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Contents

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World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 13 May 6, 2021

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 13 May 6, 2021

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 13 May 6, 2021

Contents

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Editorial Board Member of *World Journal of Clinical Cases*, Rama R Vunnam, MBBS, MD, Assistant Professor, Department of Medicine, Penn State Health Milton S. Hershey Medical Center, Hershey, PA 17033, United States. rvunnam@pennstatehealth.psu.edu

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CASE REPORT

Sodium-glucose co-transporter-2 inhibitor-associated euglycemic diabetic ketoacidosis that prompted the diagnosis of fulminant type-1 diabetes: A case report

Taro Yasuma, Yuko Okano, Soichiro Tanaka, Kota Nishihama, Kazuhito Eguchi, Chisa Inoue, Kanako Maki, Akihiro Uchida, Mei Uemura, Toshinari Suzuki, Corina N D'Alessandro-Gabazza, Esteban C Gabazza, Yutaka Yano

ORCID number: Taro Yasuma 0000-0002-9117-5679; Yuko Okano 0000-0002-8441-423X; Soichiro Tanaka 0000-0002-8240-6180; Kota Nishihama 0000-0002-0471-5164; Kazuhito Eguchi 0000-0002-4968-0217; Chisa Inoue 0000-0002-7022-9156; Kanako Maki 0000-0001-7061-0291; Akihiro Uchida 0000-0003-2589-8761; Mei Uemura 0000-0002-9140-0311; Toshinari Suzuki 0000-0003-0980-1763; Corina N D'Alessandro-Gabazza 0000-0003-2164-5775; Esteban C Gabazza 0000-0003-2536-898X; Yutaka Yano 0000-0003-0234-1207.

Author contributions: Yasuma T, Tanaka S, and Nishihama K were responsible for clinical treatment and clinical follow-up; Yasuma T prepared the first draft of the manuscript; Eguchi KC, Inoue CC, Maki KC, Okano Y, and Uchida A contributed with resources and acquisition of data; Suzuki T, D'Alessandro-Gabazza CN, Yano Y, and Gabazza EC contributed to the interpretation of the data and made an intellectual contribution to the manuscript's preparation.

Informed consent statement: Written informed consent was obtained from the patient to publish clinical details and images

Taro Yasuma, Yuko Okano, Department of Diabetes, Metabolism, and Endocrinology and Immunology, Mie University, Tsu 514-8507, Japan

Soichiro Tanaka, Kota Nishihama, Kazuhito Eguchi, Chisa Inoue, Kanako Maki, Akihiro Uchida, Mei Uemura, Toshinari Suzuki, Department of Diabetes, Metabolism, and Endocrinology, Mie University, Tsu 514-8507, Japan

Corina N D'Alessandro-Gabazza, Department of Immunology, Mie University School of Medicine, Mie University, Tsu 514-8507, Japan

Esteban C Gabazza, Department of Immunology, Mie University Faculty and Graduate School of Medicine, Tsu 514-8507, Japan

Yutaka Yano, Department of Diabetes, Mie University Graduate School of Medicine, Tsu 514-8507, Japan

Corresponding author: Esteban C Gabazza, MD, PhD, Director, Full Professor, Department of Immunology, Mie University Faculty and Graduate School of Medicine, Edobashi 2-174, Tsu 514-8507, Japan. gabazza@doc.medic.mie-u.ac.jp

Abstract

BACKGROUND

Fulminant type 1 diabetes mellitus (FT1DM) is a subtype of type 1 diabetes mellitus characterized by an abrupt onset and a rapid and complete functional loss of islet β cells. It is a very rare disease generally associated with ketoacidosis and the absence of circulating pancreatic islet-related autoantibodies. Diabetic ketoacidosis with normal blood glucose levels has been reported during sodium-glucose co-transporter 2 (SGLT2) inhibitor therapy.

