Round 1

Dear Dr. Lian-Sheng Ma:

Thank you very much for your letter, the helpful comments and advice from the reviewers for our manuscript "Systemic autoimmune abnormalities complicated by cytomegalovirus-induced haemophagocytic lymphohistiocytosis: A case report". We learn many valuable new things from the process of answering comments.

We have revised the manuscript according to the comments from the reviewers.

Peer-review report(s)

Reviewer #1:

The manuscript needs a list of abbreviations as they are a lot.

1) Abstract: Conclusion: this conclusion cannot be drawn from a case report: "HLH patients who have positive ANA accompanied with CMV infection may completely recover when CMV is removed".

We have re-phrased the part of conclusion of abstract: The case emphasizes that thoroughly early etiological screening and removal of CMV infection is significant for the prognosis of HLH. (p 2 lines 72-74 of the manuscript).

2) Outcome and follow-up: The patient was discharged after her symptoms, and laboratory abnormalities, have improved, and she felt better. She was readmitted twice for fever caused by an autoimmune disease on February 26, 2015, and June 3, 2015 (Figure 3). Her symptoms had relieved after anti-inflammatory and glucocorticoid treatment. The patient was cured with no relapse for six years. What was her autoimmune disease in view of the

positive ANA 1:320; was she diagnosed with SLE?

As we described in manuscript, the patient tested positive for ANA (titer higher than 1:320) and was diagnosed with HLH. According to the 1997 revision of the criteria for the diagnosis of SLE by the American College of Rheumatology <Marc C. Hochberg MD, MPH. Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus[J]. Arthritis & Rheumatism,1997,40(9)>, the patient did not meet the diagnosis of SLE (p 4 lines 132-134 of the manuscript) and the physician did not make a definitive diagnosis of other autoimmune diseases. However, the patient responded well to the treatments, the titer of ANA antibodies decreased to 1:100 and continued until the following two hospitalizations, and no evidence of HLH recurrence was observed for six years.

3) Treatment: The treatment the patient received did not include etoposide which is considered the standard of care sine 1980s. Can the authors comment?

Most HLH patients are treated based on the HLH-94 and HLH-2004 protocols with dexamethasone and etoposide, although both protocols were pediatric studies. Due to the heterogeneity of adult HLH, its treatment cannot be completely based on a certain regimen. In the clinical treatment of HLH patients, in addition to the guidelines, more will be targeted at removing triggers, combined with clinical experience and expert opinion. What's more, it has been recommended that etoposide is more used in EBV infection related and lymphoma associated HLH. References include <Marc Arca,Laurence Fardet,Lionel Galicier,Sébastien Rivière,Christophe Marzac,Cédric Aumont,Olivier Lambotte,Paul Coppo. Prognostic factors of early death in a cohort of 162 adult haemophagocytic syndrome: impact of triggering disease

and early treatment with etoposide[J]. British Journal of Haematology,2015,168(1)> and <La Rosée Paul,Horne AnnaCarin,Hines Melissa,von Bahr Greenwood Tatiana,Machowicz Rafal,Berliner Nancy,Birndt Sebastian,Gil-Herrera Juana,Girschikofsky Michael,Jordan Michael B,Kumar Ashish,van Laar Jan A M,Lachmann Gunnar,Nichols Kim E,Ramanan Athimalaipet V,Wang Yini,Wang Zhao,Janka Gritta,Henter Jan-Inge. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults.[J]. Blood,2019,133(23)>. This case was not treated with etoposide and the patient was clinically cured (without recurrence for 6 years).

4) Discussion: autoimmune abnormalities (AAHS), what does AAHS stand for? infection-associated HLH (IAHS), what does IAHS stand for?

AAHS stands for autoimmune-associated haemophagocytic syndrome, and IAHS stands for Infection-associated haemophagocytic syndrome. Since all expressions in this paper are Hemophagocytic lymphohistiocytosis, we have deleted these two abbreviations (P6 line 190 and line 193 of the manuscript).

5) Discussion: Gao et al.[25] demonstrated that ALB and GA levels increase with the recovery from the disease, and this was confirmed in our case (Figure 3). The authors related the low albumin as part of liver affection and did not explain how it returned to normal with recovery.

This may be the result of a variety of factors, including increased albumin production after liver function recovery, decreased albumin consumption after the disease has improved, and because ALB is a negative acute-phase reactant that decreases with inflammation and normalizes upon recovery. We have added these to manuscript (P8 lines 237-241 of the manuscript).

6) Conclusion: In summary, we report a case of systemic autoimmune abnormalities complicated by CMV-induced HLH. This statement is very vague and needs re-phrasing. The rest of the conclusion is really not a conclusion of the authors' work, it is rather literature with references: " Compared to the reported median overall survival of HLH patients being only six months[23], our patient was cured after eliminating the CMV infection, and had no recurrence of HLH for six years, even though her ANA titer remained positive (titer of 1:100). Reviewing previous studies on successful treatment of CMV-related HLH[8,20,27], only one patient was treated with a specific antiviral agent (Ganciclovir), while the others were treated with immunomodulatory and supportive therapy, including IVIG, similar to our patient. It shows us that thorough early screening and timely treatment aimed at removing the triggers (mainly infection) and inhibiting the inflammatory response, along with providing supportive therapy, are of great significance for the prognosis of HLH patients."

We have re-phrased the part of conclusion: In summary, we report a case of HLH caused by systemic autoimmune abnormalities and CMV infection. The patient was successfully cured with a combination of immunomodulatory, chemotherapy, and supportive treatments. This case suggests that thorough early screening, timely treatment aimed at removing the infection (CMV infection in our case), and inhibition of the inflammatory response, along with supportive therapy, are of great significance for the prognosis of HLH patients. (P8 lines 251-257 of the manuscript).

Editorial Office's comments

1) The "Author Contributions" section is missing. Please provide the author contributions;

We have supplemented the author contributions (P1 lines 16-17 of the manuscript).

2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

We have uploaded the approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s).

3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

We have provided the original figure documents.

4) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

We have provided the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

Best wishes,

Hua-Guo Xu

Round 2

Dear Dr. Jia-Ru Fan:

Thank you very much for your letter, the helpful comments and advice from the reviewers for our manuscript "Systemic autoimmune abnormalities complicated by cytomegalovirus-induced haemophagocytic lymphohistiocytosis: A case report". We learn many valuable new things from the process of answering comments.

We have revised the manuscript according to the comments from the reviewers.

1) Abstract: Conclusion: This case emphasizes that thorough early removal of the CMV infection were significant for the prognosis of this HLH patient. Change to: “This case emphasizes that thorough early removal of the CMV infection is significant for the prognosis of this HLH patient.

We have changed it (p 2 lines 62-64 of the manuscript).

2) No list of abbreviations was added.

We have added the list of abbreviations (p 1 lines 30-36 of the manuscript).

3) Not all points answering the comments were changed in the text, e.g. 2) and 3).

We have supplemented these in manuscript (p 6 lines 168-169 and p 7 lines 211-213 of the manuscript).

Best wishes,

Hua-Guo Xu