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Dear editor,

Thank you very much for your letter and advice. We have revised the paper, and would like to submit the revised version for your consideration. We have addressed the comments raised by the reviewers, and the amendments are underlined and highlighted in the revised manuscript. This manuscript has been edited and proofread by American Journal Experts.

We read the CrossCheck report carefully, and found that a few sentences cited from previously published papers may be responsible for a relatively high similarity index. For example, in Page 7, we cited two sentences from a recent review in Lancet to explain the mechanism of “cytokine storm” in hemophagocytic lymphohistiocytosis. In Page 10, we cited a few sentences from two in-depth reviews in the “how I treat” section of the Blood journal. In these circumstances, citations were provided to facilitate the readers with a sound evidence base. Thus these citations are necessary part of a research paper. After all, a similarity index of 18% according to the CrossCheck report may be acceptable, since most academic journals would demand a similarity index under 20-30%. We will do our best to improve the quality of our paper to meet the high standard of the journal. We also really appreciate that you give us the opportunity to make revisions. We managed to revise the cited sentences without changing the original meanings. The amendments are underlined and highlighted. Please let me know if further revisions are needed.

We hope that the revision is acceptable, and I look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Yang Guo



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We would like to express our sincere thanks to the reviewers for the constructive and positive comments.

ANSWERING REVIEWERS

Name of journal: World Journal of Clinical Cases

Manuscript NO: 40615

Title: Successful rescue of acute liver failure and hemophagocytic lymphohistiocytosis following varicella infection: A case report

Reviewer's code: 01548565

Reviewer's country: China

Science editor: Ying Dou

Date sent for review: 2018-08-07

Date reviewed: 2018-08-12

Review time: 5 Days

SPECIFIC COMMENTS TO AUTHORS

Accumulating evidence pointed towards a similar immune dysregulation pattern - a plasma "cytokine storm" in HLH and ALF. Viral infection, especially herpes viruses may trigger HLF, cy in y, in which the cytolytic activit is defect and results in uncontrolled activation of macrophages, histiocytes and T cells. This activation produces an exaggerated inflammatory response caused by hyper-secretion of pro-inflammatory cytokines. Acute liver failure associated with HLH is extremely fatal and rarely reported. In this study, the author reported a case of acute liver failure (ALF) and hemophagocytic lymphohistiocytosis (HLH) induced by varicella infection, successfully rescued by a combination therapy of acyclovir and immunosuppression with dexamethasone and etoposide. In recent years, HLH first presenting as acute liver failure was becoming



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increasingly noticed while the mortality remained high. Given the rarity, high mortality, and complexity of HLH in the context of ALF, it is important to maintain a high suspicion for HLH in ALF with or without an identified trigger. Early initiation of specific therapy targeting the underlying etiology, and watchful immunosuppression such as dexamethasone and etoposide, together with supportive therapy, are of crucial importance in this life-threatening disorder.

Replies to Reviewer 01548565

Answer: Thank you for your positive comments and encouragement. Your comments have pointed out the most innovative and important findings of the paper. These findings were summarized in the “Core tip”.



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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 40615

Title: Successful rescue of acute liver failure and hemophagocytic lymphohistiocytosis following varicella infection: A case report

Reviewer's code: 03340448

Reviewer's country: Japan

Science editor: Ying Dou

Date sent for review: 2018-08-16

Date reviewed: 2018-08-21

Review time: 5 Days

SPECIFIC COMMENTS TO AUTHORS

This is an attractive and rare case report with VZ-HLH. Received 16th Aug, 2018, and reviewed until 21th Aug, 2018. Main comments The authors did not explain the general and physical conditions, nor vital signs of the patient – most of the explanations are laboratory data. Please explain those. Minor comments Page 4) “acyclovir was started” to “intravenous acyclovir was started” Page 4) acyclovir of 10 mg/kg/day was too small for any cases. Page 4) Show the amount (IU/L) of lactate dehydrogenase (LDH) Page 4) Add also total bilirubin by “mg/dl” Page 5) Show total duration of acyclovir Page 5) Did the authors use antibiotics? If so, please explain. Page 5) Show the total observation period after discharge. No relapse for how many months or years? How are the authors going to monitor the VZV-PCR? Page 8) “On the other hand” to “In contrast” See above



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Replies to Reviewer 03340448

Thank you for your constructive comments and advice. They are very important to help us improve the quality of our paper.

1.Main comments. The authors did not explain the general and physical conditions, nor vital signs of the patient – most of the explanations are laboratory data. Please explain those.

