Journal of Gynecological Oncology

Case Report
Published: 25 May, 2020

Advanced Pelvic Malignancy Causes Syndrome of Inappropriate Antidiuretic Hormone Secretion: A Case Report

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Abstract

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) is defined as an array of clinical syndromes resulting from improper secretion of endogenous diuretic hormone or renal hypersensitivity to Antidiuretic Hormone (ADH). The cardinal feature for SIADH is hyponatremia, which represents a prognostic factor correlated with survival in cancer patient. SIADH has been closely linked with cancer, including small cell lung cancer, leukemia ureteral and prostate carcinoma, and bladder carcinoma. Here, we present a first case report of SIADH caused by advanced pelvic malignant tumor. The patients with persistent hyponatremia, although we conducted hypertonic saline treatment and chemotherapy to reduce tumor burden, the patient failed to respond and died within 17 days since hospital admission. This case suggests pelvic malignant tumors as a cause for SIADH, and prompt diagnose and accurate treatment is crucial for patient survival.

Keywords: SIADH; Pelvic Malignant tumor; Hyponatremia; Survival

Introduction

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) is a complex complication defined as the body continuing to secret Antidiuretic Hormone (ADH) at a high level or exhibiting renal hypersensitivity to ADH. High ADH levels result in hyponatremia with disrupted water secretion, leading to water retention that aggravates hyponatremia with concomitant hypo-osmolality and high urine osmolality [1]. In 1963, Amatruda et al. [2] demonstrated that SIADH in patients with small-cell lung cancer resulted from ectopic production of Arginine Vasopressin (AVP) in tumors [2]. Subsequently, SIADH was reported to causatively correlate with malignancies, medication, pulmonary infections, pain and nausea, mental trauma, anxiety and Central Nervous System (CNS) disorders [3-7]. Although many causes of SIADH have been described, oncologists should be always aware of cancer patients may accompany with SIADH [7-9]. Here, we present a first report of a patient with advanced pelvic malignant tumor who developed SIADH. Despite the diagnosis being carried out at the terminal stage of this patient and the treatment not being successful, it remains valuable to report this case to promote awareness of this syndrome and provide medical information and guidance for gynecological oncologists to improve efficacy and accuracy when designing clinical strategies so as to prolong survival of cancer patients.

Case Presentation

A 74-year-old woman was admitted on December 2019, exhibiting high fever, severe abdominal pain and distension, and was subsequently diagnosed as advanced pelvic malignancy with lots of ascites. The patient then underwent abdominal cavity puncture fluid drainage with daily release of 1000 ml ascites for 7 consecutive days, while being subscribed to anti-inflammatory and pain killer treatment. This greatly alleviated fever, abdominal pain and distention. No anti-neoplastic treatment was administered after the patient went home, but the patient was able to continue to release ascites at 1000 ml per day for 2 days at home. In the next few days, however, the high fever started to occur again, with vomiting and abdominal pain. The patient was then admitted to gynecology department of our hospital on January 13th, 2020 (referred to Day 1). The patient exhibited fever, abdominal pain, abdominal distension, and physical examination showed abdominal tenderness and rebound pain. Further laboratory tests found increased white blood cells (10.06×10^9/L), neutrophils (80.6%) and C Reactive Protein (CRP) (54.34 mg/L), which was suggestive of abdominal infection.

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Received Date: *07 May 2020*
Accepted Date: *21 May 2020*
Published Date: *25 May 2020*

Citation:
Xiaolin L, Fenge L, Yumei Z, Jing L, Zhonge T, Quanxin Q. Advanced Pelvic Malignancy Causes Syndrome of Inappropriate Antidiuretic Hormone Secretion: A Case Report. J Gynecol Oncol. 2020; 3(3): 1034.

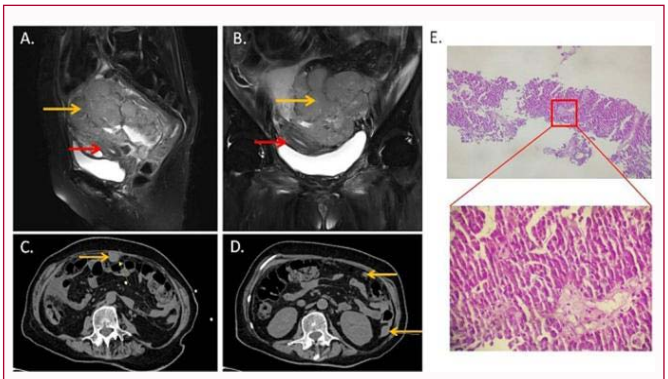

Figure 1: A) Pelvic nuclear magnetic sagittal view of uterine atrophy surrounded with solid mass shadow. Yellow arrow indicates tumor, whereas right arrow indicates uterine. B) Pelvic nuclear magnetic coronal position to visualize atrophy of the left uterine surrounded with solid mass shadow. C, D) Multiple peritoneal metastases were identified in PET-CT scan. E) Pathologic diagnosis of the patient showing malignant tumor cells. The magnification of the top image was 10x, and the bottom image was 40x.

