

**Case Report**

# Hepatitis B Virus (HBV) Reactivation Following Immunosuppression in HBsAg(+) Carriers

Richard M. Wu, MD, MPH;<sup>1</sup> Hie-Won L. Hann, MD, FAASLD<sup>1,2\*</sup>

<sup>1</sup> Division of Gastroenterology and Hepatology, Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA

<sup>2</sup> Liver Disease Prevention Center Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA

**HBV reactivation occurs in HBsAg(+) carriers who have undergone immunosuppressive therapy such as Rituximab treatment, chemotherapy or corticosteroids for malignancy or other diseases that require immunosuppression. Immunosuppression induces rapid HBV replication and increasingly infects hepatocytes. Reactivation usually occurs after discontinuation or withdrawal of immunosuppression when the immune system is reconstituted and attacks infected hepatocytes. This leads to acute hepatitis characterized by increased levels of alanineaminotransferase (ALT) and serum HBV DNA. Rarely it can be life threatening.**

[*NA J Med Sci.* 2015;8(4):196-198. DOI: 10.7156/najms.2015.0804196]

**Key Words:** HBV reactivation, immunosuppression, chemotherapy, Rituximab, HBsAg(+) carriers

## INTRODUCTION

With the influx of immigrants from HBV endemic regions, there has been an increase of chronic HBV infection in the United States over the last 20 years. Of the 2 million chronic HBV infections currently in the United States, 1.6 million of these individuals are foreign born. However, only 600,000 patients are aware of their HBV infection. Without knowledge of their HBV status or having been asymptomatic HBsAg(+) carriers, these individuals receive immunosuppressive therapy and may develop acute hepatitis that can be life threatening. There is a great need for educating the immigrant community regarding the necessity of HBV screening and also for physicians, especially oncologists, rheumatologists and primary care physicians.

Here we report three cases of HBV reactivation in previous asymptomatic HBsAg(+) carriers.

## CASE REPORT

### Case #1: HBsAg(+) Carrier with Lymphoma

A 69 year old Asian male asymptomatic HBsAg(+) carrier developed follicular lymphoma in the ileocecal region. He underwent Rituximab therapy with cyclophosphamide, etoposide, procarbazine, and prednisone. Two months after completion of therapy, he developed jaundice, disorientation with sluggish speech, abdominal pain, nausea and vomiting. Lamivudine 100 mg/day was started 10 days before. Adefovir 10 mg/day was added 5 days prior to his visit to our 4.4 mg/dL, platelets  $133 \times 10^3/\mu\text{L}$ , HBV DNA > 17 million IU/ml, and HBeAg(+), Anti-HAV IgM(-), Anti-HCV(-). Physical exam was notable for mild asterixis and jaundice without ascites. An abdominal MRI showed a normal appearing liver. His Adefovir regimen was switched to tenofovir and lamivudine was continued concurrently. Nine months later, the patient displayed HBeAg loss with normal ALT and undetectable HBV DNA. On return of care to his local family physician, the patient discussed the option of stopping HBV treatment and eventually did stop for several days with a subsequent HBV DNA serology rebounding to  $1.9 \times 10^3$  IU/ml. Monotherapy with lamivudine 150mg/day was restarted for financial reasons. Since adhering to treatment, he has remained well with an undetectable HBV DNA, normal ALT and platelets. He is currently HBeAg(-)/anti-HBe(-) and HBsAg(+).

