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CASE REPORT

Anti-GAD antibody-positive fulminant type 1 diabetes developed following SARS-CoV-2 vaccination

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Abstract

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been used worldwide since the 2020 coronavirus pandemic. However, several negative side-effects of these vaccines have been reported. Herein, we present a case of a patient with fulminant type 1 diabetes that developed shortly after administration of the SARS-CoV-2 vaccine. A 47-year-old man with no medical history presented with hyperglycemia-related symptoms shortly after receiving the third messenger ribonucleic acid SARS-CoV-2 vaccine. Based on hyperglycemia, diabetic ketoacidosis at onset, relatively low hemoglobin A1c levels, and complete depletion of endogenous insulin secretion, the patient was diagnosed with fulminant type 1 diabetes and insulin therapy was initiated. Through human leukocyte antigen genotyping, the disease-susceptible alleles for type 1 diabetes, DRB1*04:05 and DQB1*04:01, were identified. The patient tested positive for serum anti-glutamic acid decarboxylase antibodies, which are normally negative for fulminant type 1 diabetes, implying that immunomodulation triggered by SARS-CoV-2 vaccination influenced the onset of type 1 diabetes.

Keywords SARS-CoV-2 · Vaccine · Fulminant type 1 diabetes · Diabetic ketoacidosis

Introduction

Since the outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), various types of vaccines, including messenger ribonucleic acid (mRNA), adenoviral vectors, and inactivated vaccines against SARS-CoV-2 have been used globally. While transient side effects such as fever, general fatigue, and local pain at the injection site are common following SARS-CoV-2 vaccinations, immune-mediated adverse events that include myocarditis [1], neurological diseases [2], hematological disorders [3], autoimmune thyroid diseases [4], and type 1 diabetes (T1D) have also been reported [5–12].

Fulminant type 1 diabetes (FT1D) is a subtype of T1D, characterized by rapid total or near-total loss of pancreatic beta cells, resulting in hyperglycemia-related symptoms with relatively low hemoglobin A1c levels [13]. Abnormal immune responses are fundamental to the pathogenesis of FT1D, and the involvement of specific viral infections to play a role in this pathogenesis has been proposed [14]. Furthermore, it is becoming clear that conditions that cause immunological changes, such as the use of immune checkpoint inhibitors (ICIs) for cancer treatment, may contribute to the development of FT1D [15].

Herein, we present a case of FT1D that developed immediately after receiving the third mRNA SARS-CoV-2 vaccine. Although the patient exhibited several key features of FT1D, he was positive for anti-glutamic acid decarboxylase antibodies (GADAbs), which are typically negative in FT1D patients [16], indicating that SARS-CoV-2 vaccination affected the onset of T1D.

Case report

A 47-year-old Japanese man with no significant medical history, including no history of diabetes, received his first and second doses of BNT162b2 (Pfizer/BioNTech), an mRNA SARS-CoV-2 vaccine, 9 and 8 months before presenting to the emergency room, respectively, and showed no symptoms. However, he developed high fever, severe thirst, lower

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abdominal pain, and diarrhea several hours after receiving his third BNT162b2 dose. These symptoms persisted, and the patient visited the emergency department 3 days later. His height, weight, and body mass index were 172.0 cm, 72.0 kg, and 24.3 kg/m^2, respectively. The patient did not have a family history of diabetes or autoimmune diseases, and no abnormalities in glucose tolerance were noted during his medical check-up a year prior (postprandial plasma glucose, 105 mg/dL; hemoglobin A1c, 5.4%). Laboratory tests performed in the emergency room revealed elevated plasma glucose levels (661 mg/dL), nearly normal hemoglobin A1c levels (5.8%), and acidemia (pH 7.149) with increased urinary ketone bodies. After an intravenous saline infusion, the patient was transferred and admitted to our hospital with suspected diabetic ketoacidosis.

