Gynecologic Oncology Reports 58 (2025) 101704

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Small cell carcinoma of the cervix with syndrome of inappropriate antidiuretic hormone secretion following chemotherapy: A case report and literature review

Isabelle Lauzon [a], Lara deGuerké [b], Suzanne Fortin [b], Marie-Hélène Auclair [b], Sabrina Piedimonte [b,*]

[a] Department of Medicine, University of Montreal, Montreal H3T 1J4, Canada
[b] Division of Gynecologic Oncology, Maisonneuve-Rosemont Hospital, CIUSSSEMTL, Montreal H1T 2M4, Canada

ARTICLE INFO

Keywords:
Cervical cancer
SIADH
Hyponatremia

ABSTRACT

Objective: This report aims to present a rare case of severe hyponatremia induced by syndrome of inappropriate antidiuretic hormone secretion (SIADH) following chemotherapy in a patient with small cell carcinoma of the cervix (SCCC). It also reviews the existing literature on this rare phenomenon.
Case: A 45-year-old female with SCCC developed acute symptomatic hyponatremia (sodium level 110 mmol/L) three days following cisplatin-based chemotherapy. SIADH was diagnosed, and the patient required intubation and admission to the intensive care unit due to severe agitation and confusion. Despite initial correction of sodium levels, the patient developed recurrent hyponatremia after subsequent chemotherapy cycles that was refractive to first line agents. She required the use of Tolvaptan, a vasopressin type 2 receptor antagonist, for the management of hyponatremia.
Conclusions: This case highlights the rare occurrence of severe SIADH in a patient with SCCC, underscoring the complexity of managing electrolyte disturbances in the context of both paraneoplastic syndromes and chemotherapeutic side effect. The severity of our patient's presentation calls attention to the importance of early recognition of SIADH in the differential diagnosis of oncology patients with altered mental status and confusion. Post chemotherapy sodium surveillance could lead to improved patient outcomes, as well as monitoring for signs and symptoms of hyponatremia.

1. Introduction

Small cell carcinoma of the cervix (SCCC), also termed small cell neuroendocrine carcinoma of the cervix, is a rare and aggressive histologic subtype of cervical cancer, representing 2 % of all cervical malignancies (Crowder and Tuller, 2007). It is considered an extrapulmonary variant of small cell lung carcinoma (SCLC). The clinical presentation consists of vaginal bleeding, pelvic pain, pressure or symptoms of metastatic disease. As with small cell carcinoma of the lung, SCCC has a higher incidence of nodal metastases and tends to have early hematogenous dissemination compared to the more common cervical squamous cell cancer or adenocarcinoma. It is also associated with a worse prognosis than other common histologic subtypes, such as squamous cell and adenocarcinomas (Chen et al., 2008).

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a rare paraneoplastic syndrome that is classically associated with SCLC. There have been only a few reports of SIADH in patients with SCCC (Sørensen et al., 1995). Severe, chronic and refractory SIADH associated with chemotherapy and tumor breakdown in patients with SCCC is a rare condition.

We hereby present the case of a 45-year-old female with SCCC diagnosed, with severe acute hyponatremia from SIADH, three days following the first cycle of cisplatinum and etoposide doublet chemotherapy, requiring intubation and admission to the intensive care unit. We also performed a literature review and report all similar cases described.

* Corresponding author at: Division of Gynecologic Oncology, Maisonneuve-Rosemont Hospital, CIUSSSEMTL, Montreal H1T 2M4, Canada.
E-mail addresses: isabelle.lauzon.3@umontreal.ca (I. Lauzon), sabrina.piedimonte@gmail.com (S. Piedimonte).

https://doi.org/10.1016/j.gore.2025.101704
Received 28 December 2024; Received in revised form 14 February 2025; Accepted 15 February 2025
Available online 17 February 2025

2. Case

2.1. Background

The patient's past medical history consisted of an uncomplicated cesarean section and cholecystectomy. There was no prior pap test history. She presented to the emergency room in September 2023 with intermenstrual bleeding and foul-smelling vaginal discharge. A palpable mass on the cervix, extending to the posterior lower-third vaginal wall was biopsied and the pathology report showed small cell carcinoma, oat cell subtype. Further imaging revealed a 6.2 × 7.2 cm mass centered to the cervix with a posterior extension of the parametria, anterior and posterior vaginal fornix, recto-vaginal septum, bilateral pelvic iliac lymphadenopathy and a IIIC2 radiological stage was determined (see Fig. 1: MRI). Upon multidisciplinary tumor board consensus, Neo-adjuvant Cisplatinum and Etoposide chemotherapy was administered but to small cell histology.

