

# A 61-Year-Old Man With Asymptomatic, Bilateral Lung Masses

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### TARGET AUDIENCE

The November/ December Clinical Case of the Month is intended for students, general practitioners, internists and medical subspecialties specifically pulmonologists, infectious disease specialists and immunologists.

### EDUCATIONAL OBJECTIVES

The Clinical Case of the month is a regular educational feature presented by the Louisiana State University Department of Medicine. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these manuscripts. After reading this article, physicians should be better able to: 1) Increase awareness of the incidence and types of opportunistic infections which may be associated with immune compromised states; 2) Identify the immunocompromised state induced by treatment with tumor necrosis factor-alpha antagonists and the increased risk of cryptococcal pneumonia in patients receiving such agents. Estimated time to complete this activity is one (1) hour.

### CME INFORMATION

### CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) *AMA PRA Category 1 Credit*<sup>TM</sup>. Physicians should only claim credit commensurate with the extent of their participation in the activity.

### DISCLOSURE

Drs. Rehman and Ali have nothing to disclose.

Dr. Lopez discloses that he is a member of the *Journal* Board of Trustees. He is also on the *Journal* Editorial Board.

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A 61-year-old man with a 10-year history of Crohn's disease was referred to pulmonary clinic for pre-operative evaluation prior to hip surgery. His Crohn's disease was relatively well-controlled, with a disease activity index of 130.8, consistent with current remission [Crohn's disease activity index (CDAI) equal to or < 150 = remission; CDAI > 150 = active disease; CDAI > 450 = extremely severe disease].<sup>1</sup> He was being treated with prednisone (20 mg/day, orally), budesonide (9 mg/day, orally), and azathioprine (200 mg/day, orally) and had a 5-year history of worsening right hip pain, controlled with celecoxib and hydrocodone/acetaminophen. It was strongly suspected that this pain was due to steroid-induced necrosis of the right femoral head. Two and a half years ago, he was started on infliximab infusions every six weeks. A prolonged prednisone taper was initiated. The lowest prednisone dose required to maintain his Crohn's disease in remission remained at 20 mg/day, and attempts at lower doses or discontinuation of prednisone resulted in acute flares of his Crohn's disease. Subsequent imaging of the right hip confirmed advanced collapse of the femoral head, consistent with severe osteonecrosis. A right total hip arthroplasty was planned.

During pre-operative evaluation, a chest radiograph revealed a mass in the lower lobe of the right lung. On inquiry, the patient reported no respiratory symptoms. He denied any recent history of cough, shortness of breath, chest pain, hemoptysis, fever, chills, night sweats, weight loss, or weakness. There was no history of environmental exposure, recent travel, or contact with patients with tuberculous lung infections. A tuberculin skin test prior to initiation of infliximab therapy was negative. He had no known occupational exposures and quit smoking tobacco 10 years ago after a 60 pack-year smoking history. He had no known drug allergies and no family history of lung cancer or inflammatory bowel disease. Past surgical history was significant for an appendectomy 10 years ago. There was no history of alcoholism or illicit drug use.

On physical examination, vital signs included a temperature of 98.1°F, heart rate of 60 beats per minute, blood pressure of 116/69 mm Hg, and respiratory rate of 18 breaths per minute with arterial oxygen saturations of 100% breathing air. Chest examination showed no apparent deformities. Chest expansion was normal and symmetric, and percussion revealed no abnormalities. On auscultation, breath sounds were noted to be mildly decreased in the

right lung base with occasional crackles. Cardiovascular, abdominal, neurologic, extremities, and skin examinations were unremarkable. Initial labs including complete blood count and metabolic profile were within normal limits. A human immunodeficiency virus (HIV) test was negative.

A chest radiograph showed a 6 cm, irregularly shaped opacity within the right lower lobe (Figure 1a). A computed tomogram (CT) of the chest without contrast revealed multiple bilateral, noncalcified pulmonary nodules of varying sizes and shapes (Figure 1b). A dominant mass was noted in the right lung base which measured 4.3 cm in diameter and contained air bronchograms. No mediastinal, hilar, or axillary lymphadenopathy was identified. Bronchoscopy did not reveal any endobronchial lesions. Cytology, brushing, and bronchoalveolar lavage samples were obtained but proved unsuccessful in yielding a diagnosis. Later, a CT-guided transthoracic needle biopsy of the right lower lobe mass confirmed the presence of numerous rounded, encapsulated organisms in alveoli and alveolar septa. Grocott-Gomori methenamine silver, mucicarmine, and immunohistochemical staining patterns were consistent with *Cryptococcus neoformans* (Figure 2). The same organism was later grown from fungal culture of the biopsy specimen. Acid-fast bacilli smear and culture of the biopsy specimen were negative, and no malignant cells were seen.

