Delayed-onset Fulminant type 1 Diabetes Mellitus after the Discontinuation of Pembrolizumab Immunotherapy: A Case Report

Shohei Kitayama (kitayama.shohei1@gmail.com)
Itoigawa General Hospital https://orcid.org/0000-0002-7786-8997
Naokatsu Nakata
Itoigawa General Hospital and Itoigawa Community Medical Unit, Toyama University Hospital
Minoru Iwata
Itoigawa General Hospital and Itoigawa Community Medical Unit, Toyama University Hospital

Research Article

Keywords: Type 1 Diabetes Mellitus, Hyperkalemia, Immune checkpoint inhibitors, Diabetic Ketoacidosis

Posted Date: May 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-517777/v1

Abstract

Introduction:

Immune checkpoint inhibitors (ICI) have become an essential component of several cancer therapies, but the increasing use of such drugs has led to an increasing number of reports on immune-related adverse events (IRAEs). Although type 1 diabetes mellitus (T1DM) and its subtype, fulminant T1DM, have been reported as potential IRAEs, the development of these diseases with a delayed onset after the cessation of ICI administration is uncommon. We present the first case of delayed-onset fulminant T1DM precipitated by pembrolizumab, an ICI.

Case Presentation:

A 75-year-old Japanese man, who received 10 cycles of pembrolizumab as adjuvant chemotherapy for urothelial carcinoma, presented in our emergency department with polyuria and worsening dyspnea nine weeks after the discontinuation of pembrolizumab. The laboratory data showed hyperglycemia (1349 mg/dL), metabolic acidosis, HbA1c 8.1%, and serum β-hydroxybutyrate 13.9 mmol/L. The patient was diagnosed with diabetic ketoacidosis (DKA). His symptoms improved by intravenous hydration and an insulin drip. Additional workup showed his absence of insulin-secreting capacity and negative for anti-glutamic acid decarboxylase antibody.

Conclusions:

Fulminant T1DM as an IRAE is an oncologic emergency characterized by abrupt-onset ketoacidosis with severe hyperglycemia. In addition to the potential onset of fulminant T1DM during the course of pembrolizumab treatment, clinicians should consider the possibility of delayed-onset fulminant T1DM with DKA, even after the discontinuation of pembrolizumab.

Introduction

Immune checkpoint inhibitors (ICI) have become an important component of cancer therapies, with both the use of such treatments and reports of immune-related adverse events (IRAEs) increasing. Type 1 diabetes mellitus (T1DM) and its subtype, fulminant T1DM, have been reported as IRAEs. In general, these are known to develop during the period of ICI treatment. Delayed onset of these diseases after drug discontinuation is rare, and there are no reports of delayed-onset T1DM with diabetic ketoacidosis (DKA) caused by pembrolizumab, an ICI. Herein, we present the first case of the development of fulminant T1DM with severe DKA nine weeks after the discontinuation of pembrolizumab therapy.

Case Presentation

A 75-year-old Japanese man with a history of type 2 diabetes mellitus, the activity of which had been well controlled (HbA1c, 5.5%-6.3%) using only voglibose, presented in the emergency department (ED) with a

one-day history of polyuria and worsening dyspnea. Seventeen months before the ED visit, he had been diagnosed as having right urothelial carcinoma. He had received adjuvant chemotherapy (three cycles of gemcitabine/carboplatin) after a right radical nephroureterectomy (postoperative serum creatinine level, 1.48–1.77 mg/dL). Then, he had received ten cycles of pembrolizumab treatment. However, this treatment had been discontinued nine weeks before the ED visit because of disease progression. Ten days before the ED visit, the patient's blood glucose and HbA1c levels were 91 mg/dL and 6.4%, respectively. At presentation in the ED, his blood pressure was 110/46 mm Hg, his heart rate was 60 bpm, his respiratory rate was 29/min, his body temperature was 35.8^{o}C, and his oxygen saturation was 99% while breathing ambient air. A laboratory analysis showed the following results: glucose 1349 mg/dL, HbA1c 8.1%, blood urea nitrogen 48.9 mg/dL, creatinine 2.82 mg/dL, arterial blood gas pH 7.01, carbon dioxide pressure of 28.5 mm Hg, potassium 9.1 mmol/L, bicarbonate 6.9 mEq/L, anion gap 24.1 mmol/L and serum β-hydroxybutyrate 13.9 mmol/L (reference range < 0.1 mmol/L). Electrocardiography revealed an absence of P waves, a wide QRS complex, a complete right bundle branch block, and tall, sharp T waves. Therefore, we diagnosed the patient as having DKA and hyperkalemia with electrocardiogram changes based on the laboratory findings. He was started on an intravenous insulin infusion and intravenous fluids, and preparations for defibrillation were made in case of a lethal arrhythmia. He was then admitted to the endocrinology department for additional workup. His serum c-peptide level was 0.2 ng/mL (reference range 0.8–2.5 ng/mL), urine c-peptide was 2.4 μg/day (reference range 22.8-155.2 μg/day) and he tested negative for anti-glutamic acid decarboxylase antibody. By day 2, the DKA had resolved and the electrolyte abnormalities had been corrected. He was discharged three weeks after admission while continuing to receive subcutaneous insulin basal and bolus therapy.

