

Severe Symptomatic Hyponatremia Caused by Low Dose Oral Cyclophosphamide: A Case Report

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Cyclophosphamide (CY), an alkylating agent, is frequently used in the treatment of various autoimmune disorders and malignancies. Acute hyponatremia is a well-known side effect of moderate to high dose intravenous CY treatment, but is rare in patients treated with low dose intravenous CY. We report the case of a severe symptomatic hyponatremia in a 68-year-old woman with renal impairment who was treated with oral CY (100 mg/day) for anti-neutrophil cytoplasmic antibody (ANCA) associated glomerulonephritis (GN). This case demonstrates that even oral CY could be associated with life threatening acute hyponatremia and should be used with caution.

Key Words: Hyponatremia, Cyclophosphamide, ANCA associated vasculitis

INTRODUCTION

Cyclophosphamide (CY), an alkylating agent, is frequently used in the treatment of various autoimmune disorders and malignancies. Acute hyponatremia after intravenous CY treatment is an infrequent but potentially life-threatening complication. Development of symptomatic hyponatremia is usually associated with high-dose intravenous CY treatment and has rarely been reported with low-dose treatment. Moreover, only one case of symptomatic hyponatremia following low-dose oral CY treatment has been reported so far¹⁾. We report a patient with ANCA-positive glo-

merulonephritis who developed severe symptomatic hyponatremia following 3 weeks of oral CY (1.6 mg/kg/day) administration.

CASE REPORT

A 68-year old woman who was treated for ANCA-associated GN was admitted to the emergency department (ED) due to nausea, vomiting and lethargy that had persisted for several days. Six weeks before the ED visit, she had previously been hospitalized in Hematology Division for evaluation of anemia and fever of unknown origin. During this admission period there was a rapid increment in her serum creatinine from 0.75 mg/dL to 3.22 mg/dL. Further investigations revealed positive anti-myeloperoxidase (750 AAU) and anti-proteinase 3 (483 AAU) (normal cutoff for both ANCA ≤ 150 AAU). She underwent percutaneous renal biopsy which demonstrated multiple cellular crescents and focal segmental glomerulosclerosis. She was diagnosed as having ANCA-associated GN and

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3 days of methylprednisolone pulse therapy (750 mg/day) was initiated. After the steroid pulse therapy, she was given oral CY (100 mg/day) and oral prednisolone (60 mg/day). Low dose oral loop diuretics and losartan was given to control edema and proteinuria, respectively. She initially tolerated her medications well and was discharged from the hospital without any complaints. At discharge, her serum creatinine level was 3.07 mg/dL and her serum sodium level was 137 mmol/L. However, 3 weeks after discharge from the hospital she complained of nausea, vomiting and severe lethargy and visited ED.

At ED, she was confused and disoriented. Her blood pressure was elevated to 150/90 mmHg and the pulse rate was 72 beat per minute. Tongue was mildly dried and skin turgor was also slightly decreased; however, the patient showed no signs of pitting edema. Chest X-ray demonstrated no signs of pulmonary edema or significant decrease of heart size, which means there was no significant decrease of volume status (Fig. 1). Serum sodium was decreased to 102 mmol/L with decreased plasma osmolality (218 mOsm/kg) (reference value 278–298 mOsm/kg), while urinary Na excretion was 40 mmol/L with urinary osmolality of 238 mOsm/kg (reference value 50–1400 mOsm/kg). Urinary creatinine was 32.5 mg/dL and fractional excretion of sodium was 3.7%. Laboratory examination

revealed as follows: hemoglobin 11 g/dL, serum creatinine 3.04 mg/dL (estimated GFR by Modification of Diet in Renal Disease equation 15.7 mL/min/1.73m²), blood urea nitrogen 41.8 mg/dL, potassium 4.5 mmol/L, chloride 65 mmol/L, bicarbonate 24 mmol/L, calcium 8.0 mg/dL, uric acid 5.7 mg/dL, total protein 5.8 g/dL, albumin 3.6 g/dL, plasma glucose 88 mg/dL, cholesterol 229 mg/dL and triglyceride 79 mg/dL. Calculated osmolality was 223.8 mOsm/kg and osmolar gap was 5.8 mOsm/kg, precluding the possibility of pseudohyponatremia.

