Hyperaldosteronemia and hypogammaglobulinemia secondary to atopic dermatitis-induced exudation in an infant presenting with growth failure

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The present case is a 5-month-old female with atopic dermatitits who was brought to hospital for growth failure noted upon regular health examination. Laboratory examinations revealed hyponatremia, hyperkalemia, hypoproteinemia, hypogammaglobulinemia, elevated plasma renin activity and hyperaldosteronemia. Immune function was normal. Composition of the exudate collected from the skin lesions of atopic dermatitis was similar to that of plasma. Application of a steroid ointment improved the lesions as well as all laboratory values. These findings indicate that voluminous exudation caused by extensive atopic dermatitis can lead to hypotonic dehydration, electrolyte abnormalities, hypoproteinemia, hypogammaglobulinemia and, finally, to growth failure in infants. We conclude that intensive treatment is important for severe atopic dermatitis in infants to prevent serious complications.

Key words : Atopic dermatitis, growth failure, hyperaldosteronemia, hypogammaglobulinemia , infant

INTRODUCTION

Atopic dermatitis is a highly common disease [1]. In severe cases, exudate from wet lesions can be voluminous. A few reports have described cases of atopic dermatitis associated with electrolyte abnormalities and/or hypoproteinemia [2-9] and discussed its cause. We encountered an infant with severe atopic dermatitis and growth failure. Laboratory findings and outcome of topical steroid treatment indicate that exudation from the lesions of atopic dermatitis was responsible for electrolyte abnormalities, hypoproteinemia, hypogammaglobulinemia and growth failure.

CASE DESCRIPTION

Present case was a 5-month-old female infant. She was delivered at the 38th week of gestation, with a birth weight of 2648 g. The mother's history of pregnancy and delivery showed no notable problems. Family history revealed no allergic diseases. The infant was fed on breast milk, and generalized eczema developed one month after birth. She was diagnosed with atopic dermatitis and treated at a nearby clinic, with no improvement. Therefore, she was brought to the Department of Dermatology of our hospital 2 months after birth. Since the initial visit to the department, eczema associated with exudation and desquamation was noted on the entire body, centering on the face and trunk. At 4 months of age, growth failure was indicated on health examination at a health center. Thus, the infant was referred to the Department of Pediatrics of our hospital.

At presentation, her weight was 5190 g (− 1.8 SD), eczema was noted on the entire body, and humectation and erosion were marked. While the disease course was observed at the outpatient clinic, her weight decreased to 4900 g (−2.5 SD) by 5 months of age and generalized eczema became more prominent, with exudates, erosion and desquamation observed on the entire body. Normal areas of the lips and skin were dry, and turgor of the skin was decreased. Blood biochemistry disclosed hyponatremia and hypoproteinemia (Table 1). Because endocrinological examinations performed for hyponatremia revealed hyperaldosteronemia (Table 2), the infant was hospitalized for detailed examinations and treatment.

Physical Findings at Admission

Weight was 4900 g (−2.5 SD), and blood pressure was 124/34 mmHg. Eczema associated with exudation and desquamation was observed on the skin of the entire body, including the face, trunk, elbows and lower extremities. The skin of unaffected areas was dry, with no apparent pigmentation. Neither anemia nor jaundice was observed. The abdomen was flat, and the liver was palpable three finger-breadth. No edema or sign of hirsutism was evident. The external genitalia appeared normal female, and no findings suggestive of masculinization, such as enlarged clitoris, were found.

The Clinical Course Following Admission

Findings of laboratory examinations on day 1 of hospitalization included increased white blood cells, increased eosinophils, hyponatremia, mild hyperkalemia, hypoproteinemia and hypogammaglobulinemia (Table 1). Urinary sodium excretion was reduced.

Endocrinological examinations performed on day 1 of hospitalization for hyponatremia and hyperkalemia showed advanced hyperreninemia (20.0

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Table 1 Laboratory findings at admission*.

