Digestive Diseases and Sciences, Vol. 31, No. 7 (July 1986), pp. 700–704

HB_sAg Clearance in Chronic Active Hepatitis B

A Possible Cause of Cryptogenic Cirrhosis

TIMOTHY R. MORGAN, MD, ALLAN G. REDEKER, MD, SUYENORI YAMADA, MD, and MARY ASHCAVAI

Three patients with chronic hepatitis B infection, two with chronic active hepatitis and cirrhosis, and the third with quiescent cirrhosis, cleared HB_sAg from their serum and eventually developed anti-HB_s. All three were asymptomatic and had nearly normal serum aminotransferases following loss of HB_sAg. Liver biopsy revealed cirrhosis in each patient. With the development of anti-HB_s, these patients became serologically indistinguishable from patients with a cryptogenic cirrhosis who had prior unrelated exposure to hepatitis B. Remote chronic hepatitis B infection may be a more common cause of cryptogenic cirrhosis than is commonly appreciated.

For many years it had been assumed that the duration of hepatitis B surface antigenemia in chronic carriers was life long. Recently, Lindsay and others (1) described several patients who recovered from chronic persistent hepatitis B (CPH-B) after one to eight years of continuous infection. Recovery was associated with permanent loss of HB_sAg, development of anti-HB_s, and normalization of aminotransferases. At this point, these patients would be indistinguishable from patients who had recovered promptly and uneventfully from acute hepatitis B. Clearance of HB_sAg has been reported in patients with chronic active hepatitis B (CAH-B) (2, 3). Reports of such instances have been rare, and the patients have not been well described. However, despite the loss of HB_sAg, development of anti-HB_s, and normalization of aminotransferase values, if cirrhosis had already developed, liver biopsies would continue to be abnormal.

Manuscript received September 7, 1984; revised manuscript received September 30, 1985; accepted November 8, 1985.

From the Liver Unit, Departments of Medicine and Pathology, University of Southern California School of Medicine, Rancho Los Amigos Hospital, Downey, California 90242.

We report two patients with chronic active hepatitis B and cirrhosis and one patient with inactive cirrhosis who lost HB_sAg and developed anti-HB_s. Without knowledge of the prior period of documented hepatitis B surface antigenemia, these patients would be indistinguishable from patients with cryptogenic cirrhosis who had recovered from prior unrelated hepatitis B infection.

MATERIALS AND METHODS

Prior to 1972, testing for HB_sAg was done by counterimmunoelectrophoresis (CEP) or agar gel diffusion. Since 1972, HB_sAg was tested for using both CEP and RIA (Ausria-II). Anti-HB_c was tested for by RIA (Corab). Testing for anti-HB_s was done by RIA (AusAb). Ratio units were calculated by dividing the counts per minute in the sample by the counts per minute for the control. Total delta antibody was measured by solid-phase blocking RIA (4). Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) of less than 40 units per liter and bilirubin of less that 1.3 mg/dl were considered normal.

Liver tissue was fixed in Zenker's (case 1), Bouin's (case 2), or 10% formalin (case 3), embedded in paraffin, and sectioned at 4–5 μm. The 1978 wedge biopsy in case 1 was fixed in B-5, embedded in Araldite, and sectioned at 2 μm. Staining with hemotoxylin and eosin, Masson

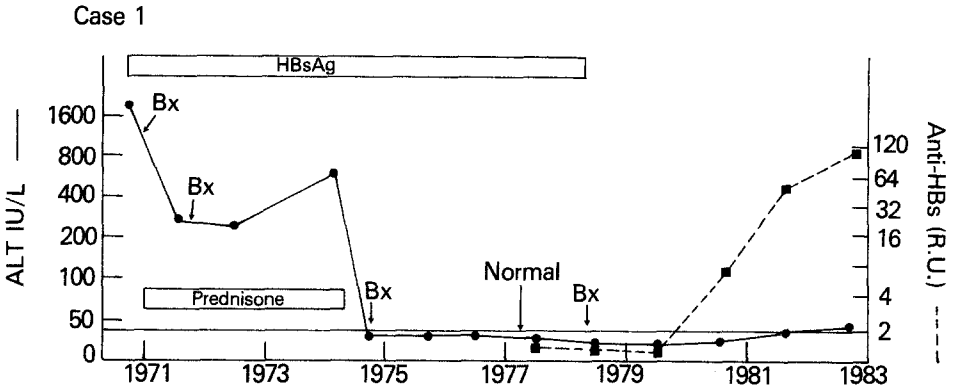

Fig 1. Alanine aminotransferase (ALT), HB_sAg, and anti-HB_s levels in case 1; Bx = biopsy.

trichrome, digested PAS, and iron stains were routinely performed. Immunoperoxidase stains for HB_cAg and orcine stains for HB_sAg were performed according to the methods described by Omata et al (5).

