

Mortality Associated with Concurrent Strongyloidosis and Cytomegalovirus Infection in a Patient on Steroid Therapy

BEVERLY Y. WANG, M.D.¹, SASHIKALA KRISHNAN, M.D.²,
AND HENRY D. ISENBERG, PH.D.³
MARCH 1999 NUMBER 2 VOLUME 66:128-132

From the Department of Pathology, Mount Sinai School of Medicine, New York, NY. ¹Department of Pathology, Elmhurst Medical Center, Elmhurst, NY; and Departments of ²Pathology and ³Clinical Microbiology, Mount Sinai Medical School of Medicine, New York, NY.

Address correspondence to Henry D. Isenberg, Ph.D., Professor of Clinical Microbiology, Center for Clinical Laboratories, Box 1122, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Abstract

Disseminated strongyloidosis has been recognized with increasing frequency, often in patients who are immunocompromised or have received steroid therapy. In addition, disease due to cytomegalovirus (CMV) is noted in immunodeficient hosts. We report on a 55-year-old Puerto Rican man who received steroid treatment for oropharyngeal pemphigus vulgaris and developed abdominal symptoms with alternating constipation and diarrhea. The clinical work-up did not reveal specific abnormalities, but the patient died of cardiopulmonary failure. At the postmortem examination, the patient had evidence of strongyloidosis and CMV disease. This report reviews both this case and the literature, and discusses the overlapping infections of strongyloidosis and CMV disease in this patient who had received steroid therapy.

Key Words: Disseminated strongyloidosis, autoinfection, cytomegalovirus, steroid therapy, cardiopulmonary failure.

Introduction

Strongyloidosis is relatively uncommon in the United States but widespread in other regions. The infection is sporadic in the southern United States and Puerto Rico. Infected patients can present with rash and various pulmonary and abdominal complaints. Parasite dissemination associated with gram-negative bacterial sepsis has been reported in immunocompromised hosts (1-5). Hyperinfection due to *Strongyloides* depends on host immunity. And host immunity can be altered by iatrogenic modalities or natural diseases such as malignancies, acquired immunodeficiency syndrome (AIDS) or other medical conditions that may require corticosteroid therapy, chemotherapy and radiation, as well as organ transplantation (2, 6-10).

The infectious form of *Strongyloides stercoralis* is the long and slender filariform larva which develops in soil (11). Infection takes place by larval penetration through the skin. The larvae are then transported by the venous circulation through the right heart to the lung, where they enter the alveoli and then migrate up to the glottis and are swallowed. The final destination is the duodenum and proximal jejunum. Following a brief cycle, the female lays eggs within the intestinal mucosa. When hatched, rhabditiform larvae enter the bowel lumen and are expelled via the feces. These develop into free-living male and female worms which eventually produce infectious filariform larvae, to repeat the process. However, this parasite can also reproduce asexually. In this situation, rhabditiform larvae in the intestine develop into filariform larvae that penetrate the bowel and gain access to the circulation to repeat the infectious cycle. This autoinfection is a unique process of *S. stercoralis* that permits reappearance of the disease for decades after departure from endemic areas (2, 5, 12–14). A substantial number of patients are asymptomatic, but overwhelming infection may occur especially in patients immunosuppressed by diseases or therapy. When it occurs, this autoinfective cycle may occasionally become fatal, since the larvae are frequently accompanied by intestinal microorganisms that initiate sepsis in all loci visited by the larvae. While the hyperinfection state is characterized by severe gastrointestinal and respiratory tract involvement along with skin rash and/or bacteremia, it is curable when diagnosed and treated promptly (1, 6, 15). When disseminated strongyloidosis occurs in patients who complain of nonspecific abdominal pain, nausea, vomiting, diarrhea and weight loss, often following steroid therapy for unrelated conditions, mortality is high, around 80% (2, 6).

Cytomegalovirus (CMV) is a DNA virus, infecting 70–90% of the population without overt disease manifestation. Serious disease is reported in neonate and immunocompromised hosts. Asymptomatic, reactivated CMV infections are commonly associated with human immunodeficiency virus (HIV) infection. Serious end-organ CMV disease (e.g., retinitis, colitis and encephalitis) is considerably less frequent (16–18). This is a report about a case of fatal disseminated strongyloidosis in a Hispanic male who lived in New York City for the past 30 years. Postmortem examination revealed disseminated strongyloidosis concurrent with CMV disease. These two etiologic agents have not been described as occurring together even in patients on various steroid regimens.

