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Strongyloides stercoralis hyperinfection: a dreaded but still missed diagnosis

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ABSTRACT

Strongyloides stercoralis (*S. stercoralis*), an intestinal nematode, is endemic in tropical and subtropical regions, being less prevalent in temperate climates. The number of infected persons worldwide ranges between 10 million and 100 million people. In Brazil the reported prevalence is 13%. Chronic infection may be asymptomatic or accompanied by gastrointestinal and respiratory symptoms. Under immunosuppressive conditions, the infection assumes serious proportions frequently accompanied by septic shock, disseminated intravascular coagulopathy and respiratory distress syndrome. The authors report a case of a 50-year-old female patient who was a chronic user of glucocorticoids and had been seeking medical attention for two months because of continuous gastrointestinal symptoms. She was admitted to the emergency room with clinical signs of septic shock and died after four days despite an adequate antibiotic regimen, vasopressor drugs, and ventilatory support. The autopsy revealed the unsuspected finding of *S. stercoralis* hyperinfection and septicemia.

Keywords: *Strongyloides stercoralis*; Glucocorticoids; Immunocompromised host; Shock, septic.

CASE REPORT

A 50-year-old female patient, coming from the rural area of a Brazilian northeastern state, sought emergency care complaining of severe lower abdominal pain irradiating to the lumbar region, nausea, vomiting, fever, and constipation during the last five days. She referred a two-month history of less severe generalized abdominal pain and diarrhea, *having sought* medical treatment in her neighborhood without any improvement. She had a history of hypertension, dyslipidemia, heart failure, and a rheumatologic disease, which she called **"**rheumatism**"** and was taking furosemide, captopril, and spironolactone. She has also been taking prednisone for 20 years in an average dose of 40 mg per day, and she had recently started herself on sodium diclofenac.

On admission, physical examination revealed an ill-looking cushingoid and pale patient, cyanotic extremities, decreased tissue perfusion,

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and marked lower limbs edema. She was also slightly disoriented. Vital signs showed: blood pressure = 50/30 mmHg, pulse = 110 beats/minute, respiratory rate = 24 respiratory movements/minute, axillary temperature = 37 °C. The abdomen was distended and diffusely tender; bowel sounds were decreased. The rebound tenderness test was negative and liver was palpable up to 1 cm below the right costal margin. The examination of the heart and lungs was unremarkable. The initial treatment consisted of extracellular volume repletion with saline through a central venous catheter, ceftriaxone, metronidazole, hydrocortisone, and noradrenaline. The patient was referred to the intensive care unit (ICU). The initial laboratory workup is shown in Table 1.

The abdominal ultrasound revealed a minimal amount of free fluid in the abdominal cavity, a diffuse and marked decrease of the small bowel peristaltic movements, and liquid distention. The anti-HIV serology was negative.

The patient remained hemodynamically unstable throughout her stay in the ICU, requiring continuous administration of norepinephrine and vasopressin. Her initial clinical presentation did not change despite all therapeutic efforts. Petechiae and ecchymoses appeared on the abdomen and upper limbs on the third day of hospitalization. During the following days, her mental status worsened requiring orotracheal intubation and mechanical ventilation. Multi sensitive *E. coli* was isolated in the blood culture. She did not present any clinical improvement and died on the fourth day of hospitalization.

AUTOPSY

Multiple petechial skin lesions were detected in the abdominal wall and limbs (Figure 1A). The patient also had generalized edema of the limbs and mild ascites, consistent with fluid therapy. Larvae of *S. stercoralis* were detected in the dermis of the skin lesions, along with foci of hemorrhage (Figure 1B). No associated inflammatory cells were seen on the skin.

The lungs were boggy and heavy. Microscopic examination revealed diffuse alveolar damage (Figure 2A), consistent with septic shock and multiple areas of recent and previous alveolar hemorrhage, with hemosiderin-laden macrophages. *S. stercoralis* larvae were detected occasionally, associated with a giant cell granulomatous reaction (Figure 2B).

