Perspective Piece

Severe Strongyloidiasis in Solid Organ Transplant Recipients: Should We Preventively Treat the Recipient, the Donor, or Both?

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Abstract. Strongyloidiasis is caused by a soil-transmitted helminth that is endemic in tropical and subtropical countries. The parasite can complete its life cycle without leaving the host, allowing autoinfection and persistence. The risk of infection in travelers is low, but the disease may become lethal following immunosuppression. In case of solid organ transplantation, the risk of donor transmission has been suspected for several years. However, the management of live donors in this context has only recently been considered, and no guidelines exist for the management of deceased donors. To highlight the complexity of diagnosing, treating, and preventing strongyloidiasis donor transmission, we describe a case of possible transmission of severe strongyloidiasis to a kidney transplant recipient with limited travel history. Taking into account the difficulty of diagnosing chronic strongyloidiasis infection and the increase in travel and immunosuppressive treatments, we recommend pragmatic management guidelines to limit the risks of infection.

INTRODUCTION

Strongyloidiasis is caused by a soil-transmitted helminth that is endemic in tropical and subtropical countries,¹ with rare cases described in southern Europe.^{2,3} The infection starts when *Strongyloides* penetrates the intact skin and is followed by an invasive phase.⁴ As *Strongyloides* has the ability to complete its life cycle without ever leaving the host, a chronic, mostly asymptomatic, life-long infection may occur, during which severe strongyloidiasis may develop in case of immunosuppression.⁵

The incidence of imported strongyloidiasis among travelers and immigrants who return from countries at risk is low (0.2%),^{4,6,7} but the absolute number of international travelers grows constantly.⁸ As a result, the prevalence of asymptomatic carriers in non-endemic countries is probably largely underestimated. In the United States, up to 5% of Latin-American immigrants and 25% of foreign-born human immunodeficiency virus patients were positive for *Strongyloides stercoralis*, either by serology or fecal quantitative polymerase chain reaction.^{9,10}

To illustrate this problem, we present a case of severe strongyloidiasis in a recipient with little travel exposure who had received a cadaveric kidney transplant.

In June 2013, two kidney transplantations (KTs) were performed in our institution, with organs from the same donor. The donor was a 59-year-old male from Réunion, a French island east of Madagascar, where strongyloidiasis is endemic.

He had died of status epilepticus, and the kidneys were the only organs that were retrieved. The recipient of the right kidney (recipient 1) was a 75-year-old caucasian woman who was born in mainland France. Her end-stage renal disease was of nephrotoxic origin (caused by gold salts and non-steroidal anti-inflammatory drugs). She previously had spent a 1-month holiday in a Caribbean island in 1992 and had taken a cruise in the Caribbean in 2000. Induction therapy consisted of intravenous methylprednisolone and rabbit anti-thymocyte globulins. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, and prednisone. Two months after the KT, the patient was admitted to the hospital because of a deteriorating general condition with cough, diarrhea, and abdominal pain. Physical examination revealed a typical periumbilical thumbprint purpura.¹¹ The C-reactive protein was at 144 mg/L (< 5 mg/L at the time of KT) and the absolute eosinophil count was 470/mm³ (0/mm³ a couple of days after the KT and following the corticosteroid treatment initiation). Other blood analyses did not show abnormalities. Computed tomography scan of the chest showed ground glass opacity of the right upper lung lobe. A bronchoalveolar lavage (BAL), skin biopsy, and feces showed the presence of *S. stercoralis* larvae. Oral ivermectin was prescribed. On day 7, hemoptysis and acute respiratory failure required orotracheal intubation for mechanical ventilation. *Strongyloides stercoralis* larvae persisted in the second BAL despite oral ivermectin. Subcutaneous veterinary ivermectin (100 µg/kg twice daily) was prescribed in association with oral albendazole (400 mg/d) for a total duration of 14 days. Fecal parasite clearance was obtained, and the patient was discharged after 2 months. The treatment was extended with repeated doses of oral ivermectin (200 µg/kg once daily, every 2 weeks) for a total of 3 months. Three years after this episode, the patient was still alive and cured from strongyloidiasis.

