Dear Editors and Reviewer:

Thank you for your letter and for the reviewer' comments concerning our manuscript entitled "Chronic Active Epstein-Barr Virus Infection Treated with PEG-aspargase: A Case Report" (Manuscript NO: 65884). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our article. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1:

1. **Comment:** I would suggest to add in the discussion that for the diagnosis of CAEBV disease Americans also require the presence of lymphocytic infiltration of tissues or organs (Cohen et al. Blood. 2011).

Response: The diagnostic criteria for CAEBV are as follows: (1) sustained or recurrent Infectious Mononucleosis-like symptoms persistent for >3 months; (2) increased amounts of EBV detected by Southern blot hybridization or EBER-positive cells in affected tissues or the peripheral blood or $\geq 10^{2.5}$ copies/μg of EBV-DNA in peripheral blood mononuclear cells (PBMCs); and (3) no evidence of previous immunological

abnormalities or other recent infection that might explain the observed condition [1]. The patient met the above three criteria. Therefore, she was diagnosed with CAEBV. Moreover, Cohen et al. have suggested that the diagnosis of CAEBV must be accompanied by lymphocytic infiltration (and EBV) in the tissues to ensure that the organ damage was attributed to EBV-infected lymphocytes [2]. However, EBER was not detected by in situ hybridization of the biopsy samples taken from the left inguinal lymph node and bone marrow of the patient. In a study by Kawamoto et al., the median count of EBER-positive cells in the affected lesion of patients with CAEBV was 53 per high power field and 86.3% (44/51) of the cases showed ≥10 positive cells per high power field [3]. Hence, in some patients, EBER may be negative in tissues, but high EBV-DNA load is detected in PBMCs.

Reference

[1] **Kimura H**, Ito Y, Kawabe S, Gotoh K, Takahashi Y, Kojima S, Naoe T, Esaki S, Kikuta A, Sawada A, Kawa K, Ohshima K, Nakamura S. EBV-associated T/NK-cell lymphoproliferative diseases in nonimmunocompromised hosts: prospective analysis of 108 cases. *Blood* 2012; **119**(3): 673-686 [PMID: 22096243 DOI: 10.1182/blood-2011-10-381921]

[2] **Cohen JI**, Jaffe ES, Dale JK, Pittaluga S, Heslop HE, Rooney CM, Gottschalk S, Bollard CM, Rao VK, Marques A, Burbelo PD, Turk SP, Fulton R, Wayne AS, Little RF, Cairo MS, El-Mallawany NK, Fowler D, Sportes C, Bishop MR, Wilson W, Straus SE. Characterization and treatment of chronic active Epstein-Barr virus disease: a 28-year experience in the United States. *Blood* 2011; **117**(22): 5835-5849 [PMID: 21454450 PMCID: 3112034 DOI: 10.1182/blood-2010-11-316745]

[3] **Kawamoto K**, Miyoshi H, Suzuki T, Kozai Y, Kato K, Miyahara M, Yujiri T, Choi I, Fujimaki K, Muta T, Kume M, Moriguchi S, Tamura S, Kato T, Tagawa H, Makiyama J, Kanisawa Y, Sasaki Y, Kurita D, Yamada K, Shimono J, Sone H, Takizawa J, Seto M, Kimura H, Ohshima K. A distinct subtype of Epstein-Barr virus-positive T/NK-cell lymphoproliferative disorder: adult patients with chronic active Epstein-Barr virus infection-like features. *Haematologica* 2018; **103**(6): 1018-1028 [PMID: 29242302 PMCID: 6058795 DOI: 10.3324/haematol.2017.174177]

We tried our best to improve the manuscript and made some changes in the manuscript. We did not list the changes but marked in red in revised paper.

We appreciate for Editors/Reviewer's warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Sincerely yours,

Zhao Wang

95 Yong An Road, Xicheng District

Department of Hematology

Beijing Friendship Hospital, Capital Medical University

Beijing 100050 China

Code: 100050

Phone: +010-80838339

E-mail: Wangzhao@ccmu.edu.cn