Abdominal Pain and Peripheral Eosinophilia

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A 69 year-old man presented to his primary care physician with abdominal discomfort. Medical history was notable for diabetes, chronic obstructive pulmonary disease with recent (one week prior) steroid use and hypertension. Surgical history was significant for a remote sigmoid hemicolectomy for diverticulitis with a synthetic mesh abdominal repair. He was admitted to the hospital for suspected gastroparesis. An upper GI series showed a distended stomach with delayed gastric motility. He underwent esophagogastroduodenoscopy and a duodenal biopsy was taken. He remained afebrile but had an elevated white blood cell count of 19.1 x 10^3/mcL (4.5 – 11.0 x 10^3/mcL) with 28.8 percent eosinophils on differential. Microscopic images of the duodenal biopsy are shown below.

What is your diagnosis?

Explication is on page 245
DIAGNOSIS: Duodenal strongyloidiasis.

DISCUSSION

Strongyloidiasis is a nematode (roundworm), parasitic infection that affects five continents and at least 70 countries. It is endemic to tropical and subtropical regions of Asia, Latin America, Africa, southern Europe and the southeastern United States; but with global travel and immigration, an epidemiologic shift is being observed. First described in the late 19th century in those with severe, persistent diarrhea, Strongyloides infection can either be clinically silent or cause a critical illness with a risk for death. With an estimated prevalence between 50 to 100 million infections worldwide, strongyloidiasis remains a major cause of morbidity and mortality. The clinical presentation, however, is often nonspecific and definitive diagnosis is frequently delayed, thus leading to malpractice which bears significant unintended iatrogenic sequelae for infected patients. As such, it is imperative to not only maintain an awareness of Strongyloides as a diagnostic consideration but also to further our knowledge base about the parasite, and its diagnostic and treatment considerations.

There are over 40 species of Strongyloides; but the main species pathogenic to humans is S. stercoralis. In the United States, studies have shown that approximately 6 percent of individuals are infected; but among immigrants that rate may approach 50 percent. Infection is initiated by filariform larvae present in soil or feces that use a histolytic protease to penetrate skin and access the venous or lymphatic vessels of the human host. The larvae are passively transported to the lungs and small intestine, where they become lodged in capillary beds. They then breach the capillary wall and invade adjacent tissue. In the lung, once within the alveoli, they are coughed up and then swallowed into the gastrointestinal (GI) tract. Once in the GI tract, the female filariform larvae molt twice and become adult female worms, living threaded and coiled within the epithelium of the small intestine, preferably the duodenum. They produce eggs which hatch in situ yielding the rhabditiform larvae. These larvae are either passed in the stool or later mature into the infective filariform larva that are capable of re-invading the host blood. In soil or feces that use a histolytic protease to penetrate skin and access the venous or lymphatic vessels of the human host, they are coughed up and then swallowed into the gastrointestinal (GI) tract. Once in the GI tract, the female filariform larvae molt twice and become adult female worms, living threaded and coiled within the epithelium of the small intestine, preferably the duodenum. They produce eggs which hatch in situ yielding the rhabditiform larvae. These larvae are either passed in the stool or later mature into the infective filariform larva that are capable of re-invading the same host's skin or mucosa, thus restarting the parasitic cycle in a process termed autoinfection. Such autoinfection can lead to widespread dissemination of the infection. The time span from dermal invasion until larvae are passed in stool is generally three-to-four weeks.

In the immunocompetent host, the main risk factor for Strongyloides infection is skin exposure to larvae-contaminated soil. Patients usually develop an asymptomatic, chronic or mildly symptomatic infection with vague abdominal discomfort, bloating and nausea as well as respiratory complaints such as cough, shortness of breath and symptoms that mimic asthma or chronic obstructive pulmonary disease (COPD). A minority of patients may present with a serpiginous, urticarial rash at the site of larval entry, known as larva currens. Endoscopic findings may include mucosal ulceration, bleeding, mucosal thickening, and focal brown discolorations as well as thickened plicae. Symptoms can be mild and persist, without progression, for up to several decades.

