Human Strongyloidiasis in Hawaii: A Retrospective Review of Enzyme-Linked Immunosorbent Assay Serodiagnostic Testing

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Abstract. Human strongyloidiasis is widely prevalent in tropical and subtropical regions worldwide but is not endemic in Hawaii. Subclinical, chronic infections may be lifelong; immunosuppressive therapy, particularly with glucocorticoids, may lead to serious or fatal disseminated disease, which is preventable. We performed a retrospective analysis of patients tested for *Strongyloides* immunoglobulin G antibody in an academic medical center in Honolulu, Hawaii, from 2005 to 2012. Of the 475 patients tested, 78 (16%) were seropositive. The largest proportion of seropositive cases was found among Micronesians (30%), Polynesians (26%), Filipinos (13%), and Southeast Asians (11%). Among the seropositive patients, the most likely reason for clinicians to order testing was blood eosinophilia. Stool parasite examination results were available for 58% of seropositive patients of which 11% were positive for *Strongyloides stercoralis* larvae. Antihelminthic therapy, usually ivermectin, was ordered for 71% of patients, respectively; both tests tended to show improvement. Travelers and immigrants from *Strongyloides*-endemic areas, including Micronesia and Polynesia, should have serodiagnostic testing for latent strongyloidiasis, and if positive, treated empirically with ivermectin, particularly when corticosteroids or other immunosuppressive therapies are anticipated.

INTRODUCTION

Strongyloidiasis is a parasitic infection of humans caused by the intestinal nematode Strongvloides stercoralis, which infects humans who had contact with soil contaminated by human feces. It is estimated to infect approximately 100 million individuals worldwide.¹ Adult worms dwelling in the human upper intestinal tract deposit eggs in intestinal mucosa, which hatch into larvae and are excreted in stool, which can contaminate soil in regions with poor sanitation. The infective filariform larvae in soil penetrate human skin, migrate to the lungs, then into the upper intestinal tract where they mature and lay eggs. The eggs, in turn, hatch into infective larvae within the gastrointestinal tract and are excreted in the stool to complete the life cycle. The life cycle resembles that of hookworm; but unlike hookworm and other intestinal worms, Strongyloides filariform larvae multiply within the human host by repeatedly penetrating the intestinal mucosa and perpetuating the life cycle indefinitely. This autoinfective life cycle is unique among nematodes and leads to latent strongyloidiasis infection that may persist for a lifetime.

The importance of diagnosing latent strongyloidiasis is, like latent tuberculosis, that the infection can become severe or fatal in patients immunocompromised by high-dose corticosteroid or immunosuppressive therapy for other diseases. Host immunosuppression can lead to disseminated strongyloidiasis in which larvae migrate into multiple organs causing multisystem failure, particularly the respiratory and gastrointestinal systems, or cause sepsis because of enteric bacterial translocation from the gastrointestinal tract. Mortality rates associated with disseminated strongyloidiasis are high approaching 70%.² The diagnosis of disseminated strongyloidiasis is often unsuspected and delayed until the larvae are detected incidentally during bronchoalveolar lavage or intestinal endoscopy.² Strongyloidiasis is difficult to diagnose, so prevalence rates in various geographic regions can only be estimated. Seroepidemiologic studies conducted in regions with large immigrant populations, such as Australia and Canada, demonstrated prevalence rates of 11–77%, depending on the geographic region of origin of those screened.^{3–5} Infections are common in tropical and subtropical areas with poor sanitation, including the Asia-Pacific region, South America, and Africa. Other persons at risk for strongyloidiasis include persons living in low-income rural Appalachia, military veterans, and others who may have been exposed while traveling to endemic areas.

The gold standard for the diagnosis of strongyloidiasis is serial stool examinations; however, traditional stool examinations are insensitive.⁵ A more sensitive, but less specific enzyme-linked immunosorbent assay (ELISA) is available from several commercial laboratories and can be confirmed by advanced methods at the Centers for Disease Control (CDC).⁶ If diagnosed, chronic infections can be effectively treated with 2 days of oral ivermectin with up to 100% success rates,⁷ which is believed to be a cost-effective strategy.^{8,9} Consequently, the CDC and other experts recommend *Strongyloides* screening tests, and subsequent treatment of those with recent or remote travel histories to *Strongyloides*-endemic areas¹⁰; however, in clinical practice, this is seldom carried out.¹¹

The first reported case of *Strongyloides* infection in Hawaii was an imported case published in 1993.¹² No further cases have been reported since then. Although the parasite is not endemic in Hawaii, the state is host to a large immigrant population from the Asia-Pacific region. The goal of this study was to evaluate the rates and risk factors for *S. stercoralis* infection among patients who had serodiagnositic testing in a tertiary academic medical center in Honolulu, Hawaii.

