

Syndrome of Inappropriate ADH Secretion (SIADH) During Chemotherapy with Carboplatin/Paclitaxel for Metastatic Fallopian Tube Cancer

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Introduction

The syndrome of inappropriate ADH secretion (SIADH) is attributed to excessive ADH release. It is defined as less than maximally dilute urine in the presence of plasma hyposmolality (hyponatremia), without volume depletion or overload, emotional stress, pain, diuretics or other drugs that stimulate ADH secretion. The exclusion of abnormalities in cardiac, hepatic, renal, adrenal and thyroid functions is also essential before SIADH can be diagnosed.

Since its initial description 1957 by Schwartz et al., SIADH has been related to a wide range of causes, such as pulmonary, central nervous system (CNS) and endocrine disorders, cytotoxic agents, malnutrition, fluid overload, various drugs and surgical interventions. Malignancies associated with clinically relevant SIADH are CNS, gastrointestinal tract, bladder, endometrial, adrenal cortex, breast cancer, thymoma, lymphoma, and most frequently small cell lung cancer [1].

The association of SIADH with gynecological cancer is rare and has been described in four cases of ovarian cancer since 1985 [2-5]. In two of them SIADH occurred in timely relation to chemotherapy: the first one (1985) [2] described a case of SIADH associated with cisplatin first line chemotherapy for endometrioid ovarian cancer. Yokohama et al. [3] described 2005 a similar case of SIADH during carboplatin-based therapy for recurrent serous-papillary ovarian cancer. The other two cases described SIADH as prodromal clinical manifestation of ovarian cancer either at primary diagnosis [4] or at the time of recurrence [6]. We describe the first case of a patient with high grade epithelial fallopian tube cancer and pulmonary metastases experiencing SIADH postoperatively during first line chemotherapy with carboplatin and paclitaxel.

Case Report

A 79 year old female patient presented with acute dyspnea, as well as abdominal bloating and malnutrition since two weeks. She had no medical history except from permanent atrial fibrillation. Transvaginal ultrasound (TVUS) revealed a 46 mm adnexal mass on the left side, with malignant sonographic features and ascites in the Douglas pouch. Due to the dyspnea, ultrasound of the thorax was performed and detected a unilateral right sided pleural effusion. Thoracocentesis revealed high grade serous carcinoma cells, most likely of ovarian origin. CT- and PET-CT Scan showed bilateral pulmonary metastasis (i.e., 12 mm diameter in the right medial lobe, 18 mm in the left inferior lobe, 6 mm in the left superior lobe), a suspect precordial lymph node of 12 mm, suspect paraaortic and pelvic lymph nodes up to 15 mm in maximum diameter, and signs of peritoneal

carcinomatosis. Colonoscopy and mammography were normal. Radiological diagnosis including second review interpreted that the pulmonary metastases were highly unlikely to be caused by primary lung cancer.

Further work-up included a diagnostic laparoscopy. The situs intraabdominally showed a tumor mass of almost 5 cm diameter emerging from the left fallopian tube and a diffuse peritoneal carcinomatosis. A salpingectomy was performed and several peritoneal biopsies were taken. Pathology revealed a high grade serous fallopian tube cancer with serous tubal in situ carcinoma (STIC). Further immunohistochemical analyses demonstrated no neuroendocrine differentiation of the primary tumor. All other lesions contained the same tumor and the final diagnosis of epithelial fallopian tube cancer stage FIGO IVB was defined. Due to irresectability of bilateral pulmonary metastases in combination with mediastinal and retroperitoneal lymph node metastasis and a diffuse visceral and parietal carcinomatosis we started chemotherapy with carboplatin AUC5 and paclitaxel 175 mg/m².

