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***Strongyloides stercoralis* Transmission by Kidney Transplantation in Two Recipients from a Common Donor**

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Abstract

Strongyloides stercoralis hyperinfection in an immunocompromised host has a high mortality rate but may initially present with non-specific pulmonary and gastrointestinal symptoms. Donor-derived *S. stercoralis* by kidney transplantation is an uncommon diagnosis and difficult to prove. We report two renal allograft recipients on different immunosuppressive maintenance regimens that developed strongyloidiasis after transplantation from the same donor. Recipient 1 presented with a small bowel obstruction. Larvae were demonstrated on a duodenal biopsy and isolated from gastric, pulmonary, and stool samples. Serologic testing for *S. stercoralis* was negative at a referral laboratory but positive at the Centers for Disease Control. The patient's hospital course was complicated by a hyperinfection syndrome requiring subcutaneous ivermectin due to malabsorption. Recipient 1 survived but the allograft failed. Recipient 2 had larvae detected in stool samples after complaints of diarrhea and was treated. On retrospective testing for *S. stercoralis*, pre-transplant serum collected from the donor and Recipient 1 was positive and negative, respectively. Donor-derived strongyloidiasis by renal transplantation is a preventable disease that may be affected by the immunosuppressive maintenance regimen. Subcutaneous ivermectin is an option in the setting of malabsorption. Finally, routine screening for *S. stercoralis* infection in donors from endemic areas may prevent future complications.

Keywords

Strongyloides stercoralis; donor-derived infection; hyperinfection syndrome; kidney transplantation

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Introduction

Strongyloides stercoralis is an intestinal nematode estimated to infect 30 million people worldwide and is prevalent in tropical and subtropical regions.(1) Infection with larvae usually occurs through exposure to contaminated soil and direct penetration of skin. Larvae are transported to the lungs through the circulatory system and then are expectorated, swallowed, and mature in the intestine. Larvae subsequently penetrate the intestinal mucosa and reenter the bloodstream initiating a unique autoinfection cycle that may persist undetected for years in an immunocompetent host.(2) Patients with uncomplicated infections may be asymptomatic or present with vague pulmonary and gastrointestinal complaints making the diagnosis difficult.

Immunocompromised patients are at risk of a hyperinfection syndrome (HIS) that is associated with increased morbidity and mortality and characterized by an overwhelming parasitic burden. There may also be dissemination to other organ systems outside the lungs and gastrointestinal tract with translocation of intestinal bacteria and possible sepsis. Risk factors include steroid use and solid organ transplantation.(3) A review of *S. stercoralis* infection in renal transplant recipients reported a crude mortality rate of 49%.(4)*S. stercoralis* transmission by renal transplantation is uncommon and difficult to prove. We report two cases of donor-derived strongyloidiasis in patients who received renal allografts from the same donor. We highlight the different maintenance regimens, awareness of potential testing center variability, and make note of the donor's demographic background as a possible risk factor for strongyloidiasis.

Case Report

Donor

A 46 year-old man suffered complications after being struck by a car. The patient experienced cardiac arrest and was intubated. Phenylephrine was started and blood products were administered. Computed tomography (CT) showed diffuse cerebral edema and tonsillar herniation. Neurosurgical intervention was felt to be futile on hospital day two and the patient was pronounced dead by brain death criteria.

History provided by the family revealed that the patient was a welder and emigrated from Honduras before arriving in the United States (US) seven years earlier. The family agreed to organ donation and the patient was given cefazolin and methylprednisolone 1 gm. The next day, both kidneys were -procured after administration of levothyroxine and another dose of methylprednisolone 1 gm. No other organs were used. There was no peripheral eosinophilia. Retrospective testing for *Strongyloides* antibody at the Centers for Disease Control (CDC) using banked donor serum was positive at 8.24 units/ μ L (reference range 1.7 units/ μ L negative).

