INTERNAL MEDICINE

□ CASE REPORT □

Mild Lung Tuberculosis in a Patient Suffering from Status Epilepticus Caused by the Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)

Mitsuo Hashimoto, Saki Kuriiwa, Ayako Kojima, Kyota Shinhuku, Akihito Sato, Ryoko Sasaki, Tsukasa Hasegawa, Akihiko Ito, Hirofumi Utsumi, Haruhiko Yanagisawa, Hiroshi Wakui, Shunsuke Minagawa, Jun Kojima, Takanori Numata, Hiromichi Hara, Jun Araya, Yumi Kaneko, Katsutoshi Nakayama and Kazuyoshi Kuwano

Abstract

A 76-year-old woman was diagnosed with lung tuberculosis. On the second day of anti-tuberculosis treatment, she became unconscious and developed status epilepticus accompanied by hyponatremia. The hyponatremia was caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Detailed examinations revealed that the patient's status epilepticus had occurred due to hyponatremia, which was caused by lung tuberculosis-associated SIADH. Previous case reports noted that patients with tuberculosis-associated SIADH showed mild clinical manifestations. They also reported that extensive lung involvement was associated with SIADH development. We herein report a rare case of SIADH complicated with status epilepticus that was caused by tuberculosis with mild lung involvement.

Key words: lung tuberculosis, SIADH, status epilepticus, hyponatremia

(Intern Med 56: 429-433, 2017)
(DOI: 10.2169/internalmedicine.56.7224)

Introduction

Hyponatremia is one of the most common electrolyte imbalances. It is important that healthcare professionals recognize the imbalance promptly to prevent potential morbidity or mortality, since it is often a marker of underlying disease (1). The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most common cause of hyponatremia in patients suffering from pulmonary diseases. The main causes of SIADH are central neurological diseases, malignant diseases, medication-related adverse effects, and pulmonary diseases such as pneumonia and pulmonary tuberculosis (2). Several cases of pulmonary tuberculosis complicated with SIADH have been documented (3-5). Minami et al. summarized eight case reports of tuberculosis-associated SIADH and showed that seven of the reports were caused by severe tuberculosis, implying that extensive lung involvement is associated with the development of SIADH in patients with pulmonary tuberculosis (4). Furthering this finding, Nishizawa et al. summarized five case reports of tuberculosis with SIADH and showed that SIADH associated with pulmonary tuberculosis resulted in mild symptoms, including headache, nausea and vertigo (5). We herein report a rare case of SIADH complicated with status epilepticus that was caused by tuberculosis with mild lung involvement.

Case Report

A 75-year-old woman was admitted to the Jikei University Hospital due to impaired consciousness and status epilepticus. She was referred to the hospital's outpatient clinic 24 days before admission to investigate a progressive mass-like lesion with a maximum diameter of 30 mm that was located on her left upper lung. Positive results from an

Division of Respiratory Disease, Department of Internal Medicine, The Jikei University School of Medicine, Japan
Received for publication February 3, 2016; Accepted for publication June 27, 2016
Correspondence to Dr. Mitsuo Hashimoto, mitsuoha-georgetown@live.jp

Table. Laboratory Data on Admission.

Hematology			Serology			Endocrinology		
WBC	15,900	/uL	CRP	0.29	mg/dL	TSH	0.7	uIU/mL
Hb	14	g/dL	PCT	0.1	mg/dL	FT4	0.92	pg/mL
Ht	40.6	%				ACTH	32.3	pg/mL
Plt	$25.9x10^4$	/uL				Cortisol	21.4	ug/mL
			Tumor markers			PAC	73.4	pg/mL
Biochemistry			sIL-2R	388	U/mL	PRA	1.2	ng/mL/hr
AST	24	U/L	CEA	1.1	ng/mL	Ad	63	pg/mL
ALT	12	U/L	SLX	34	U/mL	NA	527	pg/mL
CK	247	U/L	ProGRP	26.2	pg/mL	ADH	3.3	pg/mL
BUN	3	mg/dL	KL-6	155	U/mL			
Cr	0.45	mg/dL				Urinalysis		
Na	120	mEq/L	Blood Gas Analysis(room air)			Na	81	mEq/L
K	3.5	mEq/L	PH	7.416				
Cl	87	mEq/L	$PaCO_2$	30.4	Torr	Osmolality		
Vit. B6	5.8	ug/dL	PaO_2	73.8	Torr	Serum	253	mOsm/kg
BS	164	mg/dL	HCO_3^-	19.6	mEq/L	Urine	458	mOsm/kg

