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CASE REPORT

New-onset fulminant type 1 diabetes after severe acute respiratory syndrome coronavirus 2 vaccination: A case report

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ABSTRACT

Fulminant type 1 diabetes is characterized by a rapid progression of insulin deficiency triggered by viral infection. Here, we report a case of a 45-year-old Japanese woman with fulminant type 1 diabetes that developed 8 days after receiving messenger ribonucleic acid vaccine against severe acute respiratory syndrome coronavirus 2. She had been healthy and had no symptoms suggestive of viral infection before the vaccination. Laboratory tests showed exhaustion of insulin secretion and negative results for islet autoantibodies. Human leukocyte antigen genotype analysis showed the DRB1*04:05 and DQB1*04:01 alleles. This is the first case report of new-onset fulminant type 1 diabetes after severe acute respiratory syndrome coronavirus 2 vaccination, and suggests that a severe acute respiratory syndrome coronavirus 2 vaccine might trigger the onset of fulminant type 1 diabetes in susceptible individuals. However, a causal relationship remains to be identified, and further studies are required to determine the incidence of such cases.

INTRODUCTION

Fulminant type 1 diabetes is a subtype of type 1 diabetes characterized by rapid onset with ketoacidosis, hyperglycemia with almost normal hemoglobin A1c level and the absence of islet-associated autoantibodies[1]. Abnormal immune response triggered by viral infection is suggested as the pathogenesis of the disease, although the precise mechanism remains unclear[1]. Under the current pandemic of coronavirus disease 2019 (COVID-19), over 4 billion people worldwide have received at least one dose of vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2]. Recently, cases of several kinds of immune-mediated disorders[3–5], including type 1 diabetes[4,6], have been documented after SARS-CoV-2 vaccination. Although a causal relationship remains undetermined, these cases suggest an involvement of SARS-CoV-2 vaccination in the onset of autoimmune type 1 diabetes. Here, we report a case of new-onset fulminant type 1 diabetes after the first dose of SARS-CoV-2 vaccine.

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CASE REPORT

A 45-year-old Japanese woman, who had stable bronchial asthma, but had never been diagnosed with diabetes, received the first dose of the BNT162b2 messenger ribonucleic acid (mRNA) vaccine (Pfizer-BioNTech). She had a slight fever the next day, and general fatigue and thirst on the third day. Six days after the vaccination, she had nausea and abdominal pain, and visited a family doctor the following day. She was referred to the general hospital 8 days after the vaccination because of hyperglycemia (casual glucose 469 mg/dL, hemoglobin A1c 7.2%). At presentation, she was conscious and hemodynamically stable. She had lost 6 kg since the vaccination, and had a body mass index of 20.6 kg/m^2. Laboratory examinations showed hyperglycemia, metabolic acidosis with an increased anion gap (25.6 mEq/L) and ketonemia, consistent with diabetic ketoacidosis (Table 1). She promptly received intravenous saline infusion, and intensive insulin therapy with basal insulin glargine and bolus regular insulin with adjustment based on blood glucose levels.

Further examinations showed slightly elevated hemoglobin A1c level, exhaustion of endogenous insulin secretion, negative

Table 1 | Laboratory findings

Assessment	Results	Reference range
Arterial blood gas (room air)		
pH	7.175	7.35–7.45
pCO_2 (Torr)	17.9	35–45
pO_2 (Torr)	117.1	80–100
HCO_3^- (mEq/L)	6.4	22–26
Base excess (mEq/L)	−19.4	0 ± 2
Biochemistry		
Plasma glucose (mg/dL)	344	73–109
Hemoglobin A1c (%)	7.6	4.6–6.2
Immunoreactive insulin on admission ({U/mL)	2.74	≤18.7
Serum C-peptide on admission (ng/mL)	0.33	0.80–2.50
Urine C-peptide (μg/day)	≤1.5	29.2–167
β-hydroxybutyrate ({mol/L)	8,794	0–76
Acetoacetate ({mol/L)	1,815	13–69
Amylase (U/L)	45	37–124
Lipase (U/L)	82	11–59
Elastase-1 (ng/dL)	348	<300
Free T4 (ng/mL)	1.3	0.90–1.70
Thyroid-stimulating hormone ({IU/mL)	2.8	0.50–5.00
Immunological tests		
Anti-GAD antibody (U/mL)	<5.0	<5.0
Anti-IA-2 antibody (U/mL)	<0.6	<0.6
Insulin autoantibody, U/mL	<0.4	<0.4
Anti-ZnT8 antibody (U/mL)	<10.0	<15.0
Anti-thyroglobulin antibody (IU/mL)	<10	<28
Anti-thyroid peroxidase antibody (IU/mL)	<9	<16
Infection		
SARS-CoV-2 PCR	(−)	(−)
Anti-SARS-CoV-2 IgM, (C.O.I.)	0.2	<1.0
Anti-SARS-CoV-2 S-IgG (AU/mL)	3.2	<1.0
Anti-SARS-CoV-2 N-IgG (C.O. I.)	<0.1	<1.0
HLA-DNA typing		
DRB1*04:05:01/13:02:01		
DQB1*04:01:01/06:04:01		

C.O.I., cut off index; GAD, glutamic acid decarboxylase; HLA, human leukocyte antigen; IA-2, insulinoma-associated protein-2; IgG, immunoglobulin G; N, nucleocapsid protein; PCR, polymerase chain reaction; S, spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ZnT8, zinc transporter 8.

results for islet-associated autoantibodies and increased serum levels of pancreatic enzymes (Table 1). Based on these findings, we diagnosed fulminant type 1 diabetes. Immunological tests showed no evidence of recent viral infection potentially triggering type 1 diabetes (parainfluenza virus, coxsackievirus, cytomegalovirus, human herpesvirus and Epstein–Barr virus) and suggested vaccine-induced immunity against SARS-CoV-2 (Table 1). The class II human leukocyte antigen genotypes were DRB1*04:05:01/*13:02:01 and DQB1*04:01:01/*06/04:01. She eventually achieved adequate glycemic control with insulin glargine U-300 (14 units) before supper and of insulin lispro before meals (8 units, 10 units and 8 units before breakfast, lunch and supper, respectively), and was discharged 12 days after admission.

