CASE REPORT

Hyponatremia caused by water intoxication and malnutrition in a patient with metastatic oropharyngeal carcinoma

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Abstract
A 61-year old Caucasian male was diagnosed with oropharyngeal cancer and lung metastases. Initial treatment included three cycles of cisplatin-based chemotherapy. A few days after receiving the 12th cycle of methotrexate (second-line treatment), the patient was referred to the emergency department due to general malaise, muscle weakness, and inappetence. Laboratory findings revealed moderate hyponatremia and decreased osmolality. A urine spot sodium test showed low sodium level. The diagnosis of euvolemic hyponatremia due to water intoxication and malnutrition was made. The patient was advised to restrict his daily fluid intake. 2 weeks later, the serum sodium level normalized, along with improvement in performance status. Careful monitoring of serum electrolytes for dilutional hyponatremia should be performed in patients advised to drink more during chemotherapy, and the spot urinary sodium level is helpful in the differential diagnosis. Both chemo- and radiotherapy can lead to the syndrome of inappropriate antidiuretic hormone (ADH) secretion: Chemotherapy due to drug action and radiotherapy by compromising cerebral blood flow leading to increased ADH production. Both chemotherapy agents, our patient was treated with cisplatin and methotrexate can cause significant renal toxicity. It is proposed that water intoxication is a relatively common but overlooked and misdiagnosed cause of hyponatremia in everyday oncologic practice.

Key words: Hyponatremia; water intoxication; excess; head and neck; cancer
1. Introduction

Hyponatremia is important, but frequently overlooked adverse prognostic factor in cancer patients. It is commonly caused by the syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) or chemotherapy-induced renal salt wasting. This case emphasizes that the combination of excessive water intake and malnutrition may cause hyponatremia in patients with head and neck cancer. The urine spot sodium test is useful in differentiating the cause of hyponatremia, which is crucial for proper treatment.

Hyponatremia is generally defined as a serum sodium level of <135 mmol/L (normal levels are 135-145 mmol/L) and is considered severe when the level is below 120 mmol/L. Clinical presentation depends on the serum sodium level, and patients can present with very severe symptoms or be asymptomatic. Although hyponatremia is usually mild, in severe cases it can lead to confusion, seizures, and even coma with a potentially lethal outcome. Altogether, it is considered one of the most commonly seen water electrolyte imbalances. When caused by SIADH, it is typically treated with fluid restriction. Thus, although patients should generally be advised to increase water intake during chemotherapy, careful monitoring of serum electrolytes should be performed because this approach is not appropriate for all patients.

2. Case Report

A 61-year old Caucasian male was diagnosed with oropharyngeal cancer and lung metastases in February 2016. Diagnosis of stage T4aN2bM1 poorly differentiated squamous cell carcinoma was made, and the patient was presented at the multidisciplinary head and neck tumor board. Due to metastatic disease, initial treatment included three cycles of cisplatin-based chemotherapy (cisplatin with fluorouracil). Imaging studies after three cycles of therapy confirmed the progression of the lung metastases and stable locoregional disease. On May 13, 2016, second line-treatment with 12 cycles of methotrexate at a standard dose (40 mg/m²; calculated dose 70 mg) was started, and given intravenously once weekly. The patient was also treated with 3D conformal radiation therapy with daily fractions of 2 Gy. A prophylactic dose of 50 Gy was delivered to clinically uninvolved neck levels, concurrently with 70 Gy to the primary tumor site. Head and neck control examination revealed no residual disease.

A few days after receiving the 12th cycle of methotrexate, the patient was referred to the emergency department due to general malaise, fatigue, muscle weakness, lightheadedness, and inappetence. The patient reported a 20 kg weight loss in the past 3 months despite taking the prescribed nutritional oral support (Ensure twice daily; the patient could tolerate only 1x daily). At presentation, he weighed 72 kg. Although his body mass index was normal (22 kg/m²), the patient was in evident cachexia due to extensive weight loss. He also complained of nausea without diarrhea and vomiting for the past few days, although he tolerated the previous chemotherapy cycles well, with no signs of this typical side effect. Lying blood pressure was normal (120/80 mmHg), with no signs of dehydration or edema. Besides loss of tissue turgor, physical examination was unremarkable. The patient’s performance status was measured with the Eastern Cooperative Oncology Group (ECOG) scale. It describes the patients’ level of functioning in terms of ability to care for themselves, perform daily activities, and physical abilities such as working. It ranges from 0 (asymptomatic - fully active, able to carry on all predisease activities without restriction) to 5 (dead patient). At the time of admission to the hospital, the patients’ ECOG status was two (symptomatic patients <50% of waking hours in bed; ambulatory and capable of all self-care but unable to carry out any work activities). Because both the chemotherapeutic agents the patient received can cause significant renal toxicity, the patient was instructed to drink ample fluid to reduce the toxic effects on the kidney.

Detailed medical history revealed that the patient drank between 3L and 4L of fluid per day. The patient was compliant and had the close support of his family, and he measured fluid intake on a daily basis. Laboratory findings revealed moderate hyponatremia (129 mmol/L) and decreased calculated osmolality (272.1 mOsmol/kg; reference range for adults at our laboratory: 280-300 mOsmol/kg). Apart from hypochloremia (95 mmol/L), levels of other electrolytes such as calcium (2.29 mmol/L), ionized calcium (1.19 mmol/L), and potassium (4.2 mmol/L) were within the reference range. Multiple electrolyte loss from renal
tubular necrosis was also considered. However, serum urea (7.6 mmol/L) and creatinine (69 μmol/L) levels, as indicators of kidney function, were within the normal range. Apart from the previously mentioned cytostatic agents, the patient did not use any other medications, including diuretics or others drugs that might cause hyponatremia. Mild anemia (erythrocytes 3.2 × 10^{12}/L; hemoglobin 101 g/L), leukopenia (2.1 × 10^{9}/L), and high C-reactive protein levels (67.5 mg/L) were interpreted as consequences of the primary disease and its treatment. A urine spot sodium test showed a low sodium level (<20 mmol/L), confirming the diagnosis of euvolemic hyponatremia due to water intoxication. The patient was advised to restrict his daily fluid intake to 500 ml for four days and then to 1000 ml during the next 10 days until follow-up. The patient did not attend the suggested 10-day follow-up appointment, so control laboratory examination was done after 2 weeks, showing a normal serum sodium level (137 mmol/L) and normal renal function. The patient felt much better, and his ECOG performance status improved to one (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature).

