Strongyloides stercoralis Hyperinfection Presenting With Symptoms Mimicking Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Hsu-Chung Liu[1,2], Jeng-Yuan Hsu[1,3], Ki-Ming Chang[1]*

[1]*Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital,*
[2]*Division of Chest Medicine, Department of Internal Medicine, Chung-Shan Medical University Hospital, and*
[3]*Institute of Medicine, Chung-Shan Medical University, Taichung, Taiwan, R.O.C.*

Hyperinfection syndrome with *Strongyloides stercoralis* is not uncommon in immunocompromised patients. We present 2 fatal cases of *Strongyloides* hyperinfection with initial presentation mimicking acute exacerbation of chronic obstructive pulmonary disease (COPD). Both cases had a history of COPD and had received systemic steroid treatment before or during admission. The initial chest radiograph in both of these cases showed diffuse axial interstitial pattern. The sputum examinations of Gram stain both yielded larvae of *Strongyloides stercoralis* precipitously. Case 1 developed acute respiratory distress syndrome and bacteremia of *Escherichia coli* and *Klebsiella pneumoniae* soon after admission, and died even after receiving albendazole and antibiotic treatment. Case 2 received albendazole and antibiotic treatment for over 2 weeks, but developed refractory aseptic meningitis and died of septic shock. Neither case had high eosinophil count in peripheral blood during admission. Clinical manifestations of unexplained wheezing and respiratory failure, increased infiltration on chest radiograph, Gram-negative bacteremia, and aseptic meningitis may all be clues of *Strongyloides* hyperinfection. Due to the high mortality rate and severe complications in these patients, clinicians should always keep this diagnosis in mind, especially when dealing with immunocompromised patients. We suggest that a screening test be done for patients who live in endemic areas and those who are going to receive steroids for chronic disease. [*J Chin Med Assoc* 2009;72(8):442–445]

Key Words: acute respiratory distress syndrome, chronic obstructive pulmonary disease, immunocompromised patients, steroids, *Strongyloides* hyperinfection

Introduction

Strongyloides stercoralis is a human intestinal nematode that is considered a common parasitic disease in tropical and subtropical areas. It is endemic in Southeast Asia, Africa, the West Indies, South America, Bangladesh, and Pakistan.[1] Most patients become chronically infected with *S. stercoralis* but remain asymptomatic. Hyperinfection syndrome with *S. stercoralis* describes the syndrome of accelerated autoinfection and large parasite load in the host. It often occurs in patients with compromised immune systems.[2] Patients with hyperinfection syndrome often develop severe respiratory distress and Gram-negative sepsis, which may be caused by the migration of larvae from the gastrointestinal tract to the pulmonary system. Here, we present 2 cases of *Strongyloides* hyperinfection with the initial presentation of acute dyspnea mimicking exacerbation of chronic obstructive pulmonary disease (COPD), with severe complications.

Case Reports

Case 1

An 88-year-old man presented in January 2007 with exacerbated shortness of breath and dry cough. He was a farmer with a history of COPD diagnosed 5 years

*Correspondence to: Dr Ki-Ming Chang, Division of Chest Medicine, Taichung Veterans General Hospital, 160, Section 3, Chung-Kang Road, Taichung 407, Taiwan, R.O.C.
E-mail: yokoki2@gmail.com • Received: November 14, 2008 • Accepted: May 19, 2009

previously. Combination therapy with inhaled long-acting β-adrenergic agonist and inhaled steroids, and oral theophylline were prescribed regularly at our outpatient chest department. The most recent pulmonary function test had revealed a positive bronchodilator test, a post-bronchodilator FEV_1/FVC ratio of 54%, and a post-bronchodilator FEV_1 of 1.24 L (72% of predicted value). Oral prednisolone 10 mg daily for 2 weeks was prescribed for acute exacerbation of COPD at our outpatient department about 1 month before this admission.

Due to increased sputum purulence and exacerbated dyspnea, the patient visited our emergency department and was admitted. Physical examination on admission revealed a well-nourished male (body weight, 72 kg; body height, 162 cm) with moderate respiratory distress, a temperature of 38.8°C, a pulse of 108 beats/minute, and a respiratory rate of 26 breaths/minute. Diffuse wheezing breath sounds were also noted. The initial laboratory evaluation revealed hematocrit of 36.6%, white blood cell count of $7.3 \times 10^3/mm^3$ (94.3% neutrophils, 3% lymphocytes, 2.6% monocytes, 0.1% eosinophils), and platelet count of $178 \times 10^3/mm^3$. Arterial blood gas analysis demonstrated a pH of 7.43, $PaCO_2$ of 34.4 mmHg, PaO_2 of 72 mmHg, and bicarbonate of 23.1 mmol/L on room air. Chest radiography on admission showed axial interstitial pattern of bilateral lung fields (Figure 1). Medication on admission included intravenous steroids with hydrocortisone 300 mg daily, empiric antibiotic with augmentin, and nebulized bronchodilators of β-adrenergic agonists and anticholinergic agents.

