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Coronavirus Disease 2019 (COVID-19) Precipitating Diabetic Ketoacidosis in Controlled Diabetes Mellitus Patient: A Case Report

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Abstract: ***Diabetic ketoacidosis (DKA) is an acute complication for severe hyperglycemia state in diabetes mellitus (DM) patients. In pandemic situation of COVID-19 nowadays, having DM as comorbidity tend to be a poor outcomes when the patient got infected. Studies reported incidents of DKA occurred following a confirmed COVID-19 patient, since infection is the most common precipitating factor of DKA, but the causative mechanism of it is still unclear and need to be reviewed more. Early recognition and prevention of disease progressiveness helps reduce the morbidity and mortality in patient.***

Keywords: diabetic ketoacidosis, diabetes mellitus, COVID-19

1.Introduction

Diabetic ketoacidosis (DKA) is a well-known complication in diabetes mellitus (DM) patients who experience severe hyperglycemic state. Several events have causative role such as absolute or relative insulin deficiency, inadequate glucose utilization, ketone bodies production as consequence of lipolysis, and decrease in blood pH level.[1] Infection, hypersensitivity disease, kidney disease, obesity, illicit drug abuse, cardiovascular diseases, and immune suppression are the main precipitating factors for DKA incidence.[1, 2]

As the World Health Organization declared a pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe-acute-respiratory-syndrome corona virus 2 (SARS-CoV-2) since March 2020, diabetes mellitus patient tend to be identified as a risk factor for poor outcomes in patients who suffer COVID-19.[2] A high incidence of ketoacidosis has been observed in patients admitted to hospital with COVID-19, but the studies addressing relation between this still need to be peer-reviewed more.[2]

We report a case of diabetic ketoacidosis (DKA) in confirmed COVID-19 patient, which is treated and monitored in general isolation ward instead due to the outbreak situation in that time, and unavailability of intensive care ward.

2.Case Report

A 50-years-old female patient was referred to Emergency Department in Wangaya General Hospital, Bali, Indonesia on July 5th 2021 with fever followed by nausea and vomiting. The fever began 3 days prior to nausea and vomiting symptoms. Fever was fluctuating around 37.5 to 38.1 degree Celsius and was treated by taking paracetamol tablet independently at home. She was initiatively wearing mask and isolate herself in the room to prevent disease transmission. The stomach upset began around 12 hours before referred to hospital, antacid was taken to treat the symptom but there was no significant improvement and the patient began to vomit few times. There was no flu like illness symptom, sore throat, nor smelling and tasting disturbance.

The patient has a history of controlled type-2 diabetes mellitus (T2D) since 3 years ago. She took a rapid-acting Glulisin insulin 12 units three times daily and long-acting Glargine insulin, as much as 15 units once at night. She maintains her daily diet, routinely check her blood glucose at home, she said that her fasting blood glucose average was 115 to 125 mg/dL on routine check. There is no history of hypertension, cardiovascular disease, kidney disease or any other systemic disease. Similar disease or any other systemic disease in her family was denied. Any smoking or alcohol consumption habit was denied as well.

The patient said that last week she was attending a traditional ceremony in her village, where at the time there was a crowd of people, she careless took off mask and ate close to relatives. The rest she spent more time at home, out only for buying groceries. She has already received 2nd dose of Sinovac for COVID-19 vaccination.

The patient was physically weak and seemed exhausted. Vital signs examination showed the blood pressure was 113/68 mmHg, pulse rate 92 beats per minute, respiratory rate 26 times per minute, axillary temperature was 37.2 degree Celsius, oxygen saturation was 97% on room air. On physical examination, the eyes looked sunken, her lips looked dry, breath pattern was rapid and deep which depict Kussmaul pattern, decreased skin turgor and epigastric pain was also found. The remainder of physical examination was within normal limit. From laboratory result: leukocytosis (leukocytes 14.28 10^3/ul), random blood glucose 668 mg/dL, while other complete blood count finding was within normal limit. Biochemical evaluation showed an elevated liver enzyme (SGOT 60 U/L and SGPT 46 U/L), blood urea nitrogen (BUN) 78 mg/dL, serum creatinine (SC) 1.6 mg/dL, sodium and potassium level were 126 mmol/L and 6.1 mmol/L while chloride level was 95 mmol/L. Blood Gas Analysis result:

