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Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) following carboplatin-paclitaxel administration in a patient with lung cancer

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A 60-year-old female underwent right upper lobectomy of the lung and lymph node dissection under a diagnosis of cancer in the upper lobe of the right lung. Pathological examination showed stage IIIA adenocarcinoma with mediastinal lymph node metastasis. One month after the operation, adjuvant chemotherapy with carboplatin (CBDCA) and paclitaxel (PTX) was initiated. Four days after the chemotherapy, hyponatremia progressed, and central nervous system disorder developed. A diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was made. She recovered after fluid intake restriction and electrolyte correction. SIADH was considered to be due to the adverse effects of anticancer drugs. In postoperative adjuvant chemotherapy, attention should be paid to the serum Na level.

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is observed in about 10% of patients with small cell lung cancer but only in 0.7% of patients with non-small cell lung cancer (Sørensen et al. 1995). In addition, there have been no reports of SIADH associated with postoperative adjuvant chemotherapy for lung adenocarcinoma. We report a patient with drug-induced SIADH probably due to carboplatin (CBDCA), with a brief review of the literature.

In a 60-year-old female, an abnormal chest shadow was detected during follow-up after surgery for thyroid papillary carcinoma. She was a non-smoker, and her family history showed nothing of note. No recurrence of thyroid cancer was observed. Blood examination revealed normal electrolytes and normal renal and thyroid functions. Chest X-ray examination showed an abnormal shadow in the right middle lung field, and chest high-resolution CT identified a small nodule (15×8 mm) in S2 of the right lung. On the other hand, 18-fluorodeoxyglucose (FDG)-PET showed accumulation in the tumor but no accumulation in the hilar/mediastinal lymph nodes. Under a diagnosis of cancer of the right upper lobe of the lung, surgery was performed. The histopathological diagnosis was lung adenocarcinoma, and a micropapillary component was observed in 20%. The tumor (15×11 mm) was pT2aN2M0 stage IIIA, showing pleural invasion and lymph node metastasis. One month after the operation, adjuvant chemotherapy with CBDCA (AUC = 5) and paclitaxel (PTX) (175 mg/m^2) was initiated. After 4 days, the serum Na level decreased, and the intravenous administration of physiological saline was initiated. However, hyponatremia was aggravated, reaching the lowest value after 12 days. After 11 days, restlessness occurred. After 14 days, disorientation, ataxia of the four limbs, and dysphagia developed. Brain metastasis of lung cancer and cancerous meningitis were suspected, but cerebrospinal fluid examination and head MRI showed no abnormal findings. The low serum Na level (101 mEq/L), low blood osmolarity (216 mOsm/kg), hypertonic urine (309 mOsm/kg), and the persistence of natriuresis (urinary Na, 104 mEq/L) but a normal serum cortisol level and normal renal function fulfilled the diagnostic criteria of SIADH (Table). The plasma vasopressin (VAP) level after 18 days was normal (1.5 pg/mL), but based on the clinical course as well as the above findings, a diagnosis of drug-induced SIADH due to CBDCA or PTX was made. Fluid intake restriction (1,000–1,250 ml/day) and hypertonic saline administration were continued. The Na increment/day was adjusted to 8 mEq/L. The serum Na level gradually recovered, and the central nervous system disorder improved after 25 days (Fig.).

SIADH as a complication in lung cancer was first reported by Schwartz et al. in 1957. In SIADH, increased ectopic VAP secretion promotes water absorption in the distal and urinary tubules, and increases in extra- and intracellular fluid and urinary Na excretion, which result in hyponatremia and a decrease in plasma osmolarity. The diagnostic criteria for SIADH are: 1) hyponatremia (< 130 mEq/l), low blood osmolarity (< 275 mOsm/kg), 3) hypertonic urine (≥ 300 mOsm/kg), 4) persistence of natriuresis (≥ 20 mEq/L), 5) normal renal function, 6) normal adrenal gland function, 7) absence of findings of dehydration, and 8) absence of edema or ascites Schwartz et al 1957; Bartter and Schwartz 1967). This patient fulfilled all of the diagnostic criteria. The causes of SIADH include malignant tumors, respiratory diseases, central nervous system disorders, and drugs. In malignant tumors, excessive VAP secretion from tumor cells is the main factor, and SIADH associated with head and neck cancer and hematological tumors has often been reported (Ellison and Berl 2007). Concerning SIADH associated with lung cancer, SIADH has been reported in about 10% of patients with small cell carcinoma (Vanhees et al. 2000), but rarely in patients with non-small cell carcinoma (0.7%, Sørensen et al. 1995). In addition, only three patients with lung adenocarcinoma complicated by SIADH have been reported, and SIADH after postoperative adjuvant chemotherapy has not been reported. Various theories regarding the development of SIADH associated with malignant tumors and chemotherapy have been proposed, including the release of a large amount of a VAP-like hormone due to tumor lysis after chemotherapy (Sørensen et al. 1995; Levin et al. 1982) or an abnormal hypothalamic regulatory function due to afferent nerve disorder caused by tumor invasion to the vagal nerve. In this patient, the course after the operation for lung adenocarcinoma was favorable, the tumor markers were normalized, and electrolytes were stable. Therefore, the cause of SIADH is unlikely to have been tumor lysis syndrome or tumor invasion, and may have been the drugs.

