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CASE REPORT

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Water intoxication associated with moderate dose of cyclophosphamide pulse therapy in an elderly patient: a case report and literature review

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Abstract Intravenous high-dose cyclophosphamide infusion, usually performed to treat malignant neoplasms, is known to cause water intoxication. Intravenous cyclophosphamide pulse therapy (IVCY) is increasingly being employed for the treatment of rheumatic diseases as well. Recently, water intoxication has been reported to occur even after low-to-moderate doses of IVCY. In the present paper, we describe a case of polyarteritis nodosa in a patient in whom water intoxication developed after IVCY at a moderate dose. Hydration is usually performed to maintain sufficient urine flow to avoid cystitis. Based on our case and a review of the literature, it is recommended that hydration should be carefully performed during IVCY in order to avoid water intoxication, especially when treating elderly patients.

Key words Intravenous cyclophosphamide pulse therapy (IVCY) · Polyarteritis nodosa · Syndrome of inappropriate antidiuretic hormone secretion (SIADH) · Water intoxication

Introduction

Cyclophosphamide (CY) is an alkylating agent used to treat a variety of diseases including malignant neoplasms, organ transplantation and autoimmune disorders. In the field of rheumatology, intravenous cyclophosphamide pulse therapy (IVCY) is now widely employed based on evidence showing its efficacy as a treatment for systemic lupus erythematosus.[1,2] The efficiency of IVCY was also reported in vasculitic syndrome, such as polyarteritis nodosa, microscopic polyangiitis and Wegener's granulomatosis.[3,4]

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High-dose (30–50 mg/kg) IVCY, used to treat malignant neoplasms, is known to cause water intoxication that is clinically consistent with the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[5–9] Recently, life-threatening water intoxication was also reported to occur even by low (10 mg/kg) to moderate (15–20 mg/kg) doses of CY applied to treat rheumatic disorders.[10–14] Here, we describe a patient with polyarteritis nodosa demonstrating water intoxication after administration of IVCY at a moderate dose.

Case report

A 64-year-old woman was admitted to our hospital on April 9, 2003 because of general myalgia, fever, and walking difficulty. Laboratory data were as follows: hemoglobin, 10.9 g/dl; leukocyte count, 10900/μl (neutrophils 80.8%, eosinophils 0.8%); platelet count, 4.3×10^5/μl; erythrocyte sedimentation rate, 110 mm/h; C-reactive protein (CRP), 15.4 mg/dl. Antimyeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) was 461 EU/ml by enzyme-linked immunosorbent assay (normal range <10 EU/ml). Neither antinuclear antibody nor antiproteinase-3 antineutrophil cytoplasmic antibody (PR3-ANCA) was positive. Serum electrolytes were all within the normal range. Renal function and urinalysis were normal. Chest radiograph showed no major findings except for a tiny, old inflammatory change in the lower lung field. Myalgia and muscle tenderness continued, especially at lower limbs. Creatine phosphokinase was within the normal range (33 IU/ml) and there was no apparent neurological abnormality. Muscle biopsy was performed under suspicion of vasculitis. The biopsy specimen from gastrocnemius muscle revealed necrotizing vasculitis with fibrinoid necrosis of small arteries. Smaller vessels (arteriole, capillary, and venule) were intact. Clinically, there was no sign of arteriole or capillary injuries at lung, kidney, and skin. Based on histopathological and clinical findings, polyarteritis nodosa was diagnosed.

Oral steroid therapy with prednisolone 30 mg/day (0.7 mg/kg per day) was started on April 18. As CRP remained elevated around 5 mg/ml and myalgia did not disappear, steroid pulse therapy with methylprednisolone 500 mg/day for 3 days was begun since April 29. The level of CRP decreased. However, following oral prednisolone 35 mg/day, CRP again became elevated. Therefore, IVCY of 500 mg (12 mg/kg) was administered on May 14. The second IVCY was performed with an increased dose of CY, 750 mg/day (=18 mg/kg), on May 28. In each IVCY therapy, the patient was prehydrated with 500 ml of fluids containing 0.2% sodium infused over 2 h, followed by CY administration in 500 ml solution containing 0.2% sodium infused over 3 h. On the morning following the second IVCY, the patient felt nausea and vomited. Blood tests in the morning were as follows: Na 117 mEq/l, K 3.7 mEq/l, Cl 80 mEq/l, and ADH 2.5 pg/ml. Serum osmolarity was 246 mOsm/kgH_2O, whereas urine osmolarity was 528 mOsm/kgH_2O. There were neither endocrinal abnormalities nor a marked elevation of blood glucose. No signs of dehydration or edema were observed. Water intoxication associated with IVCY was diagnosed. After intravenous furosemide together with isotonic saline infusion, the patient's nausea and headache disappeared. In the evening, serum sodium concentration increased to 126 mEq/l and returned to the normal range after several days (Fig. 1). Since June 12, azathioprine (50 mg/day) was added to oral prednisolone. In September, the patient entered complete remission with normal CRP levels, negative MPO-ANCA, and no signs or symptoms of vasculitis.

