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Case Report

Severe hepatitis B reactivation during direct-acting antiviral treatment in "the absence" of hepatitis B surface antigen

Lydia Sastre[a], Pablo Ruiz[a], Josep Costa[b], Xavier Forns[a,*]

[a] Liver Unit, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), University of Barcelona, 08036, Barcelona, Spain
[b] Department of Microbiology, Hospital Clínic de Barcelona, University of Barcelona, 08036, Barcelona, Spain

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ABSTRACT

Hepatitis C virus (HCV) treatment with direct-acting antivirals (DAA) can be associated with reactivation of hepatitis B (HBV). We report a case of a kidney transplant recipient who had a fatal severe HBV reactivation during treatment for chronic hepatitis C with DAA. Diagnosis of HBV reactivation was delayed due to undetectable surface antigen (HBsAg) by standard assays. The latter was explained by the presence of HBsAg escape mutants. The case illustrates the relevance of HBV-DNA testing in transplant recipients with previous exposure to HBV, even in the absence of HBsAg, and particularly when liver test abnormalities are present.

Introduction

Direct-acting antiviral (DAA) agents have completely changed the landscape of hepatitis C virus (HCV) infection. Current treatment regimens are able to eradicate HCV infection in almost all patients, with an excellent safety profile. Among the few potential adverse events, reactivation of hepatitis B virus (HBV) has been reported in HCV/HBV co-infected patients treated with DAA (Wang et al., 2017). The mechanisms of this phenomenon are unknown but nucleoside/nucleotide analogue prophylaxis is recommended in HBsAg positive patients and ALT levels should be monitored in HBsAg negative/anti-HBc positive patients (2018) (include EASL recommendations as reference here; no authors but only contributors so I would leave it as it is, with EASL recommendations.

HBV reactivation is characterized by abrupt elevation of HBV-DNA levels in patients with inactive or previously resolved HBV infection (Londono et al., 2017). The importance of reactivation of hepatitis B relies on its potential severity and the ease of its prevention with prophylactic oral antiviral therapy. We present a case report of fatal HBV reactivation during DAA-based treatment of chronic hepatitis C in a kidney transplant recipient, which was complicated by the presence of HBsAg escape mutations.

Case report

A 48-year-old male kidney transplant recipient with chronic HCV infection (genotype 1b) was referred to our department for antiviral treatment. The patient had never been treated before. Following graft rejection, he developed end-stage renal disease and was in evaluation for a third transplant. Immunosuppression at time of evaluation in our Unit was tacrolimus prolonged release (1.5 mg/day, blood levels 6 ng/ml), mycophenolate mofetil (500 mg/12 h) and prednisone (5 mg/day). Baseline liver function tests were: alkaline phosphatase 194 IU/L, γ-glutamyltransferase 290 IU/L, and normal aminotransferases, total bilirubin and INR. HCV-RNA load was 7.000.000 IU/ml. HBV workup showed negative HBsAg and positive anti-core IgG and anti-HBs IgG (>1.000 IU/ml). Previous HBsAg determinations (since 2001) had been always negative. Transient elastography showed a value of 11 kPa and a liver biopsy (see below) excluded the presence of cirrhosis.

In September 2017, he started grazoprevir/elbasvir 100/50 mg once daily for 12 weeks. During the first weeks of DAA therapy the dose of tacrolimus was reduced to 1 mg/d due to a slight increase in blood levels (up to 8.5 ng/ml). Six weeks after DAA initiation HCV-RNA was undetectable but there was a significant increase in aspartate aminotransferase (AST 118 IU/L) and alanine aminotransferase (ALT 147 IU/L); bilirubin remained normal and INR was 1.25. By treatment week 9, the patient had persistent elevated aminotransferases. Other viral infections (including HEV) were excluded. Considering grazoprevir as a potential cause of liver toxicity, DAA therapy was interrupted. Since a blood test revealed a positive

* Corresponding author at: Liver Unit, Hospital Clinic, IDIBAPS and CIBERehd, Villarroel 170, 08036, Barcelona, Spain.
E-mail address: xforns@clinic.cat (X. Forns).