Case Report

A 55-year-old Hispanic man was admitted to the Elmhurst Medical Center, Elmhurst, Queens, NY, complaining of abdominal pain for 3 weeks. The patient had been well until 5 months prior to admission, when he developed painful ulcers of the buccal mucosa and gingiva. Biopsies of those ulcers were diagnostic for pemphigus vulgaris. At that time, treatment with a daily dose of 60 mg of prednisone was begun. Two months prior to admission, the lesions had nearly resolved and a tapering dose of prednisone was instituted. Then, 3 weeks prior to admission, sharp and diffuse abdominal pain developed, with alternating diarrhea and constipation, not related to meals, and unresponsive to over-the-counter histamine (H_2) blockers. The patient became anorexic and lost about 30 pounds.

Historically, the patient was a native of Puerto Rico, residing in New York City for the past 30 years; he had visited Puerto Rico 5 years earlier. He had no history of fever, nausea, vomiting, skin rash or coughing, and denied use of tobacco or alcohol, or medication noncompliance.

On physical examination, the patient was moderately obese. His temperature was 38° C, pulse rate 80/min, and blood pressure 130/70 mmHg without orthostatic changes. There were no oral lesions. Abdominal exam was notable for diffuse tenderness on deep palpation. There was neither distention nor hepatosplenomegaly. On rectal exam, there was occult blood positive brown stool. Skin examination was normal.

The values for aspartic acid aminotransferase, alkaline phosphatase, bilirubin, amylase, and magnesium were within normal limits. The prothrombin and partial thromboplastin times were normal. The chest X-ray was also normal. The flat and upright abdominal X-rays demonstrated a large amount of stool.

The patient received normal saline infusion at 50 mL/hr, followed by furosemide intravenously. The use of oral fluid was restricted and the patient was started on intravenous solucortef 100 mg every 8 hours. Ciprofloxacin was administered intramuscularly.

Laboratory values obtained on the day following admission revealed serum osmolality 260 mOsm/L, urine osmolality 780 mOsm/L, urine sodium 48 mEq/L, urine potassium 46 mEq/L, and urine chloride 54 mEq/L.

There was some improvement in the abdominal pain. On the third hospital day, the serum sodium measured 128 mMol/L and fluid restrictions were discontinued. Blood cultures were negative and the morning serum cortisol measured 31 µg/dL.

On the fifth hospital day, the patient developed increasing abdominal pain accompanied by nausea and vomiting. The vomitus was brown and feculent, and had a coffee-ground appearance. The blood pressure dropped to 90/60 mmHg. The abdominal X-ray showed dilated loops of small bowel. At this point, the patient went into cardiopulmonary arrest and expired. A postmortem examination was performed.

Results

Autopsy examination revealed heavily congested and consolidated lungs weighing 2 kg. The small intestine showed mucosal hyperemia, and the cecum was dilated with areas of ulceration. The colonic mucosa was hyperemic with multiple, large, irregular ulcerations. Some of these ulcers appeared hemorrhagic and linear, particularly in the areas of sigmoid, along with several diverticula. Microscopic sections of the lungs showed diffuse alveolar change with features of adult respiratory distress syndrome (ARDS). In addition, the right lung showed acute pneumonia (postmortem culture grew *Klebsiella pneumoniae*). An unexpected, striking finding was the presence of disseminated strongyloidosis involving multiple organs: lungs (**Fig. 1A**), large intestines (**Fig. 1C**), and mesenteric

lymph nodes (**Fig. 1D**). Other organs involved were the heart, liver, pancreas, esophagus, and small intestines, as well as skeletal muscle. In addition, many CMV inclusions were identified in the lungs (**Fig. 1B**) and throughout the gastrointestinal tract.

