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A rare case of paraneoplastic syndrome of inappropriate secretion of antidiuretic hormone in cervical squamous cell carcinoma; A case report and literature review

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CASE REPORT

A Rare Case of Paraneoplastic Syndrome of Inappropriate Secretion of Antidiuretic Hormone in Cervical Squamous Cell Carcinoma; A Case Report and Literature Review

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Abstract

SIADH is more commonly associated with small cell lung cancer but has also been associated with other malignancies such as oropharyngeal, gastrointestinal, genitourinary, endocrine, lymphomas, and sarcomas. There have been few reports of small cell carcinoma of the cervix complicated by SIADH; however, not many cases are associated with squamous cell carcinoma of the cervix. We present a case of a patient with squamous cell carcinoma of the cervix with a paraneoplastic syndrome of inappropriate secretion of antidiuretic hormone. The pathophysiology, clinical picture, and treatment are also discussed.

Keywords: Syndrome of inappropriate secretion of antidiuretic hormone, Squamous cell carcinoma of cervix, Paraneoplastic syndrome, Hyponatremia

1. Introduction

Paraneoplastic syndromes (PNS) are known rare disorders that range in presentation but essentially are an abnormal immunological response to tumors or malignancies or excessive production of a hormone. These syndromes are more commonly seen in lung, ovarian, lymphatic, and breast cancers. Syndrome of inappropriate antidiuretic hormone (SIADH) secretion can be a paraneoplastic process and occurs in 10%−45% of small cell lung cancer.[1−3] Most SIADH cases have been associated with small cell lung cancer. In contrast, associations between SIADH and gynecological malignancies are rare, with only a small number of cases reported in small cell carcinoma of the cervix and one case in squamous cell carcinoma of the cervix.[5−7] We present here the second known case of squamous cell carcinoma of the cervix complicated with SIADH.

2. Case report

This is an 84-year-old G9P5 female with a past medical history of hypertension, vertigo, pre-diabetes, and newly diagnosed p16 positive-HPV associated squamous cell carcinoma of the cervix by colposcopy (Fig. 1). The patient was sent to the hospital for pelvic examination under anesthesia for clinical staging of the cancer. The patient denied past surgical history or known family history of cancer. She denied any smoking history, alcohol, or illicit drug use. The patient denied receiving daily diuretics and was only taking Nifedipine 30 mg, Losartan 100 mg, vitamin b12 and aspirin 81 mg. Denied the use of any other medications. Additionally, the patient denied drinking excessive amounts of water or fluids.

The patient was hemodynamically stable with blood pressure 115/80 mmHg, with positive orthostasis, heart rate 98 beats per minute, and temp 36.5

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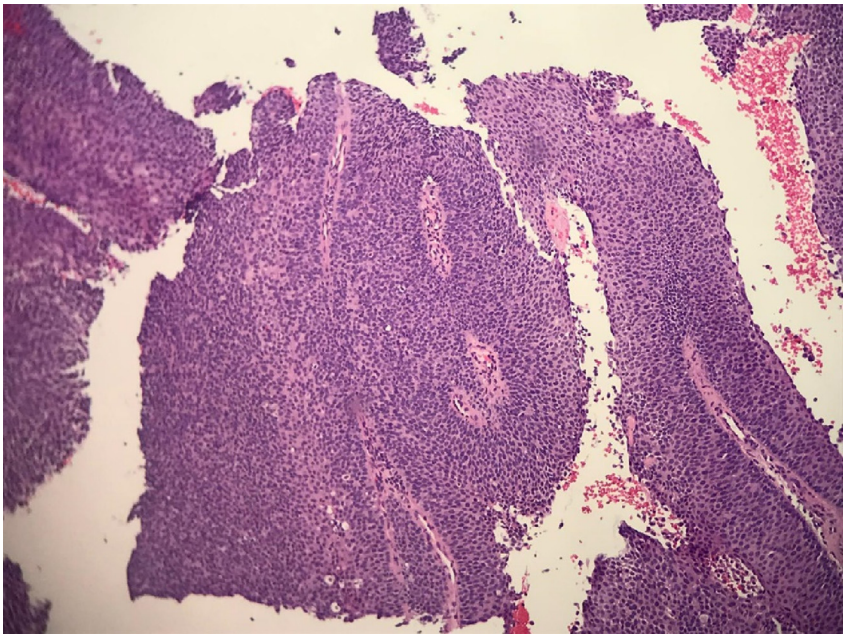

Figure 1. Cervical biopsy showing squamous cell cancer with positive p16 staining.

