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Case Report: Central Nervous System Strongyloidiasis: Two Cases Diagnosed Antemortem

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Abstract. Central nervous system (CNS) strongyloidiasis is a known but rare form of disseminated infection. The diagnosis is often made postmortem, with only five published cases of an antemortem diagnosis. We report two fatal cases of CNS strongyloidiasis diagnosed antemortem, with *Strongyloides stercoralis* larvae visualized in the CNS sample in one case. Risk factors for disseminated strongyloidiasis common to both cases included origination from the Caribbean, underlying human T-lymphotropic virus-1 infection, and recent prednisone use. Both cases occurred in Canada, where the occurrence of *Strongyloides* is uncommon, and serve as a reminder to maintain a high index of suspicion in patients with epidemiologic or clinical risk factors for dissemination.

INTRODUCTION

Strongyloides stercoralis, a nematode prevalent in tropical and subtropical regions, is thought to infect 30–100 million people worldwide.[1] Although most people with strongyloidiasis remain asymptomatic, severe and fatal clinical presentations such as hyperinfection or disseminated disease can occur.[2] *Strongyloides stercoralis* possesses the unique ability to autoinfect and multiply within the host by penetrating the intestinal mucosa or perianal skin to regain entry into the circulatory system, leading to an enormous worm burden and lifelong persistence, if untreated.[1,2] Hyperinfection refers to accelerated autoinfection with increased gastrointestinal and pulmonary symptoms.[2,3] Disseminated infection refers to migration of larvae outside of the gastrointestinal-pulmonary autoinfective cycle.[2,3] Impaired cellular immunity is a major risk factor for dissemination, especially due to immunosuppressive therapy (such as corticosteroids or posttransplant medications), hematologic malignancies, or human T-lymphotropic virus-1 (HTLV-1) infection.[2,4,5]

Central nervous system (CNS) strongyloidiasis is a known but rare form of disseminated infection, first described in 1973 as a postmortem diagnosis.[6] Since then, five published cases of antemortem diagnosis of CNS strongyloidiasis have been reported,[5,7–10] with other cases diagnosed postmortem. We report two cases of CNS strongyloidiasis diagnosed antemortem, with *S. stercoralis* larvae visualized in the CNS sample in one case. Both cases occurred in Canada, where the occurrence of *Strongyloides* is uncommon, and serve as a reminder to maintain a high index of suspicion in patients with epidemiologic or clinical risk factors for dissemination.

CASE 1

A 67-year-old Trinidadian male presented to the hospital in August 2014 with a 1-day history of headache, confusion, drowsiness, and seizure, following a period of anorexia, nausea, vomiting, abdominal pain, diarrhea, and weight loss. His background health history included rheumatoid arthritis, systemic lupus erythematosus, benign prostatic hyperplasia, previous prostate cancer, and bilateral knee replacement. For his rheumatologic conditions, he had been recently treated with methotrexate and various doses of prednisone, and had previously also been treated with leflunamide and hydroxychloroquine. On initial presentation to the emergency department, he had an elevated temperature and was suspected to have pneumonia.

After a series of nondiagnostic investigations during his early hospital stay, he developed worsening confusion and decreasing level of consciousness. Computed tomography (CT) of the abdomen revealed a nonspecific colitis. A lumbar puncture revealed the cerebrospinal fluid (CSF) to have a white blood cell (WBC) count of 22×10^6/L (91% lymphocytes, 2% neutrophils, and 7% monocytes), protein 0.46 g/L, and glucose 8.6 mmol/L. The cerebrospinal fluid culture was positive for *Escherichia coli* (*E. coli*), which prompted specific testing for *S. stercoralis*. *Strongyloides stercoralis* filariform larvae were found in this initial CSF sample (Figure 1) and also in stool and sputum examinations. *Strongyloides* serology was positive. Subsequent serology was positive for HTLV-1 and negative for human immunodeficiency virus. Magnetic resonance imaging (MRI) revealed scattered nonspecific white matter changes consistent with microangiopathy.

