Pulmonary *Cryptococcus* Presenting as a Solitary Pulmonary Nodule

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Figure 1. Computed tomography of the lung revealing the nodule of 4 mm (A) with rapid growth to 9 mm (B) in a 3-month period without other nodules, infiltrates, or lymphadenopathy.

Figure 2. Positron emission tomography–computed tomography scan demonstrating fluorodeoxyglucose-avid nodule in the left upper lobe.

A 74-year-old man with stage IV mantle cell lymphoma was referred for a gradually enlarging solitary pulmonary nodule noted on imaging. Prior therapy for his lymphoma included rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and bortezomib. Although he had not received any of these therapies for 3.5 years, he had been receiving ibrutinib therapy for the prior 5 months. He denied any respiratory or constitutional symptoms. He had a remote smoking history but no pets or recent travel. His hobbies included walking in the park and doing yardwork. Physical examination was unremarkable. Computed tomography (CT) of his chest revealed a 9-mm nodule (Figure 1) in the left upper lobe that had increased from 4 mm on imaging from 3 months prior, but no other infiltrates or lymphadenopathy were noted. Positive emission tomography–CT scan demonstrated uptake in the nodule with a standardized uptake value of 3.1 (Figure 2). Laboratory data revealed a white blood cell count of 2.6 K/ μ L, with 47% neutrophils, 33% lymphocytes, 18% monocytes, 1% eosinophils, and 1% basophils. CT-guided biopsy of the lesion revealed lung parenchyma with numerous organisms compatible with *Cryptococcus* (Figure 3), but culture of tissue remained negative. Lumbar puncture and serum cryptococcal antigen and HIV antibody were negative. The patient was treated with fluconazole. Repeat imaging 4 months later revealed a slight decrease in the nodule, and repeat positive emission tomography–CT scan 5 months later demonstrated a stable nodule with a reduced standardized uptake value of 2.4.

Cryptococcal infections have been most commonly reported in patients with HIV, but, after excluding those, malignancy was the underlying risk factor in 5 to 27% of cryptococcal infections (1). The predominant malignancies reported with cryptococcal infections are hematologic, particularly lymphoma. Two large series have reported invasive fungal infection with *Cryptococcus* in 1.5 to 2.8% of hematologic malignancies (1). Infection results from inhalation of soil contaminated by pigeon droppings in immunocompromised

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Figure 3. Computed tomography-guided biopsy of left upper lobe nodule. (A) Core needle biopsy histology (hematoxylin and eosin stain, 400×); (B) touch preparation cytology of core needle biopsy (Papanicolaou stain, 400×). Both preparations show abundant, variably sized, round to oval yeast forms, most of which have a mucinous capsule. The mucinous capsule is better demonstrated on the touch prep and appears as a fuzzy smudge surrounding the yeast. Because of formalin fixation and paraffin embedding, the yeast appears slightly smaller on the core biopsy, which also show significant retraction artifact (spaces) around the yeast (blue arrows). The touch prep shows narrow-based budding in one yeast (red arrow), and some of the smaller yeast appears unencapsulated (yellow arrow). The morphologic features demonstrated in these preparations are characteristic of *Cryptococcus*.

individuals, and the most common disease manifestation is meningitis, because the organism has a predilection to metastasize to the central nervous system (2).

As in our case, symptoms from pulmonary cryptococcal infection may be absent or may include fever, dyspnea, cough, or pleurisy. Radiographic findings typically include patchy infiltrates, multiple nodules, widespread infiltrates, or focal consolidation, and these may be fluorodeoxyglucose avid (3, 4). Multiple nodules and/or masses are often mistaken for primary or metastatic malignancy. Risk factors include lymphopenia, previous steroid use, and lymphoma.

A high index of clinical suspicion is often needed for pulmonary cryptococcal disease. Isolation of *Cryptococcus* from a respiratory sample is significant, because it is not part of normal respiratory flora, especially in immunocompromised individuals. Definitive diagnosis is made by culture and identification of the organism, and it may grow on most bacterial and fungal culture media after 2 to 7 days. Yield may be enhanced with more invasive procedures, such as bronchoscopy with bronchoalveolar lavage, transthoracic or transbronchial biopsy, or surgical lung biopsies. Although identification is plausible on routine hematoxylin and eosin staining, special staining with Gomori methenamine silver or periodic acid-Schiff is recommended in cases in which *Cryptococcus* is suspected but not identified using hematoxylin and eosin. Diagnosis may be confirmed with biopsy, and subsequent serum testing and lumbar puncture for cryptococcal infection is recommended (5). Selection of antifungal therapy is based on disease severity. Our case highlights the importance of considering pulmonary cryptococcosis in immunocompromised patients with a rapidly growing solitary pulmonary nodule. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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