2.2. Case presentation

Three days later, she was brought to the emergency room by a family member, for acute decreased mental awareness, severe agitation and confusion. Preliminary work up revealed a sodium level of 110 mmol/L, compared to 139 mmol/L prior to starting chemotherapy (normal range 135–145 mmol/L). Other blood tests showed the following results: hemoglobin 124 g/L, white blood cell 9.6 G/L, platelet 292G/L, potassium 4.6 mmol/L, calcium 2.05 mmol/L, magnesium 0.69 mmol/L, phosphorus 0.84 mmol/L. Renal, liver and thyroid function tests were all normal as well as the coagulation profile. CRP was < 0.5 mg/L. The initial differential diagnosis for this patient's acute hyponatremia included SIADH from cisplatin as well as paraneoplastic SIADH. Renal salt wasting from cisplatin was deemed less probable considering the patient did not present signs of hypovolemia.

2.3. Management and treatment plan

Rapid correction with 3 % NaCl was initiated by the emergency service and continued as per consultation with the nephrology team. The critical care team was consulted, and a decision was made to intubate and admit to the intensive care unit (ICU) due to the risk of cerebral edema. A head computed tomography scan was performed and was grossly normal. Further investigations showed an elevated urine sodium level of 241 mEq/L with an elevated urine osmolality of 645 mOsm/kg, thus SIADH was diagnosed. Excessive water consumption due to nausea post chemotherapy was initially suspected as a contributive cause of hyponatremia, but was deemed less probable in light of the elevated urine electrolyte levels. She was given intravenous hypertonic saline and was extubated two days later without any signs of neurologic deficits. She was discharged from the ICU and remained hospitalized for one week. Her sodium level proved to be difficult to correct despite oral NaCl administration, loop diuretics and a daily water restriction of 1L.

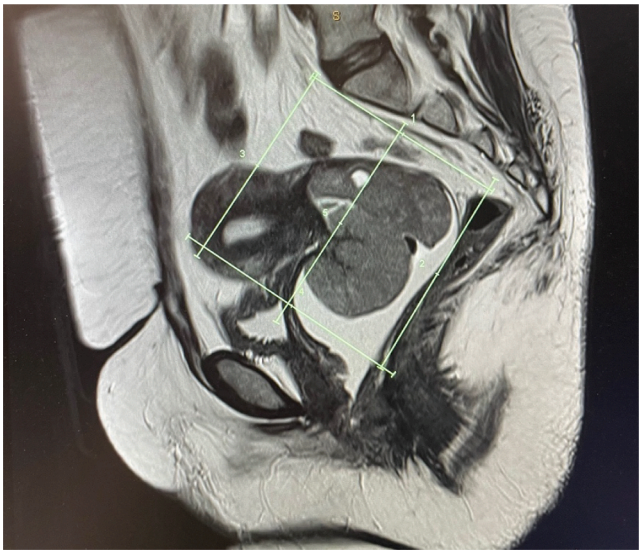

Fig. 1. Magnetic resonance imaging of the invasive cervical carcinoma.

2.4. Outcome and follow-up

Once her sodium level stabilized to 133 mmol/L, she was discharged home with oral NaCl supplementation. Furthermore, a switch of chemotherapy agent to carboplatin was arranged for the next chemotherapy cycle. However, two days following Etoposide-Carboplatin chemotherapy, close surveillance of her electrolytes revealed hyponatremia with an asymptomatic blood sodium level of 125 mmol/L (138 mmol/L pre chemo). She was readmitted to the nephrology service and investigations showed the following results: a urine sodium level of 67 mEq/L and a urine osmolality of 600 mOsm/kg. A recurrence of SIADH was suspected. Considering she showed no response to Carboplatin chemotherapy, a decision was made to give Cisplatinum chemotherapy for the next cycles. Tolvaptan, a selective vasopressin type 2 receptor antagonist was given concurrently to prevent further recurrence of SIADH. Nonetheless, following her fifth cycle, despite tolvaptan treatment, she required readmission due to her sodium levels of 122 mmol/L.

2.5. Long-term outcome

The patient completed pelvic radiotherapy and brachytherapy in March 2024. She remained disease free for 7 months. In October 2024, she had a distant recurrence diagnosed on PET scan with adrenal, pulmonary and retroperitoneal lymph node metastasis. Upon multidisciplinary tumor board consensus, the patient was started on carboplatin etoposide durvalumab and prophylactic tolvaptan and admission for observation. However, her sodium level remained normal (138–142 mmol/L), she weaned off tolvaptan and had no recurrence of neurologic symptoms. She did not require tolvaptan in subsequent cycles.

