CASE REPORT

SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE ASSOCIATED WITH STRONGYLOIDIASIS

Eiji Hayashi[1], Nobuo Ohta[1] and Hiroshi Yamamoto[2]

[1]Section of Environmental Parasitology, Department of International Health Development, Division of Public Health, Graduate School, Tokyo Medical and Dental University, Tokyo; [2]Department of Internal Medicine, Ohta Hospital, Jyohnan Welfare and Medical Association, Tokyo, Japan

Abstract. We report a case of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) with accompanying severe strongyloidiasis in a 52-year-old male. On admission, he showed drowsiness and emaciation with severe hyponatremia. We gave sodium (saline or salts) in an I.V. drip infusion and orally without improvement. A urinalysis and plasma osmotic pressure test indicated SIADH, therefore, treatment was changed to restrict his sodium intake. The hyponatremia gradually improved initially, but the appetite loss, nausea, and hyponatremia continued. Endoscopy revealed white patches on the stomach wall and histopathological examination revealed infestation of the mucosal epithelium with numerous *Strongyloides stercoralis* larvae. Ivermectin treatment was then initiated and the abdominal symptoms and hyponatremia gradually resolved. We carefully investigated the underlying cause of the SIADH, such as disease of the central nervous system, lung cancer, and other malignancies, but no abnormality or clear cause could be found. We concluded that the patient developed SIADH secondary to severe *S. stercoralis* infection.

INTRODUCTION

Strongyloidiasis is a parasitic disease caused by the intestinal nematode *Strongyloides stercoralis*. *S. stercoralis* is commonly acquired when the third-stage filariform larvae in contaminated soil or water penetrate the skin and reach the venous circulation. From the circulation, they migrate to the lungs and subsequently settle in the intestinal tract. Strongyloidiasis affects 30 to 100 million people worldwide. It is endemic to many parts of the world, including the southeastern part of United States, South Asia, Latin America, and Sub-Saharan Africa (Genta, 1989; Adedayo *et al*, 2002). Screening of stool specimens in the general population in areas of Okinawa and Amami in the southern most region of Japan, showed that 3 to 17% of the samples were positive for *S. stercoralis* (Asato *et al*, 1992). Strongyloidiasis frequently causes persistent occult infection lasting decades through an autoinfection cycle before potentially resulting in a disseminated and sometimes fatal infection. In an immunocompromized host, large numbers of rhabditiform larvae transform into invasive filariform larvae within the intestinal tract. These filariform larvae then invade the gastrointestinal tract and migrate to virtually every organ system in the body, resulting in a disseminated infection or hyperinfection. The

Correspondence: Dr Eiji Hayashi, Section of Environmental Parasitology, Department of International Health Development, Division of Public Health, Graduate School, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.
Tel: +81-3-58035194; Fax: +81-3-56842849
E-mail: ehamzoo@pref-hosp.togane.chiba.jp, eha.vip@tmd.ac.jp

features of dissemination may include severe abdominal pain, nausea, vomiting, diffuse rash, pulmonary infiltrates, ileus, Gram-negative sepsis, meningitis, and protein-losing enteropathy (Sullivan *et al*, 1992; Siddiqui and Berk, 2001). Disseminated strongyloidiasis causes increased morbidity and mortality in immunocompromized patients, especially in those who were treated with corticosteroids (Daubenton *et al*, 1998; Wang *et al*, 1999; Morimoto *et al*, 2002). Hematological and biochemical tests in cases of *S. stercoralis* hyperinfection commonly show anemia, hypoproteinemia, and hypocholesterolemia, causing protein-losing enteropathy and malnutrition from appetite loss (O'Brien, 1975).

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is induced by various dysfunctions (Robertson, 1995; Baylis, 2003) and infection is thought to be one of the important etiologies of this disease, particularly virus infections; the most frequently reported involve viruses such as the varicella-zoster virus (VSV) (Furuta *et al*, 1996; Au *et al*, 2003). Most cases of SIADH caused by these virus infections are due to nervous system disorders: meningoencephalitis by virus dissemination (Au *et al*, 2003).

Here we describe the case of an immunocompetent patient with SIADH accompanied by *S. stercoralis* hyperinfection and severe hyponatremia. The clinical symptoms improved following treatment for *S. stercoralis* using Ivermectin, and no other cause of the SIADH was identified.

CASE REPORT

Our patient was a 52-year-old male who was born in the Okinawa Islands in the southern part of Japan and moved to Bolivia and Argentina during his childhood before returning to Japan at age 42. He was transferred to the emergency room at the Ohta Hospital with symptoms of drowsiness and severe emaciation. According to the patient history, he gradually lost his appetite over the 6 months prior to admission. While he had consulted two physicians prior to this admission, the cause of his illness was unknown and he was treated as an outpatient. He became weaker and his appetite loss increased until, by the week prior to admission, he could only ingest water.

