Acute hepatitis B despite a previous high titer of anti-HBs

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Abstract

Introduction Loss of HBsAg and development of surface and core antibodies represent clinical cure. However, recent evidence suggests that hepatitis B virus (HBV) persists in a latent state even in those with mounted protective antibodies. After significant immunosuppression, anti-HBs may decrease and HBsAg may reappear (reverse seroconversion). Reverse seroconversion of HBV has been observed in association with hematopoietic stem cell transplantation, renal transplantation, intensive chemotherapy, human immunodeficiency infection, or rituximab usage.

Case report We present here a case study of a patient with a previous high titer of anti-HBs who later developed HBV reactivation following intensive chemotherapy for leukemia.

Conclusion We conclude that in immunosuppressed patients with a history of HBV infection may carry a risk for reverse seroconversion and monitoring anti-HBs levels may help recognising this risk.

Keywords Hepatitis B virus · Reverse seroconversion · Immunosuppression

Introduction

Although loss of HBsAg and development of surface and core antibodies represent clearance of the virus and clinical cure, recent evidence suggests that hepatitis B virus (HBV) persists in a latent state both in the liver and in peripheral

blood mononuclear cells [1, 2]. After significant immunosuppression, anti-HBs may decrease and HBsAg may reappear (reverse seroconversion). Reverse seroconversion of HBV has been observed in association with hematopoietic stem cell transplantation (HSCT), renal transplantation, intensive chemotherapy, human immunodeficiency infection, or rituximab usage [3–7]. In immunosuppressed patients with a history of HBV infection, monitoring anti-HBs levels may help recognising the risk of reverse seroconversion [8]. We present here a case study of a patient with a previous high titer of anti-HBs who later developed HBV reactivation following intensive chemotherapy for leukemia.

Case report

A 57-year-old female patient was admitted with 20-fold increase in alanine aminotransferase (ALT) level. She had a diagnosis of acute lymphocytic leukemia (ALL) 1 year ago and received induction chemotherapy according to the GMALL 05/93 protocol (Table 1). In the second phase of the induction, she developed fever and multiple, ill-defined hepatic lesions, which was treated with amphotericin B, followed by fluconazole, on a presumed diagnosis of hepatic candidiasis and responded well. Because no remission could be achieved after induction chemotherapy, she was given a salvage regimen consisting of mitoxantrone 12 mg/(m² day), days 1–3; cytosine arabinoside 500 mg/(m² day), days 1–3 and 8–10; and etoposide 200 mg/(m² day), days 8–10. Throughout the chemotherapy duration, she had to be supported with several units of blood products, mainly, due to the myelosuppressive effects of the treatment. After 7 months of the last dose of chemotherapy, she presented with laboratory findings of acute hepatitis.

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Table 1 Remission induction chemotherapy (modified from GMALL 88)

Induction phase I	
Vincristine	1.5 mg/(m ² day) (max. 2 mg); days 1, 8, 15, 22
Daunorubicine	25 mg/(m ² day); days 1, 8, 15, 22
Prednisolone	60 mg/(m ² day); days 1–28
L-Asparaginase	5,000 U/(m ² day); days 1–14
Induction phase II	
Cyclophosphamide	650 mg/(m ² day); days 29, 43, 57
Cytosine arabinoside	75 mg/(m ² day); days 31–34, 38–41, 45–48, 52–57
6-Mercaptopurine	60 mg/(m ² day); days 1–28
Methotrexate	12 mg (intrathecal); days 1, 8, 15, 22

GMALL The German Multicenter Acute Lymphoblastic Leukemia Study Group

Before 1 year of her last admission, when she was first diagnosed with ALL, her serologic tests were as follows: HBsAg (–), anti-HCV (–), and anti-HAV IgG (+). At that time, she had completely normal findings of liver function tests, with ALT and aspartate aminotransferase (AST) being both 17 IU/L. Another serologic study done 6 months later showed an anti-HBs titer of 237 IU/mL and was negative for HBsAg and anti-HCV.

On admission, physical examination was unremarkable. Initial diagnostic workup demonstrated a surprising positivity of HBsAg. Repeated studies confirmed the result. Other blood chemical and serologic studies were as follows: ALT 817 U/L, AST 412 U/L, alkaline phosphatase 542 U/L ($N < 306$), γ -glutamyl transpeptidase 1,165 U/L ($N = 15$ –60), HBsAg (+), HBeAg (+), anti-HBe (+), anti-HBc IgG (+), anti-HBc IgM (+), anti-HBs (–), anti-delta (–), and anti-HAV IgM (–). On follow-up, ALT/AST levels decreased gradually, returning to normal levels within 1 year without administering any treatment (Table 2). Ultrasound-guided fine-needle biopsies of both the nodular lesions and the parenchyma of the liver

revealed regenerative changes in hepatocytes with no fungal elements.

