Received: 23 October 2020 | Revised: 31 May 2021 | Accepted: 16 June 2021

DOI: 10.1002/ccr3.4574

CASE REPORT

Clinical Case Reports Open Access WILEY

Longitudinal observation of insulin secretory ability before and after the onset of immune checkpoint inhibitor-induced diabetes mellitus: A report of two cases

Noriko Fujiwara[1,2] | **Mayu Watanabe**[3] | **Akihiro Katayama**[4] | **Yohei Noda**[5] | **Jun Eguchi**[1] | **Hitomi Kataoka**[3] | **Shunsuke Kagawa**[6] | **Jun Wada**[1]

[1]Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Dentistry and Pharmaceutical Sciences, Okayama University Graduate School of Medicine, Okayama, Japan

[2]Division of Endocrinology and Metabolism, Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital, Hiroshima, Japan

[3]Department of Primary Care and Medical Education, Dentistry and Pharmaceutical Sciences, Okayama University Graduate School of Medicine, Okayama, Japan

[4]Diabetes Center, Okayama University Hospital, Okayama, Japan

[5]Department of Otolaryngology-Head and Neck Surgery, Dentistry and Pharmaceutical Sciences, Okayama University Graduate School of Medicine, Okayama, Japan

[6]Minimally Invasive Therapy Center, Okayama University Hospital, Okayama, Japan

Correspondence
Mayu Watanabe, Department of Primary Care and Medical Education, Dentistry and Pharmaceutical Sciences, Okayama University Graduate School of Medicine, Okayama, 7008558, Japan.
Email: mayu-w@okayama-u.ac.jp

Funding information
No specific funding or grant was received for this work

Abstract

Immune checkpoint inhibitor-induced diabetes mellitus is a rare immune-related adverse event. This report illustrates clinical data and insulin secretory ability before and after the onset of immune checkpoint inhibitor-induced diabetes.

KEYWORDS

C-peptide, diabetes mellitus, immune checkpoint inhibitor, insulin secretion

1 | INTRODUCTION

Immune checkpoint inhibitor-induced diabetes mellitus is a rare immune-related adverse event. This report illustrates clinical data and insulin secretory ability before and after the onset of immune checkpoint inhibitor-induced diabetes.

The programmed cell death-1 (PD-1) receptor is expressed on the surface of activated T cells and regulatory T cells, and is an immune checkpoint molecule. PD-1 interacts with two ligands, programmed cell death ligand-1 (PD-L1) and PD-L2 within the tumor microenvironment.[1] Engagement of PD-1 through PD-L1 negatively regulates T cell–mediated immune responses. Immune checkpoint inhibitor (ICI) activates T-cell immunity and suppresses tumor growth.[2] As the use of ICI therapy is expanding for treating many cancer types,[3,4] the increase in immune-related adverse events (irAEs) has been obvious. It is important for cancer patients to pay careful attention to irAEs. The most common irAEs are rash, hypothyroidism, hepatitis, and gastroenteritis.[4,5] Although the percentage of ICI-induced diabetes mellitus (ICI-induced DM) is rare (<1%), it is a life-threatening side effect without any means of early detection. Several studies reported that ICI-induced DM had several characteristics, the first was rapid-onset of severe hyperglycemia, the second was diabetic ketoacidosis (DKA) or very low to absent C-peptide levels, and

the third was persistent insulin dependence after the onset of diabetes.[6-8] Most cases are caused by anti-PD-1 or anti-PD-L1 therapy, and ICI-induced DM by anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is rare. It has also been reported that the combination of anti-PD-1 antibody and CTLA-4 inhibitor causes faster onset of ICI-induced DM than anti-PD-1 antibody monotherapy.[6,7] In non-obese diabetic mice, anti-PD1 inhibitor administration rapidly induced diabetes, but anti-CTLA-4 inhibitors did not.[9] Here, we report two cases in which insulin secretion was monitored before and after the onset of ICI-induced DM in patients treated with nivolumab.

2 | CASE REPORTS

2.1 | Case 1

A 76-year-old woman with gastric cancer had undergone total gastrectomy and pancreatoduodenectomy after preoperative chemotherapy. Although adjuvant chemotherapy was given after surgery, the gastric cancer recurred 2 years after surgery. She then received nivolumab (3 mg/kg) as a third-line therapy. She had no prior personal or family history of diabetes mellitus. At the time of nivolumab treatment, fasting blood glucose levels were 5.9 mmol/L and HbA1c 6.1%. Her body mass index (BMI) was 17.5 kg/m².

