CASE REPORT

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

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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 diseases (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

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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.

| Test                  | 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      | 34.2×10^4 | 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 phosphokinase, FT3: free triiodothyronine, FT4: free thyroxine, γ-GTP: 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.

| Test                  | Value                  | Reference Value |
|-----------------------|------------------------|-----------------|
| Thyroglobulin         | 5.4 ng/mL (<33.7)      |                 |
| Anti-TPO Ab           | 481 IU/mL (<16)        |                 |
| Anti-Tg Ab            | 82 IU/mL (<28)         |                 |
| TRAb                  | 11.9 IU/L (<2.0)       |                 |
| 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)     |                 |
| PRA                   | 1.9 ng/mL/h (0.2-2.3)  |                 |
| PAC                   | 57.1 pg/mL (4.0-8.2)   |                 |
| GH                    | 0.30 ng/mL             |                 |
| IGF-1                 | 132 ng/mL (-1.8 SD)    |                 |
| PRL                   | 17.9 ng/mL (6.12-30.54)|                 |
| LH                    | 6.01 mIU/mL            |                 |
| FSH                   | 4.29 mIU/mL            |                 |
| Dopamine              | ≤5 pg/mL (<20.0)       |                 |
| Adrenaline            | 10 pg/mL (<100)        |                 |
| Noradrenaline         | 41 pg/mL (100-450)     |                 |

Values in parentheses are reference values. ACTH: adrenocorticotropic 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.

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. 99mTc scintigraphy

Figure 2. Imaging analysis findings of the thyroid gland in the current case. A: Thyroid ultrasonography. The estimated thyroid volume was 45.2 cm³, and marked swelling was observed (left). Thyroid ultrasonography revealed diffuse hyperperfusion in the thyroid gland (right). B: 99mTc scintigraphy. Diffuse hyperaccumulation was observed in the thyroid gland (99mTc uptake 18.8% in the current case; normal range 0.5-4.0%).

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 observed in patients with autoimmune disease who received the COVID-19 vaccine.

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.
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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