Hypoglycemia as First Presentation of Immune Checkpoint Inhibitor-induced Type 1 Diabetes

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Abstract

Diabetes Mellitus is an uncommon but well-known immune-related adverse event. However, it is typically characterized by initial hyperglycemia. We report a case of a 60-year-old male diagnosed with metastatic clear cell renal cell carcinoma who developed type 1 diabetes mellitus secondary to immunotherapy with first presentation of hypoglycemia.

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Keywords: Type 1 diabetes; immunotherapy; metastatic clear cell carcinoma; immune-related adverse events

Introduction

Immunotherapy has been a trending development in the treatment of advanced cancers. While cancers may promote immune tolerance and inhibition, immune checkpoint inhibitors (ICIs) help sustain the patient's anti-tumour immune response. Monoclonal antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA-4) (ipilimumab) and programmed death protein 1 (PD-1) (nivolumab) are ICIs commonly used in combination for the treatment of metastatic cancer. The immunotherapy combination with ipilimumab (ipi) and nivolumab (nivo) has improved patient's overall survival and is associated with long term disease control in advanced melanomas[1] and other cancers including renal cell carcinoma (RCC).[2] However, patients often develop unwanted side-effects in the form of immune related adverse events (irAEs).[3] The inhibited deactivation of the immune reaction to the tumour also allows for other abhorrent immune reactions to persist. While irAEs are typically low-grade[4], severe cases can occur, often requiring treatment to be discontinued.

There have been rare instances of patients developing type 1 diabetes mellitus (T1DM) following immunotherapy.[5] Although rare, it is characterized by episodes of hyperglycemia or with diabetic ketoacidosis and may be life threatening due to its rapid onset and possibility of acute events before clinical diagnosis. Here we describe the case of a patient who developed T1DM with initial presentation of hypoglycemia as a result of immunotherapy for metastatic RCC.

Case Presentation

This case is of a 60-year-old male originally from Liverpool, England. His past medical history is positive for gastroesophageal reflux disease (GERD), resected melanoma 10 years ago, basal cell carcinoma on the neck, and knee surgery. He is currently only taking esomeprazole for GERD. He has a maternal uncle who had head and neck cancer. He is currently employed at a hardware store as a truck driver, is a non-smoker, rarely consumes alcohol and has 3 daughters.

In early March 2021, the patient was seen by a medical oncologist with a history of 20 lbs weight loss and night sweats. Workup imaging was eventually done, and an 18 cm mass of the left upper abdominal quadrant was discovered, suspicious to be malignant, without any evidence of metastatic disease. On March 24th, 2021, the patient underwent a left radical nephrectomy. Pathology identified a clear cell RCC grade 4 with clear margins and eosinophilic variant.

In May 2021, surveillance CT scans showed recurrent disease in the left renal fossa with pulmonary metastases and mediastinal lymphadenopathy. Based on International Metastatic Database Consortium (IMDC) criteria, his disease falls under intermediate risk disease. Therefore, ipi/nivo combination immunotherapy was started, with the plan for 4 cycles of the combination (1 cycle every 3 weeks) followed by maintenance nivo (1 cycle every 4 weeks).

In August 2021, after three cycles (or 9 weeks) of ipi/nivo, he developed grade 3 hypoglycemia with a glucose level of 2.7 mmol/L accompanied by abdominal pain and night sweats. His previous glucose levels were all within normal range. His 4th cycle was skipped, and he restarted on maintenance nivo in September 2021, which he continues to date. In December 2021, his glucose levels were found to be 20 mmol/L with an HbA1c of 8.7%. As a result, he was referred to

endocrinology. Based on his glucose profile and response to basal insulin, the patient appeared to be behaving clinically as a type 1 diabetic, secondary to immunotherapy. Serum C-peptide and anti-GAD65 antibody levels were done. The patient tested negative for GAD65 autoantibodies (less than 5 IU/mL), and C-peptide levels were within normal range (569 pmol/L with a reference range of 370-1470 pmol/L). In addition, his pancreatic enzymes including serum lipase and amylase were normal and CT scan revealed normal appearance of the pancreas.

He is currently on long-acting insulin, and his serum glucose levels have been under control. His most recent CT scans showed partial response as per RECIST criteria[6], and he continues maintenance nivo.

Discussion

Endocrine autoimmunity has been observed following ICI treatment, specifically with anti-PD-1 and anti-PD-L1 antibody treatments. A 2018 meta-analysis of 38 randomized clinical trials encompassing 7551 patients of the use of ICI found 13 cases of ICI-induced diabetes; 12 cases associated with the use of anti-PD-1 therapy (7 associated with the specific use of nivo) and 1 case associated with ipi, a CTLA-4 inhibitor.[7] Therefore, an incidence of 0.2% of ICI-induced diabetes was observed in clinical trials. However, in clinic observation of ICI-induced diabetes has been much higher ranging from 0.8% to 1.9% of cases.[8] A 2018 retrospective review of cases at two American institutions found 27 cases of ICI-induced diabetes accounting for 0.9% of cases.[9] Of these cases, 8 received a ipi/nivo combination, 2 received a combination of ipi and pembrolizumab (another anti-PD-1 therapy), and 7 received only nivo.[9] Another retrospective review of 1444 patient cases at an institution in the United States found 12 cases or 0.8% of patients developed ICI-induced diabetes, 1 was treated with nivo.[5] Finally, an Australian retrospective review of patient cases found 10 or 1.9% of patients developed ICI-induced diabetes, with 3 patients on a combination of ipi/nivo and 1 patient on a combination of ipi and pembrolizumab.[10] Therefore, it is established that at least the use of anti-PD-1 ICI is associated

with the incidence of ICI-induced diabetes. A meta-analysis of these studies shows that most patients presenting with ICI-induced diabetes were diagnosed with incidence of diabetic ketoacidosis and/or hyperglycemia indicated by hemoglobin A1c (HbA1c) levels.[8] The same meta-analysis found that in 45 or 43% of patients diagnosed with ICI-induced diabetes presented with HbA1c levels less than 8.7%; this coupled with the rapid onset may indicate the incidence of fulminant T1DM.[8]

Here we present a novel case of a patient presenting with hypoglycemia prior to the development of insulin dependent T1DM secondary to ICI therapy. The presentation of hypoglycemia may indicate dysfunction in glycemic regulation and pancreatitis due to autoimmune targeting of pancreatic cells. A likely mechanism for the hypoglycemia is the autoimmune attack of glucagon producing alpha cells in the pancreas, however further investigation is warranted before any confirmation can be made. Uniquely, traditional testing for the autoimmune biomarkers GAD65 was negative and C-peptide levels were normal, therefore there was no strong suggestion of autoimmunity prior to glycemic symptom presentation. This indicates the need for clinicians to monitor patients for hypoglycemia in addition to hyperglycemia as an indication of endocrine related irAE. Hypoglycemia preceding T1DM can also be an indication for the pathogenesis of fulminant T1DM following immunotherapy.

Conclusion

Immunotherapy is associated with better long-term outcomes in the treatment of patients with metastatic RCC, but at the risk of patients developing irAEs. There is mounting evidence of T1DM as a side effect of ICI treatment. A better understanding of how T1DM induced by ICI presents is necessary for clinicians to improve the management of these patients. Further research is necessary to conclude whether anti-PD-1 and anti-CTLA4 antibodies are indeed causative. Patient should be educated on the potential side effect of ICI-induced diabetes. Prescribing clinicians

should be aware of this life-threatening irAE and offer glucose monitoring systems (i.e., glucose monitors) to every patient and adjust treatment plans accordingly.

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