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CASE REPORT

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Entrectinib-induced syndrome of inappropriate antidiuretic hormone secretion in a patient with *ROS1*-rearranged non-small cell lung cancer

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Abstract

A 75-year-old woman was referred to our hospital because of a productive cough and an abnormal shadow on chest radiography. She was diagnosed as having metastatic lung adenocarcinoma harbouring ROS proto-oncogene 1 (*ROS1*). First-line therapy was instituted with entrectinib 600 mg daily, and a gradual decrease in serum sodium level was noticed on day 6, which deteriorated to Grade 3 hyponatremia on day 12. Despite a partial therapeutic response to entrectinib, she developed fatigue and dizziness, so the drug was withdrawn. The clinical findings and laboratory workup were compatible with a diagnosis of syndrome of inappropriate antidiuretic hormone secretion (SIADH) due to entrectinib. The hyponatremia subsequently improved and entrectinib was resumed at a reduced dose of 400 mg daily, which has been continued to date, with no recurrence of SIADH.

KEYWORDS

Entrectinib, hyponatremia, non-small cell lung cancer, *ROS-1*, syndrome of inappropriate antidiuretic hormone secretion

INTRODUCTION

Genetic rearrangements of the tyrosine receptor kinase ROS proto-oncogene 1 (*ROS1*) are oncogenic drivers. *ROS1* fusions are found in 1%–2% of NSCLC, and entrectinib is recommended as first-line therapy.[1] Some antineoplastic agents are known to induce the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). These include vinca alkaloids, platinum compounds, and alkylating agents. Tyrosine kinase inhibitors (TKIs) have recently been reported to cause SIADH.[2,3] We encountered a case of SIADH induced by entrectinib administered for *ROS1*-positive non-small cell lung cancer (NSCLC).

CASE REPORT

A 75-year-old woman presented to a local doctor with a 1-month history of productive cough. Medical history included cerebral infarction, cerebral aneurysm (treated by using endovascular coil embolization), hypertension, and dyslipidemia. Chest radiography showed a right lung consolidation, so she was referred to our hospital for suspected lung cancer. Contrast-enhanced computed tomography (CT) scan showed a heterogeneously enhancing mass with right middle lobe atelectasis, mediastinal and supraclavicular lymphadenopathy, with possible metastatic hepatic lesions (Figure 1). No brain metastasis was observed. 18F-fluorodeoxyglucose (FDG) positron emission tomography/CT revealed increased FDG uptake in the lung and hepatic lesions. Endobronchial ultrasound-guided transbronchial fine-needle aspiration was performed at nodal stations 4R and 10R. Histological examination revealed lung adenocarcinoma, classified as a cT2N3M1a, stage IVa. *ROS1* rearrangement was detected by using reverse transcriptase–polymerase chain reaction assay. With these results, entrectinib 600 mg daily was administered as first-line therapy.

Initially, serum sodium concentration and fluid volume status were normal, but on day 6 serum sodium was gradually decreasing. On day 10, this further decreased to 124 mmol/L, corresponding to Grade 3 hyponatremia. Urinary osmolality was 325 mmol/L with a urinary sodium concentration of 65 mmol/L. Serum osmolality was 251 mmol/L and serum ADH level was 3.0 pg/mL (0.3–4.2 pg/mL). Renal and adrenal function were normal at this time. We excluded other causes of hyponatremia, thus she fulfilled the diagnostic criteria for SIADH essentially a diagnosis of exclusion. Then, we noted tumour shrinkage on chest radiography and a partial response regarding the efficacy of entrectinib.

Entrectinib was discontinued on day 13 and we subsequently observed rapid improvement of serum sodium concentration following sodium loading and fluid restriction. Other abnormal serum and urinary indices also improved. Given this clinical course, our conclusive diagnosis was that the hyponatremia was induced by entrectinib. At 19 days after entrectinib withdrawal, hyponatremia normalized; entrectinib was resumed at a reduced daily dose of 400 mg. Treatment has since been maintained on the same entrectinib dose with no recurrence of SIADH and a sustained partial response (Figure 2).

