

Case Report: Five Cases of Recurrent Meningitis Associated with Chronic Strongyloidiasis

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Abstract. Although meningitis secondary to chronic strongyloidiasis is a rare complication, it is associated with a high mortality rate. Recurrent meningitis can occur if the underlying parasitic infection is left untreated. We report five cases of recurrent meningitis related to chronic strongyloidiasis that were associated with human T-lymphotropic virus type 1 (HTLV-1) infection. Common causative organisms are *Escherichia coli*, *Streptococcus bovis*, and *Klebsiella pneumoniae*. One patient died during the second episode of meningitis. Three patients showed significant gastrointestinal and respiratory symptoms before developing headache and fever. In four cases, patients developed multiple recurrences even with the treatment of thiabendazol. Ivermectin seems to be a better agent compared with thiabendazol to achieve eradication of strongyloidiasis.

INTRODUCTION

Recurrent bacterial meningitis is a relatively rare condition. The estimated incidence is 4–9% of patients with community-acquired bacterial meningitis. Recurrent cases are often associated with craniopharyngeal structural damage caused by previous trauma, surgical procedure, or immunocompromised state.¹

Strongyloides stercoralis is an enteric nematode with the ability to replicate within the host (autoinfection) and can cause chronic infection for many years. Impaired cellular immunity of the host, especially a result of steroids, chemotherapeutic agents, organ transplantation, human immunodeficiency virus (HIV), or human T-lymphotropic virus type 1 (HTLV-1) infection, facilitates the process of autoinfection and increases the burden of filariform larvae. This phenomenon is called hyperinfection syndrome (HIS).^{2,3} It can cause hematogenous dissemination of enteric bacteria through damaged intestinal mucosa or the invasive larvae itself can facilitate translocation of enteric bacteria.⁴ The HIS is associated with a high mortality rate (up to 87%) secondary to bacteremia or meningitis caused by enteric pathogens.^{5,6} Meningitis and bacteremia can recur unless the strongyloidiasis is successfully treated.

Strongyloidiasis affects between 10% and 40% of the population in warm, tropical, and subtropical areas such as Southeast Asia, Latin America, and sub-Saharan Africa.^{7,8} A previous report also mentioned cases in the southeastern United States including eastern Tennessee, western North Carolina, southern Virginia, and southeastern Kentucky.⁹ It is important to recognize the risk of strongyloidiasis in any developed country among the immigrant population as well as tourists and returning military personnel from endemic areas.⁷

Okinawa is a subtropical area of southern Japan known as an endemic area for both HTLV-1 infection and strongyloidiasis. We previously reported 21 cases of meningitis associated with chronic strongyloidiasis in Okinawa Chubu hospital.¹⁰ We isolated five cases of recurrent meningitis associated with strongyloidiasis from this cohort to analyze the clinical features and risk factors contributing to this coinfection and

determining optimal anthelmintic agents to prevent future recurrence of bacterial meningitis.

METHODS

This study is a retrospective chart review of recurrent meningitis associated with chronic strongyloidiasis at Okinawa Chubu Hospital from January 1990 to December 2011.

Strongyloidiasis was defined by the finding of larvae in stool, sputum, gastric juice, or any sterile body fluid. Meningitis was defined as 1) appropriate clinical features including headache, fever > 38°C, nuchal rigidity; and 2) cerebrospinal fluid (CSF) abnormality including increased cell count, low glucose, high protein.

We searched the medical record database using the keyword “meningitis” and “strongyloidiasis” for both primary and secondary diagnosis among all hospitalizations in Okinawa Chubu Hospital from January 1990 to December 2011.

RESULT

During the period, 1,012 patients were diagnosed strongyloidiasis. Forty-five cases had concomitant diagnosis of meningitis. Twenty-nine cases met the criteria written previously and five cases among them showed recurrent episodes of meningitis (Table 1). All of the patients were seropositive for HTLV-1. One patient (case 4) died during the second episode of bacterial meningitis.

The CSF cell counts ranged from 54/mm³ to 22,900/mm³. Among 20 events of meningitis, blood and CSF cultures showed various enteric pathogen including *Escherichia coli*, *Streptococcus bovis*, *Klebsiella pneumoniae*, *Lactococcus lactis*, and *Streptococcus sanguis*.