3. Discussion

In malnourished patients with head and neck cancer receiving chemotherapy, water intoxication is a relatively common but overlooked and misdiagnosed cause of hyponatremia in everyday oncologic practice. The most common causes of hyponatremia in cancer patients are SIADH and chemotherapy-induced renal salt wasting. Adrenal metastases causing adrenocortical failure with hyponatremia should also always be considered in patients with malignant disease. All three of these clinical entities are associated with hypoosmolar hyponatremia and high urinary sodium levels (>40 mmol/L) [1-4]. The prevalence of hyponatremia in patients with head and neck cancer has been estimated to be 4.2%, and approximately two-thirds of these patients are considered to have SIADH [2]. The exact cause of hypoosmolar hyponatremia in the rest of these patients is left unclear. The presence of hyponatremia in cancer patients is a negative prognostic factor associated with decreased the quality of life and overall survival [5]. Chemo- and radiotherapy by compromising cerebral blood flow leading to increased ADH production [6].

Both chemotherapeutic agents, our patient was treated with cisplatin and methotrexate can cause significant renal toxicity [7]. Cisplatin can cause SIADH by stimulating arginine vasopressin secretion, but it can also directly damage the renal tubules and interfere with sodium reabsorption, which in rare cases may lead to hyponatremia via salt-wasting nephropathy [8-10]. The proposed mechanisms of methotrexate-induced hyponatremia include a toxic effect on the neurosecretory areas of the cerebrum, activation of natriuretic peptides or changes in the distribution of body fluid volumes [11]. To reduce the toxic effects of chemotherapeutic agents to the kidney, patients are instructed to drink plenty of fluids. There is a major association between ectopic ADH secretion and small cell lung cancer and head and neck tumors [12]. Symptoms such as nausea/vomiting and pain are also significant causes of ADH release. Patients with head and neck cancer also often suffer from chronic malnutrition, which is caused by dysphagia and a catabolic state associated with malignant disease [13]. Malnutrition and other chronic diseases can “reset the osmostat.” The threshold for ADH secretion is reset downward, and ADH is secreted at a lower osmolality. In an uncomplicated condition, the kidneys retain the ability to compensatory concentrate and dilute the urine [14]. A reset osmostat classically occurs in neurologic conditions such as epilepsy and paraplegia, in addition to pregnancy, malignancy, and malnutrition; however, this can develop into any other chronic debilitating disease. The reset osmostat variation of the SIADH is thought to occur in up to one-third of these patients [15]. In addition, acute symptomatic hyponatremia can occur in psychogenic polydipsia, caused by various mental disorders. It is most commonly found in patients with schizophrenia and is usually accompanied by the sensation of dry mouth. Cheng et al. have found that early “rapid” correction of acute symptomatic hyponatremia produced no long-term neurologic sequelae [16]. In addition, the use of other drugs, such as antiepileptics and antidepressants (e.g. carbamazepine, used for neuropathic pain, as an anticonvulsant or as a mood stabilizer), can also cause hyponatremia, and physicians should be careful when prescribing these drugs [17,18].
We conclude that increased water intake by these patients, who may already be predisposed to hypo-osmolality, can cause dilutional hyponatremia, which may be overlooked or misdiagnosed. A urine spot sodium test is mandatory for differentiating the cause of hyponatremia, which is crucial for proper treatment. In our case, a urine spot sodium test successfully excluded the two most common cases of hyponatremia in cancer patients: SIADH and drug-induced renal salt wasting. This test has excellent diagnostic accuracy in the diagnosis of SIADH and is usually sufficient to make treatment decisions [19]. Methotrexate-induced hyponatremia would also present with laboratory findings consistent with SIADH, which can be excluded if the urinary sodium spot test shows urinary Na <20 mmol/L.

Case study limitations: There is still a possibility that the patient had methotrexate-induced hyponatremia, and that the urinary sodium spot test was performed in the phase of corrective salt retention which could potentially lead to a falsely low urinary sodium. Furthermore, the urine spot sodium test was done on only one occasion. Magnesium, glucose, triglyceride, protein levels, and urine osmolality were not measured in the presented patient.

Fluid restriction in our patient led to normalization of serum sodium levels and complete recovery of his performance status. Our case emphasizes the need for regular serum electrolyte monitoring in cancer patients because they are commonly malnourished with low dietary sodium intake and advised excessive fluid intake to prevent cytotoxic acute kidney injury. Further studies in this field are mandatory to improve the quality of life and outcomes of cancer patients.

4. Conclusions

Excessive water intake and malnutrition may cause hyponatremia in patients with cancer. Careful monitoring of serum electrolytes should be performed in all cancer patients. A urine spot sodium test should be used in patients with hyponatremia to differentiate the cause of hyponatremia, which is essential for proper treatment.

Author Contributions

MP, NP, DK, and AF participated in patient follow-up, drafted the manuscript and gave their final approval. GM proposed the concept and design of the article and gave her final approval.

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