

Peer Review File

Article information: <https://dx.doi.org/10.21037/tcr-22-1595>

**Reviewer A**

1. Would describe MRI findings in more detail (how large were the ischemic infarcts) and their possible contribution, if any, to the patient's neurological symptoms.

**Reply:** MRI report showed a few abnormal dotted signals in white matter of bilateral frontal lobe with T1WI equal signal, T2WI/FLAIR high signal, and DWI no abnormal dispersion signal. These ischemic infarcts are too small to explain those severe symptoms. The ischemic infarcts' location in the brain doesn't square with this patient neurological symptoms. We suppose there are not direct relationship between the ischemic infarcts and his neurological symptoms.

**Changes in the text:** We have modified our text as advised (see Page 4, line 70-73).

2. Refrain from using descriptive words like "huge" - try more professional synonym such as 'large'

**Reply:** Thanks for your suggestion. It has been refined with less descriptive words.

**Changes in the text:** We have modified our text as advised (see Page 4,5,13, line 81, 88, 261)

3. It is unclear - did the patient achieve complete response after only 2 cycles of chemotherapy?

**Reply:** After two cycles of chemotherapy, the gastroscopy in follow-up showed no lesions in the stomach but an inadequate assessment of the distal duodenum; However, the repeat PET/CT was carried out after four cycles of chemotherapy, showing no abnormal foci of increased radioactivity in the stomach wall and focal increased radioactivity in the ascending duodenum, with an area of 0.9\*1.3\*1.5cm, SUV max 13.6. For these reasons, I suppose the therapy was effective, but the patient didn't achieve a complete response after two cycles of chemotherapy.

**Changes in the text:** We have modified our text as advised (see Page 6, line 109-110,

115-118).

4. Did you employ a lumbar puncture with CSF evaluation for the patient at any point? Did the patient receive IT chemo for CNS prophylaxis? Why or why not?

**Reply:** The patients received a full assessment of CSF right after admission, before the first cycle of chemotherapy, and before the second cycle of chemotherapy respectively. The result of the first CSF test is shown in the table 1 in manuscript. The patient didn't receive any intrathecal prophylactic therapy due to repeated negative findings in CSF and brain enhancement MRI.

**Changes in the text:** We have made no changes.

5. Was a paraneoplastic panel test sent on serum or CSF?

**Reply:** Both serum and CSF paraneoplastic panel tests showed negative results. These results are added to table 1 in the manuscript.

**Changes in the text:** We have modified our table as advised (see Table 1).

6. Discussion is very good however 2nd to last paragraph is not needed as it related more to the presentation of gastric lymphoma rather than PCD which is your primary topic.

**Reply:** We appreciate your suggestion a lot. It is worth mentioning that the topic we focus on is PCD. But the major reason we wanted to include this paragraph is to raise awareness among gastroenterologists reading this article about deep excavation biopsies of lesions. Medicine diagnosis relies on pathology, while pathology diagnosis relies on biopsy technique. The patient also had a multi-point biopsy taken at another hospital without any positive findings due to the superficiality of the biopsy taken. The gastroenterologists at our hospital used deep excavation biopsies and the result of every piece turned out to be positive, contributing to the patient's timely and accurate diagnosis. Besides, hematologists may miss a few lymphoma diagnoses in time and elongate therapeutic time windows if they only rely on pathology for a definitive diagnosis of lymphoma without realizing the quality of biopsy plays a key role sometimes for gastrointestinal lymphoma.

**Changes in the text:** We have made no changes.

Overall well written and interesting case. I would add more to case report body described patient work up as requested above.

### Reviewer B

This paper is a case report of double-hit high-grade B-cell lymphoma with gastroduodenal lesions complicated by PCD. I think this paper discusses the very significant content that the chemotherapy regimen was changed to R-EPOCH and the response of double-hit lymphoma improved the patient's neurological symptoms. The following is a list of items that I would like you to reconsider.

#### Major Point

1. Is this case a malignant lymphoma originating from the stomach and duodenum? Please add a PET image to the figure. If the main lesion is the stomach and duodenum, please change the title to 'Primary gastroduodenal high-grade B-cell lymphoma' instead of 'with gastroduodenal involvement'.

**Reply:** This is a great question we have been thinking about for a period of time. At the beginning, our article title was 'primary gastroduodenal high-grade B-cell lymphoma', but we found it may not be that accurate later. The first PET evaluation showed some high uptake lymph nodes around the lesions (SUVmax 2.84), but much lower than the FDG uptake level of its gastroduodenal lesions (SUVmax 26.49-31.77). They were probably reactive hyperplasia of lymph node. The biopsy of these lymph nodes was quite hard to operate on and not beneficial for this patient since the final pathology diagnosis is confirmed. Therefore, we suppose that the definitive diagnosis of 'primary gastroduodenal high-grade B-cell lymphoma' cannot be ruled out, while the description 'with gastroduodenal involvement' shall be more precise without a biopsy of these lymph nodes. In addition, as the PET/CT was carried out in another hospital, we could only obtain the paper image, which has a low resolution and couldn't be presented in the manuscript.

**Changes in the text:** We have made no changes.

#### Minor Points

1. The term gastroscopy is used multiple times in Key words and manuscript, but esophagogastroduodenoscopy (EGD) is a common notation.