Flat lesions consistent with healing ulcers were detected along with petechial foci of hemorrhage in small bowel mucosa. Multiple small foci of hemorrhage were also seen on abdominal serous surfaces. *S. stercoralis* larvae were detected in duodenal mucosa (Figure 3A) and occasionally in omentum (Figure 3C). Larvae were not detected in other organs or tissues.

Table 1 – Admission laboratory workup

		RV			RV
Hemoglobin	12.6	12.3-15.3 g/dL	Creatinine	2.9	0.4-1.3 mg/dL
Hematocrit	37.4	36.0-45.0%	Potassium	4.7	3.5-5.0 mEq/L
Leucocytes	19100	4.4-11.3 10^3/mm^3	Sodium	110	136-146 mEq/L
Bands	17	1-5%	ALT	28	9-36 U/L
Segmented	72	45-70%	AST	44	10-31 U/L
Eosinophils	1	1-4%	LDH	336	120–246
Basophils	0	0-2.5%	CK	933	26-140 U/L
Lymphocytes	8	18-40%	Amylase	11	30-118 U/L
Monocytes	2	2-9%	Lipase	15	<60 U/L
Platelets	382.10^3	150-400$10^3$/mm^3	Total protein	4.9	7-8 g/dL
CRP	142	<5 mg/L	Albumin	2.3	3-5 g/dL
BUN	62	5-25 mg/dL	PT (INR)	1.21	1

AF = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine phosphokinase; CRP = C reactive protein; INR = international normalized ratio; LDH = lactic dehydrogenase; PT = prothrombin time; RV = reference value.

Acute hematogenous pyelonephritis with multiple small subcapsular abscesses was grossly evident on the left kidney (Figures 4A and 4B).

Bacterial hematogenous spread was also seen in the spleen, which showed acute inflammation, septic emboli and areas of acute infarction (Figures 5A and 5B).

Systemic findings of sepsis and shock were also observed in the adrenal glands (lipid depletion and hemorrhagic foci), liver (necrosis on zone 3), renal cortex (acute tubular necrosis), pancreas (foci of ischemic pancreatitis), and heart (diffuse dilatation of chambers and softening of the myocardium consistent with sepsis-induced cardiomyopathy). Focal hyaline thrombi, consistent with disseminated intravascular coagulation, were detected in the lungs and glomeruli.

Altogether, the autopsy findings were consistent with *S. stercoralis* hyperinfection syndrome with superimposed Gram-negative bacterial septicemia and septic shock.

DISCUSSION

The nematode *S. stercoralis* was discovered and first described by Louis Norman and Bavay en 1876 in France,[1] and reported by Ribeiro da Cruz as the etiologic agent of strongyloidiasis in 1880 in Brazil.[2] This intestinal nematode is endemic in tropical and subtropical regions, being less prevalent in temperate climates.[3] The number of infected persons worldwide ranges between 10 million and 100 million people. In Brazil, the reported prevalence is 13% in a randomly examined population.[4,5] Low socioeconomic status,[6] institutionalization in mental

