A case of renal salt-wasting syndrome induced by cisplatin and 5-FU during treatment of esophageal squamous cell carcinoma

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Abstract
The combination regimen of cisplatin (CDDP) and fluorouracil (5-FU) (FP) is a standard regimen for definitive chemoradiotherapy, neoadjuvant chemotherapy, and for treatment of unresectable or recurrent esophageal squamous cell carcinoma (ESCC). Here, we report a patient with FP-induced renal salt-wasting syndrome (RSWS) who presented with severe hyponatremia with disturbance of consciousness and was admitted to the intensive care unit (ICU). A 66-year-old man with recurrent ESCC was admitted and started on chemotherapy with FP. From day 3 of the first course of FP, he presented with anorexia and vomiting (grade 3). At day 6, he experienced disturbance of consciousness and blood test showed severe hyponatremia (sodium (Na): 119 mmol/L) accompanied with excessive urinary excretion of Na (181 mmol/L). He was diagnosed with RSWS because of CDDP and was transferred to the ICU. Through intensive monitoring and 3% NaCl infusion, serum Na level and symptoms recovered with no sequelae and he was discharged from the ICU after a 4-day stay.

RSWS is sometimes difficult to diagnose because of its low recognition and is misdiagnosed as the syndrome of inappropriate secretion of antidiuretic hormone. During chemotherapy with platinum-based agents, RSWS should be kept in mind as a disorder that causes hyponatremia.

Keywords: renal salt-wasting syndrome, hyponatremia, cisplatin, esophageal squamous cell carcinoma

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Introduction
Cisplatin (CDDP) is an anticancer agent used worldwide for treating various solid tumors. CDDP causes nephrotoxicity with a decline in glomerular filtration rate, and CDDP-based regimens require high-volume hydration to reduce nephrotoxicity. Because of CDDP nephrotoxicity and the required high-volume hydration, electrolyte disorders including hyponatremia occur frequently. Hyponatremia can cause severe problems if appropriate treatment based on an accurate diagnosis is not provided. Renal salt-wasting syndrome (RSWS) is a pathological condition that causes hyponatremia. However, its low recognition makes it difficult to accurately diagnose, and it is susceptible to misdiagnosis as the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Here, we report a case who developed severe hyponatremia because of treatment with CDDP and fluorouracil (5-FU), the FP regimen, and was diagnosed with RSWS.

Case report
A 64-year-old man with past medical history of acute pancreatitis and hepatitis B was newly diagnosed with esophageal squamous cell carcinoma (ESCC) with symptom of epigastric discomfort. He was diagnosed with clinical stage III disease (T3N1M0, 8th edition UICC) by esophagogastroduodenoscopy and computerized tomography. After neoadjuvant chemoradiotherapy (NAC-RT) (two courses of FP; CDDP was administered at 70 mg/m² on day 1 and 5-FU was administered at 700 mg/m²/day on days 1–5, radiotherapy; 40Gy/20fr), he underwent radical subtotal esophagectomy with three-field lymphadenectomy. Occasionally, grade 2 anorexia was observed following treatment with the NAC-RT regimen, although hyponatremia was not. Pathological examination lead to diagnosis of final stage III (T3N1M0) with histological evaluation of grade 1b.

Two years after surgery, when the patient was 66 years old, he experienced recurrence with multiple pleural metastases and was admitted for reintroduction on FP. Upon admission, results of physical examination, level of consciousness, and laboratory data were unremarkable.
After prehydration with 2,000 mL of Ringer’s acetate solution, CDDP and 5-FU were administered at 80 mg/m² on day 1 and at 800 mg/m² on days 1–5, respectively. Fosaprepitant meglumine and palonosetron hydrochloride were used as antiemetics.

From day 3 of the first course of FP, he presented with anorexia and vomiting (grade 3) and was administered oral metoclopramide (5 mg per dose). At day 6, he experienced disturbance of consciousness, and blood test revealed severe hyponatremia with serum sodium (Na) level of 119 mmol/L accompanied with excessive urinary excretion of Na (181 mmol/L) (Table 1). Simultaneously, laboratory data indicated normal cortisol level of 11.5 µg/dL, normal adrenocorticotropic hormone level of 57.3 pg/mL, normal plasma renin activity less than 0.2 ng/mL/h, and normal antidiuretic hormone (ADH) level of 0.7 pg/mL. Intravascular dehydration was suspected from body weight loss (from 45.5 kg upon admission to 43.8 kg on day 6) despite 5 days of intravenous maintenance infusion at 2,500 mL/day and administration of CDDP. Renal function decline appeared with elevated blood urea nitrogen (BUN) of 49.8 mg/dL and serum creatinine (Cre) level of 1.48 mg/dL (which were 16.7 mg/dL and 0.8 mg/dL, respectively, upon admission). The patient was diagnosed with RSWS caused by treatment with CDDP and was transferred to the intensive care unit (ICU) where Na correction was started under sustained monitoring of vitals. He was treated with normal saline (3,000 mL/day) and 3% saline (480 mL/day) from days 6–8. Serum Na level normalized gradually and symptoms recovered with no sequelae. At day 10, the patient was discharged from the ICU and 3% saline infusion was switched to internal use of 4 g of NaCl per day which was continued until he was discharged on day 24. Changes in urine volume, body weight, serum Na level, BUN, and Cre from days 0–13 of the first course of FP are shown. BUN: blood urea nitrogen, Cre: creatinine, ACTH: adrenocorticotropic hormone, ADH: antidiuretic hormone.

