Strongyloides Stercoralis Infection in Hispanic Veterans Living in Puerto Rico: A Tropical Issue or a Global One?

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Objective: Strongyloidiasis is a parasitic infection classified by the World Health Organization as a neglected tropical disease. Although predominantly asymptomatic, it can become a life-threatening disease in an immunocompromised host. Epidemiologic studies in the Western Hemisphere are scarce, but even more scarce are descriptions of the natural course of this disease. Our objectives were to identify the different manifestations and outcomes of *Strongyloides stercoralis* infection in the Hispanic veteran population in Puerto Rico. We also discuss the importance of pursuing a timely diagnosis in high-risk patients migrating from or traveling to endemic areas, regardless of their symptomatic status.

Methods: This was a single-center, retrospective record review study involving patients diagnosed with *S. stercoralis* via serology, stool samples, or organ biopsies, from 2008 through 2014.

Results: A total of 270 patients tested positive; 210 (77.8%) were asymptomatic. The mean age at diagnosis was 75.4 years old. Symptomatic patients had pulmonary (n = 25), gastrointestinal (n = 21), and dermatologic (n = 5) symptoms; 9 had multiple symptoms. Five had hyperinfection, mostly after treatment with systemic steroids or preexisting immunosuppression. The most common laboratory abnormality was eosinophilia. Reasons for testing were eosinophilia, asthma, diarrhea, screening for parasites, and unexplained skin rash.

Conclusion: Our study highlights the importance of being aware of this potentially fatal infection, especially when treating patients traveling from endemic countries. It also highlights the importance of timely screening, diagnosis, and treatment of *S. stercoralis* infection in order to prevent potentially fatal outcomes, especially when considering immunosuppressive drugs. [*P R Health Sci J 2021;40:174-179*]

Key words: Strongyloides, Neglected disease, Parasitic

Strongyloidiasis is a soil-transmitted parasitic infection caused by *Strongyloides stercoralis*, an intestinal nematode that can infect both immunocompetent and immunocompromised hosts. In comparison to that of other major soil-transmitted parasitic worms, information on *S. stercoralis* is scarce (1). It was first described in 1876 in fecal samples of French soldiers with diarrhea who were returning from Vietnam (2,3). However, it was not until the 1930s that its full life cycle and pathogenesis were fully described (4). *S. stercoralis* is an exception among parasitic worms in that it can reproduce within a human host, where the non-infective larvae survive in the feces and give rise to infective larvae (5). Humans are infected when the filariform larvae (infective stage) penetrate the host's unbroken skin; these larvae are typically acquired through the feet's skin since this organism's habitat is contaminated soil. The parasitic cycle begins when the organism is transported to the lungs via the bloodstream and lymphatic system. From there, the larvae ascend the tracheobronchial tree, where they are eventually ingested and enter the gastrointestinal tract. Ultimately, they invade the mucosa of the duodenum and jejunum, where they mature to become adult female worms (5). These adult worms produce eggs that become rhabditiform (non-infective) larvae that can either be passed into the feces and transform into filariform larvae (starting the free-living cycle described above) or mature into filariform larvae in the gastrointestinal tract, causing autoinfection.

Strongyloidiasis infection can range from an asymptomatic presentation to various clinical manifestations, including a

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life-threatening hyperinfection. Patients may present non-specific symptoms such as nausea, vomiting, abdominal pain, diarrhea, fever, and anorexia or severe symptoms involving the gastrointestinal or pulmonary systems (3). Severe gastrointestinal manifestations include bleeding or obstruction, and lung involvement may result in cough, asthma, and/or alveolar bleeding. Local skin reactions include a band-like urticaria, a long burrow with edema, and erythema with petechial eruption—also termed *larva currens*—which is the result of cutaneous invasion (6). Another dermatologic manifestation, termed periumbilical thumbprint parasitic purpura, may be seen in the advanced stage of the disease (i.e., hyperinfection) and correlates with a poor prognostic value (7). The term *hyperinfection* describes a syndrome of accelerated autoinfection that is generally the result of an alteration in immune status (8). The most common risk factors for hyperinfection include corticosteroid therapy and human T lymphotropic virus-1 infection (2). The widespread dissemination of larvae to organs that are outside the realm of the parasite's normal life cycle is termed *disseminated strongyloidiasis*. These organs may include the lymph nodes, gallbladder, liver, heart, diaphragm, pancreas, skeletal muscle, kidneys, ovaries, and brain, according to autopsy studies (8). In most patients, the outcome is almost always fatal (9). The risk of hyperinfection and disseminated strongyloidiasis in an undiagnosed or high-risk patient with recent travel to an endemic area becomes more relevant during the current coronavirus 2019 (COVID-19) pandemic, in which corticosteroid therapy has become one of the few therapies shown to reduce mortality (10).