Endocrine hormone examination showed normal cortisol level and euthyroid status. Plasma antidiuretic hormone (ADH) was 10.65 pg/mL (normal, 0–6.7 pg/mL), despite the presence of severe hyponatremia. The patient denied of any overzealous fluid intake or herb medication use.

Symptomatic hyponatremia precipitated by oral CY was suspected in view of decreased serum sodium level, inappropriately high urine osmolality and chronologic association with CY administration.

After admission, free water intake was restricted and the patient was treated with intravenous hypertonic saline and injections of furosemide. Her consciousness fully recovered after 12 hours and hypertonic saline and intravenous furosemide administrations were continued for 3 more days to correct her serum sodium

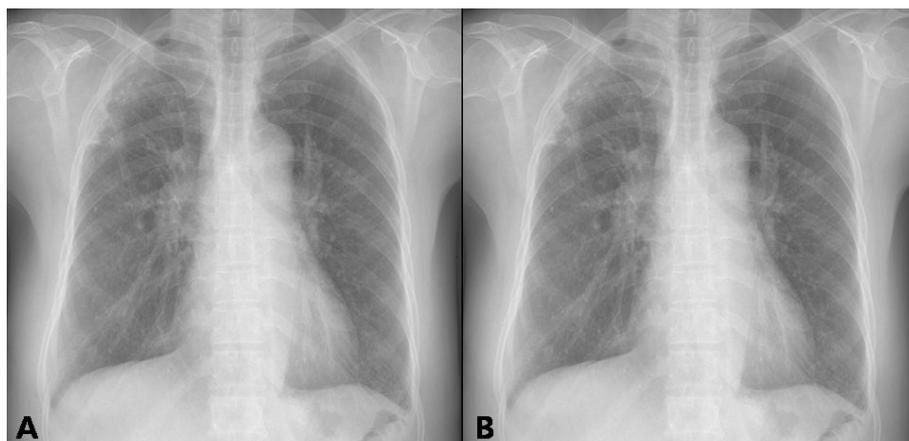


Fig. 1. Chest X-ray taken 3 weeks before (A) and on the day of emergency department admission (B). Chest X-ray shows no signs of pulmonary edema or significant decrease of heart size.

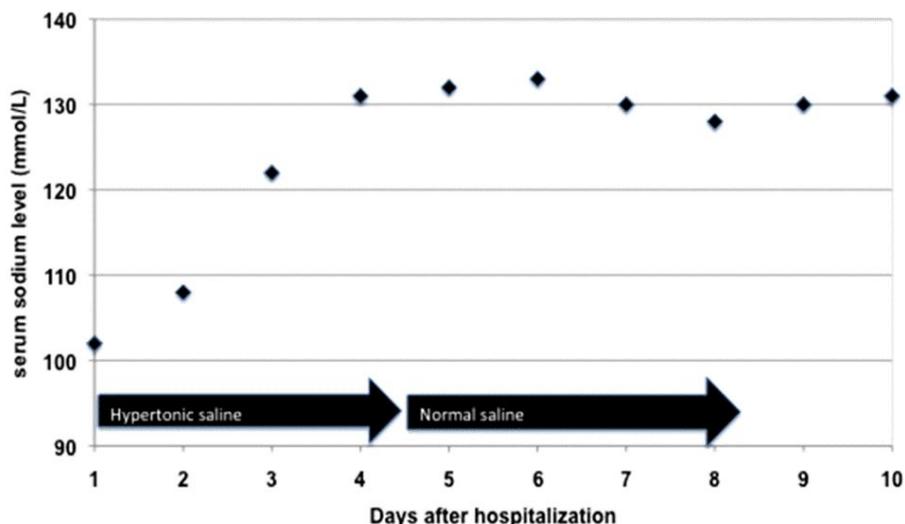


Fig. 2. Changes in the serum sodium level during hospitalization. Hypertonic saline was administered for first 3 days and replaced with normal saline. Her mentality was fully recovered 12 hours after hypertonic saline infusion. Intravenous hydration was continued for 7 days and she was discharged on 10th day of hospitalization.

level up to 131 mmol/L (Fig. 2). Thereafter she was treated conservatively with 0.9% saline 1 L/day for 4 more days. She was discharged 10 days after admission. It remains unknown whether the treatment with oral CY can be safely reinstated after an episode of acute hyponatremia. Therefore, the patient was switched to oral mycophenolatemofetil (2 g/day) and steroids. She has not experienced any more electrolyte derangements.

