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CASE REPORT

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Spontaneous HBsAg seroconversion after severe flare of chronic hepatitis B infection

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ABSTRACT

The results of the acute exacerbations of hepatitis B virus are varied from silent to severe acute hepatitis. HBsAg seroconversion induced by either antiviral drugs or occurred spontaneously, as a targeted end point of HBV infection management is infreaquent. The affect of the severe hepatitic flare on HBsAg seroconversion was reported before, however the predictive markers of HBsAg seroconversion are not clear yet. The reasons of the spontaneously HBV re-activations, or its usual results are not known well. We, herein reported a case, with the high serum HBV DNA titer during an acute spontaneously induced severe exacerbation of HBV infection which spontaneously resulted in total HBV recovery.

Key words. Spontaneous HBsAg seroconversion, Chronic hepatitis B infection. Spontaneous HBV recovery.

INTRODUCTION

Spontaneous reactivations of hepatitis B virus (HBV) were determined in different state of chronic HBV infections, varied from prior resolved HBV infection to chirrhotic state as a rate of 27% for HBeAg (+),10% for HBeAg (-).[1] Chemotherapy induced HBV reactivation rates were 25-85% in patients with HBsAg (+), and 4-29% in patients with HBsAg (-).[2] And also, it is known that most of the HBV reactivations triggered by immunosuppressive drugs.[3] The rate of the hepatitic flare of lamivudin withdrawal was about 17%,[4] and of after emergence of YMDD mutations was 40.6%.[1]

The reactivations of HBV can lead to either HBV reactivations without clinical hepatitis or severe acute hepatitis. Most of the spontaneously flares of HBV are subclinic, and resolve silently, whereas a half of the HBV reactivations in patients with HBsAg positive taking monoclonal antibody are died of hepatitis flares.[3,5]

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HBsAg seroconversion, as a sign of resolved HBV infection is the targeted end point of chronic HBV infection treatment. However, both of antiviral drugs induced and spontaneously occurred HBsAg seroconversion were infrequent (the rates of the seroconversion of HBsAg in HBeAg positive group were 1-2%/year, 3-7.8%/year, and 0-2%/year in the groups of spontaneously occurred, interferon induced, and lamivudine, adefovir or entecavir induced, respectively).[6]

In our knowledge, this is a seldom well determined case that HBV-DNA clearance and HBsAg seroconversion were achieved after a spontaneously occurred severe hepatitic flare of chronic HBV infection.

CASE REPORT

A 38-year-old man was admitted to the hospital for weakness, jaundice and pruritis at the beginning of March 2009. Clinical examinations on admission were showed mild confusion and jaundice on skin, but not sign of ascites, peripheral oedema, abdominal tenderness, or fever. When he was admitted to hospital, laboratory examinations was detected as fallows; Aspartate aminotransferase (AST) 2530 (U/L) (0-40), alanine aminotransferase (ALT) 3620 (U/L) (0-41), alkalen phosphotase (ALP) 400 (U/L) (0-270), gammaglutamyl transpherase (GGT) 230 (U/L) (0-55), lactate dehydrogenase 1660 (U/L) (207-414),

total protein 6.7 g/l (6.4-8.3), albumin 3.9 g/dL (3.8-5.1), and total bilirubin (T Bil) 11.8 mg/dL (0-1), direct bilirubin (D Bil) 9.7 mg/dL (0-0.30), creatinin 0.8 mg/dL (0.9-1.3), haemoglobin 14.9 g/dl, leucocytes 4.1x 10^3/mL, platelet 108x10^3/mL, prothrombin time 16.10 (10.5-14.5) sec, INR 1.23 (0.8-1.2) . Serology for HAV, HCV, HDV, HIV, and HbcIgM gave negative results, whereas HBsAg, HBcIgG and HBeAg were positive (performed by ALISEI SEAC RADIM - automated equipment for immunoenzymatic assays, Pomezia, Italy), and the serum HBV-DNA titer was 4.130.000.000 IU/mL (performed by real time PCR, Qiagen). Hepatobiliary ultrasound did not reveal any pathological findings, besides any sign of chronic HBV infection. In his history, he has not any surgery, or any medication using. He refused taking any herbal drugs, or alcohol abuse. We were unable to do liver biopsy due to he had not accepted.