3. Methods

A literature review was conducted using multiple databases including Medline, Embase, and Google Scholar. The search strategy focused on terms related to Cisplatin, small cell carcinoma, SIADH, and hyponatremia. The Medline and Embase searches combined keywords and mesh terms for Cisplatin, small cell carcinoma, inappropriate ADH secretion, and hyponatremia, with limits applied to human studies. Additional resources such as PubMed were also consulted to ensure a thorough review of the relevant literature.

4. Discussion

Hyponatremia caused by SIADH from a paraneoplastic process, results from ectopic production of ADH by the tumor leading to intravascular water retention. It is associated with certain malignancies, the most common being SCLC (List et al., 1986). SIADH can be diagnosed based on certain clinical criteria which are summarized in Table 1. Treatment recommendations vary depending on the severity of hyponatremia. It is estimated that 11 % of patients with SCLC have SIADH and hyponatremia is associated with poor prognosis (List et al., 1986; Hansen et al., 2010). In contrast, only a small number of cases of SIADH have been reported in gynecologic oncology, specifically in patients with SCCC (Sørensen et al., 1995). Some authors have hypothesized that in cervical neuroendocrine carcinomas, the hormones secreted by the tumor are in an inactive form or in insufficient quantity to produce a paraneoplastic syndrome (Silva et al., 1984). We performed a literature

Table 1
Summary table on SIADH (Adrogué et al., 2022);(Warren et al., 2023) .

DIAGNOSTIC CRITERIA
Serum sodium < 135 mmol/L
Serum osmolality < 275 mOsm/kg
Urinary sodium level > 30 mmol/L
Urine osmolality > 100 mOsm/kg
Euvolemic clinical state
Normal thyroid and adrenal function
Normal renal function and absence of diuretic use
MECHANISMS
Excess release of Vasopressin (AVP) despite serum hypotonicity, leading to water retention by kidneys and hyponatremia
TREATMENT
Severe, symptomatic (seizures, altered sensorium) hyponatremia requires urgent treatment
Chronic SIADH:
– Hypertonic saline (100 mL of NaCl 3 %, up to 3 doses)
o Correction target: initial increase of 4–6 mmol/L of sodium level to reverse cerebral edema manifestations
– First-line therapy: fluid restriction < 1000 mL/day
– Second-line therapies: salt tablets, tolvaptan, urea, sodium-glucose co-transporter 2 inhibitors (SGLT2i)
– Correction limit of 10 mmol/L/24 h due to increased risk of osmotic demyelination with overly rapid correction

review of reported cases of SIADH in patients with small cell carcinoma, 6 cases were reported in patients with SCCC (see Table 2). In 5 of the 6 cases, hyponatremia due to SIADH was present at the initial diagnosis. This concurs with the findings of SIADH in SCLC. List et al (List et al., 1986) reviewed 350 patients with SCLC and found only 1 patient with a normal sodium level upon diagnosis, who then subsequently developed hyponatremia after one cycle of chemotherapy. In our patient, electrolyte levels and renal function were completely normal at the time of diagnosis.

Hyponatremia due to SIADH can also be induced by certain cytotoxic drugs, including cisplatin, vincristine, vinblastine and cyclophosphamide (Adrogué et al., 2022; Warren et al., 2023).Vinca alkaloids, such as vincristine, and alkylating agents, such as cyclophosphamide, are thought to stimulate or potentiate the release of vasopressin (Adrogué et al., 2022). Platinum compounds, like cisplatin, act as natriuretic agents, increasing urinary sodium concentration (Adrogué et al., 2022). Vinca alkaloids, such as vincristine, and alkylating agents, such as cyclophosphamide, are thought to stimulate or potentiate the release of vasopressin(Adrogué et al., 2022). Platinum compounds, like cisplatin, act as natriuretic agents, increasing urinary sodium concentration (Adrogué et al., 2022). In the present case, our patient developed profound hyponatremia three days following the administration of cisplatin-based chemotherapy. However, there was a recurrence of hyponatremia from SIADH following a change of chemotherapy to carboplatin, albeit to a lesser extent. This suggests that cisplatin was not responsible for the SIADH in our patient, or that there may be some cross-reactivity between cisplatin and carboplatin.

In our patient, the hyponatremia was less severe in terms of sodium level after the second chemotherapy cycle and the patient was was asymptomatic. A few similar cases were found in the literature. Garoute et al (Garoute et al., 2015) presented the case of a patient with SCLC who had severe hyponatremia with subsequent intubation and need of intensive care unit on day 2 post cisplatin-based chemotherapy with milder episodes of hyponatremia every second day following the next

Table 2
Review of all cases of SIADH in small cell carcinoma of the cervix.

