Anti-programmed death ligand 1 therapy-induced type 1 diabetes presenting with multiple islet-related autoantibodies

An immune-related adverse event is a new disease entity that occurs after the introduction and extensive use of anti-cancer immune agents, such as anti-programmed cell death protein 1 (PD-1) or anti-programmed death ligand 1 (PD-L1) antibodies. Anti-PD-L1-related type 1 diabetes is the immune-related adverse event that typically presents as fulminant type 1 diabetes, characterized by an absence of anti-islet autoantibodies.

We are presenting a case of anti-PD-L1 therapy-related type 1 diabetes with highly positive anti-GAD and anti-islet antigen 2 antibodies.

The present patient was a 66-year-old Japanese man with type 2 diabetes diagnosed at the age of 57 years. Since then, he had been treated with nateglinide, teneligliptin and biphasic insulin aspart 30. He was diagnosed with squamous cell lung carcinoma in the right lower lobe at the age of 63 years. His lung cancer was initially treated with concurrent chemotherapy and radiation therapy. After a recurrence, the anti-PD-L1 antibody, atezolizumab, was introduced at the age of 64 years. Although his biopsied lung cancer tissue specimens showed negative PD-L1 expression, the atezolizumab had been effective. The diameter of the primary nodule changed from 43 to 34 mm. Two months after starting atezolizumab, his glycated hemoglobin level rapidly increased from 7.8 to 10.0%. The serum C-peptide level, which was 4.3 ng/mL (normal range <5.0 U/mL), and anti-islet antigen 2 autoantibody, with a titer >30.0 U/mL (normal range <0.6 U/mL).

The results were negative regarding anti-zinc transporter 8, anti-thyroid peroxidase and anti-thyroglobulin autoantibodies. Conforming to the provisions of the Declaration of Helsinki, written informed consent was obtained before examining the patient’s human leukocyte antigen (HLA) types. HLA deoxyribonucleic acid typing detected by polymerase chain reaction sequenced-based typing methods were as follows: DRB1 01:01:01 and 09:01:02, and DQB1 05:01:01 and 03:03:02.

As the limitation of the present study, islet autoantibodies were not checked before, and there still exists the possibility of undiagnosed slowly progressive type 1 diabetes. However, clinical features strongly suggested the patient had type 2 diabetes with middle-aged onset, obesity and family history of type 2 diabetes. The rapid progression of type 1 diabetes from the introduction of atezolizumab should also be discussed. Usui et al.1 reviewed and reported that eight out of 13 patients presented with newly onset type 1 diabetes within 10 weeks from the introduction of anti-PD-1/PD-L1 antibodies. In summary, we considered that the present patient developed newly onset type 1 diabetes, during type 2 diabetes, as a result of anti-PD-L1 therapy.

Baden et al.2 explored 22 cases of anti-PD-1 therapy-related type 1 diabetes, and only one example showed the single islet-related autoantibody, anti-GAD-antibody. Out of all the cases we have examined, this is the first case of type 1 diabetes with HLA-DR9 related to immune checkpoint blockade therapy, presenting multiple islet-related autoantibodies. Although Clotman et al.3 reported five cases of anti-PD-L1-related type 1 diabetes showing multiple autoantibodies, no case showed HLA-DR9. As HLA-DR9 is unique to Asian individuals, immunological backgrounds were different from the present patient.

The present patient had phenotypically acute-onset autoimmune type 1 diabetes. Interestingly, Tsutsumi et al.4 reported that patients with HLA-DRB1 09:01 and DQBI 03:03 are susceptible to fulminant type 1 diabetes, and those with DRB1 01:01 are resistant to it, but might develop classical type 1 diabetes with positive anti-islet autoantibodies. Although it is scientifically meaningless to discuss the association of clinical phenotypes in an individual case with the HLA haplotype, clinical findings on this case suggest the possible reflection of the mixture of class II HLA genotypes and the contribution of medications affecting chronic inflammations, such as dipeptidyl peptidase-4 inhibitors.

DISCLOSURE
The authors declare no conflict of interest.

Hisae Honoki1, Kunimasa Yagi1*, Kenta Kambara1, Daisuke Chujo1,2, Masataka Shikata1, Asako Enkaku1, Akiko Takikawa-Nishida1, Jianhui Liu1, Shihou Fujisaka1, Kazuyuki Tobe1,1* 1st Department of Internal Medicine, and 2Medical Research Management Center, University of Toyama, Toyama, Japan
REFERENCES

1. Usui Y, Udagawa H, Matsumoto S, et al. Association of serum Anti-GAD antibody and HLA haplotypes with type 1 diabetes mellitus triggered by nivolumab in patients with non-small cell lung cancer. J Thorac Oncol 2017; 12: e41–e43.

2. Baden MY, Imagawa A, Abiru N, et al. Characteristics and clinical course of type 1 diabetes mellitus related to anti-programmed cell death-1 therapy. Diabetol Int 2018; 10: 58–66.

3. Clotman K, Janssens K, Specenier P, et al. Programmed cell death-1 inhibitor-induced type 1 diabetes mellitus. J Clin Endocrinol Metab 2018; 103: 3144–3154.

4. Tsutsumi C, Imagawa A, Ikegami H, et al. Class II HLA genotype in fulminant type 1 diabetes: a nationwide survey with reference to glutamic acid decarboxylase antibodies. J Diabetes Investig 2012; 3: 62–69.

Doi: 10.1111/jdi.13099