A case of primary adrenal diffuse large B cell lymphoma presenting with severe hyponatremia

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Abstract We herein report a case of primary adrenal lymphoma with severe hyponatremia. The patient was admitted for an evaluation of severe hyponatremia and an enlarged bilateral adrenal mass, which were found in a previous examination for causes of general fatigue and anorexia. Laboratory data, including the serum levels of sodium (115 mEq/L), osmolality (239 mOsm/kgH₂O), ADH (5.8 pg/mL), cortisol (11.6 µg/dL), free T3 (2.42 pg/mL), urinary Na (117 mEq/L) and urine osmolality (490 mOsm/kgH₂O), fulfilled the diagnostic criteria for the syndrome of inappropriate secretion of ADH (SIADH). An abdominal computed tomography scan revealed a large bilateral adrenal mass. A biopsy of the enlarged left adrenal mass revealed diffuse large B cell lymphoma, which was negative for ADH protein. Hydrocortisone treatment normalized the patient's body temperature and serum sodium concentration. In this case, hyponatremia developed when both adrenal glands were involved and was normalized

with hydrocortisone. These findings suggest that adrenal insufficiency was the cause of hyponatremia, although the basal serum cortisol was normal. The current case suggests that the administration of hydrocortisone is recommended if suspicious clinical signs or symptoms are found in severe hyponatremia, even if hyponatremia is associated with a normal serum cortisol level and fulfills the diagnostic criteria for SIADH.

Keywords Primary adrenal lymphoma · Hyponatremia · Adrenal insufficiency · SIADH

Introduction

Primary adrenal lymphoma (PAL) is rare and fewer than 200 cases have so far been reported in the English literature [1]. PAL is bilateral in approximately 75 % of cases [1] and severe hyponatremia has been known to develop in patients with bilateral PAL [2–5]. However, the causes of hyponatremia associated with bilateral PAL have not been fully investigated.

Antidiuretic hormone (ADH) production by lymphoma cells was previously reported [6, 7], which suggests that sustained production of ADH may induce hyponatremia in PAL. Adrenal insufficiency is another potential cause of hyponatremia, since adrenal insufficiency is known to occur frequently in bilateral PAL [1, 2].

Because hyponatremia induced by adrenal insufficiency is readily corrected by the administration of hydrocortisone, the evaluation of the adrenal function is imperative in the differential diagnosis of hyponatremia. In addition, the diagnostic criteria for the syndrome of inappropriate secretion of ADH (SIADH) require the confirmation of normal adrenal function [8, 9].

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In general, the adrenal function is evaluated by the basal serum cortisol level. However, the diagnostic criteria for adrenal insufficiency in patients under unusual stress remain controversial [10].

We herein report a case of bilateral PAL associated with severe hyponatremia. The patient's hyponatremia fulfilled the diagnostic criteria for SIADH proposed by a team of experts supported by the Japanese Ministry of Health, Labour and Welfare [11], which is widely used in Japan. Although his basal cortisol level was normal, hyponatremia was rapidly normalized by the administration of hydrocortisone.

Table 1 Laboratory data on admission

Hematology	
White blood cell	7530/mm ³
Neutrophil	73.0 %
Eosinophil	8.0 %
Basophil	0.0 %
Monocyte	10.0 %
Lymphocyte	8.0 %
Red blood cell	395 × 10 ⁴ /mm ³
Hemoglobin	10.9 g/dL
Platelet	29.1 × 10 ⁴ /mm ³
Blood biochemistry	
Total protein	6.6 g/dL
Albumin	2.6 g/dL
BUN	10.4 mg/dL
Creatinine	0.69 mg/dL
AST	60 IU/L
ALT	39 IU/L
LDH	410 IU/L
γ-GTP	132 IU/L
CPK	176 IU/L
Na	115 mEq/L
K	4.1 mEq/L
Cl	84 mEq/L
Ca	8.4 mg/dL
P	2.9 mg/dL
Glucose	93 mg/dL
CRP	10.29 mg/dL
s-IL-2R	1533 U/mL
Urinalysis	
pH	7.0
Protein	–
Sugar	–
Occult blood	±
Urine chemistry	
Na	117 mEq/L
K	12.6 mEq/L
Cl	107 mEq/L

