Fulminant type 1 diabetes: recent research progress and future prospects

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Received: 19 August 2020 / Accepted: 9 September 2020 / Published online: 16 September 2020
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Abstract

To clarify the clinical and etiological characteristics of fulminant type 1 diabetes, we reviewed data from patients who had developed type 1 diabetes following anti-programmed cell death 1/programmed cell death ligand 1 (anti-PD-1/PD-L1) therapy, and research on pancreatic beta cells derived from induced pluripotent stem (iPS) cells from patients with fulminant type 1 diabetes. As determined from the disease classifications and clinical and genetic characteristics, anti-PD-1/PD-L1 therapy-related type 1 diabetes includes both fulminant type 1 diabetes and acute-onset type 1 diabetes. Using insulin-positive cells derived from iPS cells, beta-cell fragility to inflammatory cytokines, but not its regeneration failure, was observed in fulminant type 1 diabetes. Moreover, severe hyperglycemia was reported as a risk factor of sudden death or cardiac arrest at disease onset, diffusion-weighted magnetic resonance imaging was suggested as an additional tool for making a diagnosis, and the *CSAD/Inc-ITGB7-1* locus was genetically associated with fulminant type 1 diabetes. To fully understand fulminant type 1 diabetes, it is important to clarify the molecular mechanisms step by step through multifaceted approaches such as through analyses of the genetic factors, clinical features, histological findings, and cell biology. The careful and detailed study of patients is a great means for clarifying the etiology and pathophysiology of the disease.

Keywords Fulminant type 1 diabetes · Immune checkpoint molecules · PD-1 · Induced pluripotent stem cells

Introduction

Typical type 1 diabetes can be further subtyped as fulminant type 1 diabetes on the basis of serological (very low serum C-peptide concentration) and histological (almost no beta cells in the pancreas) findings [1–5]. Hyperglycemia progresses rapidly in parallel with the loss of insulin secretion following the onset of fulminant type 1 diabetes. The former is proven by the findings of hyperglycemia (800 mg/dL on average) with a near-normal HbA1c value (< 7.0% on average). Furthermore, islet-related autoantibodies are usually not detected in patients with fulminant type 1 diabetes, and a specific class II HLA haplotype is instead closely associated with the disease. Reports of patients with fulminant type 1 diabetes are common in East Asia, whereas there are only a few reported cases from other Asian countries and almost none from other areas of the world.

To clarify the mechanism of beta-cell destruction in fulminant type 1 diabetes, we have been taking a multifaceted approach to the study of this disease. In particular, we have been investigating the genetic factors (including HLA) [6–8], viral infections of the pancreas [9, 10], antiviral immune mechanisms [11], immune regulatory factors [12–14], and beta-cell regeneration failure [15]. Herein, we summarize the results of recent studies on patients who developed fulminant type 1 diabetes.

Immune checkpoint molecules

Because the immune reaction is accelerated in patients with fulminant type 1 diabetes, leading to rapid beta-cell loss, we hypothesized that immune checkpoint molecules might contribute to this event. That is, the reduced function of immune checkpoint molecules might accelerate the immune reaction against beta cells. Immune checkpoint molecules negatively control the immune reaction of T cells, where the suppression of T-cell activation occurs mainly via the anti-programmed cell death 1/programmed cell death ligand 1

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(PD-1/PD-L1) or cytotoxic T lymphocyte antigen 4 (CTLA-4)–B7 pathways [16]. We previously reported a significant reduction in CTLA-4 expression levels in CD4⁺ T cells from patients with long-standing fulminant type 1 diabetes compared those of patients with autoimmune type 1 diabetes or type 2 diabetes and healthy controls [12].

