Diabetic ketoacidosis induced by nivolumab in invasive mucinous adenocarcinoma of the lung: a case report and review of the literature

Juan Yan[1], Zheng-Zheng Xie[2], Teresa Moran[3,4,5,6], Cesare Gridelli[7], Mao-Dong Zheng[1], Su-Juan Dai[8]

[1]Department of Pharmacy, The First Affiliated Hospital of Hebei North University, Zhangjiakou, China; [2]Department of Pharmacy, Beijing Shijitan Hospital, Beijing, China; [3]Medical Oncology Department, Catalan Institute of Oncology Badalona, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; [4]Institut Germans Trias i Pujol, Barcelona, Spain; [5]Badalona Applied Research Group in Oncology, Barcelona, Spain; [6]Department of Medicine, Universitat Autònoma de Barcelona (UAB), Campus Can Ruti, Barcelona, Spain; [7]Division of Medical Oncology, 'S. G. Moscati' Hospital, Avellino, Italy; [8]Department of Pharmacy, Zengchen District People's Hospital of Guangzhou (Boji-Affiliated Hospital of Sun Yat-sen University), Guangzhou, China

Contributions: (I) Conception and design: J Yan, ZZ Xie; (II) Administrative support: MD Zheng; (III) Provision of study materials or patients: J Yan; (IV) Collection and assembly of data: T Moran, C Gridelli; (V) Data analysis and interpretation: SJ Dai; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Zheng-Zheng Xie. Department of Pharmacy, Beijing Shijitan Hospital, No. 10 Tieyi Road, Haidian District, Beijing, China. Email: xie_zhengzheng@126.com.

Background: Nivolumab is the first programmed cell death receptor 1 (PD-1) inhibitor approved in China. Compared with chemotherapy, nivolumab has shown advantages of good efficacy and safety in the treatment of a variety of tumors. However, due to its short time of use in China and lack of safety experience, clinical understanding of its adverse reactions has not been sufficiently elucidated. In recent years, cases of diabetic ketoacidosis caused by nivolumab have been reported in the emergency department, which has aroused our concern.

Case Description: Here we present a serious case of diabetic ketoacidosis in a 69-year-old woman with invasive mucinous adenocarcinoma of the lung, which occurred following therapy with the PD-1 inhibitor nivolumab and dendritic cell/cytokine-induced killer cell (DC/CIK) immunotherapy. She presented with diabetic ketoacidosis 5 days after the second cycle of nivolumab administration. The patient presented with dry mouth symptoms, a maximum blood glucose of 511.2 mg/dL, hemoglobin A1c (HbA1c) level of 7.4%, urine ketone body value of 3+, and extracellular fluid residual alkali level of –3.8 mmol/L. Normal saline and insulin was initiated. The patient had no history of obesity or family history of diabetes. She received a single dose of 3.75 mg of dexamethasone treatment during this period of time which resulted in cough improvement, but did not explain the onset of the diabetes. She was treated with insulin, sitagliptin phosphate tablets and acarbose tablets. Diabetic ketoacidosis was considered an immune-related toxicity caused by nivolumab, and consequently, treatment with nivolumab was suspended. Patient was maintained under insulin treatment with a blood glucose levels normalization.

Conclusions: The incubation period of nivolumab-induced diabetic ketoacidosis is dispersive and the clinical risk is high. Patients need life-long insulin therapy. Blood glucose and HbA1c should be monitored routinely before and during nivolumab immunotherapy to avoid the occurrence of diabetic ketoacidosis. After the occurrence of diabetic ketoacidosis, insulin should be used to actively control blood glucose and do a good job in medication education to ensure long-term compliance of patients. Nivolumab should only be initiated if the patient has a clinical benefit under stable glucose control.

Keywords: Diabetic ketoacidosis; immunotherapy adverse effects; nivolumab; programmed cell death receptor 1 inhibitor (PD-1 inhibitor); case report

Submitted Aug 25, 2022. Accepted for publication Nov 10, 2022.
doi: 10.21037/atm-22-5211
View this article at: https://dx.doi.org/10.21037/atm-22-5211

Introduction

With the advent of immunotherapy, an increasing number of patients are receiving this type of therapy as part of their antitumor treatment. Immune checkpoint inhibitors (ICIs), which differs from traditional chemotherapy both in its mechanism of action and toxicity, arise new medical problems and challenges for oncologists and other health care providers.

Nivolumab is a human monoclonal antibody that blocks the interaction between programmed cell death receptor 1 (PD-1) and its ligands, namely PD-L1 and PD-L2 (1). Nivolumab related adverse events (AEs) were documented in 74–85% of patients (2). Endocrine related AEs represent the most common form of immune related (IR)-AE, being thyroid alterations the most prevalent (3). However, *de novo* diabetes induced by treatment with immunotherapy occurs at low frequency (<1%) (4).

