

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) In *Strongyloides stercoralis* Hyperinfection

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ABSTRACT

Strongyloides stercoralis (*S. stercoralis*) is a soil transmitted intestinal roundworm that has a unique ability to multiply within the human host and reinfect the human carrier by a process of autoinfection. By this property, *S. stercoralis* can persist as an occult infection for many decades. In situations of immunosuppression or other permissive gastrointestinal conditions, there occurs a massive increase in parasite multiplication. The parasites penetrate through the intestinal mucosa and are carried in circulation and can cause multisystem involvement. We report a case of a 76-year-old Columbian male who presented with intractable vomiting and hyponatremia who was then diagnosed to have syndrome of inappropriate antidiuretic hormone (SIADH). The patient's symptoms improved after treatment with two doses of ivermectin and his serum sodium levels returned to normal. *S. stercoralis* infection should be suspected in patients from endemic regions who present with gastrointestinal symptoms and unexplained hyponatremia.

Key words: Disseminated strongyloidiasis, Hyponatremia, Parasite, Strongyloides hyperinfection, *Strongyloides stercoralis*, Syndrome of inappropriate antidiuretic hormone secretion

INTRODUCTION

Stercoralis is an intestinal nematode or roundworm which causes an infection that can manifest as an asymptomatic eosinophilia in the immunocompetent host to fatal disseminated disease in the immunocompromised host. An unusual characteristic of *S. stercoralis* is its ability to multiply within the human host.^[1-3] By this unique property, this parasite can persist for many decades as occult infection through an autoinfection cycle where mature rhabditiform larvae transform into infective filariform larvae within the intestinal tract.^[2] Humans acquire *S. stercoralis* when infective filariform larvae found in fecally contaminated soil penetrate skin or mucus membranes. Prior reports state up to 50% of infected individuals remain asymptomatic^[2,3] or may have symptoms such as abdominal pain; nausea; vomiting; and diarrhea; or pulmonary symptoms such as dry cough, dyspnea, or wheezing. Massive multiplication of parasites within the

gastrointestinal tract, known as hyperinfection, can occur in situations of immunosuppression or local gastrointestinal conditions such as achlorhydria, blind loops, and diverticulosis. Disseminated strongyloidiasis occurs when these infective filariform larvae invade through the gastrointestinal tract and migrate to other organs and cause multisystem involvement. Bacteremia and septicemia occur due to migration of bowel organisms through damaged intestinal epithelium.^[2] Features of dissemination include severe abdominal pain, nausea, vomiting, diffuse rash, pulmonary infiltrates, ileus, gram negative sepsis, meningitis, and protein losing enteropathy.^[2,4] Majority of patients with disseminated strongyloidiasis (83-87%) have a fatal outcome.^[2]

We report a case of a 76-year-old Colombian male patient presenting with gastrointestinal symptoms, hyponatremia, and *S. stercoralis* hyperinfection after being recently treated with corticosteroids. SIADH associated with *S. stercoralis* infection is vastly under-reported though it may be a common occurrence. There are only four previously reported cases in literature of SIADH being associated with disseminated strongyloidiasis.

It is therefore important to acknowledge this clinical entity in order to recognize the various manifestations of

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disseminated strongyloidiasis and institute appropriate treatment early to prevent fatal complications.

CASE REPORT

A 76-year-old Hispanic male presented to our hospital with a 2-month history of fatigue, nausea, intractable vomiting and a 30-pound weight loss. Past medical history was significant for idiopathic thrombocytic purpura (ITP) diagnosed 4 months ago, which was treated with steroids for 3 weeks. The patient had immigrated to the United States from Columbia 17 years ago and had travelled to Venezuela a month prior to presentation. He had a history of smoking 1 pack per day for 40 years.

On physical examination there was nonpalpable purpurae. Abdominal examination revealed a soft nondistended abdomen with mild epigastric tenderness, with no associated guarding, rigidity, rebound tenderness, or organomegaly.