Family search results on HBV serology showed that his 7 year old child got HBsAg and anti-HBc Ig G positivity within normal range of ALT level, and the titer of HBV DNA was < 2000 IU/L, whereas his wife had negative for all HBV markers. There were no history of the presence of HBsAg in his parents, parenteral drug abuse, and risky sexually habits.

He was hospitalized and monitorized closely. Because of the rapid resolved of confusion that taking several days, followed by prothrombin time normalization in 6 days thereafter any antiviral treatment was not started. In coming days, the serum liver enzymes, HBV DNA titers reduced dramatically, therefore we had decided to follow the patient without any antiviral treatment. HBeAg seroconversion was achieved at the end of the first month follow up. Laboratory findings were summarized in Table 1.

DISCUSSION

HBV reactivations may eventually develop either spontaneously or triggered by cytotoxic chemotherapy. In the latter group, the death of fulminant hepatitis was happened in the half of the patients, however in the former group, silently occurred and resolved hepatitis were common. Moreover, among survived patients, the total recovery of HBV infection was reported to be not unusual, whereas chronic HBV infection is a frequently result of silent HBV reactivation.[2]

The hepatitic flare period is a difficult time to differentiate of the HBV infection state. The cases of past HBsAg negativity with ALT peak can be diagnosed as an acute hepatic exacerbation of varied etiology. Acute hepatitis B infection can be characterized with HBsAg and/or IgM antibody against HBV core Ag positivity with ALT peak and low level of HBV DNA level. With the absence of anti-HBc IgM, and the low serum titer of HBV DNA, the other etiological reasons (acute HAV, HCV, HDV infections, or Wilson disease, and hemachromatosis) should also be investigated. Moreover, IgM anti-HBc test should not decided to be a diagnostic test due to the positivity in both state of acute hepatitis and acute exacerbations of chronic hepatitis B.[7] With the diagnosis of HBsAg positivity in our patient, a family search was performed. Both of HBsAg, anti-HBs, and anti-HBc IgG were negative in his wife, but his 7 year old child was diagnosed in healthy HBV carrier state. In the light of the HBV positivity in his family, and the high titer of the serum HBV DNA level in the period of the ALT peak, and the presence of anti HBcIgG, we suggested that our patient took the diagnosis of acute exacerbation of chronic HBV infection rather than an acute HBV infection.

The HBV reactivation was divided in to three phases which was started with increasing of serum

Table 1. The follow-up the laboratory results of the patient.

Date	12.03	17.03	25.03	27.03	13.04	18.05	02.09
ALT (U/L)	3620	1745	312	175	36	20	18
AST (U/L)	2530	714	117	67	14	18	18
T/D.Bil (mg/dL)	11.8/9.7	16.6/11.6	3.6	2.8/1.6	2.5/0.9	1.4/0.4	1.2/0.4
INR/PT (sec.)	1.23/15.6	1.20/15.3	1.08/12.9	1.0/12.1	0.94/12.2	1.0/11.9	1.1/12.0
HBV DNA (IU/mL)	4.1x 10^{10}		4.2 x 10^5		4 x 10^4	134	0
HBsAg	+				+	-	-
HBeAg	+				-	-	-
Anti-HBe	-				+	+	+
Anti-HBs	-				-	-	+

10^{10}: 10,000,000,000. 10^5: 100,000. 10^4: 10,000.

