JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
CASE REPORT

Type 1 diabetes mellitus following COVID-19 RNA-based vaccine

Kanako Sakurai[1]*, Daiki Narita[1], Naomi Saito[1], Takayuki Ueno[1], Ryota Sato[1], Satsuki Niitsuma[1], Kazuhiro Takahashi[2], Zenei Arihara[1]

[1]Department of Endocrinology and Metabolism, National Hospital Organization Sendai Medical Center, Sendai, Japan, and [2]Department of Endocrinology and Applied Medical Science, Tohoku University Graduate School of Medicine, Sendai, Japan

Keywords
COVID-19 RNA-based vaccines, Type 1 diabetes, Ketoacidosis

***Correspondence**
Kanako Sakurai
Tel.: +81-22-293-1111
Fax: +81-22-291-8114
E-mail address:
kanasakurai-dm@umin.ac.jp

J Diabetes Investig 2022; 13: 1290–1292

doi: 10.1111/jdi.13781

ABSTRACT

The epidemic of coronavirus disease-2019 (COVID-19) is the major public health issue in the world. COVID-19 vaccines are one of the most effective strategies against COVID-19. Here we report a 36-year-old female patient who had thirst, polydipsia, polyuria, palpitations, loss of appetite, and fatigue 3 days after the first dose of COVID-19 RNA-based vaccines without a prior history of diabetes. Ten days after vaccination, she visited our hospital with diabetic ketoacidosis and was diagnosed with type 1 diabetes. Hyperglycemia (501 mg/dL), anion gap metabolic acidosis and ketonuria were observed. The glycated hemoglobin level was 7.0%. Islet-related autoantibodies were all negative. The glucagon tolerance test revealed attenuated secretion of insulin. Human leukocyte antigen was haplotype DRB1*0405-DQB1*0401, which was associated with type 1 diabetes in Japan. The present case suggests that COVID-19 RNA-based vaccines might trigger the onset of type 1 diabetes, even in subjects without prior histories of diabetes.

INTRODUCTION

The epidemic of coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), is the major public health issue in the world. COVID-19 vaccines are one of the most effective strategies against COVID-19. However, adverse effects of COVID-19 vaccines, such as cerebral venous thrombosis and myocarditis, have been reported, although they are rare[1,2]. Type 1 diabetes is triggered by COVID-19[3]. Graves' disease and type 1 diabetes occurred in a patient with type 2 diabetes 4 weeks after the administration of COVID-19 vaccine[4]. However, there has been no report on type 1 diabetes triggered by COVID-19 vaccines in subjects without prior histories of diabetes.

Here we report a patient who had hyperglycemic symptoms 3 days after COVID-19 RNA-based vaccine without a prior history of diabetes. Ten days after vaccination, she visited our hospital with diabetic ketoacidosis and was diagnosed with type 1 diabetes.

CASE REPORT

A 36-year-old woman visited the emergency department of our hospital with a 7-day history of thirst, polydipsia, polyuria, palpitations, loss of appetite, and fatigue, which occurred 3 days after the first dose of COVID-19 RNA-based vaccines (BNT162b2, Pfizer-BioNTech). She was previously a healthy woman, and had no history of diabetes, allergy, or autoimmune disease. No family history of autoimmune disease or diabetes mellitus was noted. In addition, there was no history of over-drinking of carbonated beverage just before the onset of ketoacidosis.

At her first visit to our hospital, hyperglycemia (501 mg/dL), anion gap metabolic acidosis (pH 7.177), and ketonuria were noted, with elevated serum levels of β-hydroxybutyrate (2,190 μmol/L; reference range < 85 μmol/L) and acetoacetic acid (5,060 μmol/L; reference range < 55 μmol/L) (Table 1). She was diagnosed with diabetic ketoacidosis and admitted to our hospital. Management was initiated with intravenous fluid replacement and insulin infusion. The glycated hemoglobin (HbA1c) level was relatively low (7.0%) compared with the marked hyperglycemia, suggesting that hyperglycemia had occurred rapidly. She had no fever, upper respiratory symptoms, arthralgia, nor abdominal pain just before the onset of diabetes mellitus.

Anti-glutamic acid decarboxylase, insulinoma-associated antigen-2, zinc transporter 8, and insulin autoantibodies were all negative (Table 1). Amylase (147 IU/L; reference range 44–

Received 11 December 2021; revised 14 February 2022; accepted 24 February 2022

TABLE 1 | Laboratory test results

Hemoglobin A1c	7.0	%	(4.6–6.1)
Glucose	501	mg/dL	
Urinary ketone	(4+)		
pH	7.177		(7.35–7.45)
pCO_2	10.1	mmHg	(32–48)
pO_2	139	mmHg	(83–108)
HCO_3^-	3.6	mmol/L	(21–28)
Anion gap	10.1	mmol/L	(7.0–16.0)
Amylase	147	U/L	(44–132)
Lipase	208	IU/L	(6–48)
Acetoacetic acid	2190	μmol/L	(<55)
3-OHBA	5060	μmol/L	(<85)
Serum C-peptide	0.35	ng/mL	(0.8–2.3)
Urinary C-peptide	11.6	μg/day	(29.2–167)
GAD antibody	Negative		
IA-2 antibody	Negative		
ZnT8 antibody	Negative		
Insulin autoantibodies	Negative		
Glucagon stimulation test			
C-peptide (0 min)	0.55	ng/mL	
C-peptide (6 min)	1.03	ng/mL	
HLA haplotype			
DRB1	04:05	08:03	
DQB1	04:01	06:01	

The ranges of the reference values are indicated in parentheses. Abbreviations: HCO_3^-, bicarbonate ion; 3-OHBA, 3-hydroxybutyric acid; GAD, glutamic acid decarboxylase; IA-2, insulinoma-associated antigen-2; ZnT8, zinc transporter 8

132 IU/L) and lipase (208 IU/L; reference range 6–48 IU/L) were elevated (Table 1). No abnormal findings were observed in the pancreas on the computed tomography (data not shown).

