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# Painless Thyroiditis and Fulminant Type 1 Diabetes Mellitus in a Patient Treated with an Immune Checkpoint Inhibitor, Nivolumab

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The programmed cell death-1 (PD-1) pathway is a novel therapeutic target in immune checkpoint therapy for cancer. Nivolumab, an anti-PD-1 monoclonal antibody, blocks PD-1 and can restore anti-cancer immune responses by disrupting the signal that inhibits T-cell activation. Nivolumab may induce endocrine-related adverse events, including hypophysitis, autoimmune thyroiditis, and type 1 diabetes mellitus. Here we report a 68-year-old female patient with advanced renal cell carcinoma who was treated with nivolumab. She had positive anti-thyroglobulin antibodies and anti-thyroid peroxidase antibodies with slightly elevated thyroid-stimulating hormone (9.048 $\mu$U/mL), and was diagnosed as chronic thyroiditis with subclinical hypothyroidism before nivolumab therapy. She developed painless thyroiditis after the first cycle of the therapy (Day 14). At the 7th cycle of nivolumab therapy (Day 98), hyperglycemia (473 mg/dL) was noted, whereas glycated hemoglobin level was 6.9%. Islet-related autoantibodies were all negative. The glucagon tolerance test showed complete depletion of insulin. Human leukocyte antigen typing showed haplotype DRB1*09:01-DQB1*03:03, which was reported to be closely associated with type 1 diabetes mellitus in Japan. Fulminant type 1 diabetes mellitus was diagnosed, and she was immediately treated with multiple daily injections of insulin. Fulminant type 1 diabetes mellitus is characterized by rapid-onset diabetic ketoacidosis, and negative islet-related autoantibodies, and was proposed as a novel subtype of non-autoimmune diabetes. Preceding painless thyroiditis with positive thyroid autoantibodies observed in the present case, however, raises the possibility that autoimmune mechanisms are involved in the pathogenesis of nivolumab-induced fulminant type 1 diabetes mellitus.

**Keywords:** autoimmune; fulminant type 1 diabetes mellitus; immune checkpoint inhibitor; nivolumab; painless thyroiditis
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## Introduction

Immune checkpoint inhibitors have an anticancer effect by removing a negative regulatory signal for T-cell activation from the tumor microenvironment. They include antibodies against cytotoxic T-cell-associated antigen (CTLA-4), programmed cell death protein-1 (PD-1), and programmed cell death ligand-1 (PDL-1). These immune checkpoint inhibitors were associated with endocrine-related adverse events, including hypophysitis, thyroiditis, and type 1 diabetes mellitus (Corsello et al. 2013; Ryder et al. 2014; Haanen et al. 2015; Hughes et al. 2015; Martin-Liberal et al. 2015). Nivolumab, one of the immune checkpoint inhibitors, is an IgG4 monoclonal antibody against the PD-1 receptor, achieving disinhibition of tumor-specific immune responses.

Fulminant type 1 diabetes mellitus is characterized by rapid-onset diabetic ketoacidosis, low glycated hemoglobin (HbA1c) value, undetectable serum C-peptide, and negative islet-related autoantibodies (Imagawa et al. 2000), and is proposed as a novel subtype of idiopathic (type 1B) diabetes mellitus (American Diabetes Association 2014). Idiopathic (type 1B) diabetes mellitus was considered to be caused by non-autoimmune mechanism (American Diabetes Association 1998). However, some reports suggested the involvement of autoimmune mechanism in the onset of fulminant type 1 diabetes mellitus (Taniguchi et al. 2001, 2005; Shimada et al. 2002a, b). The etiology of fulminant

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type 1 diabetes mellitus has been still unclear.

Here we report a patient with advanced renal cell carcinoma (RCC) who developed painless thyroiditis, followed by fulminant type 1 diabetes mellitus during nivolumab therapy against RCC.

