□ CASE REPORT □

Septic Ketoacidosis

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Abstract

Various unmeasured anions other than lactate appear in the blood of septic patients, including ketones. However, the occurrence of sepsis-induced ketoacidosis without diabetes mellitus has not been reported to date. We herein describe severe ketoacidosis in a patient with septic shock despite the absence of diabetes, alcohol and starvation. A 76-year-old woman presented with septic shock due to acute obstructive cholangitis. She exhibited ketoacidosis and a remarkably strong ion gap, except for ketones. Sepsis alone may lead to ketoacidosis in patients without diabetes under specific conditions. The accumulation of ketones and other strong anions can occur in cases involving a decreased metabolic function. There may be a pathological condition called septic ketoacidosis.

Key words: septic ketoacidosis, sepsis, ketoacidosis, strong ion gap

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Introduction

Metabolic acidosis is the most frequently observed acid-base disorder in critically ill patients (1) and those with severe sepsis and septic shock (2). A high level of lactate, the main source of acidosis in such patients, is associated with increased mortality (3). However, various unmeasured anions other than lactate appear in the blood of septic patients (4) and are also associated with mortality (5). These anions can be evaluated using the Stewart-Figge method as a strong ion gap SIG (6). The apparent strong ion difference (SIDapp) and effective strong ion difference (SIDEff) are calculated using the following formula (the SIG is then calculated as the difference):

$$\text{SIDapp} = [\text{Na}^+] + [\text{K}^+] + [\text{Mg}^{2+}] + [\text{Ca}^{2+}] - [\text{Cl}^-] - [\text{lactate}^-]$$

$$\text{SIDEff} = 2.46 \times 10^{(\text{pH}-8)} \times \text{PCO}_2 + [\text{Alb}] \times (0.123 \times \text{pH} - 0.631) \\ + [\text{Phosphate}] \times (0.309 \times \text{pH} - 0.469)$$

$$\text{SIG} = \text{SIDapp} - \text{SIDEff}$$

We herein describe a case of severe metabolic acidosis without lactate elevation in a patient with septic shock due to acute obstructive cholangitis that arose primarily from blood ketones despite the absence of diabetes mellitus and a habit of alcohol consumption. Sepsis-induced ketoacidosis in

a patient without diabetes mellitus has not been reported to date. However, sepsis can produce various anions (7), and the accumulation of ketones can occur under specific conditions in patients without diabetes mellitus.

Case Report

A 76-year-old woman presented with a fever and generalized pain lasting for 15 hours. She had undergone surgery involving cholecystectomy and bile duct construction more than ten years previously. She had no diabetes mellitus and did not drink any alcohol. She reported having a good appetite until the onset of symptoms and exhibited no history of starvation or consumption associated with a low-carbohydrate diet. She did not take drugs to induce ketosis. Her height was 160 cm and her body weight was 80 kg. A physical examination showed a body temperature of 39°C, a blood pressure of 80/37 mmHg, a heart rate of 124 beats/min and a Glasgow Coma Scale of E2V4M5. The results of a blood gas analysis and laboratory examination performed on admission are shown in Table. The patient presented with liver and kidney dysfunction. Typical anion-gap metabolic acidosis was detected, primarily due to ketoacidosis, although the glucose level was normal. The calculated strong

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Table. Laboratory Findings

ABG		Chemistry		Diabetes	
pH	7.218	TP	5.5 g/dL	Glucose	126 mg/dL
PCO ₂	18.7 mmHg	Albumin	3.2 g/dL	HbA1c	5.7 %
PaO ₂	100.5 mmHg	Bilirubin	4.2 mg/dL	IRI	2.75 µU/mL
HCO ₃	7.6 mEq/L	AST	1,923 U/L	IRG	297 pg/mL
BE	-20.1 mEq/L	ALT	1,131 U/L	HOMA-R	0.86
Anion gap	26.5 mmol/L	LDH	1,314 U/L	HOMA-β	15.71
lactate	1.3 mmol/L	γGTP	310 U/L		
		ALP	609 U/L	Total cholesterol	148 mg/dL
		Amylase	194 U/L	Triglyceride	283 mg/dL
CBC		CK	445 U/L	Free fatty acid	1,155 µEq/L
WBC	30,500 cells/µL	Na	140 mmol/L		
Hb	13.0 g/dL	K	3.0 mmol/L	Ketone	
Platelet	67,000 cells/µL	Cl	106 mmol/L	acetoacetate	2,549 µmol/L
		Ca	9.0 mg/dL	3-hydroxybutyrate	9,856 µmol/L
Coagulation		P	6.2 mg/dL		
PT	14.4 sec	BUN	55.6 mg/dL	Pyruvic acid	0.37 mg/dL
APTT	32.7 sec	Creatinine	2.4 mg/dL		
FDP	12.3 µg/mL	CRP	19.73 g/dL	BNP	1,227.6 pg/mL
		Ammonia	73 µg/dL		

ABG: arterial blood gas, BE: base excess, CBC: complete blood cell count, WBC: white blood cell count, Hb: hemoglobin, TP: total protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, CK: creatine kinase, BUN: blood nitrogen, CRP: C reactive protein, IRI: immunoreactive insulin, IRG: immunoreactive glucagon, HOMA-R: homeostasis model assessment of insulin resistance, HOMA-β: homeostasis model assessment of β-cell function, BNP: brain natriuretic peptide

ion gap was 17.2 mmol/L, and the sum of acetoacetate and 3-hydroxybutyrate was 12.4 mmol/L. These findings indicated that the anion gap primarily involved ketones, although other strong anions were certainly present. An amino acid analysis showed increases in two amino acids: 2-methylhistidine at 21.1 nmol/mL and α-aminobutyric acid at 47 nmol/mL. However, the levels of other amino acids were within the normal limits.

