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Strongyloides stercoralis, Human T-cell Lymphotropic Virus Type-1 and *Cytomegalovirus* Coinfection in an Allogeneic Hematopoietic Stem-Cell Transplant Recipient

Farah Rahman, DO,[1] Aaron Mishkin, MD,[2] Samantha E. Jacobs, MD,[1] Daniel Caplivski, MD,[1] Stephen Ward, MD,[3] and Sarah Taimur, MD[1]

Strongyloides stercoralis is a soil-transmitted intestinal nematode endemic to the tropical and subtropical regions of the world, with an estimated prevalence of 30–100 million infected individuals worldwide.[1] *S. stercoralis* has the unique ability to establish autoinfection in the human host, allowing it to sustain subclinical chronic infection that can reactivate in the setting of immunosuppression and lead to life-threatening hyperinfection syndrome.[2,3] Human T-cell lymphotropic virus type-1 (HTLV-1) is known to have epidemiologic overlap and an immunologic relationship with *Strongyloides*[4]; coinfection is associated with higher likelihood of severe strongyloidiasis and more advanced HTLV-1 infection.[5] *Cytomegalovirus* (CMV) is well recognized as an immunomodulatory pathogen that plays a role in prompting allograft rejection and gastrointestinal graft-versus-host disease (GvHD) and leads to a state of systemic immunosuppression with risk of opportunistic infections due to reactivation of latent pathogens.[6] We describe herein a case of coinfection due to *S. stercoralis* and CMV in a patient who underwent allogeneic hematopoietic stem-cell transplantation (allo-HSCT) for HTLV-1–associated peripheral T-cell lymphoma.

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[1] *Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.*

[2] *Section of Infectious Diseases, Department of Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, PA.*

[3] *Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, NY.*

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Correspondence: Farah Rahman, DO, Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mt Sinai, One-Gustave L. Levy Pl, New York, NY 10029. (farah.rahman@mssm.edu).

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CASE REPORT

A 60-year-old woman originally from Jamaica with HTLV-1–associated peripheral T-cell lymphoma presented 62 days post–allo-HSCT, with a 2-day history of epigastric pain and diarrhea. She denied any recent travel or sick contacts and reported adherence to thrice-weekly trimethoprim-sulfamethoxazole prophylaxis. Her posttransplant course was significant for gastrointestinal GvHD, for which she had been receiving oral budesonide with improvement in symptoms. On day + 47, she was noted to have CMV viremia (at 50 925 IU/mL) on routine infection surveillance and was started on treatment with valganciclovir and mycophenolate mofetil was discontinued. On posttransplant day 61, she presented to the hospital for this case description with 2 days of intermittent diarrhea and epigastric pain as well as an 8-pound weight loss during the past 2 weeks. *Clostridioides difficile* stool polymerase chain reaction was performed, which returned positive, and oral vancomycin therapy was promptly initiated. Esophagogastroduodenoscopy and colonoscopy were performed the following day to evaluate for GvHD, notable for a mildly erythematous mucosa in the left colon, as well as well as erythematous mucosa in the gastric body. Biopsies were taken with pathology revealing duodenal mucosa with *S. stercoralis* larvae and mildly active colitis with increased eosinophils and CMV inclusions (Figure 1). Immunohistochemical stains for CMV were positive in the duodenum, transverse colon, and descending colon. There was also increased apoptotic activity in which mild GvHD could not be excluded. Diarrhea improved on oral vancomycin therapy; however, epigastric pain and dyspepsia persisted. Treatment was initiated for *Strongyloides* infection based on the pathologic diagnosis with ivermectin at a dose of 200 µg per kg daily. Stool ova and parasite examination was performed with visualization of the larval form of *S. stercoralis* (Figure 2). Serum was assessed for *Strongyloides* IgG using a commercial ELISA and returned negative. Of note, baseline pretransplant *Strongyloides* serology had not been obtained. Treatment continued with daily ivermectin, and at 4 weeks, a repeat stool ova and parasite sample was collected. After stool sample was confirmed to be negative, ivermectin was discontinued. Treatment was continued with valganciclovir with weekly monitoring of serum quantitative CMV polymerase chain