CASE SUMMARY

The patient was a 43-year-old woman that consulted a medical practitioner for malaise, thirst, and vomiting. Blood analysis showed high blood glucose levels (428 mg/dL), a mild increase of hemoglobin A1c (6.6%), and increased ketone bodies in urine. The patient was diagnosed with type 2 diabetes mellitus. The patient was initially treated with insulin, which was subsequently changed to an

oral SGLT2 inhibitor. Antibodies to glutamic acid decarboxylase were negative. Four days after receiving oral SGLT2 inhibitor, she consulted at Mie University Hospital, complaining of fatigue and vomiting. Laboratory analysis revealed diabetic ketoacidosis with almost normal blood glucose levels. The endogenous insulin secretion was markedly low, and the serum levels of islet-related autoantibodies were undetectable. We made the diagnosis of FT1DM with concurrent SGLT2 inhibitor-associated euglycemic diabetic ketoacidosis. The patient's general condition improved after therapy with intravenous insulin and withdrawal of oral medication. She was discharged on day 14 with an indication of multiple daily insulin therapy.

CONCLUSION

This patient is a rare case of FT1DM that developed SGLT2 inhibitor-associated diabetic ketoacidosis with almost normal blood glucose levels. This case report underscores the importance of considering the diagnosis of FT1DM in patients with negative circulating autoantibodies and a history of hyperglycemia that subsequently develop euglycemic diabetic ketoacidosis following treatment with a SGLT2 inhibitor.

Key Words: Euglycemic diabetic ketoacidosis; Sodium-glucose cotransporter 2 inhibitors; Fulminant type 1 diabetes; Case report

Core Tip: Fulminant type 1 diabetes mellitus (FT1DM) is characterized by a rapid functional loss of islet β cells and ketoacidosis. Herein, we report a rare case of FT1DM wrongly diagnosed by a medical practitioner as a type 2 diabetes mellitus for the absence of circulating autoantibodies and treated with an oral sodium-glucose co-transporter 2 (SGLT2) inhibitor. This treatment was associated with diabetic symptoms and euglycemic diabetic ketoacidosis. Insulin therapy and SGLT2 inhibitor withdrawal ameliorated the patient's clinical condition. This case report underscores the importance of considering FT1DM in patients with negative circulating autoantibodies and hyperglycemia that develop euglycemic diabetic ketoacidosis during SGLT2 inhibitor treatment.

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INTRODUCTION

Fulminant type 1 diabetes mellitus (FT1DM) is a rare subtype of type 1 diabetes mellitus[1]. Abrupt onset of the disease with a rapid and complete loss of islet β cell function is a characteristic finding of FT1DM[1]. Although this metabolic disorder's clinical manifestations are nonspecific, it can lead to diabetic ketoacidosis and increase death risk if not promptly diagnosed and treated with insulin[1]. Unlike patients with acute-onset type 1 diabetes mellitus, patients with FT1DM are negative for circulating pancreatic islet-related autoantibodies[1]. Therapy with sodium-glucose co-transporter 2 (SGLT2) inhibitor may trigger diabetic ketoacidosis with normal blood glucose levels. Here, we report a case of diabetic ketoacidosis with almost normal blood glucose levels following therapy with SGLT2 inhibitor that prompted the diagnosis of FT1DM.

when she was alive.

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CASE PRESENTATION

Chief complaints

The patient was a 43-year-old woman that consulted the Mie University Hospital because of fatigue and vomiting.

History of present illness

The patient first consulted a medical practitioner because of sudden malaise, thirst, and vomiting in April 2019. A laboratory analysis disclosed increased blood glucose levels (428 mg/dL), a mild increase of hemoglobin A1c (6.6%), and increased ketone bodies in urine. She received insulin therapy for four days. Because the serum anti-glutamic acid decarboxylase antibody was negative, she was diagnosed with type 2 diabetes mellitus. The treatment was then switched from insulin therapy to oral medication with metformin 500 mg/d, empagliflozin 10 mg/d, and vildagliptin 100 mg/d. The patient's general condition improved, and she was discharged two days after switching to oral treatment when her one-point blood glucose level decreased to 203 mg/dL.

