Chronic Hepatitis B Reactivation Subsequent to Chronic Hepatitis C Treatment: A Case Report

Habip Gedik1*, Florida Parcaoglu2

Abstract

Patients, who are coinfected with hepatitis B and C, are at high risk for a progression to severe liver disease (cirrhosis, decompensated liver disease), hepatocellular carcinoma, and unresponsiveness to treatment. In this article, a case who developed a reactivation of chronic hepatitis B subsequent to Chronic Hepatitis C (CHC) treatment is presented. A 42-year-old woman with HBV and HCV was admitted to infectious diseases clinic with a major complaint of fatigue for three months. Laboratory tests revealed an elevated alanine transaminase of 182 IU/L (Normal range: 0-55 IU/L), elevated aspartate transaminase (AST) of 150 IU/L (Normal range: 0-34 IU/L), and unresponsiveness to treatment. In this article, a case with reactivated CHB subsequent to CHC treatment is presented.

Keywords:
HBV/HCV coinfection; Pegylated interferon; Reactivation; Chronic hepatitis B; Chronic hepatitis C

Introduction

Chronic Hepatitis B (CHB) and chronic Hepatitis C (CHC) are still a major public health challenge. Hepatitis B virus (HBV) is mainly transmitted by sexual contact; sharing needles, syringes, or other drug-injection equipments, and blood transfusions with the blood, semen, or other body fluids [1]. Hepatitis C virus (HCV), a blood-borne virus, is mainly transmitted by sharing needles, syringes, or other drug-injection equipments and blood transfusions [2]. Hepatitis B infection is seen as an acute or chronic infection form and usually begins with a general-ill status, while hepatitis C infection is seen usually as an asymptomatic chronic infection leading to severe liver damage over the years [3]. Globally, an estimated 257 million and 71 million people are living with HBV and HCV [4,5].

CHB and CHC infections are the important global health problems. Because of their shared modes of transmission, co-infection with HBV and HCV is frequent. Unfortunately, the exact number of patient infected with both HCV and HBV is poorly defined. Patients who are coinfected have a higher risk of progression to severe liver disease (cirrhosis, decompensated liver disease), increased risk of hepatocellular carcinoma, and unresponsiveness to treatment [6-10].

In this article, a case with reactivated CHB subsequent to CHC treatment is presented.

Case Report

A 42-year-old woman with HBV and HCV was admitted to infectious diseases clinic with a major complaint of fatigue for three months. There was no sense of the patient’s history and family history. There was no smoking, alcohol, and any drug in the history. Her physical examination and vital signs were normal at the admission. The patient had no history of drug hypersensitivity, liver diseases, blood transfusion, or surgery. She refused to use an over-the-counter and traditional Chinese medicine. Laboratory tests revealed an alanine transaminase (ALT) of 182 IU/L (Normal range: 0-55 IU/L), aspartate transaminase (AST) of 150 IU/L (Normal range: 0-34
IU/L), HCV-RNA of 2080195 IU/mL, HCV genotype 1b, Hepatitis B surface antigen (HBs Ag), HBV-DNA of 1184 IU/mL, whereas the results of other tests were within the normal range (Table 1). She was negative for serum markers of Epstein–Barr virus, human immunodeficiency virus, cytomegalovirus, autoimmune hepatitis (liver cytosol type 1, antinuclear antibody, soluble liver antigen, smooth muscle antibody, liver/kidney microsome type 1, and antineutrophil cytoplasmic antibody), and primary biliary cirrhosis (antimitochondrial antibody). Ultrasound examination displayed no obvious changes. Pegylated interferon (Peg-IFN) alpha-2a 180 mcg/week and ribavirin (RBV) tablet 1200 mg/day were initiated in April 2015 for CHC treatment.

