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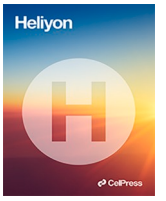

Case report

A case of new-onset Fulminant type 1 diabetes after secondary SARS-CoV-2 infection

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A B S T R A C T

Fulminant type 1 diabetes is a subtype of type 1 diabetes characterised by a rapid progression to diabetic ketoacidosis combined with a background of rapid and almost complete pancreatic islet destruction. FT1D induced by secondary SARS-CoV-2 infection is rare. Herein, we present the case of a 42-year-old male patient with new-onset FT1D after a secondary SARS-CoV-2 infection, with recurrent hyperglycaemia and ketosis as the primary manifestations. Eventually, the patient responded well after receiving more than 50 units of insulin daily. This case illustrates the importance of paying attention to severe hyperglycaemia accompanying recurrent ketosis, particularly among patients with secondary SARS-CoV-2 infection.

1. Introduction

Fulminant type 1 diabetes (FT1D) is a severe subtype of type 1 diabetes which progresses rapidly, resulting in near-complete destruction of the islet cells within a short period. FT1D is characterised by slightly elevated HbA1c levels, exhaustion of endogenous insulin secretion, and negative results for islet-associated autoantibodies [1]. The causative factors for FT1D vary, and include susceptibility genes, immunological factors, immune checkpoint inhibitor therapies, viral infections, vaccine inoculation, drug-induced hypersensitivity syndrome and pregnancy [2]. Understanding these triggers and promoting factors will play an important role in the prevention and treatment of FT1D. The triggering factors of this disease have been previously reported, and include vaccine inoculation, viral infections such as SARS-CoV-2 infection, and pregnancy [3]. However, no cases of SARS-CoV-2 secondary infection triggered by FT1D have yet been reported.

Herein, we present the first case of new-onset FT1D with recurrent hyperglycaemia and ketosis after secondary SARS-CoV-2 infection.

1.1. Case presentation

A 42-year-old man with no notable medical history experienced diabetic ketosis following a secondary infection with severe acute respiratory syndrome coronavirus 2(SARS-CoV-2). On 20 May 2023 the patient exhibited flu-like symptoms and tested positive for SARS-CoV-2 by polymerase chain reaction (PCR). Remarkably, the PCR result was negative after one week without any pharmacological intervention. Five weeks later, the patient presented with polydipsia and polyuria, accompanied by a weight loss of 10 kg prior to admission. Subsequently, the patient promptly sought care in our Endocrinology ward due to the presence of hyperglycaemia (blood glucose (BG), 21.4 mmol/L) and ketosis (serum ketone (SK) 2.4 mmol/L, urine ketone 2+, pH:7.35). Laboratory examinations revealed

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the presence of hyperglycaemia and ketosis, all antibody-negative, relatively lower levels of HbA1c (7.3 %), and extremely low fasting C-peptide level (0.14ng/mL). Physical examination was normal without special circumstances. The patient was developing normally, well-nourished and no yellowing of the skin and mucous membranes throughout the body. The visual examination, palpation, percussion, and auscultation of the heart, lungs, and abdomen were all normal. This patient had negative mobility dullness, with no palpable subcostal lesions in the liver and spleen and had no oedema in both lower limbs. His pathological signs were all negative and the muscle strength and tension of the limbs were normal. Special examination for diabetes: Body weight 89.0kg, Height 183.0cm, BMI 26.6kg/m^2. Normal acupuncture sensation, normal position/vibration sensation, cold and warm sensation symptoms, and normal pulsation of the dorsal arteries of both feet. The patient had been infected with SARS-CoV-2 twice, the first on April 19, 2022 and the second on May 20, 2023. Moreover, the patient was received three times vaccination for SARS-CoV-2. First dose vaccination time was

Table 1
The patient's Laboratory findings during hospitalization.

