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Case Report
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New-Onset Fulminant Type 1 Diabetes Following SARS-CoV-2 Protein Subunit Vaccine: A Case Report and Literature Review

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ABSTRACT

The ravages of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide have sped up the development of relevant vaccines, which is accompanied by public concerns over possible adverse effects. We report a rare case of a 39-year-old woman who suffered from severe hyperglycemia and ketoacidosis with normal hemoglobin A1c four days after SARS-CoV-2 protein subunit vaccine, which is consistent with the diagnosis of fulminant type 1 diabetes (FT1D). She received insulin therapy and recovered after 24 days from onset of the symptoms. This is the first case of new-onset FT1D after SARS-CoV-2 protein subunit vaccination and one of only six that developed after any form of SARS-CoV-2 vaccination. We hope to raise awareness of this potential adverse consequence and recommend careful monitoring after vaccination in patients even without a medical history of diabetes.

Keywords: Fulminant Type 1 Diabetes; SARS-CoV-2 Vaccine; Protein Subunit Vaccine; Adverse Effects

INTRODUCTION

With the outbreak of the coronavirus disease 2019 (COVID-19) across the world, vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have achieved accelerated clinical development to alleviate the burden of COVID-19 on public health. More than 11 billion SARS-CoV-2 vaccine doses have been administered in the world.[1] According to World Health Organization statistics,[2] the protein subunit vaccine has become the predominant category (accounting for 32% of all vaccines), followed by the RNA-based vaccine (23%), the non-replicating viral vector (14%), and the inactivated virus (12%).

Considering the unprecedented health burden induced by the COVID-19 pandemic, most vaccines have received emergency use authorization, though they have not been extensively whetted for their possible adverse effects. Therefore, public concerns over the possible adverse effects of these vaccines have emerged. A series of reports about autoimmune/inflammatory diseases induced by SARS-CoV-2 vaccines have attracted more and more attention, such as Graves' disease,[3] autoimmune hepatitis,[4-6] systemic lupus erythematosus,[7] and so on. Fulminant type 1 diabetes (FT1D) is a rapidly progressing and severe subtype of

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Liang M, He Y. Data curation: Huang L. Formal analysis: Huang L. Funding acquisition: Huang L. Investigation: Huang L. Methodology: Huang L. Project administration: Huang L. Resources: Huang L. Supervision: Liang M, He Y. Validation: Liang M, He Y. Visualization: Liang M. Writing - original draft: Huang L. Writing - review & editing: Liang M, He Y.

type 1 diabetes (T1D) with high mortality and disability rate. Recently, several cases have been reported about new-onset FT1D following SARS-CoV-2 vaccination, but only limited to mRNA vaccine[8-11] and inactivated vaccine.[12] Up to now, no cases have been reported about FT1D followed by SARS-CoV-2 protein subunit vaccination.

Herein, we reported a 39-year-old Chinese woman with new-onset FT1D four days after SARS-CoV-2 protein subunit vaccination. Meanwhile, we conducted a systematic review on the comparison between FT1D and autoimmune T1D followed by SARS-CoV-2 vaccination, so as to gain a better understanding of SARS-CoV-2 vaccine-related FT1D. We highly acknowledge the importance and benefits of mass SARS-CoV-2 vaccination, but we still hope to raise public awareness of its possible adverse effects and attach importance to the pharmacovigilance in guiding treatment.

CASE DESCRIPTION

We reported a 39-year-old woman with a family history of diabetes. She had no medical history of diabetes and the fasting blood glucose from her annual physical examination report seven weeks ago was 104.4 mg/dL. She attended a nearby hospital six days after the fourth dose of SARS-CoV-2 vaccination (Zifivax/ZF2001, Protein subunit vaccine) and complained of general fatigue, thirst, nausea and vomiting for 2 days. At presentation, the laboratory tests reported hyperglycemia (plasma glucose: 508.50 mg/dL) and ketoacidosis with a decreased bicarbonate and an increased anion gap (anion gap = [Sodium – {Bicarbonate + Chloride}] = 18.23 mmol/L, normal range ≤ 16 mmol/L). It was worth noting that the onset hemoglobin A1c (HbA1c) (5.9%) was below the threshold of diabetes. Pancreatic enzymes and thyroid function were normal. The initial diagnoses were diabetes and diabetes ketoacidosis (DKA). Then she received massive fluid infusion and intravenous insulin infusion and her symptoms relieved during a 10-day hospitalization in the nearby hospital.