Two days after discharge from the medical practitioner's clinic, she consulted Mie University Hospital's outpatient department complaining of fatigue and vomiting. The clinical findings on examination were as follows: Height 159.3 cm; body weight 58.6 kg, body mass index 23.0 kg/m^2, blood pressure 128/83 mmHg, heart rate 107 beats/min, body temperature 37.4 ˚C, and peripheral oxygen saturation (SpO2; normal level > 95%) at room air 98 %.

History of past illness

She had no medical history of any disease.

Physical examination

The patient's physical examination showed notable dryness of the oral cavity.

Laboratory examinations

Table 1 showed the results of the laboratory analysis performed at Mie University Hospital. Arterial blood gases demonstrated metabolic acidosis (pH, 7.18; pCO_2, 18 mmHg; HCO3, 6.6 mEq/L; base excess, -19.3 mmol/L; A-gap, 27.6 mmol/L), with normal level of lactic acid (1.0 mmol/L). Fasting blood glucose (184 mg/dL) was mildly elevated with increased glycated hemoglobin/hemoglobin A1c (HbA1c) (7.3%). Urinalysis showed high levels of glucose (2000 mg/dL) and ketone bodies (3+). The plasma levels of 3-hydroxybutyric acid (6585 μmol/L) were markedly high. The renal function markers (blood urea nitrogen 9.1 mg/dL; serum creatinine 0.40 mg/dL) were within the normal range. These findings were compatible with the diagnosis of diabetic ketoacidosis with mild hyperglycemia.

Further diagnostic work-up

Additional laboratory analysis showed reduced urinary C-peptide level (8.6 μg/d) and decreased fasting serum C-peptide level (0.3 ng/mL). However, islet-related autoantibodies, including anti-glutamic acid decarboxylase antibody, insulin autoantibody, islet cell antibody, insulinoma-associated protein-2 antibody, and zinc transporter-8 autoantibody, were undetectable. An abdominal computed tomography showed a normal pancreas, and the blood level of pancreas exocrine enzymes, including amylase and lipase, were within the normal range.

FINAL DIAGNOSIS

We made the diagnosis of FT1DM based on the laboratory findings at Mie University Hospital and the severe hyperglycemia (≥ 16.0 mmol/L), and a mild increase in HbA1c (< 8.7%) observed at the medical practitioner's clinic.

TREATMENT

On the first day of hospitalization at Mie University Hospital, besides suspending oral antidiabetic agents, the patient received intravenous fluid infusion (1500 mL),

Table 1 Laboratory data

Blood cell count		Normal range	Units	Biochemical examination		Normal range	Units	Arterial blood gas analysis (room air)		Normal range	Units
White blood cell	11440	3300-8600	/μL	Total protein	8.2	6.6-8.1	g/dL	pH	7.182	7.350-7.450	mmHg
Red blood cell	489	386-492	× 10^4 /μL	Albumin	4.5	4.1-5.1	g/dL	$paCO_2$	18	35.0-45.0	mmHg
Hemoglobin	14.7	11.6-14.8	g/dL	BUN	9.1	8.0-20.0	mg/dL	paO_2	115.2	> 80	mmol/L
Hematocrit	43.6	35.1-44.1	%	Creatinine	0.4	0.46-0.79	mg/dL	HCO_3^-	6.6	22.0-26.0	mmol/L
Platelet	28.3	15.8-34.8	× 10^4 /μL	Uric acid	5.3	2.6-5.5	mg/dL	Base excess	-19.3	-2.0-+2.0	mmol/L
				Na	131	138-145	mEq/L	Anion gap	27.6	10.0-18.0	mmol/L
Urinalysis				K	4.5	3.6-4.8	mEq/L	Lactic acid	1.0	0.9-1.7	mmHg
Specific gravity	1.015	1.005-1.030		Cl	102	101-108	mEq/L				
pH	5.5	4.5-7.5		Ca	8.7	8.8-10.1	mg/dL	Blood ketone bodies			
Glucose	2000	< 50	mg/dL	P	2.6	2.7-4.6	mg/dL	Acetoacetate	1784	< 55	μmol/L
Protein	100	< 30	mg/dL	AST	20	13-30	U/L	3-Hydroxybutyrate	6585	< 85	μmol/L
Ketone body	(3+)	(-)		ALT	6	7-23	U/L				
Blood	(±)	(-)		LDH	251	124-222	U/L	Autoantibodies			
				γ-GTP	43	9-32	U/L	GAD autoantibody	< 5.0	< 5.0	U/mL
Diabetic parameters				ALP	178	106-322	U/L	IA-2 autoantibody	< 0.6	< 0.6	U/mL
HbA1c	7.3	4.9-6.0	%	T-Bil	0.5	0.4-1.5	mg/dL	Insulin autoantibody	< 0.4	< 0.4	U/mL
Glycoalbumin	23.2	11.0-16.0	%	CRP	0.12	< 0.14	mg/dL	Islet cell antibody	(-)	(-)	
Blood glucose	184	73-109	mg/dL	Total-cholesterol	242	142-248	mg/dL	ZnT8 autoantibody	< 10.0	< 15.0	U/mL
Serum C-peptide	0.3	0.6-2.1	ng/mL	Triglyceride	230	30-117	mg/dL				
Urine C-peptide	8.6	22.8-155.2	μg/d	Amylase	35	44-132	U/L				
				Lipase	23	12-51	U/L				

