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【 CASE REPORT 】

Syndrome of Inappropriate Antidiuretic Hormone Secretion as the Initial Presentation in a Patient with Stage I Small-cell Lung Cancer

Tomonobu Koizumi[1], Takashi Kobayashi[1], Shintaro Kanda[1], Toshirou Fukushima[1], Futoshi Muranaka[2], Kentaro Miura[3] and Shiho Asaka[4]

Abstract:
A 67-year-old man with a history of esophageal cancer resection was referred to our hospital because of nausea and appetite loss. Laboratory findings showed severe hyponatremia and were compatible with syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Chest computed tomography (CT) revealed a nodule measuring 13 mm in the lower lobe of the right lung. Right thoracotomy was performed, and the histopathological diagnosis was small-cell lung cancer (T1bN0M0; Stage 1b). Although SIADH is frequently associated with small-cell lung cancer, it is extremely rare as the initial clinical feature in stage I small-cell lung cancer.

Key words: hyponatremia, sodium, limited disease, antidiuretic hormone

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Introduction

Syndrome of inappropriate antidiuretic hormone (SIADH) is a well-recognized paraneoplastic syndrome associated with small-cell lung cancer (SCLC) (1-9). Several prospective and retrospective studies have indicated an SIADH incidence rate of 9.1%-15% in patients with SCLC (1-3). However, most cases of SIADH occur during chemotherapy and/or in cases of advanced disease, such as those with brain metastasis, which can also contribute to the development of this syndrome (1-7). Concomitant presentation of SIADH at the initial diagnosis of SCLC was also reported (7-12). However, SIADH as the initial presentation prior to the detection of SCLC is extremely rare.

We encountered a case of SIADH during regular follow-up following resection of esophageal cancer. A subsequent systemic examination revealed stage I SCLC, which was successfully resected and resulted in improvement of the serum sodium concentration. Precedent SIADH as in the present case may be an index for searching for malignancies. We herein report the clinical course of this case along with a brief review of the relevant literature.

Case Report

A 67-year-old man was referred to the emergency unit of our hospital because of nausea and appetite loss. He had received insulin therapy for type I diabetes mellitus for over 40 years and had a history of esophageal cancer resection 2 years previously in our hospital.

A physical examination revealed no remarkable findings, including dehydration and edema. Laboratory findings showed severe hyponatremia (121 mEq/L), although the blood sodium level had been normal 6 months earlier (Fig. 1). On admission, laboratory findings revealed a further decreased sodium level of 112 mEq/L, serum osmolarity of 240 mOsm/kg, and urine osmolarity of 468 mOsm/kg

[1]Department of Hematology and Medical Oncology, Shinshu University School of Medicine, Japan, [2]Department of Surgery, Division of Gastroenterological, Hepato-Biliary-Pancreatic, Transplantation and Pediatric Surgery, Shinshu University School of Medicine, Japan, [3]Department of Surgery, Division of Thoracic Respiratory, Shinshu University School of Medicine, Japan and [4]Department of Laboratory Medicine, Shinshu University School of Medicine, Japan
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Correspondence to Dr. Tomonobu Koizumi, tomonobu@shinshu-u.ac.jp

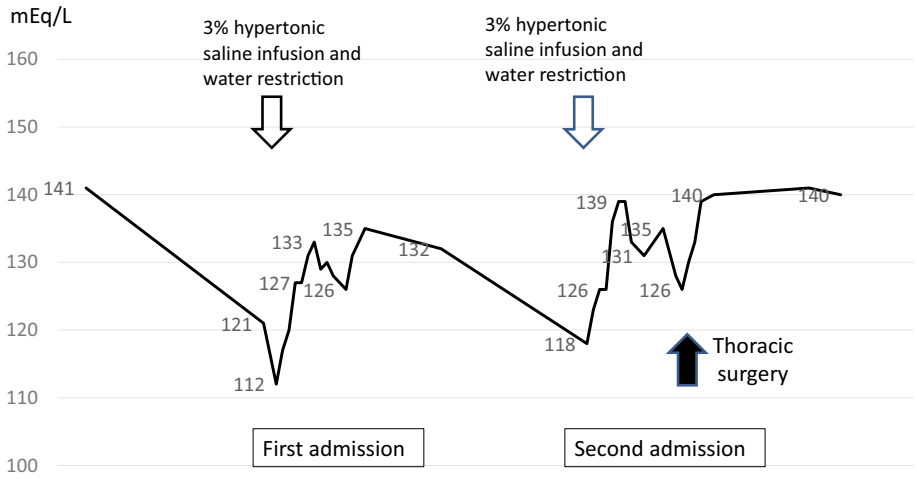

Figure 1. **Changes in the serum sodium level during the clinical course in the present case.**

