Endocrinology, Diabetes & Metabolism CASE REPORTS

R Son and others | HypoNa with hourly fluctuating U-Osm

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Hyponatremia presenting with hourly fluctuating urine osmolality

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Summary

The etiology of hyponatremia is assessed based on urine osmolality and sodium. We herein describe a 35-year-old Asian man with pulmonary tuberculosis and perforated duodenal ulcer who presented with hyponatremia with hourly fluctuating urine osmolality ranging from 100 to 600 mosmol/kg, which resembled urine osmolality observed in typical polydipsia and SIADH simultaneously. Further review revealed correlation of body temperature and urine osmolality. Since fever is a known non-osmotic stimulus of ADH secretion, we theorized that hyponatremia in this patient was due to transient ADH secretion due to fever. In our case, empiric exogenous glucocorticoid suppressed transient non-osmotic ADH secretion and urine osmolality showed highly variable concentrations. Transient ADH secretion-related hyponatremia may be underrecognized due to occasional empiric glucocorticoid administration in patients with critical illnesses. Repeatedly monitoring of urine chemistries and interpretation of urine chemistries with careful review of non-osmotic stimuli of ADH including fever is crucial in recognition of this etiology.

Learning points:

- Hourly fluctuations in urine osmolality can be observed in patients with fever, which is a non-osmotic stimulant of ADH secretion.
- Repeated monitoring of urine chemistries aids in the diagnosis of the etiology underlying hyponatremia, including fever, in patients with transient ADH secretion.
- Glucocorticoid administration suppresses ADH secretion and improves hyponatremia even in the absence of adrenal insufficiency; the etiology of hyponatremia should be determined carefully in these patients.

Background

Hyponatremia is the most common electrolyte disturbance observed in hospitalized patients and is associated with increased mortality (1); however, identifying the etiology of hyponatremia is complex. Clinical guidelines suggest a focus on urine chemistries (osmolality and sodium) rather than volume status assessment (2). The urine chemistry parameters are more objective and easier to interpret compared with the volume status and thus facilitate a more precise diagnosis of the hyponatremia etiology compared with the traditional volume status assessment. However, the diagnosis of hyponatremia remains challenging in patients with multifactorial etiologies.

We herein present a challenging case of hyponatremia in a patient with hourly fluctuating urine osmolality, which turned out to be caused by non-osmotic ADH secretion and empiric exogenous glucocorticoid administration. We also review the potential causes of highly variable urine osmolality and approaches in interpretation of this complicated presentation.

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Case presentation

A 35-year-old homeless Asian male with no significant medical history presented with 1 week of cough and hemoptysis and 1 day of right lower quadrant abdominal pain. He was admitted with the diagnoses of pulmonary tuberculosis and perforated duodenal ulcer. He underwent emergent surgery for perforation closure on the admission day. Postoperatively, he had persistent hypotension despite high-dose vasopressors, accompanied with hypoglycemia (blood glucose, 60 mg/dL) and hyponatremia (serum sodium, 128 mEq/L). Hydrocortisone at 100 mg three times daily was initiated for critical illness-related corticosteroid insufficiency, in addition to the standard tuberculosis treatment with rifampicin, isoniazid, pyrazinamide, and streptomycin. Additionally, he was administered acetaminophen as needed for spiking fever episodes due to either tuberculosis or possible drug allergy. Hydrocortisone was tapered over 5 days, and his serum sodium level, which was 140 mEq/L at the time of corticosteroid discontinuation, gradually decreased to 125 mEq/L over the next week. On day 13 of admission, he was referred to the nephrology department for consultation regarding the management of progressive hyponatremia.

At the time of the consultation, he denied any pain including headache, nausea, or vomiting. In addition to the anti-tuberculosis medications, he was on levofloxacin, meropenem, and famotidine. He was on total parenteral nutrition and supplementation for potassium, phosphate, and magnesium. Physical examination revealed that he was poorly nourished and had a nasogastric tube and tracheotomy. His vital signs were as follows: height, 165 cm; weight, 44.6 kg (compared with the presumed body weight of 42.6 kg on admission); BMI, 16.5 kg/m^2; temperature, 37.9°C; blood pressure, 106/61 mmHg in supine position; heart rate, 110 beats/min; and oxygen saturation, 95% on ventilator (FiO_2, 0.25; positive end-expiratory pressure, 5 cmH_2O; pressure support, 6 cmH_2O). He was alert and oriented, with a Glasgow Coma Scale score of E4TM6. He had moist mucous membranes, normal skin turgor, and slight edema on both upper extremities. The rest of the examination findings were unremarkable.