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; T-Bil: Total bilirubin; CRP: C-reactive protein; GAD: Glutamic acid decarboxylase; IA-2: Insulinoma-associated protein-2; BUN: Blood urea nitrogen; LDH: Lactate dehydrogenase; HbA1c: Glycated hemoglobin/hemoglobin A1c.

including 20 g of dextrose and 2 units of regular insulin. After this treatment, her metabolic acidosis substantially (pH, 7.32; pCO_2, 25.9 mmHg; HCO_3^- 12.9 mmol/L) improved. Because the patient had reduced blood potassium levels (2.8 mEq/L), 10 mEq/d potassium was administered together with 2000 mL/d of intravenous fluid infusion, including 60 g dextrose and 6 units of regular insulin. Blood glucose level fluctuated between 156 mg/dL and 195 mg/dL during the first two days after hospitalization. On the third day of hospitalization, oral food intake and multiple daily injections of insulin were initiated together with a gradual reduction in fluid administration. Urinary ketone bodies became negative on day 7.

OUTCOME AND FOLLOW-UP

The patient was discharged on day 14 with the therapeutic indication of subcutaneous injection of insulin glargine (18 U) before sleep and subcutaneous injection of insulin aspart (12U-6U-10U) before each meal.

DISCUSSION

F1DM is a severe subtype of type 1 diabetes mellitus characterized by extremely rapid and almost complete destruction of pancreatic β-cells that may eventually lead to diabetic ketoacidosis[1]. It was first reported in Japan by Imagawa *et al*[1], and since then, it has been mainly reported in East Asia. Approximately 20% of acute-onset type 1 diabetes in Japan is F1DM. The Committee of the Japan Diabetes Society reported the diagnostic criteria of FT1DM in 2012[1,2]. There are three criteria for the diagnosis of FT1DM: (1) Occurrence of diabetic ketoacidosis or ketosis soon (within seven days) after the onset of hyperglycemic symptoms, including elevation of urinary and serum ketone bodies during the first visit; (2) Plasma glucose level of ≥ 16.0 mmol/L (288 mg/dL) and HbA1c level of < 8.7% during the first visit; and (3) Urinary C-peptide excretion of < 10 μg/d or fasting serum C-peptide level of < 0.3 ng/mL (0.10 nM) and < 0.5 ng/mL (0.17 nM) after intravenous glucagon (or 2 h after a meal) load[3]. Circulating pancreatic islet-related autoantibodies are generally negative in FT1DM[1].

