**Hepatitis B surface antigen clearance long after starting hemodialysis in a 70-year-old maintenance hemodialysis patient—a retrospective study on hepatitis B virus markers and liver function for 10 years—**

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**key words**: maintenance hemodialysis, hepatitis B, hepatitis B surface antigen, seroconversion

**Abstract**

In general, the number of maintenance hemodialysis (HD) patients who became hepatitis B surface antigen (HBsAg) positive and/or develop hepatitis B virus (HBV)–associated hepatitis has been gradually decreasing. It has been considered, however, that most HD patients who are HBsAg positive 12 months after the HBV infection have little chance of eliminating the virus in the future. Therefore, hepatitis B (HB) still remains a serious hazard to HD patients. We treated a 70-year-old male on maintenance HD; he was originally a HBsAg carrier, but he completely seroconverted to negative 5 years after the initiation of HD. The clinical course, liver function and major HBV markers in this maintenance HD patient were retrospectively examined for a period of 10 years, including the time of the start of HD. When HBsAg titers began to decrease, alanine aminotransferase (ALT) was suddenly and transiently elevated to 100 U/l. There are few case reports on HD patients who were persistently HBsAg positive before the initiation of dialytic treatment yet could terminate the chronic HBsAg carrier state long after the start of HD. Therefore, the seroconversion of HBsAg in this rare case seems clinically meaningful to report.

**Introduction**

Many patients on maintenance hemodialysis (HD) have acquired hepatitis B virus (HBV) after they started HD1–6). However, the number of maintenance HD patients who became hepatitis B surface antigen (HBsAg) positive and/or develop HBV–associated hepatitis has been gradually decreasing with the protective measures for HBV infection such as glove techniques and hepatitis B (HB) vaccination6), but recently there has been a report that five outpatients on maintenance HD at a dialysis unit in Tokyo contracted HBV infection successively, and four of them died of fulminant hepatitis7): similar epidemic problems associated with HBV have previously occurred, although rare. Therefore, HBV infection is still a serious hazard to both HD patients and medical personnel. In addition, once HD patients contract HBV most of them become permanently HBsAg carriers because they are immunocompromised and cannot readily eliminate HBV4,6).

To the best of our knowledge, there are few reports of HD patients who were persistently HBsAg positive before the initiation of dialytic treatment yet could terminate the chronic HBsAg carrier state long after the start of HD8). We treated a maintenance HD patient who had been originally a HBsAg carrier but seroconverted to negative...
later. He was followed for 10 years, including the
time of the start of HD. We think this rare case is
clinically meaningful to report as it is suggestive of
many HBV-associated problems encountered when
treating HD patients with chronic HB antigenemia
and evaluating HBsAg carrier states.

Case report

A 70-year-old male patient undergoing mainte-
nance HD was referred to the International Univer-
sity of Health and Welfare Hospital (IUHW Hospi-
tal) from an outpatient HD unit in July 1999.
Because the location of the previous HD unit was
far from his home he decided to change to a closer
place. He reported to the HD center of IUHW
Hospital that he had been HBsAg positive, but a
blood test disclosed that he becomes HBsAg nega-
tive, when he started HD at this HD center in
July 1999. Therefore, we decided to retrospectively
review his medical records and laboratory tests for
the past 10 years in cooperation with two other HD
facilities where he had previously been hemodial-
yzed.

On Feb. 16, 1990, at the age of 61, the patient
started HD at Jichi Medical School Hospital. It was
speculated there that the cause of end-stage renal
failure was chronic glomerulonephritis. Hyperten-
sion, gout and chronic renal failure but not liver
dysfunction were pointed out. Up to the start of HD
he had daily consumed 1,300 to 2,000 ml of beer,
but he had never received a blood transfusion. His
parents did not have liver dysfunction, though
whether or not they had been HBsAg carriers could
not be determined. When he first underwent HD at
Jichi Medical School Hospital, he was HBsAg posi-
tive, hepatitis B antibody (HBsAb) negative, hepati-
tis B envelope antigen (HBeAg) negative, hepatitis
B envelope antibody (HBeAb) positive, and hepati-
tis B core antibody (HBcAb) negative (Table). After
HD was started, in April 1990 he was soon referred
to the outpatient HD unit of Okuda Clinic, where he
underwent regular hemodialysis care. When he first
visited the outpatient HD clinic, HBsAg and HBsAb
were analyzed by reversed passive hemagglutina-
tion (RPHA) and passive hemagglutination (PA)
methods, respectively. His HBsAg titer was 1:
256 (positive), and HBsAb was negative. HBeAg
was negative and HBeAb was positive as they had
been at Jichi Medical School of Medicine (Table).
HBcAb, however, became positive (%inhibi-
tion 100%). HBsAg and HBsAb were often
examined at the outpatient HD unit using the above
methods. The values of serum aspartate amino-
transferase (AST) and alanine aminotransferase
(ALT) are shown in Fig., as well as the major
changes in HBsAg titers and HBsAb. Until March
1994, HBsAg had been obviously positive, but the
titer gradually been decreasing from Septem-
ber 1992, and it finally became negative in Septem-
ber 1995 (Fig.). HBsAb had always been negative,
but it became positive in March 1998. It could be
speculated that the HBsAg carrier status was ter-
minated at that time. HBeAb and HBcAb were
again examined in June 1993, but both were as
positive as in April 1990 (Table). HBV DNA analy-
sis had not been carried out prior to referral to
IUHW Hospital.