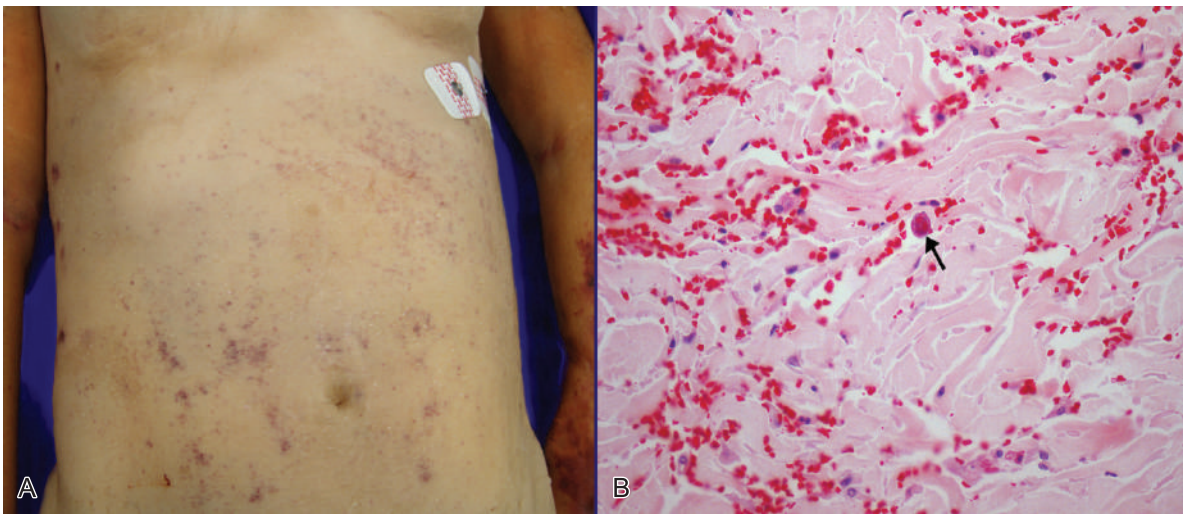

Figure 1 – A - Petechial lesions on abdominal skin; **B -** Larvae of *S. stercoralis* (arrow) in the dermis within foci of hemorrhage (H&E, 400x).

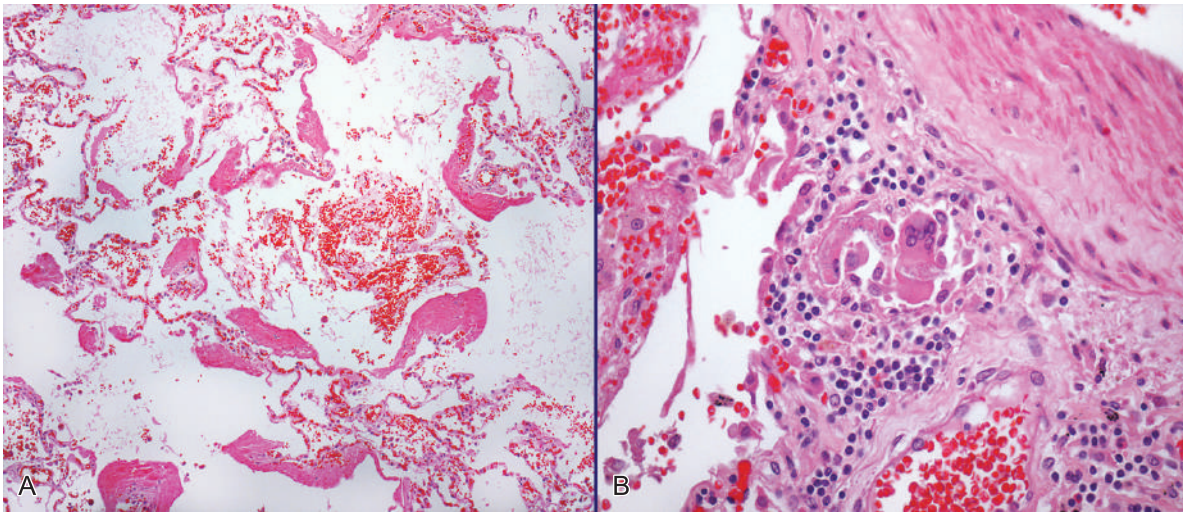

Figure 2 – A - Hyaline membranes and hemorrhage on alveoli (H&E; 200×); **B -** Giant cell reaction to *S. stercoralis* larvae in the interstitium of the lung (H&E, 400×).