Hematological findings			
WBC	27800/μl	RBC	490×10^4/μl
Neu	8.0%	Hb	13.5 g/dl
Ly	15.0%	Hct	38.0%
Eo	7.0%	Plt	60.5×10^4/μl
Blood biochemical findings			
Glucose	93 mg/dl	LDH	371 U/l
UN	9 mg/dl	ALP	242 U/l
Cr	0.2 mg/dl	Total bilirubin	0.3 mg/dl
Na	126 mEq/l	AST	49 U/l
K	5.5 mEq/l	ALT	31 U/l
Cl	97 mEq/l	Total cholesterol	139 mg/dl
Ca	4.8 mEq/l	Triglyceride	538 mg/dl
IP	5.5 mg/dl	CRP	0.3 mg/dl
Total protein	4.6 g/dl		
Albumin	2.6 g/dl		
Protein fractions			
$\alpha 1$	5.7%		
$\alpha 2$	13.9%		
β	9.7%		
γ	4.3%		
Immunoglobulins			
IgG	102 mg/dl		
IgA	<20 mg/dl		
IgM	21 mg/dl		
Urinalysis			
UNa	<10 mEq/l		
UCr	27.3 mg/dl		

* Blood and urine were sampled on the day of hospitalization. Blood was sampled before breakfast with the patient in supine position.

Table 2 Endocrinological findings at admission*.

ACTH	14.0 pg/ml (9-52)
Cortisol	14.2 μg/dl (4.0-18.3)
Plasma renin activity	>20.0 ng/ml/h** (0.3-2.9)
Aldosterone	>4000.0 pg/ml** (26.6-159)
Testosterone	<5.0 ng/dl (10-60)
Urine osmolarity	197 mOsm/kgH_2O
Plasma osmolarity	259 mOsm/kgH_2O

* Blood and urine were sampled the day of hospitalization. Blood was sampled before breakfast while the patient was in supine position. ** denotes a value outside the normal range. Normal range is indicated in parentheses.

ng/ml/h or higher) and hyperaldosteronemia (4000 pg/ml or higher) (Table 2). Plasma ACTH and serum cortisol were normal at 14.0 pg/ml and 14.2 mg/dl, respectively. Cell surface markers of white blood cells and cellular immune function tests, performed for hypoproteinemia and hypogammaglobulinemia on day 14 of hospitalization, were both normal, excluding primary immunodeficiency (Table 3).

Fluid therapy was performed for hypotonic dehydration from day 1 to 5 of hospitalization, and hyponatremia was improved. However, hypoproteinemia and hypogammaglobulinemia progressed and, by day 3 of hospitalization, total protein concentration and IgG were decreased to 3.0 g/dl and 48 mg/dl, respectively (Fig. 1). Because generalized edema and retention of ascites appeared, possibly through hypoproteinemia, administration of albumin and gammaglobulin products was initiated on day 7 and 10 of hospitalization, respectively. Although concentrations of total protein and IgG were improved, their levels declined within a few days, indicating rapid elimination of the administered albumin and gammaglobulin from the circulation (Fig. 1) Suspecting leak of proteinaceous components, exudate was sampled on day 13 and 21 of hospitalization from the wet lesions of atopic dermatitis and analyzed with concurrently sampled plasma (Table 4). The analysis demonstrated that the concentrations of electrolytes were all similar between the exudate and plasma. However, the total protein and IgG concentrations were both higher in

Table 3 Immunological findings.

Cell surface markers	
CD3	76.6% (58-84)
CD4	47.6% (25-56)
CD8	29.1% (17-44)
CD4/CD8	1.64 (0.6-2.9)
CD19	14.2% (5-24)
Proliferative activity	
PHA+	53507 (26000-53000)
control	351 (70-700)
Con A	33500 (20000-48000)
control	351 (70-700)

These examinations were performed on day 14 of hospitalization.
Normal range is indicated in parentheses.

Table 4 Electrolytes and proteins in exudate and plasma*.