At this point, infliximab was discontinued, and the patient was started on amphotericin B and flucytosine for induction therapy against *C. neoformans*. To rule out central nervous system (CNS) involvement, a lumbar puncture and a CT of the head were performed. Cerebrospinal fluid (CSF) staining with India ink was negative. CSF cultures did not grow any organism, and the head CT was normal. CSF and blood cryptococcal antigen assays were negative.

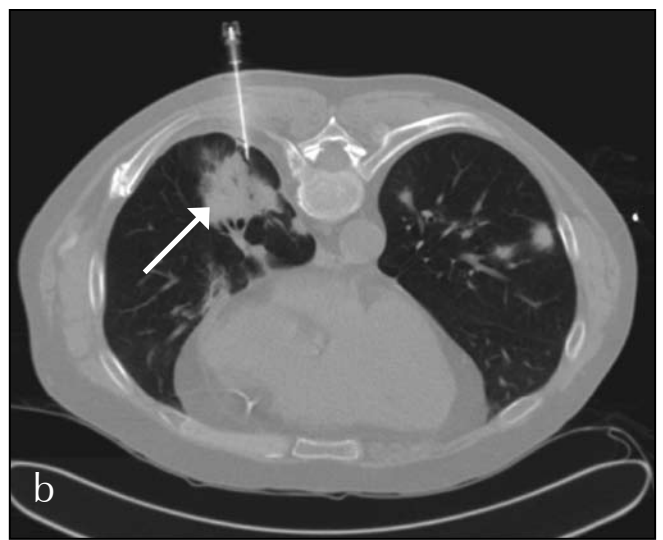
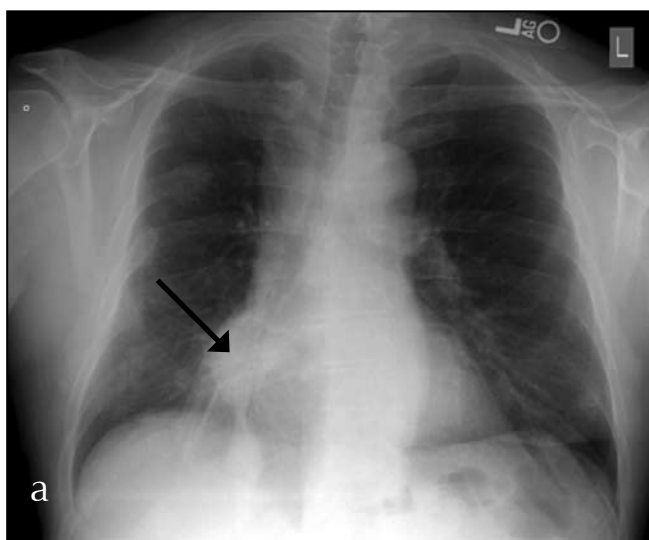
Two days after starting induction therapy, the patient developed renal insufficiency. Oral fluconazole at high doses was substituted for the amphotericin B. Eventually, the patient was discharged to continue fluconazole as an outpatient. A repeat chest radiograph at six months showed improvement and reduction in the size of the pulmonary nodules.