He was treated with albendazole (GlaxoSmithKline) 400 mg orally twice daily and ivermectin (Merck & Co., Inc.) 200 mcg/kg subcutaneously daily for disseminated *Strongyloides* infection, as well as antibiotics for *E. coli* meningitis. Initially, he did not show any signs of neurologic improvement. Repeat CT and MRI brain imaging showed leptomeningeal enhancement of both cerebral convexities consistent with ongoing meningitis, as well as new subdural collections along the right cerebral convexity and cortical infarcts.

He suffered severe neurological impairment resulting in over 1.5 years in hospital. His course was complicated by thrombosis of his cephalic veins bilaterally, upper gastrointestinal bleed with stress ulcer, *Clostridium difficile* infection, and recurrent bacteremia with several different organisms. He received intermittent treatment courses with oral ivermectin with no recurrence. Ultimately, the patient passed away in April 2016 with no autopsy performed.

CASE 2

A 55-year-old previously healthy Jamaican man presented to the hospital in August 2016 with 1 month of abdominal pain

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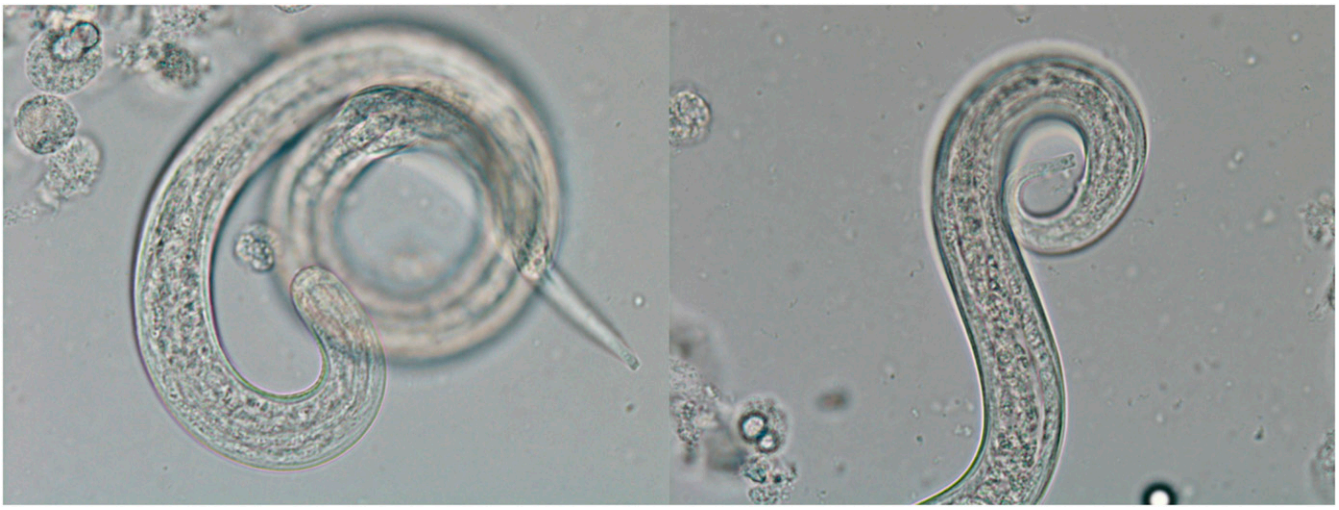

FIGURE 1. *Strongyloides stercoralis* filariform larvae in the cerebrospinal fluid of the patient in Case 1. Photos courtesy of the Public Health Ontario Laboratory. This figure appears in color at www.ajtmh.org.

with intermittent fever. He had multiple emergency department visits with no clear diagnosis despite investigations including abdominal X-ray, abdominal ultrasound, CT abdomen, and chest X-ray. He did not have any skin findings. He had immigrated to Canada in 1981 with no other relevant travel history.