A physical examination performed on admission revealed severe emaciation, dry skin, and slightly anemic conjunctiva. Although he was drowsy, his orientation was good. His body weight was 45 kg, height was 165 cm, blood pressure was 98/60 mmHg, body temperature was 36.5ºC, and pulse rate was 104 beats per minute.

Laboratory data on admission showed the following values: hemoglobin 10.7 g/dl, hematocrit 29.6% and leukocyte count 5,590/ml (71.6% neutrophils, 21.6% lymphocytes, 5.7% monocytes, 0.9% eosinophils, and 0.2% basophils). The total protein concentration was 4.9 g/dl, and he had an albumin level of 2.5 g/dl, a serum sodium level of 116 mEq/l, a serum potassium level was 2.7 mEq/l, a plasma chloride level was 81 mEq/l, and a blood sugar level was 296 mg/dl. Other laboratory findings, including a C-reactive protein (CRP) level, were normal.

Intravenous drip infusion therapy was performed to normalize the electrolyte levels. This was initially successful but the plasma sodium and potassium levels continued to decrease even with continuous infusion. To determine the cause of this, we measured the plasma and urinary osmotic pressures and concluded that the hyponatremia and hypokalemia were caused by the SIADH (Table 1). We thus changed the treatment to restrict his water intake (Schwanrtz *et al*, 1957; Kaomi *et al*, 1999).

Because he continued to have nausea and diarrhea from the time of admission, gastric endoscopy was performed which revealed

Table 1
Laboratory data for the definitive diagnosis of SIADH and data of other hormones.

	Normal range	day 2	day 13	day 58
Plasma osmotic pressure	(282~300) mOsm/kg	262 ↓	235 ↓	
Urinary osomotic pressure	(300~1,300) mOsm/kg	423 ↑	452 ↑	
Urinary sodium	(170~350) mEq/day	172	96 ↓	33 ↓
Urinary potassium	(50~65) mEq/day	17.0 ↓	42.0 ↓	6.0 ↓
Urinary chloride	(170~340) mEq/day	157 ↓	152 ↓	26 ↓
Other hormones				
TSH	(0.35~0.94) μlU/ml	0.376		
F-T3	(1.71~3.71) pg/ml	1.13		
F-T4	(0.7~1.48) ng/dl	0.81		
Renin activity	(0.2~2.7) ng/ml/h	1.1		
Aldosterone	(29~159) pg/ml	46		
Cortisol	(3.9~11.8) μg/dl	23.8		
ACTH	(6~36) pg/ml	22		

abnormal patches in the duodenum (Fig 1). The *S. stercoralis* hyperinfection was histopathologically confirmed via a biopsy of the lesion (Fig 2). The nausea was aggravated 14 days after admission, and an abdominal radiograph examination was performed which revealed an ileus (Fig 3). Stool examination revealed the presence of numerous *S. stercoralis* rhabditiform larvae. He simultaneously developed a fever, and methicillin-resistant *Staphylococcus aureus* (MRSA) was detected by a blood culture examination.

Six milligrams of Ivermectin were given 14 days apart. Vancomycin hydrochloride and imipenem/cilastatin sodium in combination were administered for the MRSA infection. His stool larvae tests were negative after the second dose of Ivermectin and his body temperature and CRP value returned to normal. His serum sodium and potassium values also returned to normal. Fig 4 shows the clinical course.

The patient's human T-lymphotropic virus type 1 (HTLV-1) antibody titer was positive and a small percentage of atypical lymphocytes was detected on the peripheral white blood cell count. While it did not indicate a definitive diagnosis of adult T-cell leukemia (ATL), an examination of the surface marker showed that 30% of the lymphocytes were CD4/CD25 double-positive. While the Southern blotting method was needed to establish a definitive diagnosis of ATL by detecting the integration of the HTLV-1 provirus gene, we decided to follow up the patient carefully to detect and treat any opportunistic infection.

