www.nature.com/clinicalpractice/neph

Respiratory hyperinfection with *Strongyloides stercoralis* in a patient with renal failure

Mohan Rajapurkar*, Umapati Hegde, Mahesh Rokhade, Sishir Gang and Kalpesh Gohel

SUMMARY

Background A 40-year-old female presented to hospital with rapidly progressive renal failure secondary to antineutrophil cytoplasmic antibody (ANCA)-positive crescentic glomerulonephritis. She was started on immunosuppressive therapy (oral steroids and oral cyclophosphamide) and hemodialysis. She re-presented with persistent fever, persistent vomiting and dry cough 135 days after starting immunosuppression. A chest X-ray revealed left lower zone consolidation. Repeated sputum Gram stains were negative, and both sputum and blood cultures were sterile. A sputum smear was negative for acid-fast bacilli. The patient's fever did not respond to empirical antibiotics or antitubercular therapy. Bronchoscopic alveolar lavage and stool examination revealed larval forms of *Strongyloides stercoralis*.

Investigations Physical examination, urine and blood analyses, chest X-ray, bronchoscopy and bronchoalveolar lavage examination.

Diagnosis Respiratory hyperinfection syndrome due to *S. stercoralis*.

Management Ivermectin, albendazole and empirical broad-spectrum antibiotics for bacterial superinfection (amoxicillin and clavulanic acid for 5 days followed by piperacillin and tazobactam plus levofloxacin).

KEYWORDS albendazole, hyperinfection syndrome, ivermectin, nonresolving pneumonia, *Strongyloides stercoralis*

CME

M Rajapurkar is Medical Director and Head of Nephrology, U Hegde is a Consultant Nephrologist, M Rokade is a Resident in Nephrology, S Gang is a Consultant Nephrologist, and K Gohel is a Consultant Nephrologist, all at the Muljibhai Patel Urological Hospital, Nadiad, Gujarat, India.

Correspondence
*Muljibhai Patel Urological Hospital, Dr Virendra Desai Road, Nadiad, Gujarat 387001, India
mmr@icenet.net

Received 26 February 2007 **Accepted** 16 July 2007
www.nature.com/clinicalpractice
doi:10.1038/ncpneph0598

Vanderbilt Continuing Medical Education online
This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

THE CASE

A 40-year-old female presented to a private hospital having had a low-grade fever for 2 months, a cough for 7 days and poor appetite, nausea and vomiting for 3–4 days. She also had watery stools and had been anuric for 2 days. She had no history of hemoptysis, hematemesis or melena. Notable past medical history included pain in both knees and in the small joints of her hands since the age of 3 years. The patient had no history of analgesic abuse. No associated urinary symptoms were observed. On admission to the private hospital her serum creatinine level was 194.5 μmol/l (2.2 mg/dl). Urine examination showed grade 2+ proteinuria with microscopic hematuria. She was treated with empirical antibiotic therapy (cefuroxime) for 7 days, which resulted in an improvement in her symptoms.

Physical examination on admission to a second hospital 2 days after the completion of the course of antibiotic therapy revealed bipedal edema, a temperature of 38.9 °C (102 °F), a blood pressure of 180/100 mmHg and normal sensorium. Cardiovascular examination revealed an S3 gallop and chest examination revealed bibasilar crepitations. The patient also had congestive hepatomegaly and moderate ascites.

Laboratory evaluation at the second hospital revealed that the patient was anemic with a hemoglobin level of 80 g/l (8 g/dl) and a white blood cell count of 17.38×10^9/l (neutrophils 72%, lymphocytes 24%, eosinophils 2% and monocytes 2%). Urinalysis revealed grade 3+ proteinuria, 5–10 white blood cells per high-power field, numerous red blood cells and occasional granular casts. The patient's serum creatinine level was 671.8 μmol/l (7.6 mg/dl); she was started on thrice-weekly hemodialysis in view of this finding and because of her anuria.