Laboratory examination revealed elevated white cell count of 11,400/ μ l, with a normal eosinophil count of 1%. Biochemistry revealed sodium of 122 meq/l. Other significant laboratory abnormalities were a total protein level of 4.5 g/dl and albumin level of 1.7 g/dl. The rest of laboratory examination was normal [Table 1]. Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain were unremarkable. The patient tested negative for both HIV and human T-lymphotropic virus (HTLV).

The patient was initially treated with 0.9 normal saline infusions suspecting hypovolemic hyponatremia due to persistent vomiting, but showed only minimal improvement

in serum sodium levels. A diagnosis of SIADH was then made based on his high urine osmolality, 564 mOsm/kg and low plasma osmolality 261 mOsm/kg. Fluid restriction increased his serum sodium to 133 meq/l.

To evaluate his symptoms of intractable vomiting, an esophagogastroduodenoscopy (EGD) was performed which showed erythema in the stomach and duodenum. Histopathology showed acute and chronic duodenitis, with marked blunting of villi and reactive cellular changes, active gastritis, and presence of parasites consistent with *S. stercoralis* [Figures 1 and 2]. Stool examination showed many *S. stercoralis* larvae.

The patient was treated with two doses of ivermectin 12 mg (calculated at 200 μ g/kilogram) following which his nausea and vomiting improved and serum sodium increased to 139 meq/l. Repeat stool examination after 2 weeks of ivermectin therapy did not show any *S. stercoralis* larvae.

DISCUSSION

S. stercoralis is a soil transmitted intestinal nematode that is endemic to many humid, tropical parts of the world including south eastern United States, south Asia, Latin America, and sub-Saharan Africa.^[5] In the United States, it is found most commonly among immigrants from endemic areas.^[6] It affects 30 to 100 million people worldwide.^[1] It is uncommon in regions with temperate climate. The highest noted prevalence in USA is among residents of south eastern states and in individuals who have resided at or travelled to endemic areas.^[1,7-9] Our patient had migrated to the USA 17 years ago from South America, an endemic region for *S. stercoralis* infections and had also recently travelled to Venezuela. Life

Table 1: Laboratory examination results

Hemoglobin	13.5	(13.5-17.5) g/dl
Hematocrit	40.3	(41-53) %
Platelet count	265,000	(140-440)/ μ l
Prothrombin Time (PT)	14.6	(12.2-14.9) seconds
Activated Partial Thromboplastin Time (aPTT)	26.7	(21.3-35.1) seconds
International Normalized Ratio (INR)	1	
Potassium	3.6	(3.5-5) meq/l
Blood Urea Nitrogen (BUN)	10	(7-23) mg/dl
Creatinine	0.8	(0.6-1.3) mg/dl
Total protein	4.5	(6.4-8.4) g/dl
Serum albumin	1.7	(3.5-5.7) g/dl
Erythrocyte Sedimentation Rate (ESR)	102	(0-10) mm/hr
BNP	110	(0-100) pg/ml
TSH	0.669	(0.35-5.60) μ IU/ml
Triglycerides	41	(< 150) mg/dl
Serum uric acid	2.5	(4.4-7.6) mg/dl
Serum cortisol level (AM)	16.2	(4.3-22.4) μ g/dl
Serum osmolality	261	(283-299) mOsm/kg
Urine osmolality	564	(332-1276) mOsm/kg

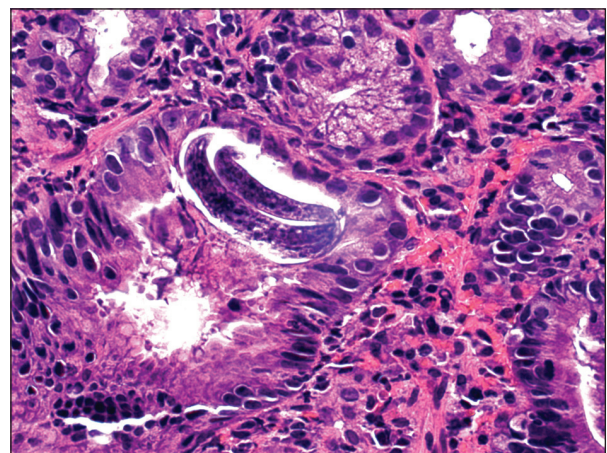


Figure 1: Hematoxylin and eosin stain of a duodenal biopsy specimen showing inflammatory cell infiltrate, marked blunting of villi and *Strongyloides stercoralis* larvae (\times 100)