DISCUSSION

SIADH is caused by the over-secretion of arginine vasopressin (AVP), and causes an excess in the amount of total water in the body, hyponatremia, coma, convulsions, nausea, and vomiting (Schwanrtz *et al*, 1957; Kaomi *et al*, 1999). Inappropriate secretion of AVP is classified into two groups: ectopic production and that from release by the posterior pituitary gland closely related to disorders of the central nervous system. Pulmonary disorders and drug administration can also cause this syndrome. Ectopic AVP-producing tumor is evident if AVP is found in cancer tissue by immunocytochemistry. In contrast, the mecha-

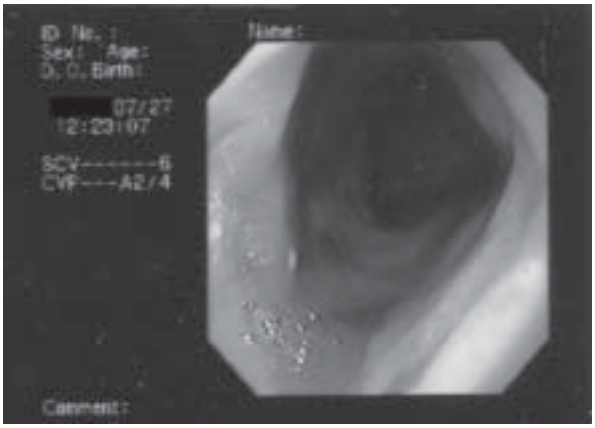
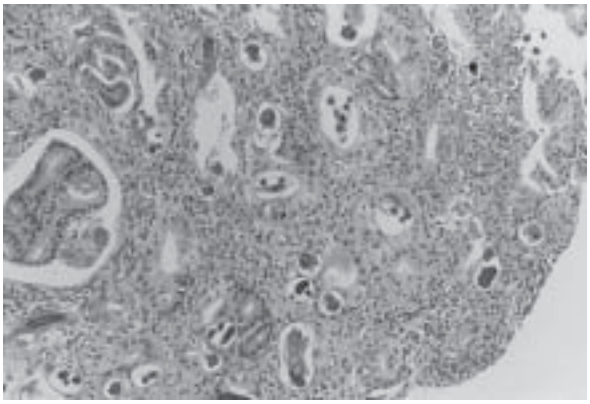


Fig 1–Gastric endoscopy revealed white patches in the duodenum.



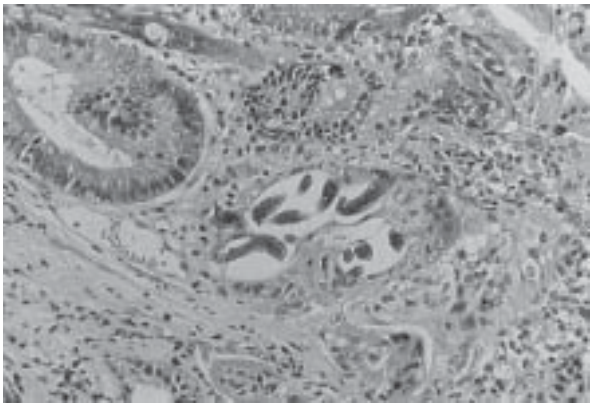


Fig 2–Cross-section of a lesion with white patches in the duodenum showed hyperinfection of *S. stercoralis*.

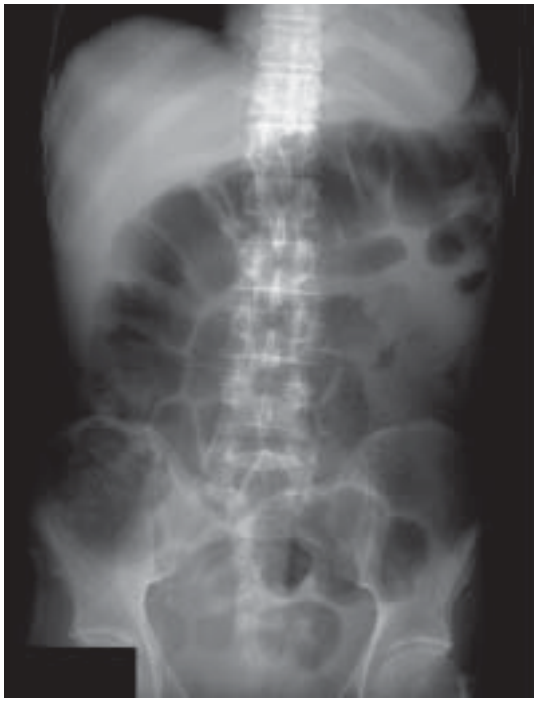


Fig 3–Abdominal radiography revealed gas in the small and large intestine.

nism of AVP release from the posterior pituitary is not clear in disorders of the central nervous system. There is no evidence for stimulatory factors or afferent pathways to the posterior pituitary.

