Case Report

Failure of Hepatitis B Surface Antibody to Protect Acute Fulminating Hepatitis in a Renal Transplant Recipient

Abhasnee Sobhonslidsuk MD*,
Pattana Sornmayura MD**, Vasant Sumethkul***

** Division of Gastroenterology, Department of Pathology, Ramathibodi Hospital, Mahidol University*
*** Department of Pathology, Ramathibodi Hospital, Mahidol University*
**** Division of Nephrology, Department of Medicine, Ramathibodi Hospital, Mahidol University*

A 58-year-old man who had a living-related kidney transplantation (KT) 13 years ago and had received a double-dosage course of hepatitis B virus (HBV) vaccination prior to KT developed acute liver failure. An exhaustive work-up for the cause of acute liver failure revealed that HBsAg was negative but anti-HBs and anti-HBcAbs were positive. HBV DNA was 535,000 copies/ml. The strongly positive staining of HBsAg and HBcAg of liver biopsy was shown by immunohistochemistry examination. HBV harboring surface mutant of hepatitis B surface gene was thought to be the cause of acute fulminant hepatitis despite the presence of protective immunity to wild-type HBV. The patient expired from acute liver failure even though an antiviral drug was started promptly. This is the first case report of liver biopsy suggestive of acute fulminating HBV that developed in a long-term kidney recipient despite the presence of high anti-HBsAb titer.

Keywords: *Hepatitis B, Liver failure, Kidney transplantation*

J Med Assoc Thai 2006; 89 (Suppl 2): S257-61
Full text. e-Journal: *http://www.medassocthai.org/journal*

Hepatitis B virus (HBV) has been a major health problem globally, and of the 350 million patients chronically infected with HBV worldwide. Eight to twenty-eight percent of long-term survivors after kidney transplantation (KT) were death due to liver disease[1]. HBV infection is also an important cause of liver disease leading to high morbidity and mortality in KT patients[1]. The prevalence of HBV infection in the patients with chronic renal failure, hemodialysis, and KT was very high prior to routine HBV blood screening and the implementation of vaccination policy by the Center for Disease Control and Prevention of the United States. The prevalence of surface gene mutant of HBV increases strikingly after universal HBV vaccination and the widely use of hepatitis B immunoglobulin prophylaxis after liver transplantation[2]. In the present report, the authors describe a patient who developed clinical manifestation of acute liver failure from HBV infection 13 years after KT despite the presence of anti-HBsAb.

Correspondence to : Sobhonslidsuk A, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, 270 Praram 6 Rd, Rajathevi, Bangkok 10400, Thailand. Phone: 0-2201-1304, 0-1349-8438, Fax: 0-2201-1387, E-mail: teasb@mahidol.ac.th

Case Report

A 58 year-old, post-KT male was admitted to Ramathibodi Hospital because of progressive jaundice and alteration of consciousness. Thirteen years ago, he underwent living-related KT due to end-stage renal disease. He received a kidney graft from his identical HLA typing brother. Prior to the transplantation, the patient had negative testing for HBsAg and anti-HBsAb (Abbott Laboratories, North Chicago, IL, USA) and had received three double-dosages (2 x 20 mg) of hepatitis B vaccination (HB Vac II). It is unfortunate that pre-KT HBV markers of the patients were not known. HBV markers of the donor were negative for HBsAg and positive for both anti-HBsAb and anti-HBcAb. The achieved nadir of serum creatinine since KT was done was 1.5 mg/dl. Maintenance immunosuppressions consisted of cyclosporin and prednisolone. Seventy-two months prior to admission (PTA), his creatinine level was 2.5 mg/dl. So, the dosage of cyclo-

