Hypothermia-Induced Acute Kidney Injury in a Diabetic Patient with Nephropathy and Neuropathy

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Abstract

Hypothermia is a life-threatening medical condition defined as an unintentional fall in body temperature below 35°C. Exposure to cold environment stimulates the thermoregulatory system to maintain the body temperature within the physiological range. Patients with malnutrition and/or diabetes mellitus are at high risk for accidental hypothermia, and acute kidney injury, which is mainly caused by pre-renal factors, occurs in relation to hypothermia. However, acute exacerbation of pre-existing chronic kidney disease has been rarely reported. Here, we present a patient with diabetes mellitus and malnutrition who developed two separate episodes of hypothermia followed by acute exacerbation of chronic kidney disease.

Key words: acute kidney injury, chronic kidney disease, diabetes mellitus, diabetic neuropathy, hypothermia, malnutrition

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Introduction

Hypothermia is a life-threatening condition defined as an unintentional fall in core body temperature below 35°C (1). Exposure to cold environment usually stimulates the thermoregulatory system to maintain body temperature within the physiological range, preventing falls in body temperature below life-threatening level (2). However, some populations such as elderly individuals and patients with debilitating diseases, malnutrition, diabetes mellitus (DM), chronic kidney disease (CKD) and congestive heart failure (CHF) are at high risk of hypothermia because of impairment of the effector mechanisms involved in the control of body temperature (2, 3).

Acute kidney injury (AKI), seen in over 40% of patients with accidental hypothermia, is a serious complication in hypothermia (4). Pre-renal factors including cold-induced diuresis are considered the main cause of hypothermia-induced AKI (5), although the precise mechanism remains undetermined. However, acute exacerbation of pre-existing CKD has been rarely reported.

Case Report

A 70-year-old man with type 2 DM was admitted to Kyushu University Hospital in December for treatment of severe hypothermia. He was first diagnosed as type 2 DM at the age of 59 years and started to receive diet therapy followed by oral hypoglycemic agents. He started to receive medical follow up for CKD probably due to diabetic glomerulosclerosis at the age of 67. Three months before the current admission, he visited our hospital for regular follow-up, and the laboratory data at that time showed serum creatinine of 3.87 mg/dL, blood urea nitrogen (BUN) 65 mg/dL, and serum albumin 3.3 g/dL. At that time, he received only diet therapy and his hemoglobin A1c (HbA1c) was 5.2%. He had no history of drug abuse, narcotic drug use, dementia, or psychiatric illness which can be an indirect cause of hy-

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hypothermia. One hour prior to admission, he was found comatose at home with slight bleeding from his head, and was transferred to our hospital. On that day, the outside temperature was 5°C.

On admission, the patient was in deep coma (JCS III-200), blood pressure was 60/38 mmHg measured in supine position, heart rate 30 beats/min, respiratory rate 15/min, and body temperature 25.6°C. Body weight was 65.0 kg, height 170 cm, and body mass index was 22.5 kg/m². Physical examination showed severe undernourishment with extremely low muscle mass, anisocoria (unequal size of the pupils), decreased deep tendon reflex, and bilateral pretilial and subcutaneous edema. Laboratory tests showed serum albumin 2.7 g/dL, BUN 61 mg/dL, creatinine 3.89 mg/dL, hemoglobin A1c 4.5%, blood glucose 37 mg/dL, C-reactive protein 0.6 mg/dL. Dipstick urine test was 3+ for proteinuria and 2+ for microhematuria, and 24-hour creatinine clearance was 22.64 mL/min/1.73 m² by Cockcroft-Gault’s equation, and 24-hour urinary protein excretion was 6.3 g/day. Urinary concentrations of sodium, potassium and chloride were 61, 33.4 and 33 mmol/L, respectively. Urinary sediment revealed red blood cells (1-5 cells/high power field, HPF), white blood cells (1-5 cells/HPF), epithelial cells (5-10 cells/whole field) and granular casts (5-10/whole field). Hormonal assays showed plasma cortisol 14.9 µg/dL (normal; 4-18.3), TSH 6.85 µIU/mL [0.27-4.20], free T4 of 1.15 ng/dL [2.20-4.40], free T3 of 1.24 pg/mL [1.00-1.80], and normal antecedent pituitary hormones, suggesting that endocrinological disorders were not involved in the development of hypothermia.

