Acute Respiratory Failure Associated With Pulmonary Cryptococcosis in Non-AIDS Patients*

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Purpose: To determine the incidence of acute respiratory failure (ARF) in non-AIDS patients with pulmonary cryptococcosis (PC).

Design: Retrospective cohort study.

Setting: University of Pittsburgh Medical Center, Pittsburgh, PA.

Subjects: All patients in whom PC without HIV infection was diagnosed between February 1989 and March 1999.

Results: Thirty-three patients with PC were identified, and 11 of those patients (33%) developed ARF and comprised the study group. Underlying diseases included solid-organ transplant recipients (seven patients; 64%) and other underlying medical conditions (four patients; 36%). The most common symptoms were cough, shortness of breath, and temperature elevation. Extrapulmonary involvement was seen in six patients (meningitis, four patients; peritonitis, one patient; laryngeal mass, one patient). Six of the 11 patients (55%) died.

Conclusion: ARF may develop in one third of non-AIDS patients with PC. This clinical syndrome is associated with the dissemination to extrapulmonary sites and high mortality rates. PC should be recognized as a possible cause of respiratory failure in non-AIDS patients.

(CHEST 2001; 119:1865–1869)

Key words: acute respiratory failure; HIV status, negative; pulmonary cryptococcosis

Abbreviations: ARF = acute respiratory failure; CSF = cerebrospinal fluid; PC = pulmonary cryptococcosis; PEEP = positive end-expiratory pressure

Cryptococcus neoformans is a ubiquitous saprophytic fungus with a characteristic polysaccharide capsule. Its ecologic niche is poorly defined, but it has been associated with pigeon and other bird droppings. The point of entry for most cryptococcal infections is thought to be the lung. The organism is tropic for the CNS, and meningitis is the most common presentation of the disease. Pulmonary involvement in non-AIDS patients has been reported in 10 to 29% of patients in whom cryptococcosis is diagnosed. However, acute respiratory failure (ARF) associated with pulmonary cryptococcosis (PC) has been given little emphasis in the literature and has been alluded to only in the setting of HIV infection.

The aim of the present study was to determine the incidence of ARF associated with PC in non-AIDS patients and to identify the predictors of outcome among these patients.

Materials and Methods

Identification of Cases

Patients with PC associated with ARF were selected from an existing database of patients with cryptococcosis at The University of Pittsburgh Medical Center. Patients were identified by the recovery of C. neoformans from BAL fluid or lung histology/pathology specimens. Patients were excluded from the study if they had known HIV infection.

Definitions

Proven PC required abnormal findings on chest radiographs or chest CT scans and isolation of C. neoformans from BAL fluid and/or lung histopathology specimen confirmation. Presumptive
PC required abnormal findings on chest radiographs or chest CT scan and isolation of *C neoformans* from at least one extrapulmonary site. ARF was defined as hypoxemia (ie, PO₂ < 60 mm Hg) requiring mechanical ventilation. Cryptococcus-related mortality was defined as death that was directly attributed to cryptococcosis (ie, *C neoformans* had been recovered from autopsy specimens). Patients who did not have an autopsy but whose death occurred within 4 weeks of receiving a diagnosis of PC also were considered to have Cryptococcus-related mortality.

**Chart Review**

The medical records of the study population were obtained and reviewed for data collection from the electronic information database of the hospital (Medical Archival Retrieval System). Included in this database were the admission history and physical examination results, the discharge summary, the dictated progress notes, the record of medications that had been dispensed from the pharmacy, and all laboratory data, including microbiology and pathology reports.

Demographic data including race, birth date, sex, dates of admission and discharge, dates of organ transplant operations, diagnostic procedures, and the outcome of the present hospitalization were obtained. The admission history and the physical examination results were reviewed for the presence and duration of fever, cough, and dyspnea, and patients were assessed for the presence of respiratory failure and their requirement of mechanical ventilation.

Recorded microbiology data included the date, specimen site, and results of cultures of all specimens, and the results of testing of the Cryptococcus antigen in serum and cerebrospinal fluid (CSF). Pathology data obtained included the date, specimen type, and results of Grocott-Gomori methanamine-silver stains. The cause of death was obtained from the discharge summary or the autopsy report.

**Chest Radiology**

Chest radiographs and CT scans were reviewed by two thoracic radiologists for the locations and types of pulmonary infiltrates and for the presence of nodules, masses, pleural effusions, and lymph node enlargement.

**Statistical Analysis**

Continuous variables were presented as the mean and SD, and categoric variables were presented as proportions. The standard two-sample *t* test was used to test differences between means, while differences in proportions were tested using Fisher’s Exact Test.

**Results**

Between February 1989 and March 1999, 33 patients with PC who did not have AIDS were identified for study enrollment. The group included 22 recipients of solid-organ transplants and 11 non-transplant patients. Eleven patients (33%) developed ARF, and they comprised the study group. The incidence of ARF was equivalent between the transplant group (7 of 22 patients) and the nontransplant group (4 of 11 patients). Of the 11 patients with ARF, 7 had proven cases of PC and 4 had presumptive cases. Eight patients were men and three were women. The mean age was 48 years (age range, 29 to 68 years). All 11 cases occurred in white individuals.

