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【 CASE REPORT 】

New-onset Type 1 Diabetes after COVID-19 mRNA Vaccination

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Abstract:

During the ongoing coronavirus disease 2019 (COVID-19) pandemic, it is critical to ensure the safety of COVID-19 vaccines. We herein report a 51-year-old Japanese woman who developed acute-onset type 1 diabetes with diabetic ketoacidosis six weeks after receiving the first dose of a COVID-19 messenger ribonucleic acid (mRNA) vaccine. Laboratory tests indicated exhaustion of endogenous insulin secretion, a positive result for insulin autoantibody, and latent thyroid autoimmunity. Human leukocyte antigen typing was homozygous for DRB1*09:01-DQB1*03:03 haplotypes. This case suggests that COVID-19 vaccination can induce type 1 diabetes in some individuals with a genetic predisposition.

Key words: COVID-19, SARS-CoV-2, mRNA vaccine, hyperglycemia, type 1 diabetes, autoimmunity

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Introduction

Under the ongoing coronavirus disease 2019 (COVID-19) pandemic, it is critical to ensure the safety of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19. A number of SARS-CoV-2 vaccines have been approved for emergency use (1), and as many as 3.8 billion people worldwide have been vaccinated thus far (2). Most of the SARS-CoV-2 vaccines administered globally have been messenger ribonucleic acid (mRNA)-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech), which are mRNA-based vaccines encoding the full-length spike protein of SARS-CoV-2 (1, 3, 4).

In the latest reports on the safety of the SARS-CoV-2 vaccines (3, 4), hyperglycemia has not been documented as a potential adverse event within six months after vaccination. However, accumulating cases of acute hyperglycemia or new-onset diabetes have been reported in patients following COVID-19 infection, some of which include cases of type 1 diabetes (5-7). Such findings suggest that COVID-19 infection induces the autoimmunity associated with type 1 diabetes (6, 8). Therefore, it is reasonable to assume that vaccination against SARS-CoV-2 also induces type 1 diabetes; however, only a limited number of reports are available on cases of new-onset diabetes after COVID-19 vaccination (9, 10).

We herein report a case of new-onset type 1 diabetes in a Japanese woman complicated by diabetic ketoacidosis after COVID-19 mRNA vaccination.

Case Report

A 51-year-old woman experienced general fatigue, thirst, polyuria, and polydipsia 28 days after the first injection of Moderna mRNA-1273 SARS-CoV-2 vaccine. She reported no systemic or local symptoms just after the first injection. She received the second injection of the Moderna mRNA-1273 vaccine two days after the onset, and then her symptoms significantly worsened, accompanied by a daily intake of 1-2 liters of sugar-sweetened soda.

She noticed weight loss of 3 kg and visited her family doctor 12 days after the onset of her symptoms. She had been healthy without a history of dysglycemia or diabetes until this episode. The results of her annual routine medical checkup 45 days before the first vaccination had shown a

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Table. **Laboratory Findings.**

Assessment	Results	Reference range
Arterial blood gas (room air)		
pH	7.113	7.35-7.45
pCO_2, Torr	13.7	35-45
pO_2, Torr	142	80-100
HCO_3^-, mEq/L	4.2	22-26
Base excess, mEq/L	-25.3	0±2
Biochemistry		
Plasma glucose, mg/dL	648	73-109
Hemoglobin A1c, %	10.3	4.6-6.2
Immunoreactive insulin (on admission), μU/mL	5.1	≤18.7
C-peptide (on admission), ng/mL	1.72	0.80-2.50
Fasting C-peptide, ng/mL	0.40	0.80-2.50
Glucagon-stimulated C-peptide, ng/mL	0.53	-
β-hydroxybutyrate, μmol/L	10,772	0-76
Acetoacetate, μmol/L	3,190	13-69
Free T4, ng/mL	1.12	0.90-1.70
Thyroid stimulating hormone, μIU/mL	1.34	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	1.6	<0.4
Anti-ZnT8 antibody, U/mL	<10.0	<10.0
Anti-thyroglobulin antibody, IU/mL	404	<4.11
Anti-thyroid peroxidase antibody, IU/mL	6.14	<5.11
Anti-thyrotropin receptor antibody, IU/L	<0.8	<2.0
Infection		
SARS-CoV-2 PCR	(-)	(-)
Anti-SARS-CoV-2 IgM, C.O.I.	2.7	<1.0
Anti-SARS-CoV-2 S-IgG, AU/mL	361	<1.0
HLA-DNA typing		
DRB1*09:01:02/09:01:02		
DQB1*03:03:02/03:03:02		

GAD: glutamic acid decarboxylase, IA-2: insulinoma-associated protein-2, ZnT8: zinc transporter 8, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, PCR: polymerase chain reaction, HLA: human leukocyte antigen, IgM: immunoglobulin M, C.O.I.: cut off index

normal glucose metabolism (fasting glucose, 90 mg/dL; hemoglobin A1c, 5.6%). Regarding her family history, her father had type 2 diabetes, but no one in her family had an autoimmune disease. Two days after the visit (i.e. six weeks after the first vaccination), she was referred to our hospital because hyperglycemia (casual glucose, 455 mg/dL) was detected by her family doctor.

