

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Treatment of gastric carcinoma with lymphoid stroma by immunotherapy: case report and literature review" (ID:75428). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. 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. Response to comment: There is missing data in the history and patient examination can you please discuss these items in detail.

Response: We thank the reviewer for pointing this out. We have made the change. See the "CASE PRESENTATION" section for details.

2. Response to comment: Regarding the figures, can you add annotations, magnifications, scale bar.

Response: We have made the corresponding revisions. Pathological pictures are also scaled.

Reviewer #2:

1. Response to comment: What is the mechanism of the healing pathway of the cancer cell? Please discuss considering tumor micro environment.

Response: Based on studies, we speculate that the possible reasons why this patient has a good effect on immunosuppressive therapy: on the one hand, the inflammatory factors dominated by IFN- γ released by a large number of infiltrated CD8⁺ T cells in the GCLS microenvironment induce PD-L1 high expression; on the other hand, EBV can also enhance the expression of PD-L1. Its unique tumor microenvironment confers immunotherapy sensitivity.

These contents are also added to the article, see the "Discussion" section for details.

2. Response to comment: Is the immuno-therapeutic pathway inducible or constructive? Also, inflammatory or non-inflammatory? Discuss that citing the following article. Characterization of PD-1/PD-L1 immune checkpoint expression in soft tissue sarcomas. Eur J Histochem. 2021 Jul 2;65(3):3203. doi: 10.4081/ejh.2021.3203. PMID: 34218652; PMCID: PMC8273625.

Response: For this comment, we made the following additions (details can be found in "Discussion" section): The TCGA study identified some characteristics that suggest that EBV tumors are potential candidates to immunotherapy with PD-1/PD-L1 pathway inhibitors, as genomic amplification of chromosomal region 9p24.1 (the locus of genes encoding PD-1 ligands PD-L1 and PD-L2) and IFN- γ released by tumor infiltrating T cells, which can directly induce PD-L1 expression. At the same time, a study on soft tissue sarcoma also suggested that many inflammatory factors in the tumor microenvironment can up-regulate the expression of PD-L1, of which IFN- γ is the most important stimulator. In addition, EBV positivity may also constitute a reliable biomarker for the efficacy of GCLS immunotherapy. Recent studies have shown that Epstein-Barr virus can promote the immune escape mechanism by enhancing the expression of PD-L1 in tumor cells. Based on the above studies, we speculate that the possible reasons why this patient has a good effect on immunosuppressive therapy: on the one hand, the inflammatory factors dominated by IFN- γ released by a large number of infiltrated CD8⁺ T cells in the GCLS microenvironment induce PD-L1 high expression; on the other hand, EBV can also enhance the expression of PD-L1. Its unique tumor microenvironment confers immunotherapy sensitivity. Therefore, the immunotherapy of GCLS mainly works through inducible or

inflammatory immune mechanisms.

Science editor:

1. Response to comment: The number of total references is few and a bit outdated, maybe a little more related references could also be cited.

Response: GCLS is a rare disease, so there are relatively few references in this area, but we also try to increase the number of literature and update some relatively new literature, see the “references part” for details.

2. Response to comment: The pathological pictures in the manuscript need to be marked with a scale bar.

Response: We thank the editor for pointing this out. We have revised.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

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

Thank you and best regards.

Sincerely,

[Hongzhen Zhang, PhD Professor, Department of Oncology, Hebei General Hospital]