cycle of *S. stercoralis* is more complex than other nematodes in the same class with its ability to alternate between free living and parasitic cycles and its capacity to autoinfect and multiply within the host.^[1-3] In the gastrointestinal tract of the human host, the infective stage of *S. stercoralis*, the filariform larva matures into the adult worm, which then lives within the mucosa of the duodenum or jejunum. The adult worm produces eggs from which develop the rhabditiform larvae, which are either passed in stool or mature into infective filariform larvae. These infective filariform larvae cause internal autoinfection by penetrating through the intestinal mucosa or external autoinfection by penetrating the skin of the perianal region.^[1,2]

Autoinfection is usually restricted by an intact immune response and a low level of autoinfection may allow the organism to persist for decades.^[1,7] However, in the

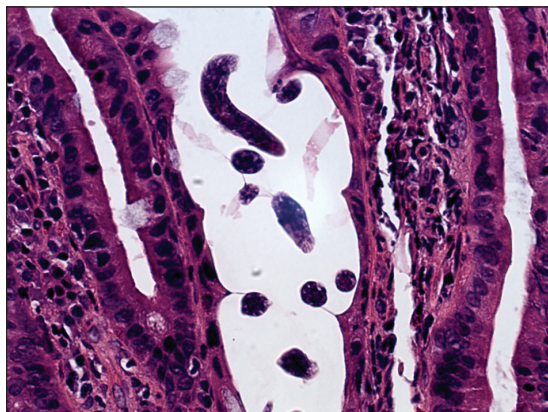


Figure 2: Longitudinal and cross-sectional view of a duodenal biopsy specimen stained with hematoxylin and eosin showing several *S. stercoralis* larvae lying within a crypt (x40)

setting of a depressed immune system, the autoinfection process can lead to a large increase in the parasite burden, causing a hyperinfection syndrome, which can then result in massive dissemination of filariform larvae into heart, lungs, central nervous system (CNS), liver, and endocrine organs ensuing in disseminated strongyloidiasis.^[10,11] Immunocompromised conditions which have been noted to predispose to *S. stercoralis* hyperinfection and dissemination include disorders such as protein-calorie malnutrition,^[12] hematologic malignancies (especially lymphoma)^[12,13] immunosuppressive therapy (particularly steroids),^[13] kidney transplantation,^[14] and viral infections such as human T-cell lymphotropic virus type 1 (HTLV-I).^[15]

S. stercoralis hyperinfection has also been reported with chronic variable immunodeficiency, chronic renal failure,^[12] burns,^[12,16] and diabetes.^[17] Local factors such as impaired bowel motility,^[16] constipation, and diverticulosis as well as achlorhydria^[18] can all cause an unrestricted increase in parasitic multiplication and maturation. Furthermore, severe disseminated strongyloidiasis may develop in immunocompromised patients leading to sepsis, respiratory failure, and death. Our patient was treated with oral corticosteroids for ITP which could have predisposed him to develop disseminated strongyloidiasis.

In patients with decreased cell mediated immunity, the case fatality rate of disseminated disease has been reported to range between 50 and 86%.^[13] Interestingly there are only a few cases reported of *S. stercoralis* hyperinfection in patients infected with HIV-1.^[19] Prior case reports mentioning the association of disseminated strongyloidiasis and SIADH consisted of patients who were on steroid therapy for

Table 2: Comparison of laboratory examination results of patients in previously reported cases

