Clinical and Experimental Rheumatology 2007; 25: 888-889.

Fatal hepatic failure associated with hepatitis B virus reactivation in a hepatitis B surface antigen-negative patient with rheumatoid arthritis receiving low dose methotrexate

G.-Y. Gwak, K.C. Koh, H.-Y. Kim

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

Geum-Youn Gwak, MD; Kwang Cheol Koh, MD; Hye-Young Kim, MD.

Please address correspondence and reprint requests to: Dr. K.C. Koh, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-Gu, 135-710, Seoul, South Korea.
E-mail: kc.koh@samsung.com

Received on December 15, 2006; accepted in revised form on May 4, 2007.

Key words: Hepatitis B virus, reactivation, rheumatoid arthritis, methotrexate.

Competing interests: none declared.

ABSTRACT

A 66-year-old female patient with rheumatoid arthritis, who had been HBsAg-negative and anti-HBs-positive, developed hepatic dysfunction following low-dose methotrexate therapy. Serologic testing for HBsAg, HBeAg, IgM HBc and HBV DNA were positive. Despite antiviral therapy with lamivudine, the hepatic condition gradually deteriorated until the patient died. Since HBV replication persists in the liver even in individuals with resolved HBV infection (i.e., HBsAg-negative, anti-HBspostive), HBV reactivation may occur in these patients with immunosuppression. Therefore, especially in endemic areas, all patients being considered for immunosuppressive therapy should be closely monitored with liver function tests and evaluated for HBV reappearance even when HBsAg-negative.

Introduction

Low-dose methotrexate (MTX) therapy is an effective treatment for rheumatoid arthritis (RA), with a low side effect profile (1). MTX has marked immunosuppressive effects with high doses; given in low doses its effects on immunity are less well defined. However, several opportunistic infections have been recognized during low-dose MTX therapy (2, 3); this suggests that the immunosuppressive effect of this regimen may not be fully appreciated. In addition, a few reports showed that low-dose MTX therapy induced hepatitis B virus (HBV) reactivation in hepatitis B surface antigen (HBsAg)-positive patients, leading to fulminant hepatitis (4-7).

Recently, we experienced an RA patient who was HBsAg-negative and anti-HBs-positive, and subsequently developed fatal hepatic failure due to HBV reactivation following low-dose MTX therapy. Herein, we describe the case and discuss the possible mechanism of HBV reactivation and its clinical significance especially in HBV endemic areas.

Case report

A 59-year-old woman was diagnosed with RA in 1999, when she had normal liver function tests. The patient had never received HBV vaccination, and had HBsAg-negative and anti-HBs-positive serologic results. She was treated with oral MTX 10mg weekly and prednisolone 5mg daily. The MTX was well tolerated and its use was accompanied by marked improvement of joint signs and symptoms. During the following 7-year course of MTX and prednisolone she was followed-up with liver function test at intervals of 1 or 2 years and did not experience any significant liver function deterioration. In September 2006 the patient developed malaise, anorexia and fatigue, which progressed gradually over the next several weeks. On October 20, 2006, she visited local clinic, where serum levels of aspartate transaminase (AST) and alanine transaminase (ALT) were found to be markedly elevated (680 and 378 IU/L, respectively). The serum total bilirubin level was 5.7 mg/dL. The serologic test for HBsAg revealed a positive reversion. The patient denied alcohol or other hepatotoxic drugs. HBV-related hepatitis was diagnosed and lamivudine at a daily dose of 100mg was started. MTX and prednisolone were discontinued, and then she was referred to our hospital.

On admission, the patient was alert and hepatomegaly was not evident on the physical examination. Serum AST, ALT, and total bilirubin were further raised to 837 IU/L, 451 IU/L and 29.5 mg/dL, respectively. Hypoalbuminemia (2.9 g/dL) and prolongation of the prothrombin time (34.3 seconds, 3.42 INR) were also found. HBsAg, hepatitis B envelope antigen (HBeAg), IgM hepatitis B core antibody (anti-HBc) and high serum HBV DNA levels (15,828,190 copies/mL) were detected in the serum. There was no evidence of hepatitis A (anti-HAV IgM) and C virus (anti-HCV antibody), Epstein-Barr virus (anti-EBV-VCA IgM), cytomegalovirus (anti-CMV IgM) or herpes simplex virus (anti-HSV type I/II IgM) infection. Despite continued antiviral therapy with lamivudine, the hepatic condition continued to deteriorate until liver function failed and encephalopathy developed. On November 14, 2006, 8 weeks after the onset of symptoms, the patient died of hepatic failure.

Discussion

Reactivation of HBV replication is a well-recognized complication in patients with chronic HBV infection who receive cytotoxic or immunosuppressive therapy (8). In HBsAg-positive patients, HBV reactivation occurs in 20% to 50% of cases receiving cytotoxic or immunosuppressive therapy (9), with a mortality rate of 10% to 40% (10). Therefore, many clinicians recommend a prophylactic antiviral treatment such as lamivudine before cytotoxic or immunosuppressive therapy in HBsAg-positive patients.

However, even in individuals with resolved HBV infection (*i.e.*, HBsAg-negative, anti-HBs-postive and/or anti-HBc-positive), HBV replication persists in the liver and in peripheral blood mononuclear cells (11, 12). Theoretically, it is likely that reactivation of HBV occurs in these patients; a few reports have described the reactivation of HBV in HBsAg-negative patients following cytotoxic or immunosuppressive therapy (13). However, without exception, all of these cases were patients who had hematological malignancies subjected to intense immunosuppressive treatment. Thus, the present case is noteworthy in that HBV reactivation occurred in an HBsAg-negative patient receiving low-dose MTX without other powerful immunosuppressive agents.