One hundred and 3 days after initial treatment with nivolumab, the patient was admitted to our hospital after 5 days of progressive general fatigue, thirst, and polyuria. She had no fever or other symptoms, suggesting she was free from a focal infection or systemic inflammation. On physical examination, she was alert. Laboratory data at the time of admission revealed hyperglycemia (blood glucose levels of 33.5 mmol/L) with ketosis (arterial blood pH 7.35, ketone body concentration 7620 μmol/L, the concentration of acetoacetate 1019 μmol/L, and the concentration of β-hydroxybutyrate 5925 μmol/L). HbA1c was 9.0%, and serum C-peptide levels were 0.05 nmol/L. Her pancreatic enzymes, thyroid hormones, and cholesterol levels were within the normal ranges. Abdominal computed tomography imaging showed porta hepatis and para-aortic lymph node swelling, but no significant findings in the pancreas. Upon additional blood testing, she was not found to have serum anti-glutamic acid decarboxylase, anti-insulinoma-associated antigen-2, anti-zinc transporter antibody 8, or anti-islet cell antibodies. Her human leukocyte antigen typing was DRB1 *08: 02-DQB1 *03: 02 and DRB1 *14: 54-DQB1 *05: 03. She did not have the type 1 DM-associated genotype. Acute-onset ICI-induced DM was diagnosed from her clinical course and laboratory data.

The levels of HbA1c and serum C-peptide levels were monitored before and after the onset of ICI-induced DM. HbA1c increased from 6.1 to 9.0% during 103 days of her course. Fasting C-peptide levels increased from 0.53 to 0.78 nmol/L, fasting blood glucose levels decreased from 5.9 to 5.2 mmol/L (Figure 1), 0–28 days after the start of nivolumab treatment, then serum C-peptide levels decreased to 0.05 nmol/L at the onset of ICI-induced DM. After admission, serum C-peptide levels were depleted (Figure 1). She was initially treated with intravenous fluids and continuous insulin infusion, which was changed to subcutaneous multiple daily injections with a combination of rapid and long-acting insulins.

2.2 | Case 2

A 68-year-old woman with stage IVA gingival cancer had been receiving tegafur, gimeracil, oteracil potassium therapy, and neoadjuvant chemotherapy. Tegafur, gimeracil, oteracil potassium therapy, and radiation therapy were conducted after surgical resection of the hemimandible; however, gingival cancer spread to cervical lymph nodes and larynx, and she felt difficulty in swallowing. Then, she was treated with nivolumab (3 mg/kg) as a third-line therapy. At the time of nivolumab treatment, fasting blood glucose levels were 6.7 mmol/L and HbA1c 5.2%. Her BMI was 16.8 kg/m². Three hundred days after the first nivolumab administration, she presented to our hospital complaining of persistent appetite loss and general fatigue for several days. She had acute airway obstruction and cardiopulmonary arrest due to mucous sputum filling in larynx when waiting for a medical examination. Even after cardiopulmonary resuscitation, hypoxic encephalopathy led to prolonged unconsciousness. Blood glucose levels were 36.3 mmol/L, and HbA1c was 9.5%. Serum C-peptide levels were 0.13 nmol/L, and urinary C-peptide level excretion was 11.9 μg/day. Her pancreatic enzymes were within the normal range. The ketone body measurements were not performed at onset. Abdominal computed tomography imaging showed no significant findings in the pancreas. Anti-glutamic acid decarboxylase and anti-IA-2 antibodies were negative. Human leukocyte antigen typing showed DRB1*04:03-DQB1*03:02, DRB1*15:01-DQB1*06:02, and she did not have the type 1 DM-associated genotype. We could not evaluate ketosis but diagnosed acute-onset ICI-induced DM from her clinical course and laboratory data.

Because she did not recover from the comatose state, a nasogastric tube was inserted for feeding. Multiple daily injections of long-acting and ultra-rapid insulin were used to control her blood glucose levels. Although nivolumab was effective for preventing cancer progression, this treatment was discontinued.

The time courses of HbA1c and serum C-peptide levels were monitored before the onset of ICI-induced DM. HbA1c