Administration of corticosteroids to a patient who harbors chronic Strongyloides infection can precipitate hyperinfection and dissemination of the parasite, yielding a 50-80 percent mortality rate, depending on other host conditions. In the Unites States, most fatal cases of Strongyloides are, in fact, iatrogenic in nature due to prescription of steroids to those who unknowingly had chronic disease. Additional fatalities, however, are seen in association with certain immunosuppressive conditions such as cancer and organ transplant recipients. In a large scale study in 2010, Croker et al. retrospectively reviewed all Strongyloides-related deaths in the United States from 1991 through 2006. Among the nearly 350 fatal cases reviewed, the authors concluded that the most prevalent health condition predictive of mortality was COPD (identified in 28.7 percent of fatal cases), due in large part to corticosteroid use. They also identified AIDS in 12.5 percent of the fatal cases. The impact of AIDS on Strongyloides, however, is controversial in that the CDC reports that the presence of HIV/AIDS is neither a risk factor nor an indicator for a worse prognosis in strongyloidiasis patients. The cause of death in fatal Strongyloides is most frequently gram negative sepsis and/or meningitis presumably due to the barrier breach caused by the larval penetration through the gastrointestinal wall that thus facilitates the entry of enteric bacteria in host blood. In the United States, nearly half of strongyloidiasis deaths occur in the southeastern states, most predominantly in Florida, Louisiana, and Kentucky. Fortunately, in the current case presented, despite recent corticosteroid use, the patient did well with treatment. Future steroid use will be avoided.

There is no gold standard for diagnosing S. stercoralis and diagnosis is often delayed. A number of tests including stool studies and cultures, enzyme linked immunosorbent assays (ELISA), PCR-based molecular techniques and gastrointestinal biopsy for histopathology have all been employed each with varied specificity and sensitivity. Visualization of S. stercoralis larvae, worms and/or eggs may be possible through a variety of techniques such as the inexpensive and simple stool study or via the swallowed string test; but both the reliability and the sensitivity are low. Histopathologic examination, as seen in the current case, does yield good specificity but requires invasive tissue sampling for the patient and, again, can bear a diminished sensitivity due to sampling error and low parasitic burden.

Laboratory findings frequently found in strongyloidiasis, and depicted well by the current case, include peripheral eosinophilia. An elevated total serum IgE may also be seen. There are only a limited number of serologic tests commercially available for strongyloidiasis and, among those, there is frequent cross reactivity with the other nematodal infections and an inability to discriminate between current and remote infections. Promising is the recent development of several real-time PCR tests in highly endemic regions, with reported sensitivities and speci-
The histopathologic appearance of *S. stercoralis* is well depicted in the current case. Typically, microscopy reveals larvae, eggs and some adult round worms nested within the gastric or duodenal crypts. Further, there is often an associated inflammatory infiltrate rich with eosinophils throughout the lamina propria. Nonspecific findings can include blunted villi and increased intraepithelial lymphocytes.

Treatment with an antihelminthic drug such as ivermectin, 200µg/kg orally, repeated at two weeks, has an 83-100 percent efficiency in eradication of *Strongyloides* infection. Hyperinfection and disseminated infections may require higher and more frequent dosing, a longer treatment course, and subcutaneous delivery of ivermectin. Follow-up stool exams are recommended to confirm resolution of strongyloidiasis and eosinophil count normalization is a reassuring surrogate marker for treatment success. The patient presented here was treated with the usual course of ivermectin dual dosing as well as with albendazole. His peripheral eosinophil count decreased to 2 percent; stool studies have remained normal.

Increasing global travel and immigration rates in the US that exceed one million annually mandate that health care providers remain educated on *Strongyloides*. *S. stercoralis* should be considered in any patient with peripheral eosinophilia >5 percent or >400/µL, especially if abdominal complaints or respiratory symptoms are elicited. Care must be taken not only to avoid misdiagnosis but also to prevent any unintended iatrogenic effects of maltreatment that can occur in immunocompromised patients, particularly those with COPD and potentially HIV/AIDS.

**REFERENCES**

6. Suputtamongkol Y, Premasathian N, Bhumimuang K, et al. Efficacy and safety of single and double doses of ivermectin versus 7-day high dose albendazole for chronic strongyloi-

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