Case Report

Cortisone Acetate Induced Acute Flare-Up of HBV Infection in a Growth Hormone Deficient Patient

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Abstract
Reactivation of hepatitis B virus is a known complication of immunosuppressive therapy and may cause liver failure and even death. A twenty-year-old male patient visited the endocrinology department because of short stature and diagnosed as growth hormone deficient. Somatropin and cortisone acetate were initiated. After six months, HBV reactivation was occurred. Antiviral treatment with lamivudine was initiated after the increase in transaminases. After a six months’ initiating lamivudine therapy, his physical examination and laboratory test results were found to be normal. In conclusion, every patient who are planned to be received immunosuppressive therapy should be screened for HBV infection.

Introduction
It is widely accepted that reactivation of the hepatitis B virus occurs after chemotherapy or immunosuppressive therapy (1). This condition can lead to progressive liver failure and even death, therefore immediate antiviral treatment is recommended before immunosuppressive therapy (1). But in many cases, because of failure to check the hepatitis serology before immuno-suppressive treatment, antiviral agents are initiated after the reactivation of HBV (1,2). On the other hand, most reactivation cases are related to high doses of steroids or chemotherapeutic agents, and there are only a few reports of acute flare up after long term and low dose steroid treatment in HBV carriers (3,4). We present a case of an inactive 20-year-old HBV carrier with an acute flare up of HBV after 6 months of low dose steroid therapy due to growth hormone deficiency.

Case Report
A twenty year old male patient, was admitted to the endocrinology department because of short stature. At first evaluation, the anthropometric measurements of the patient showed: height 154 cms; weight 42 kgs. Investigations showed no abnormalities in routine blood, stool and urine examinations. Initial laboratory studies revealed the following: IGF <25 ng/mL, T3:2.97 pg/mL (2.97 pg/mL), T4:0.91 pg/mL (0.88-1.72 pg/mL), TSH:1.84 pg/mL (0.4-4 pg/mL), GH:0.191 ng/mL (0-3 ng/mL), Prolactin:14.55 ng/mL (2.7-18.3 ng/mL), LH:4.71 IU/L (1.7-9.6), Cortisole:7.18 µg/dL (7.18 µg/dL), ACTH:3.78 IU/L (1.9-18.93 IU/L). An insulin tolerance test was performed. The evaluation of GH secretion showed a partial GH deficiency (GH peak response to insulin: 0.104 ng/mL). The patient was diagnosed as growth hormone deficient. Somatropin by injection at 0.2 mg and peroral cortisone acetate 5 mg were initiated by the endocrinologists. By the end of six months after the cortisone acetate started; he noted anorexia, nausea and jaundice. He applied to Endocrinology Department again. On physical examination, the patient was alert and oriented; his body temperature was 36.5 °C, heart rate 80 beats/minute and arterial blood pressure was 120/80mmHg. His skin was jaundiced and he had scleral icterus. He applied to Endocrinology Department again. On physical examination, the patient was alert and oriented; his body temperature was 36.5 °C, heart rate 80 beats/minute and arterial blood pressure was 120/80mmHg. His skin was jaundiced and he had scleral icterus. His lungs were clear to auscultation bilaterally. The abdomen was soft and he had a moderately enlarged liver. He had no
altered mental status, skin rashes, palmar erythema or spider angiomas.

The biochemical tests showed leukocyte: 5200/mm³; hemoglobin: 14.1 gr/dl; hematocrit: 43.1; trombocyte: 227,000/mm³; ESR: 20mm/hour; CRP: 20mg/l AST: 1752 U/L; ALT: 2132U/L; direct bilirubin: 2.76 mg/dL; total bilirubin: 4.59 mg/dL; serum albumin: 3.81 g/dL, prothrombin time: 15 sec; INR: 1.2; BUN: 32 mg/dL; creatinine mg/dL: 0.51; blood glucose: 63 mg/dL; ALP: 256 U/ml; GGT: 117 U/ml. In urine analysis, protein was negative, elevated levels of bilirubin and urobilinogen were detected. The viral panel for anti-HCV, anti-HAV IGM, anti-HAV IGG, and anti HBs, anti HBe was negative and HBsAg, IgM anti-HBc, IgG anti-HBc, and HBeAg were found to be positive. HBV DNA was also positive (249,303 IU/ml) (Figure 1). He had negative serology for CMV, EBV, HSV, VZV, Rubella, Rubeola, ANA, AMA, ASMA, and anti dsDNA. Because the patient did not define risk factors for acute hepatitis B virus, we thought that this condition was an acute flare up of HBV infection caused by cortisone acetate treatment and the patient was hospitalized to the department of infectious disease. Antiviral treatment with lamivudine was started after the hospitalization. After treatment, the patient was clear of all his previous symptoms. He was discharged from the hospital on 100 mg of lamivudine and follow-up visits at the infectious disease and internal medicine department were scheduled. After two weeks, his PE and laboratory test results were normal. After six-month of following this treatment, HBsAg, HBeAg, HBV DNA level of the patient were negative, anti HBs, anti HBe were found to be positive (16 IU/mL) and liver enzymes were found to be normal (Figure 1).

