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Case report

An unexpected cause of hyponatremia in a cancer patient: Trimethoprim-sulfamethoxazole

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ABSTRACT:

Background: Hyponatremia is one of the most common electrolyte abnormalities seen in hospitalized patients. In cancer patients, it's generally related to syndrome of inappropriate ADH secretion (SIADH).
Case Report: Here, we report a breast cancer patient with hyponatremia related to high dose trimethoprim-sulfamethoxazole use for pneumonitis cariini pneumonia.
Conclusion: It is important to be aware that all hyponatremias are not related to SIADH in cancer patients. For proper treatment strategies, a proper differential diagnosis is needed.

1. Introduction

Hyponatremia is defined as serum sodium concentration below 135 mEq/L and is the most common electrolyte abnormality in hospitalized patients.[1] Mostly, it is associated with low serum osmolality, an osmolality less than 275 mosmol/kg. There are two classification systems for etiology of hyponatremia. One is according to serum ADH (antidiuretic hormone) level and the second is related to volume status (hypovolemia, normovolemia, or hypervolemia). Urinary excretion of water requires reduction of serum osmolality which can suppress ADH release. An inability to suppress ADH release is the most common cause of hyponatremia and can be seen in conditions like; true volume depletion, decreased tissue perfusion and in the syndrome of inappropriate ADH secretion. Most patients with hyponatremia have a single cause, but occasionally multiple factors contribute to etiology. Cancer or its treatment can cause a variety of renal diseases and a variety of electrolyte disturbances. Reported incidence of hyponatremia in cancer patients is 3.7%[2] and mostly related to SIADH, reduced intake of sodium or gastrointestinal losses. SIADH is defined as dilutional hyponatremia with excessive natriuresis. Many drugs we use in our daily clinical practice can cause hyponatremia, too. Trimethoprim-sulfamethoxazole (TMP-SMX) is an antimicrobial agent, commonly used for *Pneumocystis carinii* infection.

Here, we report a case with severe symptomatic hyponatremia due to treatment with high dose trimethoprim-sulfamethoxazole for suspicious Pneumocystis carinii pneumonia (PCP) infection after adjuvant chemotherapy. The hyponatremia did not respond to the saline infusion and was at the acceptable level after cessation of TMP-SMX.

2. Case report

A 65 year old woman with stage IIIA (T3N2M0) breast cancer diagnosis was admitted to the emergency service with dyspnea and cough. She had been given adjuvant 4 cycle doxorubicin plus cyclophosphamide therapy previously and took her first cycle of docetaxel and trastuzumab adjuvant therapy twelve days prior to her admission. She was febrile (temperature, 39° C) and had bilateral diffuse crackles without respiratory sounds in the left lung base. Laboratory results showed marked elevation of CRP (120.6 mg/dl, normal range 0–3). Chest computed tomography showed diffuse ground-glass opacities and left sided pleural

Abbreviations: ADH, Antidiuretic hormone; PCP, Pneumocystis carinii pneumonia; SIADH, Syndrome of inappropriate ADH secretion; TMP-SMX, Trimethoprim-sulfamethoxazole.

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effusion. She was consulted with an experienced thoracic radiologist and differential diagnosis included docetaxel induced capillary leak syndrome and Pneumocystis carinii pneumonia (PCP). High dose corticosteroid and TMP-SMX 15 mg/kg, 4 times a day in equally divided doses were started on the first day of hospitalization. On the 10th day, serum sodium level decreased abruptly to 120 mg/dl from 136 mg/dl, urinary sodium excretion was 170 mEq/L, serum and urine osmolality was 254 mosm/kg and 529 mosm/kg respectively on the same day. SIADH diagnosis was presumed and the patient was started on fluid restriction. In the second day of the fluid restriction, there was no rise in the serum sodium level despite the effective fluid restriction which was confirmed with the high plasma renin activity of 35.8 (reference range: 0.3–1.9), and therefore saline infusion was started. After 4 days of saline infusion, serum sodium concentration was still 120 mg/dL. Because there was no response to saline infusion, patient was consulted with the Infectious Diseases Department and TMP-SMX was stopped on the 14th day of hospitalization. After 4 days of cessation, the serum sodium concentration increased to 133 mg/dl. One month after the hospital discharge, the serum sodium level was in the normal range (Fig. 1).