sporin was reduced by 50% and mycophenolate mofetil (MMF) (1.5 gm/day) was added. Twenty-six months PTA, his creatinine level was 2.9 mg/dl. Cyclosporin was gradually eliminated and the dose of MMF was increased to 2 gm/day. In addition, sirolimus (2 mg/day) was added while the dosage of prednisolone was kept at 5 mg/day. Sirolimus level was 5.1 ng/ml. Subsequently, serum creatinine level declined to 2.3 mg/dl. Eight weeks PTA, his creatinine level was 2.6 mg/dl. A few weeks after that, he developed fatigue and had ALT of 219 IU/l without jaundice. He denied alcohol drinking, recent new drugs or herbal medicine usage. Three weeks PTA, ALT was 418 IU/l, total bilirubin was 1.1 mg/dl and he felt increasingly fatigued. The HBsAg assay by Ortho Vitros ECi was negative. Anti-HBsAb was positive at 40 mIU/ml. Anti-HBcIgG was positive as well. All potential hepatotoxic agents and sirolimus were stopped. Cyclosporin and prednisolone were continued as a maintenance immunosuppression.The patient had progressive jaundice, loss of appetite, nausea, vomiting, and abdominal discomfort. On admission, physical examinations revealed deep jaundice, ascites, bilateral leg edema, and grade II hepatic encephalopathy. Laboratory tests showed AST of 253 IU/l, ALT of 192 IU/l, total bilirubin of 20 mg/dl, direct bilirubin of 14.4 mg/dl, and prothrombin time of 20 sec (control =10-13 sec.). Anti-HBcIgM, anti-HAVIgM and antibody to hepatitis C (anti-HCV) markers were all negative. Anti-HBcIgG and anti-HBs Abs were positive (with the rising of anti-HBsAb titer to 400 mIU/ml). HBeAg and anti-HBeAb were negative and positive, respectively. HCV RNA was negative but HBV DNA was positive by qualitative polymerase chain reaction. HBV DNA (Amplicor HBV Monitor test, Roche Diagnostic Systems, Branchburg, NJ) was 535,000 copies/ml. Repeated HBsAg by enhanced chemiluminescence assay (Ortho Vitros ECi) was 0.17 signal/cutoff (s/c) or negative (i.e. less than 1.00 s/c) but it was positive (0.31 IU/ml; cut off 0.05 IU/ml) by automated chemiluminescent microparticle immunoassay (Architect

