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

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Reviewer: Kenji Ashida

Reviewer's report:

Review

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

Article type: Case report

General comments to the authors:
Authors described two cases of acute onset type 1 diabetes mellitus (T1DM) with diabetic ketoacidosis induced by combined immune-checkpoint inhibitors (ICI), anti-PD-1 antibody and anti-CTLA4 antibody. In addition, authors review the literature which described the patients with type 1 diabetes mellitus induced by combined therapy with anti-PD-1(Nivolumab) and anti-CTLA4 antibody (Ipilimumab). This manuscript described about clinically interesting and relevant issues. I recommend authors to revise the manuscript with additional and critical examinations to be clarified.

Minor comments:

Title and abstract
This is reviewer's opinion that "conversion from a type 2 diabetes mellitus (T2DM) to a T1DM" is interesting, however is not adequate (Lines 31 to 32, page 2). Could you show the pathogenesis of the conversion? Only the nivolumab (anti PD-1 antibody) and ipilimumab (anti CTLA4 antibody) combined therapy was used in the present case report and past literature reviews. I recommend authors to delete PDL1, because they did not show. (Line 33, page 2) We could diagnose ICI induced T1DM in early-stage and prevent DKA progression, however we could not prevent DKA development because insulin excretion exhausted rapidly in this type DM. (Lines 35 to 37, page 2)

Background
As I mentioned above, the phrase "conversion from T2DM to acute onset T1DM" seems strange, while physicians should not be look over the T1DM development even in the T2DM patients. (Lines 57 to 58, page 3) Is the diagnosis "autoimmune pancreatitis" adequate for the present case according to the guideline for autoimmune pancreatitis? (Line 58, page 3)

Case presentation
Authors should add "and" to the sentence. "His diabetes was diagnosed and treated…", Line 65 of page 3. Because authors described the present cases as acute-onset T1DM resulted in diabetic ketoacidosis, they should describe the disturbed insulin secretion. How about the serum or urine C-peptide or IRI? In addition, how about the urinary or blood ketones, and serum free fatty acid? (case 1 and case2, case
presentation section and table 2) The present cases probably developed T1DM due to autoimmune mechanism as irAEs. However, is the diagnosis "autoimmune pancreatitis" adequate for describe? How about the IgG4 levels, to rule out type 1 autoimmune pancreatitis? How about the time course of serum lipase level? (Lines 71 to 72, pages 3 to 4)

Discussion
The phrase "Random glycaemia" had better to be revised to "casual plasma glucose" (Line 80, page 4) Authors discuss with literature review and citation, and describe that anti GAD antibody (GADA) titer is positively correlated with the severity of fulminant T1DM. However, although usual patients with fulminant T1DM do not show high-titer GADA, they show severe ketoacidosis and severe decline of insulin secretion. In addition, the patient with high-titer GADA sometimes show slowly progressive T1DM. How about this discrepancy. Do authors intend to describe that combined ICI therapy related high-titer GADA T1DM is caused by the mechanism same with the spontaneous GADA-positive fulminant T1DM? (Lines 113 to 115, page 5) Authors describe ICI-induced DKA is more severe in patients with T2DM. Had this issue been confirmed by any investigations? (Lines 126 to 127, page 5) This is a reviewer's opinion that the strength of this manuscript is combined ICI therapy quickly induced T1DM as an irAE. Authors should describe the features about combination ICI therapy related irAEs. ICI related endocrinological irAEs with ICI related T1DM patients had been already reported and have no novelty. (Lines 129 to 133, pages 5 to 6) The case 1 could be diagnosed as autoimmune pancreatitis? (Line 132, page 6) Authors should describe the HLA-type of the present cases, as they describe HLA-typing could give clue to diagnose and show risk of T1DM development. In addition, HLA-typing may give clues to show pathogenesis of combination ICI induced T1DM to compare with other type T1DM. (Lines 134 to 138, page 6)

Clinical practice issues
Authors should show the C-peptide levels in the present case report.

Tables and Graphics
Table 1: Site of metastasis has scarce meaning. Correct the italic body.

References
Please revise again carefully to complete the manuscript, because some mistyping was observed, such as "p.17-0146" (Line 268, page 14), "p.89-p.89" (Line 271, page 14), and "NOD-<em>Pdcd1</em>-/-" (Line 310, page 16). In addition, check the reference style.

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.

Yes

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

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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