PCT: Procalcitonin, PAC: Plasma Aldosterone Concentration, PRA: Plasma Renin Activity, CRP: C-Reactive Protein, sIL-2R: soluble interleukin-2 receptor

interferon-gamma-release assay (T-spot.TB assay, Oxford Immunotec Ltd. Marlborough, MA, USA) and a tuberculosis polymerase chain reaction (PCR) led to a diagnosis of pulmonary tuberculosis 16 days before admission. A sputum culture showed that the patient was positive for tuberculosis, and the diagnosis was later confirmed. The patient was prescribed four anti-tuberculosis medications (isoniazid, rifampicin, ethambutol, and pyramide). She did not start taking full doses of the medications until two days prior to her admission due to anxiety over the side effects. Her medical history included hypertension, gastric ulcer and hyperlipidemia, but she had been healthy until admission. On the day of admission, she was found lying on the floor at her home and was transported to the hospital. At the emergency room, she developed generalized seizures five times and was admitted to the intensive care unit to undergo treatment for statue epilepticus.

On admission, the patient was unconscious (Glasgow Coma Scale, E1V1M3) with a body temperature of 37℃, a heart rate of 108/min, a respiratory rate of 18 breaths/min, a saturation level of 99% on room air and a blood pressure of 160/90 mmHg. Physical examinations showed normal breath and heart sounds and no swelling of her extremities. Neurological examinations revealed an increase of muscle tonus, especially in the lower limbs. Biochemical examinations showed hyponatremia (120 mEq/L) with low serum osmolality (253 mOsm/kg), high urinary osmolality (458 mOsm/kg), and a normal urinary sodium concentration (81 mEq/L) (Table). Despite the patient's severe hyponatremia, her serum antidiuretic hormone (ADH) level was not decreased (3.3 pg/mL); it was close to the upper limit of the normal range (0.3-4.2 pg/mL). The patient's thyroid, kidney, and adrenal functions were normal. The fact that her blood urea nitrogen (BUN) to creatinine (Cr) ratio was 6.6 and the fact that she did not experience severe diarrhea or vomiting implied that she was clinically euvolemic. Based on these laboratory findings, this patient met the criteria for SIADH, which were as follows: decreased effective osmolality; urinary osmolality, >100 mOsm/kg of water; clinical euvolemia; urinary sodium concentration, >40 mmol/L; and normal thyroid and adrenal functions (2). Chest radiography and computed tomography (CT) showed a wedge-shaped infiltrative shadow with small tree-in-bud satellite lesions in the left upper lobe of the lung (Fig. 1). With the exception of pulmonary tuberculosis, contrast-enhanced CT of the whole body did not reveal any malignant or infectious diseases. Brain magnetic resonance imaging (MRI) revealed no abnormalities and electroencephalograms, which were taken three times, were all normal. A cerebrospinal fluid examination (CSF) showed no increase in the cell count (0 cells/uL) or the total protein level (47 mg/dL), no decrease in the glucose (102 mg/dL), and was culture-negative for tuberculosis and bacteria. Repeated blood cultures were also negative for bacteria. She was not taking any medicines that have previously been reported as a potential cause of SIADH. It was therefore concluded the patient's SIADH was caused by pulmonary tuberculosis. Among the prescribed medications, only isoniazid has the potential to lead to seizures. However, this possibility was excluded due to a lack of complications during re-administration. Accordingly, we concluded that the patient's status epilepticus could be attributed to hyponatremia, which had caused by pulmonary tuberculosis-associated SIADH.

