Syndrome of Inappropriate Antidiuretic Hormone Secretion in Patients with Adult Still's Disease

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Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a rare complication of adult Still's disease (ASD). We experienced a male ASD patient who complained of arthralgia and intermittent fever. Chest radiograph and pleural fluid analysis revealed pleurisy with effusion. We diagnosed this patient with SIADH and confirmed the disappearance of hyponatremia and pleurisy after starting treatment with nonsteroidal anti-inflammatory drugs. In this study, we reviewed previous literature and the case of our ASD patient with hyponatremia. This reported case is the fourth case of SIADH in an ASD patient. Further, we found that hyponatremia is a relatively common complication of ASD, and pleurisy has a possibility to develop SIADH in patients with ASD.

Key words: adult Still's disease, syndrome of inappropriate antidiuretic hormone secretion, hyponatremia, pleurisy

INTRODUCTION

Adult Still's disease (ASD) is an inflammatory disorder characterized by high fever with daily spikes, arthritis, and an evanescent rash. A number of characteristic laboratory findings are observed in ASD patients: elevation in the serum levels of aspartate aminotransferases (AST) and lactate dehydrogenase (LDH), increase in the erythrocyte sedimentation rate (ESR), extremely high serum levels of ferritin, leukocytosis with at least 80% granulocytes, serological tests negative for antinuclear antibody (ANA) and rheumatoid factor (RF) [1]. Inflammatory diseases such as infection and collagen vascular disease lead to an increased extra-renal loss of sodium, which in turn gives rise to dilutional hyponatremia [2]. Mild hyponatremia has been reported in ASD patients [3], but the incidence and pathophysiology of hyponatremia and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in these patients remain unknown. Here, we report the case of an ASD patient who developed SIADH. We reviewed the cases of ASD patients with or without hyponatremia during the last decade.

CASE REPORT

A 61-year-old man complained of migratory pain in both the shoulders and knees and intermittent high fever. He was referred to a hospital near his home in early June 2005. Because he did not respond to several courses of antibiotics and intermittent use of acetoaminophen, he was transferred to our hospital for persistent fever, elevated leukocyte counts, and elevated levels of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GTP). At the time of admission, his body temperature was 40°C. Examinations for the heart, lungs, and abdomen revealed normal findings. Pain was elicited on palpation of the shoulders, elbows, and knees; these joints had a slight limitation in the range of motion. There was no evidence of rash or arthritis. Complete blood cell count analysis showed a leukocyte count of 17500/μL with 84% neutrophils, hemoglobin concentration of 12.3 g/dL, and platelet count of 35.7×10^4/μL. The results of the liver function tests were as follows: AST, 79 U/L; alanine transaminase, 48 U/L; LDH, 393 U/L; ALP, 740 U/L; and gamma-GTP, 119 U/L. Serum electrolyte concentrations were as follows: sodium, 134 mEq/L; potassium 3.9 mEq/L; chloride, 97 mEq/L. The serum creatinine concentration was 0.7 mg/dL. The levels of blood urea nitrogen and uric acid were low: 6 mg/dL and 1.9 mg/dL, respectively. ESR was 103 mm/h; the C-reactive protein concentration, 23.78 mg/dL; the serum ferritin concentration, 24175 ng/dL. All serological tests were negative, including ANA, RF, perinuclear antineutrophil cytoplasmic antibodies (P-ANCA), and cytoplasmatic antineutrophil cytoplasmic antibodies (C-ANCA). Urinalysis showed the presence of protein (1+) but no glucose, red blood cells, or casts. Cultures of blood, throat swabs, and urine were sterile. Chest radiograph and computed tomography (CT) scan showed bilateral pleural effusion (Fig. 1a and 1b). The right pleural fluid (PF) examination revealed a cell count of 2310/μL with 51% neutrophils, 12% lymphocytes, 31% histiocytes, and 7% eosinophils and a total protein concentration of 3.8 g/dL. Pleurisy was suspected because PF analysis showed exudative effusion according to Light's criteria: PF to serum protein ratio, 0.6; PF to serum LDH ratio, 2.1; and PF LDH level, 762 U/L. On the second day of hospitalization, the patient developed fever with chills and a transient pink rash resembling measles on the extremities. The patient was diagnosed with ASD on