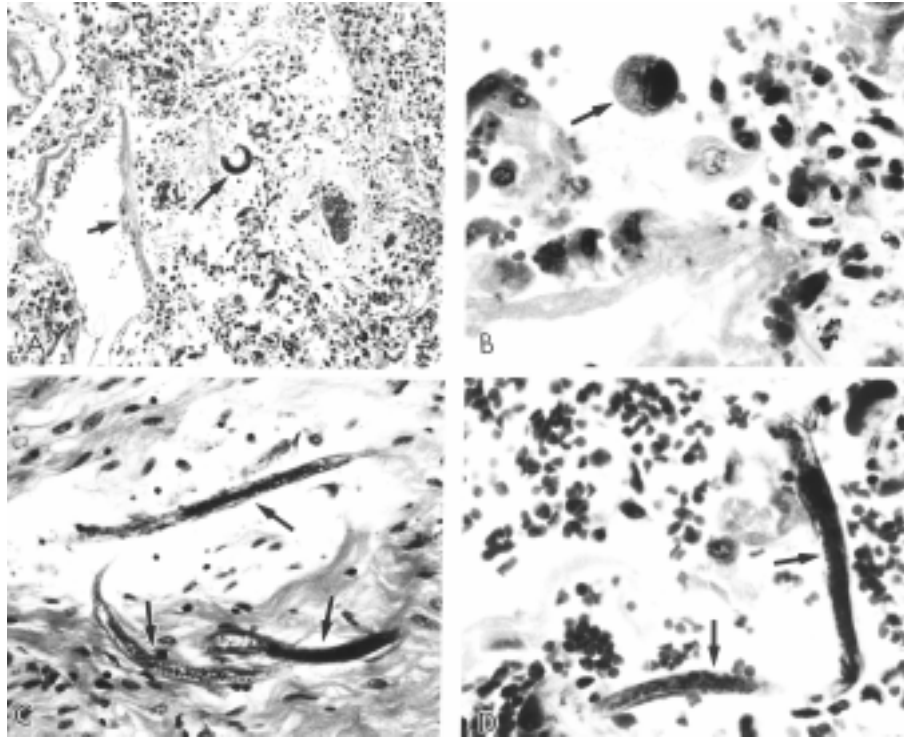


Fig. 1. A. Section of the lung showing extensive acute pneumonia with diffuse alveolar changes of ARDS. A rhabditiform larva of *Strongyloides* migrating through the lung parenchyma (arrow), adjacent alveolar space lined by hyaline membrane (arrowhead) (H-E, x200). B. High magnification of lung section showing a large cell containing a classic CMV inclusion with background of acute pneumonia (arrow) (H-E, x800). C. Section of large intestinal wall showing three larvae (arrows) (H-E, x400). D. Section of mesenteric lymph node showing two larvae (arrows) (H-E, x400). The 2 liters of peritoneal fluid did not yield any larvae.

Discussion

Most of the mainland U.S. patients in whom *S. stercoralis* has been diagnosed originally came from the Caribbean region (4, 5, 12–14). Over the past 2 decades, cases of unsuspected strongyloidosis following corticosteroid therapy have become more frequent (19–22); when overwhelming infection with *S. stercoralis* accompanies unrelated conditions that are treated with corticosteroids, this treatment leads to the activation of dormant parasites and autoinfection. Reasonable caution should be exercised when patients who have resided for prolonged periods in

areas endemic for the parasites receive therapy that leads to immunosuppression. Clinically, overt CMV disease also results from the depression of immunocompetence. Nevertheless, the concurrent emergence of strongyloidosis and CMV has not been described, in the immunosuppressed population at risk.

The diagnosis of strongyloidosis can be made quickly and noninvasively if clinically suspected (2). Laboratory examinations of at least 3 consecutive stool specimens, using direct and concentration methods, should be performed. A reliable and inexpensive serological test (ELISA) is available to detect anti-*Strongyloides* antibodies (23–26). In systemic strongyloidosis, routinely stained Papanicolaou smears of sputum can reveal the filariform larvae of *S. stercoralis* (10, 27). Duodenal aspirates, sometimes obtained with a string-test capsule, can lead to detection of rhabditiform larvae of *S. stercoralis*. Various culture methods may also be used (24).

Patients may present with vague abdominal symptoms such as anorexia, nausea, vomiting, and bloating and cramping with alternating constipation/diarrhea, attributable to various etiologies, but the diagnosis of strongyloidosis is made most often at necropsy, as in this case. This diagnosis may be missed primarily for lack of clinical suspicion, especially with patients from endemic areas (2, 21).

The respiratory symptoms in strongyloidosis are caused by the migrating larvae producing alveolar hemorrhage, edema and inflammatory changes. Adult worms are known to cause chronic bronchitis or asthma-like symptoms (19). Very often, the larvae carry intestinal microorganisms that further complicate the pulmonary lesions caused by the parasites. Enteropathy due to direct mucosal damage, impairment of intestinal lymphatic function and overwhelming presence of worms may impair absorption (2, 14, 20); involvement of liver results in elevated alkaline phosphatase and bilirubin (28).

