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Case Report

Case study of HBV-related Disasters in a High-risk Family

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Hepatitis B virus (HBV) is one of the most common intracellular parasites, of which 350 million people worldwide are chronic carriers. It also related to a high incidence of hepatocellular carcinoma. In general, it has been well known that HBV is a noncytolytic virus, so not the virus itself but any unfavorable response by host immune cells and inflammatory cytokines mainly result in chronic liver injury. From this viewpoint, we hopefully assume that Oriental therapies based on immunologic strategies may be able to provide a therapeutic alternative for caring for these illnesses. We also need to be thoroughly familiar with information about HBV epidemiology and the pathologic process of chronic HBV carriers. In this study, to clarify the important considerations of HBV infection and the high risk of HBV induced life-threatening diseases, we introduced our pilot practices given to the patients and the possibility of Oriental therapies as a novel strategy for chronic HBV carriers.

Key Words: HBV, liver disease, hepatocellular carcinoma, Oriental medicine

Introduction

Hepatitis B virus (HBV) is one of the most common intracellular parasites with which 350 million people worldwide are chronic carriers[1)]. Two-thirds of these subjects are prospective to develop chronic liver diseases such as chronic viral hepatitis, liver cirrhosis or hepatocellular carcinoma (HCC)[2)]. Accordingly, to care for a chronic HBV carrier is important to minimize the HBV-related progression of diseases or the spread of the virus. Currently, even though systemic treatment with interferon-α or nucleotide analogues, such as lamivudine, provide a therapeutic effect, they are still not curative therapies because of a low response rate and emergence of resistance against the drugs[3)].

In Korea, liver disease is the 5th most common cause of death[4)], and this is closely connected with a high carrier rate of HBV(5-6%) although an intensive nationwide vaccination program has reduced the occurrence. Especially, HCC is very prevalent and has shown an incidence of 46.5 per 100,000, similarl to other Asian countries[5)].

On the other hand, Oriental medicine has served practical therapies for patients suffering from liver disease for thousands of years. From a decade ago, it has been well known that HBV is a noncytolytic virus, so not the virus itself but any unfavorable response by host immune cells and inflammatory cytokines mainly

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result in chronic liver injury[6]. We hopefully assume that Oriental therapies based on immunologic strategies may provide a therapeutic alternative for caring these illnesses. At the present, we need to be thoroughly familiar with information about HBV epidemiology and the pathologic process of chronic HBV carriers. Therefore, we here aim to study the general considerations of the HBV infection and the high risk of HBV induced life-threatening diseases by using a family case showing all the features of the dangerous invisible creature, HBV.

The case of Kim's family

Kim OO, a thirty-nine-year-old man, was a heavy drinker and received his first diagnosis of chronic B type viral hepatitis when feeling somewhat fatigued in 1986.

He stopped drinking alcohol and received medication, Zepix, for one and a half years. However, during a regular physical examination, his doctor found a single hepatic tumor, having 3cm diameter with high serum AFP (Alpha-fetoprotein) in 1998. The doctor applied TACE (Transarterial Chemoembolization) to him eight times and another two times to different regions by 2002 because of several recurrences. His AFP level had been maintained within the normal range before he was informed as showing new two other cancerous masses followed by treatment of RITA (radiofrequency interstitial tissue ablation) at the end of November in 2004.

He visited our hospital for receiving Oriental therapies to care for his serious liver disease on January of 2005.

We located all of his health histories and picked out the stereotypical traits of a chronic HBV-carrier outcome, including familial considerations in medical managements. The following diagram is a Kim's family tree showing three generations of them(Fig. 1.).