We thought that there may have been some trig-
ger to induce the HBsAg seroconversion from Sep-
to his previous medical record, he frequently com-
plained of night sweating in November 1992 when
AST and ALT were suddenly elevated to 36 U/l
and 100 U/l, respectively. In January 1993 the night
sweating became infrequent but an occasional
cough was noticed. Basically, his general condition
was good and he had a good appetite and no emacia-
tion at this time. In October 1993 his productive
cough became severe, and sputum culture was car-
ried out. On chest X ray no abnormality suggestive
of marked pulmonary tuberculosis was found. A
test with purified protein derivative of tuberculin
(PPD) was similarly positive (15 × 15 mm) as in
1991 (15 × 14 mm). However, one colony of tubercle'
baccillus was detected on the sputum culture test,
which was confirmed by a polymerase chain reac-
tion (PCR) DNA technique. Based on the diagnosis
of probable tuberculosis, he was treated primarily
with rifampicin, secondarily with kanamycin, and
finally with capreomycin though no serious clinical
problems suggestive of definite tuberculosis, such as
pleural effusion or pulmonary cavity formation, were detected. Administration of rifampicin was started on Nov. 25, 1993, before the positive culture result for tubercle bacillus was obtained. Rifampicin, however, was stopped because the tubercle bacillus was insensitive to rifampicin. Kanamaicin was started on Jan. 6, 1994 and discontinued because a hearing impairment was found. Instead, capreomycin was started from March 15, 1994 and discontinued on Sept. 29, 1994. Since then no sputum culture has disclosed tubercle bacillus, but the period when HBsAg titer began to gradually decrease coincided with the period when pulmonary symptoms suggesting tuberculosis appeared and he was treated for the pulmonary disease (Fig.). A test with PPD was markedly positive in May 1996 (20 × 20 mm) as well as in July 1999 (28 × 23 mm).

According to the earlier medical records, the regular laboratory data showed no marked abnormality when tuberculosis was diagnosed in November 1993. At this time he underwent dialysis 3 times per week, and his HD session length was 4 hours.

### Table: HBV-associated markers and liver function

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Laboratory data were obtained at Jichi Medical School of Medicine*, Okuda Clinic** and the International University of Health and Welfare Hospital***. ND means not done.
The dry weight was 67.5 kg as previously determined. The dialyzer used was AM-SD-15 M (Asahi Medical Co., Ltd. Tokyo, Japan). The blood flow rate and the dialysis solution flow rate were 200 ml/min and 500 ml/min, respectively. Heparin was used as an anticoagulant during HD.

All through this period treponema pallidum hemagglutination assay (TPHA) and hepatitis C virus antibody (HCV Ab) were always negative. Since September 1995, HBsAg has been consistently negative. HBsAb changed from negative to positive in March 1998. HBsAb was mildly positive when he moved to IUHW Hospital in July 1999 (Table). HBcAb was as positive as it had been. HBV DNA quantification was carried out with transcription mediated amplification in February 2000, and no HBV DNA was detected. The possible presence of HBV mutants in the precore and core promoter was further analyzed, but no mutants for those were detected. HCV Ab was still negative in July 1999.

Discussion

Recently, the frequency of HBV infection in HD patients has been decreasing partly because blood donors have been screened for HBsAg since 1972 in Japan and partly because HBsAg carriers on HD have often been separated from HBsAg negative patients. Moreover, glove techniques and HB vaccine may reduce the incidence of clinical disease. In fact, according to epidemiological surveys, the risk of HBV-associated liver diseases is low and the number of HBsAg positive patients has been reduced in dialysis centers.

HB, however, still remains a serious hazard to HD patients. In Japan, recently two HB epidemics in outpatient HD units occurred in 1994 and 1999, which greatly shocked many HD patients and the community. In the earlier outbreak, 5 patients successively contracted HBV infection in the same maintenance HD unit and 4 of them died of fulminant hepatitis. In the other epidemic six HD outpatients died of hepatitis, although this epidemic was not reported in the English language literature. Therefore, HBV infection is a potentially serious risk for maintenance HD patients even if it occurs rarely. In addition, most HD patients newly infected with HBV cannot eliminate the virus and become HBsAg carriers. The viral persistence might lead to chronic hepatitis B and to a reservoir of infectious dialyzed patients in HD units.

