

Dear editor,

Thank you very much for giving us an opportunity to revise our manuscript. We appreciate the editor and reviewers very much for their constructive comments and suggestions on our manuscript entitled “A case of pembrolizumab-induced Stevens-Johnson syndrome in advanced squamous cell carcinoma of the lung”.

The following is the reply to the reviewers.

To reviewer1:

(1)and not anti-PD-L1 - Line 12: I would say anti-PD-1/anti-PD-L1 - .

Response: Thank you for your modification and I have revised it.

(2)Line 13: you mention 5 case reports but refer to 8 reports? There are more case reports than the one you mention, so I'd rather say several case reports. You can also refer to a recent systematic review (Maloney et al, doi:10.1111/ijd.14811).

Response: I have revised it to There have been several reports of anti-PD-1/anti-PD-L1 therapy inducing SJS[6-14,32]

(3)Case: - Staging: please mention which TNM was used,

8th edition? I guess it is M1b and stage IVA? based on solitary extrathoracic metastasis?

Response: I have revised it to according to the American Joint Commission on Cancer (AJCC) 8th edition staging system, she was clinically diagnosed with stage IVA lung squamous cell carcinoma (cT4N2M1b).

(4)- p.5 line 19: I believe liver metastasis? as it was a solitary metastasis?

Response: Yes, it was a solitary metastasis.

(5)- Physical examination: it would be interesting if the authors can mention if the patient had any mucous lesions?

Response: There were some ulcers around the lip. Her oral ulcers were too painful to allow her to eat anything. No other apparently positive signs were found.

(6)- p.6 line 23: the authors mention 3-month treatment? I thought the patient only received one cycle of chemo-immunotherapy? Or was it the 3-month evaluation?

Response: In terms of lung carcinoma, the pulmonary nodule was smaller than the baseline and remained stable during the 6-month evaluation.

(7)Discussion: - Improved survival in case of irAEs has also already been described in lung cancer patients, so I

would refer to those reports instead of renal cancer/melanoma. (e.g., Shankar et al, doi:10.1001/jamaoncol.2020.5012)

Response: Bairavi and his colleagues demonstrated that NSCLC patients with one irAE and multisystem irAEs incrementally improved OS and PFS. Longer immune checkpoint inhibitor durations were an independent risk factor for the development of irAEs. In our case, it was rare that such severe AEs occurred after just one cycle of immunotherapy[23]. Susana also indicated that the median PFS was 9.49 months in the group with irAEs versus 1.99 months in the group without irAEs ($P < 0.0001$) in NSCLC treated with nivolumab[24]. In our case, the condition of the patient was stable for up to 6 months just after one cycle of the treatment.

(8)Unfortunately, there are many vocabulary and grammar errors: Abstract: - Line 1: abstract instead of abtrast - Line 3: have instead of has - Line 5: remove while - Line 10: a 68-year-old female - Line 11: remove syndrome - Line 13 it is unclear what the authors want to say? Prednisone, symptomatic, anti-infectious, gamma globulin, and antipruritic therapy? - Line 14: remove and so on; did

the skin toxicity reduce or disappear? Maybe the authors meant reduced and eventually disappeared? - Line 16: patient instead of patients Intro: - Line 7: and included especially cutaneous side-effects Case: - Line 3: she instead of he - Line 7: clearly instead of obviously (also on p.6 line 3) - One cycle instead of cycles (p.5 line 5 and 7) - p.5 line 12: or other instead of and so on, line 22: which were instead of with - Itchiness instead of itching (p.6 line 6, figure 10 and 11) - p.6 line 16: remove without further delay - p.6 line 19: remove symptoms of Conclusion: - line 2: remove be (to overcome)

Response: Thank you for your modification and I have revised all of them in the manuscript.

(9)Please note the correct use of abbreviations: Abstract: once abbreviated, there is no need to abbreviate again (abstract line 4 ICI) or use the full word again (abstract line 9); intro: mention SJS as abbreviation (line 8); case: p.4 line 5 chest computed tomography (CT), line 6 magnetic resonance imaging, line 8 CT, p.6 line 12 remove Stevens-Johnson syndrome; discussion: non-small cell lung cancer (NSCLC), p.7 line 7 remove Stevens-Johnson syndrome, p.7 line 18 toxic epidermal necrolysis instead of TEN, p.8 line 3 overall survival, p.8 line 4 irAEs, line 18 tumor necrosis factor

instead of TNF.

Response: Thank you for your modification and I have revised all of them in the manuscript.

To Reviewer #2:

1. Please avoid "... and so on" in scientific writing.

Response: Thank you for your modification and I have deleted "...and so on".

**2.Does the patient have any known drug allergies?
Taking any traditional Chinese medicines or herbal
supplements?**

Response : Family and personal history were unremarkable. She had no significant medical history or drug allergy.

3.What about documented Nikolsky's sign or Koebner phenomenon?

Response: Nikolsky' s sign was positive. Koebner phenomenon was negative.

4.What was the SCORTEN scoring for this patient?

Response: SCORTEN (severity-of-illness score for TEN) score of 4 points.

5.Please provide the relevant biochemical results (and

reference ranges) in a table format.

Response: Table 1 has already listed some of blood tests.

6. Apart from corticosteroids, there is actually good (and perhaps better) emerging evidence to support the use of cyclosporine in SJS/TEN (citation: ncbi.nlm.nih.gov/pmc/articles/PMC5880515). The results of these studies suggest that the administration of cyclosporine 3 to 5 mg/kg per day as early as possible in SJS/TEN may be beneficial. This should be at least briefly mentioned.

Response : over the last several years, several retrospective trials have advocated the benefits of cyclosporine in the treatment of SJS/TEN[29,30]. Cyclosporine inhibits the activation of CD4+ and CD8+ T cells in the early phase, subsequently inhibiting the secretion of granulysin, granzyme, and perforin[31]. Despite a lack of randomized control trials, cyclosporine has proven to have a mortality benefit in the treatment of SJS/TEN without a low risk of side effects. In our case, we did not use cyclosporine due to the lack of experience in the early phase of treatment for SJS.

7. Please rephrase "Through our medical records and relevant treatment schemes, we can provide a little treatment

basis for clinical treatment."

Response: However, there is still a long way to go for immune-related adverse events, such as predictors for adverse events and ways to prevent them in advance. In future studies, we might focus more on the prediction, prevention, and treatment of irAEs, although immunotherapy is in full swing.

8.Please suggest some concrete recommendations and areas for future research.

Response: However, there is still a long way to go for immune-related adverse events, such as predictors for adverse events and ways to prevent them in advance. In future studies, we might focus more on the prediction, prevention, and treatment of irAEs, although immunotherapy is in full swing.

To Reviewer #3:

1.The grammar needs significant editing as there are several deficiencies in writing format. It needs to also be written in scientific format rather than casual.

Response: Thank you for your suggestion and The language company has been found to correct the syntax error.

2. While an expert consultation with Dermatology had yielded a clinical diagnosis of SJS, it is entirely unclear what led them to the diagnosis. Was there mucosal involvement? Was there a skin biopsy? It is unclear as simply severe skin rash as an adverse effect of Pembrolizumab is a known and common complication and it is important to highlight how you distinguished between the two in this case.

Response: We arranged an urgent consultation with a dermatologist. According to the skin and mucous membrane performance of the patient during these days, the rapid development of the disease, and history of PD-1 inhibitor use, pembrolizumab-induced SJS was diagnosed.