**Case #2: Breast Cancer in an Asymptomatic HBsAg(+) Carrier**

A 48 year-old Asian woman, who was a HBsAg(+) carrier for 20 years, developed breast cancer. Following a right mastectomy she underwent 6 cycles of chemotherapy. On the day of last chemotherapy, she noticed dark yellow urine. She received radiotherapy for the next 3 weeks while being followed by her gastroenterologist. Her laboratory studies showed a bilirubin of 15.4 mg/dL, ALT 1253 IU/L, AST 758 IU/L, Anti-HAV IgM(-) /anti-HAV total(+), HBsAg(+), Anti-HBc IgM(-), Anti-HBc total(+), HBeAg(-), anti-HBe(+), HBV DNA  $7.7 \times 10^4$  IU/ml and alpha fetoprotein (AFP) 155 ng/ml. Abdominal ultrasound was normal. On her first visit to our institution, physical exam was pertinent for alopecia and jaundice, without hepatosplenomegaly or ascites. She was started on Telbivudine 600mg daily (available from an access program). Following discussion with her oncologist, 6 weeks of radiotherapy was resumed. Six weeks later, her lab

Received: 09/12/2015; Revised: 10/03/2015; Accepted: 10/13/2015

\*Corresponding Author: 1025 Walnut Street, College Bldg 906, Philadelphia, PA 19107. Tel: 215-955-5806. Fax: 215-955-0770. (Email: hie-won.hann@jefferson.edu)

results were ALT 21 IU/L, bilirubin 0.6 mg/dL, HBV DNA < 20 IU/ml, AFP 4 ng/ml. Six months later, she was initiated on tamoxifen 20 mg daily by her oncologist while concurrently taking Tenofovir 300 mg daily. She continues to have normal liver function and undetectable HBV DNA on followup.

### Case #3: ALT Flare with Steroid Therapy in a HBV Carrier

A 65 year-old Asian woman developed severe rheumatoid arthritis. Her rheumatologist initiated therapy with methotrexate (MTX) and prednisone 10 mg daily for 6 months. During therapy, the patient felt unwell and took an unspecified amount of Ginseng over the next 5 months. Because of nausea, labs were obtained and showed

HBsAg(+), ALT 886 IU/L and HBV DNA  $9 \times 10^6$  IU/ml. MTX was discontinued, and prednisone was decreased to 7 mg/day by her rheumatologist. At her visit to our institution, nausea remained her main symptom. She was icteric and her right knee appeared consistent with active synovitis. Her labs showed an ALT of 1,131 IU/L, AST 916 IU/L, total bilirubin 3.5 mg/dL. She was started on Lamivudine 150 mg daily. In a month, her ALT decreased to 202 IU/L and subsequently to 40 IU/L with total bilirubin 0.3 mg/dL. Because of severe arthritis, she was maintained on prednisone 5 mg daily. HBV DNA became < 20 IU/ml 4 months later. Due to suboptimally controlled arthritis, she received MTX at half the original dose along with prednisone 7 mg daily while continuing Lamivudine 150 mg daily. Her ALT has remained normal with HBV DNA < 20 IU/ml during this period.

**Table 1.** HBsAg+ Antiviral Prophylactic Guidelines for Immunosuppression (IS) by Society.

Society	Population (HBV DNA)	Prophylaxis	Prophylaxis type
AASLD, 15	Baseline HBV DNA <2,000 IU/ml	Antiviral prophylaxis recommended	LAM or Telbivudine (if IS<12 months) or ETV > adefovir (if IS>12 months)
	Baseline HBV DNA >2,000 IU/ml	Antiviral prophylaxis recommended	LAM or Telbivudine (if IS<12 months) or ETV > adefovir (if IS>12 months)
EASL, 16	Baseline HBV DNA <2,000 IU/ml	Antiviral prophylaxis recommended	LAM
	Baseline HBV DNA >2,000 IU/ml	Antiviral prophylaxis recommended	Antiviral w/ high barrier to resistance
AGA, 17	High risk (>10% HBVr incidence)	Antiviral prophylaxis recommended	Antiviral w/ high barrier to resistance
	Moderate risk (1-10% HBVr incidence)	Antiviral prophylaxis suggested or monitor	Antiviral w/ high barrier to resistance
	Low risk (<1% HBVr incidence)	None	N/A
APASL, 18	All HBsAg+ patients	Antiviral prophylaxis recommended	ETV/TDF >LAM