	1st sample		2nd sample	
	exudate	plasma	exudate	plasma
Na (mEq/l)	173	137	189	137
K (mEq/l)	5.7	5.1	8.8	5.2
Cl (mEq/l)	136	111	147	147
Total protein (g/dl)	5.0	3.4	6.8	3.7
IgG (mg/dl)	103	54	312	144

* Exudate from the skin lesions and plasma were sampled on day 13 (1st sample) and 21 (2nd sample) of hospitalization and analyzed for electrolyte and protein composition. Blood was drawn while the patient was in supine position.

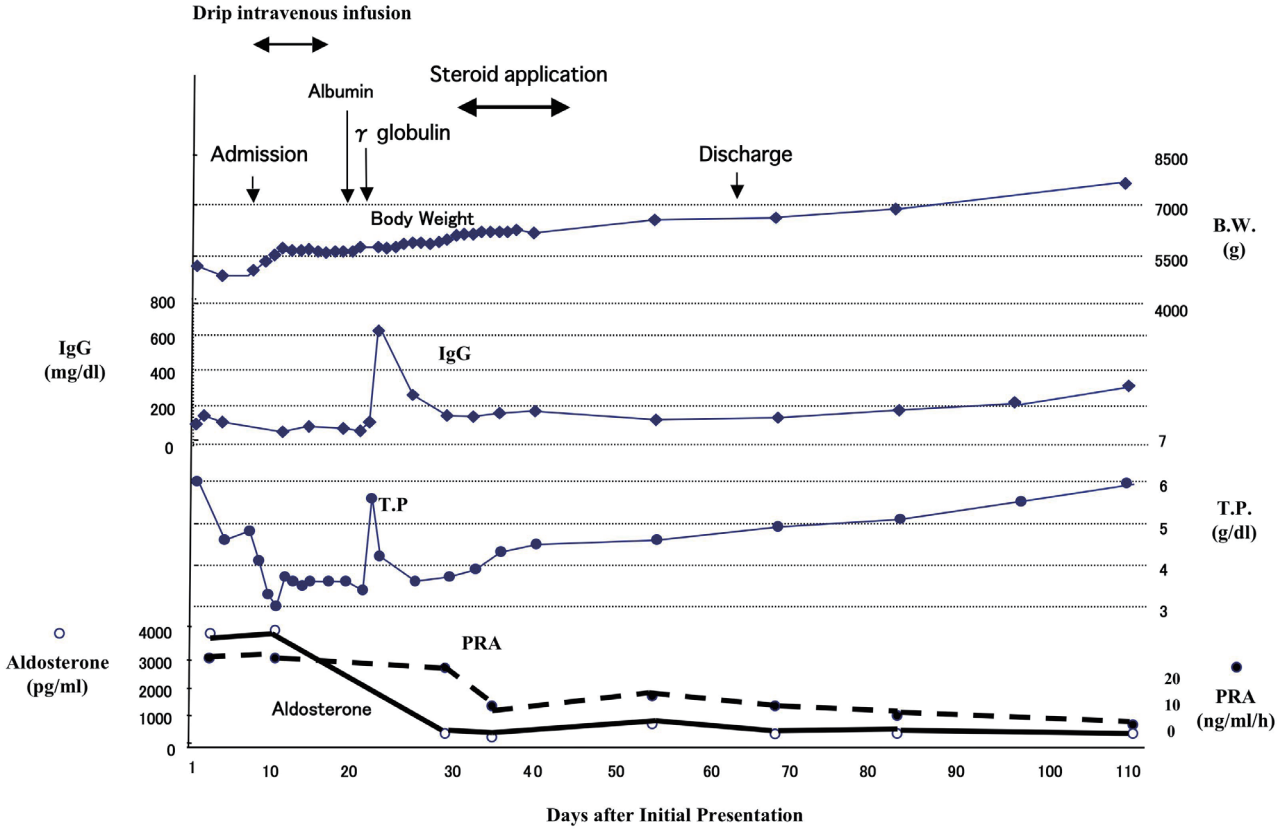

Fig. 1 Clinical course of the patient.
The patient's body weight (B.W; kg), plasma IgG (mg/dl) and total protein (T.P.; g/dl) concentrations, plasma aldosterone (pg/ml) and renin activity (PRA; ng/ml/h) were monitored from the day of the initial presentation for 110 days. During this period, the patient was hospitalized 10 days after the initial presentation (day 10 in the figure), received drip intravenous infusion of 3/4 physiological saline for hypotonic dehydration for 5 days from the day of hospitalization, administered with albumin and gammaglobulin (γ globulin) on day 17 and 20, respectively, underwent whole-body application of a steroid ointment from day 30 to 42, and was discharged on day 65.
Administration of albumin and gammaglobulin products significantly raised IgG and total protein levels. However, these increases were transient, followed by a rapid decline. Once a colloidal cream of steroid was applied to the entire body, skin exudation was decreased, endocrinological abnormalities were corrected, and the patient's weight turned to a gradual gain.

the exudate than in the plasma. Of note, the second analysis, performed after administration of albumin and gammaglobulin, revealed further increases in the total protein and IgG concentrations.

Considering that hyponatremia, hyperreninemia, hyperaldosteronemia, hypoproteinemia and hypogammaglobulinemia were ascribable to voluminous exudation and loss of fluid from the skin, we consulted with a dermatologist and initiated whole-body application of a steroid ointment on day 20 of hospitalization and continued until day 32. As a result, exudation was markedly reduced in association with the improvement

