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Two types of fulminant type 1 diabetes mellitus: Immune checkpoint inhibitor-related and conventional

Fulminant type 1 diabetes is characterized by a markedly rapid onset of hyperglycemia[1]. According to the "criteria for the definite diagnosis of fulminant type 1 diabetes mellitus (2012)"[2], fulminant type 1 diabetes mellitus is confirmed when all the following three findings are present: (i) occurrence of diabetic ketosis or ketoacidosis soon after (within approximately 7 days) the onset of hyperglycemic symptoms (elevation of urinary and/or serum ketone bodies at the first visit); (ii) plasma glucose level ≥16.0 mmol/L (≥288 mg/dL) and glycated hemoglobin (HbA1c) level <8.7% (National Glycohemoglobin Standardization Program value; this value is not applicable for patients with previously diagnosed glucose intolerance) at the first visit; and (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. A rapid course in the medical history is being indicated by (i) and (ii); that is, (hyper) glycemia and almost normal HbA1c levels show a rapid rise in blood glucose concentration in the laboratory findings. This means that (i) and (ii) are synonymous with each other. The rapid rise in blood glucose concentration is indirectly proven by the relatively low (near normal) level of HbA1c at the onset, and in a few patients, the blood glucose levels before the onset were measured, and the rapid rise in blood glucose concentration was directly proven[3]. Of course, (iii) indicates complete destruction of β-cells.

Recently, antibodies to immune checkpoint inhibitors (ICIs) have been widely used as cancer immunotherapy, and many patients who were diagnosed with fulminant type 1 diabetes have been reported during the treatment[4]. Four patients have also been reported in this journal. The first patient is the first reported patient with fulminant type 1 diabetes in Asia that developed during ICI therapy[5]. The second patient developed fulminant type 1 diabetes during ICI treatment, but his endogenous insulin secretory capacity slightly improved with the discontinuation of ICI[6]. The third patient developed fulminant type 1 diabetes during the administration of ICI of programmed cell death 1 ligand 1 antibody, but not programmed cell death 1 (PD-1) antibody[7]. The fourth patient showed a particularly rapid decrease in insulin secretory capacity during the development of fulminant type 1 diabetes[8]. In this article, we discuss the similarities and differences between fulminant type 1 diabetes after administration of ICIs and conventional fulminant type 1 diabetes.

First, regarding the rate of β-cell destruction, it might progress more rapidly in conventional fulminant type 1 diabetes than in ICI-related fulminant type 1 diabetes. One rationale is that the rapid decline of C-peptide levels was more frequently observed in conventional fulminant type 1 diabetes than in ICI-related fulminant type 1 diabetes, when C-peptide levels were directly and continuously measured. Sekine *et al.*[3] analyzed presymptomatic preserved serum with conventional fulminant type 1 diabetes patients, and reported that C-peptide concentrations decreased from the normal value to below the measurement sensitivity in just 1 day in a patient. We have previously reported that a patient suffered from fulminant type 1 diabetes 6 days after hypoglycemia with endogenous hyperinsulinemia, which might be due to the destruction of β-cells[9]. As the onset is almost unpredictable with conventional fulminant type 1 diabetes, there are few reports in which the course of C-peptide levels can be followed, including before the onset. In contrast, in ICI-related fulminant type 1 diabetes, there have been multiple reports in which blood C-peptide levels decreased from the normal value to below the measurement sensitivity in approximately 2 weeks[4,5], even though a patient whose insulin secretion decreased in just 1 day was also reported[8]. Another rationale is that, in a larger number of patients, HbA1c levels at the onset of diabetes were higher in ICI-related type 1 diabetes patients than in conventional fulminant type 1 diabetes patients[4]. The former was 8.1%[4], and the latter was 6.8%[2] on average. It is speculated that low (near normal) HbA1c levels correlate with a high rate of blood glucose elevation and also with a high rate of β-cell destruction at the onset of type 1 diabetes. In the aforementioned patient[3], the HbA1c level at onset was 5.9%, indicating that β-cell destruction progressed particularly rapidly. As there are some differences in HbA1c values at the onset of both conventional fulminant type 1 diabetes and ICI-related fulminant type 1 diabetes, the rate of β-cell destruction might vary within each subtype. It is also noted that a proportion of patients with ICI-related diabetes fulfill the criteria for acute-onset type 1 diabetes. Figure 1 illustrates type 1