3. Discussion

In cancer patients, hyponatremia is generally related to SIADH which occurs as a paraneoplastic syndrome or as a complication of chemotherapeutics.[3] While SIADH is most commonly seen in small cell lung carcinoma,[4] it can occur in any cancer. Chemotherapeutics reported to cause hyponatremia are cyclophosphamide, ifosfamide, vinca alkaloids, bortezomib, carboplatin, and cisplatin.[4] Although hyponatremia in a cancer patient is generally attributable to these causes, in our daily practice we use many other drugs for co-morbidities which can cause hyponatremia. Diuretics, anti-hypertensives, antibiotics, antidepressants, anti-epileptics, proton pump inhibitors, and *etc.* can be blamed as the cause of hyponatremia.[5] TMP-SMX is an antimicrobial agent, effective against Pneumocystis carinii infection and mostly excreted from the kidney. TMP-SMX is suggested to act on distal tubules of nephrons and cause hyperkalemia and less frequently hyponatremia by decreasing renal sodium absorption.[6]

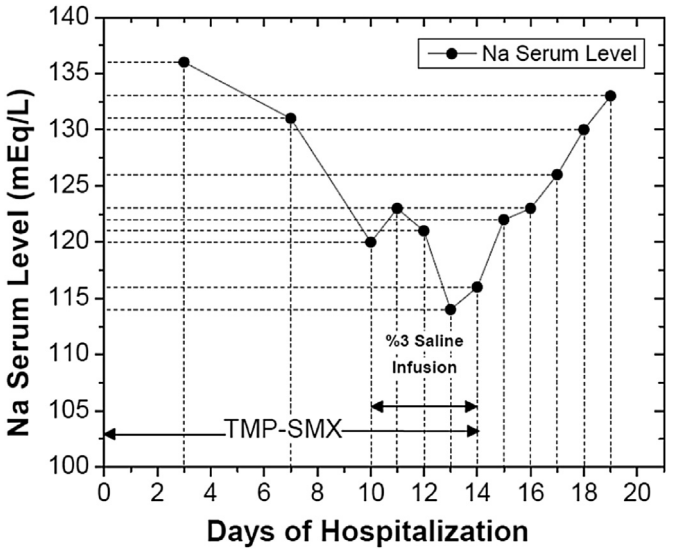

Fig. 1. Correlation of serum sodium concentration with high dose TMP-SMX use

The first case of hyponatremia with trimethoprim was reported in 1984 in a 75 year old woman with a dose of 200 mg twice daily.[7] Hyponatremia improved after the cessation of the therapy and reoccurred with re-challenge of trimethoprim. In 1995, Noto et al, reported two patients, one with Hodgkin's disease and the other with acute myeloblastic leukemia. Both patients developed severe hyponatremia and hyperkalemia with high dose of TMP-SMX given for P. cariini pneumonia.[8] Severe hyponatremia was resolved after the cessation of the therapy in the first case and replacing of TMP-SMX with pentamidine in the second case. Sheehan et al, reported hyperkalemia without hyponatremia related with TMP-SMX therapy.[9] In 2003, Mori et al, retrospectively examined the electrolyte disturbances of 77 patients treated with standard dose of TMP-SMX. They reported electrolyte disturbances in 17.5% of patients with normal renal function and 85.7% of patients with abnormal renal functions.[10]

Because biochemical results of salt wasting due to TMP-SMX are similar to SIADH, it is important to distinguish these two conditions with different treatment strategies. Treatment of SIADH includes restriction of free water and administration of vasopressin antagonists. Hyponatremia related to TMP-SMX treatment can respond to saline infusion, however, most of the time, cessation of the treatment is necessary to correct the serum sodium concentration. In our patient, there was no response to saline infusion.

This is the first case of hyponatremia related to TMP-SMX in a patient receiving chemotherapy for a solid tumor. It is important to be aware that all hyponatremias are not related to SIADH in cancer patients. For proper treatment strategies, a proper differential diagnosis is needed.

Conflicts of interest

All authors have no conflict of interest.

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