Celsius. On the physical exam, the patient was euvolemic with moist mucous membranes, no lower extremities edema and normal breath sounds. Initial preoperative labs were significant for hyponatremia of 127 mEq/L, potassium 4.3mEq/L, chloride 94 mE/L, blood urea nitrogen 14 mg/dL, Creatinine 1.20 mg/dL. The patient's baseline sodium based on prior labs was 132 mEq/L. Complete blood count showed white blood count of 7.1 × 103/mm3 without any left shift, hemoglobin of 13.3 g/dL, hematocrit of 40.0% and platelet count of 399 K/mm3. The patient was admitted for further work-up and correction of hyponatremia. She was initially started on intravenous normal saline with an appropriate maintenance fluid adjusted for her weight. However, the fluid infusion was discontinued when repeated laboratory tests showed a worsening drop in sodium concentration to 125 mEq/L.

Subsequent labs which were drawn prior to fluid initiation showed serum osmolality of 272 mOsm/Kg, urine osmolality of 357 mOsm/Kg, urine sodium of 74 mmol/L. The patient had normal renal function and morning cortisol and TSH levels were within normal limits, excluding adrenal insufficiency and hypothyroidism as causes for her hyponatremia (Table 1). There was no evidence of acid-base disorders. The patient's laboratory studies were consistent with a diagnosis of SIADH. Ultimately, the patient was placed on a fluid restriction of less than 1 L/day, and her sodium level improved to 130 mEq/L, which appeared to be closer to her baseline.

CT chest, abdomen, pelvis without contrast was obtained for staging purposes and revealed no convincing evidence of metastatic disease. Subsequently, she was able to tolerate general anesthesia for clinical staging through cystoscopy and proctosigmoidoscopy with biopsies. The final stage of her cancer was determined to be cervical cancer stage 1B1. After the procedure, the patient remained on a fluid-restricted diet, and sodium level further improved to 132 mEq/L on the day of discharge. The patient was ultimately discharged and was instructed to follow up with the primary clinic for newly diagnosed SIADH, follow up with OB-GYN and oncology for initiation of radiation, and was advised to limit fluid intake to less than 1 L per day. The

Table 1. Patient's baseline data.

	Value	Reference Range
AM Cortisol	10.3 mcg/dL	4.3–22.4 mcg/mL
TSH	1.881 uIU/mL	0.450–5.330 uIU/mL
Sodium	127 mEq/L	135-145 mEq/L
Potassium	4.3 mEq/L	3.5–5.0 mEq/L
Chloride	94 mE/L	98-107 mE/L
BUN	14 mg/dL	7–23 mg/dL
Creatinine	1.20 mg/dL	0.60–1.30 mg/dL
WBC	7.1 × 10^3/mm3	4.5–11.0^3/mm3
Hgb	13.3 g/dL	12.0–16.0 g/dL
HCT	40.0%	36.0–46.0%
Platelets	399 K/mm3	140–440 K/mm3
Serum osmolality	272 mOsm/kg	283–299 mOsm/kg
Urine osmolality	357 mOsm/kg	50-1200 mOsm/kg
Urine Sodium	74 mmol/L	15–237 mmol/L

patient received her first radiation therapy, and her follow-up labs were obtained nine days after the session, revealing significant improvement of her sodium level to 137 mEq/L, which is the highest sodium level the patient had based on prior labs.

3. Discussion

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) occurs when there is an increase of arginine, vasopressin, or other similar peptide causing intravascular water retention, and hyponatremia.[2] SIADH is a rare paraneoplastic syndrome (PNS) that can be present in a variety of malignancies; however, some malignancies have a higher incidence of SIADH than others. For instance, SIADH is most associated with lung cancer, specifically accounting for 10%–45% with small cell lung carcinoma (SCLC).[1–3] Occasionally, SIADH can precede the diagnosis of SCLC, and generally is associated with a worse prognosis.[4] In contrast, SIADH rarely presents in cervical cancer.[5] Small cell carcinoma of the cervix is a rare malignant tumor, and it is estimated that 10% of this cancer may present with symptoms of neuroendocrine tumor (most commonly SIADH).[1–6] SIADH is rarely reported in patients with non-small cell lung cancer (NSCLC).[4] Over the past twenty years, only three cases of SIADH have been reported in patients with NSCLC.[4] Additional cancers with SIADH include lymphoma, mesothelioma, thymoma, Ewing's sarcoma, and squamous cell carcinoma (SCC) of the head and neck.[16] Per literature review, the PNS of SIADH has been identified in squamous cell carcinoma (SCC) of head and neck as well as the respiratory tract; however, only one case of SIADH has been reported for SCC of the cervix.[5–7] Our patient represents the second reported case of SIADH presenting in squamous cell carcinoma of the cervix, a rare phenomenon.

The pathophysiology of SIADH in small cell lung cancers has been well identified. The mechanism is considered due to ectopic antidiuretic hormone (ADH) production by malignant cells that is independent of a negative feedback loop.[4] In a study of patients with SCLC, both ADH and atrial sodium diuretic peptide (ANP) were shown to result in SIADH. It has also been noted that ADH is more closely related to the development of hyponatremia.[8] In contrast, for patients who develop SIADH secondary to a malignancy other than SCLC, as with our patient, the etiology is not currently well understood.

