

Dear Reviewers

Thank you very much for inviting us to revise and resubmit our manuscript, **'Tegafur-uracil-induced rapid development of advanced hepatic fibrosis'**. You provided excellent suggestions and guidance and we have revised the manuscript accordingly. The text changes and revised areas are highlighted in red to enable easier reviewing of the revised paper. We have attempted to address all the concerns found in the reviewers' comments. In addition, we improved language problems again by Nature Publishing Group Language Editing. We hope the revised manuscript will be considered for publication. The following are point-by-point responses to the paraphrased reviewers' comments and suggestions.

Sincerely yours,

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COMMENTS TO AUTHORS

- 1) *Tegafur-uracil has been reported to have only minor adverse effects and is associated with liver injury in only 1.79% of Japanese patients; one "only" may be deleted.*

As suggested, one "only" was deleted.

2) *Are 8 months considered as “short-term administration”? What is considered long-term in years /months?*

As we described in the original version, only five cases of tegafur-uracil-induced hepatic fibrosis with portal hypertension have been described in the literature ^[1, 3, 4] (Table 2). These patients were treated with tegafur-uracil for a long period (23–54 months; mean 39.6 months) while in the present case, massive ascites, esophageal varices, and splenomegaly appeared 8 months after drug administration. Based on these findings, we described 8 months were considered as a short-term administration when compared to previous publication. However, as you suggested 8 months do not directly mean the short-term. We therefore added the word “relatively” in the revised version and added the explanation in “DISCUSSION”.

3) *“serum transaminase levels, prothrombin activity.” Please add “and”*

As suggested, we revised as follows, “serum transaminase levels and prothrombin activity.”

4) *“improved to 6.5 ng/mL and 112.2 ng/mL,” please also give initial values.*

As suggested, we revised as follows, “the patient’s type IV collagen 7S and hyaluronic acid levels were improved from 16 ng/mL to 6.5 ng/mL and from 653.4 ng/mL to 112.2 ng/mL, respectively” in “CASE REPORT”.

5) *“Laboratory examination revealed low platelet counts, liver dysfunction,*

and high hepatic fibrosis markers.” In principle there are no “fibrosis markers” to be measured in serum.

Type 4 collagen 7S and hyaluronic acid were measured as the hepatic fibrosis markers. We have revised the description “her blood examination showed low platelet counts, persistent liver dysfunction, and increased levels of fibrosis markers such as type 4 collagen 7S and hyaluronic acid.” in “CAES REPORT” and “Laboratory examination revealed low platelet counts, liver dysfunction, and high hepatic fibrosis markers such as type 4 collagen 7S and hyaluronic acid.” in “*Laboratory diagnosis*”.

6) “MR elastography, and VTQ” should be listed in Imaging diagnosis.

MR elastography and VTQ were listed in *Image diagnosis*, Figure 2A, Figure 2B, and Figure legend.

7) Legend table 1, all abbreviations have to be explained.

Thank you for pointing this out. We explained all abbreviation, in Legends and Table 1.

COMMENTS TO AUTHORS

This is nicely done. A few questions and comments:

1) *I gather the ursodeoxycholic acid was prescribed because of suspicion of PBC, but the manuscript implies it was prescribed because of elevated serum transaminase levels. I would clarify the reason.*

Thank you for your comment. Our description might confuse readers. The ursodeoxycholic acid was prescribed as a supportive liver therapy for the elevated serum transaminase levels induced by tegafur-uracil. We revised as follows, "her blood examination revealed increased serum transaminase levels. She was therefore prescribed ursodeoxycholic acid as a supportive liver therapy because of a suspicion of drug-induced liver injury." in "CASE REPORT".

2) Was a ceruloplasmin done, especially in view of liver biopsy findings?

As the liver biopsy finding did not indicate copper and iron accumulation in the liver tissue, we did not examine a serum ceruloplasmin level. We added the description "There was no pathological copper or iron accumulation." in "CASE REPORT".

3) In the last paragraph before the Discussion, the type IV collagen 7S and hyaluronic acid levels are given for after discontinuation but not before. I would say they improved from 16 ng/ml and 653.4 ng/ml to ...

As suggested, we revised as follows, "the patient's type IV collagen 7S and hyaluronic acid levels were improved from 16 ng/mL to 6.5 ng/mL and from 653.4 ng/mL to 112.2 ng/mL, respectively" in "CASE REPORT".