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Case report

Severe toxicity of chemotherapy against advanced soft tissue sarcoma in Werner's syndrome: Ifosfamide-induced encephalopathy with central diabetes insipidus

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1. Introduction

Werner's syndrome is an autosomal recessive disorder characterized by premature aging [1]. Werner's syndrome patients have genetic disorders such as mutations in the WRN gene that cause rapid replicative senescence, chromosomal instability and sensitivity to various DNA damaging agents [2]. Severe toxicity following induction chemotherapy in a patient with Werner's syndrome has been reported previously [3]. Patients with Werner's syndrome develop a variety of benign and malignant tumors, predominantly of mesenchymal origin. The most common tumor type is sarcoma [4]. Despite the high incidence of sarcoma, there is little information regarding optimal treatment for these patients.

Ifosfamide is used in the treatment of various cancers. Common side effects are encephalopathy, myelosuppression, hemorrhagic cystitis, acute renal failure, Fanconi's syndrome, and interstitial pneumonia.

Diabetes insipidus (DI) is a condition characterized by excessive thirst and excretion of large amounts of severely diluted urine, with reduction of fluid intake having no effect on urine concentration. The most common type of DI in humans is the neurological form, called central DI, and the second is nephrogenic DI. Although three cases of ifosfamide-induced nephrogenic DI have been reported in the literature [5–7], no case of central DI has been reported.

Here we report on a patient with Werner's syndrome with retroperitoneal undifferentiated pleomorphic sarcoma (UPS) who was treated with a regimen of ifosfamide and doxorubicin, and showed severe toxicity, acute respiratory distress syndrome, central DI and encephalopathy after ifosfamide infusion. Consent for the publication of this case was obtained from the patient's family.

2. Report of the case

A 55-year-old man presented with Werner's syndrome and a history of surgery for UPS of the right leg three years previous and lung cancer one year previous. He had neither a history of chemotherapy nor radiotherapy. He also underwent resection of retroperitoneal UPS 6 months earlier.

Typical metastasis from the right leg was not observed, but might have been an asynchronous and multifocal tumor or a new primary tumor. The tumor recurred as unresectable because of the large size at 6 months after initial resection.

An 8 g/m^2 course of ifosfamide and 50 mg/m^2 course of doxorubicin (a 20% reduction in the standard dose) were planned. Administered doses of ifosfamide and doxorubicin were 2.5 g/m^2 and 19 g/m^2 on day 1, and 1.9 g/m^2 and 19 mg/m^2 on day 2. Encephalopathy with delirium and disturbance of consciousness (GCS 12 = E3, V4, M5) occurred on day 2, and an intravenous infusion of methylene blue (50 mg/8 h) was subsequently administered to treat the encephalopathy. Administration of methylene blue was approved by our Institutional Review Board and we obtained the consent of the patient's family. Simultaneously, polyuria was noted, with a urinary output of 8 L/day. Chemotherapy was stopped on day 3, and abnormal physical findings, including disturbance of

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consciousness (GCS 12 = E3, V4, M5) and decreased skin turgor were observed.

Laboratory testing showed increased white blood cell and platelet counts and C-reactive protein level and decreased hemoglobin and albumin levels (Table 1). No increase in serum creatinine concentration from his baseline concentration of 1.14 mg/dL was observed. Urinary sediment examination and urine N-acetylglutamate were normal. The data suggested no kidney tubule cell damage. Elevated urine β_2-microglobulin was from the huge tumor and inflammation.

Brain computed tomography showed no abnormal findings such as tumor, inflammation and trauma that would result in central DI in the pituitary gland and hypothalamus (Fig. 1).

With no medical history of diabetes mellitus and normal fasting blood sugar, osmotic diuresis was excluded from causes of excess urination. The presence of hypernatremia (serum sodium 152 mEq/L), urine osmolality/plasma osmolality ratio 1.022 > 1 and poor increase in urine osmolality (319 mOsm/kg H_2O) despite high plasma osmolality (312 mOsm/kg H_2O) suggested a suspicious disorder in urine concentration. Central DI was suspected by the presence of polyuria that occurred rapidly accompanied by the disturbance of consciousness. Although urine osmolality (319 mOsm/kg/H_2O) fell short of diagnostic criteria (<300 mOsm/kg/H_2O), we considered that sodium was loaded by chemotherapy and, as a result, urinary sodium excretion increased and urine osmolality increased (Fig. 2A).

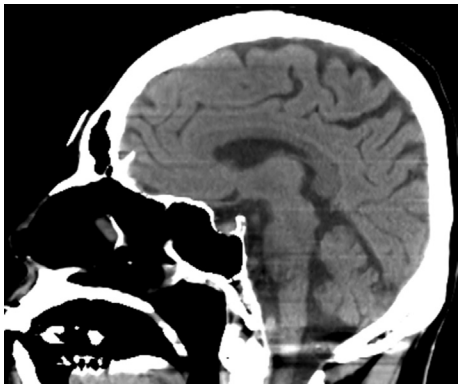

Fig. 1. Brain computed tomography showed no abnormal findings.

To distinguish between central and nephrogenic DI, 2.5 μg desmopressin was given by nasal spray on day 5. Desmopressin reduced urine output and increased urine osmolality (Fig. 2B). These findings were consistent with a diagnosis of central DI, and 2.5 μg desmopressin was continued. Encephalopathy improved (GCS 15) on day 6.

On day 9, the patient's body temperature was elevated over 38 °C, while blood pressure was 159/71 mmHg. His oxygen saturation level reduced to 98% under 2 L/min O_2 and fine crackles appeared in both lung fields.

Table 1
Laboratory data on the occurrence of central DI (Day 3).

Laboratory test	Result	Normal range
Serum		
White blood cell (/μl)	14,500[a]	3900–9800
Red blood cell (10^4/μl)	270[a]	427–570
Hemoglobin (g/dl)	7.3[a]	13.5–17.6
Blood platelet (10^4/μl)	50[a]	13.1–36.2
Total protein (g/dl)	6.4	6.4–8.1
Albumin (g/dl)	2.2[a]	4.0–5.1
Blood urea nitrogen (mg/dl)	17	8–20
Creatinine (mg/dl)	1.12[a]	0.53–1.01
Aspartate aminotransferase (U/L)	12	12–32
Alanine aminotransferase (U/L)	18	5–36
Lactate dehydrogenase (U/L)	169	116–230
Sodium (mEq/L)	149	137–146
Chloride (mEq/L)	105	98–107
Potassium (mEq/L)	4.3	3.6–4.8
Bicarbonate (mmol/l)	30[a]	21–28
Calcium (mg/dl)	7.6[a]	8.7–10.3
Glucose (mg/dl)	97	60–100
Osmolarity (mOsm/l)	299[a]	275–290
Urine		
Urinary volume (l/24 h)	8.5[a]	0.8–2
Glucose (mg/dl)	11[a]	< 0.5
pH	8.5	–
Osmolarity (mOsm/l)	315	250–1300
Sodium (mEq/l)	150	110–250
Potassium (mEq/l)	13[a]	35–90
Chloride (mEq/l)	123[a]	127–257
Calcium (mg/dl)	5.5	–
Phosphorus (mg/dl)	7	–
Creatinine (mg/dl)	7.4	–
Uric acid (mg/dl)	3	–
Total protein (mg/dl)	4.6	–
Specific gravity	1.01	–
Protein	–	
Sugar	–	
Occult blood	–	
Ketone	–	
β_2-Microglobulin (μg/L)	5984[a]	< 300
N-acetylglutamate (U/L)	3.6	0.3–11.5

[a] Abnormal value.