Table. **Laboratory Findings in the Present Case.**

		1st SIADH	2nd SIADH
Na (mEq/L)		112	118
K (mEq/L)		5.7	6.1
Cl (mEq/L)		80	85
Glu (mg/dL)		259	191
BUN (mg/dL)		12.9	18.3
Cre (mg/dL)		0.83	0.8
plasma osmolarity (mOsm/kg)		240	
urine osmolarity (mOsm/kg)		468	
urine Na (mEq/L)		75	156
ADH (pg/mL)	(<2.8)	1.6	3.4
ACTH (pg/mL)	(7.2-63.3)	64.9	
cortisol (μg/dL)	(5.0-15.0)	20.2	
renin activity (ng/mL/h)	(0.3-2.9)	0.3	
aldosterone (pg/mL)	(35.7-240.0)	159	
TSH (μIU/mL)	(0.500-5.000)	0.809	
fT3 (pg/mL)	(2.30-4.00)	2.33	
fT4 (ng/dL)	(0.90-1.70)	1.63	

SIADH: syndrome of inappropriate antidiuretic hormone

with an increased renal excretion of sodium (75 mEq/L) and normal renal function (Table). In addition, there were no significant findings on thyroid or adrenal functions tests, which was consistent with SIADH (Table). Inflammatory markers were also negative (white blood cell count: 7,120/μL, C-reactive protein level: 0.07 mg/dL).

We treated the patient with 3% hypertonic saline infusion and water restriction. His blood sodium levels return to 136 mEq/L during the first admission (Fig. 1). A systematic review was performed to determine the underlying disease of SIADH. The values of serum tumor markers were as follows: carcinoembryonic antigen (1.6 ng/mL), squamous cell carcinoma related antigen (2.0 ng/mL), and pro-gastrin-releasing peptide (Pro-GRP; 220.7 pg/mL). Chest computed tomography (CT) revealed a 13-mm nodule in the lower lobe of the right lung (Fig. 2A) that had not been detected 6 months earlier (Fig. 2B). The mass was positive on positron emission tomography with fluorodeoxyglucose-CT (Fig. 2C), and hilar and mediastinal lymphadenopathy and distant metastatic sites were not observed, including on brain magnetic resonance imaging.

During these examinations, the serum potassium level decreased again three weeks after the initial onset of hyponatremia (second admission, Fig. 1), and the laboratory findings were re-evaluated (Table). The diagnosis of SIADH was confirmed, and the antidiuretic hormone (ADH) level was slightly increased (Table). After supplementing serum potassium with 3% hypertonic saline infusion, thoracic surgery was performed for the lung nodule. Hematoxylin and Eosin staining of the resected specimen indicated irregularly shaped sheets and nests of tumor cells, and a diagnosis of SCLC was made (Fig. 3A). On immunohistochemical staining, the tumor cells were positive for synaptophysin (Fig. 3B) and thyroid transcription factor-1 (Fig. 2C). The