Ten days later, she was transferred to our hospital due to poor blood glucose control and hoped for a definite diagnosis. On admission, her body mass index (BMI) was 17.97 kg/m^2. Oral glucose tolerance test showed exhaustion of endogenous insulin secretion (fasting C-peptide: 0.01 ng/mL, 120-minute C-peptide: 0.13 ng/ml). In terms of islet-specific pancreatic autoantibodies, anti-glutamic acid decarboxylase (GAD) antibody, anti-islet cell antibody (ICA), insulin autoantibody, insulinoma-associated antigen-2 (IA-2) antibody and zinc-transporter 8 (ZnT8) antibody showed all negative. In light of the characteristics at onset and results above, she was diagnosed with FT1D. Further immunological tests showed a significantly reduction in T lymphocyte count. The CD4+ and CD8+ T lymphocyte count were both at a lower level though within the normal range (**Table 1**). We applied the continuous glucose monitoring after admission, and found high glucose variability (time in range [TIR]: 55.2–65.0%; time below range [TBR]: 10.4–33.3%; time above range [TAR]: 1.7–34.4%; glucose range: 2.2–25.0mmol/L; coefficient of variation [CV]: 45.05–70.02%) and recurrent hypoglycemia, which frequently occurred in the early morning. In order to control the blood glucose, insulin pump (Medtronic, Minneapolis, MN, USA) was used for five days. The dosage and category of insulin used in the insulin pump was 8.1 units of insulin aspart per day (the hourly dosage of insulin: 0.4 units per hour from 8 a.m.to 10 p.m., 0.2 units per hour from 10 p.m. to 3 a.m. of the next day and 0.3 units per hour from 3 a.m. to 8 a.m. of the next day). Five days later, she gained a more stable blood glucose curve (TIR: 76.1%; TBR: 0%; TAR: 23.9%; glucose range: 7.4–14.0 mmol/L; CV: 15.52%), so we switched the insulin pump

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to subcutaneous injection of insulin four times per day. Two weeks later, the blood glucose curve remained stable (TIR: 88.3%; TBR: 0%; TAR: 11.7%; glucose range: 4.7–15.6mmol/L; CV: 36.34%) and we completed the continuous glucose monitoring.

Table 1. Laboratory findings

Assessment	Results	Reference range
Peripheral blood		
White blood cell, $\times 10^9$/L	7.64	4.00–10.00
Red blood cell, $\times 10^{12}$/L	4.79	3.50–5.50
Hemoglobin, g/L	132.00	110.00–160.00
Hematocrit, %	40.10	35.00–50.00
Platelet, $\times 10^9$/L	230.00	100.00–300.00
Biochemistry		
ALT, U/L	7.00	0–40.00
AST, U/L	17.95	0–40.00
GGT, U/L	13.30	7.00–45.00
ALP, U/L	53.59	35.00–100.00
Albumin, g/L	32.71	35.00–55.00
BUN, mmol/L	6.57	1.70–8.30
Creatinine, μmol/L	76.14	35.00–80.00
Creatine kinase, U/L	93.16	24.00–170.00
Bicarbonate, mmol/L	12.87	20.00–29.00
Potassium, mmol/L	4.44	3.50–5.30
Sodium, mmol/L	137.10	135.00–147.00
Chloride, mmol/L	106.00	96.00–108.00
Free thyroxine, ng/dL	0.83	0.70–1.48
TSH, μIU/mL	2.64	0.35–4.94
Plasma amylase, U/L	109.54	10.00–120.00
Glucose, mg/dL	508.50	60.48–109.98
HbA1c, %	5.90	4.27–6.07
Plasma ketone, mmol/L	2.90	
Serum insulin, pmol/L		13.00–161.00
0 min	0.01	
30 min	2.07	
60 min	3.42	
120 min	5.60	
180 min	5.90	
Serum C-peptide, ng/mL		0.93–3.73
0 min	0.01	
30 min	0.03	
60 min	0.07	
120 min	0.13	
180 min	0.13	
Immunological data		
GAD antibody	Negative	
IA-2 antibody	Negative	
ZnT8 antibody	Negative	
Insulin autoantibody	Negative	
Anti-islet cell antibody	Negative	
T lymphocyte count, /μL	1,078	1,185–1,901
CD4+ T lymphocyte count, /μL	665	561–1,137
CD8+ T lymphocyte count, /μL	367	220–1,030
IL-6, pg/mL	2.77	0–7.00
Ferritin, ng/mL	24.53	4.63–204.00
Urinary test		
Urinary glucose	4+	
Urinary ketone	3+	
Urinary protein	Negative	
Urinary occult blood	Negative	
Urinary amylase, U/L	269.51	120.00–1,100.00

ALT = alanine aminotransferase, AST = aspartate transaminase, GGT = glutamyl transpeptidase, ALP = alkaline phosphatase, BUN = blood urea nitrogen, TSH = thyroid-stimulating hormone, HbA1c = hemoglobin A1c, GAD = glutamic acid decarboxylase, IA-2 = insulinoma-associated antigen-2, ZnT8 = zinc-transporter 8, IL-6 = interleukin-6.