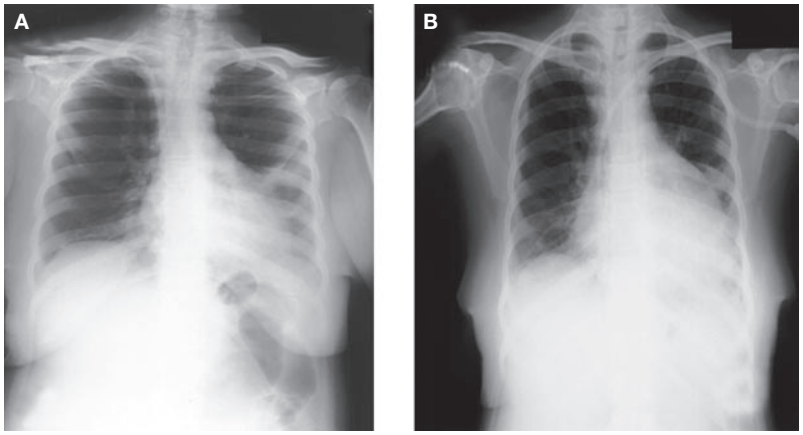

Figure 1 Chest radiographs of the patient. (**A**) Chest X-ray at presentation showing inhomogeneous opacity over the left lower zone suggestive of left lower lobe consolidation. (**B**) Chest X-ray showing complete resolution of left lower lobe consolidation after anthelmintic treatment.

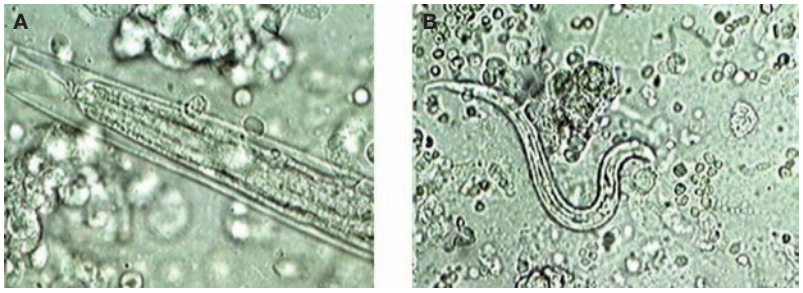

Figure 2 Larval forms of *Strongyloides stercoralis* isolated from bronchoalveolar lavage. (**A**) Magnification ×40. (**B**) Magnification ×20.

A left percutaneous renal biopsy performed 2 days after initiation of hemodialysis showed 100% glomerular crescents as well as IgM and complement component C3 deposition on immunofluorescence. The patient's serum sample was positive for cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA), and antinuclear antibody (ANA), and weakly positive for antiglomerular basement membrane antibody (5.1 U/ml). The patient received treatment with methylprednisolone 1 g/day for 3 days and was then started on oral cyclophosphamide 125 mg/day and prednisolone 50 mg/day. She was discharged 16 days after starting this treatment and continued to receive thrice-weekly dialysis on an outpatient basis along with immunosuppression (cyclophosphamide and prednisolone). Her renal function was assessed at weekly intervals.

Three weeks after being discharged, the patient presented again to the second hospital with fever, cough and vomiting. The cause of the fever was unknown, but it responded to intravenous antibiotics. Cyclophosphamide was discontinued and steroids were tapered off over the subsequent 3 weeks in view of the crescents in 100% of glomeruli on renal biopsy, because of the occurrence of infection while the patient was on immunosuppressive therapy and because there were no signs of renal recovery.

The patient continued to receive maintenance hemodialysis twice weekly as an outpatient, but 3 months later she again presented with high-grade fever, cough and vomiting. She was poorly dialyzed and was malnourished. Her subclavian catheter was found to be infected and was removed. A chest X-ray revealed left lower zone consolidation (Figure 1A). The patient was started on empirical broad-spectrum antibiotics, initially amoxicillin and clavulanic acid for 5 days, and then piperacillin and tazobactam plus levofloxacin for 12 days. Despite sufficient duration and dosage of appropriate antibiotics and adequate dialysis, the patient's fever, low appetite, cough and vomiting continued for 20 days. Blood cultures drawn on multiple occasions were sterile and the patient's sputum smear was negative for acid-fast bacilli. As a result of her lack of response to intravenous antibiotics, the patient was started on empirical four-drug antitubercular therapy (isoniazid, rifampicin, pyrazinamide and ethambutol).

