

## Syndrome of Inappropriate Secretion of ADH (SIADH) due to Small Cell Lung Cancer with Extremely High Plasma Vasopressin Level

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A 76-year-old man with small cell lung cancer associated with the syndrome of inappropriate secretion of ADH (SIADH) visited our hospital. The serum Na level was normal on the first visit, but 2 weeks later it decreased to 114 mEq/L with an extremely high plasma vasopressin (VP) level of 1520 pg/ml. Serum Na was normalized after the reduction of the tumor size by chemotherapy, but the plasma VP level remained between 150 to 600 pg/ml. On gel filtration of plasma VP two peaks of immunoreactive VP were eluted at the positions of a larger molecule than authentic VP and authentic VP, and VP in urine gave only one peak compared to that of authentic VP. The dilution curve of plasma VP was almost parallel and that of urine was completely parallel to the standard curve. These findings suggest that a larger VP with low physiological activity was predominantly secreted in the present patient and manifested relatively mild symptoms despite the extremely high plasma VP level.

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**Key words:** syndrome of inappropriate secretion of ADH (SIADH), small cell lung cancer, vasopressin, gel filtration

### Introduction

Syndrome of inappropriate secretion of ADH (SIADH) is characterized by a sustained release of VP in the absence of either osmotic or nonosmotic stimuli, and is most commonly due to ectopic VP secretion by malignancies of several kinds. Small cell lung cancer is known to ectopically produce various peptide hormones including VP. We experienced a 76-year-old man with small cell lung cancer associated with SIADH. The SIADH disappeared and the serum Na level became normal after reduction of the tumor size by chemotherapy, while the plasma VP level remained rather high. On gel filtration of VP in plasma and urine a large molecule of VP was predominantly eluted compared to authentic VP, suggesting a low physiological activity of this larger VP.

### Case Report

A 76-year-old man visited the Anan Kyoei Hospital on December 5, 1991 with complaints of chest pain, and cough with sputum for three months.

His height was 146.5 cm, weight 45 kg, blood pressure, 130/60 mmHg, pulse 84 beats/min and regular, and body temperature 37.0°C. Neither dehydration nor edema was detected. The lymph nodes were not palpable. No abnormal findings were observed in his chest, abdomen and nervous system.

Laboratory tests at the time of admission revealed the following results (Table 1): urinalysis was normal, but mild anemia was observed; BUN 17 mg/dl, serum Creatinine 0.8 mg/dl, sodium level 145 mEq/L, potassium 4.0 mEq/L, chloride 109 mg/dl, thyroid and adrenal functions were normal. The levels of tumor markers were high (neuron-specific enolase 49.8 ng/ml and SCC 2.3 ng/ml).

The chest radiogram showed a tumor-like shadow in the left upper lung field and a scar from pleuritis in the right lung (Fig. 1). The chest CT scan showed a mass lesion in S<sub>3</sub> of the left lung and swelling of the mediastinal lymph nodes. Broncho-fiberscopic biopsy demonstrated tumor cells of small cell lung cancer (Fig. 2).

Two weeks after admission he developed nausea and drowsiness, and his serum Na level decreased to 114 mEq/L. At that time, the plasma VP level was extremely high (1520 pg/ml), and

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Table 1. Laboratory Findings on Admission (Dec. 20, 1991)

Urinalysis	glucose (-)	TP	7.4g/dl
	protein (-)	BUN	17mg/dl
ESR	80mm/hr	Creatinine	0.8mg/dl
Peripheral blood		Uric acid	6.3mg/dl
RBC	$385 \times 10^4/\text{mm}^3$	Na	145mEq/L
Hb	11.9g/dl	K	4.0mEq/L
Ht	38.5%	Cl	109mEq/L
WBC	$4,790/\text{mm}^3$	FBS	102mg/dl
Platelet	$20.9 \times 10^4/\text{mm}^3$	Tumor marker	
Blood chemistry		CEA	3.7ng/ml
GOT	29IU/L	NSE	48.9ng/ml
GPT	17IU/L	SCC	2.3ng/ml

FBS: fasting blood sugar, CEA: carcinoembryonic antigen, NSE: neuron-specific enolase, SCC: squamous cell carcinoma-related antigen.