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serum cytomegalovirus viral load (1.710 IU/ml), treatment with valganciclovir was initiated.

In January 2018, he was admitted to our hospital with fever and jaundice. Laboratory tests showed: AST 712 IU/L, ALT 436 IU/L, γ-glutamyltransferase 303 IU/L, alkaline phosphatase 224 IU/L, total bilirubin 5.7 mg/dl and INR 2. Positive HBsAg was detected, with presence of both HBeAg and anti-HBe and HBV-DNA level of 170.000.000 IU/ml (Table 1). HCV-RNA was still undetectable. Liver biopsy showed a severe acute hepatitis with necroinflammatory pattern and moderate perisinusoidal fibrosis. Immunohistochemical staining by the indirect immunoperoxidase technique depicted abundant HBV core antigen (HBcAg) in the nucleus and cytoplasm of hepatocytes.

A retrospective analysis of stored serum samples revealed the presence of HBsAg (using a different diagnostic test) and HBV-DNA before DAA initiation; both markers peaked dramatically a few weeks after the start of grazoprevir/elbasvir (Table 1). Sequence analysis of the S region demonstrated the presence of HBsAg escape mutants. As soon as the diagnosis of HBV reactivation was evident, antiviral therapy with entecavir was initiated (0.5 mg/72 h). However, liver function deteriorated, and the patient died from multi-organ failure 33 days after the initiation of entecavir.

Discussion

This is a case of severe hepatitis B reactivation during anti-HCV therapy with grazoprevir and elbasvir. Several studies have shown the association between DAA therapy (and the rapid drop in HCV viral load) with the reactivation of latent viral infections, such as HBV or Herpesvirus (Perello et al., 2016; Londono et al., 2017). In a recent review, the proportion of patients who had HBV reactivation associated with DAA treatment was around 25% in those with chronic HBV infection (9% with hepatitis) and only 1–4% in patients with resolved HBV (Mucke et al., 2018). Indeed, clinical guidelines advise the use of prophylactic NA treatment in patients who are HBsAg positive (EASL, 2018; Terrault et al., 2018) EASL Recommendations 2018. In our case, and despite the slight increase in tacrolimus levels due to the administration of a protease inhibitor, we believe that HBV reactivation can be explained by the potential immunomodulatory effect of DAA therapy.

The relevance of our case was the presence of HBsAg escape mutations (and high anti-HBs antibody titers) which made it difficult to reach the diagnosis of HBV reactivation. HBsAg mutations are prevalent in nucleoside analogue (NA) exposed patients, due to overlap between the genes encoding the reverse transcriptase and the HBsAg. HBsAg escape mutations can also be present in patients not exposed to NA (Colagrossi et al., 2018). The presence of escape mutations can reduce the binding affinity for neutralizing antibodies and alter HBsAg binding to antibodies in diagnostic assays. The latter explains the negative result of HBsAg determination by using the Advia Centaur HBsAg assay (Siemens®). When samples were retested with the Architect System HBsAg assay (Abbott®), HBsAg was weakly positive before DAA therapy (Table 1). Since the sensitivity of the different diagnostic assays may vary depending on the type of mutation, determination of HBsAg by a second diagnostic test and/or HBV-DNA may be necessary in patients in whom HBV reactivation is suspected.

The fatal outcome of this case cannot be solely attributed to liver failure. Indeed, the patient did not have an underlying cirrhosis, and HBV reactivation, although severe, was only one of the several events complicating the short-term evolution. Most likely, the presence of a profound immunosuppression associated with a septic shock had a major contribution to the outcome.