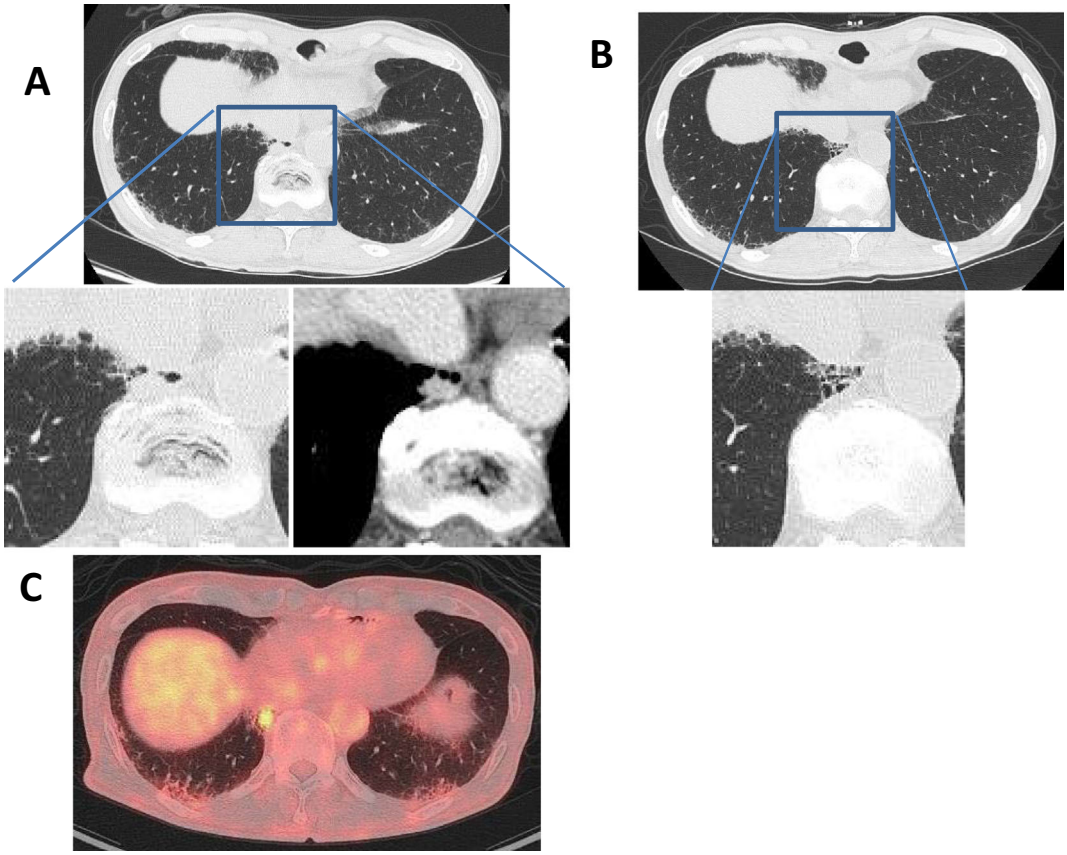

Figure 2. **Chest computed tomography (CT) showed a mass lesion in the lower lobe of the right lung (A) that had not been observed six months earlier (B). The mass was positive on positron emission tomography with fluorodeoxyglucose-CT (C).**