blood pH 6.91, low pCO2 (13 mmHg) and elevated pO2 (104 mmHg), bicarbonate 3 mmol/L, base excess level-30 mmol/L. The urinalysis showed +3 ketones and +3 glucose, protein was negative. The patient was also confirmed SARS-CoV-2 positive by nasopharynx swab RT-PCR test. The chest x-ray was within normal limit.

Table 1: Laboratory result at ED

Investigation	Result	Reference Range
Blood glucose (mg/dL)	668	80 – 200
Arterial Blood Gas		
pH	6.91	7.35 – 7.45
pCO2 (mmHg)	13	35 – 45
pO2 (mmHg)	104	80.0 – 100.0
cHCO3 (mmol/L)	3	23 – 33
BE (mmol/L)	-30	(-2) – (+2)
Biochemical		
SGPT (U/L)	46	0 – 42
SGOT (U/L)	60	0 – 37
BUN (mg/dL)	76	10 – 50
Creatinine (mg/dL)	1.6	0.3 – 1.2
Electrolytes		
Sodium (mmol/L)	126	130 – 145
Potassium (mmol/L)	6.1	3.5 – 5.5
Chloride (mmol/L)	95	95 – 108
Urinalysis		
Protein	Negative	Negative
Glucose	+3	Negative
Ketone	+3	Negative
Bacteria	Negative	Negative

Therefore, she was diagnosed tipe II diabetes with diabetic ketoacidosis (DKA), confirmed COVID-19, acute kidney injury (AKI), hyperkalemia, hyponatremia and transaminitis. As the first treatment, the patient was rehydrated by giving an intravenous fluid resuscitation of NaCl 0.9%. Ondansetron and omeprazole were given intravenously as symptomatic treatment, paracetamol tablets were given as well. Blood gas analysis and electrolytes evaluation as shown in table 2.

Image 1: Chest x-ray evaluation

Following the treatment, intravenous fluid was continued with adjusting the drops, a broad spectrum antibiotic, ceftriaxone, was given 1 gram every 8 hours after ensuring no allergic response. Intravenous insulin (IVI) drip of a rapid-acting Aspart insulin, given 4 units with hourly glucose monitoring. Oxygen via nasal canula was put on with flow of 3 liters per minute. At the time was COVID-19 cases outbreak in Bali, so referring to another hospital was difficult. The ICU capacity was full, then she was transferred to general isolation ward instead. It was planned to ask for help from patient's family in the ward to check blood glucose while in iv insulin treatment as well due to insufficient number of nurses unlike ICU. Personal protective equipment is prepared for them, and test for COVID-19 done periodically.

Table 2: Lab result after fluid resuscitation

Investigation	Result		Reference Range
	I	**II**	
Arterial Blood Gas			
pH	7.01	7.23	7.35 – 7.45
pCO2 (mmHg)	15	32	35 – 45
pO2 (mmHg)	162	188	80.0 – 100.0
cHCO3 (mmol/L)	4	13	23 – 33
BE (mmol/L)	-28	-13	(-2) – (+2)
Electrolytes			
Sodium (mmol/L)	134		130 – 145
Potassium (mmol/L)	4.5		3.5 – 5.5
Chloride (mmol/L)	100		95 – 108

Fortunatelly, the patient showed improvements. Blood pressure was 120/60 mmHg, pulse rate 92 bpm, respiration rate 20 times per minute with normal pattern, axillary temperature was 36.8 degree Celsius, oxygen saturation 99% with nasal canula 3 lpm. Blood Gas Analysis evaluated again as shown in table 2. As she was getting better and eat well, iv insulin treatment was stopped (blood glucose was 246 mg/dL) thus a long-acting Glargine insulin was given 8 units at night subcutaneously. Nasal cannula was taken off due to good oxygen saturation, iv sodium bicarbonate no longer given.

