

CASE REPORT

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Reactivation of hepatitis B (reverse seroconversion) after melphalan/dexamethasone therapy for primary amyloidosis: a case report

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Abstract

Introduction: Hepatitis B virus (HBV) reactivation (so-called reverse seroconversion) is a rare but known complication of hematopoietic stem cell transplantation, immunosuppressive therapy, or high-dose chemotherapy plus rituximab. This event is linked to a treatment-related fall in titers of antibodies to hepatitis B surface antigen (HBsAb) below the protective threshold level.

Case presentation: A 77-year-old Korean man diagnosed with primary amyloidosis was started on melphalan/dexamethasone combination therapy. During treatment, laboratory indices of hepatic function suddenly deteriorated, and he developed acute hepatitis through reverse HBV seroconversion, becoming positive for hepatitis B surface antigen (HBsAg) and negative for HBsAb. HBV DNA was also detectable in serum to a profound extent. Normal liver function was gradually restored during the course of antiviral therapy (entecavir).

Conclusions: HBV reactivation may lead to fatal liver disease in a significant percentage of patients. As a result, physicians often screen for HBsAg and HBsAb prior to initiating chemotherapy, advising antiviral treatment in patients seropositive for HBsAg, even in the absence of hepatitis B e antigen. Here, a case of HBV reactivation is described, involving a patient given relatively low-dose chemotherapy (melphalan/dexamethasone) for primary amyloidosis.

Keywords: Hepatitis B, Immunity, Innate, Amyloidosis, Dexamethasone, Melphalan

Introduction

Instances of hepatitis B virus (HBV) reactivation (so-called reverse seroconversion) have been reported after hematopoietic stem cell transplantation or high-dose chemotherapy plus rituximab and are seldom-observed consequences of multiple myeloma. However, there are no known published accounts of HBV reactivation following melphalan/dexamethasone treatment of primary amyloidosis [1-5].

Case presentation

A 77-year-old Korean man presented to our hospital with an axillary mass. The presence of amyloid in the subsequent excisional biopsy prompted a bone marrow

biopsy, related laboratory tests, and pertinent imaging studies, including computed tomography (CT). Ultimately, a diagnosis of primary amyloidosis was rendered.

Despite the patient's advanced age, melphalan/dexamethasone combination therapy was elected. After three cycles of this regimen, detectable masses grew smaller and his serum kappa/lambda ratio normalized, so treatment continued. However, serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) rose precipitously after six cycles of therapy.

Our patient denied use of other medications (including herbal or dietary supplements), smoking, or consumption of alcohol, and there was no history of blood transfusion. On physical examination, he was alert, with normal blood pressure, pulse, and respiratory rate. No direct or rebound tenderness of the abdomen was evident.

