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A Case of Diabetic Ketoacidosis Induced by Covid-19 Successfully Treated with Continuous Glucose Monitoring

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ABSTRACT

We report the case of a 77-year-old Japanese man with coronavirus disease 2019 (COVID-19) who developed diabetic ketoacidosis (DKA). He is administered oral agents for type 2 diabetes mellitus, which he was diagnosed with 35 years ago by a home doctor. Three years before his COVID-19 infection, his glycemic control deteriorated, and he started multiple daily insulin injections. He presented to our emergency outpatient department with fatigue and respiratory distress. The patient was diagnosed with COVID-19 concomitant with DKA. Dexamethasone is the recommended treatment for COVID-19 infection. The patient was treated with an intravenous fluid infusion and continuous insulin administration for DKA. The patient's clinical course was followed up with arterial blood gas and serum glucose monitoring using intermittently scanned continuous glucose monitoring (isCGM). We successfully treated DKA using isCGM and reduced the exposure of the medical staff to infected patients. Although DKA was in remission, the COVID-19 infection worsened, and the patient eventually died. The necessity for alternative methods for the management of patients with DKA and COVID-19 infection is paramount during the pandemic period.

Keywords: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); COVID-19; Diabetic ketoacidosis; Dexamethasone; Continuous Glucose Monitoring

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INTRODUCTION

DKA is a hyperglycemic emergency in patients with diabetes mellitus that arises from relative or absolute insulin deficiency. Although DKA is more common in type 1 diabetes mellitus (T1D), it can also occur in type 2 diabetes mellitus (T2D) with severe illness.[1] There are increasing reports of DKA in patients with T1D or T2D who have

developed COVID-19.[2-4] DKA complicated by COVID-19 has been reported to have more severe complications and worse mortality than uncomplicated DKA in the United States.[5]

However, it is also recommended that DKA management be tailored to reduce the exposure of medical staff to infected patients and save medical resources during the COVID-19 pandemic.[6] Here, we report the clinical course of a Japanese patient who developed severe DKA complicated by COVID-19 during the pandemic period.

CASE PRESENTATION

We present the case of a 77-year-old Japanese man. Oral agents for diabetes mellitus were prescribed upon diagnosis by his home doctor 35 years ago. Three years ago, he was referred to our hospital because of poor glycemic control, with serum glucose and hemoglobin A1c (HbA1c) levels of 546 mg/dL and 10.6%, respectively. He was admitted, and a multiple daily insulin injection (MDI) regimen (four times a day) was administered instead of oral agents. After glucose toxicity was dealt with, his laboratory examinations revealed that his fasting serum glucose level, C-peptide reactivity (CPR) level, and CPR index were 89 mg/dL, 0.45 ng/mL, and 0.51, respectively. Anti-GAD antibodies were not detected, and liver and pancreatic diseases were not detected. The patient was diagnosed with T2D with inadequate insulin secretion, and the MDI regimen was continued (Aspart: three times a day before every meal and Glargine: once a day).

His HbA1c level was maintained between 8% and 10%. He had no retinopathy, nephropathy with microalbuminuria (estimated glomerular filtration rate of 50 mL/min/1.73 m^2), and neuropathy with category IV clinical staging as diabetic complications. Two months before his next admission, he was diagnosed with ascending colon cancer, and a curative tumor resection was performed. However, the possibility of micrometastasis could not be ruled out, and adjuvant chemotherapy was thus initiated. He had not received the COVID-19 vaccine because it coincided with a surgery for colon cancer. Five days before his visit to our emergency department, he reported a history of general fatigue, appetite loss, and altered consciousness. He simultaneously demonstrated polyuria and polydipsia. He discontinued the insulin injections at his discretion because of a complete loss of appetite. He visited the emergency department because of fever and exacerbation of dyspnea.

