CLINICAL VIGNETTE

A 55-year-old male immigrant with lymphoma and Gram-negative sepsis

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CASE PRESENTATION

A 55-year-old male immigrant from Iraq presented with progressive shortness of breath and hypotension. The illness started with diarrhea and headache, and began three weeks after the first cycle of chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) was administered for the patient's newly diagnosed lymphoma. On presentation, he was in septic shock and respiratory failure requiring mechanical ventilation. The patient had altered sensorium and neck rigidity. He had no rashes and no lymphadenopathy. His white blood cell count was 16.9×10^9 cells/L with 8% eosinophilia. Chemistry tests showed acute kidney injury with a creatinine level of 168.0 µmol/L. Chest x-ray showed multilobar pneumonia. His blood and sputum cultures grew *Escherichia coli*. Lumbar puncture performed 24 h after presentation showed pleocytosis and elevated protein level; however, the culture was negative. A diagnostic test was performed.

What is your diagnosis?

DIAGNOSIS

A stool wet mount was performed and revealed *Strongyloides* larvae (Figure 1). He was diagnosed with *E coli* septic shock incited by *Strongyloides* hyperinfection and dissemination. Chemotherapy, particularly steroids, was the trigger behind this syndrome. Despite aggressive supportive measures including ivermectin, the patient succumbed to multiorgan failure in the second week of his illness.

DISCUSSION

There are >50 species of *Strongyloides*, with *Strongyloides stercoralis* (threadworm) being the most common in humans (1). These helminthes affect millions of individuals worldwide and are most endemic in tropical and subtropical regions of the globe (2). The majority of reported infections in North America occur in immigrant populations; however, sporadic cases have been reported in the southeastern regions of the United States (3).

Infection begins when the filariform larva penetrates the skin (4). This event usually goes unnoticed although, on occasion, the patient may report localized, pruritic, erythematous, papular rash soon after larval penetration (larva currens). The larvae hematogenously spread to the lungs, where they migrate to the tracheobronchial tree, are coughed up and swallowed. Invasion of the lungs can cause asthma-like symptoms and pneumonitis. In the small intestine, the larvae burrow in the mucosa and molt twice to become adult worms. Through parthenogenesis, the adult female worm produces eggs that hatch into rhabditiform larvae, subsequently migrate to the colon and are mostly excreted in feces (4). Infection of the gastrointestinal (GI) tract is asymptomatic, although some patients may report nonspecific symptoms such as nausea and chronic diarrhea. A small percentage of the larvae mature into infective filariform larvae, which penetrate the colonic mucosa or perianal skin and reinfect the host. Larva currens is more likely to occur at the time of reinfection as opposed to the time of original infection. This cycle of maturation and autoinfection within the host leads to the persistence of this infection and may last for decades (4). It is worth mentioning that *Strongyloides* is the only clinically important helminthic parasite that can complete its entire life cycle within the human host (4).

Chronic *S stercoralis* infection is often asymptomatic and rarely presents with the nonspecific dermatological, GI or pulmonary symptoms described above (5). It carries low mortality unless the host's immunity wanes and, subsequently, the parasitic infestation progresses to more serious forms of infection (hyperinfection syndrome and/or disseminated disease) (5). The above two entities can be distinguished as follows.

In hyperinfection, the parasite burden increases and the cycle of autoinfection accelerates; however, the *Strongyloides* larvae continue to be confined to the organs normally involved in the autoinfection cycle (ie, GI tract and lungs). Severe GI symptoms, including abdominal pain, intestinal obstruction and ileus, may occur, and severe bronchospasm and acute respiratory failure requiring mechanical ventilation have been reported (6-9).

On the other hand, disseminated disease results from the migration of *Strongyloides* larvae to organs beyond the GI tract and lungs such as the brain, liver, kidneys and skin. Dissemination carries a formidable risk for morbidity and mortality (5). As the worm burrows through the intestinal mucosa, it carries with it colonic commensal organisms, mainly Gram-negative bacteria and, rarely, Gram-positive bacteria, such as *Streptococcus bovis*, and *Candida* (10). This causes bacteremia, meningitis and other secondary infections and, consequently, contributes to organ damage.