Taken together, it is crucial to pay attention to HBV infection in HD facilities and prevent epidemic outbreaks of fulminant hepatitis. Although some reports indicated that a small proportion of newly infected patients with HBV on maintenance HD could convert to HBsAg negative, there has never been a long-term follow-up case report that a chronic HBsAg carrier already at the start of HD could eliminate the viral antigen long after the start of HD. According to the previous reports, it has been considered that HD patients who are HBsAg positive 12 months after the HBV infection have little chance of eliminating the virus in the future. It was also reported that the majority of HD patients who developed HBV infection and later converted to HBsAg negative did so within 6 months of becoming HBsAg positive. A controversial report stated that more patients terminated the chronic HBsAg carrier state long after the acquisition of HBV than previously thought. In that letter, however, the clinical courses of the patients who eliminated HBsAg were not described in detail. Here, we presented a maintenance HD patient who had been a chronic HBsAg carrier before starting HD but could terminate the carrier state more than 5 years after the initiation of HD.

The HBsAg seroconversion does not necessarily mean that all particles of HBV including precore mutants have been completely eliminated in the sera of HBV-infected patients; it still leaves a slight possibility of severely infecting others. In the present case, however, the clearance of HBV was certainly demonstrated by the DNA PCR technique and other analyses.

The probable and general causes of HBsAg seroconversion have previously been suggested. Spontaneous seroconversion of HBsAg might occur with the appearance of protecting HBsAb in some HBV-infected patients. Hepatitis A virus and hepatitis delta virus superinfection might induce clearance of HBsAg in serum. HBsAg and HBcAg ser-
oconversion was observed in one patient after an episode of acute HCV superinfection\(^{26}\). Administration of alpha-interferon was effective in eradicating the carrier state in some patients with chronic HB infection\(^ {26}\). A limited number of patients with chronic HBsAg could sustain clearance of HBV infection after bone marrow transplantation (BMT), which was considered to be an adoptive immunity transfer\(^ {27}\). In the present case, however, neither interferon was administered nor HCV superinfection occurred. He has never undergone BMT. No specific drugs greatly modifying immunity were administered. Examining the medical records retrospectively, we found the coincidence of the period when HBsAg seroconversion occurred and when tuberculosis and its preceding signs of the disease started. It has often been suggested that tuberculosis has a potential to enhance immunity against other exogenous antigens. It is also considered that the potential of cellular immunity can be evaluated based on the response to PPD. In the present case a test with PPD was always positive, and the grade of the reaction became greater and greater after tuberculosis was diagnosed. Therefore, we speculate that the onset of tuberculosis may have been associated with the termination of the HBsAg carrier state in this HD patient.

Interestingly, AST and especially ALT levels were elevated during the same period when signs suggesting tuberculosis appeared and HBsAg titers began to decrease. The elevation of ALT levels before the clearance of HBV was pointed out in previous reports: two patients who had sustained clearance of HBV infection after BMT had a flare in the ALT level around the time of HBsAg clearance\(^ {27}\), and the mean ALT levels were elevated and hepatitis acutely exacerbated before seroconversion of HBsAg in 13 patients out of 19 patients who had been chronic HBsAg carriers and HBsAg seroconverted\(^ {28}\). The reason why ALT levels are transiently elevated before the carrier status is terminated in HB carriers remains to be elucidated. However, it is noteworthy that the ALT level was transiently elevated in the present HD patient who terminated the HBsAg carrier state as well as in the previously reported cases with different medical conditions and without undergoing HD.

**Conclusion**

We reported a 70-year-old maintenance HD patient who had been a chronic HBsAg carrier and underwent HBsAg clearance 5.5 years after the start of HD. This 10-year follow-up case report retrospectively studied the results of major HBV markers and liver function tests in this HBsAg seroconverted patient. It may be suggested, based on the present study, that tubercle bacillus infection might induce seroconversion of HBsAg in chronic HBsAg carriers undergoing HD and that the ALT level seems to increase before HBsAg clearance in HD patients as well as in other previously reported cases with different medical conditions.

**References**


<和文要旨>
一般にB型肝炎は、B型肝炎ウイルスの解明と治療の確立により少しずつ減少し、以前に比べると維持透析患者
でもB型肝炎表面抗原（hepatitis B surface antigen）が陽性化したりB型肝炎ウイルスによって肝炎を起こす頻度が減少してきている。しかし、血液透析患者がB型肝炎ウイルスの感染によってB型肝炎表面抗原が陽性化した場合、免疫能が弱いため、12か月経過しても駆逐できていなければほとんどがそのままキャリアーになってしまうともいわれている。今回我々は、透析導入時にB型肝炎ウイルスキャリアーであることが確認されていたものの、数年後にB型肝炎表面抗原が陰性化した70歳男性の維持透析症例を経験し、ウイルスマーカーや肝機能などについてretrospective studyを施行した。本症例では、透析導入後、B型肝炎コア抗体（hepatitis B core antibody）が陽性となったが、5年後にはB型肝炎表面抗原が陰性化し現在に至るまで陰性のままであった。B型肝炎表面抗原のtiterが下がり始めた時期に一致して一過性の血清ALT値の上昇が認められた。透析患者におけるB型肝炎表面抗原のseroconversionは比較的珍しい現象であるだけでなく、その臨床経過を10年間の長期にわたって調査した報告はなく、今後、B型肝炎キャリアーの取り扱いや病状の進展、予後を予測したり評価したりするうえで臨床的に意義深いものと考え報告する。