On following day, less nausea and no fever found. She treated with maintained drop of iv NaCl 0.9%, rapid-acting Aspart insulin 8 units subcutaneously every 8 hours, iv omeprazole once daily, iv ondansetron 4mg every 8 hours, changing the antibiotic to iv Levofloxacin 750mg with addition of Azithromycin tablet 500mg each once per day, and Remdesivir according COVID-19 protocol. She also given iv vitamin C with dose of 600mg twice daily and a 5000IU vitamin D3 tablet.

Laboratory evaluation showed BUN 31 mg/dL, SC 1.2 mg/dL, HbA1C 13.3%, PT 9.5 seconds, APTT 25 seconds, INR 0.9 and an increased D-Dimer level of 921 ng/mL. Hence, a Low Molecular Weight Heparin (LMWH), Enoxaparin, was given to the patient subcutaneously with dose of 0, 4cc (4000 anti-Xa IU) once daily. Insulin administration was modified according to blood glucose level in regular monitoring to prevent hypoglycemic and hyperglycemic state. For the patient's accompanying family, fortunately, got a negative result for COVID-19 test. Anticoagulant administration was stopped when D-Dimer level was 375 ng/mL. Once, the patient experienced hypoglycemia so the insulin administration postponed,

dextrose infusion was given, and blood glucose rechecked periodically before restarting insulin treatment again.

Image 2: Chest x-ray on 9th day

Chest x-ray reevaluation was showed pneumonia, which didn't appear in first result, dehydration state of DKA presumptively was the cause. After 10 days of hospitalization, patient's condition was stable with no symptom, laboratory evaluation within normal limits, therefore she was able to discharge from hospital.

3.Discussion

Diabetic Ketoacidosis (DKA) is a state of hyperglycemic crisis in diabetes mellitus (DM) patient that occurs when glucose utilization is reduced in the setting of relative or absolute insulin deficiency, lipolysis which leads excessive ketone body formation, thus the blood become acidic. DKA is often accompanied by an underlying severe illness or condition.[3] DKA clinical sign and symptoms are based on its effect in metabolism. A persistent increase of blood glucose level in the blood as well as excessive ketones production due to lipolysis, might cause metabolic acidosis. Furthermore, altered mental status might occur as well in several cases.[4]

In this case, presented a patient with chief complaints of nausea and vomiting, which also experienced fever since few days prior that. She has a history of controlled T2D with insulin treatment. From patient's blood examination showed leukocytosis, blood glucose level was 668 mg/dL, blood pH of 6.91 with low level of pCO2, bicarbonate and base excess. Urinalysis showed positive for ketone, indicated that there was formation of ketone bodies in the circulation. Those indicated a ketoacidosis was occurring in case presented patient. The RT-PCR for SARS-CoV-2 by using nasopharynx sample was also positive, so she confirmed as COVID-19 patient as well. Interesting thing was, in the chest x-ray evaluation the result was within normal limit.

After examination, she was diagnosed with DKA, which is presumptively precipitated by COVID-19. Studies theorize that SARS-CoV-2 infection in COVID-19 uses angiotensin-converting enzyme 2 receptors (ACEs-2 receptors) to enter into the cells, pancreatic islet cells is one of several location which ACEs-2 receptors are present, where it is preferentially expressed in subsets of insulin producing β-cells.[1, 4] Transient damage to the pancreatic islet during acute infection suspected as the cause of crisis hyperglycemia state in diabetic patient who suffer COVID-19, nevertheless further studies are needed to explore this potential effect on pancreatic β-cells.[1, 4] This is hypothesized to occur in the patient in this case as well.