The PD-1–PD-L1 pathway plays an important role in tumor immunity [16, 17]. Various tumor cells express PD-L1 on their surface and thereby escape the immune response by inactivating T-cell functions. Thus, anti-PD-1/PD-L1 antibodies are now widely used as anti-cancer drugs in clinical settings. Because the PD-1 pathway also suppresses any excessive immune response to regulate immune diseases, the treatment of patients with anti-PD-1 antibodies might cause immune-related adverse events, including type 1 diabetes. According to reports from pharmaceutical companies, the incidence of type 1 diabetes (including acute-onset type 1 diabetes and fulminant type 1 diabetes) caused by nivolumab and pembrolizumab was 0.33% and 0.14%, respectively [14]. Furthermore, the development of rare fulminant type 1 diabetes following anti-PD-1 antibody administration in Caucasian patients has been reported [18]. In our immunohistochemical analysis of pancreatic tissue samples from patients with PD-1-related diabetes, we found a few residual beta cells and a predominance of CD8⁺ T lymphocyte infiltration in the islets, suggesting that beta-cell destruction in PD-1-related diabetes might be caused by T-cell activation [19]. As T-cell infiltration is observed in the pancreas of patients with fulminant type 1 diabetes, development of the disease may be controlled by immune checkpoint molecules.

Because the clinical features of type 1 diabetes related to anti-PD-1/PD-L1 antibodies are not clear, the Japan Diabetes Society (JDS) conducted an epidemiological survey of type 1 diabetes related to such antibody therapy. This study is ongoing; data on patients with type 1 diabetes related to anti-PD-1/PD-L1 therapy are being collected through the JDS homepage and from a literature search, and results from the first 22 patients were recently published [14].

The mean period from the date of the first anti-PD-1 antibody injection to the development of type 1 diabetes was 155 days (range 13–504 days) [14]. Among these 22 patients, 11 met the criteria for acute-onset type 1 diabetes and 11 met the criteria for fulminant type 1 diabetes. The average glucose level was 617 mg/dL, the average HbA1c was 8.1% at diagnosis, and the median serum and urinary C-peptide levels were 0.46 ng/mL and 4.1 µg/day, respectively. The clinical course of decreasing endogenous insulin secretion became evident in some of the patients who were developing type 1 diabetes (Fig. 1) [14]. Diabetic ketosis and diabetic ketoacidosis were frequently presented (85% and 39%, respectively). Among islet autoantibodies, the anti-glutamic acid decarboxylase antibody was positive only in one patient.

The HLA phenotype was determined in several case reports whereupon HLA-DR9 (an allele conferring susceptibility to type 1 diabetes) was frequently observed in the patients with type 1 diabetes related to anti-PD-1/PD-L1 therapy (Table 1) [20–37].

On the basis of the disease classifications and the clinical and genetic characteristics, we concluded that anti-PD-1/PD-L1 therapy-related type 1 diabetes includes both the fulminant type 1 diabetes and acute-onset type 1 diabetes subtypes. Moreover, our findings suggest that immune checkpoint molecules may contribute, at least in part, to the development of fulminant type 1 diabetes.

Beta-cell regeneration failure

Research has shown that beta cells are dynamic rather than static and have an unexpectedly high turnover rate. In fulminant type 1 diabetes, the losses of both the beta cells and insulin secretion are almost complete and do not recover over the clinical course. Therefore, we hypothesized that beta-cell regeneration failure may contribute to disease development [15].

Insulin-positive beta cells derived from the induced pluripotent stem (iPS) cells of patients with the disease were used to characterize the beta cells in fulminant type 1 diabetes, because the patients' original beta cells had been destroyed at disease onset. Initially, episomal vectors were used to generate iPS cells from the fibroblasts obtained from three patients with fulminant type 1 diabetes. Subsequently, a three-step differentiation method was used to generate insulin-positive beta cells from the iPS cells through SRY-box transcription factor 17 (SOX17)-positive endoderm cells and pancreatic and duodenal homeobox 1 (PDX-1)-positive pancreatic progenitor cells. In these insulin-positive beta cells, C-peptide secretion was significantly increased by the presence of KCl rather than high glucose in the medium [15]. This finding suggests that these insulin-positive beta cells could produce insulin molecules, but did not possess glucose responsiveness.

The induction ratio of the prepared insulin-positive beta cells was approximately 4% on average, and did not differ significantly between the patient- and control-derived iPS cells [15]. This suggests that our hypothesis of beta-cell regeneration failure was not evident in fulminant type 1 diabetes.