On arrival, he presented with severe hypoxia, with an oxygen saturation value of 80% in ambient air, and tachypnea with a respiratory rate of 42/min. Oxygen administration was immediately initiated. A clinical examination revealed a body weight of 57 kg, height of 157 cm, and body mass index (BMI) of 23.1 kg/m^2. Laboratory testing revealed DKA. Arterial blood gas (ABG) showed a pH of 7.021, HCO_3^- less than the detectable sensitivity, and an anion gap of 32. Biochemical examination revealed that his serum levels of glucose, CPR, and 3- hydroxybutyric acid were 595 mg/dL, 0.52 ng/mL, and 12279 μmol/L, respectively. Simultaneously, a nasopharyngeal swab detected SARS-CoV-2 by polymerase chain reaction, resulting in the diagnosis of COVID-19. Detailed laboratory data are presented in Table 1. Chest radiography revealed ground-glass attenuation in the right lung, suggesting pneumonia

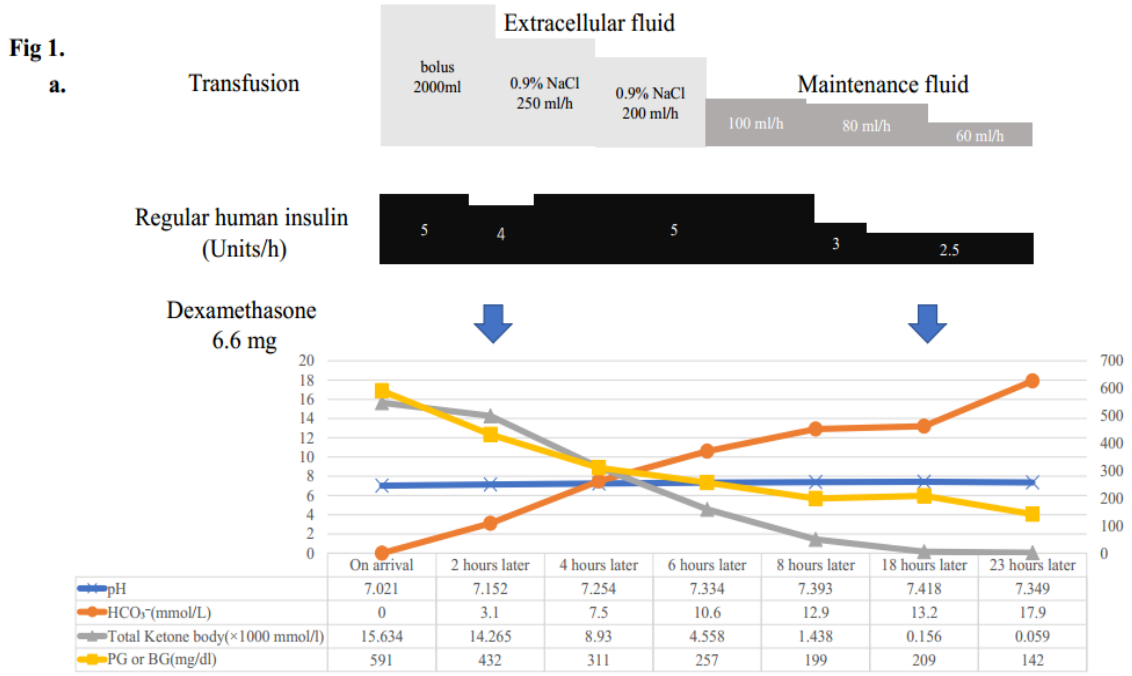
due to COVID-19. His oxygen saturation level was 90% under 2 L/min of oxygen provided by a nasal cannula. Although his oxygen supplementation was increased to 15 L with the reservoir mask, oxygen saturation did not improve. We initiated high-flow nasal cannula oxygen therapy (HFNC) and intravenous administration of 6.6 mg dexamethasone once a day. No treatment other than dexamethasone was administered to treat the COVID-19. The patient was admitted to the COVID-19 containment ward. He was started on intravenous extracellular fluids, with a continuous intravenous infusion of 0.1 units/h of regular human insulin immediately for the treatment of DKA. The dose was adjusted according to the insulin infusion instructions for non-COVID-19 patients. We followed up with the ABG and electrolytes approximately every 2 h.

Table 1: Laboratory findings on arrival.

