Case report: pembrolizumab-induced acute type 1 diabetes mellitus and diabetic ketoacidosis in a perioperative esophageal squamous cell carcinoma patient

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Background: Immune checkpoint inhibitor (ICI) therapy rarely results in severe immune-related adverse events (irAEs). Autoimmune diabetes, an uncommon but serious irAE, can be life-threatening if not promptly treated. Although ICIs have been widely used in cancer therapy, there have been no reported cases in China of autoimmune diabetes developing during the perioperative treatment of esophageal squamous cell carcinoma (ESCC). This case report provides a significant clinical contribution by presenting the first documented instance of such an occurrence, emphasizing the need for vigilance and appropriate management strategies.

Case Description: We present a 52-year-old male with locally advanced stage III locally advanced lower thoracic ESCC who developed type 1 diabetes mellitus (DM1) leading to diabetic ketoacidosis (DKA) after pembrolizumab treatment. The patient had no prior history of diabetes mellitus. He initially presented with progressive dysphagia and underwent two cycles of chemo-immunotherapy with albumin paclitaxel, carboplatin, and pembrolizumab as neoadjuvant therapy, followed by maintenance pembrolizumab after minimally invasive esophagectomy. Following the fifth course, he was admitted to the hospital in a comatose state and quickly diagnosed with DKA. Hemoglobin A1c (HbA1c) was 7.3%, and fasting C-peptide and insulin assays were significantly low. Detailed blood glucose levels and HbA1c were monitored before pembrolizumab initiation, and pre-treatment levels were normal. Pathological examination confirmed a moderately differentiated ESCC with no signs of metastatic disease. The patient received prompt multidisciplinary treatment and has been under follow-up for 10 months with no recurrence of ESCC but requiring ongoing management of diabetes.

Conclusions: In summary, this case highlights the rare but potentially life-threatening risk of autoimmune diabetes following pembrolizumab therapy in ESCC patients. The unique clinical contributions of this case include identifying the onset of DM1 during the perioperative period and emphasizing the importance of early detection of DKA symptoms. Clinicians should remain vigilant for such irAEs, ensuring regular monitoring of blood glucose and thyroid function in patients undergoing ICI therapy. Further research is needed to clarify the pathogenesis of pembrolizumab-induced diabetes and develop guidelines for monitoring and managing these adverse events in ESCC patients.

Keywords: Case report; pembrolizumab; diabetes mellitus; esophageal squamous cell carcinoma (ESCC); immune-related adverse events (irAEs)

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Introduction

In recent years, immune checkpoint inhibitors (ICIs) have made remarkable achievements in the treatment of solid tumors (1). While ICIs significantly improved prognosis and cancer survival, they were also associated with immune-related adverse events (irAEs) (2-4). Few patients taking pembrolizumab reported type 1 diabetes mellitus (DM1) or even diabetic ketoacidosis (DKA). Only 0.1% of patients enrolled in clinical trials were reported to develop DKA after pembrolizumab treatment (5). Additionally, very few cases of endocrinopathies, particularly in perioperative patients with esophageal cancer, have been documented. In this case report, we describe perioperative patient with locally advanced lower thoracic esophageal squamous cell carcinoma (ESCC) who developed pembrolizumab-induced DM1, resulting in DKA after treatment. We present this article in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-159/rc).

Highlight box

Key findings

- There are currently no reports of autoimmune diabetes in perioperative treatment of esophageal cancer in China, and we are the first to report the development of autoimmune diabetes in the perioperative period for locally advanced thoracic esophageal squamous cell carcinoma (ESCC).

What is known and what is new?

- Immune checkpoint inhibitor (ICI) therapy can result in autoimmune diseases, including type 1 diabetes mellitus.
- Immune checkpoint inhibitors can cause a rare form of autoimmune diabetes with ketoacidosis, which can be severe and potentially life-threatening.

What is the implication, and what should change now?

- Clinicians should consider the potential immune-related adverse events when patients are treated with ICIs. During the ICIs therapy, patients' blood glucose levels should be monitored dynamically and tightly.

