中文題目：使用免疫抑制劑後產生糖尿病酮症酸中毒

英文題目：Diabetic ketoacidosis secondary to treatment with immune checkpoint inhibitors

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Introduction:

Immune checkpoint inhibitors(ICI) are targeting programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1), or cytotoxic T-lymphocyte－associated antigen-4 and have been effective against several types of cancer, such as lung cancer or melanoma(**). Immune checkpoints can regulate the function of T cell and PD-1 pathway is one of the inhibitory pathways. The PD-1 protein, which is expressed on T cells, can inhibit T cell proliferation when its ligands PD-L1 and PD-L2. Pembrolizumab is one of the PD-1 inhibitory is used to treated patients with metastatic non-small cell lung cancer (NSCLC) and it makes T cell reactivation not only anti-tumor but also affect normal cells. The inflammatory side effects are often termed immune-related adverse events. The immune-related adverse events most commonly involve the gastrointestinal tract, endocrine glands, skin, and liver. And endocrine toxicity is most commonly targeting the thyroid, pituitary, or adrenal glands (**). New-onset diabetes mellitus with ketoacidosis (DKA) has been reported in fewer than 1% of patients(**). Here, we describe our patient presenting DKA after ICI therapy in real-world practice.

Case presentation:

A 49-year-old man was a smoker with 1.5 pack per day and denied systemic diseases such as type 2 diabetic mellitus or hypertension. His initial presentation was low back pain with bilateral lower limbs weakness and the final pathology showed lung adenocarcinoma, with lung to lung, liver, rib, spine metastasis, cT4N3M1c, Stage IVB, epidermal growth factor receptor and Anaplastic lymphoma kinase showed both negative, Kirsten rat sarcoma mutation with G12D. He received chemotherapy (platinum plus pemetrexed, pemetrexed maintenance therapy) plus pembrolizumab (200mg, 2.4mg/kg) regularly. After 10 months treatment course of pembrolizumab, the patient was admission to our ward due to fever with abdominal fullness and shortness of breath for one day. Acute respiratory failure with endotracheal tube insertion was noted on the third day of admission. The lab data showed blood glucose was 570 mg/dL (31.67 mmol/L), with ketoacidosis. His serum HbA1C was 7.3%, and C-peptide levels was 0.42 ng/mL and glutamic acid decarboxylase(GAD) antibody was below 0.59 IU/mL. The thyroid function and cortisol level were within normal range. The computed tomography and abdominal ultrasound showed no pancreatitis or abnormal pancreas size. He received intravenous fluids and continuous insulin infusion and was extubated on the fourth day of intensive care unit admission. According to the lab examination and history, he did not have high serum anti–glutamic acid decarboxylase antibodies, diabetic history or alcoholism. The diagnosis of pembrolizumab-associated type 1 diabetic mellitus was made. The blood sugar

was controlled well under insulin using and we also hold the pembrolizumab. Disease progression with lung lesion enlargement was noted and we used chemotherapy (gemcitabine plus carboplatin) and bevacizumab and now he was under stable condition.

Discussion:

We describe a patient with rapid onset of diabetes mellitus with ketoacidosis associated with the checkpoint inhibitor pembrolizumab. We confirm that diabetes mellitus is an important, yet rare, side effect. Similar to our case, these patients often present with a fulminant onset of diabetes mellitus and the presence of ketoacidosis at the time of diagnosis. Its onset ranges from a few weeks, sometimes even after the first or second cycle of immunotherapy, up to more than a year after the initiation of immunotherapy. This immune-related adverse events are predominantly found in patients exposed to blockade of the PD-1/PD-L1 pathway.

Conclusion:

Checkpoint blockade-induced diabetes mellitus is a rare but potentially lethal adverse effect, as diabetic ketoacidosis is often the first presentation. Despite its rarity, health-care professionals should be aware and patients need to be educated. This is crucial since a growing number of patients are treated with checkpoint blockade. In particular, in patients who have no history of diabetes, hyperglycemia without DKA is likely to be the very beginning of anti-PD-1 antibody-induced T1D. Therefore, such patients must be considered for either hospitalization or frequent outpatient visits with insulin injections and self-monitoring of blood glucose.