Case Report

Water intoxication induced by low-dose oral cyclophosphamide in a patient with anti-neutrophil cytoplasmic antibody-related glomerulonephritis

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Abstract
We reported the case of a 70-year-old woman with moderate renal failure due to anti-neutrophil cytoplasmic antibody-related glomerulonephritis who developed symptomatic water intoxication (serum Na: 108 mEq/L) following treatment with oral low-dose cyclophosphamide (CY) (50mg/day). Estimated glomerular filtration rate was 29.5 mL/min/1.73 m². She had drunk >2 L of fluid in 12 h prior to the development of cerebral oedema. This rare case suggests that oral low-dose CY could be an occult cause of water intoxication in patients with chronic kidney disease taking large fluid volumes.

Keywords: chronic kidney disease; cyclophosphamide; fluid intake; symptomatic hyponatraemia

Introduction

Cyclophosphamide (CY) is an alkylating drug often used for rheumatologic diseases such as anti-neutrophil cytoplasmic antibody (ANCA)-related glomerulonephritis (GN). Water intoxication following intravenous low-dose CY is reported rarely to cause life-threatening water intoxication [1–4]. Herein, we report the case of an elderly woman with ANCA-related GN who developed symptomatic water intoxication following low-dose oral CY treatment for 1 month.

Case report

A 70-year-old woman with ANCA-related GN was emergently readmitted to our hospital due to the development of nausea, vomiting, confusion and mental disorientation concomitantly on 9 January 2006. She had previously been admitted to our hospital due to anaemia and a rapid increment of serum creatinine from 0.69 to 3.08 mg/dL in the previous 3 months on 28 October 2005. After admission, serum creatinine had maximally increased to 5.22 mg/dL. Due to the presence of 123 EU of serum myeloperoxidase (MPO)—ANCA titre and crescentic GN in the kidney biopsy—we diagnosed her as having ANCA-related GN. After twice methylprednisolone pulse therapy (500 mg/day), we had started 30 mg/day of oral prednisolone (PSL) on 7 November and subsequently added oral CY [50 mg/day, 1.4 mg/kg body weight (BW)/day] since 6 December. She had been discharged from our hospital on 20 December, with 20 mg/day of PSL and 50 mg/day of CP. At discharge, her serum creatinine had decreased to 1.98 mg/dL with normal serum sodium (Na)

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Hyponatraemia associated with oral cyclophosphamide

Fig. 1. Cerebral oedema due to water intoxication. Plain brain CT scan revealed marked swelling of the sulcus at the frontal lobe and narrowing of cerebral ventricles at re-admission. Following the discontinuation of CY treatment and fluid restriction, hyponatraemia was promptly restored by 72 h without any disorientation. CT scan also revealed no cerebral oedema at hospital Day 10. Abbreviations are CT: computed tomography and CY: cyclophosphamide.

glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) Study equation [5]. Plain brain computed tomography (CT) scan revealed brain oedema such as swelling of the sulcus at the frontal lobe and ventricular narrowing (Figure 1A).

Endocrine hormone examination at early morning on 10 January disclosed as follows: plasma ACTH 155 pg/mL (normal, 7.4–55.7), cortisol 17.7 µg/dL (normal, 5.3–11.0) and aldosterone 311 pg/mL (normal, 29.9–159). Thyroid function was within normal range. Plasma renin activity was suppressed to 0.2 ng/mL/h (normal, 0.3–2.9), and plasma human atrial natriuretic peptide (ANP) was elevated to 80 pg/mL (normal, ≤40), a compatible finding with overhydration. Plasma antidiuretic hormone (ADH) was 2.7 pg/mL (normal, 0.3–3.5), despite the presence of hyponatraemia (Na: 119 mEq/L).

We diagnosed the patient as having water intoxication in view of hyponatraemia with an inappropriately high urine osmolality. We first suspected the CY-induced water intoxication combined with massive hydration. After stopping oral CY, the fluid intake was restricted by 1 L/day of 0.9% saline solution. By 72 h after readmission, she was fully oriented with normal electrolyte concentrations. In retrospective, she reported that she had drunk >2 L of fluid in the 12 h prior to the readmission. Plain brain CT scan on day 10 showed the improvement of sulcus swelling and ventricular narrowing (Figure 1B).

