Invasive Enteric Infections in Hospitalized Patients With Underlying Strongyloidiasis

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Key Words: Strongyloidiasis; Enteric infections; Sepsis; Fungemia

Abstract

Disseminated strongyloidiasis is often associated with enteric bacterial infections. This study was undertaken to determine if enteric organisms caused extraintestinal infections in patients infected with Strongyloides stercoralis but without apparent dissemination. The medical records of hospitalized patients from central Kentucky with strongyloidiasis (1993-2003) were examined to determine the occurrence of extraintestinal infections with enteric organisms. Of 30 patients with S stercoralis, 16 had invasive infections, including sepsis, meningitis, pneumonia, peritonitis, and endocarditis caused by enteric bacteria and Candida organisms. Infections were seen in 8 (62%) of 13 patients with disseminated strongyloidiasis and 8 (47%) of 17 with disease apparently limited to the gastrointestinal tract. Fifteen patients were receiving corticosteroids or other immunosuppressive therapy. Peripheral eosinophilia was seen in only 23% (7/30). Infection with S stercoralis, even without obvious dissemination, may predispose to invasive infections caused by enteric organisms. In Strongyloides-endemic areas, patients with invasive infections caused by enteric organisms should be examined for coinfection with S stercoralis.

Strongyloides stercoralis (SS) is an intestinal nematode that is endemic to the southeastern United States.1,2 Prevalence studies in eastern Kentucky demonstrated asymptomatic intestinal strongyloidiasis in 4% to 5% of school-aged children and college students surveyed.3,4 Although gastrointestinal infections are often transient, some patients may remain asymptomatically infected for decades.

The complex life cycle of SS is responsible for the broad spectrum of disease manifestations seen with this infection.5 In the acute infection, filariform larvae invade through intact skin and may cause local cutaneous irritation and rashes. The larvae then gain access to the venous system, from which they invade through the capillary walls of the lungs and into the alveolar space, producing respiratory symptoms. The larvae are ultimately coughed up and swallowed and take up residence in the duodenal epithelium where they mature into egg-producing adult worms. Rhabditiform larvae hatch in the duodenum and are shed in the stool to initiate the free-living phase of parasite development in the environment.

People with chronic gastrointestinal SS (GISS) often are asymptomatic, but some patients may have intestinal symptoms associated with the parasitism, such as diarrhea, nausea, and nonspecific abdominal pain.6 World War II veterans who were infected during service in Southeast Asia reported intermittent urticarial skin eruptions associated with larval migration, pruritus ani, abdominal pain, and diarrhea that recurred for decades following infection.7-10 In patients with chronic infection, disseminated disease may develop with superinfection syndrome in which the patients become immunocompromised.11,12 In superinfection syndrome, the rhabditiform larvae mature into filariform larvae in the gut and are capable of reinfecting the host without the environmental maturation...
step. Transplant recipients and people treated with systemic corticosteroids are at greatest risk for dissemination and superinfection.13-20

Symptoms in patients with disseminated SS (DSS) are primarily pulmonary, consistent with the ongoing transmigration through the lungs.6 The mortality rate of DSS has been as high as 80% in some series.11,21 Several case reports and literature reviews showed an association between DSS infection and enteric gram-negative bacterial infections that was explained by bacterial translocation on the nematode’s surface as it penetrates the intestinal mucosa.12,21-23

In previous studies, 30% to 45% of patients with DSS had serious secondary bacterial or fungal infections, including bacteremia, meningitis, peritonitis, and endocarditis.11,24,25 Bacterial infections in association with GISS in the absence of dissemination are rarely reported.26 The present study was undertaken to determine whether enteric organisms caused serious infections in persons with SS with no obvious evidence of dissemination. It is our hypothesis that patients may have significant infection due to enteric organisms without fulfilling the classic features of dissemination.

