-B) develop CH-B (31), while it is reportedly rare in Japan to develop CH-B following AH-B (7, 30). However, it was recently reported in Japan, that the number of patients acutely infected with HBV/A has been increasing, and some of these patients have subsequently developed CH-B (32, 33). Because genotype A is associated with a higher percentage of developing CH-B following AH-B in adults, there is rising concern over the increasing number of HBV/A carriers in Japan. The fact that HBV/A is frequent in northwest Europe, Sub-Saharan Africa, India and North, Central and South America, supports the notion that CH-B will develop more frequently after AH-B as the number of HBV/A carriers increases (31).

With regard to factors related to development of chronic HBV infection following AH-B in genotype A, HBV/A has a greater tendency to have C substituted for T at 1862 in the precore region, but also has a slight tendency to have A substituted for G at 1896 in the precore region. These changes



HBsAg	>10000	>10000	>10000	>10000				
HBsAb	<10.0	<10.0	<10.0	<10.0				
HBeAg	123.5	170.2	122.0	144.2	5.9	2.9	2.7	2.1
HBeAb	0.0	0.0	0.0	0.0	56.8	86.5	90.4	92.6
HBcAb	101.0	100.8	100.8	100.5				
HBcAb x200	99.9	99.8	99.9	99.9				
HBV-DNA	8.6	8.7	8.6	8.5	8.0	8.6	8.7	8.7
HBV-polymerase	3056							

Figure 2. **Clinical course.**

lead to HBeAg being continuously produced, thereby making suppression of HBV more difficult (34).

The present patient was thought to be a case of MN associated with CH-B occurring in a short period after acute HBV infection. To date, there have been no similar reports in adults. Therefore, this case is particularly significant, as it was followed from acute HBV infection through to the onset of HBV-associated nephropathy.

Though the relationship between HBV-associated nephropathy and viral factors, particularly genotype, has yet to be determined in detail, it is interesting to note that some reports on HBV-associated nephropathy have been published in South Africa, where HBV/A1 is the most prevalent (20, 22). Moreover, Kusakabe et al reported that among six patients reported to have HBV-associated nephropathy, four carried HBV/A (35). The high incidence of HBV/A thus suggests it is the predominant genotype in HBV-associated nephropathy, particularly considering the results of previous molecular epidemiological studies showing that only 1.7% of patients with CH-B in Japan carried genotype A (30).

Because most cases with HBV-associated nephropathy have HBeAg, and because there is thought to be a significant correlation between the disappearance of proteinuria and HBeAg (5, 9, 14, 21), the administration of corticosteroids and IFN-α have been attempted, with the aim of eradicating HBV and eliminating HBeAg through antiviral and host immunostimulatory activity. However, administration of corticosteroids for the purpose of controlling renal vasculitis has not produced satisfactory results (5, 14, 18, 36-38). IFN-α however is thought to be useful in some pediatric cases based on the results of several clinical trials (14, 22). It has also been reported that lamivudine, a nucleic acid analog, has proven to be beneficial in HBV-associated nephropathy (39-42), but as the efficacy of lamivudine against HBV-associated nephropathy had not been adequately evaluated when our patient was treated, and because of the issue of breakthrough hepatitis occurring via mutation of the YMDD motif (43), we selected IFN-α as the present treatment.

Though decreases in HBV-DNA were not observed and exacerbation of proteinuria occurred, the present case suggests that IFN-α is useful in HBV/A-associated nephropathy, as temporary improvement of proteinuria was observed. At the moment, clinical research has revealed that genotype A more frequently develops drug-resistant mutations against the YMDD motif in the polymerase region of HBV during administration of lamivudine (44), and that it is more sensitive to interferon than other genotypes (45, 46). Thus, though further elucidation of the efficacy of nucleic acid analogs such as adefovir and entecavir, IFN-α should be considered as a treatment option for HBV/A-associated nephropathy.

In Japan, particularly in the metropolitan areas, the number of patients with acute hepatitis due to HBV/A, treated as transmission through homosexual contact and heterosexual promiscuity, has been gradually increasing and some of these patients have progressed to chronic hepatitis (47). Therefore, we should closely follow cases of both chronic HBV infection following acute HBV infection and cases of early-onset HBV-associated nephropathy.

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