Dear editor,

RE：Manuscript **NO.** 53611

We would like to thank World Journal of Clinical Cases for giving us the opportunity to revise our manuscript.

We thank the reviewers for their careful read and thoughtful comments on previous draft.

We have carefully taken their comments into consideration in preparing our revision, the following summarizes how we responded to reviewer comments.

Thans for all the help.

Best wishes,

Dr. Nan Li

Replies to Reviewer#1:

1) There are many unclear points in the presentation of this patient, and the diagnosis is not clear. It seems that EB virus infection is currently active, but what about the results of immunostaining for EBNA-2, LMP-1, CD30, TIA1, etc.? Also, were T-cell clonality and hemophagocytosis observed? Pictures are not required and should be explained in writing. (In addition, I could not find the pathological photograph in Fig. 2) I did not understand the basis of your diagnosis as to whether this case should be NK/T-cell lymphoma with chronic EB virus infection, or a combination of the two.

RE：We checked the EBER positive in immunohistochemistry, which supported the EBV infection. Due to space limitations, I deleted some immunohistochemical results and pathological pictures when editing the article. This part has been added back to the article (Further treatment and diagnostic work part and Fig. 2). The two items of EBNA-2 and LMP-1 are unconventional testing items, which have not been carried out in our hospital. This is indeed very regrettable, but combined with his clinical manifestations,

laboratory tests, imaging tests and immunohistochemistry, we believe that the diagnosis of NKTL has been basically clear.

2) Regarding the discussion: First, the diagnosis as above mentioned, should be carefully considered. So should this case be a gray zone for chronic EBV infection and NK/T-cell lymphoma? Can this condition be transferred? Strict differential diagnosis may be difficult, but how did the author understand this condition? The author should comment on the condition, giving a general concepts. This is the most important point of this paper.

RE：I agree with you that the accurate identification of the two diseases is very difficult. Through the male's repeated fever, lymphadenopathy, increased liver function, EB virus antibody and DNA positive for more than 3 months, we confirm that the diagnosis of CAEBV; And our case progresses faster, starting with solid tumors, but CAEBV rarely develops into solid tumors in the literature, so we are also more inclined to the final diagnosis of NKTL. However, for this case, whether the lymphoma has progressed from CAEBV, we do not have enough evidence to make a judgment, but as I stated in the discussion, it is generally believed that the history of TNKLPDC is prolonged and progress is slow, but the male showed a solid tumor shortly after onset,, so we think this possibility is not high. However, this judgment is difficult. On the one hand, this male has been ill for nearly a month when he came to our hospital, lacking early medical records and examination data, on the other hand, the distinction between the two is difficult itself. This is reinforced in the article (Discussion section, paragraph 4), and I hope to get your approval.

3) I considered extremely rare that a 3-year-old infant would develop the disease. Has there been a similar case report in the past? Also, as the authors state, long-term survival seems to be quite severe without allogeneic hematopoietic stem cell transplantation, but the patient has survived successfully without recurrence for more than two years. I wanted you to explain this reason. As mentioned above, this patient is considered to be a

very valuable case, but a significant reconsideration is required before publishing the paper.

RE: The 3-year-old male suffered from this disease, and involved the intracranial, and ultimately survived cases are indeed extremely rare, I have not retrieved relevant reports; based on this, our initial assessment of the prognosis of this male is not optimistic. Due to the lack of relevant experience, out of my shallow understanding, immune dysfunction plays a key role in the development of CAEBV. On the one hand, this male has not detected known pathogenic gene mutations, although there is a heterozygous mutation in the ITK gene, but the mother who also carries heterozygous mutations is healthy; on the other hand, CAEBV itself can have a clinical remission period, and chemotherapy also has a certain effect, but there is a possibility of long-term recurrence, and it is generally believed that it can only be cured by transplantation. This male was relieved from the tumor by chemotherapy. Although he has survived disease-free for more than two years, we cannot rule out the possibility of a future recurrence, a long-term follow-up is also required (Discussion section, paragraph 4). But this is just my personal understanding, there is no clinical evidence, which is why I think this case is very special, and I hope to share it.

Replies to Reviewer#2:

Considering of positive IgM antibody for EBV and entire clinical course, this infant is considered to have contracted primary severe EBV infection. In this context, it seems not adequate to conclude that his lymphoma was progressed from chronic active EBV infection. Although rare, it has been reported that fatal EBV primary infection resembles lymphoma clinically. (For the diagnosis of CAEBV, it is necessary that mononucleosis-like symptoms continue for more than three months.) In fatal or severe primary EBV infection including EBV-HLH, EBV infection in B or T cells is polyclonal or oligoclonal. Authors should check monoclonality of EBV infection in the

lymphoma cells. Also, monoclonality of NK/T lymphoma cells should be determined.

RE : First of all, through the male's repeated fever, lymphadenopathy, increased liver function, EB virus antibody positive and EB-DNA positive greater than 3 months, we confirm that the diagnosis of CAEBV is established, which cannot be explained by the primary infection of infant EBV ; Through his occupation of solid masses and pathological immunohistochemical results, we believe that it is also consistent with the diagnosis of NKTL, and the positive EBER in the pathological tissue suggests that EB virus infection may be related to NKTL. The main clinical finding of simple CAEBV infection is inflammation, and it has rarely been reported as a solid tumor. In CAEBV infection, EBV-positive T-cell lymphoid tissue proliferative disease grade III is equivalent to lymphoma, due to the consistency of the two in the course of disease, and a hospital pathology directly reported EBV-positive T-cell lymphoid tissue proliferative disease grade III, we have considered the correlation between the two, but as you said, we have no direct evidence to confirm the absolute relationship between the two. However, as I stated in the discussion, it is generally believed that the history of TNKLPDC is prolonged and progress is slow, but this male showed a solid tumor shortly after onset, so we think this possibility is not high. Regarding this part of the discussion, I have re-intensified the thesis and hope to get your approval. We also consider the monoclonal test for EBV infection in lymphoma cells, but on the one hand, there was no institution in my city to carry out this test. In addition, due to the unoptimistic assessment of the prognosis, the parents of the male refused some complicated examination, radiotherapy and transplantation. This is also a very regrettable part of this case. Regarding the above, I made changes in the discussion section, paragraph 4 and the final conclusion, and hope to get your approval.