Author's response to reviews

Title: Passive transfer of hepatitis B antibodies from intravenous immunoglobulin

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Dear Reviewers,

Re: Case Report: Passive transfer of hepatitis B antibodies from intravenous immunoglobulin

Many thanks for your time and comments. I have made changes accordingly. Below, I have listed the comments from each reviewer in turn, and beneath each a brief indication of how/where I have addressed the issue in the manuscript. I hope you see an improvement and look forward to hearing any further thoughts.

Kind regards
Simon Parker

Points to be addressed from Reviewer 1

1. The timing of the case report is confusing. It appears that the patient had been immunocompromised for 4.5 years before IV IgG was given. The immunosuppression increased in March 2009 with Rituximab. At that time, checks on HBV markers should have been done but are not mentioned. IV IgG given in 2012 might have been indicated for both hypogammaglobulinaemia and polyarthritis. What is unclear is that, apparently, the patient screening for HBV markers was done after the initiation of IV IgG treatment prior to ‘initiating immunosuppressive therapy’, meaning in 2012 but the authors do not indicate the reason(s) for such immunotherapy in a patient already receiving Rituximab. Instead of their Table 1, the authors should present a Figure showing the immunosuppressive therapy received starting in 2008 as well as the HBV markers at time points 2008, 2009 and 2012 including levels of anti-HBs.

   a. Figure 1 has been included, illustrating the timeline of events and serology profiles at given times. Paragraph 2 of the Case Report has been edited to more clearly indicate that the sulfasalazine was initiated as an immunosuppressant for
treatment of his polyarthritis.

2. The case history suggested that the patient being HBV marker negative in 2008 but positive in 2012, a recent HBV infection had occurred while the patient was immunodeficient both by immunosuppressive drugs and possibly intrinsic hypogammaglobulinaemia. The authors should provide data regarding IgG level prior to transplant to clear that point. In such circumstances, the clinicians should have been puzzled that a recent infection was not accompanied by clinical symptoms and did not result in a chronic infection. The authors might point out such 'anomaly'

a. Addressed in paragraph 4 of the Case Report. Exact IgG levels prior to bone marrow transplant in 2008 are unfortunately not available. Exact levels are given for his admission during 2012 in Figure 1.

3. In the discussion regarding testing plasma as IgG source material, the authors should point out that anti-HBc is screened only in a few countries such as the USA and Germany. They should identify the country (ies) where the source plasma of the Vigam used came from (UK or USA or both? presumably UK as anti-HBc blood screening has been denied approximately 10 years ago).

a. Addressed in paragraphs 1, 2 and 3 of Discussion and Conclusions.

Points to be addressed from Reviewer 2

1. The description of the case provides too much unnecessary detail on many clinical events. Obviously, all details are probably very important in the clinical management of this complicated disease but the authors should try to simplify as much as possible events that may not have had any importance with regard to the covered topic. For instance, "Sputum samples at different points grew both Haemophilus influenzae and Candida albicans, and he received appropriate anti-microbials."; I am not convinced so much detail is relevant to the management of HBV infection or hepatic disease.

a. Attempts have been made throughout the Case Report to remove unnecessary detail.

2. By contrast, when describing the serological markers of this patient, all details should be provided regarding all tested markers. In the same line, it is unconceivable to read: "serology and HBV DNA testing of both donor and recipient were negative"; a "negative" serology for HBV, does not mean anything unless you provide clear results for all tested markers. In a specific report on a possible HBV reactivation, all serological results have to be provided.

a. Values have now been included in paragraph 2 of the Case Report and figure 1

3. Is it enough to state "with no evidence of a hepatitic illness" when dealing with a potential liver illness? Certainly not! It is suggested to provide values of some liver function tests.
a. Live function tests have now been included in paragraph 2 of the Case Report.

4. If the hypothesis of HBV infection was raised, why were HBc IgM antibodies not tested? Indeed, if a recent infection was suspected, recommendation would be to test for HBc IgM that could be present after the loss of HBsAg and before possible appearance of anti-HBs. This situation should be discussed.

a. Addressed in paragraph 4 of discussions and conclusions

5. Table 1 is not really informative and can be found (except maybe for the last line) in all text books on HBV. However, a recap chart providing all sequential events of this case and the observed serological profiles is missing and would certainly be more appropriate.

a. Figure 1 has been included as a timeline of events and serological profiles

6. In clinical practice, what should be done to avoid this kind of situation?

a. Addressed in the final two paragraphs

7. What are the risks of providing a false positive or negative anti-HBc serology?

a. Addressed in paragraph 3 of Discussion and conclusions

8. What products contain anti-HBc antibodies? And for what indications are they prescribed?

a. Addressed in paragraph's 1 and 3 of Discussion and conclusions

9. What are the most common situations leading to such erroneous serological profiles?

a. By giving examples of other products and the conditions they are used to treat in answering the issue above, I feel this point has also been addressed.

10. I doubt the sentence "the patient was advised to start lamivudine, a nucleoside analogue with the most suitable for the treatment of those with low (<2000IU/ml) HBV DNA levels" is correct.

a. Corrected