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【 CASE REPORT 】

Graves' Disease after Administration of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine in a Type 1 Diabetes Patient

Mayu Sakai[1,2], Ken Takao[1,2], Takehiro Kato[1,2], Kodai Ito[1,2], Sodai Kubota[1-3], Tokuyuki Hirose[1,2], Yanyan Liu[1,2], Masami Mizuno[1,2], Takuo Hirota[1,2], Tetsuya Suwa[1,2], Yukio Horikawa[1,2] and Daisuke Yabe[1-5]

Abstract:
Although there is a great demand for increased coronavirus disease 2019 (COVID-19) vaccination worldwide, rare side effects of the vaccine in susceptible individuals are attracting attention. We recently treated a patient with type 1 diabetes who had HLA-A*240201/A*020101, B*5401/B*5601, DRB1*0405/DRB1*0405, DPB1*0501/DPB1*0501 and DQB1*0401/DQB1*040 and developed Graves' disease soon after the administration of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine. While causal relationships between vaccinations and adverse events are difficult to discern due to both confounding and masking factors, our findings suggest that attention to possible adjuvant-related endocrinological diseases in certain individuals receiving SARS-CoV-2 vaccines is appropriate.

Key words: coronavirus disease 2019, vaccination, Graves' disease, type 1 diabetes

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Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic is ongoing, affecting millions of people worldwide (1). Several vaccines have been developed and are helping to contain the infection; the efficacy and safety of the Pfizer-BioNTech severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine, for example, have been reported (2). Rare side effects in genetically susceptible individuals also attract attention; autoimmune disease can reportedly be activated by inoculation along with the immune response to COVID-19 vaccination in certain individuals (3, 4), thus creating another life-threatening disease.

There are several reports of Graves' disease developing after the administration of SARS-CoV-2 vaccine (5-9). It has been speculated that ribonucleic acid (RNA) itself and/or lipid nanoparticles that encapsulate RNA might act as an adjuvant that could cause "autoimmune/inflammatory syndrome induced by adjuvants (ASIA)." Adjuvants are generally additives added to vaccines to enhance the immunogenicity of the antigen when administered together with the antigen (10). However, in some recipients, an adjuvant can impair immunological balance and induce autoimmune disease. In 2011, Shoenfeld et al. proposed the acronym *ASIA* for autoimmune diseases caused by adjuvanted vaccination (11). An analysis of 500 subjects in the ASIA International Registry strongly suggested that exposure to adjuvants could cause autoimmune disease (12). Previously, ASIA has been reported after vaccination against human papillomavirus (HPV), influenza virus and hepatitis B virus (HBV). In a cohort study after HPV vaccination, it was also reported that

[1]Department of Diabetes, Endocrinology and Metabolism, Gifu University Graduate School of Medicine, Japan, [2]Department of Rheumatology and Clinical Immunology, Gifu University Graduate School of Medicine, Japan, [3]Yutaka Seino Distinguished Center for Diabetes Research, Kansai Electric Power Medical Research Institute, Japan, [4]Center for Healthcare Information Technology, Tokai National Higher Education and Research System, Japan and [5]Division of Molecular and Metabolic Medicine, Kobe University Graduate School of Medicine, Japan
Received for publication December 17, 2021; Accepted for publication January 30, 2022
Correspondence to Dr. Ken Takao, k_takao@gifu-u.ac.jp

