Medical Journal of the
Islamic Republic of Iran

Volume 20
Number 2
Summer 1385
July 2006

Case Report

HEPATITIS B VIRUS INFECTION IN AN ANTI-HBC NEGATIVE PATIENT: A CASE REPORT

SEDIGHEH AMINI KAFI-ABAD, MD*, AND ALI TALEBIAN, MD**

From the Research Center of the Iranian Blood Transfusion Organization, Tehran, Iran.

ABSTRACT

One of the best reliable markers of hepatitis B virus infection is antibodies to the core antigen (Anti-HBc).

A first-time blood donor with HBsAg positivity was identified as an HBV carrier that was anti-HBc negative. The patient was followed for 24 months in order to investigate the evolution of his HBV serological profiles and HBV-DNA (PCR).

In the follow-up for 24 months, HBsAg, HBeAg and HBV-DNA (PCR) were positive but all the time anti-HBc remained negative. HBV DNA viral load was 3.4×10^6 copies per mL. In the immunohistochemical study on the needle liver biopsy, the hepatocytes were positive for HBcAg and HBsAg.

For this immunological situation, the most probable hypothesis is an immunotolerance to HBV due to an in utero HBV infection. This situation does not impose a risk of HBV transmission by blood transfusion, because HBsAg positive donations are excluded and discarded by HBsAg screening tests.

MJIRI, Vol. 20, No.2, 98-100, 2006.
Keywords: Anti-HBc, Hepatitis B Virus (HBV), Tolerance, Immunity.

INTRODUCTION

Hepatitis B virus produces several protein antigens such as HBsAg and HBeAg. HBcAg is produced by hepatitis B virus and is detected in liver tissue.[1-2] Antibodies to each of these antigens can be measured in blood.[1-4] 3-4 weeks after the appearance of HBsAg, anti-HBc can be detected and persists for many years.[5-8]

In the Iranian Blood Transfusion Organization a sample from each donation is tested for HBsAg, Anti-HIV, anti-HCV and a serologic test for syphilis like RPR. All positive donation units are excluded and discarded. The positive results are confirmed, then donors are notified and they are followed-up by the Iranian Blood Transfusion Organization hepatitis clinic.

CASE REPORT

The first-time blood donor was a man. He was 30 years old, born and living in Tehran. At his first donation on June 2001 he was positive for HBsAg and negative for anti-HIV, anti-HCV and RPR so this unit was discarded.

Four blood samples were obtained during nearly 24 months. The results obtained from the HBV serological markers included HBsAg, anti-HBc, HBeAg, HBeAb that are shown in detail in Table I. The results remained stable through-out the follow-up.

HBV DNA was analyzed using polymerase chain reaction (PCR). HBV DNA was positive by PCR method and detected by gel electrophoresis (Fig 1). The HBV DNA viral load was 3.4×106 copies per ml.

The needle liver biopsy on August 2001 was studied, and no significant pathologic changes were observed.

The histological activity index, according to modified HIA score was A: 0, B: 0, C: 1, D: 0, Total=1 and stage: 0.[9]

Immunohistochemical studies were performed using HBcAg and HBsAg markers and detected by avidin-biotin-peroxides complex method. The needle liver biopsy demonstrated strong nuclear reactivity for HBcAg and cytoplasmic positivity for HBsAg[10, 11] (Fig. 2 and 3).

In order to evaluate the status of the immune system especially an efficient antiviral cellular and humoral immune response, several serological markers were studied. The results of immunoglobulin G, A and M were in references interval according to age and sex. The patient

Table I. Hepatitis B Virus (HBV) serological markers through-out the follow-up

Date of bleed/Marker	April 6, 2001	April 15, 2001	June 8, 2002	May 6, 2003
HBsAg	Positive	Positive	Positive	Not done
Anti-HBc	Negative	Negative	Negative	Negative
HBeAg	Positive	Positive	Positive	Positive
Anti-HBe	Negative	Negative	Negative	Negative

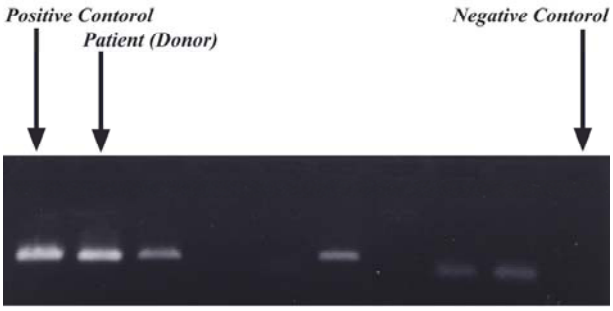

Fig 1. Detection of HBV DNA by PCR followed by gel electrophoresis.

exhibited antibodies to cytomegalovirus (6.8 IU/mL, Reference Value: Immunity>1.1 Iu/ml).

