

A Case of *de novo* Hepatitis B Complicated due to Lack of Comprehensive Interventional Approach

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ABSTRACT

Here, we report a case of *de novo type B hepatitis* in a patient with hepatitis B surface antigen (HBsAg) negative but positive for low titer of anti-HBc antibody (anti-HBc titer; dilution 200; negative). As the disease was anticipated in advance, the patient received nucleos(t)ide analogs, but *de novo type B hepatitis* was developed, because of discontinuation of antiviral drugs. A 59-year-old male with a history of T cell rich diffuse large B-cell lymphoma (DLBCL) and was treated with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). The patient responded to anticancer therapy and his complete responder status was confirmed by PET-CT on October 4, 2010. As the patient was expressing low levels of anti-HBc (anti-HBc titer; dilution 200-negative), he was given lamivudine to block HBV reactivation, but the drug was continued after 1 year due to apparent improvement. Stoppage of antiviral drug resulted in detectable HBV DNA and evidences of liver damages and he was referred to our department for specialized consultation about liver-related complications. He was given entecavir at a dose of 1 gm/day from May 2012. However, the parameters of liver function test showed anomaly indicating progressive liver damages. Subsequently, he was given steroid pulse therapy with 1,000 mg of prednisolone and tapered successively. The levels of HBV DNA decreased and parameters of liver function test were improved. A biopsy specimen taken in July 2012 showed the findings compatible with resolved acute hepatitis. To prevent *de novo type B hepatitis*, critical observation and timely management of the patients are necessary. The administration with nucleoside analogs at least 1 year after R-CHOP therapy is recommended in guideline of Japanese Society of Hepatology. However, we should reconsider the term of administration with nucleoside analogs after R-CHOP therapy.

Keywords: HBV, *de novo* hepatitis, Rituximab, HBV reactivation, Nucleoside analogs, Interdisciplinary approach.

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INTRODUCTION

It is estimated that 2 billion people worldwide have been infected with Hepatitis B Virus (HBV).¹ In Japan, it is reported that 23.2% of blood donors are positive for HBc antibody and/or HBs antibody.² Reactivation of HBV is a well-recognized complication in hepatitis B surface antigen (HBsAg) positive patients who are undergoing immuno-

suppressive chemotherapy including anti-CD20 antibody for malignancies. The clinical manifestation ranges from subclinical hepatitis to severe and potentially fatal fulminant hepatic failure.³⁻⁶ In this decade, HBV reactivation has been observed in patients with resolved infection who have undergone intensive immunosuppressive chemotherapy, such as rituximab plus steroid-containing chemotherapy. This usually happens in patients expressing HBsAg and HBV DNA in peripheral blood. Here, we report a case of *de novo type B hepatitis* in a patient with HBsAg negative but positive for low titer of anti-HBc antibody (anti-HBc titer; dilution 200; negative). The patient developed *de novo type B hepatitis* even after the prophylactic administration of nucleos(t)ide analogs for more than 1 year and 4 months after stopping of R-CHOP therapy. The present case report would contribute about importance of comprehensive approach to prevent *de novo* hepatitis. Also, some insights would be provided about duration of antiviral therapy in these circumstances.

CASE REPORT

A 59-year-old male with a history of T cell rich diffuse large B-cell lymphoma (DLBCL) is presented. The patient revealed a history of general malaise, low-grade fever, skin itching and weight loss from February 2010. Lymph node enlargement was shown in the right cervix, and biopsy specimen of right cervical region showed T-cell rich DLBCL (stage III). The patient was administered an anticancer therapy with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) for eight courses from March 2010 to August 2010. The patient responded to anticancer therapy and his complete responder status was confirmed by PET-CT on October 4, 2010. As the patient was expressing low levels of anti-HBc (anti-HBc titer; dilution 200 negative), he was given lamivudine to block HBV reactivation from May 2010. Administration of lamivudine was stopped in October 26, 2011 after the prophylactic administration of lamivudine for more than 1 year and 4 months after stopping of R-CHOP therapy. Subsequently, HBV DNA became detectable in the sera from February 29, 2012. The amount of HBV DNA was increased to 8.4 log copies/ml on May 30, 2012. Just after