At the presentation, her consciousness was clear, and her temperature was 35.5 °C. Her body height, weight, and body mass index were 150.3 cm, 41.5 kg, and 18.3 kg/m^2, respectively. Her respiratory rate, blood pressure, and oxygen saturation were 20/min, 155/94 mmHg, and 98% in room air, respectively. No obvious ketone smell was detected on her breath. She was hemodynamically stable but in low spirits with tachycardia (pulse rate, 108 bpm) and reduced skin turgor, suggesting mild dehydration. Laboratory examinations revealed hyperglycemia with elevated hemoglobin A1c level, metabolic acidosis with an increased anion gap (31.8 mEq/L), and ketonemia, which were consistent with a diagnosis of diabetic ketoacidosis (Table).

After admission, she received 4.0 L of intravenous saline and intravenous infusion of regular insulin, which was started at 0.1 unit/kg/h and was adjusted thereafter, in the first 27 hours. Subsequently, her blood glucose levels gradually decreased, her metabolic acidosis was corrected, and her ketosis significantly improved. Diabetic ketoacidosis completely resolved 20 hours after admission, and she was transitioned to subcutaneous insulin therapy. A further examination revealed exhaustion of endogenous insulin secretion, a positive insulin autoantibody, and autoimmunity against the thyroid gland with normal levels of thyroid hormones (Table). Immunological tests showed no evidence of a recent viral infection potentially triggering type 1 diabetes (coxsackievirus, mumps virus, rubella virus, cytomegalovirus,

varicella-zoster virus, human herpesvirus, and Epstein-Barr virus) and suggested vaccine-induced immunity against SARS-CoV-2 (Table). Human leukocyte antigen (HLA) class II genotyping indicated DRB1*09:01-DQB1*03:03 homozygosity, which is known to confer susceptibility to type 1 diabetes in the Japanese population (11, 12). Based on these findings, she was diagnosed with acute-onset type 1 diabetes and achieved adequate glycemic control with a subcutaneous injection of insulin glargine U-300 (14 units) before supper and of insulin lispro before meals (6 units, 4 units, and 6 units before breakfast, lunch, and supper, respectively) at discharge.

Discussion

With COVID-19 vaccination now spreading around the world (2), only a few reports have been published concerning cases of new-onset diabetes following COVID-19 vaccination (9, 10). Abu-Rumaileh et al. (9) reported a case of new-onset type 2 diabetes presenting as hyperglycemic hyperosmolar syndrome that developed three weeks after the first dose of BNT162b2 SARS-CoV-2 vaccine. Since the patient was a 58-year-old African man with a family history of type 2 diabetes, the authors speculated that the vaccine had triggered an immune response to unmask the patient's underlying prediabetes (9). Patrizio et al. (10) reported a 52-year-old man from Italy who showed new onset Graves' disease and the conversion of pre-existing type 2 diabetes into type 1 autoimmune diabetes that developed four weeks after the second dose of BNT162b2 SARS-CoV-2 vaccine. Based on the findings that the patient had a history of vitiligo vulgaris and evidence of autoimmunity to the thyroid gland and pancreatic islets, the authors speculated that the occurrence of these disorders could be explained partly by autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome) (13). Although the causal relationship remains to be clarified, these cases suggest that the exposure to SARS-CoV-2 mRNA vaccine has the potential to activate autoimmune reaction to induce serious endocrine disorders in previously healthy individuals.

In our patient, it cannot be ruled out that the COVID-19 vaccination may have induced type 1 diabetes, as there was no evidence of recent viral infection before the onset of hyperglycemia. Given that her hemoglobin A1c level on admission was significantly increased, similar to the two cases reported previously (9, 10), it is speculated that hyperglycemia developed soon after she received the first dose of the vaccine. In addition, because the C-peptide level was detectable on admission (1.72 ng/mL), polydipsia due to sugar-sweetened soda may have accelerated the progression of hyperglycemia and ketoacidosis in this case.

Another important aspect is that our patient had HLA DRB1-DQB1 haplotypes susceptible to type 1 diabetes in Japanese (11, 12) and showed autoimmunity to insulin and the thyroid gland, as in the previously reported case (10). These findings suggest that our patient was genetically susceptible and predisposed to developing type 1 diabetes. Taken together, it is speculated that COVID-19 mRNA vaccination triggered the development of type 1 diabetes in our patient, who had a genetic predisposition to the disease. In addition, considering the shared genetic susceptibility to type 1 diabetes and autoimmune thyroid disease (14), latent thyroid autoimmunity in this patient may also have been associated with COVID-19 vaccination. Indeed, several cases of autoimmune thyroid disease that developed after COVID-19 vaccination have been reported (15).

However, we should be careful in interpreting causality, as whether or not COVID-19 vaccination is associated with the development of type 1 diabetes remains unclear. Of note, no cases of new-onset type 1 diabetes after COVID-19 vaccination have been reported thus far, even though many people who are genetically susceptible to type 1 diabetes have surely been vaccinated against COVID-19 worldwide. Therefore, it may also be possible that the onset of type 1 diabetes simply coincided with the COVID-19 vaccination.

Conclusions

This case along with prior cases (9, 10) suggests that vaccination against SARS-CoV-2 can induce type 1 diabetes in some individuals with a genetic predisposition. Prospective and large-scale studies are required to clarify the incidence of new-onset type 1 diabetes associated with COVID-19 vaccination and the causal relationship between them. Because widespread vaccination is critical to bringing the COVID-19 pandemic to an end, it is necessary to ensure the safety of various vaccines. For susceptible individuals, screening for hyperglycemia may be considered following COVID-19 vaccination.

Written informed consent has been obtained from the patient to publish this report.

The authors state that they have no Conflict of Interest (COI).

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