DISCUSSION

SIADH is a common challenge for clinicians in the management of lung cancer. Distinguishing between SIADH secondary to malignancy and that caused by antineoplastic drugs is difficult. We report on a case of SIADH induced by

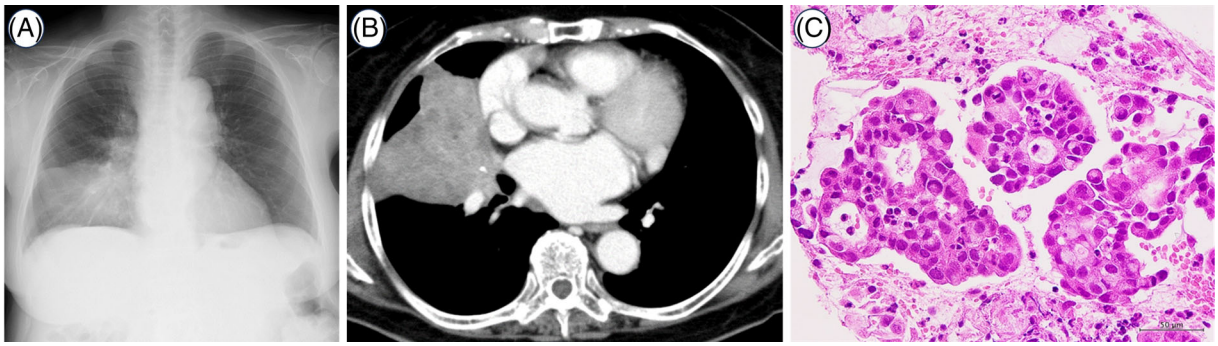

FIGURE 1 Representative Images. Chest radiography showing consolidation in the right middle-to-lower lung fields (A). Contrast-enhanced computed tomography showing a right middle-lobe mass (B). Histopathological findings from endobronchial ultrasound-guided fine-needle aspiration lymph node biopsy showing tumour cells with glandular luminal structures (Haematoxylin–Eosin stain). Scale bar represents 50 μm (C).