Recently, cases of diabetic ketoacidosis have been reported in patients treated with nivolumab. Here, we report a case of diabetic ketoacidosis following treatment with nivolumab and dendritic cell/cytokine-induced killer cell (DC/CIK) immunotherapy. This case study suggests this infrequent endocrine IR-AEs might occur early after immunotherapy administration, and biochemical and imaging examinations should be carried out regularly. For patients with normal results, it is recommended that blood glucose levels be tested every 2 to 3 weeks. We present the following article in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5211/rc).

Case presentation

A 69-year-old female was admitted to Beijing Shijitan Hospital on October 7, 2018, 2.5 years after she was diagnosed with nodules in her lower left lung, 1.5 years after her left lung surgery which confirmed a lung cancer diagnosis. The patient had a prior history of hypertension for more than 20 years, gallstones, and kidney stones, and no history of diabetes. She had always been in good health and denied any history of smoking or drinking. She also denied any history of drug or food allergies. Her family history was unremarkable. Since the onset of the disease, she had been asymptomatic.

Her oncology medical history started in September 2016, when a chest CT detected nodules in the left lower lung. Patient denied cough, sputum, hemoptysis, chest pain, or fever. In March 2017, a follow-up chest CT which found an enlargement of such lung nodules which measured 41 mm × 23 mm. She underwent a lobectomy and mediastinal lymph node dissection. Postoperative pathology report indicated infiltrative mucinous adenocarcinoma. The tumor reached subpleural tissue and did not break through the elastic layer. The results of pathological were as follows: Lymph nodes 0/6, NapsinA(–), TTF-1 (individual +), P40 (–), ck5/6 (–), ALK (–). The tumor stage was postoperative stage T2aN0M0, IB. She has been taking Chinese medicine since her operation. In October 2017, a follow up CT showed a left partial pleural thickening accompanied by a small amount of pleural effusion, and both lungs were scattered with chronic inflammation images. In April 2018, she developed a cough and had blood in her sputum. She received several courses of antibiotic with no improvement. In May 2018, additional molecular testing was performed in the surgical tissue specimens. BRAF and ROS1 results came back as negative, and EGFR was wild type. In August 2018, a PET-CT showed that the left thoracic surgical cavity was covered with hydrops, and the surrounding tissue of the hydrops had diffused thickening with small nodules and increased FDG metabolism, suggesting pleural infiltration. Additionally, small intraparenchimatous nodules in left lung tip, suggesting intrapulmonary metastasis were identified, as well as a metabolism increase in both supraclavicular and bilateral mediastinal lymph nodes. Further findings consisted of a solid density patchy lesion, with no increase in metabolism consistent with inflammatory lesion.

On September 6, 2018, the pleural fluid inside the left chest cavity was sticky and difficult to extract. Pleural microorganism testing found *Bacillus cereus* and no fungal growth. On September 13, bronchoscopy revealed that the right bronchus and the branch lumen were unobstructed, the mucosa was smooth, there were many white serous secretions in the lumen, and no hemorrhage or new organisms were found. With full informed consent, the patient was treated with nivolumab and DC/CIK cells. On

September 18, she was given an intravenous injection of nivolumab (140 mg) with no relevant AEs. On September 21, her peripheral blood was extracted for DC/CIK cell culture.

The patient was admitted for the second cycle of treatment. On October 9, she was given an intravenous injection of nivolumab (140 mg) for the second time. The first cycle of DC/CIK cells was administered intravenously on October 10, 12, and 15. On October 14, she presented severe dizziness after getting up in the morning, and her blood sugar levels were 426.6 mg/dL. Results of blood routine examination showed ketone body (2+). These findings suggested a diabetic ketosis. Under the Endocrinologist supervision, treatment with an intravenous infusion of 0.9% Sodium chloride injection (500 mL) plus insulin (4 U) intravenous infusion was started and blood glucose levels were closely monitor. After a short-term infusion, blood glucose dropped below 325 mg/dL. Supportive therapy with an intravenous infusion of 5% glucose injection (500 mL) plus insulin injection (6 U) and potassium chloride (10 mL) was adjusted.

On October 15, her blood sugar rose again to 500.4 mg/dL. The Endocrinology Department was consulted again, and a new panel confirmed diabetic ketoacidosis according to high blood glucose, a hemoglobin A1c level of 7.4, urine ketone body value of 3+, extracellular fluid residual alkali level of −3.8 mmol/L, residual alkali level of −3.3 mmol/L, and lactic acid level of 2.1 mmol/L. At that moment, the treatment regimen consisted of 8 IU of neutral insulin injection intravenously administered at 10 AM and 6 IU of neutral insulin injection intravenously administered at 11 AM, 1 PM, 3 PM, and 4 PM.

On October 16, her blood sugar was 290.16 mg/dL and she had a ketone body value of 2+. Subsequently, insulin therapy was adjusted at 6 IU of neutral insulin injection was intravenously administered at 10 AM, 1 PM, 4 PM, and 9 PM. On October 17, she had a ketone body value of 1+, and 6 IU of neutral insulin injection was intravenously administered at 9 AM. Her blood sugar was 264.6 mg/dL and she felt well enough to be discharged. She was recommended to start on oral antidiabetics with sitagliptin phosphate tablets (100 mg) taken before breakfast and acarbose tablets (100 mg, tid). She was advised to monitor her blood sugar levels every day.