Discussion

Reactivation of the hepatitis B virus is a complication of immunosuppressive therapy, especially seen after chemotherapy. This condition can lead to hepatocellular injury, elevated liver enzyme levels, symptoms of acute hepatitis, liver failure and even death (1). Many physicians who commence immunosuppressive therapy unfortunately do not check the risk factors and the serological markers of hepatitis before initiating immunosuppressive therapy.

In our case, when the patient was first admitted to the hospital, he was not checked for hepatitis. Moreo-

Figure 1. Clinical course of the patient. HD, hospital day.
ver, the patient was living in a village and he did not realize that he had the hepatitis B virus until being admitted to our hospital.

Information regarding previous HBV infection and serology (HBsAg, Anti-HBs, HBV DNA, Ig G Anti-HBc), would have made differentiating between acute hepatitis B (AHB) and chronic hepatitis B with acute exacerbation easier. However, the patient did not define any risk factors for acute hepatitis B infection such as injecting drug use, high-risk sexual practices, and surgical operations. In addition, considering the high prevalence of hepatitis B infection in the area where the patient lives, a thorough family history which would have revealed individual carriers of hepatitis among family members, an abrupt rise in liver transaminase enzymes right after cessation of immunosuppressive therapy and the onset of clinical symptoms would have rather raised the suspicion of chronic hepatitis B with acute flare (CHB-AF) instead of acute hepatitis.

Furthermore, IgM anti-HBc titers are also important to make the diagnosis but it is necessary to seek other parameters to assist IgM anti-HBc to distinguish AHB from CHB-AF in patients with no prior history of HBV infection whose diagnosis could not be made by IgM anti-HBc alone during hospitalization (5). It has been reported that HBV-DNA <0.5 pg/mL (equivalent to 28,000 IU/mL) at initial presentation had a sensitivity of 95.9% and a specificity of 86.6% for predicting AHB in a previous study (6).

Our patient’s IgM anti-HBc was found to be positive. As previously reported in the literature, Ig M anti-HBc positivity can also be seen in CHB-AF patients as in patients with AHB (5). The high levels of HBV DNA in our patient as reported above shows a clinical picture of CHB-AF and not acute Hepatitis B.

In the literature, HBV reactivation was reported by Yeo et al. in patients receiving chemotherapy for hematologic cancer (2). Most cases of HBV reactivation occur in patients who are HBsAg positive, yet it has also been reported in patients who are HBsAg negative and anti HBc positive, particularly when Rituximab is used (7). In another study by Carroll et al., they described reactivation in patients receiving treatment with TNF-alfa inhibitors and long-term steroid therapy. In the literature we did not observe any flare up of HBV cases related to immunosuppressive treatment due to growth hormone deficiency (8). Our case was admitted to the department of endocrinology service and was treated with cortisone acetate and somatropin because of growth hormone deficiency, and after the six month therapy we observed reactivation of HBV in clinical and laboratory results of the patient; we initiated immediate antiviral treatment after the increase in transaminases. Clinical studies show that initiating prophylactic antiviral treatment before immunosuppressive therapy is more effective than deferred lamivudine treatment (9, 10).

In our case we had no chance to start treatment before immunosuppressive therapy because he wasn’t aware of his illness and he didn’t report any risk factors. Also, in the department of endocrinology HBV screening was not routinely implemented and such a case hasn’t been experienced before. But we initiated the anti-viral therapy as soon as we realized the reactivation of HBV. After our treatment, PE and laboratory results of our patient were found to be normal.

Glucocorticoid is known as an important predisposing factor for HBV reactivation. In patients with chronic hepatitisB, long-term prednisolone treatment increases levels of HBsAg, HBcAg, and HBV DNA in hepatocytes (3). Immunosuppression is thought to enhance viral replication with a subsequent spread in hepatocytes. In addition, glucocorticoids may cause a direct reactivation of the latent HBV infection (11). However, in patients with chronic HBV infection, limited data exists in the literature on the effect of the various immunosuppressive regimens given for long periods of time in lower doses. Although there have been some case reports of acute flare-up of HBV after high dose steroid therapy, only a few patients have been reported with low dose immunosuppressive therapies (3). When whole literature has been scanned our case appears to be the first reactivation of hepatitis B case that is related with utilization of low dose steroid due to growth hormone deficiency. In this regard, this rare case has been found to be precious as being the subject matter of our presentation.

In conclusion, reactivation of HBV is an important condition and that can cause hepatic failure and even death. Therefore, we should control hepatitis markers not only in patients receiving chemotherapy but also in other patients receiving immunosuppressive therapies in other clinics such as rheumatology and endocrinology. Further multidisciplinary study is required to prevent reactivation of HBV and to provide more precise data.
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