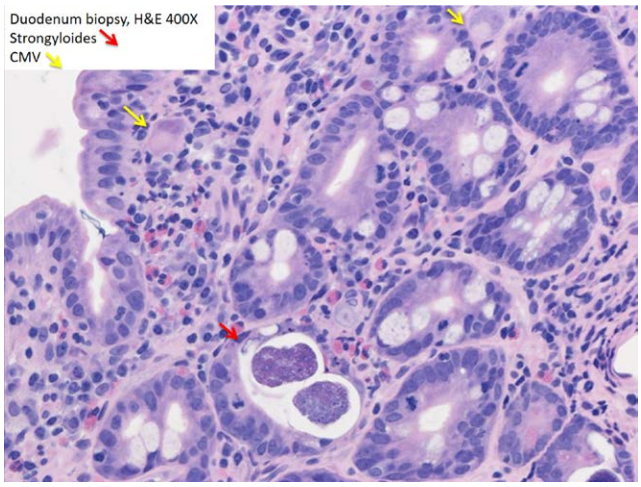

FIGURE 1. Duodenum biopsy with *Strongyloides stercoralis* and CMV inclusions. CMV, *Cytomegalovirus*; H&E, hematoxylin and eosin.

FIGURE 2. Larval form of Strongyloides from patient's stool ova and parasite specimen.

reaction, which declined below the level of detection over 4 weeks, after which valganciclovir was discontinued. She continues to follow with hematology and has not had any recurrences in her gastrointestinal symptoms through 2 years of follow-up. The timeline of infectious complications and patient's clinical course is shown in Figure 3.

DISCUSSION

S. stercoralis is an emerging pathogen in the developed world due to increase in global migration and travel. In the United States, 347 deaths (0.79 per 10 million deaths, 14–29 deaths per y) related to strongyloidiasis were reported from 1991 to 2006.[7] Recognition of epidemiologic risk and the immunologic relationship of *Strongyloides* with HTLV-1 and CMV infection is vital to prevent life-threatening complications such as hyperinfection syndrome. In this patient's case, although the more apparent risk factors for strongyloidiasis included allo-HSCT, GvHD, and iatrogenic immunosuppression, we cannot exclude the impact of concomitant CMV infection. The association between CMV and strongyloidiasis is often not recognized to the same degree as with HTLV-1. Both HTLV-1 and CMV trigger a predominant Th-1 cytokine immune response which causes downregulation of the Th-2–dependent immune responses against *Strongyloides* including degranulation of mast cells, activation of eosinophils, and production of IgE, placing the host at increased risk of more severe strongyloidiasis.[3] In the setting of HTLV-1 and *Strongyloides* coinfection, the normal age-related increase in serum IgE levels in *Strongyloides* seropositive persons is blunted.[8] Similarly, HTLV-1 proviral DNA integration into host monocytes has been shown to correlate with greater severity of strongyloidiasis suggesting increased risk of hyperinfection with more advanced HTLV-1 infection.[5] Consistent with these immunologic observations, severe strongyloidiasis has been reported in persons with HLTV-1 coinfection and testing should be considered in cases of treatment-refractory infection.[9,10] Interestingly, *S. stercoralis* itself promotes HTLV-1 infection by polyclonal proliferation of infected cells and has been postulated as a cofactor in progression toward adult T-cell leukemia/lymphoma.[11-13] A decrease in HTLV-1 proviral DNA following antiparasitic treatment for strongyloidiasis is also suggestive of the immunologic interaction between the pathogens.[13] Although the epidemiologic overlap between HTLV-1 and *Strongyloides* is well described in the literature, this case highlights a need for continuing education of clinicians on this issue because despite diagnosis of an HTLV-1–associated malignancy, *Strongyloides* serology was not obtained before allogeneic-HSCT. This case also calls for better recognition of the risk of *Strongyloides* hyperinfection in patients from endemic areas, in relation to immunomodulation from CMV. CMV is a commonly encountered pathogen in the immunosuppressed host and induces a systemic inflammatory state both during primary and latent infection, with prominence of Th-1 type cytokines.[14] Consistent with these immunologic observations, there are several reports of *Strongyloides* hyperinfection in patients with concurrent CMV infection.[15,16]