His white blood cell count 1 month before admission was 16.9×10^9/L with 0.46×10^9/L eosinophils (normal range 0–0.8×10^9/L). During the present admission, eosinophils were 0, but WBC had increased to 42.6×10^9/L (37.49×10^9/L neutrophils). A repeat chest X-ray was normal. On August 4, a colonoscopy suggested possible Crohn's disease with focal crypt architectural distortion and inflamed granulation tissue; he was started on prednisone, ciprofloxacin, and metronidazole on August 10. On August 13, he suddenly developed decreased level of consciousness and hypoxia. Repeat chest X-ray showed bilateral pulmonary infiltrates. Blood cultures were positive for *Streptococcus oralis* and coagulase-negative *Staphylococcus*. Sputum and stool parasite examinations showed many larvae suspicious for *S. stercoralis*. Bronchoalveolar lavage samples were positive for *Strongyloides* filariform larvae, whereas stool samples were positive for *Strongyloides* rhabditiform larvae. Cerebrospinal fluid showed WBC 180×10^6/L (50% polymorphonuclear leukocytes and 0% eosinophils), red blood cell (RBC) $10{,}220 \times 10^6$/L, protein 0.32 g/L, and glucose 7.6 mmol/L. Bacterial cultures were negative and no parasites were seen on CSF examination. Computed tomography head suggested hypoxic ischemic encephalopathy, but MRI was normal. *Strongyloides* serology was reactive, with an optical density of 0.5 (reactive: > 0.3). He was also found to be positive for HTLV-1.

Given that CSF cultures were negative for bacteria and that both the protein and glucose were within normal ranges, the neurological state was best explained by either deep delirium secondary to medical illness or direct CNS involvement from strongyloidiasis in the setting of proven disseminated *Strongyloides* infection. The CSF findings were not supportive of a bacterial CNS infection and there were no other likely explanations for the neurological state.

Parenteral ivermectin, 12 mg (200 mcg/kg) subcutaneously, was given daily for 2 weeks, then increased to 15 mg because of the lack of response and persistent *Strongyloides* filariform larvae in sputum. Ivermectin drug levels at this dose were 154 ng/mL. Also, he received albendazole 400 mg twice daily for 1 month.

Although his stool and sputum eventually cleared of *Strongyloides* larvae (by August 31 and September 6, respectively), he did not have any neurological improvement and care was withdrawn. He died at the end of September 2016, 7 weeks after admission. No autopsy was performed.

DISCUSSION

The two cases of CNS strongyloidiasis highlight the clinical presentation of an uncommon but devastating form of disseminated strongyloidiasis. The mechanism of CNS strongyloidiasis has been hypothesized to occur by 1) direct entry of migrating larvae through the arterial circulation, 2) a reaction to substances produced by dead or dying larvae, or 3) immune complex deposition in the meninges.[8] The latter two mechanisms may explain why it is rare to find larvae in the CSF.

In both cases, epidemiological and clinical risk factors for disseminated strongyloidiasis were present. Regions with the highest risk for *Strongyloides* exposure include Southeast Asia, Oceania, sub-Saharan Africa, South America, and the Caribbean.[2] Both our patients were originally from the Caribbean (Trinidad and Jamaica). Although both had already spent decades in Canada, the unique ability of *Strongyloides* spp. to autoinfect means that strongyloidiasis can persist lifelong if not treated.[1,2]

Key clinical risk factors for dissemination include corticosteroid therapy (equivalent to 20 mg/day of prednisone for ≥ 2 weeks), other immunomodulatory agents (including agents used in the management of solid-organ transplants and other agents affecting cellular immunity), hematologic malignancies, and HTLV-1 infection.[2,4,5] It has been shown that impairment in cell-mediated immunity leads to a lack of granulomatous immune reaction to *Strongyloides* larvae in tissues.[11] Both our patients had HTLV-1 infection and both received prednisone in immunosuppressant doses. Case 1 received a prolonged course of prednisone, whereas case 2 received prednisone only 4 days before presenting with disseminated disease.

TABLE 1

Published cases of *Strongyloides stercoralis* disseminated infection involving the CNS diagnosed antemortem with the presence of *Strongyloides* larvae in CSF

