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

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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 hypoxic 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.²³
Strongyloidiasis 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.9,10 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, Glaxo SmithKline) 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 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.
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. Further studies are needed to define the benefits of routine prophylaxis in high-risk patients.

References


**Figure 2.** Life cycle of *Strongyloides stercoralis*.

Disseminated Disease

Hyperinfection Syndrome and Strongyloides stercoralis

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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

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 poten
cosinophilic inflammation, resulting in eosinophilic pneumonia.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
A unique feature of some nematodes, including *Strongyloides*, is their ability to cause autoinfection. This means that the parasite never reaches the soil; instead, it re-enters the host via enteral circulation (endautointection) or perianal skin (exoautointection). In addition, hands (eg, dirty fingers and fingernails) or food contaminated with stool can carry infective filariform larvae from the anus back to the host (the fecal-oral route). Thus, parasites can remain in the human body for the remainder of the host’s life. One study found strongyloidiasis in a patient who had previously undergone colectomy for suspected ulcerative colitis; this finding is important, as it demonstrates the occurrence of disease in a patient who no longer lived in an endemic area.

Hyperinfection syndrome and disseminated strongyloidiasis can ensue in patients with impaired cell-mediated immunity (such as transplant patients, patients receiving steroids or immunosuppressants, or patients infected with human T-cell lymphophitropic virus type 1). As previously mentioned, hyperinfection syndrome represents an acceleration of the normal life cycle of *S. stercoralis*, leading to excessive worm burden within the traditional reproductive route (the skin, gut, and lungs), while disseminated strongyloidiasis involves widespread dissemination of larvae outside of the gut and lungs, often involving the liver, brain, heart, and urinary tract. Occasionally, strongyloidiasis is associated with gut translocation of bacteria and bacteremia. Commonly reported organisms include gram-negative rods such as *Escherichia coli* and gram-positive cocci such as *Streptococcus bovis*. Thus, the presence of *S. bovis* bacteremia should prompt a search for strongyloidiasis, in addition to a search for GI malignancies.

The clinical presentation of hyperinfection syndrome is similar to that of classic strongyloidiasis, which includes nausea, vomiting, diarrhea, weight loss, abdominal pain, GI hemorrhage, cough, fever, and dyspnea. However, due to increased parasite turnaround and dissemination, patients with hyperinfection syndrome and disseminated disease often have catastrophic clinical manifestations such as shock, disseminated intravascular coagulation, meningitis, renal failure, and/or respiratory failure. This presentation was shown in the case reported by Grover and associates, in which a computed tomography scan of the chest revealed diffuse ground-glass opacities in both lung fields, prompting the performance of a bronchoscopy; the procedure noted signs suggestive of alveolar hemorrhage.

Diagnosis of *Strongyloides* hyperinfection syndrome and/or disseminated disease often can be difficult to establish and entails a high level of suspicion. We believe that any immunosuppressed patient with eosinophilia who even briefly visits or lives in tropical or subtropical areas of the world or areas of the United States where *Strongyloides* is endemic should garner suspicion of possible strongyloidiasis. Some experts argue that the mere presence of eosinophilia is enough reason to search for this parasite. Although most studies focus on finding the parasite via stool examination (which has a yield that does not exceed 46%, even after 3 stool examinations), my colleagues and I focus on searching for the parasite in various tissues, particularly in the bronchi or GI tract. Indeed, due to the large parasitic burden present at the time of parasite dissemination, the yield in lung, bronchial, or small bowel biopsies is very high. In the case presented by Grover and coworkers, an esophagogastroduodenoscopy (EGD) was performed because of the patient’s unrelenting nausea and vomiting, and mild erythema was found in the fundus and antrum of the stomach. Examination of up to the third portion of the patient’s duodenum showed endoscopically unremarkable findings. Biopsies obtained from the patient’s duodenum and gastric antrum suggested active chronic duodenitis and chronic gastritis, with nematodes most suggestive of *Strongyloides stercoralis* visualized within the crypts. The endoscopic manifestations of strongyloidiasis are broad, ranging from normal-appearing mucosa to ulcerative and catarrhal duodenitis (Figure 1). Patients with a clinical and histopathologic diagnosis of “idiopathic” eosinophilic gastroenteritis should also be thoroughly evaluated for *Strongyloides* because larvae may not always be apparent on initial evaluation, and therapy with corticosteroids may lead to fatal hyperinfection if the diagnosis of strongyloidiasis is missed. Thus, evaluation should include several stool examinations.
examinations and EGD procedures with duodenal biopsies. Multiple biopsy specimens should be taken to increase the histopathologic yield, even if the duodenal mucosa does not manifest any major abnormalities. Other effective agents include thiabendazole (mintezol, Merck) and albendazole (albenza, GlaxoSmithKline). Often, a single course of treatment is insufficient. Thus, if symptoms do not resolve after the initial therapy, it is imperative that diagnostic studies (stool, duodenal fluid, and/or endoscopy) be repeated to determine the persistence of the Strongyloides infection and whether a second course of therapy should be given. Resolution of eosinophilia does not always indicate clearance of Strongyloides. Because it is difficult to clinically confirm eradication of the infection, many experts prefer to repeat a 2-day course of therapy 1 week after the initial course, with careful follow-up in patients with persistent symptoms and/or infection.

Because of the often lethal course of disseminated strongyloidiasis, a strong case can be made that clinicians should search for this parasite in patients awaiting transplantation. Indeed, the Infectious Diseases Society of America, the American Society of Transplantation, the Centers for Disease Control and Prevention, and the American Society of Blood and Bone Marrow Transplantation recommend testing for Strongyloides immunoglobulin G enzyme-linked immunosorbent assay antibodies in patients from endemic areas and patients with unexplained GI symptoms or eosinophilia before solid organ or hematopoietic transplantation is performed. Unfortunately, screening for this parasitic infection is still not a routine practice, and physicians often miss opportunities to identify patients with chronic strongyloidiasis, as occurred in the case reported by Grover and colleagues.

**Summary**

Strongyloidiasis can involve many organs and, therefore, can have unspecific and unusual clinical manifestations, making the infection difficult to diagnose. Furthermore, lack of familiarity with this condition can have catastrophic consequences. Due to its unique life cycle, Strongyloides is capable of infecting a host until death of the host. Strongyloidiasis can be a severe disease, causing both hyperinfection syndrome and disseminated disease, particularly in transplantation patients. Thus, any patient who came from or traveled to an endemic area of the world may potentially be infected with this parasite, particularly if symptoms and blood and/or tissue eosinophilia are present. Clinicians should search for strongyloidiasis in any patient awaiting transplantation who has epidemiologic risk factors or clinical or laboratory signs of the condition.

**References**