# Cisplatin-induced syndrome of inappropriate antidiuretic hormone (SIADH) in a patient with neuroendocrine tumor of the cervix: a case report and review of the literature

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**Summary**

We present a case of the syndrome of inappropriate antidiuretic hormone (SIADH) secondary to cisplatin therapy in a patient with advanced-stage large cell neuroendocrine carcinoma of the cervix. This occurred after the first cycle of cisplatin and then again after the second cycle. Carboplatin was substituted for cisplatin, and there were no further episodes of SIADH.

*Key words:* Cisplatin; SIADH; Cervix; Syndrome of inappropriate antidiuretic hormone; Neuroendocrine tumor.

## Introducton

Cisplatin is the most commonly used agent in patients diagnosed with cervical carcinoma requiring systemic therapy. Cisplatin is associated with known toxicities, primarily neuropathy and nephropathy. The nephropathy associated with cisplatin usually results in acute elevations in serum blood urea nitrogen (BUN) and creatinine as well as loss of potassium and magnesium. Severe hyponatremia secondary to cisplatin is rare. The syndrome of inappropriate antidiuretic hormone (SIADH) leads to severe hyponatremia and water intoxication with central nervous system changes and has been reported in assocation with cisplatin use [1-4]. We present a case of cisplatin-induced SIADH.

## Case Report

A 40-year-old G2P2002 woman with no significant past medical history presented to the emergency room with complaints of vaginal bleeding and was found to have a large, 10 cm necrotic cervical mass on pelvic examination. The cervical mass extended to the upper half of the vagina, bilateral fornices and parametria. Cervical biopsies showed poorly differentiated carcinoma with squamous features and extensive necrosis. Immunostains chromogranin and synptophysin were consistent with large cell neuroendocrine carcinoma. Computed tomography (CT) scans of the chest, abdomen, and pelvis revealed liver lesions and pelvic and aortic adenopathy. The treatment plan for the International Federation of Gynecology and Obstetrics (FIGO) Stage IVB large cell neuroendocrine carcinoma of the cervix consisted of six cycles of cisplatin/etopside, each cycle administered over three days.

The patient underwent her first cycle of cisplatin/etoposide without incident. Three days after chemotherapy, she presented to the emergency room (ER) with complaints of lethargy, nausea, vomiting, and dizziness. Her physical examination was unremarkable, with no neurological deficits. Laboratory values revealed a severely decreased sodium level compared to her prechemotherapy level. A head CT revealed no significant abnormalities, and random cortisol level was within normal limits. She was admitted and treated with fluid restriction to slowly correct her sodium level, and was discharged home with a sodium level of 127 meq/l and serum osmolarity of 260 mOsm/kg. Outpatient laboratory values later revealed a sodium level of 140 meq/l. The patient underwent a second course of cisplatin/etoposide and again presented to the ER with weakness, dizziness, and lethargy. Laboratory values revealed a serum sodium level of 117 meq/l. She was again admitted to the hospital for five days for correction of hyponatremia and was discharged home with a serum sodium level of 133 meq/l and no additional electrolyte derangements. The chemotherapy regimen was subsequently changed from cisplatin/etoposide to carboplatin/etoposide. The patient was given carboplatin/etoposide for the remainder of her treatments and had no additional adverse reactions requiring hospitalization.

## Discussion

Antidiuretic hormone (ADH) is synthesized in the posterior pituitary and primarily exerts its effects on the collecting tubule of the nephron. It is controlled by a complex system including receptors in the kidney, hypothalamus, pulmonary vein, and left atrium. Excessive secretion of ADH results in impaired water excretion, which can result in water intoxication and hyponatremia. Severe hyponatremia can lead to central nervous system alternations, including confusion, fatigue, seizures, coma, and even death.

The exact mechanism by which cisplatin causes the syndrome of inappropriate antidiuretic hormone (SIADH) is unknown; however, there are known renal and neurotoxin effects of cisplatin. Cisplatin is associated with both proximal and distal tubule damage due to activation of cisplatin in the renal tubules. Impaired sodium reabsorption in the proximal tubule leads to increased fluid in the

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descending loop of Henle. Reabsorption of fluid in the distal nephron is insufficient to overcome the fluid overload, and sodium and water excretion increases. Increased sodium in the distal tubule causes a reduction in renal blood flow and glomerular filtration rate (GFR) due to increased vascular resistance. The decrease in GFR further decreases sodium and water resorption. Neurotoxicity due to cisplatin may be due to cisplatin-induced damage to Schwann cells, which comprise the myelin sheath surrounding nerves. DNA damage and segmental cell loss is a possible explanation of demyelination seen in cisplatin-induced neuropathies.

SIADH as a result of chemotherapeutic agents has been previously reported in the literature, usually in association with vincristine/vinblastin and other alkylating agents. Cases of cisplatin-induced SIADH have been reported in the literature as early as the 1980s. In 1982, Levin reported a case of SIADH in a patient with a malignant thymoma following cis-dichlorodiammineplatinum (CDDP) administration [1]. Porter reported a case of SIADH following cisplatin therapy for ovarian cancer in 1985 [2]. Numerous cases have been reported in Japan, including a case of SIADH associated with intrathoracic cisplatin infusion in a patient with a malignant thymoma reported in 1996 [3].

Another potential cause of hyponatremia following chemotherapy administration is Renal Salt Wasting Syndrome (RSWS). Cao *et al*. reported a case of cisplatin-induced hyponatremia in a patient with squamous cell carcinoma of the esophagus [4]. The patient was subsequently diagnosed with RSWS, which is characterized by hyponatremia, excessive sodium excretion, and abnormal renal function. To distinguish between SIADH and RSWS, the urinary excretion of sodium should be checked as the urinary excretion in RSWS is excessive and the urinary excretion in SIADH is normal or decreased. This is an important distinction as the treatment of RSWS is different from that of SIADH. The treatment of RSWS is sodium supplementation.

We believe the cisplatin was the cause of this patient's SIADH as she had no adverse reactions to the carboplatin regimen. Recognizing SIADH as a cause of post-chemotherapy hyponatremia could expedite proper treatment and prevent life-threatening seizures, coma, and death. RSWS should also be considered as a differential diagnosis of post-chemotherapy hyponatremia.

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