Risk factors that are known to promote the evolution of strongyloidiasis to hyperinfection syndrome and/or disseminated disease include: immunosuppressive therapy and the use of steroids in particular; hematological malignancies, especially lymphoma, bone marrow and renal transplantation; human T cell lymphotropic virus type 1 infection; HIV infection; hypogammaglobulinemia; and malnutrition (11,12).

Strongyloidiasis is largely unrecognized due to the low level of clinical suspicion and the low sensitivity of diagnostic tools (6). Eosinophilia is common in asymptomatic and symptomatic cases but is nonspecific (7). The diagnostic sensitivity of examining three stool samples for *S stercoralis* is approximately 50% (13). *Strongyloides* serology testing is available, with a reported sensitivity of 80% to 97% (14). Unfortunately, it cannot differentiate between previous, active or treated infections, although assessing trends in titres may be useful. Furthermore, it can be falsely negative in immunocompromised patients and falsely positive in the presence of other helminthic infections (15). In addition to the abovementioned tests, filariform larvae multiply exponentially in hyperinfection syndrome, and respiratory

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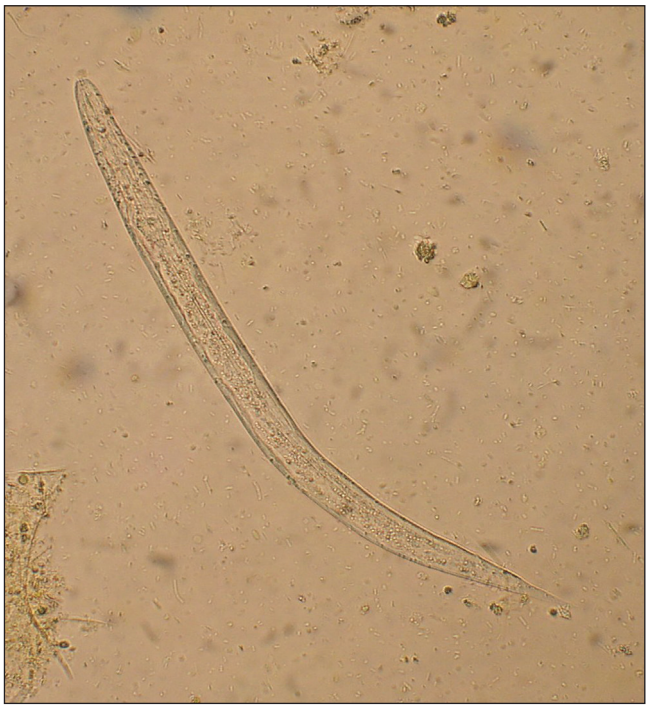

Figures 1) *Stool wet mount showing* Strongyloides stercoralis *larvae. Original magnification ×40*

fluid, peritoneal fluid, blood, bone marrow and cerebrospinal fluid should be examined for the presence of larvae (8,13).

Untreated hyperinfection syndrome is fatal and mortality remains >25% even with optimal therapy (16). Ivermectin is the drug of choice, with reported eradication rates of 80% (17). It is advisable to repeat the two-day course one week after the initial course with follow-up. Thiabendazole and albendazole are acceptable, although less effective, alternatives. Treatment efficacy can be documented after two weeks by examining the stool or the fluid of the upper small bowel for larvae (3). The trend in anti-*Strongyloides* antibody titres can also be used to confirm the adequacy of treatment (3). Furthermore, patients with *S stercoralis* hyperinfection are infectious and contact precautions are recommended to prevent nosocomial transmission (13).

Therapeutic failures are more common in immunosuppressed patients, and some experts recommend longer courses of treatment or albendazole and ivermectin combination therapy in this patient population (3). In the case of disseminated infection, albendazole and ivermectin may be continued until there is evidence of complete parasitic clearance (3).

Although there are no standard recommendations for screening patients for strongyloidiasis, it appears to be reasonable to screen patients at high risk for hyperinfection syndrome (14). Patients who have unexplained eosinophilia or who migrated from or travelled to endemic areas should be screened with serological testing for *Strongyloides* before initiating immunosuppressive therapy. Patients with positive serology can be treated empirically with ivermectin (3,5).

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