Despite the potentially fatal outcomes of disseminated strongyloidiasis and its high prevalence in endemic areas, there is a significant shortage of epidemiologic data, contributing to the non-existent implementation of global policies and guidelines for the diagnosis, treatment, and prevention of the disease. Methods for testing and diagnosis include agar plate culture, direct smear examination, polymerase chain reaction, and serology, but none of them are standardized, and they have different degrees of sensitivity and specificity, contributing to incomplete and inconsistent data that may underestimate the true prevalence of the disease (11). Furthermore, the availability of these diagnostic tests is scarce in many countries where *S. stercoralis* is endemic, limiting adequate screening and diagnosis. Its classification as a neglected tropical disease by the Centers for Disease Control and Prevention and the World Health Organization (WHO) makes evident the lack of awareness towards this disease. Latin America, being largely composed of tropical and subtropical rural countries, is presumed to have high endemicity for strongyloidiasis. However, a meta-analysis that explored the prevalence of strongyloidiasis in Latin America concluded that for most countries a reliable estimation of prevalence could not be made because of the scarceness of studies (12).

In Puerto Rico, a tropical island and territory of the United States, there are few studies addressing this important parasitic infection. Moreover, most of the information comes from studies focused on the prevalence of intestinal parasites in general and are not consistent in terms of the methods used for detection or the sampled populations. In 1945, Weller and Dammin estimated a prevalence of 10.6% by performing an island-wide survey of 19,139 Selective Service registrants aged 18–37 years by sampling 1g of feces from each individual (13). This group was not considered representative of the total population, as it consisted mainly of healthy, well-educated adult males and a few farm laborers. From 1953 through 1955, Maldonado and Oliver studied a total of 23,262 fecal samples in 6 selected areas of Puerto Rico, where the estimated prevalence of *S. stercoralis* was 5.0%, with that prevalence increasing with age (14). In 1973, Knight et al. estimated the prevalence of parasitic infections in 1,000 inhabitants in a rural community in eastern Puerto Rico, with the specific prevalence of *S. stercoralis* being less than 2% (15). In 1986, Rivera-Marrero conducted a study in 9 rural elementary schools located in 7 towns in southwest Puerto Rico; the study examined 852 children aged 8–12 and calculated the prevalence of *S. stercoralis* to be less than 1% (16). The last known study reporting the prevalence of *S. stercoralis* in Puerto Rico was published in 1990 by Hillyer et al. and assessed 83 individuals living in a rural community in north-central Puerto Rico and correlated the prevalence of intestinal parasitic infections with the presence of eosinophilia. *S. stercoralis*, which was found in the stool samples of only 2 of the 83 individuals (2.4%). In both samples, the eosinophilia level was 16% but did not correlate with the number of larvae per gram found in those samples (36 and 755, respectively). Other reports on *S. stercoralis* in Puerto Rico are limited to case studies focusing on disease presentation in individual patients rather than prevalence (17,18,19).

The present study was conducted at the Veterans Affairs Caribbean Healthcare System (VACHS) in San Juan, Puerto Rico, with data collected from 2008 through 2014. The primary aim of the study was to identify the different clinical presentations of and the outcomes associated with *S. stercoralis* infection in our Hispanic population.

Methods

This is a retrospective record review using the computerized patient record system at the VACHS, which contains records of patients from Puerto Rico and the United States Virgin Islands, ranging from 2008 through 2014. The study was approved by the VACHS Institutional Review Board. The inclusion criteria were as follows: patients had to be veterans, Hispanic, and aged 21 to 89 years old. In addition, they had to possess a positive diagnosis of *S. stercoralis* established by one of the following: IgG testing via enzyme linked immunosorbent immunoassay, the observation of *S. stercoralis* larvae in a stool sample, or an organ biopsy. Patients with negative *S. stercoralis* tests were excluded from the study. Records were reviewed for demographics, indications for testing, comorbidities at the

time of diagnosis, laboratory values (white blood cell count, hemoglobin levels, and eosinophil count), and the presence of symptoms. Gastrointestinal symptoms were defined as diarrhea, intestinal obstruction or other manifestations. Pulmonary symptoms included asthma, exacerbation of chronic obstructive pulmonary disease or others. Cutaneous manifestations included rash. Other manifestations included hyperinfection. The sample size was based on the number of cases diagnosed during the study period. The primary objective was to provide an accurate description of the clinical characteristics of *S. stercoralis* infection and identify those patients at increased risk of testing positive after undergoing an assessment of comorbidities, symptoms, and certain laboratory parameters.

