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CASE REPORT

Successful use of subcutaneous ivermectin for the treatment of *Strongyloides stercoralis* hyperinfection in the setting of small bowel obstruction and paralytic ileus in the immunocompromised population

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SUMMARY

Severe *Strongyloides stercoralis*, such as hyperinfection syndrome, carries a high mortality risk. Even with appropriate treatment, patients may experience infectious complications and failure of therapy. Currently, there are no Food and Drug Administration–approved parenteral therapies available for treatment in patients who develop gastrointestinal complications from hyperinfection, including small bowel obstruction. A veterinary form of ivermectin is available as a subcutaneous injection, although current literature in humans is limited. We report on the successful treatment of two surviving immunocompromised patients with *S. stercoralis* hyperinfection syndrome after prompt recognition and initiation of veterinary subcutaneous ivermectin therapy.

BACKGROUND

Strongyloidiasis is an infection caused by *Strongyloides* species, a parasite common in tropical, subtropical and warm temperate climates.[1–3] Strongyloidiasis has been identified in the USA, predominantly in the southeastern region, as well as in travellers and immigrants from South America or sub-Saharan Africa.[4] This organism can migrate through the skin and mucosa into the intestinal tract and travel to other organs, frequently affecting the skin, lungs and gastrointestinal (GI) tract.[2 5] Hyperinfection can result in disruption of mucosa, ulcerations and ileus.[1] In these situations, the organism can travel through the systemic circulation to the lungs causing bronchospasm, diffuse alveolar haemorrhage or respiratory failure.[6] Hyperinfection can also be precipitated in the setting of an immunocompromised host. In particular, glucocorticoid use and human T-lymphotropic virus type 1 infection (HTLV-I) have been identified in promoting hyperinfection.[7] Glucocorticoids may blunt the eosinophil response while HTLV-I can impair the function of the T-cell lymphocytes.[7]

The Centers for Disease Control and Prevention (CDC) recognises ivermectin as the first-line agent for the treatment of strongyloidiasis as well as *Strongyloides* hyperinfection. In the USA, ivermectin is available in oral and parenteral formulations, but the Food and Drug Administration (FDA) has approved only the oral formulation for human use.[8] The CDC recognises the use of veterinary subcutaneous ivermectin may be a therapeutic option when oral and/or rectal administration of the drug is not possible[9]; however, this use requires an investigational new drug (IND) exemption from the FDA.

We present individual cases of two immunocompromised patients diagnosed with *Strongyloides* hyperinfection syndrome who developed GI complications, including small bowel obstruction and ileus, during the course of their hospital stay. Both patients were critically ill in the intensive care unit (ICU), and it was unclear if enteral absorption of oral ivermectin was optimal. Thus, therapy with veterinary subcutaneous ivermectin was pursued for each patient. This case series adds to the body of literature regarding the use of veterinary subcutaneous ivermectin in human for the treatment of *Strongyloides* hyperinfection as well as the importance of early recognition and diagnosis of this infection.

CASE PRESENTATION

Case 1

Our first patient was a 42-year-old Cuban-American man, who relocated to Florida when he was 6 years old. His medical history was significant for asthma and deep vein thrombosis. He presented with diffuse abdominal pain, anorexia, vomiting, diarrhoea and dizziness for approximately 1 week. He was taking oral dexamethasone 6 mg by mouth daily for treatment of asthma. His physical examination was remarkable for diffuse abdominal tenderness and an erythematous, maculopapular rash with occasional pustules over the anterior abdomen. Laboratory values on admission are shown in table 1. Abdominal CT scan demonstrated bowel wall thickening and inflammatory stranding involving the caecum, ascending colon and transverse colon concerning for colitis. Concentrated examination of the stool with iodine staining demonstrated many *Strongyloides* parasitic larvae (figure 1). He was diagnosed with hyperinfection syndrome and started on albendazole. Colonic biopsy revealed active colitis with focal architectural changes and focal granulomas associated with *Strongyloides*. On admission day

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Table 1 Laboratory and clinical details of both cases

Laboratory value (units)	Case 1	Case 2
White blood cell count ($\times 10^9$/L)	14.7	24.6
Eosinophils (%)	0.5	0.9
Sodium (mEq/L)	126	129
Potassium (mmol/L)	3.4	4.1
Albumin (g/dL)	2.6	2.7
Total bilirubin (mg/dL)	0.9	4.4
Procalcitonin (ng/mL)	NA	<0.05
Duration of subcutaneous ivermectin therapy (days)	6	26
Total duration of admission (days)	17	104
Outcome	Alive; discharged	Alive; discharged

NA, not applicable.

