Acute respiratory distress syndrome due to strongyloides stercoralis in Lupus nephritis

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Abstract
Strongyloides stercoralis is an intestinal helminth that infects humans transdermally, endemic in tropical and subtropical rural regions. In immunocompetent subjects, pulmonary disease caused by the parasite most commonly is asymptomatic to mild disease, but the same can be life threatening in immunocompromised subjects. A 21-year-old male suffering from class IV lupus nephritis was started on steroids and cyclophosphamide. After 1.5 months’ therapy, he presented with diarrhoea, abdominal pain and dyspnea, rapidly worsened to acute respiratory distress syndrome (ARDS) needing ventilation. Bronchoalveolar lavage (BAL) showed Strongyloides stercoralis. He was treated with IV antibiotics, Ivermectin and albendazole with good results.

Keywords: Acute Respiratory Distress Syndrome, Strongyloides stercoralis, Hyper infection, Lupus Nephritis.

Introduction
Strongyloides stercoralis is an intestinal helminth that infects humans transdermally, contracted by humans on walking in barefoot on soil in tropical and sub-tropical regions.¹ Sixty million people are estimated to be infected worldwide. It is mainly encountered in areas where sanitary facilities are poor or in moist environments, such as in mines or tunnels. Low socioeconomic status, alcoholism, white race and male gender are associated with higher prevalence of S. stercoralis stool positivity.² The life cycle includes 2 forms: a free-living rhabditiform larvae (in the soil) and a parasitic infective filariform. 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. Its hosts include reptiles, birds and primates, including humans. This nematode is capable of autoinfection. It causes minimal clinical manifestations in an immunocompetent host. In an immunocompromised host, hyperinfection may be associated with bacterial infection usually of gastrointestinal origin and multiorgan involvement can occur. In immunocompetent subjects, pulmonary disease is unremarkable; however, S. stercoralis infection though rare can be life threatening in immunocompromised subjects. It is associated with the use of corticosteroids in conditions like vasculitis, nephrotic syndromes or organ transplantation, neoplastic diseases, with severe malnutrition and alcoholism. Even though infection is common in tropical regions, hyper-infection with S. stercoralis leading to ARDS in India is rare. We report one such patient of lupus nephritis treated with Prednisolone and cyclophosphamide presenting with hyperinfection, ARDS.

Case
The 21-year-old male presented with generalized edema, anorexia, decreased urine for 3 months and he was diagnosed as lupus nephritis. Historically he had malar rashes, fever and a joint pain 4 years back (Serum Creatinine- 0.8 mg/dl; Anti-nuclear antibody (ANA) and Anti-double stranded deoxyribonucleic acid (Anti-dsDNA) +ve, low C3, proliferative urine sediment) and was treated with Prednisolone, Hydroxychloroquine and Azathioprine. He became symptomatically better, but he had stopped treatment on his own after 2 years of therapy. He underwent renal biopsy this time which revealed Diffuse Proliferative Glomerulo-Nephritis with activity index of 14/24. His serum creatinine was 1.14mg/dl with proteinuria of 7gm per day and was treated with Euro lupus protocol with 3 doses of Methyl
Prednisolone followed by oral prednisolone and injection cyclophosphamide 500mg every 15 days. After 1.5 months of initiation of immunosuppression, he presented with dyspnea on exertion, loose motion, nausea, vomiting and abdominal pain for 2 days. There was no fever or cough. He was a febrile with pulse rate 88/minutes with respiratory rate of 24/minutes. His blood pressure was maintained at 130/90mmHg. He had edema feet and minimum free fluid in the abdomen. Stool examination showed Strongyloides. Dyspnea worsened and he needed ventilation within 2 days. X-ray chest showed miliary shadows and in 2-3 days progressed to ARDS. Computed tomography of the chest was consistent with ARDS. He was treated with intravenous antibiotics and supportive care. BAL effluent showed free living Strongyloides larvae. Mycobacteria were not seen, BAL culture showed E. coli.

Hypoxia needing ventilation with radiological finding of diffuse bilateral infiltrates and patchy opacity and BAL showing Strongyloides, led us to the diagnosis of ARDS due to hyperinfection with Strongyloides stercoralis. He was treated with steroids, broad spectrum antibiotics, fluconazole, albendazole (5 days) & Ivermectin. Ivermectin was continued (12 mg daily for 15 days) till the stool examination showed no larvae. With this, he improved & could be extrubated. His 24 hours’ urine protein excretion was found to be 9.2gms despite steroids so was then started with cyclosporine. Dose was adjusted as per Cyclosporine trough (C0) levels. Edema was managed with fluid restriction & diuretics.

**Discussion**

This case illustrates that Strongyloides stercoralis infection in the immunosuppressed individual may lead to dissemination and present with pulmonary disease as ARDS. The most common and globally distributed human pathogen of clinical importance is Strongyloides stercoralis. The other species, Strongyloides fuelleborni, is found sporadically in Africa and Papua New Guinea. Strongyloidiasis affects anywhere from 30 to 100 million people worldwide and is endemic in Southeast Asia, Latin America, sub-Saharan Africa, and parts of the southeastern United States.

