Review

Strongyloidiasis: A Multifaceted Disease

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Strongyloidiasis is a parasitic infection caused by 2 species of the intestinal nematode *Strongyloides*. The more common and clinically important pathogenic species in humans is *Strongyloides stercoralis*. The other species, *Strongyloides fuelleborni,* is found sporadically in Africa and produces limited infections in humans.[1,2] Strongyloidiasis affects approximately 100 million individuals worldwide, and this infection is endemic to many parts of the world, including the Southeastern United States, South Asia, Latin America, and sub-Saharan Africa.[1,3-5] In some rural areas of the Appalachian region and the Southeastern United States, the prevalence of strongyloidiasis can reach 4%.[6]

The unique and complex life cycle of this parasite starts when invasive filariform larvae in contaminated soil, water, or feces penetrate the skin and proceed via venous circulation to the lungs. After penetrating the alveoli, the larvae ascend the tracheobronchial tree and are swallowed. Once in the gastrointestinal tract, the larvae mature into adult females, which live threaded in duodenal and proximal jejunal mucosa.[1,5-7]

Adult females of this parasite can produce up to 40 eggs per day. These eggs hatch into rhabditiform larvae, which can either be passed in stool—continuing the soil-based cycle—or remain in the host and cause autoinfection. Autoinfection involves the premature transformation of noninfective rhabditiform larvae into infective filariform larvae. Infective larvae can penetrate intestinal mucosa (internal autoinfection) or the perineal skin area (external autoinfection), thus perpetuating the infection. The autoinfection phenomenon can lead to a dormant but persistent infection.[1,7] Of note, *S. stercoralis* is the only helminth that secretes larvae in stool. Thus, the identification of eggs in a fecal smear is unlikely.

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The term "hyperinfection syndrome" is defined as an amplification of the normal life cycle of *S. stercoralis* without the spread of larvae outside of the usual migration pattern (eg, gastrointestinal tract, lungs). Disseminated disease, in contrast, refers to the massive migration of infective larvae from the gastrointestinal tract not only to the lungs, but also to other organs that are not involved in the normal helminthic life cycle.[1] In this situation, the mortality rate can be as high as 80%.[1] Several risk factors are associated with the development of disseminated strongyloidiasis, including immune deficiency, hematologic malignancies, administration of steroids, human T-lymphotropic virus-1 infection, chronic alcoholism, renal failure, HIV infection, diabetes, advanced age, and transplantation.[7,8]

Approximately half of *Strongyloides* infections are asymptomatic.[1,7] The most common clinical manifestations are usually related to the gastrointestinal tract. These symptoms are vague and nonspecific, and they include—but are not limited to—anorexia, diarrhea, abdominal pain, flatulence, and constipation. In advanced cases, malabsorption syndromes, paralytic ileus, intestinal/duodenal obstruction, and gastrointestinal bleeding may occur.[1,6,7] Respiratory symptoms, such as coughing and wheezing, occur during the larvae's primary migration phase in the pulmonary parenchyma (Löffler syndrome). Severe pulmonary symptoms, such as dyspnea, pleuritic pain, pleural effusion, and hemoptysis, are observed only with disseminated disease.[1,6,7] If strongyloidiasis is suspected, the skin should be examined systematically, as *Larva currens* (racing larva) is a pathognomonic cutaneous manifestation of *Strongyloides* external autoinfection.[1,9]

Few cases of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and *Strongyloides* infection have been reported in the literature. Interestingly, in most of these cases, an extensive involvement of the lung parenchyma or central nervous system is present. However, in the case presented by Khanna and associates, the mechanism through which *S. stercoralis* caused SIADH remains unknown.[10-14]

Laboratory findings are usually nonspecific and may include intermittent eosinophilia (mainly in the acute phase), anemia, hypocholesterolemia, hypoalbuminemia, and increased serum immunoglobulin (Ig)E concentration. In patients with chronic and disseminated disease, eosinopenia and low IgE levels have been associated with poor prognosis.[1,8]

The presence of larvae in stool is diagnostic of strongyloidiasis. This method of parasite detection is easily performed, broadly available, and inexpensive. However, the diagnostic yield of a single specimen is approximately 30%. Examining 5 or more stool samples at different time points could increase the sensitivity of fecal smear

testing 3-fold.[15] To enhance larvae recovery, special tools can be used, such as Baermann funnels, Harada-Mori filter paper, and agar plates.