Discussion

In the 1970s, several reports showed that high-dose IVCY caused water intoxication or SIADH.[5–9] In those days, water intoxication was considered to barely occur when CY was administered at doses less than 30 mg/kg.[6] However, as listed in Table 1, patients with water intoxication associated with lower doses of CY have been reported since the 1980s, probably due to the increasing numbers of patients receiving low to moderate doses of CY which targets nonmalignant disorders such as rheumatic diseases.[10–14] Bressler and Huston first reported that water intoxication developed after a moderate dose of CY in a patient with systemic lupus erythematosus.[10] Webberley and Murray reported a patient with multiple myeloma, in whom water intoxication developed following treatment with oral indomethacin and low-dose IVCY.[11] Water intoxication was also observed after low-dose CY in patients with systemic lupus erythematosus[12,14] and Sjögren's syndrome.[13] In the present paper, we report that a moderate dose of IVCY (18 mg/kg) caused water intoxication in a patient with polyarteritis nodosa.

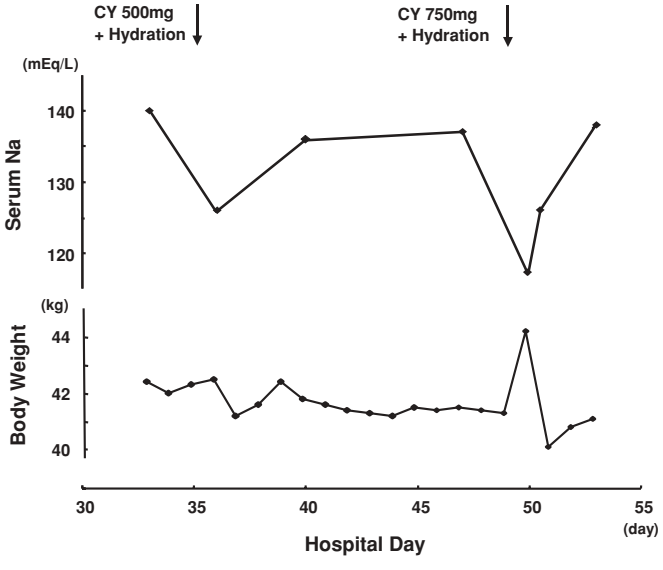

Fig. 1. Serum sodium concentration and body weight in the course of intravenous cyclophosphamide pulse therapy (IVCY)

As stated by Spital and Ristow,[13] the potential risk of water intoxication following IVCY has not been well recognized among rheumatologists. Retrospectively, our patient showed mild hyponatremia (126 mEq/l) with mild nausea on the morning following the first IVCY (Fig. 1). This episode was overlooked and the patient exhibited severe hyponatremia after the second IVCY with a 50% increased dose. So rheumatologists should be aware of the potential risk of water intoxication after a low to moderate dose of IVCY.

The exact mechanism of water intoxication associated with IVCY remains unknown. Affected patients showed minimum findings indicating SIADH, which are hyponatremia, serum hypoosmolarity, and urinary hyperosmolarity characterized by continued sodium excretion.[15] The plasma ADH level was reported to be unchanged during water retention after IVCY,[6,7,10] including our patient. Although the unchanged level of ADH despite plasma hypotonicity might reflect the effect of CY on the hypothalamus, the ADH level seems too low to explain acute and severe water retention and hyponatremia that developed soon after CY administration. The most possible explanation is that CY or its metabolites directly affect renal tubules permitting increased water reabsorption or indirectly increasing the sensitivity of the tubules to ADH.[5–9,15]

Interestingly, the ages of patients in whom water intoxication developed following a low to moderate dose of CY were all 48 years or older (Table 1). Four out of seven patients were given CY for the treatment of systemic lupus erythematosus. In general, the peak ages of disease onset in systemic lupus erythematosus are between the second to fourth decades of life. Although younger lupus patients are expected to be equally likely to receive IVCY, there is no patient under the fourth decade of life reported to have developed water intoxication. So it is suggested that water intoxication by CY more frequently develops in elderly patients. The reason for higher prevalence of water intoxication after IVCY in elderly patients remains to be clarified.