Cases 1–4 showed recurrent episodes of meningitis after treatment with thiabendazole. *Case 1.* An Okinawan female, who was used at the local city hall with history of appendicitis and otitis media, had four episodes of meningitis from 1981 to 2000. Her first episode of bacterial meningitis occurred when she was 21 years of age. The CSF culture showed *E. coli*. Stool specimen showed *S. stercoralis*. In addition to the appropriate antibiotic treatment, thiabendazole was administered for 3 days. The HTLV-1 infection was diagnosed at the age of 27. The second episode occurred when she was 31 years of age during which time the patient presented with 9 days of abdominal distention and oral herpes before developing symptoms of

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TABLE 1
Clinical presentation and outcomes of all cases

Case	Sex	Age	HTLV-1	Comorbidities	CSF culture	Blood culture	<i>Strongyloides</i>	Gastrointestinal symptoms	Respiratory symptoms	Anthelmintics	Outcome
1	F	21	(+)	Otititis media	<i>E. coli</i>	Negative	Stool			Thiabendazole	Recovery
		31			<i>E. coli</i>	Negative	Stool, gastric juice	Abdominal distention		Thiabendazole	Recovery
		38			<i>L. lactis</i>	<i>L. lactis</i>	Stool	Weight loss, appetite loss, diarrhea	dry cough	Thiabendazole	Recovery
		40			<i>S. bovis</i>	<i>S. bovis</i>	Stool			Thiabendazole, Ivermectin	Recovery
2	M	38	(+)	HBV infection	<i>S. sanguinis</i>	Negative	Stool	Diarrhea		Thiabendazole	Recovery
		43			Negative	Negative	Stool	Weight loss, diarrhea		Thiabendazole	Recovery
		45			Negative	Negative	Stool	Diarrhea		Thiabendazole	Recovery
		45			Negative	Negative	Negative	Diarrhea		Thiabendazole	Recovery
		46			Negative	Negative	Stool			Thiabendazole	Recovery
49	Negative	Negative	Stool, sputum	Weight loss	Hemoptysis	Ivermectin	Recovery				
3	F	60	(+)	Cervical cancer	Negative	Negative	Stool			Thiabendazole	Recovery
		60			<i>E. coli</i>	Negative	Negative			Thiabendazole	Recovery
		62			Negative	<i>E. coli</i>	Stool			Thiabendazole	Recovery
		63			Negative	<i>E. coli</i>	Negative			Thiabendazole	Recovery
		64			Negative	Negative	Negative			Thiabendazole	Recovery
		65			Negative	<i>E. coli</i>	Negative			Thiabendazole, Ivermectin	Recovery
4	M	76	(+)	Smoldering ATL	Negative	<i>K. pneumonia</i>	Stool, gastric juice			Thiabendazole	Recovery
		76			<i>K. pneumonia</i>	<i>K. pneumonia</i>	Negative			Thiabendazole	Death
5	M	49	(+)		Negative	Negative	Not performed			None	Recovery
		49			<i>S. bovis</i>	Negative	Stool	Diarrhea	Sore throat, wet cough	Ivermectin	Recovery

HTLV-1 = human T-lymphotropic virus type 1; HBV = hepatitis B virus; ALT = adult T-cell leukemia.

meningitis including headache and fever. The CSF culture again showed *E. coli*. Stool and gastric juice showed *S. stercoralis*. Five days of thiabendazole was administered. Because of recurrence, monthly thiabendazole was started. The third episode occurred at the age of 38. Patient again presented with gastrointestinal symptoms including loss of appetite, 3 kg weight loss, and dry cough for seven days prior to developing a fever and worsening headache. The CSF culture and blood cultures showed *L. lactis*. During this hospitalization, the patient developed recurrent oral herpes. The last episode occurred at the age of 40. This time, blood cultures, and CSF cultures showed *S. bovis*. Ivermectin was started and no recurrence was observed. Colonoscopy was not done.