Authors and year of publication	Year of case	Age/ gender	Risk factors for disseminated strongyloidiasis	Clinical presentation	Relevant investigations	Antiparasitic treatment	Outcome
Bradley et al.[5]	1977	30/M	Lymphoma, chemotherapy, prednisone Born in West Indies; other travel history unknown	Shortness of breath 1 month after diagnosis of lymphoma, and chemotherapy and prednisone initiation, shortly followed by intestinal obstruction and progressive unresponsiveness and meningismus	White blood cell count: 36.8 × 10^9/L with 1% eosinophils CXR: extensive bilateral infiltrates Bronchoalveolar lavage: *S. stercoralis* larval forms cerebrospinal fluid: *S. stercoralis* filariform larvae, Gram-negative bacilli	Thiabendazole 1.5 g NG	Death
Meltzer et al.[7]	1977	56/F	Prednisone (up to 60 mg/day) for ITP for 9 months before presentation Born in Southern Italy and lived there until age 6, then visited 6 months before presentation; also lived in Florida for 10 years	Abdominal distension, fever, headache 1 week after splenectomy for ITP and 9 months of prednisone, followed by worsening mental status Had eosinophilia with abdominal cramping of unknown etiology for 7 years prior	White blood cell count: 15.8 × 10^9/L (eosinophilia % on admission not reported, but was 12% previous year) CXR: extensive bilateral infiltrates Blood: *Escherichia coli* Urine: *E. coli* and *Pseudomonas aeruginosa* Sputum, stool, CSF: *S. stercoralis* filariform larvae Cerebrospinal fluid also grew *Pseudomonas aeruginosa*, *Enterococcus faecium*, and *Candida albicans* at various times during admission	Thiabendazole 25 mg/kg BID × 8 days + levamisole 150 mg on days 1, 2, 7, 8 and 14	Death (septic shock from *Klebsiella pneumoniae* on DOA 56)
Belani et al.[8]	1985	46/F	Prednisone (5 mg BID) for presumed asthma Born in Kentucky and mainly lived in Florida for last 22 years, working as a sharecropper and frequently walking barefoot Treated for *Strongyloides* in 1979 with thiabendazole × 3 days when found in stool during work-up for eosinophilia	Headache, stiff neck, nausea, vomiting, fever, vague abdominal pain; eventually became more confused with generalized weakness and bilateral extremity pain, wheezing Had two episodes of neutrophilic meningitis in 1977 and 1978 with negative bacterial and fungal cultures	White blood cell count: 9.5 × 10^9/L with 3% eosinophilia CXR: few granulomatous densities, but no infiltrate Computed tomography head: cerebral atrophy with slightly dilated ventricles Magnetic resonance imaging brain: periventricular areas of high signal, no abscess Sputum, stool, CSF: *S. stercoralis* filariform larvae Cerebrospinal fluid was 97% neutrophilic	Thiabendazole 25 mg/kg/day divided BID × 8 days	Survived (continued with monthly stool examinations and prophylactic 2-day courses of thiabendazole monthly while on steroids)
Dutcher et al.[9]	1985	45/M	Non-Hogdkin's Burkitt-like lymphoma with CNS involvement with chemotherapy started 8 months before presentation; human immunodeficiency virus positive Born and raised in Puerto Rico, moved to and resides in the United States for the last 22 years	Right 3rd cranial nerve palsy, right Babinski sign positive, urinary retention → thought to be lymphomatous involvement so WBI and IT chemotherapy → developed hyponatremia, seizures, and respiratory distress shortly after 3 months prior, had been noted to have 20% eosinophilia of unclear etiology	Cerebrospinal fluid: malignant cells, *S. stercoralis* filariform larvae Bronchoalveolar lavage, gastric washings, stool: *S. stercoralis* filariform and rhabditiform larvae Blood: *E. coli*	Thiabendazole 1.5 g NG BID × 14 days	Death
Dokmeci et al.[10]	?	75/F	High-dose corticosteroids for presumed asthma with intermittent steroids twice in the last 4 months Lived in Angola for 7 years 4 decades ago before coming to US	Respiratory distress refractory to steroids followed by mental status deterioration, progressive lethargy, seizure, and bradycardic arrest Had chronic intermittent diarrhea for years without clear etiology despite colonoscopy with biopsy	White blood cell count: 19.7 × 10^9/L (no eosinophilia, but 11% the week prior) CXR: unremarkable Cerebrospinal fluid: WBC 2074/mm^3 with 100% neutrophils, rare *S. stercoralis* organisms Sputum, stool: many *Strongyloides* organisms Brain imaging: no gross hemorrhage or structural abnormalities	Ivermectin 200 mcg/kg/day via NG × 7 days	Death (DOA 12)

