Dear editors and reviewers:

It is very nice to hear from you, and we are grateful to you for the efforts that you have afforded on our paper. In addition, we thank you for the valuable comments and suggestions from editors and reviewers, which have helped us improve the paper's quality and learn more in this field. Accordingly, we have revised the manuscript. All amendments are highlighted in red in the revised manuscript. Following are our point-by-point answers to the questions and comments raised by the reviewers. We will make further improvements if needed. Thank you.

Yours sincerely

All of the authors

Replies to Reviewers

Reviewer 1

1) To improve the manuscript, I recommend to make a table describing the diagnostic criteria of the 3 conditions, and highlight the criteria present in this cases.

Answer: Thank you for your advice. We have revised it as you suggested in Table1, add it to *FINAL DIAGNOSIS* in P5L125, and put it at the end of the text.

Table1. The diagnostic criteria of Diffuse large B cell lymphoma, Guillain-Barre Syndrome and Hemophagocytic Syndrome.

	Diffuse large B cell lymphoma	Guillain-Barre Syndrome[1]	Hemophagocytic Syndrome[2]
Diagnostic criteria	Diagnosis is based on WHO Classification of Tumours of Haematpoietic and Lymphoid Tissues.	Bilateral and flaccid weakness of limbs Decreased or absent deep tendon reflexes in weak limbs Monophasic course and time between onset-nadir 12 h to 28	The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled (1) A molecular diagnosis consistent with HLH (2) Diagnostic criteria for HLH fulfilled (five out of the eight criteria below) (A) Initial diagnostic criteria (to be

	days *CSF cell count < 50/ul *CSF protein concentration > normal value NCS findings consistent with one of the subtypes of GBS Absence of alternative diagnosis for weakness	evaluated in all patients with HLH) Fever Splenomegaly Cytopenias (affecting 2 of 3 lineages in the peripheral blood): Hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100 g/L). Platelets <100 10^9/L. Neutrophils <1.0 10^9/L Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides 3.0 mmol/L (i.e., 265 mg/dl) Fibrinogen <1.5 g/L Hemophagocytosis in bone marrow or spleen or lymph nodes No evidence of malignancy (B) New diagnostic criteria Low or absent NK-cell activity (according to local laboratory reference) Ferritin 500 mg/L Soluble CD25 (i.e., soluble IL-2 receptor) 2,400 U/ml

NCS = nerve conduction studies; GBS = Guillain-Barre´ syndrome.

*If CSF is not collected or results not available, nerve electrophysiology results must be consistent with the diagnosis Guillain-Barre´ syndrome.

References:

1 **Fokke C,** van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. *Brain* 2014; **137**(Pt 1): 33-43.

Doi:10.1093/brain/awt285

2 **Henter JI,** Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; **48**(2): 124-131. Doi:10.1002/pbc.21039

2) Is it possible to make differential diagnosis with other entities?

Answer: We feel great thanks for your professional review work on our manuscript. The diagnosis of DLBCL was based on spleen biopsy, and the diagnosis of GBS and HPS met the diagnostic criteria, so we think it is possible to make differential diagnoses with other entities. Detailed diagnostic criteria are shown in Table 1.

3) Was the EB virus responsible to triggering GBS?

Answer: Thank you for this insightful question. In our case, despite the normal level of EBV- DNA, EBV-encoded small RNA (EBER) was positive in spleen biopsy by situ hybridization test. EBV is a possible pathogenic factor to GBS, it had been reported in several studies. The study of Cheng H *et al*.[1] showed that GBS in 15 cases (16.9%) was caused by EBV. Ostman C *et al*.[2] systematically review cases of GBS in renal transplant patients to evaluate causative pathogens or triggers, they found in 15 cases (88%), an infectious etiology was postulated as a triggering factor, EBV was 7%.

References:

1 **Cheng H,** Chen D, Peng X, Wu P, Jiang L, Hu Y. Clinical characteristics of Epstein-Barr virus infection in the pediatric nervous system. *BMC Infect Dis* 2020; **20**(1): 886. Published 2020 Nov 25. Doi:10.1186/s12879-020-05623-1.

2 **Ostman C,** Chacko B. Guillain-Barré syndrome post renal transplant: A systematic review. *Transpl Infect Dis* 2019; **21**(1): e13021. Doi:10.1111/tid.13021

4) Which was the cause of the HPS?

