

Early detection of euglycemic ketoacidosis during thoracic surgery associated with empagliflozin in a patient with type 2 diabetes: A case report

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Keywords

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ABSTRACT

We report the first case of intraoperatively detected euglycemic diabetic ketoacidosis (DKA) associated with sodium–glucose cotransporter 2 inhibitors during thoracic surgery. A 59-year-old man had a 12-year history of type 2 diabetes mellitus treated with insulin and empagliflozin. The patient developed bacterial empyema and was initiated with antibiotics at a local hospital. Owing to the persistence of his symptoms, he was transferred to our hospital after the medication of empagliflozin the day before surgery. After overnight fasting, the patient underwent thoracoscopic debridement and intrathoracic lavage surgery. During this surgery, he was noted to have euglycemic ketosis and acidosis, and diagnosed as euglycemic DKA. Immediately after the consultation in our department, the patient underwent treatment for DKA. He awoke from anesthesia normally and showed no symptoms of DKA. DKA gradually resolved over the next 24 h. Early identification and management are critical for rapid recovery from perioperative euglycemic DKA associated with sodium–glucose cotransporter 2 inhibitors, especially during thoracic surgery.

INTRODUCTION

Sodium–glucose cotransporter 2 inhibitors (SGLT2is) are widely used in patients with diabetes mellitus. However, regulatory agencies issued a warning that SGLT2is could cause diabetic ketoacidosis (DKA)¹. DKA associated with SGLT2is can even occur when glucose levels are lower than expected, known as euglycemic DKA (eDKA), and often occurs during the perioperative period^{1,2}. Cases of eDKA associated with SGLT2is have been reported after surgery^{1,2}, but there is no report of occurrence during the surgery. Here, we present a patient with type 2 diabetes and bacterial empyema, who underwent surgery without a sufficient period of empagliflozin withdrawal. He developed intraoperative eDKA, but rapidly recovered after its early identification and management.

CASE REPORT

A 59-year-old man had a 12-year history of type 2 diabetes mellitus initiated with 10 mg of empagliflozin 18 months

earlier, and clinically titrated to 25 mg along with intensive insulin therapy. During the period of treatment with empagliflozin, uric ketone had not been detected at every visit. The patient presented with high fever and chest pain for 2 weeks, and was admitted to a neighboring hospital. He was diagnosed as having left bacterial empyema, and treated with antibiotics for 4 days; however, as his symptoms persisted, he was transferred to Wakayama Medica University (Wakayama, Japan) for surgical treatment. He had a fever of 37.2°C, and weak pulmonary sound on the left side. The patient's bodyweight, height and body mass index were 69 kg, 169 cm and 24.1 kg/m², respectively. Laboratory data showed a severe infectious state (Table 1). Chest radiography and computed tomography images showed a large pleural effusion (Figure 1). On the day the patient was transferred to our hospital, he was treated with empagliflozin and insulin for diabetes at the former hospital (day 0; Figure 2). Empagliflozin was taken for the last time 28 h before surgery. He had no appetite loss nor digestive symptoms on that day. He was treated with insulin glargine 13 h before surgery.

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Table 1 | Laboratory data on admission

Hematology/biochemistry			
WBC	15,620/ μ L	AMY	39 U/L
RBC	357×10^4 / μ L	Na	139 mEq/L
Hb	11.2 g/dL	K	4.8 mEq/L
Plt	27.3×10^4 / μ L	Cl	103 mEq/L
TP	5.4 g/dL	PG	209 mg/dL
Alb	2.2 g/dL	HbA1c	9.4%
AST	70 U/L	C-peptide	0.95 ng/mL
ALT	47 U/L	Lactate	10.6 mg/dL
LDH	219 U/L		
Serological examination			
CPK	364 U/L	C-reactive protein	29.8 mg/dL
γ -GTP	81 U/L	Anti-GAD Ab	<5.0 U/mL
BUN	16.6 mg/dL	Anti-IA-2 Ab	<0.6 U/mL
Cr	1.11 mg/dL		

γ -GTP, gamma-glutamyl transpeptidase; Ab, antibodies; Alb, albumin; ALT, alanine aminotransferase; AMY, amylase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CPK, creatine kinase; Cr, creatinine; GAD, glutamic acid decarboxylase; Hb, hemoglobin; HbA1c, glycated hemoglobin; IA-2, islet antigen 2; LDH, lactate dehydrogenase; PG, plasma glucose; Plt, platelets; RBC, red blood cells; TP, total protein; WBC, white blood cells.

