Background: Overwhelming strongyloidiasis defined by multi-organ dissemination causes severe morbidity and high mortality.

Objective: To report a case of disseminated strongyloidiasis presenting with unusual gastrointestinal manifestations in an immunocompromised host.

Methods: A Thai girl with myasthenia gravis treated by chronic administration of corticosteroids presented with disseminated strongyloidiasis. Pulmonary and gastrointestinal symptoms were the clinical manifestations of hyperinfection or disseminated strongyloidiasis.

Results: Strongyloides larvae were found in her sputum, stool, and peritoneal fluid. They were present in all layers of the intestinal wall. She did not respond to oral antihelminthic drugs (albendazole). Subcutaneous ivermectin was administered. She succumbed to unresponsive cardiac arrest that was unresponsive to standard resuscitation protocols due to severe septicemia. Pulmonary and gastrointestinal symptoms were the clinical manifestations of hyperinfection or disseminated strongyloidiasis.

Conclusion: Serial stool examination should be performed prior to the onset and during immunosuppressive treatment.

Keywords: Strongyloides stercoralis, Hyperinfection, Disseminated strongyloidiasis, thiabendazole, Ivermectin

Clinical report

Overwhelming strongyloidiasis

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Strongyloides stercoralis is a small nematode found in tropical countries including Thailand and causes a disease called strongyloidiasis. The life cycle of S. stercoralis is complex encompassing self-sustaining and parasitic stages. Adult females, embedded in the intestinal mucosa, lay eggs that hatch internally. Rhabditiform larvae (L1) are excreted in the feces and develop into L2 and L3 (filariform larvae) stages in the soil; hence, strongyloidiasis is classified as a soil transmitted disease. Humans are infected transcutaneously. The clinical syndromes of strongyloidiasis comprise a wide spectrum ranging from asymptomatic, acute, or chronic infection to hyperinfection or dissemination. Strongyloidiasis is often asymptomatic in otherwise healthy hosts. On the other hand, disseminated disease is commonly found in immunocompromised hosts such as in patients with hematologic malignancies and in immunodeficiency syndrome or in patients receiving organ transplantation or corticosteroid treatment. Acute strongyloidiasis is defined by symptoms from local reactions at the site of larva entry, which occur almost immediately and may last up to several weeks. Chronic strongyloidiasis is mainly asymptomatic, with occasional mild symptoms manifesting in the pulmonary and gastrointestinal system [1, 2]. During the asymptomatic stage, eosinophilia is the only clinical indicator. The term “hyperinfection” or “overwhelming infection” is defined by signs and symptoms attributable to large amounts of larvae migration. The hallmark of hyperinfection is development or exacerbation of gastrointestinal and pulmonary symptoms and increase numbers of larvae in stool and/or sputum. Larvae in hyperinfection are confined to the organs involved in the pulmonary auto-infective cycle such as lung, gastrointestinal tract, and peritoneum. The term “disseminated strongyloidiasis” refers to the migration of larvae to many organs beyond the range of a pulmonary auto-infective cycle. Gastrointestinal symptoms include abdominal bloating, abdominal cramps, diarrhea, vomiting, and weight loss [2-4].
Hematochezia or melena is caused by extensive intestinal ulceration found in heavy infection. The intestinal manifestations can mimic an acute surgical abdomen such as small bowel obstruction, paralytic ileus or perforating peptic ulcers [5,6]. The most common dermatologic manifestations are localized, pruritic, erythematous maculopapular rash at the site of larva penetration. The pathognomonic sign for *Strongyloides* infestation is larva currens defined as migratory, short, erythematous linear or serpiginous papules which may progress to urticaria [7]. The crucial step in establishing the diagnosis of strongyloidiasis is the identification of larvae in stool. The rate of larva excretion in stool is fluctuation. Microscopic stool examination should be repeated to increase test sensitivity if strongyloidiasis is suspected. Stool samples can be microscopically examined for larvae employing various methods such as simple direct smear (sensitivity 0-52%), formalin ether concentration method (sensitivity of 13-55%), agar plate culture with a high sensitivity of 78-100% [8-10]. Another diagnostic method for strongyloidiasis is by serology to identify the presence of strongyloid antibody in the serum. This method can be applied in asymptomatic patients with eosinophilia or mildly symptomatic patients. In addition, diagnosis can be accomplished by methods such as Enzyme-linked Immunosorbent Assay (ELISA), Gelatin Particle Indirect Agglutination (GPIA), and Western Blot analysis (WBA) [8, 11, 12]. Medications of choice for treatment of strongyloidiasis are oral thiabendazole, albendazole, and ivermectin [13, 14]. Albendazole is a broad-spectrum antihelminthic drug used for treatment of many gastrointestinal parasitic infestations and visceral larva migrans. It is absorbed rapidly by the gastrointestinal tract and maintained at a high tissue level. The recommended dose of thiabendazole for intestinal strongyloidiasis is 25 mg/kg twice daily for two days with the maximum dose being three grams per day [1, 4]. This regimen can effectively eradicate intestinal strongyloidiasis in 90-100% of patients. A five-day course of treatment is recommended for disseminated disease. Daily sputum and stool examinations for larvae of *Strongyloides* should be performed to assess duration of therapy. The major adverse effects of thiabendazole therapy are anorexia, nausea, vomiting, diarrhea, abdominal discomfort, confusion, dizziness, leukopenia, transient elevations in aspartate aminotransferase and neuropsychiatric symptoms [15]. The response to antihelminthic drugs requires an intact immune system and thus, immunocompromised hosts are commonly refractory to treatment. Currently, ivermectin is preferred over thiabendazole due to its improved rate of larva clearance from stool when compared with albendazole and thiabendazole and less adverse side effects. Its mechanism of action is based on blockage of chemical transmission across motor nerve synapses, causing paralysis in nematodes. The orally administered drug is 60% absorbed [16]. This drug is not recommended for children below the age of 5 years and for lactating women [17]. Ivermectin binds to albumin with high affinity and hence, hypoalbuminemia may cause poor absorption and increased clearance of unbound drug [16, 18]. For patients with disseminated strongyloidiasis and bowel ileus who cannot absorb oral drugs, the simultaneous oral and rectal administration of ivermectin and oral albendazole represents an effective treatment regimen [19]. In severe cases of strongyloidiasis with other multiple gastrointestinal problems, oral medications cannot be used effectively due to hypoalbuminemia, paralytic ileus, and increased drug clearance [16, 18]. The alternative treatment is subcutaneous administration of ivermectin. Provided there are no further complications, the disease is treated with ivermectin 200 μg/kg once daily for one or two days. In Thailand, ivermectin is recommended for the treatment of parasitic infestation in animals. It has not yet been approved by the Thai FDA for use in humans. Steroid withdrawal has been advocated, but may not be effective in decreasing parasite infestation. Coinfection by *S. stercoralis* and other enteric gram negative bacteria is common. They are thought to enter the bloodstream together with the larvae that penetrate the bowel wall [20, 21].