Case presentation

A 52-year-old male patient with a history of locally advanced lower thoracic ESCC, classified as cT3N1M0 according to American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) 8th edition, and no history of diabetes mellitus, was admitted with progressive dysphagia. Detailed blood glucose levels and HbA1c were monitored before pembrolizumab initiation, and pre-treatment levels were normal. The patient completed two cycles of chemotherapy and immunotherapy before surgery and underwent radical resection of esophageal cancer as scheduled. The protocol of neoadjuvant therapy was albumin paclitaxel 300 mg + carboplatin 300 mg + pembrolizumab 200 mg per cycle. The postoperative pathological stage was ypT2N1M0 AJCC/UICC 8th.

The patient continued immunomaintenance therapy after surgery. After the fifth cycle of immunotherapy, the patient developed a generalized rash, which was relieved after the patient applied dexamethasone ointment. He was subsequently admitted to hospital in a coma and was quickly diagnosed with DKA (*Figure 1*). In this patient, fasting C-peptide assay was significantly low, C-peptide was significantly decreased 2 hours after meals, fasting insulin assay was low, insulin was normal 2 hours after meals (*Figure 2A*), thyroid stimulating hormone was decreased (*Figure 2B*), urine sugar was 4+, hemoglobin A1c (HbA1c) was 7.3%, testosterone was normal, follicle stimulating hormone was doubled, anti-insulin antibody was negative, insulin autoantibody was negative, and glutamic acid decarboxylase antibody was negative (*Figure 2C*).

During the hospitalization, the patient underwent treatment using Mealtime Recombinant Human Insulin Lispro Injection (Humalog Mix25) and insulin glargine, however, achieving adequate glycemic control was challenging. To address this, the mealtime insulin was switched from Humalog to Humulin, and the insulin glargine was replaced with basal insulin. Nevertheless, the patient experienced episodes of nocturnal hypoglycemia

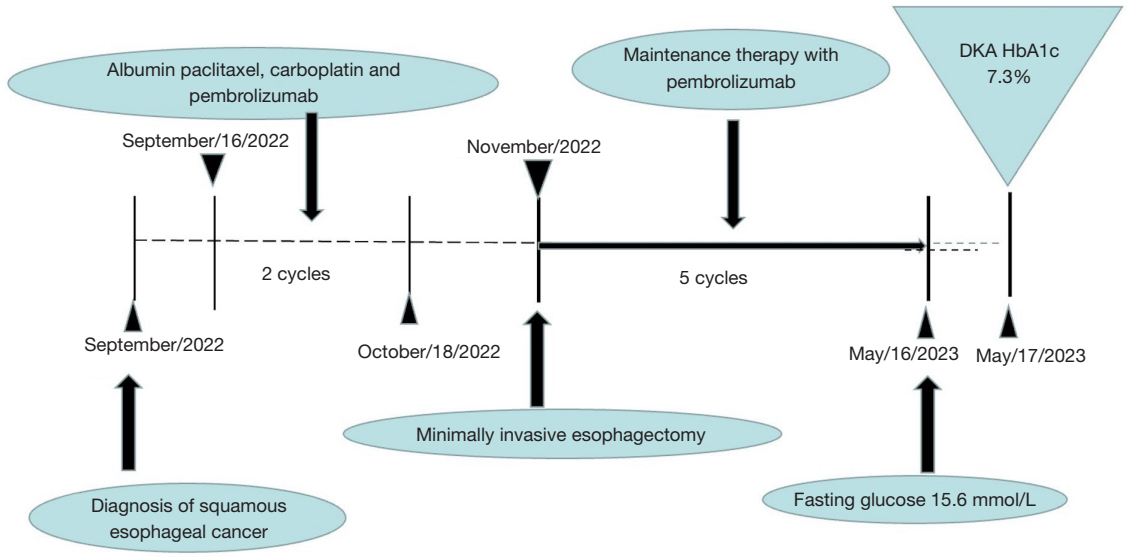

Figure 1 Timeline of treatment from diagnosis of esophageal squamous carcinoma to development of autoimmune diabetes mellitus. DKA, diabetic ketoacidosis; HbA1c, hemoglobin A1C.