On admission, high plasma glucose levels and acidemia persisted, computed tomography revealed no evidence of pancreatitis, and the serum amylase levels were within the normal limits (Table 1). The SARS-CoV-2 polymerase chain reaction test results were negative. A continuous intravenous insulin infusion was initiated. On the third day of hospitalization, we switched to subcutaneous basal-bolus insulin therapy with insulin lispro and degludec. His insulin secretion capacity was exhausted; his fasting serum C-peptide immunoreactivity (CPR) was below the detectable range and 24-h urinary C-peptide excretion was 0.5 µg/day according to additional tests performed after admission (Table 1). Based on these findings, we diagnosed him with FT1D. The patient tested positive for GADAbs, but negative for anti-insulinoma-associated antigen 2, anti-thyroglobulin, and anti-thyroid peroxidase antibodies (Table 1). There was no evidence of recent viral infections, such as with coxsackievirus, enterovirus, cytomegalovirus, Epstein-Barr virus, or human herpesvirus 6, which have been shown to cause T1D [17]. Through human leukocyte antigen (HLA) genotyping, the disease-susceptible alleles for T1D, DRB1*04:05 and DQB1*04:01, were identified (Table 1). The patient was discharged 17 days after admission with adequate blood glucose levels controlled by basal-bolus insulin therapy.

Discussion

We have presented a case of FT1D that developed immediately after mRNA SARS-CoV-2 vaccination. The most characteristic feature of FT1D is the rapid destruction of pancreatic beta cells, which leads to ketosis or ketoacidosis within several days of the onset of hyperglycemia-related symptoms with relatively low hemoglobin A1c levels [13]. Although certain cases of FT1D are known to be caused by viral infections or the use of ICIs for cancer treatment [15], the current patient had no obvious signs of viral infection or ICI administration prior to the development of ketoacidosis. Therefore, the SARS-CoV-2 vaccination might have triggered an abnormal immune response, resulting in the development of FT1D in this case.

Various types of immune-related adverse events have been reported since the start of global SARS-CoV-2 vaccination. Recently, several cases of T1D have been reported following SARS-CoV-2 vaccinations [5–12]. Similar to the

Table 1 Laboratory data

Arterial blood gas (room air)			**Immunological tests**		
pH	7.149		Anti-GAD antibody	18.7	U/mL
pCO_2	25.0	mmHg	Anti-IA-2 antibody	< 0.6	U/mL
pO_2	87.3	mmHg	Anti-Tg antibody	11.0	IU/mL
HCO_3^-	8.5	mmol/L	Anti-TPO antibody	< 9.0	IU/mL
Biochemistry			**HLA genotyping**		
Plasma glucose	658	mg/dL	DRB1*04:05:01/13:02:01		
Hemoglobin A1c	5.8	%	DQB1*04:04:01/06:04:01		
Serum C-peptide	< 0.1	ng/mL			
Urine C-peptide	0.5	µg/day			
BUN	42	mg/dL			
Creatinine	1.45	mg/dL			
Amylase	56	IU/L			
Na	130	mmol/L			
K	7.0	mmol/L			
Cl	94	mmol/L			
Free T4	1.17	ng/dL			
TSH	1.50	µIU/mL			

BUN blood urea nitrogen, *TSH* thyroid-stimulating hormone, *GAD* glutamic acid decarboxylase, *IA-2* insulinoma-associated protein-2, *Tg* thyroglobulin, *TPO* thyroid peroxidase, *HLA* human leukocyte antigen

current case, some of these cases presented with clinical features of FT1D [7, 8, 10], the characteristics of which are summarized in Table 2. The involvement of mRNA-based [7, 10] or inactivated [8] SARS-CoV-2 vaccines has been implicated. While one patient had received ICI treatment prior to the SARS-CoV-2 vaccination [10], there were no other obvious potential causative factors besides the vaccines in the other cases. From the viewpoint of genetic factors, the most prominent genomic region that contributes to a higher susceptibility to T1D is the Class II HLA [18]. T1D is associated with haplotypes DRB1*04:05-DQB1*04:01 and DRB1*09:01-DQB1*03:03 in Japanese and East Asian populations [19]. Intriguingly, except for one case of receiving ICI treatment before FT1D onset, all cases, including the current patient, exhibited one of these class II HLA haplotypes [7, 8], indicating that SARS-CoV-2 vaccinations increase the risk of developing FT1D in a genetically predisposed population.

