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【 CASE REPORT 】

New-onset Fulminant Type 1 Diabetes Following COVID-19 Vaccination

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Abstract:

A 31-year-old Japanese man was admitted with a slight fever and epigastric pain. He had received his third Moderna Coronavirus disease 2019 (COVID-19) vaccine dose (Spikevax, mRNA-1273) 16 days before his visit. His serum amylase level was elevated, and computed tomography found pancreatic enlargement. Acute pancreatitis was diagnosed, and the patient was treated with fasting and intravenous fluids. However, on day 3 of hospitalization, his blood glucose level had increased to 320 mg/dL. His serum and urinary C-peptide were remarkably low (≤0.03 ng/mL and ≤0.6 μg/day, respectively). Finally, fulminant type 1 diabetes mellitus caused by the COVID-19 mRNA vaccine was diagnosed.

Key words: fulminant type 1 diabetes mellitus, COVID-19 RNA vaccine, pancreatic enlargement, autoimmune disease

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Introduction

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, in December 2019 and then quickly spread throughout the world, causing many deaths. Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were produced in 2020, and vaccination was started in Japan in 2021. These vaccines have improved the morbidity and mortality associated with COVID-19. However, immune-mediated disorders (1-3) related to SARS-CoV-2 mRNA vaccines, including type 1 diabetes (4-11), have recently been reported.

We herein report a case of fulminant type 1 diabetes following vaccination against SARS-CoV-2 and pancreatic changes at the onset of diabetes observed on computed tomography (CT).

Case Report

A 31-year-old Japanese man visited the emergency department of the study center with a 4-day history of a slight fever (around 37°C) and epigastric pain. The patient was previously healthy and had no history of diabetes or drug allergies. He had received a third dose of the Moderna COVID-19 vaccine [mRNA-1273; Spikevax, (Moderna, Cambridge, USA)] 16 days before his current visit. He had a slight fever the day after he was vaccinated but soon improved and experienced no other symptoms.

Laboratory tests revealed elevated pancreatic enzyme and C-reactive protein (CRP) levels. At presentation, his blood glucose level was slightly high, but his HbA1c level was normal (Table 1). CT revealed diffuse enlargement of the pancreas and an increased density of adipose tissue due to inflammation. Inflammation extends beyond the inferior pole of the kidney (Figure a, b). Acute pancreatitis was diagnosed, and the patient was admitted for treatment with fasting and intravenous fluids.

The epigastric pain and fever improved, but on hospital day 3, the patient reported dizziness and discomfort in the groin. His fasting glucose level was high (320 mg/dL), and his serum β-hydroxybutyrate and acetoacetic acid levels

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Table 1. Laboratory Data.

Complete blood count		Biochemistry	
WBC	3,500 /μL	AST	28 U/L
Neut	40.1 %	ALT	25 U/L
Baso	1.2 %	BUN	13.5 mg/dL
Lym	25.8 %	Cr	0.68 mg/dL
Mono	13.5 %	Na	136 mEq/L
Eo	19.4 %	K	4.6 mEq/L
Hb	14.4 g/dL	Cl	99 mEq/L
Plt	201,000 /μL	Amylase	284 U/L
		CRP	4.5 mg/dL
Endocrine examination		HbA1c	5.2 %
TSH	0.8 μIU/mL	Total ketone body	4,031 μmol/L
Free T3	3.02 pg/mL	Acetoacetic acid	663 μmol/L
Free T4	1.28 ng/dL	3-Hydroxybutyric acid	3,367 μmol/L
		GA	15.4 %
Immunological tests		Insulin	0.4 μU/mL
IgG4	74.2 mg/dL	C-peptide	≤0.03 ng/mL
GADAb	7.4 U/mL		
IA-2Ab	<0.6 U/mL	Urinalysis	
IAAb	<0.4 %	24h urinary C-peptide	≤0.6 μg/day
TgAb	<10 IU/mL		
TPOAb	2.1 IU/mL		
HLA typing analysis			
DRB1*04:10/15:01	DQB1*04:02/06:02		
Glucagon loading test (performed 1 month after discharge)			
(Before loading)		(After loading)	
C-peptide	≤0.03 ng/mL	C-peptide	≤0.03 ng/mL
Plasma glucose	104 mg/dL	Plasma glucose	138 mg/dL

