**CLINICAL VIGNETTE**

# Diabetes in a Patient Treated with PD-l Inhibitor

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## *Case*

A 73-year-old female with history of BRCA1 mutation, recurrent and metastatic papillary serous fallopian tube carcinoma (stage III), prediabetes, and hypothyroidism presented to the ED with two weeks of progressive symptoms of abdominal pain, nausea, vomiting, poor food tolerance, increased thirst, and shortness of breath. She had seen her oncologist four days earlier and was newly started prednisone 60mg daily, in anticipation of initiating additional cancer treatment. Prior to admission, she was living independently and alone at her home.

Her vital signs were notable for blood pressure of 164/74 mmHg, heart rate 120 beats per minute, respiratory rate of 25 breaths per minute, oxygen saturation of 100% on nasal cannula and temperature of 36.1℃. On examination, she was thin, pale, and ill-appearing. She was alert but disoriented. She had severely dry mucus membranes and was tachypneic with full air movement, bilaterally. Her heart rate was rapid without murmurs. Her abdomen was tender to moderate palpation with hypoactive bowel sounds. She had no lower extremity edema.

Emergency department laboratory studies included serum glucose of 1084 mg/dL, sodium of 122 mmol/L (uncorrected), potassium 5.8 mmol/L, chloride 94 mmol/L, bicarbonate 10 mmol/L, anion gap 18, creatinine 1.0 mg/dL, BUN 37 mg/dL, moderate serum ketones, serum osmolality 356 mOsm/kg, venous pH 7.08, WBC 19.46 x $10^3$/mL, Hemoglobin 11.8 g/dL and platelets 554 x $10^3$/mL. Urinalysis showed 2+ ketones and 3+ glucose, and 1+ blood. She was diagnosed with diabetic ketoacidosis and endocrinology was consulted. Additional evaluation included lipase 76 U/L, TSH 3.0 mcIU/mL, Troponin < 0.04 ng/mL, Lactate 38 mg/dL, blood cultures which were negative and chest x-ray without acute process. Hemoglobin A1c resulted at 9.1%. (Hemoglobin A1c was 6.3%, 6 months prior.)

The patient was treated with IV fluid resuscitation, IV insulin infusion, potassium repletion and admitted to the medical ICU. She required extended intravenous insulin treatment secondary to fluctuating mental status and poor dietary intake. On the fourth day of admission, she was transitioned to basal-bolus insulin regimen of Lantus and Aspart. She had low insulin requirements after transition off insulin drip, which prompted additional evaluation. Glutamic Acid Decarboxylase-65 antibody returned negative (< 5.0 U/mL) but C-peptide was undetectable (< 0.2) with concurrent serum glucose of 257.

Prior cancer treatment was fully reviewed. Patient had been treated with Nivolumab five months prior to admission. Nivolumab was administered for a 3-month course until a PET-CT demonstrated fullness in the pancreatic tail and part of the body concerning for pancreatitis. At that time, pancreatic markers were elevated to peak lipase of 1522 U/L. Nivolumab was held and lipase normalized. The patient had not taken Nivolumab for two months prior to her presentation with hyperglycemia. It is presumed that exposure to Nivolumab precipitated the onset of the patient's diabetes.

She was discharged to a rehabilitation unit. Diabetes regimen at time of discharge was Lantus 3 units every 12 hours, Aspart with carbohydrate to insulin ratio of 1 unit for every 20 grams of carbohydrates and correction factor of 1:50 over capillary glucose of 175. Over the subsequent three months, insulin was adjusted to Lantus 5 units in the morning and 4 units in the evening. Insulin to carbohydrate ratios increased to 1 unit of insulin for every 12 grams of carbohydrate.

## *Discussion*

Cancer immunotherapy is a rapidly growing field of oncology with wide reaching applicability. While initially approved for metastatic melanoma and squamous non-small cell lung carcinoma, cancer immunotherapy drugs have since shown antitumor activity in genitourinary carcinomas, gastrointestinal malignancies, hematologic malignancies as well as head and neck carcinoma.[1,2]

Currently, cancer immunotherapy includes two approved classes of medication: CTLA-4 and PD-1 inhibitors. Through unique mechanisms, these inhibitors prevent

deactivation of T cells resulting in increased immune recognition of malignant cells.[3,4] As a consequence, the immune system also develops increased recognition of auto-reactive cells resulting in immune related adverse events (IRAEs). Endocrine IRAEs have included thyroid dysfunction, adrenal insufficiency, hypophysitis, and rarely diabetes.[1]

In previously reported cases, the anti-PD-1 inhibitor induced diabetes is consistently insulin deficient. Patients present with diabetic ketoacidosis with low or undetectable c-peptide and require long-term insulin treatment.[5-8] Incidence of diabetes in PD-1 Inhibitor therapy is low. In a cohort of 496 patients with metastatic melanoma, PD-1 inhibitor treatment (Nivolumab or Pembrolizumab) was complicated by insulin requiring diabetes in 0.8%.[5] Antibodies to GAD and ICA can be either positive or negative,[5-8] and there may be a factor of underlying HLA haplotype predisposition.[7,8] It may also occur in the context of pre-existing type 2 diabetes as was the case in our patient.[5,7]

In the same cohort study of 496 patients, pancreatitis occurred in 1.8% with only 1 case of subsequent pancreatic insufficiency that was diagnosed by exocrine deficiency without diabetes.[5] While pancreatitis is a relatively rare complication, elevations in lipase are more common with rates ranging 4-17% with Nivolumab therapy and even higher (13-25%) when combined with Ipilumumab.[1] Of note, autoimmune activation may have a direct relationship with pancreatic destruction. In type 1 diabetics, there is evidence to suggest that the autoimmune process leads to islet inflammation which promotes pancreatic duct hyperplasia. Pancreatic duct hyperplasia may cause obstruction leading to local areas of pancreatitis.[9]

Our patient's presentation is especially interesting because she experienced complications of both pancreatitis and insulin-deficient diabetes as a result of her PD-1 therapy. This, in addition to her underlying pre-diabetes, suggests that her insulin deficient diabetes was likely multifactorial from both direct pancreatic destruction and autoimmune mechanisms.

With increased use, physicians in both outpatient and inpatient clinical settings should be aware of potential IRAEs, which can result in significant endocrinopathies. Insulin deficient diabetes is a rare IRAEs but a life threatening complication that requires rapid diagnosis.

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