Case report	Patient age	Clinical history	Hemoglobin (g/dl)	Hematocrit	WBC 10 ³ /mm ³	Eosinophils (%)	Platelets 10 ³ /mm ³	Serum sodium (mEq/L)	Serum osmolarity (mosm/kg)	Urine osmolarity (mosm/kg)	Total protein (g/dl)	Albumin (g/dl)	TSH (μIU/ml)	Cortisol (μg/dl)
Reddy, Myers, 2003	66	Prednisone for vasculitis		25%	7,400	1	246,000	123	248	960	4.6	1.9 g/dl	"normal"	not reported
Seet, Gong, 2005	55	chemotherapy (with adjunctive steroids) for multiple myeloma	14.3	—	12,900	0.3	220,000	119	—	—	—	—	—	—
Hayashi, Yamamoto, 2007	52	travel to endemic area	10.7	29.6	5590	0.9	—	116	262	423	4.9	2.5	0.376	23.8
Aregawi, Lopez, 2009	51	chemotherapy (with adjunctive steroids) for glioblastoma multiforme	—	—	—	—	—	—	—	—	—	—	—	—
Nag Chowdhury, Dhadham, 2013	76	prednisone for ITP	13.5	40.3	11,400	1	265,000	122	261	564	4.5	1.7	0.669	16.2

various conditions. Their laboratory examination results are compared for review [Table 2].

Peripheral eosinophilia, which is known to be an important clinical marker for helminthic infection, is very nonspecific and is seen in only 5-15% of infected patients.^[7,8,18] Eosinophilia may be absent in disseminated *S. stercoralis* infection and also after corticosteroid therapy,^[7] as seen in our patient who had an eosinophil count of 1% or 1,000/mm³. Absence of eosinophilia is a poor prognostic sign.^[12]

Hypoproteinemia in *S. stercoralis* hyperinfection may occur as a result of hemorrhage, edema, and capillary leaks in the intestinal mucosa causing a protein losing enteropathy^[4] which was also noted in our patient who had a total protein of 4.5 g/dl and albumin of 1.7 g/dl.

Skin lesions such as nonpalpable purpura, seen in our patient, resemble vasculitis and have been attributed to a hypersensitivity reaction to *S. stercoralis* larvae in the dermis.^[20,21]

SIADH is thought to occur by various dysfunctions and infections, particularly virus infections, which may cause meningoencephalitis by virus dissemination. SIADH has been associated with systemic strongyloidiasis; the mechanism is unknown, although it has been attributed to CNS or pulmonary involvement.^[20,22-25] In one report, diffuse pulmonary interstitial infiltrates was reported to be responsible for the development of SIADH;^[20] while another report identified anorexia, as a result of chronic *S. stercoralis* infection to be responsible for increased ADH secretion.^[25] However, our patient did not have CNS features or pulmonary infiltration, and the mechanism by which *S. stercoralis* causes SIADH remains unclear.

Definitive diagnosis of strongyloidiasis is usually made on direct visualization of larvae in stool or in clinical specimens such as duodenal or jejunal aspirates and/or biopsies obtained via endoscopy. However, these may be negative in approximately 25% of infected patients. A low parasite burden or intermittent excretion^[2,26] in stool may be responsible for a large percentage of false negative results. Specialized testing of the stool sample with the Baermann concentration technique or a modified agar plate method may increase the yield. Considering the possibility of intermittent excretion, repeated examinations with up to 3-7 stool samples may increase sensitivity.^[27,28] Diagnosis can also be made with serological testing.^[1] In disseminated strongyloidiasis, filariform larvae can also be found in sputum, pleural and peritoneal fluid, and bronchoalveolar lavage fluid in addition to stool.^[29-33] We diagnosed strongyloidiasis in

our patient by means of esophagogastroduodenoscopy and biopsy of gastric and duodenal mucosa which showed many *S. stercoralis* larvae. *S. stercoralis* larvae was also directly visualized on stool examination.

Treatment with ivermectin has shown good results in this condition, including patients who did not respond adequately to thiabendazole. Ivermectin is highly effective when given orally (200 µg/kg per day for 1-2 days) for complicated intestinal strongyloidiasis. In one study, complete parasitological cure was obtained in 24 of the 29 patients treated with ivermectin 200 µg/kg as a single dose (83%) and in nine of the 24 patients who were given albendazole 400 mg/day for 3 days (38%). Both treatment groups suffered from minimal clinical or biological adverse effects.^[34] Our patient achieved cure after two doses of ivermectin verified by a stool testing.