Materials and Methods

A search was performed in the medical records computer database for the words “Strongyloides” and “strongyloidiasis” as a primary or secondary discharge diagnosis for the period January 1, 1993, to December 31, 2003. The microbiology records of all patients identified were reviewed to confirm the presence of SS in clinical specimens during hospitalization. Outpatients with strongyloidiasis were excluded from the study so that chart review could be performed.

Identification of strongyloidiasis was made on the basis of morphologic identification of organisms on formalin acetate concentration specimens from stool or sputum. Identification of migrating larvae on stool and respiratory cultures aided in the detection of organisms, although specific Strongyloides culture techniques were not undertaken. Two patients with the presumptive clinical diagnosis of strongyloidiasis had no microbiologic confirmation and were excluded from the study.

A tool designed to abstract patient health information was developed and used to summarize that data from the retrospective record review. Patient charts were reviewed in detail for underlying medical conditions, medications, symptoms, signs, relevant laboratory and microbiology findings, clinical course, and mortality rate at that particular admission. Cases were divided into patients who had DSS defined as the presence of SS in sputum, other body fluids, or invasion of larvae into tissues as seen on biopsy27 and patients with GISS defined as the identification of SS larvae only in stool samples.

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Results

Demographics

Thirty patients were identified for inclusion in the study. Of the 30 patients, 19 (63%) were males. The median age was 61 years (range, 17-79 years). Of the 30 patients, 13 (43%) had DSS, and the remaining 17 patients (57%) had SS infection apparently confined to the intestinal tract. The demographics of patients with DSS and GISS did not differ significantly. All patients were residents in the Commonwealth of Kentucky.

Underlying Conditions

The underlying conditions in patients with strongyloidiasis are summarized in Table 1. Patients with GISS and DSS were not statistically different in diagnoses of chronic lung or renal disease, malignancy, transplantation, or connective tissue disease. Although 35% of patients (6/17) with GISS had no underlying medical conditions compared with only 8% of patients (1/13) with DSS, this difference was not statistically significant. Corticosteroid use, with or without other immunosuppressive agents, was more common in patients with DSS than in patients with GISS (P = .002).

Clinical Manifestations

The clinical signs and symptoms for patients with GISS and DSS are summarized in Table 2. The most common

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symptoms and signs of SS infection were gastrointestinal (nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal bleeding). These symptoms were independent of DSS or GISS status. Fever was likewise very common in both groups ($P = .26$). Patients with DSS were more likely to have respiratory symptoms (ie, dyspnea, cough, chest pain, or respiratory failure) than patients with GISS ($P < .001$). There were no patients in this study who were totally asymptomatic for infection.

Laboratory Findings

The most common laboratory abnormality was hyponatremia, which was noted in 60% of patients (18/30) in this study. The mean sodium level for patients with hyponatremia was 127 mEq/L (127 mmol/L). Hyponatremia was more commonly diagnosed in patients with DSS (9/13 [69%]); however, even patients with GISS were noted to be hyponatremic more often than not (9/17 [53%]). Peripheral eosinophilia was noted in only 7 patients in the study population (23%), a finding that was independent of DSS or GISS status ($P = 1$). Of 30 patients, 8 (27%) had elevated liver enzyme levels.

Diagnosis

The diagnosis of GISS was made by a positive stool sample for ova and parasites in 16 patients and a duodenal aspirate in 1 patient. In patients with DSS, the diagnosis was made by sputum ova and parasite examination for 8 patients and bronchoalveolar lavage (BAL) fluid for 1. Of the 9 patients, 5 had SS identified in multiple sites, including stool and various tissue biopsy specimens, in addition to sputum or BAL fluid. Two patients with DSS had positive stool examinations for ova and parasites in addition to tissue biopsy. In the remaining 2 patients with DSS, the diagnosis was made only by biopsy. Tissues in which SS was identified by biopsy included the following: lung, 4; stomach, 3; skin, 1; and appendix, 1. In 1 patient with DSS, larval forms of the nematode were detected on autopsy in almost every organ tissue, including lungs, brain, heart, gastrointestinal tract, bladder, prostate, and lymph.