## DISCUSSION

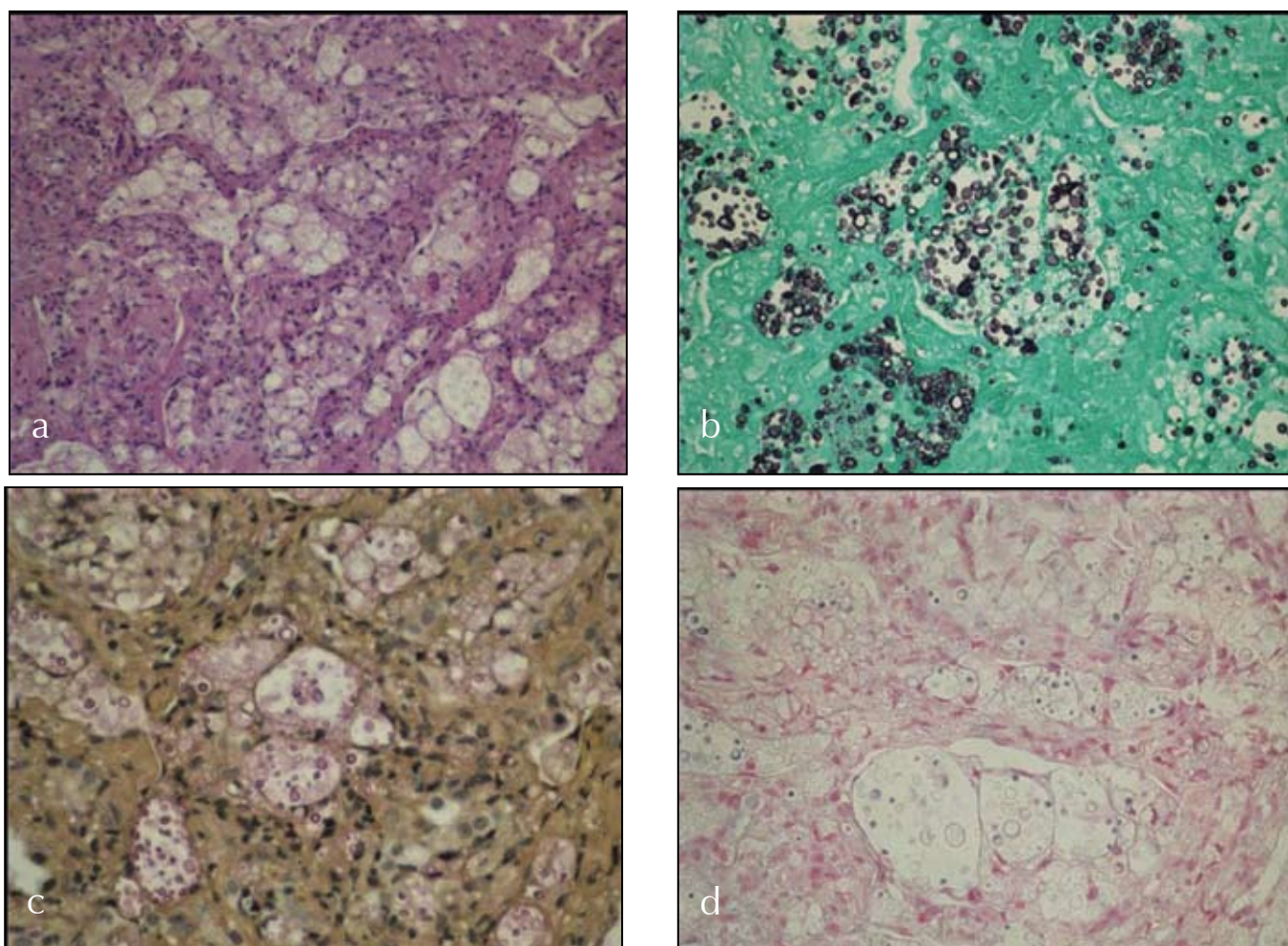
Tumor necrosis factor (TNF)-alpha antagonists comprise a relatively new class of drugs with evolving clinical indications and adverse-effect profiles. Their main mechanism of action involves immunomodulation by blocking the biologic activities of TNF-alpha. Infliximab is a chimeric, monoclonal antibody directed against TNF-alpha. It is indicated for the treatment of immunologic disorders such as Crohn's disease and rheumatoid arthritis. An important side-effect of infliximab is impairment of T-cell-mediated immunity with predisposition to serious opportunistic infections. Reactivation of latent tuberculosis in infliximab-treated patients is well-described.<sup>2</sup> Pulmonary and extrapulmonary cryptococcosis is being increasingly observed in association with this agent. This case highlights the immunocompromised state induced by infliximab with the development of an opportunistic *C. neoformans* infection.

### Early Pulmonary Immune Response

Inhaled microbes are initially intercepted by macrophages and other phagocytes patrolling the alveolar membranes. They form the first line of defense against air-borne pathogens. Macrophages have receptors for recognizing domains on microbial surfaces, leading to



**Figure 1.** (a) Posterior-anterior chest radiograph shows a large mass (black arrow) in the lower lobe of the right lung. (b) Prone, non-contrast, computed tomogram of the chest at the time of a transthoracic needle biopsy of the right lower lobe mass. Note multiple bilateral nodules of varying shapes and sizes. The dominant right lower lobe mass (white arrow) has air bronchograms within it.