【CBC】		【Coagulation】		
WBC	12670 µL	PT(%)	69	
Neutrophil	76%	PT-INR	1.2	
Lymphocyte	18.5%	APTT	27.4	seconds
Eosinophil	0%	Fbg	366	mg/dl
Hemoglobin	15.5 g/dL	D-dimer	4.8	µg/ml
Platelet	13.6 µL			
		【Arterial Blood Gas (nasal 2L/min)】		
【Biochemistry】		pH	7.021	
Total protein	6.9 g/dL	pO_2	83.4	mmHg
Albumin	3.8 g/dL	pCO_2	undetectable	
AST	59 IU/L	HCO_3^-	undetectable	
ALT	28 IU/L	Lactate	3.4	mEq/L
LDH	645 IU/L	Anion Gap	32	
CK	276 IU/L			
BUN	51 mg/dL	【Urinalysis】		
Creatinine	1.76 mg/dL	Protein	100	mg/dl
e-GFR	30 ml/min/1.73m^2	Glucose	>1000	
Na	125 mEq/L	Occult blood	3+	
K	5.4 mEq/L	Ketone body	3+	
Cl	93 mEq/L			
CRP	6.15 mg/dL	【COVID-19】		
Plasma glucose	595 mg/dL	SARS-CoV2 PCR	(+)	
HbA1c	10.1%			
Serum CPR	0.52 ng/mL			
Total ketone bodies	15634 µmol/L			
3-OHB	12279 µmol/ L			
Serum osmolality	315 mOsm			
Anti-GAD Ab	<5.0 U/ml			

CPR; C-peptide immunoreactivity, 3-OHB; 3-hydroxybutyric acid Anti-GAD Ab; anti-glutamic acid decarboxylase antibody,
SARS-CoV-2; severe acute respiratory syndrome coronavirus PCR; Polymerase Chain Reaction

We utilized intermittently scanned continuous glucose monitoring (isCGM) to minimize the contact time of medical staff with COVID-19-positive patients. The isCGM was administered for 12 days, from admission until the day of death and discharge. The glucose sensor worn at the time of administration was maintained for the entire period. The isCGM was scanned using an attached dedicated reader. In Japan, the sensor glucose level using isCGM cannot be used as a substitute for clinically measured blood glucose levels and/or the SMBG because of its accuracy. Therefore, we confirmed the accuracy of the isCGM by performing blood gas analysis every 2 hours until DKA achieved remission, at least once a day until the glycemic control stabilized following the remission of DKA, and every 2–3 days thereafter. When isCGM indicated a low glucose level, the SMBG was checked for hypoglycemia, and glucose was administered if the SMBG level was less than 70 mg/dL. We did not use Libre View® or Libre Link® for the data management. All of the data were managed on a computer after the sensor was removed. The treatment course is shown in Figure 1. Approximately 24 h after the start of treatment, his serum HCO_3^- level improved, and DKA was in remission. On the 4th day of hospitalization, he started eating, and intravenous insulin infusion was switched to MDI.



	On arrival	2 hours later	4 hours later	6 hours later	8 hours later	18 hours later	23 hours later
pH	7.021	7.152	7.254	7.334	7.393	7.418	7.349
HCO_3^-(mmol/L)	0	3.1	7.5	10.6	12.9	13.2	17.9
Total Ketone body(×1000 mmol/l)	15.634	14.265	8.93	4.558	1.438	0.156	0.059
PG or BG(mg/dl)	591	432	311	257	199	209	142

Figure 1a: Clinical course of the patient. Approximately 24 h after the initiation of treatment, the remission of DKA occurred.

