A Comatose State in Disseminated Strongyloidiasis due to an Anti-Parasitic Drug

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Abstract

A 48-year-old Hispanic male patient with follicular non-Hodgkin’s lymphoma was admitted with an incarcerated inguinal hernia. This event was followed by sepsis by *Klebsiella* and *Candida* sp. by disseminated strongyloidiasis bacterial translocation involving the skin, intestines, and lungs. The patient lived in a non-endemic area. The lung involvement consisted of diffuse alveolar hemorrhage and acute respiratory distress syndrome (ARDS) requiring intubation and mechanical ventilation. Ivermectin neurotoxicity caused a comatose state. The patient recovered from the comatose state after ivermectin removal. He was weaned from mechanical ventilation.

Keywords: Strongyloides Stercolaris Hyperinfection; Ivermectin Neurotoxicity; Acute Respiratory Distress Syndrome; Diffuse Alveolar Hemorrhage

Abbreviation

CT: Computed Tomography; ARDS: Acute Respiratory Distress Syndrome; PEEP: Positive End-Expiratory Pressure; PaO₂: Arterial Pressure of Oxygen; FIO₂: Inspired Fraction of Oxygen; EEG: Electroencephalogram; MRI: Magnetic Resonance Imaging; CDC: Centers of Disease Control; WHO: World Health Organization; PCR: Polymerase Chain Reaction

Introduction

*Strongyloides* spp. infection involves approximately 30 - 100 million people mostly from endemic areas in tropical and subtropical zones. Infection occurs after direct exposure to *Strongyloides* spp. larvae through contaminated soil. After entering the host, the larvae migrate to the intestine and enter the lung. From the lung, the larvae travel to the throat and are swallowed entering into the gastrointestinal system. This organismal auto-cycle can last for a lifetime; the infection may go unnoticed as patients are asymptomatic. The current diagnostic technology has not the optimal sensitivity. When the host enters an immunocompromised state, such as chemotherapy or organ transplantation, the larvae may become aggressive to the host. In these immunocompromised hosts, *Strongyloides* spp. may further disseminate to multiple organs and carry bacteria from the gut to the bloodstream.

Case Presentation

A 48 years old Hispanic male patient with follicular non-Hodgkin’s lymphoma, post-chemotherapy status about three weeks before admission was admitted with nausea, vomiting, right testicular pain, and swelling.

The physical exam was remarkable for the following: chronically ill, underweight with general pallor, multiple purpuric rashes at the periumbilical, chest and hip areas. The right inguinal area had a mass with tenderness.

A computed tomography (CT) scan showed an incarcerated inguinal hernia. A surgical repair corrected the inguinal hernia. Upper endoscopy showed gastritis with negative biopsies. Urine cultures tested positive for drug multi-sensitive *Klebsiella pneumonia*. The therapy consisted of ciprofloxacin and piperacillin/tazobactam as continued from admission.

He started with hypoxemia, and bilateral lung infiltrates which required non-invasive mechanical ventilation. After five days, he developed acute respiratory failure requiring intubation with mechanical ventilation. Bronchoscopy with bronchoalveolar lavage showed dif-
fuse alveolar hemorrhage with the aliquots color progression from pink to bloody. Multiple *Strongyloides stercoralis* larvae were present in the cytology exam of the bronchoalveolar lavage (Figure 1). A skin biopsy at the periumbilical area was done also showing *S. stercoralis* larvae.

Ivermectin 200-mg/kg/day started after identification of the *S. stercoralis*. After five days from ivermectin, he had refractory hypoxemia with diffuse alveolar infiltrates with acute respiratory distress syndrome (ARDS) and septic shock requiring norepinephrine as the vasopressor. The patient had PaO$_2$/FiO$_2$ = 188 (low) with a positive end-expiratory pressure (PEEP) = 15 cmH$_2$O (high) consistent with acute respiratory distress syndrome (ARDS).

He became unresponsive two days after manifesting ARDS. There was no sedation. The electroencephalogram (EEG) was consistent with metabolic encephalopathy without seizures. The brain magnetic resonance imaging (MRI) was unremarkable. The spinal fluid analysis was negative for parasites, fungi, bacteria, or malignant cells. The urine cultures grew *Candida cruzei* and the patient was started on fluconazole 200-mg daily intravenously (IV) with defervescence.

The discontinuation of Ivermectin occurred after concern of neurotoxicity. Two days after discontinuation, the patient opened his eyes spontaneously. A rechallenge drug administration with ivermectin induced the comatose state again and documented as an adverse drug reaction. Albendazole, the secondary drug of choice of the Centers for Disease Control and Prevention (CDC), was effective in treatment continuation.

**Figure 1**: Bronchoalveolar lavage smear stained with hematoxylin and eosin (H&E) stain showing *Strongyloides stercoralis* larvae. Arrows point to larvae.
The acute respiratory failure resolved after two weeks. After four months of physical therapy with critical illness myopathy, the patient was able to move but with limitations (inability to walk). Flow cytometry of the blood showed active follicular non-Hodgkin's lymphoma.

Discussion

*Strongyloides stercoralis*, a roundworm also known as threadworm in some countries, is a nematode present in the soil. Humans acquire the parasite through the skin in contaminated soil. *Strongyloides stercoralis* reproduces in the gastrointestinal tracts of mammals.