On November 2, the patient was admitted to hospital for further anticancer treatment, and her blood glucose before sleep was 243 mg/dL. Between November 5 and 7, her blood sugar levels were 85.8, 66.6, and 84.6 mg/dL, respectively, and her blood sugar levels were still higher than normal after meals. Doctors fully communicated with the patient, and according to the patient's disease and physical condition, treatment with nivolumab was suspended, and only DC/CIK immunotherapy was used to treat lung cancer. During the treatment, the patient's fasting blood glucose was within the normal range, and no AEs occurred. After discharge, the patient was followed up on December 2. She took her medication regularly and her fasting blood glucose was in the normal range. Since no complications appeared after the third course of therapy with DC/CIK, nivolumab was definitively halted. After 5 cycles of DC/CIK immunotherapy, the patient was treated in another hospital due to disease progression (see *Figure 1*).

Diabetic ketoacidosis is one of the hyperglycemic crisis and one of acute complications of diabetes mellitus. The main clinical manifestations were hyperglycemia, hyperketone and metabolic acidosis. When the condition is serious, acidosis and water electrolyte metabolic disorder are aggravated, it may lead to varying degrees of consciousness disturbance and coma, and even lead to death. There was a large time difference from the onset of ICIs to diabetic ketoacidosis. All patients receiving ICIs should be on high alert for ICIs-related diabetes when they present with typical symptoms of diabetes such as polyphagia, polydipsia, weight loss, and fatigue. If the patient has normal blood glucose in the past, the admission with hyperglycemia, outbreak of diabetes mellitus and other laboratory results and clinical manifestations can be basically confirmed. This case report provides essential clinical information and reference for diagnosis of ICIs induced diabetes ketoacidosis.

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 Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Here, we report the case of a patient treated with an intravenous injection of nivolumab (140 mg) on September 18 with good tolerance. She was given an intravenous injection of nivolumab (140 mg) for the second time on October 9 in combination with DC/CIK cells was administered intravenously the following day. On October

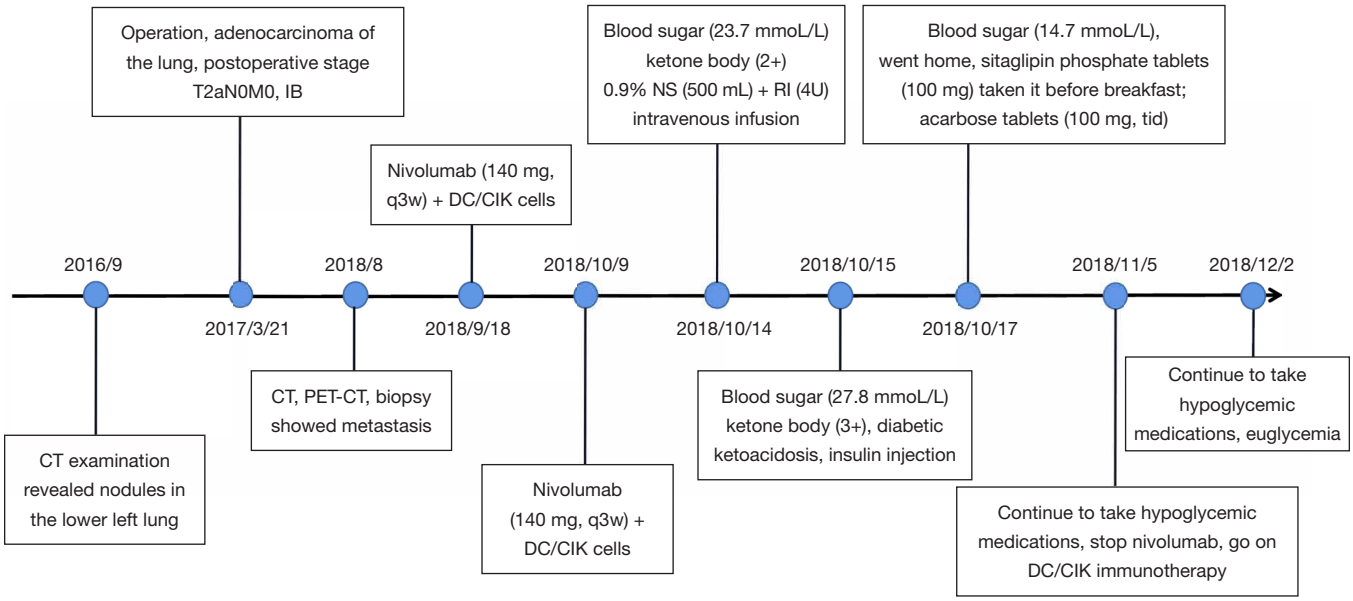

Figure 1 The timeline of diagnosis, treatment, and follow-up. PET-CT, positron emission tomography-computed tomography; DC/CIK, dendritic cell/cytokine-induced killer; NS, normal saline; RI, regular insulin.

