Strongyloides stercoralis Infection in a Non-Endemic Area

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CLINICAL HISTORY

Patient: 75-year-old Caucasian male.

Chief Complaint: Frequent diarrhea.

History of Present Illness: The patient had a history of Crohn’s disease, initially diagnosed in 1976 with a positive test for toxigenic Clostridium difficile (C. difficile) in August 2011, successfully treated with metronidazole (500 mg PO bid ×10 d). There was a concern that diarrhea may be a result of C. difficile recurrence.

Past Medical History: The patient had an extensive medical history, including eosinophilia (8%, normal 0%-7%) in October 2011, gastroesophageal reflux disease, anemia secondary to Crohn’s disease, coronary artery disease, hypertension, osteoarthritis, and Type II diabetes mellitus. Additionally, the patient has severe Crohn’s disease which involves the terminal ileum and colon, and has undergone multiple small bowel resections as well as a colectomy. Medications included immunomodulatory therapy with balsalazide (Colazal), azathioprine (Imuran), infliximab (Remicade), ranitidine, and prednisone for both Crohn’s disease and osteoarthritis.

Travel History: The patient was originally from Louisiana, and briefly lived in Las Vegas, NV. For approximately 40 years, he has lived in western Iowa. The patient did not have a history of foreign travel nor had he recently traveled outside of Iowa or Nebraska. He drives a bus for a local business.

Principle Laboratory Findings: Loose brown stool was collected in December 2011 and submitted for laboratory testing for toxigenic C. difficile and cultured for enteric pathogens. An ova and parasites exam was not ordered at that time. Salmonella, Shigella, and Campylobacter species, as well as Shiga toxin producing–Escherichia coli, were not detected; the toxigenic C. difficile assay was negative. A laboratory technologist noted the presence of small trails of displaced bacteria on the blood agar plate from the original stool culture (Image 1). From this, a full ova and parasites exam was performed on the stool specimen.

Keywords: Strongyloides stercoralis, Crohn’s disease, diarrhea, strongyloidiasis, prednisone

Questions

1. What are the most striking laboratory findings?
2. What is the most likely diagnosis?
3. What is the epidemiological distribution and pathogenesis of the disease?
4. What are the risk factors for development of this condition?
5. What are the various forms of clinical presentation for this disease?
6. What laboratory methods are available to diagnose this infection?
7. What therapy was used and what other treatment options are available?

Abbreviations

C. difficile, Clostridium difficile; ELISA, enzyme-linked immunosorbent assay; L3, third-stage; µg, microgram; Kg, kilogram; TNF-alpha, tumor-necrosis factor alpha; H2, histamine; ARDS, adults respiratory distress syndrome

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Possible Answers

1. After noting the presence of small trails of displaced bacteria on the blood agar plate (Image 1), a full ova and parasites exam was performed. A few Strongyloides stercoralis (S. stercoralis) rhabditiform larva were detected microscopically on a concentrated wet mount of the stool as shown in Image 2.
2. Gastrointestinal strongyloidiasis. Symptoms of chronic intestinal infection can include nonspecific symptoms such as abdominal pain or discomfort, malabsorption, fluctuating eosinophilia, nausea, and diarrhea.\textsuperscript{1-3} \textit{S. stercoralis} can remain undetected within an individual for many years or possibly the individual’s lifespan. This nematode is asymptomatic in as many as 50% of infected individuals.\textsuperscript{1,6-7} Individuals with the above conditions and negative results for other enteric pathogens should be examined for ova and parasites. Often \textit{S. stercoralis} colitis may mimic inflammatory bowel disease (such as ulcerative colitis or Crohn’s disease) with untreated infection having a mortality rate of >50%. Additionally, misdiagnosis as inflammatory bowel disease can lead to unnecessary resections of the colon and terminal ileum.\textsuperscript{5,9}

3. \textit{S. stercoralis} is endemic in subtropical and tropical regions, including the southeastern Appalachian region of the United States.\textsuperscript{3,6,7,10} Although western Iowa is not known to be an endemic area with \textit{S. stercoralis}, the patient’s birthplace in Louisiana is endemic for the pathogen. Due to the lower endemicity across the United States, strongyloidiasis is frequently misdiagnosed for an average of 5 years before being properly recognized.\textsuperscript{1} In a study of 204 U.S.-born individuals who died due to strongyloidiasis, 26 were born in Louisiana (12.7%).\textsuperscript{6} Infection with this

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**Image 1**

Trails of bacterial colonies on a blood agar plate inoculated with fresh patient stool.