5, he developed acute hypoxic respiratory failure and was intubated. A bronchoscopy with bronchoalveolar lavage (BAL) was performed, which revealed diffuse friable mucosa. Additionally, *Strongyloides stercoralis* was isolated in the wet preparation in parasitic larvae form and a send-out *Strongyloides* IgG serum antibody test was found to be positive. The patient was switched to oral ivermectin 200 µg/kg/day (13 mg) via nasogastric tube; however, due to paralytic ileus, ivermectin was changed to rectal suspension retention enema (tablets crushed and suspended in 30 cc Ora-Plus; Perrigo, Minneapolis, Minnesota, USA) administered daily as a bridge while awaiting emergency IND approval (IND no. 128369) from the FDA in addition to expedited institutional review board approval at our institution for the use of subcutaneous ivermectin (1%, 50 cc). The patient was extubated on admission day 10 but remained nothing by mouth due to paralytic ileus. On admission day 11, he was transitioned from rectal retention enema to subcutaneous ivermectin 200 µg/kg/day given in two divided syringes, one to each arm, every 48 hours.

Case 2

Our second patient was a 33-year-old Ethiopian woman living in Florida with a medical history of HIV infection. She emigrated from Ethiopia when she was 18 years old. Three months prior to admission, the patient had a CD4 count >500 cells/mm^3 and

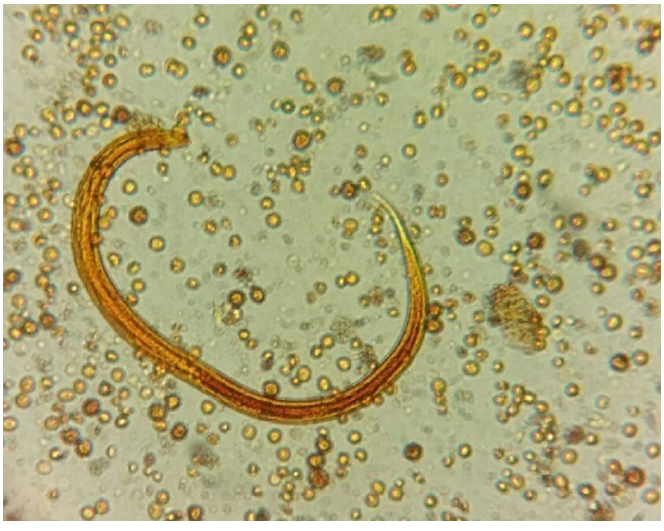

Figure 1 Stool demonstrating *Strongyloides stercoralis* in ova and parasite specimen.

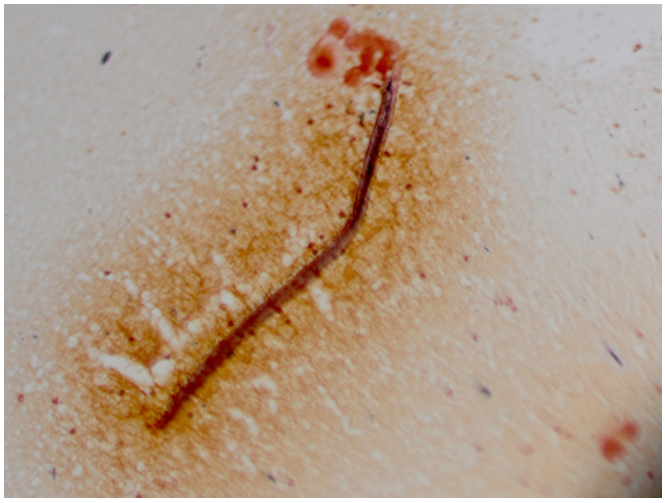

Figure 2 Bronchoalveolar lavage washings with *Strongyloides stercoralis*.