The patient suffered acute respiratory failure with desaturation several days after admission. Follow-up chest radiography showed diffuse alveolar infiltration, and acute respiratory distress syndrome (ARDS) was considered from his serial data and clinical course. Sputum examination and Gram stain were performed after endotracheal intubation, which revealed several rhabditiform larvae of *S. stercoralis* (Figure 2). A subsequent stool examination was also positive for rhaditiform larvae. The anthelmintic agent oral albendazole 400 mg daily was prescribed for *Strongyloides* hyperinfection. At this time, *Escherichia coli* and *Klebsiella pneumoniae* were twice isolated from blood culture. The empiric antibiotic was changed to ceftriaxone according to a drug sensitivity test, but the patient died 2 days later due to disease progression and refractory septic shock.

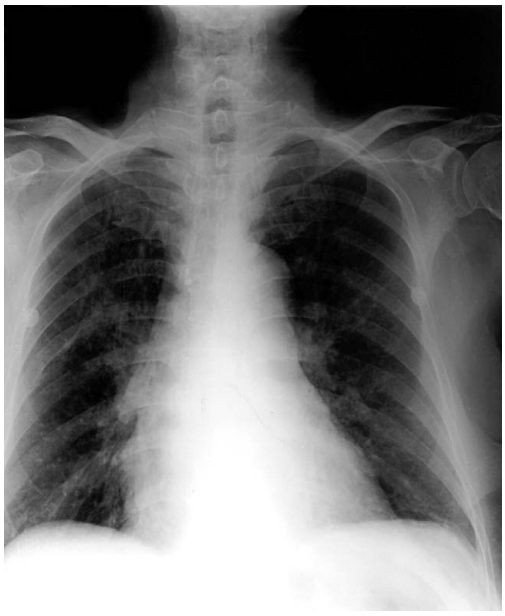

Figure 1. Case 1: posteroanterior radiography shows axial interstitial pattern of bilateral lung fields.

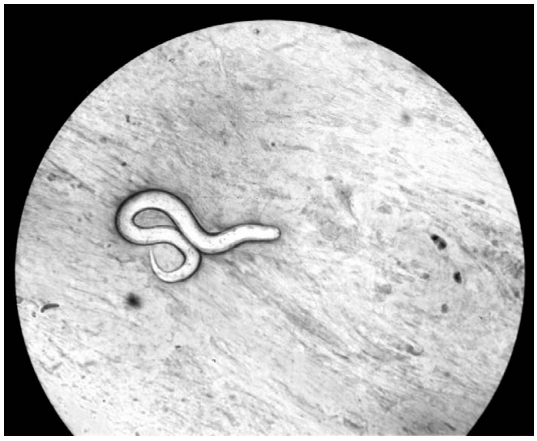

Figure 2. Case 1: sputum examination and Gram stain show rhabditiform larvae of *Strongyloides stercoralis* with few neutrophils (original magnification, 100×).

Case 2

A 76-year-old man presented in August 2004 with exacerbated shortness of breath, poor appetite, and abdominal distension. He was a retired soldier and had a history of COPD that had been diagnosed over 10 years ago. The most recent pulmonary function test showed a negative bronchodilator test, a post-bronchodilator FEV_1/FVC of 61%, and a post-bronchodilator FEV_1 of 1.42 L (77% of predicted value). Medication with inhaled bronchodilators and prednisolone 20 mg daily for 2 weeks were prescribed at our outpatient department before admission.

On review of systems, the patient denied diarrhea, constipation, and abdominal pain, but said he had had a poor appetite for a long time. Physical examination on admission showed a poorly-nourished male (body

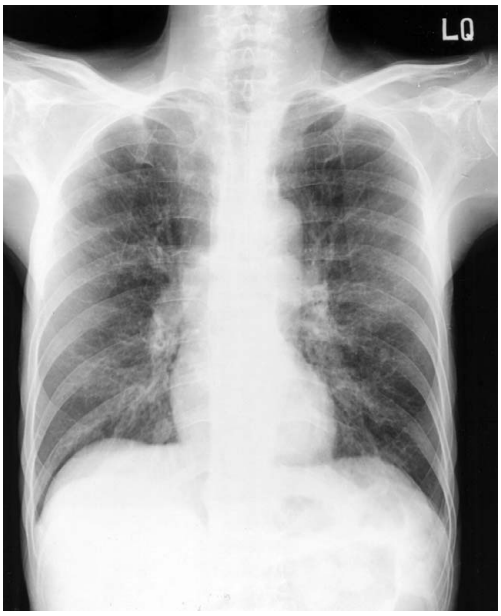

Figure 3. Case 2: posteroanterior radiography shows diffuse axial interstitial pattern.

