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The Worm that Clogs the Lungs: Strongyloides Hyper-Infection Leading to Fatal Acute Respiratory Distress Syndrome (ARDS)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 70
Final Diagnosis: Acute respiratory failure
Symptoms: Cough • fever • lethargy
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine

Objective: Rare co-existance of disease or pathology

Background: *Strongyloides stercoralis* is an intestinal helminth. Parasitism is caused by penetration of the larvae through the skin. It is endemic in tropical and subtropical regions of the world and in the United States occurs in the southeastern region. It has a tendency to remain dormant or progress to a state of hyper-infection during immunosuppression.

Case Report: We present the case of a 70-year-old Nigerian who developed fatal ARDS secondary to *Strongyloides* infection after been treated with steroids for treatment of autoimmune necrotizing myopathy. Despite adequate management with mechanical ventilation and appropriate antifungal therapy, the patient died on day 19 of hospitalization.

Conclusions: *S. stercoralis* is known to affect every organ in the body. ARDS is often an overlooked complication of *Strongyloides* hyper-infection, which is often deadly. Immediate diagnosis and treatment are important for patient survival.

MeSH Keywords: Methylprednisolone • Respiratory Distress Syndrome, Adult • Strongyloides

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Background

Strongyloidiasis is an infection caused by *Strongyloides stercoralis* and about 30 million people worldwide are estimated to be affected by this parasite [1–3]. The prevalence of the disease is estimated to be 30–100 million people worldwide, and it is found in all continents except Antarctica [4]. In the United States, *Strongyloides* is relatively common in the southeastern region [5]. Studies in the United States have shown prevalence rates ranging from 0% to 6.1% in the general population and much high rates in immigrants, ranging from 0% to 46.1% [4]. It is associated with low socioeconomic status, rural areas, and agricultural activities [4].

The life cycle includes 2 forms: a free-living rhabditiform larvae (outside the host in the soil) and a parasitic infective filariform [6]. The filariform larvae are able to penetrate the skin, migrate to the submucosa of the host, making its way to the venous circulation, right heart, and lungs, larynx, and gastrointestinal tract [6]. Its hosts include reptiles, birds, and primates, including humans [4].

The parasite has a unique ability to live dormant in the human host, remaining asymptomatic and can be re-activated or cause disseminated infection, especially during an impaired state of cell-mediated immunity. It is known to result in severe illness and occasional death [7]. Hyper-infection of the organism can easily occur in immunosuppressed patients, people with HIV, and those on steroids. Hyper-infection syndrome represents an acceleration of the normal life cycle of *S. stercoralis,* leading to excessive worm burden within the organs. The most common manifestations are gastrointestinal symptoms, diarrhea, nausea, vomiting, loss of appetite, abdominal pain, and dyspnea, and coughing seems to be the most common pulmonary symptom. These non-specific clinical presentations can delay early diagnosis, with attendant poor outcome.

Acute respiratory distress syndrome (ARDS) may be common, but there are few reported cases of ARDS due to *Strongyloides stercoralis.* Therefore, ARDS is an uncommon complication which can be overlooked, resulting in delayed treatment. The use of steroids is known to increase the risk of hyper-infection in patients with strongyloidiasis.

Case Report

Our patient was a 70-year-old Nigerian man who immigrated to the USA about 1 year prior to presentation. His past medical history was significant for controlled hypertension, insulin-dependent diabetes mellitus, hyperlipidemia (on statin therapy), and sickle cell trait. He presented with a 3-month history of progressive bilateral upper- and lower-extremity weakness. Associated symptoms included difficulty rising from a sitting position, fatigue, subjective weight loss, and decreased appetite. He denied any skin changes, previous trauma, sick contacts, recent immobilization/hospitalization, dysphagia, or discoloration of urine. Pertinent physical exam findings included 3/5 strength in all 4 extremities. The patient had no fever, rash, tenderness, or swelling. Significant laboratory findings were elevated liver enzymes (AST/ALT of 266 U/L and 234 U/L), CPK of 8497U/L, Hgb 10 g/dl MCV of 95 fl, and eosinophilia of 10%. In reviewing his medication record, he stated that his statin therapy was discontinued 4 months ago (due to severe myalgia). A right quadriceps muscle biopsy showed elevated 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) levels, consistent with autoimmune necrotizing myopathy, and these findings were suggestive of long-standing inflammatory myopathy. A diagnosis of autoimmune necrotizing myopathy was made, for which he received treatment consisting of weekly methotrexate, prednisone twice daily, and intravenous immunoglobulin. He was discharged on prednisone 20 mg twice daily and oral methotrexate 7.5 mg weekly, and the above medication was continued for 3 months.

