Pulmonary *Cryptococcus* Infection After Mono-Chemotherapy With Gemcitabine

Yu-Guang Chen MD, Te-Yu Lin MD, Gen-Min Lin MD, and Jung-Chung Lin MD PhD

Mono-chemotherapy with gemcitabine (difluorodeoxycytidine) is an effective cancer chemotherapy, and is often used instead of a more effective but more toxic combination chemotherapy regimen. Infection associated with gemcitabine is very rare. We present a case of *Cryptococcus neoformans* pneumonia that developed after 5 courses of gemcitabine for advanced bladder carcinoma. Lung biopsy and antigens demonstrated *C. neoformans*. The pneumonia resolved after antifungal therapy. Key words: gemcitabine; pneumonia; *Cryptococcus neoformans*. [Respir Care 2011;56(3):339–341. © 2011 Daedalus Enterprises]

Introduction

Fungal infections have become a worldwide healthcare problem over the last decade. The most common community-acquired pathogens in fungal pneumonia are *Aspergillus* species, followed by *Candida* species.¹ Based on those analyses, pulmonary *Cryptococcus* infections are rare. Mono-chemotherapy with gemcitabine (difluorodeoxycytidine, brand name Gemzar) effectively treats non-small-cell lung, pancreatic, bladder, and breast cancers, and has been used in patients who do not tolerate more effective but more toxic chemotherapy agents.^{2,3} There have been

few reports of *Cryptococcus* in non-hematologic malignancies treated with cytotoxic therapy. We present a case of acute *Cryptococcus neoformans* pneumonia that developed after mono-chemotherapy with gemcitabine for 5 weeks, in a patient with advanced bladder carcinoma.

Case Report

A 75-year-old man with type 2 diabetes mellitus and advanced urothelial carcinoma of the bladder was admitted for chemotherapy and radiotherapy in December 2006. On admission he underwent chest radiograph. No specific infiltration was observed. He received weekly gemcitabine (1,500 mg) mono-chemotherapy for 5 weeks. At the end of that treatment period he presented with a productive cough, intermittent fever, and chills.

Physical examination found an oral temperature 38.4°C, a heart rate 108 beats/min, a respiratory rate 26 breaths/min, and basilar crackles over both lungs. Laboratory tests showed a white-blood-cell count of 6.1×10^9 cells/L, with 74% neutrophils, and C-reactive protein of 15.23 mg/dL (normal < 0.5 mg/dL). Plain chest radiograph showed new diffuse interstitial markings, patchy consolidation, and ground-glass opacities in both lungs (Fig. 1). Chest computed tomogram revealed multiple nodules, with ill-defined consolidated patchy air spaces in both lungs, predominantly in the sub-pleural region (Fig. 2). Empirical antibiotics (piperacillin and tazobactam) were administered intravenously.

Sputum cultures showed no pathological bacteria. Tuberculosis culture, polymerase chain reaction test for *Pneumocystis carinii*, and test for *Cytomegalovirus* antigen were

Yu-Guang Chen MD is affiliated with the Department of Internal Medicine, Tri-Service General Hospital, Taipei, Republic of China. Te-Yu Lin MD and Jung-Chung Lin MD are affiliated with the Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, Taipei, Republic of China. Gen-Min Lin MD is affiliated with the Division of Cardiology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Republic of China, and with the Division of General Medicine, Department of Internal Medicine, Hualien Armed Forces General Hospital, Hualien, Taiwan, Republic of China.

The authors have disclosed no conflicts of interest.

This research was partly supported by Tri-Service General Hospital grants TSGH-C97-83 and TSGH-C97-84.

Correspondence: Jung-Chung Lin MD PhD, Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, No. 325, Section 2, Cheng-Gong Road, Neihu 114, Taipei, Republic of China. E-mail: jclin@ndmctsgh.edu.tw.