## Case Report

A 68-year-old woman with metastatic RCC was visited to our outpatient endocrine clinic for the thyroid function test before nivolumab therapy in April 2017. She was diagnosed as left RCC and underwent resection of the left kidney in June 2004. Lung metastasis of RCC was diagnosed in May 2010, and she was treated with interferon $\alpha$ (intron A: 600 units, three times a week) for 5 months, followed by sunitinib (a tyrosine kinase inhibitor) (50 mg/day for 2 weeks, followed by 2 weeks off) for 25 months. Bone metastasis of RCC occurred in August 2014, and she was treated with axitinib (a tyrosine kinase inhibitor) (3 mg/day) and received radiation therapy. Because of the liver metastasis of RCC, she received transcatheter arterial embolization in February 2017. After the transcatheter arterial embolization, nivolumab therapy (3 mg/kg, once every 2 weeks) was planned.

Before the administration of nivolumab (Day 0), free triiodothyronine (FT3) (2.54 pg/mL; reference range 2.13-4.07 pg/mL) and free thyroxine (FT4) (1.24 ng/dL; reference range 0.95-1.74 ng/dL) levels were normal, with a slightly elevated level of thyroid-stimulating hormone (TSH) (9.048 $\mu$U/mL; reference range 0.55-4.78 $\mu$U/mL) (Fig. 1). Anti-thyroglobulin antibodies (> 4,000 IU/mL;

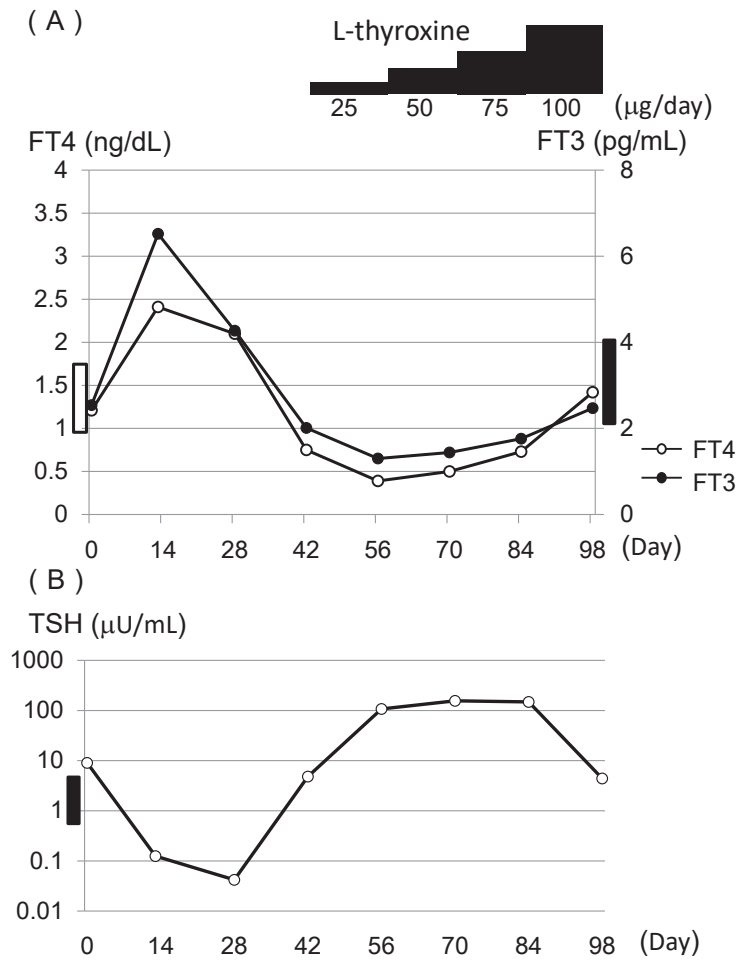


Fig. 1. Serum levels of free thyroxine, free triiodothyronine, and thyroid-stimulating hormone during the nivolumab treatment.

A. Serum levels of free thyroxine (FT4) and free triiodothyronine (FT3). The open bar and the closed bar denote the reference ranges for FT4 and FT3, respectively. Serum FT4 (open circles) and FT3 levels (closed circle) increased to the level higher than the reference range 14 days after the first administration of nivolumab (Day 14), followed by subsequent hypothyroidism at Day 42. Levothyroxine (L-thyroxine) replacement therapy (25 $\mu$g daily) was started at Day 42 (shown in the graph at the right upper).

