Dear Director Wang

Re: Manuscript NO: 70126

Thank you for your letter and the reviewers'comments concerning our manuscript entitled "Primary adrenal diffuse large B-cell lymphoma with normal adrenal cortex function： A case report " (70126). Those comments are valuable and very helpful. We have read through comments carefully and have made corrections. Based on the instructions provided in your letter, we uploaded the file of the revised manuscript. The responses to the reviewer's comments are marked in red and presented following.

We would love to thank you for allowing us to resubmit a revised copy of the manuscript and we highly appreciate your time and consideration.

Sincerely.

Zhi-Nan Fan

Reviewer #1:

Q1. There is a key-point that may be reconsidered in my opinion. The concept that the combination of surgery and chemotherapy could be a therapeutic approach for primary adrenal DLBCL is incorrect to me. The international guidelines (NCCN and ESMO) do not suggest surgery as part of the treatment for DLBCL but just as a diagnostic tool. The backbone for front-line treatment of this disease is R-CHOP (or R-CHOP-like regimens) that represents the worldwide accepted standard of care, nowadays (see NCCN guidelines, ESMO guidelines, Kim YR et al. Prognostic factors in primary diffuse large B-cell lymphoma of adrenal gland treated with rituximab-CHOP chemotherapy from the consortium for improving survival of lymphoma (CISL). J Hematol Oncol 2012"). In addition, the poor prognosis of the disease cited in the manuscript (1-year OS of 17%) is affected by the inadequate treatment approach. Data from patients with adrenal DLBCL treated with immunochemotherapy show much higher rates of responses and survival (54% of complete responses and 2-year OS over 68%) (see Zhou L et al. Primary adrenal lymphoma: radiological; pathological, clinical correlation. Eur J Radiol 2012;81:401-405) In my view, due to the same concept this sentence may be revised: '[…]This is due to the adherence of the tumor to the surrounding tissues, which hinders its complete removal during surgery, resulting in recurrence and metastasis soon after surgery[…]. The complete surgical removal of the disease is never curative for DLBCL and systemic

treatment is required. Moreover, the term 'metastasis' is not appropriate to describe lymphoma dissemination that is a systemic disease by definition.

Response: We are grateful for the suggestion. As surgeons, we did subconsciously exaggerate the role of surgical treatment in the original manuscript. Then we further studied the NCCN guidelines and relevant literature. As a systemic disease, lymphoma is difficult to achieve radical cure by surgical resection, and systemic treatment is the most critical. We have made appropriate corrections in the manuscript.The reference to adverse prognosis in the manuscript (1-year OS of 17%) is indeed unrepresentative and I have changed to other reference.

The revised text reads as follows on :

'Kim et. al., reported 31 cases of primary adrenal DLBCL with overall 2-year and progression-free survival rates of 68.3% and 51.1%, respectively'

"Currently, there is no unified treatment regimen for PADLBCL. Most of the therapeutic strategies are developed based on the summary and comparison of the treatment experiences of lymphoma. PADLBCL is usually treated as a systemic disease, and early diagnosis and treatment can significantly prolong the patient's survival. Since lymphoma is a systemic disease, the invasiveness of PADLBCL is generally extends beyond the visual limit, and it is difficult to achieve complete resection . Therefore, surgery is mainly used to diagnose the disease, and further immunochemotherapy is recommended post-surgery."

Q2. In my understanding the time from the diagnosis to the beginning of the immunochemotherapy has been of around 1 month. If this is correct there has been a delay in the systemic treatment administration considering the aggressive behavior of DLBCL and this should be stated or at least analyzed in the text, since could has affected the outcome for the patient.

Response: We are grateful for the suggestion. After the pathological diagnosis was confirmed, the patient was immediately notified telephonically. However, due to the patient's personal reasons, the return visit was delayed, and the patient returned to the hospital for further treatment a month later.. We have added this addition to the manuscript.

Q3."Hematologists did not rule out lung damage caused by chemotherapy drugs […]". This should be stated with more caution or with more details on the rationale.