Risk factors for systemic strongyloidosis include leukemia, lymphoma, chronic infection, transplantation and immunosuppressive therapy (6, 20, 21, 29, 30). Eosinophilia, if present, is an alarming clue. However, eosinophil counts tend to be lower in systemic infection and with the hyperinfection syndrome after corticosteroid therapy (2, 14, 25).

Prevention of disseminated strongyloidosis can be achieved in patients when an early diagnosis is made and prompt medical intervention is applied. Successful treatment in cases of disseminated strongyloidosis is achieved with conventional drugs like thiabendazole and mebendazole (31), but mortality in disseminated strongyloidosis remains at about 80% (1). Death is frequently the result of either secondary bacterial infections or respiratory failure .

In retrospective autopsy series, CMV inclusions have been observed in the lungs of more than 90% of AIDS patients. Both strongyloidosis and CMV are considered to be opportunistic infections in these patients (7, 8, 17, 32). However, the relationship between strongyloidosis and CMV is unknown; the coexistence of CMV with other opportunistic pathogens has not been fully

elucidated. In Jacobson's experience (16), CMV pneumonitis is almost always an incidental diagnosis after bronchoscopy performed on patients with symptomatic interstitial lung disease. The isolated presence of CMV in bronchoscopy specimens may or may not be associated with progressive clinical pneumonitis (16). CMV infections of the GI tract include colitis, esophagitis and gastritis. Successful use of ganciclovir to prevent and treat CMV infection has been widely accepted. Foscarnet, another antiviral agent, may also be used in the treatment of CMV infection, often in combination with ganciclovir for immunosuppressed patients, or with zalcitabine for therapy of AIDS patients (33–35).

The possibility that CMV or other viruses may be carried by the migrating larvae is an intriguing factor, despite our inability to support this view in this HIV-negative patient, who had resumed steroids for an unrelated condition (3, 16, 17, 22). This case illustrates the need to consider carefully the combination of therapeutic regimens to be used in those patients at risk, even though the clinical manifestations are subtle. To the best of our knowledge, this report represents the first case in which both *S. stercoralis* and CMV were found. This suggests that some viruses may join enteric bacteria as companions of migrating larvae (18, 20, 21).

Acknowledgment

The authors greatly appreciate the valuable suggestions and comments of Dr. Noam Harpaz and the excellent photographic assistance of Mr. Norman Katz and Mr. Micha Zeffren.

References

1. Simpson WG, Gerhardstein DC, Thompson JR. Disseminated *Strongyloides stercoralis* infection. *South Med J* 1993; 86:821–825.
2. Scowden EB, Schaffner W, Stone WJ. Overwhelming strongyloidiasis. An unappreciated opportunistic infection. *Medicine (Baltimore)* 1978; 57:527–544.
3. Igra-Siegman Y, Kapila R, Sen P, et al. Syndrome of hyperinfection with *Strongyloides stercoralis*. *Rev Infect Dis* 1981; 3:397–407.
4. Genta RM. Global prevalence of strongyloidiasis: Critical review with epidemiologic insights into the prevention of disseminated disease. *Rev Infect Dis* 1989; 11:755–767.
5. Vermund SH, LaFleur F, MacLeod S. Parasitic infections in a New York City hospital: Trends from 1971 to 1984. *Am J Public Health* 1986; 76:1024–1026.
6. Purtilo DT, Meyers WM, Connor DH. Fatal strongyloidiasis in immunosuppressed patients. *Am J Med* 1974; 56:488–493.

