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Case Report

A case of Hyperglycemic Hyperosmolar State with Hyponatremia and Subsequent Gastrointestinal Bleeding due to Acute Gastric Mucosal Lesions

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SUMMARY

We present a case of hyperglycemic hyperosmolar state with hyponatremia and subsequent bleeding from acute gastric mucosal lesions. An 84-year-old man with a long history of type 2 diabetes was repeatedly hospitalized for treatment of congestive heart failure due to coronary artery disease during the past decade and therefore received combination therapy with loop and thiazide diuretics. He was admitted for hyperglycemic hyperosmolar state with hyponatremia and, while hospitalized, developed anemia and bloody stools. Gastroscopy showed gastrointestinal bleeding due to acute gastric mucosal lesions (erosions and ulcers). Clinicians should keep in mind that acute gastric mucosal lesions can develop as a complication of hyperglycemic hyperosmolar state.

Keywords : hyperglycemia, hyperosmolar, hyponatremia, gastrointestinal bleeding, acute gastric mucosal lesions

INTRODUCTION

Hyperglycemic hyperosmolar state (HHS) is a life-threatening metabolic decompensation in diabetes that presents with severe hyperglycemia and profound dehydration with prerenal failure and is typically accompanied by alterations in consciousness ranging from lethargy to coma[1~3]. HHS frequently occurs in elderly people with type 2 diabetes who have a serum osmolality greater than 340 mOsm/kg and blood glucose levels greater than 600 mg/dL[1~3]. HHS sometimes induces temporal acute kidney injury due to marked dehydration. Hyperglycemia-induced osmotic diuresis can cause hypernatremia, a process that occurs mostly in patients with HHS[4]. Here, we describe a case of HHS with hyponatremia and subsequent gastrointestinal bleeding from acute gastric mucosal lesions (AGML).

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CASE PRESENTATION

An 84-year-old man with long-standing type 2 diabetes was admitted to our hospital with marked hyperglycemia and hyperosmolality. He had undergone coronary artery bypass surgery for unstable angina 10 years ago. At the same time, atrial fibrillation was observed, so an antiplatelet drug (aspirin 100 mg/day) and anticoagulant (apixaban 5 mg/day)

Table 1 Laboratory data on admission

Biochemical analysis		**Blood cell counts**	
Plasma glucose	555 mg/dL	WBC	11,700/μL
HbA1c	7.1%	Neutro	94.0%
Na	130 mmol/L	Eosino	0.0%
K	4.5 mmol/L	Baso	0.1%
Cl	94 mmol/L	Mono	2.6%
Ca	8.8 mmol/L	Lympho	3.3%
Mg	2.6 mmol/L	RBC	$494\times10^4/\mu$L
BUN	207 mg/dL	Hemoglobin	14.7 g/dL
Creatinine	3.85 mg/dL	Hematocrit	41.6%
eGFR	12.4 ml/min/1.73 m^2	Platelets	$15.8\times10^4/\mu$L
Uric acid	7.1 mg/dL	**Arterial blood gas analysis**	
Plasma osmolarity	375 mOsm/kg	**(1L/min O_2 inhaled)**	
Calculated osmolarity	368 mOsm/kg	pH	7.328
AST	32 U/L	PCO^2	19.5 mHg
ALT	35 U/L	PO^2	132.0 mmHg
LDH	220 U/L	HCO^{3-}	9.9 mmol/L
CPK	88 U/L	Base excess	−14.1 mmol/L
Amylase	211 U/L	Anion gap	19.1 mmol/L
CRP	＜0.04 mg/dL	**Coagulation fibrinolysis examination**	
Triglyceride	92 mg/dL	PT	14.9 sec
HDL cholesterol	44 mg/dL	PT-INR	1.33
Albumin	4.6 g/dL	PT%	63%
BNP	95.4 pg.mL	APTT	42.7 sec
Endocrinology		D dimer	0.4 μg/mL
Intact PTH	164.8 pg/mL	Fibrinogen quantity	227 mg/dL
Free-T4	1.05 ng/dL	FDP	2.0 μg/mL
Free-T3	1.76 pg/mL	**Urinalysis**	
TSH	1.02 μIU/mL	pH	5
ACTH	34.5 pg/mL	Glucose	500 mg/dL
Cortisol	22.2 μg/dL	Ketone bodies	(−)
Renin activity	12 ng/ml/hr	Blood	(3+)
Aldsterone	195 pg/mL	Protein	(−)
ADH	15.3 pg/mL	Na	34 mmol/L
		K	62 mmol/L
		Cl	79 mmol/L
		Ca	3.8 mg/dL
		P	8 mg/dL
		Creatinine	28 mg/dL