Answer: We have concentrated on abnormal findings on physical examination, such as skin rashes and ecchymosis, as well as laboratory data, which made up the whole story of acute liver failure, varicella infection, and the more subtle condition of hemophagocytic lymphohistiocytosis. The patient was stable, alert, and oriented on admission. But his liver function deteriorated overnight with coagulopathy and grade 2 encephalopathy, revealing a devastating clinical course. As many case reports did^[1,2], we omitted the general physical conditions, or vital signs if they were normal. We now realize it may be important for the readers to capture this information and we really appreciate your advice to add the general and physical conditions, and vital signs of the patient. These amendments were underlined and highlighted. (Page 4)

2.Minor comments

①Page 4) “acyclovir was started” to “intravenous acyclovir was started”.

Answer: In the revised manuscript, we replaced it with “intravenous acyclovir was started”.

②Page 4) acyclovir of 10 mg/kg/day was too small for any cases.

Answer: On physical examination, there were papulovesicular rashes on the face and



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trunk. The typical features of skin rash led us to suspect chickenpox, but the diagnosis was not confirmed until the varicella-zoster virus (VZV) PCR amplifications showed positive findings. Nor did we relate VZV infection to the progressive liver injury on admission. Moreover, at that time we were concerned about the liver dysfunction and slightly decreased estimated glomerular filtration rate (eGFR) of $78\text{ml/min}\cdot 1.75\text{m}^2$ (Normal: >90). Thus, only a small dosage of acyclovir of 10 mg/kg/day was administered (from May 31 to June 2nd). As soon as VZV-PCR was confirmed positive and the patient was deemed as having varicella-induced acute liver failure, the dose of acyclovir was increased to 10 mg/kg every 8 hours (June 3rd to June 12).

③Page 4) Show the amount (IU/L) of lactate dehydrogenase (LDH)

Answer: In the revised manuscript, we added the amount of lactate dehydrogenase (LDH).

④Page 4) Add also total bilirubin by “mg/dl”

Answer: In fact, we showed total bilirubin by “ $\mu\text{mol/L}$ ”(Page 4). According to the “Common Usage of Quantities and Units” provided by *World Journal of Clinical Cases*, “ $\mu\text{mol/L}$ ” may be suitable. In many medical journals, “ $\mu\text{mol/L}$ ” is an acceptable unit for bilirubin^[3,4]. Furthermore, it will be more convenient for us to draw a figure based on bilirubin in “ $\mu\text{mol/L}$ ”.(Page 16, Figure 2) If the unit be changed to “mg/dl”, I’m afraid we have to work on Figure 2 all over again. The new figure may not appear as succinct and intact as the original one. I’d be grateful if you would understand our difficulty.

⑤Page 5) Show total duration of acyclovir.

Answer: Intravenous acyclovir was started at a dose of 10 mg/kg/day from May 31 to June 2nd when chickenpox was suspected. As is mentioned above, as soon as VZV-PCR was confirmed positive and the patient was deemed as having varicella-induced acute liver failure, the dose of acyclovir was increased to 10 mg/kg every 8 hours (June 3rd to June 12). This information was added in the text.(Page 5, Page 16)

⑥Page 5) Did the authors use antibiotics? If so, please explain.

Answer: Yes, we used antibiotics when the febrile patient developed neutropenia. Since immunosuppression therapy with dexamethasone and etoposide was in urgent need to treat hemophagocytic lymphohistiocytosis, antibiotics were administered concomitantly. At first, imiperem was used, and de-escalation of antibiotics was applied in the following days. We consider antibiotics as a part of supportive therapy. We also added the information of antibiotics usage in Page 5.

⑦Page 5) Show the total observation period after discharge. No relapse for how many months or years? How are the authors going to monitor the VZV-PCR?

Answer: In page 5, we mentioned that the patient remained healthy without any recurrence for 3 years. He was followed up regularly after discharge. Since chickenpox is known to be non-infectious after the rashes crust over, we carefully observed the regression of the rashes (Page 15, Figure 1), accompanied by improvement of laboratory data (Page 16, Figure 2). From these observations, we concluded that the patient had recovered. Furthermore, the patient was followed up regularly and remained healthy for 3 years after discharge. In fact, VZV-PCR was not monitored.



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⑧Page 8) “On the other hand” to “In contrast”

Answer: In the revised manuscript, we replaced it with “In contrast”.



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- [3] Slusher TM, Vreman HJ, Brearley AM, et al. Filtered sunlight versus intensive electric powered phototherapy in moderate-to-severe neonatal hyperbilirubinaemia: a randomised controlled non-inferiority trial. *Lancet Glob Health* 2018. doi: 10.1016/S2214-109X(18)30373-5. [Epub ahead of print]
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