The patient did not develop seizures after infusion of fosphenytoin sodium hydrate. Her level of consciousness improved after an infusion of saline to treat her abnormal serum sodium concentration, and she became conscious on the second day after admission (Fig. 2). Rhabdomyolysis occurred due to the patient's status epilepticus, and her creatine kinase (CK) levels increased (6,630 IU/L). SIADH did

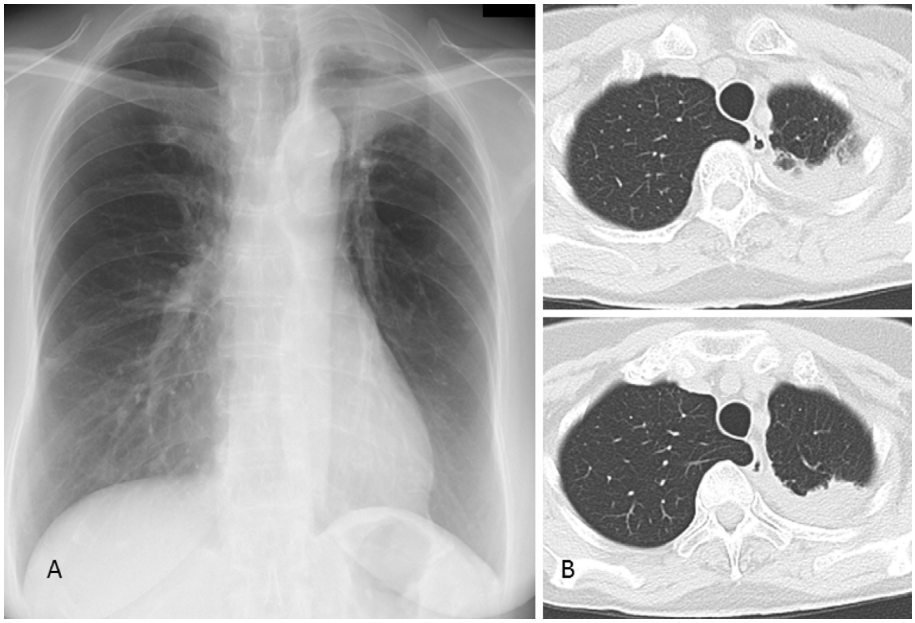

Figure 1. **A: chest radiography on admission showed mass-like shadow in the left upper lung field. B: CT on admission showed wedge-shaped infiltrative shadow with small tree-in-bud satellite lesions in the left upper lobe.**