Pathologic interpretation was made according to standard criteria (6).

Case 1. A 38-year-old white hospital administrator was seen in August 1970 for a routine physical exam. His only complaint was mild fatigue. Physical exam was normal. Laboratory tests showed elevated AST and ALT and HB_sAg testing the following month was positive (Figure 1). He had not received any blood products. He had had no recent dental work, tatoos, or acupuncture. He denied IV drug use or homosexual activity and was only an occasional user of alcohol. Liver biopsy done in October 1970 was fragmented and showed focal necrosis and exudate with fibrosis and collapse. This was interpreted as chronic active hepatitis or impaired regeneration in someone beyond the optimum age of regenerative capacity of the liver. He was started on 30 mg prednisone per day but continued to complain of fatigue. Repeat biopsy in 1971 was fragmented and inadequate for diagnosis. During the next three and a half years, several attempts to stop prednisone were deemed unsuccessful because of flares in his aminotransferases. During this time his liver edge gradually became palpable below the costal margin and was slightly firm. Several spider angiomas appeared and the spleen also became palpable. He continued to feel fatigued and gained 50 pounds in three years.

Prednisone was stopped in April 1974, and the patient lost 20 pounds and felt somewhat better. In July, 1974 he had an elective cholecystectomy. The liver looked finely nodular and the spleen was two to three times enlarged. Liver biopsy showed cirrhosis with little activity. Wedged hepatic vein pressure in September 1974 was 15 mm Hg above the inferior vena cava pressure (nl: 1–5 mm Hg). He continued to feel well off prednisone and his aminotransferases remained less than 60 IU/liter. HB_sAg was weakly positive in April 1978, and he underwent an open liver biopsy. Histologically, a quiescent, coarsely nodular cirrhosis was seen. Immunoperoxidase stains for HB_cAg and orcine stains for HB_sAg were negative. Serum HB_sAg was first noted to be negative in June 1979. He felt completely well, and all routine liver tests were normal. Anti-HB_s was absent in October 1979 but present in high titers in July 1981. Retrospective testing for delta antibody was negative on several occasions during the period of hepatitis B surface antigenemia. Tests for HB_eAg were negative in 1977, 1978, and 1981. Anti-HB_e was absent in September 1982.

Case 2. A 32-year-old black security guard was admitted to hospital in April 1974 with an episode of hemorrhoidal bleeding. He had never had upper gastrointestinal bleeding. He was a practicing homosexual but denied intravenous drug use, prior hepatitis, or receiving blood transfusion. He consumed one to two glasses of wine per week. Physical examination revealed multiple spider angiomas and a firm liver edge 3 cm below the right costal margin. The spleen was not palpable. Bilirubin was 3.5 mg/dl; AST was 188 IU/liter (Figure 2). HB_sAg was positive while ANA and mono spot tests were negative. Technetium sulfur colloid liver spleen scan showed hepatosplenomegaly with redistribution to the spleen and bone marrow. Needle biopsy of the liver two weeks later revealed chronic active hepatitis without cirrhosis. Barium swallow four months later was negative for varices. He was followed without treatment and remained well except for easy fatiguability. His physical exam was unchanged.

HB_sAg, which had been positive on repeated testing through July 1976, was first noted to be negative in April 1977. He felt well, and his AST and ALT had returned to normal. Aspiration needle biopsy in June 1977 showed fragments of liver with a few focal areas of hepatocellular necrosis and chronic inflammatory cell infiltrate but was consistent with cirrhosis. Immunoperoxidase stains for HB_cAg and orcine stains for HB_sAg were negative. He continued to feel well and have nearly normal bilirubin and AST. In September 1979, he had a two to three week illness when AST reached 1000 IU/liter and bilirubin peaked at 4.5 mg/dl. No etiology was found for this episode. He has felt completely well since then and maintained nearly normal AST and normal bilirubin. Anti-HB_s was negative in October 1980 but was strongly positive in September 1982. Delta antibody was negative on several occasions during the period of hepatitis B surface antigenemia (1976, 1980, 1982). Tests for HB_eAg