Laboratory tests also showed moderately decreased serum levels of sodium for the patient (125.3 mmol/l), accompanied by low plasma osmolality (271.8 mOsm/kg), low creatinine (31 μmol/l) and low uric acid (109.1 μmol/l). Thyroid function and cortisol levels were normal. We initially considered this electrolyte disturbance attributed to insufficient intake of food and water. Therefore, the patient was treated with anti-infection, 2% sodium supplementation, antiemetic treatment, and venous nutritional supplements. Diuretic treatments were not considered.

Positron Emission Tomography-Computed Tomography (PET-CT) results on Day 3 revealed high density of soft tissues in the pelvic cavity and multiple metastatic nodules were found around the liver, spleen, parietal peritoneum, omentum, mesenteric and pelvic peritoneum with high metabolism signals (Figure 1A-1D). Surgery was not considered at this stage due to the high-performance status score of 3. Ultrasound guided needle biopsies were performed and assessed by a pathologist on day 3, confirming a pelvic malignant tumor with Performance Status (PS) of 3 (Figure 1E). These imaging and pathology results indicate advanced pelvic cancer for the patient. We continued the treatment as before, which greatly alleviated abdominal pain, abdominal distension, nausea and vomiting and slowly increased serum levels of sodium.

We found a sodium level at 126.1 mmol/L on day 8 for the patient, who indicated that insufficient intake of food and water may not be accountable as the serum level of sodium was not increased accordingly. The urine level of sodium was 189.2 mmol/l (normal range <30 mmol/L), then the patient was diagnosed as SIADH on day 9. The NCCN guideline suggests removing tumors or controlling tumor growth immediately as the primary strategy for SIADH treatment. Surgical removal of the tumor was not an option for the patient due to the advanced disease status and high score of personal performance. Chemotherapy with paclitaxel 90 mg and carboplatin 200 mg was administered on day 10. However, the patient appeared increasingly tired and exhausted, and chose to give up further medical treatments when the patient was in coma on day 14. The serum level of sodium was back to normal (138.9 mmol/L) on day 16, with serum osmolality at 299.6 mOsm/L, when the patient was infused with significant less fluid. At this time, the blood sodium and plasma osmotic pressures were back to normal (Table 1 and Figure 2). This result further confirmed SIADH for the patient, who died on day 17 resulting from brain edema coma due to prolonged hyponatremia.

Discussion

SIADH is a disorder of impaired water management and increased urinary sodium excretion from excess release of Antidiuretic Hormone (ADH) that results in hyponatremia. ADH is also known as Arginine-Vasopressin (AVP), which is secreted by cells within the supraoptic and paraventricular nuclei of the neurohypophyseal system and stored in the posterior lobe of the pituitary gland [10,11]. AVP physiologically functions in the distal and collecting tubules of the nephron of the kidney [12]. AVP binds to the V2 Receptor subtype (V2R) in the kidney, activates transduction cascades to develop antidiuresis. This enhances reabsorption of solute-free water in the kidney, aggravates excretion of excessive urinary sodium, lowers volume of concentrated urine and leads to hyponatremia [13]. The secretion of AVP is normally stimulated by increased plasma osmolality *via* activation of osmoreceptors located in the anterior hypothalamus, as well as by decreased blood volume or pressure *via* activation of high and low-pressure baroreceptors located in the cardiovascular system [14]. However, malignant tumors can also produce AVP, including small cell lung cancer [15], prostate cancer, testicular cancers, and pancreatic cancer [16]. Sustained stimulation of AVP retains water and leads to hyponatremia.

Hyponatremia is the main clinical complication for SIADH, which is characterized by anorexia, nausea, generalized weakness, respiratory suppression, ataxia, tremor, asterixis, dysarthria, and convulsions [17,18]. Mental disorder is also often observed, ranging from mild to severe lethargy. The clinical symptoms of SIADH are not specific, thus presenting a particular challenge for early and accurate diagnosis [13]. The patient in the current report was diagnosed as SIADH 28 days after the initial symptoms were documented, and was admitted to our hospital with mild cachexia and apathy after a total of 9000 ml of ascites were released. The patient exhibited