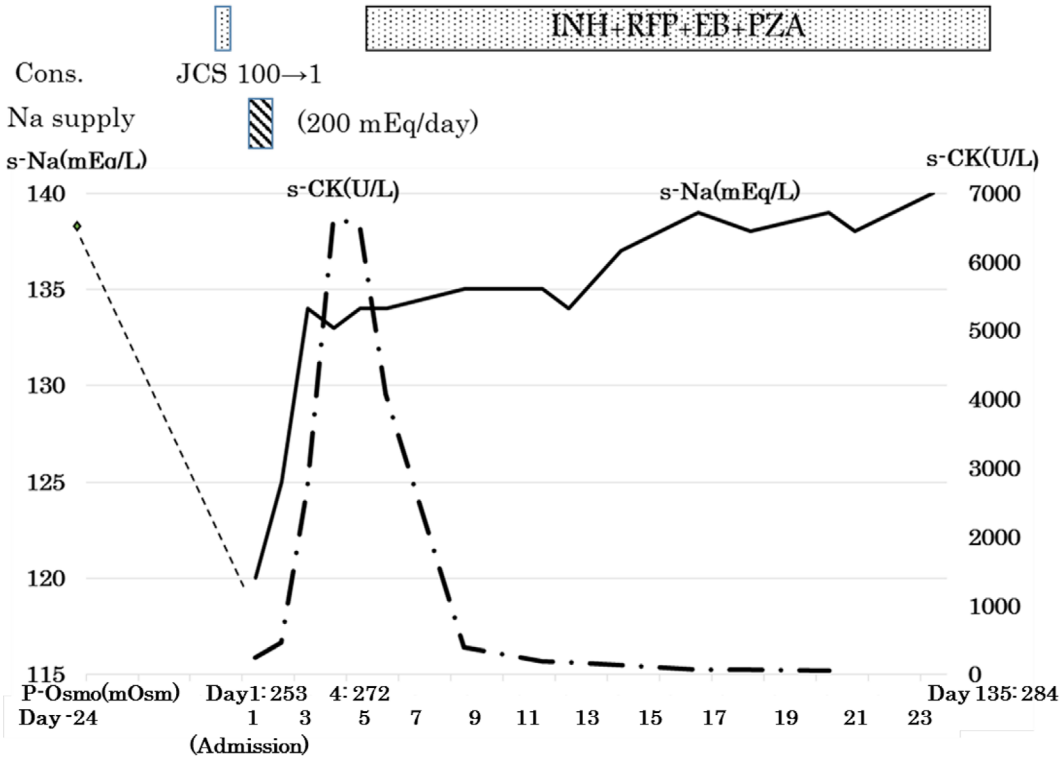

Figure 2. **Clinical Course. INH: isoniazid, RFP: rifampicin, EB: ethambutol, PZA: pyrazinamide, JCS: Japan coma scale, Cons: consciousness, P-Osmo: Plasma osmolality**

not recur after the patient resumed taking the anti-tuberculosis medicines and she was discharged from the hospital on the 22nd day after admission. The fact that she improved with treatment verified our diagnosis.

Discussion

SIADH is characterized by the excessive release of ADH, which results in dilutional hyponatremia and an increase in the blood volume. This form of hyponatremia is associated

with neurological symptoms such as headaches, confusion, weakness, seizures, and coma (2). The causes of SIADH include, but are not limited to, central nervous system diseases, malignant diseases, drug-induced diseases, and pulmonary diseases. It is estimated that about 2.1% of pulmonary disease-related SIADH cases can be attributed to pulmonary tuberculosis (3).

Hyponatremia is commonly associated with tuberculosis. It has been reported that 10.7% of patients with newly diagnosed active pulmonary tuberculosis have hyponatremia (6). Although it is not clear what percentage of hyponatremia cases are associated with SIADH, Nakamata et al. reported that approximately 29% of lung tuberculosis patients had high plasma ADH, suggesting the existence of a potential causal relationship between pulmonary tuberculosis and SIADH (7). ADH is released from the posterior pituitary in response to a decrease in the intravascular volume or an increase in the serum osmolality (8); however the cause of the inappropriate release of ADH in patients with pulmonary tuberculosis is not fully understood.

There are several possible mechanisms for abnormal ADH levels in patients with tuberculosis. First, although our patient was not suffering from tuberculous meningitis, ADH production may be triggered by cerebral insults, including infections and malignancies, which suggests that non-specific inflammation may stimulate the release of ADH from the posterior pituitary (1, 9). Moreover, recent reports have suggested that interleukin-6 (IL-6) has an important role in the release of ADH in response to inflammatory diseases such as pneumonia and tuberculosis (10). Ogawa et al. reported that the monocytes or macrophages of tuberculosis patients showed higher levels of IL-6-production than those of healthy subjects (11). These reports suggest that IL-6 could play important roles in causing hyponatremia in tuberculosis patients. However, our patient's C reactive protein level was only slightly increased, implying that there was low inflammation. Secondly, decreased blood flow in the intrathoracic vessels due to the destruction of the lung by extensive pulmonary tuberculosis can be sensed by the mechanoreceptors in the left ventricle, leading to the non-osmotic release of ADH (12). However, in the present case, the patient's pulmonary tuberculosis was limited. Finally, another intriguing possibility is the direct release of ADH from lungs infected with tuberculosis. Vorherr et al. detected high concentrations of ADH in tuberculous lung tissue, suggesting the production of ADH in the local lung or that the tuberculous lung tissue had adsorbed an inappropriately released hormone from the posterior pituitary (13). Moreover, Lee et al. reported a case of tuberculosis and proven diabetes insipidus in a patient who had an elevated ADH level in the presence of hyponatremia even without using desmopressin, which suggested ectopic ADH production (14). In our case, SIADH occurred two days after the initiation of anti-tuberculosis treatment. The bactericidal property of the medications might have affected the integrity of the tuberculous lung tissue, which may have resulted in the release of ADH. Thus, although it is still not clear whether ADH is produced in tuberculous lung tissue or whether it accumulates there, we hypothesize that the accelerated temporary release of ADH from tuberculous lung tissue due to anti-tuberculosis medications may have caused SIADH in the present case.

