Author's response to reviews

Title: Anticoagulant therapy for nodular regenerative hyperplasia in a HIV-infected patient

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Author's response to reviews: see over
Dear Dr. Graham,

You informed us that our manuscript “MS1413374552288259 - Anticoagulant therapy for nodular regenerative hyperplasia in a HIV-infected patient” has been reviewed and you requested revisions of the manuscript.

Hence, we herein submit a revised version of the manuscript that takes into account all concerns raised by the reviewers, as well as a point-by-point discussion of their comments.

We would like to thank you and the reviewers for your comments and we strongly feel that by addressing all concerns, the quality of the manuscript has improved very much.

We thank you in advance and are looking forward to hear from you.

Sincerely,

Florian Bihl MD
**Point-to-point reply:**

**Reviewer 1:**

1. The authors write in discussion that perhaps changing therapy from DDI to another ARV resulted in improvement in portal hypertension. The exposure of ARV medication to this patient needs to be clarified. The authors should provide more history of ARV exposure including start date of ARV therapy, changes in the ARV regimen over time and how that correlated with improvement of portal hypertension. It is entirely possible that reversal of portal hypertension occurred as a result of ARV therapy and not anticoagulation therapy.

   **Author’s reply:** We added all information about HAART in the text (drug start and stop date and switches) and added in figure 2 the HIV viral load and CD4 counts. We discussed in more detail in the discussion section the correlation between DDI and portal hypertension as suggested by reviewer 2.

2. This patient had peritoneal tuberculosis. Peritoneal tuberculosis is another cause of ascites. The authors need to clarify the status of peritoneal TB. They should also outline the relevant therapy used for TB and the timeline of use of TB medications. I have not come across TB medications causing NRH and authors should state that it is not an etiology particularly if the timeline between TB therapy and symptoms was simultaneous. It will be prudent to include ascitis fluid analysis as well to show that it was consistent with portal hypertension based on a SAAG ratio.

   **Author’s reply:** The diagnosis of miliary tuberculosis with peritoneal involvement was made in August 2005. The PMN count in the ascites fluid was $<250 \text{ cells/mm}^3$ excluding a SBP. The SAAG was 24 gr/L (pointing towards portal hypertension and not infectious peritonitis) but bacterial culture of the ascites became positive for Mycobacterium tuberculosis. The treatment was initially with Rifampin, INH (Isoniazid) and ethambutol for 6 months and thereafter with INH and rifampin (based on the antibiogram) for 7 more months until end of September 2006. We added these information to the case report accordingly.

3. Please provide the work up for liver disease in the case report. What were the hepatitis viral serologies. Also was autoimmune work up done including ANA and quantitative immunoglobulins. Autoimmune diseases have been associated with NRH as well.

   **Author’s reply:** We added a whole paragraph in the beginning of the case report describing in detail the work up for liver disease including the serologies (HAV, HBV, HDV, HCV, HEV, CMV and EBV) and autoimmune work up (antinuclear antibodies, anti-mitochondrial antibodies, anti-actine antibodies, quantitative Ig).

4. The status of HIV disease should also be mentioned with T cell count and HIV viral load as this is pertinent as well.

   **Author’s reply:** As stated for question #1, we added the HIV viral load and CD4 counts in the text and figure 2.
Reviewer 2:

The case of a Human Immunodeficiency Virus (HIV)-infected patient with nodular regenerative hyperplasia (NRH) and severe portal hypertension that improved under anticoagulants is presented. The patient had been previously exposed to didanosine and harbored protein S deficiency. This case adds further evidence that HIV-associated NRH is linked to thrombophilia, but still, there is not enough data to recommend the use of anticoagulants in HIV-associated NRH. The manuscript should be modified to focus on the putative mechanism(s) of HIV-associated NRH. With their observation, the authors should highlight the relation between thrombophilia and HIV-associated NRH which is, to date, not so clear.

Author’s reply: We modified the introduction and discussion section in the light of the newly discovered putative pathophysiologic mechanism in HIV-associated NRH. We highlighted in the discussion the relation between thrombophilia and HIV-related NRH and adapted the discussion accordingly.

1. Major revisions

This patient had several episodes of gastrointestinal hemorrhage, one of them under vitamin K antagonist (VKA). Please explain and discuss how you managed these complications before and under anticoagulants.

Author’s reply: We thank the reviewer for pointing this out. We added in the case report the management of the variceal bleeding (repetitive band ligation and sclerosis of cardial varices).

The following mechanisms: HIV-1 vasculotropism and toxicity, didanosine and thrombophilia (especially Protein S deficiency) should be better discussed. Please reference the recent studies on the subject.

Author’s reply: As stated above, we extended the discussion accordingly and added the suggested references.

The conclusion of this paper is that anticoagulants should be evaluated in controlled studies.

Author’s reply: This message was added accordingly to the discussion section and the abstract.

2. Minor revisions:

Please reference the recent papers on the subject [1-5].


Author’s reply: We added these references accordingly

In the introduction, first paragraph, it is inaccurate to state that the central veins are squeezed by the enlarged hepatocytes in NRH, especially in HIV-associated NRH where obliterative venopathy seems to be the main mechanism [3, 6].

Author’s reply: We thank the author for this comment and we changed this statement based on the findings from the references suggested by the reviewer.