Response: Thank you for your careful review. Drug-induced lung injury caused by chemotherapy is an exclusive diagnosis, and there is still a lack of effective objective diagnostic criteria, and its histological and imaging manifestations are also lack of specificity. Therefore, the clinical diagnosis of drug-induced lung injury requires comprehensive consideration of drug history, clinical characteristics, histopathology and imaging manifestations. The patient developed severe lung infection during the fourth chemotherapy, and had no previous lung disease. Granulocytopenia occurred during chemotherapy, and the patient was prone to concurrent infection during this period. The chest CT reexamination indicated diffuse patchy fuzzy shadows in both lungs. In addition, an increased incidence of interstitial pneumonia has been reported in DLBCL patients receiving rituximab immunochemotherapy(Huang et al. Low absolute lymphocyte count and addition of rituximab confer high risk for interstitial pneumonia in patients with diffuse large B-cell lymphoma. Annals of Hematology.2011). In view of this, We did not exclude the possibility of drug-induced lung injury due to immunochemotherapy.We think this part is not related to the theme of the manuscript, so it is not reflected in the manuscript.

Q4. The adrenal gland involvement is related to high risk of CNS lymphoma involvement or CNS relapse. Diagnostic lumbar puncture at baseline in order to rule out CNS involvement and CNS prophylaxis with systemic methotrexate or intratecal chemotherapy should be always considered in this scenario. This theme may be further developed in the manuscript.

Response: We are grateful for the suggestion.We have added content related to the central nervous system in the manuscript, as follows:

"In addition, adrenal lymphoma is one of the major risk factors for the recurrence of central nervous system (CNS) lymphoma. In the study by Kim *et. al.*, 13% of patients with adrenal lymphoma had CNS lymphoma recurrence. Therefore, systemic methotrexate or intrathecal injection of methotrexate may be administered during the treatment to prevent the involvement and recurrence of the central nervous system."

Q5. In the discussion the definition of GCB and non-GCB subtypes is imprecise.

Response：We apologize for the problem in the original manuscript.We have revised the relevant content as follows:

"Immunohistochemistry can also be used to classify the molecular types of PADLBCL. For this purpose, Hans algorithm is most extensively used in routine practice, and it consists of three markers (CD10、Bcl6、MUM1). Based on the combination of these three markers, Hans algorithm could divide DLBCL into two groups (GCB and non-GCB subtype). "

Q6.non-GCB patients are often characterized by a higher expression of the proliferation index (Ki-67), with standard R-CHOP chemotherapy regimen being ineffective in such patients'. I would suggest the term 'less effective' instead of ineffective.

Response： Thank you for your suggestion.We have replaced "ineffective" with "less effective".

Q7. For CD30-positive patients, the use of the anti-CD30+ antibody brentuximab vedotin has been recommended'. The efficacy of Brentuximab vedotin on DLBCL is moderate both as single agent and in combination with R-CHOP. This recommendation should be stated with more caution.

Response： Thank you for the suggestion.This recommendation is really not prudent, and I have deleted it.

In addition, I have replaced "chemotherapy" with "immunochemotherapy" and "vindesine" with "vincristine".Thank you again for pointing out our mistakes.

Reviewer #2:

Q1. Please explain in more detail how the final diagnosis was obtained.

Response: We deeply appreciate the reviewer's suggestion.The patient's final diagnosis was based on Pathological examination. We have described the pathological section manifestations and immunohistochemical results in detail in this paper, and attached corresponding pictures.

Q2.please provide more details about surgical procedure. The right adrenal gland was not touch?

Response: Thank you for your precious comments and advice. I have added more details of the operation in the manuscript.The main purpose of this operation was to clarify the diagnosis and make a plan for subsequent treatment, so we chose unilateral adrenal resection, so the right side was not treated.

The revised text reads as follows on :

"We performed a left adrenalectomy under laparoscopic surgery. During the surgery, an irregular mass was observed in the left adrenal area. The mass was strongly adhered to the upper pole of the left kidney, and it pressurized the left kidney in forward and downward direction. No detectable lymph node enlargement was observed. The upper pole of the left kidney was damaged during the laparoscopic separation of the mass, so the wound surface was sutured continuously with 3-0 absorbable suture. After the separation of the tumor from the upper pole of the left kidney, due to excessive blood on the wound surface and compromised visibility, the tumor vessels were perturbed during the operation leading to the rupture of associated blood vessels. Due to the excessive blood loss, the laparoscopic surgery was reallocated to open abdominal surgery. The intraoperative blood loss was approximately 1300 ml, and blood transfusion was prescribed to overcome the loss."