Short Report: Strongyloidiasis Hyperinfection in a Patient with a History of Systemic Lupus Erythematosus

Evan E. Yung,* Cassie M. K. L. Lee, Joshua Boys, Daniel J. Grabo, James L. Buxbaum, and Parakrama T. Chandrasoma
Department of Pathology, Department of Surgery, and Department of Gastroenterology, Los Angeles County-University of Southern California Medical Center, Los Angeles, California

Abstract. Strongyloidiasis is a parasitic disease caused by *Strongyloides stercoralis*, a nematode predominately endemic to tropical and subtropical regions, such as Southeast Asia. Autoinfection enables the organism to infect the host for extended periods. Symptoms, when present, are non-specific and may initially lead to misdiagnosis, particularly if the patient has additional co-morbid conditions. Immunosuppressive states place patients at risk for the *Strongyloides* hyperinfection syndrome (SHS), whereby the organism rapidly proliferates and disseminates within the host. Left untreated, SHS is commonly fatal. Unfortunately, the non-specific presentation of strongyloidiasis and the hyperinfection syndrome may lead to delays in diagnosis and treatment. We describe an unusual case of SHS in a 30-year-old man with a long-standing history of systemic lupus erythematosus who underwent a partial colectomy. The diagnosis was rendered on identification of numerous organisms during histologic examination of the colectomy specimen.

Strongyloidiasis is an infection caused predominantly by the helminth *Strongyloides stercoralis*. This nematode is endemic to tropical and subtropical regions such as Southeast Asia, but is also present in more temperate climates, such as the northern United States and Canada.¹ Infection can rarely occur in areas thought to be non-endemic for the disease. Most chronically infected persons are asymptomatic. Clinical manifestations, when present, are usually mild and non-specific.²

Immunosuppression places infected persons at risk for the *Strongyloides* hyperinfection syndrome (SHS), where the organism proliferates unchecked. This syndrome can cause exacerbation of the patient's symptoms related to an increased parasite load in the intestine and lungs. Additional symptoms may arise as the organism involves organs not normally associated with the auto-infective life cycle.^{2,3} We describe an unusual case of SHS in a patient undergoing chronic corticosteroid treatment for systemic lupus erythematosus (SLE). We review the literature regarding SLS in immunosuppressed patients, with emphasis on those with a history of SLE.

A 30 year-old Hispanic man with an eight-year history of poorly controlled SLE came to an emergency department with fever, diffuse generalized pain, and bilateral upper and lower extremity edema. He was treated with antibiotics and methylprednisolone for presumed sepsis and lupus flare. The patient's symptoms eventually resolved, but he was found to have nephrotic range protein and erythrocyte casts in his urine. He underwent an ultrasound-guided left renal biopsy, which later confirmed class IV G lupus nephritis. The next day, the patient's systolic blood pressure decreased to 90 mm of Hg, and he began to experience diffuse abdominal pain, rebound tenderness, guarding, rigidity, and emesis. His leukocyte count and lactate dehydrogenase level were increased, and his hemoglobin level decreased significantly.

Based on the clinical examination and findings of a computed tomographic (CT) angiography of the abdomen and pelvis (Figure 1), the patient underwent an emergent exploratory celiotomy. Blood clots were visualized in the peritoneal cavity,

as well as active slow bleeding from the gastrocolic ligament and the base of the transverse mesocolon. Hematomata were identified in the omental bursa, pelvis, and hepatic flexure. No additional source of peritoneal bleeding was identified. The combined operative and CT findings suggested that the vascular supply to the distal transverse colon was compromised. An extended right hemicolectomy with a colonic mucous fistula and end ileostomy was performed.

Grossly, the serosa of the colon was covered by dark red-brown blood but was otherwise unremarkable. Several blood clots were seen within the mesentery and the omentum. The colonic mucosa was diffusely edematous with patches of yellow-tan exudate. There was a mild loss of the mucosal folds with focal edema. No lesion, ulceration, or perforation was identified. Microscopically, there were patchy areas of acute inflammatory cells and cellular debris overlying eroded mucosa. The lamina propria was markedly expanded by a lymphoplasmacytic infiltrate with scattered neutrophils and eosinophils.

