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CASE REPORT

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Duloxetine-induced syndrome of inappropriate antidiuretic hormone secretion in a patient with neuropathic pain

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Key Clinical Message

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) induces hyponatremia accompanied by uric acid reduction. We report a case of a patient with small-cell lung cancer who developed SIADH with hypouricemia after duloxetine treatment and discuss the potential underlying mechanisms. SIADH and hypouricemia improved after duloxetine was switched to mirogabalin.

KEYWORDS

duloxetine, neuropathic pain, small-cell lung cancer, syndrome of inappropriate antidiuretic hormone secretion, uric acid

1 | INTRODUCTION

Duloxetine, a serotonin and norepinephrine reuptake inhibitor, has been reported as a culprit of syndrome of inappropriate antidiuretic hormone secretion (SIADH) in several case reports.[1–7] Patients with SIADH are observed to have hyponatremia without fluid loss, followed by decreased renin activity and uric acid levels.[8] Previously, reports on hyponatremia caused by duloxetine-induced SIADH have been published. However, the occurrence of hyponatremia followed by hypouricemia is not well documented. Here, we present a rare case of duloxetine mediated SIADH followed by hypouricemia.

2 | CASE HISTORY AND EXAMINATION

A 71-year-old man (body weight: 69.1 kg, height: 169.0 cm, smoking behavior: 20 cigarettes/day for 48 years, and alcohol consumption: none) was admitted to our hospital with a history of chronic myocardial infarction, prostatic hypertrophy, asymptomatic gallstones, dyslipidemia, and hypertension.

One month prior to admission, the patient experienced pain in the midline of the lumbar region. An electric numbing sensation persisted from the buttocks to the toes, which gradually turned into pain. In addition, the patient had a loss of appetite and had lost 10 kg of body weight in a period of 2 months. The patient also noted dysuria and gait disturbance.

3 | CASE PRESENTATION

On Day 2, 900 mg/day acetaminophen was administered for low back pain. The pain was not relieved by Day 3; hence, we initiated treatment with 20 mg/day duloxetine (Figure 1). Suspecting subacute neuropathy, we administered 27,500 mg/day intravenous immunoglobulin on Days

3–7. On Day 8, the patient's serum sodium level decreased to 120.3 mEq/L (reference value, 138.0–147.0 mEq/L) compared with 134.7 mEq/L on admission. And plasma osmotic pressure decreased to 251 mOSm/kg (reference value, 274–299 mOSm/kg). This decrease was accompanied by a slight reduction in the uric acid level from 4.4 mg/dL to 3.5 mg/dL (reference value, 2.1–6.9 mg/dL). The patient did not exhibit central nervous system manifestations related to a low sodium level, and there was no apparent improvement in neuropathic pain. Furthermore, he did not present with dehydration or suppression of antidiuretic hormone (ADH) nor abnormal renal and adrenocortical functions (serum creatinine and cortisol levels: 0.48 mg/dL (reference value, 0.6–1.20 mg/dL) and 14.9 μg/dL (reference value, 6.4–21.0 μg/dL), respectively). Urinalysis revealed urine osmolarity of 680 mOSm/kg and a urinary sodium level of 38.2 mEq/L; other observations included plasma renin activity of 2.6 ng/mL/h. Based on the clinical course and laboratory data mentioned above, a diagnosis of SIADH was made and duloxetine, a drug most suspected as the cause of SIADH (Table 1), was discontinued on Day 8. We administered 1000 mL of amino acids, glucose, vitamin B1, and sodium-containing injections, ensuring the provision of 35 mEq/day of sodium, to treat anorexia and hyponatremia. Additionally, oral fluid intake was restricted to 500 mL/day from Day 9. On Day 11, oral sodium chloride (NaCl) was administered at 153 mEq, and the dose was adjusted based on monitored sodium levels. The uric acid decreased to 2.3 mg/dL after the discontinuation of duloxetine, which occurred after the decrease in sodium levels. The patient's condition continued to deteriorate over time. After a period of 1 week following intravenous immunoglobulin administration, there was no improvement in gait disturbance, and he reported worsening pain in his left foot. On Day 14, the neuropathic pain in the left foot had further intensified, leading to the re-initiation of duloxetine at 20 mg/day. On Day 15, the serum sodium level improved to 133.5 mEq/L and the urinary sodium level was 80.5 mEq/L. On Day 23, the water intake restriction was discontinued. The patient's medications, including prasugrel (3.75 mg/day), vonoprazan (10 mg/day), rosuvastatin (5 mg/day), benidipine (2 mg/day), and silodosin (8 mg/day), remained unchanged throughout the period.