weight, 38 kg; body height, 161 cm) with moderate respiratory distress, temperature of 37.8°C, pulse of 134 beats/minute, and respiratory rate of 24 breaths/minute. Diffuse wheezing breath sounds, hypoactive bowel sounds and tympanic abdominal percussion were noted. There was no focal tenderness or rebounding pain on the abdomen. The initial laboratory evaluation revealed hematocrit of 33.8%, white blood cell count of $11.3 \times 10^3/mm^3$ (93.1% neutrophils, 4.4% lymphocytes, 2.3% monocytes, 0.1% eosinophils), and platelet count of $240 \times 10^3/mm^3$. The chemistry data showed serum sodium of 124 mg/dL, potassium of 2.5 mg/dL, albumin of 2.7 mg/dL, and normal liver function. Arterial blood gas analysis demonstrated pH of 7.51, $PaCO_2$ of 37.6 mmHg, PaO_2 of 65 mmHg, and bicarbonate of 30.6 mmol/L on room air. Chest radiography showed diffuse axial interstitial pattern of the lungs (Figure 3). Abdominal radiography revealed ileus of the intestine. The medication on admission included nebulized bronchodilators, empiric antibiotics with ampicillin and sulbactam, and theophylline.

The patient developed respiratory failure 2 days after admission and received intubation and mechanical ventilation. Serial chest radiograph showed collapse of the left lower lung, which was reopened the next day. The initial sputum examination revealed many neutrophils with few Gram-negative bacilli. One week after admission, the patient continued to suffer from intermittent fever. A lumbar puncture was performed due to his drowsy consciousness and neck stiffness. Examination of cerebrospinal fluid revealed a white blood cell count of $360/mm^3$ (66% neutrophils, 34% lymphocytes), glucose of 45 mg/dL, protein of 220 mg/dL, and lactate of 70 mg/dL. The empiric antibiotic was changed to ceftriaxone under the suspicion of bacterial meningitis. After that, repeated sputum examinations revealed unexpected rhabditiform larvae of *S. stercoralis*, which were also found in stool examinations. The fever subsided gradually after anthelmintic treatment with albendazole 400 mg daily. However, the fever recurred even though he had received albendazole for 2 weeks. Subsequent sputum and stool examinations did not reveal any detectable larvae. At this time, his consciousness had not improved and another lumbar puncture showed no improvement in meningitis. Cultures and examinations of cerebrospinal fluid revealed no bacteria and no parasites. Nevertheless, his condition deteriorated and he developed septic shock even after the antibiotic was changed to piperacillin. He died 1 month after admission.

Discussion

The ability to replicate in the human host permits autoinfection of *S. stercoralis* leading to chronic infection. Chronic infection in patients can remain undetected for decades due to few or no symptoms. However, hyperinfection syndrome can occur in immunocompromised patients, and it has a high mortality rate (up to 87%).[2] The immunocompromised population includes those undergoing steroid therapy or chemotherapy, and those with hematologic malignancy, kidney transplants, bone marrow transplants, human T-lymphotropic virus type 1 infection, and hypogammaglobulinemia.[3] The 2 cases presented here had both been receiving systemic steroids for COPD control. Case 1 was a farmer and so had a history of contact with soil. Case 2 was emaciated (body mass index, $14.7\ kg/m^2$) and had had abdominal symptoms for a long time prior to admission. We presume that they had both been previously chronically infected with *S. stercoralis* but had subtle symptoms only. The transformation of chronic infection to hyperinfection syndrome may have been caused by the steroid therapy they had been prescribed from the outpatient department. In Case 1, after admission, the intravenous steroids prescribed for the symptoms that mimicked COPD exacerbation may have worsened his hyperinfection syndrome.

Complications of hyperinfection and disseminated disease include bacterial and fungal infections, sepsis, and meningitis. Secondary bacterial infection occurs because of the leakage of gut flora from an ulcerative

bowel mucosa or as a result of bacteria carried on the surface of the larvae when they migrate into the host's circulation. Therefore, blood cultures commonly grow *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas*, and *Enterococcus fecalis*. Case 1 developed a typical manifestation of bacteremia caused by *Strongyloides* hyperinfection. Case 2 ultimately developed septic shock without definite bacterial evidence; however, he developed meningitis, which is the most common central nervous system involvement of *Strongyloides* hyperinfection. In patients with meningitis associated with *S. stercoralis*, cerebrospinal fluid may show parameters of aseptic meningitis,[4] Gram-negative bacterial meningitis,[5] or parasitic meningitis.[6] Our patient developed aseptic meningitis that was refractory to treatment.