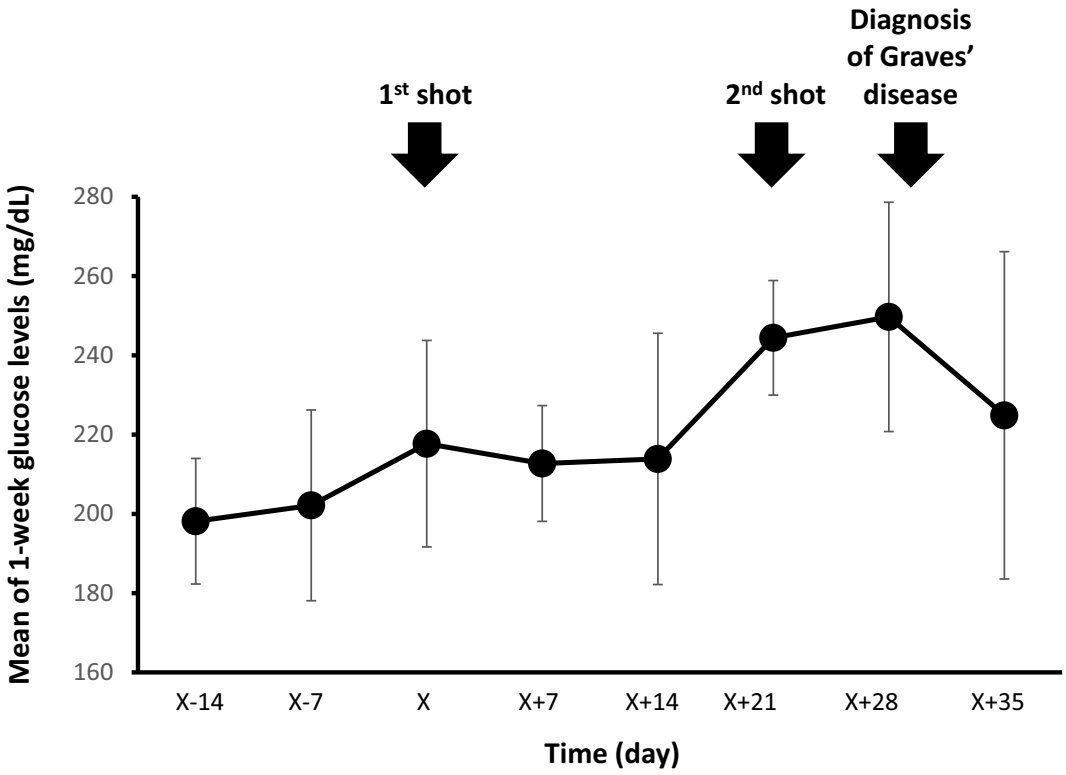


Figure 1. **Changes in mean one-week glucose levels estimated by factory-calibrated glucose monitoring before and after vaccination. The patient's glucose levels were estimated by factory-calibrated glucose monitoring, and the mean one-week glucose levels between each indicated date and the consequent six days were plotted as the mean±SD. The patient received the Pfizer-BioNTech SARS-CoV-2 vaccine (COMIRNATY) twice with a 3-week interval between the two shots (Day X and Day X+21). Her glucose levels became elevated as soon as the first day after the first shot (Day X+1) and remained high despite the total daily insulin dose being increased to approximately 60-80 units.**

15% of vaccinated people met the diagnostic criteria for ASIA, including 0.6% with an autoimmune disease, predominantly thyroiditis and rheumatoid arthritis (13). In a cross-sectional study, 76% of ASIA adverse events occurred during the first 3 days after vaccination (14), possibly because the concentration of viral protein reaches its peak within a few days after inoculation (15). Although the genetic predisposition to ASIA remains largely unexplored, it has been suggested that HLA-DRB1 and HLA-DQB1 may be involved (16). Thus far, 54 cases of subacute thyroiditis, 2 cases of Hashimoto's disease, 11 cases of primary ovarian failure/primary ovarian dysfunction, 13 cases of type 1 diabetes, and 1 case of adrenal failure have been reported as ASIA-associated endocrine diseases (16).

We herein report a type 1 diabetes patient in whom Graves' disease developed after the administration of a SARS-CoV-2 vaccine.

Case Report

The patient was a 31-year-old woman with type 1 diabetes. Before the diagnosis of diabetes, she had been naturally healthy and shown no abnormalities at school health check-ups. At 20 years old, she developed thirst, polydipsia, and polyuria after symptoms of a cold and began losing body weight (5 kg in 1 month) before she consulted a nearby doctor.

Her plasma glucose and hemoglobin A1C (HbA1c) levels were 366 mg/dL and 12.2%, respectively, and she was positive for urinary ketone bodies. She was referred to our institution and hospitalized for treatment. She was diagnosed with acute-onset type 1 diabetes due to positivity for anti-glutamic acid decarboxylase (GAD) antibody (141 U/mL) and a severely impaired β-cell function in the glucagon stimulation test (serum C-peptide levels 0.37 and 0.52 ng/mL and plasma glucose levels 124 and 169 mg/dL before and after intravenous administration of 1 mg glucagon, respectively). She was negative for anti-thyroid autoantibodies. She began receiving multiple daily injections (MDIs) with a total daily insulin dose (TDD) of approximately 40 units.

