Case Report: A Case of Recurrent *Strongyloides stercoralis* Colitis in a Patient with Multiple Myeloma

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Abstract. *Strongyloides stercoralis* chronic infection is frequently subclinical and thus under-recognized, although its increasing prevalence in nonendemic regions has implications for immunocompromised hosts. We present a 75-year-old male with stage II multiple myeloma who presented with relapse of *Strongyloides* infection after initial treatment, negative surveillance testing, and subsequent resumption of chemotherapy for his multiple myeloma. The optimal regimen for secondary prophylaxis against recurrent infections is unknown. Secondary prophylaxis should be considered for patients who recur and/or remain at high risk of recurrence because of ongoing immunosuppression. We implemented a prophylactic regimen of ivermectin 200 mcg/kg once monthly. In addition, improved laboratory assays for strongyloidiasis are needed to aid with diagnosis, monitoring of treatment response, and early detection of relapse.

INTRODUCTION

We present a case of recurrent *Strongyloides stercoralis* colitis in a patient with multiple myeloma who relapsed after initial treatment and reinitiation of immunosuppressive therapy, without reexposure.

CASE

A 75-year-old Puerto Rican-born male with stage II IgA lambda multiple myeloma treated with 13 cycles of carfilzomib, pomalidomide, and dexamethasone presented to an outside facility with 3 days of confusion, fatigue, fever of 102.8°F, and mild leukocytosis. The physical examination was unremarkable with no signs of neck stiffness or rigidity. The patient was covered empirically with vancomycin, cefepime, and trimethoprim-sulfamethoxazole. A computed tomography (CT) of his head was negative. Blood, urine, and cerebrospinal fluid (CSF) cultures were obtained, with the initial Gram stain of the CSF showing gram-positive cocci, and blood and CSF cultures growing *Streptococcus bovis*. Antibiotics were de-escalated to ampicillin on day 3. Contrasted CT of the abdomen and pelvis showed circumferential wall thickening in the region of the ascending colon and cecum, concerning for colitis or neoplasm. With concern for the link between *Streptococcus bovis* and colon cancer, a colonoscopy was performed. The biopsies revealed colonic mucosa with parasitic larvae consistent with *S. stercoralis* infection, which was treated with 2 days of ivermectin. Both the initial *Strongyloides* IgG enzyme-linked immunoassay (EIA) (Quest Diagnostics, Sacramento, CA) and a single stool ova and parasite examination were negative; however, peripheral blood eosinophilia was present.

At follow-up, he continued to have a negative *Strongyloides* antibody 1 month after discharge, negative stool microscopy on single stool samples obtained at 1 and 2 months after his discharge, and resolution of his peripheral eosinophilia. He then resumed chemotherapy with carfilzomib, pomalidomide, and dexamethasone 4 months after the initial infection. Another 4 months later, and before starting a new

chemotherapy regimen with elotuzumab, lenalidomide, and dexamethasone, it was again confirmed that there was no evidence of *Strongyloides* by stool microscopy and antibody assay with IgG EIA (LabCorp, Dayton, OH).

Four months into this new regimen, he became progressively fatigued and dyspneic, and he developed cramping abdominal pain and foul-smelling bowel movements. He was referred for upper and lower endoscopy, during which multiple biopsies were obtained. Two days later, he presented to our facility with two bouts of profuse watery diarrhea, emesis, and hypokalemia of 1.9 mmol/L (lower limit of normal of 3.5 mmol/L). CT of the abdomen and pelvis was consistent with diffuse colitis. *Clostridium difficile* assay was negative on admission, and he was started on empiric ciprofloxacin in addition to supportive care. Stool culture grew *Aeromonas hydrophila*, stool microscopy was positive for *S. stercoralis*, and he seroconverted to a positive *Strongyloides* IgG on EIA (LabCorp). Pathology from the preadmission biopsies showed eosinophilic inflammation and immature worms within his gut mucosa (Figures 1 and 2). Of note, he had not traveled outside the country between episodes, and his only household contact was tested for strongyloidiasis and found to be negative. In addition to 3 days of ciprofloxacin for *Aeromonas*, he received ivermectin 12 mg daily (200 mcg/kg/day) and albendazole 400 mg twice daily for strongyloidiasis in light of his relapse after prior treatment with ivermectin. He responded quickly with formed stools within 72 hours. However, on day 3 of treatment, his platelets significantly dropped and albendazole was discontinued because of the temporal relationship and its side-effect profile, and he completed a 5-day course of treatment with ivermectin. Because of his relapse on chemotherapy and the anticipated high risk for future relapse with ongoing chemotherapy, he was transitioned to ivermectin 200 mcg/kg once monthly for secondary prophylaxis. No recurrences have occurred to date, with seroreversion to a negative *Strongyloides* IgG EIA at 6 months (LabCorp) and no gastrointestinal symptoms at 10 months of follow-up despite ongoing chemotherapy.