Laboratory studies at the time of admission and during the consultation are presented in Table 1. Whole trunk CT scan with contrast on admission revealed pulmonary infection and abdominal abscess. No calcification or enlargement of the adrenal glands was noted.

Table 1 Laboratory studies on admission and consultation.

Parameter	Value on admission (day 1)	Value on consultation (day 13)
Blood chemistries		
Sodium (mEq/L)	125	125
Potassium (mEq/L)	4.5	3.7
Chloride (mEq/L)	88	91
Serum urea nitrogen (mg/dL)	10.2	5.7
Creatinine (mg/dL)	0.50	0.23
Glucose (mg/dL)	68	105
Serum osmolality (mosmol/L)	–	249
Calcium (mg/dL)	7.3	6.4
Magnesium (mg/dL)	1.7	1.9
Phosphorus (mg/dL)	3.9	1.6
Albumin (g/dL)	1.3	1.3
Uric acid (mg/dL)	–	1.7
CRP (mg/dL)	16.70	13.28
Atrial blood gases		
pH	7.262	7.463
PCO_2 (mmHg)	53.4	37.6
PO_2 (mmHg)	171.0 (FiO_2: 0.6)	69.7 (FiO_2: 0.25)
Bicarbonate (mEq/L)	23.4	26.5
Complete blood count		
Hemoglobin (g/dL)	12.8	7.5
Hematocrit (%)	38.2	21.8
WBC count (×10^3/μL)	15.2	13.0
Platelets (×10^3/μL)	171	199
Urinary chemistries		
Sodium (mEq/L)	–	169
Potassium (mEq/L)	–	34
Urine urea nitrogen (mg/dL)	–	297
Creatinine (mg/dL)	–	35
Osmolality (mosmol/L)	–	529
FE_{Na} (%)	–	0.9
FE_{UA} (%)	–	12.9
FE_P (%)	–	12.1

Conversion factors for units: serum and urine urea nitrogen from mg/dL to mmol/L, 0.357; calcium from mg/dL to mmol/L, 0.2495; phosphorus from mg/dL to mmol/L, 0.3229.
CRP, C-reactive protein; FE_{Na}, fractional excretion of sodium; FE_P, fractional excretion of phosphate; FE_{UA}, fractional excretion of uric acid; PCO_2, partial pressure of carbon dioxide; PMN, polymorphonuclear; PO_2, partial pressure of oxygen; WBC, white blood cell.

Investigation

The adrenocorticotropic hormone (ACTH) stimulation test using i.v. tetracosactide acetate (250 μg) on admission day 9 after hydrocortisone discontinuation ruled out adrenal insufficiency, with peak cortisol value of 28.17 μg/dL (3). The thyroid function tests were not significant. The levels of plasma renin activity, serum aldosterone, α-human atrial natriuretic polypeptide,

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and amino-terminal pro-brain natriuretic peptide were 5.6 ng/mL/h, 61 pg/mL, 28.7 pg/mL, and 457.4 pg/mL, respectively. His antidiuresis hormone (ADH) was elevated at 1.7 pg/mL despite hyponatremia. Further calculations revealed that the patient had been administered 3000 mL fluid per day, including total parental nutrition and antibiotics for several days, which comprised 97 mEq/L sodium and 13 mEq/L potassium. Based on the volume status assessment and the repeatedly high urine osmolality and urine sodium levels, the patient was diagnosed with the syndrome of inappropriate antidiuresis hormone (SIADH).

Treatment

Since water restriction and increased solute intake would change the composition of total parental nutrition, furosemide (5 mg intravenously) was chosen as the initial SIADH treatment, which failed to dilute the urine osmolality. Although the patient was asymptomatic, his sodium level dropped to 124 mEq/L overnight after the consultation. Tolvaptan (7.5 mg) was administered for progressive hyponatremia; however, the urine chemistries revealed an unexpectedly diluted urine before the tolvaptan administration with no apparent cause, accompanied by changes in urine sodium level and urine osmolality from 190 to 20 mEq/L and from 515 to 155 mosmol/L, respectively. The urine sodium level was increased rapidly with a large volume of urine output (1200 mL in 2 h). The overcorrection of the hyponatremia was prevented by 75 µg desmopressin administered via a nasal spray. The urine osmolality was fluctuating hourly between 100 and 600 mosmol/kg, resembling the alternating urine osmolality observed in typical polydipsia and SIADH (Fig. 1).