At 23 years old, she experienced thyrotoxicosis (TSH < 0.01 μIU/mL, free T3 2.16 pg/mL and free T4 1.34 ng/dL). She was negative for first-generation TSH receptor antibody (TRAb) (10.1%) but positive for anti-thyroglobulin antibody (205 IU/mL). She was diagnosed with painless thyroiditis; her thyroid function was normalized without any medication, but she remained insulin-dependent (casual plasma glucose level 252 mg/dL and serum C-peptide level undetect-

Table 1. Biochemistry, Complete Blood Count and Thyroid Function before and after 1st and 2nd Shots of Pfizer-BioNTech SARS-CoV-2 Vaccination.

	Reference value	Month X-8	Day X-14	Day X+21	Day X+28	Month X+3
Biochemistry						
TP	6.6-8.1 g/dL	7.0	6.8	5.3	6.0	6.5
Albumin	4.1-5.1 g/dL	4.6	4.4	3.3	3.6	4.1
A/G ratio	1.1-2.3	1.9	1.8	1.7	1.5	1.7
CPK	41-153 U/L	62	61	43	44	42
AST	13-30 U/L	10	12	18	62	21
ALT	7-23 U/L	13	14	20	86	32
ALP	38-113 U/L	N.A.	N.A.	66	97	166
γ-GTP	9-32 U/L	8	10	11	25	28
Total bilirubin	0.4-1.5 mg/dL	N.A.	N.A.	N.A.	0.8	N.A.
LDL-C	65-140 mg/dL	127	127	67	100	128
HDL-C	48-103 mg/dL	78	75	44	51	89
TG	30-117 mg/dL	56	53	107	93	107
Casual PG	<200 mg/dL	130	142	369	317	381
HbA1c	4.9-6.2 %	8.3	8.8	8.3	8.3	8.4
Complete blood count						
WBC	3,300-8,600 /μL	7,540	3,990	3,790	3,940	6,330
Hb	11.6-14.8 g/dL	12.9	14.1	12.4	13.6	14.2
Platelet	158-348×10^3/μL	335	321	327	34.2×104	42.8
Thyroid function						
TSH	0.61-4.23 μIU/mL	2.35	N.A.	<0.005	<0.005	<0.005
FT3	2.3-4.0 pg/mL	2.89	N.A.	28.7	>32.5	4.20
FT4	0.9-1.7 ng/dL	0.92	N.A.	7.47	>7.77	1.03

A/G: albumin/globulin ratio, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CPK: creatine phosphorus kinase, FT3: free triiodothyronine, FT4: free thyroxine, γGTP: γ-glutamyltransferase, Hb: hemoglobin, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, PG: plasma glucose, TP: total protein, TSH: thyroid-stimulating hormone, WBC: white blood cells. Day X and Day X+21 are the dates that the patient received the 1st and 2nd shots of Pfizer-BioNTech SARS-CoV-2 vaccination, respectively.

Table 2. Basal Levels of Various Hormones upon Admission to Our Institution 7 Days after the 2nd Shot of Pfizer-BioNTech SARS-CoV-2.

Thyroglobulin	5.4 ng/mL (<33.7)	GH	0.30 ng/mL
Anti-TPO Ab	481 IU/mL (<16)	IGF-1	132 ng/mL (-1.8 SD)
Anti-Tg Ab	82 IU/mL (<28)	PRL	17.9 ng/mL (6.12-30.54)
TRAb	11.9 IU/L (<2.0)	LH	6.01 mIU/mL
		FSH	4.29 mIU/mL
ACTH	29.3 pg/mL (7.2-63.3)		
Cortisol	11.5 μg/dL (7.07-19.6)		
DHEA-S	236 μg/dL (23-266)	Dopamine	≤5 pg/mL (<20.0)
PRA	1.9 ng/mL/h (0.2-2.3)	Adrenaline	10 pg/mL (<100)
PAC	57.1 pg/mL (4.0-82.1)	Noradrenaline	41 pg/mL (100-450)