**Figure 2.** Photomicrographs of the lung biopsy specimen. (a) Hematoxylin and eosin stain shows alveolar inflammatory infiltrate. (b) Grocott-Gomori methenamine silver stain: fungal organisms demonstrated are morphologically consistent with cryptococci. (c) Mucicarmine stain & (d) Cryptococcus- in situ hybridization: clear halos around intracellular cryptococci represent polysaccharide capsules. Courtesy of Alfred Hew, MD, Medical Director, Pathology, Ochsner Medical Center, Kenner, LA; and Bernardo Ruiz, MD, Department of Pathology, Louisiana State University Health Sciences Center, New Orleans, LA.

their activation and secretion of cytokines that regulate downstream immune responses. The cytokine environment during these initial stages plays a crucial role in determining the evolution of immune responses to a particular pathogen.

TNF-alpha is an early cytokine product of activated macrophages. It regulates the generation of the cell-mediated immune response by stimulating IL-12 and interferon (IFN)-gamma production. With early IL-12 predominance, naïve helper T (Th0) cells differentiate into type 1 helper T (Th1) cells (Figure 3). Th1 cells produce IFN-gamma which further activates macrophages and recruits them to the site of infection. IFN-gamma also guides the immune response away from antibody production by inhibiting the Th0 to type 2 helper T (Th2) cell transformation. On the other hand, early IL-4 predominance favors Th0 to Th2 differentiation. The main cytokine products of Th2 cells, IL-4, IL-5 and IL-10, channel the immune response toward antibody production and away from cell-mediated immunity.<sup>3,4</sup>

### Role of TNF-Alpha in Pulmonary Immune Response to *C. Neoformans*

Fungal lung infections may induce humoral and cell-mediated immunity. Antibody production is usually ineffective in clearing pulmonary mycoses; delayed-type hypersensitivity (DTH) reaction is required for their successful eradication and control. Generation of DTH reactions is impaired in conditions with underlying defects in cell-mediated immunity which may predispose to serious infections with opportunistic and non-opportunistic fungi.

Inhalation of *C. neoformans* promotes TNF-alpha production which then generates a cell-mediated immune response through stimulation of IL-12 and IFN-gamma secretion. In murine models of cryptococcal pneumonia, TNF-alpha expression is observed as early as two days after infection and precedes the development of the inflammatory response.<sup>5,6</sup> When treated with anti-TNF-alpha monoclonal

antibody at the time of infection, such mice show markedly reduced expression of TNF-alpha. Further downstream, early TNF-alpha neutralization results in reduced IL-12 and IFN-gamma production<sup>5</sup> and a greater than 98% reduction in pulmonary macrophages on day 13 post-infection.<sup>6</sup> A single dose of anti-TNF-alpha antibody on day 0 is enough to prevent the development of DTH reaction to *C. neoformans* for up to 35 days.<sup>6</sup> There is an overall deflection of the immune response toward the Th2 pathway, evidenced by elevated levels of IL-4, pulmonary eosinophils, and serum IgE levels.<sup>5</sup> The end result is absence of DTH reaction and impaired clearance of infection.

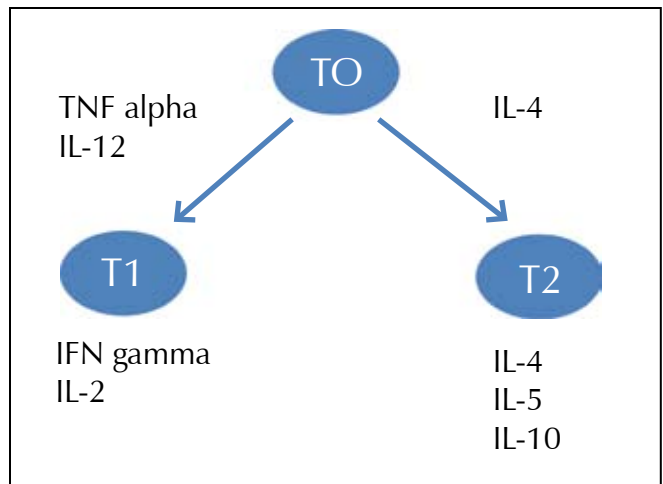
These animal studies suggest that TNF-alpha is an essential pre-requisite for the development of an effective T-cell-mediated immune response to *C. neoformans*. Cell-mediated immunity may fail to develop in the absence of an appropriate early rise in TNF-alpha levels after exposure to *C. neoformans*.