In the present patient, the clinical and laboratory features were consistent with the diagnostic criteria of SIADH by Bartter and Schwartz (1967). He had hyponatremia, hypoosmolality, and hypertonic urine; he had neither dehydration nor edema and both his renal and adrenal functions were normal. While we tested for disorders of the central nervous system and pulmonary disorders, we could find no abnormality except for the *S. stercoralis* hyperinfection in the duodenum.

Reddy (2002) reported a case of a female having SIADH and nonpalpable purpura with *S. stercoralis* hyperinfection. In this case, pulmonary hyperinfection manifested as a cough,

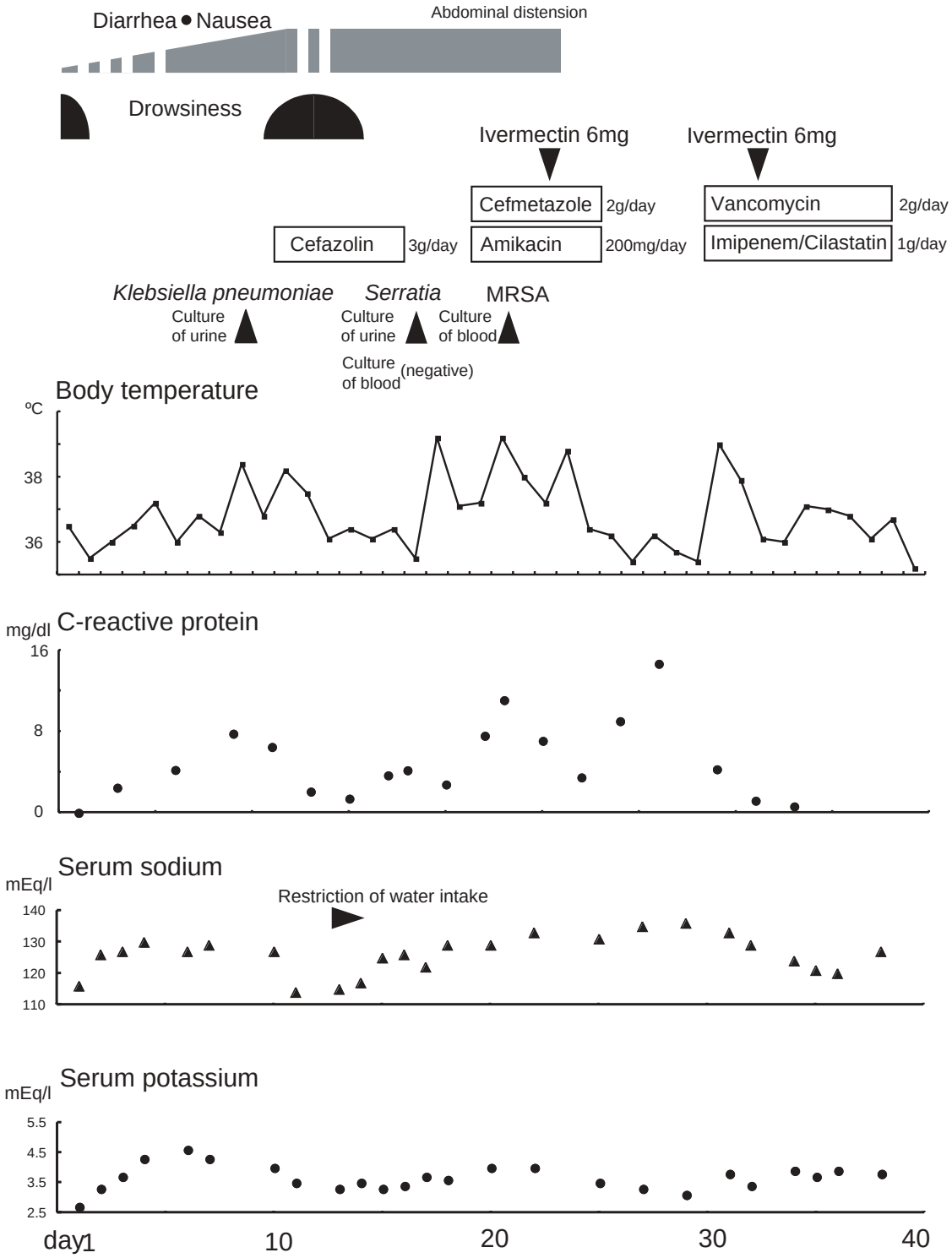


Fig 4–The clinical course of our patient.

dyspnea, bronchospasm, chronic bronchitis, and adult respiratory distress syndrome. Chest radiographs revealed diffuse interstitial changes in the lungs, which were considered to be responsible for the manifestation of the SIADH. In the present case, in contrast, there were no remarkable changes in the respiratory system, suggesting the presence of another mechanism of over secretion triggered by *S. stercoralis* hyperinfection.