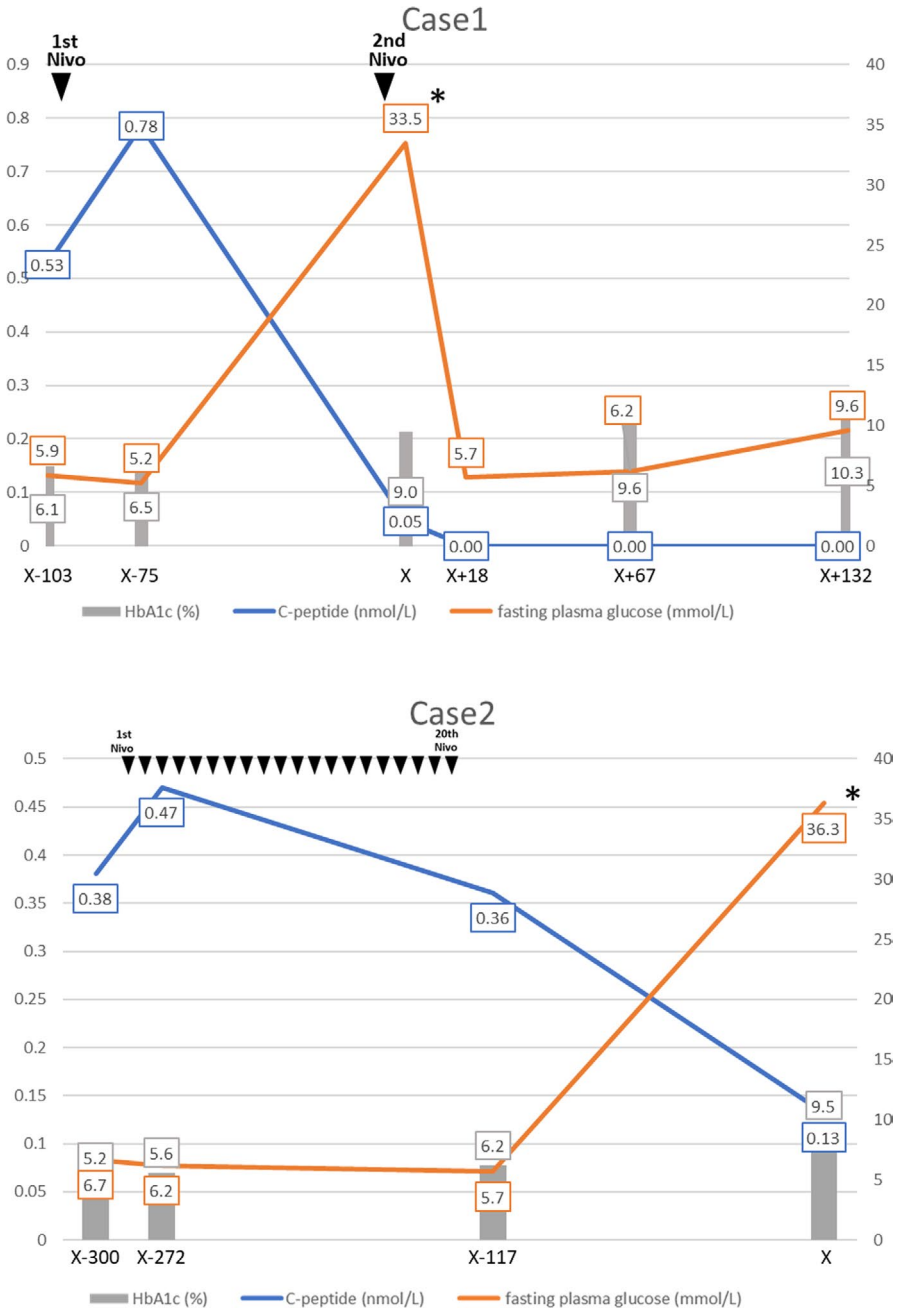

FIGURE 1 Longitudinal course of HbA1c, serum C-peptide levels, and fasting blood glucose levels. HbA1c increased from 6.1 to 6.5%, the fasting C-peptide levels increased from 0.53 to 0.78 nmol/L and fasting blood glucose levels decreased from 5.9 to 5.2 mmol/L, 0–28 days after the start of nivolumab (Nivo) treatment, then HbA1c increased to 9.0%, serum C-peptide levels decreased to 0.05 nmol/L and fasting blood glucose levels increased to 33.5 mmol/L at the onset of immune checkpoint inhibitor-induced diabetes. After admission, serum C-peptide levels were depleted (Case 1). HbA1c increased from 5.2 to 5.6%, the fasting C-peptide levels increased from 0.38 to 0.47 nmol/L and fasting blood glucose levels decreased from 6.7 to 6.2 mmol/L, 0–28 days after nivolumab treatment, then HbA1c increased to 9.5%, serum C-peptide levels decreased to 0.13 nmol/L and fasting blood glucose levels increased to 36.3 mmol/L at the onset of immune checkpoint inhibitor-induced diabetes (Case 2). X: at admission. *: random plasma glucose

increased from 5.2 to 9.5% in the period of 300 days. Fasting C-peptide levels increased from 0.38 to 0.47 nmol/L, and fasting blood glucose levels decreased from 6.7 to 6.2 mmol/L, 0–28 days after nivolumab treatment, then serum C- peptide levels decreased to 0.13 nmol/L at the onset of ICI-induced DM (Figure 1).