B. Serum levels of thyroid-stimulating hormone (TSH). The closed bar denotes the reference ranges for TSH. The slightly elevated serum TSH level before the nivolumab treatment (Day 0) decreased and reached the nadir at Day 28, and then increased to the level higher than the reference range. Finally, 100 $\mu$g daily of L-thyroxine was needed to normalize serum TSH level.

Table 1. Laboratory test results 14 days after the first administration of nivolumab (Day 14).

| | | |
|---|---|---|
| TSH | 0.125 μU/mL | (0.55 - 4.78) |
| FT3 | 6.52 pg/mL | (2.13 - 4.07) |
| FT4 | 2.41 ng/dL | (0.95 - 1.74) |
| C-reactive protein | 0.1 mg/dL | (< 0.3) |
| TSH receptor antibody | 0.5 IU/mL | (< 2.0) |
| Anti-thyroglobulin antibody | > 4000 IU/mL | (0 - 28) |
| Anti-thyroid peroxydase antibody | 105 IU/mL | (0 - 16) |
| $^{123}$I uptake | 0.0 % | |

The ranges of reference values are indicated in the parentheses.
TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine.

reference range 0-28 IU/mL) and anti-thyroid peroxidase (TPO) antibodies (77 IU/mL; reference range 0-16 IU/mL) were positive. Thyroid ultrasonography demonstrated an inhomogeneous pattern (data not shown). Subclinical hypothyroidism due to chronic thyroiditis was diagnosed. She was followed without Levothyroxine (L-thyroxine) treatment. She had been treated with telmisartan for hypertension for three years. She had no history of allergy or autoimmune disease. There was no family history of autoimmune disease or diabetes mellitus.

After the first cycle of nivolumab treatment (Day14), she complained of palpitations and fatigue without a significant weight loss. The thyroid function test showed a decreased level of TSH (0.125 $\mu$U/mL), and elevated levels of FT3 (6.52 pg/mL) and FT4 (2.41 ng/dL) (Table 1). Anti-TSH receptor antibodies were negative whereas anti-thyroglobulin antibodies (> 4,000 IU/mL) and anti-TPO antibodies (105 IU/mL) were positive (Table 1). The $^{123}$I uptake of the thyroid gland at 24 h was low (0.0 %) (Table 1). Thyroid ultrasonography demonstrated a diffuse heterogenous goiter without increased blood flow signal (data not shown). Serum C-reactive protein was normal (0.1 mg/dL; reference range < 0.3 mg/dL) (Table 1). Painless thyroiditis induced by nivolumab therapy was diagnosed. She was followed without treatment. At the third cycle of nivolumab therapy (Day 42), thyroid function tests showed hypothyroidism (Fig. 1). L-thyroxine (25 $\mu$g daily) was then initiated, and the dose was gradually increased to 100 $\mu$g daily to normalize serum TSH level.

At the 7th cycle of nivolumab therapy (Day 98), hyperglycemia (473 mg/dL) without metabolic ketoacidosis was noted (Table 2). HbA1c and random blood glucose levels during nivolumab therapy are summarized in the Fig. 2. Blood glucose levels and HbA1c were normal before the 6th cycle of nivolumab (Day 84). In spite of marked hyperglycemia, HbA1c level was relatively low (6.9 %), suggesting the rapid onset of hyperglycemia. She had no flu-like symptoms such as fever, upper respiratory symptoms and arthralgia, or abdominal pain prior to the onset of diabetes mellitus.