(continued)

TABLE 1
Continued

Authors and year of publication	Year of case	Age/ gender	Risk factors for disseminated strongyloidiasis	Clinical presentation	Relevant investigations	Antiparasitic treatment	Outcome
Case 1 of this paper	2014	67/M	Prednisone, HTLV-1 infection Born in Trinidad with multiple subsequent visits	Headache, confusion, decreased level of consciousness, seizures; also history of nausea, vomiting, diarrhea, abdominal pain, anorexia; suspected pneumonia	White blood cell count: 9.7 × 10^9/L (no eosinophilia) Computed tomography abdomen: colitis Computed tomography head/MRI brain: leptomeningeal enhancement with subdural collections Cerebrospinal fluid: WBC 22 × 10^6/L with 91% lymphocytes; *E. coli*, *S. stercoralis* Stool, sputum: *S. stercoralis* larvae	Ivermectin Albendazole	Death

BID = twice daily; CNS = central nervous system; CSF = cerebrospinal fluid; CXR = chest X-ray; DOA = day of admission; HTLV-1 = human T-lymphotropic virus-1; IT = intrathecal; ITP = idiopathic thrombocytopenic purpura; MRI = magnetic resonance imaging; NG = nasogastric; WBC = white blood cell; WBI = whole brain irradiation.

The relationship between HTLV-1 and *Strongyloides* infection appears to be bidirectionally influential. That is, strongyloidiasis appears to accelerate the disease course of HTLV-1 to become T-cell leukemia, possibly due to increased levels of $CD4^+$ $CD25^+$ T cells in coinfected patients yielding increased circulating proviral DNA. Concurrently, HTLV-1 infection appears to render patients more tolerant to *Strongyloides* infection by biasing the immune system toward the Th1 system, thereby producing more gamma interferon and less polyclonal and parasite-specific immunoglobulin E.[3,12]

Corticosteroids are implicated in most cases of hyperinfection and dissemination of *Strongyloides* infection, with reports of low-dose steroids, high-dose steroids, locally injected steroids, and adrenocorticotropin being associated with hyperinfection.[3] This may be due to the acute suppression of eosinophilia and lymphocyte activation by corticosteroids, and/or possibly direct effects of corticosteroids on the parasite by either accelerating the rhabditiform to infective filariform larvae transformation or increasing the reproduction of adult females.[3]

Five previously published cases of antemortem diagnosed CNS strongyloidiasis with confirmed larvae found in the CSF are outlined in Table 1, along with Case 1 of this paper. All previous reports were from the United States. Of note, similar to our patients, most cases did not have peripheral eosinophilia during disseminated *Strongyloides*, although there was often eosinophilia before the dissemination stage. The most common presenting symptoms were meningeal signs, usually with a neutrophilic rather than eosinophilic CSF profile; this may be because of the fact that disseminated strongyloidiasis is often complicated by concomitant spread of enteric organisms during the autoinfective cycle when filariform larvae penetrate the intestinal mucosa.[4,8] Only one patient survived. All previous cases in the literature were predisposed to disseminated strongyloidiasis by epidemiological and clinical risk factors.

Current Canadian recommendations for treatment of disseminated strongyloidiasis include ivermectin 200 μg/kg/day orally or subcutaneously once daily plus albendazole 400 mg orally twice daily until clinical improvement and cessation of larval shedding.[2]

The Centers for Disease Control and Prevention in the United States recommends ivermectin 200 μg/kg/day orally until stool and/or sputum tests are negative for 2 weeks.[1]

Despite advances in treatment over time, mortality remains high with a fatality rate of up to 86%[13]; timely diagnosis and treatment remain paramount. Disseminated *Strongyloides* can be prevented by screening those from endemic countries with serology and stool for ova and parasite examination before starting corticosteroids or other immune suppressive medications, especially when eosinophilia is present.

In conclusion, CNS strongyloidiasis is a rare but severe form of disseminated infection with high morbidity and mortality. Central nervous system strongyloidiasis should be considered in patients presenting with neurological, respiratory, and gastrointestinal signs when there are epidemiological and clinical risk factors for disseminated strongyloidiasis.

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