At the medical practitioner's clinic, the patient showed an extremely high blood glucose level and a slight increase of HbA1c with a trace of ketone bodies in urine. Symptoms improved after starting insulin therapy. Subsequent laboratory analysis showed a negative test for circulating anti-glutamic acid decarboxylase antibodies. Based on this negative test, the patient was wrongly diagnosed with type 2 diabetes mellitus. Therefore, insulin therapy was stopped, and oral administration of biguanide, dipeptidyl peptidase-4 inhibitor, and SGLT2 inhibitor was initiated. However, discontinuation of insulin and therapy with oral SGLT2 led to the development of diabetic ketoacidosis. During the first visit of the patient at the medical practitioner's clinic, the laboratory findings of severe hyperglycemia (≥ 16.0 mmol/L), a light increase of HbA1c (< 8.7%), and ketosis (urinary ketones) are compatible with the diagnosis of F1DM. However, the patient was not diagnosed with F1DM at the first clinic she consulted, probably because the data on C-peptide levels in blood and urine were unavailable. Once admitted to Mie University Hospital, laboratory analysis showed abnormal levels of urinary C-peptide, indicating a remarkable decrease of endogenous insulin secretion, thus strongly suggesting the diagnosis of F1DM. Pancreatic swelling and elevated blood levels of pancreatic enzymes have also been reported in patients with F1DM[4,5]. However, the pancreas CT findings and the blood levels of pancreas exocrine enzymes were normal. It is worth noting that in the present case, diabetic ketoacidosis occurred despite the slight increase in blood glucose level during the treatment with an SGLT2 inhibitor.

SGLT2 inhibitors are a new class of anti-hyperglycemic medications first introduced in 2013 to treat type 2 diabetes[6]. SGLT2 inhibitors lower the serum glucose levels by increasing urinary glucose clearance[6,7]. These therapeutic drugs may induce diabetic ketoacidosis[8]. In 2015, the United States Food and Drug Administration issued a warning statement regarding the risk of diabetic ketoacidosis during treatment with SGLT2 inhibitors[9]. Several mechanisms may explain the increase of blood ketone bodies by SGLT2 inhibitors. SGLT2 inhibitors stimulate glucagon secretion from pancreatic α cells by lowering blood glucose and binding directly to SGLT2 expressed in pancreatic α cells[10]. This hyperglucagonemia accelerates lipolysis leading to increased release of free fatty acids in the blood[8]. The amelioration of hyperglycemia by SGLT2 inhibitors also suppresses the endogenous secretion of insulin. Inhibition of hepatic acetyl-CoA carboxylase by the increased blood levels of glucagon and the decreased insulinemia decreases malonyl CoA, increases carnitine palmitoyl-transferase type I, and accelerates β-oxidation leading to enhanced production of ketone bodies from free fatty acids[8]. The significant reduction of endogenous insulin secretion observed in our current case further increases the risk of developing diabetic ketoacidosis. A normal or mildly elevated blood glucose level referred to as euglycemic diabetic ketoacidosis is another characteristic finding in diabetic ketoacidosis induced by SGLT2 inhibitors[11]. This laboratory finding makes the diagnosis of diabetic ketoacidosis even more difficult, and it is a frequent cause of missed diagnosis or delayed treatment. In our present case, the discontinuation of insulin therapy and administration of SGLT2 inhibitor might have contributed to the acceleration of diabetic ketoacidosis.

CONCLUSION

Here, we report a case of F1DM with diabetic ketoacidosis. This case report underscores the importance of considering the diagnosis of F1DM in all patients with

severe hyperglycemia even in the absence of circulating autoantibodies and the possibility of euglycemic diabetic ketoacidosis in patients treated with SGLT2 inhibitors. SGLT2 inhibitors are frequently used as antidiabetic drugs for their cardiovascular[12-14] and renal benefits[15,16]. Recently, Japan approved the use of dapagliflozin and ipragliflozin in combination with insulin for type 1 diabetes, and in May 2020, the United States Food and Drug Administration approved the indication of dapagliflozin for heart failure. The major availability of SGLT2 inhibitors predicts an increase in the number of medical indications of SGLT2 inhibitors in the coming future. Therefore, major awareness of the potential adverse events of SGLT2 inhibitors is fundamental to avoid misdiagnosis in daily clinical practice.

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