DISCUSSION

Strongyloides stercoralis is an intestinal parasitic nematode that is estimated to infect 30–100 million people worldwide, and its prevalence is likely underestimated.^{1,2} It was first

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FIGURE 1. The lamina propria (LP) of the colonic mucosa is occupied by abundant eosinophils. Frequent neutrophils and plasma cells are also present. The eosinophils infiltrate into the surface epithelium and coalesce with neutrophils in crypts (C) to create eosinophilic abscesses (A). Occasionally, neutrophils also infiltrate into the surface and crypt epithelium ("epithelitis" and "cryptitis"). These are features of active eosinophilic colitis. H&E stains, 200 $\times$ and 400 $\times$. This figure appears in color at www.ajtmh.org.

reported in 1876 in French soldiers with severe diarrhea who were returning from what is now Vietnam.³ Prevalence rates of strongyloidiasis are as high as 50% in areas where moist soil and improper disposal of human waste coexist, including West Africa, the Caribbean, Southeast Asia, tropical regions of Brazil, Cambodia, and temperate regions of Spain.⁴ Still very uncommon in the United States, there are foci within rural areas of the southeastern states and the Appalachian region, including eastern Tennessee, Kentucky, and West Virginia.⁵ However, there is still a higher prevalence among immigrants and refugees from tropical and subtropical countries,⁶ and in veterans of World War II and the Vietnam War.⁷

Strongyloides self-perpetuates in cycles of autoinfection over years to decades in a chronic disease state that tends to be subclinical for most immunocompetent individuals.^{8,9} For those who develop symptoms, the most prominent manifestations are gastrointestinal in the form of intermittent to persistent diarrhea or abdominal pain; pulmonary in the form of wheezing, cough, or throat irritation, and dermatologic in the

FIGURE 2. Antral-type gastric mucosa showing longitudinal and cross sections of *Strongyloides stercoralis* occupying most crypts. The worms feature pointed tails and prominent genital primordia. In addition, the lamina propria (LP) contains numerous eosinophils, neutrophils, and plasma cells. The neutrophils frequently infiltrate into the gastric epithelium (GE), whose cells are large, dark, and reactive in response. H&E stains, 200 $\times$ and 400 $\times$. This figure appears in color at www.ajtmh.org.

form of rash or pruritus.^{10,11} Recently, *Strongyloides* has received increased attention because of an emerging association with immunosuppressive diseases such as those caused by human T-lymphotropic virus type 1, human immunodeficiency virus, and hematological malignancies,^{12,13} as well as with immunosuppressive agents used in organ transplant recipients and as disease modifiers in autoimmune diseases, especially corticosteroid therapy.¹⁰ In such patients, there is decreased immunologic control of the autoinfection cycle, with increased risk for complications of strongyloidiasis, including hyperinfection syndrome and disseminated infection.⁸

Our patient falls in line with this growing body of evidence; yet his case is important for consideration in that it leads to the question of how best to monitor for and prevent recurrent infection in patients at high risk for relapse. In addition, it is one of only a small number of case reports describing *S. bovis* meningitis and/or bacteremia as a complication of strongyloidiasis; all of these cases have been described in immunocompromised hosts.^{14–18}

Relapse after apparent clearance has been described,¹⁹ but there was retrospective concern whether his initial presentation was actually one of undertreated hyperinfection syndrome. In contrast to the 1–2 daily doses of ivermectin 200 mcg/kg recommended by the Centers for Disease Control for chronic strongyloidiasis or ivermectin 200 mcg/kg daily for 2 days and repeated at 2 weeks for primary prophylaxis in high-risk hosts,¹⁹ standard treatment of hyperinfection is ivermectin 200 mcg/kg daily until stool and/or sputum samples are negative for 2 weeks.²⁰ On review of the literature, hyperinfection syndrome is loosely defined.¹⁹ It is differentiated from autoinfection by the development of worsening gastrointestinal and pulmonary symptoms with the presence of a significant increase of rhabditiform or filariform larvae in the stool or sputum.^{21,22} Prior cases of bacteremia as a complication of *Strongyloides* infection have been attributed to hyperinfection or hyperinfestation syndrome.^{14–16} The proposed mechanism of bacteremia has been translocation of bacteria from the intestinal lumen through lesions in the colonic mucosa or migration of colonic flora on/in the migrating helminths. Although helminth invasion of the intestinal wall and migration also occur as part of the typical autoinfection cycle, the increase in the number of larvae during hyperinfection increases the risk of bacteremia.^{15,19} It is notable that he had serially negative stool examinations for *Strongyloides* larvae, thus meeting an endpoint for treatment of hyperinfection, although stool microscopy has limited sensitivity for diagnosis.^{8,14} However, in this immunocompromised host, the likely reason for his relapse was undertreated hyperinfection syndrome. Recognition of bacteremia as a manifestation of hyperinfection syndrome can facilitate an appropriate treatment duration and thus decrease the risk for relapse.²³