Ivermectin also appears to be devoid of the side effects seen with thiabendazole therapy, and achieves cure rates of up to 88% in immunocompetent patients.^[34] Immunocompromised patients with systemic disease may require multiple dose regimens.^[29] Patients who experience frequent relapses may benefit from monthly treatment regimens.^[2]

CONCLUSION

Ill-defined gastrointestinal symptoms, obscure hyponatremia, hypoproteinemia, and purpuric rash in immunocompromised patients who have lived in an endemic region for *S. stercoralis* should prompt the suspicion of strongyloidiasis as one of the differential diagnoses. All patients who possess risk factors for the development of *S. stercoralis* infection must be screened for the presence of the parasite before starting any immunosuppressive therapy even if exposure was many decades ago. SIADH may occur in patients with disseminated strongyloidiasis and is a frequently unrecognized complication of the disease. Healthcare professionals need to be aware of this fatal complication to institute early and appropriate treatment.

REFERENCES

1. Siddiqui AA, Berk SL. Diagnosis of *Strongyloides stercoralis* infection. Clin Infect Dis 2001;33:1040-7.
2. Concha R, Harrington W, Rogers AI. Intestinal strongyloidiasis: Recognition, management, and determinants of outcomes. J Clin Gastroenterol 2005;39:203-11.
3. Bannon JP, Fater M, Solit R. Intestinal ileus secondary to *Strongyloides stercoralis* infection: Case report and review of the literature. Am Surg 1995;61:377-80.
4. Sullivan PB, Lunn PG, Northrop-Cleaves CA, Farthing MJ. Parasitic infection of the gut and protein-losing enteropathy. J Pediatr Gastroenterol Nutr 1992;15:404-7.