she was compliant with her antiretroviral therapy. She presented with nausea, vomiting and epigastric pain. Her physical examination was benign except for abdominal tenderness. Laboratory values from admission are shown in table 1. Right upper quadrant ultrasound was significant for a slightly dilated common bile duct; a subsequent hepatobiliary iminodiacetic acid scan was normal. The patient underwent an oesophagogastroduodenoscopy, which revealed diffuse, severe gastric inflammation with oedema and friable mucosa in the second portion of the duodenum. On admission day 4, she developed acute hypoxic respiratory failure from presumed acute respiratory distress syndrome. She was transferred to the ICU and was intubated. A bronchoscopy showed progressively bloodier aliquots consistent with diffuse alveolar haemorrhage. BAL cytology revealed numerous *S. stercoralis* in both parasitic larvae and adult forms (figure 2). Subsequent CT of chest and abdomen imaging showed diffuse ground-glass opacities bilaterally, small bowel obstruction, colitis and urinary bladder wall thickening with emphysematous cystitis. A concentrated stool examination with iodine staining demonstrated *S. stercoralis* in adult forms. Additionally, a duodenal biopsy noted abundant *Strongyloides* in parasitic larvae and adult form. She was diagnosed with *Strongyloides* hyperinfection. Ivermectin therapy was initiated orally at 200 µg/kg/day (12 mg). Unfortunately, the patient developed a small bowel obstruction and due to concern for malabsorption, FDA approval and an emergency IND application (IND no. 131494) were submitted for subcutaneous dosing. On receiving approval, the patient was transitioned to subcutaneous ivermectin (1%, 50 cc), obtained from a local veterinary hospital, at the same dose of 200 µg/kg/day given in two divided syringes, one to each arm, every 48 hours. Stool and sputum samples were sent every few days to document clearance of infection.

TREATMENT

See above.

OUTCOME AND FOLLOW-UP

Case 1

Stool and sputum were sent for *Strongyloides* every 3 to 4 days, and by admission day 13, *S. stercoralis* was no longer detected on sputum gram stain, although it was still present in the stool at discharge. The patient received three doses of subcutaneous ivermectin and was

restarted on oral ivermectin by admission day 17. At the time of discharge, he had received 12 days of ivermectin and was sent home with an additional 2-week course of oral therapy.

Case 2

She continued on subcutaneous therapy for 26 days before transitioning to oral ivermectin, as directed by the medical team due to her slow response to therapy. Due to depressed mental status and concern for further disease dissemination, a lumbar puncture was performed to rule out central nervous system involvement; this work-up was negative. Additionally, HTLV-I/II antibodies were ordered; tests were non-reactive. By day 39 of ivermectin therapy, larvae were no longer seen in her stool or sputum cultures and she was deemed to have completed therapy. She continued to have a prolonged hospital course and was eventually discharged home.

DISCUSSION

In this case series, we highlight the successful use of non-oral ivermectin for the treatment of *S. stercoralis* hyperinfection syndrome in two immunocompromised patients. In the available literature, at least 22 cases of subcutaneous ivermectin use have been reported, with 11 patients surviving treatment.[10] In an immunocompromised patient from an endemic area, a strong clinical suspicion for strongyloidiasis is warranted, as symptoms may be vague and delays in diagnosis can negatively impact a patient's outcome. Strongyloidiasis has been commonly encountered in patients living in tropical and subtropical climates. A 2010 publication identified 347 strongyloidiasis-related deaths in the USA; of note, over 50% of cases occurred in patients born in the southeastern region.[11] Thus, it is important for healthcare professionals in this area of the USA to be vigilant for this infection when evaluating patients presenting with respiratory and/or GI symptoms consistent with strongyloidiasis. Consistently, high mortality (up to 90%) has been documented due to the underdetection of this infection along with its wide range of clinical presentations.[12] However, the CDC provides guidance to healthcare professionals in *Strongyloides* screening and identifies the following individuals at risk: initiating or currently receiving corticosteroids or other immunosuppression medication, history of HTLV-I infection, those who are being evaluated or have a history of organ transplantation, persistent peripheral or unexplained eosinophilia, and recent or remote travel history to endemic areas.[12] In our two patients, they each met at least one screening criteria outlined by CDC as well as residence in the southeastern region of the USA. Our cases reinforce the need for early screening in at-risk individuals as well as promoting awareness of this infection and its risk factors to healthcare professionals practising in the southeastern USA.

