Manuscript ID: 73251

Title: Recurrence of infectious mononucleosis in adults after remission for three years: A case report and literature review

Journal: *World Journal of Clinical Cases*

Response to Reviewers' comments

Dear Dr Wang

We thank you for your careful consideration of our manuscript. We appreciate your response and overall positive initial feedback and modifications to improve the manuscript. After carefully reviewing the comments made by the reviewers, we have modified the manuscript to improve the presentation of our results, therefore providing a full context for the research that may be of interest to your readers.

We hope you will find the revised paper suitable for publication, and we look forward to contributing to your journal. Please do not hesitate to contact us with other questions or concerns regarding the manuscript.

Best regards

Reviewer #1

This manuscript has been written on a well designed study and interesting topic. There are no major issues I can point to.

Response: We thank the Reviewer for the positive and encouraging comments.

Reviewer #2

In the current manuscript, the authors present a case with recurrence of infectious mononucleosis (IM). The manuscript is well written, and the readers can follow the clinical course of this rare case.

Response: We thank the Reviewer for the positive and encouraging comments.

However, the authors need further consideration of the diagnosis, especially considering the possibility of chronic active EBV infection (CAEBV).

Response: We thank the reviewers for reminding us that we considered the possibility of CAEBV in our diagnosis. Although the patient had IM-like symptoms again after three years, his EBV-DNA titer was less than 1000 copies/ml, titers of VCA-IgG showed that it was not detected, which were both lower than the lowest value hat could be detected in the laboratory, and there were no clinical symptoms that other chronic diseases could not explain. Under the current medical conditions of our hospital and the hint of guidelines [1] [2], we consider that all the current clinical evidence is insufficient for the diagnosis of CAEBV.

When the patient was admitted to the hospital for the second time, there were the following symptoms: fever, pharyngitis, cervical lymph node enlargement and splenomegaly. Laboratory examination showed that atypical lymphocytes were 0.1, and the absolute value of lymphocytes was more than 5*10^9/L, which met the diagnostic basis of clinical diagnosis of IM [2]. In the follow-up laboratory examination, both EBV-CA-IgG and EBV-CA-IgM were positive, and we were more inclined to diagnose the patient as recurrence of IM.

The authors need to check EBV viral load and show the titers of VCA-IgG. Additionally, the authors need to check the clonality of expanded T-cells to exclude the possibility of CAEBV.

Response: We thank the reviewers for their comments. We checked the DNA titer of EBV and the titer of VCA-IgG, which are lower than the lowest value could be detected in our laboratory. Unfortunately, the patient refused the lymph node biopsy, so we could not obtain a biopsy to examine the clonality of expanded T-cells. In gene rearrangement, IM is polyclonal, CAEBV is polyclonal, oligoclonal or monoclonal, so we think that gene rearrangement cannot completely distinguish the two.

Minor concerns: 1. Why do the authors need to show the nationality of this case?
Response: We thank the reviewer for the kind reminder. When we looked up the literature, we found that the incidence of adult cases of CAEBV and IM in East Asia was significantly higher than that in Europe and the United States. We believe that the patient's nationality may be associated with his recurrence of IM.

Figure 2E shows biopsy results of bone marrow, not the smears. Did the authors check EBER in the bone marrow slide?

Response: Thank you very much for pointing out the language translation errors in our article. We have revised it to bone marrow biopsy in this article. We were unable to EBER in the bone marrow.

Reviewer #3

Dear Author, your topic was interesting and it is essential in the clinical practice. Furthermore, it is given a future direction for the clinician and researcher in working further in the proactive diagnosis, management and prevention of the IM.

Response: We thank the reviewer for the positive and encouraging comments.

Science editor:

This manuscript reports a case of recurrence of infectious mononucleosis (IM). It is of guiding significance for the active diagnosis, management and prevention of IM. Please show the titer of VCA IgG and check the clonality of amplified T cells.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Response: We thank the Science Editor. We revised the manuscript according to the Reviewers' comments. We examined the DNA titer of the patient's EBV and the titer of VCA-IgG, but because the patient refused a lymph node biopsy, we could not obtain a biopsy to examine the clonality of expanded T-cells.

We want to add that in gene rearrangement, IM is polyclonal, CAEBV is polyclonal, oligoclonal or monoclonal, and the results of the two tests overlap, so we believe that gene rearrangement cannot completely distinguish the two.

We considered the possibility of CAEBV in the diagnosis. Although the patient had IM-like symptoms reappeared after three years, the patient met condition 1 of the CAEBV diagnostic criteria in guideline [1] and had persistent or recurrent IM symptoms but did not meet the latter two. His V-DNA titer and VCA-IgG were lower than the lowest value that could be detected in the laboratory, and there were no clinical symptoms that other chronic diseases could not explain. Under the current medical conditions of our hospital and the hint of guidelines [1] [2], we consider that all the current clinical evidence is insufficient for the diagnosis of CAEBV.

At the same time, there were the following symptoms: fever, pharyngitis, cervical lymph node enlargement and splenomegaly. Laboratory examination showed that heteromorphic lymphocytes were 0.1, and the absolute value of lymphocytes was greater than 5*10^9 / L, which met the diagnostic basis of clinical diagnosis of IM [2][3]. In follow-up laboratory tests, both EBV-CA-IgG and EBV-CA-IgM were positive, so we were more inclined to diagnose the recurrence of IM.

Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before its final acceptance, the author(s) must provide the Signed Consent for Treatment Form(s) or Document(s). Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". 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. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response: We thank the Editor-in-Chief. All tables are three-line tables. The rows are aligned. Returns were not used to align the text in the tables.

References

[1] Okano M, Kawa K, Kimura H, Yachie A, Wakiguchi H, Maeda A, Imai S, Ohga S, Kanegane H, Tsuchiya S, Morio T. Proposed guidelines for diagnosing chronic active Epstein-Barr virus infection. American journal of hematology. 2005 Sep;80(1):64-9.

[2] 中华医学会儿科学分会感染学组, 全国儿童 EB 病毒感染协作组. 儿童主要非肿瘤性 EB 病毒感染相关疾病的诊断和治疗原则建议. *中华儿科杂志* 54.008(2016):563-568.

[3] Luzuriaga, K. and J.L. Sullivan, Infectious mononucleosis. New England Journal of Medicine, 2010. **362**(21): p. 1993-2000.

Round 2

The authors provided additional data and changed the manuscript according to the comments from Reviewers. The changes have made the manuscript clearer. Discussion about the possibility of CAEBV including how the authors excluded the disease will be welcomed for the readers.

As the patient had IM-like symptoms again after three years, we considered the possibility of CAEBV and recurrent IM in our diagnosis. His EBV-DNA titer and titers of VCA-IgG were both lower than the lowest value that could be detected in the laboratory, and there were no clinical symptoms that IM or other chronic diseases could not explain. Under the current medical conditions of our hospital and the hint of guidelines [23], we consider that all the recent clinical evidence is insufficient for the diagnosis of CAEBV. Therefore, based on the clinical manifestations of the patient (lymphadenopathy and pharyngitis) and the laboratory test results (atypical lymphocytes ≥10% and positive EBV VCA antibodies), we confirmed the diagnosis of recurrent IM in the patient.