Strongyloides Infection in a Cardiac Transplant Recipient: Making a Case for Pretransplantation Screening and Treatment

Inderpreet S. Grover, MD[1]
Rene Davila, MD[1]
Charu Subramony, MD[2]
Sumanth R. Daram, MD[1]

[1]*Division of Digestive Diseases, Department of Medicine,*
[2]*Department of Pathology, University of Mississippi Medical Center, Jackson, Mississippi*

Solid organ transplantation has become the therapy of choice for various types of organ failure. Two major complications, infection and malignancy, result from the lifelong immunosuppression needed to maintain allograft function. Most commonly, post-transplantation infections result from reactivation of latent infections in the donor organ or the recipient; *Strongyloides stercoralis* is one example of an organism that can exist in an asymptomatic host. The risk of reactivating a latent infection is related to the degree of post-transplantation immune suppression, particularly suppression of cell-mediated immunity. We describe a case of fatal *Strongyloides* hyperinfection syndrome in a patient who had previously undergone orthotopic heart transplantation.

Case Report

Our patient was a 51-year-old white male with a history of severe ischemic cardiomyopathy, emphysema, and hypothyroidism. After successful heart transplantation, the patient was placed on immunosuppressants, including corticosteroids, mycophenolate, and tacrolimus. The patient presented to us with severe nausea and vomiting 4 weeks after his transplantation. Initial diagnostic imaging showed unremarkable findings, and laboratory data were significant only for an elevated tacrolimus level (22.9 ng/mL; normal, 5–20 ng/mL). The patient's initial symptoms were attributed to supratherapeutic tacrolimus levels, but his nausea and vomiting persisted despite stopping tacrolimus treatment and use of antiemetics. The patient's disease course in the hospital deteriorated, with worsening dyspnea and hypoxemic respiratory failure. Acute transplantation rejection was ruled out via ventricular biopsies. A computed tomography scan of the chest revealed diffuse ground-glass opacities in both lung fields, prompting the performance of a bronchoscopy, which revealed signs suggestive of alveolar hemorrhage. The gastroenterology service was consulted for further work-up of the patient's unrelenting nausea and vomiting. A review of the patient's laboratory data revealed peripheral blood eosinophilia (up to 20%) for several months preceding the transplantation, which raised concerns of a parasitic infestation. An esophagogastroduodenoscopy was performed, and mild erythema was found in the fundus and antrum of the stomach. Examination of up to the third portion of the duodenum was endoscopically unremarkable. Biopsies obtained from the duodenum and gastric antrum suggested active chronic duodenitis and chronic gastritis, with nematodes most suggestive of *S. stercoralis* visualized within the crypts (Figure 1). Ivermectin (stromectol, Merck) therapy was recommended. However, the patient died several days later.

Discussion

S. stercoralis infection was first reported in 1876 in French soldiers. After approximately 50 years, more was known about the unique and characteristic feature of autoinfection that occurs in this parasite's life cycle.[1] The earliest description of disseminated infection dates to 1966, when the first cases of fatal strongyloidiasis associated with immunosuppression were reported.[2,3]

Address correspondence to:
Dr. Sumanth R. Daram, Division of Digestive Diseases, Department of Medicine, University of Mississippi Medical Center, 2500 N. State Street, Jackson, MS 39216; Tel: 601-984-4540; Fax: 601-984-4548; E-mail: sdaram@umc.edu

