On examination, there was no finger clubbing or central cyanosis, but he had bilateral basal late inspiratory crackles. His initial FEV/FVC was 3.1/4.4 (predicted 3.3/4.9) L with a TLC of 6.7 L (predicted 7.2), RV of 2.3 L (predicted 2.9) and KCO of 1.26 (predicted 1.1-1.6). His chest x-ray film showed patchy shadowing in both lower zones (Fig 2). He had no blood eosinophilia and ANF and RA latex test results were negative. Sputum was negative for acid-fast bacilli on three occasions. Fiberoptic bronchoscopy findings were normal, and transbronchial biopsies were nondiagnostic. He underwent an open lung biopsy which showed interstitial fibrosis with fibroblasts and chronic inflammatory cells in the alveolar walls with type 2 cell hyperplasia and areas of fibro-myoid connective tissue within the alveoli. There was no vasculitis or granuloma.

He was treated with prednisolone 40 mg daily, and after one month, his chest x-ray film findings had returned to normal. His FEV/FVC was then 3.1/5.2 L with a TLC of 7.5 L. RV 2.3 L and KCO 1.17. His prednisolone dose was gradually reduced until it was discontinued in July, 1988. He has remained asymptomatic with normal chest x-ray findings during two years of follow-up, during which time he has continued to take sulfasalazine 2 g daily. He has had no exacerbations of his ulcerative colitis since his chest symptoms appeared.

**DISCUSSION**

Bronchial inflammation and bullae are well recognized in association with ulcerative colitis, but diffuse chest x-ray film shadowing is much less common. It may be due to vasculitis or an eosinophilic infiltrate which may or may not be caused by sulfasalazine. The few previous case reports resembling cryptogenic fibrosing alveolitis either do not include histologic confirmation of colitis or alveolitis, or involve predominantly the upper zones.

In case 1, the diagnosis of alveolitis was established histologically and the illness took an acute form. The patient responded unusually quickly and completely to a course of prednisolone and did not suffer a relapse when his ulcerative colitis appeared almost two years later or during subsequent follow-up.

Patient 2 differed slightly in that the chest x-ray film shadowing was more patchy, although it was also mainly in the lower zones. Sulfasalazine is unlikely to have been the cause of this shadowing since he had no eosinophilia, the drug had been taken for 11 years, and administration continued following his chest illness without it recurring. His symptoms, chest x-ray film findings and respiratory function improved promptly after prednisolone was given.

In neither of these patients did the appearance of the alveolitis coincide with an exacerbation of the colitis. The natural history of the alveolitis is uncertain, but it was extremely sensitive to prednisolone and did not show relapse after treatment was discontinued. Complete radiologic resolution of "cryptogenic" fibrosing alveolitis is unusual and these patients suggest that if this does occur, the alveolitis may be associated with the presence or subsequent development of ulcerative colitis.

**REFERENCES**


**Complex Cryptococcal Empyema**

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*Cryptococcus neoformans* continues to present diagnostic and treatment challenges in patients with underlying malignant neoplasms. Cryptococcal empyema is a relatively rare complication of cryptococcal disease. It is important to distinguish whether uncontrolled malignancy or cryptococcal infection is responsible for the effusion. We used both traditional diagnostic approaches, bronchoscopy and transbronchial fine needle aspiration, to verify the presence of the organism but continued to have treatment failure until adequate drainage was established.

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**Cryptococcus neoformans** is a ubiquitous fungus found in the soil. On inhalation, a complex, incompletely understood series of host responses begins that determines whether the infection will be controlled or will progress to local or disseminated disease. The frequency of cryptococcal disease in steroid-treated individuals, allograft recipients, and acquired immunodeficiency syndrome (AIDS) victims highlights the importance of T lymphocyte-dependent host defenses. We are witnessing an evolution in pulmonary cryptococcal infection, both in clinical presentations and advances in diagnostic laboratory testing, as illustrated by the following case.

**CASE REPORT**

A 46-year-old man was admitted to the hospital with a chest roentgenogram with multiple pleural-based nodules considered suspicious for metastatic cancer. A year earlier, he had undergone total laryngectomy and left radical neck dissection for squamous cell carcinoma of the larynx. He was not otherwise immunocompromised.

Bronchial brushes and a transbronchial biopsy specimen from

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TFNA = transthoracic fine needle aspiration

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Suspicion arose that coexistent cancer accounted for some of his lesions or the advancing pleural process. Transthoracic fine needle aspiration (TFNA), using a 22-gauge spinal needle, was performed with computed tomography guidance. The aspirate, a few drops of fluid, contained numerous cryptococci. Six hours after TFNA, the patient had dyspnea, fever (temperature, 38.7°C), and right-sided pleuritic pain. A repeat chest roentgenogram showed progressive increase in the large loculated right pleural effusion (Fig 2).

Chest tube placement yielded 1,100 ml of cloudy serosanguineous fluid with numerous cryptococci (Fig 3). The drainage slowly decreased and the chest tube was removed three weeks later. After completion of intravenous amphotericin and flucytosine therapy, the patient was discharged on a regimen of oral ketoconazole (400 mg orally every day). Six weeks later, he was readmitted to the hospital with generalized weakness and rapidly enlarging nodules in his neck; biopsy specimens of these neck nodules revealed squamous cell carcinoma. The bilateral intraparenchymal lung masses, attributed to cryptococcosis, had significantly regressed. He had progressive inanition and died. An autopsy was not granted.