WBC: white blood cell, Neut: neutrophil, Baso: basophil, Lym: lymphocyte, Mono: monocyte, Eo: eosinophil, RBC: red blood cell, Hb: hemoglobin, Plt: platelet, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, Cr: creatinine, Na: sodium, K: potassium, Cl: chloride, CRP: C-reactive protein, HbA1c: hemoglobin A1c, GA: glycoalbumin, TSH: thyroid-stimulating hormone, IgG: immunoglobulin G, GADAb: anti-glutamic acid decarboxylase antibody, IA-2Ab: anti-insulinoma-associated antigen 2 antibody, IAAb: insulin autoantibody, TgAb: anti-thyroglobulin antibody, TPOAb: anti-thyroid peroxidase antibody, HLA: human leukocyte antigen

were elevated (3,367 μmol/L and 663 μmol/L, respectively) (Table 1). No blood gas test was performed, and acidemia was not assessed. Insulin therapy was immediately initiated. The anti-glutamic acid decarboxylase antibody level was slightly elevated (7.4 U/mL), but anti-insulinoma-associated antigen-2 antibody and anti-insulin antibody levels were negative (Table 1).

His serum and urinary C-peptide levels were below measurement sensitivity, and his HbA1c level was low (5.2%) relative to his hyperglycemia (320 mg/dL). Based on these findings, the patient was diagnosed with fulminant type 1 diabetes mellitus. His blood glucose level was controlled using multiple subcutaneous insulin injections, and he was discharged 10 days after admission.

Interestingly, CT performed on hospital day 6 revealed that pancreatic enlargement had improved (Figure c). Human leukocyte antigen (HLA) typing revealed haplotypes DRB1*04:10-DQB1*04:02 and DRB1*15:01-DQB1*06:02, which were previously not known to be associated with type 1 diabetes (Table 1).

Discussion

The patient was initially admitted with a diagnosis of acute pancreatitis, which was based on CT findings on admission for pancreatic enlargement and blood test findings of elevated pancreatic exocrine enzymes. CT and other imaging studies have demonstrated temporary pancreatic enlargement in fulminant type 1 diabetes mellitus. An autopsy performed immediately after the onset of fulminant type 1 diabetes mellitus revealed lymphocytic infiltration of the pancreatic exocrine glands and pancreatic islets (12). In contrast, a pathological study of the pancreas one month after the onset of fulminant type 1 diabetes reported no insulitis

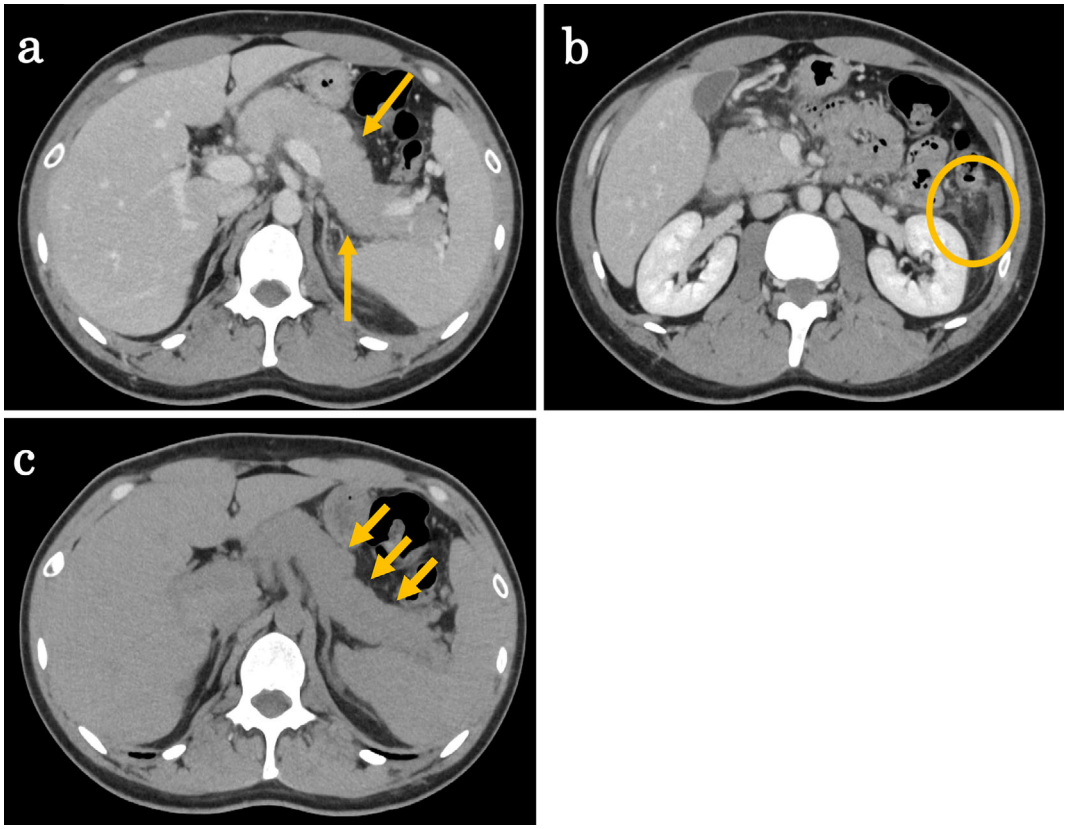

Figure. **a: Diffuse enlargement of pancreas (orange arrows). b: Fatty tissue concentration around the pancreas was elevated and the inflammation extended beyond the inferior pole of the kidney (orange circle). c: The pancreatic enlargement was improved (orange arrows).**

