Author’s response to reviews

Title: Amiodarone-induced reversible and irreversible hepatotoxicity: a case report

Authors:
Toyonobu Tsuda (tttsuda0329@yahoo.co.jp)
Hayato Tada (ht240z@sa3.so-net.ne.jp)
Yoshihiro Tanaka (littlechild0626@gmail.com)
Naoto Nishida (abcing4410@gmail.com)
Taiji Yoshida (tjyd27@gmail.com)
Takeshi Sawada (sawada1046@gmail.com)
Kenji Sakata (kenjis@yu.incl.ne.jp)
Kenshi Hayashi (kenshi@med.kanazawa-u.ac.jp)
Masa-aki Kawashiri (mk@med.kanazawa-u.ac.jp)
Takeru Oyama (takeruoyama@staff.kanazawa-u.ac.jp)
Motoko Sasaki (m8sasaki@med.kanazawa-u.ac.jp)
Nozomu Kurose (k-nozomu@kanazawa-med.ac.jp)
Masakazu Yamagishi (myamagi@med.kanazawa-u.ac.jp)

Version: 1 Date: 13 Feb 2018

Author’s response to reviews:

Answers to Reviewer 1

Thank you very much for your favorable and constructive comments. We have revised our manuscript according to your suggestions point by point.

Page 2 line 45: "....liver CT imaging during treatment with amiodarone and liver biopsy results should be considered when amiodarone-induced hepatotoxicity is suspected". Could the authors clarify if the suggestion is to guide therapy (continuation or discontinuation of amiodarone)
based on the findings of liver CT imaging and liver biopsy as it is currently unclear what the authors are trying to suggest in the conclusion section.

Our response: Thank you for your great comment. We revised conclusion section according to the suggestion.

Page 3 line 63: "After initiation of amiodarone, liver enzymes were gradually exacerbated....". I would recommend changing exacerbated to elevated and to give a time period over which such an elevation happened including the peak and the lowest values; also was the trend towards slow progressive AST/ALT elevation or was the elevation intermittent.

Our response: Actually, his liver enzymes gradually as well as intermittently elevated over 13 years. We revised our manuscript according to the suggestion.

Page 5 line 88: Would change the word exacerbated to elevated and provide a timeline of elevation of LFTs (would also provide the values up to which AST/ALT were elevated and if they were indeed $> 5$ times above upper limit of normal) since initiation of amiodarone.

Our response: We revised our manuscript according to the suggestion.

Page 6, line 122: was the liver enzyme elevation in the second patient more than 5 times above upper limit of normal?

Our response: The answer is NO. We added the peak value as well as the period of the elevation of liver enzymes in the manuscript.

Page 7 line 133: Would mention the signs associated with hepatotoxicity with amiodarone (e.g. hepatomegaly, weakness, ascites, jaundice) and the current recommendations for discontinuation of amiodarone therapy.
Our response: We added words suspecting hepatotoxicity with amiodarone, and recommendations to discontinue amiodarone in our manuscript according to the suggestion.

Answers to Reviewer 2

Thank you very much for your favorable and constructive comments. We have revised our manuscript according to your suggestions point by point.

Reviewer #2: In this paper, Authors reported the clinical, imaging, and histological features of 2 contrasting cases of reversible and irreversible Amiodarone-induced hepatotoxicity.

In general, the paper is interesting and well-written. However, there are a few points that may need further clarifying or revision:

- In the 1st patient:
  *there was concomitant use of corticosteroid since years. Please specify its type, corticosteroids might also cause liver injury or accelerate an underlying liver disease. Please add to discussion.

Our response: We added the specification of the corticosteroid in our manuscript, and added a sentence describing the possibility of liver injury or accelerating his underlying liver disease in discussion as suggested.

  *This patient started chronic amiodarone therapy at a young age (49 years) for VT in cardiac sarcoidosis, based on clinical decision likely made 13 years ago without any re-analyzing through the following years. Nowadays, TV catheter ablation and ICD implantation are, even being invasive, but still viable alternative in young patients rather than the potentially harmful chronic amiodarone therapy, particularly when the latter' side effects occur. Please add to discussion.
Our response: Thank you for your great comment from the clinical point of view. We fully agree with this comment. We added a sentence describing this point in discussion section.

- In the 2nd patient: *specify please the type of ventricular arrhythmia (sustained VT?), and if there was an underlying structural heart disease.

Our response: We added those information in our manuscript as suggested.

*was liver biopsy repeated to confirm the regression of liver injury after amiodarone suspension?

Our response: Thank you again for your great comment. The second liver biopsy was not performed.

- In both patients specify more the AST, ALT levels and the normal ranges (did they reach 2, 3 times of the upper normal limit or more?). This point is important clinically to know when to stop amiodarone therapy, since many patients may show minimal transaminase alterations on amiodarone.

Our response: Thank you for your good comment. Actually, this point is also suggested by the reviewer 1. We added those information in our manuscript.

- Both patients have comorbidities, please mention the other drugs used since many might also participate to liver injury.

Our response: We added those information in our manuscript as suggested.

- Is CT imaging showing liver hyper-density specific for hepatoxicity, or it is related to chronic amiodarone use/metabolism.
Our response: We believe that this is related to amiodarone use. We added this point in discussion section.

- Few typos:

Conclusions: an importance>>> importance

page 6 - line 114: leads >>> lead

page 6 line 120: fetal hepatic failure >>> fatal hepatic failure

on the other hands >>> on the other hand

Our response: We revised them as suggested.