Electrocardiography (ECG) showed normal sinus rhythm with a heart rate of 40 beats/min. No lethal arrhythmias was detected by Holter ECG. There was no sign for J-wave, which is occasionally seen in patients with severe hypothermia (6). Chest roentgenography revealed bilateral hydrothorax and congestive lung fields. Cardiothoracic ratio was 57%. Ultrasonography showed massive ascites and pericardial effusion. Computed tomography of the head revealed only old brain infarcts. Arterial blood gas analysis under 3 L/min O₂ showed pH 7.358, pCO₂ 40.3 mmHg, pO₂ 110 mmHg and HCO₃⁻ 22.2 mmol/L.

Upon hospitalization, he was wrapped in a warm blanket and infused with warmed saline. Eight-hour rewarming resulted in a rise of body temperature to 35.4°C and regaining of consciousness. Twenty-four hours later, his body temperature rose to 37°C, without any signs of rewarming shock, which is occasionally seen in patients with hypothermia (7). However, serum creatinine level gradually increased from 3.69 to 5.86 mg/dL on the 5th hospital day, though it decreased later to 3.44 mg/dL on the 16th hospital day with supportive treatment (Fig. 1A). Post-renal factors were excluded by ultrasonography. The patient was discharged after 3 months of hospitalization.

Three months after his discharge from hospital in a warm day in March (outside temperature, 23.5°C), he was again found at home in deep coma and was transferred to our hospital. On admission, this body temperature was 24.6°C. He was again hospitalized and the body re-warmed, and on the second hospital day he regained consciousness. At that time, blood glucose was 128 mg/dL. The serum creatinine level rose from an initial value of 4.05 mg/dL on admission to 6.82 mg/dL on the 7th hospital day, but gradually decreased to 4.00 mg/dL with supportive treatment (Fig. 1B). He was discharged on the 26th hospital day and transferred to another hospital for rehabilitation.

Discussion

We described here a rare case of incidental hypothermia with DM who developed acute exacerbation of CKD. The serum creatinine was about 1.5 times the baseline level in each of the two hypothermic events, and it decreased to baseline level within 2 weeks with only appropriate medical treatment. In the present case, hypothermia induced acute exacerbation of CKD probably through pre-renal mechanism. It is possible also that an accumulation of multiple risk factors explains the two separate episodes of hypothermia.

Clinically, AKI is seen in over 40% of patients with accidental hypothermia (4).

In mild hypothermia, there is a cold diuresis as a consequence of resistance to anti-diuretic hormone, then in moderate to severe hypothermia, the glomerular filtration rate falls as cardiac output and hence renal blood flow falls (5). Moyer et al (8) reported that dogs exposed to cold environment developed systemic hypotension, low glomerular blood flow, glomerular hypofiltration and became oliguric. Yoshitomi et al (9) described obtaining a renal biopsy from a patient with acute renal failure associated with accidental hypothermia caused by water immersion. Histopathological examination of the biopsy specimen showed only mild tubular and interstitial changes, suggesting that the acute renal failure in their case was mainly caused by acute tubular necrosis associated with vasoconstriction. On the other hand, it has also been reported that AKI sometimes occurs after rewarming because the rewarming therapy itself can cause acute tubular necrosis via apoptosis and necrosis (10). Actually, involvement of ischemic AKI was suspected in the present case because granular casts and epithelial cells, suggestive of acute tubular necrosis, were also observed in the urinary sediment. Based on the present case and previous reports, AKI induced by hypothermia can be regarded as transient pre-renal injury especially caused by ischemia and hypovolemia that can be reversed and prevented to some extent by careful volume replacement and supportive care (11). However, the possibility of “rewarming shock” should be always considered in the development of hypothermia-related AKI because rewarming shock can lead to AKI; rewarming shock is a fatal circulatory derangement often observed in victims of accidental hypothermia induced by re-warming and recognized by falling cardiac output and a sudden drop in blood pressure, probably due to peripheral vasodilatation.
Figure 1. Serial changes in serum urea and creatinine during hospitalization for each event of accidental hypothermia. Serial changes in serum creatinine and urea nitrogen levels (A) during the first admission to the hospital, and (B) during the second hospitalization. Serum levels of urea and creatinine increased 1.5 times the baseline levels and almost completely returned to the baseline level within a relatively short duration. Black bars show the period of re-warming using warmed saline infusion and a blanket (for almost 24 hours). BUN: blood urea nitrogen, Cre: serum creatinine