As the patient's symptoms persisted despite 2 weeks of antitubercular therapy, she was diagnosed as having nonresolving pneumonia. At this point, she underwent bronchoscopy and bronchoalveolar lavage. Examination of her bronchoalveolar lavage fluid revealed *Strongyloides stercoralis* larvae (Figure 2) and scanty growth of amikacin-sensitive and gatifloxacin-sensitive *Klebsiella* species, but no acid-fast bacilli or fungi. Her sputum and stool samples were positive for larval forms of *S. stercoralis*. In view of the patient's symptoms, pneumonia, and the fact that her bronchoalveolar lavage fluid and stool showed larval forms of *S. stercoralis*, a diagnosis of hyperinfection syndrome due to *S. stercoralis* infection was made. She was treated with a single dose of ivermectin (200 μg/kg) and a 2-week course of twice-daily albendazole 400 mg. The patient improved clinically and was discharged from hospital after completion of the albendazole course. Fifteen days after completion of therapy, however, she returned to hospital with a fever and a dry cough. Stool

and sputum samples again revealed larval forms of *S. stercoralis*. A repeat course of ivermectin (200 μg/kg) daily for 5 days followed by 2 weeks of albendazole 400 mg twice daily was initiated. The patient's symptoms improved and a repeat stool and sputum examination after 2 weeks of therapy showed no evidence of strongyloidiasis. Her chest X-ray showed complete resolution of the left lower zone consolidation (Figure 1B). The patient underwent renal transplantation 6 months later. Strongyloidiasis did not recur, but the patient died a month after transplantation as a result of loss of graft function.

Box 1 Differential diagnosis of nonresolving pneumonia in an immunosuppressed individual.

Legionella infection
Tuberculosis
Aspergillus fungi
Resistant bacterial pathogens such as *Streptococcus pneumoniae* (pneumococcus), multidrug-resistant *Haemophilus influenzae*, multi-drug-resistant *Pseudomonas aeruginosa* and meticillin-resistant *Staphylococcus aureus*
Parasitic infections such as respiratory hyperinfection syndrome due to *Strongyloides stercoralis, Toxoplasma gondii*, *Toxocara canis*, and *Ascaris suum*
Endobronchial carcinoma

DISCUSSION OF DIAGNOSIS

Differential diagnosis

The case presented here is one of crescentic glomerulonephritis in a patient in a tropical setting who received short-term immunosuppression and presented with nonresolving pneumonia. The differential diagnosis of nonresolving pneumonia in an immunosuppressed individual is summarized in Box 1. Most of these diagnoses were excluded by the patient's clinical history and laboratory examination (sterile blood cultures and sputum negative for acid-fast bacilli). Bronchoalveolar lavage, sputum and stool examination revealed numerous *S. stercoralis* larvae. A diagnosis of hyperinfection syndrome due to *S. stercoralis* infection was made on the basis of these findings. It is important to note that the patient did not have eosinophilia at her initial presentation; such a finding would have raised a suspicion for a parasitic infection.

Epidemiology and life cycle of *Strongyloides stercoralis*

About 30 million people in 70 countries are infected with *S. stercoralis*. This parasite is endemic in tropical and subtropical regions worldwide.[1,2] *S. stercoralis* has a complex life cycle in which parthenogenetic females embedded in the intestinal mucosa of the host lay embryonated eggs, which hatch in the intestine. The resultant rhabditiform larvae are excreted in the feces and either develop directly into free-living adult worms or develop into filariform larvae. The filariform larvae mature into adult worms, which initiate the infection by burrowing into the mucosa of the duodenum and jejunum. Free-living adult worms live for up to 5 years. These worms reproduce sexually to produce eggs, from which rhabditiform larvae hatch, and in turn develop into another generation of free-living adults or filariform larvae. Filariform larvae can penetrate the skin of the human host to gain access to the blood. These larvae then spread to the lungs hematogenously, ascend the tracheobronchial tree to reach the pharynx, are swallowed, and finally reach the duodenum, where they mature into adult egg-laying females. The resulting rhabditiform larvae are either passed out in the feces, or cause autoinfection. Autoinfection involves rhabditiform larvae developing into infective filariform larvae within the gastrointestinal tract. These infective filariform larvae then penetrate the intestinal mucosa and migrate to the definitive site in the small intestine or to parenteral sites such as the lungs, liver, heart, central nervous system or endocrine glands.[2,3]

