A Rare Cause Of Hyponatremia: Cyclophosphamide

Hiponatreminin Nadir Bir Nedeni: Siklofosfamit

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Abstract

Hyponatremia is the most common electrolyte disorder and occurs in %10-15 of hospitalized patient. SIADH is a frequent cause of normovolemic hyponatremia and mostly induced by malignancy and many drugs. Cyclophosphamide is a rare agent among this drugs. In this article, we aimed to report the case of acut hyponatremia due to cyclophosphamide and point to this rare cause.

Key words hyponatemia, SIADH, cyclophosphamide

Öz

Hiponatremi en sık görülen elektrolit bozukluğu olup hastanede yatan hastaların %10-15'inde görülmektedir. SİAD ise övolemik hiponatreminin sık bir nedenidir ve başta maligniteler ve bazı ilaçlar olmak üzere pek çok faktöre bağlı görülebilir. Bu ilaçlar arasında siklofosfamit oldukça nadir görülen bir ajandır. Bu yazıda siklofosfamit kullanımına ikincil olarak gelişen akut hiponatremi olgusunu sunmayı ve bu nadir nedene dikkat çekmeyi amaçladık.

Anahtar Kelimeler hiponatremi, siad, siklofosfamit

Intoduction

Hyponatraemia, defined as a serum sodium concentration <135 mmol/L, is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. %10-15 of the hospitalized patient suffer from hyponatremia. Hyponatraemia is primarily a disorder of water balance, with a relative excess of body water compared to total body sodium and potassium content (1,2). In response to hypovolemia, antidiuretic hormone (ADH) is synthesized in hypotalamus. ADH stimulates V2 receptors in distal tubule and increases water reabsorption (3). The syndrome of inappropriate antidiuretic hormone secretion (SIADH), was first described by Scwartz et al in two patients with bronchogenic carcinoma in 1955 (4). SIADH is a disorder of sodium and water balance characterized by urinary dilution impairment and hypotonic hyponatremia, in the absence of renal disease or any identifiable non-osmotic stimulus able to induce ADH release; according to its definition, it is diagnosed through an exclusion algorithm (5). Diagnostic criteria is shown in table 1 (6). Nervous system disorders, neoplasia, pulmonary diseases, and drugs are the major causes of SIADH. Cyclophosphamide is a chemotherapeutic and ımmunosuppressive agent which rarely cause SIADH. We report a female patient with breast cancer got SIADH caused by cyclophosphamide.

Table 1: Diagnostic criteria of SIADH

Absolute criteria	Helpful criteria
Plasma osmolality < 275 mOsm/kg	Plasma uric acid< 4 mg/dl
Urine osmolality > 100 mOsm/kg	Plasma urea< 10 mg/dl
Urine sodium concentration >40 mEq/L	Fractional Excretion of sodium > %1, Fractional Excretion of urea >%55
Patient clinically euvolaemic	No recovery of serum sodium with isotonic NaCl infusion
Normal thyroid, adrenal, renal function	Fractional Excretion of uric acid > %12
No diuretic use	Correction of hyponatremia by fluid restriction
	Abnormal response to water loading test
	Increase of plasma ADH level

Case Report

56 years-old female patient was brought to emergency clinic with the complain of unconsciousness. The patient was consulted our clinic for acute hyponatremia. Her complain started 6 hours ago and proceeded progressively. On her medical history, 20 days before she had undergone left mastectomy operation with the diagnosis of ductal invasive adenocarcinoma and 2 days ago first line chemotherapy treatment was performed. She does not have chronic disease and medication. On her physical examination; vital parameters was normal, GKS was 11 with no cooperation and orientation. Other system examinations were normal. Cranial tomography and diffusion MR was normal. She was clinically euvolemic and serum sodium level was 114 mmol/L with normal renal and liver function tests, CBC and other electrolyte parameters was normal. The examination which was performed one week ago, serum sodium level was 140 mmol/L. The patient was admitted to the intensive care unit. The central venous pressure was 5 cm H2O. The patient was received hypertonic salin infusion treatment for euvolemic hyponatremia. Laboratuary tests were performed for differantial diagnosis. Renal and thyroid function tests, levels of anterior pituitary hormones, serum and urine cortisol levels were normal. Serum osmolality and urine osmolality were respectively 272 and 415 mOsm and spot urine sodium concentration was 86 mmol/L. Se-

rum uric acid level was 2.6 mg/dl. The patient got a SIADH diagnosis. We continued fluid restriction and diuretic treatment for 3 days. When the patient's old examinations were analysed, there were no metastasis in preoperative craniel, torax, abdominal CT scan and no malignant cell in sentinel lymph node biopsy with clean surgical margin. Two days before admission to the hospital, first line chemoterapy was performed with cyclophosphamide and adriamycin in oncology clinic. Cyclophosphamide related SIADH was considered for the patient who has no residual malignancy. After 4 days intensive care follow up, serum sodium level was 137 mmol/L and there was no abnormality at neurologic pyhsical examination. The patient was consulted to the oncology clinic and performed PET-CT scan. There was no evidence of malignancy. After 2 days follow up in internal medicine service the patient was discharged.

Discussion

Our case is a classical examplary of SIADH, both with clinical and laboratory findings. A frequent cause of SIADH is malignancies. Even so we mostly come across as a paraneoplastic syndrome in small cell lung cancer, it might be rarely seen in breast cancer[7]. In our case, although there is a history of breast cancer, tumor burden did not exist at the time of symptom occurance and diagnosis. As it is known, paraneoplastic endocrine syndromes are developed as a result of bioactive molecules produced from tumor cells affecting target tissues[8]. So it is difficult to say that the cause of the present condition in our case is malignancy. Our patient received cyclophosphamide and adriamycin treatment two days before the admission. Cyclophosphamide is a nitrogen mustard type alkylating agent. It becomes effective by converting to phosphoramidmustard in liver, which is the active metabolite. By binding to DNA and alkylation, it corrupts replication and transcription of the DNA. It is not a phase spesific agent[9]. Cyclophosphamide, which is used in the treatment of various autoimmune and malign diseases, is a chemotherapeutic agent that has been used in breast cancers for many years. Most side effects are bone marrow suppression, alopecia, infertility, susceptibility to infections, hemorrhagic cystitis. Another side effect that is rare compared to these side effects is SIADH and it is considered to increase both ADH release and reduce the ability of the kidney to excrete water[10]. Cyclophosphamide induced hyponatremia was first defined in 1974 and considered it retains water[11]. The mecanism is still unclear but previously physicians has observed and reported many cases[12,13,14]. Elazzazy et al reported a case which got breast cancer and hyponatremia caused by cyclophospamide similar to our case[15]. Altough we could not reach cyclophosphamide dose which our patient had received, there are many cases which both low or high dose cyclophosphamide induced hyponatremia in literature[16,17]. In this case report, we tried to attract notice to a rare side effect of cyclophosphamide which is used in various autoimmune and malign diseases. For the patients who receive this treatment, monitorization of sodium levels before and after the treatment might be useful but also more studies are needed to understand identify the patophysiology and frequency of cyclophosphamide induced SIADH.

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