BUN, blood urea nitrogen ; eGFR, estimated glomerular filtration ; AST, aspartate transaminase ; ALT, alanine transaminase ; LDH, lactate dehydrogenase ; CPK, creatine phosphokinase ; CRP, C-reactive protein ; HDL, high-density lipoprotein ; BNP, brain natriuretic peptide ; PTH, parathyroid hormone ; TSH, thyroid stimulating hormone ; ACTH, adrenocorticotropic hormone ; ADH, antidiuretic hormone ; WBC, white blood cell ; RBC, red blood cell ; PT, prothrombin time ; INR, international normalized ratio ; APTT, activated partial thromboplastin time ; FDP, fibrinogen and fibrin degradation products.

were administered. He was also administered rabeprazole sodium to prevent aspirin-induced gastric mucosal damage. The patient had been repeatedly hospitalized for treatment of congestive heart failure during the past decade and was receiving combination therapy with loop and thiazide diuretics and an aldosterone blocker. And he was instructed by his doctor to limit fluid intake for chronic heart failure. He was also taking both linagliptin 5 mg/day and mitiglinide 30 mg/day as anti-diabetic drugs. He did not have dementia

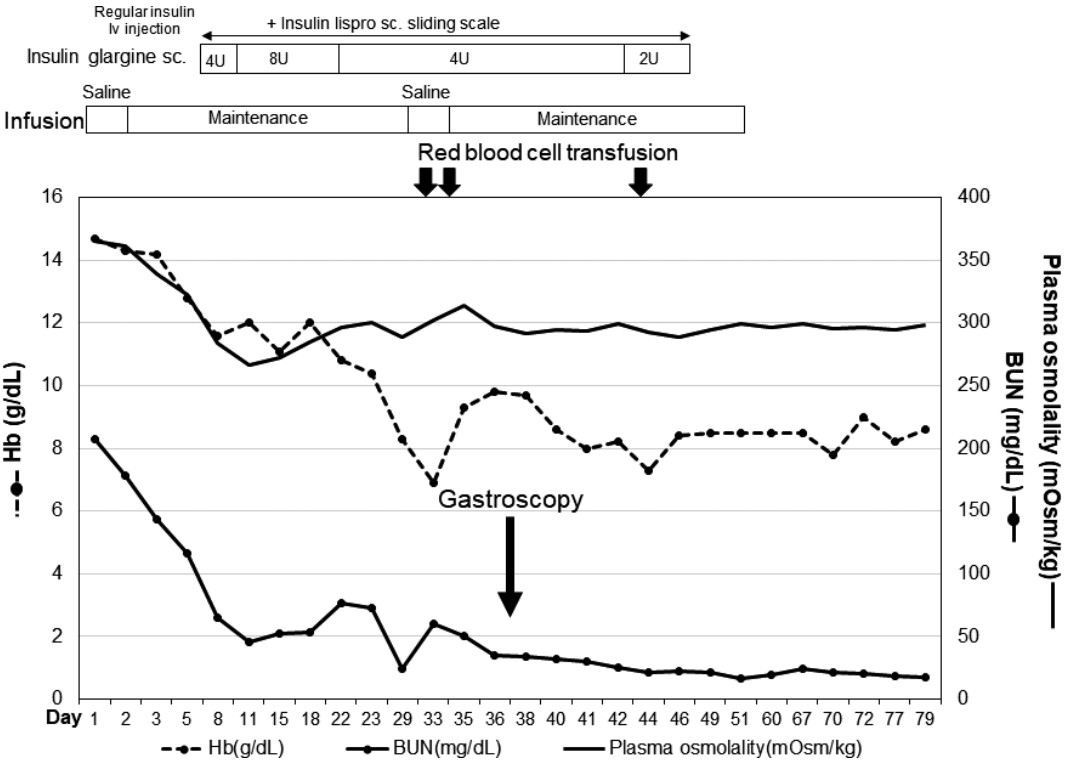

Fig. 1

Clinical course of serial changes in serum blood urea nitrogen (BUN), plasma osmolality, and hemoglobin during the hospitalization.