Case report

An 81-year-old man was admitted to our hospital after a 3-month history of a slight fever, general fatigue and anorexia. He had a past history of hypertension and cerebral infarction. A physical examination at the time of admission showed a body height of 154.0 cm, weight 46.7 kg, body temperature 37.2 °C, blood pressure 104/58 mmHg, and pulse rate of 74 beats/min. Neither lymphadenopathy nor hyperpigmentation was observed. Laboratory data on admission showed anemia, eosinophilia, hyponatremia, hypoalbuminemia, and elevated serum levels of LDH, CRP and soluble interleukin-2 receptor (sIL-2R) (Table 1). The plasma osmolality was low, while the urinary osmolality and plasma ADH were high. Basal serum levels of cortisol (11.6 µg/dL) and ACTH (59.5 pg/mL) obtained at 2:30 pm were normal (Table 2). An abdominal computed tomography (CT) scan taken 1 month before this admission detected a bilateral adrenal mass (Fig. 1c). A left adrenal mass biopsy revealed diffuse large B cell lymphoma. Because the patient did not have a prior history of lymphoma and invasion of lymphoma cells to other lymph nodes or other organs was not observed, we diagnosed him with PAL. An immunohistochemical analysis of the lymphoma cells using vasopressin antibody (Sigma-Aldrich, St. Louis, MO, USA) was negative for ADH protein.

Previous medical records from another hospital 15 months before this admission showed a nodular mass in the left adrenal gland (Fig. 1a), which was diagnosed as adenoma at that time. A CT scan taken 12 months before this admission showed the enlargement of the left adrenal mass (Fig. 1b). No obvious abnormality was found in the

Table 2 Endocrinological data

Blood	
ADH	5.8 pg/mL
ACTH	59.5 pg/mL
Cortisol	11.6 µg/dL
Adrenaline	<5 pg/mL
Noradrenaline	802 pg/mL
Dopamine	25 pg/mL
Aldosterone	46.9 pg/mL
Plasma renin activity	1.7 ng/mL/h
Free T3	2.42 pg/mL
Free T4	1.63 ng/dL
TSH	3.13 µU/dL
Plasma osmolality	239 mOsm/kgH ₂ O
Urine	
Cortisol	116.2 µg/day
Creatinine	822 mg/day
Urine osmolality	490 mOsm/kgH ₂ O

Fig. 1 Abdominal CT. A small nodule was found in the left adrenal gland 15 months before admission (a). The left adrenal mass increased in size 3 months later (12 months before the admission) (b). An enlarged right adrenal mass appeared in addition to the enlarged left adrenal mass 1 month before admission (c). The bilateral adrenal mass further increased in size 3 weeks after admission (d)

right adrenal gland on these CT scans. The serum sodium level (141 mEq/L) was normal 8 months before this admission.

The intravenous administration of 17 g of sodium chloride in 1060 mL for 3 days and 21 g of sodium chloride in 1120 mL for 4 days increased the serum sodium level slightly, but did not normalize it. However, the administration of hydrocortisone sodium succinate (200–300 mg/day) rapidly normalized the body temperature and serum sodium level and improved the patient's appetite and general condition. Normal body temperature and serum sodium levels were then maintained with 30 mg of hydrocortisone. However, the adrenal mass increased in size and his general condition deteriorated at 3 weeks after admission. He died after 8 weeks due to disease progression.

Discussion

In this patient, diffuse large B cell lymphoma was found as a large bilateral adrenal mass. Because the patient did not have a previous history of lymphoma and invasion of the lymphoma cells to other lymph nodes or other organs was not observed, he was diagnosed with bilateral PAL.

Several cases of severe hyponatremia in bilateral PAL have been reported [2–5]. However, the causes of hyponatremia associated with bilateral PAL have not been fully investigated.