After overnight fasting for 18 h, the patient underwent thoracoscopic debridement and intrathoracic lavage (day 1; Figure 2). His surgery was initiated with drip infusion of extracellular fluid with 1% glucose without insulin. Based on the information of having diabetes from the former hospital, his arterial blood gas was measured during surgery. Approximately 2 h after the initiation of surgery, he was found to be acidotic on arterial blood gas with 162 mg/dL of blood glucose level (Figure 2). A urine test for ketone showed a positive result. Laboratory tests showed elevated levels of total ketone bodies, acetoacetic acid and 3-hydroxybutyric acid in serum (Figure 2). Subsequently, the patient was started on an insulin infusion with drip infusion of 5% glucose immediately after the consultation from the anesthesiologist to the first department of medicine. He awoke from anesthesia normally and showed no digestive symptoms. After the continuous insulin infusion, his acidosis and ketosis gradually resolved over the next 24 h. Approximately 2 weeks later, his bacterial empyema had almost resolved. During these 2 weeks, he was treated with insulin alone for diabetes and did not present ketosis or acidosis.

Written informed consent was obtained from the patient.

DISCUSSION

SGLT2is are widely used as excellent agents for managing diabetes, while providing metabolic, cardiovascular and renal benefits^{1,3,4}. However, several adverse effects are concerned. DKA is a significant risk for patients taking SGLT2is, especially when there are precipitating factors, such as illness, infection and surgery^{1,2}. In several countries, it is recommended that SGLT2is be discontinued preoperatively. The half-life of 25 mg

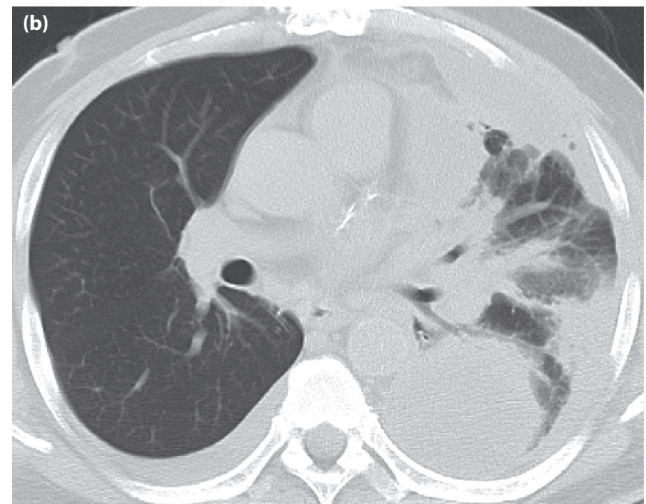
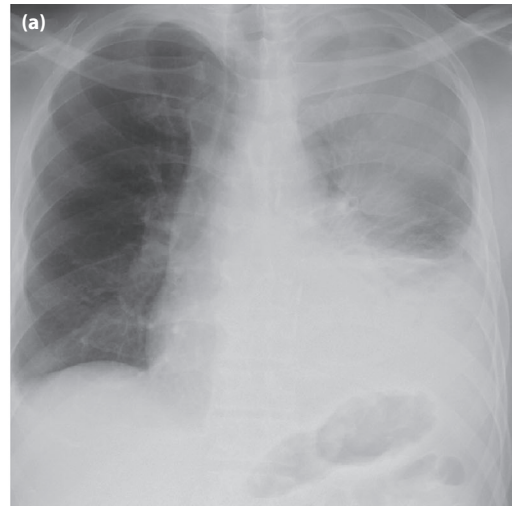


Figure 1 | Chest radiography (a) and computed tomography (b) before thoracoscopic debridement and intrathoracic lavage (day 0).

empagliflozin is reported to be 18.0 h according to the package insert. In the present case, empagliflozin was taken for the last time 28 h before surgery. However, in the case of surgery, it might be necessary to consider the potential effects of anesthesia and muscle relaxants on the half-life. In Australia, for example, cessation at least 3 days preoperatively is recommended based on the half-life and dose-dependent offset time of SGLT2is¹. In the present case, besides the use of SGLT2is with an insufficient withdrawal period, the patient was speculated to have infection with empyema and surgery as risk factors of DKA. In particular, as the present patient initially showed mixed acidemia, possibly as a result of the retention of carbon dioxide under the isolated one-lung ventilation in addition to accumulation of ketone, it is necessary to pay attention to the management of DKA during thoracic surgery. In addition, the initial drip infusion during surgery was at a