Results

From 2008 through 2014, a total of 270 patients tested positive for *S. stercoralis*; most were men. The mean age at diagnosis was 75.4 years old. Most of the patients had one or more comorbidities, most commonly hypertension, diabetes mellitus, or pulmonary disease. Approximately one-fourth of the patients had a diagnosis of cancer. Laboratory tests were essentially unaltered; the most common findings were an elevated eosinophil count (defined in our laboratory as > 0.1 x103/ul) and, consequently, an elevated eosinophil percent (defined in our laboratory as > 7%). The most common reasons for testing were the presence of eosinophilia, a diagnosis of asthma, diarrhea, an unexplained skin rash, and for screening, among others. Refer to Table 1 for the detailed study results.

Most (78%) of the patients were asymptomatic. Of those with symptoms, most had pulmonary manifestations (asthma (26), chronic obstructive pulmonary disease (4), or other (1)) or gastrointestinal manifestations (diarrhea (26) or intestinal obstruction (2)). Dermatologic manifestations were present in 4% of the cases. Hyperinfection was the initial presentation in 5 (2%) patients, of which 4 (80%) died. Three of the deaths were directly associated with dissemination of the infection (Table 2).

Table 1. Characteristics of Hispanic veterans with *S. stercoralis* infection (n = 270).

Age (mean)	75.4	
Sex	N	Percent
Male	269	99.6%
Female	1	0.4%
Comorbid diagnosis*	N	Percent
Hypertension	209	77%
Diabetes mellitus	106	39%
Pulmonary disease	98	36%
Cancer	74	27%
Congestive heart failure	32	12%
Laboratory results	Result	Normal values
White blood cell count	8.7 x103/ul	4.3–9.3 x103/ul
Eosinophil count	1.4 x103/ul	0–0.1 x103/ul
Eosinophil percent	15.5%	0–7%
Hemoglobin	13.0 g/dL	12.6–17.8 g/dL
Indications for testing*		
Eosinophilia	236	87%
Asthma	21	8%
Diarrhea	20	7%
Rash	10	4%
Screening	11	4%
Other	19	7%
Presenting symptoms*	N	Percent
Asymptomatic	210	78%
Pulmonary symptoms	31	11%
Gastrointestinal	28	10%
Dermatologic	11	4%
Hyperinfection	5	2%

*Patients had 1 or more comorbidities, indications for testing, and/or presenting symptoms.

Table 2. Characteristics of patients with hyperinfection

Subject	Comorbidities	Diagnosis	Initial presentation	Timing of steroid administration	Cause of death	Attributed to *S. stercoralis*
1	UC, HTN, multiple sclerosis	Serum ELISA	General malaise, night sweats, fever, chills	1 month prior for recently diagnosed ulcerative colitis	Severe ARDS, DIC, MOF	Yes
2	HTN, asthma, ITP, hemolytic anemia	Serum ELISA, larvae in stool	Septic shock, nausea, vomiting, worsening ITP	2 months prior for ITP	Septic shock, RF	Yes
3	DM, HTN, emphysema, thymoma	Jejunal biopsy, bronchoalveolar lavage	GI obstruction, jejunitis, intractable vomiting	Did not receive glucocorticoids	N/A	No
4	HTN	Serum ELISA	SOB, fever, diarrhea, abdominal pain	1 month prior for temporal arteritis	MOF, ARDS, DIC, RF	Yes
5	CLD, COPD, RBC aplasia	Serum ELISA, larvae in stool	Persistent diarrhea, abdominal pain	1 month prior for RBC aplasia	DIC	No

