Asymptomatic Solitary Pulmonary Nodules Due to *Cryptococcus neoformans* in Patients Infected with Human Immunodeficiency Virus

Kirk D. Miller, Jo Ann M. Mican, and Richard T. Davey

We report the cases of three HIV-positive patients with solitary pulmonary nodules caused by *Cryptococcus neoformans*. Although human infection with *C. neoformans* occurs via the respiratory tract, isolated pulmonary infection in HIV-positive patients, in contrast with HIV-negative patients, has been thought to be relatively rare. When isolated pulmonary disease in HIV-infected patients has been described, most of the patients have been symptomatic (symptoms have included fever, cough, and dyspnea). In addition, these patients have had diffuse interstitial infiltrates, alveolar infiltrates, or nodular infiltrates that have often been associated with hilar adenopathy and occasionally with pleural effusions. None of the patients in the previously reported series have had lesions described as small, asymptomatic, isolated pulmonary nodules.

Although the CNS is the most common site of HIV-associated cryptococcosis, pulmonary disease has also been well described. However, most patients reported to have pulmonary disease also have had concurrent disease of the CNS or other evidence of dissemination [1–10]. When isolated pulmonary cryptococcal infections among HIV-infected patients have been reported, patients have generally presented with an acute illness characterized by fever, marked respiratory symptoms, and significant radiographic evidence of pneumonitis [1–11]. We report cryptococcal pulmonary infections in three essentially asymptomatic HIV-infected patients with small isolated pulmonary nodules.

**Case Reports**

All three patients described in this report were enrolled in ongoing protocols at the National Institutes of Health. Each was found to have a lesion on a routine surveillance chest roentgenogram performed as per protocol requirements, and a CT scan of the chest was subsequently performed for each patient (figure 1). In all three cases, evaluations led to the diagnosis of cryptococcosis (table 1). Repeated roentgenograms taken 3 months (patient 1), 6 months (patient 2), and 1 month (patient 3) after therapy with oral fluconazole was started demonstrated resolution of the lesions. All three patients continued to receive fluconazole as ongoing prophylaxis against reactivation and dissemination of cryptococcosis.

**Case 1.** A 38-year-old homosexual male who was participating in a protocol evaluating combination antiretroviral therapy for HIV infection presented for his monthly visit. He denied any respiratory symptoms, headache, or fever. His only medical condition, other than antiretrovirals, was trimethoprim-sulfamethoxazole (TMP-SMZ) for *Pneumocystis carinii* pneumonia (PCP) prophylaxis. He was afebrile. His CD4+ lymphocyte count at the time of his visit was 146 cells/mm³ (13% of total lymphocytes). Findings on a chest roentgenogram taken 6 months before presentation were normal.

**Case 2.** A 44-year-old homosexual male who had been participating in protocols evaluating IFN-α therapy for Kaposi’s sarcoma presented for a routine 6-month follow-up visit. In addition to antiretrovirals, his medications included acyclovir for herpes prophylaxis, inhaled pentamidine for PCP prophylaxis, and ethambutol and rifabutin for treatment of *Mycobacterium avium-Mycobacterium intracellulare* that had previously been isolated from his stool.

At the time of the visit the patient complained of a mild cough, which he attributed to a recent upper respiratory infection with persistent postnasal drip, and an occasional sensation of chest tightness with exertion. He denied headache or fever and was afebrile at the time of his visit. His CD4+ lymphocyte count at the time of his visit was 144/mm³ (8% of total lymphocytes). Reevaluation of a chest roentgenogram taken 6 months before presentation showed a noncavitated nodular density in the same area as the current cavitated lesion (his CD4+ cell count at that time was 169/mm³); however, there was no lesion on a roentgenogram taken 12 months before the current roentgenogram.

**Case 3.** A 42-year-old homosexual male who had been participating in an evaluation of IL-2 therapy for HIV infection presented for his monthly follow-up visit. He denied any respiratory symptoms, headache, or fever. In addition to antiretrovirals, his medications included TMP-SMZ for PCP prophylaxis and occasional clotrimazole troches. He was afebrile. His CD4+ lymphocyte count at the time of his visit was 116/mm³ (16% of total lymphocytes). A chest roentgenogram taken 16 months before presentation was normal.

**Discussion**

The clinical presentations of the three patients we describe in this report differ from those previously reported for patients...
with pulmonary infections due to *Cryptococcus neoformans*. The underlying reason for this difference undoubtedly lies in the way in which our patients were identified as compared with the way that the patients described in previous series were identified: those patients were identified because signs and symptoms prompted a pulmonary evaluation that ultimately led to the diagnosis of cryptococcosis, whereas our patients were identified because routine periodic chest roentgenograms were performed as a surveillance requirement for ongoing participation in an investigational protocol [1–11].

