

# Syndrome of inappropriate secretion of antidiuretic hormone after chemotherapy with vinorelbine

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## Abstract

**Purpose** To describe a case of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) after administration of vinorelbine (VNB) for recurrence of lung cancer.

**Case** A 76-year-old man underwent bronchial arterial infusion (BAI) of VNB for postoperative recurrence of lung cancer. Seven days later, hyponatremia and natriuresis developed. Based on his clinical and laboratory findings, we diagnosed him with SIADH. He improved within a couple of days with fluid restriction only.

**Conclusions** Administration of VNB may potentially cause SIADH. This is the second report of the SIADH caused by VNB. It is important to monitor the serum sodium level and clinical findings after chemotherapy with VNB.

**Keywords** Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) · Vinorelbine (VNB) · Non-small cell lung cancer · Chemotherapy

## Introduction

We present a case of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in a 76-year-old man after administration of vinorelbine (VNB). He underwent bronchial arterial infusion (BAI) of VNB for postoperative

recurrence of lung cancer. Seven days later, hyponatremia and natriuresis developed.

Based on his clinical and laboratory findings, we diagnosed him with SIADH. He improved within a couple of days with fluid restriction only. This is the second report of the SIADH caused by VNB therapy for lung carcinoma.

## Case report

A 76-year-old man underwent left upper lobectomy for lung adenocarcinoma (pathological staging T3N1M0, stage IIIA) and 14 months later, chest computed tomography (CT) showed bilateral pulmonary metastases. Five courses of chemotherapy with docetaxel (DOC) 100 mg and gemcitabine (GEM) 1,400 mg resulted in stable disease (SD) and he was begun on modified chemotherapy with vinorelbine (VNB 40 mg). After three courses of VNB, he was admitted to hospital, complaining of left chest pain and cough.

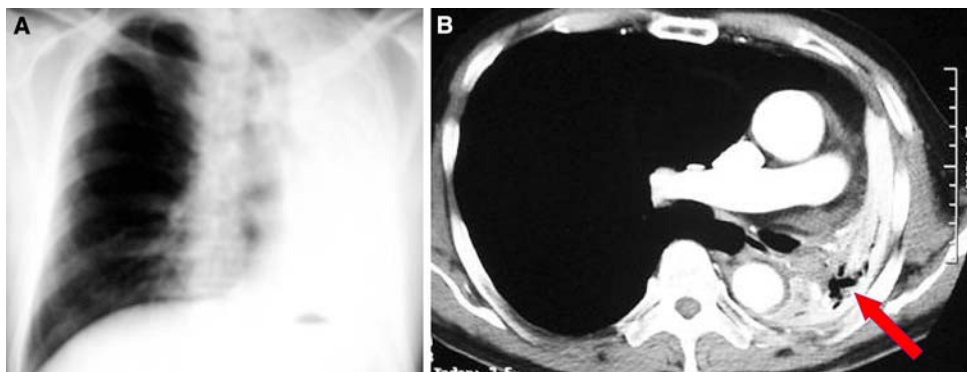
Chest X-ray and CT on admission showed the tumor occluding in the left main bronchus and complete atelectasis of the remaining left lower lobe (Fig. 1a, b).

Transbronchial interventions, such as tumor resection, injection of ethanol and YAG laser ablation, were performed repeatedly, after which the chest X-ray showed gradual restoration in his remaining left lobe. Irradiation (total 50 Gy) of the recurrent tumor was performed for 5 weeks and then chemotherapy with VNB 40 mg (BAI 20 mg + intravenous 20 mg) was repeated.

Seven days after administration of 40 mg VNB, he complained of anorexia, nausea and lethargy. His consciousness was clear. His physical and neurogenic examinations were almost intact. His plasma sodium concentration was 113.1 mEq/l, serum osmolality was 242 mOsm/kg lower

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**Fig. 1** **a** Chest X-ray on admission shows complete atelectasis of remaining left lobe. **b** Chest computed tomography scan shows the tumor occluding the left main bronchus (arrow)

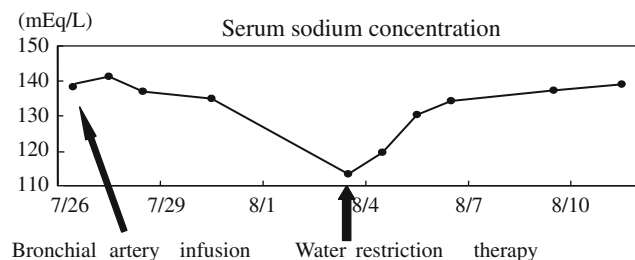


than normal limit of 270 mOsm/kg and urine osmolality was 309 mOsm/kg higher than normal limit of 300 mOsm/kg. Urine sodium value was 20.2 mEq/l higher than normal limit of 20 mEq/l. His cortisol concentration value was normal. The plasma arginine vasopressin (AVP) concentration was 0.59 pg/ml, which was within normal limits, as were other parameters. Clinically, there were no symptoms related to adrenal or anterior pituitary dysfunction. The patient was euvoletic and renal function tests were within normal limits. VNB is considered to be strongly associated with SIADH, so he was diagnosed as having SIADH because his clinical features and laboratory data satisfied all standard criteria.