Discussion

S. stercoralis is a soil-transmitted parasitic worm that is endemic to tropical and subtropical countries. It mainly presents as an asymptomatic disease with non-specific laboratory findings. In a subset of patients, the infection may present with gastrointestinal, pulmonary, or dermatologic manifestations. However, in the immunosuppressed host, there is a risk for widespread dissemination and hyperinfection, both of which have consistently proven to be fatal. Despite the potentially fatal outcomes of disseminated disease, there is a lack of essential epidemiologic data of *S. stercoralis*, which contributes to the failure of the implementation of global policies and guidelines for the diagnosis, treatment, and prevention of the disease. Furthermore, evolving trends of globalization have increased migratory rates around the globe. With increasing capabilities and more accessible mobility, people from endemic countries can easily travel to places where *S. stercoralis* is not endemic. Demographic forces, globalization, and environmental degradation result in increased migration pressures, resulting in massive population movements of people looking for better opportunities. Natural disasters also account for the increased translocation of people from endemic to non-endemic areas. In September 2017, Hurricane Maria struck Puerto Rico and the Caribbean. In its aftermath, nearly 400,000 Puerto Ricans left the island and established themselves in the continental United States, a crisis documented in multiple newspaper articles, columns, and news outlets. A New York–based technological company tracked data that were harvested from a sample of nearly 500,000 smartphones and developed a map that reflected where Puerto Ricans moved between October 2017 and February 2018 (20). Most of those who left moved to Florida (43%), New York (9%), Texas (7%), and Pennsylvania (6%). The 2018 United States Census Bureau reports that the number of people living in Puerto Rico decreased by 4.4% after the passage of Hurricane Maria in 2017, while the number of movers from Puerto Rico to the continental United States increased by 30%.

In the United States, *S. stercoralis* is relatively uncommon, with its few endemic foci localized in the Appalachian region (2). This poses epidemiological challenges regarding screening and treatment of endemic diseases like strongyloidiasis in a setting where such diseases are not common. In terms of epidemiology and what concerns us in the medical community, specific populations of patients who have traveled from endemic countries (e.g., tourists, immigrants, military personnel) require different approaches to healthcare and should be highly considered for testing prior to receiving immunosuppressive care, regardless of the presence or absence of symptoms. This is especially relevant in the case of solid-organ transplant patients who routinely receive corticosteroids to achieve immunosuppression and prevent rejection. Donor-derived strongyloidiasis is a rare occurrence but has been reported in the literature, with most such cases leading to fatal hyperinfection or disseminated disease in transplant recipients (21). Several case reports have described strongyloidiasis in recipients receiving organs from Puerto Rican donors. In 1 case series, 3 transplant recipients were infected after receiving organs from a common Puerto Rican donor (22). In another case report (23), a transplant recipient presented with fatal hyperinfection after receiving corticosteroids. Pre-transplantation records demonstrated transient eosinophilia. Retrospectively, a pre-transplant blood sample was evaluated and was found to be positive for the *Strongyloides* antibody. In all these cases, the donors had asymptomatic *Strongyloides* infection and the risk for strongyloidiasis was not recognized until the transplant recipients presented with hyperinfection. Guidelines from the American Society of Transplantation strongly recommend evaluating both transplant recipients and donors with epidemiological risk factors and/or individuals with unexplained eosinophilia for *Strongyloides* (24).

Adequate travel and residence histories have become particularly significant during the COVID-19 era. Increasingly, more cases of disseminated *Strongyloides* that emerge after the administration of corticosteroids for COVID-19 are being reported (25, 26, 27). The WHO recently published an article describing the risks of disseminated strongyloidiasis in patients with COVID-19 and who had previously traveled or migrated from countries where *Strongyloides* is endemic; the article emphasized the need to address these risks prior to the initiation of corticosteroids (28). The outcome of disseminated strongyloidiasis in patients who receive corticosteroids is so adverse that several authors have proposed the initiation of empirical treatment with ivermectin in COVID-19 patients who are considered to be at high-risk for exposure (25, 26).