The use of footwear lowers the risk of infection [1]. The World Health Organization (WHO) classifies the parasite as a neglected tropical disease affecting 30 - 100 million worldwide [2]. *Strongyloides stercoralis* is a fast-crawling cruiser in the soil. Olfaction mechanism by *Strongyloides* allows detecting skin sweat odorants which cause chemotaxis to the skin. Interestingly, these specific chemotactic odorants are the same that attract mosquitoes. The olfactory mechanism is host-specific, preferentially for humans. Chemotaxis is accelerated by increased temperatures, causing convulsive movements [3]. A high carbon dioxide concentration repels *Strongyloides stercoralis*.

Immunosuppressed patients may develop a hyperinfection, often fatal if not recognized early [4-6]. Blood cancer patients may develop an aggressive infection after chemotherapy [7,8]. The genomes of four *Strongyloides* species have been sequenced and published in 2014 [9].

Gastrointestinal bleeding has been described in *Strongyloides* hyperinfection by the mucosal invasion of the larvae into the antrum of the stomach [10]. In our case, we could not identify the larvae in the gastric mucosa in the upper endoscopy biopsies. Translocation from the intestinal mucosa to the blood by the larvae causes septicemia of bacteria or fungi with an acute increase in proinflammatory cytokines [11,12]. *Klebsiella pneumoniae* and *Candida* spp. have been identified in these cases, probably from intestinal source [13]. Impaired intestinal motility with an intestinal obstruction may cause hyperinfection [4] like in this case report.

Diffuse alveolar hemorrhage happens with pulmonary invasion [14,15]. Periumbilical and proximal thigh petechial purpuric eruption ("thumbprint purpura") occur rarely. The hyperinfection, commonly, has the absence of eosinophilia [16] as in this case report. Bacterial meningitis with *Escherichia coli*, *Streptococcus bovis*, *Enterococcus* spp. occurred in disseminated strongyloidiasis [17-19].

Serologic tests are more sensitive than stool analysis. Real-Time Polymerase Chain Reaction (PCR) tests are sensitive in 64% cases, compared to parasitic stool exam that has a sensitivity of 54%. A meta-analysis published in 2018 suggested that PCR tests are not suitable for screening but may be useful as a confirmatory test due to the low sensitivity of the current technology [20]. Seroconversion occurs with response to treatment [21]. A novel test of urine DNA detection was proven to be superior to stool sample analysis [22]. Through visualization of the larvae through repeated examinations (up to seven) of the stool under the microscope remains the gold-standard diagnostic test. It is challenging to capture larvae due to the low, irregular output inside the intestines.

Nematicides used in environmental soil control of the parasite with fluensulfone had less environmental toxicity and involved most larval stages. However, studies are limited to *Caenorhabditis elegans* in veterinary studies [23,24].

Ivermectin has a statistically significantly higher parasitical cure than albendazole to treat strongyloidiasis (Risk Ratio = 1.79, 95% Confidence Interval = 1.55 to 2.08, n = 478 participants), though adverse events to ivermectin vs albendazole are not statistically significantly different (RR = 0.80, 95% CI = 0.59 to 1.09, n = 518 participants) [25]. For that reason, ivermectin is the drug of choice. Thiabendazole, albendazole, and mebendazole are members of the antiparasitic family of drugs called benzimidazoles. The antiparasitic effect mechanism consists of the inhibition of the beta-tubulin polymerase. The inhibition causes an abnormal synthesis of the microtubule formation, thus paralyzing the nematode by decreasing its energy production [26].

Ivermectin is a macrocyclic lactone working in stimulating membrane permeability using glutamate-gated chloride channels dependent neurotransmission causing defective movement in the nematode with paralysis [24,27]. The filariform adult stage is more resistant to ivermectin effect. Other gated receptors bind to ivermectin in the parasite whose relevance is undetermined. These receptors include the P2X4 receptors, seven acetylcholine receptors, glycine receptors, and histamine-gated chloride channels. Ivermectin decreased the levels of eosinophil and neutrophil count and mast cell granular proteins [28].

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Ivermectin-associated encephalopathy [29] includes stupor, coma, persistent vegetative stage that reverses after removal of the drug. The patient’s improvement effect after drug withdrawal is known as a positive dechallenge test. If the symptoms recur after re-administration, then it is called a positive rechallenge test. Both scenarios occurred, in this reported case, validating drug neurotoxicity using both challenges tests.

Ivermectin does not cross the blood-brain barrier by the protective barrier effect of the transporter P-glycoprotein in the brain. However, a decreased activity of the mcr-1 gene allows crossing to the blood-brain barrier. Up to 28 cases reported in a series concluded that polymorphisms or mutations in the mcr-1 gene increased the permeability of the blood-brain barrier to ivermectin. This last effect caused neurotoxicity and increased accumulation of the drug in the brain that may cause death [30]. Also, drug interactions may cause neurotoxicity by drugs using the elimination pathway of CYP3A4 and may occur with albendazole. For that reason, Ivermectin was discontinued allowing further treatment with albendazole used as the second drug of choice in this case presented.

**Conclusion**

Patients receiving ivermectin may become comatose due to ivermectin induced neurotoxicity. Albendazole is a suitable alternative to ivermectin in these rare cases. Positive rechallenge and dechallenge tests are crucial in the assessment. Assuming brain invasion of the nematode as the cause of coma should be an exclusion diagnosis.

**Bibliography**


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