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

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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 rare1,2. Type 1 diabetes is triggered by COVID-193. Graves’ disease and type 1 diabetes occurred in a patient with type 2 diabetes 4 weeks after the administration of COVID-19 vaccine4. 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 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.
CASE REPORT
Type 1 diabetes and COVID-19 vaccine

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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. 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.

Table 1: Laboratory test results

| Test                        | Result          |
|-----------------------------|-----------------|
| Hemoglobin A1c              | 7.0%            |
| Glucose                     | 501 mg/dL       |
| Urinary ketone              | (44+)           |
| pH                          | 7.177           |
| pCO₂                        | (32–48) mmHg    |
| pO₂                         | (83–108) mmHg   |
| HCO₃⁻                      | (21–28) mmol/L  |
| Anion gap                   | (7.0–16.0) mmol/L |
| Amylase                     | (44–132) U/L    |
| Lipase                      | (6–48) U/L      |
| Acetoacetic acid            | (55) µmol/L     |
| 3-OHBA                      | (85) µmol/L     |
| Serum C-peptide             | (0.8–2.3) ng/mL |
| Urinary C-peptide           | (292–167) µg/day |

The ranges of the reference values are indicated in parentheses. Abbreviations: HCO₃⁻, bicarbonate ion; 3-OHBA, 3-hydroxybutyric acid; GAD, glutamic acid decarboxylase; IA-2, insulinoma-associated antigen-2; ZnT8, zinc transporter 8.

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.

Patrizio et al. reported a case of Graves’ disease and type 1 diabetes following BNT162b2 mRNA COVID-19 vaccine. 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. 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. Melanoma differentiation-associated protein 5 (MDA5), is an innate pathogen recognition receptor. Because MDA5 regulates the innate immune response 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.

Kanduc and Shoenfeld demonstrated the molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes. 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.
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