Three months later, he was readmitted for lethargy and inability to speak and follow commands. His family reported initial onset of a dry cough and occasional fever and diarrhea, with subsequent deterioration in his overall condition despite being adherent to his medication. Physical examination revealed a febrile patient with temperature of 39.3°C (102.7°F), tachypnea, and tachycardia. Blood pressure was 109/56 mmHg. A lung examination revealed presence of crackles with reduced breath sounds at the lung bases. Cardiac examination was only significant for tachycardia. Oral thrush was also noted. Significant laboratory findings included Na+ 122 mmol/l, hemoglobin 8 g/dl, leukopenia with eosinophilia, and CPK of 163U/L. ABG showed pH 7.57/pCO2 of 27/pO2 89, and lactic acid was 4.5 mmol/L. Computerized tomography (CT) of the head and cerebrospinal fluid from lumbar puncture were both within normal limits, while initial chest X-ray was pertinent for bilateral infiltrates. Upon admission, blood cultures were obtained and patient was started on broad-spectrum antibiotics. On the second day of admission, patient became severely hypoxic, had a cardiopulmonary arrest, and was intubated for hypoxic respiratory failure. ABG showed severe acidosis pH 7.18/PCO_2, 43/PO_2, and 67/HCO_3 15. Return of spontaneous circulation was achieved after 2 min of cardiopulmonary resusitation. A chest X-ray showed bilateral worsening of lower lobe infiltrates (Figure 1A). CT chest, abdomen, and pelvis showed bilateral dense consolidation with air bronchograms consistent with acute respiratory distress syndrome (Figure 1B) in the setting of PaO2/FiO2 of 96 and no cardiac cause. CT was negative for pulmonary embolism. Bronchoscopy with bronchoalveolar lavage (BAL) was performed due to worsening of chest imaging and continued hypoxia despite adequate ventilation

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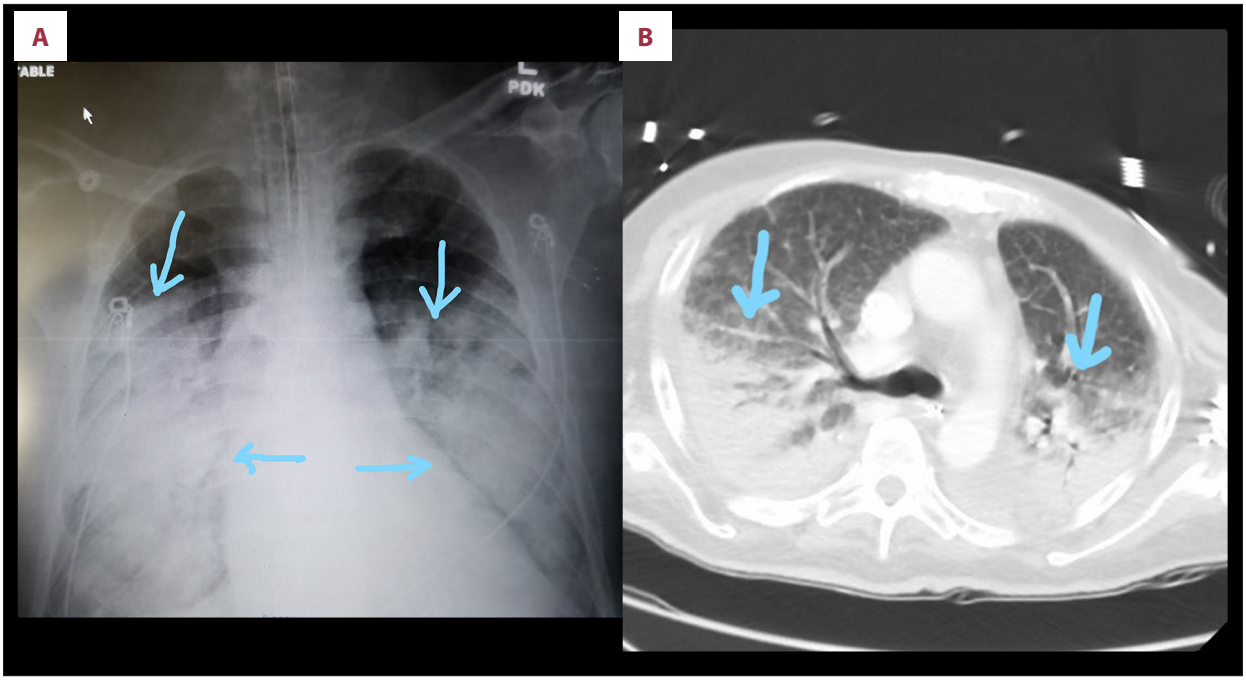