HBV DNA titer, followed by elevation of serum ALT level, with/without symptoms of hepatitis or jaundice.[3] The end of HBV reactivation was described with recovery of HBV, decreasing of the serum HBV DNA and ALT levels to the baseline values, and in a small amount of cases with total recovery of HBsAg. Knöll et al reported four HBsAg negative patients with HBV reactivations during cytotoxic therapy.[8] Hepatitis was pointed in only one of four, and also HBsAg clerence was happened just in this unique patient, whereas the remains were persisted with HBsAg positivity. The high amount of death after hepatitis reactivation due to chemotheraupotic agents was reported before[2] in HBsAg negative patients (%50 of the receiving monoclonal agents, and about %4 of the classical anticancer drugs). But the more challenging point was the percentages of resolved of HBsAg in surviving patients among the exacerbation of hepatitis occurred (%60 of patients in receiving monoclonal antibody therapy, and 67.8% of taking classical anticancer therapy).[2]

Clerences of HBsAg and moreover presence of anti-HBs were achieved in two HBsAg positive patients with taking immunupressive drugs.[9] The intrestingly point was both of them had severe hepatic exacerbations. HBeAg seroconversion was notted in %75 of patients whom a peak of ALT level determined after an emergence of the YMDD mutant, whereas no one was realized in HBsAg seroconversion in the group of patients without a hepatitis flare inspite of the emergence of the YMDD mutant.[1] Massetto B et al. described a young patient with active chronic hepatitis B who succeded in HBsAg and HBV DNA negative, and anti-HBs positive state after three hepatitic flares of different origin.[10] And also a case whom seroconversion of HBeAg was achieved after the third hepatic flare in the end of 11 years of chronic HBV infection was notted by Villeneu et al.[11] However these recurrent flares resulted in not only HBeAg seroconversion but also in chirrosis. Our case supported the association of the high ALT peak and the total HBsAg recovery occurred in surviving patients. But, our case is unique because of its spontaneously occurred severe hepatitis flares resulted in totally recovery of HBV infection without any anti-viral therapy as not reported before.

The presence of the HBsAg positivity in the past history of the patient will change the pre-diagnoses of ALT peaks. Thereafter, the reasons of the acute exacerbations in patients with chronic HBV infection should be investigated (eg. acute HAV, HCV, HDV infections, or Wilson disease, and hemachromatosis or acute exacerbation of the HBV infection). The high level of the serum HBV DNA in such patients with acute ALT flare in chronic hepatitis B can be happened in patients undergoing an antiviral therapy with the resistant to the agent or with a pre-core/core-promoter mutation of the HBV genome. In contrast, low serum HBV DNA was seen in patients of hepatitis reactivation taking interferon therapy due to the chronic HBV infection.[3] Among these patients taking interferon, ALT peaks were happened because of the immune-activation and mostly resulted in HBeAg seroconversion.[12] Although, such an HBeAg seroconversion can be seen in therapy naïve patients, a high level of HBV DNA during the period of ALT flare have not been published in recent cases. Our patient was the first case reported in the literature, showed the high level of serum HBV DNA during the severe hepatitic flare, and followed by total HBV recovery.

A hepatitic flare with both high viremia, and ALT levels resulted in spontaneously recovery of HBV infection has not been diagnosed before. Because of the knowledge about each acute flares in patients diagnosed in CHB infection is an increasing risk factor of HCC/cirrhosis, it is hard to recommend to wait without any antiviral therapy in patients with acute hepatic exacerbation in the light of our case. However, the courage signs get us waiting for a while without any targeted antiviral treatment were the rapid resolved of confusion, the normalization of prothrombin time in a several days, the declining of the serum liver enzymes, and the bilirubin levels, the dramatic reduction of the serum HBV DNA titer, and perhaps the most important sign was HBeAg seroconversion.

CONCLUSION

In spite of the well knowledge about the HBV infection, the ongoing process of chronic HBV infection has been still full of question marks. Our observation give rise to thought important role of severe flares in the progress of chronic hepatitis B and suggest that firm observations without any antiviral treatment in such kind of patients can be a good quality steps forward. We hope a give a new data to define this complex infection that pursued with or without treatment.

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