METHODS

This was a retrospective descriptive study of human strongyloidiasis using medical chart review at an academic medical center that includes a tertiary care hospital and its

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outpatient clinic in Honolulu, Hawaii. We included patients who, during routine clinical care, had *Strongyloides* serological testing from January 1, 2005 to May 31, 2012. We examined medical records for baseline demographics, clinical findings, serological testing, blood eosinophil counts, and stool parasite examinations. Serodiagnostic testing for *Strongyloides* immunoglobulin G (IgG) antibody immunoassay by ELISA was performed by Quest Diagnostics, Infectious Diseases Inc., San Juan Capistrano, CA (formerly Focus Diagnostics). The laboratory states that the assay shows 92% sensitivity and 100% specificity compared with the CDC assay. Some cross-reactivity may be observed with filarial and nematode infections.

Eosinophilia was defined by our clinical laboratory as a differential white blood cell blood cell count with greater than or equal to 7% eosinophils. Fecal specimens were collected, placed in commercial polyvinyl alcohol containers, and submitted to the hospital laboratory for routine stool ova and parasite studies with formalin concentration and microscopic examination of permanent stained smears. We reviewed the electronic medical records (EMRs) of the seropositive patients for demographic and clinical characteristics. We also reviewed the treatment history and subsequent changes in eosinophil counts and *Strongyloides* antibody levels following treatment. This study was given expedited approval by the Research and Institutional Review Committee of The Queen's Medical Center (Protocol RA 2013-028).

RESULTS

During the 7-year and 5-month study period, a total of 475 patients had *Strongyloides* serological testing. As shown in Table 1, among the 475 patients who had serodiagnostic testing, the highest proportion of seropositive patients was found in Micronesians (30%), non-Hawaiian Polynesians (26%), and Filipinos (13%). Nine patients (12%) were being

TABLE 1

Characteristics of 475 patients with Strongyloides serodiagnostic testing

| Characteristic | Total <i>N</i> = 475 <i>N</i> (%) | Seropositive N = 78 N (%) |
|-----------------------------|--------------------------------------|------------------------------|
| Age (years) median | 65 | 54 |
| Range | 12–104 | 27–99 |
| Female | 260 (55) | 19 (24) |
| Male | 215 (45) | 59 (76) |
| Race/ethnicity‡ | (), | |
| Micronesian | 151 (32) | 46 (30) |
| Filipino | 69 (15) | 9 (13) |
| Asian* | 69 (15) | 2 (3) |
| Polynesian† | 53 (11) | 14 (26) |
| White | 44 (9) | 3 (7) |
| Part-Hawaiian | 41 (9) | 1 (2) |
| Southeast Asian | 18 (4) | 2 (11) |
| Okinawan | 12 (3) | 1 (8) |
| Other/unspecified | 18 (4) | 0 Í |
| Immunosuppressed | ., | |
| Corticosteroids | | 4 (5) |
| Chemotherapy + steroid | | 3 (4) |
| Methotrexate | | 2 (3) |
| HTLV-1, N positive/N tested | | 0/4 |
| HIV, N positive/N tested | | 0/8 |

HIV = human immunodeficiency virus; HTLV = human T-lymphotrophic virus. * Chinese, Japanese, and Korean.

+ Samoan and Tongan.

[‡] Presented as row percentages for seropositive patients to show antibody prevalence within race/ethnic groups.

treated with immunosuppressive agents. Eight (10%) were tested for human immunodeficiency virus and four (5%) were tested for human T-lymphotrophic virus-1; all of whom were negative.

The clinical features of the 78 seropositive patients are shown in Table 2. The clinicians' reasons for ordering Strongyloides serodiagnostic testing and tests for other parasitic infections were not clear in all cases from our EMR review. However, of the 78 seropositive patients, eosinophilia was present in 69 (88%) patients before serological testing. Many patients also had respiratory and/or gastrointestinal symptoms, which with or without eosinophilia, may have also led to Strongyloides serodiagnostic testing as shown in Table 2. Stool ova and parasite examination results were available for 45 (58%) patients. Twelve (27%) patients were positive for parasites, of which five (11%) were S. stercoralis larvae. Additional serodiagnostic testing was positive for Toxocara antibodies in seven of nine patients. The clinical features of these patients did not distinguish if the results were due to primary infection with Toxocara, cross-reactivity with Strongyloides, or co-infection with both parasites.