### TNF-Alpha in Crohn's Disease

Crohn's disease is a chronic inflammatory bowel disease that can involve any part of the gastrointestinal tract from the mouth to anus. Grossly, the disease produces transmural lesions with a discontinuous pattern of gut involvement. Histologically, it is characterized by the presence of noncaseating granulomas in the bowel mucosa. Crohn's disease has an immunologic basis, and immune dysregulation due to excessive Th1 pathway stimulation has been implicated. This is suggested by elevated levels of Th1 pathway cytokines such as TNF-alpha, IL-12, and IFN gamma in the involved gut regions.<sup>4</sup> The activities of TNF-alpha particularly relevant to Crohn's disease include recruitment of inflammatory cells and formation of granulomas in the mucosa and lamina propria.<sup>7</sup> Helper T cells from animal models of inflammatory bowel disease were found to produce a predominant Th1 cytokine response in vitro. Neutralization of TNF-alpha with anti-TNF alpha monoclonal antibody reduced the incidence of severe disease.<sup>8</sup> In clinical trials of Crohn's disease, infliximab has been found to be efficacious for the induction and maintenance of remission; for the treatment of severe, refractory and fistulizing disease; and as a steroid-sparing measure in long-term treatment and control.<sup>9-13</sup>

### Cryptococcal Pneumonia in the Setting of TNF-Alpha Blockade With Infliximab

Although *C. neoformans* may cause disease in immunocompetent hosts,<sup>14</sup> infections are usually seen in immunocompromised patients. Defects in cell-mediated immunity are particularly associated with a greater predisposition to cryptococcal infection. Treatment with TNF-alpha blockers may induce impairment of cell-mediated immunity. Patients receiving these agents may thus be at higher risk of developing serious infections with *C. neoformans*.



**Figure 3.** Schematic representation of cytokine regulation in early immune response. See text.

For the purpose of this discussion, a literature search was performed for reported cases of cryptococcosis in infliximab-treated patients. "Pubmed" and "Google Scholar" were searched using terms "Infliximab and *Cryptococcus neoformans*", "Infliximab and Cryptococcosis" and "Infliximab and Cryptococcal infection". The results are summarized in the Table.<sup>15-21</sup>

Our search revealed seven previous reports of cryptococcal infection in patients receiving infliximab. Of the eight cases including the present one, five were men, and three were women. All except two were patients over 60 years of age. In five cases, the disease appeared after administration of five or fewer doses of infliximab. The present case documents the longest reported interval (2.5 years) between the initiation of infliximab therapy and the diagnosis of *C. neoformans* infection. The lung was the only site of infection in all but one patient, who also had CNS involvement. Resolution of the disease was observed with treatment in all cases. Rheumatoid arthritis was the primary indication for infliximab in 7 out of 8 cases. To the best of our knowledge, the present case is the first complete report of cryptococcal pneumonia in an infliximab-treated patient with Crohn's disease.

### Management Strategies

The clinical presentation of cryptococcal pneumonia in infliximab-treated patients may be subtle and is highly variable. A high index of suspicion is thus required to make the diagnosis. Any change in functional status or new onset of shortness of breath, cough, fever, hemoptysis or weight loss should prompt aggressive investigation. Chest imaging may be indicated at an early stage. If pulmonary lesions are identified and the symptoms are severe or persistent, a trial of empiric antibiotics may be warranted. Lack of response to empiric treatment may prompt a search for histologic diagnosis through a bronchoscopic or transthoracic approach.

Serum cryptococcal antigen assay is not reliable in ruling out either primary lung infection or extrapulmonary dissemination. In confirmed cases of cryptococcal pneumonia, CNS involvement must be ruled out with lumbar puncture and a CT of the head, even if there are no signs or symptoms of CNS infection.

Once the diagnosis of cryptococcal pneumonia is made, infliximab should be stopped. Fluconazole/ itraconazole, amphotericin B, and flucytosine are the treatment options that may be used. In the eight patients reviewed above, five were treated with fluconazole alone, two with amphotericin B and fluconazole, and one with amphotericin B and flucytosine initially, followed by fluconazole. All cases were associated with favorable outcomes.

