Reviewer’s report

Title: Combined immune checkpoint inhibitor therapy with nivolumab and ipilimumab causing acute-onset type 1 diabetes mellitus following a single administration: two case reports

Version: 0 Date: 07 Oct 2019

Reviewer: BRIGITTE VELKENIERS

Reviewer's report:

Title:
- I would suggest to remove the words "and instructive" from the title, as this is an obvious goal of a case report.

Abstract:
- Line 26: While it is true that most cases have been reported in the setting of anti-PD-1 therapy, from a physiological standpoint, this is probably explained by the fact that PD-1 inhibitors were introduced earlier than PD-L1 inhibitors, as PD-L1 inhibitors are also capable of inducing autoimmune diabetes mellitus. Perhaps the authors should mention that autoimmune diabetes has only been described during PD-1/PD-L1 inhibition up until this point, yet not so during anti-CTLA-4 therapy?
- Line 26: I would tend to disagree with the statement that most cases occur after ten weeks of therapy, as demonstrated by a recent systematic review by de Filette et al., EJE 2019. I would rather mention that most cases occur early-on, often during the first three to six months of therapy.
- The development of autoimmune diabetes related to immune checkpoint blockade in a patient with known type 2 diabetes is indeed an interesting feature. Are the authors aware of other cases described in the literature?
- Finally, in the Conclusion, I would advise the authors to emphasize the particularities of their own two patients. Currently, this section contains rather their own opinion on the subject of autoimmune diabetes related to checkpoint blockade therapy, which is not supported by their personal findings.

Background:
- Lines 44-45: the authors should also list the currently FDA-approved PD-L1 inhibitors (atezolizumab, avelumab, durvalumab) and the drug cemiplimab (anti-PD-1).
- Line 45: I would check this sentence for spelling, and suggest adding the word "the" between the words "enhances" and "immune system response".
- Case 1: The authors presume the development of autoimmune pancreatitis related to immune checkpoint therapy. What were their criteria for this diagnosis? Is the elevated serum lipase level sufficient to pose the diagnosis of autoimmune pancreatitis, or is this phenomenon rather a bystander effect of the acute onset of autoimmune diabetes, in which elevated lipase levels can also be observed? Did the authors assess the patient's exocrine function?
- Case 1: What was the rationale to start high-dose glucocorticosteroids (HDG) in this patient? I would personally be cautious with the administration of HDG in patients on immune checkpoint therapy, as a recent article by Faje et al., Cancer 2018, has demonstrated a reduced survival in patients treated with HDS for ipilimumab-induced hypophysitis. Could the authors comment?
- Case 1 and 2: Where other pancreatic autoantibodies apart from GADA assessed? Did the authors perform HLA analysis?
Discussion:
- Lines 94, 100, 103, 106, … : Please check the article carefully for spelling mistakes (i.e. PD-L1 and not PDL-1).
- Lines 153-154: This is a rather preliminary conclusion, as patients should be followed for all possible autoimmune side effects and not only diabetes mellitus, that this should also include patients on mono-immune checkpoint therapy, and that this is strictly expert-opinion based. For instance, in a retrospective review by Magis et al. J Immunother. 2018, no benefit of routine glucose monitoring during PD-1 blockade was found.
- Lines 157-158: The authors should mention that assessment of A1c levels and pancreatic autoantibodies could be useful, but is in no way essential, as A1c levels are often not very elevated due to the brisk onset of insulitis, and autoantibodies are negative in about half of cases.
- Line 163: The authors propose a target HbA1c of <8.0% in patients who develop autoimmune diabetes related to checkpoint blockade therapy. Did the authors consider the adjuvant use of immune checkpoint therapy, in patients with an earlier disease stage, which is associated with a better prognosis? Should the glycemic target rather be individualized?

Conclusion:
- See final remark in the 'Abstract' section.

Table 2:
- The authors could refer to the article by de Filette et al., EJE 2019, as according to their review, at least 14 cases of autoimmune diabetes related to combination checkpoint blockade therapy have been described in the literature.
- Is a definitive discontinuation of immune checkpoint blockade therapy required? Could the authors comment?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript
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