After 1 year, when her liver enzyme levels were normal and negative for HBV-DNA, her leukemia relapsed. She was then treated with fludarabine 30 mg/(m² day), days 1–5; cytosine arabinoside 200 mg/(m² day), days 1–5; and idarubicine 8 mg/(m² day), days 1–3. Anti-HBs antibodies showed negative findings during the all follow-up period. Because the HBsAg still showed positive findings, this therapy was administered under lamivudine prophylaxis. Her liver enzyme findings remained normal throughout the chemotherapy cycle. She died of a probable bacterial infection during an episode of febrile neutropenia following the last chemotherapy.

Discussion

Reverse seroconversion is a rare event and generally seen in the patients undergoing bone marrow transplantation. It is occasionally observed after chemotherapy for leukemia [9]. Uhm et al. [10] reported 7 of 129 patients (5%) who were initially negative for HBsAg and were then identified as positive for HBsAg after autologous HSCT; five of those seven patients developed acute hepatitis, thus indicating reverse seroconversion. They observed that reverse seroconversions were associated with multiple myeloma more frequently than any other disease. No statistical correlation was found between reverse seroconversion and thalidomide/dexamethasone maintenance therapy in patients with multiple myeloma. This finding may support the critical role of humoral immunity against the risk of reverse seroconversion in patients with multiple myeloma. Previously, it has been shown that in cases of allogeneic HSCT, reverse seroconversion hepatitis is caused by the loss of recipient-derived IgG and naive donor immunity against HBV [8, 11].

Table 2 Laboratory findings of the patient

	Admission	Mo. 1	Mo. 4	Mo. 6	Mo. 7	Mo. 8	Mo. 12	Mo. 13
ALT (U/L)	817	346	137	109	147	111	58	24
AST (U/L)	412	198	90	73	85	109	46	18
ALP (U/L)	542	239	145	145	132	115	79	82
GGT (U/L)	1,165	397	127	115	105	70		
T.Bil. (mg/dL)	1.34		0.7	0.45	0.62	0.35	0.58	0.95
D.Bil. (mg/dL)								0.21
Alb. (g/dL)	3.8		3.7	3.8	3.9	3.7	3.6	2.97
PT (s)	14			14.3			14.2	
HBV-DNA (method)		+ (PCR)		3,334 pg/mL (Hib.)		– (Hib.)		

Mo. months, ALP alkaline phosphatase, GGT γ -glutamyl transpeptidase, T.Bil total bilirubin, D.Bil. direct bilirubin, Alb. albumin, PT prothrombin time, Hib. hybrid capture

The timing of reverse seroconversion is controversial. Kempinska et al. [12] reported a patient and reviewed previous 11 patients who had adequate information. They concluded that the reactivation of HBV infection following bone marrow transplantation appears to occur almost exclusively in patients who have received marrow from an anti-HBs-negative donor and have experienced graft-versus-host disease, the onset of which is associated with the tapering of immunosuppressive therapy. However, because some patients were still receiving immunosuppressive therapy at the time of reverse seroconversion, it is difficult to conclude that the reduction or cessation in immunosuppression is a necessary trigger for clinical reactivation. In addition, our patient developed reverse seroconversion while she was receiving immunosuppressive therapy.

Monitoring anti-HBs levels can provide a reliable estimate of reverse seroconversion. Knöll et al [13] monitored seven patients with pre-transplant anti-HBs and anti-HBc levels for HBV reactivation after allo-HSCT: after allo-HSCT, all seven recipients showed progressive decline in anti-HBs titer. Reverse seroconversion was observed in six recipients occurring 12, 14, 16, 22, 31, and 39 months after allo-HSCT, respectively, and the only patient without HBV reactivation had the highest pre-transplant anti-HBs titer. Onozawa et al. [8] retrospectively studied HBV markers in 14 recipients with pre-transplant anti-HBs. Progressive decline in anti-HBs levels were observed in all cases. In 12 cases, anti-HBs titer had decreased to levels under the protective limit and reverse seroconversion occurred in 7 cases after disappearance of anti-HBs.

Patients, who were given immunosuppressive therapy, especially those with lymphoproliferative disorders, have to be accurately tested for all serum markers of HBV and not only for HBsAg. Those who have markers of a previous exposure to HBV (anti-HBs and/or anti-HBc IgG) should be closely monitored if treated with an intensive chemotherapy regimen. A progressive decline in anti-HBs titers should alert the care takers on the risk of reverse seroconversion.

Conflict of interest statement None.

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