Table 1
Underlying Medical Conditions in Patients With Strongyloides stercoralis Infection*

<table>
<thead>
<tr>
<th>Underlying Condition</th>
<th>DSS (n = 13)</th>
<th>GISS (n = 17)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lung disease</td>
<td>7 (54)</td>
<td>5 (29)</td>
<td>.18</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4 (31)</td>
<td>4 (24)</td>
<td>.70</td>
</tr>
<tr>
<td>Transplant recipients</td>
<td>4 (31)</td>
<td>2 (12)</td>
<td>.36</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>1 (8)</td>
<td>4 (24)</td>
<td>.35</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>2 (15)</td>
<td>2 (12)</td>
<td>1</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>10 (77)</td>
<td>3 (18)</td>
<td>.002</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>5 (38)</td>
<td>3 (18)</td>
<td>.24</td>
</tr>
<tr>
<td>Corticosteroids and/or immunosuppressive therapy</td>
<td>11 (85)</td>
<td>4 (24)</td>
<td>.003</td>
</tr>
<tr>
<td>No underlying medical conditions</td>
<td>1 (8)</td>
<td>6 (35)</td>
<td>.10</td>
</tr>
</tbody>
</table>

DSS, disseminated S. stercoralis; GISS, gastrointestinal S. stercoralis.
* Data are given as number (percentage).
† The Fisher exact test was used to calculate the $P$ values, except for the first value, which was calculated using the $\chi^2$ test.

Table 2
Most Common Symptoms and Signs of Strongyloides stercoralis Infection*

<table>
<thead>
<tr>
<th>Symptom or Sign</th>
<th>DSS (n = 13)</th>
<th>GISS (n = 17)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and/or vomiting</td>
<td>5 (38)</td>
<td>11 (65)</td>
<td>.15</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (23)</td>
<td>10 (59)</td>
<td>.07</td>
</tr>
<tr>
<td>Abdominal pain or tenderness</td>
<td>6 (46)</td>
<td>7 (41)</td>
<td>.79</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>3 (23)</td>
<td>2 (12)</td>
<td>.63</td>
</tr>
<tr>
<td>Any gastrointestinal symptom or sign</td>
<td>10 (77)</td>
<td>14 (82)</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (31)</td>
<td>2 (12)</td>
<td>.36</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (23)</td>
<td>0 (0)</td>
<td>.07</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2 (15)</td>
<td>0 (0)</td>
<td>.18</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>10 (77)</td>
<td>5 (29)</td>
<td>.025</td>
</tr>
<tr>
<td>Any respiratory symptom or sign</td>
<td>13 (100)</td>
<td>6 (35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fever or chills</td>
<td>10 (77)</td>
<td>9 (53)</td>
<td>.26</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3 (23)</td>
<td>2 (12)</td>
<td>.63</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0)</td>
<td>3 (18)</td>
<td>.24</td>
</tr>
<tr>
<td>Mental status changes</td>
<td>1 (8)</td>
<td>2 (12)</td>
<td>1</td>
</tr>
<tr>
<td>Skin rash</td>
<td>1 (8)</td>
<td>1 (6)</td>
<td>1</td>
</tr>
</tbody>
</table>

DSS, disseminated S. stercoralis; GISS, gastrointestinal S. stercoralis.
* Data are given as number (percentage).
† The Fisher exact test was used to calculate the $P$ values, except for the first and third values, which were calculated using the $\chi^2$ test.
nodes. The present study design did not allow for the distinction between acute and chronic SS infection.