Blood levels of $\beta$-hydroxybutyrate (227 $\mu$mol/L; refer-

Table 2. Laboratory test results 98 days after the first administration of nivolumab (Day 98), glucagon stimulation test (Day 109), and serum C-peptide levels during Day 84-109.

| | | |
|---|---|---|
| HbA1c | 6.9 % | (4.6 - 6.1) |
| Glucose | 473 mg/dL | |
| Urinary ketone | (-) | |
| pH | 7.389 | (7.35 - 7.45) |
| $pCO_2$ | 42.1 mmHg | (32 - 48) |
| $pO_2$ | 75.5 mmHg | (83 - 108) |
| $HCO_3^-$ | 24.8 mmol/L | (21 - 28) |
| Anion gap | 7.2 mmol/L | (7.0 - 16.0) |
| Amylase | 107 U/L | (37 - 120) |
| Lipase | 50 IU/L | (6 - 48) |
| Acetoacetic acid | 114 μmol/L | (< 55) |
| 3-OHBA | 227 μmol/L | (< 85) |
| Acetoacetic acid / 3-OHBA | 0.5 | (> 0.7) |
| Serum C-peptide | 0.24 ng/mL | (0.8 - 2.3) |
| Urinary C-peptide | 1.4 μg/day | (29.2 - 167) |
| GAD antibody | negative | |
| IA-2 antibody | negative | |
| ZnT8 antibody | negative | |
| Insulin autoantibody | negative | |

| **Glucagon stimulation test (Day 109)** | |
|---|---|
| C-peptide (0min) | < 0.03 ng/mL |
| C-peptide (6min) | 0.04 ng/mL |

| **Time-series data of serum C-peptide** | |
|---|---|
| Day 84 | 2.65 ng/mL |
| Day 98 | 0.24 ng/mL |
| Day 99 | 0.16 ng/mL |
| Day 105 | 0.06 ng/mL |
| Day 109 | < 0.03 ng/mL |

The ranges of reference values are indicated in the parentheses.
HbA1c, glycated hemoglobin; $HCO_3^-$, bicarbonate ion; 3-OHBA, 3-hydroxybutyric acid; GAD, Glutamic Acid Decarboxylase; IA-2, Insulinoma-associated Antigen-2; ZnT8, Zinc transporter 8.

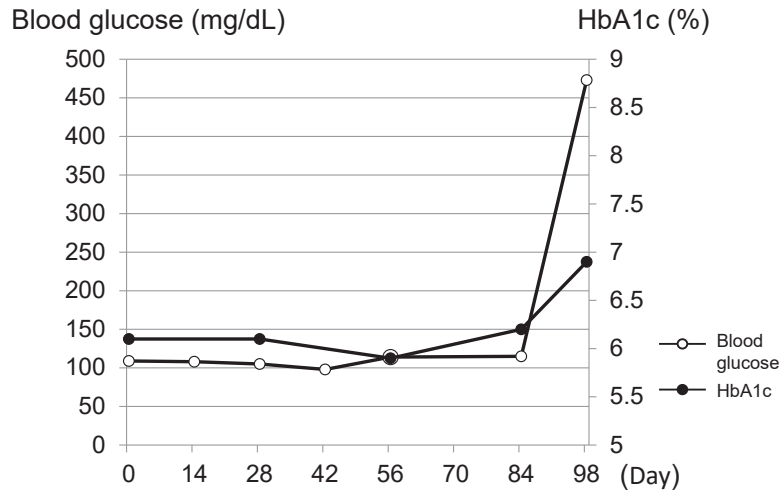


Fig. 2. Blood glucose levels and glycated hemoglobin (HbA1c) during the nivolumab treatment.
Blood glucose levels (open circles) and HbA1c (closed circles) were normal before the 6th cycle of nivolumab therapy (Day 84). At the 7th cycle of nivolumab therapy (Day 98), hyperglycemia was noted, whereas HbA1c level was relatively low, suggesting the rapid onset of hyperglycemia.