of humectation and erosion, and laboratory findings including plasma aldosterone and renin activity were gradually improved and normalized by about day 40 of hospitalization. In addition, the infant's weight dramatically turned to a gain.

The infant was discharged on day 55 of hospitalization. Follow-up until day 110 of the initial presentation showed that plasma IgG and total protein concentrations continued to improve, and plasma aldosterone level and renin activity remained normal.

DISCUSSION

In the present case, we evaluated the possibility that the patient's hyponatremia, hyperkalemia, growth failure, hypoproteinemia and hypogammaglobulinemia could be explained in terms of exudation due to atopic dermatitis and associated loss of fluid, electrolytes and plasma protein components.

ACTH and cortisol levels were normal in our patient, which excluded adrenal insufficiency. Since hyperreninemia and hyperaldosteronemia associated with hyponatremia were observed, we considered pseudohypoaldosteronism type I (PHA-I). PHA-I exhibits symptoms of aldosterone deficiency because of the unresponsiveness of aldosterone receptors, and has no abnormalities in aldosterone production or secretion. Yoshida *et al.* [4] analyzed infants with concurrent atopic dermatitis and PHA-I and reported that PHA-I could cause electrolyte abnormalities. In the present case, urinary sodium excretion was below detectable range; thus, aldosterone unresponsiveness was ruled out.

Although the period around the age of 4 months is the time when IgG is physiologically at its trough level, values at 250 mg/dl or below necessitate consideration of immunodeficiency and associated increase in susceptibility to infections. Since serum IgG level of the present case was extremely low at 102 mg/dl, we examined for possible severe combined immunodeficiency (SCID). Immunodeficiency was ruled out by the examinations of cellular immune function and white blood cell surface markers.