At the third and sixth months of CHC treatment, the liver enzymes were slightly elevated and HCV-RNA negative. But the patient was followed up by endocrinology clinic due to anemia and hyperthyroidism related to Peg-IFN+RBV with the complaints of nervousness, anxiety, rapid heartbeat, hand tremor, excessive sweating, weight loss, and sleep problems. The endocrinology clinic has suggested to discontinue the CHC treatment. After three months, CHC treatment was started again with the suggestion of the endocrinology clinic and completed the 48-week treatment. HCV-RNA was negative at the end of treatment. Her hyperthyroidism has recovered, but the anemia continued. Anemia was associated with CHC treatment and did not need a treatment. HCV-RNA remained to be negative in the first year after the treatment of CHC. Patients presented with fatigue once again and elevated liver enzymes to our department after one year of CHC treatment. A liver biopsy was performed according to the health insurance guideline of Turkey in order to receive CHB treatment due to a HBV-DNA of 878215 IU/ml and elevated liver enzymes. The histopathological examination of liver tissue revealed a mildly active histologic activity (6/18) and a mildly active histological activity (1/6) according to ISHAK scoring. Tenofovir tablet 245 mg/day was administered for the CHB treatment. The patient is still followed up without any complaint at the ambulatory clinic of infectious diseases.

Table 1: Laboratory findings of the patient.

|                      | April 2015 | May 2015 | June 2015 | August 2015 | October 2015 | November 2015 | January 2016 | March 2016 | April 2016 | March 2017 | May 2017 |
|----------------------|------------|----------|-----------|-------------|--------------|---------------|--------------|------------|------------|------------|----------|
| Alanine aminotransferase | 182        | 59       | 52        | 49          | 42.7         | 29.7          | 31.2         | 23         | 43.6       | 120.5      |
| (ALT, N: 0-55 IU/L)   |            |          |           |             |              |               |              |            |            |            |          |
| Aspartate aminotransferase | 150        | 64       | 59        | 61          | 53           | 33            | 32           | 30         | 34         | 66         |
| (AST, N: 0-34 IU/L)   |            |          |           |             |              |               |              |            |            |            |          |
| Gamma-glutamyl transpeptidase (GGT, N: 0-55 IU/L) | 34 | 24 | 44 | 17 | | | | | | |
| Alkaline phosphatase (ALP, N: 30-120 IU/L) | 85 | 75 | | 65 | | | | | | |
| Lactate dehydrogenase (LDH, N: 135 – 214 IU/L) | 341 | 267 | 291 | | 320 | | | | | |
| Creatinin (N: 0.5-1.1 mg/dL) | 0.67 | 0.64 | 0.53 | 0.7 | 0.8 | 0.59 | 0.62 | 0.58 | 0.64 |
| Urea (N: 17 – 43 mg/dL) | 27 | 42 | 30 | 31 | 28.3 | 36.4 | 22 | 29.7 | 22 |
| Glucose (N: 74 – 106 mg/dL) | 87 | | | | | | | | | |
| Thyroid-stimulating hormone (TSH, N: 0.36 – 5.36 μIU/mL) | 1.07 | | | | | 0.252 | | 6.34 |
| White Blood Cells (WBC, 10^3 mm3) | 7.97 | 6.55 | 7.43 | 5.58 | 9.36 | 6.23 | 5.6 | 8.29 | 12.07 |
| Red Blood Cells (RBC, 106/mm3) | 4.4 | 3.67 | 3.03 | 2.87 | 3.35 | 2.95 | 3.3 | 3.38 | 4.29 |
| Platelet (PLT, 10^3 mm3) | 315 | 275 | 338 | 315 | 261 | 323 | 255 | 315.9 | 398.3 |
| Hematocrit (Htc, %) | 37.2 | 32.9 | 29.2 | 29.5 | 34.1 | 30 | 33.3 | 35.36 | 34.86 |

This article is available from: http://hepatitis.imedpub.com/archive.php
### Discussion

HBV/HCV-coinfected patients are very heterogeneous through the world. Most patients from Asia acquire HBV infection at birth and HCV infection as a superinfection, while patients from Europe and the USA acquire HBV on HCV as either coinfection or a superinfection. The diverse mechanisms have been assumed in the development of HBV- or HCV-related Hepatocellular Carcinoma (HCC) that both viruses could play an active role at the different stages of the carcinogenic process, when they are present together in the hepatocytes. In the most advocated evidence, HBV is capable of introducing the neoplastic process, while HCV could treat as a promoter, and they may be synergistic in the development of HCC [12]. However, the retrospective cohort study of Liu et al. reported that Peg-IFN +RBV significantly reduced the risk of HCC and improved the overall survival [13]. Sustained Virological Response (SVR) rates were reported to be 72.2% in the HBV and HCV co-infected patients at 24 weeks (SVR24) after Peg-IFN+RBV treatment versus 77.3% in the HCV mono-infected patients [11]. Our case has achieved an SVR in spite of HCV genotype 1b, which was reported to achieve lower SVR than other genotypes.