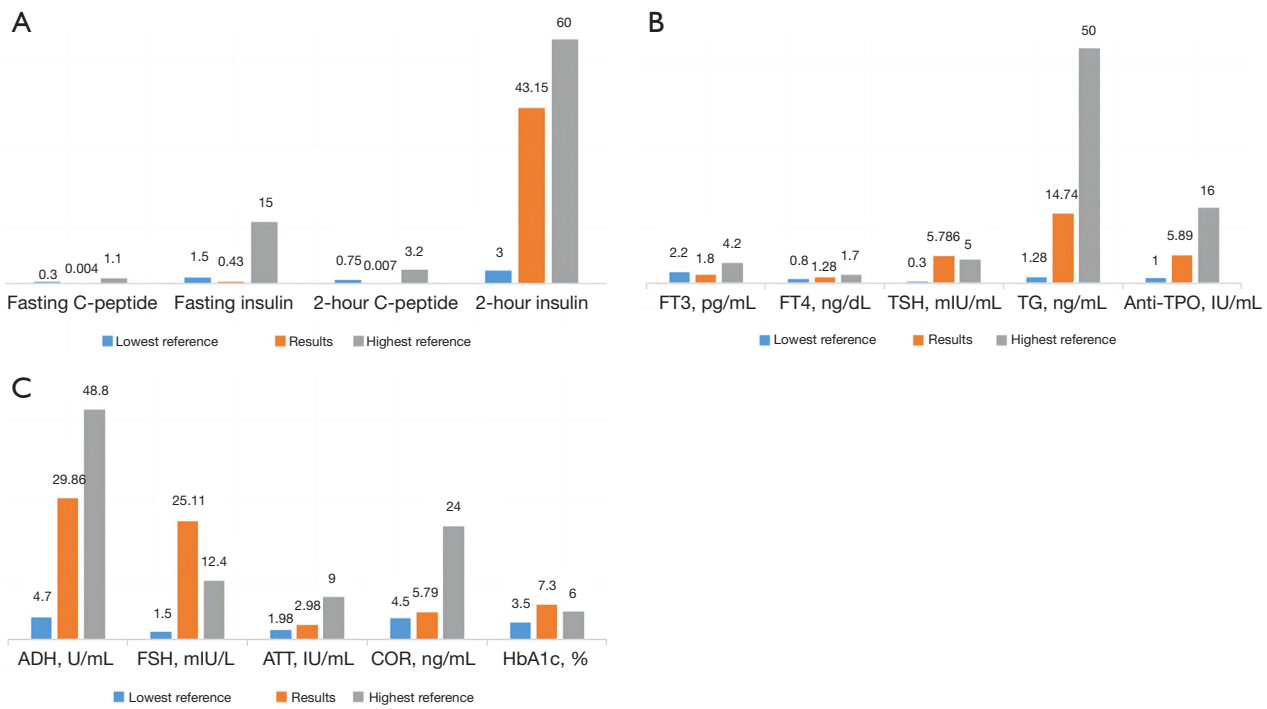

Figure 2 Laboratory tests and results. (A) Insulin (μIU/mL) and C-peptide (nmol/L) levels. (B) Thyroid stimulating hormone and relevant hormones. (C) Sex hormones and glycosylated hemoglobin. ADH, antidiuretic hormone; Anti-TPO, thyroid peroxidase antibody; ATT, glutamic acid decarboxylase antibody; COR, corticosterone; FT3, free triiodothyronine; FT4, free thyroxine; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1C; TG, triglyceride; TSH, thyroid stimulating hormone.

or low fasting blood sugar levels in the morning. Consequently, the basal insulin was discontinued, and an oral hypoglycemics agent, empagliflozin, was introduced. With this adjustment, the patient's blood sugar levels stabilized, and subsequently, the patient was discharged. Presently, the patient continues insulin therapy to manage glycemic control.