Severe hypoalbuminemia in the present patient may have been caused by protein-losing enteropathy. *S. stercoralis* hyperinfection results in heavy infestation of the intestinal mucosa, causing hemorrhage or edema, and capillary leaks leading to protein loss from the gastrointestinal tract.

The patient was born in Okinawa then moved to South America in childhood. Since *S. stercoralis* is endemic in both those areas we could not determine when or where he was infected (Asato *et al*, 1992). Disseminated strongyloidiasis frequently develops in patients with immunodeficiencies caused by poor nutrition, drug therapy (including steroid therapy) for autoimmune diseases, chronic alcoholism, advanced age, diabetes mellitus, collagen disease, postoperative status, or a high titer of HTLV-1 (Longworth and Weller, 1986; Saito, 1995). On admission, this patient was severely emaciated because of continuous appetite loss lasting 6 months. It is not clear whether his appetite loss was caused by the SIADH. He was immunocompetent and not an alcoholic. On admission, he was afebrile, the C-reactive protein was negative, and no other evidence of infection was noted. His chief complaint after admission was epigastric pain and nausea. While he was treated with supplementary electrolytes by drip infusion after admission, his symptoms continued and he still had appetite loss. Pyrexia then developed, a bacterial infection was seen on blood culture examination, and dissemination of *S. stercoralis* was suspected following gastric endoscopy. We assumed that the dissemination was triggered by poor nutrition.

The onset of dissemination did not correspond with the onset of SIADH, and thus it is unlikely the SIADH was triggered by *S. stercoralis* dissemination. We were unable to identify the cause of SIADH. In addition, there was no history of pharmaceutical use that may have caused the SIADH. It has been reported that mild cases of strongyloidiasis pathologically develop eosinophilic pneumonia. The characteristic pathological change in the lung is alveolar bleeding in response to dissemination and hyperinfection. Thus, while no lung disease was found in the present case, the undetectable bleeding lesion on the chest radiograph may have played a role in the development of SIADH.

The intensity of the pulmonary alveolar hemorrhage in a serious case does not relate to the number of infecting *S. stercoralis* (Harper *et al*, 1984), but is thought to be related to the pulmonary changes, changes in oxygen partial pressure, abnormalities of the activation system of kallikrein, and abnormalities of the coagulation cascade due to the influence of filariform larval protease acting on the basal membranes in the pulmonary capillary system (Shiroma and Sato, 1997). While no clear cause of SIADH could be identified in the present case, there was a persistent chronic infection of *S. stercoralis* in the alimentary tract identified by patient history. We assumed that anorexia played a role in the chronic infection with *S. stercoralis*, and this accelerated AVP secretion directly or indirectly.

Adachi *et al* (1994) reported a case of adult T-cell leukemia (ATL), a unique type of T-cell malignancy closely associated with HTLV-1. They presented an unusual case of ATL with various abnormalities in the endocrine and metabolic systems involving anterior pituitary function, thyroid function, lipid metabolism, and calcium metabolism. Some of these abnormalities were considered to arise from the

infiltration of leukemic cells in systemic organs. In the present case, the HTLV-1 antibody titer was positive and only a low percentage of atypical lymphocytes was detected on the peripheral white blood cell count. While there was not a definitive diagnosis of adult T-cell leukemia (ATL), examination of the surface marker showed that 30% of the lymphocytes were CD4/CD25 double-positive. There were few leukemic cells in the peripheral blood, and no organ invasion was detected. Due to this, the cause of SIADH was deemed not due to HTLV-1 infection.

Many cases of *S. stercoralis* have general constitutional symptoms, such as general fatigue or emaciation persisting for a long time. It has been reported that 20-30% of patients with chronic infection complain of arthralgia, abdominal pain, borborygmus, or numbness of limbs, and these subjective symptoms improve following treatment for *S. stercoralis* (Shiroma *et al*, 1990; Zaha *et al*, 1992). In the present case, the SIADH developed following chronic infection with *S. stercoralis* accompanied by anorexia, malnutrition, and emaciation which, in turn, was followed by the dissemination of *S. stercoralis*. These symptoms and hyponatremia improved following treatment for *S. stercoralis*.

It is unknown how many cases of strongyloidiasis are accompanied by abnormalities of serum electrolytes, as in the present case. Further research is required to determine the relationship between strongyloidiasis and SIADH. These studies should involve a sufficient number of cases of persistent mild infection with *S. stercoralis* along with animal model studies.

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