Cyclophosphamide is well known to cause hemorrhagic cystitis. Hydration is usually performed to maintain sufficient urine flow to avoid cystitis. All reported patients received high volume hydration during IVCY (Table 1). Most

Table 1. List of patients with water intoxication associated with low to moderate dose of intravenous cyclophosphamide pulse therapy (IVCY)

First author, year[Ref.]	Age (years)	Sex	Disease	Minimal serum sodium concentration (mEq/l)	Dose of IVCY	First clinical manifestation (interval after IVCY)	Later clinical manifestation (interval after IVCY)	Hydration before/after IVCY
Bressler, 1985[10]	54	F	SLE	112	20 mg/kg	Somnolence (18 h)	Generalized seizures (28 h)	Intravenous infusion of 5% dextrose in water at a rate of 100 ml/h for 28 h after IVCY
Webberley, 1989[11]	68	M	Multiple myeloma	108	500 mg/body (<10 mg/kg)	Restless, confused, disorientated, pulmonary edema (48 h)		Oral hydration with 3 l of fluid a day after IVCY
McCarron, 1995[12]	59	F	SLE	116	10 mg/kg	Headache, nausea, vomiting (12 h)	Confusion, somnolent (not described)	Intravenous infusion at 100 ml/h for 24 h after IVCY
Spital, 1997[13]	57	F	SS	117	780 mg/body (500 mg/m^2)	Nausea (soon after IVCY)	Incoherent, disoriented (16 h)	Pretreatment with several glasses of water, instruction to drink at least 32 oz. of water over the next 6 h
Salido, 2003[14]	48	F	SLE	119	12.5 mg/kg	Confused, disoriented, incoherent (8 h)	Generalized seizures (14 h)	Instruction to drink at least 3 l of water a day after IVCY
Salido, 2003[14]	53	F	SLE/SS	119	500 mg/body	Vomiting, diarrhea, generalized seizures (7 h)		Drank 3 l of fluid before IVCY
Present case	64	F	PN	117	18 mg/kg	Nausea, vomiting (16 h)		Intravenous infusion 1 l of low-salt infusion during IVCY, drunk a large volume of water after IVCY

SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; PN, polyarteritis nodosa

patients were hydrated with sodium-free fluid, such as an infusion of 5% dextrose in water or drinking water. Our patient was administered 1 liter of low-salt fluid during IVCY. Moreover, it turned out retrospectively that she also drank a large volume of water due to a fear of hemorrhagic cystitis. Increased body weight of about 3 kg the next morning indicated that this patient was overloaded with water. Therefore, given the potential risk of water retention following CY, which may be caused by a direct effect of CY or its metabolites on renal tubules, inadequate hydration was considered to be associated with water intoxication after IVCY.

Although water intoxication after IVCY is not predictable, the following points would be important to avoid or minimize it. First, special attention should be paid to patients 50 years or older. These days, IVCY is being used in the treatment of vasculitic diseases. MPO-ANCA-associated vasculitis or polyarteritis nodosa is more common in the elderly, so IVCY should be cautiously performed in the treatment for these patients. Second, hydration for the protection of cystitis should be performed carefully. The risk of SIADH can be reduced by infusion of isotonic saline instead of hypotonic saline.[7,13] Limiting free water intake can also diminish the risk of water retention. Administration of furosemide together with isotonic saline would be useful to maintain urine flow without inducing hyponatremia. Third, patients should be monitored closely not to miss the signs and symptoms of water intoxication, such as headache, nausea, weakness, or alteration in mental status.[13] Two of three patients with generalized seizure were reported to show a change in mental status, such as somnolence or disorientation 7–10 h prior to the appearance of grand mal seizure (Table 1). If any signs or symptoms are noted, serum sodium concentration should be examined immediately, especially in patients 50 years or older.

In summary, we reported the case of a patient with polyarteritis nodosa who developed water intoxication after IVCY. Although hydration seems important during IVCY to prevent cystitis, it should be performed carefully in order to avoid water intoxication, especially in elderly patients.

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