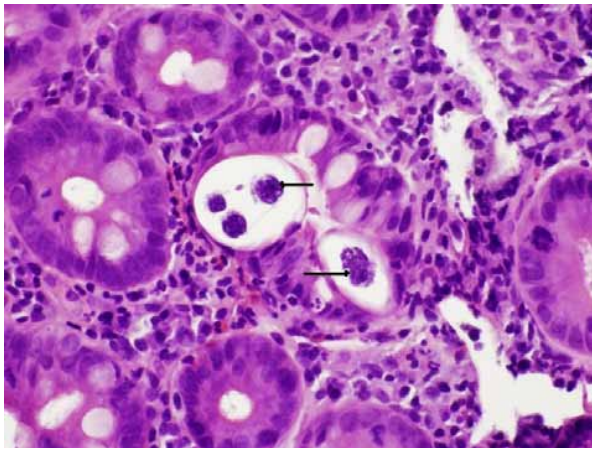

Figure 1. Duodenal biopsy showing *Strongyloides stercoralis* infection within the crypts (marked with arrows; hematoxylin and eosin stain, 200× magnification). The underlying lamina propria shows abundant neutrophils, eosinophils, and chronic inflammatory cells.

Strongyloides is endemic in tropical and subtropical areas as well as in the Appalachian region of the United States, particularly eastern Tennessee, Kentucky, and West Virginia. Immigrants and travelers from endemic areas and veterans of World War II and the Vietnam War are at risk for this infection. A prevalence rate of up to 4% has been reported for *Strongyloides* in the Southeastern United States.[4,5]

Strongyloidiasis is usually acquired via direct skin contact with filariform larvae. After entering a human host, the larvae migrate to the small intestine, where the female worm lays eggs that hatch into rhabditiform larvae. The larvae are either released into the stool or molt into filariform larvae that reinfect the host, resulting in chronic infection that can persist for several years (Figure 2). Peripheral eosinophilia is a frequent finding; it is seen in 50–80% of infested patients.[6]

Once the host's immunity is compromised, the parasite exponentially increases in number, resulting in a potentially fatal hyperinfection syndrome. This syndrome is characterized by infective filariform larvae in the stool and sputum, leading to clinical manifestations of increased parasite load and migration (such as gastrointestinal bleeding, respiratory distress, and septic shock).[7] The 2 most common settings associated with hyperinfection are corticosteroid treatment and human T-lymphotropic virus type 1 infection; however, cases of hyperinfection have also been reported in association with solid organ transplantation, hematologic malignancies, and AIDS. In fact, many cases of hyperinfection that have recently been reported in the literature involve solid organ transplantation recipients. Hyperinfection can develop months to years after transplantation, but severe disease usually occurs within the first 3 months.[8]

Prior to organ transplantation, patients are routinely evaluated for the presence of certain infections; however, screening for parasitic infection is not routine.[8,9] We believe that patients from endemic areas and/or patients with risk factors for subclinical parasitic infestation should undergo further evaluation for the presence of active or latent infection before transplantation. In addition, systemic eosinophilia before transplantation should prompt a detailed work-up for parasitic infection.

Ivermectin (200 mcg/kg/day) is the treatment of choice for strongyloidiasis; albendazole (albenza, GlaxoSmithKline) is an alternative treatment option. In patients with hyperinfection or disseminated infection, treatment should be administered for at least 7–10 days or until symptom resolution.[10] In immunocompromised hosts, the use of secondary prevention, such as a 2-day course of ivermectin every 2 weeks, may prevent hyperinfection or disseminated infection.[11] In patients receiving steroids, curative treatment is difficult, and relapses of infection are common. Disseminated disease carries a mortality rate of almost 80%, so early detection and treatment are imperative.[12]

Our patient had peripheral eosinophilia prior to transplantation but was not evaluated for parasitic infestations; he likely had latent *Strongyloides* infection. He was a resident of the Southeastern United States, where *S. stercoralis* is endemic. The clinical outcome in our patient could have been different if *S. stercoralis* had been diagnosed and treated prior to transplantation. This case is an example of a potentially preventable infection in a patient undergoing organ transplantation.