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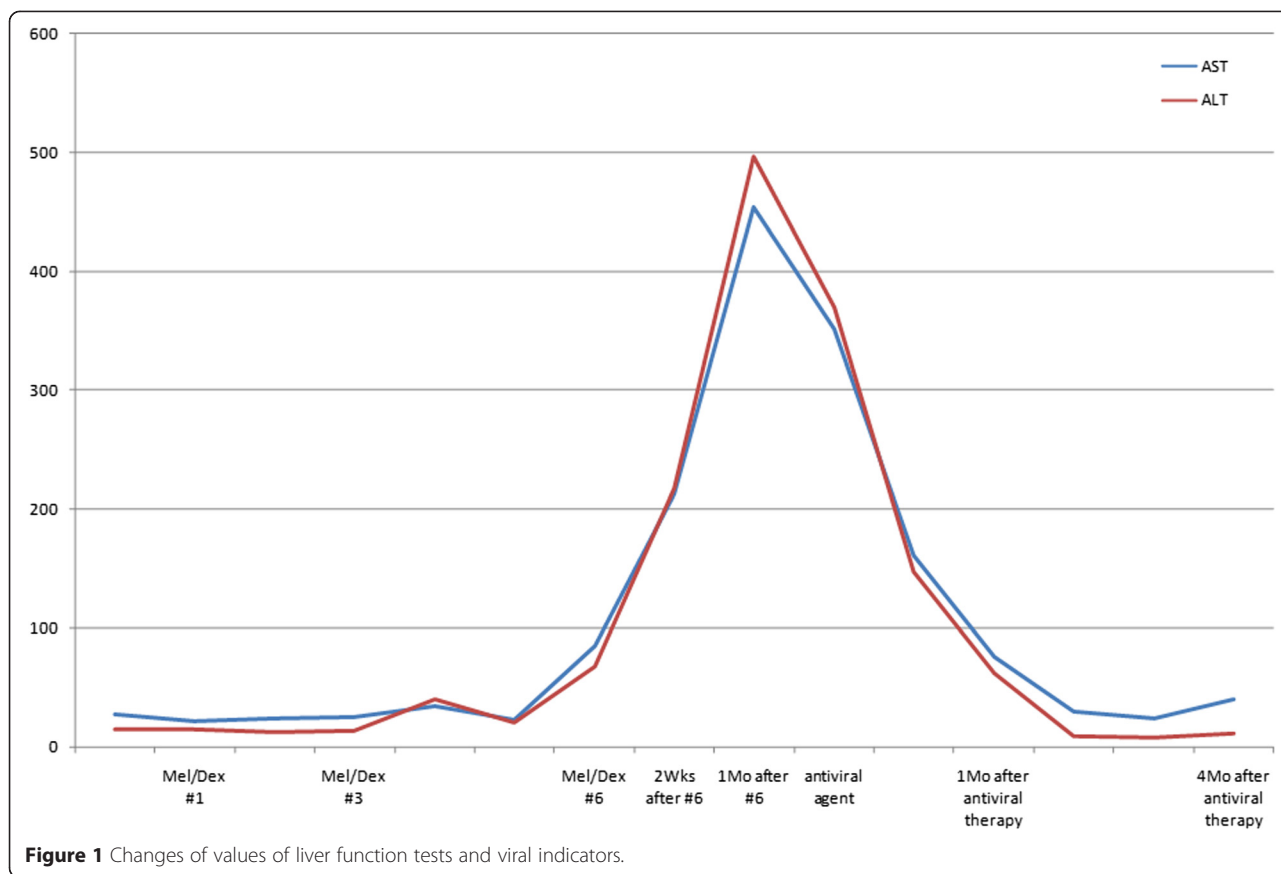


Figure 1 Changes of values of liver function tests and viral indicators.

Laboratory tests yielded the following values: white blood cell count, 2,720/mm³ (40.1% neutrophils, 43.5% lymphocytes, 1.4% eosinophils); hematocrit, 10.6g/dL; platelet count, 111,000/mm³; prothrombin time, 11.8 seconds; AST level, 454.1IU/L; ALT level, 496.3IU/L; total bilirubin, 1.34mg/dL; direct bilirubin, 1.04mg/dL; albumin, 3.11g/d; alkaline phosphatase (ALP), 142U/L; gamma-glutamyl transferase (rGTP), 126U/L; blood urea nitrogen (BUN), 17.2mg/dL; and creatinine (Cr), 1.28mg/dL.

Prior to initiating chemotherapy, our patient had been screened twice for hepatitis, testing negative for hepatitis B surface antigen (HBsAg, 0.41S/Co) and positive for antibodies to HBsAg (HBsAb, 55.0mIU/mL). No further serologic testing was pursued at this juncture, but after

receiving chemotherapy, HBsAg seroconversion (5,592S/Co) and loss of HBsAb (0.62mIU/mL) were documented. Repeat testing generated the same results, so screening was expanded to include hepatitis B envelope antigen (HBeAg, negative (0.27S/Co)), antibodies to HBeAg (HBeAb, positive (0.02S/Co)), and antibodies to hepatitis B core antigen (immunoglobulin M (IgM) HBcAb, negative (0.27S/Co); immunoglobulin M (IgG) HBcAb, positive (2.2S/Co)). A massive HBV DNA burden (67,322,328 copies/mL) was also determined by real-time polymerase chain reaction (PCR).

Given a lack of HBV vaccination by history, the patient's baseline HBsAb positivity was attributed to innate (naturally acquired) immunity. Hence, this acute bout of

Table 1 Values of viral indicators

	HBsAg (S/Co)	HBsAb (mIU/mL)	HBeAg (S/Co)	HBeAb (mIU/mL)	IgM-HBcAb (S/Co)	IgG-HBcAb (S/Co)	HBV DNA PCR (copies/mL)
Before CTx	(-) 0.40	(+) 85.2					
	(-) 0.41	(+) 55.0					
Mel/Dex#6	(+) 5,592	(-) 0.62					
	(+) 5,667	(-) 0.09	(-) 0.27	(+) 0.02	(-) 0.27	(+) 12.2	67,422,428
After antiviral agent							3,600