Discussion

In a large case series, the incidence of ICI-induced T1DM was 0.9%. The mean age at the time of diagnosis was 66 years, and the median time to disease onset was six cycles of ICI treatment [1]. The pathogenesis of ICI-induced T1DM is not fully understood, although ICI-induced disruption of peripheral immune tolerance to pancreatic β-cells is considered to be a potential contributory factor [2]. Pembrolizumab, an anti-programmed cell death protein 1 (PD-1) antibody that acts as an ICI, inhibits the PD-1 pathway, which is involved in immune tolerance. In fact, several cases of T1DM development during pembrolizumab treatment have been reported. Fulminant T1DM is a subtype of T1DM, and several ICI-related cases have been reported. It is characterized by abrupt-onset hyperglycemia with severe ketoacidosis due to rapid β-cell destruction. Our case fulfilled the Japanese diagnostic criteria for fulminant T1DM [3]. In addition, Hyperkalemia in patients with DKA frequently results from a combination of several factors. In this case, insulin deficiency due to drastic reduction of β-cell function and renal impairment were considered to be major contributory factors.

Although IRAEs generally occur during the period of ICI treatment, our patient developed fulminant T1DM nine weeks after the discontinuation of pembrolizumab treatment. To the best of our knowledge, this is the first case report describing the development of T1DM with DKA after the cessation of pembrolizumab

therapy. Recently, Couey et al. proposed the concept of delayed immune-related events (DIRE) after ICI discontinuation [4], and Mae et al. reported a case of DKA as a DIRE after the discontinuation of nivolumab, another ICI [5]. Furthermore, it has been pointed out that the occupancy rate of PD-1 receptors remains high for more than 12 weeks after a single anti-PD-1 antibody injection [4]. Therefore, T1DM could theoretically develop after the discontinuation of pembrolizumab. In general, the etiology of fulminant T1DM is known to include both genetic and environmental (e.g., viral infection) factors [6]. We cannot exclude the possibility that the fulminant T1DM in this case was caused by a generally speculated etiology, nor can a direct causal relationship between pembrolizumab and fulminant T1DM be proved from the case report. However, the above reports support the possibility that this patient developed delayed-onset fulminant T1DM due to pembrolizumab treatment.

Conclusions

There is a growing awareness of T1DM, especially fulminant T1DM, as an emergent IRAE. In addition to the potential onset during the course of pembrolizumab treatment, clinicians should consider the possibility of delayed-onset fulminant T1DM with DKA, even after the cessation of pembrolizumab.

Declarations

Acknowledgments:

We express our deep thanks to Dr. Akira Matsuki for his continuous support.

Funding:

The authors declare that they have no financial supports.

Conflicts of interest/Competing interests:

The authors declare that they have no conflict of interest.

Ethics approval:

All procedures were performed in accordance with the institutional ethics committee.

Consent for publication:

The patient has consented to submission of this case report to the journal.

Availability of data and material:

Not applicable

Code availability:

Not applicable

Authors' contributions:

Shohei Kitayama designed and conceived the manuscript, analyzed the data. Naokatsu Nakata and Minoru Iwata conceived the manuscript and revised the text for intellectual content.

References

1. Stamatouli AM, Quandt Z, Perdigoto AL, Clark PL, Kluger H, Weiss SA, et al. Collateral Damage: Insulin-Dependent Diabetes Induced With Checkpoint Inhibitors. Diabetes. 2018;67(8):1471-80.
2. Youssef N, Noureldein M, Daoud G, Eid AA. Immune checkpoint inhibitors and diabetes: Mechanisms and predictors. Diabetes Metab. 2020; https://doi.org/10.1016/j.diabet.2020.09.003
3. Imagawa A, Hanafusa T, Awata T, Ikegami H, Uchigata Y, Osawa H, et al. Report of the Committee of the Japan Diabetes Society on the Research of Fulminant and Acute-onset Type 1 Diabetes Mellitus: New diagnostic criteria of fulminant type 1 diabetes mellitus (2012). J Diabetes Investig. 2012;3(6):536-9.
4. Couey MA, Bell RB, Patel AA, Romba MC, Crittenden MR, Curti BD, et al. Delayed immune-related events (DIRE) after discontinuation of immunotherapy: diagnostic hazard of autoimmunity at a distance. J Immunother Cancer. 2019;7(1):165.
5. Mae S, Kuriyama A, Tachibana H. Diabetic Ketoacidosis as a Delayed Immune-Related Event after Discontinuation of Nivolumab. J Emerg Med. 2020; https://doi.org/10.1016/j.jemermed.2020.09.023
6. Kawabata Y, Ikegami H. Genetics of fulminant type 1 diabetes. Diabetol Int. 2020;11(4):315-322.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CAREchecklist.pdf