DISCUSSION

To our knowledge, this is the first case of new-onset fulminant type 1 diabetes after SARS-CoV-2 vaccination. Under the current mass SARS-CoV-2 vaccination, there have been a limited number of cases of new-onset type 1 diabetes after vaccination[4,6] (Table 2). Patrizio *et al.*[4] reported a case of a 52-year-old man from Italy who developed Graves' disease and type 1 diabetes 4 weeks after the second dose of BNT162b2 vaccine. We also recently experienced a case of a 51-year-old Japanese woman with acute-onset type 1 diabetes and latent autoimmune thyroiditis 6 weeks after the first dose of Moderna mRNA-1273 vaccine[6]. Although the causal relationship remains undetermined, those two cases suggest that the exposure to

Table 2 | Comparison of the cases of new-onset type 1 diabetes after severe acute respiratory syndrome coronavirus 2 vaccination

Authors	Patrizio *et al.*[4]	Yano *et al.*[6]	Present case
Age and sex	52 years, male	51 years, female	45 years, female
Viral infection before the onset	None	None	None
SARS-CoV-2 vaccine	BNT162b2 (Pfizer-BioNTech)	mRNA1273 (Moderna)	BNT162b2 (Pfizer-BioNTech)
Period from vaccination to onset	4 weeks after second dose	6 weeks after first dose	8 days after first dose
Onset pattern of type 1 diabetes	Acute-onset	Acute-onset	Fulminant
Plasma glucose on admission	ND	648 mg/dL	344 mg/dL
Hemoglobin A1c on admission	10.1%	10.3%	7.6%
Plasma C-peptide on admission	1.0 ng/mL	1.72 ng/mL	0.33 ng/mL
β-Hydroxybutyrate on admission	ND	10,772 μmol/L	8,794 μmol/L
Islet autoantibodies	GAD Ab (+)	GAD Ab (−)	GAD Ab (−)
		IA-2 Ab (−)	IA-2 Ab (−)
		IAA (+)	IAA (−)
		ZnT8 Ab (−)	ZnT8 Ab (−)
Thyroid autoantibodies	TgAb (+)	TgAb (+)	TgAb (−)
	TPOAb (+)	TPOAb (+)	TPOAb (−)
	TRAb (+)	TRAb (−)	
Class II HLA genotype	ND	DRB1*09:01/09:01	DRB1*04:05/13:02
		DQB1*03:03/03:03	DQB1*04:01/06:04

Ab, antibody; GAD, glutamic acid decarboxylase; HLA, human leukocyte antigen; IA-2, insulinoma-associated protein-2; IAA, insulin autoantibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Tg, thyroglobulin; TPO, thyroid peroxidase; TR, thyrotropin receptor; ZnT8, zinc transporter 8.

SARS-CoV-2 mRNA vaccine induces type 1 diabetes in healthy individuals, albeit rarely.

Unlike the aforementioned two cases, the present case experienced hyperglycemic symptoms from just 3 days after the first dose of vaccination. Furthermore, our case showed a rapid progression to ketoacidosis, relatively low hemoglobin A1c level and extremely low serum C-peptide level on admission (Table 2). These features suggest a severe immune response causing rapid β-cell destruction and insulin deficiency, consistent with fulminant type 1 diabetes[1]. Because no evidence of viral infection was identified before the onset of hyperglycemia, it cannot be excluded that the SARS-CoV-2 vaccine might have triggered fulminant type 1 diabetes. Of importance, the present case had the human leukocyte antigen DRB1*04:05 and DQB1*04:01 alleles, which confer susceptibility to fulminant type 1 diabetes in Japanese individuals[7]. Thus, it is speculated that a SARS-CoV-2 mRNA vaccination triggers the onset of fulminant type 1 diabetes in genetically susceptible individuals.

The present case is also interesting in terms of the relationship between vaccinations and the development of type 1 diabetes[8]. There is one case report of fulminant type 1 diabetes that developed in a 54-year-old Japanese man 7 days after influenza vaccination[9]. As in the present case, that case had the human leukocyte antigen DRB1*0405 and DQB1*0401 alleles[9]. Currently, it is unknown whether mRNA vaccines are more likely to induce autoimmune disorders than other vaccines. As the mRNA vaccine has a unique self-adjuvant property triggering innate immune responses[10], future studies are required to compare the incidence of autoimmune disorders, including type 1 diabetes, after different types of vaccination.

In summary, we report a case of fulminant type 1 diabetes diagnosed 8 days after the first dose of BNT162b2 SARS-CoV-2 vaccine. This case suggests that SARS-CoV-2 vaccination might be a trigger for the development of fulminant type 1 diabetes in genetically susceptible individuals. However, it remains unclear whether SARS-CoV-2 vaccination is causally associated with fulminant type 1 diabetes or it just coincided with the mass COVID-19 vaccination. Further studies are required to determine the incidence of fulminant type 1 diabetes associated with SARS-CoV-2 vaccination and the causality. To ensure the safety of COVID-19 vaccination, screening for hyperglycemia might be considered after vaccination for susceptible individuals.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: The patient has provided informed consent to publish this case and the identity of the patient has been protected.
Registry and the registration no. of the study/trial, N/A.
Animal studies: N/A.

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