Several possible mechanisms by which SARS-CoV-2 vaccines induce autoimmune diseases have been postulated. These mechanisms include molecular mimicries between SARS-CoV-2 proteins and human tissue antigens and dysregulation of the immune system following exposure to adjuvants contained in the vaccines [4]. Antibodies against SARS-CoV-2 proteins (e.g., spike proteins, nucleoproteins, and membrane proteins) cross-react with human GAD65 and thyroid peroxidase [20], which may induce autoimmune responses in pancreatic beta cells and thyroid tissues, leading to T1D and autoimmune thyroid diseases, respectively. Regarding the latter mechanism, it has been suggested that several excipients in SARS-CoV-2 vaccines, such as the aluminum hydroxide contained in inactivated vaccines and polyethylene glycol lipid conjugates in mRNA vaccines, act as adjuvants and trigger autoimmune responses [21]. Interestingly, there is a case report of FT1D development following influenza vaccine administration, which may support the latter mechanism [22]. However, the precise mechanism has not been fully elucidated, and further investigations are warranted.

The most notable aspects of the present case are the presence of GADAbs, which is usually negative in FT1D patients, and the extremely rapid onset of the disease within one day of SARS-CoV-2 vaccination. According to a Japan Diabetes Society committee survey, the positivity of GADAb in cases that meet the diagnostic criteria for FT1D is as low as 4.8% [16], which is remarkably low compared to other subtypes of T1D, such as acute-onset T1D (89% positivity in the same study). Indeed, except in our case, GADAbs were not detected in all cases reported to develop FT1D following SARS-CoV-2 vaccination (Table 2). Differences in GADAb positivity between T1D subtypes have generally been thought to highlight differences in the clinical course and underlying mechanisms involved in disease development [23]. It should be noted that in patients with acute-onset

Table 2 Characteristics of cases of fulminant type 1 diabetes that developed following SARS-CoV-2 vaccination

No. (Ref.)	1 [10]	2 [8]	3 [7]	4
Authors	Sato et al	Tang et al	Sasaki et al	Present case
Age	45	50	45	47
Gender	Male	Male	Female	Male
Type of SARS-CoV-2 vaccine	mRNA	Inactivated virus	mRNA	mRNA
Dose	2nd	1st	1st	3rd
Time to onset	2 days	5 days	8 days	Within 1 day
Preceding infectious disease symptoms	None	None	None	None
Plasma glucose	655 mg/dL	ND	344 mg/dL	658 mg/dL
Hemoglobin A1c	8.0%	Near normal	7.6%	5.8%
Serum C-peptide	0.13 ng/mL	0.10 ng/mL	0.33 ng/mL	< 0.1 ng/mL
Autoantibodies	GAD Ab (−)	GAD Ab (−)	GAD Ab (−)	GAD Ab (+)
	IA-2 Ab (−)	IA-2 Ab (−)	IA-2 Ab (−)	IA-2 Ab (−)
	ZnT8 Ab (−)	ZnT8 Ab (−)	ZnT8 Ab (−)	TgAb (−)
			TgAb (−)	TPOAb (−)
			TPOAb (−)	
HLA genotype	DRB1*11:01/13:02	DRB1*09:01/09:01	DRB1*04:05/13:02	DRB1*04:05/13:02
	DQB1*03:01/06:04	DQB1*02:03/03:03	DQB1*04:01/06:04	DQB1*04:01/06:04
Other factors	Use of nivolumab	None	None	None

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, *mRNA* messenger ribonucleic acid, *Ab* antibody, *GAD* glutamic acid decarboxylase, *IA-2* insulinoma-associated protein-2, *ZnT8* zinc transporter 8, *Tg* thyroglobulin, *TPO* thyroid peroxidase, *HLA* human leukocyte antigen, *ND* not described