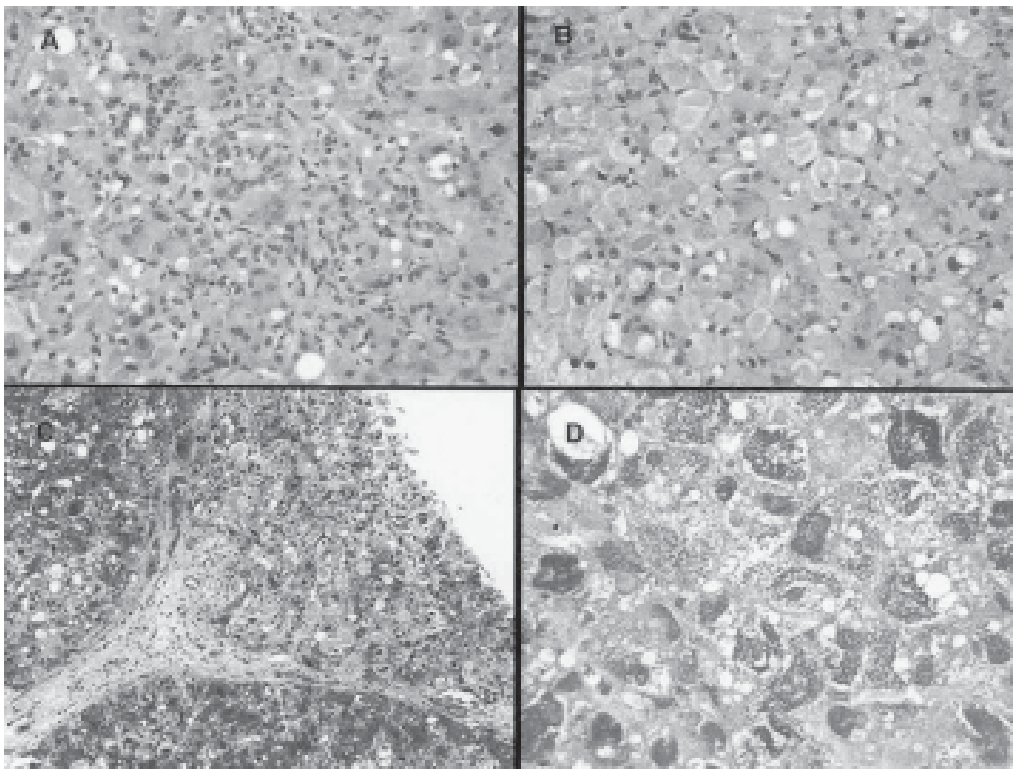

Fig. 1 Staining of liver biopsy: (A) Diffused ground glass appearance of hepatocytes, hepatocyte drop-out and some lobular infiltrations of lymphocytes (HE; original magnification, x200); (B) Diffused ground glass of hepatocytes with intrahepatic cholestasis (HE; original magnification, x200); (C) Expanding portal fibrosis is showed by Masson trichrome (original magnification, x400); (D) Presence of HBsAg in some hepatocytes is confirmed by the Orcein stain (original magnification, x400)

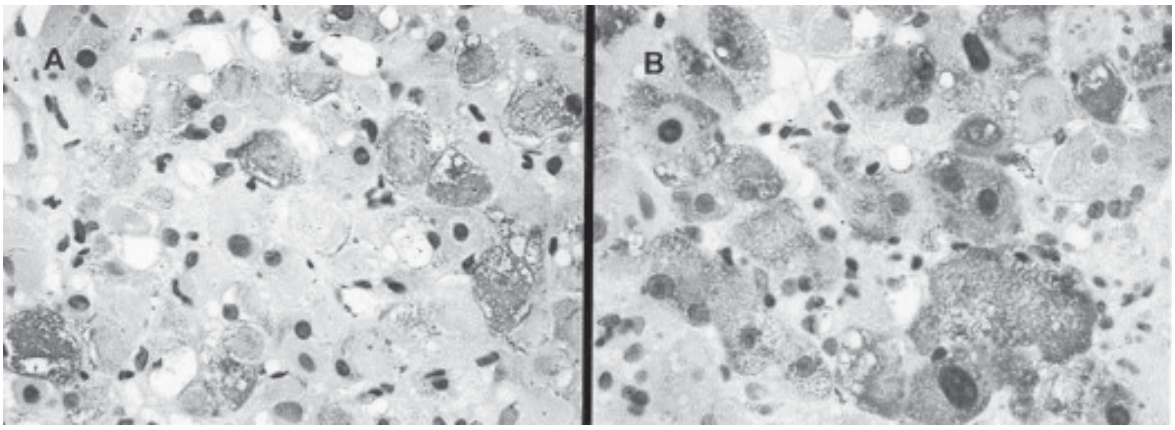

Fig. 2 Immunohistochemical study of the liver: (A) Staining of HBsAg in the cytoplasm of some hepatocytes (original magnification, x400); (B) Intense nuclear staining and weaker cytoplasmic staining of HBcAg in several hepatocytes (original magnification, x400)

HBsAg QT). Diffused ground-glass hepatocytes, cholestasis with some infiltrations of lymphocytes and expanding portal fibrosis was revealed from the liver pathology (Fig. 1). Immunohistochemistry examination showed strongly positive staining of HBsAg and HBcAg in hepatocytes (Fig. 2). Lamivudine (100 mg/day) was started promptly and fully supportive treatment was given. Nevertheless, his clinical course of fulminant hepatitis deteriorated with the development of hepatic coma and renal failure. He was listed for liver transplantation but the liver organ was not available in time. He expired from multiple organ failure at one month after lamivudine therapy.

Discussion

Death from liver diseases is still a challenging problem for KT recipients. Liver failure becomes a leading cause of death in patients with HBsAg after 10 years of KT[3]. HBV replication increases by the impact of immunosuppression and the liver damage can progress.

In the present case report, the positive anti-HBcAb, the detectable HBV DNA, and marked staining of HBsAg and HBcAg on liver histology demonstrated by immunohistochemistry confirmed that HBV was the cause of acute hepatitis.