or inflammation in the surrounding, pancreatic tissue (13). In fulminant type 1 diabetes mellitus, inflammation occurs not only in the islets but also in the pancreatic exocrine glands immediately after disease onset. This is thought to account for the elevated pancreatic exocrine enzymes in the blood and the pancreatic enlargement seen on CT, with inflammation occurring only during the acute phase of the disease (at most one month). In the present case, the possibility of autoimmune pancreatitis was considered but eventually ruled out because the IgG4 level was normal (74.2 mg/dL) (Table 1), the pancreatic swelling improved, and the serum amylase normalized without glucocorticoid therapy.

In Japan, seven cases of fulminant type 1 diabetes mellitus observed with CT, including the present case, have been reported thus far (Table 2). Half of the patients experienced pericardial pain and abdominal symptoms. The serum amylase level fluctuated but was higher than the reference value in all cases. In most instances, pancreatic enlargement preceded the rise in blood glucose and improved within a few days to two weeks.

The present patient was a young man with no history or family history of diabetes. He had no symptoms suggestive of a past infection characteristic of fulminant type 1 diabetes or a history of drug use, such as immune checkpoint inhibitor therapy, that might have caused fulminant type 1 diabetes. The patient had received his third COVID-19 vaccine [mRNA-1273; Spikevax, (Moderna)] 16 days prior to experiencing diabetic symptoms, raising the index of suspicion for fulminant type 1 diabetes mellitus resulting from a COVID-19 vaccine. To date, four cases of fulminant type 1 diabetes have been reported following COVID-19 mRNA vaccination. All patients received one to three doses of the vaccine before the onset of fulminant type 1 diabetes. The duration from vaccination to disease onset ranged from 3 days to 15 weeks. Unlike most patients (4/5) who experienced diabetes onset after COVID-19 vaccination, patients with fulminant type 1 diabetes are usually negative for anti-glutamic acid decarboxylase (GAD) antibody. However, the mechanism underlying this association remains unknown (Table 3).

The frequencies of HLA types DRB1*04:05-DQB1*04:01 and DRB1*09:01-DQB1*03:03 are high in Japanese patients with fulminant type 1 diabetes (20). All patients who experienced fulminant type 1 diabetes onset after receiving the COVID-19 mRNA vaccine had either or both HLA types (one patient was not assessed for HLA types) (Table 3).

In this case, the HLA types were DRB1*04:10-DQB1*04:02 and DRB1*15:01-DQB1*06:02. DRB1*15:01-DQB1*06:02, which the present patient had, is known to confer resistance to acute-onset type 1 diabetes and slowly progressive type 1 diabetes but not to fulminant type 1 diabetes (20). There have been previous reports of their occurrence in the context of this disease (21). The haplotype difference may be related to the difference between cases in which this re-

Table 2. Characteristics of Japanese Patients with Fulminant Type 1 Diabetes Mellitus Evaluated by CT over Time.

No. (Ref.)	1 (14)	2 (15)	3 (16)	4 (17)	5 (18)	6 (19)	7
Age (years)	55	31	23	38	55	30	31
Sex	Male	Female	Male	Female	Male	Male	Male
Drinking history (per day)	Rice wine 540 mL	Beer 700 mL Cocktail 700 mL	Social	Rice wine 360 mL	None	Social	Cocktail 500 mL
Chief complaint	Fever, abdominal distension	Epigastric pain, back pain	Disturbance of consciousness	Vomiting, epigastric pain	Thirst, polyuria, erythema over the entire body	Left-sided abdominal pain	Epigastric pain
Presence of abdominal pain	No	Yes	Yes	Yes	No	Yes	Yes
Serum amylase	1,071 IU/L	465 IU/L	1,014 IU/L	507 IU/L	150 IU/L	N/A	284 IU/L
BG on admission	107 mg/dL	91 mg/dL	2,149 mg/dL	92 mg/dL	807 mg/dL	45 mg/dL (day 2)	182 mg/dL
BG (maximum value)	344 mg/dL (day 6)	703 mg/dL (day 5)	2,149 mg/dL (on admission)	498 mg/dL (day 12)	807 mg/dL (on admission)	400 mg/dL (day 4)	320 mg/dL (day 3)
Time to improvement of pancreatic enlargement*	10 days	7 days	3 days	13 days	36 days	9 days	6 days

*Pancreatic enlargement was confirmed by computed tomography on admission or before hospital transfer in all the patients.