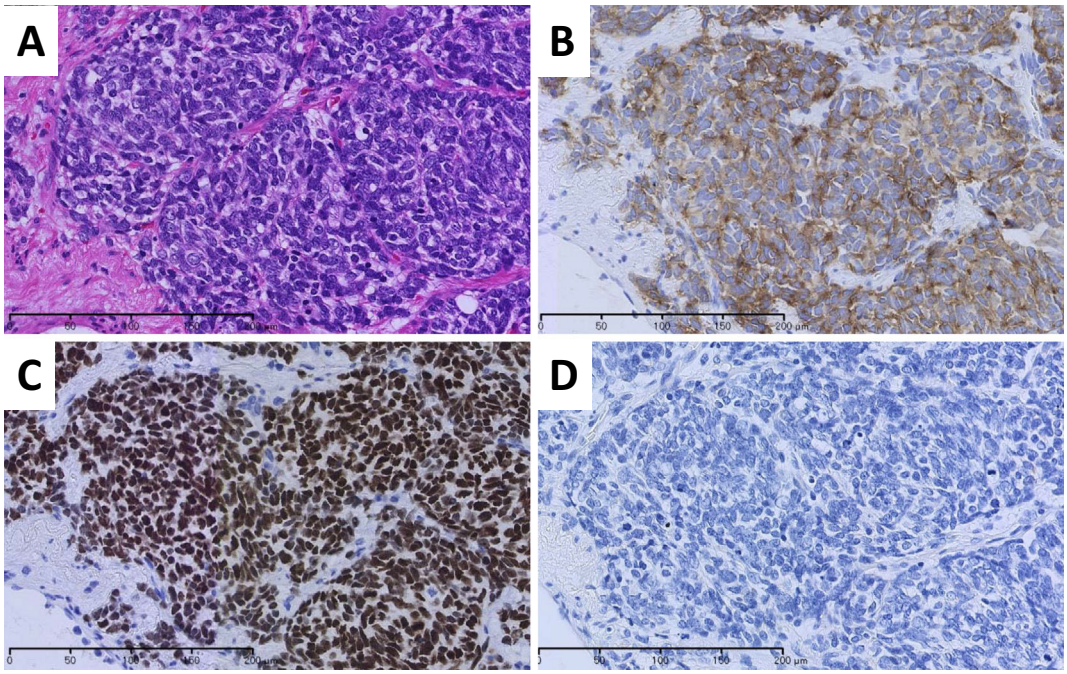

Figure 3. **Hematoxylin and Eosin staining of the resected specimen showed irregularly shaped sheets and nests of tumor cells (A). Immunohistochemical staining indicated that the tumor cells were positive for synaptophysin (B) and thyroid transcription factor-1 (C). Immunohistochemical staining for ADH was negative in the cells of the resected tumor (D).**

stage was T1bN0M0; Stage 1b (8th edition of WHO classification). After surgery, the serum potassium level returned to normal and remained within the normal range (Fig. 1). The serum ADH and Pro-GRP levels also decreased postoperatively (3.1 pg/mL and 152.3 pg/mL, respectively). The patient received four cycles of adjuvant chemotherapy using platinum+etoposide. Hyponatremia (minimum value of 126 mEq/mL) was observed during adjuvant chemotherapy, but the serum potassium level remained almost within the normal range after chemotherapy (136-140 mEq/L), and no recurrence of esophageal cancer and/or SCLC was noted over one year after thoracic surgery. The tumor cells in the resected specimen were negative for ADH on immunohistochemical staining with anti-vasopressin antibody (AB1565; Merck Millipore, Tokyo, Japan) (Fig. 2D).

Discussion

We encountered a case of initially presented SIADH in a patient with stage I SCLC. After relevant examinations, a diagnosis of SCLC was eventually made, and surgery was successfully performed. SIADH as the initial presentation is extremely rare in patients with stage I SCLC.

SIADH is often regarded as a diagnosis of exclusion (3, 4). The adrenal and thyroid function in the present case were normal. Although the patient received insulin therapy, his medications were not changed, and no additional agents were administered during the development of SIADH. In addition, there were no increases in the hypothalamic production of ADH-like substances associated with neurological disorders (infections, Guillain-Barre syndrome, and brain tumors). The diagnosis of SIADH in the present case was confirmed by laboratory findings, including symptomatic hyponatremia with corresponding serum hyposmolality, urine osmolality greater than serum osmolality, and continued renal excretion of sodium. In addition, the hyponatremia improved following removal of the tumor, suggesting that the SIADH in our case was related to the presence of SCLC tumor cells.

However, the plasma ADH level (3.4 pg/dL) just before surgery was too low compared with other reports of ectopic ADH-producing SCLC (6, 7, 13). Furthermore, the resected tumor cells were negative for ADH on an immunohistochemical examination. Although the increased level of ADH might have been below the level of detection on an immunohistochemical analysis in tumor cells, we had to consider that SIADH might have developed as an accidental manifestation due to causes other than ADH-producing SCLC. There were many predisposing factors of SIADH, including intrathoracic disorders and/or increases in intrathoracic pressure, such as infections, pneumothorax, positive-pressure ventilation, and conditions involving a decreased left atrial pressure (1-7). In our case, intrathoracic disorder related to the retrosternal route of gastric tube reconstruction and pleural adhesion due to prior thoracic surgery may have contributed to the development of hyponatremia, in addition to the presence of SCLC and/or excess of water intake. Thus, the etiology of SIADH in our case remains unclear, but an appropriate diagnosis of hyponatremia is essential in such a clinical situation.

Several studies have shown positive and favorable survival rates in early-stage SCLC initially treated with surgery (14, 15). The frequency of these SCLC patients was 1.8-2.4% among cases of lung cancer treated with surgery in Japan, and better surgical outcomes have been observed in asymptomatic SCLC patients and patients with stage I disease than in others. We therefore emphasize that SIADH may be an initial presentation in patients with malignancies, especially those with early-stage SCLC, and clinicians should be aware of the presence of initial manifestations of hyponatremia and/or SIADH in patients with malignancies.

In summary, our case indicates that hyponatremia and/or SIADH is an important index for detecting underlying malignancies.

Author's disclosure of potential Conflicts of Interest (COI).
Tomonobu Koizumi: Honoraria, AstraZeneca, Ono Pharmaceutical and Chugai Pahrmaceutical.

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