DISCUSSION

In this case, a dramatic complication followed TFNA within 6 h. The temporal proximity suggests that the needle punctured either a large liquefied lung lesion or a loculated empyema that then drained through a small tear to involve the right inferior pleural space (Fig 2). Cryptococcal paren-

**Figure 1.** Posteroanterior chest roentgenogram demonstrates multiple bilateral and pleural-based pulmonary masses and blunting of both costophrenic angles.

The right upper lobe contained numerous yeasts characteristic of cryptococci. Culture yielded *Cryptococcus neoformans*. Despite intravenous amphotericin B therapy, he showed no clinical or roentgenographic improvement. Repeated bronchoscopy specimens continued to show numerous cryptococci and no evidence of malignant neoplasm. Flucytosine was added to the therapy, but right costophrenic blunting appeared on the chest roentgenogram (Fig 1).

**Figure 2.** The postprocedure chest roentgenogram shows an increase in the large loculated right pleural effusion without pneumothorax. There is a distended loop of bowel gas under the right hemidiaphragm.

**Figure 3.** Cell block section, right pleural effusion (hematoxylin-eosin, original magnification, × 400). Round cryptococcal organisms are surrounded by neutrophils. *Inset,* Same specimen, with electron microscopy of a Cryptococcus (original magnification, × 1,500). Note the clearly defined electron-dense wall and the less dense, multilayered, thick capsule.
chymal lesions often consist almost entirely of thickly encapsulated organisms, with little or no inflammatory response. These masses can be gelatinous or cavitary and thus susceptible to spillage. They may even present as a lung abscess as has been described in a *Cryptococcus laurentii* infection. In pulmonary coccidioidomycosis, a somewhat analogous phenomenon sometimes occurs—spontaneous rupture of a cavity and resulting pyopneumothorax. Since slight fever often follows bronchoscopy or TFNA, it is important to recognize that a clinical presentation similar to this heralds a more serious complication. The virulence of sudden spread into the pleural space, as in this case, is unclear. The patient did respond to closed chest drainage and died later, from his underlying malignant neoplasm rather than from progressive cryptococcal infection. This complication appears to be exceptional and may even have been a spontaneous event. It should not deter the careful use of TFNA for the diagnosis of suspected cryptococcosis and other infections.

Between 40 percent and 85 percent of patients with cryptococcal infections also have severe underlying diseases or immunodeficiencies. Common predisposing factors include hematogenously malignant neoplasms (especially Hodgkin’s disease), long-term corticosteroid therapy, diabetes mellitus, and sarcoidosis. About 7 percent of patients with AIDS have disseminated cryptococcosis as a complicating infection.

Most pulmonary infections in apparently healthy subjects are asymptomatic or mildly symptomatic but self-limited; antifungal therapy is seldom required. Infections usually remain localized and either resolve spontaneously or encapsulate. On the other hand, patients with progressive pulmonary cryptococcosis usually present with chronic cough, low-grade fever, chest pain, which may be pleuritic, scant mucoid or bloody sputum, malaise, and weight loss. The clinical course is subacute or chronic and is frequently complicated by concomitant extrapulmonary infection. Because the symptoms and roentgenographic findings are not pathognomonic, the diagnosis is based on the demonstration of *C neoformans* in respiratory secretions or lung biopsy specimens, and on the isolation and identification of the fungus in culture. Tissue invasion rather than culture from sputum is necessary for the diagnosis of *C neoformans* pneumonia because this fungus may be a saprophyte as well as a pathogen. Antigen detection in pleural fluid and in the serum of three patients with focal *C neoformans* pneumonitis has proved useful in documenting infection. Attenuated capsular material can also be identified by transmission electron microscopy. Although not necessary for diagnosis, transmission electron microscopy is also a valuable adjunct to confirm the presence of a capsule. The capsule, regardless of its width, appears as radiating filaments embedded in a granular matrix that surrounds the laminated cell wall of the cryptococcal cell. Phagocytic cells often contain phagolysosomes distended with capsular material in addition to degenerated yeast forms (Fig 3).

Pleural effusion in pulmonary cryptococcosis by any mechanism is uncommon and does not by itself portend a poor prognosis. Cell counts vary from 1 to 10,000 with a predominant lymphocytosis (80 to 90 percent). The culture is negative in 50 percent of the cases described. It is possible that the intense cellular response (Fig 3) renders the organisms nonviable. Ineffectual phagocytosis and impaired fungal cell killing are major factors to consider whenever there is interference with the “priming function” of the T lymphocyte. The potential for cryptococcal disease to result in complex clinical problems is often manifest whenever the host’s underlying condition is not controlled or a coexistent malignant neoplasm is present. Despite evidence for active cellular response (Fig 3), our patient was refractory to standard treatment regimens and required surgical drainage. Prolonged antifungal therapy combined with early consideration of surgical drainage procedures is warranted when these situations are recognized.

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