3 | DISCUSSION

We report two cases of acute-onset ICI-induced DM in which the longitudinal course of fasting C-peptide levels and corresponding fasting blood glucose levels was assessed before and after the administration of nivolumab therapy. As far as we are aware, most of previous reports have measured blood glucose levels and serum C-peptide levels after the onset of ICI-induced DM. Few literatures have reported the longitudinal course of C-peptide levels and corresponding fasting blood glucose levels before and after the onset of ICI-induced DM. Our cases showed that insulin secretion increased 1 month after nivolumab administration and remained in the normal range until the onset of ICI-induced DM. Furthermore, fasting plasma glucose level slightly decreased and the HbA1c level increased in both cases without any change in nutritional status before the onset. Nivolumab therapy also aggravates pre-existing diabetes with incompletely deficient insulin secretion.[10] It was suggested that mild glucose intolerance may have

TABLE 1 Cases of immune checkpoint inhibitor-induced diabetes mellitus with outcomes after anti-PD-1 antibody therapy

Literature	Clinical tumor response to anti-PD−1 antibody	Islet-related autoantibodies	Age/sex	Primary diagnosis	Anti-PD−1 antibody	Occurrence in days after initiation of Nivo	Plasma Glucose at onset (mmol/L)	HbA1c at onset (%)	HLA
Gauci, M. L., et al. 2017[14]	CR	Positive	73/m	Melanoma	Nivo	42	27.8	8.8	N/A
Lowe, J. R., et al. 2016[15]	CR	N/A	54/m	Melanoma	Ipi, Nivo	133	N/A	N/A	N/A
Hofmann L., et al. ① 2016[16]	CR	Negative	70/f	Melanoma	Nivo	42	N/A	N/A	N/A
Zezza, M., et al. ① 2019[17]	CR	Positive	60/m	Melanoma	Ipi, Nivo	14	46	7.5	N/A
Hong, A. R., et al. ③ 2020[18]	CR	Positive	78/f	Melanoma	Pembro	28	27.4	11.4	N/A
Takagi, T., et al. 2018[19]	PR	N/A	72/m	Renal cell carcinoma	Nivo	182	N/A	N/A	N/A
Miyoshi, Y., et al.2016[20]	PR	Negative	66/f	Melanoma	Nivo	121	29.5	7.3	DRB1*11:01-DQB1*03:01 DRB1*13:02-DQB1*06:04
Telo, G. H., et al. 2017[21]	PR	Negative	51/m	Renal cell carcinoma	Ipi, Nivo	45	42.4	7.2	N/A
Hatakeyama, Y., et al. 2018[22]	PR	Negative	60/m	Lung cancer	Nivo	491	23.1	9.1	N/A
Usui, Y., et al. ① 2017[23]	PR	Positive	31/ m	Lung cancer	Nivo	13	41.2	6.4	DRB1*04:05-DQB1*04:01
Usui, Y., et al. ② 2017[23]	PR	Negative	62/f	Lung cancer	Nivo	42	13.7	6.5	DRB1*09:01-DQB1*03:03
Chae, Y. K., et al. 2017[24]	PR	Positive	76/m	Lung cancer	Pembro	28	34.2	N/A	N/A
Yamamoto, N., et al. 2019[25]	PR	Negative	77/m	Renal cell carcinoma	Nivo	85	21.0	6.2	DRB1* 09, DRB1*12 DQB1* 03, DQB1* 03
Hong, A. R. et al. ① 2020[18]	PR	Negative	76/m	Lung cancer	Pembro	77	27.4	10.4	N/A
Hong, A. R. et al. ④ 2020[18]	PR	Negative	65/f	Billary cancer	Pembro	147	28.4	5.8	N/A
Yilmaz, M. 2020[26]	PR	Negative	49/m	Renall cell carcinoma	Nivo	300	44.5	10.9	N/A
Wen, L., et al. 2020[27]	PR	Negative	56/m	Hepatocellular carcinoma	sintilimab	168	22.2	7.8	DRB1* 12, DRB1*12 DQB1* 05, DQB1* 03
Sakaguchi, C., et al. 2019[28]	SD	Negative	68/f	Melanoma	Nivo	420	17.4	8.2	DRB1*09:01

(Continues)

TABLE 1 (Continued)