Since Flowers *et al*. first described HBV reactivation in an HBsAg-positive RA patient receiving MTX in 1990 (4), 3 additional similar cases have been reported (5-7). They all developed severe hepatitis linked to HBV reactivation after discontinuation of low-dose MTX. HBV is a non-cytopathic virus and causes liver injury by the host's immune reactions. Therefore, it has been postulated that immunosuppression caused by MTX enhances HBV replication and permits widespread infection of hepatocytes, and subsequently, withdrawal of MTX leads to restoration of immune function, resulting in rapid destruction of infected hepatocytes. Interestingly, the present case developed severe hepatitis during the treatment without interruption for several years. Although the mechanism remains unclear, in part, this phenomenon might be explained by a direct cytopathic effect of HBV on hepatocytes. Recently, Meuleman *et al*. demonstrated that HBV causes dramatic hepatocellular damage in a severely immune deficient mouse, indicating that HBV might be directly cytopathic in conditions of severe immune suppression (14). Thus, in the present case, it is plausible that HBV, which have accumulated within hepatocytes gradually during a long period of MTX therapy, might have led to a sudden overwhelming liver injury through a direct cytopathic effect. However, further investigation is required to determine whether HBV exerts a direct cytopathic effect with relatively mild immunosuppressive conditions such as low-dose MTX therapy.

In conclusion, the present case implicates that low-dose MTX therapy may cause HBV reactivation during treatment regardless of the HBV serological status. However, the incidence of HBV reactivation in HBsAg-negative patients is likely to be much lower than that in HBsAg-positive patients. HBV infection is one of the most common viral infections in human; in highly endemic areas such as Korea, more than half of the population is infected with HBV throughout their lives. Therefore, a universal adoption of the prophylactic antiviral therapy in HBsAg-negative patients is unlikely to be cost-effective and practically impossible. A close monitoring for HBV reappearance during or after treatment in these patients are needed and further investigations are warranted to elucidate the incidence, clinical significance and risk factor of HBV reactivation in HBsAg-negative patients.

References

1. BALDINI C, DELLE SEDIE A, BOMBARDIERI S: From clinical trials to the bedside: how can we treat patients with rheumatoid arthritis and concurrent morbidities who are generally excluded from randomised controlled clinical trials? *Clin Exp Rheumatol* 2005; 23: 893-904.
2. LANG B, RIEGEL W, PETERS T, PETER HH: Low dose methotrexate therapy for rheumatoid arthritis complicated by pancytopenia and Pneumocystis carinii pneumonia. *J Rheumatol* 1991; 18: 1257-9.
3. LYON CC, THOMPSON D: Herpes zoster encephalomyelitis associated with low dose methotrexate for rheumatoid arthritis. *J Rheumatol* 1997; 24: 589-91.
4. FLOWERS MA, HEATHCOTE J, WANLESS IR *et al*.: Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. *Ann Intern Med* 1990; 112: 381-2.
5. NARVAEZ J, RODRIGUEZ-MORENO J, MARTINEZ-AGUILA MD, CLAVAGUERA MT: Severe hepatitis linked to B virus infection after withdrawal of low dose methotrexate therapy. *J Rheumatol* 1998; 25: 2037-8.
6. ITO S, NAKAZONO K, MURASAWA A *et al*.: Development of fulminant hepatitis B (precore variant mutant type) after the discontinuation of low-dose methotrexate therapy in a rheumatoid arthritis patient. *Arthritis Rheum* 2001; 44: 339-42.
7. HAGIYAMA H, KUBOTA T, KOMANO Y, KUROSAKI M, WATANABE M, MIYASAKA N: Fulminant hepatitis in an asymptomatic chronic carrier of hepatitis B virus mutant after withdrawal of low-dose methotrexate therapy for rheumatoid arthritis. *Clin Exp Rheumatol* 2004; 22: 375-6.
8. HOOFNAGLE JH, DUSHEIKO GM, SCHAFER DF *et al*.: Reactivation of chronic hepatitis B virus infection by cancer chemotherapy. *Ann Intern Med* 1982; 96: 447-9.
9. YEO W, CHAN PKS, ZHONG S *et al*.: Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000; 62: 299-307.
10. YEO W, LAM KC, ZEE B *et al*.: Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. *Ann Oncol* 2004; 15: 1661-6.
11. REHERMANN B, FERRARI C, PASQUINELLI C, CHISARI FV: The hepatitis B virus persists for decades after patients' recovery from acute viral hepatitis despite active maintenance of a cytotoxic T-lymphocyte response. *Nat Med* 1996; 2: 1104-8.
12. LEUNG NWY, TAM JSL, LAU GTC, LEUNG TWT, LAU WY, LI AKC: Hepatitis B virus DNA in peripheral blood leucocytes - a comparison between hepatocellular carcinoma and other hepatitis B virus-related chronic liver diseases. *Cancer* 1994; 73: 1143-8.
13. WANDS JR, CHURA CM, ROLL FJ, MADDREY WC: Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders. *Gastroenterology* 1975; 68: 105-12.
14. MEULEMAN P, LIBBRECHT L, WIELAND S *et al*.: Immune suppression uncovers endogenous cytopathic effects of the hepatitis B virus. *J Virol* 2006; 80: 2797-807.