Many cases of *S. stercoralis* infection are unrecognized, as diagnosis is often difficult. Diagnosis requires the examination of at least 2 stool specimens to check for the presence of rhabditiform larvae; testing of serial samples is recommended because of the low sensitivity of such testing. Larvae have also been identified in bronchial aspirates, sputum, serum, cerebrospinal fluid, and peritoneal fluid.[13-18] Newer diagnostic methods include the luciferase immunoprecipitation system, which has increased sensitivity and specificity for the detection of *S. stercoralis*–specific antibodies, as well as real-time quantitative polymerase chain reaction testing for the detection of *S. stercoralis* in fecal samples.[19] Although detection of anti–*S. stercoralis* immunoglobulin G4 antibodies via enzyme-linked immunosorbent assay is sensitive, this method cannot distinguish between past or present infection, is cross-reactive with other helminthic infections, and can produce negative results in patients with disseminated infection.[20]

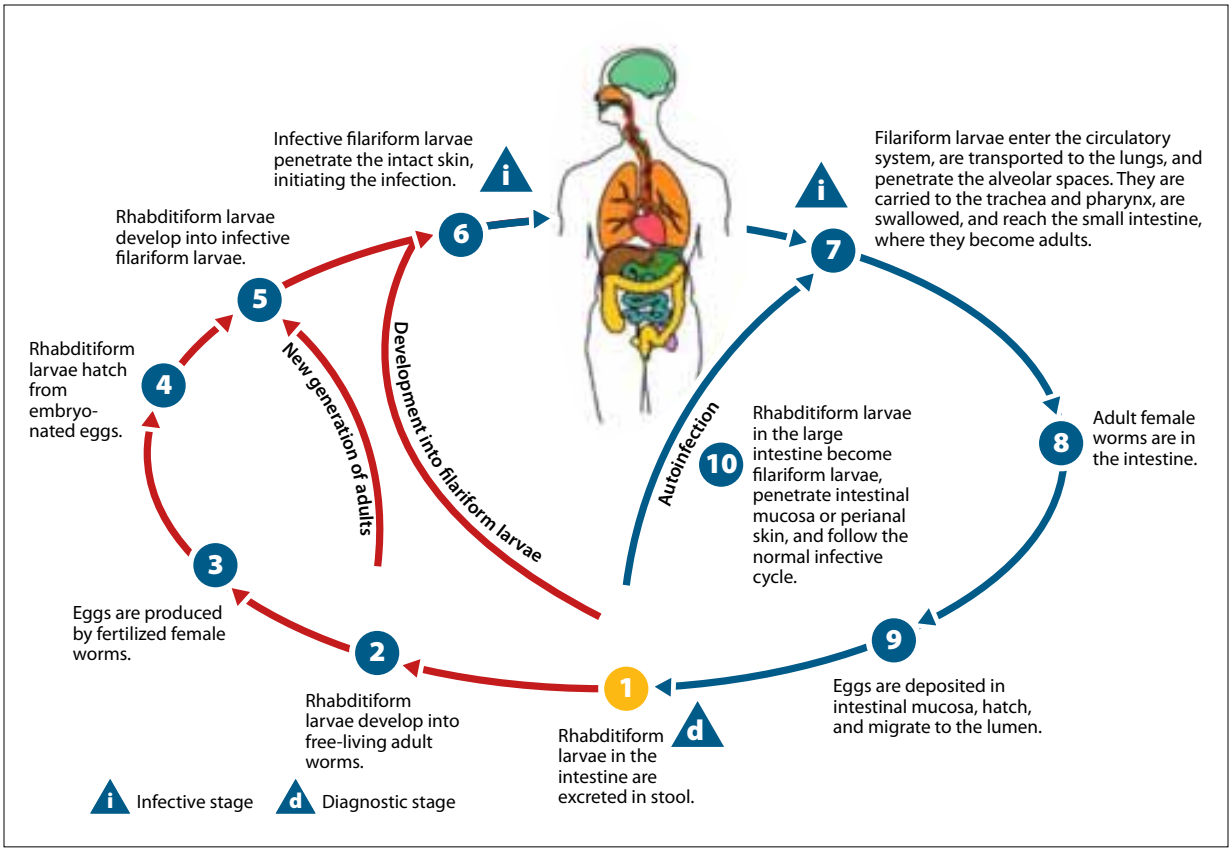

Figure 2. Life cycle of *Strongyloides stercoralis*.

