Syndrome of inappropriate secretion of anti-diuretic hormone following carboplatin-paclitaxel administration in a patient with recurrent ovarian cancer

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Summary

This is the first report on a syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) in a patient with recurrent ovarian cancer following carboplatin and paclitaxel administration. A 63-year-old woman received chemotherapy combining carboplatin and paclitaxel for recurrent ovarian serous papillary adenocarcinoma. Four days after the chemotherapy, she suffered decreased mental awareness and lost consciousness. Blood chemistry tests showed serum sodium of 109 mmol/l. Plasma osmolarity was reduced to 232 mOsm/kg while urine osmolarity was high at 430 mOsm/kg, strongly suggesting the presence of SIADH. Because hyponatremia was not observed in the subsequent cycle of chemotherapy consisting of weekly paclitaxel and cisplatin, carboplatin was thought to be responsible for the condition. Clinicians should be aware of the possibility that carboplatin may cause SIADH, and should carefully monitor electrolyte balance after chemotherapy.

Key words: SIADH; Carboplatin; Paclitaxel; Ovarian cancer.

Introduction

The syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) is a disorder related to impaired water excretion resulting in dilutional hyponatremia and giving rise to central nervous system symptoms. It is characterized by reduction in plasma osmolarity with inappropriately concentrated urine. The causes of SIADH include central nervous system disorders, pulmonary and endocrine diseases, malignancies and some drugs [1]. Anticancer agents such as vincristine, cyclophosphamide and cisplatin (CDDP) are well documented to induce SIADH by direct or indirect stimulation of vasopressin release from the posterior pituitary gland [2-6], although the mechanism remains unclear. We report here a patient with recurrent ovarian cancer complicated by SIADH following intravenous carboplatin and paclitaxel administration. This is, to our knowledge, the first report describing SIADH onset following carboplatin and paclitaxel administration for ovarian cancer.

Material and Methods

A 64-year-old woman received chemotherapy combining CDDP, epirubicin and cyclophosphamide as adjuvant chemotherapy under a diagnosis of IIc stage ovarian serous papillary adenocarcinoma following staging laparotomy and obtained complete remission in 1996. Although she had been healthy and well for approximately eight years, she was admitted to our hospital on May 17, 2004 for cancer chemotherapy administration suffering from recurrence of the disease. Her previous medical history was unremarkable. She was scheduled to receive chemotherapy consisting of AUC 5 of carboplatin and 175 mg/m^2 of paclitaxel in a salvage chemotherapy. On May 27, 2004, carboplatin and paclitaxel treatment was conducted after pretreatment of H_2 receptor antagonist, histamine H_1 receptor antagonist and dexamethasone. Four days after the chemotherapy, she became dizzy, suffered decreased mental awareness and lost consciousness. She also felt physically drained but had no neurological paralysis. Blood pressure was 143-93 mmHg and heart rate was 60 beats per minute. The presence of brain metastasis, intracranial hemorrhage and subarachnoid hemorrhage was excluded on the basis of a computed tomography scan. Blood chemistry tests demonstrated that her serum sodium was 109 mmol/l (her pretreatment sodium level was 139 mmol/l), her serum potassium was 4.4 mmol/l, and her serum chloride was 75 mmol/l. Plasma osmolarity was reduced to 232 mOsm/kg while urine osmolarity was inappropriately high at 430 mOsm/kg, with a urine sodium of 99 mmol/l. Serum concentration of blood urea nitrogen, creatinine, cortisol, free-T3 and free-T4 was normal at 17 mg/dl, 0.6 mg/dl, 18.7 μg/dl, 2.40 pg/ml and 1.42 ng/dl, respectively, and plasma arginine vasopressin (AVP) concentration was high at 0.85 pg/ml compared with plasma hypoosmolarity, suggesting a diagnosis of SIADH. She did not have diarrhea or vomiting, did not experience overhydration and was not dehydrated since her skin was moist. Her fluid intake was restricted to less than 20 ml/kg/day and sodium chloride was replaced. The serum sodium was returned to 137 mmol/l and she was gradually restored to health over the next seven days. In the subsequent cycle of combination chemotherapy consisting of weekly paclitaxel administration and low-dose consecutive CDDP, hyponatremia was not observed, strongly suggesting that the SIADH might be directly caused by carboplatin administration.