Some studies said about 50% to 75% of DKA patients present with GI tract symptoms such as nausea, vomiting, and abdominal pain.[3, 5] The exact pathogenesis for these symptoms remains unclear, but it is possible that hyperglycemia increases circulating catecholamine and glucagon level due to response of hyperglycemic stress, which play a role in gastric motility.[4] Samewise as the patient in this case, symptoms of nausea and vomiting were experienced when administered to emergency department. She also showed a rapid and deep breathing pattern, known as Kussmaul Breathing in order to compensate occurring metabolic acidosis.[5, 6]

Other findings were hyperkalemia, elevated blood urea, creatinine serum and transaminase level. Based on theory, in the state of insulin deficiency and metabolic acidosis, potassium will shifts into the extracellular space. Giving fluid administration as well as insulin therapy, will helps shifting potassium back to intracellular space.[3, 7] Elevated BUN-SC might indicate the patient suffering an acute kidney injury (AKI) due to acute dehydration state. Increased lipolysis which resulting in deposits of free fatty acid in the liver, as well as oxidative stress from ketone bodies, stated to be the cause of hepatocyte damage thus increasing hepatic enzymes.[3, 5, 7]

The principal of DKA managements are based on mechanism of how it occurs. Those mechanisms include insulin deficiency resulting in decreased glucose utilization by peripheral tissues, increased counter regulatory hormones thus increasing hepatic glucose production as well as lipolysis, and excessive oxidation of free fatty acid in the liver resulting excessive ketone bodies leads to ketoacids, [7, 8] For years, the management of DKA still have not changed, which is include the triad of fluid resuscitation, electrolytes correction, and insulin therapy.[8, 9] The patient in this case was given fluid resuscitation with isotonic fluid (NaCl 0.9%) in order to expand intravascular volume. Symptomatic treatments were also given after that. Sodium bicarbonate were given as well, but then it was not given regularly due to patient's improvement. Hyperkalemia was also corrected after fluid resuscitation. The following treatment was intravenous insulin (IVI) with hourly monitoring. As infection is one of the most precipitating factors in DKA, a broad spectrum antibiotic was also given to this patient.

The most common hospital setting utilized to administer DKA is the ICU, since frequent glucose monitoring is required due to simultaneous therapies (fluids and insulin), a risk of hypoglycemia risk in patient is extremely high.[3, 7] Furthermore, the patient in this case was suffering COVID-19 as well which need to be closely monitored. But the situation that time, ICU for COVID-19 was full and referring the patient was difficult, because other

hospital experienced same situation as well. She was administered to the general isolation ward instead. Fortunatelly, the patient's clinical features were getting better as the DKA gradually resolved. Close monitoring of blood glucose level was not a simple task, since the patient was not monitored in the ICU; patient's family help has an important role to it.

The treatment for COVID-19 was done simultaneously in the ward as well as DKA monitoring. For patient presented in this case, according to guidelines of COVID-19 management by Indonesian Ministry of Health, it is suggested giving antibiotics for pneumonia such as azithromycin and/or levofloxacin based on evaluation, vitamin C 600mg to 1200mg per day, vitamin D3 5000 IU per day, antiviral treatment using Favipiravir or Remdesivir, LMWH based on evaluation given as treatment for coagulopathy, as well as other supportive and comorbid treatment.1[0] Patient in this case has been treated according to the guidelines for COVID-19 by Indonesian Ministry of Health. It is presumed that patient's history of controlled T2D as well as COVID-19 vaccination help prevent poor outcome.

There is not enough data yet on studies whether patients with diabetes who infected by SARS-CoV-2 tend to experience DKA. Further studies are needed to explore the incidence and pathogenesis of DKA in diabetic patients with SAR-CoV-2 infection.[8, 9] Considering that the patient in this report was with controlled T2D, even so she experienced ketoacidosis state when she got infected by SAR-CoV-2.

4.Conclusion

DKA is a complication of hyperglycemic crisis state in diabetes mellitus patients which often accompanied by an underlying disease or condition. In COVID-19 pandemic era, SAR-CoV-2 infection is said to be one of precipitating factor in DKA occurrence. Further studies of relation of COVID-19 with DKA incidence in diabetic patients are needed. Early recognition, proper treatments and close monitoring greatly helps reduce the morbidity and mortality.

Conflict of Interest

The authors declare no conflicts of interest.

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