Case 2. An Okinawan male who worked as a heavy equipment operator with a past medical history of chronic hepatitis B infection had six episodes of meningitis from 1991 to 2000. Strongyloidiasis was diagnosed when he was 21 years of age. Monthly thiabendazole was initiated, however he was not compliant with the treatment because of nausea. Thiabendazole was eventually discontinued when he was 37 years of age. The first episode of meningitis occurred at the age of 38. His symptoms started with 2 weeks of diarrhea and low grade fever before he developed symptoms of meningitis. Blood cultures showed *S. sanguis*. Stool specimen showed *S. stercoralis*. Thiabendazole was administered and HTLV-1 serology was noted to be positive at that time. Subsequently, he developed culture-negative meningitis five times within a 6-year period. In each case, he complained about preceding gastrointestinal

symptoms of appetite loss, abdominal distention, and diarrhea. Duration of these symptoms ranged from 5 days to a month. Significant weight loss was observed during the third episode with a 5 kg weight loss and a 17 kg weight loss during the sixth episode. During each episode, he was treated with monthly thiabendazole, however despite this his meningitis recurred. During the sixth episode, at 49 years of age, he was given a dose of ivermectin, which resulted in clinical cure.

Case 3. The patient was an Okinawan female with a history of cervical cancer status post total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) when she was 59 years of age, and otitis media and six episodes of meningitis from 1991 to 1995. She was diagnosed with strongyloidiasis at the age of 54. The HTLV-1 infection was diagnosed at the age of 59. She developed her first episode of bacterial meningitis at the age of 60. The CSF and blood cultures were negative during this episode. Stool specimen showed *S. stercoralis* and she was treated with thiabendazole for 5 days. Even with thiabendazole, the patient had five cases of meningitis in 5 years. *Escherichia coli* was isolated from blood culture and/or CSF culture during the second, third, fourth, and sixth episodes. Stool specimen showed *S. stercoralis* again during the 3rd episode. Patient's symptoms include fever, headache, and on occasion altered mental status. No significant preceding gastrointestinal or respiratory symptoms were documented. Each time when she developed meningitis, she was treated with thiabendazole, however recurrence was observed. Because her last episode of meningitis, patient continued to

take thiabendazole every 2 months, however, despite this she developed diarrhea at the age of 72 with positive stool *S. stercoralis*. She was given ivermectin and clinical cure achieved.

Case 4. The 76-year-old Okinawan male with a history of smoldering adult T-cell leukemia (ATL), HTLV-1 infection, stroke, hypertension, and tuberculosis presented with two cases of bacterial meningitis in a 1-month period and unfortunately died. He was 76 years of age when he had the first episode of bacterial meningitis. On the day of admission, patient was found mentally altered and incontinent. He was taken to the emergency department by his wife. Lumbar puncture was performed, which showed elevated cell counts. The CSF culture was negative, but blood cultures revealed *K. pneumoniae*. Stool and gastric juice was positive for *S. stercoralis*. The patient was treated with ceftriaxone for 12 days and thiabendazole for 8 days and was discharged. Two days after his discharge, his altered mental status recurred and blood cultures and CSF culture showed *K. pneumoniae* again. Unfortunately, the patient did not respond to appropriate antimicrobial therapy with the addition of thiabendazole and he died on hospital Day 4.

Case 5. The Okinawan male who worked as a carpenter developed two episodes of meningitis within a 10-month period. His first episode of meningitis occurred when he was 49 years of age. The CSF and blood culture were negative at that time. The patient was discharged without any complications. Ten months later he was readmitted because of fever and headache. Preceding this second episode, the patient had watery diarrhea for 1 week and a sore throat with wet cough for 5 days. The CSF gram stain showed gram-positive cocci in chains, therefore he was initially treated with dexamethasone with antibiotics. A CSF culture eventually showed *S. bovis*. A stool specimen showed *S. stercoralis*. Ivermectin was administered during the hospitalization. The HTLV-1 serology was positive. No recurrence was observed. Colonoscopy was done after discharge, which showed benign adenoma.

DISCUSSION

Because HIS is associated with a high mortality rate, early diagnosis and treatment of strongyloidiasis is crucial. Previous case reports pointed out difficulties in the recognition of strongyloidiasis and HIS in non-endemic areas. Mak and others¹¹ reported one patient with 10 episodes of recurrent meningitis. *Strongyloides* was identified, but connection between strongyloidiasis and meningitis was not made for over 10 years. Somin and others⁵ reported a fatal case associated with four episodes of bacterial meningitis within a 3-month period. The patient was treated with steroids for possible Tuberculosis meningitis during the recurrent episodes. When he developed a fourth episode of meningitis, he had diarrhea and peripheral eosinophilia. Five stool examinations were negative for parasites, but duodenal biopsy eventually revealed a *S. stercoralis*. Vandebosch and others¹² reported a case of small bowel ileus complicated with syndrome of inappropriate antidiuretic hormone secretion (SIADH) caused by strongyloidiasis. This patient had five episodes of recurrent meningitis without diagnosis of strongyloidiasis.