The ova of the female S. stercoralis hatch into rhabditiform (non migratory) larvae that are capable of maturing into non-infectious adults or moulding into filariform (infective) larvae. On walking bare feet on contaminated soil, the filariform larvae invade the patients skin and penetrate the dermis to migrate through the venous system to the lungs, ascend to the trachea. They are swallowed into the digestive tract and infect the small intestinal mucosa. Individuals with an intact immune system are able to control the parasitic burden and the organism can persist for years after the initial inoculation. Autoinfection happens when some larvae, re-enter the blood stream through the bowel wall and migrate through lungs bypassing the soil cycle. Massive autoinfection leads to disseminated strongyloidiasis, the so called hyperinfection syndrome (HS), which can result in severe pulmonary disease with associated septicemia. Pulmonary strongyloidiasis usually manifests as cough, dyspnea, wheezing and

**Fig. 1:** Strongyloides stercoralis larva in the bronchoalveolar lavage

**Fig. 1:** A. X-Ray chest showing military mottling. B. Computerised Tomography chest showing diffused interstitial infiltrates with ground glass opacities in both lung fields.
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hemoptysis along with peripheral eosinophilia. With the development of heavier infection, bronchopneumonia with scattered, patchy alveolar opacities, segmental opacities, lobar opacities or diffuse parenchymal involvement may be present. Patients with altered cellular immunity, especially those receiving long-term steroid therapy, malnutrition, patients with malignancies, kidney allograft recipients, achlorhydria, the use of antacids / H2 blockers, prisoners and other institutionalized people, the parasitic burden increases, the infection disseminates to other tissues and hyperinfection can occur. If the worm molting rate (Rhabditiform larva to filariform larva to adult egg-laying females) is low, hyperinfection might only clinically manifest later, only after steroids are discontinued, once the worm load becomes large.

The first case of ARDS caused by S. stercoralis infection was reported in 1987 and thereafter there are several reports showing that Strongyloides as the cause of ARDS. One of the mechanisms of development of ARDS is due to direct lung parenchymal damage by the parasite. Bacterial and fungal infections often occur in cases of hyperinfection because of the leakage of gut flora from a bowel damaged by moving larvae. The lung injury is also caused by the endotoxin mediated injury from associated bacterial sepsis. Intense inflammatory response evidenced by massive cytokine release following intrapulmonary destruction of the large number of larvae following administration of anthelmintic agents, leading to capillary permeability, can also lead to ARDS. Patients with HTLV-1 seropositivity have been shown to be more likely to develop hyper infective strongyloidiasis, as there is decreased production of IL-4, IL-5, IL-13 and IgE, which are needed for the host defense against helminths. This is postulated to be due to even lower IgE levels in these patients than seen in HTLV-1 negative patients. In the present case, the development of ARDS was possibly due to a combination of heavy parasitic load and superadded bacterial infection of E. coli.

Definitive diagnosis of strongyloidiasis is usually made on the basis of detection of larvae in the stool/sputum/BAL sample. Single stool examination fails to detect larvae in up to 70% of cases due to low larvae output in stool. Repeated examinations of stool specimens improve the chances of finding parasites (sensitivity increases to 50% with 3 and 100% if 7 serial stool samples are examined). Several techniques, such as Baermann concentration method, formalin-ethyl acetate concentration, and direct smear of feces in salined Lugol iodine stain, and nutrient agar plate cultures, are much more sensitive than single stool smear, but they are rarely used in standard in clinical parasitology laboratories. Molecular diagnosis of Strongyloides stercoralis can be made by real-time polymerase chain reaction method targeting the small subunit of the rRNA gene for the detection of S. stercoralis DNA in fecal samples, and this may increase the detection rate. 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. Peripheral eosinophilia is seen in about 16% of disseminated infection. In patients with pulmonary symptoms diagnosis is done by serology testing with ELISA is a very useful tool especially in a immunocompetent patients with sensitivity of 84-88%. Serology can cross-react with other parasites, remain positive for years after successful treatment. Serology may be false negative in immunocompromised patients. Performing BAL and revealing the presence of filariform larvae confirms the diagnosis but is a late finding. X-ray chest findings of diffuse shadows, like butterfly pulmonary opacities, looks similar to pulmonary edema.

Thiabendazole 25 mg/kg orally twice daily for 2 days (uncomplicated infection) to 5 days (disseminated disease) was the drug of choice earlier. Ivermectin (200µg/kg/day for 1–2 days) is more effective and better tolerated than thiabendazole and is the current drug of choice for disseminated strongyloidiasis. A broad-spectrum anthelmintic, Albendazole has a variable therapeutic efficacy with cure rate 45–55%. Mebendazole (200 mg twice daily for 28 days) might be of use in strongyloidiasis but has high risk of development of liver dysfunction. Treatment should be continued until the clinical symptoms resolve and the larvae are no longer detectable. In a systematic review by Buonfrate D et al. showed that cases treated with albendazole or thiabendazole had an increased percentage of deaths among patients than cases treated...
with Ivermectin. Segarra-Newnham recommend that treatment for HS is to administer Ivermectin daily until symptoms resolve and stool tests have been negative, for at least two weeks. The prognosis varies depending on the severity of the strongyloidiasis, but the mortality rate exceeds 70% despite appropriate treatment. In patients with HS complicated by secondary bacterial infection, mortality may exceed 80%.  

In general, screening for asymptomatic carriers is not required. However, many clinicians think that patients in endemic areas who are being considered for corticosteroid or immunosuppressive therapy should be screened via examination of repeated stool samples or ELISA before starting the therapy. Either Ivermectin for 1-2 days or Albendazole for 3 days cures intestinal infestation and prevents HS.

### Conclusion

Strongyloides infection is causes serious disease in immunosuppressed patients. Given the high mortality rate with late diagnosis, Strongyloides infection should be ruled out in patients with ARDS, elevated eosinophils, who are 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 and Cyclophosphomide to prevent serious complication.

### Conflict of Interest

The authors declare that there have no competing interests.

### Source of Funding

None.

### References


### How to cite