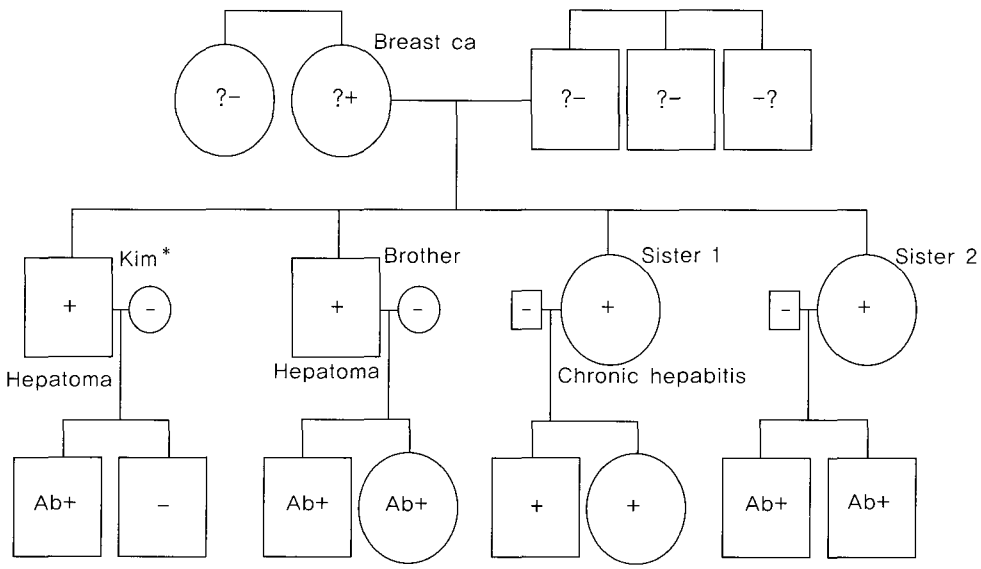

Fig. 1. Kim' s family tree
□ : male, ○: female, +: HBsAg positive, -: HBsAg negative, Ab+: HBsAb positive

Discussion

Perinatal transmission: As shown in the above diagram, Kim's mother passed away with breast cancer when she was 58 years old. But, we can tell that she must have been an active HBV-carrier during her child-bearing years because both her two sons and both her two daughters have carried HBV. When the mother is both HBsAg-positive and HBeAg-positive, the incidence of perinatal infection is around 70-90%[7,8]. This is a mode known as perinatal transmission, which has been the most serious and common HBV infection route in Korea and other Southeast Asian countries[9]. Among three possible routes of transmission of HBV from infected mothers to infants, natal transmission during delivery is the most common compared to two other ways, transplacental transmission of HBV or postnatal transmission during care or through breast milk.

Accordingly, prevention of HBV infection is an intensive medical issue for the infant from the HBV-carrier mother. Combination of HBIG (0.13ml/kg, immediately after delivery or within 12 hours after birth) with recombinant vaccine is currently recommended. This protocol results in protection higher than 90% against perinatal acquisition of HBV10). As showed in the above diagram, Kim's nephew and niece from sister 1 have been chronic HBV carriers because, unfortunately, they were born under non-professional medical care. On the contrary, others from sister 2 have kept the HBs Ab positive due to HBIG and HBV vaccination.

HBV-induced chronic liver disorder: HBV, a noncytophatic virus, induces cellular destruction through immunopathologic mechanisms, which can result in clearance of the virus when it is efficient or in persistent necroinflammatory disease when it is not proficient[11,12]. This HBV-related outcome is determined by many factors such as genotype or titer of virus, time or route of infection, and condition of host protective immunity. Among these, infection of HBV at birth or in the first year of life usually causes one to become a chronic carrier in up to 90% of the cases. Also, this group is mainly subjected to developing chronic liver disease (chronic viral hepatitis, liver cirrhosis or hepatoma) composing two thirds of the chronically infected contrast to one third of healthy carrier[2,13].

Kim and his one brother' have developed HCC, and one sister has been prescribed for treatment of chronic viral hepatitis. Only another sister has been under careful medical observation by normal serum transaminase. Interestingly, nobody had liver cirrhosis in spite of the fact that 80% of HCC occurrences develop from liver cirrhosis14). This can be explained by new reports that showed the risk of HCC occurrence may be relevant with not liver cirrhotic state but period of HBV-infection[15,16].