Answer: We would like to thank you for your careful and thorough reading of our manuscript. Epstein-Barr virus (EBV) is the most commonly reported trigger of HPS[1]. Lymphoma is one of the most important factors leading to HPS[2]. EBV is also closely related to lymphoma. We think this

patient presented as secondary HLH due to the both factors.

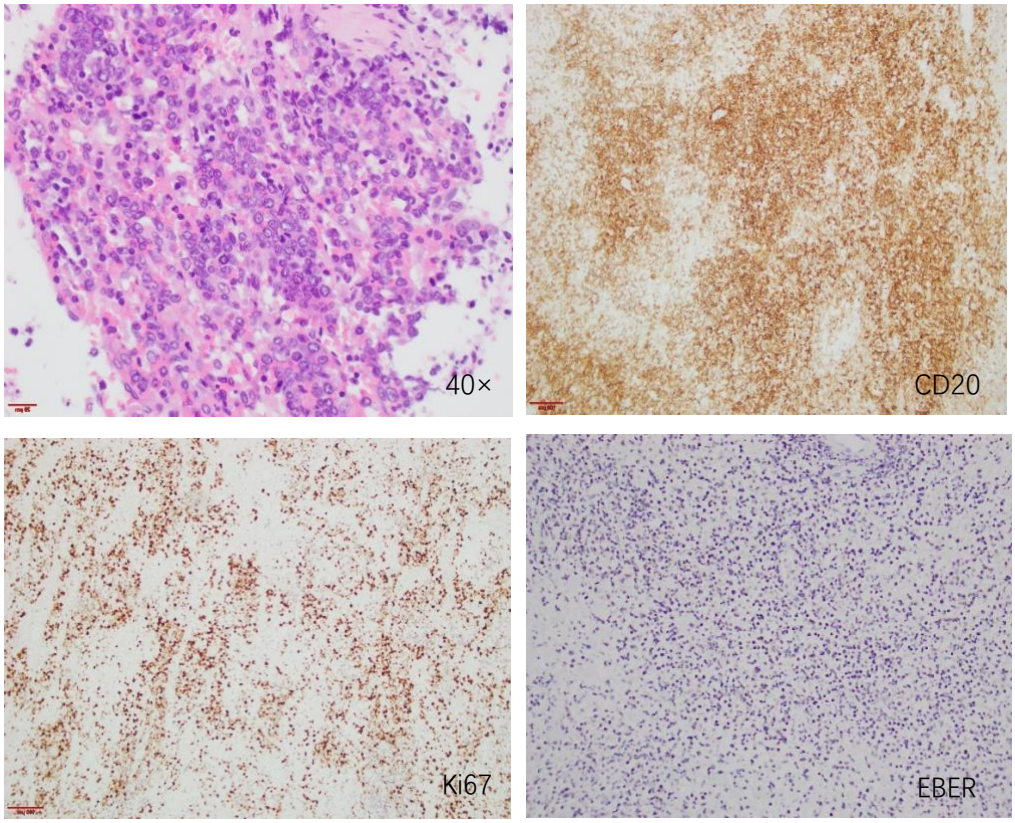
Reference

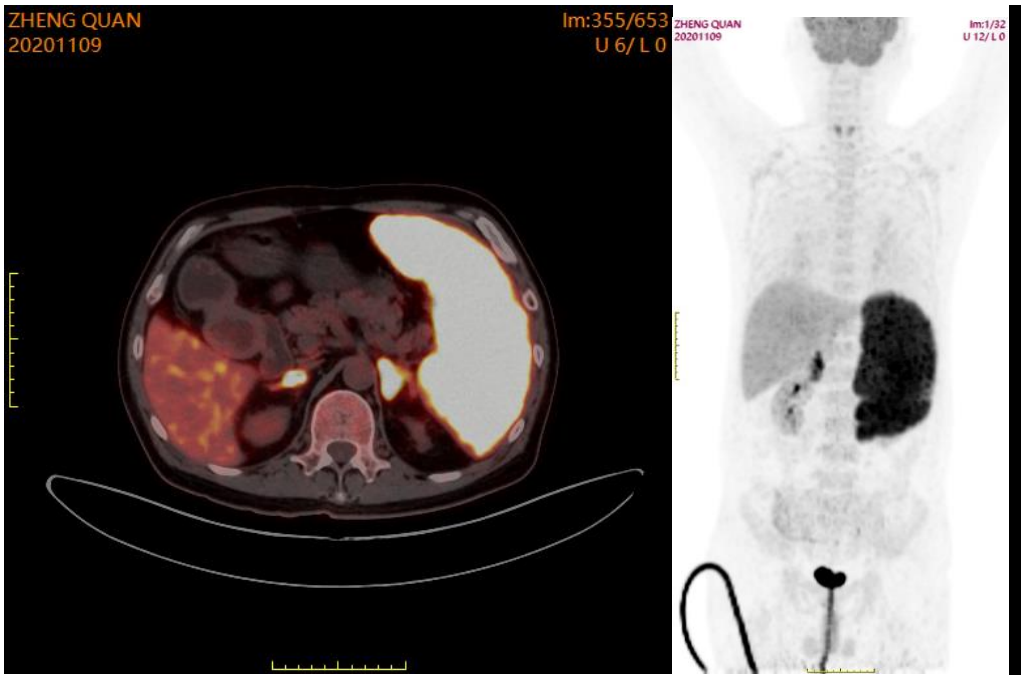
1 **Ricard JA,** Charles R, Tommee CG, Yohe S, Bell WR, Flanagan ME. Epstein Virus Barr-Positive Diffuse Large B-Cell Lymphoma Associated with Hemophagocytic Lymphohistiocytosis. *J Neuropathol Exp Neurol* 2020; **79**(8):915-920. doi:10.1093/jnen/nlaa061.