There were numerous filariform larvae and sharply pointed, curved tailed adult worms present within luminal acellular debris overlying the ulcerated mucosa. Similar organisms were seen in the lamina propria infiltrating into and running alongside intact crypts (Figure 2). Numerous organisms were seen in the lymphatics (Figure 3).

Treatment of the patient's *Strongyloides* hyperinfection was started with a 21-day course of ivermectin and albendazole. The patient then showed development of diffuse alveolar hemorrhage causing acute respiratory distress syndrome. A transbronchial lung biopsy was performed, which showed evidence of cytomegalovirus pneumonia, verified by immunohistochemical stainings. The lung biopsy specimen was remarkable for the presence of a giant cell granulomatous inflammatory response surrounding a filariform larva that presumably died secondary to the anti-helminthic agents (Figure 4). His cytomegalovirus pneumonia was treated with intravenous ganciclovir. His previously mentioned class IV lupus nephritis was treated with intravenous immunoglobulin and pulse steroids with steroid taper.

The resolution of his infection was confirmed with triplicate negative stool ova and parasites studies. Finally, on hospital day 60, he was discharged to a long-term rehabilitation facility. To date, he has no documented sequelae from his infection with *Strongyloides*.

*Address correspondence to Evan E. Yung, Department of Pathology and Laboratory Medicine Los Angeles County-University of Southern California Medical Center, 1200 North State Street, Clinic Tower A7E, Los Angeles, CA 90033. E-mail: evan.yung@usc.edu

FIGURE 1. Computed tomographic (CT) image of the patient's abdomen. Identified are a mesenteric hematoma with fluid density consistent with fresh blood (A), markedly edematous ascending and proximal transverse colon (B), perihepatic fluid consistent with old blood (C), and a defect in the posterior left kidney, consistent with biopsy site (D). There is no perinephric fluid or soft tissue changes to suggest acute hemorrhage of the renal biopsy site. There was no definitive CT evidence of acute vascular injury, pseudoaneurysm, contrast extravasation, perivascular contained hematoma, or dissection.

The interest in this case stems from histopathologic diagnosis of SHS in a patient without any relevant medical history. The patient's medical history was remarkable only for SLE. The patient indicated a history of professional boxing, which may imply a history of extensive travel; however, this notion is speculative at best. The patient's condition at admission closely mimicked symptoms described in the patient's rheumatologic disorder. Accordingly, the index for suspicion for parasitic infections was low to non-existent. Were it not for the series of events that lead to the eventual histopathologic diagnosis, the patient likely would have experienced progression of the hyperinfection syndrome and eventual death.

The life cycle of *Strongyloides* can either be an isolated free-living cycle where the helminth lives independently in soil, as well as a parasitic cycle in which the infective filariform larvae enter the host via intact skin, mature to adults, and proliferate. The rhabditiform larvae created in the parasitic

FIGURE 3. High-power magnification of colon, showing a *Strongyloides* larva within a lymphatic space (arrowhead).

cycle are either passed in the stool or re-enter the circulation as filariform larvae by penetrating bowel mucosa or perianal skin to perpetuate the parasitic life cycle. This autoinfection cycle differentiates *S. stercoralis* from many other helminths,^{1,4-6} and enables the organism to reside within the host for years, or even decades.

Most persons infected with *S. stercoralis* are asymptomatic. Clinical manifestations, when present, are often mild and involve the intestine (abdominal pain, diarrhea, constipation, nausea, and weight loss), the skin (rash and pruritus, particularly at the site of entry of the larvae), and the lungs (cough, tracheal irritation, wheezing, and asthma).^{2,3} The lack of specificity of the clinical syndrome, combined with a lack of sufficiently sensitive diagnostic tests, suggest that the current estimated prevalence of 3–100 million infected persons worldwide^{1,4} is likely to be a significant underestimate.

Immunosuppressive states place patients at risk for SHS. Although the diagnosis of hyperinfection is not clearly defined, it generally occurs when the immune status of the patient changes, and the organism proliferates unchecked and enters organs not normally involved in the worm's normal intra-host life cycle. The patient may then show systemic manifestations, or more localized symptoms related to each

FIGURE 2. Medium power view of colon, showing filariform larvae consistent with *Strongyloides* (arrowheads).