Literature	Clinical tumor response to anti-PD−1 antibody	Islet-related autoantibodies	Age/sex	Primary diagnosis	Anti-PD−1 antibody	Occurrence in days after initiation of Nivo	Plasma Glucose at onset (mmol/L)	HbA1c at onset (%)	HLA
Matsuura, N., et al. 2018[29]	SD	Positive	78/m	Lung cancer	Nivo	40	29.3	6.1	DRB1*0301-DQB1*0803 DRB1*0601-DQB1*1406
Capitao, R., et al. 2018[30]	SD	Positive	74/f	Lung cancer	Nivo	25	58.8	8.7	DRB1*04
Araujo, M., et al. 2017[31]	SD	Positive	73/f	Lung cancer	Nivo	11	>55.5	7.2	DRB1*0301-DQB1*0201 DRB1*0401-DQB1*03:02
Godwin, J. L., et al 2017[32]	SD	Positive	34/m	Lung cancer	Nivo	28	41.0	7.1	DR9
Hofmann, L., et al. ② 2016[16]	SD	Positive	78/f	Melanoma	Ipi, Nivo	18	N/A	N/A	N/A
Kapke, J., et al. 2017[33]	SD	Positive	N/A	Head and neck cancer	Nivo	90	23.6	N/A	DRB1*08, DRB1*11 DQB1*03, DQB1*04
Tohi, Y., et al. 2019[34]	SD	Negative	75/m	Ureteral cancer	Pembro	50	60.6	6.7	N/A
Hong, A. R. et al. ② 2020[18]	SD	Negative	67/m	Urothelial cancer	Atezolizumab	189	29.4	9.8	N/A
Current study Case 1	SD	Negative	76/f	Gastric cancer	Nivo	107	33.5	9	DRB1*08:02-DQB1*03:02 DRB1*14:54-DQB1*05:03
Current study Case 2	SD	Negative	68/f	Head and neck cancer	Nivo	300	36.3	9.5	DRB1*04:03-DQB1*03:02 DRB1*15:01-DQB1*06:02
Li, W., et al. 2020[35]	SD	Negative	73/m	Lung cancer	Anti-PD−1 monoclonal antibody	221	51.0	7.6	N/A
Zaied, A. A., et al. 2018[36]	PD	N/A	N/A/m	Renal cell carcinoma	Nivo	38	48.7	8.4	N/A
Li, L., et al. 2017[37]	PD	Positive	63/m	Lung cancer	Nivo	27	32.9	7.2	N/A
Teramoto, Y., et al. 2017[38]	PD	Negative	63/f	Melanoma	Nivo	189	36.7	8.9	N/A
Zezza, M. et al. ② 2019[17]	PD	Positive	80/f	Melanoma	Ipi, Nivo	35	48.4	N/A	N/A

Abbreviations: CR, complete response; Ipi, ipilimumab; N/A, not available; Nivo, nivolumab; PD, progressive disease; Pembro, pembrolizumab; PR, partial response; SD, stable disease.

TABLE 2 Clinical characteristics of immune checkpoint inhibitor-induced diabetes mellitus

	Akturk. H. K., et al, 2019[40] *n* = 71	Baden, M., et al, 2019[a] [39] *n* = 22
Age, years (SD)	61.7 (12.2)	63 (12)
Gender (Female; %)	45	41
immune checkpoint inhibitor (nivolumab; %)	53.5	100
Duration to the onset of immune checkpoint inhibitor-induced diabetes mellitus, days (SD)	83.5 (88.5)	121(21)
Diabetic ketoacidosis (%)	76	39
Plasma glucose, mmol/L (SD)	33.4 (11.5)	34.2 (13.8)
HbA1c, % (SD)	7.8 (2.2)	8.1 (1.3)
Presence of islet-related autoantibody (%)	50.7	4.8

[a]all patients were Japanese.

occurred while insulin secretion was maintained in the normal range before insulin secretion decreased markedly. The contribution of postprandial hyperglycemia is predominant in patients with well-controlled HbA1c, over fasting hyperglycemia.[11] Postprandial glucose levels could not be assessed in our cases; however, we speculate that increased HbA1c and serum C-peptide levels reflect elevated postprandial blood glucose levels.

Some studies have demonstrated that irAEs are associated with improved survival in melanoma or non-small cell lung cancer patients treated with nivolumab.[12,13] 33 isolated reports of ICI-induced DM that included the effectiveness of anti-PD-1 antibody therapy can be found in the literature (Table 1). The overall response rate (complete plus partial response) was 52% (5 complete and 12 partial responses in 33 cases). ICI-induced DM may be a predictive marker for durable clinical benefit in cancer patients, although the mechanisms underlying the association of ICI-induced DM with the outcome of anti-PD-1 antibody therapy are unknown. In our cases, although no recurrence was observed and the response to anti-PD-1 antibody therapy was stable disease, anti-PD-1 antibody treatment was discontinued because of a patient or family's request.