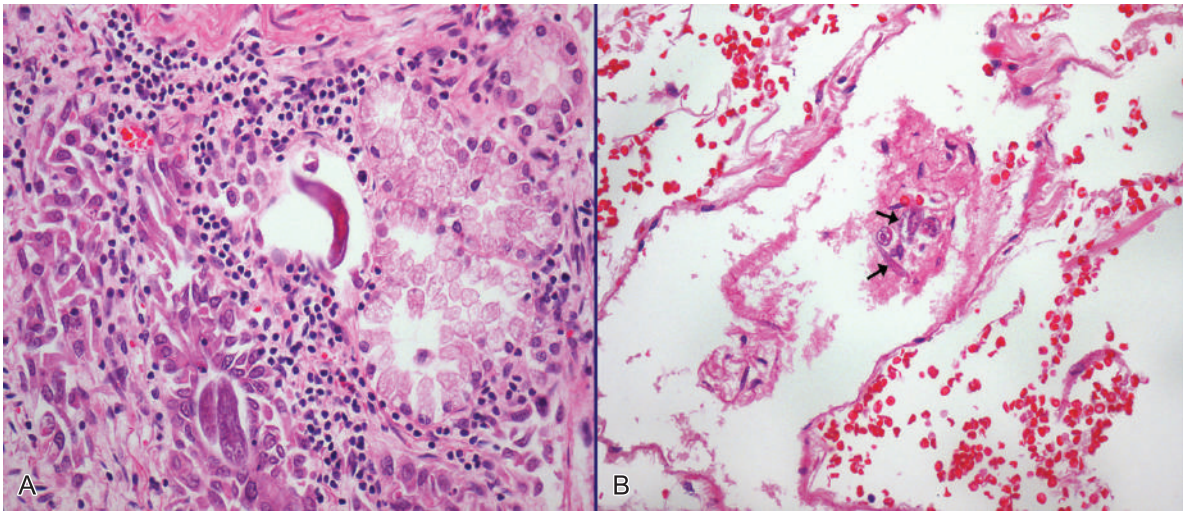

Figure 3 – A - *S. stercoralis* larvae in duodenal mucosa (H&E, 400×); **B -** *S. stercoralis* larvae and histiocyte reaction within omental tissue (H&E, 400×).

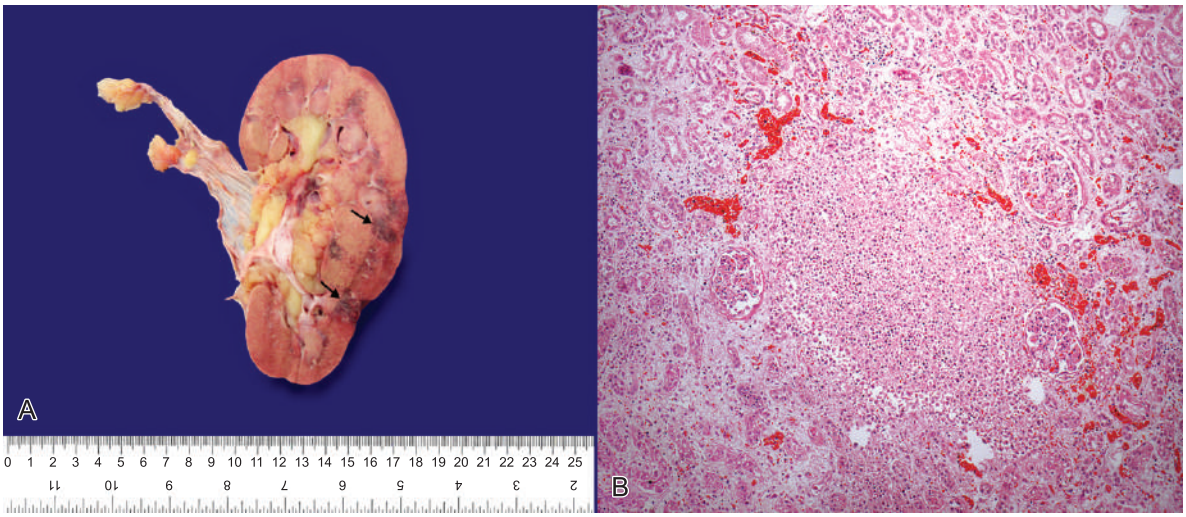

Figure 4 – A - Longitudinal section of the left kidney. Note cortical abscesses and hemorrhage (arrows); **B -** Hematogenous abscess within renal cortex (H&E, 200×).

