Author’s response to reviews

Title: Isolated adrenocorticotropic hormone deficiency and thyroiditis associated with nivolumab therapy in a patient with advanced lung adenocarcinoma: A case report and literature review

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RESPONSES TO THE REVIEWERS’ COMMENTS

Thank you very much for your excellent advice. Our individual responses to each comment raised are listed below.

Reviewer reports:

Reviewer #1:

4. Does the article report the following information? Where information is missing, please specify.

a. The relevant patient information, including De-identified demographic information (age, gender, ethnic) and demographic data is complete except for the occupation, which could be relevant in case the author considers it.
Response: We agree to your advice and have added the information of the patient’s occupation in the first paragraph of the Case Presentation section.

‘The patient had been a housewife since her 20s,’

TimeLine: It is strongly suggested by the complexity of the changes in antineoplastic therapy and for better reader's understanding of chronologic order of the events to make a table in chronological order or flowchart of time from the time of diagnosis of the Lung cancer until the last hospital admission.

Response: Thank you for your excellent opinions. We agree and have added the flowchart of time from the diagnosis of the lung cancer until the last hospital admission in the Figure 3.

5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?

Comments:

The literature review of similar to the current report described similar cases and those related to the evolution and therapy of immunological antineoplastic therapy is appropriate. It is interesting that not all cases have positivity of anti-thyroid antibodies or against the pituitary gland, as well as the present case, where there is no laboratory evidence of autoimmunity, despite a predisposition to pathology immune-compatible HLA. IT would be interesting to discuss if the lesion of thyroid tissue and pituitary wouldn't be by direct toxicity of the product and not by the generation of new antibodies. It would be interesting to issue some opinion on this point and perhaps make some reference to strengths and weaknesses of the case presentation.

Response: Thank you for your excellent advice. We agree and have added the following sentences in the first paragraph of the Discussion section.

‘Other than those regarding nivolumab, there have been few reports on thyroid or pituitary dysfunction associated with the anti-cancer agents that our patient took, including bevacizumab and ramucirumab (Fig. 3) [26-29]. External brain radiotherapy can produce pituitary dysfunction that is usually associated with GH deficiency, but it seldom causes IAD [30]. These findings suggest that our patient exhibited both ICI-related thyroiditis and IAD induced by nivolumab.’

7. Is the Abstract representative of the case presented?

Comments:

* Introduction: In this report while stressing that there is previous experience of the inhibitor of immune control and its association with autoimmune endocrinological pathology and especially with thyroiditis and to a lesser extent with deficiency of
pituitary function complete or partial (with deficit of isolated ACTH production) (Panhypopituitarism), the distinctive character of this case is the time of the occurrence and the fact related to an autoimmune polyglandular disease-associated HLA. This issue should be more clearly expressed in the speech of the Abstract.

Response: Thank you for excellent opinions. We agree and have revised the abstract in order to describe more clearly the time of the occurrence of thyroid and pituitary disorders and its possible relation to an autoimmune polyglandular disease-associated HLA.

Reviewer #2:

9. Additional comments for the author(s)?

Well presented, following the guidelines for a case report.

Lengthy, may need to be concise with important findings.

Response: Thank you for your advice. We agree and have reduced the number of words so that readers can understand the manuscript as easily as possible.