T1D, GADAbs have been shown to become positive months to years before the onset of overt hyperglycemia [24], indicating that the presence of GADAbs reflects a persistent autoimmune process leading to beta cell damage for a certain period of time. Therefore, it is unlikely that the rapidly emerging GADAbs directly affected the onset of FT1D. In the context of ICI-related T1D, a case report has confirmed the seroconversion of GADAbs following combination therapy with nivolumab and ipilimumab, leading to the development of newly-developed FTID [25]. However, in that case, it took approximately 4 months to develop FT1D from the initial ICIs administration. In contrast, another case of GADAb-positive insulin-dependent diabetes (IDDM) with complete loss of insulin secretion that developed as rapidly as in one week after the initial nivolumab administration has been reported [26]. Although it is unknown whether GADAbs were present before ICI treatment in that case, there is a possibility that the patient had already been under the course of slowly progressive T1D or latent autoimmune diabetes in adults, prior to the initiation of ICI administration, since the patient had been receiving medications for type 2 diabetes before developing IDDM [26]. In that case, it is possible that ICI-triggered aberrant autoimmune responses accelerated beta cell destruction, resulting in IDDM development immediately after ICI treatment. Considering these findings, although it remains unclear whether GADAbs were present prior to SARS-CoV-2 vaccination in our case due to the lack of pretreatment evaluation, it can be speculated that autoimmune processes leading to beta cell destruction had been ongoing before the vaccination, and the immune alteration caused by SARS-CoV-2 vaccination accelerated the destruction of pancreatic beta cells.

In conclusion, we described a case of FT1D that developed immediately after mRNA SARS-CoV-2 vaccination. Further similar cases would help to elucidate the relationship between T1D and vaccines, resulting in a better understanding of the pathological mechanisms of T1D.

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Data availability There are no associated data available.

Declarations

Conflict of interest All the authors declare that they have no conflicts of interest.

Ethical approval This study was conducted in accordance with the 1964 Declaration of Helsinki and its later versions. This article does not contain any studies with animal subjects by any of the authors. The patient's identity is protected. Informed consent was obtained from the patient included in the study.

References

1. Lee ASY, Balakrishnan IDD, Khoo CY, Ng CT, Loh JKX, Chan LL, et al. Myocarditis following COVID-19 vaccination: a systematic review (October 2020–October 2021). Heart Lung Circ. 2022;31:757–65. https://doi.org/10.1016/j.hlc.2022.02.002.
2. Kaulen LD, Doubrovinskaia S, Mooshage C, Jordan B, Purrucker J, Haubner C, et al. Neurological autoimmune diseases following vaccinations against SARS-CoV-2: a case series. Eur J Neurol. 2022;29:555–63. https://doi.org/10.1111/ene.15147.
3. Mingot-Castellano ME, Butta N, Canaro M, Del Castillo G, Solano MDC, Sánchez-González B, Jiménez-Bárcenas R, et al. COVID-19 vaccines and autoimmune hematologic disorders. Vaccines. 2022. https://doi.org/10.3390/vaccines10060961.
4. Caron P. Autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines: from etiopathogenesis to clinical management. Endocrine. 2022;78:406–17. https://doi.org/10.1007/s12020-022-03118-4.
5. Patrizio A, Ferrari SM, Antonelli A, Fallahi P. A case of Graves' disease and type 1 diabetes mellitus following SARS-CoV-2 vaccination. J Autoimmun. 2021;125: 102738. https://doi.org/10.1016/j.jaut.2021.102738.
6. Yano M, Morioka T, Natsuki Y, Sasaki K, Kakutani Y, Ochi A, et al. New-onset type 1 diabetes after COVID-19 mRNA vaccination. Intern Med. 2022;61:1197–200. https://doi.org/10.2169/internalmedicine.9004-21.
7. Sasaki K, Morioka T, Okada N, Natsuki Y, Kakutani Y, Ochi A, et al. New-onset fulminant type 1 diabetes after severe acute respiratory syndrome coronavirus 2 vaccination: a case report. J Diabetes Investig. 2022;13:1286–9. https://doi.org/10.1111/jdi.13771.
8. Tang X, He B, Liu Z, Zhou Z, Li X. Fulminant type 1 diabetes after COVID-19 vaccination. Diabetes Metab. 2022;48: 101324. https://doi.org/10.1016/j.diabet.2022.101324.
9. Bleve E, Venditti V, Lenzi A, Morano S, Filardi T. COVID-19 vaccine and autoimmune diabetes in adults: report of two cases. J Endocrinol Invest. 2022;45:1269–70. https://doi.org/10.1007/s40618-022-01796-5.
10. Sato T, Kodama S, Kaneko K, Imai J, Katagiri H. Type 1 diabetes mellitus associated with nivolumab after second SARS-CoV-2 vaccination, Japan. Emerg Infect Dis. 2022;28:1518–20. https://doi.org/10.3201/eid2807.220127.
11. Ohuchi K, Amagai R, Tamabuchi E, Kambayashi Y, Fujimura T. Fulminant type 1 diabetes mellitus triggered by coronavirus disease 2019 vaccination in an advanced melanoma patient given adjuvant nivolumab therapy. J Dermatol. 2022;49:e167–8. https://doi.org/10.1111/1346-8138.16304.
12. Aydoğan Bİ, Ünlütürk U, Cesur M. Type 1 diabetes mellitus following SARS-CoV-2 mRNA vaccination. Endocrine. 2022;78:42–6. https://doi.org/10.1007/s12020-022-03130-8.
13. Imagawa A, Hanafusa T. Fulminant type 1 diabetes mellitus. Endocr J. 2006;53:577–84. https://doi.org/10.1507/endocrj.kr-72.
14. Hosokawa Y, Hanafusa T, Imagawa A. Pathogenesis of fulminant type 1 diabetes: genes, viruses and the immune mechanism, and usefulness of patient-derived induced pluripotent stem cells for future research. J Diabetes Investig. 2019;10:1158–64. https://doi.org/10.1111/jdi.13091.
15. Baden MY, Imagawa A, Abiru N, Awata T, Ikegami H, Uchigata Y, et al. Characteristics and clinical course of type 1 diabetes

