VIA MEDICA
CASE REPORT
ISSN 2450–7458

Kevin Wibawa[1], Ferica Valentine Kuhuwael[2], Caesar Rio Julyanto Putra[1], Sandra Utami Widiastuti[2], Leonardo Paskah Suciadi[3]

[1]Research Associates, Siloam Heart Institute, Jakarta, Indonesia
[2]Internal Medicine, Siloam Hospitals Kebon Jeruk, Jakarta, Indonesia
[3]Cardiology and Vascular Medicine, Siloam Heart Institute / Siloam Hospitals Kebon Jeruk, Jakarta, Indonesia

Euglycemic diabetic ketoacidosis associated with empagliflozin in patients hospitalized with acute pulmonary embolism

ABSTRACT

Euglycemic diabetic ketoacidosis (Eu-DKA) is a rare but life-threatening complication in diabetic patient treated with sodium-glucose cotransporter 2 inhibitors (SGLT2i). A 71-year-old diabetic female treated with empagliflozin presented to the ED with shortness of breath. Diagnosis of acute pulmonary embolism was confirmed initially. She was treated conservatively with subcutaneous enoxaparin 60 mg bidaily. and oxygen therapy. Respiratory distress associated with anion gap — metabolic acidosis and ketosis developed on the following days however her blood glucose levels were always within normal limit. Clinical recovery was gained after stopping the drug, administering rehydration, and insulin drip. Complication of DKA without hyperglycaemia should be considered while evaluating ketoacidosis in diabetic patients treated with SGLT2i, particularly in critical illness cases. (Clin Diabetol 2021; 10; 2: 204–208)

Key words: euglycemic diabetic ketoacidosis, diabetes mellitus, SGLT2i, empagliflozin, acute pulmonary embolism

Address for correspondence:
Kevin Wibawa
Research Associates, Siloam Heart Institute,
Jakarta, Indonesia
e-mail: kevin.wibawa24@gmail.com
Clinical Diabetology 2021, 10; 2: 204–208
DOI: 10.5603/DK.a2021.0010
Received: 18.09.2020 Accepted: 28.12.2020

Introduction

Diabetic ketoacidosis (DKA) is an acute life-threatening complication of diabetes. It is classically characterized as a clinical triad comprising anion-gap metabolic acidosis, hyperglycemia and increased ketone bodies in the blood and urine. Typically, plasma glucose level is > 250 mg/dL in DKA. This situation is usually triggered by other critical illness or infection. However, it is also reported that DKA could occur in a subset of patients with the serum glucose levels within the normal limits, termed as euglycemic DKA (Eu-DKA) [1].

Sodium glucose co-transport 2 inhibitors (SGLT2i) is a novel class of antidiabetic medications which act as insulin-independent glucose lowering agents by blocking selectively the SGLT2 in renal tubules, resulting in glucose elimination by urine. Rare side effect of Eu-DKA associated with this agent has been recently reported [2].

Here we describe a case of Eu-DKA which occurred in a diabetic patient treated with empagliflozin who was hospitalized du to acute pulmonary embolism.

Case illustration

A 71-year-old female admitted to emergency room (ER) with symptoms of progressive malaise and shortness of breath since the last several days. She had experienced recurrent thromboembolism events in the past 6 months including deep vein thrombosis (DVT) at the right lower extremity and acute pulmonary embolism. Additionally, she had been diagnosed with a significant coronary artery disease but percutaneous coronary intervention (PCI) was unsuccessful. Her current medications were edoxaban 60 mg/d, empagliflozin 25 mg/d, valsartan 80 mg/d, and atorvastatin 20

Table 1. Laboratory results at admission

Parameters	Value	Reference range	Unit
Haemoglobin	11.2	12.0–16.0	d/dL
Leucocyte	8,500	4,000–10,000	/uL
Platelets	227,000	150,000–400,000	/uL
SGOT	29	5–34	U/L
SGPT	34	< 55	U/L
Random blood glucose	149	80–180	mg/dL
Ureum	32	10–50	mg/dL
Creatinine	1.26	0.6–1.1	mg/dL
Estimated GFR	43		mL/min/1.73 m^2
Sodium	138	135–145	mmol/L
Potassium	3.4	3.5–5.0	mmol/L
Chloride	105	97–111	mmol/L
D-Dimer	7,720	0–550	ng/mL
Albumin	3.3	3.5 – 5.0	g/dL
Osmolality	285	280–295	mOsmol/kg H_2O
NT-proBNP	10,958	< 300	pg/mL
HbA_{1C}	8.3	< 6.0	%