Disseminated strongyloidiasis was diagnosed in one of 78 patients. This patient was a 79-year-old Chinese immigrant woman who had recently been treated elsewhere with

| TABLE 2 |
|---|
| Characteristics of 78 Strongyloides-seropositive patients |

| Characteristic | N (%) |
|--|----------|
| Inpatients | 22 (28) |
| Outpatients | 46 (59) |
| Site unknown | 10 (13) |
| Infectious diseases consult | 6 (8) |
| Blood eosinophilia | 69 (88) |
| Median, range | 14, 7–38 |
| Stool parasite test results | |
| Patients tested | 45 (58) |
| Strongyloides* | 5 (11) |
| Hookworm | 1 (2) |
| Clonorchis | 1 (2) |
| Blastocystis | 5 (11) |
| Serological test results for other parasites | |
| Toxocara, $N = 9$ | 7 (78) |
| Schistosomiasis, N = 1 | 0 |
| Filariasis, <i>N</i> = 1 | 0 |
| Symptoms† | |
| Respiratory | 36 (46) |
| Gastrointestinal | 33 (42) |
| Unspecified rash | 7 (9) |
| Disseminated strongyloidiasis | 1 (1) |
| Disseminated strongyloidiasis, probable | 1 (1) |
| Antiparasitic treatments ordered, $N = 55$ | |
| Ivermectin | 50 (91) |
| Mebendazole‡ | 3 (5) |
| Albendazole | 2 (4) |
| Posttreatment laboratory tests | |
| Eosinophilia | 42 (76) |
| Decreased/normalized | 33 (79) |
| Persistent | 9 (21) |
| Serology titer after 10 days to 29 months | 19 (35) |
| Normalized | 1 (5) |
| Decreased | 14 (74) |
| Unchanged§ | 3 (16) |
| Increased | 1 (5) |
| + For Mission and an Obligation | |

† Includes patients with multiple symptoms.

‡ One patient with hookworm, treated with mebendazole only.

§ Two patients untreated, one patient's second test carried out 7 weeks posttreatment.

|| Patient was treated with mebendazole (unclear if medication was taken before or after posttreatment laboratory test).

high-dose corticosteroids for repeated episodes of acute respiratory failure attributed to chronic obstructive pulmonary disease (COPD). She was admitted to our intensive care unit because of severe dyspnea, three days of diarrhea, and a petechial-purpuric rash of her right abdomen and both legs. Clinical evaluation was remarkable for tachypnea, tachycardia, fever of 40°C, and hypoxia. She was intubated for respiratory distress. Initial laboratory results were remarkable for normal white blood cell counts with zero eosinophils, and persistent thrombocytopenia. Chest imaging demonstrated a right upper lobe infiltrate and evidence of COPD. Blood and sputum cultures, and tests for tuberculosis, were subsequently negative. She was treated for pneumonia and sepsis with broad-spectrum antibiotics and 40 mg of intravenous methylprednisolone per day for a COPD exacerbation. On hospital day 9, an infectious diseases consultant considered the diagnosis of strongyloidiasis and ordered stool parasitic studies and serodiagnostic testing. Her pulmonary infiltrates became generalized, and on hospital day 9, she had gross hemoptysis, septic shock, and multiorgan failure. On hospital day 11, three sputum cytology studies incidentally detected S. stercoralis larvae; two fecal examinations were also positive for S. stercoralis larvae. She was treated with ivermectin, but expired on day 11. The family declined an autopsy. This patient had the typical clinical features of disseminated strongyloidiasis.² She had immigrated from a Strongyloides-endemic area and was immunosuppressed with corticosteroid therapy for COPD. She had multiple symptoms involving the respiratory and gastrointestinal tract, petechial-purpuric skin lesions, and the presence of Strongyloides larvae in the sputum and stools. The lack of eosinophilia was likely due to high-dose corticosteroid therapy. Despite the latter, her antibody levels shown by serodiagnostic testing were elevated. This case demonstrates the common lack of clinicians' awareness of the consequences of immunosuppression in patients from Strongyloides-endemic regions who have untreated latent strongyloidiasis.¹¹

Table 2 shows the anthelminthic therapies that were ordered and the posttreatment laboratory test results. Although treatment compliance could not be confirmed for the ambulatory patients, 42 individuals were retested for eosinophilia, which decreased or normalized in 33 (79%) and was unchanged or higher in nine (21%). Nineteen serologically positive patients had repeat *Strongyloides* serological testing after an interval that varied between 10 days and 29 months. The antibody titer decreased in 14 (74%), normalized in one (5%), was unchanged in three (16%), and increased in one (5%).