14, she presented the first episode of diabetic ketosis. She had no prior history of personal or family history of diabetes. There was a total of 28 days between the first administration and the occurrence of the patient's severe symptoms. After insulin treatment, the patient's symptoms were reduced and blood sugar levels became normal. Although diabetes is a rare IR-AE, it has been reported that it generally appears 6 weeks after medication. Type 1 diabetes may occur after 4 weeks. In our case, Hemoglobin A1c levels were not tested before use of nivolumab.

ICI affect T cell immune function. T cells infiltrate the organ and cause an immune activation response (5,6), which destroys pancreatic beta cells and leads to absolute insulin deficiency, namely type 1 diabetes. Type 1 diabetes can be divided into delayed type 1 diabetes, acute type 1 diabetes, or fulminant type 1 diabetes. Among the IR toxicity of patients treated with ICI, fulminant type 1 diabetes is more common, and some cases have been reported in patients with lung cancer and melanoma (7-9). The onset of fulminant type 1 diabetes is sudden and life-threatening, and the degree of ketoacidosis is relatively severe. The islets are completely destroyed in a short period of time and are difficult to recover. At present, the specific etiology is unknown. If the patient is not diagnosed and treated timely, it often leads to death in a short time, which is mostly common in East Asian people.

The patient had no history of obesity or family history of diabetes. She received a single dose of 3.75 mg of dexamethasone treatment during this period of time which resulted in cough improvement, but did not explain the onset of the diabetes. The causal relationship between nivolumab and diabetic ketoacidosis was assessed using the Naranjo Probability of Adverse Effects Scale (10), with a score of 6 in this case. It suggested that diabetic ketoacidosis was caused by nivolumab. The main limitations to establish a causal relationship between nivolumab and diabetic onset in this case were that diabetes susceptibility genes were not tested and the risk of abnormal blood glucose was not evaluated and baseline.

We reviewed the literature and collected a total of 33 reported cases of type 1 diabetes caused by nivolumab through literature retrieval (8,11). Of the 33 cases, 16 were fulminant type 1 diabetes and ketoacidosis occurred in 21 patients. The median onset time of type 1 diabetes was 96.5 days, and the median interval from normal to abnormal blood glucose was 2 weeks. The main clinical symptoms were polyuria and polydipsia, fatigue of varying degrees, and nausea/vomiting. Blood glucose control was adequate in 27 patients after insulin treatment. Sixteen patients were restarted with nivolumab without further complications. Of the 21 patients with ketoacidosis, there were 6 patients with lung cancer. Among the lung cancer patients, there were

3 women aged 47, 34, and 56. They developed ketoacidosis 24, 28, and 33 days after using nivolumab (*Table 1*).

In the above literature analysis, it can be concluded that the incubation period of nivolumab-induced diabetic ketoacidosis is dispersive and the clinical risk is high. Patients need life-long insulin therapy. Blood glucose and HbA1c should be monitored routinely before and during nivolumab immunotherapy to avoid the occurrence of diabetic ketoacidosis. After the occurrence of diabetic ketoacidosis, insulin should be used to actively control blood glucose and do a good job in medication education to ensure long-term compliance of patients. Nivolumab should only be initiated if the patient has a clinical benefit under stable glucose control.

According to the guidelines and expert consensus related to toxicity management of The European Society for Medical Oncology and The Society for Immunotherapy of Cancer, the patient had grade 3 immune-related type 1 diabetes with ketoacidosis. In accordance with the treatment of new-onset type 1 diabetes, the patient was suspended from using nivolumab. At the same time, the patient's blood glucose were strictly managed, with the objective of maintaining her HbA1c level at <8.0% for a long time. There is no evidence that stopping nivolumab relieves diabetes, and since the onset of diabetes is usually permanent, the French guidelines recommend continuing insulin therapy even if the immunotherapy drugs are discontinued. Therefore, patients need to establish baseline endocrine function before using ICI, since in the early days after nivolumab, patients might be prone to ketoacidosis. These baseline tests may be critical for the patients management. Then considering prior recommendations, patients on nivolumab should have their blood sugar monitored regularly for the first months of clinical use (32).

In conclusion, as the first PD-1 inhibitor in China, nivolumab has brought hope for the survival of most patients with advanced cancer. However, nivolumab is also associated with a risk of ketoacidosis, a clinical risk that requires lifelong insulin treatment. In clinical practice, blood glucose should be routinely monitored before and during nivolumab treatment to avoid the occurrence of ketoacidosis. In addition, diabetes susceptibility gene testing might help to evaluate the risk of abnormal blood glucose levels. After the occurrence of nivolumab-induced diabetes, insulin should be used to actively control blood glucose and medication education should be given to ensure long-term medication compliance of patients. Restarting on nivolumab after an episode of diabetic ketoacidosis should be an individualized decision.

Questions to be further discussed and considered

Question 1: Is it necessary to test for diabetes susceptibility genes to avoid the risk of developing diabetes before using ICIs?