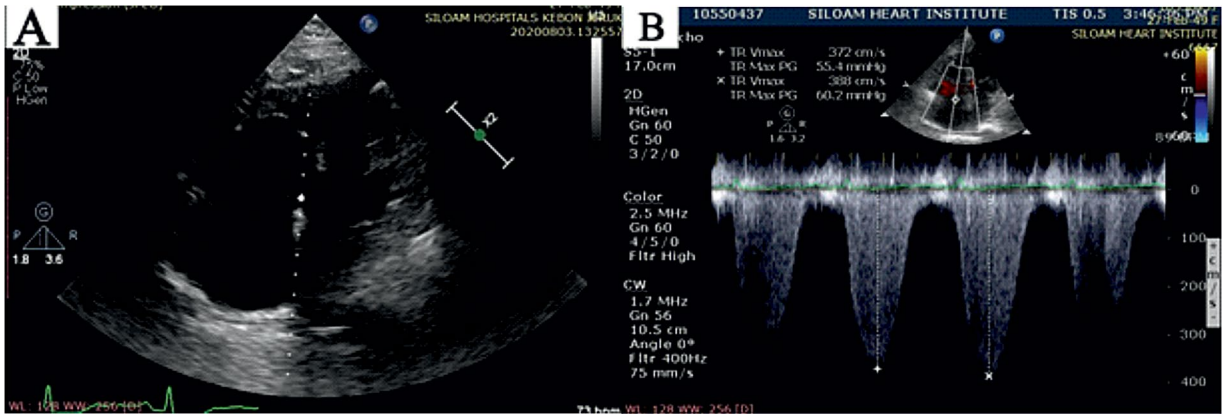

Figure 1. Echocardiography findings. **A.** Remarkable right ventricular enlargement seen from the apical 4-chamber view. **B.** Maximum velocity of the tricuspid regurgitation was around 3.8 m/s, indicating the tricuspid valve gradient of 60 mm Hg

mg/d in order to treat DVT as well as her long-standing hypertension and diabetes.

At the initial presentation she was obese with body mass index (BMI) around 33 kg/m^2 (body weight: 71 kg, body height: 1.47 m), and appeared dyspneic. Her vital signs on admission were as follows: fully awake, blood pressure 103/58 mm Hg, heart rate 90 bpm, respiratory rate 30/min; body temperature 37.0°C, and oxygen saturation 93% at room air. Other findings included slightly increased jugular vein pressure, increased the second heart sound without any murmur, clear lung sound, and swelling with tenderness at the entire right leg. ECG showed sinus tachycardia and diffuse ST depression at anteroseptal leads. Abnormalities on the initial laboratory results included increased D-Dimer 7,720 ng/mL and NTproBNP 10,958 pg/mL, HbA1C 8.3%, and slightly elevated creatinine 1.26 mg/dL (Table 1, Figure 1).

Echocardiography revealed normal left ventricle (LV) structure and preserved systolic function, an estimated pulmonary artery systolic pressure (PASP) of 70–80 mm Hg, prominent systolic septal inversion of LV, dilated RV, slightly reduced right ventricular systolic function. An obstructive thrombus with non-compressible vein were seen by Duplex Ultrasound upon right common femoral vein. Eventually, CT angiography of pulmonary artery confirmed the diagnosis of acute pulmonary embolism caused by several thrombus at both main branches of pulmonary arteries, along