Of the seven solid-organ transplant recipients, three had undergone heart transplants and four had undergone liver transplants. All seven patients received long-term immunosuppressive therapy, which included tacrolimus or cyclosporine with or without prednisone. The time intervals between transplantation and the onset of PC were from 1 month to 10 years. Among the nontransplant patients, two had chronic liver disease, one had congenital heart disease (dextrocardia), and one had lung cancer. Only one patient in the nontransplant group had received immunosuppressive therapy before the diagnosis of PC, which consisted of chemotherapy for lung cancer. Table 1 presents the clinical presentation, microbiology, radiology findings, treatment, and outcome data of each study case. Common symptoms were reported in 10 patients. The duration of symptoms ranged between 1 day and 30 days before diagnosis. Sites of extrapulmonary involvement

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Symptoms</th>
<th>Mechanical Ventilation, d</th>
<th>Culture Positive</th>
<th>Serum Cryptococcal Antigen</th>
<th>Radiology</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SOB X 14 d</td>
<td>12</td>
<td>Blood, peritoneal fluid</td>
<td>1:1024</td>
<td>Bilateral effusion</td>
<td>AMPHO B/5FC</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>SOB, cough</td>
<td>7</td>
<td>BAL</td>
<td>NO</td>
<td>Bilateral airspace disease</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>SOB X 1 d</td>
<td>6</td>
<td>BAL</td>
<td>NO</td>
<td>LUL airspace disease</td>
<td>AMPHO B</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>SOB, T 38.7°C</td>
<td>8</td>
<td>BAL, CSF</td>
<td>1:28</td>
<td>Bilateral airspace disease</td>
<td>AMPHO B/5FC</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>SOB X 10 d</td>
<td>30</td>
<td>Laryngeal mass</td>
<td>1:68</td>
<td>Bilobar airspace disease</td>
<td>AMPHO B/5FC</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>SOB, T 38.3°C</td>
<td>7</td>
<td>BAL</td>
<td>Negative</td>
<td>Right effusion</td>
<td>AMPHO B/5FC</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>Cough X 5 d, T 39°C</td>
<td>11</td>
<td>BAL, blood, CSF</td>
<td>1:1024</td>
<td>RUL airspace disease</td>
<td>AMPHO B/5FC</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>T 41°C</td>
<td>3</td>
<td>BAL</td>
<td>NO</td>
<td>Bilateral effusion</td>
<td>AMPHO B</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>NR</td>
<td>4</td>
<td>BAL</td>
<td>NO</td>
<td>Bilateral airspace disease</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>10</td>
<td>Headache</td>
<td>4</td>
<td>CSF</td>
<td>1:27,68</td>
<td>Right effusion</td>
<td>AMPHO B/5FC</td>
<td>Died</td>
</tr>
<tr>
<td>11</td>
<td>SOB, cough X 14 d, T 38.6°C</td>
<td>7</td>
<td>BAL</td>
<td>NO</td>
<td>RUL airspace disease</td>
<td>None</td>
<td>Died</td>
</tr>
</tbody>
</table>

*SOB = shortness of breath; T = temperature; LUL = left upper lobe; RUL = right upper lobe; AMPHO B = amphotericin B; 5FC = flucytosine; NO = not obtained; NR = not reported.*
were seen in six patients (55%), and they included meningitis (n = 4), peritonitis (n = 1), and laryngeal mass (n = 1).

Mechanical ventilation was initiated in all 11 patients within 24 h of hospital admission. The duration of ventilation support ranged from 3 to 30 days. Therapy with positive end-expiratory pressure (PEEP) was used in all patients and ranged between 7.5 and 10 cm H₂O. Chest radiograph findings included the following: irregular or nodular airspace disease (nine patients), segmental or lobar airspace disease (two patients), and pleural effusions (six patients). Chest CT scans were performed in six patients and provided additional information that was not readily seen on plain chest radiographs that had been performed in all patients. Chest radiographs of two of our patients in this study are shown in Figures 1, 2.

The mean values for laboratory tests at the time of diagnosis included the following: hematocrit, 30.5% (range, 24.9 to 37.3%); WBC count, 10,181/μL (range 3,900 to 15,800 μL); serum glucose level, 159.6 mg/dL (range, 93 to 322 mg/dL); serum creatinine level, 2.1 mg/dL (range, 1.0 to 5.1 mg/dL); and arterial PO₂ at a fraction of inspired oxygen of 0.21, 53 mm Hg (range, 38 to 60 mm Hg).