Hyperinfection syndrome

The term 'hyperinfection' is used to describe a condition of accelerated autoinfection. During *S. stercoralis* hyperinfection, worm numbers increase massively until they become detectable in extraintestinal regions, particularly the lungs. Signs and symptoms of increased larval migration, such as the development or exacerbation of gastrointestinal and pulmonary symptoms, are, therefore, present in patients with hyperinfection syndrome. The hallmark of hyperinfection is an increased number of larvae in stool or sputum samples.[4] Individuals with an intact immune system are able to control the parasitic burden of *S. stercoralis*, and the organism can persist for years after the initial inoculation. In patients with impaired cell-mediated immunity, however, (e.g. those using corticosteroids, and those with malignancies, malnutrition, or acquired

immunodeficiency syndrome), the parasitic burden increases, the infection disseminates to other tissues and hyperinfection can occur. Ciclosporin has activity against strongyloidiasis, but it is unknown whether its effect is sufficient to reduce the risk of hyperinfection. The clinical manifestations of *S. stercoralis* hyperinfection vary widely and the condition's onset can be acute or insidious. Fever and chills are not always present and can indicate the presence of an associated bacterial infection.[4] If the worm molting rate (i.e. the rate at which rhabditiform larvae develop intraluminally into filariform larvae and complete a cycle to become adult egg-laying females) is low, hyperinfection might only clinically manifest after steroids are discontinued, once the worm load becomes large. A low molting rate might have been responsible for the delay in hyperinfection in the patient presented here. Other factors that might have contributed to the delay in this patient include the presence of end-stage renal disease, poor dialysis and malnutrition.

Diagnosis

The diagnosis of strongyloidiasis should be suspected in patients with clinical signs and symptoms of the disease (e.g. fever, cough, vomiting, and eosinophilia), or indicative serologic findings (e.g. increased IgE and positive enzyme-linked immunosorbent assay results). Eosinophilia—the only clue to the infestation in many cases of strongyloidiasis—might be suppressed or absent in disseminated disease because of a concomitant pyogenic infection or because of steroid administration.[5] Serum IgE concentration is often elevated in patients with disseminated disease. Definitive diagnosis of strongyloidiasis is usually made by the detection of larvae in a stool sample.[1,2,6] Many uncomplicated strongyloidiasis cases, however, have a very low intestinal worm load and minimal larvae excretion.[2,7] The diagnostic sensitivity of larvae detection increases with repeated stool examinations. One study showed that diagnostic sensitivity was only 30% with one stool sample, but that it increased to 50% with three consecutive samples and 100% with seven consecutive samples.[8] Aspiration of duodenojejunal fluid or use of the string test® (Enterotest; HDC Corporation, Milpitas, CA), a method for sampling duodenal fluid, might be required to detect *S. stercoralis* larvae if they are not detectable in the stool sample.

As disseminated infections involve large numbers of worms, detection of *S. stercoralis* larvae is usually easiest in patients with hyperinfection. In patients with hyperinfection, larvae can be detected in wet preparations of sputum, bronchoalveolar lavage fluid, lung biopsy samples, or in pleural fluid stained with Gram, Papanicolaou or acid-fast stains.[9] In the absence of repeated stool examinations, a highly sensitive and specific enzyme-linked immunosorbent assay might be useful for the detection of either symptomatic or asymptomatic strongyloidiasis, but this technique can give false negative results in immunocompromised hosts.[10]

Chest X-ray findings vary widely between patients. Pulmonary infiltrates, if present, can be alveolar or interstitial, diffuse or focal, and unilateral or bilateral in nature. Pulmonary consolidation, cavitation and abscess formation have been reported in some patients with strongyloidiasis.[2] Bacterial superinfections (e.g. by Gram-negative bacilli) are often responsible for the differences in chest X-ray findings between patients.[11,12]

DISCUSSION OF TREATMENT

For many years, thiabendazole was the drug of choice for the treatment of *S. stercoralis* infections. This medication is given in 25 mg/kg doses twice daily (for 2 days for uncomplicated strongyloidiasis and for 5 days for disseminated disease), and has a cure rate of more than 90%.[13] As thiabendazole is associated with gastrointestinal adverse effects and a high rate of relapse,[2] and because it is not very effective in disseminated disease, however, it is less commonly used now.[14]

Ivermectin (200 μg/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 follow-up stool examination or duodenal aspiration 2 weeks after ivermectin therapy can be used to confirm whether the treatment has been effective. In chronic cases of strongyloidiasis, 1–2 doses of ivermectin should be given every 3 months until three consecutive stool samples, each taken 2 weeks after ivermectin therapy, are negative.[3,6,7,14]

Albendazole is a broad-spectrum anthelmintic that is poorly absorbed orally and has variable therapeutic efficacy (cure rate 45–55% in strongyloidiasis). This agent has, however, been used successfully in hyperinfection syndrome and remains a viable treatment alternative to ivermectin.[3,7,15] Albendazole is administered

orally in 400 mg doses given twice daily for 3 days for uncomplicated strongyloidiasis and for 7–10 days for hyperinfection.