DOI: 10.4187/respcare.00652

Fig. 1. Radiograph after intensive gemcitabine chemotherapy shows diffuse interstitial infiltration and patchy opacity over both lungs.

Fig. 2. Chest computed tomogram shows multiple nodules and ill-defined consolidated patches in both lungs, predominantly in the sub-pleural region, and mild to moderate pleural effusion over the right lung.

negative. The test for *Cryptococcus* antigen was positive, with a titer of 1:64.

Computed-tomography-guided lung biopsy was performed, and pathology confirmed pulmonary *C. neoformans* (Fig. 3). A subsequent lumbar puncture excluded extensive spread of *C. neoformans*. We prescribed fluconazole, 400 mg/d intravenous for one week, and orally for

Fig. 3. Lung biopsy specimen (Grocott's methenamine silver stain, magnification 400) shows interstitial pneumonia, including thickened alveolar septa and fungal spores in the alveoli.

4 weeks. His fever gradually subsided. In a series of follow-up plain chest radiographs, the pneumonia patches completely recovered. He was free of *Cryptococcus* infection 6 weeks after starting fluconazole.

Discussion

Gemcitabine is a deoxycytidine anti-metabolite, anti-neoplastic agent. It is a pyrimidine analog, and its mechanism of action is the inhibition of DNA replication and repair in tumor cells. Gemcitabine can sequentially induce programmed cell death or apoptosis, and it is most commonly used to treat non-small-cell lung, pancreatic, bladder, and breast cancers.^{2,3}

Gemcitabine's adverse effects include pancytopenia, nausea, vomiting, appetite loss, flu symptoms, and temporary elevated liver function. The pancytopenia can begin 10–14 days after initiating gemcitabine, and resistance to infection usually reaches its lowest point during that period. Infections associated with gemcitabine are rare.

Fungi are extremely common in the community, where they exist as free-living saprobes. They often reside on body surfaces as transient environmental colonizers, and usually do not infect immunocompetent people. Impaired T lymphocyte function from cancer chemotherapy and depressed neutrophil function increase the risk of fungal infection. The most common site of infection in cancer patients is the lung, and the spectrum of pulmonary infection depends upon the underlying immunologic deficiency. Several immunologic deficits can be present in one patient, which makes the patient susceptible to various opportunistic pathogens. In neutropenic patients, Gram-negative bacteria predominate early, whereas fungal infections are common if neutropenia persists. *Aspergillus* species are by

far the most common cause of fungal pneumonia in neutropenic patients, followed by *Zygomycetes* and *Fusarium*.⁴ Pulmonary *Cryptococcus* infections are very common in patients with human immunodeficiency virus, and are becoming increasingly common in patients with malignancies.^{5,6}

C. neoformans is an encapsulated, heterobasidiomycetous fungus found throughout the world. It is associated with the excreta of certain birds, including pigeons, canaries, and cockatoos, and with several species of eucalyptus tree.¹ Clinically, the most common isolates are serotype A, typically isolated from soil and avian excreta. Based on its infective mechanism, most of these infections are acquired by inhaling environmental propagules from the soil and bird droppings.

C. neoformans infection is rare in immunocompetent patients.⁷ With the increasing use of immunosuppressive anti-neoplastic therapies, organ transplantation, catheter insertion, dialysis, and other invasive procedures, *C. neoformans* infection has become more common. The clinical manifestations of *C. neoformans* infections are variable and range from asymptomatic colonization to life-threatening disease.^{1,8,9} Cryptococcal meningitis is the most frequent manifestation, and pulmonary cryptococcal infection is the second most frequent. Patients may present with evidence of acute infection, such as fever, chest pain, cough, weight loss, and sputum production. In a severely immunocompromised host, cryptococcal pneumonia can rapidly progress to acute respiratory distress syndrome.^{1,8} Patients at risk for cryptococcal infection should avoid high-risk environments.

