Reviewer's report

Title: Acute-on-chronic liver failure due to methimazole in a patient with hyperthyroidism and trilogy of Fallot: case report

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Reviewer: M Isabel Lucena

Reviewer's report:

In this manuscript Shen and coworkers describe a case of acute-on-chronic liver failure believed to be induced by methimazole in a patient with hyperthyroidism and trilogy of Fallot. This is the first report of methimazole-induced acute liver failure under the abovementioned medical conditions. The report is laid out clearly and with detailed medical information. Although the authors provide coherent evidence pointing towards methimazole as the main culprit in the case, the patient’s underlying medical conditions should not be disregarded. This manuscript would benefit from a more profound consideration of potential effects of the underlying liver condition on the case development and outcome. This case report conforms to ethical guidelines.

Suggestions for consideration and improvement of the manuscript are outlined below:

Major considerations:

Title: The authors should use the drug name specified by the Anatomical Therapeutic Chemical classification. Hence, methimazole should be referred to as thiamazole (ATC code H03B002). The use of methimazole may be confused with metamizole (N02BB02), an analgesics and antipyretics.

Page 3 (Background), first paragraph: The acronym ATDs is normally used for antidepressant drugs. To avoid confusion it would be better if the authors changed their acronym for antithyroid drugs, for example to ADs.

Page 3 (Background), first paragraph: “….. presenting with toxic hepatitis or cholestatic jaundice…” is better referred to as “… presenting with hepatocellular or cholestatic injury…”

Page 3 (Background), last paragraph: “….. caused by MMI” is better written as “….related to MMI”.

Page 4 (case report), first paragraph: The patient is said to have taken MMI for one year intermittently without noticing any adverse effects. However, when MMI was continuously administrated symptoms appeared after only two days. The authors should comment on this. Did the daily dosage increase or remain the same (20 mg/day) during the intermittent and continuous administrations? Was any concomitant drugs (including non-ATDs) taken by the patient prior to hospital admission? Was any over-the-counter drugs or herbal remedies, which may have contributed to hepatotoxicity, taken by the patient?
Page 4 (case report), first paragraph: “There was no history of liver disease”. What liver disease do the authors consider here?

Despite the lack of defined liver diseases the patient’s medical condition is known to have the ability to cause liver dysfunctions, which may have affected his susceptibility to hepatotoxicity. The authors should comment on this.

Page 4 (case report), third paragraph: The authors should include laboratory test values for alkaline phosphatase (AP). The AST values could be removed. In addition, inclusion of base line values would be preferable considering the patient’s underlying liver condition. In addition, what do the authors mean with “liver protecting preparations”? Those preparations should be specified and the active ingredients listed.

Page 4 (case report), third paragraph: How was the lymphocyte stimulation test for MMI performed?

Page 5 (case report), second paragraph: MMI was discontinued on admission and treatment with PTU, propranolol and methylprednisolone was initiated. Could this have had any effect on the progression and poor outcome of the case? The authors should comment on this.

Page 6 (conclusions), second paragraph: The authors state “only a small proportion of patients can develop liver failure”. What do they mean with “small proportion”?

Page 6 (conclusions), second paragraph: What do the authors mean with “immune agents or idiosyncratic reactions”? Idiosyncratic drug-induced liver injury can involve components of the immune system.

Page 6 (conclusions), second paragraph: It is important to state that the patient’s condition was stable prior to drug treatment.

Page 6 (conclusions), second paragraph: The biopsy data are considered to favour the MMI-induced liver injury. However, it only demonstrated cholestasis, which is not specific for drug-induced injury. More specific biopsy findings, such as eosinophils and centrolobular damage are needed to support drug-induced injury.

Page 8 (conclusions), first paragraph: The authors have stated that “ATD was proposed to be a risky approach due to the possibility of cross-reactivity between the two agents”. Comments on the significance of this and possible effects on the poor outcome should be given.

The report would benefit from inclusion of a CIOMS/RUCAM scale score.

Table 1: Converting the data in Table 1 into graph(s) could make the liver and thyroid function test data more visual and subsequently facilitate the comprehension of the progression of the various parameters during the time period of hospitalization for the reader. Indications of when new drugs were started would be beneficial, as well as baseline values and values for alkaline phosphatase (AP)

Minor considerations:
Page 2 (abstract): The background sentence is grammatically confusing and needs to be revised.

Page 2 (abstract): The first sentence in the case presentation section is grammatically incorrect and should be “……Fallot, who developed……” or “……Fallot developing……”

Page 2 (abstract): The conclusions section is grammatically incorrect. Suggestion for correction: “This case suggests that methimazole-induced hepatotoxicity in the setting of advanced fibrosis increase (or can increase) the risk of poor outcome. Regular liver function monitoring during methimazole therapy is therefore important”

Page 3 (background), line 3: …..were widely…… should be …….are widely….

Page 3 (background), line 5: ……presenting with….. should be ….. presenting as…..

Page 3 (background), line 14: This sentence reads better as: Here we report the first case of a patient with hyperthyroidism and TOF that was recently referred to our hospital for acute-on-chronic liver failure (ACLF) caused by MMI.

Page 6 (conclusions), line 2: ‘changes on liver histology’ should be ‘changes in liver histology’

Page 6 (conclusions), line 12: …..‘and only a small proportion of patients can develop as liver failure’ is better worded as ‘..‘but only a small proportion of patients develop liver failure’ or ‘but only leads to liver failure in a small proportion of patients’.

Page 6 (conclusions), line 14: in the English literature

Page 7 (conclusions), line 10: …‘can lead to the liver damage’…. should be …‘can lead to liver damage’

Page 8 (conclusions), line 17: ….‘enhance their awareness of that’…..

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'.