The recipient of the left kidney (recipient 2) was a 70-year-old caucasian male. He had no history of any travel in a country

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where strongyloidiasis is endemic. Eight weeks after the KT, he was hospitalized because of a *Pseudomonas aeruginosa* and *Aspergillus fumigatus* pneumonia. Despite three fecal examinations and a BAL which showed no evidence of *S. stercoralis*, he received a prophylactic treatment with oral ivermectin. C-reactive protein levels and absolute eosinophil counts remained low (< 200 cells/mm³) before and after KT, until he died 1 month later of *Pseudomonas* septicemia.

Strongyloidiasis serologies were retrospectively performed in the donor and both recipients on the available sera (Table 1) using the microwell enzyme-linked immunosorbent assay (ELISA) *Strongyloides* antibody assay (SCIMEDX Corporation, Dover, NJ) according to the manufacturer's recommendations, with the provided positive and negative controls. The donor serology 2 months before his death was positive, but no serology, nor a direct parasitological search for *S. stercoralis*, had been performed just before his death. None of the recipients had been screened or treated for strongyloidiasis before transplantation, as they both had very limited travel history. *Strongyloides* serology of recipient 1 was at the cutoff level before transplantation, negative on the day of transplantation, and slightly positive during severe strongyloidiasis. Serology of the second recipient was positive on the day of transplantation, but negative afterward.

DISCUSSION

This report highlights the difficulties in managing the severe strongyloidiasis risks that are associated with solid organ transplantation.

Severe strongyloidiasis can present both as a hyperinfection syndrome and as disseminated infection.¹² The former is associated with the higher numbers of larvae that result from a particularly active auto-infection; pulmonary and gastrointestinal signs are then usually present. Disseminated strongyloidiasis is defined by the presence of larvae outside the digestive and pulmonary tracts (recipient 1, in our case report) such as the blood stream and the skin.

In most cases of severe strongyloidiasis in transplant recipients, it is difficult to determine the origin of infection.^{13,14} Usually, dissemination of a recipient's own, latent infection triggered by immunosuppressive treatment is suspected. Screening of solid organ recipients for strongyloidiasis is not mandatory in France. Interestingly, recipient 1 had been treated with corticosteroids for scleroderma and arthritis in the 1990s without infectious complications. It is possible that a more profound global immunosuppression in the KT context was responsible for the patient's strongyloidiasis dissemination. It is also possible that recipient 1 acquired a donor-derived severe strongyloidiasis after transplantation.^{1,13-17} However, the donor theoretically had to suffer from disseminated strongyloidiasis at the time of organ

retrieval to transmit the disease, which is probably a rare occurrence.^{15,18}

Diagnosing chronic strongyloidiasis can be challenging, as stool examination is not a sensitive test in this setting.¹⁴ Serology by ELISA may be helpful, with a 82–95% sensitivity in immunocompetent patients,^{19,20} but its sensitivity seems lower in occasional travelers,²¹ and relying on measuring antiparasitic antibodies in immunosuppressed patients is doubtful, as exemplified by recipient 1 who did not show a clear positive serology even after proven disseminated infection.^{19,22} Moreover, serology specificity ranges from 29% to 99% because of possible cross-reactions, especially with filarial infections.¹⁹ Perhaps new *S. stercoralis* ELISAs that are based on other antigens than laboratory analogue of *Strongyloides stercoralis* will improve the detection sensitivity and specificity.

No clear recommendation exists for the treatment of severe strongyloidiasis, but parenteral ivermectin appears to be the treatment of choice.^{14,23} This should be continued until symptoms resolve and at least for 2 weeks (the duration of one autoinfection cycle).²² To prevent recurrences, one or two additional oral doses (200 µg/kg once daily) 2 weeks apart after the end of curative treatment have been proposed.^{1,14}

The systematic screening for, and treatment of strongyloidiasis before starting an immunosuppressive therapy is recommended.^{1,20,24} Presumptive treatment has been shown to be more cost-effective in immigrants in the United States than diagnostic procedures or other public health strategies.²⁵ In settings where ivermectin is not easily available, serology testing before immunosuppression should be performed. In this case, lowering the cutoff for a positive serology might be needed to increase sensitivity.¹⁹