Concurrent with the diagnosis of his relapse, he presented with another infection, *Aeromonas*-associated diarrhea, which led to decompensation and electrolyte abnormalities. He improved with ciprofloxacin for his *Aeromonas* infection in addition to 5 days of ivermectin and 3 days of albendazole for his strongyloidiasis. Although his ongoing immunosuppression placed him at increased risk for hyperinfection syndrome and he met some criteria for hyperinfection syndrome during his relapse, including increased quantity of larvae with the positive stool microscopy, he did not receive a full treatment course for hyperinfection given that the acute *Aeromonas* infection was thought to be the predominant cause of his increased gastrointestinal symptoms. This is a potential limitation of this case, although a 5-day course has been described for hyperinfection in an immunocompromised host.¹⁷

His known relapse and anticipated risk for further relapse with further chemotherapy highlight the growing need for improved laboratory detection for *Strongyloides* infection. With the limited sensitivity of stool microscopy and the invasive nature of endoscopic diagnosis, serologic markers of infection are important, especially for monitoring of treatment response. However, immunocompromised patients, especially those with hematologic malignancies such as multiple myeloma, may have false-negative serologies because of reduced antibody production.^{24,25} Although his initial and inter-episode antibody assays were negative for *Strongyloides*, he was able to mount an antibody response at the time of relapse despite ongoing chemotherapy, so a false negative is thought to be less likely in this case. Nonetheless, periodic monitoring and trending of quantitative rather than qualitative antibody assays every 3 to 6 months may have allowed for early,

preclinical detection and treatment of relapse. Indeed, a posttreatment optical density (OD) reading of ≤ 0.5 and/or a posttreatment to pretreatment OD ratio < 0.6 have been proposed as serologic markers of cure.^{26,27} Failure to reach one or the other of these goals may have triggered earlier suspicion for failure to eradicate the infection. The advent of stool real-time polymerase chain reaction (RT-PCR) may also augment diagnosis and allow for early recognition and treatment.^{8,28,29}

Given his ongoing immunosuppression after relapsed infection, concerns that “curative” therapy may not eradicate every organism, and the limitations of surveillance testing, we elected to pursue secondary prophylaxis to suppress any residual larvae.^{19,30} There is little data on longitudinal dosing of antihelminthics for secondary prophylaxis against relapse in patients with ongoing immunosuppression. A randomized control trial comparing thiabendazole 25 mg/kg twice daily versus placebo for two consecutive days monthly for primary or secondary prophylaxis of strongyloidiasis in patients with hematologic malignancies or those receiving corticosteroids for benign conditions in an endemic region revealed no difference in the incidence of strongyloidiasis; however, the study was underpowered, and only 8% of patients were enrolled for secondary prophylaxis.³¹ Case reports and series have also suggested various regimens for secondary prophylaxis in immunosuppressed patients to prevent relapse, with varying success: ivermectin 200 mcg/kg daily for 2 days every 4–6 weeks,³⁰ thiabendazole 25 mg/kg twice daily for 2 days each month,²³ or thiabendazole 3 g every 1–2 weeks.^{19,32} Expert opinion has suggested larval suppression with a prophylactic regimen of two daily doses of ivermectin every 2 weeks,³³ monthly ivermectin for at least 6 months,³⁴ or ivermectin 200 mcg/kg every 3–6 months depending on risk and degree of endemicity.^{35,36} An alternative to longitudinal prophylaxis would have been serial antibody testing followed by empiric treatment in the event of a seroconversion or uptrending titer.^{19,26} We elected for a prophylactic regimen of ivermectin 200 mcg/kg monthly, and he has remained relapse-free on this regimen for 10 months despite ongoing chemotherapy.

CONCLUSION

Strongyloides stercoralis is an intestinal parasitic nematode whose infection rate is likely underestimated. There is growing awareness of strongyloidiasis within nonendemic areas owing to refugees, travelers, veterans, and the increasing use of immune modulators, leading to more immunocompromised individuals and increased complications of strongyloidiasis, such as hyperinfection syndrome and disseminated infection. Our case adds to the growing body of literature for *Strongyloides* infections in immunocompromised hosts; particularly, our case illustrates the risk for relapsed infection in the setting of ongoing immunosuppression, the challenges of posttreatment surveillance for relapse, and a to-date successful prophylactic strategy against further relapse. Moving forward, further attention is needed to improve diagnosis and posttreatment surveillance of strongyloidiasis relapse, possibly with serial monitoring of quantitative antibody titers and stool RT-PCR in high-risk patients. Finally, consideration can be given to secondary prophylaxis with a regimen of ivermectin 200 mcg/kg once monthly in patients who have a recurrence and/or remain at high risk of recurrence due to ongoing immunosuppression.

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