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Pembrolizumab (Keytruda®) Associated Diabetic Ketoacidosis in a Previously Nondiabetic Patient

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Introduction

Pembrolizumab (Keytruda®) is an immunotherapy agent commonly used in the treatment of non-small cell lung cancer (NSCLC) and melanoma. It is a monoclonal antibody that binds and blocks the Programmed Cell Death 1 (PD-1) receptor, an immune checkpoint that inhibits T-Cell activation. While it has become essential in the treatment of various malignancies, it has been associated with multiple adverse reactions including pneumonitis, colitis, hepatitis, hypophysitis, hyper/hypothyroidism, nephritis, and type 1 diabetes. Type 1 diabetes was reported in only 0.1% of the patients in clinical trials of Pembrolizumab, the majority of whom were first diagnosed with diabetes after initial presentation in diabetic ketoacidosis (DKA).

Pembrolizumab Mechanism of Action

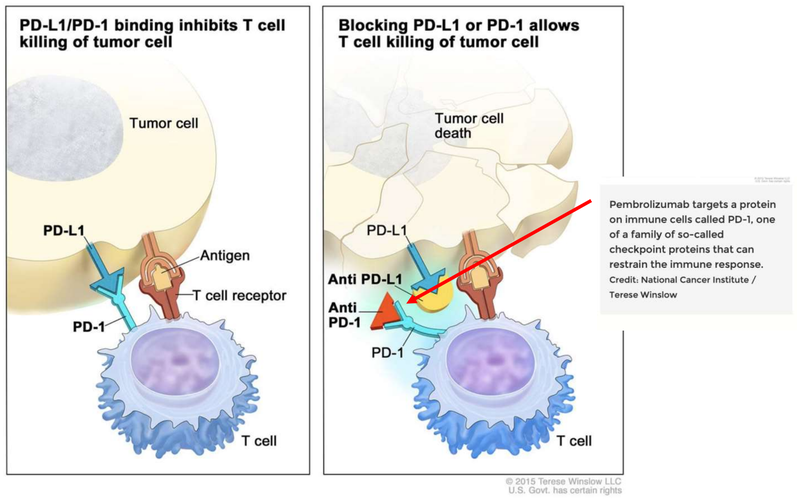

Figure 1. Immune checkpoint inhibitor. Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, help keep immune responses in check. The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells in the body (left panel). Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells (right panel).

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Case Description

Patient is a 75 year old male with a history of carcinoma in situ of the bladder, prostate cancer, carcinoma of unknown primary, chronic kidney disease presents to the hospital with fatigue, weakness, and confusion for 2 weeks.

He was previously on various chemotherapy regimen including: Atezolizumab, Enzalutamide that were started in 2017, but transitioned to Docetaxel in early 2019 due to poor response.

Patient was transitioned to Carboplatin, Docetaxel, and Pembrolizumab in late 2019 due to findings of new metastasis. One month after starting this new regimen, patient presented to the hospital with confusion, fatigue and weakness. Labs were significant for elevated glucose, lactic acid, high anion gap metabolic acidosis, beta-hydroxybutyrate, consistent with DKA. Additional workup revealed low levels of C-peptide (<0.2); however, islet-cell antibodies, insulin autoantibodies, glutamic acid decarboxylase antibodies, insulinoma associated protein, zinc transporter were all within normal limits.

Laboratory Values

Laboratory Test	Lab Value During Admission	Lab Reference Range
Lipase	162 IU/L	0-60 IU/L
Lactic Acid	2.3 mmol/L	<2.1 mmol/L
Serum Glucose	1884 mg/dsL	50-140
Beta Hydroxybutyrate	10.22 mmol/L	0.0-0.30 mmol/L
PH, Arterial	7.12	7.35-7.45
Thyroid Stimulating Hormone	0.63 uIU/mL	0.45-5.33 uIU/mL
Anti-glutamic acid decarboxylase autoantibodies	<5 IU/mL	<5 IU/mL
Insulin Antibodies	<0.4 U/mL	0-0.4 U/mL
Zinc Transporter 8 Antibody	<10 U/mL	<15 U/mL
IA-2 Antibody	<5.4 U/mL	<5.4 U/mL
Islet Cell Antibody	<1:4	<1:4
C-Peptide	<0.2 ng/mL	0.8-4.0 ng/mL
Hemoglobin A1c	7.9%	<5.7%

Discussion

Our patient has no personal or family history of diabetes with no previously documented Hemoglobin A1c. The temporal relationship of Pembrolizumab initiation and the onset of DKA suggests a correlation. With the HbA1c being 7.9, it estimates an average glucose of 180 suggesting a more acute process in a patient not on prior anti-glycemic agents. In addition, the absence of C-peptide along with lack of traditional autoimmune diabetes markers indicates a different mechanism for his diabetes.

PD-L1 inhibitors has been reported to cause diabetes when used alone or in concert with PD-1 inhibitors. The patient was on Atezolizumab (PD-L1 inhibitor) for 2 years, transitioned to Docetaxel for 1 year before starting Pembrolizumab. It was after 1 month of Pembrolizumab that patient developed diabetes. Due to the time gap between discontinuation of Atezolizumab and initiation of Pembrolizumab, it is reasonable to attribute the development of diabetes to the latter agent.

Pembrolizumab blocks and prevents binding of tumor cells to PD-1 on lymphocytes allowing T-cell mediated destruction. However, because of non specificity, non-cancerous cells are also affected. In animals, Pembrolizumab has been shown to act on beta islet cells of the pancreas and cause subsequent destruction of insulin producing cells.

Cases such as this stress the importance of monitoring patients for signs and symptoms of diabetes when starting immunotherapy targeting immune checkpoint modulators such as Pembrolizumab.

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