	Parameter	Results/1st admission	Results/2nd admission	Reference range
Arterial blood gas analysis	pH	7.35	7.28	7.35–7.45
	pCO_2, mmHg	36	38	35–45
	pO_2, mmHg	92	88	75–105
	HCO_3-, mmol/L	21.4	17.8	21.3–24.8
	Base excess, mmol/L	−3.40	−5.80	−3.00–3.00
	Lactic acid, mmol/L	1.28	1.88	0.5–2.2
Hematology	White blood cells, 10^9/L	7.68	10.05	3.5–9.5
	Red blood cells, 10^{12}/L	5.07	5.72	4.3–5.8
	Platelet, 10^9/L	191	223	125–350
Biochemistry	Plasma glucose, mmol/L	21.4	24.2	4.3–5.9
	Plasma ketones, mmol/L	2.4	1.8	<0.3
	Blood urea nitrogen, mmol/L	4.9	4.8	3.1–8.0
	Creatinine, umol/L	73	76	57–97
	Sodium, mmol/L	130.1	132.0	137–145
	Potassium, mmol/L	4.54	4.59	3.5–5.1
	Chlorine, mmol/L	96.6	99.0	99.0–110.0
	Hemoglobin A1c, %	7.3	7.6	4.5–6.3
	Fasting C-peptide, ng/mL	0.14	0.12	1.1–4.4
	Postprandial C-peptide, ng/mL	0.18	0.16	/
	Amylase, units/L	22.4	27.3	35.0–135.0
	Thyroid stimulating hormone, uIU/mL	1.87	1.90	0.35–4.94
Immunological tests	Anti-GAD antibody, IU/mL	(−)	(−)	(−)
	Anti-IA-2A, IU/mL	(−)	(−)	(−)
	Anti-insulin antibody, IU/mL	(−)	(−)	(−)
	Anti-islet cell antibody, IU/mL	(−)	(−)	(−)
	Antithyroglobulin antibody, IU/mL	(−)	(−)	(−)
	Antithyroid peroxidase antibody, IU/mL	(−)	(−)	(−)
	Total immunoglobulin IgE, IU/mL	77.90(−)	NA	0–100
	Immunoglobulin IgG, g/L	17.5	NA	7.51–15.6
	Immunoglobulin IgA, g/L	3.02(−)	NA	0.82–4.53
	Immunoglobulin IgM, g/L	0.60(−)	NA	0.46–3.04
	Serum Complement C3, g/L	0.89(−)	NA	0.79–1.52
	Serum Complement C4,g/L	0.24(−)	NA	0.16–0.38
	Rheumatoid factor, RF, IU/mL	<20.00(−)	NA	0–20
Inflammatory factors	Interleukin-1β, pg/ml	<5	NA	<5
	Human interleukin-2 receptor,U/ml	699	NA	223–710
	Interleukin-8, pg/ml	275↑	NA	<62
	Interleukin-10, pg/ml	<5	NA	<9.1
	Tumor necrosis factor-α, pg/ml	10.2↑	NA	<8.1
	Interleukin-6, pg/ml	6.47	NA	0–7
Urinalysis	Ketones	Positive(2+)	Positive(2+)	(−)
Infection	Epstein-Barr virus IgM antibody	(−)		(−)
	Antistreptolysin O	53.2(−)		(−)
	Coxsackievirus IgM antibody	(−)		(−)
	Cytomegalovirus DNA PCR	(−)		(−)
	Adenovirus	(−)		(−)
	Bordetella pertussis PCR	(−)		(−)
	Mycoplasma pneumoniae PCR	(−)		(−)
	Chlamydia pneumoniae PCR	(−)		(−)
	Influenza A virus PCR	(−)		(−)
	Influenza B virus PCR	(−)		(−)
	Respiratory syncytial virus PCR	(−)		(−)
	Secondary SARS-CoV-2 PCR	Omicron BA.5		(−)
	First SARS-CoV-2 PCR	Omicron BA5.2		(−)

GAD: Glutamic Acid Decarboxylase; IA-2A: Human Islet Antigen-2 Antibody; PCR: Polymerase Chain Reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome- Coronavirus-2.