DISCUSSION

The case presented here highlights the possible dangers of oral CY therapy in precipitating life threatening acute hyponatremia. CY is a commonly used drug in the treatment of various autoimmune or malignancy disorders. However, there are some serious adverse effects associated with the use of this agent including bone marrow suppression, bladder cancer and hyponatremia²⁾. High doses of intravenous CY (>50 mg/kg) have been clearly demonstrated to impair kidney's ability to dilute urine. Recently, low-dose (<15 mg/kg) intravenous pulse CY treatments are predominant re-

gimen used in the clinical practice. This low dose CY may reduce the risk of water intoxication but the risk of precipitating symptomatic hyponatremia is not uncommon³⁾. In contrast, symptomatic hyponatremia associated with low dose oral CY treatment has rarely been reported. To the best of our knowledge, there is only one other case of symptomatic hyponatremia associated with low dose oral CY treatment (1.4 mg/kg)¹⁾. The present case demonstrated development of symptomatic hyponatremia after 3 weeks of oral CY treatment that was initially well tolerated.

The precise mechanism of CY induced hyponatremia remains uncertain. Direct toxic effects or potentiation of the renal action of ADH by alkylating metabolites of CY have been proposed^{2, 4)}. Mildly elevated plasma ADH level noted in our patient might more likely be due to decreased urinary clearance of ADH in chronic renal failure as opposed to increased secretion by accompanying mild volume depletion⁸⁾. Moreover, some lines of evidence argue against dehydration as the major player in causing the severe hyponatremia noted in the patient. The patient was not hypotensive and did not show any signs of tachycardia that are

commonly observed in patients with volume depletion. Furthermore, the ratio between blood urea nitrogen and serum creatinine (13.7) nor calculated FENa demonstrated by the patient were compatible with severe dehydration.

Onset of clinically symptomatic hyponatremia was most common within 1–2 days of intravenous CY administration²⁾. Due to the paucity of reported cases of symptomatic hyponatremia after oral administration of CY, the time frame of development of symptomatic hyponatremia is uncertain. Compared to intravenous route, the oral route of administration might take more time for the metabolites of CY to accumulate in the body. As is in our case, the underlying renal impairment might have contributed to greater accumulation of drug metabolites and could have triggered the development of severe hyponatremia.

Previously reported cases of severe hyponatremia associated with low dose CY treatment were usually preceded by massive hydration (2–3 L/day)³⁾. Our patient denied any overzealous water intake but did report daily fluid intake of at least 1 liter. The patient denied taking any medications such as non-steroidal anti-inflammatory agents or thiazide diuretics that may provoke acute hyponatremia. The rapid improvement of hyponatremia after cessation of CY also support the role of CY in development of hyponatremia. Taken together, the progressive accumulation of CY metabolites and possible fluid retention due to patient's underlying impaired renal function could have aggravated hyponatremia.

Treatment for acute hyponatremia usually consists of removal of the inciting factor and infusion of hypertonic or isotonic saline⁵⁾. The CY treatment was stopped immediately and our patient received hypertonic saline and loop diuretics. She showed dramatic neurologic improvements within the first 24 hours and her electrolyte abnormalities improved after conservative treatment.

The present case illustrates the potential danger of acute hyponatremia following low dose oral CY treat-

ment. Two other cases of acute symptomatic hyponatremia after low dose and moderate dose of intravenous cyclophosphamide have been reported in Korea^{6,7)}. Lee et al also reviewed water intoxication after low dose intravenous CY, which were usually associated with massive intravenous hydration to prevent development of hemorrhagic cystitis³⁾. To the best of our knowledge, the present case is the first case report of acute symptomatic hyponatremia after low dose of oral CY in Korea. Greater awareness of this potentially life-threatening complication may reduce the risk of its occurrence.

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