Peer Review File

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Response to the Review Comments:

Regarding the checklist

- Checklist 3c: please add information on (1) stage of NSCLC; (2) dosage of pembrolizumab in abstract.

- Reply: We added stage information as 'recurred' NSCLC because the patient was recurred case after surgery (pT2aN2M0, stage IIIA). The dose of pembrolizumab was 2 mg/kg.

- Changes in the text:

Page 2, line 10: skin depigmentation … in a patient with stage IV NSCLC.

Page 2, line 13: pembrolizumab 2 mg/kg for 14 months with close monitoring…

Page 4, line 16: pemetrexed and cisplatin, pembrolizumab 2 mg/kg was administered…

- Checklist 4: regarding the key information "During anti-PD-1 monotherapy, cutaneous irAEs such as vitiligo, psoriasis, and lichenoid dermatitis can develop. But vitiligo-like depigmentation has been rarely reported in patients with non-melanoma malignancies" mentioned in introduction, please add relating references (for your reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5061067/).

- Reply: Thank you for your recommendation. We added the reference as #4.

- Changes in the text:

Page 3, line 21: … patients with non-melanoma malignancies (4).

Page 8, line 10: 4. Sanlorenzo M, Vujic I, Daud A, et al. Pembrolizumab Cutaneous Adverse Events and Their Association With Disease Progression. JAMA Dermatol. 2015;151(11):1206-12.

- Checklist 5c: please also add history of dermatosis and pembrolizumab use before September 6, 2017, even though there's none.

- Reply: We added the sentence as below.

- Changes in the text:

Page 5, line 1-2: There was no history of dermatosis before pembrolizumab use.

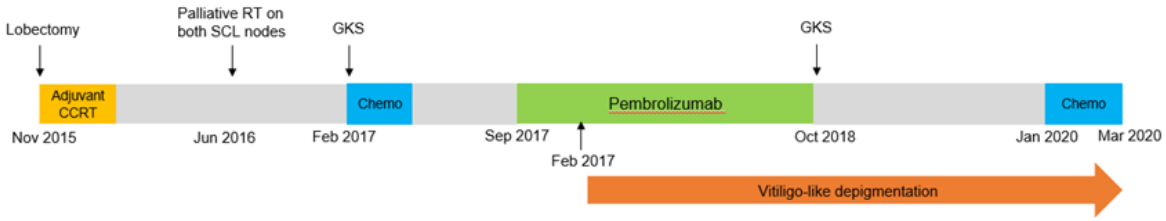
Checklist 7: please draw a timeline figure and make sure it stands alone. An example is attached.

- Reply: We added Figure 3 which contained timeline.

- Changes in the text:

Page 4, line 18: … from September 6, 2017 (Figure 3)….

Page 11, line 9-13: Figure 3. Time line and duration of each treatment….



Checklist 9b: please add dosage of pemetrexed, cisplatin, pembrolizumab and topical corticosteroid.

- Reply: We added the dosage of the drugs in abstract and body as below.

- Changes in the text:

Page 4, line 16: pemetrexed 500 mg/kg and cisplatin 60 mg/kg, pembrolizumab 2 mg/kg …

Page 5, line 5: … topical corticosteroid 45 g and …

Checklist 11a: it is highly recommended that authors use one separate paragraph to LIST BOTH strengths and limitations of this case in a logical way.

- Reply: As two reviewer's comments, we added one paragraph in discussion about strengths (we used the term 'interesting points') and limitation as below.

