Author’s response to reviews

Title: Hepatitis B virus reactivation sustained by an HBsAg immune-escape mutant isolate in an anti-HBc positive patient during treatment with sofosbuvir and velpatasvir for HCV infection: a case report

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To Editorial Board Members

Journal of Medical Case Reports

Rome August 10th, 2019
Article title: Hepatitis B virus reactivation sustained by an HBsAg immune-escape mutant isolate in an anti-HBc positive patient during treatment with sofosbuvir and velpatasvir for HCV infection: a case report

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Corresponding Author: Prof. Loredana Sarmati

Dear Editors,

A revised version of the manuscript cited below is being re-submitted to your journal. The present version has been revised according to the suggestions of the reviewer.

Attached below please kindly find our point-by-point responses to all the concerns highlighted all changed passages in the manuscript raised by the reviewers.

Reviewer reports:

Additional revisions are needed.

Add a paragraph at the end of the Introduction that explains why this case report is presented (what is unique and adds to the medical knowledge)
More information is needed:

The case report should include past medical, social, environmental, family and employment history.

What medications was the patient on prior to diagnosis? Did the patient smoke, and/or consume alcohol?

Give detailed physical and neurological examination on the primary admission. What was the temperature, pulse, blood pressure and temperature, on admission?

Give all results of laboratory findings (i.e. CBC, liver and renal functions), urinalysis, serology, microbiology etc)

Give information about follow-up for at least 6 months.

Discussion – add a paragraph at the beginning of the Discussion that summarizes the case and describes what is unique in this case compared to what is available in the literature.

Answer:

We would like to thank the reviewer for the useful and constructive comments on our case report.

Add a paragraph at the end of the Introduction that explains why this case report is presented (what is unique and adds to the medical knowledge)

We agree with the reviewer on the need to explain why our case report is presented. Therefore, we have added this paragraph at the end of introduction:
“Here, we report a case of HBVr in an HCV-infected patient, with resolved HBV infection, treated with sofosbuvir and velpatasvir for 12 weeks. Surprisingly, the patient reactivated HBV infection and the virus developed two mutations localized in an immune-active HBsAg region, thus making ineffective HBV-specific immune response and favouring HBV viral load (VL) flare. The clinical relevance of the case is also due to the difficulty in the diagnosis of HBVr since the mutations in HBsAg did not allow its detection by the usual laboratory tests.”

The case report should include past medical, social, environmental, family and employment history.

What medications was the patient on prior to diagnosis? Did the patient smoke, and/or consume alcohol?

Give detailed physical and neurological examination on the primary admission. What was the temperature, pulse, blood pressure and temperature, on admission?

Answer:

We apologize for not going properly deeper into the social and medical history of this patient. According to the suggestions of the reviewer, we have included the complete medical, social and familiar history of the patient. Moreover, we have provided further details regarding the examination at the first visit in our clinic. Consequently, we have modified the first part of the case presentation:
“A 50-year-old male, in a stable relationship and employed, was considered for HCV treatment at our centre. In 1996, during a hospitalization for jaundice, he received a diagnosis of acute hepatitis B/hepatitis D virus (HDV) infection. At that time, an HCV infection genotype 1a was also diagnosed, which had never been treated. The patient had a history of previous assumption of injected heroin and inhaled cocaine, and he was in opiate substitution therapy (OST) with buprenorphine. Except for this, he did not assume other drugs. He was a smoker, reported a previous alcohol abuse, and at the first assessment he stated to drink 1-2 drinks a day. His medical history was notable for a sinus tachycardia and he underwent inguinal hernioplasty and appendectomy. No liver disease was documented in his family history.

His serological profile at admission to our centre was HBsAg-negative, HBV core antibody (anti-HBc)-positive, HBV surface antibody (anti-HBs)-negative, and anti-HDV-positive.

On presentation, the patient did not report any symptoms and denied previous episodes of ascites, hematemesis, melena, hepatic encephalopathy, and vomiting. The physical examination excluded signs of hepatic decompensation; in particular, it did not revealed ascites, splenomegaly, leg swelling, jaundice and spider angiomas. The remainder of the examination was normal.”

Give all results of laboratory findings (i.e. CBC, liver and renal functions), urinalysis, serology, microbiology etc)

Answer:

We thank the reviewer for this observation. We have included the results of biochemical, serological and virological analysis in the text and in the table 1:
“Laboratory analysis showed that alanine aminotransferase (ALT) was 51 IU/L, aspartate aminotransferase (AST) was 52 IU/L and glucose 108 mg/dL. The count of white-cell and platelet, and levels of haemoglobin, creatinine, alpha-fetoprotein, electrolytes and liver function tests were normal. HCV viral load was 7,014,213 IU/ml and no HCV resistance-associated substitutions were found. FIB-4 score was 2.13. Other laboratory test results are shown in table 1; data regarding the HBV VL were not available.”

Give information about follow-up for at least 6 months.

Answer:

After the end-of-treatment we have monitored the patient through frequent checks to control the virological (hepatitis B and C) status. Six month after the end of treatment, we have also performed an abdomen ultrasound and a non-invasive measurement of hepatic stiffness to assess the progression of liver disease. Accordingly, we have added these informations in the manuscript:

Page 6, line 82-87:

“The patient reached a sustained virological response (SVR) for HCV at 12 and 24 weeks after the end of treatment (EOT). The abdomen ultrasound performed at the week 24 after the EOT showed hepatic steatosis but excluded the presence of nodular lesions. At the same time point, the non-invasive measurement of liver fibrosis, through the transient elastography, confirmed the starting fibrosis stage (median liver stiffness 5.0 kPa, F0/F1 Metavir stage).”

Discussion – add a paragraph at the beginning of the Discussion that summarizes the case and describes what is unique in this case compared to what is available in the literature.

Answer:

We agree with the reviewer. We have therefore added this sentence at the beginning of the discussion:
“According to our knowledge, we first report a case of HBVr characterized by the emergence of viral strains with immune-escape mutations in an HCV-coinfected patient with isolated anti-HBc positivity and on a successful treatment with the latest generation of DAAs sofosbuvir and velpatasvir”

We have already compared our case report, describing the differences, to similar case descriptions in the literature (Page 8, line 134-143)

We hope that our revised paper will be published in Journal of Medical Case Reports, and we look forward to hearing from you. I thank you and send my best regards.

Sincerely,

Loredana Sarmati, MD

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