Discussion

SIADH is a disease caused by hyponatremia due to water retention because of the persistent production of AVP despite a plasma hypoosmotic state and hypervolemic circulation [4]. The diagnosis of SIADH requires the exclusion of hyponatremic states caused by salt-depletion dehydration and adrenal and renal insufficiency

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[7]. The present hyponatremic state was diagnosed as SIADH, based on reduced osmolarity of her serum (232 mOsm/kg), increased osmolarity of her urine (430 mOsm/kg), normal adrenal and renal function, and increased excretion of urine sodium. AVP concentration of 0.85 pg/ml was considered inappropriately high for the present plasma hypoosmotic state.

There have been several reports describing the onset of SIADH following CDDP administration as well as vincristine and cyclophosphamide administration [2-6]. The potential mechanisms induced by CDDP administration have been suggested among those reports. Kagawa *et al.* suggested potentiation of the peripheral action of ADH with CDDP since AVP concentration in their patient with SIADH following CDDP administration remained within normal limits [5]. Ritch described that the occurrence of hyponatremia and inappropriately concentrated urine following CDDP administration might be caused by a central effect of CDDP on ADH secretion as well as a direct effect on renal tubular function [3] because CDDP has an adverse effect of inhibiting the solute transport by the thick ascending limb of Henle's loop [8]. It is also likely that SIADH is caused by overhydration that is mandatory for preventing renal toxicity during CDDP administration. In the present case, AVP concentration was within normal limits and vigorous hydration was not necessary because of the use of carboplatin; thus, it was most likely that the SIADH was caused by peripheral potentiation of ADH action with carboplatin or a direct effect of carboplatin or a direct effect of carboplatin on ADH secretion. Resnik and Bender reported SIADH following carboplatin and cyclophosphamide administration in peritoneal adenocarcinoma, but the mechanism of how either carboplatin or cyclophosphamide caused SIADH was not discussed [10]. Although Langer-Nitsche *et al.* reported that treatment with docetaxel, a taxane-type anticancer agent, led to the development of SIADH in metastatic breast cancer [9], involvement of paclitaxel is less possible in this case because weekly paclitaxel administration did not induce SIADH in the next cycle of the chemotherapy.

SIADH characterized by water retention and hyponatremia manifests central nervous system symptoms including nausea, vomiting, headache, weakness, lethargy, confusion, convulsion and coma. Severity of the symptoms is usually determined by the speed of onset and extent of the fluid and electrolyte disturbance. Some patients have developed convulsions or coma associated with hyponatremia following CDDP administration [2, 3, 5]. Most of the cases occurred within two days of the initiation of chemotherapy. Because our patient gradually showed the symptoms of SIADH four days after the chemotherapy, she might have been spared serious, life-threatening states such as convulsion and coma.

Chemotherapy combining carboplatin and paclitaxel has been established as the first-line treatment for ovarian cancer by a large-scale randomized clinical trial [11]. Although there have been many reported adverse effects caused by carboplatin and paclitaxel treatment, to our knowledge, SIADH is a previously unreported complication of carboplatin and paclitaxel administration. An outpatient treatment system is now becoming the mainstream for ovarian cancer chemotherapy. Hyponatremia should be considered if seizures occur or if mental status changes in patients undergoing chemotherapy. Although SIADH following carboplatin or paclitaxel administration is extremely rare, clinicians should be aware of the possibility that carboplatin or paclitaxel may cause SIADH, and should carefully monitor electrolyte balance after the chemotherapy.

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