

CASE REPORT

DISSEMINATED STRONGYLOIDIASIS SUCCESSFULLY TREATED WITH EXTENDED DURATION IVERMECTIN COMBINED WITH ALBENDAZOLE: A CASE REPORT OF INTRACTABLE STRONGYLOIDIASIS

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Abstract. We describe a patient with an overlapping syndrome disseminated strongyloidiasis and gram-negative sepsis. She was previously treated with albendazole 400 mg/day 14 days before admission without success. This admission, she was treated with a combination of oral ivermectin (injectable solution form), with a dosage of 200-400 µg/kg/day, and albendazole for 14 days. Strongyloides larvae disappeared from the stool by day 4 and from the sputum by day 10. No side effects were encountered during hospitalization or at the 1-month follow-up visit.

Strongyloidiasis has a worldwide distribution, and usually causes mild or asymptomatic infection. Hyperinfection syndrome can cause significant morbidity and mortality in immunocompromised states such as malignancy, lymphoma, HIV infection, or immunosuppressive agent administration. Oral thiabendazole is standard treatment, and ivermectin is an effective alternative antihelminthic agent; however, these drugs are not available in Thailand. We present a patient with disseminated infection that was successfully treated with albendazole and an extended duration of ivermectin injectable solution for cattle.

A 51-year-old Thai woman was admitted due to watery diarrhea one day prior to hospitalization at Ramathibodi Hospital in Thailand. In the emergency room, she was agitated with a confused mental status, and her oxygen saturation was 88%. Her blood pressure could not be measured and her heart rate was 160/minute with cold clammy extremities, with a respiratory rate that was 40/minute, and shallow. She had dry lips and tongue with flat neck veins. Endotracheal intubation was performed due to hypoxemia and he-

modynamic instability. Intravenous fluid resuscitation was started for rehydration, and she was transferred to the ICU. On physical examination, she had generalized mild tenderness and guarding of the abdomen, with decreased bowel sounds. Neck stiffness was detected. The rest of the examination was unremarkable.

The patient had been diagnosed previously with the overlapping syndrome of CNS veno-occlusive disease, GI vasculitis and strongyloides infestation. The latter was diagnosed 18 days before this admission and was treated with oral albendazole 400 mg/day for 14 days. Her medications included cyclophosphamide 100 mg/day, prednisolone 60 mg/day, methotrexate 2.5 mg once a week, and warfarin 3 mg/day.

Laboratory investigations showed a hemoglobin 10.4 g/dl, hematocrit 33.9%, Wbc 2,640/mm³, N 58%, L 31%, M 3%, E 1%, Baso1%, platelets 361,000/mm³, and ESR 67 mm/hour. Urinalysis showed trace proteinuria, positive blood with Rbc 2-3/HPF, Wbc 0-1/HPF. Blood chemistry: glucose 119 mg/dl, BUN 33 mg/dl, Cr 2.5 mg/dl, Na 130 mmol/l, K 3.32 mmol/l, CO₂ 20.5 mmol/l, Cl 90 mmol/l, Ca 9 mg/dl, P 4.5 mg/dl, TB 1.5 mg/dl, DB 0.6 mg/dl, AP 85 µl, SGOT 45 µl, SGPT 48 µl, GGT 86 µl TP 55.6 g/l, Alb 30.1 g/l, Chol 234 mg/dl, Trig 326 mg/dl,

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Mg 1.6 mg/dl. Complement levels were CH₅₀ 75% C, C₃ 773 mg/ml (750-1,400), C₄ 261 mg/ml (100-400). A coagulogram showed PTT 41.7 (33-44 seconds), PT 17.5/51.5%, TT 8.3 (5-10 seconds), INR 1.53 and a negative D-dimer study. Serum cortisol was 20 mg/dl. Fecal examination showed brown, watery stool with Wbc 10-20/HPF, Rbc 3-5/HPF, and strongyloides larvae with active movement. Fresh sputum examination showed strongyloides larvae with active movement. Chest radiograph had no definite pulmonary infiltration. Initially, she was diagnosed as having disseminated strongyloidiasis with gram-negative sepsis and meningitis.