CTx, chemotherapy; Dex, dexamethasone; HBcAb, hepatitis B core antigen; HBeAb, antibodies to HBeAg; HBeAg, hepatitis B envelope antigen; HBsAb, antibodies to HBsAg; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; Mel, melphalan; PCR, polymerase chain reaction.

hepatitis was considered HBV reactivation. Entecavir antiviral treatment was then administered, gradually restoring normal liver function within three weeks. Five months later, AST and ALT levels were 40IU/L and 12IU/L, respectively. At this point, he also tested negative for HBsAg and positive for HBsAb, with PCR-determined HBV DNA level at 3,600 copies/mL (Figure 1, Table 1). Continued chemotherapy for primary amyloidosis was declined, and he died unexpectedly seven months later.

Discussion

HBV infection remains a major cause of acute and chronic liver disease. According to the World Health Organization (WHO), 350 to 400 million people worldwide suffer from chronic HBV infection [6], with relatively greater prevalence in Korea (2 to 10%) [7]. Presence of HBsAb and HBcAb is equated with resolution of infection and HBV clearance. In addition to enabling viral clearance during acute infection, immune reactivity to HBV antigens is also responsible for disease pathogenesis [8].

Innate immunity is important in controlling HBV infection immediately after onset, generally limiting the spread of infection and instigating an efficient adaptive immune response. Organism-specific structures (for example, double-stranded RNA and bacterial wall components) of pathogens trigger pattern-recognition receptors (PRRs) to activate innate immunity. The most important PRRs in viral infections are Toll-like receptors (TLRs), RNA helicases (such as retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5)), and double-stranded RNA-dependent protein kinase (PKR) [8,9].

Adaptive immunity is responsible for immunity to HBV infection conferred by vaccine administration. Routine HBV vaccination at birth is recommended for a number of reasons. Approximately 90% of infants born to HBV-infected mothers will acquire the infection at birth; and 30 to 50% of infected youths <5 years of age become chronic HBV carriers, compared with only 6 to 10% of newly infected adults [8-10]. The series of immunizations constituting recombinant HBV vaccines are 95% effective at inducing seroimmunity. Although in use for only 20 years, their duration is likely lifelong [11,12].

Reverse seroconversion of HBV due to medical treatments, such as hematopoietic stem cell transplantation and high-dose chemotherapy plus rituximab, is an uncommon event that seldom occurs with multiple myeloma as well. During chemotherapy, amplified viral replication increases DNA polymerase activity, thereby boosting serum levels of HBV DNA, HBeAb, and HBsAg; reversing HBsAb titers; and enabling the spread of liver infection [2]. The immunologic reconstruction that follows cytotoxic treatments is marked by massive and rapid immune-mediated destruction of infected hepatocytes, reflected clinically in rising AST and ALT levels. Such scenarios

may culminate in serious and even fatal liver disease for a significant percentage of patients [1-5].

Prior to initiating any cytotoxic or immunosuppressive therapy, patients should be adequately screened for HBV infection. Antiviral treatment is advised for HBsAg-positive states (even if negative for HBeAg) [10,13].

As seen here, HBV reactivation may result from relatively low-dose chemotherapy (melphalan/dexamethasone), calling for expanded testing in similar circumstances.

Conclusions

This patient (HBsAg-negative/HBsAb-positive status at baseline) illustrates that HBV reactivation (that is reverse HBV seroconversion) may develop as an exceedingly rare consequence of melphalan/dexamethasone therapy for primary amyloidosis. Comprehensive HBV screening, including HBcAg, HBcAb, and HBV DNA serologic testing, is clearly needed in this setting.

Consent

Written informed consent was obtained from the patient and the patient's legal guardians for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Cr: creatinine; CT: computed tomography; HBcAb: hepatitis B core antigen; HBeAb: antibodies to HBeAg; HBeAg: hepatitis B envelope antigen; HBsAb: antibodies to HBsAg; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; IgG: immunoglobulin G; IgM: immunoglobulin M; MDA5: melanoma differentiation-associated gene 5; PKR: RNA-dependent protein kinase; PRRs: pattern-recognition receptors; rGTP: gamma-glutamyl transferase; RIG-I: retinoic acid-inducible gene I; PCR: polymerase chain reaction; TLRs: Toll-like receptors; WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MWR was the major contributor in writing the manuscript. KJA, MDS, YYM, CBS, and CCH were involved in drafting, writing and editing the manuscript. PSG was involved in drafting, writing and editing the manuscript, and reviewed the manuscript as corresponding author. All authors read and approved the final manuscript.

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