Teresa Moran: ICI-related T1DM is considered a rare AE. However, with an increased number of patients with any tumor exposed to ICI and ICI combinations, the number of such AE is expected to increase. A recent review in the literature investigated potential predictive risk factors, including pre-treatment islet antibodies and human leukocyte antigen (HLA) status (33). An important 60–80% of patients carried pretreatment GAD antibody. In addition, HLA-typing in these series demonstrated high risk alleles for developing T1DM in some of them.

While there is no firm clinical recommendation, we advocate for pre-treatment islet antibodies and HLA status study in a large cohort of patients including different tumor types, in different clinical stages and with different ICI and ICI combinations. This may help to clarify if ICI act as an accelerator or initiator of type 1 diabetes and may identify those patients at higher risk of developing such complication.

Question 2: What is the pathogenesis of diabetes associated with ICIs?

Teresa Moran: Type 1 diabetes mellitus (T1DM) results from the autoimmune destruction of the insulin-producing βcells of the endocrine pancreas, and this destruction occurred in a T cell dependent mechanism. A genetic background including both major histocompatibility complex (MHC) and non-MHC genes has been associated with the risk of T1DM (34,35). Several HLA genotypes have been associated with a high risk to develop autoimmune diabetes mellitus, however over 90% of type 1 diabetics carry either DR3-DQ2 or DR4-DQ8, and up to 30% have both haplotypes (DR3/DR4 heterozygotes), which is associated with the greatest risk for the development of autoimmune diabetes (36). Other non-HLA factors which regulate antiviral response, lymphocyte activation, peripheral tolerance, and chemokine and cytokine functions have been related to the risk of T1DM occurrence. In addition, several autoantigens isolated from pancreatic islet cells are associated with the development of autoimmune DM. These include including GAD, insulin, insulinoma-associated protein 2 (IA-2), and zinc transporter

Table 1 Case analysis of literature on diabetic ketoacidosis caused by nivolumab

Number (Ref.)	Sex	Age (years)	Cancer	Dose	Occurrence time	Initial symptoms	Treatment	Stop/go on nivolumab	Outcome
No. 1 (12)	Female	54	Melanoma	2 mg/kg, q3w	After 16 cycles	Excessive drinking and urination, severe fatigue, delirium, fever, cold	Insulin therapy (route of administration unknown)	Go on	Continue insulin therapy
No. 2 (13)	Female	68	Melanoma	3 mg/kg, q3w	Seven days after the 28th cycle	Abdominal pain, nausea, vomiting, severe fatigue, excessive drinking, and urination	Intravenous insulin and fluid replacement therapy	Stop	Continue insulin therapy
No. 3 (14)	Male	77	Renal cell carcinoma	3 mg/kg, q2w	Fifteen days after the 6th cycle	Fatigue, nausea, vomiting	Insulin therapy (route of administration unknown)	Go on	Continue insulin therapy
No. 4 (15)	Male	73	Lung cancer	3 mg/kg, q2w	Twenty-one days after the 11th cycle	Excessive drinking and urination, nausea, and vomiting	Insulin therapy (route of administration unknown)	Stop (aggravation of pneumonia)	Not described
No. 5 (16)	Male	31	NSCLC	Unknown	Thirteen days after the first cycle	Fatigue, excessive urination, excessive drinking	Intravenous insulin therapy	Go on	Continue insulin therapy
No. 6 (17)	Male	73	Melanoma	3 mg/kg, q2w	Before the 4th cycle	Palpitations, fatigue	Intravenous insulin and fluid replacement therapy	Go on	Continue insulin therapy
No. 7 (18)	Male	52	Melanoma	Ipi 3 mg/kg + nivo 3 mg/kg, q3w	Eighteen days after the 3rd cycle	Polyuria, polydipsia, nausea, vomiting, weight loss	Insulin subcutaneous therapy	Stop	Continue insulin therapy
No. 8 (19)	Female	74	Melanoma	2 mg/kg, q3w	Thirteen days after the 6th cycle	Nausea, vomiting, polyuria, dizziness	Intravenous insulin and fluid replacement therapy	Stop	Continue insulin therapy
No. 9 (20)	Male	51	Renal cell carcinoma	Unknown	The 45th day	Nausea, fatigue	Control blood glucose, the specific treatment plan is unknown	Stop	Continue insulin therapy
No. 10 (21)	Female	55	Melanoma	2 mg/kg, q3w	The 12th month	Vomiting, delirium, excessive drinking and urination	Insulin subcutaneous therapy	Go on	Continue insulin therapy
No. 11 (22)	Male	54	Melanoma	Ipi 3 mg/kg + nivo 3 mg/kg, q3w	After the 6th cycle	Fatigue, myalgia, nausea, vomiting	Insulin was administered intravenously and fluid rehydration was followed by subcutaneous insulin injection	Stop	Continue insulin therapy
No. 12 (23)	Male	83	Maxillary sinus squamous cell carcinoma	240 mg/kg, q2w	The 3rd month	No subjective symptoms	Insulin therapy (route of administration unknown)	Stop (because of colitis)	Continue insulin therapy
No. 13 (24)	Female	47	Lung cancer	3 mg/kg, q2w	Ten days after the 2nd cycle (24 days)	Excessive drinking and urination, weight loss, vomiting, confusion, fatigue, dehydration, low blood pressure	Insulin was administered intravenously and fluid rehydration was followed by subcutaneous insulin injection	Go on	Continue insulin therapy
No. 14 (25)	Male	66	Melanoma	2 mg/kg, q3w	Ten days after the 6th cycle	Nausea, vomiting, anorexia	Insulin was administered intravenously and fluid rehydration was followed by subcutaneous insulin injection	Go on	Continue insulin therapy
No. 15 (26)	Female	34	Lung cancer	3 mg/kg, q2w	Ten days after the 2nd cycle (28 days)	Abdominal pain, nausea, fatigue	Intravenous insulin and fluid replacement therapy	Go on	Continue insulin therapy
No. 16 (9)	Female	56	Lung cancer	Dose unknown, q2w	Five days after the 3rd cycle (33 days)	Excessive drinking and urination, coma, agitation,	Insulin was administered intravenously and fluid rehydration was followed by subcutaneous insulin injection	Go on	Continue insulin therapy
No. 17 (27)	Male	42	Lung cancer	3 mg/kg, q2w	Eighteen days after the 4th cycle	No subjective symptoms	Insulin was administered intravenously and fluid rehydration was followed by subcutaneous insulin injection	Stop (poor blood sugar control)	Continue insulin therapy
No. 18 (28)	Male	49	Renal cell carcinoma	3 mg/kg, q2w	After the 21st cycle	Fatigue, drowsiness, weight loss, and excessive drinking and urination	Insulin was administered intravenously and fluid rehydration was followed by subcutaneous insulin injection	Go on	Continue insulin therapy
No. 19 (29)	Female	59	Metastatic mucosal melanoma	Dose unknown, ipilimumab/ nivolumab	Three days after receiving the 3rd cycle	Nausea, vomiting and generalized weakness	Insulin	Do not mention it	Do not mention it
No. 20 (30)	Female	60	Advanced renal cell carcinoma	Nivolumab (3 mg/kg) and ipilimumab (1 mg/kg), q3w	Seven months (216 days) after the first administration and about half a year (174 days) after the last administration	General malaise, hyperglycemia, metabolic acidosis, and presence of ketone bodies in urine	Injections of insulin	Stop	Continue insulin therapy
No. 21 (31)	Male	77	Metastatic high-grade neuroendocrine tumor	200 mg, q2w	After 15 cycles	Worsening fatigue, polyuria, and polydipsia of 1 week's duration	Intravenous insulin	Stop	Continue insulin therapy