Duodenal biopsies are invasive. However, the examination of a duodenal specimen for ova and larvae has been shown to be the most sensitive diagnostic procedure for *S. stercoralis*, with a false-negative frequency of less than 10%.[15,16] Endoscopic findings include duodenal mucosal edema, erythema, hemorrhagic spots, ulcerations, and, in some cases, megaduodenum. Duodenal white villi are also a common endoscopic feature and should alert the physician to the possibility of strongyloidiasis.[17,18] Differential endoscopic diagnoses include tuberculosis, primary intestinal lymphoma, Crohn's disease, eosinophilic gastroenteritis, celiac sprue, Whipple disease, and gastrointestinal stromal tumor.

In cases of disseminated infection, *S. stercoralis* can also be identified in bronchoalveolar lavage, sputum, cerebrospinal fluid, skin, urine, and ascites.[19] Serologic tests are indicated when infection is suspected and *S. stercoralis* cannot be demonstrated by standard diagnostic evaluation. Although indirect hemagglutination and indirect fluorescent antibody tests have been used, the use of enzyme-linked immunosorbent assay is currently recommended, due to its greater sensitivity. Despite their high specificity and sensitivity, immunodiagnostic tests have limitations, including false-positive results due to cross-reactions with other parasitic infections, such as filariasis and acute schistosomiasis, which occur in 8–16% of cases. The enzyme-linked immunosorbent assay is also useful for monitoring response to therapy, as antibody titers decrease significantly within the first 6 months of treatment.[2,20]

Although imaging studies are nonspecific, the physician should be alerted to the possibility of strongyloidiasis upon noting abnormalities restricted to the duodenum and proximal jejunum (ie, stenosis, ulceration, or thickening of the intestinal wall) on computed tomography scans and upper gastrointestinal series.[21] In some cases in the literature, confirmation of the strongyloidiasis diagnosis was not possible, and patients underwent surgical intervention for intestinal obstruction and/or paralytic ileus, with dismal results.[22]

Medical treatment should be achieved in all cases—even in the absence of symptoms—in order to prevent dissemination of the parasite. The drug of choice for treatment of strongyloidiasis is ivermectin (Stromectol, Merck) given at a dose of 200 mcg/kg of body weight daily for at least 2 days. In cases of disseminated disease, it may be necessary to prolong or repeat the therapy 14 days after the initial treatment. Ivermectin binds selectively to glutamate-gated chloride ion channels in invertebrate nerve and muscle cells, causing cell death. Although few side effects have been reported, ivermectin should be avoided during pregnancy.[1,2,23] Alternative treatments include albendazole (Albenza, GlaxoSmithKline) and thiabendazole. In cases of disseminated strongyloidiasis, combination therapy of albendazole and ivermectin can be used. In patients with severe ileus or intestinal/duodenal obstruction, rectal administration of ivermectin or thiabendazole has been suggested.[24,25] No parenteral preparation of these anthelmintics is available for use in humans, although subcutaneous veterinary ivermectin has been successfully utilized in the treatment of strongyloidiasis unresponsive to standard oral therapy or when enteral administration is not possible (ie, severe ileus or intestinal obstruction).[26-28]

In summary, SIADH is a rare complication of *S. stercoralis* infection. The large spectrum of clinical manifestations and lack of a classic clinical syndrome make the final diagnosis of strongyloidiasis extremely difficult. Therefore, a high index of suspicion is needed for accurate and early diagnosis of this uncommon complication of *S. stercoralis* hyperinfection, particularly in patients from areas where this parasite is endemic.

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