ence range < 85 $\mu$mol/L) and acetoacetic acid (114 $\mu$mol/L; reference range < 55 $\mu$mol/L) were slightly elevated whereas ketonuria was negative (Table 2). Islet-related autoantibodies were all negative (anti-glutamic acid decarboxylase, insulinoma-associated antigen-2, zinc transporter 8, and insulin autoantibodies) (Table 2). Lipase (50 U/L; reference range 6-48 U/L) was slightly elevated at the onset of hyperglycemia, with normal levels of amylase and elastase-1 (Table 2). Computed tomography showed no abnormal findings in the pancreas (data not shown). Human leukocyte antigen (HLA) typing showed haplotype DRB1*09:01-DQB1*03:03, which was reported to be closely associated with autoimmune type 1 diabetes mellitus in Japan (Kawabata et al. 2009). The glucagon tolerance test on Day 109 showed complete depletion of insulin (Table 2). Serum C-peptide levels were decreased and were below the limit of detection on Day 109 (Table 2). Therefore, fulminant type 1 diabetes mellitus induced by nivolumab therapy was diagnosed. She was treated with multiple daily injections of insulin (23 units /day). Nivolumab therapy was continued without further adverse events.

There were no findings suggestive of adrenal insufficiency secondary to hypophysitis, such as nausea, anorexia, fatigue and hyponatremia during nivolumab therapy.

Informed consent was obtained from the subject on this case report.

## Discussion

We report a case of nivolumab-induced painless thyroiditis and fulminant type 1 diabetes mellitus. Islet-related autoantibodies were all negative in this case, whereas thyroid autoantibodies were positive before nivolumab therapy. No metabolic ketoacidosis was observed, which may be due to the early detection of hyperglycemia and subsequent prompt initiation of the treatment with insulin.

The immune checkpoint inhibitors were associated with endocrine-related adverse events, including hypophysitis, thyroiditis, and type 1 diabetes mellitus (Corsello et al. 2013; Ryder et al. 2014; Haanen et al. 2015; Hughes et al. 2015; Martin-Liberal et al. 2015). The occurrence of thyroid dysfunction was reported to be 5.0-10.1% for hypothyroidism and 3.2-6.5% for thyrotoxicosis in patients treated with nivolumab (Ribas et al. 2015; Robert et al. 2015). The occurrence of type 1 diabetes mellitus (Ishikawa et al. 2017), or hypophysitis with secondary adrenal insufficiency (Topalian et al. 2012) was much lower (about 0.1-0.2% and 0.3%, respectively) than that of thyroid dysfunction in patients treated with nivolumab.

Type 1 diabetes mellitus is classified as type 1A and type 1B diabetes, which are considered to be caused by autoimmune and non-autoimmune mechanisms, respectively (American Diabetes Association 2009, 2014). Fulminant type 1 diabetes mellitus is characterized by rapid-onset diabetic ketoacidosis, low HbA1c value, undetectable serum C-peptide, and negative islet-related autoantibodies, and is proposed as a novel subtype of type 1B (idiopathic; non-autoimmune) diabetes mellitus (American Diabetes Association 2014). Both autoimmune type 1 diabetes mellitus and fulminant type 1 diabetes mellitus have recently been reported to occur in patients treated with the immune checkpoint inhibitors (Gaudy et al. 2015; Hughes et al. 2015).

Some of the literatures reported cases of insulin-dependent diabetes mellitus with positive islet-related autoantibodies (type 1A, autoimmune diabetes mellitus) after anti-PD-1 therapy as fulminant type 1 diabetes mellitus (Lowe et al. 2016; Araujo et al. 2017). But it is difficult to conclude that these cases were typical fulminant type 1 diabetes mellitus because of the presence of positive islet-

related autoantibodies. We therefore searched the literatures of anti-PD-1 therapy-induced type 1 diabetes mellitus with negative islet-related autoantibodies (Table 3) as well as that with positive islet-related autoantibodies (Table 4). The Committee of the Japan Diabetes Society on the Research of Fulminant and Acute-onset Type 1 Diabetes Mellitus adopted the HbA1c level of < 8.7% as the diagnostic criteria of fulminant type 1 diabetes mellitus (Imagawa et al. 2012). The cases with HbA1c levels of < 8.7% are therefore marked by an asterisk in the literature of Table 3 and 4.