**Associated Bacterial and Yeast Infections**

Of the 30 patients, 16 (53%) with SS were found to have extraintestinal infections. Of these 16 patients, an enteric organism was identified in 13 (Table 3); 11 had enteric bacteria, with *Enterococcus faecalis* the most common. Other bacteria included *Escherichia coli*, *Enterobacter cloacae*, *Streptococcus mitis*, and an unidentifiable gram-negative rod. Three patients had a systemic candidal infection in association with SS infection; 1 patient had concurrent bacterial and candidal infections. *Candida parapsilosis* was found in 2 patients and *Candida glabrata* in 1 (Table 3). Three patients had septic shock diagnosed clinically and confirmed by Swan-Ganz catheter measurements with negative blood cultures; 2 of the 3 were already receiving antibiotics before blood cultures were obtained. Of the 3, 2 had clinical and radiographic findings of pneumonia with negative sputum cultures. These 3 patients were treated for presumptive gram-negative sepsis and responded to treatment.

Bacterial and fungal infections were noted in patients with DSS and in patients with only GISS. In DSS, 8 (62%) of 13 were found to have an associated infection, including sepsis or fungemia, compared with 8 (47%) of 17 in GISS (P = .43). In 6 (46%) of 13 patients with DSS, an enteric organism was isolated, compared with 7 (41%) of 17 patients with GISS (P = .79). Patients with DSS who had an associated infection with an identified enteric organism were more likely to be immunocompromised (5/6 [83%]), compared with only 2 (29%) of 7 patients with GISS who had an enteric coinfection. Because of the small numbers in both groups, this difference was not statistically significant (P = .10).

**Mortality**

The overall in-hospital mortality for all patients in this study was 23% (7/30). Patients with SS who had a superimposed enteric infection had an overall mortality of 25% (4/16); the death rate for patients with DSS was 31% (4/13) and for GISS was 18% (3/17) (P = .67).

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. of Patients</th>
<th>Sites of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>6*</td>
<td>Sepsis, bacteremia, pneumonia</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>2</td>
<td>Meningitis</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>1</td>
<td>Sepsis, spontaneous bacterial peritonitis</td>
</tr>
<tr>
<td>Gram-negative rod</td>
<td>1</td>
<td>Meningitis</td>
</tr>
<tr>
<td><em>Streptococcus mitis</em></td>
<td>1</td>
<td>Endocarditis</td>
</tr>
<tr>
<td><em>Candida parapsilosis</em></td>
<td>2*</td>
<td>Candidemia, peritonitis</td>
</tr>
<tr>
<td><em>Candida glabrata</em></td>
<td>1</td>
<td>Candidemia</td>
</tr>
<tr>
<td>No organisms identified (presumed sepsis)</td>
<td>3</td>
<td>Sepsis based on clinical manifestations</td>
</tr>
</tbody>
</table>

* One patient had infection with *C parapsilosis* and *E faecalis*.

**Discussion**

This article summarizes the cases of strongyloidiasis identified in hospitalized patients at a tertiary care facility during a 10-year period. Strongyloidiasis was decidedly uncommon in hospitalized patients, with only 30 cases diagnosed. This finding is in marked contrast with those of earlier studies performed in the region demonstrating unsuspected intestinal infection in 6.1% of hospitalized and 2.6% of domiciliary patients in Tennessee,28 between 3% and 5% of school-aged students in Kentucky,2,3 and 4% of college-aged students in Berea, KY.2 Taking these prevalence studies into consideration, it is likely that the current study population represents the “tip of the iceberg” for *Strongyloides* infections during this period with only the most symptomatic hospitalized patients being identified. In comparison with the 3-year study of patients admitted to the University of Kentucky Medical Center in Lexington (1975-1977) in which 53 patients were found to be infected with SS,2 the current 10-year rate of 30 patients suggests that the prevalence of disease with this parasite may be decreasing. In fact, SS is no longer the most common parasite to be detected in stool specimens at the University of Kentucky Medical Center.29