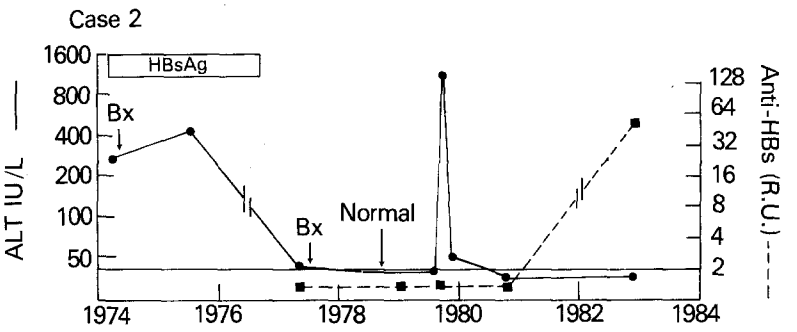

Fig 2. Alanine aminotransferase (ALT), HB_sAg, and anti-HB_s levels in case 2; Bx = biopsy.

were negative in 1978 and 1979. Anti-HB_e was absent in 1982.

Case 3. A 44-year-old white housewife was admitted to hospital in July 1979 with a three-day history of lower abdominal pain. She had received blood transfusions in 1963 and 1970 but had never been jaundiced. She drank alcohol socially. On physical exam, liver and spleen were not palpable, and there were no stigmata of chronic liver disease. She was taken to surgery where hemorrhagic ovarian cysts were found. Wedge biopsy of the liver revealed a quiescent cirrhosis. Ground glass cells, indicative of ongoing hepatitis B infection, were seen on review of the biopsy at LAC-USC Medical Center. Liver tests were normal in October and December 1979 (Figure 3). In January 1981 she had a routine physical exam. Liver and spleen were not palpable. AST and ALT were normal. Serum HB_sAg was tested for the first time and found to be positive. She was referred to LAC-USC Medical Center in May 1981 for further evaluation. She felt fine and physical exam was unremarkable. Serum amino transferases were minimally elevated and HB_sAg was again positive. During the succeeding year she was begun on disopyramide phosphate for a cardiac arrhythmia but otherwise remained healthy. Physical exam in July 1982 again revealed no signs of chronic liver disease and liver and spleen remained nonpalpable. Liver tests were normal. HB_sAg was now negative, while anti-HB_s was weakly positive. Repeat liver tests in June 1983 were normal, while anti-HB_s was strongly positive.

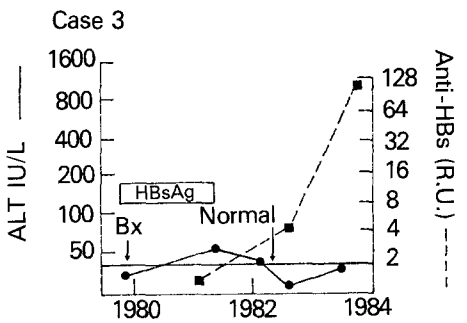

Fig 3. Alanine aminotransferase (ALT), HB_sAg, and anti-HB_s levels in case 3; Bx = biopsy.

HB_eAg was absent in 1981. Anti-HB_e was tested for the first time in 1982 and was present.

DISCUSSION

Three patients with hepatitis B-induced cirrhosis had permanent loss of HB_sAg followed by development of anti-HB_s during follow-up of four to nine years (Figures 1–3). Other investigators have reported the spontaneous loss of HB_sAg and development of anti-HB_s in patients with chronic hepatitis B. Van Waes et al (7), using CEP to measure HB_sAg, noted loss of detectable surface antigen during follow-up in 5 of 20 patients with biopsy-proven cirrhosis. Anti-HB_s testing was not performed. Viola et al (2) and Fevery et al (3) have described one or two patients with CAH-B or cirrhosis who lost HB_sAg and developed anti-HB_s. Other investigators have described the loss of HB_sAg and development of anti-HB_s in patients with chronic hepatitis without mentioning whether the underlying disease was CAH-B or CPH-B (8–10). However, in none of the reports is the clinical, biochemical, or histologic course of patients with CAH-B/cirrhosis well described, and in some reports it is unclear whether patients had CAH-B or CPH-B.