- Changes in the text:

Page 6, line 7-21: In this study, we described a case of vitiligo-like depigmentation after 5 months of pembrolizumab 2 mg/kg use in stage IV NSCLC with brain metastasis. Although the patient had gone through quite a complicated intervention history such as surgery, adjuvant chemoradiotherapy, palliative radiotherapy, gamma knife surgery and levothyroxine medication, there was no specific history of dermatosis before pembrolizumab use. So we could judge that the depigmentation was caused by pembrolizumab. The skin lesions persisted without exacerbation or improvement for 9 months. There are two interesting points in this case. First, we do could learn some message regarding whether it's a prognostic factor

for patients with NSCLC. While the depigmentation had been existing, pembrolizumab was discontinued at 14 months due to the progression of brain metastasis. Therefore, anti-PD1 inhibitor-associated vitiligo in NSCLC may not be a favorable factor unlike melanoma. Second point is that the skin lesions persisted even after pembrolizumab was finished. This suggests that anti-PD1 immunotherapy may cause irreversible skin manifestation. However, our case alone has limitation in determining the cancer prognosis and reversibility of vitiligo-like depigmentation.

Major suggestion

1. As we know and mentioned in the case, among patients with melanoma, the appearance of hypodepigmentation is a favorable prognostic factor. It's glad to see that authors have mentioned in the discussion that "labeling immunotherapy-associated vitiligo as a favorable prognostic factor in NSCLC management is yet to be confirmed". However, this is especially important and the highlight of this case. I strongly suggest the authors discuss this in detail (including related potential reasons: cancer type, stage, dosage, duration, etc.). This is because we could see from this case that the progression is poor (brain metastasis) while the hypodepigmentation had been existing. We do could learn some message regarding whether it's a prognostic factor for patients with NSCLC, from this case.

- Reply: As your comment, we added the description suggesting prognosis in NSCLC as below.

- Changes in the text:

Page 6, line 7-18: In this study, we described a case of vitiligo-like skin depigmentation after 5 months of pembrolizumab (2 mg/kg) use in stage IV NSCLC with brain metastasis. … The skin lesions persisted without exacerbation or improvement during additional immunotherapy for 9 months. … While the depigmentation had been existing, pembrolizumab was discontinued at 14 months due to the progression of brain metastasis. Therefore, anti-PD1 inhibitor-associated vitiligo in NSCLC may not be a favorable factor unlike melanoma.

2. Although it has been reported quite a few hypodepigmentation due to pembrolizumab. We also see that, in this case, the patient has gone through quite a complicated intervention history. I suggest authors add discussion to prove/persuade that the manifestation is due to

pembrolizumab instead of other interventions.

- Reply: As your comment, we added the description as below.

- Changes in the text:

Page 6, line 8-12: Although the patient had gone through quite a complicated intervention history such as surgery, adjuvant chemoradiotherapy, palliative radiotherapy, gamma knife surgery and levothyroxine medication, there was no specific history of dermatosis before pembrolizumab use. So we could judge that the depigmentation was caused by pembrolizumab.

3. Last but not the least, it's very interesting to see that the vitiligo-like lesions remained persistent for 25 months. From the information I could get, the duration of pembrolizumab would be less than 25 months, right? Therefore, I suppose this case also gives us an indication that the manifestation could last even after pembrolizumab treatment is finished. If it's confirmed (the total duration of pembrolizumab), I recommend the authors also discuss this.

- Reply: Thank you for comment, we added this description as below.

- Changes in the text:

Page 6, line 18-20: Second point is that the skin lesions persisted even after pembrolizumab was finished. This suggests that anti-PD1 immunotherapy may cause irreversible skin manifestation.

Minor suggestion

1. "However, vitiligo-like depigmentation resulting from the use of pembrolizumab has not been reported. "

Change to: However, vitiligo-like depigmentation resulting from the use of pembrolizumab in NSCLC has not been reported.

- Reply: As your comment, we modified the sentence.

- Changes in the text:

Page 5, line 17-18: vitiligo-like depigmentation resulting from the use of pembrolizumab in NSCLC has not been reported.

2. Please state in introduction that this case is written in accordance with CARE GUIDELINE.

- Reply: We added the last sentence in introduction as below.

- Changes in the text:

Page 3, line 22-23: We present the following case in accordance with the CARE guideline checklist.