DISCUSSION

The endemicity of *S. stercoralis* is well established in Asia, Southeast Asia, and Japan (particularly in Okinawa).^{13,14} However, there is a paucity of data on prevalence of *S. stercoralis* in Micronesia and Polynesia. This is the first study to address the epidemiology of *S. stercoralis* in Hawaii, and to our knowledge, the first study to address strongyloidiasis among Micronesian and Polynesian immigrants. Because *Strongyloides* is soil transmitted and favors the humid, wet climates of the tropics and subtropics, it is not surprising that we detected a large number of *Strongyloides* infections in this population.

The parasite's unique autoinfective life cycle can result in lifelong latent infection. Because of increased global mobility, individuals from endemic areas should be screened for S. stercoralis because their infection can lead to serious disseminated infections due to the common use of steroids, immunosuppressive agents, and chemotherapy. The results of this study support the CDC recommendations that all individuals with recent or remote residence in S. stercoralisendemic areas should be screened for latent strongyloidiasis.¹⁰ Asymptomatic long-term travelers or military personnel who have been in known Strongyloides-endemic areas should also be targeted.^{15–17} Patients with such histories should be screened even if their last exposure was decades prior. This is exemplified by the report of patient who developed hyperinfection syndrome following antineoplastic chemotherapy 42 years after returning from military service in Micronesia during World War 2.18 Although there were few individuals from nonendemic areas in our cohort, these individuals may be underrepresented in our sample because testing was based on provider discretion.

Diagnostic testing for larvae in standard stool examinations is insensitive. Our study was illustrative of this given only five of the 45 (11%) available stool studies exhibited S. stercoralis larvae. Serological methods are considered to be more accurate with sensitivities greater than 90%.¹⁹ Assessing the accuracy of serological tests is challenging because of the lack of sensitivity of a fecal-based reference standard. Serological methods may also be complicated by cross-reactivity with other soil-transmitted helminthes; however, newer recombinant antigen assays have shown a specificity of 100%.²⁰ Eleven Strongyloides-seropositive patients had serodiganostic testing for other parasites (Table 2). Nine patients had ELISA-based testing for Toxocara antibodies and seven were seropositive. However, Toxacara serodiagnostic tests may also have false-positive reactions in patients with other helminth infections.²¹ Even with improved ability to differentiate with newer assays, it is important to note that evidence of infection with another parasite does not exclude S. stercoralis infection. For example, ELISA-based testing samples from a reference laboratory in Ho Chi Minh City, Vietnam, revealed that roughly half of individuals had been exposed to more than one parasite.²²

Eosinophilia was the likely reason for *Strongyloides* testing, which was present either alone or in combination with additional symptoms in 88% of our seropositive patients. The presence of eosinophilia among those who were seropositive was comparable with data reported elsewhere.⁶ Although helminthic parasites are the most common cause of eosinophilia around the world,²³ our data support the finding that eosinophilia is not universally present in *S. stercoralis* infection, and cases of hyperinfection syndrome have been reported in its absence likely because of glucocorticoid suppression of eosinophilia.² Therefore, aside from eosinophilia, the diagnosis of strongyloidiasis should be based on travel history and other clinical features.

The most commonly reported symptoms of strongyloidiasis are abdominal pain, diarrhea, bloating, cough, and skin exanthemata.^{24,25} As shown in Table 2, these symptoms were also common among our seropositive patients. Such symptoms, particularly when associated with eosinophilia, probably lead to the diagnostic workup for strongyloidiasis and other parasitic infections. We noted the high prevalence of underlying lung diseases such as asthma and COPD in this cohort. While it is difficult to establish whether pulmonary symptoms are secondary to the parasite or the patient's baseline pulmonary complaints,²⁶ this finding highlights that screening is warranted among individuals from endemic areas with pulmonary complaints because of the frequent administration of corticosteroid therapy for asthma and COPD exacerbations.

Since the introduction of mebendazole, albendazole, and ivermectin, treatment of *Strongyloides* has been associated with improved efficacy and fewer side effects.⁷ A two-consecutive-day treatment with ivermectin has been shown to result in cure rates approaching 100%.⁷ In light of this, two consecutive days of ivermectin should be the treatment of choice, particularly among those undergoing immunosup-pressive therapy to maximize the likelihood of eradication. Our study demonstrates that strongyloidiasis is likely undertreated because a prescription for anthelminthic therapy was ordered for just 71% of our serodiagnosed patients.