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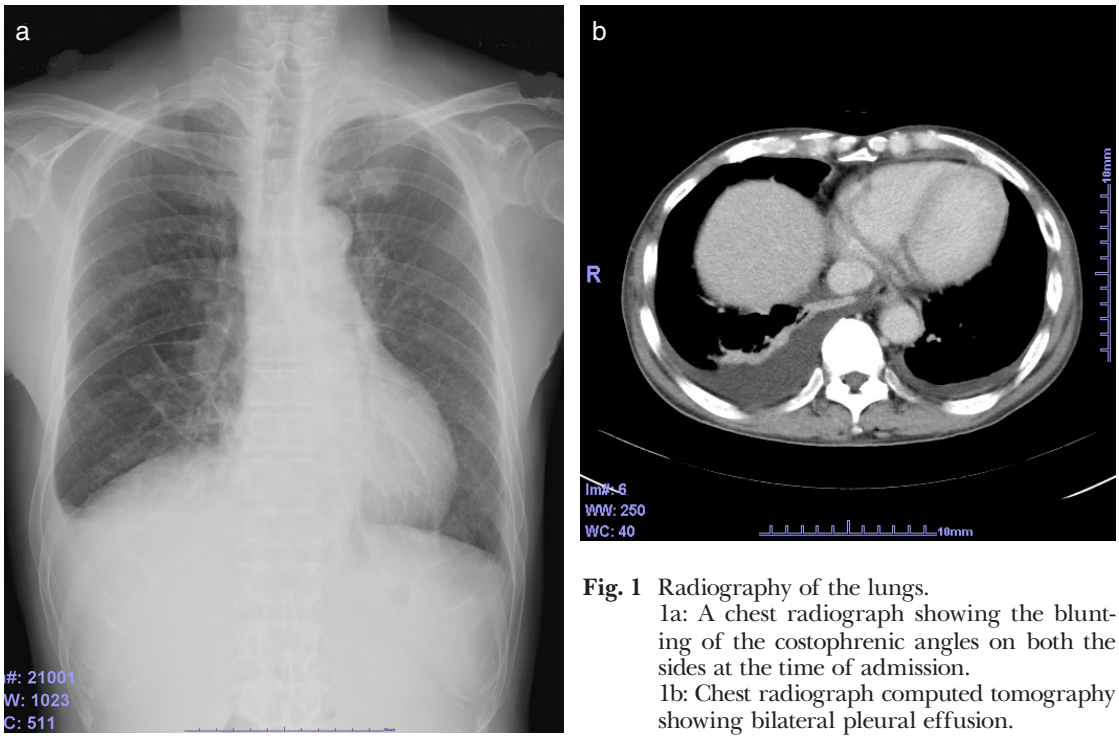

Fig. 1 Radiography of the lungs.
1a: A chest radiograph showing the blunting of the costophrenic angles on both the sides at the time of admission.
1b: Chest radiograph computed tomography showing bilateral pleural effusion.

the basis of typical symptoms and the laboratory findings as well as the absence of infection, malignancy, or other rheumatic diseases. Laboratory studies performed after 3 days of hospitalization gave the following results: serum sodium concentration, 126 mEq/L; serum osmolality, 256 mOsm/kg; urine osmolality, 462 mOsm/kg; and urinary sodium concentration, 141 mEq/L. The serum levels of thyroid and adrenal hormones were normal. Despite serum hypoosmolality, the serum level of ADH was found to be 1.0 pg/mL (normal range, 0.3–3.5 pg/mL). The patient was diagnosed with SIADH because he had hyponatremia accompanied by abnormally high urine osmolality and sodium concentration. Finally, we concluded that our patient was a complex case of ASD complicated with SIADH. We started treatment with loxoprofen sodium (60 mg) 3 times daily. After 7 days of the treatment, the pleurisy with effusion and hyponatremia disappeared, and the maximum body temperature reduced to 38°C. However, after 13 days of treatment, the fever flared up again despite the disappearance of pleurisy and hyponatremia. We immediately started treatment with prednisolone (40 mg/d); the fever improved within several days of treatment (Fig. 2).