4 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT

Following the oral NaCl intake, the serum and urinary Na levels increased to 140.2 and 87.4 mEq/L on Day 26. Although we administered immunoglobulin 27,500 mg/day (Days 26–30) and increased the dose of duloxetine to 40 mg/day from Day 26, the patient's neuropathic pain did not alleviate. Unfortunately, although he had been dosed with 6 g of oral NaCl, his serum sodium and uric acid levels decreased to 134.1 mEq/L (on Day 32) and 1.9 mg/dL (on Day 29); hence, we switched duloxetine to mirogabalin 10 mg/day from Day 33. The serum sodium level improved from Day 35 onward. On Day 36, the pain in the patient's left lower extremity was slightly relieved. However, on Day 41, the numbness in the right leg gradually worsened, making it difficult to maintain a standing position. On Day

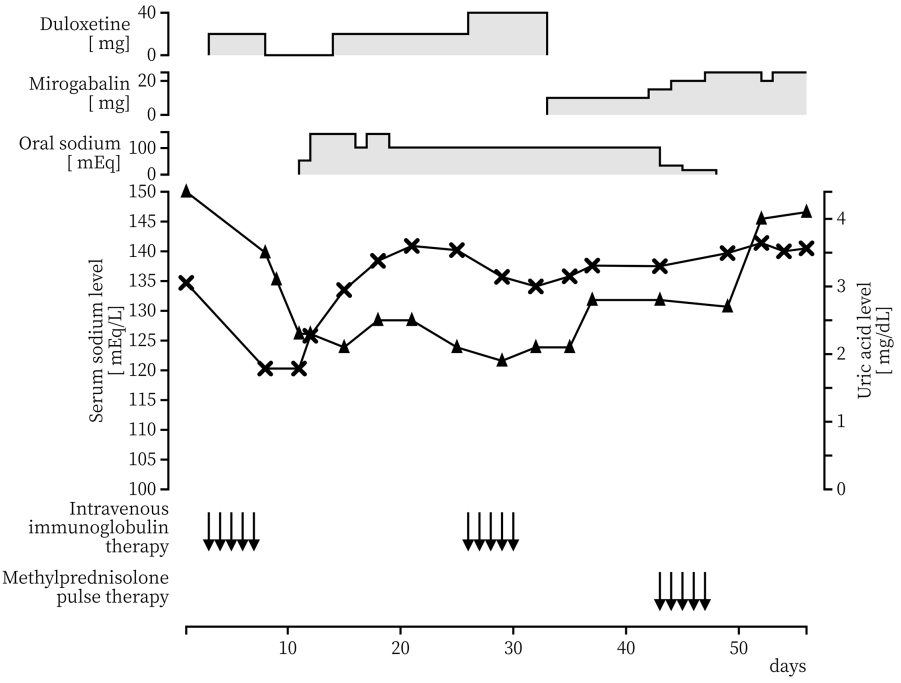

FIGURE 1 Clinical course of the present case. Triangular marks indicate the uric acid level. Cross marks indicate the serum sodium level.

TABLE 1 Diagnostic criteria for SIADH.

Diagnostic criteria
No dehydration
Serum sodium level < 135 mEq/L
Plasma osmotic pressure < 280 mOSm/kg
No ADH suppression.
Urinary osmotic pressure >100 mOSm/kg
Urinary sodium level ≧20 mEq/L
No abnormal findings in renal and adrenocortical.
Clinical findings
Plasma renin activity ≦5 ng/mL/h
Uric acid level ≦5 mg/dL

42, the patient was diagnosed with small-cell lung cancer. We suspected paraneoplastic neurological syndrome and administered methylprednisolone pulse therapy at 1000 mg/day on Days 43–47. Unfortunately, pain management became difficult due to persistent tingling pain at rest on Day 48. On Day 49, the patient was found to be positive for serum anti-Hu antibody. Finally, we assessed neuropathic pain caused by small-cell lung cancer-induced paraneoplastic neurological syndromes and SIADH caused by duloxetine during the clinical course.

5 | RESULT AND FOLLOW-UP

We succeeded in discontinuing oral NaCl from Day 49, and the serum sodium and uric acid levels improved to the corresponding baseline levels by Day 52. On Day 54, we confirmed that there was no further decrease in serum sodium levels (serum sodium level 140.0 mEq/L and urinary sodium level 31.8 mEq/L, respectively).