It is recommended to test live donors who were born or who lived in disease-endemic countries before organ donation and to treat infected live donors before organ retrieval.¹³ By contrast, the management of deceased donors is unclear and possibly somewhat different. First, the context of emergency and the frequent lack of information from the donor's relatives prevent a detailed risk stratification. Often, the donor's residency is the only available data. Second, serology cannot be performed urgently in most hospitals. Last, oral ivermectin is likely incapable of affecting parasite clearance in deceased donors. Despite the absence of evidence, treatment of both the recipient and the donor seems reasonable when the risk of transmission seems high. Taking all these parameters into account, we suggest a pragmatic and simple management scheme (Figure 1) that is based on the origin and history of both recipients and donor.

CONCLUSIONS

Because of an increase in worldwide travel and migration, cases of parasitic infection are more frequently observed in

TABLE 1
Donor and recipient *Strongyloides* serology and parasitological sample examinations

	<i>Strongyloides</i> serology* (OD)			<i>Strongyloides</i> larvae (sample examinations after KT)		
	Before KT (date)	Day of KT (date)	After KT (date)	Stools (Baerman)	BAL	Skin biopsy
Donor	1.12 (June 5, 2013)	–	–	NA	NA	NA
Recipient 1	0.21 (August 22, 2012)	0 (June 7, 2013)	0.26 (September 27, 2013)	Positive	Positive	Positive
Recipient 2	–	0.51 (June 7, 2013)	0 (September 2, 2013)	Negative	Negative	NA

* BAL = bronchoalveolar lavage; KT = kidney transplantation; NA = not available; OD = optical density. Serologies were retrospectively performed using the (SCIMEDX®) enzyme-linked immunosorbent assay *Strongyloides* Antibody assay with an OD ≥ 0.2 as the cutoff for positive testing.

FIGURE 1. Proposal for the pragmatic management of strongyloidiasis risks in solid organ transplantation based on the origin and history of both the recipient and the donor. KT = kidney transplantation.

non-endemic countries, where medical practitioners are unaccustomed to these diseases. Some of these infections, such as strongyloidiasis, may persist for a lifetime and expose the patients to potentially life-threatening reactivations.