It was reported that HBs Ag seroclearance occurred in 11.2% of 161 co-infected patients after CHC treatment, and HBV-DNA rose in 28 (36%) of the 77 co-infected patients that had undetectable pre-treatment levels of HBV DNA [13,14]. Interferons have immunomodulatory effect in patients infected with HCV or HBV as a monoinfection or co-infection [15,16]. The cumulative incidence rates of HBV reactivation were similar in patients treated with either IFN-based therapy (14.5%) or oral direct-acting antiviral agents (DAAs, 12.2%) among CHC patients with manifest HBV infection (n=779). HBV reactivation was reported to occur frequently at the end of treatment and much earlier in those treated with DAAs (during treatment) than in those treated with Peg-IFN-based therapies. DAA-based therapies were more likely to cause hepatitis due to HBV reactivation (12.2% in DAAs vs. 0% in IFN) [17]. The higher SVRs with Peg-IFN treatment were reported in patients with HBV genotype A, high levels of ALT (≥ 2 × upper limit of normal), low levels of HBV DNA (2000 IU/mL < 2.0 × 108 IU/mL), and HBe Ag, and patients that have genotypes B or C, high levels of ALT, HBe Ag, and low HBV DNA, whereas patients with Genotype D patients had a lower chance [18]. Our case was unresponsive to Peg-IFN treatment against CHB, as she had HBV-DNA (less than 2000 IU/mL), Ani-Hbe, elevated liver enzymes due to CHC, and was in the immune tolerant phase of CHB [16]. Genotype D is prevalent in Turkey, although we have not analyzed the HBV genotype of our case [19]. HBS Ag seroclearance is very rarely seen as an annual rate of 2.4–3.2% with Peg-IFN treatment, and only <1% with nucleoside/nucleotide analogues [20]. Therefore, we have not expected a HBs Ag seroclearance in our case. The 5-year cumulative incidence rates of HBs seroclearance were reported to be 53.3% in patients who had HBV-DNA negative one year after the end of the CHB treatment [21].

A reactivation of HBV is thought to be a result of an immunological response to infected hepatocytes that replicate HBV after the restoration of both innate (restoration of NK cell phenotype and function) and adaptive (improvement in CD8+ T cell function) immunological mechanisms with interferon treatment against CHC [22,23]. Spontaneous fluctuations in the HBV-DNA levels are common in patients with HBs Ag-positive. Maylin and colleagues reported to occur the spontaneous fluctuations (>0.5 log10) in 63% of 87 patients with HBs Ag-positive, normal ALT and AST [24]. Papathodoridis reported that almost 50% of patients with CHB followed during a median period of time of 7.5 months (HbeAg negative) had >1 log10IU/mL fluctuations in the HBV-DNA levels [25]. Wang and colleagues reported that only three patients had fluctuations in the 10 HBs Ag (+) and 124 anti-Hbc (+) patients that received IFN-free regimen for CHC, whereas Sulkowski and colleagues did not observe fluctuation in patients who were Anti-Hbc positive and HBs Ag negative, and treated with Ledipasvir/Sofosbuvir for CHC [26,27]. HBs Ag was a strong predictor for a development of the hepatitis B reactivation [26]. The probable risk of liver failure due to HBV reactivation, although slight, urges us to screen all patients receiving hepatitis C treatment for the presence of HBs Ag. If HBs Ag is positive, HBV-DNA monitoring during the treatment would probably be a good approach to early identify these patients, as viral replication happens before the verification of clinical signs of hepatitis [28].

There was no reported a clinically evident hepatitis in 62% of the 76 co-infected patients whose undetectable pretreatment serum HBV DNA had reappeared, and none of those patients received anti-viral therapy due to HBV reactivation in the study of Yu et al. [29]. However, Yalcin et al. reported a severe