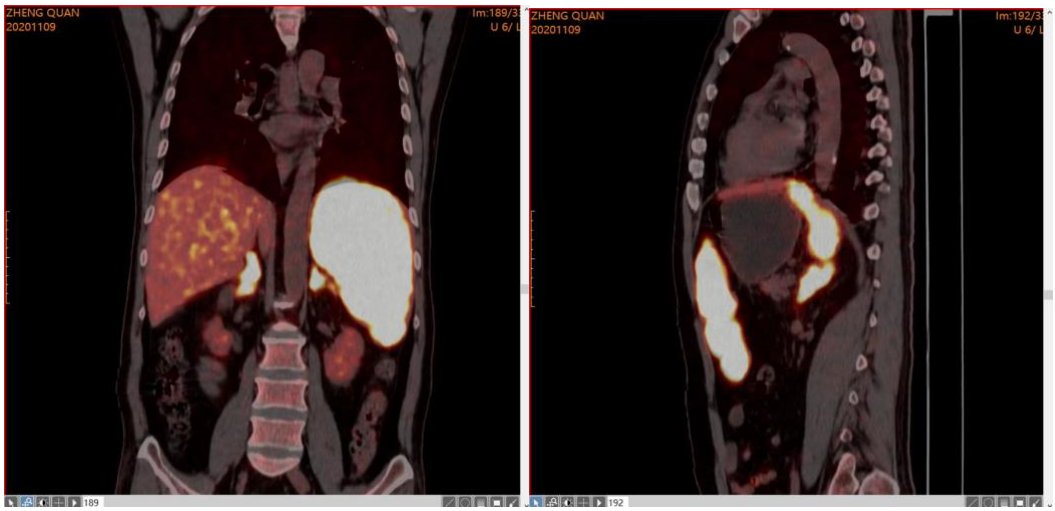
2 Wen JJ, Xu F, Zhou QL, et al. Clinical characteristics and prognostic analysis of secondary hemophagocytic syndrome in adults[J]. *Journal of Leukemia & Lymphoma*, February 2021; Vol. **30**, N. 2.

5) **Could you please show histological images, and other images such as the PET-CT scan?**

Answer: Thank you for your question. We showed the histological images and the PET-CT scan below.







6) Could you please add the normal values of the different parameters, to remind potential readers of the normal values?

Answer: Thank you for your advice. We have revised as you suggested in P4L105 - P4L119.

Reviewer 2

Thank you for your advice, our paper has been proofed by English language editors again. And we attached the language edition certification in the end (Fig. 1, Fig. 2).

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CERTIFICATE OF ENGLISH EDITING

This document certifies that the manuscript entitled "Guillain-Barre syndrome and hemophagocytic syndrome heralding the diagnosis of diffuse large B cell lymphoma: a case report and literature review" was proofread and edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the qualified scientific editors at MedSci, all of whom are native English speakers. Neither the research content nor the authors' intentions were altered in any way during the editing process.

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Fig. 1

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Manuscript title

Guillain-Barre syndrome and hemophagocytic syndrome heralding the diagnosis of diffuse large B cell lymphoma: A case report

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Fig. 2