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REFERENCES

1. Marcos LA, Terashima A, Dupont HL, Gotuzzo E, 2008. *Strongyloides* hyperinfection syndrome: an emerging global infectious disease. *Trans R Soc Trop Med Hyg* 102: 314–318.
2. Grapsa D, Petrakakou E, Botsoli-Stergiou E, Mikou P, Athanassiadou P, Karkampasi A, Ioakim-Liossi A, 2009. *Strongyloides stercoralis* in a bronchial washing specimen processed as conventional and Thin-Prep smears: report of a case and a review of the literature. *Diagn Cytopathol* 37: 903–905.
3. Valerio L, Roure S, Fernandez-Rivas G, Basile L, Martinez-Cuevas O, Ballesteros AL, Ramos X, Sabria M, 2013. *Strongyloides stercoralis*, the hidden worm. Epidemiological and clinical characteristics of 70 cases diagnosed in the North Metropolitan Area of Barcelona, Spain, 2003–2012. *Trans R Soc Trop Med Hyg* 107: 465–470.
4. Angheben A, Mistretta M, Gobbo M, Bonafini S, Iacovazzi T, Sepe A, Gobbi F, Marocco S, Rossanese A, Bisoffi Z, 2011. Acute strongyloidiasis in Italian tourists returning from southeast Asia. *J Travel Med* 18: 138–140.
5. Gill GV, Bell DR, 1979. *Strongyloides stercoralis* infection in former far east prisoners of war. *BMJ* 2: 572–574.
6. Nuesch R, Zimmerli L, Stockli R, Gyr N, Christoph Hatz FR, 2005. Imported strongyloidosis: a longitudinal analysis of 31 cases. *J Travel Med* 12: 80–84.
7. Soonawala D, Lieshout LV, den Boer MA, Claas EC, Verweij JJ, Godkewitsch A, Ratering M, Visser LG, 2014. Post-travel screening of asymptomatic long-term travelers to the tropics for intestinal parasites using molecular diagnostics. *Am J Trop Med Hyg* 90: 835–839.
8. UNWTO, 2014. *Tourism Highlights*. Madrid, Spain: World Tourism Organization.
9. Ostera G, Blum J, Cornejo C, Burgula S, Jeun R, Bryan PE, Mejia R, 2017. Strongyloidiasis in Latin American immigrants: a pilot study. *J Helminthol* 91: 262–266.
10. Hochberg NS et al., 2011. High prevalence of persistent parasitic infections in foreign-born, HIV-infected persons in the United States. *PLoS Negl Trop Dis* 5: e1034.
11. Salluh JJ, Bozza FA, Pinto TS, Toscano L, Weller PF, Soares M, 2005. Cutaneous periumbilical purpura in disseminated strongyloidiasis in cancer patients: a pathognomonic feature of potentially lethal disease? *Braz J Infect Dis* 9: 419–424.
12. Mejia R, Nutman TB, 2012. Screening, prevention, and treatment for hyperinfection syndrome and disseminated infections caused by *Strongyloides stercoralis*. *Curr Opin Infect Dis* 25: 458–463.
13. Levi ME et al., 2014. Considerations for screening live kidney donors for endemic infections: a viewpoint on the UNOS policy. *Am J Transplant* 14: 1003–1011.
14. Roxby AC, Gottlieb GS, Limaye AP, 2009. Strongyloidiasis in transplant patients. *Clin Infect Dis* 49: 1411–1423.
15. Said T et al., 2007. Hyperinfection strongyloidiasis: an anticipated outbreak in kidney transplant recipients in Kuwait. *Transplant Proc* 39: 1014–1015.
16. Roseman DA, Kabbani D, Kwah J, Bird D, Ingalls R, Gautam A, Nuhn M, Francis JM, 2013. *Strongyloides stercoralis* transmission by kidney transplantation in two recipients from a common donor. *Am J Transplant* 13: 2483–2486.
17. Hamilton KW et al., 2011. Donor-derived *Strongyloides stercoralis* infections in renal transplant recipients. *Transplantation* 91: 1019–1024.
18. Mansfield LS, Alavi A, Wortman JA, Schad GA, 1995. Gamma camera scintigraphy for direct visualization of larval migration in *Strongyloides stercoralis*-infected dogs. *Am J Trop Med Hyg* 52: 236–240.
19. Bon B, Houze S, Talabani H, Magne D, Belkadi G, Develoux M, Senghor Y, Chandenier J, Ancelle T, Hennequin C, 2010. Evaluation of a rapid enzyme-linked immunosorbent assay for diagnosis of strongyloidiasis. *J Clin Microbiol* 48: 1716–1719.
20. Lim S, Katz K, Krajden S, Fuksa M, Keystone JS, Kain KC, 2004. Complicated and fatal *Strongyloides* infection in Canadians: risk factors, diagnosis and management. *CMAJ* 171: 479–484.
21. Sudarshi S, Stumpfle R, Armstrong M, Elman T, Parton S, Krishnan P, Chiodini PL, Whitty CJ, 2003. Clinical presentation and diagnostic sensitivity of laboratory tests for *Strongyloides stercoralis* in travellers compared with immigrants in a non-endemic country. *Trop Med Int Health* 8: 728–732.
22. Segarra-Newnham M, 2007. Manifestations, diagnosis, and treatment of *Strongyloides stercoralis* infection. *Ann Pharmacother* 41: 1992–2001.
23. Turner SA, Maclean JD, Fleckenstein L, Greenaway C, 2005. Parenteral administration of ivermectin in a patient with disseminated strongyloidiasis. *Am J Trop Med Hyg* 73: 911–914.
24. Centers for Disease Control and Prevention, IDSoA, American Society of Blood and Marrow Transplantation, 2000. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recomm Rep* 49: 1–125, CE1–7. Erratum in: *MMWR Recomm Rep* 2004;53.
25. Muennig P, Pallin D, Challah C, Khan K, 2004. The cost-effectiveness of ivermectin vs. albendazole in the presumptive treatment of strongyloidiasis in immigrants to the United States. *Epidemiol Infect* 132: 1055–1063.