The patient's mother was evaluated for HBV infection and she was positive for HBcAb.

DISCUSSION

Anti-HBc negativity in HBsAg positive carrier children and blood donors has been reported in a few studies.[12-14] In one study in China the absence of anti-HBc occurred in four children who were infected perinatally. They were HBsAg and HBV DNA positive but anti-HBc never appeared.[13] Two blood donors in France exhibited such a profile.[14]

Hepatitis B infection and failure to produce anti-HBc after several months has been described in three different circumstances. First, unresponsiveness to viral infection and antigens like HBV infection and HBcAg are encountered in immunocompromised patients.[15,16] Second, some partial deletions in the core gene have been detected in HBV infection. These deletions cause the reduction of HBsAg, HBcAg and HBeAg and their antibodies or absence of anti-HBc and other antibodies.[17,18] Third, anti-HBc has been found to be negative in some infants who were HBsAg positive and were borne to HBeAg positive carrier mothers.[14,19-23] It is suggested that HBeAg can cross the placenta and establish T helper cell tolerance in utero for HBeAg and HBcAg.[14,22] These results support immune incompetency of the hepatitis B virus antigens in neonates, so HBsAg carrier infants with serum anti-HBc negativity may result from immunologic tolerance in the uterus.

In this case the first hypothesis was excluded because the patient did not have hypogammaglobulinemia and produced antibodies against other viruses like CMV. HBsAg and HBcAg were produced and detected in liver tissue and in long-term follow-up HBV antigens were detected in blood (Table I), so the second hypothesis was unlikely. The third hypothesis seems to be the probable

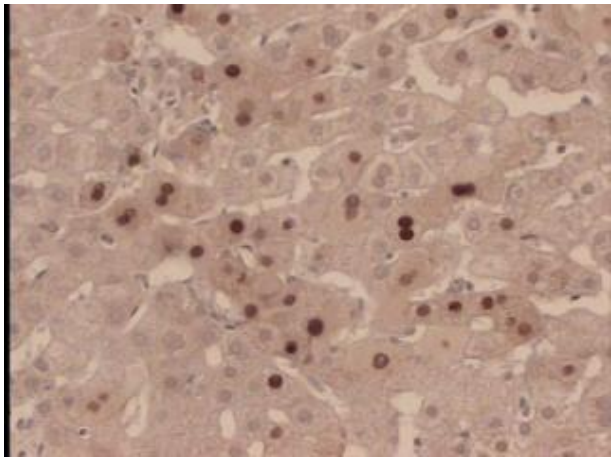

Fig 2. Hepatocytes expressed nuclear staining for HBcAg.

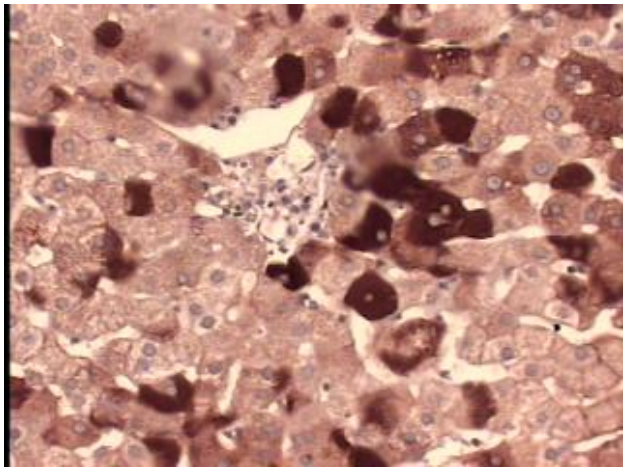

Fig 3. Hepatocytes expressed cytoplasmic staining for HBsAg.

explanation for this immunologic and clinical situation. Serological markers and results of HBV DNA viral load indicated active viral replication but no significant pathologic changes were observed in liver biopsy. These findings were in agreement with possibility with an immune incompetence to HBV infection in this subject. Long term follow-up of the patient in the future was recommended because a delayed immune response could not be definitively excluded.

This situation does not impose a risk of HBV transmission by blood transfusion because HBsAg positive donations are excluded and discarded by an HBsAg screening test.

REFRENCES

1. Bader FT: Viral hepatitis. In: Storch GA, Essentials of Diagnostic Virology. New York: Churchill Living-stone, pp.115-128, 2000.