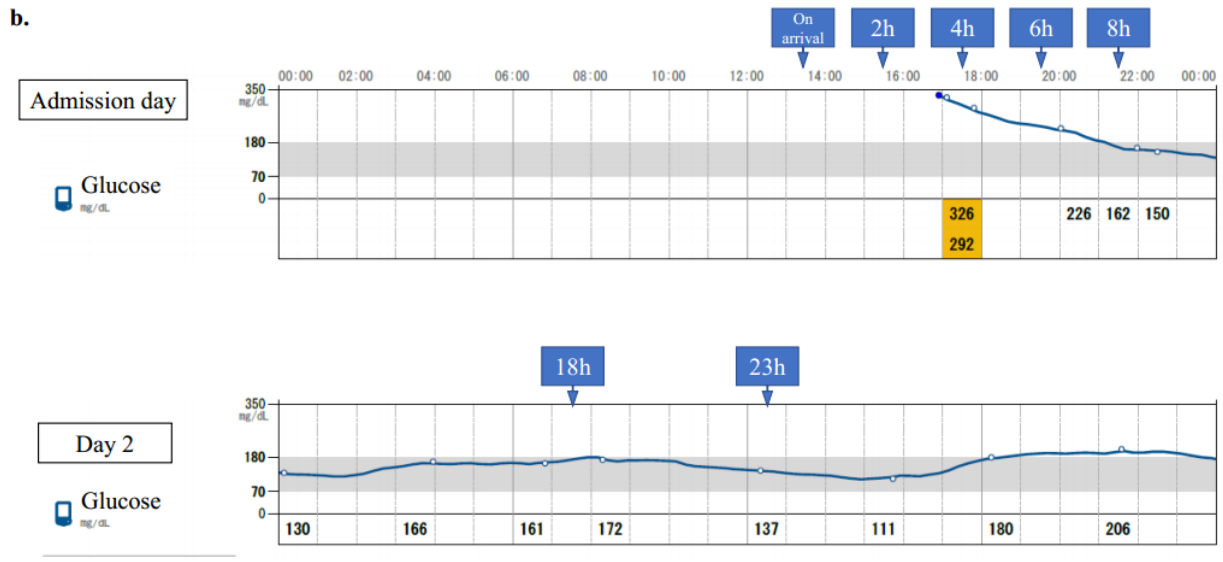


Figure b: The isCGM data from hospitalization to DKA remission.

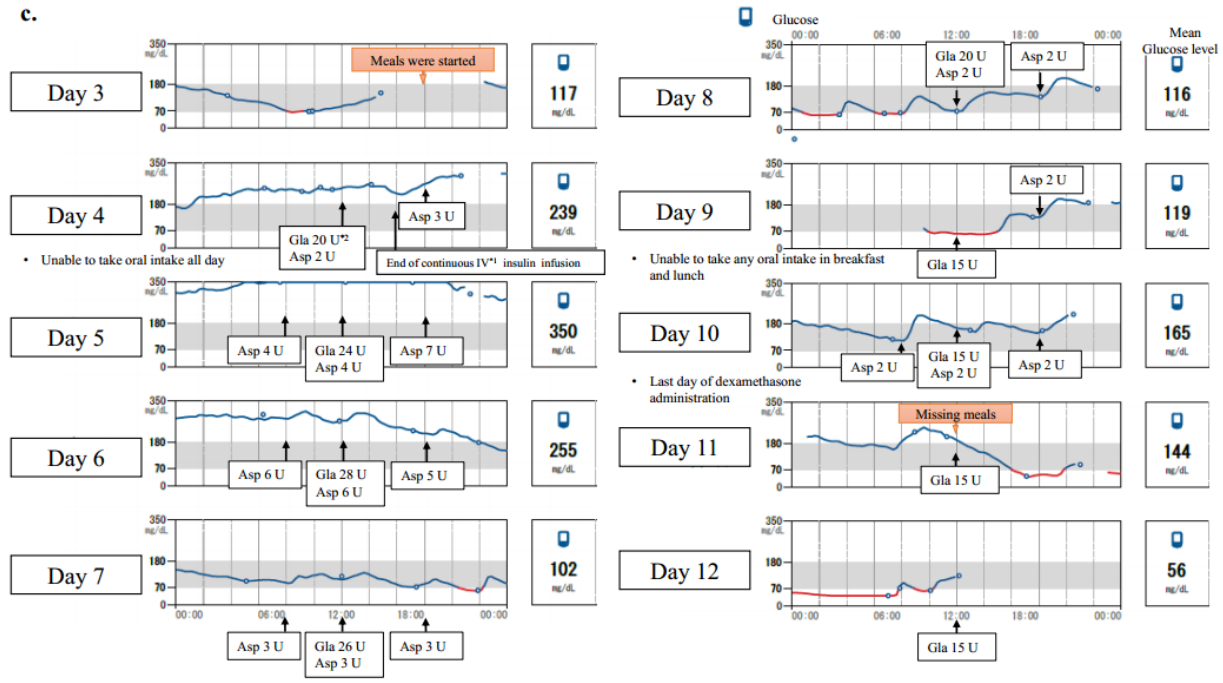


Figure 1c: The isCGM data from DKA remission to death.

* 1 IV; intravenous, *2 U; units. Between days 5 and 8, he was able to finish most of his meals.