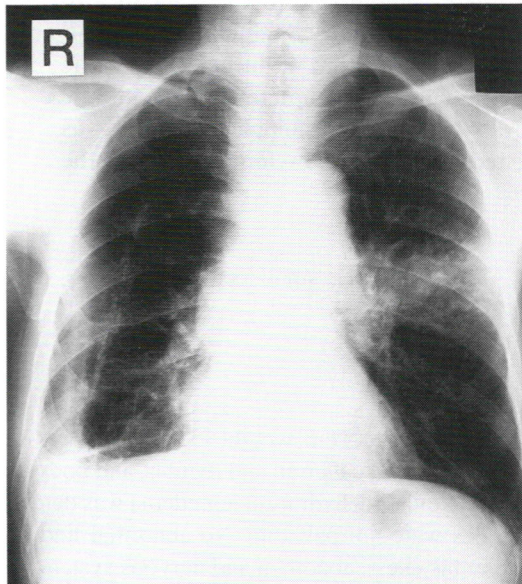


Fig. 1. Chest X-ray film on admission showing tumor-like shadow at the left hilar area.

he was diagnosed as SIADH (Table 2). With three episodes of chemotherapy using carboplatin (CBDCA), etoposide (VP-16), doxorubicin hydrochloride (ADM), vincristine sulfate (VCR), and cyclophosphamide (CPA) for the lung cancer, the tumor shadow was reduced and the serum Na level was normalized. The plasma VP level also decreased, but remained between 150 and 600 pg/ml until September 1992 when he died without any symptoms of SIADH. The lung cancer had enlarged again, metastasized to the cervical spine and liver, and he died of sudden melena and arrhythmia on September 2, 1992 (Fig. 3).

## Materials and Methods

To clarify the discrepancy between the high plasma VP level

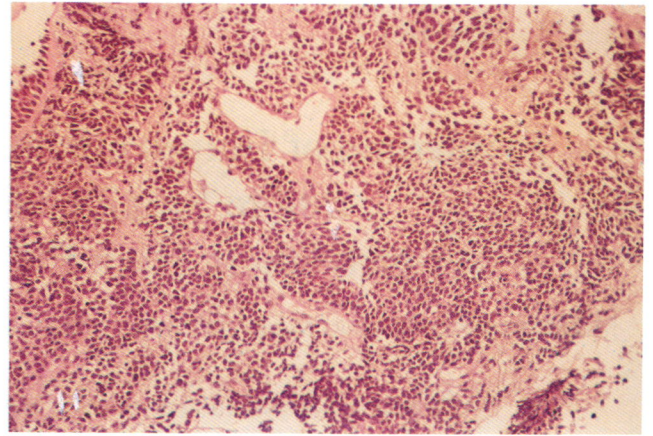


Fig. 2. Histology of the lung tumor showing small cell lung cancer, intermediate type (HE stain,  $\times 200$ ).

Table 2. Laboratory Findings on Jan. 2, 1992 when the Diagnosis of SIADH was Made

Blood chemistry		Hormonal examination	
BUN	6mg/dl	VP	1,520pg/ml
Creatinine	0.5mg/dl	GH	3.9ng/ml
Uric acid	1.4mg/dl	PRL	12ng/ml
Na	114mEq/L	TSH	1.8μU/ml
K	4.1mEq/L	LH	15mIU/ml
Cl	83mEq/L	FSH	7.5mIU/ml
Posm	225mOsm/kg	ACTH	31pg/ml
Uosm	468mOsm/kg	cortisol	16.4μg/dl
Urine Na	79.8mEq/day	PRA	0.9ng/ml/hr
(urine volume 500ml/day)		aldosterone	30pg/ml

and no SIADH symptoms after March 1992, we investigated the gel filtration pattern of immunoreactive VP (IR-VP) in the plasma and urine. VP was extracted from plasma collected on January 2, 1992 by the method of Shimizu and colleagues (1). Briefly, the plasma sample was placed on a Sep-Pak-C18 column (Water Associates, Milford, MA USA) and eluted with methanol. VP concentration was measured by the AVP-RIA kit (Mitsubishi Petrochemical Co., Tokyo, JAPAN). The recovery of VP from the plasma was 90.2% and the sensitivity of the assay was 0.3 pg/ml.

Gel filtration of VP in plasma extract and urine were performed using a Sephadex G25 column (1 $\times$ 45 cm) and eluted with 0.01 M phosphate buffer, pH7.4.

