Author's response to reviews

Title: Anastrozole-related acute hepatitis with autoimmune features: a case report.

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Author's response to reviews: see over
Dear Editor,

I have greatly appreciated the reviewers’ comments on the above mentioned case report and I have extensively revised the manuscript according to their suggestions, particularly the Discussion. As a consequence, some references have been also changed.

New paragraphs are yellow highlighted while deleted text is red crossed out. English language has been revised. Enclosed you will find also a point-by-point response to reviewers’ concerns.

I hope that in this revised form the manuscript could be considered for publication on BMC Gastroenterology.

Yours sincerely,

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CONCERNS AND ANSWERS

Reviewer # 1 (Ráoul JJ Andrade)

1. Abstract: the first 3 lines of the conclusion … should be removed

   The first 3 lines have been removed

2. Case description: normal values for liver enzymes should be listed …
   would suggest an obstructive process in biliary tract. Why did the authors not perform other imaging technique
to rule out this possibility?

   Normal values for liver function tests have been listed.
   The mild dilatation of intrahepatic bile ducts was not considered clinically significant, also because the hepatitis
   was mainly not cholestatic and it dramatically improved after anastrozole withdrawal. This last consideration
   has been added on page 5 lines 18-19

3. Discussion: this subsection needs to be more focused. Rather than general comments …, a detailed comparison
   with the other two reports published is necessary.
   … the presence of antinuclear antibodies that disappeared upon normalization of liver enzymes as compared with
   other typical instances of hetotoxicity with autoimmune features (…) is also advisable. A recent article that could
   help shed light on this area is available …

   We have really appreciated these suggestions and we have rewritten the Discussion accordingly. General
   comments have been eliminated. Comparisons have been made with the other two published reports (page 6 lines
   22-26, page 7 lines 1-12).
   The clinical relevance of the disappearance of antinuclear antibodies has been emphasized (page 7 lines 12-16)
   and the possible analogies of the case with the characteristics of drug-induced autoimmune hepatitis have been
   mentioned (page 9 lines 14-21)

Reviewer # 2 (James H Lewis)

1. The authors failed to provide any baseline liver tests … Also, no pretreatment autoantibodies are available …
   The apparent positive De-challenge cannot be verified.

   The baseline liver function tests have been provided, but we cannot provide pretreatment values of
   autoantibodies since these tests are not included in the baseline evaluation of breast cancer patients starting
   anastrozole.
   We considered the disappearance of antinuclear antibodies after anastrozole withdrawal suggestive of a link
   with exposure to the drug and we have addressed this issue on page 7 lines 11-16

2. The word “flogistic” does not appear …
   … did the biopsy have any features that are accepted as autoimmune hepatitis-like, such as plasmacell infiltrate,
   …?

   The word “flogistic” has been substituted with “inflammatory”.
   We agree that liver biopsy did not show histological features typical of autoimmune hepatitis, but it did not
   exhibit any specific pattern and the absence of a typical histology does not categorically exclude the possibility of
   a hepatitis with autoimmune features. These issue is discussed on page 9 lines 7-10

3. Did the authors apply any standard causality assessment methodology … such as RUCAM; and given the
   possibility of autoimmune injury, did they attempt to apply the international autoimmune hepatitis scoring
   system …? What values …? And would those scores allow classification of the case of at least “probably
   related”? …
RUCAM was calculated obtaining a score of 7 that allows us to consider the event as “probably related” (page 6 lines 16-21). Unfortunately, we did not determine serum immunoglobulins, thus a complete score according to the widely used simplified criteria for the Diagnosis of Autoimmune Hepatitis is unavailable. A comment on this issue is included (9 lines 10-12).