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: Hideaki Miyoshi

Reviewer's report:

The authors reported two cases of acute-onset type 1 diabetes mellitus induced by combined immune checkpoint inhibitor therapy with nivolumab and ipilimumab. This report was very important to hold the attention to the very rapid onset T1DM within a few weeks after ICI therapy.

#1: A curious weakness which the authors themselves admit is that they did evaluate neither anti thyroid antibody, nor GADA before initiating ICI therapy. A recent study (J Endocr Soc 2018, 2(3), 241-251) showed that the patients with positive TgAbs and/or TPOAbs before ICI therapy were associated with developing destructive thyroiditis as an irAE. I wonder if the authors showed the course of diabetes treatment of case 1 before initiating ICI therapy, it would be unconvincing to completely exclude a possibility of having existed GADA before initiating ICI therapy.

#2: According to Table 2, neither case 1 nor case 2 were measured C-Peptide levels at DKA onset. Did you evaluate insulin secretory ability (ex. glucagon loading testing, urine collection testing) of these patients after the treatment of DKA?

#3: Did these cases have an antecedent infection before the onset of DKA?

#4: The authors discussed some factors which were able to develop T1DM earlier as an irAE, IPI-NIVO combination therapy, GADA positive, and extremely high GADA titres. Reference No. 34 showed that higher GADA titres linked to the earlier onset and greater clinical severity of diabetes. This reference fully supported the pathogenesis of case 1. Although in the study, the patients with anti-thyroid autoantibody-positive cases were excluded because GADA titres tend to be higher in the patients with autoimmune thyroid disease. The pathogenesis of the patients with T1DM as an irAE who were both positive with anti-thyroid antibodies and GADA should be discussed further.

#5: In line 136-138, the authors noticed a possibility of the need to determine the baseline genotyping to predict the risk of ICI-induced diabetes. They did not examine HLA haplotype of these two patients and could not show the relationship between some HLA haplotypes and the very rapid onset of T1DM as an irAE. I wonder this was an extraordinary sentence, when considering the previous texts.

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