Peer Review File

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Reviewer A

Comment 1: AD term is used in the abstract without full name.
Reply 1: We added the full name of AD term (autoimmune disease) when it was first used in the abstract (see Page 2, Line 36).
Changes in the text: Page 2, Line 36.

Comment 2: Abstract conclusion language (line 14-15) is very strong. This perhaps can be less strong. As this report is based on only 2 patients.
Reply 2: We have modified our text as advised. 'May be predictive for HLH' was replaced by 'are worthy of attention to the presence of HLH' (see Page 2, Line 35-36). In fact, although we just report 2cases, we find the same phenomenon in other reported cases, and we discussed it (see Page 10, Line 199-200).
Changes in the text: 2, Line 35-36.

Comment 3: Overall language of the report need to be revised by professional editor. It seems like more of a story than scientific report. Sentences are judgmental and biased towards diagnosis.
Reply 3: We have revised our manuscript to improve the language. In addition, we sought assistance from a professional English language editing service (AME Editing Service) to ensure that our manuscript meets the required language standards.
Changes in the text: Changes were marked in the manuscript.

Comment 4: Both patients have autoimmune diseases from the start, symptomatic (n=1) and asymptomatic and non-characterized (n=1). History of autoimmune disease is a well established risk factor to predict irAE including HLH. So authors conclusion and claim perhaps can be less strong or mild. Overall this report definitely enrich the literature towards this challenging complication of ICI.
Reply 4: Thanks for appreciating our work. Increasing the awareness of HLH being an adverse event of ICI is the aim we wrote this case report. The associated irAEs of ICIs did occur more frequently in patients with autoimmune diseases, but are most mild and manageable (1). We discuss this in our manuscript (Page 7, Line 144-148). We underline HLH being a 'threshold' disease, aiming to increasing the cautiousness of using ICIs in patients with two or more predisposing factors, which may be a new idea. We have modified our text to stress this idea (see Page 9, Line 180-185).
Changes in the text: Page 9, Line 180-185.

(1) Fillon M. Immune checkpoint inhibitors may be safe for patients with preexisting autoimmune disease. CA Cancer J Clin. 2020;70(1):3-4. doi:10.3322/caac.21587

Reviewer B

General Comment: Excellent report of HLH associated with checkpoint inhibitor
Few sugestion and remark:
Reply: We are thankful to you for appreciating our work and your insightful comments. We have considered all the comments and revised the manuscript accordingly.

Comment 1: Author could highlight HLH occurred after the first infusion of immunotherapy. It seems in litterature that HLH often (always?) occurred after the 1st or second infusion of immunotherapy. Interesting point probably to discuss.
Reply 1: We are sorry that we didn't find this phenomenon that HLH often (always?) occurred after the 1st or second infusion of immunotherapy. As the article you mentioned in Comment 5, this literature review of HLH listed 17 patients with relatively detailed immunotherapy, among which 8 patients developed HLH after 3 or more infusions of immunotherapy and 9 patients developed HLH after the first or second infusion. But we find a phenomenon that HLH, as well as other severe irAEs, often occurred after the first infusion of immunotherapy in patients with two or more predisposing factors. And we discussed it (see Page 9, Line 186-192).
Changes in the text: Page 9, Line 186-192.

Comment 2: The 2 patients reported here have previous history of autoimmune disease or condition. It should be interesting to highlight this in the discussion, regarding also in litterature. A message could be: think about screen patient for autoimmune test if they have HLH.
Reply 2: We added some discussion as you advised (see Page 9, Line 180-185).
Changes in the text: Page 9, Line 180-185.

Comment 3: L 37 "penetrating examination was denied". I do not understand what is épenetrating examination".
Reply 3: The term "penetrating examination" refers to the "labial gland biopsy". Since it is difficult to understand, and there are other inspection items helping to diagnose Sjögren's Syndrome (SS), we use the term "further examination" to replace it (see Page 4, Line 68).
Changes in the text: Page 4, Line 68.

Comment 4: "SS" abbreviation should be explained
Reply 4: We added the full name of "SS" (see Page 4, Line 67).
Changes in the text: Page 4, Line 67.

Comment 5: A reference probably to add as this report other cases of HLH associated with ICI: "Haemophagocytic lymphohistiocytosis associated with immune checkpoint inhibitors: a descriptive case study and literature review". BJH 2020. PMID 32243578
Reply 5: We added this article as a reference (see Page 8, Line 172-176) as you advised.
Changes in the text: Page 8, Line 172-176.

Comment 6: Tocilizumab, an anti-IL6 rec therapy, could be suggested in the discussion for treatment of HLH associated with autoimmune conditions. This could be discussed in the manuscript.
Reply 6: We have modified our text as advised (see Page 10, Line 201-204). Since treatments of HLH are not the essential part of our manuscript, we just gave a brief discussion.
Changes in the text: Page 10, Line 201-204.

Reviewer C

Comment: This is a nicely written case series on an important topic. The writers have addressed the nuances of the case in great detail. I would recommend compiling the existing evidence on the topic (there are a few retrospective studies looking at HLH due to ICIs) in the discussion. This will make the draft more educational for the reader. I congratulate the authors on a job well done!
Reply: We are very thankful to you for your high praise. As you advised, we compiled existing evidence on HLH induced by ICIs (reference 16/17). In addition, we added some references to enhance the credibility of our ideas (reference 15/20).
Changes in the text: Page 8, Line 169-175.

Reviewer D

This is a report of 2 cases and a literature review for hemophagocytic lymphohistocytosis after immune checkpoint inhibitor therapy.
Comment 1: The English is very bad. Full of errors and difficult to understand.
Reply 1: We have revised our manuscript to improve the language, and we sought assistance from a professional English language editing service (AME Editing Service).
Changes in the text: Changes were marked in the manuscript.

Comment 2: The description of the clinical management of the patients is poor and is not logical.
Reply 2: We have modified our clinical management of the patients (see changes in Case Presentation).
Changes in the text: see changes in Case Presentation.

Comment 3: The literature review is superficial and does not provide any significant insight.
Reply 3: We added the existing evidence of HLH induced by ICIs (see Page 8, Line 169-175). And we added some discussion to emphasize our idea that more cautiousness is needed before using ICIs in patients with two or more predisposing factors (see Page 9, Line 180-185). In addition, we find an interesting phenomenon that HLH, as well as other severe irAEs, often occurred after the first infusion of immunotherapy in patients with two or more predisposing factors (see Page 9, Line 186-191).
Changes in the text: Page 8, Line 169-175; Page 9, Line 180-191.