and was almost independent of activities of daily living. He reported started having experienced malaise and anorexia 10 days before hospitalization. He continued to take diuretics and other medications, although his diet and fluid intake were reduced. On admission, his consciousness was clear, his blood pressure was 124/90 mmHg, his pulse was irregular and 90 beats/minute, his respiratory rate was 20 /minute, and his temperature was 36.3℃. He is 159.1 cm tall and weighted 47.0 kg. On physical examination, we found exceedingly dry oral mucosa and poor skin turgor. The laboratory evaluation on admission revealed a marked hyperglycemia of 555 mg/dL with hyponatremia of 130 mEq/L ; serum blood urea nitrogen (BUN) and creatinine were significantly increased to 207 mg/dL and 3.85 mg/dL, respectively (Table 1). His plasma osmolality was markedly elevated at 375 mOsm/kg. No protein or ketone bodies were found in his urine. Plasma antidiuretic hormone (ADH) was markedly elevated. Although mild leukocytosis was found, serum C-reactive protein was less than 0.04 mg/dL (Table 1). He was diagnosed with HHS accompanied by hyponatremia and acute kidney injury.

Prompt fluid replacement and continuous intravenous insulin infusion were initiated. Simultaneously, thiazide and loop diuretics were discontinued because of the severe dehydration. On day 2, plasma glucose had decreased to 177 mg/dL, but serum BUN (178 mg/dL) and plasma osmolality (358 mOsm/kg) remained high. On day 6, serum BUN and plasma osmolality had decreased to 65 mg/dL and 276 mOsm/kg, respectively (Fig. 1). Subsequently, we switched from continuous intravenous insulin infusion to multiple subcutaneous insulin injections. On day 33, the patient complained of epigastric discomfort and noticed bloody stool. At the same time, his hemoglobin level decreased rapidly to 6.9 g/dL, so blood transfusions were given (Fig. 1). Gastroscopy showed acute gastrointestinal bleeding due to multiple acute gastric mucosal lesions (AGML) (erosions and ulcers) in the lesser curvature of the gastric corpus (Fig. 2). After stopping oral intake of food, the patient was fed intravenously for a couple of weeks. And he was continued an administration of PPI, which was changed from rabeprazole sodium to vonoprazan fumarate. His hemoglobin level was further decreased and he got a

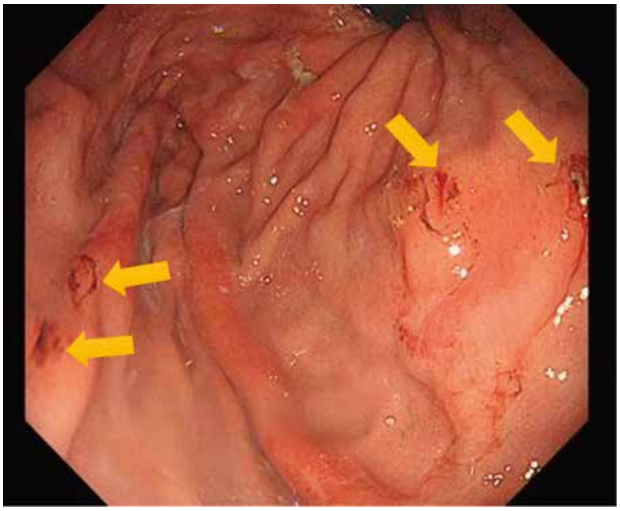

Fig. 2
Findings of gastroscopy : Multiple gastric mucosal erosion with bleeding and scarred ulcers (arrows) in lesser curvature of the gastric corpus.

red blood cell transfusion. His general condition improved slowly but steadily. On the 82nd day after being hospitalized, he was transferred to a long-stay hospital for rehabilitation.

DISCUSSIONS

We report on an 84-year-old man with HHS presenting with hyponatremia. Although our patient had severe dehydration, as shown by both plasma osmolality (375 mOsm/kg) and serum BUN (207 mg/dL), he had hyponatremia associated with acute renal failure. HHS occurs commonly in elderly patients with type 2 diabetes and is characterized by severe dehydration with hypernatremia, marked hyperglycemia, and neurological impairments[1~3]. Infection is the most frequent cause of HHS[1~3] ; however, our patient had no signs of infection. We hypothesize that the combined treatment with loop diuretics and thiazide, in particular the latter, may have been a participating factor in the development of HHS in our patient.

