REVIEW ARTICLE

Infection Due to *Strongyloides stercoralis* in Patients With Pulmonary Disease

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THE INTESTINAL NEMATODE *Strongyloides stercoralis* has gained increasing importance because of its ability to reproduce rapidly and disseminate in patients with defective cell-mediated immunity. This condition, known as the hyperinfection syndrome or disseminated strongyloidiasis, may have a greater than an 80% mortality.[1] Because patients with chronic lung disease (CLD) may frequently be treated with corticosteroids, they are at particular risk for chronic infection or hyperinfection with this organism, whether or not the lung is primarily infected. The following case presentation describes a patient who had such an infection, and whose diagnosis was complicated by his underlying lung disease. A review of reported cases of coexistent *Strongyloides stercoralis* infection and preexisting lung disease follows.

CASE REPORT

The patient is a 69-year-old white man with a long history of steroid-dependent chronic obstructive lung disease and multiple Veterans Administration Medical Center admissions for exacerbations. In August 1987, 1 month after a previous admission for similar symptoms, he had gradually worsening shortness of breath and pleuritic chest pain, without change in his usual sputum production. He denied fever, chills, or hemoptysis. Past medical history included a perforated ulcer in 1984. Medications at the time of admission included cimetidine (400 mg at bedtime), albuterol (four puffs four times daily from a metered dose inhaler), terbutaline (2.5 mg twice daily) theophylline (400 mg twice daily), ampicillin (250 mg four times daily), hydrochlorothiazide (50 mg/day), and prednisone (40 mg/day). Physical examination revealed an elderly white man in slight respiratory distress. Blood pressure was 140/90 mm Hg, pulse rate 120/min, and respiratory rate 32/min and slightly labored; he was afebrile. He had diffuse wheezes that had not cleared with nebulizer treatments in the emergency room. With the patient breathing room air, blood gas values were pH 7.57, P_{CO_2} 27 mm Hg, and P_{O_2} 106 mm Hg. White blood cell count was 16 900/mm^3 but decreased with hydration; differential count revealed 36% neutrophils, 19% monocytes, 11% lymphocytes, and 35% eosinophils. He was hydrated and given more nebulizers, which resulted in an improvement in the wheezing. He was discharged after a 4-day admission.

Over the next year he was seen three times in the pulmonary clinic. His condition was described as stable until September 20, 1988, when he was seen in the emergency room because of pain and tenderness in the right upper quadrant, nausea and vomiting, and a 20-lb weight loss. The WBC was 9200/mm^3 with 26% eosinophils. An upper gastrointestinal series, abdominal ultrasonography, and computerized tomography of the abdomen all yielded normal findings. Results of upper gastrointestinal endoscopy were also normal. A duodenal biopsy, done to detect possible giardiasis, revealed profuse infection with *Strongyloides stercoralis*. The patient was treated with thiabendazole, 25 mg/kg twice a day for 2 days, and his steroids were tapered. When seen 6 weeks after treatment, he was asymptomatic and had gained 30 lb. Stool examinations were negative for *Strongyloides* organisms.

DISCUSSION

Strongyloides stercoralis is a ubiquitous intestinal nematode that is found in every state in the US. It is most prevalent, however, in the South, especially in Tennessee, Kentucky, and the Appalachian chain. A number of unique aspects of the organism account for its ability to cause morbidity. While the initial infection is contracted through penetration of the skin, the organism may metamorphose within the host (autoinfection) and continue the infection for many years without additional exposure. Adult worms live in the upper small intestine. In most patients, the infection is asymptomatic or causes few symptoms.[2] Patients may report intermittent loose stools or diarrhea, bloating, fleeting abdominal pain, or skin rashes. The extraintestinal organ most frequently damaged by the parasite is the lung. Larval forms break out of small pulmonary vessels into the alveoli, resulting in diffuse alveolar hemorrhage with resultant dyspnea, wheezing, sputum production, or hemoptysis; there may be additional immunologically mediated vascular damage.[3]

As in most nematode infections, the majority

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TABLE. Reported Cases of *Strongyloides* Hyperinfection Syndrome in Patients With Preexisting Asthma

	Age	History of Asthma (years)	Percent Eosinophils	Organ Involvement
Ali-Khan and Seemayer[22]	58	15	"Normal"	Small bowel, CNS
Higenbottam and Heard[23]	57	37	2%	Lungs, bronchi
Ford et al[24]	60	39	2%	Lungs, small bowel
Belani et al[25]	46	40	3%	CNS, small bowel

of patients have eosinophilia; between 83% and 92% of patients will have more than 5% eosinophils, and the mean eosinophil percentage is between 13% and 18%.[2] The combination of pulmonary symptoms and eosinophilia in patients with known lung disease may be attributed to an exacerbation of their disease, and an alternative cause may not be sought.