No prospective studies have been performed to evaluate the relative efficacy and optimum duration of various treatment options for cryptococcal pneumonia in infliximab-treated patients. The Infectious Disease Society of America's "Practice Guidelines for the Management of Cryptococcal Disease" recommend treating HIV-negative, immunocompromise-associated cryptococcal disease with two weeks of induction therapy followed by a minimum of 10 weeks of consolidation treatment. In such patients, the same treatment strategy is advocated for CNS and non-CNS disease. The two week induction treatment is comprised of amphotericin B (0.7-1 mg/kg/day) and flucytosine (100 mg/kg/day). Consolidation treatment is with fluconazole (400mg/day) for a minimum of 10 weeks and may be continued for as long as the immunocompromised state lasts.<sup>22</sup>

## CONCLUSION

TNF-alpha plays a pivotal role in the generation of the cell-mediated immune response to *C. neoformans*. Treatment with TNF-alpha blockers such as infliximab produces an immunocompromised state marked by impairment of T-cell-mediated immunity. Infliximab-treated patients may thus be at higher risk of developing serious infections with *C. neoformans* than patients who are not immunocompromised. The clinical presentation in such patients is highly variable

**Table.** Reported cases of cryptococcosis in infliximab-treated patients.

Authors	Patient demographics	Immune disorder	Presentation	Doses of Infliximab prior to presentation	Site of infection	Treatment	Response/ Comments
Shrestha RK et al. (2004) <sup>15</sup>	65 y, man	Rheumatoid arthritis	Fever, pneumonia	3 doses	Lung	Fluconazole 200 mg/day x 28 days	Resolution/ Possible transmission from pet cockatiel
Hage CA et al. (2003) <sup>16</sup>	61 y, man	Rheumatoid arthritis	Shortness of breath, anemia	3 doses	Lung	Amphotericin B followed by Fluconazole	Resolution
Faress RA et al. (2003) <sup>17</sup>	73 y, man	Rheumatoid arthritis	Anorexia, weight loss	Not reported	Lung	Fluconazole	Resolution/ Caused by <i>C. albicans</i> (non-encapsulated)
Arend SM et al. (2004) <sup>18</sup>	47 y, woman	Rheumatoid arthritis	Cough, weight loss, lung infiltrates	2 doses	Lung	Fluconazole 400 mg/day, stopped after 5 months	Resolution/ Cavitating pneumonia
Munoz P et al. (2007) <sup>19</sup>	67 y, woman	Rheumatoid arthritis	Headache, confusion, hallucination, agitation	12 doses (~2 y)	Central nervous system	Fluconazole 400 mg/day	Resolution
True DG et al. (2002) <sup>20</sup>	69 y, woman	Rheumatoid arthritis	Fever, lung infiltrates, pancytopenia	5 doses	Lung	Amphotericin B and fluconazole	Resolution
Starrett WC et al. (2002) <sup>21</sup>	44 y, man	Rheumatoid arthritis	Pneumonia, clinical & radiographic	3 doses	Lung	Fluconazole	Resolution
Present case (2007)	61 y, man	Crohn's disease	Lung mass, otherwise asymptomatic	~2.5y	Lung	Amphotericin B, flucytosine and later fluconazole	Resolution

and may even be asymptomatic with only radiographic evidence of disease. A high index of suspicion and aggressive investigation may be required to make the diagnosis.

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## CME QUESTIONS

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Choose the answer that is most correct for each question.

1. True/False  
Reactivation of latent tuberculosis is a well-known complication of treatment with TNF-alpha blocking agents.
2. A chest radiograph in cryptococcal pneumonia may show:
  - a. Bilateral pulmonary nodules.
  - b. Cavitory lesions.
  - c. Consolidation with air bronchograms.
  - d. All of the above.
3. True/False  
In immunocompromised patients with cryptococcal pneumonia, central nervous system (CNS) involvement should be ruled out with lumbar puncture and cerebrospinal fluid (CSF) analysis, even in the absence of signs of meningeal irritation.
4. Which of the following may be used in the treatment of cryptococcal pneumonia?
  - a. Fluconazole.
  - b. Amphotericin B.
  - c. Flucytosine.
  - d. All of the above.