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**Case Report**                                                                                        **Open Access**

# A Case of Nivolumab-Induced Fulminant Type 1 Diabetes with Steroids and Glucagon-Like Peptide 1 Administration during the Early Onset

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## Abstract

**Background:** Nivolumab is a humanized IgG4 anti-programmed cell death protein-1 (PD-1) antibody. In recent years, type 1 diabetes associated with anti-PD-1 immunotherapy has been reported.

**Case report:** We report a 62-year-old woman with primary choroidal melanoma who developed fulminant type 1 diabetes after anti-PD-1 immunotherapy (nivolumab). She had elevated levels of blood glucose and total blood ketone body. Her hemoglobin A1c level was at the upper limit of normal, and she had decreased endogenous insulin secretion. Anti-glutamic acid decarboxylase and anti-islet antigen 2 antibody tests were negative. Endogenous insulin was still being secreted at the time of diagnosis; therefore, we administered steroids and glucagon-like peptide-1 (GLP-1). However, insulin secretion did not recover. Approximately 10 months after onset, her diabetes was under control with intensive insulin therapy and voglibose treatment.

**Discussion**: The mechanism of diabetes caused by nivolumab is unclear, but it may involve the excessive autoimmune response associated with PD-1 inhibition. GLP-1 has a protective effect on the pancreas by promoting differentiation and proliferation of pancreatic β cells and suppressing pancreatic β cell apoptosis. We attempted to treat with steroids and GLP-1 before depletion of endogenous insulin to suppress the hyperimmunization and protect the pancreatic β cells. Insulin secretion did not recover. However, no reports have described using these therapies to treat diabetes associated with immune checkpoint inhibitors during early onset to date. We consider this case is the meaningful report as a negative data.

## Introduction

Nivolumab is a humanized IgG4 anti-programmed cell death protein-1 (PD-1) antibody, which inhibits the binding of PD-1 to programmed cell death ligand-1 (PDL-1). In recent years, type 1 diabetes associated with anti-PD-1 immunotherapy has been reported [1-5]. We describe a patient who developed fulminant type 1 diabetes after the fifth administration of nivolumab and whom we attempted to treat with steroids and glucagon-like peptide 1 before depletion of endogenous insulin.

## Case Report

A 62-year-old woman with primary choroidal melanoma of the right eye underwent gamma knife radiosurgery with no tumor recurrence. Approximately 7 years later, 18F-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) imaging revealed multiple bone metastases and pleural lesions. Therefore, we administered nivolumab (2 mg/kg, every 3 weeks) with zoledronic acid (0.08 mg/kg, every 3 weeks) for prevention of skeletal related event. The patient had no past history or family history of diabetes. She received a total of five treatments (days 1, 24, 45, 73, and 94).

On day 130, she complained of mild fatigue and discomfort in the epigastric region, which lasted for 1 week, and no fever, signs of infection, or other symptoms were seen prior to the onset of diabetes. No gastrointestinal symptoms such as diarrhea, nausea, and vomiting were seen either. She had a blood glucose level of 469 mg/dL (hyperglycemia), a total blood ketone body level of 334 μmol/L (ketosis), and was admitted. Her hemoglobin A1c (HbA1c) level was 5.8%, but her immunoreactive insulin was 3.4 μU/mL, serum C-peptide immunoreactivity (CPR) was 0.70 ng/mL, urine CPR was 7.7 μg/day,

and she had decreased endogenous insulin secretion. Anti-glutamic acid decarboxylase and anti-islet antigen 2 antibodies were negative. Abdominal CT revealed no pancreatic abnormalities (Figure 1). The
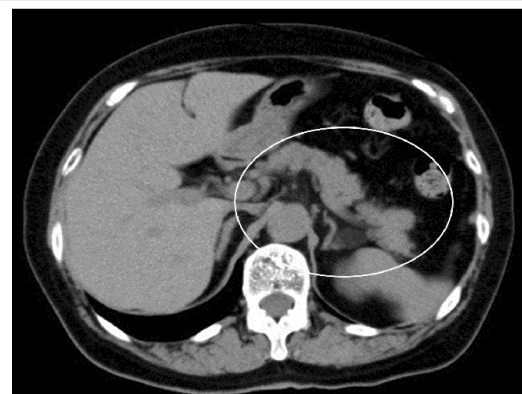