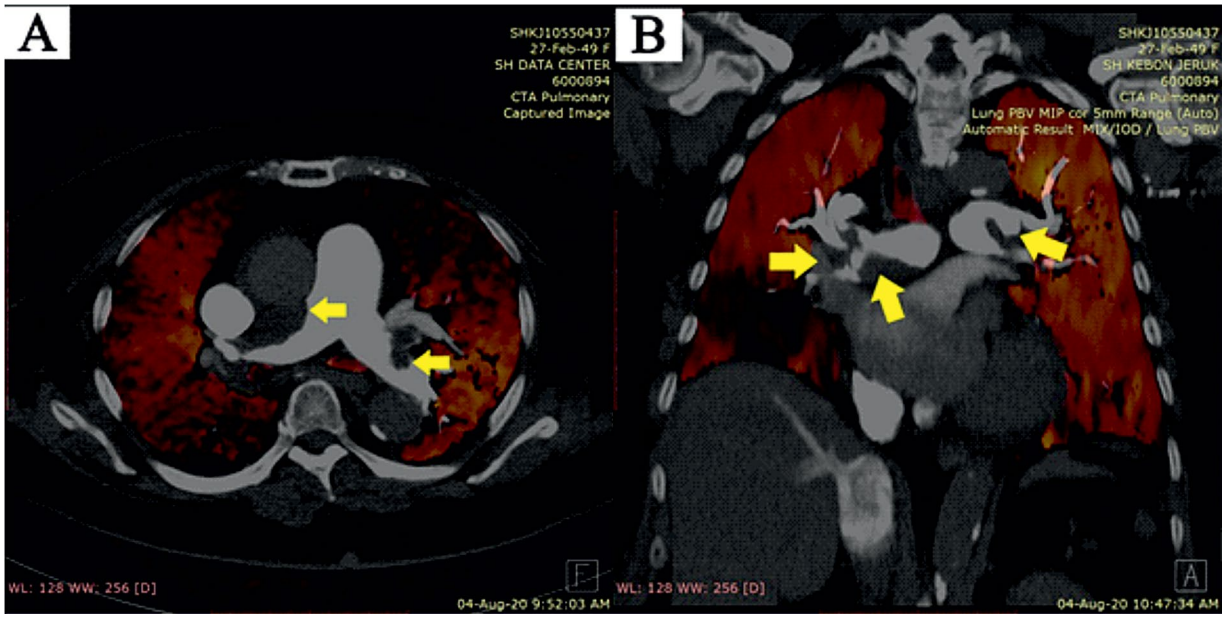

Figure 2. Computed tomography angiography of the pulmonary arteries revealed large thrombus (yellow arrows) at both main branches of pulmonary arteries and the distal branches. **A.** Axial plane. **B.** Coronal plane

Table 2. Laboratory results at worsening symptoms

Parameters	Value	Reference range	Unit
Random blood glucose	142	80–180	mg/dL
Lactic acid	5.4	0.7–2.5	mmol/L
Blood keton	2.9	0.0–0.6	mmol/L
pH	7.14	7.35–7.45	
pO^2	75.0	80.0–105.0	mm Hg
pCO_2	36.7	35.0–45.0	mm Hg
Bicarbonate	12.1	21.0–28.0	mmol/L
Base excess	-17.0	-2.5 ± 2.5	
T CO_2	13.0	19.0–25.0	mmol/L
O2 Saturation	88	95.0–100	%
SGOT	34	5–34	U/L
SGPT	26	< 55	U/L
Ureum	28	10–50	mg/dL
Creatinine	1.37	0.6–1.1	mg/dL
Estimated GFR	38		mL/min/1.73 m^2
Sodium	141	135–145	mmol/L
Potassium	4.1	3.5–5.0	mmol/L
Chloride	111	97–111	mmol/L

with multiple chronic segmental embolisms. Based on these findings, she was treated with subcutaneous enoxaparin 60 mg bidaily and high-flow nasal oxygen (Optiflow) (Figure 2).

During the next 48 hours, she developed increased work of breathing and loss of consciousness, although the hemodynamic and oxygenation remained stable, urging her to get intubated and mechanical ventilated. The blood test showed random blood glucose 142 mg/dL, pH 7.14, base excess -17, pCO_2 36.7 mm Hg, calculated anion gap 17.9 mEq/L, as well as increased levels of blood ketone 2.9 mmol/L and lactate 5.5 mmol/L. Notably, her urea and creatinine levels were relative steady at 28 mg/dL and 1.37 mg/dL, respectively (Table 2).

Table 3. Laboratory results after insulin administration and other corrections

Parameters	Value	Reference range	Unit
Random blood glucose	136	80–180	mg/dL
Lactic acid	1.6	0.7–2.5	mmol/L
Blood keton	0.2	0.0–0.6	mmol/L
pH	7.54	7.35–7.45	
pO_2	92.9	80.0–105.0	mm Hg
pCO_2	28.6	35.0–45.0	mm Hg
Bicarbonate	25.0	21.0–28.0	mmol/L
Base excess	3.8	-2.5 ± 2.5	
T CO_2	25.8	19.0–25.0	mmol/L
O_2 Saturation	98.2	95.0–100	%
Ureum	26	10–50	mg/dL
Creatinine	1.35	0.6–1.1	mg/dL
Estimated GFR	39.5		mL/min/1.73 m^2
Sodium	145	135–145	mmol/L
Potassium	4.5	3.5–5.0	mmol/L
Chloride	109	97–111	mmol/L

Meanwhile, there was no significant ECG changes than the previous recording, except sinus tachycardia. Moreover, follow-up echocardiography indicated improvement of right ventricular size and function, and reduced PASP (around 55–65 mm Hg) as well.

A diagnosis of Eu-DKA presumably related to empagliflozin was considered. Empagliflozin was withheld, then rehydration and administration of bicarbonate as well as small dose of insulin drip along with dextrose solution were managed. Rapid resolution of metabolic acidosis, lactate and ketone levels along with the clinical improvement was achieved on the following days (Table 3). Predischarge echocardiography demonstrated reduction of PASP to 55–65 mm Hg and right ventricle size, as well as an increased tricuspid annular plane systolic excursion (TAPSE). Finally, she was discharged in the next week with rivaroxaban 20 mg od., sildenafil 25 mg tid., and atorvastatin 20 mg/d.