consulting with hepatologist, he was administered entecavir at a dose of 1 gm/day. However, the parameters of liver function test showed downhill trends and referred to us. Physical findings on admission: Height: 174 cm; weight: 58.3 kg, BMI: 19.3 he was not icteric; lung; no abnormality detected. The abdomen was flat, smooth, soft and non-tender. The liver and spleen was not palpable. There was no flapping tremor. Laboratory data was shown in Table 1. The patient showed general malaise and loss of appetite. Hepatomegaly and yellowing of the eyes were not shown. The parameters of liver function test in June 25, 2012, was AST, 322 U/l; ALT, 390 U/l; LDH, 373 U/l; ALP, 283 U/l, γ -GTP, 38 U/l, total bilirubin; 0.8 gm/dl; direct bilirubin, 0.1 mg/dl and prothrombin time, 76.8 %. The level of HBV DNA was 6.1 log copies/ml (HBV genotype B). The patient was expressing HBsAg (36,360 IU/ml) and HBeAg in the sera. HBsAg became for positive on June 30, 2012. His HBV was wild-type. Positivity of HBV-DNA was observed after 1 year and 7 months, HBs antigen became positive after 1 year and 10 months, abnormality of AST/ALT was after 1 year and 11 months after cease of R-CHOP therapy. Clinical course of present case was shown in Figure 1. In spite of antiviral therapy, progressive liver damages continued as evident from values of ALT and AST. In June 2012, steroid pulse therapy was started with 1,000 mg of prednisolone and tapered successively. The levels of HBV DNA, AST and ALT fell due to integrated therapy. The levels of HBV-DNA decreased and subjective symptoms disappeared, and the parameters of liver function test became normalized. A liver biopsy was done in July 30, 2012, the liver specimen showed in Figures 2A and B. Liver-cell damage, cell death and inflammatory cells infiltration were seen predominantly in central area, but there was no bridging necrosis. There was few abnormal finding in periportal area. These findings indicate resolved acute hepatitis. The patient discharged from hospital on 15th August 2012.

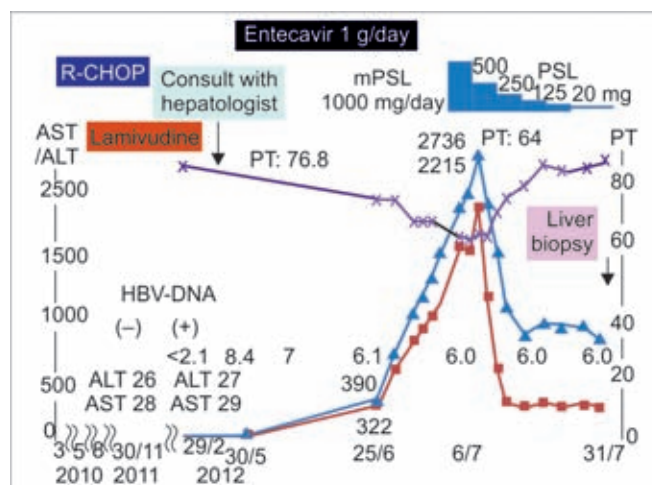


Fig. 1: Clinical course of present case

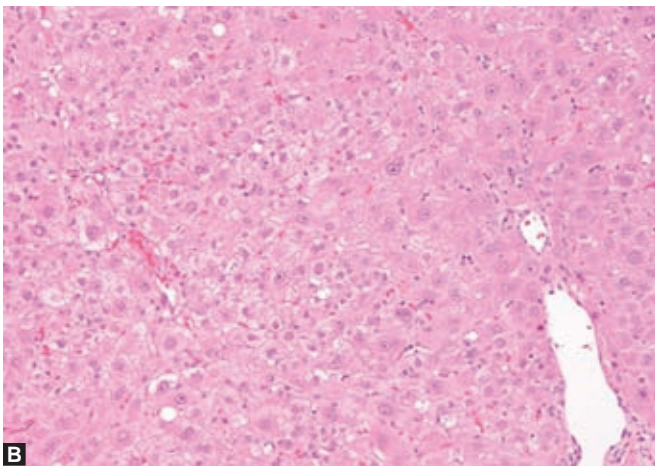
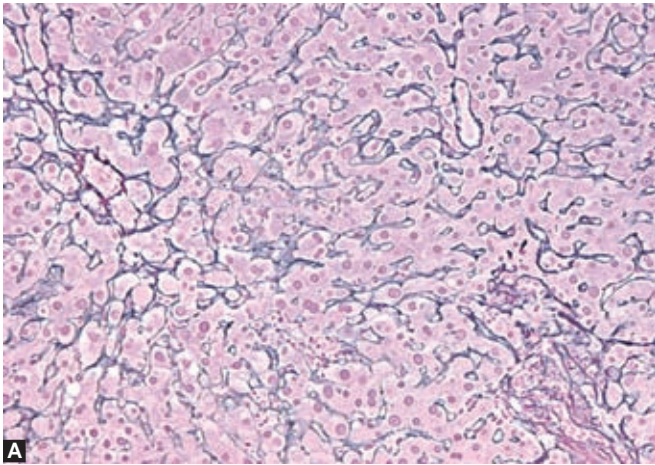
DISCUSSION