According to the Lund and Browder chart, the area of exudation of the present infant reached approximately 30%. Thus, the volume of exudation, although not determined, was substantially large. Fluid therapy improved hyponatremia, while IgG and total protein concentrations were markedly decreased, a possible reflection of hypoproteinemia occurring through the improvement of dehydration-induced hemoconcentration. Administration of albumin and gammaglobulin elevated total protein and IgG levels, followed by a rapid decline. Considering the half-life of gammaglobulin products, this rapid decrease was apparently abnormal. We found that the composition of the exudate was similar to that of the plasma. However, it should be noted that the total protein and IgG concentrations were both higher in the exudate, and their values were further elevated after the administration of albumin and gammaglobulin products. Because the volume of sample recovered at one time was very small, samples collected on separate occasions had to be combined for analysis. Therefore, the exudate sample was possibly concentrated during the handling. Nevertheless, these findings suggest that substantial amounts of fluid, electrolytes and plasma proteins were lost in the exudate. Following application of a steroid ointment, the exudation was decreased in association with improvement of the skin lesions. Simultaneously, electrolytes abnormalities, hypoproteinemia, hypogammaglobulinemia and hyperaldosteronemia, were all improved, indicating that the voluminous exudation from the skin lesions was the underlying cause of the patient's abnormalities.

Nomura *et al.* [8] analyzed 15 pediatric patients with atopic dermatitis who had serum protein levels of 3.2-5.8 g/dl and reported that their skin discharges contained almost the same protein concentration as serum. Abrahamov *et al.* [6] published a detailed report on hypoproteinemia, edema and anemia in a 10-month-old infant with infantile atopic dermatitis, pointing out a link between exudation and hypoproteinemia. Parving *et al.* [7] reported adult cases of hypoproteinemia in skin diseases, suggesting a similar possibility for adults. Our study also showed that loss of plasma proteins from the skin lesions caused hypoproteinemia and hypogammaglobulinemia.

As per a possible link between loss of fluid and electrolyte and endocrine abnormalities, Anand *et al.* [10], in their analysis of a 3.5-year-old girl with repeated episodes of dehydration, hyponatremia and hyperkalemia, proposed that excessive loss of sodium from the sweat and salivary glands causes pseudohypoaldosteronism. In this connection, Maeyama *et al.* [2] reported hyponatremia and hyperkalemia in an infant with atopic dermatitis, and Yoshida *et al.* [4] described a 7-month-old girl with atopic dermatitis complicated with PHA-1. More recently, Takiyama *et al.* [3, 5] presented their analysis of infants with atopic dermatitis who developed similar electrolyte abnormalities, hypoproteinemia and growth failure. On the extension of the proposal by Anand *et al.* [10], Maeyama *et al.* [2] as well as Takiyama *et al.* [3, 5] speculated on the pathogenesis of electrolyte and endocrine abnormalities in atopic dermatitis as follows: excessive loss of fluid and electrolytes from the skin lesions of atopic dermatitis causes hyponatremia and hypovolemia, which lead to elevated renin and aldosterone levels; sodium delivery to distal tubules, however, is reduced and, with potassium secretion in exchange for sodium suppressed, hyperkalemia develops in the face of hyperaldosteronemia. In parallel, loss of plasma proteins from the skin lesions leads to hypoproteinemia and, eventually, growth failure. By endocrinological examinations and analysis of the exudate, we substantiated the hypothesis that in severe and extensive atopic dermatitis, a large loss of body fluid and plasma components can cause dehydration, hypoproteinemia and hyponatremia, leading to secondary hyperaldosteronemia and hyperreninemia,

The principle of the treatment for atopic dermatitis of infants is external application therapy and skin care. Occasionally, cases have been reported in which use of steroids was denied for their adverse effects, and skin lesions were not improved, leading to complications such as electrolyte abnormalities and hypoproteinemia [3, 5]. Nomura *et al.* [8] discussed that improvement of skin lesions is important in the

treatment of severe complications of atopic dermatitis, such as hypoproteinemia and electrolyte abnormalities. In order to avoid these complications, we also stress the importance of intensive treatment of atopic dermatitis.

CONCLUSIONS

In severe atopic dermatitis, a large volume of exudation from exanthema can lead to severe complications such as electrolyte abnormalities, hypoproteinemia, hypogammaglobulinemia and growth failure. Results can be life threatening. We advocate that in severe atopic dermatitis of infants, excessive concern for adverse effects of steroid products should be avoided, and intensive treatment should be performed.

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