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Ethics statement

Ethical review of the present case report was waived by the review board of the First Affiliated Hospital of Guangxi Medical University. Informed consent for data collection and publication of the study was obtained from the patient.

DISCUSSION

To the best of our knowledge, this is the first case of FT1D induced by SARS-CoV-2 protein subunit vaccine. Although we could not confirm the objective causal relationship, the temporal relationship indicated a strong link between SARS-CoV-2 protein subunit vaccine and FT1D.

New-onset T1D has been observed following SARS-CoV-2 infection.[13,14] This phenomenon could be explained by the fact that the spike protein on the surface of SARS-CoV-2 virus can facilitate viral entry into islet cells via angiotensin converting enzyme 2 (ACE2), a membrane-bound receptor, and then initiate the imbalance of T lymphocytes and the activation of cytokine storm, thus inducing islet beta cell apoptosis and DKA.[15-18] As an emerging and promising SARS-CoV-2 vaccine, the protein subunit vaccine utilizes recombinant protein technology to produce the extracellular portion of the spike protein of SARS-CoV-2.[19,20] Due to structural homology, molecular mimicry could be proposed to cause hyperglycemia after SARS-CoV-2 vaccination. It is possible that the spike protein in the SARS-CoV-2 vaccines could cross-react with the ACE2 receptors of islet cells target proteins due to molecular mimicry to cause islet cells damage. The mechanism of molecular mimicry has been also proposed to prove the causal relationship between thyroid dysfunction and SARS-CoV-2 vaccination.[21] However, the mechanism of FT1D induced by SARS-CoV-2 vaccination still needs further research.

We further conducted searches in PubMed, Web of Science, and MEDLINE database for existing reported cases of FT1D induced by SARS-CoV-2 vaccination in order to have a better understanding of the clinical characteristics of SARS-CoV-2 vaccine-related FT1D. Five related cases were finally included. As shown in **Table 2**, patients with FT1D followed by SARS-CoV-2 vaccination were predominantly female (four female vs. two male), young and middle-aged (range from 36 to 59 years old) and thin (BMI range from 17.97 to 20.6 kg/m^2). These reported vaccines included four mRNA vaccines and one inactivated vaccine while our present case was the first case with respect to the protein subunit vaccine. The duration from symptoms onset to diagnosis among these cases were all within seven days. The levels of serum pancreatic enzyme were slightly elevated in some cases,[8,10,12] corresponding to previous reported cases of FT1D.[22,23] This phenomenon could be explained by leukomonocyte infiltration in exocrine pancreatic acinar cells rather than insulitis.[24] As for islet-specific pancreatic autoantibodies, there were only two cases with positive GAD antibody. We further compared the cases with positive and negative GAD antibodies, and found that positive GAD antibodies were significantly associated with more complete destruction and worse secretion capacity of islet beta cells. Kawasaki et al. have showed that the proportion of GAD antibody accounted for 9% of FT1D patients,[23] which shared a similarity with these cases. This indicated that islet-associated autoimmune processes may partake in the pathogenesis of FT1D patients with positive GAD antibodies.[22]

Moreover, we conducted a systematic review on the comparison between FT1D and autoimmune T1D followed by SARS-CoV-2 vaccination. After searching PubMed, Web of

