Author's response to reviews

Title: Autoimmune hepatitis type 2 associated with an unexpected and transient presence of primary biliary cirrhosis-specific antimitochondrial antibodies: a case study and review of the literature

Authors:

Pietro Invernizzi (pietro.invernizzi@humanitas.it)
Maria G Alessio (mgalessio@ospedaliriuniti.bergamo.it)
Daniel S Smyk (daniel.s.smyk@gmail.com)
Ana Lleo (ana.lleo@humanitas.it)
Aurelio Sonzogni (asonzogni@ospedaliriuniti.bergamo.it)
Luca Fabris (luca.fabris@libero.it)
Manila Candusso (manila.candusso@opbg.net)
Dimitrios P Bogdanos (dimitrios.bogdanos@kcl.ac.uk)
Raffaele Iorio (riorio@unina.it)
Giuliano Torre (giuliano.torre@opbg.net)

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Author's response to reviews: see over
Dr Christopher L Bowlus  
Section Editor  
BMC Gastroenterology  

Dear Dr Bowlus  

Re-Submission of a Case Report Reference # 8876490176667433  

We re-submit an article entitled “Autoimmune hepatitis type 2 associated with and unexpected and transient presence of primary biliary cirrhosis-specific antimitochondrial antibodies: a case study and review of the literature”, previously submitted as "Pediatric Primary Biliary Cirrhosis and Type 2 Autoimmune Hepatitis Overlap Features in a 3-Year-Old Girl: A Case Study and Review of the Literature on AMA Positivity in Pediatric Age" by Invernizzi et al. to be considered for publication in BMC Gastroenterology.

We appreciate the comments of the Editor and the Reviewers, and have made the following changes:

Editor  

Comment: "The paper is felt to be a description of an interesting case of AIH with a transient AMA but not a clinical case of overlap. This issue should be addressed along with the other issues raised by the reviewers."

Response: We appreciate the comment of the editor and the Reviewers. We made several changes in the title, abstract and the revised context of the case study, to make sure that the issues raised are satisfactorily addressed (see point-by-point response to Reviewers).

Reviewer 1:  

Comment: An increase of serum IgG levels, but normal IgM levels were recorded at onset of the liver disease. High serum IgG levels with normal IgM levels is a particular sign of AIH. Increase of serum IgM, absent in this patient (see table 1), is generally observed in patients with PBC....  

Initial response to treatment and further evolution were typical of an AIH, without any sign in favour of PBC.
in the long term follow-up. As the authors mentioned in the description of the case: “the cholangiopathic component “of PBC” does not respond to immunosuppressive treatment.

This case report does not justify the title of the article : “Primary Biliary cirrhosis... overlapping...” The title may be change to : “AIH type 2 associated with an unexpected and transient presence of AMA”.

Response: We appreciate the comments of the Reviewer and seriously take into account his view that the evidence is not in support of a definitive case of AIH type 2-PBC overlap. As such, we have changed the context of the case report to reflect the likelihood that this is a case of AIH type 2 with concomitant PBC-specific AMA positivity. These changes can be found throughout the text in the underlined positions. We have also changed the title as well as the abstract in accordance with these alterations.

Comment: Histological findings described were compatible with an AIH under treatment, however, no signs to believe that this girl had a PBC were found (“only hepatic lesion diagnostic of PBC is the granulomatous destruction of septal of interlobular bile ducts”, Oxford Textbook of Clinical Hepatology). Figure 3 does not allow to propose a possible PBC.

Response: We agree with the comments of the Reviewer in regards to the histological data. We have made changes to indicate that the histology did not confirm a PBC-AIH overlap, but demonstrated AIH with overlapping biliary features. We also made clear that histological lesions typical of PBC, like granulomatata, were not observed. These changes can be found on page 5 lines 5-7 from the bottom, page 8 lines 9-14 from the top, and page 9 lines 8-12 from the top.

Reviewer 2:

Comment: My major issue is that I do not see evidence for PBC; I see evidence for immunoserologic overlap. I would interpret the presentation as serologic overlap with AMA in the context of severe acute autoimmune hepatitis, with biliary overlap features. I do not see classic PBC and the AMA titre falls in keeping with resolving acute liver injury. The images provided do not show convincing PBC lesions.

Therefore I think this paper is useful and the review component helpful, but I would favour that the title, abstract and emphasis is adjusted very clearly to discuss the findings in the context as above.

Response: We appreciate the positive feedback from the Reviewer. We agree with the comments of the Reviewer, and have made the relevant changes, underlined throughout the text and abstract (see response to Reviewer 1). The emphasis of this report is now on AIH-2 with serological evidence of con-current PBC-specific AMA positivity.

Comment: Do the authors have AMA-MIT3 results and gp210 or sp100 titres? Can t they stain tissue for AMA (biliary phenotype).

Response: We appreciate the questions of the Reviewer, and have highlighted the methodology used in this case. This can be found in the abstract on page 3 lines 14-15, and page 16 lines 8-9. Unfortunately, we did not stain the tissue for AMA. Also, our main aim was to test for responses to individual mitochondrial antigens, as tests assessing reactivity to the MIT-3 hybrid molecule do not provide information as to
whether positive tests are due to reactivity to PDC-E2, OGDC-E2, or BCOADC-E2 (in isolation or in combination) and therefore found not very informative to test for AMA-MIT3. Nevertheless, we have performed an additional set of experiments testing the samples for autoantibodies using an IgG ELISA based on a mixture of recombinant MIT3/sp100 & gp210 synthetic peptides (Quanta Lite, INOVA Diagnostics), and revised the text accordingly.

Additional Comment:
Please note the underlined affiliation detail changes in the author list.

We hope that is review will now be suitable for publication in BMC Gastroenterology.

The Authors have read and agreed to BMC Gastroenterology Research Copyright and Licence Agreement. The article’s publication has been approved by all the other Co-authors.

Yours Sincerely

Pietro Invernizzi, MD, PhD