One month after the cessation of CY, we conducted a water-loading test (20 mL/kg body weight) by infusing 5% glucose solution for 30 min (Scr: 1.54 mg/dL, eGFR: 26.8 ml/min/1.73 m²). By 4 h, a total of 85% of the loaded volume was excreted into the urine, and urinary osmolality decreased from 369 to 150 mOsm/kg H₂O. Plasma ADH also decreased to 1.2 pg/mL with 130 mEq/L of serum Na at 2 h after the loading. Until April 2008, she has not experienced any episode of hyponatraemia.

Discussion

It was initially thought that water intoxication developed in doses >50 mg/kg BW of CY [6]. However, this is not true, since some observations have shown that low-dose CY also, but rarely, causes water intoxication [1–4]. To the best of our knowledge, there were five cases that developed symptomatic water intoxication following low-dose CY (<15 mg/kg BW) (Table 1). In all of the cases, the drug was given intravenously. In this case, we first experienced severe hyponatraemia in an elderly women with oral administration of low-dose CY (daily dose: 1.4 mg/kg) for 1 month.

That CY was responsible for hyponatraemia in this patient is supported by some observations. First, her hyponatraemia had first become evident 1 month after oral CY treatment. By stopping CY and water restriction, her hyponatraemia soon dissolved and have not occurred again. Second, the water-loading test at 1 month after CY cessation revealed normal excretion of free water, indicating no prior impairment of water excreting ability. Third, no other cause of hyponatraemia was apparent. Nausea is a potent stimulus to release ADH, but her plasma ADH remained within normal range. In addition, nausea soon dissolved concomitantly with the correction of hyponatremia by water restriction. Other study also showed that no rise of plasma is
Table 1. Patient characteristics of water intoxication following low-dose CY

| Age (years) | Sex | Original diseases | CY dosage | Scr (mg/dL) | Serum Na (mEq/L) | Fluid intake | Ref. |
|------------|-----|-------------------|-----------|------------|-----------------|-------------|-----|
| 68         | M   | MM                | 500 mg, iv| 0.96       | 108             | 3 L/day     | [1] |
| 59         | F   | SLE               | 10 mg/kg, iv| 0.63       | 116             | 2.4 L/day   | [2] |
| 57         | F   | Sjögren           | 780 mg, iv| 0.6        | 117             | >0.95 L/6 h| [3] |
| 48         | F   | SLE               | 750 mg, iv (12.5 mg/kg)| 0.72       | 119             | 3 L/day     | [4] |
| 53         | F   | SLE               | 750 mg, iv| ND         | 119             | 3 L/2 h     | [4] |
| 70         | F   | ANCA-related GN   | 50 mg (1.4 mg/kg)| 1.31       | 108             | >2 L/12 h  | This case |

CY: cyclophosphamide, MM: multiple myeloma, SLE: systemic lupus erythematosus, ANCA-related GN: anti-neutrophil cytoplasmic antibody-related glomerulonephritis, Scr: serum creatinine, Na: sodium and ND: not determined.

observed during moderate-dose CY infusion [7]. However, the water-loading test when recovered from hyponatraemia decreased plasma ADH to 1.2 pg/mL, indicating that the level of plasma ADH (2.7 pg/mL) at readmission was relatively high in association with CY therapy. Since a case has been reported of an 8-year-old girl with established diabetes insipidus with hyponatraemia caused by CY infusion despite an inability to secrete ADH [8], one or more CY metabolites may directly alter water permeability in the kidney.

One certain factor that possibly may contribute to water intoxication was excess fluid intake in this case. Previously reported cases that developed severe hyponatraemia by low-dose CP also received oral hydration >2–3 L of fluid a day. Other causative factors responsible for water intoxication were the presence of renal failure and hypoalbuminaemia. Moderate renal failure (Ccr: 25–50 mL/min) prolongs the half-life of CY (50–100 mg/m² as a 1-h infusion) from 4.8 to 6.4 h [9]. Since hyponatraemia was already evident 3 days before re-admission, accumulated CY metabolites by continuous oral regimen may gradually progress to hyponatraemia.

In summary, we experienced the case of an elderly woman with impaired renal function who developed symptomatic hyponatraemia following oral CY administration for 1 month. In this case, the patient had been taking over 2 L of fluid per day according to the general advice to avoid the risk of cystitis, which may contribute to water intoxication. Thus, nephrologists should be aware that oral low-dose CY could be an occult cause of water intoxication in renal failure patients and should advise the patient to take sodium chloride when using oral hydration.

Conflict of interest statement. None declared.

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