2. Bendinelli M, Pistello M, Freer G, Vatteroni M, Maggi F: Viral hepatitis. In: Rose NR, Hamilton RG, Detrick B: Manual of clinical laboratory immunology. Washington, D.C, ASM Press, 696-717, 2002.
3. Robinson SW: Hepatitis B virus and hepatitis D virus. In: Mandell GL, Bennet JE, and Dolin R, (eds.), Principle and practice of Infectious Disease. New York: Churchill Livingstone, pp. 1406-1439, 2000.
4. Fagan EA, Harrison TJ, Viral hepatitis. Oxford: Bios, 89-130, 2000.
5. Neto CA, Strauss E, Sabino EC, Sucupira MCA, Chamone DAF: Significance of isolated hepatitis B core antibody in blood donors from Sao Paulo. Rev Inst Med Trop Paulo 43(4): 203-208, 2001.
6. Hennig H, Puchta I, Luhm J, Schlenke P, Georg S, and Kirchner H: Frequency and load of hepatitis B virus DNA in first time blood donors with antibodies to hepatitis B core antigen. Blood 100(7); 2637-2641, 2002.
7. Papotheodoridis GV, Hadziyannis SJ: Diagnosis and management of pre-core mutant chronic hepatitis B. J Viral Hepatol 8; 311-321, 2001.
8. Bonino F, Rosina F, Rizzetto M, Rizzi R, Chiaberge E, Tardanico R, et al: Chronic hepatitis in HBsAg carriers with serum HBV-DNA and anti-HBe. Gastroenterology 90(5); 1268-73, 1966
9. Snover DC: Non-neoplastic liver disease. In: Sternberg SS, (ed.), Diagnostic Surgical Pathology. Philadelphia: Lippincott Williams & Wilkins, pp. 1509-1552, 2003.
10. Pal J, Somogy C, Szmoleszky A, Szekeres G, Sipos J, Hegedus G, Martzinovits I, Molnar J, and Nemeth P: Immunohistochemical assessment and prognostic value of hepatitis B virus X protein hepatitis and primary hepatocellular carcinoma using anti-HBxAg monoclonal antibody. Path Onco Research 7(30); 178-184, 2001.
11. Ge JH, Zhang LZ, Li JX, Liu H, Liu HM,He J, Yao YC, Yang YJ, Yu HY, and Hu YP: Gene expression of mutant hepatitis B virus in a transgenic mouse contained complete viral genome with s gene. World J Gasteroenterol 10(21); 3141-3145, 2004.
12. Hosseini SK, Avijgan M, Mohamadinejad M: High prevalence of HBV, HCV, and HIV infections in gypsy population residing in Shahr-e-Kord. AIM 7(1): 20-22, 2004.
13. Ni YH, Hsu HY, Chang MH, Chen DS, Lee CY: Absence or delayed appearance of hepatitis B core antibody in chronic hepatitis B surface antigen carrier children. J Hepatol 17(2): 150-154, 1993.
14. Laperche S, Guitton C, Smilovici W, Courouce M: Blood donors infected with the hepatitis B virus but persistently lacking antibodies to the hepatitis B core antigen. Vox Sang 80: 90-94, 2001.
15. Costello M: Yungbluth M, Viral infections. In: Henry JB, (ed), Clinical Diagnosis and Management by Laboratory Methods. New York: W.B. Saunders, pp. 1045-1071, 2001.
16. Preikschat P, Meisel H, Will H, Gunther S: Hepatitis B virus genomes from long-term immunosuppressed virus carriers are modified by specific mutations in several regions. J Virol 80: 2685-2691,1999.
17. Wakita T, Kakumu Sh, Shibata M, Yoshioka K, Ito Y, Shinagewa T, Ishikawa T, Takayanagi M, Morshima T: Detection of Pre-C and Core region mutants of hepatitis B virus carriers. J Clin Invest 88: 1793-1801, 1999.
18. Yuan TT, Lin MH, Qiu SM, Shih Ch: Functional characterization of naturally occurring variants of human hepatitis B virus containing the core internal deletion mutation. J Virol 72(3): 2168-2176, 1998.
19. Chisari FV: Virus, immunity, and cancer: lessons from B. American J Pathol 156(4): 1118-1132, 2000.
20. Roh S, Kim K, Overcoming tolerance in hepatitis B virus transgenic mice: a possible involvement of regulatory T cells. Microbiol Immunol 47(6): 453-460, 2003.
21. Diepolder HM, Jung MC, Wierenga E, Hoffmann RM, Zacholva R, Gerlach TJ, et al: Anergic TH1 clones specific for hepatitis B virus (HBV) core peptides are inhibitory to other HBV core-specific CD4+ T cells in vitro. J Virol 70(11): 7540-7548, 1996.
22. Milich DR, Schodel F, Hughes JL, Jones JE, Peterson DL: The hepatitis B virus core and e antigens elicit different Th cell subsets: antigen structure can affect Th cell phenotype. J Virol 71(3): 2192-2201, 1997.
23. Milich DR, Jones JE, Hughes JL, Price J, Raney AK, McLachlan A: Is a function of the secreted hepatitis B e antigen to induce immunologic tolerance in utero? Proc Natl Acad Sci USA 87: 6599-6603, 1990.