Strongyloidiasis remains a challenging diagnosis, and pathogen-specific IgG serology is often performed in cases of suspected infection. In this patient's case, serology checked in the setting of active *Strongyloides* infection was negative. This is not surprising given the well-known variability in diagnostic yield of commercially available assays. Gonzaga et al[17] reported that results of IgG avidity assay could vary depending on multiple factors, including infection severity, parasite and host interaction, larval output, and IgG maturation. The diagnostic yield of *Strongyloides* serology appears to be further diminished in patients with hematologic malignancies. Schaffel et al[18] reported a sensitivity of 68% and specificity of 89%, concluding that the IgG assay may be a better test to rule out diagnosis of strongyloidiasis in patients with hematologic malignancies and that there might be false-negative results due to lower sensitivity.[18] We decided to treat this patient with ivermectin 200 mg per kg daily until symptoms had resolved and stool microscopy was negative for parasites. Ivermectin is the drug of choice for treatment of *Strongyloides* infection, but the exact dosing regimen and duration of treatment remain unclear, and there is wide variation in treatment practice.[19] Recent data highlight the chronic nature of infection and low rates of parasitological cure despite what is considered standard treatment with ivermectin. In the study by Repetto et al,[20] serial testing of stool following treatment with ivermectin (200 μg/kg once a day for 2 days and then repeated after 2 weeks and during the follow-up period, ivermectin was readministered only in the presence of larvae

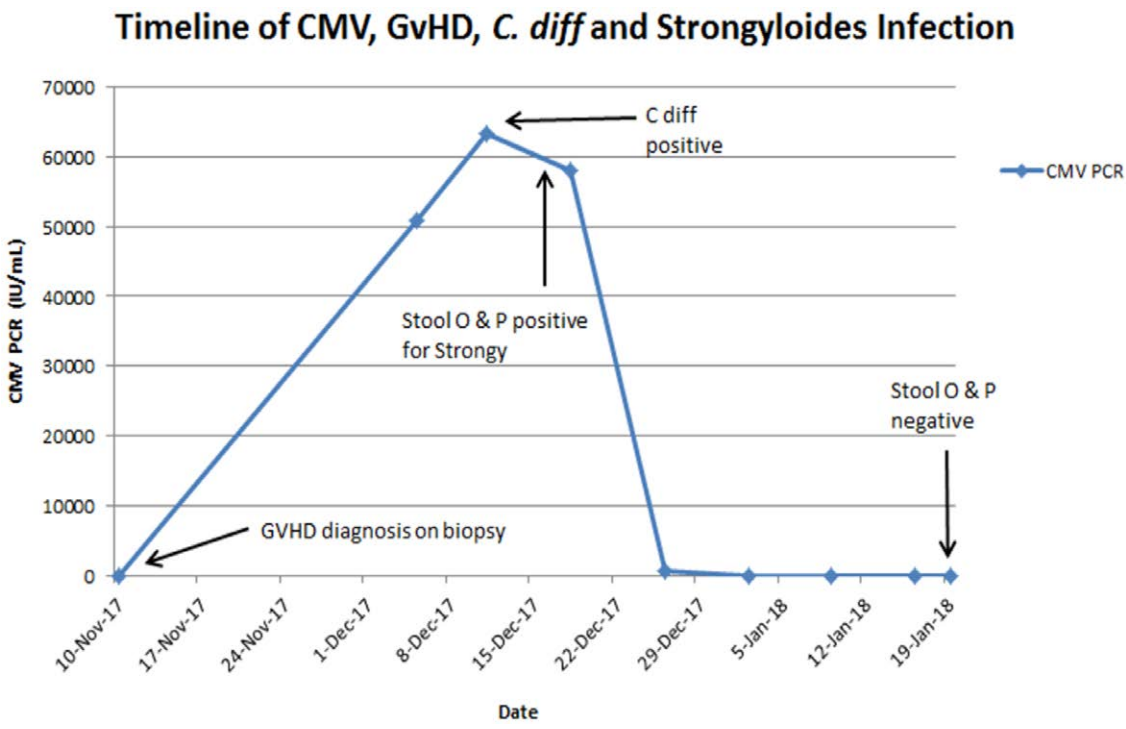

FIGURE 3. Timeline of CMV, GvHD, *Clostridioides difficile*, and Strongyloides infection. CMV, *Cytomegalovirus*; GvHD, graft-versus-host disease; PCR, polymerase chain reaction.

