Reactivation of chronic hepatitis B infection related to imatinib mesylate therapy

Shilen Lakhani · Lev Davidson · Dennis A. Prieбат ·
Averell H. Sherker

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Abstract Imatinib (Gleevec, Novartis), an inhibitor of BCR-ABL, platelet-derived growth factor, and KIT receptor tyrosine kinases, is widely used in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors. We describe a case of activation of chronic hepatitis B infection associated with imatinib therapy.

Keywords Chronic hepatitis B infection · Imatinib mesylate

Reactivation of hepatitis B virus (HBV) is a well-recognized phenomenon in chronically infected patients undergoing immunosuppressive treatment and is associated with mortality of up to 40%. Imatinib mesylate (Gleevec), an inhibitor of BCR-ABL tyrosine kinase, is widely used in the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST) and is not known to have generalized immunosuppressive properties. Here we describe the occurrence and course of HBV reactivation in a patient treated with imatinib mesylate.

A 50-year-old man with an unresectable desmoid tumor of the arm was seen in consultation for abnormal liver tests. He had been diagnosed with HBV more than 10 years earlier but was never offered treatment. He was started on imatinib

mesylate 300 mg twice daily 6 months prior to presentation. His liver tests after 3 months of treatment were normal. His aminotransferases slowly increased over the next 3 months to AST and ALT levels of 311 and 841 IU/l, respectively, at which time his imatinib mesylate was stopped. His only symptom was mild fatigue. He denied jaundice, pruritus, bleeding tendency, or increased abdominal girth. The patient denied all other medications including acetaminophen. While on imatinib mesylate therapy, the patient experienced only mild neutropenia. The lowest recorded absolute granulocyte count on treatment was $1.6 \times 10^3/\mu\text{l}$.

Laboratory investigation revealed positive HBsAg and HBcAb (total), with a negative “e” antigen and positive “e” antibody. HBV DNA was positive at a concentration of 2.9×10^7 IU/ml. Hepatitis A IgM antibody and hepatitis C antibody were negative. The ANA and immunoglobulins were normal. Bilirubin, alkaline phosphatase, albumin, and PT/INR were all normal.

The patient was followed conservatively and monitored with serial laboratory tests (Fig. 1). Over 2 weeks, he developed jaundice and experienced increasing fatigue. His ALT and AST levels peaked at 2120 and 1584 IU/l, respectively. His total bilirubin increased to a peak value of 7.1 mg/dl. His PT/INR remained normal throughout, and he never developed ascites or encephalopathy.

Symptoms and laboratory abnormalities resolved over the next 6 weeks. HBV DNA was at the lower limits of detection when repeated a month later and remained so on subsequent determinations.

Prior laboratory records were obtained from the patient's primary physician. The records confirmed repeatedly positive results for HBsAg 5 and 6 years prior to the acute presentation. Hepatitis B “e” antigen was negative with a positive “e” antibody and ALT level was slightly above the upper limit of normal. No record of prior HBV DNA testing was present.

S. Lakhani · A. H. Sherker (✉)
Section of Gastroenterology and Hepatology, Washington
Hospital Center, Georgetown University School of Medicine,
110 Irving Street NW, Washington, DC 20010, USA
e-mail: A.H.Sherker@Medstar.net

L. Davidson · D. A. Prieбат
Washington Cancer Institute, Washington Hospital Center,
Georgetown University School of Medicine, 110 Irving Street
NW, Washington, DC 20010, USA

Fig. 1 The patient was treated with imatinib mesylate for a desmoid tumor. Amino-transferases were normal at baseline and through the first three months of treatment but subsequently rose, leading to discontinuation of the drug. Following discontinuation, the patient developed fatigue and jaundice and alanine aminotransferase (ALT) peaked after six weeks off treatment. At that time HBV DNA was strongly positive. With conservative management, symptoms resolved over several weeks, ALT normalized and HBV DNA fell to a low level

Reactivation of HBV is well described following the administration of corticosteroids and immunosuppressive chemotherapy. Manifestations of the condition range from asymptomatic aminotransferase elevation to a progressive hepatitis with significant mortality. Typically, reactivation occurs upon withdrawal of the immunosuppressive agent due to a heightened immune response directed against viral antigens. A strategy comprising prophylactic treatment with antiviral agents such as lamivudine is advocated to prevent this reactivation phenomenon [1].

Imatinib mesylate is an agent that specifically inhibits the tyrosine kinase activity of ABL and BCR-ABL, as well as KIT, ARG, and platelet-derived growth factor [2]. The agent has been approved for the treatment of CML and GIST, and there have been reports of clinical responses in desmoid tumors [3]. Imatinib mesylate may impair immune responsiveness by preventing differentiation of progenitor stem cells to antigen presenting cells [4].

In this report, we describe a case of reactivation of chronic hepatitis B temporally related to imatinib mesylate therapy. The mechanism of this reactivation is unclear, but it does not appear to relate to treatment-induced neutropenia. Although tyrosine kinases are involved with HBV replication, the ABL family has not been described to play a specific role. Hepatotoxicity has rarely been described in association with imatinib mesylate therapy [5]. In this case, HBV DNA was strongly positive just prior to the peak in aminotransferase level and has remained at the lower limits of detection since the resolution of acute illness. Unfortunately, there was no

record of prior HBV DNA testing in this patient. Documentation of a rising HBV DNA level on therapy would be further supportive of HBV reactivation as the cause of the liver disease. Interestingly, there has been a recent report of an HBV-infected patient experiencing fatal liver disease during imatinib mesylate treatment of CML [6].

This case illustrates the potential for imatinib mesylate therapy to reactivate chronic hepatitis B infection. In patients undergoing imatinib mesylate therapy, screening for HBV infection and prophylactic antiviral therapy should be considered.

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