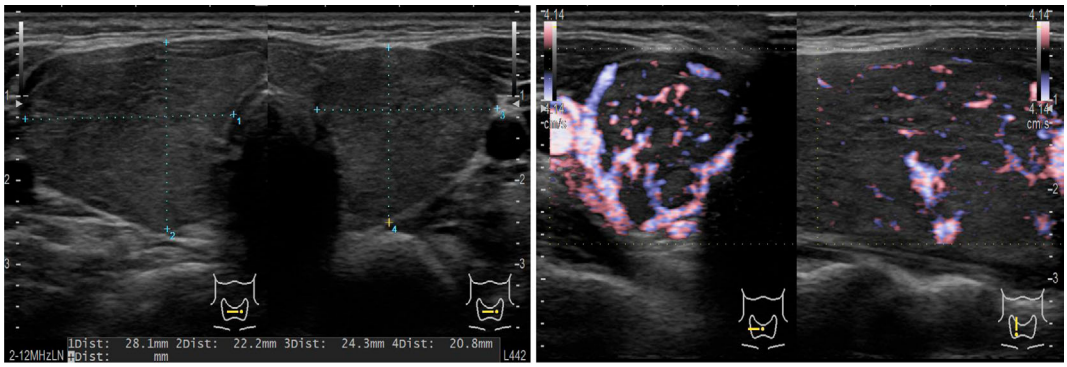
Values in parentheses are reference values. ACTH: adenocorticotropic hormone, anti-Tg Ab: anti-thyroglobulin antibody, anti-TPO Ab: anti-thyroid peroxidase antibody, LH: luteinizing hormone, FSH: follicle stimulating hormone, GH: growth hormone, IGF-I: insulin-like growth factor, PAC: plasma aldosterone concentration, PRA: plasma renin activity, PRL: prolactin, TRAb: thyroid stimulating hormone receptor autoantibody

able).

At 26 years old, she married and began receiving continuous subcutaneous insulin infusion (CSII) for planned pregnancy. At 27 years old, she delivered a healthy baby with a normal body weight (3,162 g). She continued CSII, and her HbA1c levels remained at 8-9% with a TDD of approximately 40 units after delivery. Her thyroid hormone levels were measured every 5-12 months and remained normal (TSH 2.35 μIU/mL, free T3 2.89 pg/mL and free T4 0.92 ng/dL at 8 months before vaccination).

Due to the global outbreak of COVID-19 infection, she received the Pfizer-BioNTech SARS-CoV-2 vaccine

A. Thyroid ultrasonography



B. ^{99m}Tc scintigraphy

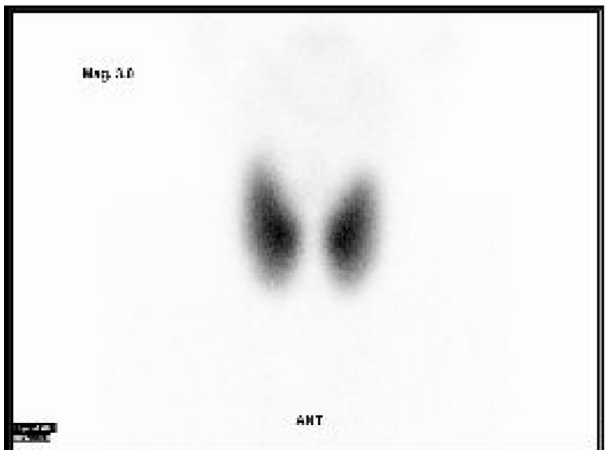


Figure 2. Imaging analysis findings of the thyroid gland in the current case. A: Thyroid ultrasonography. The estimated thyroid volume was 45.2 cm^3, and marked swelling was observed (left). Thyroid ultrasonography revealed diffuse hyperperfusion in the thyroid gland (right). B: ^{99m}Tc scintigraphy. Diffuse hyperaccumulation was observed in the thyroid gland (^{99m}Tc uptake 18.8% in the current case; normal range 0.5-4.0%).