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Table 1. Results of blood test and spot urine test at day 6 of the first course of FP.

| Blood test | Value         | Unit        | Change |
|------------|---------------|-------------|--------|
| WBC        | 8700          | /μL         | -      |
| RBC        | 386           | /μL         | ↓      |
| Hgb        | 12.2          | g/dL        | ↓      |
| Hct        | 34.5%         |            | ↓      |
| Plt        | 15.8*10⁴      | /μL         | ↓      |
| CRP        | 0.97          | mg/dL       | -      |
| AST        | 27            | IU/L        | -      |
| ALT        | 12            | IU/L        | -      |
| T-Bil      | 1.2           | mg/dL       | -      |
| BUN        | 49.8          | mg/dL       | ↑      |
| Cre        | 1.48          | mg/dL       | ↑      |
| Na         | 119           | mmol/L      | ↓      |
| K          | 5.0           | mmol/L      | -      |
| Cl         | 84            | mmol/L      | ↓      |
| Cortisol   | 11.5          | µg/dL       | -      |
| ACTH       | 57.3          | pg/mL       | -      |
| Plasma renin activity | <0.2 | ng/ml/hr | -      |
| ADH        | 0.7           | pg/mL       | -      |

| Spot urine test | Value         | Unit       |
|-----------------|---------------|------------|
| Na              | 181           | mmol/L     | ↑        |
| K               | 24            | mmol/L     | ↓        |
| Cl              | 119           | mmol/L     | ↑        |
| Cre             | 23.3          | mg/dL      | ↓        |

WBC: white blood cells, RBC: red blood cells, Hgb: hemoglobin, Hct: hematocrit, Plt: platelets, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, T-Bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine, ACTH: adrenocorticotropic hormone, ADH: antidiuretic hormone.
Discussion

CDDP-based regimens have been reported to result in hyponatremia which can cause nausea, anorexia, headache, tremor, and coma. Hyponatremia from CDDP-based chemotherapy is caused by several factors, such as extrarenal Na loss because of vomiting or diarrhea, or SIADH and RSWS (alone or in combination). Among these causes, RSWS, initially reported by Kurtzberg et al., is not widely known. Therefore, it is sometimes difficult to definitively diagnose. RSWS has been reported to be induced by platinum-containing antitumor agents including CDDP and carboplatin. RSWS is a reabsorption disorder affecting Na and H2O at the level of the proximal tubule. Compared with RSWS, in SIADH, hyponatremia occurs via excessive secretion of ADH which causes a subsequent increase in reabsorption of H2O at the proximal tubule. H2O intake should be restricted in SIADH, whereas supplementary Na and H2O are important in RSWS. The approaches to treatment of these two disorders are therefore opposing, emphasizing the need for correct diagnosis. The critical factors that distinguish RSWS from SIADH are as follows: 1) the presence of intravascular hypovolemia, 2) Na excretion exceeds intake, and 3) renal function decline. High serum ADH level is insufficient to distinguish the two disorders as serum ADH can increase in RSWS because of intravascular hypovolemia.

We diagnosed our patient with RSWS based on severe hyponatremia, body weight loss (despite administration of CDDP and hydration with over 2,500 mL/day), excessive urine output (up to 5,480 mL/day), high Na level in spot urine (up to 181 mmol/L), and normal serum ADH level. Accurate diagnosis and appropriate treatment resulted in improvement of symptoms without sequelae.

Hyponatremia during platinum agent-based chemotherapy is often observed, and accurate diagnosis of the disorders that cause hyponatremia is imperative. RSWS is sometimes difficult to diagnose because of its low degree of recognition, and is prone to misdiagnosis as SIADH. RSWS should be kept in mind as a disease that causes hyponatremia during treatment with platinum-based chemotherapeutic agents.

Conflicts of interest:
The authors declare no competing financial interests.

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