Ipi, ipilimumab; nivo, nivolumab; NSCLC, non-small cell lung cancer.

(ZnT8) (37). Postmortem histopathological studies of the pancreas from type 1 diabetics have demonstrated that the majority of infiltrating immune cells are $CD8^+$ T cells. The PD-1-PD-L1 pathway seems to provide a protective effect against βcell autoimmunity, and in some patients, blocking with ICIs may lead to autoimmune diabetes mellitus and insulin dependence (38).

However, the pathogenic mechanism underlying ICI-related T1DM remains to be fully elucidated. ICI treatment may lead to pancreatitis affecting endocrine and exocrine pancreatic function. A presumed autoimmune-mediated pancreatitis leading to hyperglycaemia has been proposed (39). Autoantigens from pancreatic islet cells positivity has been described but are not universal, and some reports have demonstrated the presence of high-risk HLA alleles for autoimmune diabetes (33).

Question 3: ICI-related diabetes is uncommon but irreversible. How do doctors educate patients in clinical practice?

Teresa Moran: A detailed personal and family history of diabetes, as well as autoimmunity should be recorded. Up to 70% of the cases of T1DM had other IRAEs and 44% had endocrine-related IRAEs prior or concurrent to the development of ICI-induced diabetes (especially primary thyroid dysfunction) (40). There is controversial data regarding pre-existing type 2 diabetes as a predictor of ICI-diabetes occurrence (33,41).

Doctors and patients should also be aware that a combination of immunotherapies and/or pre-treatment with other immunotherapies before starting ICI appeared to associate an increased risk of ICI-induced diabetes (40,42).

As with other immune related AEs, patients should be educated to recognize any sign or symptom potentially related with a T1DM onset, which should prompt them to an early consultation. Periodic test before each ICI administration should include glucose levels. New onset hyperglycaemia and worsening of hyperglycaemia in patients with pre-existing type 2 diabetes following treatment with ICI should be taken into account. This is particularly important as patients might also receive steroids that can exacerbate hyperglycaemia. Due to the rapid onset of ICI-related insulin deficiency and potential DKA development, plasma levels should be tested in all acutely unwell patients receiving ICI, and work-up should include ketosis and acidosis parameters if hyperglycaemia is detected. DKA should be managed as per standard approach. Patients with new onset hyperglycaemia without DKA should be started on subcutaneous insulin. Patients should be referred to the diabetes team for education, training on safe insulin administration and follow up (43).