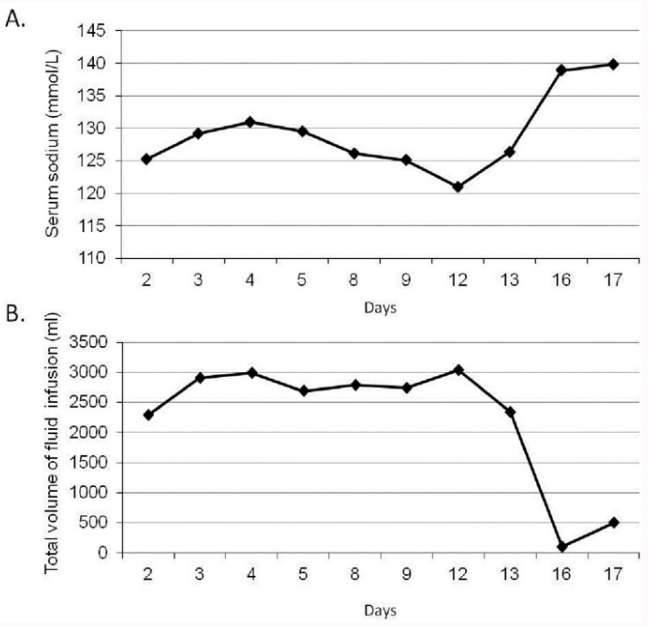

Figure 2: A) Serum levels of sodium over time during hospitalization. B) Total volume of fluid infusion of the patient over the treatment. Blood level of sodium was increased from Day 3 to Day 4, followed by a decrease with fluid rehydration. Serum level of sodium was normal after fluid infusion deduction or no infusion.

Table 1: Results of laboratory tests.

Time	Total volume of fluid infusion (ml)	Serum sodium (mmol/L)	Serum kalemia (mmol/L)	Serum chlorine (mmol/L)	Serum osmolality (mOsm/kg)
Day 2	2290	125.3	3.82	89.6	271.8
Day 3	2910	129.2	3.76	95.7	-
Day 4	2990	131	3.63	93.4	-
Day 5	2690	129.5	3.99	92.1	-
Day 8	2790	126.1	4.87	89.7	269
Day 9	2740	125.1	4.92	91.5	267.5
Day 12	3040	121	4.55	82.6	259.8
Day 13	2340	126.4	4.77	88.3	271
Day 16	500	138.9	6.57	98.3	299
Day 17	500	139.8	5.77	100	305.5

persistent hyponatremia suggesting that electrolyte disturbance was not attributed to insufficient food and water intake. Eventually, the patient was diagnosed as SIADH because of the high level of urinary Na^+ at 189.2 mmol/l. It was then observed that the serum Na^+ level returned to normality with significantly reduced volume of infusion, which further confirmed the diagnostic result of SIADH for this patient. Therefore, rapid and accurate diagnosis for SIADH with appropriately and promptly devised medical treatment is crucial for SIADH patients. SIADH can then be defined as low serum Na^+ (<135mmol/L), low serum osmolality (<280 mOsm/kg), high urine osmolality (>200 mOsm/kg) and high urine Na^+ concentration (>30 mmol/L) [4]. Importantly, these changes occur with normal adrenal and thyroid function. In the present report, laboratory tests revealed the minimum of sodium level at 121 mmol/L, minimum of serum osmolality at 259.8 mOsm/L, and the urine sodium level was at 189.2 mmol/l indicative of SIADH.

It has been established that SIADH is associated with high mortality and poor prognosis in cancer patients [1,9,15]. The median overall survival for patients with SIADH who are cancer-free is 910 days, as compared with those with malignancy at only 58 days [15]. The overall survival of the patient reported in our study was 35 days, and this would be prolonged if diagnosis of SIADH was confirmed earlier. Therefore, early diagnosis, removal of primary tumor and rationally designed medical intervention are key components of the clinical strategy for cancer patients with SIADH.

Here, we summarize multiple treatment criteria and strategies for treating SIADH. Foremost, removing or constraining the primary tumor should be considered with priority. Second, fluid intake limitation and infusion of hypertonic saline combined with furosemide could also be effective [2,4,19]. Fluid intake limitation is considered as the initial step with limited fluid intake to 800 ml to 1200 ml per day [20]. Hypertonic saline at 3% is the most commonly used concentration for SIADH treatment [14]. In addition, utilizing furosemide can discharge excessive water with great therapeutic benefit and no impact on the electrolyte. Tolvaptan is an oral antagonist of vasopressin V2 receptor with stronger binding affinity for the V2 receptor than native vasopressin [21]. It can increase urinary excretion of free water; decrease urine osmolarity, increase serum sodium concentrations, and can serve as an adjuvant to promptly increase serum sodium levels [22].

In sum, we present the first report showing that gynecological malignancy can cause SIADH. Early diagnose of SIADH is essential to for rational design of therapeutic strategies. It is highly possible that chemotherapy would prolong the survival of the patient in our study if SIADH was diagnosed at an early stage with early medical alle*via*tion of hyponatremia. We hope that our case report in the current study will help gynecological oncologists be aware of SIADH associated with gynecological malignancy and improve the efficacy of the clinical treatment for the disease.

Acknowledgment

This work was funded by Tianjin First Central Hospital. Informed consent was obtained from her family.

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