## DISCUSSION

All 3 patients were asymptomatic HBsAg(+) carriers and underwent different modalities of immunosuppression. Each case of HBV reactivation was associated with a different temporal relationship to immunosuppression and the degree of immunosuppression modulation differed in each scenario. In general, the completion of immunosuppressive medication is associated with the recovery of the host immune responsiveness and is followed by acute hepatitis.<sup>2</sup> The spectrum of chemotherapy induced HBV flares ranges from HBV reactivation (> 10 fold rise in serum HBV DNA with serum ALT elevation from baseline), HBV-related hepatitis (serum ALT > 2 times baseline and 10 fold increase in serum HBV DNA level), and HBV related liver failure (elevation of ALT with evidence of coagulopathy).

**Case 1** was an asymptomatic HBsAg(+) carrier who developed reactivation of HBV following rituximab based chemotherapy combined with high dose steroids. Rituximab is a chimeric monoclonal antibody that targets the CD 20 molecule on B cell surfaces and is highly effective for CD20-positive lymphoma. HBV reactivation due to rituximab has been widely reported. A meta-analysis found a temporal pattern of delay clinical Hepatitis B reactivation 3 months after the last administration of Rituximab; however, up to 30% of patient's presentation is delayed up to half a year after the last administration.<sup>7</sup> In general, the completion of immunosuppressive medication is associated with the

recovery of the host immune responsiveness and can be followed by acute hepatitis.

**Case 2** illustrates an asymptomatic HBsAg(+) carrier who underwent non-rituximab-based chemotherapy and radiation therapy for breast cancer treatment and subsequently developed acute hepatitis. Radiation induced liver disease is a complication of radiation therapy. In HBV carriers, there is a lower threshold dose of radiation to cause this complication. The mechanism for radiation induced HBV reactivation is not fully known. Several hypotheses exist ranging from radiation directly activating HBV in the infected hepatocytes or radiation increasing a systemic increase in cytokines associated with HBV reactivation.<sup>9-11</sup> The patient's transiently elevated AFP was not from an underlying HCC but from acute viral hepatitis. The mechanism of elevation of AFP in viral hepatitis has not been fully elucidated but possible mechanisms include liver cell retrodifferentiation during hepatic regeneration.

Most studies for HBV activation utilized Lamivudine in the past. Lamivudine has been effective for the prophylaxis of HBV reactivation during chemotherapy. Lamivudine is best suited for patients with low (< 2000 IU/mL, < 10<sup>4</sup> copies/ml) or undetectable HBV DNA level and/or receiving a short (< 6 months) course of immunosuppression. Incidentally, for compliant patients, low resistance has been observed in

patients with baseline HBV DNA ( $< 1.7 \times 10^5$  IU/ml,  $1 \times 10^6$  copies/ml) with the lamivudine dose of 150 mg daily.<sup>21</sup> On the other hand, if the patient is undergoing a prolong course of chemotherapy and has a high viral load, the recommendation is to use nucleos(t)ide analogues with low rate of drug resistance such as Tenofovir or Entecavir.

In all three cases, therapeutic immunosuppression was started without antiviral prophylaxis. **Case 1** illustrates the rapid return of HBV DNA shortly after discontinuation of antiviral therapy. The case highlights the important concept that the course of treatment for reactivated HBsAg(+) patients should be the same as for chronic hepatitis B.

In conclusion, HBV reactivation with immunosuppression is a relatively common and clinically important entity to recognize as it can be life threatening. HBV reactivation can occur in patients who have been exposed to past HBV infection. HBsAg(+) persons have a stronger risk of reactivation than those who have isolated anti-HBc(+) or anti-HBc(+)/anti-HBs(+). Those who have acquired Anti-HBs from vaccination would be negative for anti-HBc and does not carry the risk. However, it would be safe to test for anti-HBc. Education and collaboration between gastroenterologists and hepatologists with the oncology and rheumatology community is needed to screen immigrants from HBV endemic regions before initiating any form of immunosuppressive therapy and ensure adequate adherence to new guidelines of prophylaxis.