There are three interesting aspects that need to be addressed. First, the onset of acute fulminating hepatitis occurred at 13 years after KT was performed. To the authors' knowledge, this is the longest period reported in recipients with KT. It is unclear when and how the patient acquired HBV infection, however the possibilities are; the passive infection from donor graft or the infection acquired over time after KT. The first possibility has low probability since the HBV acquisition from donors with positive anti-HBcAb and anti-HBsAb was seen mainly in liver transplant recipients. Second, there was a discordant between the detection of HBsAg by a routine commercial ELISA assay using monoclonal capture/monoclonal conjugate (Ortho Vitros ECi) and a commercial automated chemiluminescent microparticle immunoassay or MEIA that use monoclonal capture/polyclonal indicator (Architect HBsAg QT). It is likely that the surface or "a" mutant of HBV occurring in the present case was the cause of viral escape from immunity of anti-HBsAb. Commercial HBsAg assays have varying sensitivity and ability to detect wild type and HBV variants[4,5]. The Architect HBsAg QT assay, which is a kit for quantitative measurement of HBsAg titer, has excellent sensitivity and good detection of HBsAg mutation[6]. Unfortunately, the authors did not have the opportunity to confirm the surface mutant of HBV by direct HBV gene sequencing in the presented case. Lastly, one month therapy of lamivudine was ineffective in halting the progression of liver injury. Occult hepatitis B infection defined by negative of HBsAg and positive of HBV DNA was found in 3.8% of adult patients in a hemodialysis unit in North America[7]. The majority of these patients (78%) had "a" determinant mutation, mostly with a substitution from glycine to arginine at the position 145 (G145R)[7-9]. The G145 R mutant has been the most common and the most stable surface mutant found after universal HBV vaccination in childhood and post-liver transplant prophylaxis with HBIG[2,8,9]. Portal fibrosis detected in liver biopsy leads to the suggestion that

the patient had chronic hepatitis B infection which explained the negative result of anti-HBcIgM. Flare of hepatitis B in the present case might result from reactivation of the preexisting wild type HBV or reactivation of mutant strain HBV infection that escape neutralization from the antibody to the surface antigen of wild-type HBV[10-12].

The relative impact of each immunosuppressive drug on the reactivation or induction of acute HBV infection in the presented patient is unclear. Interestingly, the patient did not develop HBV infection during the first eleven years after KT while he was receiving a combination of cyclosporin, MMF, and steroid. However, he did develop acute hepatitis after he was switched to a combination of sirolimus, MMF, and steroid. It is not known whether the sirolimus-base regimen is more or less potent than the cyclosporin-base regimen regarding to the enhancement of viral hepatitis replication. However, the net immunocompromise state or the changing of immune status should be considered as a key point relating to the breakthrough of HBV in the presented patient despite the presence of immunity to the wild-type HBV.

It is generally accepted that patients who had been positive for anti-HBsAb prior to transplantation, either from natural acquisition or vaccination, are less likely to be infected with the wild type of HBV. Nevertheless, some studies show that HBV infection can occur after KT even in the presence of anti-HBsAb or anti-HBcAb before transplantation with or without mutation in the "a" determinant region[10,11]. It is important to address that, in those studies, HBV infection occurred when anti-HBsAb fell below 40 IU/ml[10,11]. On the contrary, the presented patient developed HBV infection despite the anti-HBsAb level of 400 IU/ml. The clinical course of chronic hepatitis B harboring the surface gene mutation in KT patients is not known because of its rare incidence. Only one report from Lu et al[11] described a KT recipient who had de novo HBV infection caused by mutation within HBsAg like the presented case but there are dissimilarities in several points. First, the reported patient developed de novo acute HBV infection considerably earlier (25 months after KT) than the presented case[11]. Second, anti-HBsAb of the reported patient had decreased to undetectable level after the infection[11]. Finally, the clinical outcome of the reported patient was uneventful while the presented case succumbed to death. Unfortunately, the relationship between the flare of HBV and immunosuppressive drugs could not be elaborated due to the lack of the detail of immunosuppression[11]. In summary, the present study has led to an awareness of fatal HBV-related fulminant hepatitis despite the presence of anti-HBsAb[10-12]. This may occur from surface mutant of HBV infection that enables HBV to escape protective immunity from anti-HBsAb. More studies are needed to understand the mechanisms of acquired infection and the outcome of the surface mutant infection in renal transplant recipients.

Acknowledgements

The authors wish to thank Associate Professor Suda Louisirirotchanakul and Mr. Chavachol Sattsaudom for their meaningful comments and assistance.