6 | DISCUSSION

Here, we present the typical and severe clinical course of hypouricemia accompanied by hyponatremia due to SIADH after the administration of duloxetine in a patient with neuropathic pain.

In previous reports, SIADH was alleviated approximately 2–7 days after duloxetine discontinuation.[1–7] In our case, we could not discontinue duloxetine immediately because it controlled the patient's neuropathic pain. Hyponatremia, followed by hypouricemia, was noted again after duloxetine use was restarted. The Naranjo score for adverse events was 8 points, indicating that the events were likely related to the drug administered.[9] The mechanism of SIADH-induced hyponatremia followed by hypouricemia has been reported to comprise the following steps via stimulation of antidiuretic hormone receptor 1a (V1a) receptor by excessive secretion of ADH: (1) upregulation of ATP-binding cassette transporter 2 for uric acid secretion transporter in the apical membrane of renal proximal convoluted tubule cells, and Na+−dependent phosphate transporter 1 in the apical membrane of renal proximal convoluted tubule cells, and (2) downregulation of glucose transporter 9 (GLUT9) for uric acid secretion in the basolateral membrane of renal proximal convoluted tubule cells.[10] In our case, hypouricemia was observed during duloxetine treatment but not during mirogabalin treatment. This suggests that the effects on ADH secretion differ between duloxetine and mirogabalin and that the expression levels of the V1a receptor-mediated urate transporter may be altered. In addition, renal hypouricemia has been reported in 0.3% of the general Japanese population, 90% of which has urate transporter 1 (URAT1) mutations.[11] We could not determine the patient's URAT1 genotype; a mutation could have potentially enhanced the severity of his hypouricemia.

Lung cancer is a risk factor for SIADH.[12] In fact, patients with malignancies associated with SIADH are reported to have lower survival rates compared to patients with SIADH without cancer (34.5%–6.1%).[13] To consider the prognosis for the outcome after recovering from SIADH, duloxetine inducing SIADH required strictly monitoring serum sodium level when we administered duloxetine to patients with cancer.

Furthermore, neurological diseases such as chronic inflammatory demyelinating polyneuritis and Guillain–Barre syndrome can also induce SIADH, and SIADH is known to be a poor prognostic factor, especially in Guillain–Barre syndrome.[14,15] While uric acid levels were used as a reference for the diagnosis of SIADH in this case, this indicator may not be significant enough to reliably distinguish SIADH from other causes of hyponatremia.[16] In this patient, uric acid levels showed a decreasing trend after the onset of SIADH, but the change near the time of dose increase to duloxetine 40 mg/day was only 0.2 mg/dL. Although the changes in uric acid levels between the time of onset and after the drug change were strongly suggestive of a drug-related cause, these findings should be taken as informative only when genetic factors are also considered. Therefore, in identifying the cause of SIADH, it is essential to evaluate multiple factors comprehensively, including clinical symptoms, laboratory findings, imaging, and drug history, rather than relying on a single indicator.

7 | CONCLUSION

In conclusion, we reported a typical severe case of hypouricemia in a patient with SIADH. This report suggests

that the effects that lead to SIADH development differ between duloxetine and mirogabalin treatment. It should be noted that caution is needed in the interpretation of uric acid levels in the diagnosis of SIADH. In our case, the change in uric acid levels after the drug change suggested drug-induced, but the variability was small and other influences, such as genetic factors, should be considered during diagnosis.

AUTHOR CONTRIBUTIONS

Nobuyuki Takahashi: Conceptualization; data curation; investigation; writing – original draft. **Yukiko Mori:** Conceptualization; data curation; investigation; writing – original draft. **Kenji Momo:** Conceptualization; supervision; writing – original draft; writing – review and editing. **Hidetomo Murakami:** Conceptualization; writing – review and editing. **Hironori Tanaka:** Conceptualization; writing – review and editing.

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None declared.

CONFLICT OF INTEREST STATEMENT

KM received travel reimbursements from AbbVie for attending a conference. The Department of Hospital Pharmaceutics, School of Pharmacy, Showa University received funding from Ono with a contract research project according to a collaborative research agreement. As a potential conflict of interest, the Department of Hospital Pharmaceutics, School of Pharmacy, Showa University received grants from Nippon Kayaku, Ono, Shionogi, Bayer, Daiichi Sankyo, Eisai, Mochida, and Taiho, which is a potential conflict of interest. KM received honorarium fees from Eisai, Nippon-Kayaku, Sawai, and AbbVie. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All information in this case is included in this published article.

ETHICS STATEMENT

None.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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