HBV-related hepatoma (hepatocellular carcinoma): Cancer of the liver ranks almost fourth from the top in the world and third in incidence in Korea or East Asia[17]. The majority (around 85%) of instances of primary liver cancer is HCC-originated from hepatocytes, which results in a very poor prognosis associated with its bad cancerous behaviors of rapid growth or infiltration, coincidence with chronic hepatitis or cirrhosis, and clinically late diagnosis[18]. Even the roles of HBV in carcinogenesis are not clear, and there are accumulated data showing that HBV constitutes a major environmental and etiological factor for HCC[19]. Many experiments have presented the fact that HBV or its components (HBx, PreS2/S, HBV spliced protein) can regulate the proliferation, differentiation and apoptosis of liver-cells[20]. In addition, mixed pathological conditions associated with HBV-induced chronic hepatitis itself and integration of virus into hepatocyte genome can cause cancerous activities of liver cells21).

Kim and his younger brother were diagnosed as having HCC when they were forty-one and forty-six years old, respectively. Both of them hadn't cared seriously for their potentially dangerous HBV-carrier state. They endured heavy stress in their work, managing money in the bank and public office, and were high alcohol consumers. Fortunately, their livers had a single mass each 3.5 and 5.5 cm at the time of initial diagnosis with normal range of liver function because cirrhotic change was not found in clinical. evaluation The doctors decided to cure their tumors not by resection but by other therapies, TACE and/or RITA. They are now keeping themselves in a physically healthy state with no detectable mass through serial MRI imaging studies.

HBV and Alcohol consuming: What caused two brothers to have liver cancer and two sisters not to have it? We cannot find the correct answer for this question. However, the general features of difference in HCC incidence, four times higher in men than women, may be applied to this family. In addition, severe alcohol consumption should be considered as a critical factor which promoted early development of HCC in only brothers among the members of Kim's generation.

Although it is still a controversy whether alcohol itself is a cause of HCC, alcohol is generally regarded as an important carcinogen for several cancers including hepatoma. Chronic alcoholics can develop liver cirrhosis, which increases the risk of HCC incidence over than 100 times[15]. In the case of Kim and his brother, there is no evidence for existence of laboratorial or imaging- based liver cirrhosis. In contrast to HCV, HBV seems not to be involved in liver cirrhosis in alcoholics. However, HBV and alcohol consumption are thought to have a synergic affect on the appearance of hepatic tumors containing HCC. Some studies showed that chronic alcohol consumption modulates HBV antigen expression in an accelerating manner[22], and tumosr frequently contain HBV DNA sequences in heavy alcohol drinkers[23].

Strategies for chronic HBV infection or HCC using oriental therapies: Kim and his brother have regularly visited the cancer center in our hospital to achieve more effective Oriental remedies. They worried about the situation that in the future they may be told by their doctor about a recurrence of HCC. Currently, they are also in the process of regular check-ups after RITA or TACE treatments in a western hospital. Moderate complications such as mild jaundice, serum transaminase elevation, fatigue and weight loss after these therapies were overcome during hospitalization in our hospital for 30 days. We have given them three prescriptions composed of Chunggantang, Hangamdan and Myunyuckdan, which help liver integrity, anti-angiogenesis and tumor immunity, respectively. So far, they have been in a healthy state within limited examinations showing a mass-free state in their livers.

Recently, many researches have been performed for new drugs with anti-viral activities against HBV or anti-cirrhotic effects from Oriental medical resources in laboratorial and clinical fields[24-26]. We still need to gain insight more intensively into the complexity of interaction between HBV and the host reaction, as well as herbal formulas and liver environment. Thus, Oriental practices can be adapted as efficient therapies based on scientifically analyzed knowledge. We hope that Oriental strategies may give us a clue to successfully fight against HBV or HBV-related chronic liver diseases in the future.

Conclusion

We here studied the general medical issues caused by HBV through a family showing chronic HBV-carrier's typical features, such as perinatal transmission. The results demonstrate the importance of medical protection of the newborn from HBV, how HBV

carriers can progress into chronic liver disease including HCC, and how certain people are at critical risk of developing hepatic tumors through HBV infection and alcohol consumption. We briefly introduced our pilot practices given to the patients and the possibility of Oriental therapies as a novel strategy for chronic HBV carriers.