Many theories have been documented to explain the mechanism of SIADH in cancers other than SCLC. It was proposed that the etiology of hyponatremia was not due to hormonal release, as NSLC rarely has been shown to produce ADH or ANP polypeptide hormones.[4–9] Further studies in SCC tumors, as in our patient, did not demonstrate ADH gene expression.[10] Therefore, the mechanism of how our patient with cervical SCC developed SIADH remains a mystery.

In general, PNS is rarely present in gynecological primary cancers, especially cervical cancer.[5] For instance, for patients with small cell carcinoma of the cervix, it has been hypothesized that polypeptide hormones are secreted by the tumor in inactive forms and or in insufficient amounts to lead to a paraneoplastic syndrome.[5–12] In contrast, studies have shown that there are neuropeptides thought to be associated with ADH production in squamous cell carcinoma.[10] In animal studies, mice vaccinated with squamous cell carcinoma showed increased levels of neuropeptide Y, which caused increased stimulation of the posterior pituitary gland and led to the secretion of ADH hormone.[10–14] More recent studies report that higher levels of ADH in SCC (in 38% of SIADH patients with SCC) may suggest that ADH is stimulated indirectly through neuropeptide Y in patients with SCC, in comparison to direct stimulation of ADH with SCLC.[10–15] Therefore, it is important to identify the histopathology and origin of tumor in patients presenting with PNS to fully understand the mechanism of the paraneoplastic process. Our patient underwent biopsies not only for clinical staging, but also to identify the source of ADH release.

Relevant alternative theories to explain the etiology of such paraneoplastic syndrome have been reported. In one case report, a patient with NSCLC developed SIADH after completion of radiation therapy. It was hypothesized that the PNS was secondary to release of ADH from tumor lysis.[4–16] There are also several reports that SIADH is induced by certain chemotherapy for other types of cancers, such as Cisplatin infusion. Levine et al. suggested that Cisplatin administration induces SIADH by excessive central antidiuretic hormone secretion as well as via direct renal tubular injury.[2] Regardless, our patient did not receive radiation or chemotherapy prior to the diagnosis of such paraneoplastic syndrome.

When determining the prognosis of cervical SCC complicated by SIADH, we have limited information due to its rare occurrence. Paraneoplastic syndromes can be the first sign of malignancy, and can precede it by months to years, which requires further evaluation.[4] Hyponatremia may be a useful tool in early diagnosis of malignancy; however, it may indicate a poor prognosis.[1] On the other hand, if the

hyponatremia from SIADH allows for early diagnosis of the malignancy and patients are treated adequately with surgical excision of the tumor (if applicable), this may lead to better outcomes and subsequent improvement in the electrolyte disturbances of SIADH.[1–5] In terms of treatment of patients with SIADH secondary to malignancy, or in patients with SIADH in general, the overall goal of therapy is to treat the underlying condition. Therefore, patients exhibiting paraneoplastic SIADH should undergo treatment of their malignancy.[5–17] In our case, the patient's sodium levels normalized within 2 weeks following radiation, consistent with treatment of the underlying condition in order to treat SIADH. Further research is warranted in order to investigate the prognostic effect and therefore significance of early detection to treat this paraneoplastic disorder.

There are several barriers in our case, as SIADH can occur via idiopathic cause or can occur following head trauma, surgery, medications (e.g. morphine, NSAIDs, and oxytocin), various lung diseases (pneumonia, abscess and tuberculosis) and/or due to endocrine disease states (hypothyroidism and glucocorticoid deficiency).[18] However, we were unable to identify these alternative causes in our patient. It is unclear whether SIADH was a paraneoplastic syndrome or an incidental idiopathic finding. Further research is warranted to confirm and diagnose the possibility of paraneoplastic syndrome in patients with cervical SCC.

4. Conclusion

We identified a rare case of SCC of the cervix demonstrating the paraneoplastic syndrome SIADH, an unexpected finding. This case aims to identify possible etiologies of this paraneoplastic syndrome, perform thorough literature review of this phenomenon, and edify the importance of immunohistological analysis of these tumors. SIADH may provide prognostic information for these patients and may lead to earlier diagnosis and treatment. Our case supports prior evidence that treatment of the underlying malignancy remains the best management to improve paraneoplastic syndromes such as SIADH. The mechanism of SIADH in cancers other than SCLC continues to warrant further research.

Author contribution

Deniz Yucel, MD, Erinie Mekheal, MD, are the article guarantors. Deniz Yucel, MD, Erinie Mekheal, MD, Brooke Kania, DO, Polina Aron MD, performed the literature review and wrote the manuscript. Polina Aron MD, Ashima Kapoor, MD, assisted in the collection of the patient's clinical data. All authors took part in the medical management of the patient and edited the final manuscript for submission. All work was performed at St. Joseph's University Medical Center.

Consent

As this is a case report, consent was obtained for the purpose of this paper.

Conflict of Interest

The authors report no conflict of interest. Ethical review is not necessary, because this is a case report. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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