Nine cases of anti-PD-1 therapy-induced type 1 diabetes mellitus with negative islet-related autoantibodies (autoantibodies to glutamic acid decarboxylase, insulinoma-associated antigen-2 or insulin) have been reported in the literatures (Table 3) (Gaudy et al. 2015; Hughes et al. 2015; Mellati et al. 2015; Hofmann et al. 2016; Kong et al. 2016; Miyoshi et al. 2016; Okamoto et al. 2016; Munakata et al. 2017). Seven of these nine cases showed HbA1c levels of < 8.7%, indicating that these seven cases had fulminant type 1 diabetes mellitus. It is noteworthy that thyroid dysfunction accompanying by positive thyroid autoantibodies occurred in three out of these seven cases (Table 3). The present case also presented painless thyroiditis with thyroid autoantibodies, followed by fulminant type 1 diabetes mellitus with negative autoantibodies to glutamic acid decarboxylase, insulinoma-associated antigen-2 and insulin after nivolumab therapy against RCC. The Japan Diabetes Society Committee on Fulminant Type 1 Diabetes Mellitus Research reported that positive ratios of anti-thyroglobulin antibodies and anti-TPO antibodies were 7.3% and 9.4% in fulminant type 1 diabetes mellitus, and 16.9% and 27.3% in autoimmune type 1 diabetes mellitus (type 1A), respectively (Hanafusa et al. 2005). Thus, the positive ratios of thyroid autoantibodies appear to be higher in the patients with anti-PD-1 therapy-induced fulminant type 1 diabetes mellitus shown in Table 3, when compared with the report by Hanafusa et al. (2005).

In contrast, twelve cases of anti-PD-1 therapy-induced type 1 diabetes mellitus with positive islet-related autoantibodies (type 1A) have been reported in the literatures (Table 4) (Hughes et al. 2015; Martin-Liberal et al. 2015; Mellati et al. 2015; Hansen et al. 2016; Hofmann et al. 2016; Lowe et al. 2016; Li et al. 2017; Araujo et al. 2017; Chae et al. 2017). Thyroid dysfunction accompanied by positive thyroid autoantibodies occurred in at least three out of these twelve cases of type 1 diabetes mellitus with positive islet-related autoantibodies. It is also noteworthy that five out of

Table 3. Cases of anti-PD-1 therapy-induced type 1 diabetes mellitus with negative islet-related autoantibodies reported in the literatures.

| Literature | Age/sex | Primary diagnosis | Anti-PD-1 drug | Time after anti-PD-1 | Pancreatic enzyme | Clinical presentation | HbA1c (%) | Random glucose (mg/dL) | Random C-pep (ng/mL) | Thyroid autoantibodies | HLA |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gaudy et al. *2015** | 44/F | Melanoma | Pem | 5 weeks | Elevated | DKA | 6.85 | 908 | Undetectable | (+) | Not listed |
| Hughes et al. *2015** | 55/F | Melanoma | Nivo | 5 months | Not listed | DKA | 6.9 | 532 | < 0.1 | (+) | A2.1, DR4 |
| Hughes et al. *2015** | 64/F | Melanoma | Pem | < 1 month | Not listed | Diabetic ketosis | 7.4 | 703 | 0.5 | (+) | DR4 |
| Mellati et al. 2015 | 70/M | Lung cancer | (Anti-PD-1) | 15 weeks | Not listed | DKA | 9.8 | 441 | 0.3 | Not listed | Not listed |
| Hofmann et al. 2016 | 70/F | Melanoma | Nivo | 6 weeks | Not listed | Hyperglycemia | Not listed | Not listed | < 16 pmol | Not listed | Not listed |
| Kong et al. *2016** | 68/M | Lung cancer | Pem | 5 months | Not listed | DKA | 7.9 | 866 | < 0.03 | (-) | DRB1*09:01-DQB1*03:03 DRB1*14:05-DQB1*05:03 |
| Miyoshi et al. *2016** | 66/F | Melanoma | Nivo | 4 months | Elevated | DKA | 7.3 | 531 | 0.23 | (-) | DRB1*11:01, *13:02 DQB1*03:01, *06:04 |
| Okamoto et al. *2016** | 55/F | Melanoma | Nivo | 12 months | Not elevated | Diabetic ketosis | 7.0 | 580 | < 0.1 | (-) | DRB1*04:05 DQB1*04:01 |
| Munakata et al. *2017** | 72/M | Hodgkin lymphoma | Nivo | 3 months | Elevated | Hyperglycemia | 7.3 | 326 | Urine C-pep 5.0μg/day | Not listed | B*40:02 |

*Cases with HbA1c level of < 8.7% (one of the diagnostic criteria of fulminant type 1 diabetes mellitus) are marked by an asterisk in the literature.