Recipient 1

A 60 year-old man from Kenya with a history of diabetes, hypertension, and end-stage renal disease on hemodialysis for five years underwent a deceased donor renal transplantation (DDRT). The patient received induction therapy with methylprednisolone and anti-thymocyte globulin and was maintained on prednisone, mycophenolate mofetil (MMF), and tacrolimus. The recipient's clinical course was complicated by delayed graft function for the first month. Two months after transplantation, the patient was admitted with delirium, fevers, nausea, vomiting, and diarrhea. MMF was stopped due to concern for adverse gastrointestinal side effects. Symptoms resolved with volume resuscitation and MMF was restarted at a lower dose along with a course of ciprofloxacin.

The patient was re-admitted within a week due to nausea, vomiting, odynophagia, and abdominal pain. MMF was changed to azathioprine. An esophagogastroduodenoscopy revealed severe reflux esophagitis and erythematous duodenopathy. Immunohistochemistry was negative for herpes simplex virus and cytomegalovirus (CMV). A nasogastric tube was placed to suction and total parenteral nutrition was started. CT showed bibasilar pulmonary opacities, diffusely thickened small bowel wall, and a narrow zone of transition suggestive of a small bowel obstruction. The patient underwent an exploratory laparotomy and no bowel obstruction was identified although several loops of distended jejunum extended to an extremely thickened segment of small bowel. A small bowel enteroscopy showed thick exudate and friable mucosa in the distal duodenum. Biopsy specimens revealed helminthic parasites.

The Organ Procurement and Transplantation Network (OPTN) and New England Organ Bank (host organ procurement organization) were immediately notified of a potential disease transmission as required. *S. stercoralis* were subsequently isolated from stool, gastric, and pulmonary secretions. A HIS was further complicated by bacteremia with *Staphylococcus aureus* and coagulase negative *Staphylococcus*. Tacrolimus was changed to cyclosporine due to possible anti-helminthic properties.(5, 6) Serology for human T-cell lymphotropic virus (HTLV-1) was negative. Therapy was initiated with vancomycin and oral ivermectin although absorption was unclear due to an ileus.

The CDC was also contacted to review similar cases and discuss potential treatment options in the setting of malabsorption. Ivermectin per rectum was administered but the veterinary subcutaneous formulation is not approved by the US Food and Drug Administration (FDA) for human use. Permission to administer subcutaneous ivermectin under a compassionate use protocol was approved by the FDA and Institutional Review Board (IRB). This was given at 200 µg/kg for a total of 13 mg, divided into 6.5 mg per upper extremity every other day for eight days. Albendazole was also given concomitantly for three days. Testing for antibodies to *Strongyloides* at a referral laboratory using an enzyme-linked immunosorbent assay was negative but positive at the CDC (7.47 units/µL). Oral ivermectin was restarted after the larval burden was sufficiently decreased and enabling the patient to tolerate oral medications. Ivermectin was discontinued once serial testing of sputum and stool was negative for *Strongyloides*. On retrospective testing at the CDC, pre-transplant serum from Recipient 1 was negative for antibodies to *Strongyloides* (0.60 units/µL).

The recipient was discharged with a functioning renal allograft that ultimately failed over the next few months. *Strongyloides* antibodies one year later were assessed for surveillance and detected at the CDC (28.73 units/µL). The recipient was re-treated with two days of oral ivermectin and five months later antibody titers were decreased to 2.48 units/µL.

Recipient 2

A 37 year-old man with a history of end-stage renal disease presumed to be due to hypertensive nephrosclerosis was treated with hemodialysis for five years prior to undergoing a DDRT. The patient received induction therapy with methylprednisolone and anti-thymocyte globulin and was maintained on MMF and tacrolimus. One month after transplantation, the patient complained of diarrhea and the dose of MMF was reduced. Loose stools and abdominal pain continued at three months post-transplant despite further immunosuppressive dose reductions.

Upon recognition of strongyloidiasis in the first kidney recipient, the second recipient was electively admitted for further investigation. Laboratory studies showed leukopenia with bandemia, eosinophilia and newly detected CMV infection but serology for *Strongyloides* antibodies was negative. However, *S. stercoralis* was identified in stool samples. Oral

ivermectin and albendazole were started along with ganciclovir. The patient's only travel history outside of the Northeast US was for a Caribbean cruise vacation. Pre-transplant serum was not tested. Recipient 2 was discharged on a higher dose of valganciclovir and completed three days of albendazole 400mg twice daily and one week of oral ivermectin at 200 µg/kg. Surveillance stool samples were negative for *S. stercoralis*.