According to standard postoperative follow-up protocols for esophageal cancer, enhanced computed tomography (CT) scans of the neck, chest, and abdomen are performed every 3 months. However, considering the patient's ICIs-induced type 1 diabetes, we conduct monthly telephone follow-ups. Based on the latest follow-up data, the patient shows no signs of tumor recurrence or metastasis. The patient's type 1 diabetes has shown no improvement and continues to be managed with oral hypoglycemic agents. Currently, blood glucose levels are reasonably controlled.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

PD-1 inhibitor-related DM1 is often characterized by high-risk symptoms such as polydipsia, polyuria, fatigue, weight loss, acute glucose rises and even DKA. It has been reported that 80% of patients have DKA as the first symptom, which may be life-threatening if not treated in time (6-8). The median time to onset of diabetes in patients with ICI-associated diabetes included by de Filette *et al.* was about 13 weeks, and the combination of PD-1 and cytotoxic T-lymphocyte-associated-4 (CTLA-4) may accelerate the onset of diabetes (9). Previous study has shown that there is no correlation between HbA1c level and the onset time of PD-1 inhibitor-related diabetes, which may be related to the faster onset of PD-1 inhibitor-related diabetes, resulting in the failure of HbA1c level to reflect the sharp rise of blood sugar in time (10). In recent years, there have been increasing reports of Fulminant type 1 diabetes (FT1D) after treatment with PD-1 inhibitors in East Asian populations. FT1D is a subtype of autoimmune type 1 diabetes characterized by sudden ketoacidosis, which is characterized by high blood sugar but low HbA1c and low or undetectable C-peptide levels (11). In addition, studies have shown that patients with checkpoint inhibitor-associated diabetes also have associated thyroid insufficiency (9,12). Therefore, monitoring thyroid function in patients with PD-1 inhibitor-associated diabetes can also help improve the clinical judgment of this irAE. There is also a certain relationship between PD-1 inhibitor-related diabetes and type 1 diabetes autoantibodies. Byun *et al.* mentioned that GAD antibody is the most common positive among these antibodies, and about 50% of patients are positive (13). He noted that after the use of PD-1 inhibitors, antibody-positive patients were more likely to develop autoimmune diabetes than negative patients, but this was not related to the occurrence or severity of DKA. Other studies have shown that patients with anti-B-cell autoantibodies GAD, IAA, IA2, and ICA are likely to develop DKA after a short period of treatment with PD-1 inhibitors (14). At present, whether islet autoantibodies are involved in the onset or development of immune-related diabetes remains to be further studied.

PD-1 inhibitor-associated diabetes may be a new type of autoimmune disease. In DM1, the continuous activation of T lymphocytes leads to the destruction of islet B cells. PD-1 inhibitors may activate autologous reactive T cells, leading to $CD4^+$ T cytokine secretion and cytolytic $CD8^+$ T cell tissue infiltration, thereby causing an autoimmune response of islet cells (15). In addition, because programmed cell death protein 1 (PD-1) inhibitors block the binding of programmed death-ligand 1 (PD-L1) on pancreatic B cells to the PD-1 receptor on autoreactive T cells, they have a disinhibitory effect on autoreactive T cells, thereby allowing them to survive and destroy islet B cells (16). Previous study has shown that PD-1 inhibitor-related diabetes may also cause C-reactive protein and other cytokines in the body to cause damage to the pancreas, but the specific mechanism is unknown (17). It has been reported that human leukocyte antigen (HLA) genotypes HLA-DQ2 and HLA-DQ8 were more likely to develop DM1, while HLA-DR4 genotype was more common in PD-1-related diabetes patients (18). Despite the above studies, the pathogenesis of PD-1 inhibitor-induced autoimmune diabetes is still unclear and needs to be further explored.

With the increasing use of PD-1 inhibitors, adverse reactions related to immunosuppressants should be paid more attention by medical personnel. Routine blood glucose detection before each administration and close attention to the clinical symptoms and signs of hyperglycemia are helpful for early diagnosis of blood glucose abnormalities, especially DKA. In addition, C-peptide tests can be used to detect impairment of islet function, which has potential

value in future decision making. The presence of pancreatic autoantibodies can be detected in about 50% of patients, and antibody positive patients are more likely to develop PD-1 inhibitor-associated diabetes, but detection of antibodies is not an absolute requirement for diagnosis and treatment. In addition, most patients with fulminant hyperglycemia and DKA as the first symptoms, the situation is dangerous, so it is important to strengthen patients' awareness and monitoring of this adverse reaction.