Abdominal enhanced CT revealed dilatation of the common and intrahepatic bile ducts. Cardiac echography showed diffuse hypokinesis of the left ventricle. Therefore, a diagnosis of septic shock due to acute obstructive cholangitis was made. A blood culture grew *Klebsiella pneumoniae*. We performed endoscopic retrograde biliary drainage and initiated treatment with antibiotics and intensive care. Noradrenalin (maximum 0.2 µg/kg/min) therapy was started, and the patient's hemodynamics immediately stabilized. Nevertheless, her metabolic acidosis and septic state did not improved after 24 hours, and the oliguria persisted. Therefore, continuous hemodialysis and filtration were administered, after which the acidosis and anion gap normalized within six hours and the dose of noradrenalin was decreased. Subsequently, parenteral nutrition, including 100 g of glucose per day and 1 unit per hour of insulin, was also started. The ketoacidosis did not recur, and the patient gradually recovered. Later, an oral glucose tolerance test showed normal results: glucose=83 mg/dL before, 174 mg/dL after one hour, 138 mg/dL after two hours. The patient was discharged two weeks later.

Discussion

The present case of metabolic acidosis was regarded to

involve ketoacidosis, without an etiology of diabetes, alcohol consumption, starvation or intoxication. Because the patient's particular ketone bodies were considered to be produced due to a state of sepsis without diabetes, there may be a pathological condition called septic ketoacidosis.

Fasting ketosis can occur following short-term starvation (8) and should be considered a differential cause of ketoacidosis in this case. Obesity and pregnancy have also been reported to accelerate ketogenesis (9, 10), and moderate ketoacidosis (base excess -15) is known to occur after a few days of starvation in pregnant woman (11). Ketogenesis following a half a day of starvation can occur in patients with obesity, similar to the present patient (9); however, the amount of ketones produced would be quite small and the condition would not present as severe ketoacidosis. Therefore, there is likely another cause for the large amount of ketones observed in this case.

How and where were these ketone bodies produced in the present patient, in the absence of diabetes? Ketogenesis generally takes place within the mitochondria of perivenous hepatocytes in the liver, with an absolute or relative lack of insulin (12). β-oxidation of fatty acids by lipolysis is also a key factor in the production of ketones in the liver (13). The produced ketones are metabolized by the enzymes for ketolysis in the muscles, kidneys and brain (12). The laboratory findings observed in the present case demonstrated a mild relative lack of insulin according to the HOMA-β and extremely high levels of free fatty acids. Chambrier et al. reported that sepsis impairs the actions of insulin during endogenous glucose production and glucose utilization (7). The insulin level in the present case was relatively low; however, it had only decreased slightly, not enough to induce remarkable ketoacidosis alone. Hypermetabolism under a septic

state and a relative increase in the level of glucagon may be considered to have accelerated the patient's ketogenesis. In fact, the arterial ketone ratio, acetoacetate/hydroxybutyrate, is reportedly decreased in patients with hemodynamically unstable septic shock (14), as observed in the present case. Meanwhile, acetic acid overload and acetyl-CoA carboxylase inhibition have also been reported to be additional causes of ketoacidosis. The usual source of acetic acid is bacterial metabolism in the gastrointestinal tract, and acetyl-CoA carboxylase is inhibited by adrenaline; both of these conditions can induce rapid ketogenesis (15). This mechanism of ketogenesis may be involved in our rare case of septic ketoacidosis. Moreover, the patient's kidney dysfunction may have decreased the rate of ketolysis, resulting in ketoacidosis. Therefore, sepsis alone can induce remarkable ketoacidosis, even in patients without diabetes mellitus.

Various anions other than lactate are reported to appear in the blood of critically ill septic patients, some of which have been identified (16-18). Moviat et al. examined unmeasured anions in the blood of patients with a dilated strong ion gap. However, only 7.9% of the cases were found to be explainable by examined amino acids, uric acid or organic acids (19). Indeed, the present patient exhibited a remarkably strong ion gap due to factors other than ketones, which could not be explained by the results of the amino acid analysis. Kellum et al. examined the anion flux of each organ in a dog model of acute endotoxemia (20). Although the liver normally removes anions under healthy conditions, interestingly, it switches to releasing anions under a state of endotoxemia. It is believed that severe sepsis or septic shock decreases the anion clearance of the liver. In patients with severe liver failure, as in the present case, the produced anions cannot be cleared and instead accumulate in the blood, thus resulting in a remarkably strong anion gap. Kidney dysfunction and heart failure may accelerate the altered clearance.

Septic ketoacidosis can occur in cases of severe sepsis or septic shock in patients without diabetes mellitus or a history of alcohol consumption or starvation via a relative lack of insulin and poor metabolic function. Hemodialysis is a potential effective option for the management of remarkably strong ion gaps in patients with decreased metabolism.

The authors state that they have no Conflict of Interest (COI).

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