Discussion

S. stercoralis infection in kidney transplant recipients is well documented although donor transmission is uncommon and difficult to prove.(7-10) Our cases demonstrate a single donor with pre-transplant serologic evidence of *Strongyloides* whose kidney recipients both developed strongyloidiasis with negative pre-transplant serologies in Recipient 1. Subcutaneous ivermectin was well tolerated without neurotoxicity and highlights the importance of coordination with the appropriate public health authorities when treatment options are limited and malabsorption is suspected. We also observed testing center variability for detection of *S. stercoralis* serologies. Finally, our donor emigrated from an endemic area and this adds further support for establishing a routine screening program in this growing population.(11, 12)

Donor-transmission of *Strongyloides* by renal transplantation was not confirmed until recently. A review of donor-derived disease transmission events in the US from 2007 indicated that a proven case of *Strongyloides* by renal transplantation occurred but no details are known.(13) Two cases emerged in 2011 providing evidence of donor transmission based on positive donor serology.(2, 14) In the first case, a deceased Honduran woman donated both kidneys and a liver. One kidney recipient was diagnosed with strongyloidiasis. In the second report, a deceased man from the Dominican Republic also donated both kidneys and a liver. Donor preconditioning included significant steroid exposure. Both kidney recipients were maintained on prednisone, mycophenolate, and tacrolimus. They were both symptomatic from strongyloidiasis.

The current report extends the literature by providing further evidence of proven donor-transmission *Strongyloides* in two renal allograft recipients on different maintenance protocols. Corticosteroids, a reported risk factor for HIS and dissemination, are commonly used in preconditioning regimens and maintenance protocols. The steroids used for donor preconditioning, similar to the earlier confirmed case, may have contributed to transmission along with acute stress. Recipient 2 was on a steroid sparing immunosuppressive regimen and experienced a less severe course. We identified only one prior report of suspected *S. stercoralis* transmission by renal transplantation in a patient on a steroid free regimen.(15) As steroid free protocols become more common, it is unknown if this will affect the activation of *S. stercoralis* infections.

Therapeutic options for severe strongyloidiasis in renal transplant recipients with malabsorption are limited. Oral ivermectin is recommended for uncomplicated strongyloidiasis and is well tolerated.(16-18) Parenteral ivermectin is available as a veterinary formulation and has been used with some success in humans as rescue therapy but requires FDA approval. Recipient 1 suffered from an ileus and was given parenteral ivermectin with no adverse side effects. Serum levels were not measured since the effective therapeutic level is unknown. Our experience suggests that alternative routes of ivermectin administration may benefit patients who do not improve with oral therapy or suffer from gastrointestinal dysfunction.

We observed testing center variability for *S. stercoralis* serologies and this poses a diagnostic dilemma. Serum from Recipient 1 tested negative for *Strongyloides* at a referral

laboratory but the same sample tested positive at the CDC. There is no gold standard for diagnosing *S. stercoralis* and formal proficiency testing for Strongyloides antibodies is not available. A review of serologic tests highlighted multiple concerns including different assays, protocols, and reduced sensitivity of the ELISA in immunosuppressed patients.(19) A reasonable diagnostic approach may be to consider either serial sampling or multiple testing assays such as stool and serum when clinical suspicion is high. Laboratories that offer testing for Strongyloides antibodies could participate in a sample exchange registry for external validation. Communication with testing centers regarding discrepant results may also allow laboratories to implement quality control measures.