mellitus related to anti-programmed cell death-1 therapy. Diabetol Int. 2019;10:58–66. https://doi.org/10.1007/s13340-018-0362-2.
16. Imagawa A, Hanafusa T, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, et al. Fulminant type 1 diabetes: a nationwide survey in Japan. Diabetes Care. 2003;26:2345–52. https://doi.org/10.2337/diacare.26.8.2345.
17. Imagawa A, Hanafusa T. Fulminant type 1 diabetes—an important subtype in East Asia. Diabetes Metab Res Rev. 2011;27:959–64. https://doi.org/10.1002/dmrr.1236.
18. Ilonen J, Lempainen J, Veijola R. The heterogeneous pathogenesis of type 1 diabetes mellitus. Nat Rev Endocrinol. 2019;15:635–50. https://doi.org/10.1038/s41574-019-0254-y.
19. Kawabata Y, Ikegami H, Awata T, Imagawa A, Maruyama T, Kawasaki E, et al. Differential association of HLA with three subtypes of type 1 diabetes: fulminant, slowly progressive and acute-onset. Diabetologia. 2009;52:2513–21. https://doi.org/10.1007/s00125-009-1539-9.
20. Vojdani A, Vojdani E, Kharrazian D. Reaction of human monoclonal antibodies to SARS-CoV-2 proteins with tissue antigens: implications for autoimmune diseases. Front Immunol. 2020;11:617089. https://doi.org/10.3389/fimmu.2020.617089.
21. Shoenfeld Y, Agmon-Levin N. "ASIA"—autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun. 2011;36:4–8. https://doi.org/10.1016/j.jaut.2010.07.003.
22. Yasuda H, Nagata M, Moriyama H, Kobayashi H, Akisaki T, Ueda H, et al. Development of fulminant Type 1 diabetes with thrombocytopenia after influenza vaccination: a case report. Diabet Med. 2012;29:88–9. https://doi.org/10.1111/j.1464-5491.2011.03391.x.
23. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet. 2018;391:2449–62. https://doi.org/10.1016/s0140-6736(18)31320-5.
24. Tuomilehto J, Zimmet P, Mackay IR, Koskela P, Vidgren G, Toivanen L, et al. Antibodies to glutamic acid decarboxylase as predictors of insulin-dependent diabetes mellitus before clinical onset of disease. Lancet. 1994;343:1383–5. https://doi.org/10.1016/s0140-6736(94)92521-6.
25. 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.
26. Hughes J, Vudattu N, Sznol M, Gettinger S, Kluger H, Lupsa B, et al. Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. Diabetes Care. 2015;38:e55–7. https://doi.org/10.2337/dc14-2349.