Figure 1. (**A**) Chest X-ray showing bilateral lower-lobe predominant opacities. (**B**) Computed tomography of the chest revealing bilateral consolidations and ground glass opacities.

management. BAL specimen culture was positive for the larvae of *Strongyloides stercoralis*. Serology testing for *Strongyloides* was negative and HIV testing was also negative. An initial stool sample was negative for *Strongyloides* and *Clostridium*, while a second sample collected the next day was positive for the rhabditiform larvae of *Strongyloides*. All steroids previously prescribed for myopathy were suspended and Ivermectin 200 mg/kg and Albendazole 400 mg was initiated. Blood cultures returned positive for *Klebsiella pneumoniae* and appropriate antibiotics were continued. The patient died 19 days after admission, despite prone positioning, high positive end-expiratory pressure with low tidal volume, antibiotics, antifungal therapy, and aggressive critical care management.

Discussion

Strongyloides infection can be insidious in the setting of low parasitic load; however, in an immunocompromised patient, the infection can become disseminated and even result in pulmonary *Strongyloides* [8]. Infection is acquired through penetration of the skin by the filariform larvae (which is the infective stage) of *S. stercoralis*, which are found in the soil. The larvae penetrate the skin and migrates to the bloodstream and lymphatics to the lungs, where it penetrates the alveolar sac. The organism has a unique characteristic of remaining dormant in the human host and cause severe infection during immunosuppression. Our patient likely had a dormant infection prior to moving to the United States. However, the new steroid therapy for his necrotizing myopathy unfortunately resulted to a probable hyper-infection of *Strongyloides*. Immunocompromised patients on steroid therapy and those who have hematological malignancies are the most susceptible patient populations for hyper-infection syndrome and disseminated diseases. Other conditions associated with increased risk include hypogammaglobinemia, anti-tumor necrosis factor receptor therapy, and organ transplant patients [6]. Disseminated Strongyloidiasis involves widespread dissemination of larvae outside of the gut and lungs, often involving the liver, brain, heart, and urinary tract [9–11]. Symptoms of infection can involve any and all organs in the body, especially in hyper-infection. The most common manifestations of hyper-infection syndrome include but are not limited to: fever, nausea and vomiting, anorexia, diarrhea, abdominal pain, dyspnea, wheezing, hemoptysis, and cough.

Although most studies focus on finding the parasite larvae in the stool sample, this is negative in most cases due to low larvae output in stool [6]. Eosinophilia is a common laboratory finding that should raise a high index of suspicion for the presence of parasitic infections; however, this can be absent, leading to a delay in diagnosis [12]. Peripheral eosinophilia is seen in about 16% of disseminated infection [5].

In the setting of pulmonary symptoms, obtaining a BAL improves the diagnosis by revealing the presence of larva, but this can be a late finding, as in the present case. Serology testing with ELISA has been proven to be useful, especially in

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the immunocompetent population, but this can be falsely negative in immunosuppressed patients such as ours.

With *Strongyloides*, sepsis from enteric bacteria such as *Klebsiella* and *Streptococcus bovis* often occurs [13]. This coexistence is due to the translocation of enteric bacteria, resulting in sepsis [13]. All this results in massive cytokine release, leading to capillary permeability. This permeability in the lungs results in acute respiratory distress syndrome, as in our patient.

The mechanism by which *Strongyloides* induces ARDS has been attributed to direct lung parenchymal damage by the parasite [13]. In addition, given its association with bacterial sepsis, the release of endotoxin and increased permeability can also result in lung injury [13]. Published reports also attributed some of the injury to the inflammatory reaction that results from destruction on the high burden of larvae in the in the lungs after the administration of an anthelminthic [13]. In our patient, it is possible that ARDS resulted from a combination of *Strongyloides* hyper-infection and sepsis from *Klebsiella*.

Management of strongyloidiasis is usually supportive in early infection because intestinal infection needs to be established for medications to be effective. Oral therapy includes anti-parasitic agents with Albendazole 400 mg by mouth on an empty stomach twice daily for 3–7 days or Ivermectin (the optimal regimen for treatment is uncertain) standard dosing with 2 single 200 mcg/kg doses administered on 2 consecutive days or administered 2 weeks apart. However, treatment with Ivermectin can be done for 7 days in combination with Albendazole in hyper-infection, as done in our patient. When possible, immunosuppressive agents need to be stopped.

Conclusions

Given the high mortality rate with late diagnosis, *Strongyloides* infection should be ruled out in patients with ARDS, elevated eosinophils, immunosuppression, and coming from an endemic region. Furthermore, this case highlights the importance of testing patients from endemic areas prior to initiation of any immunosuppressive therapy, particularly corticosteroids.

Conflict of interest

None.

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