April 8, 2021, the second was May 7, 2021 and the third was December 1, 2021. This medical history information was necessary to rule out the possibility that FT1D of this patient is related not to vaccination for SARS-CoV-2 but infection of SARS-CoV-2.

The biochemical characteristics on admission are detailed in Table 1. Subsequently, the patient was diagnosed with FT1D. Following admission, we implemented continuous glucose monitoring and continuous intravenous insulin pump (IIP) therapy at approximate 34.3 units (IU) per day, in conjunction with approximately 1750mL of fluid infusion and acarbose administration at 50 mg Ter in die (TID). By the fifth day, blood glucose levels were improved significantly, remaining stable within the normal range and urinary ketone turned negative. The continuous glucose monitoring report shown that the coefficient of variation of glucose is 14.74 %. The IIP was discontinued owing to a consistent downward trend in BG. Subsequently, the patient was administered a basal-bolus subcutaneous insulin regimen comprising 22 IU of insulin glargine once daily and 8 IU of insulin aspart before breakfast, lunch, and dinner. This treatment was supplemented with acarbose at a TID of 50 mg.

Two weeks later, the patient presented with recurrent hyperglycaemia (BG 24.2 mmol/L) and ketoacidosis (pH 7.28, $HCO3^-$ 17.8mmol/L, Base excess −5.8mmol/L, lactate 1.88mmol/L, SK 1.8 mmol/L). The patient was readmitted to our ward. All biochemical characteristics during the 2nd admission were detailed in Table 1. He was initiated on IIP therapy, with a total daily dose of 47.1 IU, along with the oral agents pioglitazone metformin (500 mg bis in die, BID), Metformin (0.5 g QD), and acarbose (100 mg TID). After seven days, the patient achieved a more stable BG profile, and ketonuria returned to normal. The continuous glucose monitoring report shown that the coefficient of variation of glucose is 16.17 %. Consequently, we opted to transition from IIP to subcutaneous administration of insulin four times per day, including administration of 35 IU of insulin glargine once daily and 7 IU of Novorapid daily before three meals. Oral medications remained unaltered. The patient was discharged on August 4, 2023 when plasma glucose level was stabilized and glucose toxicity was completely relieved. At that time of reexamination, the fasting serum C-peptide value was 0.12ng/mL indicating completely failure of islet cell function, which was consistent with the diagnosis of FT1D. After one month, the follow-up C-peptide (fasting, 120min after meals) were 0.16ng/mL, 0.19ng/mL respectively and blood glucose (120min) was 6.8mmol/L. C-peptide was in a low and flat state whether in the fasting or non-fasting which indicating that after management of acute hyperglycemia, islet cell function was still almost completely failure.

2. Discussion

FT1D development following SARS-CoV-2 secondary infection is an exceedingly rare condition which can nevertheless endanger life due to rapid progression to diabetic ketoacidosis and almost complete failure of the pancreatic islet β cells. To date, six cases of newly diagnosed FT1D after SARS-CoV-2 vaccination have been reported [4] while only one case of new-onset FT1D caused by SARS-CoV-2 has been reported [5]. In contrast to previous reports, our case represents the sole instance aligned with the diagnosis of FT1D caused by a secondary SARS-CoV-2 infection. The patient initially experienced flu-like symptoms after initial infection of SARS-CoV-2. However, after secondary infection, the patient developed severe hyperglycaemia and ketosis, accompanied by rapid advancement of insulin deficiency. However, whether secondary SARS-CoV-2 infection increases the risk of pancreatic islet cell dysfunction remains unknown.

Table 2
Comparison of characteristics of FT1D after first and secondary SARS-CoV-2 infection.