Our study highlights several important factors about infection with *S. stercoralis*. First, it establishes the importance of high suspicion for testing and early detection since most of the patients are asymptomatic carriers (3, 29). Second, in our study group, eosinophilia was the most common clinical manifestation of occult infection and the trigger for most of the patients diagnosed with the infection. Third, there is still unawareness of the clinical implications of *S. stercoralis* infection, even in endemic regions. In our study, very few cases were diagnosed through screening prior to the administration of immunosuppressive drugs (n = 11). Fourth and most importantly, this study reveals the importance of testing in immunocompromised patients, in particular those that will receive immunosuppressive drugs such as corticosteroids. As previously established in several reports, the most common risk factors for severe disease are those that alter the body's immune response, including cancer, corticosteroid therapy, and human T lymphotropic virus-1 infection (29). We identified disseminated strongyloidiasis in 5 patients, of whom 4 had previously been treated with high-dose glucocorticoids (for an unrelated condition) and of whom 3 had had a hematological/autoimmune disorder or cancer. In none of them was the infection suspected prior to the administration of glucocorticoids.

Our study had some limitations. It was a single-center retrospective study and the studied population was mostly men. The association between parasitic infections and eosinophilia has been documented before, but the relationship between eosinophilia levels and positive *S. stercoralis* testing is unclear, as reported by a 2013 study conducted by Wang, et al. (3), in which study patients who had tested positive for *S. stercoralis* presented with elevated, normal, and even decreased eosinophil levels. However, the most common reason for *S. stercoralis* testing in our study was eosinophilia, making these findings prone to selection bias. Finally, travel histories were unavailable for our patients—as we performed a retrospective record review—and were therefore unable to be reported in this study. However, these individuals were Hispanic patients residing in Puerto Rico, where they might have acquired the organism, given the endemicity of *Strongyloides* on the island.

As demonstrated in this study, other than positive testing (via the detection of antibodies in the serum or the identification of larvae in stool or biopsy samples), factors such as comorbidities, symptoms, laboratory data (white blood cell count, hemoglobin), and even eosinophil levels do not necessarily correlate with *S. stercoralis* infection. Instead, high suspicion and decreased threshold for testing prior to treatment should be based on other factors, such as risk for exposure and traveling to or returning from an endemic country (3). This becomes of increasing importance as corticosteroids are more frequently being used for immunosuppression, pain management, and, more recently, treatment for COVID-19 infection, increasing the risk for severe complications that are known to be associated with *S. stercoralis*.

Abbreviations

UC: ulcerative colitis; HTN: hypertension; ELISA: enzyme-linked immunosorbent assay; ARDS: acute respiratory distress syndrome; DIC: disseminated intravascular coagulation; MOF: multiple-organ failure; MICU: medical intensive care unit; ITP: immune thrombocytopenic purpura; GI: gastrointestinal; RF: respiratory failure; DM: diabetes mellitus; SOB: shortness of breath; CLD: chronic liver disease; COPD: chronic obstructive pulmonary disease; RBC: red blood cell.

Resumen

Objetivo: La estrongyloidiasis es una infección causada por un nemátodo y es clasificada por la Organización Mundial de la Salud como una enfermedad tropical desatendida. Aunque predominantemente asintomática, tiene el potencial de ser mortal en pacientes inmunocomprometidos. Los estudios epidemiológicos sobre este organismo son limitados, particularmente en el hemisferio occidental, al igual que estudios sobre los distintos escenarios clínicos que puede causar. Nuestro objetivo principal fue describir las distintas manifestaciones clínicas y los resultados asociados a *Strongyloides stercoralis* en la población hispana de veteranos en Puerto Rico. Métodos: Este estudio retrospectivo se llevó a cabo en un solo centro y se basó en la revisión del expediente electrónico de pacientes que fueron diagnosticados con *S. stercoralis* a través de pruebas serológicas, estudios de escreta o biopsias en el Hospital de Veteranos de Puerto Rico. Resultados: Un total de 270 pacientes resultaron positivos, de los cuales 210 (77.8%) fueron asintomáticos. La edad media de los pacientes fue 75.4 años. De los pacientes que presentaron síntomas, 25 tuvieron manifestaciones pulmonares, 21 tuvieron manifestaciones gastrointestinales, 5 tuvieron manifestaciones dermatológicas y 9 tuvieron síntomas adicionales. Cinco presentaron con hiperinfección, de los cuales la mayoría recibieron esteroides o eran inmunocomprometidos. El hallazgo de laboratorio más común fue la eosinofilia. Las razones más comunes para hacer la prueba de *S. stercoralis* fueron eosinofilia, asma, diarrea, cernimiento antes de comenzar tratamiento immunosupresivo y salpullido. Conclusión: Nuestro estudio recalca la importancia de descartar esta infección en países endémicos debido a su potencial mortal en pacientes inmunocomprometidos.

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