Optimum anthelmintic activity of azole drugs and ivermectin requires the patient to have an intact immune system. Treatment should be continued until the clinical symptoms resolve and the larvae are no longer detectable. The most practical detection methods for *S. stercoralis* larvae only sample the intestinal compartment (i.e. the stool or duodenal aspirate). Assuming that the autoinfective cycle takes a period of at least 2 weeks, repeated courses of treatment and screening should continue until fecal cultures have been negative for at least 2 weeks after the initiation of therapy.[4]

Mebendazole (200 mg twice daily for 28 days) might be of use in strongyloidiasis, but it is not recommended because of associations with liver dysfunction.[14]

Patients with both strongyloidiasis and human T-lymphotropic virus type 1 (HTLV-1) express high levels of interferon γ and transforming growth factor β1, which are associated with a poor response to therapy.[16] HTLV-1 infection should, therefore, be ruled out in patients who do not respond well to treatment.

CONCLUSIONS

The case presented here demonstrates that a simple parasitic infection such as strongyloidiasis can cause nonresolving pneumonia in an immunosuppressed host in a tropical setting. Fatal hyperinfection caused by *S. stercoralis* can be prevented with a high index of suspicion, along with early detection and treatment of asymptomatic chronic infections. In patients at high risk of strongyloidiasis (e.g. those living in endemic areas) comprehensive assessment should include a stool sample examination and an eosinophil count to detect latent *S. stercoralis* infection before any therapy or immunosuppression is started.

References

1 Genta RM (1989) Global prevalence of strongyloidiasis: critical review with epidemiologic insights into the prevention of disseminated disease. *Rev Infect Dis* **11:** 755–767
2 Siddiqui AA and Berk SL (2001) Diagnosis of *Strongyloides stercoralis* infection. *Clin Infect Dis* **33:** 1040–1047
3 Grove DI (1996) Human strongyloidiasis. *Adv Parasitol* **38:** 251–309
4 Keiser PB and Nutman TB (2004) *Strongyloides stercoralis* in the immunocompromised population. *Clin Microbiol Rev* **17:** 208–217
5 Arsic-Arscnigevic V *et al.* (2005) Fatal *Strongyloides stercoralis* infection in a young woman with lupus glomerulonephritis. *J Nephrol* **18:** 787–790
6 Heyworth MF (1996) Parasitic diseases in immunocompromised hosts: cryptosporidiosis, isosporiasis, and strongyloidiasis. *Gastroenterol Clin North Am* **25:** 691–707
7 Liu LX and Weller PF (1993) Strongyloidiasis and other intestinal nematode infections. *Infect Dis Clin North Am* **7:** 655–682
8 Nielsen PB and Mojon M (1987) Improved diagnosis of *Strongyloides stercoralis* by seven consecutive stool specimens. *Zentralbl Bakteriol Mikrobiol Hyg [A]* **263:** 616–618
9 Siddiqui AA *et al.* (2002) Strongyloides stercoralis. In *Infections of the Gastrointestinal Tract*, edn 2, 1113–1126 (Eds Blaser MJ *et al.*) Philadelphia: Lippincott Williams & Wilkins
10 Abdalla J and Saad M *et al.* (2005) An elderly man with immunosuppression, shortness of breath, and eosinophilia. *Clin Infect Dis* **40:** 1535–1536
11 Woodring JH *et al.* (1994) Pulmonary strongyloidiasis: clinical and imaging features. *AJR Am J Roentgenol* **162:** 537–542
12 Woodring JH *et al.* (1996) Clinical and imaging features of pulmonary strongyloidiasis. *South Med J* **89:** 10–19
13 Marcos L *et al.* (2005) Thiabendazole for the control of *Strongyloides stercoralis* infection in a hyperendemic area in Peru. *Rev Gastroenterol Peru* **25:** 341–348
14 Zaha O *et al.* (2000) Strongyloidiasis—progress in diagnosis and treatment. *Intern Med* **39:** 695–700
15 Horton J (2000) Albendazole: a review of anthelmintic efficacy and safety in humans. *Parasitology* **121 (Suppl 1):** S113–S132
16 Satoh M *et al.* (2002) Reduced efficacy of treatment of strongyloidiasis in HTLV-I carriers related to enhanced expression of IFN-γ and TGF-β1. *Clin Exp Immunol* **127**: 354–359

Acknowledgments

The authors would like to thank Dr Anila Mathews for taking the photographs shown in Figure 2.

Competing interests

The authors declared no competing interests.