FIGURE 4. High-power magnification of a lung biopsy specimen, showing filariform larvae consistent with *Strongyloides* (arrowhead).

organ the worm involves (e.g., meningitis or biliary obstruction). Invasion of the larvae through the bowel mucosa may also lead to secondary gram-negative septicemia as gut flora enter the blood stream in tandem with the larvae.^{2,4,5} The patient may then undergo multi-organ dysfunction, septic shock, and die.

A significant proportion of SHS cases are secondary to immunosuppressive drugs and primary immunodeficiency states, such as genetic disorders and hematologic malignancies. Of these contributing factors, corticosteroids are by far the most common precipitating agent.^{4,7} The exact mechanism of this is unclear; hypotheses range from modulation of the T cell-mediated immune response to suppression of eosinophilia that normally occurs in response to parasitic infections.^{3,8} Other hypotheses include a possible stimulatory effect of steroids on the adult female's ability to produce eggs, or on the larval ability to mature.² Underlying infection with human T cell lymphotropic virus 1 may also affect the T helper immune response and predispose to disseminated strongyloidiasis, to the point where infection with human T cell lymphotropic virus 1 may be suspected if a patient exhibits sub-optimal response to anti-helminthic treatment.⁹ Interestingly, an association between acquired immunodeficiency syndrome and an increased risk of SHS has not yet been established. The reason for this finding remains unclear.^{3,4,8}

There is no standard method of diagnosing strongyloidiasis. As in our case, histopathologic diagnosis may be rendered by direct visualization of the larvae or adult worms in biopsy specimens. The filariform larvae can be described histologically as a tubular esophagus measuring 180–380 μm in length with a blunted buccal end and notched tail.^{1,10} Adult worms are considerably longer and are identified by one anterior esophagus and two posterior reproductive organs.¹¹ In intestinal biopsy specimens, these organisms are found in the crypt epithelium, the lamina propria, and submucosa.^{6,11} Direct detection can also be made in stool specimens. However, some authors recommend analysis of multiple stool samples because a single stool examination may have sensitivity approximating 30%.^{12,13} Examination of other specimens, such as sputum, duodenal aspirates, ascitic fluid, pleural fluid, peripheral blood smears, and cerebrospinal fluid, may be performed.^{4,10} The blood agar plate method is a unique and sensitive diagnostic method in which presence of the organism is confirmed by visualizing tracts of bacterial colonies left in the organism's wake as it travels across the agar plate's surface.³ Newer modalities to detect *Strongyloides*-specific antigens have been described, such as polymerase chain reaction, which can simultaneously test for presence of other parasitic infections, but can show false-negative results because of potential polymerase chain reaction inhibitors present within patient samples or by inconsistent shedding of the organism in the feces.¹⁴

The diagnosis of strongyloidiasis can also be made by using serologic analysis and identification of antibodies against *Strongyloides*. The enzyme-linked immunosorbent assay has been described as an effective method of testing because of its practicality, ability for automation, and its ability to detect the presence of antibody or antigen, depending on the assay.^{14,15} Similar testing methods have been described; these include dipstick assays, gelatin particle agglutination, and immediate hypersensitivity skin tests to *Strongyloides* antigens.^{3,15} Although reasonably effective, these types of tests are prone to cross-reactivity with other helminthic infections and are

incapable of differentiating current from past infections.^{4,14} Moreover, serologic assays may show false-negative results during acute infections or in immunosuppressed patients.^{3,4,14,16} Assays or studies that directly detect the organism or its antigens may prove helpful in these cases. Luciferase immunoprecipitation system assays have recently been developed and showed promise in detection of *Strongyloides*-specific antibodies because of its high sensitivity and specificity, lack of cross-reactivity with other parasitic infections, and ability to monitor changes in antibody titers over time, resulting in an effective method of assessing treatment response.^{14,16,17}

Treatment of uncomplicated cases requires standard treatment with anti-helminth drugs, such as ivermectin or albendazole. However, treatment protocols for SHS have not been well established because of lack of data. Furthermore, whether strongyloidiasis patients will benefit from concurrent reduction in immunosuppressive therapy remains debatable. Reports have generally advocated daily anti-helminthic treatment until stool ova and parasite samples are repeatedly negative for an extended period, often up to two weeks.^{2,4} Response to anti-helminthic therapy is variable in immunosuppressed patients; accordingly, treatment in these patients depends on the etiology of the patient's immunosuppression.³