Other investigators, using immunohistologic stains or HBV-DNA probes, have detected the hepatitis B virus in hepatocytes from cirrhotic patients whose serum was negative for HB_sAg. Omata et al (5) and Ray et al (11), using immunohistologic staining techniques, found HB_cAg or HB_sAg in 15–30% of cirrhotic patients whose serum was negative for HB_sAg but positive for anti-HB_c or anti-HB_s. Other reports, in which HBV-DNA probes were used, found hepatitis B viral DNA in hepatocyte nuclei from cirrhotic patients whose serum was negative for HB_sAg but positive for anti-HB_s

TABLE 1. HEPATITIS B ANTIBODIES IN CONTROL AND CRYPTOGENIC CIRRHOSIS PATIENTS

		Control			Cryptogenic cirrhosis	
Author	*Country*	*Patients*	*No.*	*Anti-HB_c/HB_s (%)*	*No.*	*Anti-HB_c/HB_s (%)*
Bassedine et al (16)	England	ALD*	56	11	20	25
		Lupoid	27	9		
		Hospital Pts	112	11		
Skinhoj et al (17)	Denmark	Blood donors	960	3.6	49	37
		Hospital Pts	1300	8.2		
Boires et al (18)	France	Blood donors (22)	64	4	65	40
Kerlin et al (19)	USA	Lupoid	23	8.7	26	50
	(Los Angeles)	nAnB	11	9.1		
Thompson (20)	(Los Angeles)	Blood donors	8200	7.1		
Sadikali and Doniach (21)	Uganda	Hospital Pts	205	34	62	48

*ALD = alcoholic liver disease; nAnB = blood transfusion-associated non-A, non-B hepatitis.

(12–14). Implied in these reports is the suggestion that hepatitis B infection may be the cause of cirrhosis despite the absence of HB_sAg in serum. Only in our patients, however, has the conversion from HB_sAg positive to acquisition of anti-HB_s been well documented. Our report now provides the direct clinical and histologic evidence to support the indirect implications of studies on liver tissue from HB_sAg-negative patients.

The course of these patients is noteworthy in three other respects. First, conversion from surface antigen positive to anti-HB_s positive was not preceded or accompanied by an episode of transaminase elevation. This is in contradistinction to loss of HB_eAg in patients with CAH-B which can be accompanied by a brief elevation of transaminases (15). However, it is in accord with the findings of Lindsay et al (1) in seven patients with CPH-B who lost HB_sAg and developed anti-HB_s without an elevation in aminotransferases. Second, anti-HB_c alone was found for more than two years in two patients and with low anti-HB_s titers (4.8 ratio units) for one year in the remaining patient. Eventually, all three patients developed high titers of anti-HB_s. Thus, these patients had a protracted "window" period similar to the window period in resolving acute hepatitis B which lasted from one to four years. Third, the final histologic pattern in all three patients is inactive cirrhosis. In two patients liver biopsies documented a change from active inflammation and necroses early in their illness to inactive cirrhosis several years later. In the remaining patient only one liver biopsy was available and it revealed inactive cirrhosis. In addition, aminotransferase levels returned to normal with loss of HB_sAg.

Had these patients been first encountered following the development of anti-HB_s and without knowledge of their prior history of chronic hepatitis B surface antigenemia, it would have been impossible to establish the hepatitis B etiology of their cirrhosis. Such patients would commonly be considered to have a cryptogenic cirrhosis. Prior CAH-B may be more common in patients with a cryptogenic cirrhosis than in other patients. Investigators from Europe, the United States, and sub-Saharan Africa have reported a higher incidence of hepatitis B antibodies in patients with cryptogenic cirrhosis than in control patients (Table 1). These findings are consistent with the possibility that prior hepatitis B is etiologically related to an important proportion of cases of cryptogenic cirrhosis.

In conclusion, we report that clearance of HB_sAg can occur in CAH-B after cirrhosis has developed. The residual lesion is then inactive cirrhosis. Without knowledge of the prior prolonged HB_sAg positivity, patients in which clearance has occurred could be inferred to have cryptogenic cirrhosis with prior unrelated hepatitis B. Such cases may be more frequent than is commonly appreciated and, thus, the full impact of hepatitis B infection as a cause of cirrhosis may be considerably underestimated.

ACKNOWLEDGMENTS

We thank Dr. Robert L. Peters for review of the liver biopsies and Dr. Telfer B. Reynolds for allowing us to study two of his patients. Thanks also to the medical media personnel at the Veterans Administration Medical Center, Tucson, Arizona, for preparation of the figures.