Discussion

Here, we presented a case of Eu-DKA occurred in patients admitted due to acute pulmonary embolism (PE). Regarding to the steady hemodynamic and oxygenation status, her clinical deterioration during hospitalization was more likely caused by the progression of metabolic acidosis, rather than the PE progression. Recent use of empagliflozin might contribute in developing DKA in this critical case.

Since symptoms of Eu-DKA are less typical compared to classical DKA, early recognition of this complication might be challenging [3]. Potential precipitating factors of developing Eu-DKA in SGLT2i use include low carbohydrate diets, restricted fluid intake, concomitant critical diseases (including acute pulmonary embolism), malnutrition, pregnancy, excessive alcohol intake, and insulin withdrawal or dose reduction [4–6].

Notably, lean individuals on SGLT2i have a higher risk compared with obese individuals since the degree of glycosuria is independent of body size [7]. In addition, type-2 diabetes mellitus patients with limited -cell function reserves, longer duration of diabetes, and poorer control of diabetes are also more prone to experience Eu-DKA [8].

The reported incidences of DKA in previous studies of SGLT2i are low, however the specific numbers of Eu-DKA events were not certainly assessed. The CANagliflozin cardioVascular Assessment Study (CANVAS) noted the incidences of this catastrophe in canagliflozin group compared to the placebo are 0.6 versus 0.3 per 1000 patients, respectively [7]. Other study, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUCTOME) showed the incidence of DKA is less than 0.1%. Similar to EMPA-REG OUTCOME, the Dapagliflozin Effect of Cardiovascular Events (DECLARE) also reported the frequencies of DKA is < 0.1% [3, 7]. Moreover, FDA indicated that the fatality rate of Eu-DKA associated SGLT2i is higher compared to classical DKA (1.54% and 0.4%, respectively) [9].

Eu-DKA in the setting of SGLT2i use is directly related to the effect of glycosuria of this agent [10]. SGLT2i increase glucose excretion contributing to approximately 50–100 mg/day. As a result, the plasma glucose levels are reduced after a meal and in fasting

state [3]. Furthermore, the plasma insulin levels are also reduced because glucose is the stimulus of insulin release. In contrast, the plasma glucagon levels are increased. The possible mechanisms of increased plasma glucagon levels are diminished paracrine inhibition of insulin and decreased SGLT-2 mediated glucose transport into pancreatic α-cells [5, 11]. Dapagliflozin had been considered for having a direct effect on pancreatic α-cells by triggering glucagon secretion, but this finding varies between studies [12, 13]. Recent study reported interindividual differences of SGLT2 protein expression and function in human pancreatic islet, which support the explanation of interindividual response among individuals with SGLT2i [14].

The reduced plasma insulin levels and increased plasma glucagon levels result in an reduced insulin-to-glucagon ratio [8]. Given that insulin have anti-lipolytic activity, lower insulin-to-glucagon ratio would potentially induce lipolysis contributing to an increased release of free fatty acid (FFA). The elevated FFA delivery to the liver might cause an increased ketone production [3, 9]. Moreover, reduced insulin levels would bring down the activity of acetyl-CoA carboxylase and then result in declined malonyl-CoA levels, a potent inhibitor of carnitine palmitoyl-transferase-I (CPT-I). This process will end up in an increased CPT-I which further promotes the transport of FFA into mitochondria and oxidation of FFA to ketone bodies, including acetoacetate and β-hydroxybutyrate [4, 7, 9].

To date, there is no specific guideline for the treatment of Eu-DKA associated SGLT2i. Basically, the approach refers to management of the classical DKA, except there is no hyperglycemia in this case [7, 9]. SGLT2i are needed to be withheld for a period of time, and intravenous isotonic fluid administration might be considered to replenish volume status [12, 13]. If the potassium level is more than 3.3 mEq/L, intravenous insulin can be safely given along with intravenous dextrose 5% to avoid hypoglycaemia [3, 5]. Bicarbonate usually is considered in severe metabolic acidosis indicated by pH level less than 6.9 [15]. The resolution of Eu-DKA is marked by 2 of the following conditions, a serum bicarbonate level $\geq$ 15 mmol/L, and anion gap $\leq$ 12 mmol/L, or venous pH $>$ 7.3 [10].

Conclusion

Eu-DKA might potentially occur in diabetic patients treated with SGLT2i during critical illness setting. Prompt recognition of this atypical clinical condition is paramount important to intervene this life-threatening complication.

Conflict of interest

None declared.

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