Outcome and follow-up

The patient did not complain of any symptoms; therefore, no further intervention was sought. His serum sodium level gradually returned to 135 mEq/L over the next 2 weeks. However, 40 days after the initial admission, his respiratory state deteriorated. He was transferred to the intensive care unit, and his serum sodium level dropped to 129 mEq/L again at the time of transfer (Fig. 1). The second ACTH stimulation test suggested possible adrenal insufficiency, with peak cortisol value of 16.47 µg/dL (3). Hydrocortisone (200 mg daily), empirically initiated by the intensive care unit team, gradually corrected the serum sodium level to 140 mEq/L. Hydrocortisone was tapered off, and he was discharged with a serum sodium level of

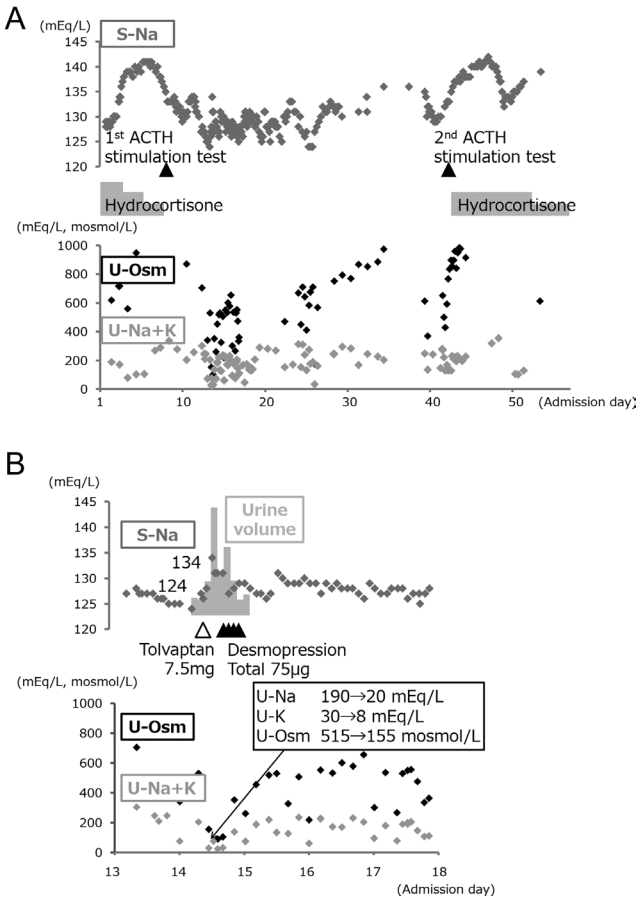

Figure 1
Clinical course of the patient including serum sodium levels, urine osmolality, and the sum of urine sodium and potassium levels (A) through the entire presentation and (B) during the 2 weeks after the consultation.

138 mEq/L and a randomly measured cortisol level of 8.49 µg/dL without corticosteroid supplementation.

Discussion

Hyponatremia is common in patients with tuberculosis, with prevalence rates reaching 62% (4). The causes of tuberculosis-related hyponatremia include SIADH directly due to infection or anti-tuberculosis medications and adrenal insufficiency related to disseminated adrenal tuberculosis (5). In the current patient, the urine osmolality and urine sodium levels were repeatedly high at the time of consultation. In addition to the urine chemistries, his euvolemic presentation and the normal ACTH stimulation test results initially supported the diagnosis of SIADH. However, his hyponatremia was overcorrected with an unexpected drop in urine osmolality to 150 mosmol/L. The erratic, hourly changes in urine osmolality could not be explained simply as a typical SIADH presentation.

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Table 2 Causes of hyponatremia associated with unintentional overcorrection (7).

Causes of hyponatremia	Mechanism of escape from antidiuresis
Hypovolemia	Volume repletion reverses baroreceptor-mediated vasopressin secretion
Beer potomania, tea and toast diet	Increased solute intake enhances delivery of glomerular filtrate to distal diluting sites
Thiazide diuretics	Discontinuation of diuretic restores diluting function of the distal tubule
SSRIs	Discontinuation of antidepressant eliminates drug-induced SIADH
Desmopressin	Discontinuation of synthetic vasopressin eliminates antidiuretic state
Hypopituitarism	Cortisol replacement restores ability to suppress vasopressin secretion
Addison disease	Volume and cortisol replacement
Hypoxemia	Correction of hypoxemia eliminates non-osmotic stimulus for vasopressin
Nausea, surgery, pain, or stress	Spontaneous resolution of SIADH

SIADH, syndrome of inappropriate secretion of antidiuretic hormone; SSRI, selective serotonin reuptake inhibitor.