Temporary hyperglycemia occurred when switching from intravenous insulin to the MDI. He was able to consume most of his meals between the 5th and 8th days of hospitalization. When his food intake stabilized, the glycemic

control gradually improved with increased basal insulin and additional insulin, including supplemental insulin. However, his fever did not improve sufficiently, and the hypoxia deteriorated. Despite completing 10 days of dexamethasone administration, the oxygen demand increased slowly. As COVID-19 worsened, his food intake became unstable, the frequency of hypoglycemia increased, and the glycemic control worsened. The patient died on the 12th day of hospitalization.

DISCUSSION

In this report, we describe the case of a patient with T2D and severe DKA triggered by COVID-19. To the best of our knowledge, this is the first report describing the treatment of DKA in COVID-19 patients using isCGM in Japan. Diabetes mellitus (DM) is frequently associated with COVID-19. According to a nationwide analysis of 1590 patients with COVID-19 across China, hypertension is the most prevalent comorbidity (16.9%), followed by diabetes mellitus (8.2%).[7] Additionally, diabetes is highly prevalent (34.9%) in patients with severe COVID-19 [7] and is associated with increased severity of complications and mortality.[8]

DKA is a life-threatening, emergent hyperglycemic condition in patients with diabetes mellitus. Similar to other severe infections, DKA has also been reported in patients with COVID-19.[9–11] Goldman et al. reported that 1.8% of patients admitted for COVID-19 presented with DKA.[2] In this case, there was insufficient endogenous insulin secretion, and the self-induced interruption of the insulin administration associated with appetite loss and increased insulin requirement associated with COVID-19 infection led to the development of DKA. Successful treatment of DKA requires correction of dehydration, hyperglycemia, and electrolyte imbalance. In other words, fluid resuscitation, potassium repletion, and insulin replacement are necessary. Monitoring every 2-4 hours is recommended until the patient is stabilized, and thus the treatment of DKA is often performed in an intensive care unit (ICU) setting.[12] For bedside blood glucose monitoring, point-of-care (POC) glucose meters remain the standard of care for hospitalized patients. However, during the COVID-19 pandemic, frequent contact with patients is a challenge from the perspective of medical personnel protection.[6] Moreover, dexamethasone administration has been recommended in cases requiring oxygen supplementation in Japan,[13] which exacerbates glucose intolerance.[14] Therefore, it is more difficult to treat severe DKA when a patient is infected with COVID-19 than when the patient is not, especially in the general ward. It is pointed out that CGM, including isCGM, offers a potential method for facilitating care in COVID-19 patients while also decreasing nurse exposure through reduced frequency of POC blood glucose testing [6]. In addition, in patients with COVID-19, there are reports of significant improvement in hyperglycemia using CGM[15] and reports that blood glucose can be controlled using CGM without increasing hypoglycemia.[16] The FDA announced that they would not object to the in-hospital use of CGM to assist in monitoring COVID-19 patients.[17] The reason why we chose isCGM among other CGM devices was that, in our case, the COVID-19-dedicated general ward was originally a surgical ward and was not accustomed to the management of diabetes. The isCGM is easier to manage and operate than Dexcom 4/6® or Guardian®, which require training for sensor puncturing and regular blood glucose calibration. In addition, the effective period of the

sensor is 14 days for isCGM, compared with 7 days for Dexcom 4/6® or Guardian®. The maximum duration of dexamethasone administration for COVID-19 is 10 days, and the sensor does not need to be changed during dexamethasone administration, which reduces the workload of nurses and facilitates the data management for the medical staff. However, it is important to keep in mind the accuracy or mean absolute relative difference (MARD) when using CGM. The MARD of isCGM has been reported to be 11.4%.[18] It is important to compare the sensor glucose level of the isCGM with the actual blood glucose level, when appropriate. In our case, intravenous insulin administration was appropriate, and the patient and his family members expressed their desire for the patient to not be treated in the ICU because of his advanced age. The patient was treated with hourly glucose monitoring in the general ward using isCGM. While isCGM and blood glucose values from blood tests were checked occasionally to confirm that there were no significant deviations (MARD in our case; 3.5–21.3%), we adjusted the insulin dosage based on the record of sensor glucose levels scanned by the dedicated reader. The utilization of isCGM was helpful not only to treat DKA, but also to manage better glycemic control after the remission of DKA and to reduce medical contact with infected patients.

In conclusion, we report a case of DKA concomitant with COVID-19. The use of CGM is relevant and can be a monitoring option during the course of DKA treatment during the COVID-19 pandemic.

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