Pulmonary cryptococcosis can manifest as acute or non-acute pneumonia. Acute cryptococcal pneumonia is rare, sometimes corresponds with symptomatic primary infection, and can be complicated by severe acute respiratory distress syndrome. Non-acute cryptococcal pneumonia is more common, and usually corresponds with reactivation, and is often associated with meningitis or other body localizations.¹⁰ Most *C. neoformans* infections are associated with impaired cell-mediated immunity.¹¹ Humoral immunity also contributes to protection against *C. neoformans*.¹²

As a consequence, isolation of *C. neoformans* in a respiratory specimen warrants the physician's attention. In some cases a *C. neoformans* isolate can indicate a pulmonary infection, either alone or in association with a disseminated disease. In other cases it may indicate an asymptomatic carrier.¹³ It was clear in our patient that sputum

fungal culture and the pellets from bronchoalveolar lavage were negative for the possibility of pulmonary *Cryptococcus* reactivation and that acute pulmonary cryptococcosis may have resulted from a massive environmental exposure to soil contaminated by bird droppings. These findings suggested less of a possibility of infection of the upper airway and lower airway colonization than acute infection.

We strongly suspect that the *C. neoformans* infection in our patient was community-acquired, and we emphasize that the environment may play a role in *Cryptococcus* infection in cancer patients, even those receiving less toxic chemotherapy. This is a very important lesson in the care and management of patients on chemotherapy.

REFERENCES

1. Duperval R, Hermans PE, Brewer NS, Roberts GD. Cryptococcosis, with emphasis on the significance of isolation of *Cryptococcus neoformans* from the respiratory tract. *Chest* 1977;72(1):13-19.
2. Bramhall SR, Schulz J, Nemunaitis J, Brown PD, Baillet M, Buckels JA. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. *Br J Cancer* 2002;87(2):161-167.
3. Xie DR, Liang HL, Yang Q, Guo SS, Jiang ZM. [Meta-analysis on gemcitabine of fixed-dose rate infusion plus oxaliplatin as first-line therapy for advanced pancreatic cancer.] *Ai Zheng* 2007;26(8):895-899. *Article in Chinese*.
4. Pagano L, Fianchi L, Leone G. Fungal pneumonia due to molds in patients with hematological malignancies. *J Chemother* 2006;18(4):339-352.
5. Friedman GD, Fessel J, Udaltsova N, Hurley LB. Smoking and cryptococcosis in AIDS patients. *Mycoses* 2006;49(1):68-69.
6. Friedman GD, Jeffrey FW, Udaltsova NV, Hurley LB. Cryptococcosis: the 1981-2000 epidemic. *Mycoses* 2005;48(2):122-125.
7. Aberg JA, Mundy LM, Powderly WG. Pulmonary cryptococcosis in patients without HIV infection. *Chest* 1999;115(3):734-740.
8. Cameron ML, Bartlett JA, Gallis HA, Waskin HA. Manifestations of pulmonary cryptococcosis in patients with acquired immunodeficiency syndrome. *Rev Infect Dis* 1991;13(1):64-67.
9. Perfect JR, Casadevall A. Cryptococcosis. *Infect Dis Clin North Am* 2002;16(4):837-842.
10. Kerkering TM, Duma RJ, Shadomy S. The evolution of pulmonary cryptococcosis: clinical implications from a study of 41 patients with and without compromising host factors. *Ann Intern Med* 1981;94(5):611-616.
11. Schop J. Protective immunity against *Cryptococcus neoformans* infection. *McGill J Med* 2007;10(1):35-43.
12. Vecchiarelli A, Casadevall A. Antibody-mediated effects against *Cryptococcus neoformans*: evidence for interdependency and collaboration between humoral and cellular immunity. *Res Immunol* 1998;149(4-5):321-333.
13. Rozenbaum R, Goncalves AJ. Clinical epidemiological study of 171 cases of cryptococcosis. *Clin Infect Dis* 1994;18(3):369-380.