The pulmonary manifestation of *Strongyloides* hyperinfection may induce bronchospasms, cough, and respiratory failure.[7] It can mimic acute exacerbation of underlying COPD or new-onset asthma.[8,9] In addition, blood counts in chronic infection often show eosinophilia, but the condition of eosinophilia is often absent in hyperinfection syndrome. In a study by Newberry et al,[7] 3 of 7 patients with *Strongyloides* hyperinfection died, and all of the fatal cases had eosinophil counts $<400/mm^3$. Neither of our cases showed eosinophilia during admission. Therefore, the absence of eosinophilia in patients cannot exclude the diagnosis. With regard to the chest imaging findings of *Strongyloides* hyperinfection, pulmonary infiltration on chest radiograph has multiple patterns. It may present as diffuse or focal interstitial infiltration, alveolar opacity, nodular lesions, and even cavitation.[10] Both of our cases presented with diffuse axial interstitial pattern on admission and Case 1 later progressed to ARDS.

The diagnosis of *Strongyloides* hyperinfection is not difficult due to the high numbers of larvae that exist in stool, sputum, and even body fluid. Except for stool examinations, the larvae can be identified in sputum, bronchoalveolar lavage fluid, bronchial brushings, lung biopsies, or pleural fluid by microscopic examinations of Gram, Papanicolaou, or acid-fast stains.[3,8,10,11] Patients in endemic areas with COPD or asthma receiving steroids are at risk of hyperinfection syndrome. Therefore, screening these high-risk patients is an important preventative measure. Although several immunodiagnostic assays have been developed for screening latent *Strongyloides* infection, a highly specific and sensitive diagnostic test is still lacking.[2]

In conclusion, the clinical manifestations of *Strongyloides* hyperinfection are diverse. Besides showing gastrointestinal symptoms, it may mimic acute exacerbation of underlying COPD or new-onset asthma, and be complicated with Gram-negative bacteremia and meningitis. Therefore, stool and sputum examinations are important when the clinical picture is suspicious for *Strongyloides* hyperinfection, with or without eosinophilia. We suggest that high-risk patients in endemic areas should receive screening tests before receiving immunosuppressant therapy.

References

1. Boulware DR, Stauffer WM, Hendel-Paterson BR, Rocha JL, Seet RC, Summer AP, Nield LS, et al. Maltreatment of *Strongyloides* infection: case series and worldwide physicians-in-training survey. *Am J Med* 2007;120:541–8.
2. Siddiqui AA, Berk SL. Diagnosis of *Strongyloides stercoralis* infection. *Clin Infect Dis* 2001;33:1040–7.
3. Keiser PB, Nutman TB. *Strongyloides stercoralis* in the immunocompromised population. *Clin Microbiol Rev* 2004;17:208–17.
4. Vishwanath S, Baker RA, Mansheim BJ. *Strongyloides* infection and meningitis in an immunocompromised host. *Am J Trop Med Hyg* 1982;31:857–8.
5. Link K, Orenstein R. Bacterial complications of strongyloidiasis: *Streptococcus bovis* meningitis. *South Med J* 1999;92:728–31.
6. Dutcher JP, Marcus SL, Tanowitz HB, Wittner M, Fuks JZ, Wiernik PH. Disseminated strongyloidiasis with central nervous system involvement diagnosed antemortem in a patient with acquired immunodeficiency syndrome and Burkitts lymphoma. *Cancer* 1990;66:2417–20.
7. Newberry AM, Williams DN, Stauffer WM, Boulware DR, Hendel-Paterson BR, Walker PF. *Strongyloides* hyperinfection presenting as acute respiratory failure and Gram-negative sepsis. *Chest* 2005;128:3681–4.
8. Smith B, Verghese A, Guiterrez C, Dralle W, Berk SL. Pulmonary strongyloidiasis: diagnosis by sputum gram stain. *Am J Med* 1985;79:663–6.
9. Nwokolo C, Imohiosen EA. Strongyloidiasis of respiratory tract presenting as "asthma". *Br Med J* 1973;2:153–4.
10. Woodring JH, Halfhill H 2nd, Reed JC. Pulmonary strongyloidiasis: clinical and imaging features. *AJR Am J Roentgenol* 1994;162:537–42.
11. Siddiqui AA, Guiterrez C, Berk SL. Diagnosis of *Strongyloides stercoralis* by acid-fast staining. *J Helminthol* 1999;73:187–8.