Pulmonary Strongyloidiasis Without Lung Disease

Mild to moderate *Strongyloides* infections may involve the lungs. Patients with the acute onset of "asthma"[4,5] or the subacute onset of "asthmatic bronchitis"[6] have been found to actually have heavy pulmonary infection with *Strongyloides*. In one instance a patient believed to have asthma was treated with steroids, and hyperinfection developed. After successful treatment, asthmatic symptoms resolved.[7] Although strongyloidiasis as a cause of asthma in the general population is probably rare, it may be reasonable to consider the diagnosis in patients from endemic areas at high risk of infection.

A series of 29 cases of pulmonary infection reported from Poland included patients with such underlying diseases as malignancy, tuberculosis, sarcoidosis, and pulmonary cysts accompanied by such complications as Löeffler's syndrome, hemoptysis, pneumonias, and cough.[8] None of the cases was diagnosed before the examination of pathologic material. Severe infections such as those seen in immunocompromised individuals may result in a spectrum of serious pulmonary disease. Persistent pulmonary infection in immunodeficient patients[9] and severe pulmonary infections with coexistent bacterial superinfection in corticosteroid-treated patients have been reported.[10,11] Acute respiratory failure due to *Strongyloides* has been reported in corticosteroid-treated patients with renal transplants[12,13] and polymyositis.[14] Adult respiratory distress syndrome due to strongyloidiasis has been reported in a renal transplant patient.[15] Lung abscess was found in two corticosteroid-treated patients.[16,17] As an opportunistic infection, strongyloidiasis frequently involves the lung and should be strongly considered in the differential diagnosis of pulmonary infections in immunocompromised patients.

Strongyloidiasis With Preexisting Lung Disease

Four surveys have investigated coexistent diseases in *Strongyloides* infection of hospitalized patients. In a retrospective study in a Nashville Veterans Administration Medical Center, 9 of 63 patients (14%) had CLD.[18] In a similar review at the University of Kentucky Medical Center, 11 of 56 patients (20%) had the previous diagnosis of CLD.[19] Neither of these studies included control groups, which might have helped in determining whether CLD could predispose to *Strongyloides* infection. Davidson et al[2] performed a case-control study of risk factors in a population of 28 patients with domestically acquired strongyloidiasis in North Carolina; the prevalence of CLD was similar in both groups (around 15%). Berk et al[20] did a prospective screening study in 229 patients hospitalized at the VA Hospital in Johnson City, Tennessee. Fourteen patients (6%) were found to have *Strongyloides* sp in their stools, and 12 of those 14 (86%) had coexistent CLD, as compared with 52% of a stool-negative control population. It is clear that a significant percentage of hospitalized patients with strongyloidiasis have coexisting lung disease (around 20% from these four studies).

In addition to provoking the hyperinfection syndrome in some patients, it is postulated that corticosteroids enhance the normal life cycle of the organism in others, resulting in internal autoinfection and a persistence or worsening of a non-disseminated infection.[21] Thus steroid use was found to be associated with the infection, in the absence of hyperinfection, in two of the studies mentioned.[2,20] The most dramatic presentation of the infection, however, is hyperinfection, and such cases are more likely to be reported.

Hyperinfection in Patients With Asthma

In four reported cases, patients with the hyperinfection syndrome were being treated with corticosteroids for asthma (Table). Their mean age was 55 years. None of the patients had eosinophilia. Two of the four patients died, 5 and 14 days after admission, and the diagnosis of *Strongyloides* infection was made post mortem. One patient died of bowel infarction and sepsis[22]; the other died of progressive respiratory failure and pneumonia.[23] Of the two patients who survived, one had a progressive lung abscess that did not respond to treatment until *Strongyloides* was discovered in postbronchoscopy sputum specimens. This patient was successfully treated with a 5-day course of thiabendazole, despite the continuance of steroid therapy.[24] The other surviving patient,[25] from the same institution that my report comes

from, had been previously treated for strongyloidiasis 6 years earlier; she had pyogenic meningitis, and *Strongyloides* larvae were found in her cerebrospinal fluid. She was successfully treated with an 8-day course of thiabendazole.