He was treated with water restriction, oral intake plus drip infusion into vein (DIV, total 750 ml/day). Within 2 days, his serum sodium concentration rose gradually and was restored to 130.3 mEq/l (Fig. 2). His mentation and appetite recovered in accordance with the increasing serum sodium concentration without central pontine myelinolysis. There was a possibility of developing SIADH again with a fifth cycle of VNB, so the chemotherapy agent was changed. He has been free of SIADH and has lived with lung cancer for 1 year.

## Discussion

Schwartz et al. first reported SIADH in patients with lung cancer in 1957 [1]. Standard criteria include (1) hyponatremia,



**Fig. 2** Clinical course of serum sodium concentration 7 days after administration of vinorelbine. The patient complained of anorexia, nausea and lethargy and the sodium concentration was 113.1 mEq/l. He was treated with oral water restriction only and 2 days later, the serum sodium concentration was restored to 130.3 mEq/l

(2) plasma hypo-osmolality and urine hyperosmolality, (3) continuous secretion of sodium in urine, (4) normal renal function without hydration, (5) no adrenal gland dysfunction and (6) hyponatremia and hyposmotic pressure that recover with water restriction therapy without change in blood pressure [2]. The present patient fulfilled these criteria.

Various causes of SIADH have been reported, such as disorders of the cerebral nervous system, malignant tumors, diseases of the thoracic cavity, medicinal side-effects and idiopathic [3]. Approximately 75% of tumor-associated cases of SIADH are related to small-cell lung cancer (SCLC) [4]. The occurrence of SIADH with non-small-cell carcinoma (NSCLC) has been only rarely reported [5]. It has been reported that SIADH is caused by the tumor invading the vagus nerve or releasing ADH-like product. In the present study, imaging showed no evidence of invasion of the vagus nerve and we identified that the serum level of AVP was normal. We do not consider that its upregulation or secretion of ADH-like material occurred because the patient never experienced other electrolytic abnormalities and his serum sodium concentration was restored rapidly by water restriction therapy alone. There was no evidence of a relationship between progression of lung carcinoma and the onset of SIADH in this case.

Another possibility is that when the extension receptors of the left atrium detect hyperthoracic pressure and abnormal hemodynamics, they decrease the suppressor signal level and induce continuous release of ADH from the posterior lobe of the pituitary. But in the present case, bronchoscopic interventions were performed to target the local recurrence and restore his remaining left lobe. Syndrome of inappropriate secretion of antidiuretic hormone developed after 5 weeks of irradiation therapy following these interventional procedures. Even if there was a change in the respiratory circulation with release of the atelectasis, it is unlikely because of the time delay.

Enhancing release of AVP, potentiating the renal action of AVP and unknown mechanisms are reported as the main causes of SIADH by drugs [3]. Syndrome of inappropriate secretion of antidiuretic hormone associated with vinca

alkaloids, especially vincristine (VCR) and vinblastine (VBL), has been reported [6–8]. Garrett and Simpson first reported that SIADH occurred after a single treatment of VNB for breast cancer [9]. In addition, they reported that there was a slight structural difference between VNB and other vinca alkaloids, however, the precise mechanism is unclear and they may possess common neural or renal adverse effect profiles. In the present case, we firmly concluded that SIADH was induced by chemotherapy with VNB because concomitant medication was steroids only. In addition, SIADH occurred after four courses and not with earlier exposures of VNB. Although we think that repeated administration or retention of VNB may have been associated with SIADH, the precise mechanism of this SIADH was unclear.

In the report by Garrett and Simpson, SIADH from VNB did not respond to fluid restriction and patient had to be given 3% NS. But in our case, patient recovered with fluid restriction only. This difference with these two mechanisms was unclear. Furthermore, they also reported that prophylactic use of demeclocycline, which interacts with ADH at the renal collecting duct, might usefully prevent recurrence of SIADH associated with continuous treatment with VNB [9]. Stuart and Cuaso reported that SIADH was prevented by rigorous water restriction [10]. For our patients, we choose an alternative because of the high possibility of SIADH caused by VNB. If chemotherapy with VNB results in complete response or partial response, we would choose to readminister VNB with restriction of water, or use demeclocycline and monitor the sodium concentration.

We consider that VNB should be regarded as very likely to cause SIADH, but as this is only the second report of SIADH associated with use of VNB alone, it is a rare occurrence.

## Conclusion

It is known that lung cancer can give rise to SIADH as a paraneoplastic syndrome and there are some anticancer agents that can potentially cause SIADH. It is important to monitor the serum sodium level and clinical findings after chemotherapy for lung cancer.

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