## Results

Gel filtration patterns of IR-VP in the plasma extract and urine are shown in Fig. 4. IR-VP in the plasma extract was eluted at the positions of void volume, with a bigger molecule than authentic VP and authentic VP. On the other hand, IR-VP in the urine sample showed one peak at the position of authentic VP. The dilution curve of IR-VP in the plasma extract was

## Large Vasopressin in SIADH

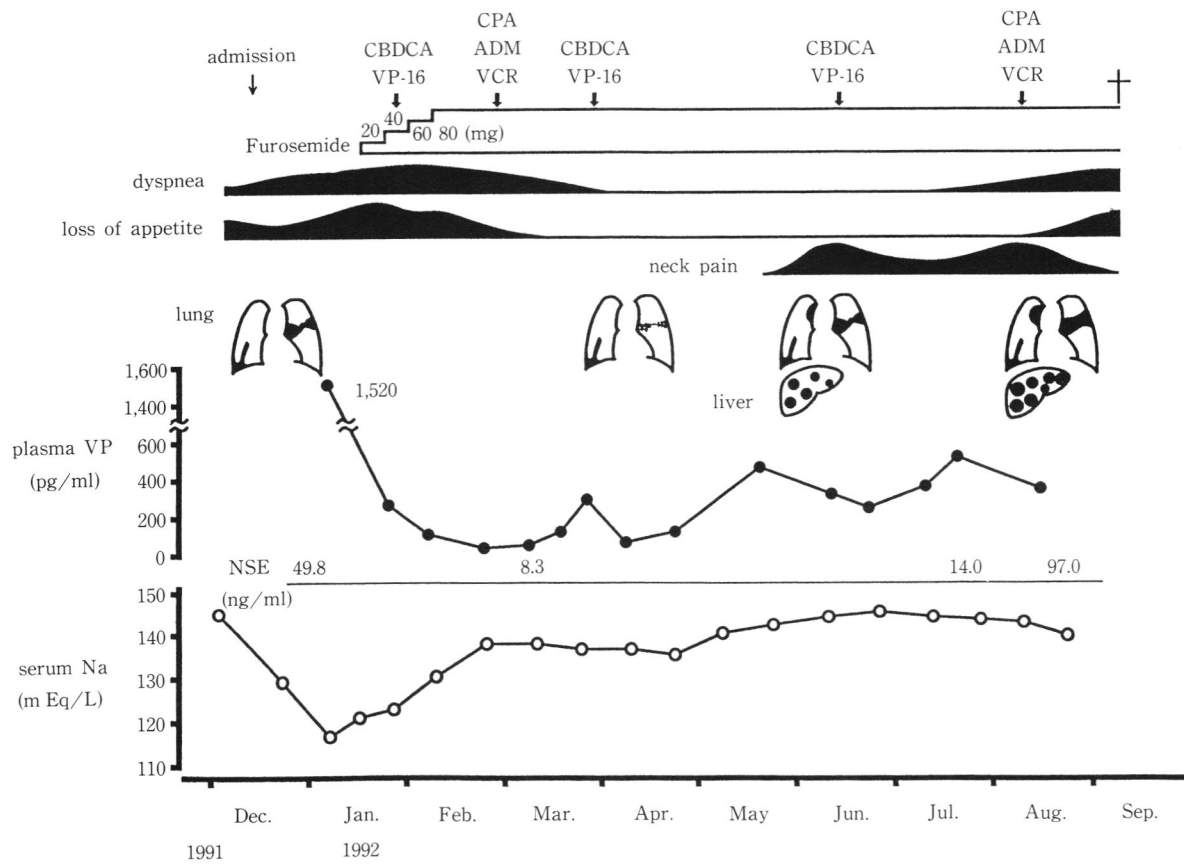


Fig. 3. Clinical course.

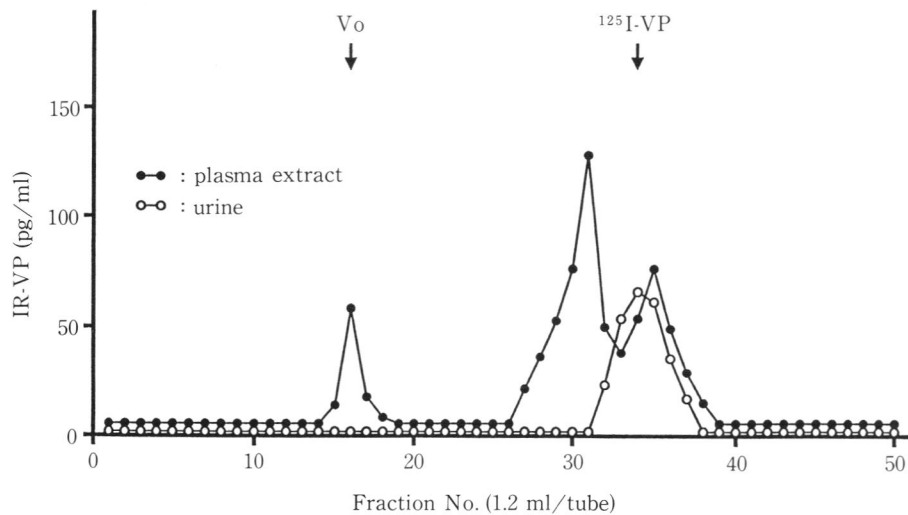


Fig. 4. Elution patterns of immunoreactive vasopressin (IR-VP) in plasma extract and urine on Sephadex G25 column (1x45 cm).