Hyperinfection in Patients With Chronic Lung Disease

The recent literature reports nine cases of serious infection with *Strongyloides stercoralis* in patients receiving corticosteroids for chronic lung disease.[26-29] All patients were male. Seven of the nine (77%) died during hospitalization. Eight of the nine were from the same institution, a VA hospital.[27-29] Three patients had no eosinophils on differential white blood cell count, and only one had eosinophilia. Although the diagnosis was made ante mortem in all patients, it was delayed; among the eight cases in which the information was reported, the average date of diagnosis was 17.5 days after admission.

The patients died of a variety of causes, including complicating *Aspergillus* infection,[26] nosocomial pneumonia,[27] sepsis,[28] and cardiorespiratory failure.[29] It is clear, given the frequency of infection in hospital-based surveys, that these patients represent only a small percentage of those who have chronic lung disease and the most severe *Strongyloides* infections. Given the extraordinarily high mortality from hyperinfection, it is essential to detect the infection at an earlier stage, when it is either latent or accelerated as in the case reported here.

Strongyloides larvae may be removed from pleural effusions.[30] Examination of sputum may reveal the presence of larvae, either in wet preparations[16,17,31,32] or by Gram's stain.[27,33] Transtracheal aspirate,[12] bronchial washings,[6,11,13] and transbronchial biopsy[13] have supplied diagnostic material. Two reports of diagnosis by bronchoalveolar lavage have been published.[15,29] In a prospective study of the utility of sputum examination in *Strongyloides*-infected patients, Berk et al[20] found 2 of 23 cases by positive sputum Gram's stains, indicating accelerated infection or hyperinfection. Both were in patients with chronic lung disease; one patient was taking corticosteroids. Both responded well to treatment.

Recently, serologic tests for *Strongyloides* infection have become available by both private laboratories and the Centers for Disease Control. The enzyme-linked immunosorbent assay (ELISA) has been reported to have a sensitivity of 84% to 88%[34-36] and has been used in two population-based screening studies.[37,38] Although the specificity of the test is good in patients without other nematode infections (99%), there may be some cross-reactivity in patients with ascariasis and other nematode infections.[34]

Infection due to *Strongyloides stercoralis* is frequently asymptomatic in immunocompetent individuals. When these patients are given corticosteroids, an exacerbation of latent infection occurs. Because accelerated infection may involve the lungs, causing dyspnea, wheezing, cough, hemoptysis, and eosinophilia, patients with preexisting lung disease may be diagnosed as having an exacerbation of their pulmonary disease. This may result in considerable delay in diagnosis, thereby exposing the patient to the risk of hyperinfection. Treatment with thiabendazole in a dose of 25 mg/kg twice a day for 2 to 10 days, depending on the immune status of the individual, is effective,[39] and as in this case report, probably prevents the development of hyperinfection in many patients with accelerated infection. Such therapy has clearly been life-saving in some patients with hyperinfection.[16,21] A concern in patients with CLD is the possibility of thiabendazole-induced theophylline toxicity[40]; careful monitoring of theophylline levels is therefore suggested.

Patients considered at high risk for latent strongyloidiasis may be screened for the infection. Davidson et al[2] found a significantly increased risk of infection in whites, men, patients using corticosteroids, and patients with underlying hematologic malignancy. Additionally, patients with previous gastric surgery were at a much greater risk of infection (inhibition of the gastric acid barrier, whether by surgery or pharmacologic means, apparently enhances the survivability of the organism). Other factors that place persons at risk include outdoor exposure to soil, previous infection with *Strongyloides,* and living in an endemic area. Berk et al[20] developed a risk factor scale for hyperinfection in patients with *Strongyloides* infection; it includes age over 65, chronic lung disease, corticosteroid therapy, and use of antacids or cimetidine.

Recommendations for screening are problematic, since careful population-based studies of test characteristics have not been done. However, the ease of the sputum Gram stain and its frequency of positivity in case reports make it an attractive method of screening for accelerated infection.[27] Stool specimens are difficult to obtain from outpatients, and their sensitivity varies,[37] but they present an accurate means of diagnosing latent infection. The ELISA appears to be relatively accurate and probably is an important addition to the diagnostic approach to this infection.[37,38]

In endemic areas it may be reasonable to screen

all corticosteroid-treated patients, including those with CLD, with an ELISA or stool examinations annually. Patients with CLD whose condition is deteriorating, especially those being treated with steroids, should routinely be suspected of having strongyloidiasis. Eosinophilia in patients taking corticosteroids should be considered unusual[21]; most frequently, patients taking therapeutic doses will have no eosinophils. The sputum Gram stain is probably the most efficient method of screening these patients for accelerated infection, despite the lack of detailed information about sensitivity or specificity of this test. The additional use of ELISA or stool examinations should be strongly considered. Physician awareness of the infection and its presentation is the most important diagnostic maneuver.

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