The clinical course of the changes in urine osmolality and serum sodium levels are shown in Fig. 1. In the current patient, type of the administered i.v. fluids, respirator settings, and medications were constant, whereas the urine osmolality fluctuated significantly. Erratic, unregulated ADH secretion is commonly observed in SIADH (6); up to 30% of the patients present with wide ADH fluctuations, accompanied with changes in urine osmolality (6). However, urine osmolality is usually not suppressed to the extent of maximum antidiuresis (6), which rendered the SIADH diagnosis less likely in the current patient. Since no clear relationship between urine osmolality and serum sodium was observed, the causes of non-osmotic ADH secretion were investigated. Non-osmotic ADH secretion is clinically important because unintentional hyponatremia overcorrection might occur following the resolution of the etiology (7) (Table 2). None of the causes summarized in Table 2 was observed in the current patient, which raised the possibility of spiking fever episodes as the cause of erratic ADH secretion.

The physiologic association between fever and ADH secretion has been well recognized in humans as well as in animal models since 1960s. Although the exact mechanism is unknown, interleukin 1-β and tumor necrosis factor-α are suggested to cause the ADH secretion (8). The current patient experienced spiking fever episodes due to either tuberculosis or drug allergy during the week after the consultation, and there was a close correlation between his body temperature and urine osmolality (Fig. 2). We therefore speculated that non-osmotic ADH secretion was caused by the spiking fever episodes, which were resolved by acetaminophen. Thus, the large fluctuations in the urine osmolality were attributed to the changes in body temperature and antipyretic use. The progressive hyponatremia following the spiking fever episodes was likely augmented due to the relatively hypotonic total parenteral nutrition. In contrast, the urine chemistries during the afebrile periods mimicked polydipsia.

Retrospectively, the improvement in hyponatremia by hydrocortisone at the time of initial admission and on day 40 after admission in the current patient raises the possibility of adrenal insufficiency. Additionally, his hyponatremia responded well to hydrocortisone. However, since exogeneous glucocorticoids suppress ADH secretion, hydrocortisone can improve hyponatremia regardless of the adrenal function (9). It is possible that the fever-induced ADH secretion in the current patient was suppressed by exogeneous glucocorticoids, resulting in the improvement of hyponatremia. Although it remains possible that the patient suffered relative adrenal insufficiency concurrently, the previously mentioned pathophysiology should be considered in addition to any abnormalities in adrenal function in patients with hourly fluctuating urine osmolality. Albeit still controversial, glucocorticoid administration in patients with fever and possible relative adrenal insufficiency is

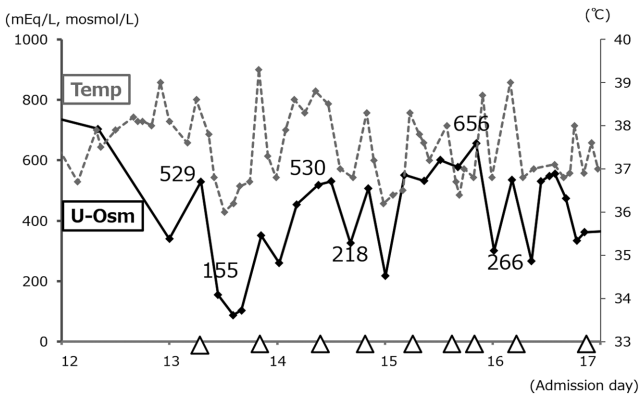

Figure 2
Clinical course of the patient's urine osmolality and body temperature within the first week following the consultation. The open triangles refer to the administration of acetaminophen.

practiced commonly in intensive care units (10). Since the diagnosis of critical illness-related corticosteroid insufficiency is sometimes based only on empiric glucocorticoid administration, transient ADH secretion and hyponatremia can be improved by glucocorticoids even in patients without underlying adrenal insufficiency. It remains possible that the etiology of transient ADH secretion and hyponatremia seen in the current patient is underrecognized.

In conclusion, we herein presented a patient with hyponatremia and highly variable urine osmolality. Although SIADH contributed to hyperosmolar urine in the current case, highly variable urine osmolality seems to be related to fever-induced ADH secretion. The spiking fever episodes were associated with non-osmotic induction of ADH secretion, which resulted in the SIADH-like presentation, whereas the ADH secretion was reduced with the fever control, resulting in the polydipsia-like presentation. It is reasonable to assume that exogenous corticosteroids suppressed transient non-osmotic ADH secretion rather than correcting the underlying adrenal insufficiency in the current case. This case highlights the importance of repeated monitoring for urine chemistries and consideration of the causes of potential, transient non-osmotic induction of ADH secretion, including spiking fever.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
The patient provided written informed consent for the publication of all data and images of this case report.

Author contribution statement
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