Thirteen other cases of SHS occurring in a patient with a history of SLE have been identified. For most of these cases, the diagnosis was either made too late in the disease course to prevent death,^{18–22} or after the patient succumbed to disease.^{8,23–25} In only four of these thirteen cases was the diagnosis made and treatment initiated sufficiently early to provide a favorable clinical outcome for the patient.^{8,10,26,27} Compounding the issue is that these diagnoses were also reported in non-endemic areas, where index of suspicion is low,⁷ made possible because of the long periods that *S. stercoralis* can reside in a host. The high percentage of asymptomatic chronic strongyloidiasis, its non-specific symptoms and similarity in clinical presentation to entities such as the SLE flare (as in our patient), and its appearance in non-endemic areas contribute to the high mortality rate for SHS.⁵

To prevent development of SHS and hyperinfection, screening for *Strongyloides* infection has been advocated for patients with a relevant medical history (such as residence or travel in disease-endemic areas) who are either in an immunosuppressed state or about to undergo immunosuppressive treatment.¹⁶ Serologic assays have been advocated as primary screening tests because of their reliability and the high sensitivity described in some assays.¹⁴ Although some assays are limited in their inability to differentiate current from past infection, some authors state that because of the persistence of strongyloidiasis, a patient with a compatible history and a positive serologic results may benefit from empiric treatment, such as a 1–2 day course of ivermectin if they are immunosuppressed or about to undergo immunosuppressive treatment.^{3,16}

In our patient, the diagnosis was based on identification of an unusual load of worms and filariform larvae detected during the routine histologic examination of the colectomy specimen. A transbronchial pulmonary biopsy obtained soon thereafter isolated larvae in the alveolar septae. In our case, the rapid initiation of anti-helminthic therapy cleared his strongyloidiasis, verified by repeatedly negative stool ova and parasite samples. Our case underscores the importance of maintaining a baseline index of suspicion of strongyloidiasis in immunocompromised patients because this disease is

potentially a fatal infection that can be treated successfully with anti-microbial agents.

Received April 12, 2014. Accepted for publication June 25, 2014.

Published online August 4, 2014.

Authors' addresses: Evan E. Yung, Cassie M. K. L. Lee, and Parakrama T. Chandrasoma, Department of Pathology and Laboratory Medicine, Los Angeles County-University of Southern California Medical Center, Los Angeles, CA, E-mails: evan.yung@usc.edu, cassiele@usc.edu, and ptchandr@usc.edu. Joshua Boys and Daniel J. Grabo, Department of Surgery, Los Angeles County-University of Southern California Medical Center, Los Angeles, CA, E-mails: joshua.boys@med.usc.edu and daniel.grabo@usc.edu. James L. Buxbaum, Department of Gastroenterology, University of Southern California, Los Angeles, CA, E-mail: james.buxbaum@med.usc.edu.