Clinical course

After she was admitted to the ICU, a CT scan of the brain was performed and showed no intracranial hemorrhages or leptomeningeal enhancement. Lumbar puncture was done which revealed an opening pressure of 11 cm H₂O, a closing pressure of 7 cm H₂O, Wbc 1,050/mm³ (PMN 100%), protein 164 mg/dl, sugar 85 mg/dl, and the CSF Gram-stain showed no organisms. She was immediately started on ceftriaxone 2 g IV q 12 h and gentamicin 200 mg iv drip qd. Hydrocortisone 100 mg/day was given intravenously. On the third day of hospitalization, she developed worsening hypoxemia and a chest radiograph showed progressive opacification of the lung fields bilaterally. The antibiotic was switched to meropenem 1 g IV q 12 h. We started treatment for disseminated strongyloidiasis on the first day of hospitalization. Ivermectin (IVOMEC®)

treatment was discussed with the patient's daughter and informed consent was given prior to starting treatment. Treatment protocol, duration of treatment and parasite examinations of stool and sputum are shown in Table 1.

Strongyloides stercoralis is a small roundworm (nematode) which can cause disease in humans in several ways. The 'direct' cycle of infection begins when the human comes in contact with soil containing the worm in its infective (filariform) larval stage. *Strongyloides* penetrates the skin and enters the circulation of the host. When the worms reach the alveolar capillaries, a pulmonary phase begins in which the parasites enter the alveoli and ascend the respiratory tract. Once in the pharynx, the organisms are swallowed. Maturation and reproduction occur in the small intestine. The fertilized adult female burrows into the mucosa of the upper small intestine and begins to lay eggs. The larvae which hatch are in a noninfectious (rhabditiform) stage; they eventually bore through the intestinal epithelium to reach the bowel lumen and are passed out in the feces. The rhabditiform larvae can transform to the infective filariform larvae in the soil, thus completing the cycle. In addition to this direct cycle, *Strongyloides* can also reproduce without a human host. In this 'indirect cycle', larvae are passed into the soil, as described above. If proper environmental conditions are present, larvae mature into adult helminths capable of reproduction. After copulation, large numbers of new larvae are produced, potentially infectious to humans. A less common but clinically important aspect of

Table 1
Treatment protocol and duration for disseminated strongyloidiasis.

Day of treatment	Stool exam	Sputum exam	Ivermectin	Albendazole
Day 1	Pos (active)	Pos (active)	8,000 µg po qd pc	400 mg po bid
Day 2	Pos (active)	Pos (active)	8,000 µg po qd pc	400 mg po bid
Day 3	Pos (active)	Pos (active)	8,000 µg po qd ac	400 mg po bid
Day 4	Neg	Pos (active)	8,000 µg po qd ac	400 mg po bid
Day 5	Neg	Pos (active) ↓	8,000 µg po bid ac	400 mg po bid
Day 6	Neg	Neg 2 time	8,000 µg po bid ac	400 mg po bid
Day 7	Neg	Pos (active) ↓ 1 /HPF	8,000 µg po bid ac	400 mg po bid
Day 8	Neg	Pos (active) ↓ 2 /HPF	8,000 µg po bid ac	400 mg po bid
Day 9-14	Neg	Neg	8,000 µg po bid ac	400 mg po bid

Pos: positive, Neg: negative

Strongyloides is its 'autoinfection cycle'. Instead of being passed in the stool, noninfectious larvae transform into infectious larvae in the lumen of the intestine. They can then reenter the host circulation either by boring through the intestinal wall or penetrating the perianal skin. This 'autoinfection' can cause repeated infections over the years and at times can be life-threatening because of the associated heavy worm burden ('hyperinfection syndrome').