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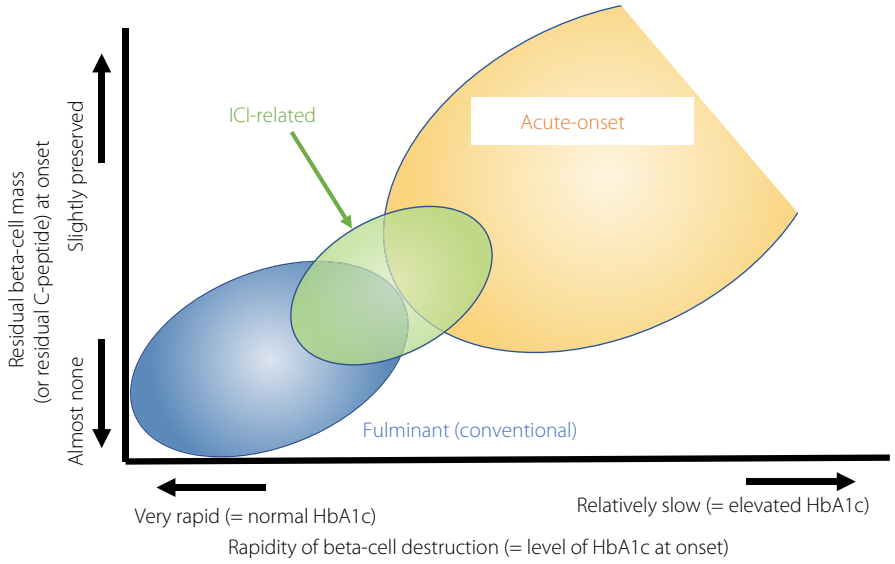

Figure 1 | Schematic figure of type 1 diabetes in relation to the rapidness of progression and residual β-cell mass at onset. β-Cells are destroyed very rapidly and are almost absent at onset in conventional fulminant type 1 diabetes, but are destroyed and remain relatively slowly in acute-onset type 1 diabetes. The immune checkpoint inhibitors (ICI)-related fulminant type 1 diabetes is placed between the two established subtypes from both aspects. HbA1c, glycated hemoglobin.

diabetes in relation to the rapidness of progression and residual β-cell mass at onset.

Next, the mechanism of β-cell destruction might be common, at least in part, in both conventional fulminant type 1 diabetes and ICI-related fulminant type 1 diabetes patients. Pathologically, mononuclear cell infiltration is observed both in the islets and exocrine areas, suggesting that cell-mediated immunity is mainly involved[10]. As for the trigger, viral infection has been primarily considered in conventional fulminant type 1 diabetes patients (Table 1). Preceding common cold-like symptoms is frequently observed in conventional fulminant type 1 diabetes[1]. β-Cell damage infected with encephalomyocarditis virus is a model in mice, and enterovirus and cytomegalovirus are candidates in humans[1]. However, the molecular mechanism of β-cell destruction has just begun to be elucidated. In contrast, in ICI-related fulminant type 1 diabetes, blocking of the PD-1/programmed cell death 1 ligand 1 pathway is the definite trigger (Table 1). As fulminant type 1 diabetes develops in programmed cell death 1 ligand 1 antibody administration, as well as in PD-1 antibody[8], it seems important to block this pathway, but not each molecule. Interestingly, β-cell damage ensues after the initial dose of ICI, but often after repeated doses of ICI in ICI-related fulminant type 1 diabetes[4-8]. This suggests that β-cell destruction could be triggered only when an additional element overlaps with ICI administration. The next question was whether immune checkpoint molecules would be involved in the destruction of β-cells in conventional fulminant type 1 diabetes. We have had no clear evidence of this issue, but it is reasonable to expect that these molecules are involved in T-cell activation, even in conventional fulminant type 1 diabetes.

We discussed ICI-related fulminant type 1 diabetes and conventional fulminant type 1 diabetes by focusing on the reports of four patients published in this journal. In the future, the mechanism of β-cell destruction in ICI-related fulminant type 1 diabetes and conventional fulminant type 1 diabetes should be clarified as a distinct subtype. This would lead to the progress of treatment in both subtypes of fulminant type 1 diabetes.

Table 1 | Two subtypes of fulminant type 1 diabetes

	ICI-related FT1D	Conventional FT1D
Rate of β-cell loss	Approximately 2 weeks	More rapid
Trigger of β-cell destruction	Administration of ICI	Viral infection

FT1D, fulminant type 1 diabetes; ICI, immune checkpoint inhibitors.

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