| Hemoglobin (Hgb, g/dL) | 12.1 | 10.8 | 9.76 | 8.41 | 10.7 | 10 | 10.8 | 10.61 | 9.99 |
|------------------------|------|------|------|------|------|----|------|------|------|
| HBV-DNA (IU/mL)        | 1184 | 145  | 878215 |
| Anti-HBc IgM            | negative | positive |
| HBs Ag                 | positive | negative |
| HBe Ag                 | negative | positive |
| ANTI-HBe               | positive | negative |
| HCV-RNA (IU/mL)        | 2080195 | negative | negative | negative | negative | negative | negative |
| ANTI-HCV               | positive | negative |
| ANTI-DELTA             | negative | negative |
hepatitis flare case after a Peg-IFN treatment for CHC [29,30]. Our case was not severe, but symptomatic with elevated liver enzymes and without hyperbilirubinemia. We have initiated tenofovir disoproxil treatment due to reactivation of CHB and HBV/HCV coinfection that may cause more severe chronic liver damage, have a high risk of development of hepatocellular carcinoma. The risk of HBV reactivation during anti-viral therapy against HCV with an interferon-free regimen (DAAs) is being pointed out. The HBV reactivation (>1 log increase in HBV-DNA levels) was reported to occur in five (50%) of 10 HBsAg positive and one (1.6%) of 64 anti-HBc positive patients. None of those patients had an increased ALT in the presentation of clinical reactivation. Şentürk et al. revealed that dual infection with HBV and delta virus is a significantly more severe condition than the dual infection with HBV and HCV in the follow-up of 51 patients with both HBsAg and anti-HCV positive and 67 patients with HDV. We do not know the previous period of CHB of our case, as she had no viral hepatitis investigation. However, we have seen that inflammation and fibrosis were mild in the liver biopsy performed one year after CHC treatment. It is not known whether Peg-IFN had beneficial effects on the liver of our case, as a liver biopsy before CHC treatment was not obligatory in Turkey at that time. Despite a 3-month interruption of CHC treatment due to hyperthyroidism and anemia related to Peg-IFN+ RBV, the absence of HCV-RNA in the first month of treatment (rapid virological response) may be a good prognostic sign for the lasting of treatment response.

As a result, patients coinfected with HBV and HCV should be followed up for the reactivation of HBV after CHC treatment with either pegylated interferon-based therapy or oral direct-acting antiviral agents in the medium-term, and the cirrhosis and hepatocellular carcinoma in the long-term.

Acknowledgement
There is no conflict of interest.