On admission, this patient presented with sepsis and disseminated strongyloidiasis, which had been previously treated with albendazole 400 mg/day for 14 days. This probably means this infection was due to an autoinfection or new infestation. She was treated with albendazole 800 mg/day and ivermectin (IVOMEC® for cattle in injectable solution form) 200 mg/kg/day via the oral route. At first, ivermectin was given after meals once a day for two days. *Strongyloides* larvae were still found in the feces and sputum. Then ivermectin was given before meals for 5 days. With this regimen, the fecal examination showed no larvae on Day 4, however the sputum examination was still positive for larvae. Finally, we doubled the dosage of ivermectin and extended the duration of treatment to 14 days and the fecal and sputum examinations became negative for parasites by 10 days of treatment (Table 1). We found no side effects in this patient during the 1 month she was admitted to our hospital. No larvae were detected after we discontinued ivermectin treatment.

In the literature, the recommended treatment for strongyloides infection is a two-day course of ivermectin tablets 200 µg/kg, or a three-day course of albendazole 400 mg/day, which may be repeated two weeks later. Thiabendazole is recommended for acute and chronic strongyloidiasis at 1.5 g PO bid for 2 days and for severe strongyloidiasis such as with hyperinfection syndrome and disseminated strongyloidiasis at 1.5 g PO bid for 7-14 days (Palenokovite, 2003), but ivermectin is not recommended. A recent comparative study demonstrated that ivermectin appeared to be as effective as thiabendazole, although the cure rates for disseminated strongyloidiasis ranged anywhere from 50% to 100% (Datry *et al*, 1994; Salazar *et al*, 1994).

Albendazole also proved to be an attractive alternative antihelminthic therapy, especially in chronic strongyloidiasis, and is virtually free of side effects (Pene *et al*, 1982; Rossignol and Maisonneuve, 1983; Pungpak *et al*, 1987; Mojon and Nielsen, 1987; Archibald *et al*, 1993; Pitisuttithum *et al*, 1995). If immunosuppression cannot be withdrawn, monthly 2-day courses of treatment, until eradication, may be necessary in order to prevent hyperinfection syndrome (Plourde *et al*, 1994).

In Thailand, ivermectin for humans and thiabendazole are not available. Most cases of strongyloidiasis are treated with albendazole with the results being unsatisfying, especially in disseminated form, and relapses commonly occur. Some patients die of disseminated strongyloidiasis and gram-negative sepsis. Ivermectin is an antiarthropoda and antinematoda agent that is used to eradicate internal and external parasites in dogs and cattle. Commercial oral forms of ivermectin for dogs and cattle are available in Thailand. A very low dosage of ivermectin in each tablet and the high cost of ivermectin are the main problems. An injectable solution of ivermectin with a higher concentration is available and cheaper. For the treatment of demodex skin infection (red mange) in dogs, ivermectin is used at a high dose (300-600 µg/kg/day, orally) for 6-8 weeks and may be extended to 40 weeks in severe cases with occasionally mild side effects (Mansfield and Schad, 1992; Prapararakul, 2001). In the large veterinarian training hospital in Thailand, the injectable form of ivermectin is used in an oral form diluted with propyleneglycol or multivitamin solution. It is effective and shows good results for the treatment of demodectic skin infection (Tynes, 1999). We used the injectable form of ivermectin orally diluted in a multivitamin solution along with albendazole, in this intractable case with disseminated strongyloidiasis which had been previously treated previously with 14-day course of albendazole 400 mg/day albendazole. That suggests that ivermectin injectable solution for cattle; used as an oral solution, can treat the hyperinfected and disseminated forms of strongyloidiasis, at the same dosage or double dosage (200-400 µg/kg/day). If ivermectin treatment is not successful in 2 days (by positive fecal examination or sputum examination), ex-

tended duration of ivermectin for 7-14 days can be an effective treatment modality.

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