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Reviewer A

Major comments

In the Methods, the authors must describe how they followed the patient' disease activity with EBV genomes, serum ferritin, cytokines, and blood phagocytosis indexes (what are these?).

- **Reply:** Disease activity was assessed according to the HLH-2004 guidelines.
- **Changes in the text:** We have modified our text (Page 5, Line 139-140; Page 6, Line 147, 168).

In Table 2 and Fig.2, cytokines were assayed only after 2022-11-02 only. why?;

- **Reply:** Cytokine testing is not usual in our hospital so these cytokines were not frequently assessed.
- **Changes in the text:** For clear information, we adjusted the date label on Figure 2 & Table 2, and the whole text as well.

In Fig.1, data during emapalumab therapy alone were graphically listed. However, for readers, it is unknown how EBV genomes, serum ferritin, cytokines and blood phagocytosis indexes fluctuated during the entire course of the disease.

- **Reply:** These laboratory parameters varied with the disease recurrence under different treatments, and the last time of the active disease was ~5 days before initiation of emapalumab and that was when we began to record the data. We aimed to describe how the EBV-DNA, ferritin, etc. changed around emapalumab.

Usually, this type of EBV-HLH in which the EBV genome resides in CD8+T cells takes a good course, not become a refractory disease. The authors did not discuss an important issue as to why this case took a refractory course.

- **Reply:** Usually, primary EBV infection has a good prognosis. If EBV virus and EBV-infected cells are not cleared well, however, HLH will relapse eventually. In this case, EBV was not well-controlled which triggered HLH recurrence.
- **Changes in the text:** We have modified our text (Page 7, Line 204-206).

PPV for the low levels of CD107a 7.14% was reported as 16.7%, and the gene screening was negative.

- **Reply:** In the local laboratory, the normal CD107a reference value is >10%. Indeed, we didn't find any HLH gene from the testing.

The authors employed various regimens- HLH-94, ruxolitinib, L-asparaginase, cisplatin, L-DEP, DEP, and PD-1 (sintilimab) besides emapalumab. The authors must tell if all of these drugs have been approved for HLH in China, or if they used some of them as off-label usage.

- **Reply:** None of these drugs were approved in China for the treatment of HLH.
- **Changes in the text:** We have modified our text (Page 4, Line 94-95).

In addition, it remains unknown if each of the regimens was employed following originally recommended doses and durations. For example, the original HLH-94 protocol did not recommend the 8-week treatment. Why did the author stop the treatment at 8 weeks? The authors only say each of them was not effective but did not mention any adverse effects of these regimens in this patient.

- **Reply:** At week 8, the patient achieved remission and was planned to further receive anti-virus treatment. Because the patient was not diagnosed as primary HLH, she was not planned to receive HSCT and did not receive maintenance therapy, per the HLH-1994 protocol. However, we finally had to decide to conduct HSCT because of the refractory/relapse disease per Chinese guidelines for HLH.
- **Reply:** We used the standard schedules for each regimen but any salvage treatment would be changed according to the statement of HLH guidelines "If patients do not display at least a partial response within 2-3 weeks of therapy initiation, salvage therapy should be considered".
- **Changes in the text:** We have added a reference in the text (Page 6, Line 147).

Most critically, EBV-HLH can occur in association with primary HLH, with other inborn errors of immunity, and as a secondary disease (associated with acute EBV infection as well as chronic active EBV disease); however, the statements in the Introduction and the Discussion appear to be misunderstood and are very confusing. Particularly, Expert opinion-style discussions don't fit a regular Case report article.

- **Reply:** Because the patient had a negative gene testing result, she was diagnosed with secondary EBV-HLH.

- **Reply:** Expert opinion-style discussion is an iMDT format of AME publishing company.
- **Changes in the text:** We have modified our text (Page 4, Line 77-79, 88; Page 7, Line 199-200).

The clinical course was also confusing because the authors used mixed actual dates, days, weeks, etc. Ideally, consistent use of days (day 0 for the disease onset) is recommended, like at Day 200, HCT was performed.

- **Changes in the text:** For clear information, we adjusted the date label on Figure 2, 3 & Table 2, and the whole text as well. Day 0 means the day for the first infusion of emapalumab.

Minor comments

1. Line 19; et.al. is not correct; should be etc.
- **Changes in the text:** We modified the text accordingly (Page 1, Line 34).