Six of the 11 patients (55%) died. All deaths occurred within 2 weeks of diagnosis. Three of the six patients who died received their diagnoses after death and did not receive treatment. The other three patients had received treatment with amphotericin B and flucytosine. An autopsy was performed in three of the patients. Microscopic findings in these patients demonstrated disseminated cryptococcosis, involving multiple lung lobes (n = 2), hilar and subcarinal lymph nodes (n = 3), esophagus (n = 1), kidney (n = 1), and CNS (n = 1).
**Discussion**

Although not conclusively documented, almost all cases of cryptococcosis are thought to be the result of the inhalation of fungi from an environmental source. Indeed, desiccated yeast cells of *C neoformans* measuring 0.6 to 3.5 mm in diameter, a size that is ideal for alveolar deposition after inhalation, have been isolated from aerosol particles generated from soil and pigeon droppings. After entry, the fungus may remain dormant in the lung or spread to another organ system with affinity to the CNS.

Before the AIDS era, the reported incidence of pulmonary disease was 10%, but most of the cases were identified histologically, and often at autopsy, with only approximately 20% diagnosed by culture. A recent study by Hajjeh et al.3 showed a 29% incidence of PC in HIV-negative patients. Cancer, a known risk factor for cryptococcosis, was the most common underlying disease, followed by diabetes mellitus. However, most patients in the study suffering from diabetes also had one or more immunocompromising conditions. Perhaps the most likely explanation for this is the increased use of immunosuppressive agents for a variety of medical conditions.

Different authors have described the broad spectrum of PC in both HIV-infected and non-HIV patients. However, reports of ARF in association with cryptococcal infection have been described only in the HIV-positive population. In a study of 210 patients with AIDS and cryptococcosis, ARF was identified in 19 patients (14%). Nine of the patients were definitively defined as having cases of PC, and 10 patients were defined as having probable cases. Definitive cases were defined as patients with ARF and bronchoscopic and/or autopsy evidence of pulmonary involvement with *C neoformans*, in the absence of any other pulmonary process. Cases were probable if, in the absence of bronchoscopic evidence, the patients with ARF had microbiological evidence of extraneural dissemination of cryptococcosis with no other concurrent diagnosis. Mechanical ventilation was used in only 7 of the 19 patients with ARF. However, no data regarding the time between the initiation of mechanical ventilation and the time of diagnosis or the use of PEEP were given. All 19 patients with ARF had evidence of extrapulmonary disease, including 10 patients who had meningitis. The predictors of ARF included black race, a lactate dehydrogenase level of > 500 IU/L, and the presence of interstitial infiltrates and cutaneous lesions. All patients died. Another report described a case of ARDS and cryptococcosis in a 45-year-old white man in whom AIDS had been diagnosed. Treatment with mechanical ventilation with PEEP was started, but the patient died < 48 h after his admission to the hospital. A postmortem histopathologic examination of the lungs showed diffuse bilateral PC.

Our cohort included non-AIDS patients who developed ARF in association with PC. All patients required the initiation of mechanical ventilation along with the addition of PEEP within 24 h after their hospital admission. This rapid clinical presentation is suggestive of an acute lung injury, which is in contrast with the subclinical pneumonitis that is more often described in most reports concerning non-AIDS patients. Possible explanations for this observation may be related to the virulence factors of *C neoformans* and its capacity to induce different lung injuries as well as the host’s immune status. Previous reports have shown that the prevalence of cryptococcosis is markedly increased among patients with defects in the cell-mediated arm of the immune system, such as those in patients with AIDS, lymphoreticular malignancy, collagen vascular disease, and sarcoidosis and in patients receiving immunosuppressive therapy. In our group, 7 of the 11 patients with ARF were solid-organ transplant recipients and were receiving immunosuppressive agents to prevent acute allograft rejection, thus placing them at risk for cryptococcal disease. Of the remaining four patients, three also had conditions that may have altered their host status, such as lung cancer and chronic liver disease. Therefore, they were also at risk for cryptococcosis. The incidence of ARF in both groups was equivalent.

Although we recognize that the etiology of ARF associated with cryptococcal disease is a multifactorial one, the extent of cryptococcosis in the lungs and other organs that is described in our study may have played an important role in the pathogenesis of respiratory failure. Our findings also confirm that nonspecific symptoms are the predominant manifestation of PC. Thus, a high index of suspicion for PC should remain in the differential diagnosis of ARF in patients at risk.

Risk factors for poor outcome despite treatment for cryptococcosis in non-AIDS patients were associated with meningitis. These factors include the following: lymphoreticular malignancy; glucocorticoid therapy; CSF with high opening pressure; low glucose level; < 20 leukocytes/μL; a positive reaction to an India ink smear; cryptococci isolated from an extraneural site; and high titers of cryptococcal antigen in the CSF or serum. In our study, the presence of ARF in patients with cryptococcal disease yielded a mortality rate of 55% and often was associated with disseminated disease. Thus, the presence of ARF with cryptococcosis is a particularly grave prognostic sign, and it could represent a marker of systemic cryptococcal infection.

In summary, ARF may develop in one third of...
non-AIDS patients with PC. Its incidence is equivalent among transplant recipients and patients with other medical conditions, and it is associated with a high mortality rate.

REFERENCES
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