Further analyses focused on the role of fragility to viral infections in the development of fulminant type 1 diabetes. To this end, the insulin-positive beta cells were treated with the inflammatory cytokines tumor necrosis factor- α , interleukin-1 β , and interferon- γ to examine their likelihood of undergoing apoptosis, which was evaluated by the caspase-3 positivity rate. The likelihood of apoptosis was

Serum C-peptide level (ng/ml)

Fig. 1 Changes in patients' serum C-peptide levels. The vertical axis shows serum C-peptide levels, and the horizontal axis shows the number of days after patients were diagnosed with anti-PD-1 antibody-related type 1 diabetes. The patient noted by the asterisk

received steroid injections as a part of chemotherapy at 21–23 days after the development of type 1 diabetes. Adapted from ref. [14], Fig. 2.

Table 1 HLA DR alleles in patients with type 1 diabetes related to anti-PD-1/PD-L1 antibodies in Japan

Patient No.	Age	Sex	Cancer type	Anti-PD-1	HLA	References
1	66	F	Melanoma	Nivolumab	DR5/DR6	[21]
2	55	F	Melanoma	Nivolumab	DR4/–	[22]
3	31	M	NSCLC	Nivolumab	DR4/–	[23]
4	62	F	NSCLC	Nivolumab	DR9/–	[23]
5	50 s	M	NSCLC	Nivolumab	DR9/–	[24]
6	73	M	NSCLC	Nivolumab	DR1/DR9	[25]
7	68	F	RCC	Nivolumab	DR9/–	[26]
8	80	F	Melanoma	Nivolumab + ipilimumab	DR4/–	[27]
9	68	M	NSCLC	Nivolumab	DR2/DR9	[28]
10	63	F	Melanoma	Nivolumab	DR9/	[29]
11	82	M	NSCLC	Pembrolizumab	DR5/	[30]
12	77	M	RCC	Nivolumab	DR5/DR9	[31]
13	79	M	NSCLC	Nivolumab	DR9/	[32]
14	48	M	Parotid gland adenoma	Nivolumab	DR4/	[33]
15	72	M	NSCLC	Pembrolizumab	DR9/	[34]
16	72	M	NSCLC	Pembrolizumab	DR4/DR8	[35]
17	52	F	Breast cancer	Nivolumab	DR14/DR14	[36]
18	68	F	Melanoma	Nivolumab	DR9/	[37]

NSCLC non-small cell lung cancer, RCC renal cellular carcinoma

found to be significantly higher in the cells derived from the patients than in those derived from healthy individuals, suggesting the vulnerability of beta cells to the tested inflammatory cytokines in patients with fulminant type 1 diabetes [15].

Although this iPS cell model did not prove our original hypothesis of beta-cell regeneration failure, it should be useful for further studies on the pathophysiology of fulminant type 1 diabetes and for the establishment of therapeutic strategies against the disease.

Other recent progress

In addition to the studies mentioned above, three recent papers of fulminant type 1 diabetes by the Japan Diabetes Society Committee on (Fulminant) Type 1 Diabetes Mellitus Research offer some new prospects and insight into the disease.

At the time of onset, fulminant type 1 diabetes mellitus can be accompanied by sudden death or cardiac arrest, representing the most severe subtype across the clinical spectrum. Comparison of patients with fulminant type 1 diabetes mellitus who experienced sudden death or cardiac arrest ($n = 17$) with patients who did not ($n = 257$), revealed that the former group had more severe hyperglycemia and acidosis. The patients with a plasma glucose level higher than 1000 mg/dL were at greater risk of cardiac arrest [38].

Another study tested the ability to diagnose fulminant type 1 diabetes based on image findings. Diffusion-weighted magnetic resonance imaging (DWI) was used to measure apparent diffusion coefficient (ADC) values of the pancreas. The results indicated that the ADC values of all parts of the pancreas were significantly lower in fulminant type 1 diabetes than those of controls. The best cut-off value indicated good sensitivity (86%) and specificity (71%), suggesting that DWI may be a useful additional tool for making a diagnosis of fulminant type 1 diabetes [39].