Following treatment, eosinophilia and antibody titers can be measured as a proxy for response to therapy. In clinical practice, patients are considered cured if their eosinophil counts return to normal levels and serodiagnostic testing for Strongyloides reverts to negative. In one report, significant reductions in eosinophil counts and serological antibody titers were observed in patients responding to therapy after an average of 96 and 270 days, respectively.¹⁶ In our cohort, 79% of patients who had follow-up complete blood cells counts experienced decreased or resolution of eosinophilia. Nineteen patients had repeat Strongyloides serological testing and titers decreased or normalized in 15. Of the four who did not show improvement in serological testing, one received mebendazole instead of the more effective ivermectin and it was unclear if the medication was taken before or after repeat laboratory testing, two had no documented treatment despite a prescription being ordered, and one had repeat testing just 7 weeks posttreatment. The latter patient's test likely did not revert to negative because testing was repeated too early.⁶

Two of our study patients had clinical sepsis: one had disseminated Strongyloides infection and another had suspected disseminated infection. Many cases of disseminated strongyloidiasis have been reported in the medical literature, including cases in the United States. However, U.S. physicians are often unfamiliar with this potentially fatal infection. Our study supports the CDC-recommended preventive measures, including prospective screening and treatment of migrants and other patient populations at risk for Strongyloides infection.¹⁰ Refugee predeparture treatment programs have also been shown to be beneficial among certain ethnic groups.²⁷ Most of our patients who were seropositive for Strongyloides were of Micronesian and non-Hawaiian Polynesian descent. These populations had previously not been recognized to be at risk for strongyloidiasis. Many Micronesians and Polynesians migrate to Hawaii and the continental United States. They should be screened for strongyloidiasis and treated if infected.

At a systems level, our study shows that improvements in *Strongyloides* testing and treatment are needed. As shown in Table 1, testing of Whites, Asians, and part-Hawaiians had low yield. From our EMR review, we could not determine if these individuals originated from high-risk areas, if they were veterans, or travelers to high-risk areas. We are also unable to determine how many Micronesians, Polynesians, Filipinos, and Southeast Asians went unscreened. Electronic medical record decision support tools could be created to assist with decision-making regarding screening, particularly where there is a high prevalence of individuals who are at high risk, which is a strategy that has been implemented for tuberculosis.²⁸ If level of risk could be established and conveyed to health-care providers, perhaps the yield of positive testing could be improved. In addition, our study demonstrates that testing did not always lead to treatment. As shown in Table 2, treatment was documented in 71% of cases. Moreover, of those who were treated, follow-up laboratory testing was lacking in approximately one quarter. Increased provider education and EMR decision support could also be implemented to improve these outcomes.

This study has several important limitations. First, given our restrospective design, testing was provider initiated. Overall, serodiagnostic testing in our patients seemed appropriate because most cases were from high-risk areas. However, we are not able to comment on population-level Strongyloides prevalence among migrants in Hawaii using this study design. Second, the cases in this study were identified using ELISAbased testing. Although this is not the gold standard, stool testing risks underdiagnosing cases of Strongyloides infection due to its insensitivity and, overall, ELISA-based testing has a low false positivity rate. Third, we are unable to confirm patient adherence to prescribed antihelminthic therapy, particularly in the oupatient setting. Last, the administrative data in the EMR described only race/ethnicity and not place of birth or history of travel to Strongyloides-endemic areas. Therefore, the precise location where Strongyloides infection was acquired cannot be definitively ascertained. However, because Strongyloides is not endemic in Hawaii, we presume that all the seropositive patients were acquired abroad.

In conclusion, our study addressed the epidemiology of Strongyloides in the population of Hawaii. To our knowledge, this study is the first to describe Strongyloides infections in immigrants from Micronesia and Polynesia. Patients with strongyloidiasis, even if asymptomatic, should be treated to prevent disseminated infection because the latter has a mortality rate of that can exceed 70%. Disseminated strongyloidiasis should be suspected in immigrants from endemic areas who present with fever, sepsis, or acute and severe multisystem disease. We recommend that consideration be made to screen all immigrants from known Strongyloides-endemic areas, including Polynesia, Micronesia, and the Philippines using commercially available Strongyloides serodiagnostic tests. In addition, if time permits, we recommend deferring immunosuppressive therapy, especially with corticosteroids, pending results of Strongyloides serodiagnostic testing, and anthelminthic treatment of seropositive patients.

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