	Reported cases		
		case1	case 2
Characteristics	Author	Pan Y et al., 2023	Present case
	Sex	female	male
	Year	46	42
	Vaccine	RNA	inactivated vaccine
	Onset	12 days	5 weeks
	BMI, kg/m2	22.31	26.6
	Plasma glucose levels, mg/dl	618.6	385.2
	HbA1c(%)	6.7	7.3
	Antibody	all negative	all negative
	fasting C-peptide, ng/mL	0.19	0.21
	previous diabetes history	(−)	(−)
	family history of diabetes	(−)	(−)
	HLA typing	NA	NA
Treatment	On admission	Insulin pump: a continuous intravenous infusion of insulin of approximately 43.6 units per day.	insulin therapy: insulin pump(basal 22.3 units), bolus 12 uints; oral agents: Acarbose, pioglitazone/metformin, metformin
	Discharge	4-split insulin regimen(Glargine 15u SC before supper daily, Novorapid 9u, 6u, 6u, SC before three meals respectively)	4-split insulin regimen(Glargine 35u SC HS, Novorapid 7u SC TID)

SC: Subcutaneous; HS: hora somni; HLA: Human Leukocyte Antigen; TID: Ter in die.

FT1D has been reported to develop following infection some viruses, such as herpesvirus, HHV-6, cytomegalovirus, and coxsackievirus B3 [6,7] and cellular autoimmunity, such as $CD8^+$ T cell responses [8]. In this case, we did not find any viral infection other than SARS-CoV-2. Based on the clinical symptoms and laboratory examinations, we confirmed the diagnosis of FT1D. SARS-CoV-2 infection causes aberrant glycometabolism, exacerbating insulin resistance, and impairing peripheral glucose uptake through the release of cytokines, lipids, and counterregulatory hormones [9]. Virus-induced inflammatory cytokines and disruption of endothelial function are believed to injure β cell functions [10]. Previous preclinical studies have shown that spike proteins on the surface of SARS-CoV-2 can directly promote viral entry into islet cells via ACE2 and activate cytokines, leading to islet beta cell apoptosis and diabetic ketoacidosis (DKA) [11,12].

Of note, the patient with severe hyperglycaemia accompanying recurrent ketosis as well as a higher insulin dosage. Hyperglycaemia was difficult to correct until the insulin dosage reached 47.1IU (Table 2) which his demand for insulin was significantly higher than that of other patients. Several possible associated factors were suggested after consulting literature. We found that high insulin dosage may be related to the degree of overweight/obesity in patients [13,14]. A 5 % increase in body weight indicates insulin sensitivity in adipose tissue, liver and muscles will decline, as well as islet cell function will also decrease, which the underlying mechanism may be related to the adipose tissue expression of genes involved in cholesterol flux, lipid synthesis, extracellular matrix remodeling, and oxidative stress [15]. Progressive weight gain can lead to a decrease in metabolic function of multiple organs and alterations in key adipose tissue biological pathways [16]. Physicians should pay attention to such clinical manifestations, especially in patients with recent SARS-CoV-2 secondary infection.

Additionally, the case had certain limitations. Although we did not find any viral infection other than SARS-CoV-2. A previous clinical study had shown that SARS-CoV-2 infection causes aberrant glycometabolism, exacerbating insulin resistance. However, only this case alone was not enough to prove that SARS-CoV-2 is related to the development of FT1D.

3. Conclusion

In this case report, we aimed to raise awareness of the potential for the development of hyperglycaemia and ketoacidosis after secondary SARS-CoV-2 infection. Inflammatory cytokines must be emphasised in hyperglycaemic ketoacidosis after secondary SARS-CoV-2 infection in patients without diabetes. Early diagnosis or prediction of new-onset FT1D after secondary SARS-CoV-2 infection is critical for the prevention and timely treatment of diabetic ketoacidosis, which can be life-threatening. Finally, this case reminds clinicians to monitor patients carefully, especially those infected with SARS-CoV-2.

Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Patient consent

Informed consent has been obtained from the patient for publication of this case. The patient consented to the publishing of all images, clinical data, and other data included in the manuscript.

CRediT authorship contribution statement

Jie Wang: Writing – review & editing, Writing – original draft. **Yiwen Huang:** Writing – review & editing, Investigation. **Feng Tao:** Project administration, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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