Not surprisingly, in the present study, clinical manifestations varied according to whether the patient had DSS or GISS. All patients with DSS had at least 1 pulmonary symptom such as cough, dyspnea, chest pain, or respiratory failure. In contrast, only 6 of 17 patients with GISS had pulmonary symptoms (P ≤ .001). Of the 13 patients with DSS, 10 required mechanical ventilation compared with 5 of 17 patients with GISS (P = .025). In 7 of 13 patients with DSS, the diagnosis was made by the finding of SS in multiple specimens from 2 or more sources. In 4 patients with DSS, the nematode was found in only 1 respiratory specimen, sputum or BAL fluid. In the remaining 2 patients with DSS, the diagnosis was more challenging and was made only by lung biopsy. We recognize that this is a retrospective study with variation in diagnostic methods used to detect infected patients. Of patients with DSS, 77% were receiving corticosteroids, a...
well-known risk factor for dissemination, compared with only 18% of patients with GISS (P = .002). This factor might have led to more extensive investigations in this group of immunocompromised patients that eventually revealed dissemination.

Of note, however, is the occurrence of invasive infections due to enteric organisms that were seen in 41% of patients with SS infection that was apparently limited to the gastrointestinal tract. Even though dissemination of the larvae was not definitively demonstrated by cytologic or tissue morphologic features, the presence of enteric organisms causing disease in nongastrointestinal sites likely indicates that larval transmigration had occurred in these patients. In a 1992 review, Genta\(^5\) suggests that a certain proportion of larvae normally molt and reinfect patients to maintain chronic infections with *Strongyloides* as part of the normal life cycle. In contrast with previous studies in which enteric gram-negative rods produced the majority of extraintestinal infections,\(^6,11,12,16,22,23,26\) the present study demonstrated that more than 70% of bloodstream infections were caused by enteric gram-positive cocci or yeast.

The mortality rate of DSS in this study was 31%, which was comparable to that seen in a 1995-1999 study (26% mortality),\(^12\) but is significantly lower than the 52% to more than 80% mortality rate in other studies.\(^11,16,26\) It should be noted that the highest mortality rates were seen in the study by Link and Orenstein,\(^26\) in which only patients with associated bacterial infections were included. The mortality rate of 18% in patients with GISS in this study seemed higher than expected for this condition and could be attributed to the serious enteric bloodstream infections.

Eosinophilia was a poor predictor for SS infections whether disease was disseminated or localized to the gastrointestinal tract. In previous studies looking at patients with DSS, eosinophilia was detected in 9% to 34% of patients,\(^6,11,16\) whereas rates of eosinophilia in patients with GISS ranged between 10% and 90%.\(^3,6,11,28\) In the present study, there was no difference in the proportion of patients with elevated eosinophil counts with GISS or DSS (23% and 24%, respectively during the entire hospital course).

This study was limited by the fact that it was retrospective and the number of patients in each group was too small to provide statistical strength. In addition, the study might have overestimated the risk of enteric coinfections in patients with GISS by excluding outpatients and including only hospitalized patients who were more likely to have such infections. As a result, a significant difference in the incidence of invasive enteric infections between DSS and GISS groups might have been obscured by this selection bias. However, our observation that underlying SS in patients admitted with serious infection due to enteric pathogens without obvious dissemination is important. The association may represent silent dissemination or asymptomatic transmigration of the parasite with resultant significant enteric infections. The presence of significant infections due to enteric pathogens, particularly in patients with no obvious reason to have such infections, should stimulate clinicians to search for SS infections.

**Conclusions**

Infection with SS predisposes to serious invasive infections caused by gastrointestinal flora, including enteric bacteria and *Candida* species. This study suggests that clinicians should look for underlying strongyloidiasis in patients with serious infections due to enteric organisms without a readily identifiable source in the presence or absence of peripheral eosinophilia. Patients with DSS and GISS in this study were found to be at risk of serious infections with enteric organisms. SS should be looked for in sputum, other body fluids, and tissue biopsy specimens of involved organs whenever possible to document dissemination. Failure to detect SS in specimens other than stool should not divert treating physicians from the fact that patients with apparent GISS remain at risk for severe extraintestinal infections caused by enteric pathogens as demonstrated in this study.

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