Empirical treatment with antimicrobial and antifungal drugs should be considered in an immunocompromised host with overwhelming strongyloidiasis. In immunocompromised hosts with decreased cellular immunity, the fatality rate of disseminated disease ranges from 50-86% due to co-infection with gram-negative bacteria that causes sepsis [22]. Most fatal infections can be prevented by early detection of strongyloidiasis by serial stool examination for the ova and parasites, and by enzyme-linked immunosorbent assay (ELISA) before and during treatment with immunosuppressive drugs [22].

Our objective is to report a case of overwhelming strongyloidiasis in a patient under prolonged corticosteroid therapy who presented with an unusual...
manifestation of gastrointestinal disease including perforation of the duodenum.

Case report

A 14-year-old girl, referred from a provincial hospital from the north of Thailand, was admitted to King Chulalongkorn Memorial Hospital with history of epigastric pain for seven days. Other symptoms included loss of appetite, non-bilious vomiting, and watery diarrhea. The past medical history was significant for systemic Myasthenia Gravis, which had been diagnosed previously. During the past two years, she has been treated with azathioprine, mestinon, and prednisolone (40 mg/day).

On physical examination, the patient was alert. Vital signs and oxygen saturation were within normal limits. She did not suffer from ptosis or respiratory distress. Her body weight and height were on the 50th-60th percentile. Abdominal examination revealed mild distension and marked tenderness at the epigastrium without guarding. Liver and spleen were not palpable. There was no lymphadenopathy. Skin examination revealed diffuse erythematous blanchable ecchymosis. The rest of the physical examination, including a detailed neurologic examination, yielded normal results. Initial baseline laboratory results included a normal complete blood count with 3% eosinophilia, normal renal function and normal electrolytes. Serum amylase and lipase were within normal limits at 46 μL and 46 μL, respectively. Stool examination was positive for occult blood. Strongyloides stercoralis larvae exceeding 100/smear was found in the stool specimen. She was treated with albendazole 400 mg twice a day. Hemoculture was negative. Cytomegalovirus viral load was below 600 units. Chest radiography displayed bilateral interstitial infiltration. Abdominal radiography displayed generalized bowel ileus. She received intravenous fluid, a dopamine infusion was initiated. On the third day of hospitalization, she developed severe epigastric pain with coffee ground stained nasogastric fluid. Emergency esophagogastro-duodenoscopy revealed mild focal acute erosive esophagitis, without any evidence of vasculitis or organisms. She was not able to receive orally administered drugs and albendazole was discontinued.