Table 1. Summary of diagnostic work-up for three patients with isolated pulmonary nodules due to *Cryptococcus neoformans*.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Results of induced sputum*</th>
<th>Result of serum cryptococcal antigen test</th>
<th>Definitive diagnostic procedure</th>
<th>Result of test for cryptococcal antigen in BAL fluid†</th>
<th>Results of cytological and histological examinations (findings)</th>
<th>Results of culture (organism isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Negative for PCP, AFB, and fungi</td>
<td>Negative</td>
<td>Percutaneous needle biopsy</td>
<td>...</td>
<td>Biopsy positive (yeast forms)</td>
<td>Biopsy positive (C. neoformans)</td>
</tr>
<tr>
<td>2</td>
<td>Negative for PCP, AFB, and fungi</td>
<td>Negative</td>
<td>Bronchoscopy with BAL and transbronchial biopsy</td>
<td>Positive</td>
<td>BAL positive (yeast forms)</td>
<td>BAL positive (C. neoformans)</td>
</tr>
<tr>
<td>3</td>
<td>Negative for PCP, AFB, and fungi</td>
<td>Negative</td>
<td>Bronchoscopy with BAL</td>
<td>ND</td>
<td>BAL negative</td>
<td>BAL positive (C. neoformans)</td>
</tr>
</tbody>
</table>

NOTE. AFB = acid-fast bacilli; BAL = bronchoalveolar lavage; ND = not done; PCP = *Pneumocystis carinii* pneumonia.
* Results listed are for both cytological examination and microbiological testing of sputum.
† Cryptococcal Antigen Latex Agglutination System (CALAR; Meridian Diagnostics, Cincinnati, OH).
‡ See [12].
Although human infection with *C. neoformans* occurs via the respiratory tract, isolated pulmonary infection in HIV-infected patients, in contrast with patients who are not infected with HIV, has been thought to be relatively rare [13–15]. Of 116 patients described in 11 different series of patients with documented pulmonary cryptococcosis, 96 (83%) had evidence of dissemination, usually to the CNS [1–10]. When isolated pulmonary disease in HIV-infected patients has been described, most of the patients have been symptomatic (symptoms have included fever, cough, and dyspnea) [1–9]. Moreover, these patients have had diffuse interstitial infiltrates, alveolar infiltrates, or nodular infiltrates that have often been associated with hilar adenopathy and have sometimes been associated with pleural effusions [2–11].

None of the patients in the previous 11 series had lesions described as small, asymptomatic, isolated pulmonary nodules such as those we report. Although asymptomatic nodules have not been previously described in HIV-infected patients, it has been suggested that they may represent the earliest stage of cryptococcal infection following exposure and that such nodules may either spontaneously resolve radiographically before later reactivation and dissemination or that these nodules may persist and gradually progress to more widespread and symptomatic pulmonary involvement and dissemination [15, 16].

It is of interest that our three patients had CD4⁺ lymphocyte counts that are higher than those previously reported for patients with pulmonary cryptococcosis. In the one reported series of patients with pulmonary cryptococcosis in which CD4⁺ lymphocyte counts were analyzed, the overall median count was 24/mm³ [1]. Although the four patients with isolated pulmonary disease in this series had slightly higher lymphocyte counts (median, 48/mm³), they were still substantially lower than those for our three patients, who each had CD4⁺ lymphocyte counts of 116, 144, or 146/mm³.

It is possible that in patients similar to ours, exposure to *C. neoformans* and initial infection occur at a time when some level of immune competence remains but that eventual reactivation or progression of pulmonary disease and dissemination to extrapulmonary sites occurs as CD4⁺ lymphocyte counts decline and immune function wanes. If true, this may help explain why the solitary pulmonary lesion in case 2 progressed little during a 6-month period in which the patient’s CD4⁺ lymphocyte count remained relatively stable. It also raises the question as to whether antiretroviral therapies that stabilize or improve CD4⁺ cell counts could also have a suppressive effect on the natural progression of untreated pulmonary cryptococcal infection.

None of the three patients we describe had detectable serum cryptococcal antigen, in contrast with patients with pulmonary cryptococcosis in most previous reports. Serum cryptococcal antigen positivity has been reported both in isolated pulmonary disease and in pulmonary disease with evidence of dissemination [2–5, 10]. However, at least one other reported series of cases suggests that serum cryptococcal antigen is usually undetectable in pulmonary disease without evidence of dissemination, as was observed in our three cases [17]. It is not known whether the degree of subclinical pulmonary involvement, in the absence of evidence of dissemination, might correlate with the presence of detectable serum cryptococcal antigen.

Lifelong maintenance therapy has been shown to be necessary to prevent relapse in HIV-infected patients with disseminated cryptococcosis [13–15]. It is not known whether similar therapy is necessary for patients with solitary pulmonary nodules, but, in the absence of information to the contrary, it would seem prudent to maintain such patients indefinitely on therapy with triazole antifungal agents.

### Acknowledgments

The authors thank the physicians and nursing staff of the National Institute of Allergy and Infectious Diseases/Critical Care Medicine Department, HIV Research Clinic for caring for the patients described in this report.

### References