Image from DPDx, Centers for Disease Control. Parasites and health: strongyloidiasis (*Strongyloides stercoralis*). http://www.dpd.cdc.gov/dpdx/html/Strongyloidiasis.htm.

Conclusion

S. stercoralis hyperinfection is a potentially fatal complication of immunosuppression that should be suspected in every organ transplantation patient who presents with abdominal and/or respiratory symptoms. Instituting early therapy is of paramount importance; effective treatment consists of total eradication of the parasite before fatal complications develop. Therefore, knowledge of endemic areas is of considerable practical importance. Although current practice guidelines recommend screening for and treatment of *Strongyloides* infection before transplantation, physicians often miss opportunities to identify patients with chronic strongyloidiasis. Screening tests have limitations, so clinical suspicion remains an important component of the pretransplantation evaluation. Monthly prophylaxis in high-risk patients is a plausible alternative but is difficult to advocate, due to the low frequency of this disease, which makes cost-effectiveness studies challenging.[21] Further studies are needed to define the benefits of routine prophylaxis in high-risk patients.

References

1. Siddiqui AA, Berk SL. Diagnosis of *Strongyloides stercoralis* infection. *Clin Infect Dis.* 2001;33:1040-1047.
2. Rogers WA Jr, Nelson B. Strongyloidiasis and malignant lymphoma. "Opportunistic infection" by a nematode. *JAMA.* 1966;195:685-687.
3. Cruz T, Reboucas G, Rocha H. Fatal strongyloidiasis in patients receiving corticosteroids. *N Engl J Med.* 1966;275:1093-1096.
4. Concha R, Harrington W Jr, Rogers AI. Intestinal strongyloidiasis: recognition, management, and determinants of outcome. *J Clin Gastroenterol.* 2005;39:203-211.
5. Simpson W, Gerhardstein D, Thompson J. Disseminated *Strongyloides stercoralis* infection. *South Med J.* 1993;86:821-825.
6. Genta R. Global prevalence of strongyloidiasis: critical review with epidemiologic insights into the prevention of disseminated disease. *Rev Infect Dis.* 1989;11:755-767.
7. Keiser PB, Nutman TB. *Strongyloides stercoralis* in the immunocompromised population. *Clin Microbiol Rev.* 2004;17:208-217.
8. DeVault GA Jr, King JW, Rohr MS, Landreneau MD, Brown ST 3rd, McDonald JC. Opportunistic infections with *Strongyloides stercoralis* in renal transplantation. *Rev Infect Dis.* 1990;12:653-671.

9. Morgan JS, Schaffner W, Stone WJ. Opportunistic strongyloidiasis in renal transplant recipients. *Transplantation.* 1986;42:518-524.
10. Igual-Adell R, Oltra-Alcaraz C, Soler-Company E, Sánchez-Sánchez P, Matogo-Oyana J, Rodríguez-Calabuig D. Efficacy and safety of ivermectin and thiabendazole in the treatment of strongyloidiasis. *Expert Opin Pharmacother.* 2004;5:2615-2619.
11. Segarra-Newnham M. Manifestations, diagnosis, and treatment of *Strongyloides stercoralis* infection. *Ann Pharmacother.* 2007;41:1992-2001.
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. Smith SB, Schwartzman M, Mencia LF, et al. Fatal disseminated strongyloidiasis presenting as acute abdominal distress in an urban child. *J Pediatr.* 1977;91:607-609.
14. Eveland LK, Kenney M, Yermakov V. Laboratory diagnosis of autoinfection in strongyloidiasis. *Am J Clin Pathol.* 1975;63:421-425.
15. Schainberg L, Scheinberg MA. Recovery of *Strongyloides stercoralis* by bronchoalveolar lavage in a patient with acquired immunodeficiency syndrome. *Am J Med.* 1989;87:486.
16. Smith B, Verghese A, Guiterrez C, Dralle W, Berk SL. Pulmonary strongyloidiasis. Diagnosis by sputum gram stain. *Am J Med.* 1985;79:663-666.
17. Williams J, Nunley D, Dralle W, Berk SL, Verghese A. Diagnosis of pulmonary strongyloidiasis by bronchoalveolar lavage. *Chest.* 1988;94:643-644.
18. Harris RA Jr, Musher DM, Fainstein V, Young EJ, Clarridge J. Disseminated strongyloidiasis. Diagnosis made by sputum examination. *JAMA.* 1980;244:65-66.
19. ten Hove RJ, van Esbroeck M, Vervoort T, van den Ende J, van Lieshout L, Verweij JJ. Molecular diagnostics of intestinal parasites in returning travelers. *Eur J Clin Microbiol Infect Dis.* 2009;28:1045-1053.
20. Abdalla J, Saad M, Myers JW, Moorman JP. An elderly man with immunosuppression, shortness of breath, and eosinophilia. *Clin Infect Dis.* 2005;40:1464, 1535-1536.
21. Abdul-Fattah MM, Nasr ME, Yousef SM, Ibraheem MI, Abdul-Wahhab SE, Soliman HM. Efficacy of ELISA in diagnosis of strongyloidiasis among the immune-compromised patients. *J Egypt Soc Parasitol.* 1995;25:491-498.

