

Answering Reviewers

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Title: Therapeutic plasma exchange and a double plasma molecular absorption system in the treatment of thyroid storm with severe liver injury: a case report

Youwen Tan, Li Sun, Kai Zhang, Li Zhu

Dear Editors and Reviewers:

Thank you very much for your comments regarding our manuscript. We have carefully revised the manuscripts per your suggestion.

Reviewer #1: The manuscript is in general very interesting and instructive. But I have several comments in order to improve the quality of the manuscript.

1. The title should be changed, because the liver lesion is caused by combination of autoimmune and hyperthyroidism-induced liver injury

A: Thanks for your very kindly comments.

We revised "Therapeutic plasma exchange and a double plasma molecular absorption system in the treatment of thyroid storm with severe immune hepatitis: a case report" to "Therapeutic plasma exchange and a double plasma molecular absorption system in the treatment of thyroid storm with severe **liver injury**: a case report"

2. The introduction should be complement with more data, or at least the discussion with more data regarding PE and treating of liver disease

A : We have added to the discussion about traditional therapies for hyperthyroidism storm and plasma exchange for liver failure in introduction. P5.

3. The case report should be presented with more details: a. Alkaline phosphatase and GGT levels are not mentioned b. Taking into account that $AST > ALT$, MCV levels should be mentioned and clearly state that alcohol abuse was excluded c. Previously and not in the end should be mentioned that viral hepatitis was excluded d. Did the patient have a history of liver disease? e. It should be stated that drug and herbal induced liver injury are excluded, as well f. Ultrasonography of the thyroid gland was mentioned, but not result of an abdominal ultrasonography examination g. Are infections by culturing are excluded as a possible cause of fever?

A: Thanks for your very kindly reminds.

a:ALP and GGT levels added in Table 1.

b: Although $AST > ALT$ in this patient, but MCV fluctuated in the normal range during the whole course of the patient's condition change, so we did not include it in detail." No alcohol abuse" added in P6.

c: "viral hepatitis was excluded" in "*History of past illness*".

d: Other liver disease (no nonalcoholic fatty liver disease history and no cholestatic liver diseases include primary biliary cirrhosis, primary sclerosing cholangitis, and secondary sclerosing cholangitis.)have excluded in "*History of past illness*".

e: We add "Drug and herbal induced liver injury are excluded" in "*Personal and family history*".

f: Abdominal ultrasonography added in "*Imaging examinations*".

g: "No pathogenic bacteria were found in blood culture" added in "*Laboratory examinations*".

Reviewer #2: The thyroid storm resistant to conventional treatments and requiring therapeutic alternatives like plasma exchange is exceptional and the

experience of the literature comes down to case reports. The clinical case presented by the authors is -original: to my knowledge there is no data in the literature about DPMAS in this indication and this treatment proposal is innovative -the case is well written, -and well documented, -the distinction between the role of thyroid storm in liver injury and an associated autoimmune hepatitis is well argued. Some points of discussion could be reinforced in order to highlight the benefit of the association of PE and DPMAS. Plasma exchange (PE) is a non-selective apheresis technique for the rapid purification of high molecular weight pathogens. It is not free of problems that it would be important to emphasize : - - The need to use alternative solutes such as human albumin and fresh frozen plasma to compensate for plasma extraction, the availability of which is limited - - Plasma exchange is adapted for 5 l of blood; the diffusion space of the T3 being approximately 30 to 40 l, the efficiency is therefore limited and transient. - Moreover, in case of cardiopathy, control of the hemodynamic state is very difficult during plasmapheresis; PE is therefore discussed in severe hyperthyroidism. Conversely, a PE treatment before DPMAS can improve the adverse effects of DPMAS on blood coagulation function and albumin levels. It would be useful to argue the previous experiences of mixed treatments in hepatology. For example, TPE and DPMAS were similar in improving 12-week survivals in HBV-ACLF in hepatitis B virus-infected acute-on-chronic liver failure treated by entecavir (PMID: 28304106 and or PMID: 30481880). Finally, it would have been interesting to have a longer-term evolution of the patient after her relapse and how the different drugs withdrawal took place, in particular to clarify the respective roles of hyperthyroidism and potential underlying AIH, in the pathophysiology of hepatic failure. In conclusion, this new approach mainly published by the Chinese teams in the context of acute liver failure should be spread in other countries.

A: Thanks for your review and recommendation.

We further elaborated and analyzed the causes and mechanisms of this combination therapy (PE+DPMAS) for thyroid storm with severe liver injury. See the discussion section of this article, in P12.

Reviewer #3:

1.Please put the normal values for table 1;

A: We added the normal values for table 1.

2.Why immune hepatitis?

A: We revised to “immunological liver injury”.

3.After 22 days, all symptoms disappeared (PLEASE DETAIL), liver function returned to normal (PLEASE DETAIL), and the hyperthyroidism index was restored (PLEASE DETAIL).

A:We revised to “liver function returned to normal (TBIL 15.2 μ mol/L, ALT 26U/L,AST 31U/L), and the hyperthyroidism index was restored (FT3 6.1pmol/L,FT4 20.4 pmol/L,TSH 0.007 μ U/ml) at first discharge.”in “Laboratory examinations”.

4.On the fourth in hospitalday, fever, palpitation, and other symptoms occurred (PLEASE DETAIL).

A:We revised to “About 40 days later, the patient was re-admitted presented similar symptoms and liver function and thyroid index abnormalities (Table 1)” .in P9.

5.In conclusion, we report a case of severe hepatic failure (PLEASE DETAIL) in a patient with severe hyperthyroidism (PLEASE DETAIL) and hyperthyroidism storm (PLEASE DETAIL). Theliver histopathology suggests that the immune damage was caused by hyperthyroidism (PLEASE DETAIL). This patient was treated with PE combined with DPMAS and achieved a good

curative effect (PLEASE DETAIL). This novel therapeutic combination may be worth popularizing.

A: Thanks for your review. However, here is a summary of the full text, details have been described in the full text.

Sincerely.

Youwen Tan, MD,

Department of Hepatology, The Third Hospital of Zhenjiang Affiliated Jiangsu University (No.300,Daijiamen,Runzhou Distinct,Zhenjiang 212003), Zhenjiang, China

Tel: +86-511-88970796;

Fax: +86-511-88970796;

E-mail: tyw915@sina.com