References
1. Nelson PK, Mathers BM, Cowie B,Hagan H, Des Jarlais D, Horyniak D, et al. (2011) Global epidemiology of hepatitis B and hepatitis C in people who inject drugs results of systematic reviews. Lancet 378: 571-583.
2. Crockett SD, Keeffe EB (2005) Natural history and treatment of hepatitis B virus and hepatitis C virus coinfection. Ann Clin Microbiol Antimicrob 4: 13.
3. Lee LP, Dai CY, Chuang WL, Chang WY, Hou NJ, et al. (2007) Comparison of liver histopathology between chronic hepatitis C patients and chronic hepatitis B and C-coinfected patients. J Gastroenterol Hepatol 22: 515-517.
4. Potthoff A, Manns MP, Wedemeyer H (2010) Treatment of HBV/HCV coinfection. Expert Opin Pharmacother 11: 919-928.
5. Sagnelli E, Coppola N, Pisaturo M, Masiello A, Tonziello G, et al. (2009) HBV superinfection in HCV chronic carriers a disease that is frequently severe but associated with the eradication of HCV. Hepatology 49: 1090-1097.
6. Shi J, Zhu L, Liu S, Xie WF (2005) A meta-analysis of case-control studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma in China. Br J Cancer 92: 607-612.
7. Nguyen LH, Ko S, Wong SS, Tran PS, Trinh HN, et al. (2011) Ethnic differences in viral dominance patterns in patients with hepatitis B virus and hepatitis C virus dual infection. Hepatology 53: 1839-1845.
8. Donato F, Boffetta P, Puoti M (1998) A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. Int J Cancer 75: 347-354.
9. Liu CJ, Liou JM, Chen DS, Chen PI (2005) Natural course and treatment of dual hepatitis B virus and hepatitis C virus infections. J Formos Med Assoc 104: 783-791.
10. Liu CJ, Chuang WL, Lee CM, Yu ML, Lu SN, et al. (2009) Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis C and B viruses Gastroenterology 136: 496-504.
11. Yu ML, Lee CM, Chuang WL, Lu SN, Dai CY, et al. (2010) HBsAg profiles in patients receiving peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. J Infect Dis 202: 86-92.
12. Chun JL, Wan LC, Chuan ML, Ming LY, Sheng NL, et al. (2009) Peginterferon Alfa-2a Plus Ribavirin for the Treatment of Dual Chronic Infection With Hepatitis B and C Viruses. Gastroenterology 136: 496-504.
13. Chuang WL, Dai CY, Chang WY, Lee LP, Lin ZY, et al. (2005) Viral interaction and responses in chronic hepatitis C and B coinfected patients with interferon-alpha plus ribavirin combination therapy. Antivir Ther 10: 125-133.
14. Chen G, Wang C, Chen J, Ji D, Wang Y, et al. (2017) Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents A systematic review and meta-analysis. Hepatology 66: 13-26.
15. Buster EH, Hansen BE, Lau GK, Piratvisuth T, Zeuzem S, et al. (2009) Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis C to peginterferon alfa. Gastroenterology 137: 2002-2009.
16. Sunburl M, Leblebicicoglu H (2005) Distribution of hepatitis B virus genotypes in patients with chronic hepatitis B in Turkey. World J Gastroenterol 11: 1976-1980.
17. Andersson KL, Chung RT (2009) Monitoring during and after antiviral therapy for hepatitis B. Hepatology 49: 166-173.
18. Serti E, Chepa-Lotrea X, Kim YJ, Keane M, Fryzek N, et al. (2015) Successful interferon-free therapy of chronic hepatitis C virus infection normalizes natural killer cell function. Gastroenterology 149: 190-200.
19. Martin B, Heennecke N, Lohmann V, Kayser A, Neumann-Haefelin C, et al. (2014) Restoration of HCV-specific CD8+T cell function by interferon-free therapy. J Hepatol 61: 538-643.
20. Maylin S, Sire JM, Mbaye PS (2015) Short-term spontaneous fluctuations of HBV DNA levels in a Senegalese population with chronic hepatitis B. BMC Infect Dis 25: 154.
21. Papaioedidou VS, Chrysanthos N, Hadziyannis E, Cholongitas E, Manesis EK (2008) Longitudinal changes in serum HBV DNA levels and predictors of progression during the natural course of HBeAg-negative chronic hepatitis B virus infection. J Viral Hepat 15: 434-441.
22. Wang C, Ji D, Chen J, Shao Q, Li B, et al. (2017) Hepatitis due to reactivation of hepatitis B virus in endemic areas among patients with hepatitis C treated with direct-acting antiviral agents. Clin Gastroenterol Hepatol 15: 132-136.

23. Sułkowski MS, Chuang WL, Kao JH (2016) No evidence of reactivation of hepatitis B virus among patients treated with ledipasvir-sofosbuvir for hepatitis C virus infection. Clin Infect Dis 63: 1202-1204.

24. Hoofnagle JH (2009) Reactivation of hepatitis B. Hepatology 49: 156-165.

25. Yeh ML, Hung CH, Huang JF, Liu CJ, Lee CM, et al. (2011) Long-Term Effect of Interferon Plus Ribavirin on Hepatitis B Surface Antigen Seroclearance in Patients Dually Infected with Hepatitis B and C Viruses. PLoS ONE 6: 20752.

26. Yalcin K, Degertekin H, Yildiz F, Kilinc N (2003) A severe hepatitis flare in an HBV-HCV coinfected patient during combination therapy with alpha-interferon and ribavirin. J Gastroenterol 38: 796-800.

27. Mrani S, Chemin I, Menouar K, Guillaud O, Pradat P, et al. (2007) Occult HBV infection may represent a major risk factor of non-response to antiviral therapy of chronic hepatitis C. J Med Virol 79: 1075-1081.

28. Londoño MC, Lens S, Mariño Z, Bonacci M, Ariza X, et al. (2017) Hepatitis B reactivation in patients with chronic hepatitis C undergoing anti-viral therapy with an interferon-free regimen. Aliment Pharmacol Ther 45: 1156-1161.

29. Senturk H, Tahan V, Canbakan B (2008) Clinicopathologic features of dual chronic hepatitis B and C infection a comparison with single hepatitis B, C and delta infections. Ann Hepatol 7: 52-58.

30. Yu JW, Wang GQ, Sun LJ, Li XG, Li SC (2007) Predictive value of rapid virological response and early virological response on sustained virological response in HCV patients treated with pegylated interferon alpha-2a and ribavirin. J Gastroenterol Hepatol 22: 832-836.