Paper	ID	Year (reference number)	Sodium level	Timing	Symptoms	Treatment
Kothe et al.	69F	1990 (Kothe et al., 1990)	Na 112 mmol/L	At SCCC diagnosis	Nausea, vomiting, lethargy	Fluid restriction, sodium chloride tablets
Ishibashi-Ueda et al.	41F	1996 (Ishibashi-Ueda et al., 1996)	Not specified	At SCCC diagnosis	Behavior changes	Not specified
Kim et al.	41F	2013 (Kim et al., 2013)	Na 124 mmol/L (pre-surgery), Na 133 mmol/L (4-month post-surgery)	Before surgery and recurrence 4 months post-surgery with recurrence of SCCC	Not specified	Fluid restriction, hypertonic saline, surveillance for recurrence
Kuriakose et al.	50F	2014 (Kuriakose et al., 2014)	Na 116 mmol/L	At the SCCC diagnosis	Vomiting, seizure, altered sensorium	Spontaneous correction of sodium level post oncologic surgery
D'Adda et al.	26F	2015 (D'Adda et al., 2015)	Na 107 mmol/L	At the SCCC diagnosis	Generalized tonic seizure, abnormal vaginal bleeding	Surgical treatment followed by chemotherapy and radiotherapy
Zhao et al.	55F	2020 (Zhao et al., 2021)	Na 123.2 mmol/L	1 month after first cycle of chemotherapy	Trembling of the limbs	Fluid restriction, hypertonic saline, intermittent diuretics. No recurrence following oncologic surgery.

chemotherapy treatments with carboplatin. They speculated that the intensity of the tumor lysis may correlate with the intensity of the hyponatremia, with more ectopic ADH being released after the first treatment. Vanhees et al. (Vanhees et al., 2000) reported a case of hyponatremia from SIADH in a patient with SCLC two days following the first cycle of chemotherapy with normal sodium levels prior to chemotherapy. They hypothesized that the transient hyponatremia was caused by the malignant cells releasing ADH during the initial tumor breakdown.

Our patient experienced recurrent hyponatremia following each chemotherapy cycle, despite adequate first-line treatment with fluid restriction, oral sodium supplementation and loop diuretics. As a result, a second-line agent, tolvaptan, was introduced for hyponatremia prophylaxis at the start of each chemotherapy cycle and was administered for 7–10 days. Tolvaptan is an oral vasopressin type 2 receptor antagonist that blocks the action of vasopressin in the kidneys, leading to water diuresis and an increase in plasma sodium concentration. It was approved in the United States in 2009 for treatment of clinically significant hypervolemic or euvolemic hyponatremia (serum sodium level $<$ 125 mmol/L), or symptomatic hyponatremia resistant to fluid restriction. Tolvaptan is typically initiated in a hospital setting to allow for close monitoring of serum sodium levels, as there is a risk of overly rapid correction, which can lead to osmotic demyelination syndrome (Adrogué et al., 2022; Warren et al., 2023).

In conclusion, this case highlights the rare occurrence of severe SIADH in a patient with SCCC, underscoring the complexity of managing electrolyte disturbances in the context of both paraneoplastic syndromes and chemotherapeutic side effect. The severity of our patient's presentation calls attention to the importance of early recognition of SIADH in the differential diagnosis of oncology patients with altered mental status and confusion. Post chemotherapy sodium surveillance could lead to improved patient outcomes, as well as monitoring for signs and symptoms of hyponatremia.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CRediT authorship contribution statement

Isabelle Lauzon: Writing – original draft, Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Lara deGuerké:** Writing – review & editing, Conceptualization, Methodology, Project administration. **Suzanne Fortin:** Conceptualization, Methodology, Writing – review & editing. **Marie-Hélène Auclair:** Conceptualization, Methodology, Writing – review & editing. **Sabrina Piedimonte:** Writing – review & editing, Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision.

References

Adrogué, H.J., Tucker, B.M., Madias, N.E., 2022. Diagnosis and management of hyponatremia: a review. J. Am. Med. Assoc. 328 (3), 280–291. https://doi.org/10.1001/jama.2022.11176.

Chen, J., Macdonald, O.K., Gaffney, D.K., 2008. Incidence, mortality, and prognostic factors of small cell carcinoma of the cervix. Obstet. Gynecol. 111 (6), 1394–1402. https://doi.org/10.1097/AOG.0b013e318173570b.

Crowder, S., Tuller, E., 2007. Small cell carcinoma of the female genital tract. Semin. Oncol. 34 (1), 57–63. https://doi.org/10.1053/j.seminoncol.2006.10.028.