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**Image 2**

Wet mount of fresh stool demonstrating rhabditiform larvae of \textit{Strongyloides stercoralis} shown at 400× magnification.
organism can remain latent for >50 years, and many of the deaths related to disseminated *S. stercoralis* have occurred in individuals either born or having previously resided in a southeastern endemic U.S. state.4,5,11

*S. stercoralis* is a nematode commonly known as roundworm. Humans are the primary host for the parasite, and become infected when bare skin is exposed to soil contaminated by *S. stercoralis*.1,12 The infected human host contaminates soil with fecal material containing the noninfectious rhabditiform larvae. The rhabditiform larvae develop into infectious filariform larvae that are able to penetrate into skin that is exposed to the soil. Once in the skin of the human host, the larvae enter the bloodstream and migrate to the heart and then to the alveoli of the lungs, subsequently ending up in the trachea where the larvae are coughed up and swallowed.7,12 Upon reaching the upper portion of the small intestine, the larvae mature into both adult male and female worms. The adult females lay eggs that are deposited in the intestinal mucosa. These eggs subsequently hatch into rhabditiform larvae which are passed in the stool to the environment to restart the life cycle. Eggs are rarely excreted in feces, as they are embryonated and hatch in the mucosa of the small intestine of the human host. The rhabditiform larvae are typically seen in the stool 2 to 4 weeks after initial skin penetration.1,12 Once in the soil, the rhabditiform larvae mature over a period of 5-7 days into third-stage infective filariform larvae. In the human host, a chronic infection can also be maintained through persistent autoinfection in which the rhabditiform larvae in the large intestine develop into filariform larvae and penetrate the intestinal mucosa or perianal skin of the infected host, allowing the normal infection cycle to proceed without the soil maturation phase.1,5

4. A noted risk factor for development of strongyloidiasis is immunosuppressive therapy, particularly therapies that alter cellular immunity through use of TNF-alpha inhibitors. Other risk factors include age (>65 years), H2 receptor antagonists such as ranitidine in this patient’s case, chronic lung disease, and diabetes mellitus.1,3,5-17,13 Other comorbidities often associated with this parasitic infection include gastric ulcers, antacid use, dilated cardiomyopathy, surgically created intestinal blind loops, and systemic rheumatic diseases.11,14 This case was complicated by a history of Crohn’s disease and steroid use.11 The progression to hyperinfection syndrome or disseminated strongyloidiasis is frequently associated with corticosteroid use (particularly prednisone).3 Individuals who are born in endemic areas are at increased risk for acquiring *S. stercoralis* infection and should be examined for the parasite before administration of immunosuppressive therapy.11

5. Strongyloidiasis may present as an acute or chronic gastrointestinal discomfort, hyperinfection syndrome, or disseminated disease.3 The most common clinical presentation for *S. stercoralis* is gastrointestinal strongyloidiasis with the presence of the larvae in the intestinal tract.7 This condition is often chronic due to autoinfection.10,15 Upon initial infection with *S. stercoralis*, an individual may present with a localized skin reaction at the site where the parasite penetrated the skin. As the parasite migrates through the host’s respiratory tract, the infected individual may present with pneumonia or Loeffler’s syndrome. At the time of larval migration through the alveoli, the parasite may be detectable in a sputum smear. Loeffler’s syndrome, an allergic reaction to the larvae, occurs in a subset of infected individuals who may present with a dry irritating cough, wheezing, shortness of breath, chest pain, and fever, which are accompanied with eosinophilic pulmonary infiltrates.16,17 Gastrointestinal symptoms typically begin 2 weeks after infection; however, the larvae may be undetectable in stool until 3 to 4 weeks after infection.2,12 Gastrointestinal symptoms of *S. stercoralis* typically mimic peptic ulcer disease, and are accompanied by abdominal pain.18 Radiographic findings of strongyloidiasis may emulate Crohn’s disease of the proximal small intestine. Leukocytosis and peripheral eosinophilia are common in infected patients (50%-75% of cases). Uncomplicated chronic gastrointestinal disturbance, such as diarrhea, constipation, bloating or abdmonal cramps, will often precede pulmonary symptoms.18 Additionally, individuals may not become symptomatic until many years after the initial exposure.

Hyperinfection syndrome is a more complicated form of *S. stercoralis* disease known as the autoinfection stage.32 This disease occurs when the parasite burden increases, facilitating rapid autoinfection. During this stage the organism will follow normal migration patterns.32,33 However, the rhabditiform larvae in the intestine develop into infectious filariform larvae in the gastrointestinal tract where the larvae can penetrate into the intestinal mucosa. In hyperinfection, the individual will generally experience severe gastrointestinal tract and pulmonary symptoms.

Immunocompromised or immunosuppressed hosts are at increased risk for a poor outcome during the hyperinfection syndrome. Those patients with hyperinfection who present with peripheral eosinophilia of 10%-40% often have a
better prognosis. The greatest concern of hyperinfection is the introduction of gram-negative bacteria into the bloodstream following disruption of the intestinal mucosa by the filariform larvae resulting in bacterial dissemination. The mortality rate associated with hyperinfection caused by *S. stercoralis* is approximately 87% in individuals age 65-74 years.