With the advent of immunosuppressive agents, the uses of these drugs have been related to some incidences of death because of reactivation of HBV and acute hepatic failure. Previous reports have clarified that this combination therapy can lead to acute hepatic failure and even death. For this reason, clinicians need to be aware of HBV reactivation not only in patients with current infection but also in those with resolved infection who are undergoing intensive immunosuppressive therapy.

The *de novo* hepatitis B could occur after the reactivation of HBV, when HBs antigen and HBV-DNA negative, but antipositive patients are treated with immunosuppressive agents. It becomes evident that the prophylactic administration of nucleos(t)ide analogs is very effective against the reactivation of HBV and occurrence of *de novo* hepatitis.⁷⁻⁹ To prevent *de novo* type B hepatitis, critical observation and timely management of the patients are necessary. Also, multidisciplinary approach is necessary. A guideline of Japanese Society of Hepatology to manage *de novo* hepatitis and reactivation of HBV during and after

Table 1: Laboratory findings on administration day (June 25th, 2012)

WBC	4200/ μ l	AST	322 U/l	HBV-DNA	6.1 log copies/ml
RBC	3.82×10^6 / μ l	ALT	390 U/l	HBs Ag	(+)
HGB	12.9 g/dl	LDH	373 U/l	HBe Ag	(+) 245
HCT	37.7%	ALP	283 U/l	HBe Ab	(-)
PLT	15.3×10^4 / μ l	γ -GTP	38 U/l	HBc Ab	X1 (\pm) 53%
PT	76.8%	Na	142 mEq/l		X200 (-)
		K	3.6 mEq/l	HBV genotype	B
TP	6.3 g/dl	Cl	103 mEq/l	HBV YMDD	
Alb	4.0 g/dl	BUN	14 mg/dl	Lamivudine	Mutant (-)
TB	0.8 g/dl	Cre	0.78 mg/dl	HBV precore	Wild type
DB	0.1 g/dl	UA	6.7 mg/dl	Core promoter	Wild type
CHE	344 U/l	CRP	0.33 mg/dl		
		Glu	102 mg/dl		



Figs 2A and B: Biopsy specimen on the 63rd clinical day. Liver-cell damage, cell death and inflammatory cells infiltration were seen predominantly in central area, but there was no bridging necrosis. These findings indicate resolved acute hepatitis

immunosuppressive drugs, was reported and became popular to use it in Japan.^{10,11} Japanese guideline that prevents reactivation *de novo* hepatitis of HBV is widely used not only by hepatologist but also by hematologist and rheumatologist. Similar guidelines were reported from Europe and USA.¹²⁻¹⁴ Japanese guideline described that prophylactic administration should be continued for at least 1 year. In present case, the patient was treated with lamivudine for 1 year and 4 months after the case of R-CHOP therapy. But after stopping administration of lamivudine, HBV-DNA became positive within 4 months, and HBsAg became positive in 7 months, then acute hepatitis occurred. It means that, in this case, the occurrence of acute hepatitis was not prevented with the administration of lamivudine for 1 year and 4 months after stopping R-CHOP therapy. Though the Japanese guideline described that nucleos(t)ide analogs should be administered 'at least 1 year', the present case showed that nucleoside analogs for more than 1 year. We think that this case is valuable to know when we should stop the prophylactic administration of nucleos(t)ide analogs and how we should observe the

patient after the stop of administration. This has become an emerging problem in every field of clinical medicine.¹⁵

CONCLUSION

Prolonged use of antiviral drugs seems to be necessary in immune suppressed patients with previous history of HBV infection. Also, a comprehensive approach is needed to tackle these patients. Periodic updating of therapeutic recommendations is also a necessity.

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