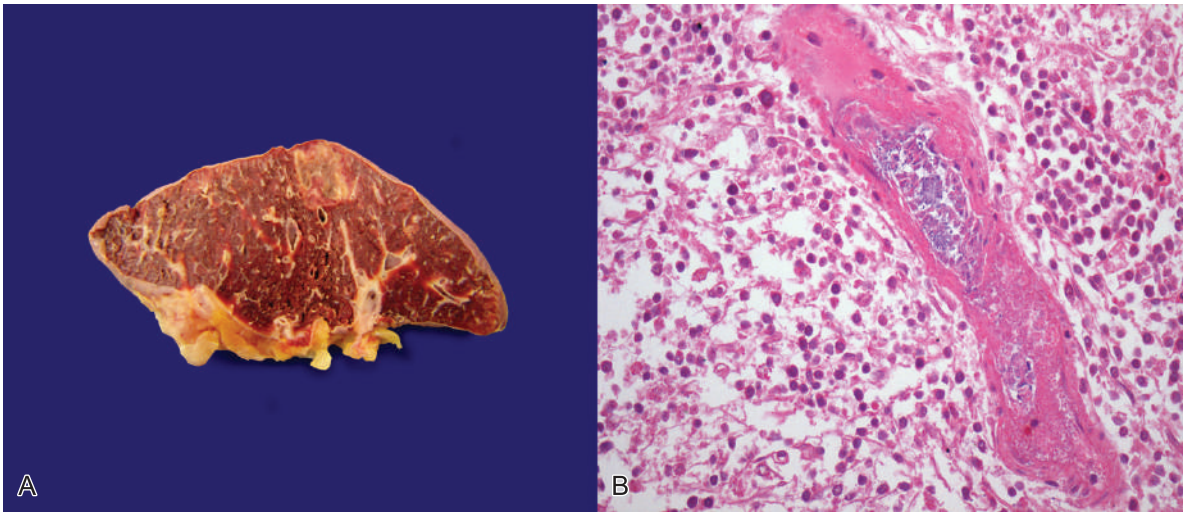

Figure 5 – A - longitudinal section of the spleen showing acute subcapsular infarction and initial cavitation; **B -** Septic embolus in arteriole of the spleen. Bluish material corresponds to bacterial colonies (H&E, 400×).

retardation clinics,[7] as well as occupations that imply close contact with contaminated soil (e.g. farming) increase the risk of infection. The patient described in this case report lived in a small village in the rural area in northeastern Brazil, a region known by its high prevalence of helminthic infections.

The *S. stercoralis* infection in humans occurs by the penetration of filariform larvae through the skin and dermis, although it has also been experimentally induced by oral administration of water contaminated by these larvae.[8] After dermal penetration, the filariform larvae reach the bloodstream and are carried to the lungs (where they may produce an eosinophilic pneumonitis), ascending the tracheobronchial tree to enter the gastrointestinal tract. The adult female worms embed themselves in the mucosa of the small bowel and produce eggs via parthenogenesis.[9-11] Within the intestinal lumen, the eggs hatch noninfective rhabditiform larvae, which are excreted, along with stool, into the environment.[12] Some rhabditiform larvae transform into invasive filariform larvae before being excreted. As such, they are capable of reinfecting the host by invading the intestinal wall or the perianal skin.[8,12] This auto infective cycle can occur at a low level throughout infection and allows subsequent generations to persist in the host indefinitely.[10,12]

Chronic infection with *S. stercoralis* is frequently asymptomatic, although symptoms may occur at the chronic stage, such as vomiting, diarrhea, constipation, weight loss, anal itching, urticaria, and asthma.[13] Under conditions associated with compromised host defenses (mainly cell-mediated immunity) the infection by *S. stercoralis* may become a fulminant fatal illness. The patient of this case report had a two-month history of abdominal pain and diarrhea, which did not improve despite medical intervention. These symptoms may represent the phase of increase in parasitic burden and intestinal invasion.