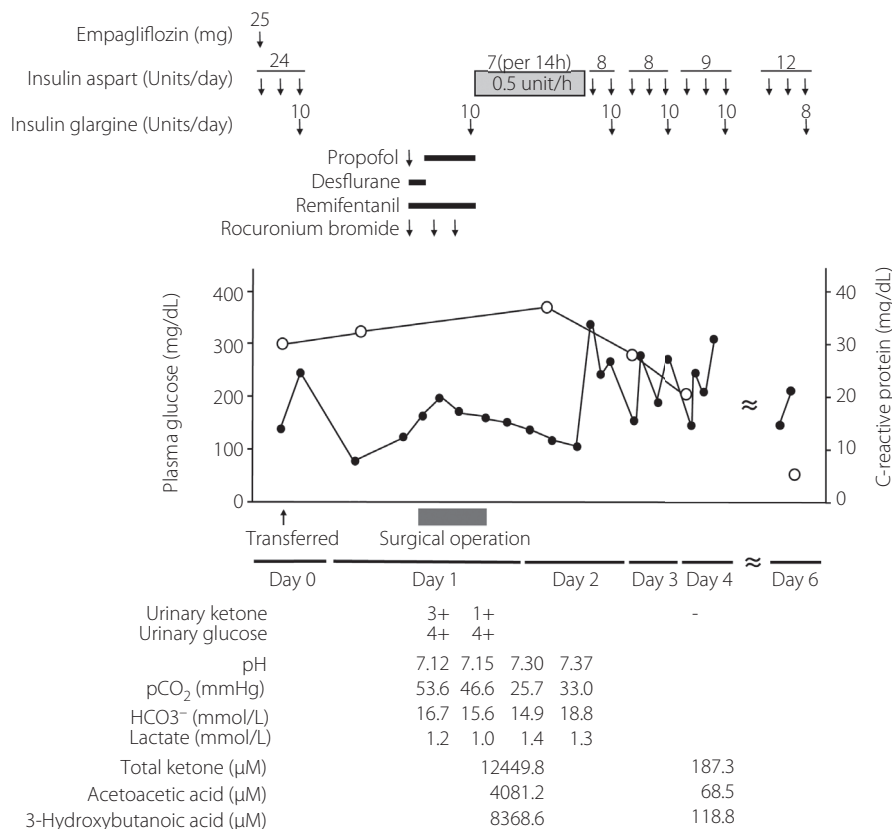


Figure 2 | Patient's clinical course. Black circles and blank circles represent blood glucose and C-reactive protein levels, respectively.

low concentration of glucose without insulin. Although insulin glargine was injected the night before, it is also possible that an insufficient dosage of glucose and insulin made the DKA worse in the present case.

Early detection and intervention are critical for management of DKA associated with SGLT2is. The US Food and Drug Administration highlighted awareness among practitioners, DKA symptoms and the potential for lower than expected blood glucose levels when precipitating factors for DKA associated with SGLT2is are present in patients⁵. However, as the symptoms are atypical and the blood glucose levels could be lower than expected, the diagnosis tends to be delayed in DKA associated with SGLT2is. In the present case, it is possible that eDKA had already developed before the surgery, although the patient had no symptoms of acidemia at that point. Thus, when it is difficult to take a sufficient withdrawal period of SGLT2is preoperatively, it is important to monitor ketone and acidosis, even before surgery, for the early detection and immediate management of DKA.

Several situations/diseases are raised as the general differential diagnosis of euglycemic ketoacidosis: pregnancy, restriction on caloric intake, glycogen storage diseases or defective gluconeogenesis as a result of alcohol abuse or chronic liver disease. As for the mechanism of eDKA associated with SGLT2is under stress, situations, such as delivery of a potentially low dose of insulin, increased secretion of counter hormones and

dehydration status on the surgical day, could be speculated^{1,6,7}. Under stress, such as surgery or illness, increased secretion of counter hormones, such as glucagon, leads to ketogenesis owing to such reasons as lipolysis providing sufficient free fatty acid substrate for production of ketone bodies or hepatic glucose production. Meanwhile, in patients treated with both SGLT2is and insulin, increased renal excretion of glucose might result in treatment with insufficient insulin to suppress lipolysis and ketogenesis, even if blood glucose levels are not increased. Therefore, sufficient insulin delivery, and careful clinical and biochemical monitoring are required to prevent perioperative eDKA in patients treated with dual SGLT2is and insulin.

In summary, we presented a patient with type 2 diabetes and bacterial empyema, who developed intraoperative eDKA associated with empagliflozin. This is the first case of eDKA associated with SGLT2is during thoracic surgery, which could be rapidly resolved by emergent intervention. When patients are taking SGLT2is, especially those with precipitating factors, it is clinically important to be aware of the potential risk of eDKA and to increase monitoring for the immediate initiation of treatment.

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DISCLOSURE

The authors declare no conflict of interest.

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