In response to active rewarming (7). In the present case, the patient did not show apparent circulatory instability after rewarming that could lead to AKI. Thus, we were able to exclude rewarming as the etiology of renal failure in our case.

Acute exacerbation of CKD associated with hypothermia has been rarely reported. Kuriyama et al (12) reported nine cases of hypothermia patients who developed acute exacerbation of pre-existing CKD. In their article, two patients showed a decline in serum creatinine after appropriate medical treatment, but seven patients died in spite of aggressive treatment. Yokoyama et al (13) reported a hypothermia patient who developed acute exacerbation of CKD. In these two reports, no specific mechanism as to the exacerbation of CKD was mentioned, and they speculated that the mechanism of AKI in hypothermic patients could be applied to the acute exacerbation of CKD. In the present case, the patient suffered from CKD caused by diabetic nephropathy (although this was not confirmed by renal biopsy), and developed hypothermia-induced acute exacerbation of CKD, which was completely resolved within 2 weeks. Probably, the acute exacerbation of CKD was caused by the same aforementioned mechanism of AKI as in hypothermia patients, and could be successfully treated with appropriate volume control and supportive management. However, renal replacement therapy should be considered in case of severe uremic state to avoid further life-threatening condition because previous reports have documented that the magnitude of AKI tends to be severe in CKD patients (12).

A variety of risk factors for hypothermia have been reported; age, exposure to cold environment, drug abuse, intoxication, endocrinological dysfunction, neurological disorders, multi-organ dysfunction, heat burn, malnutrition, exfoliative skin diseases (2, 14). In the present case, the patient was found at home and was not exposed to a cold environment: it is conceivable that hypothermia was caused by complex intrinsic factors. Actually, we propose that an accumulation of several risk factors such as old age, hypoglycemia, CKD, DM, CHF, altered autonomic nervous system state, and malnutrition could have triggered and promoted hypothermia in the present case.

First, hypoglycemia might have affected consciousness, resulting in the development of hypothermia in the present case. In addition, hypoglycemia is also known to cause neurogenic hypothermia through impairment of hypothalamic function (14). However, endocrinological studies have failed to disclose the known causes for hypoglycemia, and it
is also true that hypothermia could result in hypoglycemia. Although it remains undetermined whether hypoglycemia preceded hypothermia, hypoglycemia could have affected this patient’s consciousness and the development of hypothermia.

Second, undernourishment, occasionally seen in diabetic patients, is closely associated with decreased muscle mass and adipose tissue; muscle is an important organ for generating heat through shivering, and adipose tissues are highly associated with energy storage and protection against heat loss (15). Thus, undernourished patients cannot generate enough heat to maintain body temperature even in the presence of a functional autonomic nervous system because total muscle volume is markedly decreased in these patients. Third, the autonomic nervous system, which is often impaired in patients with diabetic neuropathy, plays important roles in the thermoregulatory system because it exerts heat production through activating muscle and adipose tissue (2). Actually, Yokoyama et al (13) reported that diabetic patients are prone to develop hypothermia due to impaired thermogenesis especially heat generation from peripheral muscles and adipose tissue, which is regulated by the autonomic nervous system. Fourth, CKD is also an important known risk factor for hypothermia (3); the uremic state itself represents accumulation of multiple risk factors that can result in the development of hypothermia. We conclude that the aforementioned factors could have resulted in the development of hypothermia in the present case.

In summary, we reported a patient with CKD and DM who on two occasions developed hypothermia followed by AKI. Based on the present case and those reported in the literature, it is conceivable that malnourished DM patients with nephropathy are prone to develop hypothermia followed by AKI or acute exacerbation of CKD, although these changes could be ameliorated with appropriate medical management.

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References