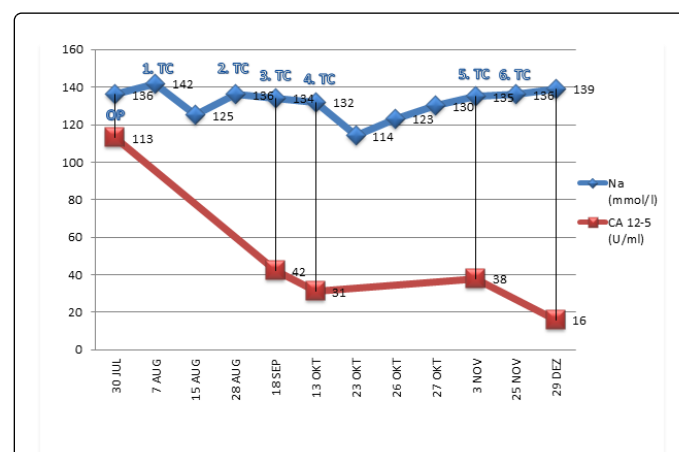
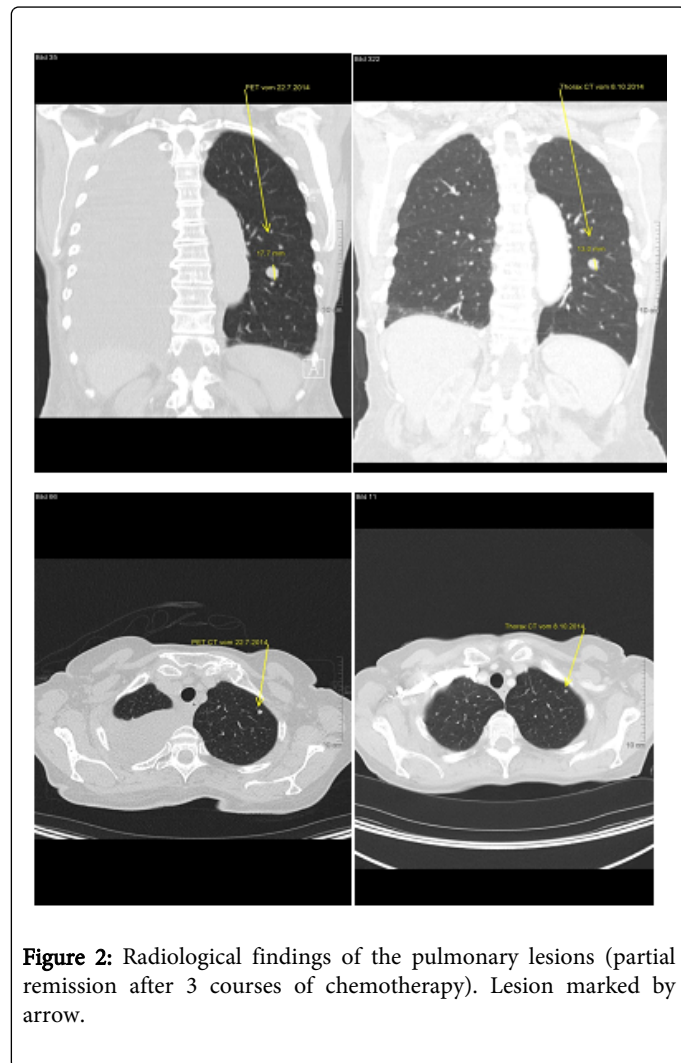


Figure 1: Longitudinal characteristics of CA-125 (U/mL) and Sodium (mmol/L) beginning at the time of surgery until the 6th cycle of Carboplatin/Paclitaxel (TC). TC=Carboplatin AUC 5 and Paclitaxel 175 mg/m².

Eight days after the 2nd course of chemotherapy the patient was readmitted with generalized fatigue. Blood tests demonstrated a hyponatremia of 125 mmol/L, which was substituted with isotonic saline infusions. Within 3 days, sodium was within the normal range

and the patient was discharged with oral sodium substitution as well as a recommendation for continuous blood testing for the next days. Chemotherapy was continued with weekly blood testing. After re-staging and radiological partial remission nach RECIST 1.1., as well as serological complete remission, we continued with the chemotherapy as planned (Figures 1 and 2).



Eleven days after the 4th course the patient was readmitted because of dizziness, fatigue and loss of mental awareness. At the time of admission the patient presented with sodium levels of 114 mmol/L, potassium levels were normal. Urine tests supported the clinical diagnosis of SIADH (low serum osmolality with high urine osmolality). Additional serological analyses revealed normal ADH copeptin levels. Within five days of slow sodium substitution aiming at maximal increase of sodium value 5 units/d to avoid osmotic demyelination syndrome the patient showed normal sodium levels. One day after administration of the 5th course, we started oral treatment with Tolvaptan – a selective competitive antagonist of the arginine-vasopressin-receptor subsequently leading to increased diuresis without the loss of sodium. Since the initiation of this medical treatment the patient's sodium level and her clinical status have remained stable. Clinical course of sodium levels and CA 125 levels are depicted above (Figure 1). After completion of chemotherapy, there have been no further SIADH episodes attended, CA 12-5 remained

until current follow up negative, radiological signs of further regression in the abdomen CT by non-measurable disease have been observed 3 months after last course of chemotherapy.

Discussion

We report here the very rare coincidence of a metastatic fallopian tumor cancer associated with SIADH. SIADH occurred while this patient received a standard chemotherapy regimen of carboplatin-paclitaxel. Thorough work up could rule out other reasons for SIADH than tumor and/or chemotherapy. The association of SIADH with fallopian tube tumor has not been described before and the association with ovarian cancer has only been reported in 4 cases. Given the low frequency of SIADH in gynecologic oncology underlines the importance to raise awareness of this serious but manageable paraneoplastic or therapy associated diagnosis.

