Peer Review File

Article information: https://dx.doi.org/10.21037/hbsn-2024-737

Review Comments:

In this article, the authors briefly describe the clinical, pathologic, and genomic features of a case of indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract (iNKLPD-GI) in which the patient died of the disease. This is the first reported death resulting from this very rare disease to my knowledge, which has previously been described to have an indolent, although occasionally persistent/recurrent, clinical course and thus conservative management is generally recommended. Because this case has the potential to alter the way this disease is approached clinically, I think more information is needed to better understand the clinical picture and confirm the diagnosis. My specific questions/recommendations are as follows:

1. Did the patient have any pertinent past medical history, such as autoimmune disease, immunodeficiency, or inflammatory bowel disease?

Reply1: Thanks for your comments. The patient did not have any pertinent past medical history and we are sorry not to mention it in the manuscript due to word limit. We have revised the sentences for better understanding as you suggested **as follows:**

*A 66-year-old man **without underlying diseases** was admitted due to 2-year diarrhea and 2-month progressive abdominal distension, with reduced exhaust and defecation.*

2. Was clinical staging performed to assess for disease outside the GI tract (e.g. full body imaging like CT or PET scan, peripheral blood studies like CBC and/or flow cytometry, bone marrow biopsy)?

Reply2: Thanks for your kind suggestions. We have conducted enhanced whole-body CT plus CT enterography, which revealed remarkable expansion of whole small intestine and gas-liquid level, without intestinal stenosis and extraintestinal involvement. In addition, the patient also taken blood routine and blood smear. He did not receive bone marrow biopsy as the patient had died before the final diagnosis was confirmed. We are sorry not to mention it in the manuscript due to word limit. We have revised the sentences for better understanding as you suggested **as follows:**

*Laboratory tests showed **decreased lymphocyte of 480 cells per μL, haemoglobin of 8.6g/dL and prominent hypoalbuminemia of 20g/L, with normal blood smear**, urinary protein and liver function. **The whole-body enhanced CT with enterography** revealed remarkable expansion of whole small intestine and gas-liquid level, without intestinal stenosis and extraintestinal involvement (Figure 1)*

3. Only a limited description of the histologic and immunophenotypic features was provided. I would recommend expanding on this to increase the reader's confidence in the diagnosis. Were cytoplasmic granules seen by H&E? I would also provide the results of additional immunophenotypic markers, in particular CD2, CD3, CD5, CD7, CD4, CD8, cytotoxic

molecules, T cell receptors, B cell markers, and markers of immaturity (e.g. TdT).

Reply3: Thanks for your kind suggestions. We have added inside H&E image of higher magnification to show the cytoplasmic granules and all the immunophenotypic markers to Figure 4 to make the diagnosis more certain. We have revised the figure legend **as follows:**

Atypical cells infiltrated the lamina propria and displaced the glands (A, HE, 400 × magnification), paranuclear eosinophilic cytoplasmic granules could be seen in some cells (A inside, HE, 800 × magnification). These tumor cells expressed CD2(B), cytoplasmic CD3(C), CD7(F), CD8(G), CD56(I) and TIA1(J), while negative for CD4(D), CD5(E), CD20(H), TdT(K) and EBER(L), Ki-67 of about 40% (M) (B-M, 200 × magnification).

4. Was T cell receptor gene rearrangement performed?

Reply4: Thanks for your kind comments. We are sorry not to mention it in the manuscript due to word limit. We have revised the sentences for better understanding as you suggested **as follows:**

Analysis for T cell receptor (TCR) gene rearrangement was negative *and next-generation sequencing (274 gene panel) revealed JAK3 K563_C565del mutation with 26.3% variant allele frequency.*

5. How was the JAK2 mutation detected (e.g. NGS, targeted analysis)? What was its allele frequency? If a panel was used, how many genes were in the panel and were any other mutations/alterations identified?

Reply4: Thanks for your kind comments. We are sorry not to mention it in the manuscript due to word limit. The JAK2 mutation was detected by NGS. The concrete information of NGS has been added in the revised manuscript **as follows:**

Analysis for T cell receptor (TCR) gene rearrangement was negative and ***next-generation sequencing (274 gene panel)*** *revealed JAK3 K563_C565del mutation with* ***26.3% variant allele frequency****.*