In a Japanese national survey of ICI-induced DM, HbA1c and blood pH were higher, and fasting plasma glucose levels tended to be lower at the onset of ICI-induced DM than conventional type 1 DM.[39] Baden M et al. reported that diabetic ketoacidosis was observed in 39% of ICI-induced DM patients in Japan, while Akturk. HK et al[40] reported that diabetic ketoacidosis was observed 76% of ICI-induced DM patients in their systematic review (Table 2). It might be one of the reasons for this difference that the higher positive rate of islet-related autoantibodies in Akturk's report than Baden's report (presence of islet-related autoantibody; 50.7% in Akturk's report vs 4.8% in Baden's report). Similar to the report of Baden, M. et al., HbA1c was as high as 9.0% or more, though diabetic ketoacidosis was not observed and islet-related autoantibodies were negative in our cases. Recent research revealed that patients who had islet-related autoantibodies were reported to develop ICI-induced DM rapidly.[6,40,41] In Table 1, islet-related autoantibodies were negative in 17 cases and positive in 13 cases. The duration to the onset of ICI-induced DM was significantly longer in islet-related autoantibody-negative cases (the average duration between ICI initiation and DM development; 176 ± 134 days in negative group vs 31 ± 20 days in positive group, $p = 0.000$, Man-Whitney test; Table 1). Our cases did not have islet-related autoantibodies, and the duration to the onset of ICI-induced DM was more than 3 months from the initial administration of nivolumab.

There is no standard version of case definitions for ICI-induced DM. ICI-induced DM often characterized by the presence of diabetic ketoacidosis or very low to absent C-peptide levels and insulin dependence after the onset of diabetes.[6-8] Baden, M. et al[39] suggested that C-peptide levels of acute-onset type 1 diabetes were 0.15 (0.07–0.23) nmol/L, while those of fulminant type 1 diabetes were 0.07 (± 0.06) nmol/L in Japanese patients with ICI treatment. Tsang V. H. M. et al[8] reported that C-peptide levels were 0.41 nmol/L several months after diagnosis of ICI-induced DM. However, specific cutoff values for C-peptide levels in ICI-induced DM have not been determined.[7] In the current cases, ICI-induced DM was diagnosed by the clinical symptoms and laboratory data. Hyperglycemia symptoms such as general fatigue, thirst, and polyuria appeared for several days in both cases. The serum C-peptide levels were inappropriately low (case1: 0.05 nmol/L and case2: 0.13 nmol/L), and both

patients were insulin dependent for over 1 year after the onset of ICI-induced DM. In case 2, although the course of insulin secretion after the onset could not be assessed, ICI-induced DM was diagnosed because the serum C-peptide levels at the onset had already markedly decreased and the patient was insulin dependent.

As ICI-induced DM is a rare, but life-threatening side effect of nivolumab, close monitoring of blood glucose levels is recommended for the early diagnosis of ICI-induced DM. Pathogenic mechanisms underlying the development of ICI-induced DM and predictive markers for selection of patients who have increased risk of the onset of ICI-induced DM have not been elucidated. Monitoring clinical data including insulin secretory ability might help in early detection of ICI-induced DM and understanding clinical features of the development of DM during ICI treatment. Our two cases showed that insulin secretion was maintained in the normal range and temporarily increased before the onset of ICI-induced DM. Accumulating cases of ICI-induced DM can be helpful to identify predictive markers for early diagnosis and prevent this side effect.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ACKNOWLEDGEMENTS

We thank the patients and all clinical staff who participated in the treatment of the patient.

AUTHOR CONTRIBUTIONS

All authors contributed significantly. Noriko Fujiwara, Mayu Watanabe and Akihiro Katayama contributed the design of the work. Noriko Fujiwara and Mayu Watanabe wrote the manuscript in consultation with Akihiro Katayama, Yohei Noda, Jun Eguchi, Hitomi Kataoka, Syunsuke Kagawa, and Jun Wada.

ETHICAL APPROVAL

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. This study was conducted with the approval of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital, Ethics Committee (No 1704–009). We obtained verbal and written informed consent were obtained from each patient.