Acknowledgments

The authors acknowledge AME Editing Service for editing the manuscript.
Funding: This study was supported by Hebei Province Foundation for "333 Talent Project" (No. A202001019).

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5211/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5211/coif). CG received honoraria as speaker bureau or advisory board member from Bristol Meyers Squibb, Roche, Astra Zeneca, Sanofi, MSD. TM declares consulting/advisory role fees from Roche, Bristol Myers, Boeringher, Astra Zeneca, Lilly, and Research funding from Kyowa Kirin. 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 Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Mikuni H, Yamamoto S, Kato K. Nivolumab for the treatment of esophageal cancer. Expert Opin Biol Ther 2021;21:697-703.
2. Meng LF, Huang JF, Luo PH, et al. The efficacy and safety of immune checkpoint inhibitor plus chemotherapy in patients with advanced non-small-cell lung cancer: a meta-analysis. Invest New Drugs 2022;40:810-7.
3. Nishino M, Ramaiya NH, Hatabu H, et al. Monitoring immune-checkpoint blockade: response evaluation and biomarker development. Nat Rev Clin Oncol 2017;14:655-68.
4. Peiró I, Palmero R, Iglesias P, et al. Thyroid dysfunction induced by nivolumab: searching for disease patterns and outcomes. Endocrine 2019;64:605-13.
5. Benesova K, Kraus FV, Carvalho RA, et al. Distinct immune-effector and metabolic profile of CD8+ T cells in patients with autoimmune polyarthritis induced by therapy with immune checkpoint inhibitors. Ann Rheum Dis 2022;81:1730-41.
6. Ding J, Zheng Y, Wang G, et al. The performance and perspectives of dendritic cell vaccines modified by immune checkpoint inhibitors or stimulants. Biochim Biophys Acta Rev Cancer 2022;1877:188763.
7. Chen X, Affinati AH, Lee Y, et al. Immune Checkpoint Inhibitors and Risk of Type 1 Diabetes. Diabetes Care 2022;45:1170-6.
8. Mae S, Kuriyama A, Tachibana H. Diabetic Ketoacidosis as a Delayed Immune-Related Event after Discontinuation of Nivolumab. J Emerg Med 2021;60:342-4.
9. Tzoulis P, Corbett RW, Ponnampalam S, et al. Nivolumab-induced fulminant diabetic ketoacidosis followed by thyroiditis. Endocrinol Diabetes Metab Case Rep 2018;2018:e18-0111.
10. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
11. Kubota T, Choda Y, Ishida M, et al. Effect on Prognosis of Immune-Related Adverse Events after Nivolumab Treatment in Gastric Cancer. Gan To Kagaku Ryoho 2020;47:1860-2.
12. Ishikawa K, Shono-Saito T, Yamate T, et al. A case of fulminant type 1 diabetes mellitus, with a precipitous decrease in pancreatic volume, induced by nivolumab for malignant melanoma: analysis of HLA and CTLA-4 polymorphisms. Eur J Dermatol 2017;27:184-5.
13. Sakaguchi C, Ashida K, Yano S, et al. A case of nivolumab-induced acute-onset type 1 diabetes mellitus in melanoma. Curr Oncol 2019;26:e115-8.
14. Yamamoto N, Tsurutani Y, Katsuragawa S, et al. A Patient with Nivolumab-related Fulminant Type 1 Diabetes Mellitus whose Serum C-peptide Level Was Preserved at the Initial Detection of Hyperglycemia. Intern Med 2019;58:2825-30.
15. Kumagai R, Muramatsu A, Nakajima R, et al. Acute-onset type 1 diabetes mellitus caused by nivolumab in a patient with advanced pulmonary adenocarcinoma. J Diabetes Investig 2017;8:798-9.
16. Usui Y, Udagawa H, Matsumoto S, et al. Association of Serum Anti-GAD Antibody and HLA Haplotypes with Type 1 Diabetes Mellitus Triggered by Nivolumab in Patients with Non-Small Cell Lung Cancer. J Thorac Oncol 2017;12:e41-3.
17. Gauci ML, Laly P, Vidal-Trecan T, et al. Autoimmune diabetes induced by PD-1 inhibitor-retrospective analysis and pathogenesis: a case report and literature review. Cancer Immunol Immunother 2017;66:1399-410.
18. Gunawan F, George E, Roberts A. Combination immune checkpoint inhibitor therapy nivolumab and ipilimumab associated with multiple endocrinopathies. Endocrinol Diabetes Metab Case Rep 2018;2018:e17-0146.
19. Takahashi A, Tsutsumida A, Namikawa K, et al. Fulminant type 1 diabetes associated with nivolumab in a patient with metastatic melanoma. Melanoma Res 2018;28:159-60.
20. Teló GH, Carvalhal GF, Cauduro CGS, et al. Fulminant type 1 diabetes caused by dual immune checkpoint blockade in metastatic renal cell carcinoma. Ann Oncol 2017;28:191-2.
21. Okamoto M, Okamoto M, Gotoh K, et al. Fulminant type 1 diabetes mellitus with anti-programmed cell death-1 therapy. J Diabetes Investig 2016;7:915-8.
22. Lowe JR, Perry DJ, Salama AK, et al. Genetic risk analysis of a patient with fulminant autoimmune type 1 diabetes mellitus secondary to combination ipilimumab and nivolumab immunotherapy. J Immunother Cancer 2016;4:89.
23. Kapke J, Shaheen Z, Kilari D, et al. Immune Checkpoint Inhibitor-Associated Type 1 Diabetes Mellitus: Case Series, Review of the Literature, and Optimal Management. Case Rep Oncol 2017;10:897-909.
24. Capitao R, Bello C, Fonseca R, et al. New onset diabetes after nivolumab treatment. BMJ Case Rep 2018;2018:bcr-2017-220999.