Cases of severe *S. stercoralis* infection have been seen more frequently in patients receiving immunosuppressive therapies as well as those with HTLV infection.[7 13 14] Although once thought to be an AIDS-defining illness, few cases of strongyloidiasis in this patient population have been detected in clinical practice.[7 15] A retrospective study of HIV-positive immigrants at two Italian hospitals between January 2000 and August 2009 noted that 11% (15/138) of patients indeed had *Strongyloides* infection, as evidenced by positive laboratory testing with either an indirect immunofluorescent antibody test and/or direct parasitological tests with or without stool culture for *S. stercoralis*; however, no cases could be classified as hyperinfection syndrome.[16] Croker and colleagues identified 12.5% of patients in their study population in the USA with HIV who died from strongyloidiasis; similar to the previous study, none of these patients were diagnosed with hyperinfection syndrome.[11] A recent publication by Geri and colleagues reviewed 133 patients with *Strongyloides* hyperinfection syndrome, noting 10.7% of this population had HIV infection; however, this was not found to be predictive of ICU mortality or shock.[17] Although not commonly encountered in the HIV population, high clinical suspicion is warranted in the appropriate context due to the high mortality associated with *Strongyloides* hyperinfection syndrome.

Ivermectin's mechanism of action focuses on its binding to glutamate chloride ion channels, resulting in hyperpolarisation of the cell leading to death of the parasite.[8] Ivermectin has high oral bioavailability and is highly protein bound (93%); therefore, free serum drug levels can be increased in individuals with hypoalbuminemia.[8 18] Neurotoxicity is a major concern and the altered pharmacokinetics in critically ill patients can affect serum levels of ivermectin.[18] Veterinary subcutaneous ivermectin, the product used for our two patients, is a sterile solution containing glycerol formal and propylene glycol.[19] These compounds are used as drug vehicles for this product due to ivermectin's insolubility in water.[20] Additionally, this non-aqueous drug formulation has been shown to have activity against internal parasites, including *Strongyloides* spp., and external parasites.[20] Use of subcutaneous ivermectin was preferred in order to ensure adequate systemic absorption and distribution to all infected areas in the body[21 22]; however, we did not use therapeutic drug monitoring for either of our patients due to limited access to levels. There is no standardised therapeutic range recognised with the use of subcutaneous ivermectin. Barrett and colleagues published a summary of previous case reports on subcutaneous ivermectin, including any use of ivermectin serum levels.[10] Values varied significantly across the publications from 2.7 to 35.4 ng/mL. The weight-based dose was the same in each case; however, the frequency of administration differed. Additionally, patient outcomes did not appear to correlate with serum ivermectin concentrations. Some in vitro data suggest 2.4 ng/mL of ivermectin is needed to paralyse 50% of other *Strongyloides* spp.[23 24]; however, the dose of 200 µg/kg/day, which was used in both of our cases, has resulted in high parasitic eradication.[25] Clinical use and pharmacokinetic studies of subcutaneous ivermectin have primarily been in animals. Unfortunately, there is little pharmacokinetic data in humans at present and further studies are needed for dose optimisation and potential licensure for human use.

Impaired immunity likely played a role in promoting hyperinfection in both of our cases. Geri and colleagues noted 83.5% of their patients with *Strongyloides* hyperinfection syndrome on corticosteroids at a median dose of 40 mg per day, highlighting the significant role of this drug therapy on infection risk.[17] Our first case involved a patient who had been receiving chronic corticosteroids, which may have led to a blunted eosinophil response. Eosinophils are known to combat parasitic infections, yet were not detected by laboratory tests in either patient. From previous cases, it has been noted that eosinophil counts are lower in individuals with severe strongyloidiasis compared with individuals who are asymptomatic.[4] The degree of immunosuppression appeared to be significant in our first case and may have accelerated the patient's hyperinfection. Our second case involved an HIV patient with a CD4 count above 500 cells/mm^3. Testing for HTLV during admission was noted to be non-reactive. Interestingly, hyperinfection is not commonly seen in the HIV population but can occur in individuals who are undergoing immune reconstitution inflammatory syndrome in endemic areas.[26] The exact mechanism is unclear, but it has been noted that HIV can decrease Th-1 lymphocytes. As the immune system reconstitutes, the increase of Th-1 lymphocytes may promote autoinfection.[26]

Our patient was from an endemic area for *Strongyloides* spp. and also exhibited GI symptoms during her hospitalisation. It is likely she had chronic strongyloidiasis that evolved into hyperinfection. In the setting of depressed immunity and residence in an endemic area, these patients were at risk for development of strongyloidiasis, including hyperinfection.

Learning points

- The use of veterinary subcutaneous ivermectin in the treatment of *Strongyloides* hyperinfection offers an option to patients with unreliable gastrointestinal absorption in order to achieve adequate drug serum levels.
- Residence in endemic areas and impaired immunity can predispose patients to infection with *Strongyloides* spp.
- Prompt recognition and diagnosis of infection along with timely initiation of appropriate treatment is paramount in the management of *Strongyloides* hyperinfection syndrome.

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