References

1. Fabrizi F, Martin P, Ponticelli C. Hepatitis B virus and renal transplantation. Nephron 2002; 90: 241-51.
2. Thomas HC. Mechanism of emergence of hepatitis B virus escape variants: approaches to prevention. J Viral Hepat 1998; 5 Suppl 2: 31-6.
3. Kliem V, Ringe B, Holhorst K, Frei U. Kidney transplantation in hepatitis B surface antigen carriers. Clin Investig 1994; 72: 1000-6.
4. Louisirirotchanakul S, Kanoksinsombat C, Theamboonlert A, Puthavatana P, Wasi C, Poovorawan Y. Mutation of the "a" determinant of HBsAg with discordant HBsAg diagnostic kits. Viral Immunol 2004; 17: 440-4.
5. Moerman B, Moons V, Sommer H, Schmitt Y, Stetter M. Evaluation of sensitivity for wild type and mutant forms of hepatitis B surface antigen by four commercial HBsAg assays. Clin Lab 2004; 50: 159-62.
6. Coleman PF, Chen YC, Mushahwar IK. Immunoassay detection of hepatitis B surface antigen mutants. J Med Virol 1999; 59: 19-24.
7. Minuk GY, Sun DF, Greenberg R, Zhang M, Hawkins K, Uhanova J, et al. Occult hepatitis B virus infection in a North American adult hemodialysis patient population. Hepatology 2004; 40: 1072-7.
8. Zuckerman JN, Zuckerman AJ. Mutations of the surface protein of hepatitis B virus. Antiviral Res 2003; 60: 75-8.
9. Francois G, Kew M, Van Damme P, Mphahlele MJ, Meheus A. Mutant hepatitis B viruses: a matter of academic interest only or a problem with far-reaching implications? Vaccine 2001; 19: 3799-815.
10. Kim KH, Ahn SH, Chung HY, Paik YH, Lee KS, Kim YS, et al. Hepatitis B virus infection after renal

transplantation in the presence of antibody to hepatitis B surface antigen immunity. J Gastroenterol Hepatol 2004; 19: 847-53.
11. Lu M, Lorentz T. De novo infection in a renal transplant recipient caused by novel mutants of hepatitis B virus despite the presence of protective anti-hepatitis B surface antibody. J Infect Dis 2003; 187: 1323-6.
12. Huo TI, Wu JC. Does antibody to hepatitis B surface antigen protect renal transplant patients from hepatitis B? J Gastroenterol Hepatol 2004; 19: 841-3.

ภูมิต้านทานไวรัสตับอักเสบบีไม่สามารถป้องกันภาวะตับวายจากไวรัสตับอักเสบบีในผู้ป่วยภายหลังการปลูกถ่ายไต

อาภัสณี โสภณสฤษฎ์สุข, พัฒนา ศรมยุรา, วสันต์ สุเมธกุล

ชายอายุ 58 ปี มาโรงพยาบาลด้วยอาการตับวายเฉียบพลันโดยมีประวัติได้รับการผ่าตัดปลูกถ่ายไตเมื่อ 13 ปีก่อน ผู้ป่วยได้รับวัคซีนป้องกันไวรัสตับอักเสบบีก่อนการปลูกถ่ายไต เมื่อทำการตรวจหาสาเหตุของตับวายเฉียบพลันไม่พบแอนติเจนของไวรัสตับอักเสบบี และพบภูมิต้านทานต่อผิวและคอร์แอนติเจนของไวรัสตับอักเสบบี ผลการตรวจชิ้นเนื้อตับโดยการย้อมอิมมูโนฮีสโตเคมมิสทีของเนื้อตับยืนยันว่าไวรัสตับอักเสบบีเป็นสาเหตุของตับวาย มีข้อสันนิษฐานว่าไวรัสตับอักเสบบีที่กลายพันธ์ที่ผิวของไวรัสเป็นสาเหตุของตับอักเสบที่รุนแรงแม้ว่าผู้ป่วยมีภูมิต้านทานต่อไวรัส ผู้ป่วยเสียชีวิตแม้ว่าได้รับการรักษาด้วยยาต้านไวรัส lamivudine รายงานนี้เป็นรายงานฉบับแรกของการเกิดโรคตับวายเฉียบพลันที่มีข้อสันนิษฐานจากการตรวจชิ้นเนื้อตับว่าเกิดจากไวรัสตับอักเสบบีในผู้ป่วยที่ได้รับการปลูกถ่ายไตมานานกว่า 10 ปี และมีภูมิต้านทานต่อไวรัส