Table 2. Comparison of characteristics of FT1D after SARS-CoV-2 vaccination

Characteristics	Reported cases					
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Author	Sakurai et al.[8]	Lin et al.[9]	Tang et al.[12]	Kobayashi et al.[10]	Sasaki et al.[11]	Present case
Sex	Female	Female	Male	Male	Female	Female
Age, yr	36	39	50	59	45	39
Vaccine	RNA	RNA	Inactivated vaccine	RNA	RNA	Protein subunit
Time from vaccination to onset	3 days	14 wk	6 days	15 wk	3 days	4 days
Time from symptom onset to DKA	7 days	≤ 7 days	1 days	6 days	5 days	2 days
BMI, kg/m^2	NA	19.2	18.1	NA	20.6	17.97
Plasma glucose levels, mg/dL	501	364	Elevated	1454	469	508
HbA1c, %	7	6.4	Elevated	7.8	7.2	5.9
Serum pancreatic enzyme, U/L	Slightly elevated	NA	Slightly elevated	Slightly elevated	NA	Normal
Fasting C-peptide	0.55	< 0.02	0.01	< 0.03	0.33	0.01
GAD antibody	(–)	(+)	(–)	(+)	(–)	(–)
IA-2 antibody	(–)	(+)	(–)	(–)	(–)	(–)
ZnT8 antibody	(–)	NA	(–)	(–)	(–)	(–)
Insulin autoantibody	(–)	NA	NA	NA	(–)	(–)
TPOAb	NA	NA	NA	(–)	(–)	NA
TgAb	NA	NA	NA	(–)	(–)	NA
Previous diabetes history	(–)	(–)	(–)	(–)	NA	(–)
Family history of diabetes	(–)	T2D	T2D	(–)	NA	T2D

FT1D = fulminant type 1 diabetes, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, DKA = diabetes ketoacidosis, BMI = body mass index, HbA1c = hemoglobin A1c, GAD = glutamic acid decarboxylase, IA-2 = insulinoma-associated antigen-2, ZnT8 = zinc-transporter 8, TPOAb = thyroperoxidase antibodies, TgAb = thyroglobulin antibodies, T2D = type 2 diabetes, (–) = negative, NA = not available.

Science, and MEDLINE database for existing reported cases of new-onset T1D following SARS-CoV-2 vaccination, six cases with FT1D and eight cases with autoimmune T1D following SARS-CoV-2 vaccination were included. The characteristics of FT1D and autoimmune T1D after SARS-CoV-2 vaccination were summarized in **Table 3**. Patients with FT1D following vaccination were predominantly younger, female, and thinner. The first symptoms of FT1D were mostly typical symptoms of DKA, and some were accompanied by adverse reactions of vaccines such as fatigue and a slight fever.[10-12] Patients with FT1D were more likely to have shorter onset time, more serious ketoacidosis, and lower HbA1c. The levels of amylase

Table 3. Comparison between fulminant T1DM and autoimmune T1DM after SARS-CoV-2 vaccination

Variables	Fulminant T1DM	Autoimmune T1DM
Age, yr		
Median (range)	42 (36–59)	54 (27–73)
Sex		
Female/Male	4/2	4/4
BMI, kg/m^2		
Median (range)	18.6 (17.97–20.6)	21.9 (18.3–27.4)
HbA1c, %		
Median (range)	7 (5.9–7.8)	10.3 (8.2–12.6)
Serum pancreatic enzyme	Slightly high/Normal	Normal
Serum C-peptide, ng/mL		
Median (range)	0.01 (0.01–0.55)	0.92 (0.4–1.5)
Severity of acidosis	Serious	Partly serious
GAD antibody		
Positive ratio	2/6	8/8
IA-2 antibody		
Positive ratio	1/6	1/3
TPOAb	Negative	Partly positive
TgAb	Negative	Partly positive

T1DM = type 1 diabetes mellitus, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, BMI = body mass index, HbA1c = hemoglobin A1c, GAD = glutamic acid decarboxylase, IA-2 = insulinoma-associated antigen-2, TPOAb = thyroperoxidase antibodies, TgAb = thyroglobulin antibodies.

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increased in some FT1D patients.[8,10,12] Most cases with FT1D reported negative GAD antibodies while all patients with autoimmune T1D had positive GAD antibodies.

In conclusion, we reported a patient with typical fulminant type 1 diabetes four days after SARS-CoV-2 protein subunit vaccination. The normal fasting blood glucose in the physical examination report seven weeks ago and normal HbA1c onset of this patient confirmed the connection between FT1D and this vaccine. We could not confirm the causal relationship between them, which requires long-term and large-scale population research. Nevertheless, we summarized the characteristics of the currently published FT1D following SARS-CoV-2 vaccination to help clinicians make early diagnosis and treatment. We highly appreciate the tremendous benefits of large-scale SARS-CoV-2 vaccination, but we still hope to alert about related adverse consequences and strengthen the pharmacovigilance and supervision during mass SARS-CoV-2 vaccination. It is important for clinicians to remain vigilant for acute deterioration of hyperglycemia and acidosis and we also recommend careful monitoring following SARS-CoV-2 vaccination even without a medical history of diabetes. Early identification and treatment can halt the progression of FT1D and prevent complications.

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