5. Agrawal V, Agarwal T, Ghoshal U. Intestinal strongyloidiasis: A diagnosis frequently missed in the tropics. *Trans R Soc Trop Med Hyg* 2009;103:242-6.
6. Weller PF, Nutman TB. Intestinal Nematodes. *Harrison's Principles of Internal Medicine*, 18th edition. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds, McGraw Hill, 1739-1744.
7. Genta RM. Global prevalence of strongyloidiasis: Critical review with epidemiologic insights into the prevention of disseminated disease. *Rev Infect Dis* 1989;11:755-67.
8. Liu LX, Weller PF. Strongyloidiasis and other intestinal nematode infections. *Infect Dis Clin North Am* 1993;7:655-82.
9. Berk SL, Verghese A, Alvarez S, Hall K, Smith B. Clinical and epidemiologic features of strongyloidiasis. A prospective study in rural Tennessee. *Arch Intern Med* 1987;47:1257-61.
10. Keiser PB, Nutman TB. *Strongyloides stercoralis* in the immunocompromised population. *Clin Microbiol Rev* 2004;17:208-17.
11. Montes M, Sawhney C, Barros N. *Strongyloides stercoralis*: There but not seen. *Curr Opin Infect Dis* 2010;23:500-4.
12. Igra-Siegman Y, Kapila R, Sen P, Kaminski ZC, Louria DB. Syndrome of hyperinfection with *Strongyloides stercoralis*. *Rev Infect Dis* 1981;3:397-407.
13. Segarra-Newnham M. Manifestations, diagnosis, and treatment of *Strongyloides stercoralis* infection. *Ann Pharmacother* 2007;41:1992-2001.
14. Morgan JS, Schaffner W, Stone WJ. Opportunistic strongyloidiasis in renal transplant recipients. *Transplantation* 1986;42:518-24.
15. Gotuzzo E, Terashima A, Alvarez H, Tello R, Infante R, Watts DM, *et al.* *Strongyloides stercoralis* hyperinfection associated with human T cell lymphotropic virus type-1 infection in Peru. *Am J Trop Med Hyg* 1999;60:146-9.
16. Scowden EB, Schaffner W, Stone WJ. Overwhelming strongyloidiasis: An unappreciated opportunistic infection. *Medicine (Baltimore)* 1978;57:527-44.
17. Coovadia YM, Rajput MC, Bhana RH. Disseminated strongyloidiasis in a diabetic patient. *Trop Geogr Med* 1993;45:179-80.
18. Grove DI. Human strongyloidiasis. *Adv Parasitol* 1996;38:251-309.
19. Gompels MM, Todd J, Peters BS, Main J, Pinching AJ. Disseminated strongyloidiasis in AIDS: Uncommon but important. *AIDS* 1991;5:329-32.
20. Reddy TS, Myers JW. Syndrome of inappropriate secretion of antidiuretic hormone and nonpalpable purpura in a woman with *Strongyloides stercoralis* hyperinfection. *Am J Med Sci* 2003;325:288-91.
21. Galimberti R, Pontón A, Zaputovich FA, Velasquez L, Galimberti G, Torre A, *et al.* Disseminated strongyloidiasis in immunocompromised patients — report of three cases. *Int J Dermatol* 2009;48:975-8.
22. Aregawi D, Lopez D, Wick M, Scheld WM, Schiff D. Disseminated strongyloidiasis complicating glioblastoma therapy: A case report. *J Neurooncol* 2009;94:439-43.
23. Seet RC, Gong LL, Tambyath PA. Image of the month. *Strongyloides stercoralis* hyperinfection and syndrome of inappropriate secretion of antidiuretic hormone. *Gastroenterology* 2005;128:8,252.
24. Vandeboosch S, Mana F, Goossens A, Urbain D. *Strongyloides stercoralis* infection associated with repetitive bacterial meningitis and SIADH: A case report. *Acta Gastroenterol Belg* 2008;71:413-7.
25. Hayashi E, Ohta N, Yamamoto H. Syndrome of inappropriate secretion of antidiuretic hormone associated with strongyloidiasis. *Southeast Asian J Trop Med Public Health* 2007;38:239-46.
26. Lim S, Katz K, Krajden S, Fuksa M, Keystone JS, Kain KC. Complicated and fatal *Strongyloides* infection in Canadians: Risk factors, diagnosis and management. *CMAJ* 2004;171:479-84.
27. Nielsen PB, Mojon M. Improved diagnosis of *Strongyloides stercoralis* by seven consecutive stool specimens. *Zentralblatt für Bakteriologie, Mikrobiologie und Hygiene. Series A: Medical Microbiology, Infectious Diseases, Virology, Parasitology*; 1987;263:616-8.
28. Poe CM, Taylor LM. Syndrome of inappropriate antidiuretic hormone: Assessment and nursing implications. *Oncol Nurs Forum* 1989;16:373-81.
29. Eveland LK, Kenney M, Yermakov V. Laboratory diagnosis of autoinfection in strongyloidiasis. *Am J Clin Pathol* 1975;63:421.
30. Schainberg L, Scheinberg MA. Recovery of *Strongyloides stercoralis* by bronchoalveolar lavage in a patient with acquired immunodeficiency syndrome. *Am J Med* 1989;87:486.
31. Smith B, Verghese A, Guterrez C, Dralle W, Berk SL. Pulmonary strongyloidiasis. Diagnosis by sputum gram stain. *Am J Med* 1985;79:663.
32. Williams J, Nunley D, Dralle W, Berk SL, Verghese A. Diagnosis of pulmonary strongyloidiasis by bronchoalveolar lavage. *Chest* 1988;94:643-4.
33. Harris RA Jr, Musher DM, Fainstein V, Young EJ, Clarridge J. Disseminated strongyloidiasis. Diagnosis made by sputum examination. *JAMA* 1980;244:65-6.
34. Detry A, Hilmarsdottir I, Mayorga-Sagastume R, Lyagoubi M, Gaxotte P, Biligui S, *et al.* Treatment of *Strongyloides stercoralis* infection with ivermectin compared with albendazole: Results of an open study of 60 cases. *Trans R Soc Trop Med Hyg* 1994;88:344-5.

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