Two cases with fulminant type 1 diabetes that developed long after cessation of immune checkpoint inhibitor treatment

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INTRODUCTION

While immune checkpoint inhibitors (ICIs), such as anti-programmed cell death 1 (PD-1), anti-PD-ligand 1 (PD-L1), and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-antibodies, are effective for treating numerous malignancies, several immune-related adverse events (irAEs), such as thyroid dysfunction, pneumonitis, colitis, cutaneous toxicities, have been reported. Type 1 diabetes (T1D), especially fulminant type 1 diabetes (FT1D), is also reportedly associated with ICI treatments\textsuperscript{2}. Because fulminant type 1 diabetes results from acute and near-total destruction of pancreatic \(\beta\) cells, it can be life-threatening if unrecognized\textsuperscript{3}. Therefore, it is important to detect its onset. Clinical ICI treatment guidelines generally recommend repeated laboratory tests, including the measurement of blood glucose levels during the treatment period\textsuperscript{4--6}. However, the necessity of monitoring glucose levels in patients in whom the ICI therapy had been terminated is not clearly described in most guidelines. One of the guidelines notes that another measurement 4--6 weeks after the last cycle of immunotherapy may be necessary\textsuperscript{7}.

We experienced two cases who developed fulminant type 1 diabetes more than 6 weeks after their last ICI treatments. In particular, one developed fulminant type 1 diabetes approximately 6 months after the last ICI infusion.

CASE PRESENTATION 1

A 74-year-old male with no history of diabetes was diagnosed as having lung adenocarcinoma with metastases in the liver, bone, and brain. He received first-line chemotherapy with gefitinib for 6 months, but with little therapeutic response. Thereafter, second-line chemotherapy with nivolumab every 2 weeks was started. Before the first infusion of nivolumab, the postprandial plasma glucose was 103 mg/dL, glycated hemoglobin (HbA1c) was 6.1%, the postprandial serum C-peptide immunoreactivity (CPR) level was 2.1 ng/mL. Computed tomography demonstrated an abnormal pericardial effusion and growth of the primary tumor. Since malignant pericarditis had worsened, nivolumab administration was terminated after its sixth cycle.

Six weeks after the last infusion of nivolumab, he became aware of thirst, polydipsia, and polyuria. His weight decreased by 3.7 kg. Laboratory data on day 44 after ICI cessation
revealed marked hyperglycemia and ketonuria and he was transferred to our hospital as an emergency.

While his postprandial plasma glucose was elevated to 507 mg/dL, HbA1c was 7.1%. Fasting serum C-peptides were below the lower limit of detection. He had ketonuria with markedly elevated 3-hydroxybutyrate and acetacetate in the blood (Table 1). Autoantibodies to glutamic acid decarboxylase (GAD) and insulinoma-associated antigen-2 (IA-2) were both negative. We diagnosed fulminant type 1 diabetes with diabetic ketosis, and suspected nivolumab to be associated with its development. Ketosis showed a prompt improvement and his blood glucose was well controlled on intensive insulin therapy. Human leukocyte antigen (HLA) typing identified no specific alleles known to be related to type 1 diabetes (Table 1).

**CASE PRESENTATION 2**

An 85-year-old male with no history of diabetes was diagnosed as having lung adenocarcinoma with carcinomatous pleurisy. He started on a treatment regimen with carboplatin, pemetrexed, and atezolizumab every 3 weeks. Before the first infusion of atezolizumab, the fasting plasma glucose and HbA1c were 86 mg/dL and 5.7%, respectively. After the sixth cycle, this treatment was stopped because of a renal function decline. On day 171 after the last infusion of atezolizumab, he complained of appetite loss and thirst. Four days later, the postprandial plasma glucose was 735 mg/dL and he had lost 1.4 kg. He was transferred to our hospital.

Although his postprandial plasma glucose was 705 mg/dL, HbA1c was 7.4%. Fasting serum C-peptide was beneath the lower limit of detection. He had ketonuria and the blood levels of both 3-hydroxybutyrate and acetacetate were increased (Table 2). Autoantibodies to GAD and IA-2 were both negative. The glucagon loading test showed no increase in CPR levels (Table 2), indicating complete β cell loss.

Based on these findings, we diagnosed fulminant type 1 diabetes and suspected atezolizumab to be involved in its development. He had type 1 diabetes-susceptible HLA types, i.e., DRB1*09:01-DQ81*03:03. He initially received continuous insulin infusion intravenously. Thereafter, he was managed with basal-bolus insulin therapy.

**DISCUSSION**

In both of our cases, the criteria for diagnosing fulminant type 1 diabetes, established by the committee of the Japanese Diabetes Society, were all met. Related findings, including undetectable islet-related autoantibodies and a diabetes duration of less than 1 week before the start of insulin treatment were also met in these two cases. Therefore, both patients were diagnosed as having fulminant type 1 diabetes. Of course, we cannot rule out the possibility that the fulminant type 1 diabetes development in these two patients was unrelated to their ICI treatments. However, neither patient exhibited symptoms suggesting viral infection, a known trigger of fulminant type 1 diabetes, just prior to its onset. In addition, pharmacodynamics reportedly indicated a sustained high occupancy of PD-1 on circulating T cells of more than 2 months following nivolumab infusion. Thus, ICIIs were deemed to be the most likely cause of their fulminant type 1 diabetes development.