References

1. Lee, W.M., Hepatitis B virus infection. N Engl J Med, 1997;337(24):1733-45.
2. Michel, M.L., et al., Immunotherapy of chronic hepatitis B by anti HBV vaccine: from present to future. Vaccine, 2001;19(17-19):2395-9.
3. Levy, P., et al., Clinical course of spontaneous reactivation of hepatitis B virus infection in patients with chronic hepatitis B. Hepatology, 1990;12(3 Pt 1):570-4.
4. KNSO. Koean motality and causes of death in 2003. 2004.
5. Park, J.W., [Hepatocellular carcinoma in Korea: introduction and overview]. Korean J Gastroenterol, 2005;45(4):217-26.
6. Perrillo, R.P., Acute flares in chronic hepatitis B: the natural and unnatural history of an immunologically mediated liver disease. Gastroenterology, 2001;120(4):1009-22.
7. Stevens, C.E., et al., HBeAg and anti-HBe detection by radioimmunoassay: correlation with vertical transmission of hepatitis B virus in Taiwan. J Med Virol, 1979;3(3):237-41.
8. Xu, Z.Y., et al., Prevention of perinatal acquisition of hepatitis B virus carriage using vaccine: preliminary report of a randomized, double-blind placebo-controlled and comparative trial. Pediatrics, 1985;76(5):713-8.
9. Hou, J., Z. Liu, and F. Gu, Epidemiology and Prevention of Hepatitis B Virus Infection. Int J Med Sci, 2005;2(1):50-57.
10. Lavanchy, D., Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat, 2004;11(2):97-107.
11. Missale, G., et al., Comparative pathogenesis of HBV and HCV. Virus Res, 2002;82(1-2):19-23.
12. Rapicetta, M., C. Ferrari, and M. Levrero, Viral determinants and host immune responses in the pathogenesis of HBV infection. J Med Virol, 2002;67(3):454-7.
13. Hyams, K.C., Risks of chronicity following acute hepatitis B virus infection: a review. Clin Infect Dis, 1995;20(4):992-1000.
14. Okuda, K., Hepatocellular carcinoma: recent progress. Hepatology, 1992;15(5):948-63.
15. Colombo, M., Screening for cancer in viral hepatitis. Clin Liver Dis, 2001;5(1):109-22.
16. Velazquez, R.F., et al., Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. Hepatology, 2003;37(3):520-7.
17. Bosch, F.X., et al., Primary liver cancer: worldwide incidence and trends. Gastroenterology, 2004;127(5 Suppl 1):S5-S16.
18. Cheon JH, P.J., Park KW, et al., The Clinical Report of 1,078 Cases of Hepatocelluar Carcinomas: National Cancer Center Experience. Koea J Hepatol, 2004;10:288-297.
19. Brechot, C., et al., Molecular bases for the development of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC). Semin Cancer Biol, 2000;10(3):211-31.
20. Terradillos, O., et al., p53-independent apoptotic effects of the hepatitis B virus HBx protein in vivo and in vitro. Oncogene, 1998;17(16):2115-23.

21. Michalopoulos, G.K. and M.C. DeFrances, Liver regeneration. Science, 1997;276(5309):60-6.
22. Ganne-Carrie, N., et al., Effects of ethanol on hepatitis B virus Pre-S/S gene expression in the human hepatocellular carcinoma derived HEP G2 hepatitis B DNA positive cell line. J Hepatol, 1995;23(2):153-9.
23. Yotsuyanagi, H., et al., Role of hepatitis B virus in hepatocarcinogenesis in alcoholics. Alcohol Clin Exp Res, 2004;28(8 Suppl Proceedings): 181S-185S.
24. Cho JH, L.Y., Seo SH, Yoo HS, Lee YW, Choi WJ, Son CG, Cho CK, A Clinical Report about 57 Patients with Chronic Liver Disease. J. Korean Oriental Medicine, 2000;21(4):111-121.
25. Son CG, Cho CK. A Study on the Immune Modulation and Hepatoprotection og Gamichunggantang. J. Korean Oriental Medicine, 2003;23(2):28-38.
26. Chang, J.S., et al., Ethanol extract of Polygonum cuspidatum inhibits hepatitis B virus in a stable HBV-producing cell line. Antiviral Res, 2005; 66(1):29-34.