We could neither confirm nor rule out that SIADH was associated rather with chemotherapy than with the underlying tumor. The timely association with chemotherapy suggests that Carboplatin or paclitaxel may be responsible and not the tumor itself. Our assumption is that SIADH in our patient probably had been caused by carboplatin. According to the literature, carboplatin is associated with a higher risk for SIADH than paclitaxel, which has not been described to be associated with SIADH so far [3]. In the literature, two ovarian cancer cases with chemotherapy induced SIADH had been described, as briefly mentioned above [2,3]. The first case, published in 1985, described a cisplatin- induced lethal SIADH causing hyponatremia 2 days after the 3rd course of chemotherapy. This patient had been treated with a premedication scheme including 2 liters of fluid volume before chemotherapy, which might have caused a fluid overload worsening the SIADH associated hyponatremia [2]. The second patient presented with SIADH induced by carboplatin during chemotherapy with carboplatin/paclitaxel for recurrent serous papillary ovarian cancer of unspecified differentiation. SIADH occurred 4 days after the 1st course of treatment [3]. The patient was subsequently switched to cisplatin/paclitaxel, under which no further relevant events had been observed.

The other two cases mentioned above described SIADH of most likely paraneoplastic origin. Interestingly, both patients – as our patient – presented with pulmonary metastases. Taskin et al (1995) described the first case of a paraneoplastic SIADH syndrome in epithelial ovarian cancer (EOC), with SIADH related symptoms being in fact its initial clinical presentation in a patient with primary high grade serous ovarian cancer. Additional analyses in this patient revealed elevated ADH serum levels as well as a focal positive ADH antibody staining ascertained by immunohistochemistry [4]. However, ADH serum levels in our patient remained within the normal limits. Normal ADH serum levels sometimes imply a hypothalamic origin of paraneoplastic ADH secretion [5], or a direct ADH- synthesis and release from neoplastic cells [7,8]. Therefore, we performed additional immunohistochemistry which did not reveal neuroendocrine differentiation in our patient's tumor, as immunohistochemical testing of NSE, Chromogranin, ADH, ANP was negative. The other published case report described symptomatic hyponatremia and SIADH as part of recurrence of a well differentiated serous papillary carcinoma of the ovary 6 months after optimal primary debulking surgery and 1st line chemotherapy. Recurrent disease presented by extraabdominal disease with diffuse pulmonary metastasis by initially solitary lesion [6,9,10]. The treatment consisted of hypertonic saline, demeclocycline, as well as 2nd line chemotherapy.

SIADH in our patient could have been caused by both, either chemotherapy induced by carboplatin or paraneoplastic syndrom due to the pulmonary metastases. In patients with ovarian cancer the rare case of severe hyponatremia caused by SIADH has to be kept in mind as a differential diagnosis when patients present with dizziness, fatigue and loss of mental awareness, even if cranial metastases or stroke seem to be more likely. Chemotherapy with carboplatin and pulmonary metastases seem to be risk factors for SIADH in fallopian tube and ovarian cancer patients.

References

1. De Troyer A, Demanet JC (1976) Clinical, biological and pathogenic features of the syndrome of inappropriate secretion of antidiuretic hormone. A review of 26 cases with marked hyponatraemia. *Q J Med* 45: 521-531.
2. Porter AT (1985) Syndrome of inappropriate antidiuretic hormone secretion during cis dichlorodiammineplatinum therapy in a patient with an ovarian carcinoma. *Gynecologic Oncology* 21: 103-5.5
3. Yokoyama Y, Futagami M, Mizunuma H (2005) Syndrome of inappropriate secretion of anti-diuretic hormone following carboplatin-paclitaxel administration in a patient with recurrent ovarian cancer. *Eur J Gynaecol Oncol* 26: 531-532.
4. Taskin M, Barker B, Calanog A, Jormark S (1996) Syndrome of inappropriate antidiuresis in ovarian serous carcinoma with neuroendocrine differentiation. *Gynecol Oncol* 62: 400-404.
5. Zerbe R, Stropes L, Robertson G (1980) Vasopressin function in the syndrome of inappropriate antidiuresis. *Annu Rev Med* 31: 315-327.
6. Murphy MC, Markham MJ2 (2015) Rare case of syndrome of inappropriate antidiuretic hormone as the initial presentation of ovarian cancer recurrence. *J Clin Oncol* 33: e48-49.
7. Yamaji T, Ishibashi M, Katayama S (1981) Nature of the immunoreactive neurophysins in ectopic vasopressin-producing oat cell carcinomas of the lung. Demonstration of a putative common precursor to vasopressin and neurophysin. *J Clin Invest* 68: 388-398.
8. Kavanagh BD, Halperin EC, Rosenbaum LC, Shannon EM, Nilaver G (1992) Syndrome of inappropriate secretion of antidiuretic hormone in a patient with carcinoma of the nasopharynx. *Cancer* 69: 1315-1319.
9. Roman H, Verspyck E, Sentilhes L, Barau G (2004) Immature ovarian teratoma with hyponatremia and low antidiuretic hormone level. *Obstet Gynecol* 103: 1108-1110.
10. Lam CM, Yu VS (2004) SIADH associated with ovarian immature teratoma: a case report. *Eur J Gynaecol Oncol* 25: 107-108.