Finally, kidney donors from endemic countries represent an increasing trend in the US and raise important questions about screening and treatment approaches for strongyloidiasis. The donor in this report was originally from Honduras where one study identified *S. stercoralis* in 16.3% (n=427) of randomly selected stool samples.(20). An expanded screening program for Hispanic transplant candidates in Chicago observed 6.0% (n=83) with positive *S. stercoralis* serology.(11) The OPTN reports that kidneys recovered from deceased donors of all ethnicities, include Hispanics, have increased since 2000 while at the same time almost half of all foreign-born US residents in 2010 were from Central and South America where *S. stercoralis* is endemic based on small studies.(1, 21, 22) Current guidelines for donor screening of *S. stercoralis* in solid organ transplantation suggest obtaining a travel history to mitigate risk.(23-25) Taken together, these findings support a potential role for either routine screening of *S. stercoralis* in kidney donors from endemic countries or empiric treatment for their recipients to potentially avoid significant complications. Additional data are needed to determine the most appropriate method for donor screening.

In conclusion, *S. stercoralis* transmission by renal transplantation is a preventable disease in which severity may be contingent upon the immunosuppressive maintenance regimen. There is testing center variability for *S. stercoralis* serology and subcutaneous ivermectin may be an option in severe cases. Reactivation of a latent *S. stercoralis* infection in immunocompromised patients is possible but treating clinicians should also consider a donor source, especially when the renal allograft was donated by an individual identified as coming from an endemic area. Further research is needed to understand *S. stercoralis* infection and renal involvement in addition to transmission risk factors in transplantation.

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References

1. Genta RM. Global prevalence of strongyloidiasis: critical review with epidemiologic insights into the prevention of disseminated disease. *Reviews of infectious diseases*. 1989; 11(5):755–767. [PubMed: 2682948]
2. Hamilton KW, Abt PL, Rosenbach MA, Bleicher MB, Levine MS, Mehta J, et al. Donor-derived Strongyloides stercoralis infections in renal transplant recipients. *Transplantation*. 2011; 91(9): 1019–1024. [PubMed: 21358367]
3. Segarra-Newnham M. Manifestations, diagnosis, and treatment of Strongyloides stercoralis infection. *The Annals of pharmacotherapy*. 2007; 41(12):1992–2001. [PubMed: 17940124]