From a practical point of view, the case illustrates the relevance of HBV-DNA determination in patients previously exposed to hepatitis B who undergo DAA therapy. The risk of HBV reactivation during immunosuppressive therapy in individuals who are HBsAg negative/anti-HBc is low and the presence of anti-HBs appears to reduce the risk significantly. However, anti-HBs do not completely prevent reactivation as shown in kidney transplant recipients and patients undergoing bone marrow transplantation (Hammond et al., 2009; Kanaan et al., 2012; Terrault et al., 2018). As recommended by AASLD and EASL clinical guidelines, aminotransferase elevations in HBsAg negative patients who were previously exposed to HBV (anti-core positive) should be followed by the determination of HBsAg but also of HBV-DNA (2018; Terrault et al., 2018). In our case, and despite the presence of high anti-HBs titers, earlier determination of HBV-DNA might have changed the outcome of HBV reactivation. Importantly, the potential infection

Table 1
Evolution of laboratory parameters and serological viral markers before, during and after DAA treatment.

	27 June 2008	13 June 2017	10 October 2017	25 October 2017	17 November 2017	22 January 2018	1 February 2018
AST (IU/L)	20	29	22	118	82	429	144
Br (mg/dL)	0.5	0.4	0.5	0.6	0.5	8.9	4
INR	N/A	N/A	N/A	1.25	1.29	2.25	1.48
HCV-RNA (IU/mL)	9.6×10^5	7×10^6	ND	N/A	ND	ND	N/A
HBsAg (ADVIA Centaur, Siemens)	Negative	Negative	N/A	N/A	N/A	Weak positive	N/A
qHBsAg (Architect Abbott) (IU/mL)	N/A	2	7.552	N/A	13.488	13.315	556
Anti-HBs (IU/L)	Positive	>1.000	N/A	N/A	N/A	842	N/A
Anti-HBc	Positive	Positive	N/A	N/A	N/A	Positive	N/A
HBeAg	N/A	Negative	ND	N/A	Positive	Positive	Positive
Anti-HBe (IU/L)	N/A	Positive	Positive	N/A	Weak positive	N/A	Weak positive
HBV-DNA (IU/mL)	N/A	21.000	87×10^6	270×10^6	236×10^6	120×10^6	120.000
DNA sequencing	N/A	Y100C, T118k, P120T, M133I, D144E	Y100C, T118k, P120T, M133I, D144E	N/A	N/A	N/A	N/A
DAA (EBV/GZV)	No	No	Yes	Yes	Yes	No	No
NA (ETV)	No	No	No	No	No	Yes	Yes
CMV DNA (IU/mL)	N/A	88	N/A	N/A	1710	85	260

Abbreviations: HCV hepatitis C virus, DAA direct-acting antiviral, EBV/GZV elbasvir/grazoprevir, HBsAg hepatitis B surface antigen, NA nucleotide analogue, ETV entecavir, qHBsAg quantitative hepatitis B surface antigen, Anti-HBc antibodies against hepatitis B core antigen, Anti-HBs antibodies against hepatitis B surface antigen, HBeAg hepatitis B e antigen, Anti-HBe antibodies against hepatitis B e antigen, HBV hepatitis B virus, AST aspartate aminotransferase, Br bilirubin, INR international normalized ratio, CMV cytomegalovirus, ND not detectable, N/A non available.

with HBsAg escape mutants highlights the relevance of HBV-DNA determination in immunosuppressed patients, even in the absence of liver test abnormalities.

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Ethical approval

This is a clinical case and no data that allow patient identification are included, so ethical approval is not necessary. However, XF received funding from Secretaria d'Universitats i Recerca, Departament d'Economia i Coneixement grant 2017 SGR 1753. XF was also supported by CERC Programme/Generalitat de Catalunya.

Conflict of interest

Xavier Forns received unrestricted grant support from AbbVie and has acted as advisor for Abbvie and Gilead. Secretaria d'', grant 2017_SGR_1753 .

Author contributions

All authors participated in data collection, analysis and drafted the manuscript. All authors read and approved the final manuscript.

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