Okinawa is an endemic area of strongyloidiasis and HTLV-1 infection. We routinely check for strongyloidiasis in any patient with bacterial meningitis or bacteremia caused by enteric pathogens without other apparent sources. Aseptic or

viral meningitis is more common than *Strongyloides*-associated culture negative meningitis, but for high risk patients, especially with recurrent episodes of meningitis or history of unexplained bacteremia, strongyloidiasis should be strongly considered.

Cases 1, 3, and 5 showed significant gastrointestinal symptoms including watery diarrhea, abdominal distention, and weight loss with or without respiratory symptoms including cough, hemoptysis, or sore throat preceding the onset meningitis. These clues should raise suspicion for HIS in high-risk patients. Immunosuppressive agents, especially corticosteroids, chemotherapeutic agents, organ transplantation and diseases like HTLV-1 or HIV infection, are known risk factors for HIS.^{2,3} Previous reports suggested patients with coinfection with strongyloidiasis and HTLV-1 may be associated with decreased IgE levels and a higher rate of refractoriness to albendazole treatment.^{13,14} We found that all of our patients were seropositive for HTLV-1 infection, however, no other concomitant risk factors were observed.

Even with various methods, diagnosis of strongyloidiasis remains challenging and there is still no gold standard. The HIS is associated with a large burden of larvae, therefore it is expected that diagnosis is relatively easy with direct stool smear.⁴ We routinely check at least 10 slide samples of stool per patient who are suspected to be infected with *Strongyloides*. Cases 2, 3, and 4 showed negative stool smears several times during recurrent episodes of meningitis. Serology could be helpful in cases where direct stool smear is negative, however, it is not yet available on a commercial basis in many places. A false positive result caused by cross-reactivity with other nematode infections and previous (cured) infection is also a problem with serologic studies.¹⁵ Confirmation of eradication is even more problematic. Various polymerase chain reaction methods showed better sensitivity, but have lower sensitivity as burden of larvae decreases.¹⁶ There are proposals for follow-up of antibody level after treatment,^{17,18} however further research is needed to assess the value of serology as a marker of eradication.

Treatment of strongyloidiasis is another important issue to address to prevent future recurrence. There is a recent report of a randomized clinical trial on ivermectin versus thiabendazole for the treatment of strongyloidiasis.¹⁹ A single dose of 200 mcg/kg ivermectin and two daily doses of 25 mg/kg thiabendazole for 2 days were compared. The study concluded that there were no significant differences. A limitation to this study is that it includes only chronic strongyloidiasis patients without HIS and there was no mention of risk factors like concomitant HTLV-1 infection. From our experience, negative stool smear was documented among cases 1–4 during each hospitalization after thiabendazole treatment. Cases 1 and 2, were also given monthly thiabendazole after discharge, however recurrence of meningitis was observed. Ivermectin was approved in 2002 for use in Japan. Interestingly, all cases who previously failed treatment with thiabendazole were successfully treated with ivermectin. Based on our series, we found that thiabendazole could suppress strongyloidiasis, even HIS, however did not accomplish eradication in patients with HTLV-1 co-infection. Grove suggested thiabendazole has no effect on larvae migrating in the tissues or adult worms in the gut through his experimental animal study.²⁰ Our cases support his observation. The low incidence of HIS makes it difficult to conduct randomized clinical trials, therefore collaborative reporting is needed to define optimal treatment and screening protocols before HIS occurs.

Dexamethasone is recommended for suspected pneumococcal meningitis. In Case 5, CSF gram stain showed gram-positive coccus in chains and the patient was given dexamethasone. For high-risk patients who may have concomitant strongyloidiasis, all clinicians should be cautious with steroid use because it can potentially aggravate HIS.

In conclusion, in areas of endemic strongyloidiasis, bacterial meningitis with significant gastrointestinal or respiratory symptoms should raise suspicion for hyperinfection syndrome. In these cases, extra caution is required before steroid use because it may potentially aggravate strongyloidiasis. We also recommend ivermectin rather than thiabendazole for strongyloidiasis eradication. Further accumulation of case reports and research is expected to establish better diagnostic methods, screening protocols, and treatment.

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