Anti-PD-1 pembrolizumab induced autoimmune diabetes in Chinese patient
A case report
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Abstract
Rationale: Programmed cell death-1 protein (PD-1) antibody is an immune-checkpoint inhibitor that triggers anti-tumor response by enhancing immune response. Although PD-1 antibody has been reported effective in some malignant tumor, it can also induce significant immune-related adverse events (irAEs) such as autoimmune diabetes.

Patient concerns: A 67-year-old male patient with non-small cell lung cancer (NSCLS) presented with polydipsia, polyuria, weakness, and weight loss after use of anti-programmed cell death-1 antibody therapy. Hyperglycemia, high serum ketone, low bicarbonate and high anion gap were compatible with the criteria of diabetic ketoacidosis (DKA).

Diagnoses: Autoimmune diabetes and diabetic ketoacidosis (DKA). The presence of low serum titers of c-peptide, high blood glucose together with diabetic ketoacidosis (DKA) that occurs shortly after the use of pembrolizumab strongly supported the diagnosis of anti-PD-1 induced autoimmune diabetes.

Interventions: The patient stopped using pembrolizumab while continuous subcutaneous insulin infusion (CSII) was started at the same time. The insulin infusion was switched to multiple daily injection (MDI) after he was discharged from hospital.

Outcomes: The patient is now a well-controlled insulin-dependent patient with palliative care of NSCLS.

Lessons: Autoimmune diabetes induced by anti-programmed cell death-1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) therapy is a rare, but life threatening immune-related side effect. Physicians should closely monitor diabetes-related indexes of patients who have been undergoing the treatment of anti-PD-1/PD-L1 therapy.

Abbreviations: BMI = body mass index, DKA = diabetic ketoacidosis, HbA1c = glycated hemoglobin (a1C), NK = nature killer, NOD = non-obese diabetic, NSCLS = non-small cell lung cancer, PD-1 = programmed cell death-1, PD-L1 = programmed cell death 1 ligand 1, PD-L2 = programmed cell death 1 ligand 2.

Keywords: anti-programmed cell death-1 antibody, autoimmune diabetes, programmed cell death-1, pembrolizumab

1. Introduction
Pembrolizumab is a humanized IgG4 anti-programmed cell death-1 (PD-1) antibody serving as an immune-checkpoint inhibitor. It was approved by the food and drug administration (FDA) in 2015 as a breakthrough drug for the treatment of non-small cell lung cancer (NSCLS). PD-1 and its ligands (PD-L1 and PD-L2) are negative co-stimulatory molecules of T cell activation. Anti-PD-1 antibody send an inhibitory signal to T cell preventing it from recognizing and attacking tumor cells.[1] Rash, pruritus, thyroiditis, diarrhea, hepatitis, and pneumonitis are main immune-related side effects of anti-PD-1 therapy. Autoimmune diabetes induced by immunotherapy are rare, but life threatening
islet-related autoantibodies. HbA1c (%) 8 (4–16) Bicarbonate, mmol/L 13.4 (24–39) Anion gap, mmol/L 26 (8–16) Blood ketones, mmol/L 5.1 (0.17–2.03) 3. Discussion

In this report, we describe a case of anti-PD-1 therapy-induced autoimmune diabetes in Chinese population, which characterized with a rapid onset of DKA. The use of pembrolizumab was considered as the cause of autoimmune diabetes, for there were no other potential factors such as personal or family history of autoimmune diseases, viral infection, pancreatic metastasis or use of drugs that induce diabetes, and only pembrolizumab could be identified.

Furthermore, blocking the PD-1/PD-L1 pathway in non-obese diabetic (NOD) mice may precipitate the onset and progression of autoimmune diabetes. Anti-PD-1/PD-L1 drugs might have the same effect. Besides, Fujisawa et al demonstrated that autoimmune diabetes patients have a significant reduction in PD-1 expression in CD4 (+) T cells compared with healthy controls. Another study suggested that decreased PD-1 expression on T cell derived from T1D patients can cause abnormal activation of T cell and then destroy the β cells. So the reduction of PD-1 on T cell may play an important role in the progressing of anti-PD-1 therapy-induced diabetes.

Although the mechanism underlying anti-PD-1/PD-L1 antibody induced autoimmune diabetes is not well understood, 42 cases have been reported that patients presented diabetes were secondary to PD-1 or PD-L1 inhibitors. Twelve out of 42 were treated with pembrolizumab. The levels of C-peptide was low in most patients (30 of 32 tested patients). The low or undetectable C-peptide indicated the rapid onset of diabetes with rapid β-cell destruction. Similarly, in our patient, there was a low C-peptide level at the onset of autoimmune diabetes.

So far, to the best of our knowledge, this is the first case report of autoimmune diabetes following the treatment of anti-PD-1 therapy in China. Many PD-1 inhibitor has officially hit the Chinese mainland this year, with thousands of patients starting to use these drugs. Autoimmune diabetes is a rare but serious side-effect of anti-PD-1/PD-L1 therapy. The US FDA has updated with a warning for the development of autoimmune diabetes following the use of pembrolizumab. Patients undergoing the treatment of anti-PD-1/PD-L1 therapy should be closely monitored about diabetes related indexes including blood glucose and glycated hemoglobin (HbA1c) before and during the treatment. Patients with sudden onset of DKA should be alert to the occurrence of PD-1 related diabetes. Further studies are required to identify the pathogenesis of anti-PD-1/PD-L1 induced autoimmune diabetes.

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Author contributions

Conceptualization: Ji Hu.
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