DISCUSSION

Hyponatremia, a condition in which the serum sodium concentration is less than 136 mEq/L, is a common and potentially serious electrolyte disorder seen in hospitalized patients. Although hyponatremia can be associated with low, normal, or high tonicity, low tonicity is the most frequent form [4]. SIADH is the most common cause of hypoosmolality and euvolemic hyponatremia, with prevalence rates of 20%–40% among all low tonicity patients [5–6]. The major causes of SIADH are central nervous system disorders, tumors, certain drugs, and pulmonary diseases. We encountered a patient with ASD complicated with SIADH; however, we have found only 3 such cases in the literature, including 1 detailed case report that described the relationship between SIADH and ASD [3, 7]. Therefore, we examined 28 patients with active ASD who were admitted to our hospital between 1997 and 2006. Fifteen patients had hyponatremia, which we defined as a condition wherein the serum sodium concentration is below 136 mEq/L and the osmolality is below 280 mOsm/kg (Table 1, 2). The incidence of hyponatremia in our patient series was 53.6% (15/28), which was slightly lower than that reported by a previous study [3]. Approximately all the hyponatremic patients (14/15) had mild to moderate hyponatremia, and their serum sodium concentrations ranged from 120 to 135 mEq/L. With respect to age, gender and laboratory data correlated with disease activity, no significant differences were found between patients with and without hyponatremia, as analyzed by Mann-Whitney's *U* test and the chi-square test for independence. In our institute, except for the case reported here, we did not notice the development of SIADH as a complication of ASD in any patient. However, in the other hyponatremic patients, the data on urine osmolality and levels of thyroid hormones, adrenal hormones, and ADH were not used for the differential diagnosis of hyponatremia, and the hyponatremia was found to improve after the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids with or without short-term administration of sodium chloride. Hence, these hyponatremic patients might have had latent SIADH or adrenal insufficiency. Further, 4 patients had pleurisy as a complication. The incidence of pleurisy in our ASD patient series was 14.2 % (4/28), which was similar to that reported by previous studies [8–9]. Pleurisy, thus, frequently develops in patients with hyponatremia.