PD-1, programmed cell death-1; Nivo, Nivolumab; Pem, pembrolizumab; DKA, diabetic ketoacidosis; HbA1c, glycated hemoglobin; C-pep, C-peptide.

Table 4. Cases of anti-PD-1 therapy-induced type 1 diabetes mellitus with positive islet-related autoantibodies reported in the literatures.

| Literature | Age/sex | Primary diagnosis | Anti-PD-1 drug | Time after anti-PD-1 | Pancreatic enzyme | Clinical presentation | HbA1c (%) | Random glucose (mg/dL) | Random C-pep (ng/mL) | Thyroid autoantibodies | HLA |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hughes et al. *2015** | 83/F | Lung cancer | Nivo | < 1 month | Not listed | DKA | 7.7 | 350 | < 0.1 | (-) | A2.1, DR4 |
| Hughes et al. *2015** | 63/M | Renal cell carcinoma | Nivo | 4 months | Not listed | Hyperglycemia | 8.2 | 247 | 1.3 | (-) | A2.1, DR4 |
| Hughes et al. *2015* | 58/M | Lung cancer | Nivo | 1 week | Not listed | DKA | 9.7 | 749 | < 0.1 | (-) | A2.1 |
| Martin-Liberal et al. 2015 | 54/F | Melanoma | Pem | 6 weeks | Not listed | DKA | Not listed | Not listed | Not listed | Not listed | DRB1*04-DQB1*03:02 |
| Mellati et al. *2015* | 66/F | Sarcomatoid squamous cell carcinoma of the jaw | ( Anti-PD-1) | 7 weeks | Not listed | DKA | 9.4 | 752 | < 0.1 | (+) | DR3-DQ2, DR4-DR8 |
| Hansen et al. *2016* | 58/M | Melanoma | Pem | 1 year | Not elevated | Hyperglycemia | 9.7 | 408 | 2.4 | Not listed | Not listed |
| Hofmann et al. *2016* | 78/F | Melanoma | Nivo | 3 weeks | Not listed | DKA | Not listed | Not listed | Low | Not listed | Not listed |
| Hofmann et al. *2016* | 58/F | Melanoma | Pem | 3 weeks | Not listed | Hyperglycemia | Not listed | Not listed | Low | Not listed | Not listed |
| Lowe et al. 2016 | 54/M | Melanoma | Nivo | 4 months | Not listed | DKA | Not listed | Not listed | < 0.1 | (+) | A2 DQB1*06:02 |
| Li et al. *2017** | 63/M | Lung cancer | Nivo | 4 weeks | Not listed | DKA | 7.2 | 592 | Not listed | (+) | A2, DR4-DQ8 |
| Araujo et al. *2017** | 73/F | Lung cancer | Nivo | 4 weeks | Not elevated | DKA | 7.2 | > 1000 | 0.06 | Not listed | DRB1*03:01-DQB1*02:01 DRB1*04:01-DQB1*03:02 |
| Chae et al. *2017** | 76/M | Lung cancer | Pem | 4 weeks | Not listed | Hyperglycemia | 5.8 | 619 | < 0.1 | Not listed | Not listed |

*Cases with HbA1c level of< 8.7% (one of the diagnostic criteria of fulminant type 1 diabetes mellitus) are marked by an asterisk in the literature.