4. DeVault GA Jr, King JW, Rohr MS, Landreneau MD, Brown ST 3rd, McDonald JC. Opportunistic infections with *Strongyloides stercoralis* in renal transplantation. *Reviews of infectious diseases*. 1990; 12(4):653–671. [PubMed: 2201067]
5. Schad GA. Cyclosporine may eliminate the threat of overwhelming strongyloidiasis in immunosuppressed patients. *The Journal of infectious diseases*. 1986; 153(1):178. [PubMed: 3941286]
6. Armson A, Cunningham GA, Grubb WB, Mendis AH. Murine strongyloidiasis: the effects of cyclosporin A and thiabendazole administered singly and in combination. *International journal for parasitology*. 1995; 25(4):533–535. [PubMed: 7635630]
7. Roxby AC, Gottlieb GS, Limaye AP. Strongyloidiasis in transplant patients. *Clin Infect Dis*. 2009; 49(9):1411–1423. [PubMed: 19807271]
8. Hoy WE, Roberts NJ Jr, Bryson MF, Bowles C, Lee JC, Rivero AJ, et al. Transmission of strongyloidiasis by kidney transplant? Disseminated strongyloidiasis in both recipients of kidney allografts from a single cadaver donor. *JAMA : the journal of the American Medical Association*. 1981; 246(17):1937–1939. [PubMed: 7026811]
9. Palau LA, Pankey GA. Strongyloides hyperinfection in a renal transplant recipient receiving cyclosporine: possible *Strongyloides stercoralis* transmission by kidney transplant. *The American journal of tropical medicine and hygiene*. 1997; 57(4):413–415. [PubMed: 9347955]
10. Said T, Nampoory MR, Nair MP, Halim MA, Shetty SA, Kumar AV, et al. Hyperinfection strongyloidiasis: an anticipated outbreak in kidney transplant recipients in Kuwait. *Transplantation proceedings*. 2007; 39(4):1014–1015. [PubMed: 17524878]
11. Fitzpatrick MA, Caicedo JC, Stosor V, Ison MG. Expanded infectious diseases screening program for Hispanic transplant candidates. *Transplant infectious disease : an official journal of the Transplantation Society*. 2010; 12(4):336–341. [PubMed: 20534036]
12. Marcos LA, Terashima A, Canales M, Gotuzzo E. Update on strongyloidiasis in the immunocompromised host. *Current infectious disease reports*. 2011; 13(1):35–46. [PubMed: 21308453]
13. Ison MG, Hager J, Blumberg E, Burdick J, Carney K, Cutler J, et al. Donor-derived disease transmission events in the United States: data reviewed by the OPTN/UNOS Disease Transmission Advisory Committee. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2009; 9(8):1929–1935. [PubMed: 19538493]
14. Weiser JA, Scully BE, Bulman WA, Husain S, Grossman ME. Periumbilical parasitic thumbprint purpura: strongyloides hyperinfection syndrome acquired from a cadaveric renal transplant. *Transplant infectious disease : an official journal of the Transplantation Society*. 2011; 13(1):58–62. [PubMed: 20525017]
15. Huston JM, Eachempati SR, Rodney JR, Cayci C, Fusco D, Mathew M, et al. Treatment of *Strongyloides stercoralis* hyperinfection-associated septic shock and acute respiratory distress syndrome with drotrecogin alfa (activated) in a renal transplant recipient. *Transplant infectious disease : an official journal of the Transplantation Society*. 2009; 11(3):277–280. [PubMed: 19392733]
16. Suputtamongkol Y, Premasathian N, Bhumimuang K, Waywa D, Nilganuwong S, Karuphong E, et al. Efficacy and safety of single and double doses of ivermectin versus 7-day high dose albendazole for chronic strongyloidiasis. *PLoS neglected tropical diseases*. 2011; 5(5):e1044. [PubMed: 21572981]
17. Detry A, Hilmarsdottir I, Mayorga-Sagastume R, Lyagoubi M, Gaxotte P, Biligui S, et al. Treatment of *Strongyloides stercoralis* infection with ivermectin compared with albendazole: results of an open study of 60 cases. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1994; 88(3):344–345. [PubMed: 7974685]
18. Gann PH, Neva FA, Gam AA. A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. *The Journal of infectious diseases*. 1994; 169(5):1076–1079. [PubMed: 8169394]
19. Requena-Mendez A, Chiodini P, Bisoffi Z, Buonfrate D, Gotuzzo E, Munoz J. The laboratory diagnosis and follow up of strongyloidiasis: a systematic review. *PLoS neglected tropical diseases*. 2013; 7(1):e2002. [PubMed: 23350004]

20. de Kaminsky RG. Evaluation of three methods for laboratory diagnosis of *Strongyloides stercoralis* infection. *The Journal of parasitology*. 1993; 79(2):277–280. [PubMed: 8459339]
21. Acosta, YD.; de la Cruz, GP. *The Foreign Born From Latin America and the Caribbean*: 2010. Washington, D.C.: U.S. Census Bureau; 2011.
22. Siddiqui AA, Berk SL. Diagnosis of *Strongyloides stercoralis* infection. *Clin Infect Dis*. 2001; 33(7):1040–1047. [PubMed: 11528578]
23. Fischer SA, Lu K. Screening of donor and recipient in solid organ transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2013; 13(4):9–21. [PubMed: 23464994]
24. Ison MG, Grossi P. Donor-derived infections in solid organ transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2013; 13(4):22–30. [PubMed: 23464995]
25. Schwartz BS, Mawhorter SD. Parasitic infections in solid organ transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2013; 13(4):280–303. [PubMed: 23465021]

Abbreviations

HIS	hyperinfection syndrome
CT	Computed tomography
US	United States
CDC	Centers for Disease Control
DDRT	deceased donor renal transplantation
MMF	mycophenolate mofetil
CMV	cytomegalovirus
HTLV-1	human T-cell lymphotropic virus
FDA	Food and Drug Administration
IRB	Institutional Review Board
OPTN	Organ Procurement and Transplantation Network