(COMIRNATY) twice at 31 years old, with a 3-week interval between the 2 shots (Day X and Day X+21). No adverse events other than injection-site pain was noted. However, her glucose levels became elevated after the first shot (Day X+1) and remained high for the next 4 weeks (Fig. 1), although her TDD was increased to approximately 60-80 units. She suffered excessive sweating, diarrhea, and shortness of breath during exertion after the second shot (Day X+21) and visited our hospital 7 days after the second shot (Day X+28). While she was not aware of cervical swelling, she experienced palpitations after the second shot that suggested tachycardia. She had diffuse goiter with no nodules or pain as well as thyrotoxicosis. Her thyroid hormone levels were high on the day of the second shot (Day X+21) and were further elevated on Day X+28 (Table 1). The patient's albumin/globulin ratio, which is sometimes associated with autoimmune disease, was reduced on Day X+28 (Table 1). She was also positive for third-generation TRAb (11.9 IU/L) on Day X+28 (Table 2).

Thyroid ultrasonography revealed diffuse hyperperfusion in the thyroid gland; Tc scintigraphy showed diffuse hyperaccumulation in the thyroid gland (Fig. 2). She had HLA-A*240201/A*020101, B*5401/B*5601, DRB1*0405/DRB1*0405, DPB1*0501/DPB1*0501 and DQB1*0401/DQB1*0401. She was diagnosed with Graves' disease and started receiving 15 mg thiamazole once daily; her thyroid function had nearly normalized by 3 months after the initiation of thiamazole (TSH <0.01 μIU/mL, free T3 2.16 pg/mL and free T4 1.34 ng/dL), and she no longer required an increased insulin dose to achieve glycemic control, similar to before the Pfizer-BioNTech SARS-CoV-2 inoculation.

Discussion

We encountered a patient with type 1 diabetes who developed Graves' disease the day after receiving the Pfizer-BioNTech SARS-CoV-2 vaccine. As the current case had a high genetic predisposition to autoimmune disease, the Pfizer-BioNTech SARS-CoV-2 vaccine may well have triggered the onset of Graves' disease in this case.

Several cases of Graves' disease plausibly associated with use of the Pfizer-BioNTech SARS-CoV-2 vaccine have been

reported (5-8), with the onset of the disease documented two to eight weeks after receiving the first shot. We cannot be certain that the current case was clinically euthyroid immediately before her first shot; however, the patient showed signs of Graves' disease within 28 days after the first shot of the Pfizer-BioNTech SARS-CoV-2 vaccine. Our patient's mean glucose levels were elevated after her first shot (Day X+1) and remained high despite the increased TDD. Furthermore, the patient's thyroid hormone levels were high on the day of the second shot (Day X+21) and were further elevated on Day X+28. The patient's albumin/globulin ratio, which is sometimes associated with autoimmune diseases, was reduced on Day X+28. Graves' disease-related symptoms, such as sweating and palpitations, became evident after the second shot on day X+21 and persisted until Day X+28.

It is difficult to clarify causal relationships between vaccinations and adverse events due to both confounding and masking factors. Furthermore, physicians may be unaware of rare, potential adverse events associated with vaccination. Currently, it is not clear how the Pfizer-BioNTech SARS-CoV-2 vaccine might elicit Graves' disease. While RNA itself and/or lipid nanoparticles that encapsulate RNA may act as an adjuvant for the Pfizer-BioNTech SARS-CoV-2 vaccine to cause Graves' disease as an ASIA, it has also been suggested that SARS-CoV-2 spike proteins encoded by the Pfizer-BioNTech mRNA might cross-react with human thyroid proteins to cause Graves' disease (12, 17). Further investigations will be required to determine the causal relationship and identify underlying mechanisms.

About 20% to 25% of patients with type 1 diabetes have thyroid antibodies, and up to 50% of them go on to develop autoimmune thyroiditis (18). HLA-DPB1*0501 carriers are reportedly susceptible to the onset of Graves' disease (odds ratio 3.16), and HLA-A*2402 carriers are protected (odds ratio 0.62) (19). Our current patient had both alleles as well as HLA-DRB1*0405 and DQB1*0401 levels that are reported to be associated with AISA (16). Thus, our patient had a genetic predisposition to Graves' disease that may well have been exacerbated by vaccination. Studies focusing on the relationship between a genetic predisposition for the development of ASIA, including Graves' disease, and the various SARS-CoV-2 vaccines are therefore warranted.

In conclusion, we encountered a patient with type 1 diabetes who developed signs of Graves' disease as soon as the day after receiving the Pfizer-BioNTech's SARS-CoV-2 vaccine. Our findings indicate that attention to ASIA-related endocrinological diseases in certain individuals receiving SARS-CoV-2 vaccines is appropriate.

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

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