**Reply:** We appreciate your advice and have refined it as you suggested.

**Changes in the text:** We have modified our text as advised (see Page 4, 5, 6, 9, line 80, 86, 107, 171)

2. Please add the interleukin-2 receptor to the laboratory findings in Table 1.

**Reply:** We suppose IL-2R (sCD25) is mainly used for the diagnosis of hemophagocytic syndrome. We did not take this examination because of no related manifestations of hemophagocytic syndrome in this patient.

**Changes in the text:** We have made no changes.

3. The anthracycline drug used in the first chemotherapy was pirarubicin, and you should write THP-COP, not CHOP.

**Reply:** We appreciate your advice and have refined it as you suggested.

**Changes in the text:** We have modified our text as advised (see Page 5, line 101 and Table 2)

Please accept this paper under the above conditions.

### **Reviewer C**

1. please mention of paraneoplastic antibody testing methodology (cell based, immunofluorescence ? etc)

**Reply:** The method is a line blot assay.

**Changes in the text:** We have modified our text as advised (see Table 1)

2. please mention the number of oligoclonal bands seen in the csf

**Reply:** I'm sorry that the detection report did not mention the specific number of oligoclonal bands, but it was clear that the type of bands was type II.

**Changes in the text:** We have modified our text as advised (see Table 1)

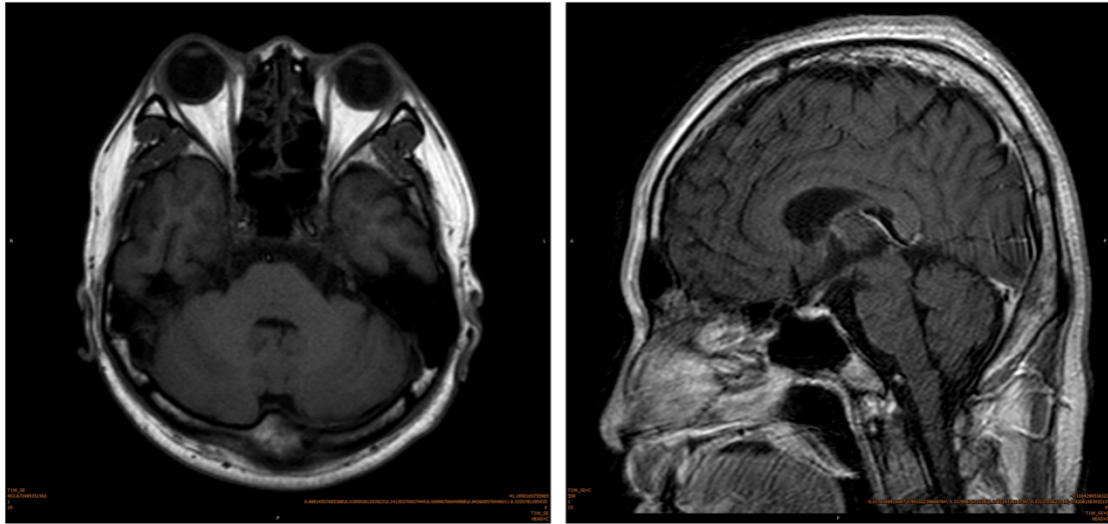
3. no need for mention of hospital (line # 27)

**Reply:** I appreciate your advice and have refined it as you suggested.

**Changes in the text:** We have modified our text as advised (see Page 3, line 54)

4. please include MRI of brain showing cerebellum & vermis (especially saggital view that includes pons)

**Reply:** Thanks for your suggestion. The MRI of the brain showing cerebellum & vermis (a sagittal view that includes pons) is shown below. The MRI image' artifacts are due to the patient's incontrollable head shaking. We do want to use these pictures, but the imaging quality is too poor to be adopted in the manuscript.



**Changes in the text:** We have made no changes.

5. if any angiogram is done please report given some ischemic lesions are seen. please also include stroke work up as well especially in a new cancer pt(MR angiogram, CT angiogram, 2 D echo, DVT) . possibility of stroke related to vasculitis exists given SSA & SSB antibodies are positive and pt has family hx of anca vasculitis is there. This could be discussed for stroke findings on MRI.

**Reply:** Thanks for your suggestion. PACNS often presents headaches, recurrent strokes, TIAs, cognitive dysfunction and ataxia. The typical cerebral angiogram shows bead-like segmental stenosis, usually in the small and medium-sized arteries. Unfortunately, this patient did not have a cerebral angiogram examination but only a TCD showed no abnormalities. It is difficult to discuss the differential diagnosis of stroke adequately. But we appreciate your question. It opens up our thinking and will be useful in our future clinical practice.

**Changes in the text:** We have modified our text as advised (see Page 4, line 70)

6. please also mention whether specific treatment for PCD is given or not (high dose

steroids, ivig, plasma exchange, tacrolimus etc). if not given, addressing cancer immediately without delay with specific chemo could help in halting progression of PCD and some reversal.

**Reply:** Thanks for your suggestion. The patients received IVIG treatment twice before and after the first cycle of chemotherapy, which is mentioned in the manuscript.

**Changes in the text:** We have made no changes.