D'Adda, E., Paletta, R., Brusaferri, F., Cagnana, A., Teresa Ferrò, M., Gennuso, M., Ghione, I., Saponara, R., Prelle, A., 2015. Rhabdomyolysis in hyponatremia and paraneoplastic syndrome of inappropriate antidiuresis. Acta Myologica: Myopathies Cardiomyopathies: Off. J. Mediterranean Soc. Myol. 34 (2–3), 139–140.

Garoute, C., Plouvier, N., Iacob, E., Cotrel, R., Suguenot, R., Lecuyer, E., Bentayeb, H., Douadi, Y., Dayen, C., 2015. Hyponatrémie sévère sous chimiothérapie du carcinome à petites cellules [Severe hyponatremia during chemotherapy for small cell carcinoma]. Rev. Mal. Respir. 32 (1), 52–57. https://doi.org/10.1016/j.rmr.2014.07.004.

Hansen, O., Sørensen, P., Hansen, K.H., 2010. The occurrence of hyponatremia in SCLC and the influence on prognosis: a retrospective study of 453 patients treated in a single institution in a 10-year period. Lung Can. (Amsterdam, Netherlands) 68 (1), 111–114. https://doi.org/10.1016/j.lungcan.2009.05.015.

Ishibashi-Ueda, H., Imakita, M., Yutani, C., Ohmichi, M., Chiba, Y., Kubo, T., Waki, M., 1996. Small cell carcinoma of the uterine cervix with syndrome of inappropriate antidiuretic hormone secretion. Modern Pathology: Off. J. United States Can. Acad. Pathol., Inc, 9(4), 397–400.

Kim, D.Y., Yun, H.J., Lee, Y.S., Lee, H.N., Kim, C.J., 2013. Small cell neuroendocrine carcinoma of the uterine cervix presenting with syndrome of inappropriate antidiuretic hormone secretion. Obstetr. Gynecol. Sci. 56 (6), 420–425. https://doi.org/10.5468/ogs.2013.56.6.420.

Kothe, M.J., Prins, J.M., de Wit, R., Velden, K.V., Schellekens, P.T., 1990. Small cell carcinoma of the cervix with inappropriate antidiuretic hormone secretion. Case Report. Brit. J. Obstetr. Gynaecol. 97 (7), 647–648. https://doi.org/10.1111/j.1471-0528.1990.tb02558.x.

Kuriakose, S., Umadevi, N., Mathew, S., Supriya, N., Aravindan, K., Smitha, D., Amritha Malini, G., 2014. Neuroendocrine carcinoma of the cervix presenting as intractable hyponatremic seizures due to paraneoplastic SIADH-a rare case report and brief review of the literature. Ecancermedicalscience 8, 450. https://doi.org/10.3332/ecancer.2014.450.

List, A.F., Hainsworth, J.D., Davis, B.W., Hande, K.R., Greco, F.A., Johnson, D.H., 1986. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in small-cell lung cancer. J. Clin. Oncol. 4 (8), 1191–1198. https://doi.org/10.1200/JCO.1986.4.8.1191.

Silva, E.G., Kott, M.M., Ordonez, N.G., 1984. Endocrine carcinoma intermediate cell type of the uterine cervix. Cancer 54 (8), 1705–1713. https://doi.org/10.1002/1097-0142(19841015)54:8<1705: aid-cncr2820540837>3.0.co;2-t.

Sørensen, J.B., Andersen, M.K., Hansen, H.H., 1995. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease. J. Intern. Med. 238 (2), 97–110. https://doi.org/10.1111/j.1365-2796.1995.tb00907.x.

Vanhees, S.L., Paridaens, R., Vansteenkiste, J.F., 2000. Syndrome of inappropriate antidiuretic hormone associated with chemotherapy-induced tumour lysis in small-cell lung cancer: case report and literature review. Ann. Oncol.: Off. J. Eur. Soc. Med. Oncol. 11 (8), 1061–1065. https://doi.org/10.1023/a:1008369932384.

Warren, A.M., Grossmann, M., Christ-Crain, M., Russell, N., 2023. Syndrome of inappropriate antidiuresis: from pathophysiology to management. *Endocr. Rev.* 44 (5), 819–861. https://doi.org/10.1210/endrev/bnad010.

Zhao, C.F., Zhao, S.F., Du, Z.Q., 2021. Small cell carcinoma of the cervix complicated by syndrome of inappropriate antidiuretic hormone secretion: a case report. J. Int. Med. Res. 49 (2), 300060520985657. https://doi.org/10.1177/0300060520985657.