Drug-induced SIADH is caused by the direct stimulation of VAP secretion or VAP activation by drugs (Ellison and Berl 2007; Reynolds and Seckl 1992). As drugs inducing SIADH, vincristine (Escuro et al. 1992), cyclophosphamide (Resnik and Bender 1992), and vinorebine (Kuroda et al. 2008) are known, and cisplatin (CDDP, Otsuka et al. 1996) and CBDCA (Yokoyama et al. 2005) as platinum anticancer drugs have also been reported. Kagawa et al. (2001) suggested that VAP activation rather than the direct stimulation of VAP secretion is the

Table: Laboratory data on manifestation of hyponatremia

Serum Chemistry		
BUN	5	mg/dL
Creatinine	0.36	mg/dL
Na	101	mEq/L
K	2.4	mEq/L
Cl	68	mEq/L
Osmolality		
Serum	261	mOsm/L
Urine	309	mOsm/L
Urine		
Na	104	mEq/L
Endocrine		
Vasopressin	1.5	pg/mL
Cortisol	13.8	μg/dL
Renin	< 0.1	ng/mL/hr
fT4	1.5 ng/dL	ng/dL

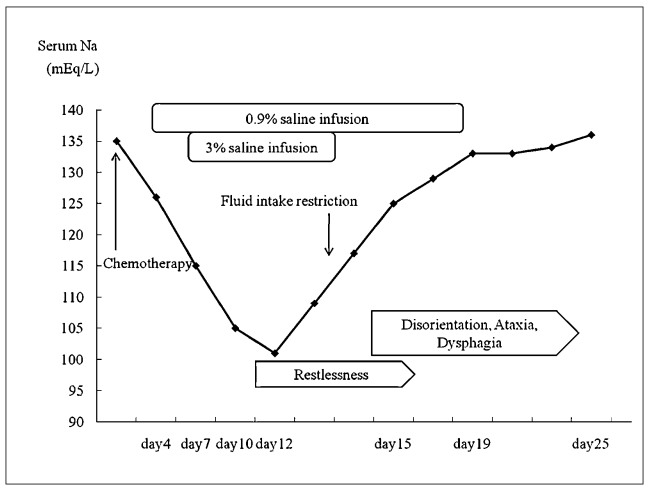

Fig.: Clinical course of serum sodium concentration after administration of carboplatin and paclitaxel. After 4 days, the serum Na level decreased, and the intravenous administration of physiological saline and hypertonic saline was initiated. Hyponatremia was aggravated, reaching the lowest value after 12 days. After 13 days, fluid intake restriction was initated, the serum Na level was restored to 133 mEq/L 7days later.

cause because the VAP level was normal after CDDP chemotherapy. Krutzberg et al. (1984) reported that nephropathy is the cause of SIADH after CDDP administration. Indeed, CDDP inhibits electrolyte transporters in the thick ascending limb of the loop of Henle, which results in persistent urinary Na excretion. When CDDP is used, fluid administration is generally performed to avoid nephropathy, which may aggravate SIADH. Otsuka et al. (1996) reported that CBDCA, which does not require fluid administration, is unlikely to induce SIADH. In this patient, the VAP level was normal, and no fluid was administered. Therefore, the cause of SIADH may have been the activation of VAP by CBDCA or nephropathy due to CBDCA. However, the possibility that PTX was the cause of SIADH cannot be completely excluded. However, there have been no reports suggesting PTX as a cause of SIADH.

Postoperative adjuvant chemotherapy for lung cancer is widely used in daily practice. CDDP tends to induce nephropathy and always requires fluid administration and diuresis, while CBDCA can be readily used in clinical practice due to its relatively mild adverse effects. However, in some patients such as the present case, even CBDCA induce SIADH, and so the use of CBDCA also requires careful attention.

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