2. Line 23: A pediatric patient; specify the age and male/female of the patient.
- **Changes in the text:** We modified the text accordingly (Page 2, Line 38).

3. Line 25; Are there any molecular-targeted drug treatment for EBV-HLH?
- **Reply:** Molecular-targeted drug means JAK inhibitor and anti-PD-1 antibody for off-label use.

4. Line 61-62; EBV-ELH develops after primary EBV infection, but is also triggered by reactivated EBV infection.
- **Changes in the text:** We modified the text accordingly. (Page 4, Line 77-79)

5. Line 69: EBV-HLH occurs in cases of primary HLH and as secondary without known genetic abnormalities.
- **Changes in the text:**We modified the text accordingly (Page 4, Line 88).

6. Line 117; Low levels of CD107a (ΔCD107a, 7.14%) were detected on NK cells. However, no genetic abnormalities. How do the authors explain this phenomenon?
- **Reply:** There are more than 100 genes relative to HLH pathogenesis but only 17 genes are confirmed to have clear mechanisms of disease process. We believe that for patients with negative gene testing results, there must be other genes that we have not found yet, or HLH could be triggered by multiple variants of genes, not a monogenic change.

7. Line 110; soluble CD25 (>2,400 U/mL), Line 126; soluble IL-2 receptor (25,722 pg/mL). Why does the unit differ?

- **Reply:** The sCD25 testing was performed by a 3rd-party laboratory with ELISA which provided a result with the unit "pg/mL", referring to the local standard value. The result "25,722 pg/mL" was higher than the normal reference.
- **Changes in the text:** We added the explanation in the text (Page 6, Line 143-144). We also deleted ">2,400 U/mL" to avoid confusion for the reader (Page 5, Line 127; Table 1).

8. Ruxolitinib (dose/day; and duration of treatment?)

- **Reply:** Ruxolitinib 5 mg/12 hours. The duration of treatment was short, around 1 week, because the patient had no response to the treatment and we changed the regimen afterward.
- **Changes in the text:** We modified the text (Page 6, Line 145-146).

9. Line; 132; what are blood phagocytosis indexes? What the actual values?

- **Reply:** It should be associated laboratory parameters, a mistranslation.
- **Changes in the text:** We have modified our text (Page 6, Line 150, 168-169).

10. As a time course related to the treatments, time is not consistent (ideally, days are preferable from onset day as 0). Table 2 uses date, Figure 1 uses days, Figure 2 uses date (such as 2022-11-2), Figure 3 uses weeks (However, readers must calculate total weeks from the date presented).

- **Changes in the text:** We have modified the date label in the whole text, including Figure 2 & 3.

11. Line 237 and below; This type of discussion is very unusual, thus, is better deleted.

- **Reply:** Expert opinion-style discussion is an iMDT format of AME publishing company for case reports.

Reviewer B

This is a well-written and elaborate manuscript, describing the use of emapalumab in a 5-year-old Chinese girl, however there are few points which have to be addressed.

1. Why HLH-1994 protocol was used for the index child while HLH-2004 protocol is being practiced for years now and it is the standard treatment guideline for patients waiting for HSCT.

- **Reply:** Comparing HLH-1994 study and HLH-2004 study, early use of CsA didn't significantly improve the survival of patients but brought more toxicities. In addition, Chinese guideline for HLH also recommends HLH-1994 regimen as the 1st-line treatment for HLH.

2. There are several reports of using emapalumab in patients with refractory HLH and the mechanism of action of emapalumab is already established. What is unique about this case ?

- **Reply:** This the the first case report of emapalumab in patient with secondary EBV-HLH as a bridging treatment before allo-HSCT.

3. Although the pathogenesis and cytokine profile of primary HLH and EBV-driven HLH are the same, is there any added advantage of emapalumab in patients with EBV-driven HLH? Is there any literature regarding that ?

- **Reply:** Emapalumab has a favored safety profile that could be used in heavily treated patients with EBV-HLH (Lounder DT, et al. Blood Adv. 2019;3(1):47-50.).

4. Discussion part can be shortened.

- **Changes in the text:** We have deleted some redundant text in discussion (Line 195 – Line 251).
- **Reply:** Expert opinion-style discussion (Line 253 and below) is an iMDT format of AME publishing company for case reports.