In our case, the patient had suffered a loss of appetite for 3 months when severe hyponatremia was found. Thus it is

possible that volume depletion due to the decreased intake might be the cause of hyponatremia. However, the urine sodium concentration was high and sodium chloride loading of more than 15 g/day for several days did not normalize the serum sodium. Therefore, it is unlikely that hyponatremia was caused by volume depletion alone in the current case.

In this case, serum ADH was not suppressed and the urine osmolality was higher than the serum osmolality, despite the low levels of serum sodium and serum osmolality. These findings suggest that ADH secretion was stimulated independently from the serum osmolality.

Nonosmotic stimuli to induce ADH secretion, such as vomiting, pain and medicines, were not observed in this case. In addition, the serum levels of thyroid hormone and basal serum cortisol were within the normal limits. These findings indicate that hyponatremia in this case fulfilled the diagnostic criteria for SIADH [11].

Lymphoma is listed as one of the malignant diseases that cause SIADH [8]. In addition, ADH production by the lymphoma cells was previously reported in hyponatremic lymphoma patients who were diagnosed with SIADH [6, 7]. However, the immunohistochemical analysis demonstrated that the lymphoma cells were negative for ADH protein in the current case.

In this case, hyponatremia was noted when enlargement of the bilateral adrenal glands was observed on an abdominal CT scan, which was associated with the patient's subjective symptoms, such as the fever, general malaise and appetite loss. Furthermore, adrenal insufficiency is known to develop in bilateral PAL at a high rate [2]. When we initiated

hydrocortisone treatment, rapid normalization of the body temperature and serum sodium concentration occurred.

The diagnostic criteria for SIADH require the confirmation of normal adrenal function. However, the plasma cortisol level for excluding adrenal insufficiency is not clearly defined in most textbooks [9].

In general, the adrenal function is evaluated by the basal serum cortisol level and the response to ACTH administration when the basal serum cortisol is at the borderline level [9]. However, the ACTH stimulation test is not routinely performed for the diagnostic purpose of SIADH in clinical settings. The diagnostic criteria for SIADH widely used in Japan [11] proposed the use of a basal cortisol level higher than 6 µg/dL as the criterion for normal adrenal function in the diagnosis of SIADH. With the use of this criterion, the adrenal function of this patient, whose basal cortisol was 11.6 µg/dL, was judged to be normal, and adrenal insufficiency as the cause of hyponatremia was excluded.

Because stress may stimulate the secretion of cortisol, recent consensus statements from an international task force by the American College of Critical Care Medicine recommended a random total cortisol level of less than 10 µg/dL for the diagnostic criterion of corticosteroid insufficiency in critically ill patients [12]. Smith et al. recommended the use of the higher morning cortisol concentration (>18.1 µg/dL in most cases and >25.3 µg/dL in acutely ill patients with major trauma or severe sepsis) for excluding adrenal insufficiency [10]. In addition, by reviewing severe hyponatremia due to hypopituitarism, Diederich et al. [13] recommended the consideration of hyponatremia due to hypopituitarism and adrenal insufficiency in cases with basal cortisol concentrations less than 15.9 µg/dL.

These findings suggest that the diagnostic criteria for SIADH proposed by a team of experts supported by the Japanese Ministry of Health, Labour and Welfare [11], which is widely used in Japan, may falsely diagnose hyponatremia due to adrenal insufficiency as SIADH.

Since the present patient was under unusual stress caused by lymphoma, hyponatremia, appetite loss and severe general malaise, his basal cortisol concentration (11.6 µg/dL) may reflect the poor response of the ACTH–adrenal axis to these stresses. Taken together, hyponatremia in our case was likely caused by adrenal insufficiency rather than by SIADH.

Shibata et al. [14] reported a similar case with severe hyponatremia in which the basal serum cortisol level was 12.1 µg/dL. The patient's hyponatremia fulfilled the criteria of SIADH used in Japan, but was normalized by the administration of hydrocortisone.

In summary, the current case suggests that the administration of cortisol is recommended if suspicious clinical signs or symptoms are found in patients with severe hyponatremia, even if the patient fulfills the diagnostic criteria of SIADH.

Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

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