Transplant patients, patients receiving immunosuppressants, patients with cancer, acquired immunodeficiency syndrome (AIDS) or infection with HTLV-I, malnutrition, chronic alcoholism with liver disease, advanced age, diabetes mellitus, hypogammaglobulinemia, collagen diseases (e.g. rheumatoid arthritis and systemic lupus erythematous), sarcoidosis, postsurgical state, are more likely to develop severe forms of the disease.[14-20]

Glucocorticoids are the immunosupressor drugs most specifically associated with the transformation of chronic strongyloidiasis into hyperinfection,[21] doubling or tripling this risk.[22] Hyperinfection is a life-threatening condition with an approximately 50% mortality rate, generally due to Gram-negative septicemia.[23]

A TH2-type cellular immune response is normally required to control parasite infections[24-26] through the production of cytokines and Immunoglobulin E, which eliminate the organism.[26,27] Corticosteroids increase apoptosis of lymphocytes, reduce circulating numbers of eosinophils and ultimately decrease the mast cell response to *S. stercoralis* antigens in the intestines.[28] The first blood cell count of this patient showed a low eosinophil count, which, unfortunately, may have lowered the suspicion of the helminthic hyperinfection. This low eosinophil count in the presence of the helminthic infection may have resulted from chronic corticoid usage.

Some authors have also suggested that glucocorticoids may have a direct effect on the parasites, accelerating the transformation of rhabditiform to invasive filariform larvae or by rejuvenating reproductively latent adult females.[16] The effect of these drugs could also be similar to ecdysteroid (the hormone that triggers the process of moulting), triggering the dreaded outcome of severe infections.[14,16,17]

Gram-negative bacteria and other bowel flora may gain access to the bloodstream through ulcers in the bowel or by transport on the surface of migrating larvae.[21,28,29]

The severe and potentially fatal infections caused by *S. stercoralis* are known as hyperinfection syndrome and disseminated strongyloidiasis,[14] rarely observed in immunocompetent individuals. The hyperinfection syndrome is characterized by an acceleration of life cycle and hyperinfection, and by an increased parasite burden within the sites of the nematode cycle. The disseminated strongyloidiasis is defined by the presence of parasites in organs outside their habitual life cycle, such as liver, central nervous system, and urinary tract.[19]

The clinical features of *S. stercoralis* hyperinfection may vary widely; the onset may be acute or insidious. Most cases are similar to chronic strongyloidiasis associated with bacteremia and

sometimes septic shock, disseminated intravascular coagulation, renal and respiratory failure.[30,31] Disseminated infection refers to the migration of larvae to organs beyond the range of pulmonary auto infective cycle, but does not imply a greater severity of disease.[16] At the admission of our patient to the emergency department, the clinical picture was compatible with septic shock, confirmed by the autopsy findings and the positive blood culture for *E. coli,* one of the most frequent bacteria associated with *S. stercoralis* hyperinfection.

Dermatologic manifestations, in either hyperinfection or disseminated disease, comprise linear streaks, plus petechial and pruritic rashes on trunk, thighs, and buttocks. Biopsies of skin lesions may reveal the presence of larvae, as in the case presented here.

Many cases of strongyloidiasis are mistaken for pneumonia,[32] inflammatory bowel disease[33] or systemic lupus erythematous.[34] Thus, physicians should always have a high degree of suspicion of strongyloidiasis when facing nonspecific gastrointestinal symptoms such as abdominal pain, diarrhea, vomiting, or newly diagnosed asthma, especially when associated (but not necessarily) to eosinophilia, as well as cases of Gram-negative septicemia of unclear origin .[35] Since there are reports of cases that occurred 20-50 years after exposure to the parasite, the lack of a history of recent travel or residence in endemic areas may not be relevant.[36] Even when suspected, the diagnosis may be missed due to the low sensitivity of stool examination. Eggs and larvae are present in less than 50% of the confirmed cases.[4] Other tests, such as duodenal biopsy or a search for larvae in duodenal aspirate, by endoscopy, are far more sensitive and reliable, but unfortunately not widely available. For this reason, empirical treatment is recommended for patients who will undergo some degree of immunosuppression, regardless of the presence of symptoms or history of exposure to endemic areas.[21]

Early diagnosis of *Strongyloides stercoralis* infection, a challenge to practitioners working in nonendemic areas, is associated to a favorable outcome even in the presence of hyperinfection.

Due to the low suspicion of *Strongyloides stercoralis* infection, patients in developed centers are exposed to the risk of underdiagnosis and of hyperinfection, when immunosuppressed, besides other medical errors.[21]

This case report reminds us of the danger of forgetting to include common diseases, such as helminthiases, in our differential diagnoses

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