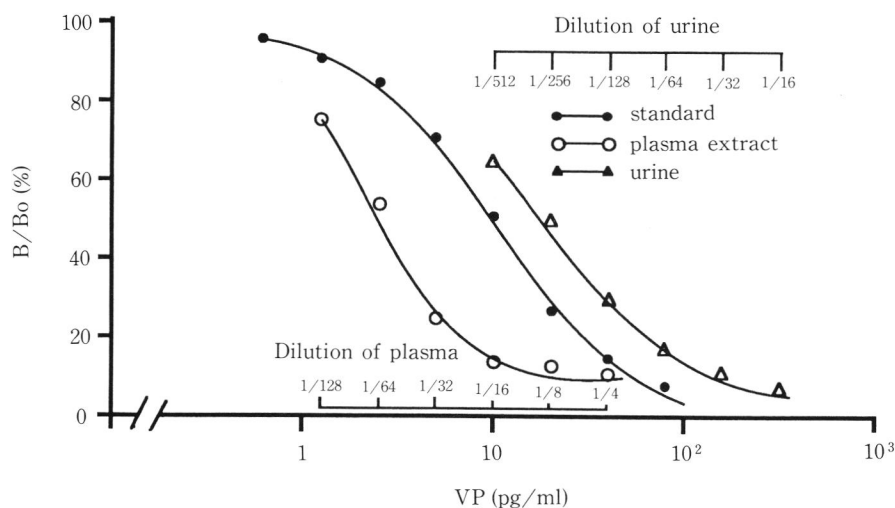


Fig. 5. Standard curve of VP radioimmunoassay and the dilution curves of IR-VP in plasma extract and urine.

almost parallel to the standard curve and that of IR-VP in the urine was completely parallel (Fig. 5).

## Discussion

SIADH is a clinical entity proposed by Schwartz and colleagues (2) in 1957, and caused by pulmonary diseases, cerebrospinal diseases and ectopic ADH-secreting tumors, etc. Lung cancer occupies 84% of ADH-secreting tumors, with 94% as small cell lung cancer (1).

On the other hand, SIADH is seen in 7–39% of patients with small cell lung cancer, and hyponatremia is detected in 90% of cases at initial diagnosis (3). In the present case, the plasma VP concentration was remarkably high, but later decreased with reduction of the tumor after chemotherapy. These findings suggested that the production and secretion of VP was caused by the cancer. The present patient's serum Na level was normal at the first visit, then two weeks later an extremely high plasma VP level was found with SIADH. After chemotherapy the SIADH disappeared, but the plasma VP level remained at the levels of 150–600 pg/ml.

To clarify the reason for the discrepancy between the high plasma VP level and normal serum Na level, the nature of the plasma VP was investigated. Gel filtration study showed two peaks of plasma IR-VP besides a molecule at the position of the void volume, a large VP and an authentic VP. IR-VP in the urine gave only one peak at the position of the authentic VP. Furthermore, the dilution curve of plasma IR-VP was almost parallel to the standard curve, and that of urinary IR-VP was completely parallel. These findings suggested that the cancer predominantly produced high molecular weight VP rather than authentic VP. There are some reports of gel filtration study on the tissue extract of small cell lung cancer with SIADH. In compari-

son with these studies, the present case is characteristic for its extremely high plasma VP level, and the different elution pattern of the IR-VP in the plasma and urine. A high molecular weight VP in the present case seemed to be smaller in molecular size than the VP precursor (high molecular weight neurophysin) reported by Yamaji and colleagues (4) and to have almost the same size as the neurophysin fragment attached to the C-terminus of VP (5). Plural enzymes participate in the complete conversion of the precursor to VP and neurophysin (4). This large VP produced by the tumor may be processed in a different manner from authentic VP. Furthermore, the ratio of large VP to authentic VP was higher in the present case compared to the case reported by Shimizu (1). The physiological activity of this large VP is not known, but should be much lower than authentic VP. The structure and physiological activity of this large VP remains to be studied.

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