Hypernatremia is common in HHS and is causally associated with an osmotic diuresis-induced hypotonic loss, which results in water being lost at a faster rate than sodium. Hypernatremia is closely associated with a profound hyperosmolarity in HHS. Whether hypo- or hypernatremia develops in HHS is dependent on which factor is more prominent, ie, in hyponatremia, increased plasma osmolality drives free water into the extracellular space, leading to dilutional hyponatremia ; and in hypernatremia, the loss of that free water through osmotic diuresis leads to a deficit of free water and hypovolemia with true hypernatremia[4].

Our patient presented with hyponatremia despite a marked hyperosmolar state (plasma osmolarity 375 mOsm/kg) due to severe dehydration (extremely high serum BUN level of 208 mg/dL), and we propose two possible explanations why we did not observe hypernatremia despite the marked hyperosmolality. One possible explanation is the presence of severe renal insufficiency, evidenced by an estimated glomerular filtration rate of 12.3 ml/min/1.73 m^2 on admission. Osmotic diuresis can lead to a significant loss of free water in excess of sodium and can cause or at least contribute to the development of hypernatremia. In patients with severe renal failure, osmotic diuresis is either markedly curtailed or nonexistent, so serum sodium levels do not rise[5]. In a similar fashion, in our patient the ability to develop and sustain osmotic diuresis was impaired because of acute renal failure, so no hypernatremia developed. The second possible explanation is the combined treatment with several diuretics, including thiazide and loop diuretics : Such treatment increases the excretion of sodium into the urine, so the serum sodium level does not increase. Pseudohyponatremia caused by hyperglycemia and azotemia also clearly contributed to the hyponatremia observed in our HHS patient.

Interestingly, after hospitalization, the patient developed gastrointestinal bleeding from multiple AGML (erosions and ulcers) in the gastric corpus. To the best of our knowledge, this is the first report of AGML after treatment for HHS in a hospitalized patient. Critically ill patients are at increased risk of developing stress-related mucosal disease and subsequent gastric ulcer bleeding as a result of an underlying disease[6]. Cook et al. demonstrated that both respiratory failure (mechanical ventilation for at least 48 hours) and coagulopathy were strong independent predictors for stress-related mucosal disease[7]. Our elderly patient was critically ill because of HHS, and he was also taking both an antiplatelet drug and an anticoagulant for treatment of coronary artery disease and atrial fibrillation. Furthermore, he was at high

risk for gastrointestinal bleeding because of multiple AGML.

The mechanism responsible for gastrointestinal bleeding in our patient remains unclear. In critically ill patients, hypovolemia and hypotension due to severe dehydration are associated with a significant increased risk of gastrointestinal bleeding[6] because splanchnic hypoperfusion may cause a breakdown of the mucosal protective defenses, leading to injury of the gastrointestinal wall and ulceration[6]. In addition, decreased microcirculation induced by vasoconstriction through activation of the sympathetic nervous system or increased catecholamine release or both may contribute to gastrointestinal bleeding[6]. In our patient, HHS may have been associated with both marked dehydration and sympathetic overactivity induced by stress, leading to development of AGML. Previous reports showed that the anticoagulants were increased in blood concentration by renal impairment[8]. Therefore, in cases with renal dysfunction, the risk of bleeding may increase, and it is necessary to reduce or discontinue the anticoagulant. This case is an elderly person with renal impairment who has a high risk of bleeding due to anticoagulants. Apixaban was administered at a reduced dose of 5 mg / day. However, the rapid progression of renal dysfunction associated with HHS may have increased blood concentration of apixaban. Clinicians should be aware of the occurrence of bleeding complications in the management of oral anticoagulants. If there are findings suggestive of renal dysfunction, it is very important to monitor renal function frequently and reduce or discontinue anticoagulants or switch to other drugs.

In conclusion, we present an elderly diabetic patient with HHS and hyponatremia and subsequent gastrointestinal bleeding from AGML. Critically ill patients such as those with HHS are at increased risk of developing stress-related mucosal disease and subsequent gastric ulcer bleeding. Clinicians should keep in mind that AGML can develop as a complication of HHS.

Disclosure statement

YA has received speaker fees from Mitsubishi Tanabe Pharma, Sumitomo Dainippon Pharma Co., Novo Nordisk Pharma, and Takeda Pharmaceutical Company.

Other authors state that they have no Conflict of Interest.

Author contributions

SS, SH : were treated the patient, and drafted the manuscript. TI, TT, TJ, IU : reviewed the manuscript. YA : wrote the manuscript. All authors read and approved the final manuscript.

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