DISCLOSURE

Jun Wada receives speaker honoraria from Astra Zeneca, Daiichi Sankyo, MSD, Novartis, Tanabe Mitsubishi, Taisho Toyama and receives grant support from Baxter, Chugai, Dainippon Sumitomo, Ono, Teijin.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Mayu Watanabe https://orcid.org/0000-0003-4253-3465
Akihiro Katayama https://orcid.org/0000-0002-9729-7343

REFERENCES

1. Ribas A. Tumor immunotherapy directed at PD-1. *N Engl J Med*. 2012;366(26):2517-2519. https://doi.org/10.1056/NEJMe1205943
2. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252-264. https://doi.org/10.1038/nrc3239
3. Myers G. Immune-related adverse events of immune checkpoint inhibitors: a brief review. *Curr Oncol*. 2018;25(5):342-347. https://doi.org/10.3747/co.25.4235
4. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378(2):158-168. https://doi.org/10.1056/NEJMra1703481
5. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012;366(26):2455-2465. https://doi.org/10.1056/NEJMoa1200694
6. Quandt Z, Young A, Anderson M. Immune checkpoint inhibitor diabetes mellitus: a novel form of autoimmune diabetes. *Clin Exp Immunol*. 2020;200(2):131-140. https://doi.org/10.1111/cei.13424
7. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. *Endocr Rev*. 2019;40(1):17-65. https://doi.org/10.1210/er.2018-00006
8. Tsang VHM, McGrath RT, Clifton-Bligh RJ, et al. Checkpoint inhibitor-associated autoimmune diabetes is distinct from type 1 diabetes. *J Clin Endocrinol Metab*. 2019;104(11):5499-5506. https://doi.org/10.1210/jc.2019-00423
9. Ansari MJ, Salama AD, Chitnis T, et al. The programmed death-1 (PD-1) pathway regulates autoimmune diabetes in nonobese diabetic (NOD) mice. *J Exp Med*. 2003;198(1):63-69. https://doi.org/10.1084/jem.20022125
10. Matsumura K, Nagasawa K, Oshima Y, et al. Aggravation of diabetes, and incompletely deficient insulin secretion in a case with type 1 diabetes-resistant human leukocyte antigen DRB1*15:02 treated with nivolumab. *J Diabetes Investig*. 2018;9(2):438-441. https://doi.org/10.1111/jdi.12679
11. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care*. 2003;26(3):881-885. https://doi.org/10.2337/diacare.26.3.881
12. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. *Clin Cancer Res*. 2016;22(4):886-894. https://doi.org/10.1158/1078-0432.CCR-15-1136