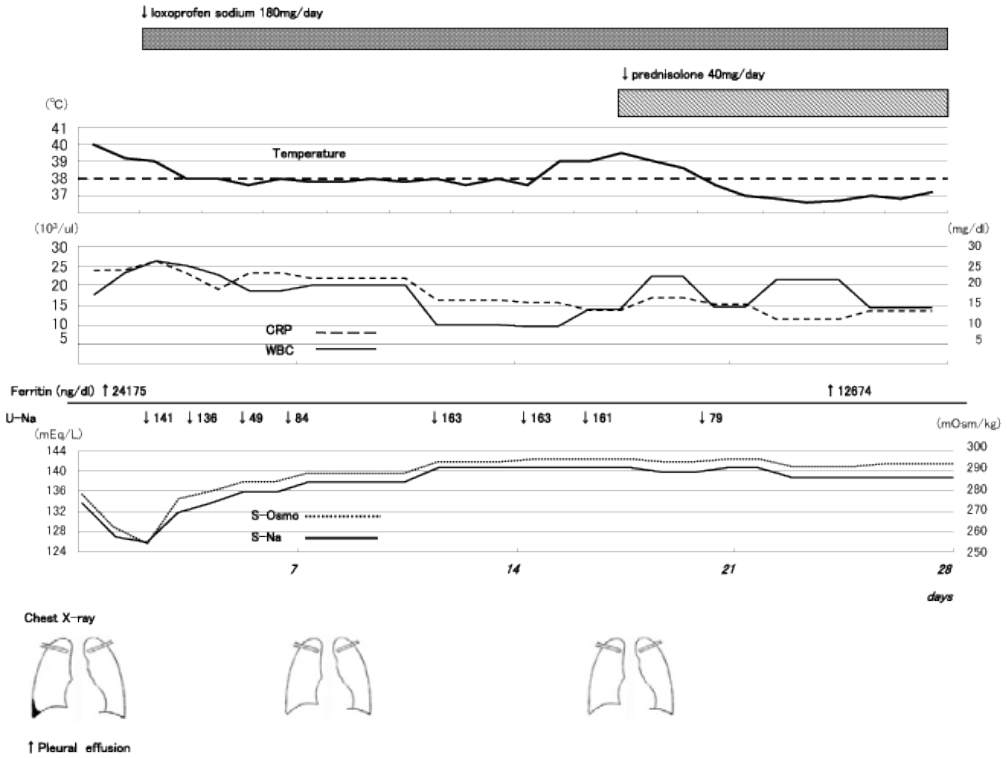

Fig. 2 Clinical course and changes in the temperature and key laboratory parameters. S-Osmo indicates serum osmolality; S-Na, serum sodium concentration; U-Na, urinary sodium concentration.

Table 1 Laboratory data and frequency of pleurisy in patients with or without hyponatremia

	Hyponatremia (n=15)	Non-hyponatremia (n=13)
Male (%)	8 (53)	6 (46)
Age	40±16*	36±11*
Pleurisy (%)	4 (26)	0 (0)
WBC [/μL]	15393±6630*	15955±8509*
CRP [mg/dL]	13.70±8.55*	15.30±10.54*
Ferritin [ng/dL]	6198±8860*	7225±9830*
AST [U/L]	44±27*	53±38*
ALT [U/L]	45±30*	52±55*
LDH [U/L]	561±334*	772±597*
ALP [U/L]	480±210*	504±562*
Gamma-GTP [U/L]	129±107*	49±40*

*the standard deviation of the mean

Table 2 Degree of hyponatremia in patients with or without pleurisy

	Pleurisy		n
	+ (n=4)	- (n=11)	15
Severe [<120 mEq/L] (%)	0 (0)	1 (9)	1
Moderate [120-129 mEq/L] (%)	1 (25)	0 (0)	1
Mild [130-135 mEq/L] (%)	3 (75)	10 (90)	13

Honjoh et al have discussed the relationship between ASD and SIADH [7] and have indicated the possibility of vasculitis in a hypothalamo-pituitary lesion. Unfortunately, we did not examine the hypothalamo-pituitary system by using magnetic resonance imaging (MRI) or CT and hormone-stimulating tests. In the case of our patient, hyponatremia improved immediately after NSAID treatment. Therefore, our patient could not have developed vasculitis. Honjoh et al also mentioned that steroid therapy was effective for pleurisy and hyponatremia. We found that NSAIDs were simultaneously effective for both pleurisy and hyponatremia. We observed that the incidence of pleurisy was higher in hyponatremic patients than in non-hyponatremic patients in our institute. Therefore, pleurisy may develop SIADH in patients with ASD, although the exact cause of this relationship is unknown.

In conclusion, hyponatremia is a relatively common complication of ASD. In patients with this complication, it is important to assess fluid volume; measure urinary electrolytes and urine osmolality; and determine the serum levels of thyroid hormones, adrenal hormones, and ADH. When hyponatremia is present along with pleurisy, SIADH should be considered in the differential diagnosis. Further clinical studies with a large number of patients will reveal the true incidence and pathogenesis of SIADH in ASD patients.

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