**Figure 1:** Abdominal computed tomography (CT) revealed no pancreatic abnormalities.

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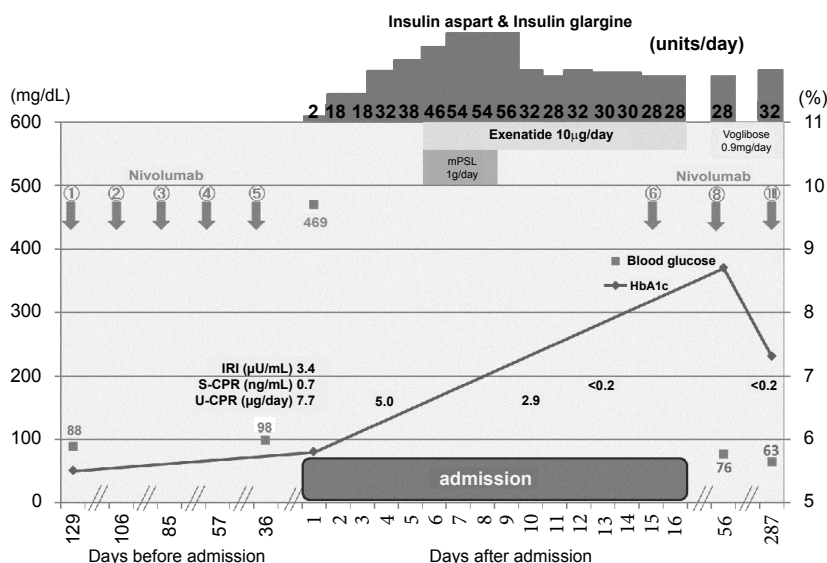
**Figure 2:** Clinical course of nivolumab-induced fulminant type 1 diabetes.

other laboratory findings were as follows; total white cell (WBC) count, 9300/μL with 85.4% neutrophils, 7.5% lymphocytes, 5.1% monocytes, 1.4% eosinophils, and 0.6% basophils; red blood cell (RBC) count 42.5 × 10⁴/μL; platelet count, 22.7 × 10⁴/μL; amylase, 51 IU/L; lipase 45 U/L, and elastase-1 88 ng/dL. Thus, serum amylase, lipase, and elastase-1 levels were not elevated. Thyroid and pituitary hormones were within the normal range, and the shape of the pituitary gland was normal on magnetic resonance imaging (MRI, data not shown). HLA DRB1*13:02 and DQB1*06:04, *06:09 were positive in class II HLA typing.

We initiated intensive insulin therapy. We assumed autoimmune system involvement in the nivolumab-induced decrease in insulin secretion. Therefore, we initiated pulse steroid therapy on hospital day 6 (methylprednisolone: 1 g/day for 3 days) and administered exenatide, a glucagon-like peptide-1 receptor agonist (10 μg/day for 11 days). However, endogenous insulin secretion remained decreased; on hospital day 13, laboratory findings revealed serum CPR <0.20 ng/mL (Figure 2). Insulin doses were adjusted after admission to achieve pre-prandial and pre-sleep blood glucose levels of 100 mg/dL to 150 mg/dL, and doses were increased approximately 1.5 to 2 fold around the time of steroid administration. No major problems such as symptoms of hyperglycemia or infection occurred. Blood examinations were performed on the day steroid administration was started and on hospital day 13, and liver function, electrolytes, blood cell counts, and differential leukocyte count were all within the respective normal ranges.

In addition to intensive insulin therapy, we continued nivolumab treatment because of its effective anti-tumor action. We added voglibose to improve glycemic control. Approximately 10 months after onset, her diabetes was under control with an HbA1c level of 7.3% with insulin (32 units/day) and voglibose (0.9 mg/day) treatment. Disease control rate (DCR) of melanoma keeps partial response (PR) in World Health Organization (WHO) standard.

## Discussion

Some cases of type 1 diabetes in which pancreatic β cells are rapidly destroyed, insulin secretion decreases, and hyperglycemia and ketosis develop in a short period of time are fulminant type 1 diabetes with a

