ANSWER THE COMMENT

Dear editor

We revised the manuscript as much as possible according your comment. I wish our revision is satisfied your mind even if insufficient. But if you have still comment, please let me know. So I hope that you will consider this paper as suitable publication in your journal. Thank you

Reviewer #1: Dear author,

I appreciate for your careful review. Your comment is so good to me.

I answered for your comment followed and we revised the manuscript according your comment

Comments)

The authors reported a case of squamous NSCLC treated with platinum doublet with PR for 12 weeks and then PD per RECIST. Subsequent pembro treatment for 9 weeks led to CR, but quickly was discontinued due to SAE. Unfortunately, the patient presented URT infection and increased WBC count, and was then diagnosed having AML. The pulmonary complications and fast clinical deterioration of this patient are consistent with a subset of AML patients who have hyperleukocytosis defined by >100K/μL WBC counts. The origin of the AML is still unknown, given the clinical evidence described here without any molecular characterization of the malignancies from both the NSCLC and AML. The authors believe that this is an AE related to pembro treatment.

However, I don't think the evidence presented here is strong enough to either prove or disapprove this, nor could they prove or disapprove any other possibilities. Most critically, as the authors pointed out themselves, "among the adverse events observed with pembrolizumab treatment, acute myeloid leukemia (AML) has not been reported", isn't it true that extra caution needs to be taken when they tried to build this case without published precedence? This is the burden and responsibility the authors need to bear.

I suggest **two possible paths** for this manuscript.

One is **to provide stronger evidence to support the possibility that the AML is pembro-related,** or

they should tone down the whole manuscript about the relationship between AML and the pembro treatment, and balance it by discussing other possibilities in more details.

They did discuss briefly two other possibilities, one of being related to prior doublet treatment. The other one is that the AML is a separate malignancy that grew out of a pre-clinical scale into hyperprogression after pembro. **Metachronous or synchronous presentation of AML and lung cancer** was already well-documented.

However, defining the current clinical course as hyperprogression is quite questionable for two reasons.

First, most documented hyperprogression describes a longitudinal evolution of a malignancy, particularly there are tumor assessments before AND after the immunotherapy, so the dynamics of the progression can be clearly defined. In this case, there is no assessment of the AML before pembro, so how can the authors be sure this is not the natural course of the malignancy?

Secondly, if there are prior documented cases of AML that became hyperprogressive after immunotherapy, please describe it as a supporting evidence. If there was no such prior case, then the likelihood would be small.

- ⇨ **Thank you for your valuable comment**.
- ⇨ We reported a case of AML occurred suddenly during pembrolizumab treatment for NSCLC.
- ⇨ As mentioned in the discussion, the precise underlying mechanism remains unknown. So, three hypothetical explanations were presented in the discussion.

    1) In our case, AML occurred during the use of pembrolizumab, and it was necessary to review the association with the drugs (Pembrolizumab, cytotoxic drug). Although we reviewed the relationship between Pembrolizumab side effects (especially, immune-related adverse events) and AML, no side effects or mechanisms related to AML were found. So, we described, ‘The relationship between AML and immune-related adverse events associated with pembrolizumab remains controversial.’ **To reduce the link**

between Pembrolizumab and AML following the reviewer's opinion, the paragraph 'Hence, we could consider our patient's diagnosis as an immune-related adverse event rather than therapy-related AML' in the discussion was deleted.

2) In our case, the latency interval for the development of therapy-related AML was 4 months that the latency was shorter than in a report from the Swedish acute leukemia registry.

3) As the reviewer's comment, we found the case report that hyperprogression of AML after immunotherapy. Ratner et.al. reported that PD-1 inhibitor, nivolumab, led to rapid progression of adult T-cell leukemia-lymphoma after treatment. And they confirm and characterize a suppressive role for PD-1 in indolent ATLL, report the discovery of similar gene expression profile between tumor-associated Tregs and ATLL cells after PD-1 blockade.

   (reference:

   Rapid progression of adult t-cell leukemia–lymphoma after pd-1 inhibitor therapy. New England Journal of Medicine 2018;378:1947-1948.

   Rapid progression of adult t-cell leukemia/lymphoma as tumor-infiltrating tregs after pd-1 blockade. Blood 2019;134:1406-1414.)

4) Although AML was not diagnosed before chemotherapy and immunotherapy, we suggested a hyperprogression as a hypothesis considering the above evidence. We added the above evidence to the manuscript.

Additional questions to the manuscript:

1) Is this patient a current or past smoker? If yes, please document the smoking history and habit. Smoking is associated with both AML and squamous NSCLC.

⇨ He was a non-smoker. He had no history of alcohol abuse

2) Was there any cytogenetic and/or molecular analysis being performed in addition to the karyotyping? AML with normal karyotyping is not that unusual. AML with hyperleukocytosis and normal karyotypes was also documented before.

- ⇨ Routine cytogenetic analysis revealed a normal male karyotype (46, XY[20]) A multiplex, nested reverse transcription PCR assay for BCR/ABL, AML1/ETO, and PML/RARA gene rearrangement associated with acute leukemia did not detect any abnormalities.

2-1)How about the SQ NSCLC biopsy that was taken? Any analysis being done on that biopsy?

- ⇨ Squamous cell carcinoma was confirmed by biopsy of the cervical lymph node. No evidence of suspected head and neck cancer was seen. The contrast-enhanced chest CT showed 2 cm sized heterogeneously enhanced nodules in the anterior segment of left upper lobe and large periosteal mass formation involving the lateral arc of the 7^{th} left rib. So we was diagnosed with squamous cell carcinoma of the lung.

3) If the panels C and D in the Figure 2 have the same magnification as A and B, please specify. I can see where the panel B is inside the panel A, but for clarity to the readers, please either demarcate the panels A and C, or at least describe it clearly.

- ⇨ The contents of the legend in the figure 2 have been changed more clearly.

4) Figure 4 legend, is “hypogranuleation” a typo?

- ⇨ We changed from “hypogranuleation” to “hypogranulation”.

5) The headers of Table 1 are unclear. Please describe what Pem #1, #2, and #3 are in the legend. HD is hospital day, but is it possible to describe the relationship between the “Pem” days and the HD, for example, how many days away from the Pem#3? Please also include the reference (normal) values for each test for clarity to the readers.

- ⇨ We changed followed;
- ⇨ the headers of table, Pem #, relationship between the Pem days and the HD, and the reference values

6) For describing PD-L1 IHC staining result, please use the exact terms in the interpretation manual approved for 22C3 in NSCLC by Agilent, the TPS system.

- ⇨ Thank you for your valuable comment.
- ⇨ So I changed followed;
- ⇨ **The Programmed death-ligand 1 tumor proportion score was ≥50%**