Most recently, the results of the first genome-wide association study of fulminant type 1 diabetes in Japanese individuals were published [8]. Associations above a genome-wide significance level were observed in the class II HLA (DR) region and CSAD/Inc-ITGB7-1 on chromosome 12q13.13. The latter region was associated with susceptibility to fulminant, but not autoimmune type 1 (type 1A) diabetes. These findings suggest that fulminant type 1 diabetes is a distinct subtype of type 1 diabetes.

Indeed, the new World Health Organization classification of diabetes describes fulminant type 1 diabetes as an independent subtype within type 1 diabetes [40]. This clinical entity has been widely observed in East Asia, whereas there have only been a few reported cases in other Asian countries and other areas of the world. According

to the recent wide use of immune checkpoint inhibitors as anti-cancer drugs, this subtype has become increasingly reported worldwide [18, 41–43].

Future prospects

To fully understand fulminant type 1 diabetes, it is important to clarify the molecular mechanisms step by step through multifaceted approaches such as through the analyses of genetic factors, clinical features, histological findings, and cell biology. For physician scientists, the careful and detailed study of patients is a great means for clarifying the etiology and pathophysiology of the disease. For example, patients with anti-PD-1 antibody-related type 1 diabetes have offered a new picture of the disease etiology. Clinically, a course of decreasing endogenous insulin secretion is sometimes visualized, as shown in Fig. 1. In a similar context, it is important to learn more using new research tools effectively, such as iPS cell technology. We hope that the accumulation of such efforts will eventually lead to the development of a cure for fulminant type 1 diabetes.

Acknowledgements We would like to express our sincere thanks to the doctors, Hanafusa T (Sakai City Medical Center), Terasaki J, Murase-Mishiba Y, Matsumoto H, Sano H, Haseda F, Tsutsumi C, Shibasaki S, Fujisawa R (Dept. of Internal Medicine (I), Osaka Medical College), Shimomura I, Iwahashi H, Okita K, Kozawa J, Fukui K, Uno S, Sayama K, Nakata S, Tokunaga A, Yoshikawa A, Yoneda S, Hosokawa Y, Baden MY, Ishibashi C. (Dept. of Metabolic Medicine, Osaka Univ, Graduate School of Medicine), Osafune K, Toyoda T (Center for iPS Cell Research and Application (CiRA), and Kyoto University), for the collaboration. We would also like to thank the members of the Committee on Type 1 Diabetes, the Japan Diabetes Society, including Abiru N (Nagasaki University), Awata T (Saitama Prefectural University), Ikegami H, Kawabata Y (Kindai, University), Oikawa Y, Shimada A (Saitama Medical University), Osawa H (Ehime University), Kajio H (National Center for Global Health and Medicine), Kawasaki E (Shin-Koga Hospital), Takahashi K (Iwate Prefectural University), Chujo D (University of Toyama), Fukui T (Showa University), Miura J (Tokyo Women's Medical University), Yasuda K (Kyorin University), Yasuda H (Kobe University), and Kobayashi T (Okinaka Memorial Institute for Medical Research), and the diabetes specialists affiliated with the Japan Diabetes Society for answering the questionnaire. We also thank Editage for editing a draft of this manuscript. This work was supported in part by JSPS KAKENHI Grant Number 18K08529 received by AI.

Compliance with ethical standards

Conflict of interest In connection with this manuscript, we disclose COI with the following companies/organizations: honoraria for lectures: Eli Lilly Japan K.K., Ono Pharmaceutical Co. Ltd., and Astellas Pharma Inc.; research funding: Astellas Pharma Inc., Astra-Zeneca K. K., Bristol-Myers Squibb Company, Chugai Pharmaceutical Co. Ltd., Soiken Holdings Inc., and Taiho Pharmaceutical Co. Ltd.; scholarship donations: Takeda Pharmaceutical Company Limited, Astellas Pharma Inc., Kyowa Hakko Kirin Co. Ltd., and Ono Pharmaceutical Co. Ltd.

Ethical approval All data reviewed in this article have already been published.

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