mild increase in HbA1c at onset [6]. The patient complained of mild fatigue and discomfort in the epigastric region, which lasted for 1 week, and had a blood glucose level of 469 mg/dL, a total blood ketone body level of 334 μmol/L, HbA1c level of 5.8% and urine CPR of 7.7 μg/day on admission. So, she was diagnosed after meeting all of the following fulminant type 1 diabetes diagnostic criteria (2012) 1-3 of the Japan Diabetes Society [7] at the time of admission as follows; [i] Occurrence of diabetic ketosis or ketoacidosis soon (approximately 7 days) after the onset of hyperglycemic symptoms (elevation of urinary and/or serum ketone bodies at first visit). [ii] Plasma glucose level ≥16.0 mmol/L (≥288 mg/dL) and glycated hemoglobin level <8.7% at first visit [iii] Urinary C-peptide excretion <10 μg/day or fasting serum C-peptide level <0.3 ng/mL (<0.10 nmol/L) and <0.5 ng/mL (<0.17 nmol/L) after intravenous glucagon (or after meal) load at onset. The onset of immune checkpoint inhibitor-induced type 1 diabetes has been reported with nivolumab and other drugs, such as another PD-1 inhibitor, pembrolizumab, and a PDL-1 inhibitor [1-5]. Reports of fulminant type 1 diabetes such as the present case exist among previous reports of diabetes associated with immune checkpoint inhibitors. The mechanism of diabetes caused by immune checkpoint inhibitor is unclear, but it may involve the excessive autoimmune response associated with PD-1 inhibition. Some previous reports have described that T cell-related autoimmunity is involved in the onset of autoimmune type 1 diabetes. This theory is supported by PD-1 expression decreases in peripheral CD4-positive T-lymphocytes in autoimmune type 1 diabetes [8]. In addition, cases of other autoimmune diseases, including thyroiditis and hypophysitis, interstitial pneumonia, pancreatitis, and hepatitis, associated with nivolumab also have been reported [9]. In this case, apoptosis and acute destruction of pancreatic β cells by T cells activated by nivolumab were thought to be involved in the onset of diabetes. Steroid administration is generally recommended for side effects induced by hyperimmunization of nivolmab, including hypophysitis, interstitial pneumonia, pancreatitis, and hepatitis. On the other hand, steroid therapy reportedly improved control of diabetes induced by impaired insulin secretion in autoimmune pancreatitis [10].

GLP-1 has a protective effect on the pancreas by [i] promoting differentiation and proliferation of pancreatic β cells, and [ii] suppressing pancreatic β cell apoptosis. Possible mechanisms of this

include enhanced expression of insulin receptor substrate 2 (IRS2) and cyclin D1 for [i], and enhanced expression of B-cell lymphoma 2 (Bcl-2) and endoplasmic reticulum (ER) stress reduction for [ii] [11]. To date, few reports have discussed protection of the pancreas by GLP-1 from a clinical perspective; however, some other report has described that administration of exenatide increased the rate of insulin withdrawal after transplantation in type 1 diabetes patients who required re-implantation following pancreatic islet transplantation [12].

HbA1c levels were lower in this patient, compared with previous reports of fulminant type 1 diabetes [1,3,5]. The HbA1c level was 5.5% when nivolumab was first administered, 5.8% at hospital admission, and her blood glucose level was 98 mg/dl at the fifth administration of nivolumab. Diabetes was diagnosed extremely early in our patient; endogenous insulin was still being secreted at the time of diagnosis. We attempted treatment with methylprednisolone and exenatide to suppress the hyperimmunization and protect the pancreatic beta cells and with enough units of insulin for glycemic control. The administration of steroids and GLP-1 in this case was not a treatment with established efficacy but was performed following careful consideration of advantages and disadvantages, its applications, and methods by several physicians from the departments of clinical oncology and diabetes and endocrinology. Three days of pulse steroid therapy was chosen because steroids are known to affect blood glucose and are not desirable to administer for a long term unless there is a specific purpose. The treatment was performed at the wish and with the appropriate and sufficient explanations and consent of the patient. Although steroids and GLP-1 may have been effective if administered at an earlier stage when endogenous insulin secretion remained, these drugs were not effective in this case. To date, no reports have described using these therapies to treat diabetes associated with immune checkpoint inhibitors. Although we consider this case is the meaningful report as a negative data, no report to date has demonstrated the specific efficacy of these therapies. In 2016, the Japan Diabetes Society issued a statement saying, "The administration of steroids is not currently recommended" [13]. We also do not currently recommend administering steroids and GLP-1 to similar patients. The indications for nivolumab now include types of cancer other than malignant melanoma, such as non-small cell lung cancer and renal cell carcinoma. Therefore, attention should be paid to the sudden onset of hyperglycemia and ketoacidosis in Asians, who are particularly vulnerable to fulminant type 1 diabetes.

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