25. Miyoshi Y, Ogawa O, Oyama Y. Nivolumab, an Anti-Programmed Cell Death-1 Antibody, Induces Fulminant Type 1 Diabetes. Tohoku J Exp Med 2016;239:155-8.
26. Godwin JL, Jaggi S, Sirisena I, et al. Nivolumab-induced autoimmune diabetes mellitus presenting as diabetic ketoacidosis in a patient with metastatic lung cancer. J Immunother Cancer 2017;5:40.
27. Tassone F, Colantonio I, Gamarra E, et al. Nivolumab-induced fulminant type 1 diabetes (T1D): the first Italian case report with long follow-up and flash glucose monitoring. Acta Diabetol 2019;56:489-90.
28. Yilmaz M. Nivolumab-induced type 1 diabetes mellitus as an immune-related adverse event. J Oncol Pharm Pract 2020;26:236-9.
29. Cao Y, Afzal MZ, Shirai K. Ipilimumab and nivolumab induced immune-related adverse events in metastatic mucosal melanoma. BMJ Case Rep 2021;14:243713.
30. Yaura K, Sakurai K, Niitsuma S, et al. Fulminant Type 1 Diabetes Mellitus Developed about Half a Year after Discontinuation of Immune Checkpoint Inhibitor Combination Therapy with Nivolumab and Ipilimumab: A Case Report. Tohoku J Exp Med 2021;254:253-6.
31. Delasos L, Bazewicz C, Sliwinska A, et al. New onset diabetes with ketoacidosis following nivolumab immunotherapy: A case report and review of literature. J Oncol Pharm Pract 2021;27:716-21.
32. Illouz F, Briet C, Cloix L, et al. Endocrine toxicity of immune checkpoint inhibitors: essential crosstalk between endocrinologists and oncologists. Cancer Med 2017;6:1923-9.
33. Galligan A, Xu W, Fourlanos S, et al. Diabetes associated with immune checkpoint inhibition: presentation and management challenges. Diabet Med 2018. [Epub ahead of print]. doi: 10.1111/dme.13762.
34. Steck AK, Rewers MJ. Genetics of type 1 diabetes. Clin Chem 2011;57:176-85.
35. Todd JA. Etiology of type 1 diabetes. Immunity 2010;32:457-67.
36. Davies JL, Kawaguchi Y, Bennett ST, et al. A genome-wide search for human type 1 diabetes susceptibility genes. Nature 1994;371:130-6.
37. Morran MP, Vonberg A, Khadra A, et al. Immunogenetics of type 1 diabetes mellitus. Mol Aspects Med 2015;42:42-60.
38. Rajasalu T, Brosi H, Schuster C, et al. Deficiency in B7-H1 (PD-L1)/PD-1 coinhibition triggers pancreatic beta-cell destruction by insulin-specific, murine CD8 T-cells. Diabetes 2010;59:1966-73.
39. Cramer P, Bresalier RS. Gastrointestinal and Hepatic Complications of Immune Checkpoint Inhibitors. Curr Gastroenterol Rep 2017;19:3.
40. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. JAMA Oncol 2018;4:173-82.
41. Magis Q, Gaudy-Marqueste C, Basire A, et al. Diabetes and Blood Glucose Disorders Under Anti-PD1. J Immunother 2018;41:232-40.
42. Byun DJ, Wolchok JD, Rosenberg LM, et al. Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies. Nat Rev Endocrinol 2017;13:195-207.
43. Nogueira E, Newsom-Davis T, Morganstein DL. Immunotherapy-induced endocrinopathies: assessment, management and monitoring. Ther Adv Endocrinol Metab 2019;10:2042018819896182.

(English Language Editor: C. Betlazar-Maseh)

Cite this article as: Yan J, Xie ZZ, Moran T, Gridelli C, Zheng MD, Dai SJ. Diabetic ketoacidosis induced by nivolumab in invasive mucinous adenocarcinoma of the lung: a case report and review of the literature. Ann Transl Med 2022;10(22):1256. doi: 10.21037/atm-22-5211