REFERENCES

- Murray PR, Rosenthal KS, Pfaller MA, eds. 2013. *Nematodes. Medical Microbiology*. Seventh edition. Philadelphia, PA: W. B. Saunders, 778–795.
- Concha R, Harrington W Jr, Rogers AI, 2005. Intestinal strongyloidiasis: recognition, management, and determinants of outcome. *J Clin Gastroenterol* 39: 203–211.
- Keiser PB, Nutman TB, 2004. *Strongyloides stercoralis* in the immunocompromised population. *Clin Microbiol Rev* 17: 208–217.
- Ramanathan R, Nutman T, 2008. *Strongyloides stercoralis* infection in the immunocompromised host. *Curr Infect Dis Rep* 10: 105–110.
- Lam CS, Tong MK, Chan KM, Siu YP, 2006. Disseminated strongyloidiasis: a retrospective study of clinical course and outcome. *Eur J Clin Microbiol Infect Dis* 25: 14–18.
- Al Samman M, Haque S, Long JD, 1999. Strongyloidiasis colitis: a case report and review of the literature. *J Clin Gastroenterol* 28: 77–80.
- Buonfrate D, Requena-Mendez A, Angheben A, Muñoz J, Gobbi F, Van Den Ende J, Bisoffi Z, 2013. Severe strongyloidiasis: a systematic review of case reports. *BMC Infect Dis* 13: 78.
- Mora CS, Segami MI, Hidalgo JA, 2006. *Strongyloides stercoralis* hyperinfection in systemic lupus erythematosus and the antiphospholipid syndrome. *Semin Arthritis Rheum* 36: 135–143.
- Hirata T, Uchima N, Kishimoto K, Zaha O, Kinjo N, Hokama A, Sakugawa H, Kinjo F, Fujita J, 2006. Impairment of host immune response against *Strongyloides stercoralis* by human T cell lymphotropic virus type 1 infection. *Am J Trop Med Hyg* 74: 246–249.
- Kothary NN, Muskie JM, Mathur SC, 1999. *Strongyloides stercoralis* hyperinfection. *Radiographics* 19: 1077–1081.
- Overstreet K, Chen J, Rodriguez JW, Wiener G, 2003. Endoscopic and histopathologic findings of *Strongyloides stercoralis* infection in a patient with AIDS. *Gastrointest Endosc* 58: 928–931.
- Siddiqui AA, Berk SL, 2001. Diagnosis of *Strongyloides stercoralis* infection. *Clin Infect Dis* 33: 1040–1047.
- Moghadam KG, Khashayar P, Hashemi M, 2011. Gastrointestinal strongyloidiasis in immunocompromised patients: a case report. *Acta Med Indones* 43: 191–194.
- Levenhagen MA, Costa-Cruz JM, 2014. Update on immunologic and molecular diagnosis of human strongyloidiasis. *Acta Trop* 135: 33–43.
- van Doorn HR, Koelewijn R, Hofwegen H, Gilis H, Wetsteyn JC, Wismans PJ, Sarfati C, Vervoort T, van Gool T, 2007. Use of enzyme-linked immunosorbent assay and dipstick assay for detection of *Strongyloides stercoralis* infection in humans. *J Clin Microbiol* 45: 438–442.
- 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.
- Ramanathan R, Burbelo PD, Groot S, Iadarola MJ, Neva FA, Nutman TB, 2008. A luciferase immunoprecipitation systems assay enhances the sensitivity and specificity of diagnosis of *Strongyloides stercoralis* infection. *J Infect Dis* 198: 444–451.
- Livneh A, Coman EA, Cho SH, Lipstein-Kresch E, 1988. *Strongyloides stercoralis* hyperinfection mimicking systemic lupus erythematosus flare. *Arthritis Rheum* 31: 930–931.
- Hughes R, McGuire G, 2001. Delayed diagnosis of disseminated strongyloidiasis. *Intensive Care Med* 27: 310–312.
- Setoyama M, Fukumaru S, Takasaki T, Yoshida H, Kanzaki T, 1997. SLE with death from acute massive pulmonary hemorrhage caused by disseminated strongyloidiasis. *Scand J Rheumatol* 26: 389–391.
- Arsić-Arsenijević V, Dzamić A, Dzamić Z, Milobratović D, Tomić D, 2005. Fatal *Strongyloides stercoralis* infection in a young woman with lupus glomerulonephritis. *J Nephrol* 18: 787–790.
- Finkelstein JD, Grinberg AR, Paz LA, Plana JL, Benchetrit GA, Nicastro MA, Roncoroni AJ, 1996. Case report: reactive hemophagocytic syndrome associated with disseminated strongyloidiasis. *Am J Med Sci* 312: 37–39.
- Lemos LB, Qu Z, Laucirica R, Fred HL, 2003. Hyperinfection syndrome in strongyloidiasis: report of two cases. *Ann Diagn Pathol* 7: 87–94.
- Reiman S, Fisher R, Dodds C, Trinh C, Laucirica R, Whigham CJ, 2002. Mesenteric arteriographic findings in a patient with *Strongyloides stercoralis* hyperinfection. *J Vasc Interv Radiol* 13: 635–638.
- Rojo-Marcos G, Cuadros-González J, González-Juárez MJ, Gómez-Ayerbe C, 2009. *Strongyloides stercoralis* hyperinfection syndrome in a Colombian patient receiving immunosuppressive treatment [in Spanish]. *Enferm Infecc Microbiol Clin* 27: 432–434.
- Wachter RM, Burke AM, MacGregor RR, 1984. *Strongyloides stercoralis* hyperinfection masquerading as cerebral vasculitis. *Arch Neurol* 41: 1213–1216.
- Hayden GM, Atlas SA, 1995. Strongyloidiasis masquerading as inflammatory bowel disease in a patient with lupus erythematosus: a case report. *Conn Med* 59: 649–650.