The most severe form of clinical presentation caused by *S. stercoralis* is disseminated strongyloidiasis. The term “disseminated” is usually restricted to infections with systemic spread of invasive filariform larvae to sites outside of their normal migration pattern including extensive invasion of organs or cerebral spinal fluid. Although it’s possible for the hyperinfection syndrome to occur without dissemination, it is during disseminated disease that fatal gram-negative sepsis, meningitis, and adult respiratory distress syndrome (ARDS) are more common. A noted clinical symptom of disseminated disease is the presence of external migratory tracks of infective larvae beneath the skin, known as larva currens. Larva currens is defined as the presence of serpiginous creeping and pruritic eruption along the skin. These areas represent parasite migration under the skin’s surface. Although hyperinfection syndrome without dissemination responds well to therapy, disseminated strongyloidiasis is fatal in 70%-90% of cases.

6. In suspected cases of strongyloidiasis, sputum, stool, and duodenal aspirates should be examined for the presence of the parasite. These specimens are particularly important in patients with peripheral blood eosinophilia or immunosuppression. During acute or chronic disease, the larvae may be passed sporadically in the stool because of an intermittent parasite burden. Parasite concentration procedures, fecal cultures, and the duodenal capsule technique often have higher sensitivity compared to microscopic examination of fecal material. Examination of a single stool sample will detect rhabditiform larvae in only 25% of cases; however, multiple stool examinations utilizing concentrated stool, the Baermann technique, or an agar-plate method increase the sensitivity to >85%. In comparison, serology has a sensitivity of 64%-100%. The rhabditiform larvae are the diagnostic stage of the organism in feces. *S. stercoralis* closely resembles the causative agents of hookworm (*Ancylostoma duodenale* and *Necator americanus*); the ability to recognize the differentiating characteristics is important. As seen in Image 2, the rhabditiform larvae of *S. stercoralis* have a short buccal chamber with a prominent genital primordium and a notched tail; whereas human hookworms have a long buccal chamber, an inconspicuous genital primordium, and a pointed tail.

Culture of *S. stercoralis* involves inoculation of an agar plate with fresh stool from an infected patient. After incubation at room temperature for about 2 days, the larvae will be visualized by the trails of tiny bacterial colonies following migration of the larvae. The presence of larvae is confirmed by washing a scrapping from the agar plate in 10% formalin and observing the sediment with a wet mount under a light microscope. Agar plate techniques increase sensitivity to 96%, as there may be <25 larvae per gram of stool. Agar trailing is most indicative and has higher sensitivity than does the traditional ova and parasites screen. This is due to a low organism load in asymptomatic patients.

Another method for examining a stool specimen for the presence of *S. stercoralis* larvae is the Baermann technique. In this technique, fresh fecal material is placed on multiple layers of gauze supported by a wire mesh over a funnel apparatus containing tap water. Larvae migrate through gauze material into water and settle at the bottom of the funnel where they are collected and examined microscopically. The Harada-Mori filter paper strip culture is conceptually similar to the Baermann technique. Other techniques utilized in microscopic examination for larvae are direct aspiration of duodenal contents or the Entero-test (string-test) method. Both methods allow direct examination of duodenal contents. To perform the Entero-test a string attached to a gelatin capsule is swallowed while the upper portion of the string is attached to the person’s cheek, allowing the capsule to reach the duodenum. The string is then later removed through the oral cavity and the mucous is examined microscopically for larvae. Research shows that positive detection for the presence of *S. stercoralis* increases to 91% with examination of duodenal aspirates.

Serology for *S. stercoralis* is performed using an enzyme-linked immunosorbent assay (ELISA) to detect the presence of IgG antibodies against *S. stercoralis* third-stage (L3) antigen. Serology is typically negative 6 months after successful treatment; however, seroconversion may not occur in infected or chronically colonized individuals. The ELISA has been shown to have a sensitivity of 84%-92% and specificity of 94%, but cross-reactions with antibodies for *Wuchereria bancrofti, Onchocerca volvulus, Schistosoma mansoni, Schistosoma
haematobium, Schistosoma japonicum, and Ascaris lumbricoides infections have been reported.\textsuperscript{11,16,20}

7. The preferred treatment for strongyloidiasis in both adults and children is ivermectin at 200 µg/Kg/orally for 2 days. Albendazole is an alternative treatment and is recommended at 400 mg orally twice per day for 7 days in adults and children.\textsuperscript{20} Thiabendazole and albendazole may be used; however, there is a lower cure rate with these agents compared to ivermectin.\textsuperscript{1,2} In the U.S. the cure rate for ivermectin is considered 100%, and for thiabendazole is 94%. Internationally, cure rates are reported as 64% for ivermectin and 87% for thiabendazole. The difference in cure rates between the United States and international studies may be due to the administration of a 1-day treatment regimen instead of the 2-day treatment typically used in the United States.\textsuperscript{1} In our patient, adult worms were seen in the stool after administration of ivermectin. However, three post-therapy stool specimens collected approximately 2, 4, and 9 weeks after treatment, were negative by the ova and parasites assay.

References