Conclusions

We firstly presented a perioperative patient who developed DM1 that resulted in DKA after pembrolizumab treatment for locally advanced lower thoracic ESCC. Clinicians should consider the potential occurrence of irAEs in patients undergoing treatment with ICIs.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-24-159/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-24-159/coif). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Kubli SP, Berger T, Araujo DV, et al. Beyond immune checkpoint blockade: emerging immunological strategies. Nat Rev Drug Discov 2021;20:899-919.
2. Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ 2018;360:k793.
3. Huang Y, Ma W, Wu D, et al. Prognostic relevance of immune-related adverse events in lung cancer patients undergoing immune checkpoint inhibitor therapy: a systematic review and meta-analysis. Transl Lung Cancer Res 2024;13:1559-84.
4. Li S, Wang T, Lai W, et al. Prognostic impact of sarcopenia on immune-related adverse events in malignancies received immune checkpoint inhibitors: a systematic review and meta-analysis. Transl Cancer Res 2021;10:5150-8.
5. Cheema A, Makadia B, Karwadia T, et al. Autoimmune Diabetes Associated With Pembrolizumab: A Review of Published Case Reports. World J Oncol 2018;9:1-4.
6. de Filette J, Andreescu CE, Cools F, et al. A Systematic Review and Meta-Analysis of Endocrine-Related Adverse Events Associated with Immune Checkpoint Inhibitors. Horm Metab Res 2019;51:145-56.
7. Ferrari SM, Fallahi P, Elia G, et al. Autoimmune

Endocrine Dysfunctions Associated with Cancer Immunotherapies. Int J Mol Sci 2019;20:2560.
8. Onodera R, Chiba S, Nihei S, et al. High level of C-reactive protein as a predictive factor for immune-related adverse events of immune checkpoint inhibitors in non-small cell lung cancer: a retrospective study. J Thorac Dis 2023;15:4237-47.
9. de Filette JMK, Pen JJ, Decoster L, et al. Immune checkpoint inhibitors and type 1 diabetes mellitus: a case report and systematic review. Eur J Endocrinol 2019;181:363-74.
10. Gauci ML, Boudou P, Squara PA, et al. Checkpoint inhibitor treatment induces an increase in HbA1c in nondiabetic patients. Melanoma Res 2019;29:328-32.
11. Haller MJ, Long SA, Blanchfield JL, et al. Low-Dose Anti-Thymocyte Globulin Preserves C-Peptide, Reduces HbA(1c), and Increases Regulatory to Conventional T-Cell Ratios in New-Onset Type 1 Diabetes: Two-Year Clinical Trial Data. Diabetes 2019;68:1267-76.
12. Lin W, Huang Y, Zhu L, et al. Pembrolizumab combined with paclitaxel and platinum as induction therapy for locally advanced esophageal squamous cell carcinoma: a retrospective, single-center, three-arm study. J Gastrointest Oncol 2022;13:2758-68.
13. Byun DJ, Wolchok JD, Rosenberg LM, et al. Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies. Nat Rev Endocrinol 2017;13:195-207.
14. Changizzadeh PN, Mukkamalla SKR, Armenio VA. Combined checkpoint inhibitor therapy causing diabetic ketoacidosis in metastatic melanoma. J Immunother Cancer 2017;5:97.
15. Quandt Z, Young A, Anderson M. Immune checkpoint inhibitor diabetes mellitus: a novel form of autoimmune diabetes. Clin Exp Immunol 2020;200:131-40.
16. Akturk HK, Michels AW. Immune Checkpoint Inhibitor-Induced Type 1 Diabetes: An Underestimated Risk. Mayo Clin Proc 2020;95:614-5.
17. Ying L, Zhang Y, Yin J, et al. Classic Type 1 Diabetes Mellitus and Fulminant Type 1 Diabetes Mellitus: Similarity and Discrepancy of Immunological Characteristics and Cytokine Profile. Diabetes Metab Syndr Obes 2021;14:4661-70.
18. Stamatouli AM, Quandt Z, Perdigoto AL, et al. Collateral Damage: Insulin-Dependent Diabetes Induced With Checkpoint Inhibitors. Diabetes 2018;67:1471-80.

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