BG: blood glucose, CT: computed tomography

Table 3. Characteristics of Patients with Fulminant Type 1 Diabetes Developing after SARS-CoV-2 mRNA Vaccination (Excluding Those with a History of Immune Checkpoint Inhibitor Therapy).

No. (Ref.)	1 (8)	2 (9)	3 (10)	4 (11)	5
Age (years)	59	39	45	47	31
Sex	Male	Female	Female	Male	Male
History of infection	Fever 4 days prior to onset	None	Fever 2 days prior to onset	None	None
Dose	2nd	3rd	1st	3rd	3rd
Time to onset	15 weeks	14 weeks	3 days	8 days	16 days
Plasma glucose	1,514 mg/dL	364 mg/dL	344 mg/dL	658 mg/dL	320 mg/dL
Hemoglobin A1c	7.8%	6.4%	7.6%	5.8%	5.2%
Autoantibodies	GAD Ab (+) IA-2 Ab (-) ZnT8 Ab (-) Tg Ab (-) TPO Ab (-)	GAD Ab (+) IA-2 Ab (-)	GAD Ab (-) IA-2 Ab (-) ZnT8 Ab (-) Tg Ab (-) TPO Ab (-)	GAD Ab (+) IA-2 Ab (-) Tg Ab (-) TPO Ab (-)	GAD Ab (+) IA-2 Ab (-) IA Ab (-) Tg Ab (-) TPO Ab (-)
Imaging findings	Magnetic resonance imaging (MRI) 8 days after onset showed no pancreatic enlargement	N/A	N/A	N/A	CT on admission showed pancreatic enlargement, which improved on day 6 of hospitalization
Pharmaceutical company	Pfizer-BioNTech	Pfizer-BioNTech	Pfizer-BioNTech	Pfizer-BioNTech	Moderna
HLA genotype	DRB1*04:05/09:01 DQB1*03:03/04:01	N/A	DRB1*04:05/13:02 DQB1*04:01/06:04	DRB1*04:05/13:02 DQB1*04:01/06:04	DRB1*04:10/15:01 DQB1*04:02/06:02

GAD Ab: anti-glutamic acid decarboxylase antibody, IA-2 Ab: anti-insulinoma-associated antigen 2 antibody, IA Ab: insulin autoantibody, ZnT8 Ab: zinc transporter 8 antibody, TgAb: anti-thyroglobulin antibody, TPOAb: anti-thyroid peroxidase antibody

action occurs acutely and those in which it does not. Furthermore, the vaccine administered in the present patient was manufactured by Moderna, unlike the vaccines in other reports, which were manufactured by Pfizer-BioNTech.

In addition to type 1 diabetes mellitus, other autoimmune diseases known to occur after COVD-19 mRNA vaccination include thyroid disease [subacute thyroiditis (n=54), painless thyroiditis (n=5), and Basedow disease (n=63)], Guillain Barré syndrome, and autoimmune hepatitis (1-3). The mechanism by which autoimmune diseases develop after COVID-19 vaccination involves the mRNA itself or polyethylene glycol acting as an adjuvant, triggering an autoimmune reaction (ASIA syndrome). It has also been suggested that monoclonal antibodies against the COVID-19 spike protein and nuclear protein may cross-react with human target proteins, including GAD65, which is associated with many forms of autoimmune disease (7). However, its precise mechanism of action has not yet been elucidated.

Care was required in interpreting the cause of the present case. Whether or not COVID-19 vaccination is associated with the development of fulminant type 1 diabetes remains unclear; only a few cases of new-onset fulminant type 1 dia-

betes following COVID-19 vaccination have been reported thus far despite the large number of vaccinations against COVID-19 which have been administered globally. The continued accumulation of data on this issue may help elucidate the underlying pathomechanism.

Conclusion

The present report describes a case of fulminant type 1 diabetes mellitus with acute pancreatitis-like symptoms and laboratory findings following COVID-19 vaccination. The present case is the first reported instance of fulminant type 1 diabetes mellitus in a patient with HLA subtypes atypical for this disease following the administration of the Moderna mRNA vaccine. There have been several reports of autoimmune disease development following COVID-19 mRNA vaccination. More cases are required to determine whether or not these autoimmune diseases, including fulminant type 1 diabetes, are associated with SARS-CoV-2 vaccination. When treating acute pancreatitis of unknown etiology, the possibility of fulminant type 1 diabetes mellitus should be considered, and blood glucose levels should be carefully monitored.

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

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