Several cases of tuberculosis-associated SIADH have been reported in Japan. However, most of the cases were caused by severe lung tuberculosis or tuberculous meningitis and the symptoms were generally mild (5). In contrast, our patient had mild lung tuberculosis complicated with SIADH, which caused serious symptoms such as impaired consciousness and status epilepticus. The manifestations of hyponatremia are more prominent when a patient's serum sodium concentration rapidly decreases (15); we therefore assumed that the severe symptoms in our case occurred due to a rapid decrease in the serum sodium concentration. This rapid decrease in the serum sodium concentration could be explained by a rapid release of ADH. We hypothesize that the accelerated and temporary release of ADH was from the tuberculous lung tissue, and that it was induced by the bactericidal property of the anti-tuberculosis medicines.

We believe that close observation is required to detect symptoms of SIADH, even in cases of mild lung tuberculosis, especially when a patient begins to take anti-tuberculosis medications.

The authors state that they have no Conflict of Interest (COI).

References

1. Esposito P, Piotti G, Bianzina S, et al. The syndrome of inappropriate antidiuresis: pathophysiology, clinical management and new therapeutic options. Nephron Clin Pract **119**: c62-c73, 2011.
2. Ellison DH, Berl T. The syndrome of inappropriate antidiuresis. N Engl J Med **356**: 2064-2072, 2007.
3. Saito T. The syndrome of inappropriate secretion of antidiuretic hormone. J Jpn Soc Int Med **85**: 1705-1710, 1996.
4. Minami T, Wakamatsu K, Kumazoe H, et al. A case of mild lung tuberculosis complicated with the syndrome of inappropriate antidiuretic hormone secretion which caused impaired consciousness. AJRS **49**: 607-611, 2011.
5. Nishizawa Y, Yamamori C, Nishimura Y, et al. A case of lung tuberculosis initially presented with syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Kekkaku **78**: 27-31, 2003 (in Japanese, Abstract in English).
6. Chung DK, Hubbard WW. Hyponatremia in untreated active lung tuberculosis. Am Rev Res Dis **99**: 595-597, 1969.
7. Nakamata M, Tsukioka K, Kondo A, Hashimoto T. Plasma ADH in patients with lung tuberculosis. Kekkaku **62**: 635-639, 1987 (in Japanese).
8. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. Am J Med **120**(11 Suppl 1): S1-S21, 2007.
9. Park SJ, Shin JI. Inflammation and hyponatremia: an underrecognized condition? Korean J Pediatr **56**: 519-522, 2013.
10. Swart RM, Hoorn EJ, Betjes MG, Zietse R. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. Nephron Physiol **118**: 45-51, 2011.
11. Ogawa T, Uchida H, Kusumoto Y, Mori Y, Yamamura Y, Hamada

S. Increase in tumor necrosis factor alpha- and interleukin-6-secreting cells in peripheral blood mononuclear cells from subjects infected with *Mycobacterium tuberculosis*. Infect Immune **59**: 3021-3025, 1991.

12. Reddy P, Mooradian AD. Diagnosis and management of hyponatraemia in hospitalized patients. Int J Clin Pract **63**: 1494-1508, 2009.

13. Vorherr H, Massry SG, Fallet R, et al. Antidiuretic principle in tuberculous lung tissue of a patient with lung tuberculosis and hyponatremia. Ann Intern Med **72**: 383-387, 1970.

14. Lee P, Ho KK. Hyponatremia in pulmonary TB: evidence of ectopic antidiuretic hormone production. Chest **137**: 207-208, 2010.

15. Luis CG, Maria DC, Jose MLC, et al. Electrolytes disturbances and seizures. Epilepsia **47**: 1990-1998, 2006.