Human leukocyte antigen (HLA) typing revealed haplotype DRB1*0405-DQB1*0401. It was reported that DRB1*0405-DQB1*0401 was closely associated with three types of type 1 diabetes; acute-onset type 1 diabetes, slowly progressive type 1 diabetes, and fulminant type 1 diabetes in Japan[5]. The glucagon tolerance test showed attenuated secretion of insulin (Table 1). The serum C-peptide level decreased to 0.13 ng/mL 14 days after admission, suggesting a possibility of fulminant Type 1 diabetes. Subcutaneous multiple daily injection of insulin was initialized. Then 15 days after admission, she was discharged in a stable condition.

Informed consent on this case report was obtained from the subject.

DISCUSSION

We report a case of type 1 diabetes following COVID-19 RNA-based vaccine. She had no history of diabetes, but presented rapid-onset diabetic ketoacidosis with low HbA1c value and negative islet-related autoantibodies 10 days after the first dose of COVID-19 RNA-based vaccines. Fulminant type 1 diabetes is characterized by rapid-onset diabetic ketoacidosis, low HbA1c level, undetectable serum C-peptide, and negative islet-related autoantibodies. Because the serum C-peptide level decreased to 0.13 ng/mL 14 days after the admission, there is a possibility that she had fulminant Type 1 diabetes. It should be noted that she has haplotype DRB1*0405-DQB1*0401, which is closely associated with fulminant Type 1 diabetes in Japan[5].

Patrizio *et al.* reported a case of Graves' disease and type 1 diabetes following BNT162b2 mRNA COVID-19 vaccine[4]. This case was characterized by the previous history of diabetes, positive autoantibodies against glutamic acid decarboxylase 65, and co-occurrence of Graves' disease. In contrast, our case had no co-occurrence of Graves' disease, nor previous histories of diabetes.

The hyperglycemic symptoms occurred 3 days after the first administration of mRNA COVID-19 vaccines in our case. Therefore, we cannot deny the possibility that the onset of Type 1 diabetes just coincided with the timing of the COVID-19 vaccination. Whereas, Yasuda *et al* reported a case of fulminant Type 1 diabetes that developed after seasonal influenza vaccination[6]. In their case, hyperglycemic symptoms occurred 4 days after vaccination. Another possible pathogenesis of the present case may therefore be fulminant Type 1 diabetes triggered by COVID-19 RNA-based vaccine.

Innate immune responses to viral infection accelerates aggressive β-cell destruction and associated with the onset of fulminant Type 1 diabetes[7]. Melanoma differentiation-associated protein 5 (MDA5), is an innate pathogen recognition receptor. Because MDA5 regulates the innate immune response to SARS-CoV-2[8], it is likely that MDA5 recognizes RNA derived from COVID-19 RNA-based vaccines. Recognition of RNA by MDA5 induces the synthesis of type I interferons, which impair insulin production, proinsulin conversion and mitochondrial function in pancreatic β-cells[9].

Kanduc and Shoenfeld demonstrated the molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes[10]. Molecular mimicry means a significant similarity between certain pathogenic elements in the vaccine and specific human proteins. However, bystander activation may also be associated with the COVID-19 RNA-based vaccine and the development of Type 1 diabetes.

The present case suggests that Type 1 diabetes should be added to the list of the possible adverse effects of COVID-19 vaccination, and should be surveyed carefully after COVID-19 vaccination, even in subjects without prior histories of diabetes.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: Informed consent was obtained from the subject.
Approval date of registry and the registration no. of the study/-trial: N/A.
Animal studies: N/A.

REFERENCES

1. Perry RJ, Tamborska A, Singh B, *et al*. Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study. *Lancet* 2021; 398: 1147–1156.
2. Witberg G, Barda N, Hoss S, *et al*. Myocarditis after Covid-19 vaccination in a large health care organization. *N Engl J Med* 2021; 385: 2132–2139. https://doi.org/10.1056/NEJMoa2110737
3. Rubino F, Amiel SA, Zimmet P, *et al*. New-onset diabetes in Covid-19. *N Engl J Med* 2020; 383: 789–790.
4. Patrizio A, Ferrari SM, Antonelli A, *et al*. A case of Graves' disease and type 1 diabetes mellitus following SARS-CoV-2 vaccination. *J Autoimmun* 2021; 125: 102738.
5. Kawabata Y, Ikegami H, Awata T, *et al*. Differential association of HLA with three subtypes of type 1 diabetes: fulminant, slowly progressive and acute-onset. *Diabetologia* 2009; 52: 2513–2521.
6. Yasuda H, Nagata M, Moriyama H, *et al*. Development of fulminant Type 1 diabetes with thrombocytopenia after influenza vaccination: a case report. *Diabet Med* 2012; 29: 88–89.
7. Aida K, Nishida Y, Tanaka S, *et al*. RIG-I- and MDA5-initiated innate immunity linked with adaptive immunity accelerates beta-cell death in fulminant type 1 diabetes. *Diabetes* 2011; 60: 884–889.
8. Yin X, Riva L, Pu Y, *et al*. MDA5 governs the innate immune response to SARS-CoV-2 in lung epithelial cells. *Cell Rep* 2021; 34: 108628.
9. Blum SI, Tse HM. Innate viral sensor MDA5 and coxsackievirus interplay in type 1 diabetes development. *Microorganisms* 2020; 8: 993.
10. Kanduc D, Shoenfeld Y. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. *Immunol Res* 2020; 68: 310–313.