#### CONFLICT OF INTEREST

Wu: none.

Hann: serves on Advisory Board for Gilead Sciences and receives clinical grant supports from Gilead and Bristol-Myers Squibb.

#### REFERENCES

1. Kusumoto, S, Tanaka Y, Ueda R, et al. Reactivation of hepatitis B virus following rituximab-plus-steroid combination chemotherapy. *J Gastroenterol.* 2011; 46:9-16.
2. Hoofnagle, JH, Dusheiko GM, Schafer DF, et al. Reactivation of Chronic Hepatitis B Virus Infection by Cancer Chemotherapy. *Ann Intern Med.* 1982; 96:447-449.
3. Mastroianni CM, Lichtner M, Citton R, et al. Current trends in management of hepatitis B virus reactivation in the biologic therapy era. *World J Gastroenterol.* 2011; 17: 3881-3887.
4. Cohen C, Evans AA, London WT, et al. Underestimation of chronic hepatitis B virus infection in the United States of America. *J Viral Hepatol.* 2008;15:12-13.
5. Kim, WR. Epidemiology of hepatitis B in the United States. *Hepatology.* 2009;49 (5 Suppl):S28-34.
6. Cohen C, Holmberg SD, McMahon BJ, et al. Is chronic hepatitis B being undertreated in the United States? *J Viral Hepat.* 2011;18:377-383.
7. Evens AM, Jovanovic BD, Su Y-C, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Ann Oncol.* 2011;22:1170-1180.
8. Chou, CH, Chen P-J, Lee P-H, et al. Radiation-Induced Hepatitis B Virus Reactivation in Liver Mediated by the Bystander Effect from Irradiated Endothelial Cells. *Clin Cancer Res.* 2007; 13: 851-857.
9. Belyakov OV, Mitchell SA, Parikh D, et al. Biological effects in unirradiated human tissue induced by radiation damage up to 1mm away. *Proc Natl Acad Sci USA* 2005;102:1420-1428.
10. Cheng AL, Hsiung CA, Su IJ, et al. Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. *Hepatology* 2003;37:1320-1328.
11. Locarnini S. Molecular virology of hepatitis B virus. *Semin Liver Dis* 2004;24 Suppl 1:3-10.
12. Cheng AL, Hsiung CA, Su IJ, et al. Lymphoma Committee of Taiwan Cooperative Oncology Group. Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. *Hepatology.* 2003;37:1320-1328.
13. Nair PV, Tong MJ, Stevenson D, et al. Effects of short-term, high-dose prednisone treatment of patients with HBsAg-positive chronic active hepatitis. *Liver* 1985;5:8-12.
14. Watanabe K, Takase K, Ohno S, et al. Reactivation of hepatitis B virus in a hepatitis B surface antigen-negative patient with rheumatoid arthritis treated with methotrexate. *Mod Rheumatol.* 2012;22:470-473.
15. Lok ASF, McMahon BJ. Chronic hepatitis B: Update 2009. *Hepatology.* 2009;45:507-539.
16. European Association for the Study of Liver Disease. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol.* 2012;57:167-185.
17. Reddy KR, Beavers KL, Hammond SP, et al. American Gastroenterological Association Institute Guideline on the prevention of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology.* 2015;148:215-219.
18. Liaw Y-F, Kao J-H, Piratvisuth T, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: 1 2012 update. *Hepatol Int.* 2012;6:531-561.
19. Tong MJ, Pan CQ, Hann HW, et al. The management of chronic hepatitis B in Asian Americans. *Dig Dis Sci.* 2011;56:3143-3162.
20. Civan J, Hann HW. Giving rituximab in patients with occult or resolved hepatitis B virus infection: are the current guidelines good enough? *Expert Opin Drug Saf.* 2015;14:1-11.
21. Chae HB, Hann HW. Baseline HBV DNA level is the most important factor associated with virologic breakthrough in chronic hepatitis B treated with lamivudine. *World J Gastroenterol.* 2007;14; 13(30): 4085-4090.