Most cases who developed ICI-associated irAEs were reported during the period of ICI treatment, while several irAEs, such as pneumonitis, hepatitis, colitis, and cutaneous toxicities, were reported to have developed despite ICI treatments having already been discontinued. Clinical ICI treatment guidelines recommend repeated laboratory tests, including the measurement of blood glucose levels, during the treatment period. In many guidelines, however, a concrete description is lacking of how long these laboratory tests should be continued after treatment cessation. The guidelines promulgated by the European Society for Medical Oncology note that another measurement 4–6 weeks after the last cycle of immunotherapy may be necessary. However, our two patients developed fulminant type 1 diabetes more than 6 weeks after receiving their last ICI.

### Table 1 | Laboratory results of case 1

| Biochemistry | TSH | FT4 | FT3 | Lipase | Amylase | Elastase 1 | Acetacetate | 3-Hydroxybutyric acid | Total ketone bodies | Complete blood count |
|--------------|-----|-----|-----|--------|---------|-----------|------------|---------------------|-------------------|---------------------|
| T-Bil (mg/dL) | 0.8 | 1.1 | 1.25 | 26 U/L | 57 U/L | 326 ng/dL | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| γ-GTP (U/L) | 33 | 125 | 26 U/L | 57 U/L | 326 ng/dL | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| AST (U/L) | 23 | 26 U/L | 57 U/L | 326 ng/dL | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| ALT (U/L) | 25 | 26 U/L | 57 U/L | 326 ng/dL | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| LDH (U/L) | 161 | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| BUN (mg/dL) | 26 | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| Cre (mg/dL) | 0.69 | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| UA (mg/dL) | 5.8 | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| TP (mg/dL) | 68.9 | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| Alb (g/dL) | 3.4 | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| Na (mmol/L) | 137 | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| K (mmol/L) | 3.6 | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| Cl (mmol/L) | 98 | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| Ca (mg/dL) | 9 | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| P (mg/dL) | 3.5 | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| CRP (mg/dL) | 0.89 | 1,144 mol/L | 1,894 mol/L | 3,038 mol/L | Complete blood count |
| Arterial blood gas analysis | 0.439 μU/mL | 11.9 g/dL | 119.9 g/dL | 160 × 10^3 {L} | Complete blood count |
| pH | 7.369 | 119.9 g/dL | 160 × 10^3 {L} | Complete blood count |
| PCO₂ | 39.8 mmHg | 119.9 g/dL | 160 × 10^3 {L} | Complete blood count |
| HCO₃⁻ | 22.4 mmol/L | 119.9 g/dL | 160 × 10^3 {L} | Complete blood count |
| Base Excess | −2.1 mmol/L | 119.9 g/dL | 160 × 10^3 {L} | Complete blood count |
| Diabetes-related data | HbA1c (7.1%) | 5.0 U/mL | 0.01 ng/mL | Complete blood count |
| GA | 29% | 5.0 U/mL | 0.01 ng/mL | Complete blood count |
| FPG | 227 mg/dL | 5.0 U/mL | 0.01 ng/mL | Complete blood count |
| Serum CPR | <0.1 ng/mL | 5.0 U/mL | 0.01 ng/mL | Complete blood count |
| Anti-GAD antibody | <5.0 U/mL | 5.0 U/mL | 0.01 ng/mL | Complete blood count |
| Anti-IA-2 antibody | <0.6 U/mL | 5.0 U/mL | 0.01 ng/mL | Complete blood count |
| HLA typing (day 11) | HLA-A31, A01 | Complete blood count | Complete blood count | Complete blood count |
| HLA-B54, B39 | Complete blood count | Complete blood count | Complete blood count | Complete blood count |
| HLA-DRB1*1302 | Complete blood count | Complete blood count | Complete blood count | Complete blood count |
| HLA-DQB1*0604 | Complete blood count | Complete blood count | Complete blood count | Complete blood count |
Table 2 | Laboratory results of case 2

| Biochemistry | Lipase | 29 U/L |
|--------------|--------|--------|
|              | Amylase| 124 U/L |
|              | Elastase 1 | 180 ng/dL |
|              | Acetoacetate | 729 μmol/L |
|              | 3-Hydroxybutyric acid | 2,688 μmol/L |
|              | Total ketone bodies | 3,417 μmol/L |
| Complete blood count | WBC | 6,100/μL |
| | Hb | 11.4 g/dL |
| | Plt | 167 x 10^3/μL |

Arterial blood gas analysis

| pH | 7.406 |
| PCO2 | 38.3 mmHg |
| HCO3^- | 23.5 mmol/L |
| Base excess | -0.4 mmol/L |

Diabetes-related data

| HbA1c | 7.4% |
| GA | 29% |
| FPG | 223 mg/dL |
| Serum CPR | <0.01 ng/mL |
| Anti-GAD antibody | <5.0 U/mL |
| Anti-IA-2 antibody | <0.6 U/mL |
| Urinary CPR (day 8) | 0.61 μg/day |

Glucagon loading test (day 13)

| CPR 0 min | <0.01 ng/mL |
| CPR 6 min | <0.01 ng/mL |

HLA typing (day 12)

| HLA-A24*02, 31:01 |
| HLA-B35*01, 44:03 |
| HLA-DRB1*09:01, 13:02 |
| HLA-DQB1*03:03, 06:04 |

Informed consent: We informed the patient or patient’s family of the case report, and they gave their consent.

Approval date of registry and the registration No. of the study/trial: October 19, 2021, No. 23579.

Animal studies: N/A.

Approval of the research protocol: N/A.

DISCLOSURE

The authors declare no conflict of interest.

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