REFERENCES

1. Lindsay KL, Redeker AG, Ashcavai M: Delayed HBsAg clearance in chronic hepatitis B viral infection. Hepatology 1:586–589, 1981

2. Viola LA, Coleman JC, Fluker JL, Barrison IG, Paradinas FJ, Evans BA, Murray-Lyon IM: Natural history of liver disease in chronic hepatitis B surface antigen carriers. Lancet 2:1156–1159, 1981
3. Feverey J, Desmet VJ, De Groote J: Long term follow-up and management of asymptomatic chronic active hepatitis. *In* Chronic Active Liver Disease. S Cohen, RD Soloway (eds). New York, Churchill Livingston, 1983, pp 51–64
4. Rizzetto M, Shih JWK, Gerin J: The hepatitis B virus associated delta antigen: Isolation from liver, development of solid-phase radioimmunoassays for delta antigen and antidelta and partial characterization of delta antigen. J Immunol 125:318–324, 1981
5. Omata M, Afroudakis A, Liew C, Ashcavai M, Peters R: Comparison of serum hepatitis B surface antigen (HB_sAg) and serum anticore with tissue HB_sAg and hepatitis B core antigen (HB_cAg). Gastroenterology 75:1003–1009, 1978
6. Edmonson HA, Peters RL: Liver. *In* Pathology, 8th ed. WAD Anderson, JM Kissone (eds). St. Louis, C.V. Mosby, 1985, pp 1124–1127
7. Van Waes L, Segers J, Van Egmond J, Van Nimmen L, Barbier F, Wieme R, Demeulenaere L: Chronic liver disease and hepatitis-B antigen: A prospective study. Br Med J 3:444–446, 1974
8. Hoofnagle JH, Seeff LB: Natural history of chronic type B hepatitis. *In* Progress in Liver Disease, Vol VII. H Popper, F Shaffner (eds). New York, Grune and Stratton, 1982, pp 469–494
9. Sampliner RE, Hamilton FA, Iseri OA, Tabor E, Boitnott J: The liver histology and frequency of clearance of hepatitis B surface antigen (HB_sAg) in chronic carriers. Am J Med Sci 277:17–22, 1979
10. Krugman S, Giles JP: Viral hepatitis, type B (MS-2-strain), further observations on natural history and prevention. N Engl J Med 288:755–760, 1973
11. Ray M, Desmet V, Fevery J, DeGroote J, Bradburne A, Desmyter J: Hepatitis B surface antigen (HB_sAg) in the liver of patients with hepatitis: A comparison with serological detection. J Clin Pathol 29:89–93, 1976
12. Brechot C, Nalpas B, Courouce A, Duhamel G, Callard P, Carnot F, Tiollais P, Berthelot P: Evidence that hepatitis B virus has a role in liver-cell carcinoma in alcoholic liver disease. N Engl J Med 306:1384–1387, 1982
13. Brechot C, Hadchouel M, Scotto J, Fonck M, Potet F, Vyas G, Tiollais P: State of hepatitis B virus DNA in hepatocytres of patients with hepatitis B surface antigen-positive and -negative liver diseases. Proc Natl Acad Sci USA 78:3906–3910, 1981
14. Figus A, Blum H, Vyas G, Virgilis S, Cao A, Lippi M, Lai E, Balestrieri A: Hepatitis B viral nucleotide sequences in non-A, non-B or hepatitis B virus-related chronic liver disease. Hepatology 4:364, 1984
15. Hoofnagle J: Chronic type B hepatitis. *In* Chronic Hepatitis and Primary Biliary Cirrhosis. AASLD Post-Graduate Course, 1982, pp 199–215
16. Bassendine MF, Della Seta L, Salmeron J, Thomas HC, Sherlock S: Incidence of hepatitis B virus infection in alcoholic liver disease, HB_sAg-negative chronic active liver disease and primary liver cell cancer in Britain. Liver 3:65–70, 1983
17. Skinhoj P, Nielsen JO, Dietrichson O: Serological evidence of hepatitis B infection in patients with chronic liver diseases: Radioimmunology of HB_sAg and anti-HB_s. Scand J Gastroenterol 12:615–619, 1977
18. Bories P, Coursaget P, Goudeau A, Degott C, Maupas P, Benhamou JP: Antibody to hepatitis B core antigen in chronic active hepatitis. Br Med J 1:396–397, 1978
19. Kerlin P, Ashcavai M, Redeker A, Peters R, Jones M: Anti-HB_c and anti-HB_s in HB_sAg negative chronic liver disease. Gastroenterology 77:A22, 1979
20. Thompson P: Medical director, Los Angeles and Orange Counties, Red Cross, unpublished data
21. Sadikali F, Doniach D: Autoimmune factors in African cirrhosis: Correlation with hepatitis B surface antigen and antibody. Am J Gastroenterol 64:484–489, 1975
22. Corusaget P, Maupas PH, Goudeau A, Millman I: Automated complement fixation test for the detection of antibodies against the core of hepatitis B virus (HB_c). J Immunol Methods 13:21–27, 1976