and/or symptoms), revealed the presence of larvae in stool in 64% and 72% of immunosuppressed and immunocompetent patients, respectively, demonstrating that parasitological cure is unlikely and testing should be performed frequently, especially in those who are immunocompromised. Additionally, based on cases of recurrent hyperinfection syndrome in patients with malignancy and HTLV-1 infection, the need for prophylaxis following treatment has been postulated.[21,22] Until there are more clinical data available to guide treatment, we feel ivermectin should be continued until symptom resolution and negative microscopy. Following the completion of treatment, risk of recurrent infection must be kept in mind with preemptive monitoring versus a period of prophylaxis with an antiparasitic medication. This patient was also treated for *C. difficile* infection with clinical improvement in diarrhea. However, endoscopic findings were not suggestive of *C. difficile*. The association between CMV and risk of other bacterial infections has been well described in stem-cell transplant recipients.[23] Based on reports of concomitant infection in solid organ transplant population, the possibility of immunomodulation due to CMV predisposing immunocompromised patients to *C. difficile* has been raised.[24] While *C. difficile* infection was deemed not proven, we feel this is a noteworthy point in relation to this case.

To the best of our knowledge, this is the first reported case of CMV, HTLV-1, and *Strongyloides* coinfection in a stem-cell transplant recipient. This case highlights complexities of coinfection and the importance of screening for endemic pathogens in the immunosuppressed host. International society guidelines recommend screening for *Strongyloides* infection in stem-cell transplant candidates with endemic risk, but the extent to which institutions adhere to this practice in nonendemic areas such as the United States is unclear.[25,26] To prevent potentially life-threatening complications secondary to endemic pathogens, it is imperative that a detailed history of epidemiologic exposures is obtained in the pretransplant period, with targeted screening and treatment. Medical practitioners should be educated on the epidemiologic and immunologic relationship between *S. stercoralis* and HTLV-1. Future guidelines should highlight the impact of CMV infection on risk of strongyloidiasis and recommend *Strongyloides* screening in all cases of HTLV-1–associated malignancies.

REFERENCES

1. World Health Organization. *Strongyloidiasis*. Available at www.who.int/intestinal_worms/epidemiology/strongyloidiasis/en/. Accessed August 30, 2016.
2. Krolewiecki A, Nutman TB. Strongyloidiasis: a neglected tropical disease. *Infect Dis Clin North Am.* 2019;33:135–151.
3. Marcos LA, Terashima A, Canales M, et al. Update on strongyloidiasis in the immunocompromised host. *Curr Infect Dis Rep.* 2011;13:35–46.
4. Nakada K, Kohakura M, Komoda H, et al. High incidence of HTLV antibody in carriers of Strongyloides stercoralis. *Lancet.* 1984;1:633.
5. Nakada K, Yamaguchi K, Furugen S, et al. Monoclonal integration of HTLV-I proviral DNA in patients with strongyloidiasis. *Int J Cancer.* 1987;40:145–148.
6. Varani S, Landini MP. Cytomegalovirus-induced immunopathology and its clinical consequences. *Herpesviridae.* 2011;2:6.
7. Croker C, Reporter R, Redelings M, Mascola L. Strongyloidiasis-related deaths in the United States, 1991-2006. *Am J Trop Med Hyg*. 2010;83:422–426.
8. Robinson RD, Lindo JF, Neva FA, et al. Immunoepidemiologic studies of *Strongyloides stercoralis* and human T lymphotropic virus type I infections in Jamaica. *J Infect Dis.* 1994;169:692–696.
9. Ashraf M, Gue CL, Baddour LM. Case report: strongyloidiasis refractory to treatment with ivermectin. *Am J Med Sci.* 1996;311:178–179.
10. Terashima A, Alvarez H, Tello R, et al. Treatment failure in intestinal strongyloidiasis: an indicator of HTLV-I infection. *Int J Infect Dis.* 2002;6:28–30.
11. Yamaguchi K, Matutes E, Catovsky D, et al. Strongyloides stercoralis as candidate co-factor for HTLV-I-induced leukaemogenesis. *Lancet.* 1987;2:94–95.
12. Satoh M, Toma H, Sugahara K, et al. Involvement of IL-2/IL-2R system activation by parasite antigen in polyclonal expansion of CD4(+)25(+)