On the ninth day of hospitalization, she went into septic shock and was intubated and transferred to the pediatric intensive care unit. After several boluses of intravenous fluid, a dopamine infusion was initiated. She underwent an abdominal re-exploration one day after the first operation. During the second operation, another perforation of the second part of the duodenum of 1.5 cm in diameter was repaired and a perforation at the duodeno-jejunal junction of 5 cm in diameter was resected followed by an end-to-end anastomosis. Meropenem was discontinued in favor of intravenous sulperazone, vancomycin, metronidazole, gancyclovir, and fluconazole. Two days after the second operation (gastrojejunostomy) Strongyloides stercoralis were found in sputum, nasogastric fluid and intraperitoneal fluid (Fig. 1). She was diagnosed as disseminated strongyloidiasis and subsequently, 200 μg of ivermectin was administered subcutaneously once a day. Since ivermectin had not yet been approved by the Thai FDA, Ministry of Public Health, informed consent from parents was obtained prior to its administration.

On the fourteenth day of hospitalization, the patient developed swelling of the left leg. Doppler ultrasound of lower extremities revealed complete obstruction of the common femoral vein and partial obstruction of the distal saphenous vein, consistent with deep vein thrombosis. Coagulation tests yielded normal results with a D-Dimer level of 5.6 μg/mL, a plasma fibrinogen level of 110 mg/dL and a fibrin degradation product level of 160 μg/mL. However, heparinization was not started due to coagulopathy. Hence, supportive treatment including leg elevation and compression was initiated. The specimens obtained during the operation revealed moderate growth of Pseudomonas spp., coagulase negative Staphylococcus spp., and Enterococcus faecalis. The esophageal biopsy from the esophagogastro-duodenoscopy revealed mild focal acute erosive esophagitis, without any evidence of vasculitis or organisms. She was not able to receive orally administered drugs and albendazole was discontinued.

On the sixteenth day of hospitalization, she developed swelling of the left leg. Doppler ultrasound of lower extremities revealed complete obstruction of the common femoral vein and partial obstruction of the distal saphenous vein, consistent with deep vein thrombosis. Coagulation tests yielded normal results with a D-Dimer level of 5.6 μg/mL, a plasma fibrinogen level of 110 mg/dL and a fibrin degradation product level of 160 μg/mL. However, heparinization was not started due to coagulopathy. Hence, supportive treatment including leg elevation and compression was initiated. The specimens obtained during the operation revealed numerous Strongyloid larvae in all layers of the intestinal wall, muscular necrolysis and fibrinonecrotic inflammatory materials (Fig. 2). Her condition did not improve and she succumbed to unresponsive cardiac arrest, which was unresponsive to standard resuscitation protocols, on day 17 of hospitalization.
Discussion

This patient, who had received two immuno-suppressive drugs including steroid and azathioprine, developed gastrointestinal manifestations of strongyloidiasis in the form of abdominal pain and upper gastrointestinal bleeding. After the third day since admission, her condition deteriorated and she developed disseminated strongyloidiasis. Esophagogastroduodenoscopy revealed esophagitis and duodenitis. Skin manifestations indicative of vasculitis were also present during hyperinfection [23]. While on steroid therapy, this patient had suppressed eosinophilia probably due to glucocorticoids therapy, which may have a direct effect on parasites by accelerating the transformation of rhabditiform to invasive filariform larvae or by rejuvenating reproductively latent adult females [24, 25]. This patient did not respond to three days of albendazole treatment and subsequently developed clinical disseminated strongyloidiasis. The response to antihelminthic drugs depends on an intact immune system and immunosuppressed hosts have been reported unresponsive to multiple courses of commonly used agents (thiabendazole and ivermectin) [1, 26–28]. Combination therapy with ivermectin plus thiabendazole or ivermectin plus albendazole has been recommended for patients with disseminated disease [22, 29]. Due to postoperative bowel ileus, oral administration of antihelminthic drugs to this patient was not possible. Since ivermectin injection

Fig. 1 A photomicrograph of a histological section from duodenal biopsy of small bowel demonstrating longitudinal and transverse cross sections of several worms (arrowhead) lying within crypts. The adults display a single intestine and double reproductive tubes. The mucosa shows lymphoplasmacytic and eosinophilic infiltration. (Hematoxylin and eosin stain, original magnification, x400).

Fig. 2 Strongyloid rhabditiform larvae seen in sputum and ascitic fluid.
for humans is not available in Thailand, a veterinary formulation was used. Cause of sepsis in this patient was transmission of enteric bacteria through the bowel wall by invading filariform larvae. Follow-up stool examinations should be performed over a period of three months after treatment to ensure the infection has been cleared.

In conclusion, immunocompromised conditions have been associated with hyperinfection with strongyloidiasis. Stool examination should be repeated periodically during immunosuppressive therapy. Physicians should be aware of the unusual manifestations of disseminated strongyloidiasis. Inhabitants of endemic areas should be educated on modes of parasite transmission to avoid recurrent infection.

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