Case Report

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

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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 of 150 IU/L, serum HCV-RNA levels of 2080195 IU/mL (genotype 1b), and HBV-DNA of 1184 IU/mL. The results of other laboratory tests were within the normal range and remained to be normal during the follow-up. Pegylated interferon alpha-2a (180 mcg/week) and ribavirin (1200 mg/day) were administered for the treatment of CHC for 48 weeks. After one year of CHC treatment, our case was admitted with the elevation in liver enzymes and HBV-DNA of 878215 IU/mL. 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 disoproxil tablet (245 mg/day) was initiated for the chronic hepatitis B treatment. The patient is followed up at the ambulatory clinic of infectious diseases. 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.

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, coinfection 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 refuted 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	January 2016	March 2016	April 2016	March 2017	May 2017
Alanine aminotransferase (ALT, N: 0-55 IU/L)	182	59	52	49	42.7	29.7	31.2	23	43.6	120.5
Aspartatae aminotransferase (AST, N: 0-34 IU/L)	150	64	59	61	53	33	32	30	34	66
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 U/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

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									
HBs Ag	positive									positive
HBe Ag	negative									negative
ANTI-HBe	positive									positive
HCV-RNA (IU/mL)	2080195	negative	negative		negative	negative		negative	negative	
ANTI-HCV	positive				positive					
ANTI-DELTA	negative						negative			negative

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 seroclearence 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]. Papatheodoridis 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, Yalçın et al. reported a severe

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 HBs Ag 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 HBs Ag 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.

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