13. Haratani K, Hayashi H, Chiba Y, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. *JAMA Oncol*. 2018;4(3):374-378. https://doi.org/10.1001/jamaoncol.2017.2925
14. 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(11):1399-1410. https://doi.org/10.1007/s00262-017-2033-8
15. Lowe JR, Perry DJ, Salama AK, Mathews CE, Moss LG, Hanks BA. 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. https://doi.org/10.1186/s40425-016-0196-z
16. Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer*. 2016;60:190-209. https://doi.org/10.1016/j.ejca.2016.02.025
17. Zezza M, Kosinski C, Mekoguem C, et al. Combined immune checkpoint inhibitor therapy with nivolumab and ipilimumab causing acute-onset type 1 diabetes mellitus following a single administration: two case reports. *BMC Endocr Disord*. 2019;19(1):144. https://doi.org/10.1186/s12902-019-0467-z
18. Hong AR, Yoon JH, Kim HK, Kang HC. Immune checkpoint inhibitor-induced diabetic ketoacidosis: a report of four cases and literature review. *Front Endocrinol*. 2020;11:14. https://doi.org/10.3389/fendo.2020.00014
19. Takagi T, Yoshida K, Kobayashi H, et al. Durable response after discontinuation of nivolumab therapy in patients with metastatic renal cell carcinoma. *Jpn J Clin Oncol*. 2018;48(9):860-863. https://doi.org/10.1093/jjco/hyy106
20. 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(2):155-158. https://doi.org/10.1620/tjem.239.155
21. Telo GH, Carvalhal GF, Cauduro CGS, Webber VS, Barrios CH, Fay AP. Fulminant type 1 diabetes caused by dual immune checkpoint blockade in metastatic renal cell carcinoma. *Ann Oncol*. 2017;28(1):191-192. https://doi.org/10.1093/annonc/mdw447
22. Hatakeyama Y, Ohnishi H, Suda K, Okamura K, Shimada T, Yoshimura S. Nivolumab-induced acute-onset type 1 diabetes mellitus as an immune-related adverse event: a case report. *J Oncol Pharm Pract*. 2019;25(8):2023-2026. https://doi.org/10.1177/1078155218816777
23. 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(5):e41-e43. https://doi.org/10.1016/j.jtho.2016.12.015
24. Chae YK, Chiec L, Mohindra N, Gentzler R, Patel J, Giles F. A case of pembrolizumab-induced type-1 diabetes mellitus and discussion of immune checkpoint inhibitor-induced type 1 diabetes. *Cancer Immunol Immunother*. 2017;66(1):25-32. https://doi.org/10.1007/s00262-016-1913-7
25. 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(19):2825-2830. https://doi.org/10.2169/internalmedicine.2780-19
26. Yilmaz M. Nivolumab-induced type 1 diabetes mellitus as an immune-related adverse event. *J Oncol Pharm Pract*. 2020;26(1):236-239. https://doi.org/10.1177/1078155219841116
27. Wen L, Zou X, Chen Y, Bai X, Liang T. Sintilimab-induced autoimmune diabetes in a patient with the anti-tumor effect of partial regression. *Front Immunol*. 2020;11:2076. https://doi.org/10.3389/fimmu.2020.02076
28. Sakaguchi C, Yano S, Ashida K, et al. A case of acute exacerbation of chronic adrenal insufficiency due to ipilimumab treatment for advanced melanoma. *Am J Case Rep*. 2019;20:106-110. https://doi.org/10.12659/AJCR.913021
29. Matsuura N, Koh G, Konishi C, et al. Fulminant onset of insulin-dependent diabetes with positive anti-GAD antibody titers during treatment with nivolumab in a patient with NSCLC. *Cancer Immunol Immunother*. 2018;67(9):1417-1424. https://doi.org/10.1007/s00262-018-2203-3
30. Capitao R, Bello C, Fonseca R, Saraiva C. New onset diabetes after nivolumab treatment. *BMJ Case Rep*. 2018;2018;bcr-2017-220999. https://doi.org/10.1136/bcr-2017-220999
31. Araujo M, Ligeiro D, Costa L, et al. A case of fulminant Type 1 diabetes following anti-PD1 immunotherapy in a genetically susceptible patient. *Immunotherapy*. 2017;9(7):531-535. https://doi.org/10.2217/imt-2017-0020
32. 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. https://doi.org/10.1186/s40425-017-0245-2
33. Kapke J, Shaheen Z, Kilari D, Knudson P, Wong S. Immune checkpoint inhibitor-associated type 1 diabetes mellitus: case series, review of the literature, and optimal management. *Case Rep Oncol*. 2017;10(3):897-909. https://doi.org/10.1159/000480634
34. Tohi Y, Fujimoto K, Suzuki R, Suzuki I, Kubota M, Kawakita M. Fulminant type 1 diabetes mellitus induced by pembrolizumab in a patient with urothelial carcinoma: a case report. *Urol Case Rep*. 2019;24:100849. https://doi.org/10.1016/j.eucr.2019.100849
35. Li W, Wang H, Chen B, et al. Anti PD-1 monoclonal antibody induced autoimmune diabetes mellitus: a case report and brief review. *Transl Lung Cancer Res*. 2020;9(2):379-388. https://doi.org/10.21037/tlcr.2020.03.05
36. Zaied AA, Akturk HK, Joseph RW, Lee AS. New-onset insulin-dependent diabetes due to nivolumab. *Endocrinol Diabetes Metab Case Rep*. 2018;2018:17-0174. https://doi.org/10.1530/EDM-17-0174
37. Li L, Masood A, Bari S, Yavuz S, Grosbach AB. Autoimmune diabetes and thyroiditis complicating treatment with nivolumab. *Case Rep Oncol*. 2017;10(1):230-234. https://doi.org/10.1159/000456540
38. Teramoto Y, Nakamura Y, Asami Y, et al. Case of type 1 diabetes associated with less-dose nivolumab therapy in a melanoma patient. *J Dermatol*. 2017;44(5):605-606. https://doi.org/10.1111/1346-8138.13486
39. Baden MY, Imagawa A, Abiru N, et al. Characteristics and clinical course of type 1 diabetes mellitus related to anti-programmed cell death-1 therapy. *Diabetol Int*. 2019;10(1):58-66. https://doi.org/10.1007/s13340-018-0362-2

40. Akturk HK, Kahramangil D, Sarwal A, Hoffecker L, Murad MH, Michels AW. Immune checkpoint inhibitor-induced type 1 diabetes: a systematic review and meta-analysis. *Diabet Med*. 2019;36(9):1075-1081. https://doi.org/10.1111/dme.14050
41. Stamatouli AM, Quandt Z, Perdigoto AL, et al. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. *Diabetes*. 2018;67(8):1471-1480. https://doi.org/10.2337/dbi18-0002

How to cite this article: Fujiwara N, Watanabe M, Katayama A, et al. Longitudinal observation of insulin secretory ability before and after the onset of immune checkpoint inhibitor-induced diabetes mellitus: A report of two cases. *Clin Case Rep*. 2021;00:e04574. https://doi.org/10.1002/ccr3.4574