HTLV-1-infected T-cells in human carriers of both HTLV-1 and S. stercoralis. *Oncogene.* 2002;21:2466–2475.
13. Ratner L, Grant C, Zimmerman B, et al. Effect of treatment of Strongyloides infection on HTLV-1 expression in a patient with adult T-cell leukemia. *Am J Hematol.* 2007;82:929–931.
14. van de Berg PJ, Heutinck KM, Raabe R, et al. Human cytomegalovirus induces systemic immune activation characterized by a type 1 cytokine signature. *J Infect Dis*. 2010;202:690–699.
15. Elzein FE, Alsaeed M, Ballool S, et al. Strongyloides hyperinfection syndrome combined with cytomegalovirus infection. *Case Rep Transplant.* 2016;2016:1786265.
16. Rathor N, Khillan V, Sarin SK. Strongyloides stercoralis hyperinfection in patient with autoimmune hepatitis and purpura fulminans. *Indian J Crit Care Med.* 2016;20:52–54.
17. Gonzaga HT, Ribeiro VS, Feliciano ND, et al. IgG avidity in differential serodiagnosis of human strongyloidiasis active infection. *Immunol Lett.* 2011;139:87–92.
18. Schaffel R, Nucci M, Carvalho E, et al. The value of an immunoenzymatic test (enzyme-linked immunosorbent assay) for the diagnosis of strongyloidiasis in patients immunosuppressed by hematologic malignancies. *Am J Trop Med Hyg.* 2001;65:346–350.
19. Keiser J, Utzinger J. The drugs we have and the drugs we need against major helminth infections. *Adv Parasitol.* 2010;73:197–230.
20. Repetto SA, Ruybal P, Batalla E, et al. Strongyloidiasis outside endemic areas: long-term parasitological and clinical follow-up after ivermectin treatment. *Clin Infect Dis.* 2018;66:1558–1565.
21. Peters L, McCarthy AE, Faught C. Secondary Strongyloides stercoralis prophylaxis in patients with human T-cell lymphotropic virus type 1 infection: report of two cases. *Int J Infect Dis.* 2009;13:e501–e503.
22. Glenn K, Lindholm DA, Meis G, et al. Case report: a case of recurrent Strongyloides stercoralis colitis in a patient with multiple myeloma. *Am J Trop Med Hyg.* 2017;97:1619–1622.
23. Nichols WG, Corey L, Gooley T, et al. High risk of death due to bacterial and fungal infection among cytomegalovirus (CMV)-seronegative recipients of stem cell transplants from seropositive donors: evidence for indirect effects of primary CMV infection. *J Infect Dis.* 2002;185:273–282.
24. Florescu DF, Mindru C, Chambers HE, et al. Clostridium difficile and cytomegalovirus colitis co-infection: search for the hidden 'bug'. *Transpl Infect Dis.* 2011;13:411–415.
25. Tomblyn M, Chiller T, Einsele H, et al.; Center for International Blood and Marrow Research; National Marrow Donor Program; European Blood and MarrowTransplant Group; American Society of Blood and Marrow Transplantation; Canadian Blood and Marrow Transplant Group; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America; Association of Medical Microbiology and Infectious Disease Canada; Centers for Disease Control and Prevention. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15:1143–1238.
26. Requena-Méndez A, Buonfrate D, Gomez-Junyent J, et al. Evidence-based guidelines for screening and management of Strongyloidiasis in non-endemic countries. *Am J Trop Med Hyg.* 2017;97:645–652.