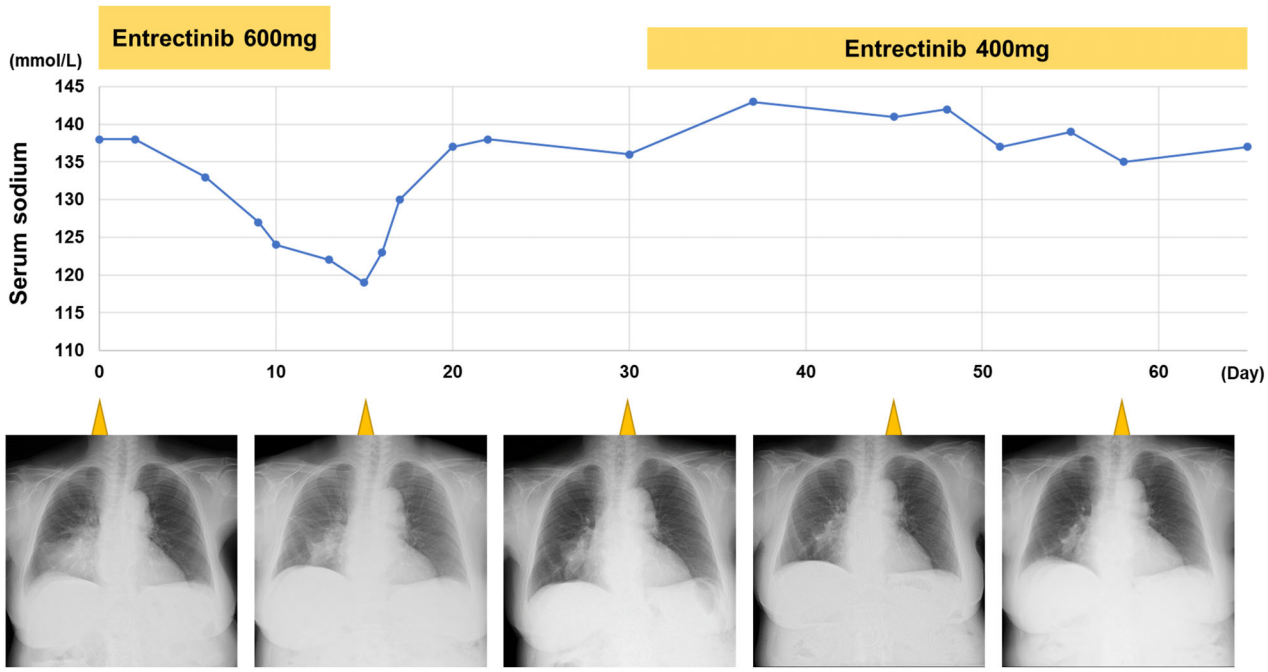

FIGURE 2 Clinical course showing hyponatremia and a dose-dependent response to entrectinib.

entrectinib for treatment of *ROS1* fusion-positive NSCLC, successfully treated by dose reduction. To our knowledge, this is the first reported case of entrectinib-induced SIADH.

Entrectinib is a TKI that potently and selectively inhibits *ROS1*. An integrated analysis of three phase I/II trials (ALKA-372-001, STARTRK-1 and STARTRK-2), reported an overall response rate of 67.1%, with a median progression-free survival of 15.7 months in *ROS1* rearrangement NSCLC. Other studies report drug-induced hyponatremia as an adverse effect of entrectinib in a few cases. Further, the phase II basket study of entrectinib (STARTRK-2), which included *ROS1* fusion-positive NSCLC and *NTRK* fusion-positive solid tumours, reported hyponatremia in 0.9% of patients.[1]

The pathogenesis of SIADH can be attributed to several mechanisms. These include stimulation of the hypothalamus–pituitary axis by central nervous system disease or drugs, derepression of the inhibitory ADH secretory pathway by pulmonary disease, and ectopic secretion of ADH/ADH-like substances from tumours. In SIADH due to lung cancer, the frequency of small cell lung cancer is relatively high (15%), while that due to NSCLC is low (0.7%).[4] There is a seeming paucity of consistent reports on the relationship between specific gene mutations in NSCLC and the frequency of SIADH in the literature. Regarding drug-induced SIADH, there have been reports of SIADH due to various antineoplastic agents. These include TKIs among which antileukemic agents imatinib and dasatinib and epidermal growth factor receptor-TKIs gefitinib and osimertinib were reported to cause SIADH.[2,3] The tyrosine kinase activity transduction pathway is a step in the downregulation of glial cells, and its inhibition by TKIs causes increased/inappropriate secretion of ADH.[3]

In this case, SIADH progression was observed despite shrinkage of the primary and metastatic lesions after entrectinib, but this rapidly improved after drug discontinuation. This suggests entrectinib caused the SIADH. Entrectinib is a novel TKI designed to cross the blood–brain barrier (BBB) efficiently with high CNS penetration and brain distribution. This is because entrectinib interacts weakly with and is a poor substrate of P-glycoprotein, a potent BBB transporter.[5] Although the mechanism of entrectinib-induced SIADH is currently unknown, plausibly SIADH could be attributed to the same mechanism as that caused by osimertinib because of its superior intracerebral translocation. Furthermore, it has been reported that imatinib-induced SIADH is dose-dependent.[2] In our case, SIADH induced by entrectinib did not recur after dose reduction suggesting a dose-dependent association in entrectinib induction of SIADH.

In conclusion, we have described the first case of entrectinib-induced SIADH administered for ROS1-fusion NSCLC; treatment has been continued to date by dose reduction with no SIADH recurrence. Although TKIs such as entrectinib are usually highly effective with mild side effects, it is requisite to pay attention to dyselectrolytemia as observed in this case.

AUTHOR CONTRIBUTIONS

Chiaki Kato and Muneyuki Sekiya: Conception and design. **Chiaki Kato, Muneyuki Sekiya, and Ryo Sekiguchi**: Data acquisition, analysis, and interpretation. **Chiaki Kato, Akira Yamasaki, and Takahiro Yoshizawa**: Drafting the manuscript. **Kazutoshi Isobe, Naobumi Tochigi, Kazutoshi Shibuya, and Kazuma Kishi**: Manuscript revision critically for important intellectual content. All authors contributed to and have given final approval of this submission to be published.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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