PD-1., programmed cell death-1; Nivo, Nivolumab; Pem, pembrolizumab; DKA, diabetic ketoacidosis: HbA1c, glycated hemoglobin; C-pep, C-peptide.

twelve cases of anti-PD-1 therapy-induced type 1 diabetes mellitus with positive islet-related autoantibodies had HbA1c levels of < 8.7%, suggesting that pancreas $\beta$ cell destruction progressed at a rapid rate comparable to fulminant type 1 diabetes mellitus. Indeed, the case reported by Chae et al. (2017) (Table 4) showed a rapid decrease of serum C-peptide levels (from 0.81 ng/mL at the onset of diabetes mellitus to less than 0.1 ng/mL 14 days later). Further studies are therefore required to clarify whether such cases with positive islet-related autoantibodies and lower HbA1c levels of < 8.7% represent a novel subtype of fulminant type 1 diabetes mellitus.

The etiology of fulminant type 1 diabetes mellitus is still unclear. Fulminant type 1 diabetes mellitus characterized by negative islet-related autoantibodies was proposed as non-autoimmune (idiopathic) diabetes mellitus (type 1B) (American Diabetes Association 2009, 2014). However, the involvement of T-cell autoimmunity in this disease has also been reported previously (Taniguchi et al. 2001, 2005; Shimada et al. 2002a, b). Moreover, Hamasaki et al. (2006) reported that fulminant type 1 diabetes and painless thyroiditis presented simultaneously in a 47-year-old woman without treatment of the immune checkpoint inhibitor. Painless thyroiditis is generally considered to be an autoimmune disorder (Dayan and Daniels 1996). Therefore, the case reported by Hamasaki et al. (2006) suggested participation of autoimmune mechanisms at the onset of fulminant type 1 diabetes. Occurrence of fulminant type 1 diabetes mellitus was also observed after nivolumab-induced painless thyroiditis in the present case. This finding raises the possibility that T-cell-mediated autoimmunity is involved in the pathogenesis of nivolumab-induced fulminant type 1 diabetes mellitus.

Recently, Araujo et al. (2017) reported a genetically susceptible patient who developed fulminant type 1 diabetes following anti-PD-1 immunotherapy. They indicated that DR3-DQ2 and DR4-DQ8 genotypes of HLA-II (DRB1*03-DQB1*02:01 and DRB1*04-DQB1*03:02) were high risk genotypes. Although these genotypes are strongly associated with type 1 diabetes in the Caucasian population, they are very rare in the Japanese people (Kawabata et al. 2002). In contrast, in the Japanese people, haplotype DRB1*04:05-DQB1*0401 and DRB1*09:01-DQB1*03:03, which are rare in the Caucasian populations,

confer susceptibility to type 1 diabetes (Awata et al. 1992; Ikegami et al. 1992; Yasunaga et al. 1996).

In our case, the HLA typing showed haplotype DRB1*09:01-DQB1*03:03 (DR9-DQ9), which is the haplotype closely associated with autoimmune type 1 diabetes in Japan (Kawabata et al. 2009). Recent case reports of nivolumab-induced type 1 diabetes mellitus have also shown certain high-risk HLA genotypes for autoimmune or fulminant type 1 diabetes (Martin-Liberal et al. 2015; Mellati et al. 2015). HLA genotypes might therefore be one of the predicting factors of occurrence of fulminant type 1 diabetes mellitus.

Fulminant type 1 diabetes mellitus is a life-threatening disease if prompt insulin therapy is not initiated. Predictive factors of anti-PD-1 therapy-induced fulminant type 1 diabetes mellitus have yet to be clarified. Further studies are required to identify predictive biomarkers for the risk of anti-PD-1 therapy-induced fulminant type 1 diabetes mellitus, and to clarify possible involvement of the autoimmune mechanism in its pathogenesis. We could not exclude the possibility that anti-PD-1 therapy-induced type 1 diabetes mellitus has a pathogenesis different from previously known autoimmune type 1 diabetes mellitus (type 1A) or fulminant type 1 diabetes mellitus (type 1B). Moreover, periodic surveillance of thyroid function and blood glucose is mandatory during the treatment with immune checkpoint inhibitors.

## Conflict of Interest

The authors declare no conflict of interest.

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