7. Glezerov V, Masci JR. Disseminated strongyloidiasis and other selected unusual infections in patients with the acquired immunodeficiency syndrome. In: Rotterdam H, editor. Progress in AIDS Pathology. Vol. II. Philadelphia: Field & Wood Inc.; 1990. pp. 137–142.
8. Climent C, DeVinatea ML, Lasala G, et al. Geographical pathology profile of AIDS in Puerto Rico: The first decade. *Mod Pathol* 1994; 7:647–651.
9. Yim Y, Kikkawa Y, Tanowitz H, Wittner M. Fatal strongyloidiasis in Hodgkin's disease after immunosuppressive therapy. *J Trop Med Hyg* 1970; 73:245–249.
10. Scoggin CH, Call NB. Acute respiratory failure due to disseminated strongyloidiasis in a renal transplant recipient. *Ann Intern Med* 1977; 87:456–458.
11. Piekarski G. *Medizinische Parasitologie in Tafeln*. 2nd ed. Berlin: Springer Verlag; 1973.
12. Aziz EM. *Strongyloides stercoralis* infestation: Review of the literature and report of 33 cases. *South Med J* 1969; 62:806–810.
13. Imperato PJ, Shookhoff HR, Marr JS, et al. Parasitic infections in New York City: Incidence and epidemiology. *N Y State J Med* 1977; 77:50–56.
14. Milder JS, Walzer PD, Kilgore G, et al. Clinical features of *Strongyloides stercoralis* infection in an endemic area of the United States. *Gastroenterology* 1981; 80:1481–1488.
15. Thompson JR, Berger R. Fatal adult respiratory distress syndrome following successful treatment of pulmonary strongyloidiasis. *Chest* 1991; 99:772–774.
16. Jacobson MA. Cytomegalovirus disease in acquired immunodeficiency disease. In: Opportunistic infections in patients with the acquired immunodeficiency syndrome. Leoung G, Mills J, editors. New York and Basel: Marcel Dekker Inc.; 1989. pp. 195–213.
17. Waxman AB, Goldie SJ, Brett-Smith H, Matthay RA. Cytomegalovirus as a primary pathogen in AIDS. *Chest* 1997; 111:128–134.
18. Grigg A, Chapman R, Szer J. Fatal CMV pneumonia associated with steroid therapy after autologous transplantation in patients previously treated with fludarabine. *Bone Marrow Transplant* 1998; 21:619–621.
19. Sen P, Gil C, Estrellas B, et al. Corticosteroid-induced asthma: A manifestation of limited hyperinfection syndrome due to *Strongyloides stercoralis*. *South Med J* 1995; 88:923–927.

Wang

20. Cruz T, Reboucas G, Rocha H. Fatal strongyloidiasis in patients receiving corticosteroids. *N Engl J Med* 1966; 275:1093–1096.
21. Willis AJP, Nwokolo C. Steroid therapy and strongyloidiasis. *Lancet* 1966; 1:1396–1398.
22. Kaslow JE, Novey HS, Zuch RH, Spear GS. Disseminated strongyloidiasis: An unheralded risk of corticosteroid therapy [letter]. *J Allergy Clin Immunol* 1990; 86:138 .
23. Eveland LK, Kenney M, Yermakov V. Laboratory diagnosis of autoinfection in strongyloidiasis. *Am J Clin Pathol* 1975; 63:421–425.
24. Garcia LS, Bruckner DA. Intestinal nematodes. In: *Diagnostic medical parasitology*. 3rd ed. Washington (DC): ASM Press; 1997. pp. 240–245.
25. Nutman TB, Ottesen EA, Leng S, et al. Eosinophilia in southeast Asian refugees: Evaluation at a referral center. *J Infect Dis* 1987; 155:309–313.
26. Genta RM, Douce RW, Walzer PD. Diagnostic implications of parasite-specific immune responses in immunocompromised patients with strongyloidiasis. *J Clin Microb* 1986; 1099–1103.
27. Kenney M, Webber CA. Diagnosis of strongyloidiasis in Papanicolaou-stained sputum smears. *Acta Cytol* 1974; 18:270–273.
28. Poltera AA, Katsimbura N. Granulomatous hepatitis due to *Strongyloides stercoralis*. *J Pathol* 1974; 113:241–245.
29. Rogers WA, Nelson B. Strongyloidiasis and malignant lymphoma. *JAMA* 1966; 195:685–687.
30. Davidson RA, Fletcher RH, Chapman LE. Risk factors for strongyloidiasis. *Arch Intern Med* 1984; 144:321–324.
31. Coulter C, Walker DG, Gunsberg M, et al. Successful treatment of disseminated strongyloidiasis. *Med J Aust* 1992; 157:331–332.
32. Murray JF, Garay SM, Hopewell PC, et al. Pulmonary complications of the acquired immunodeficiency syndrome: An update. *Am Rev Respir Dis* 1987; 135:504–509.
33. McCormack JG, Bowler SD, Donnelly JE, Steadman C. Successful treatment of severe cytomegalovirus infection with ganciclovir in an immunocompetent host. *Clin Infect Dis* 1998; 26:1007–1008.

Wang

34. Van Droogenbroeck J, De Ceuninck M, Snoeck HW, et al. Successful treatment of cytomegalovirus encephalitis in a patient with Hodgkin's disease in remission. *Ann Hematol* 1998; 76:179–181.
35. Aweeka FT, Brody SR, Jacobson M, et al. Is there a pharmacokinetic interaction between foscarnet and zalcitabine during concomitant administration? *Clin Ther* 1998; 20:232–243.