Review

Strongyloides stercoralis Hyperinfection Syndrome and Disseminated Disease

Marco Kassalik, MD, PhD[1]
Klaus Mönkemüller, MD, PhD, FASGE[1,2]

[1]Department of Internal Medicine and Gastroenterology, Marienhospital, Bottrop, Germany;
[2]Division of Gastroenterology and Hepatology, University of Magdeburg, Germany

Strongyloides is a parasite that is very prevalent in the tropical and subtropical regions of the world and is endemic in the Southeastern United States.[1-3] Strongyloidiasis is caused by the female nematode *Strongyloides stercoralis*.[1-3] In its classic life cycle, *Strongyloides* travels from the skin to the lungs and then to the gastrointestinal (GI) tract of its host. In hyperinfection syndrome, this classic life cycle is exaggerated (ie, the parasite burden and turnaround increase and accelerate).[1,4] Disseminated disease is defined by the presence of parasites outside of the traditional life cycle (ie, in organs other than the skin, GI tract, or lungs).[4,5] Although hyperinfection syndrome can occur in any host, disseminated disease occurs mainly in immunocompromised individuals.[4-6] Nonetheless, many experts equate hyperinfection syndrome with disseminated disease.[7-9]

Address correspondence to:
Dr. Klaus Mönkemüller, Marienhospital, Josef-Albers-Str. 70, 46236 Bottrop, Germany; Tel: +49 (0) 241-106-1001; Fax: +49 (0) 241-106-1009;
E-mail: moenkemueller@yahoo.com

The life cycle of *Strongyloides* is basically comprised of 2 parts: a free-living cycle outside of the host as rhabditiform larvae and a parasitic life cycle as infective filariform larvae (filariae).[1-4] During the free-living cycle in the soil, *Strongyloides* transform from rhabditiform larvae into infective filariform larvae, which penetrate the human skin and proceed into the submucosa, then into the venous circulation, and then toward the right heart and lungs.[1-3,5] During the maturation process, *Strongyloides* larvae induce alveolar capillary bleeding and potent eosinophilic inflammation, resulting in eosinophilic pneumonitis.[1,3,5] From the alveoli, the larvae continue to migrate up the pulmonary tree and trachea. The cough reflex helps to push the larvae out of the bronchial tree and trachea. However, once the larvae reach the larynx, they are swallowed and travel to the stomach and small bowel.[1,3] Inside the GI tract, *Strongyloides* larvae mature into diminutive adult females that measure approximately one tenth of one inch (ie, 220–250 µm).[1,2] Adult female worms embed themselves in the mucosa of the small bowel and produce eggs via parthenogenesis. Within the intestinal lumen, the eggs hatch into noninfective rhabditiform larvae, which are excreted, along with stool, into the environment (ie, soil).[1]