

Pleural Effusion as a Manifestation of Pulmonary Cryptococcosis

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Introduction

Cryptococcosis is an opportunistic fungal disease caused by *Cryptococcus neoformans*, an encapsulated dimorphic fungus. It has two subspecies: *Cryptococcus neoformans* var. *neoformans* and *Cryptococcus neoformans* var. *gattii*. Each subspecies cause disease in humans. *C. neoformans* var. *neoformans* has been connected to infection in immunosuppressed patients worldwide; *C. neoformans* var. *gattii* has been described in relation to infections in immunocompetent patients but its distribution is limited to tropical and subtropical countries.

Infection occurs by inhaling the microorganism present in bird excrement, most commonly from pigeons. This produces an initial infection in the lungs, from where it can spread by hematogenous dissemination to other organs—mainly meninges and the central nervous system—causing meningitis and encephalitis. [1,2] It also may remain latent and reactivate when immunity mechanisms fail. The most common manifestation of this fungus, both in immunosuppressed and immunocompetent patients, is neurological.

Isolated pulmonary cryptococcosis occurs in approximately 10-30% of cases, and is more frequent in immunosuppressed patients. [3,4] Existing literature is focused on the HIV population, and descriptions of this disease in non-HIV patients are scarce. [5]

We present a patient with lymphoma on chemotherapy, with pulmonary and pleural involvement with *C. neoformans* in the pleural fluid, with an unfavorable clinical course.

Clinical case

We present a 65-year-old patient, former smoker, with hypertension, gallstones, and stage III mantle cell lymphoma admitted with respiratory symptoms. He had undergone his first cycle of scheduled chemotherapy a week previously. He was admitted with worsening cough, expectoration, fever and concern for bacteremia. Upon physical examination, he was febrile and tachypneic. He had good bilateral air entry, bilateral isolated rhonchi, right-sided basilar crackles, and painless bilateral lateral cervical, supraclavicular, axillary and inguinal lymphadenopathy. His complete blood count (CBC) showed his hematocrit was 22 %, hemoglobin 7.8 g/dl, white blood cells 9,700/mm³ and platelets 522,000/mm³. Tests for HIV, Hepatitis B and Hepatitis C were negative. A chest computerized tomography (CT) scan was abnormal. (**Figure 1**)

The patient was initially felt to have hospital-acquired pneumonia. Blood cultures and sputum tests were ordered. An empiric treatment with piperacillin-tazobactam was started with a satisfactory clinical response. All cultures were initially negative. A week after admission, fever and hypoxemia recurred. A CT chest scan was repeated. (**Figure 2**)

A thoracentesis was performed, with results as follows: slightly bloody pleural fluid, 175/mm³ red blood cells, 740/mm³ white blood cells (lymphocyte predominant), glucose 100 mg/dl, protein 2.1 g/dl, and LDH 233 U/L. These results were consistent with uncomplicated effusion.

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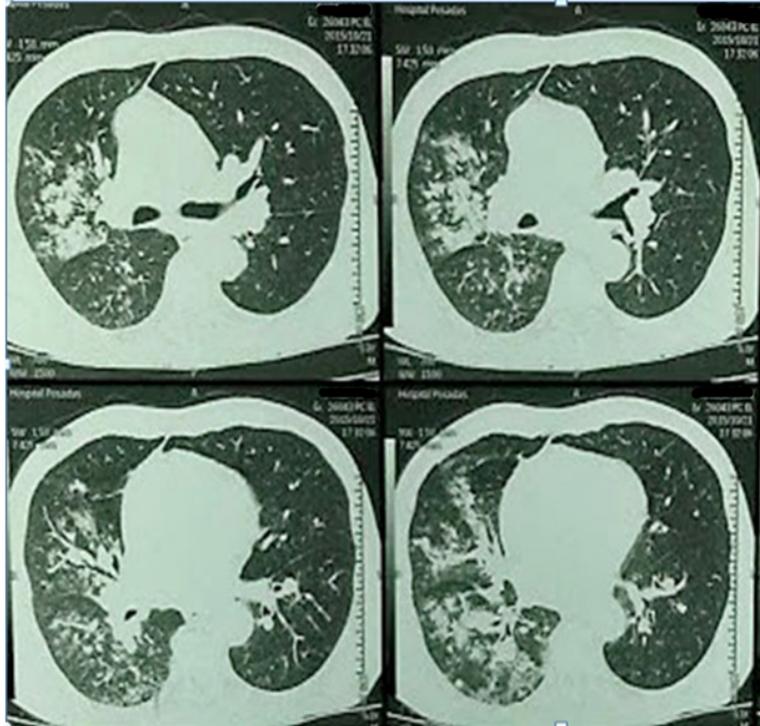


Figure 1. Alveolar infiltrates with right upper, middle and lower lobe involvement, with consolidation areas, ground-glass areas and diffuse micronodules.

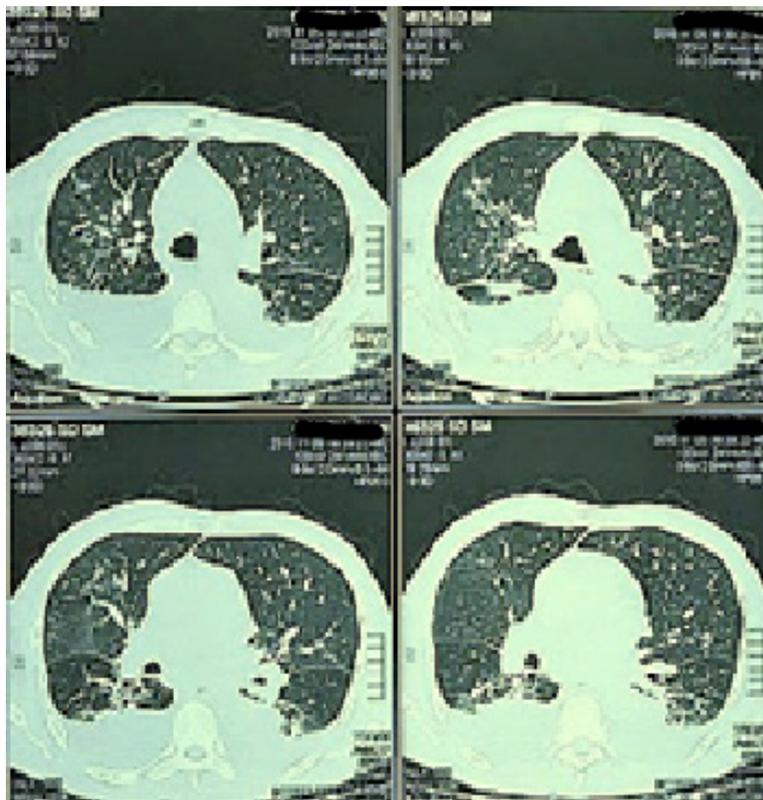


Figure 2. Bilateral pleural effusion with a right predominance and associated bibasilar consolidated areas and pleuro-pulmonary fibrous tracts.

Pleural fluid culture tested negative for common organism pathogens and positive for *Cryptococcus neoformans*. Cryptococcal antigen in the blood and fungal blood cultures remained negative. Treatment with Amphotericin B was initiated. The patient's condition continued to worsen, with acute respiratory distress requiring orotracheal intubation and respiratory mechanical ventilation until he died due to multi-organ failure.

Discussion

Pulmonary cryptococcosis may develop in immunocompetent or immunocompromised patients- such as those with HIV or other underlying medical conditions, such as lymphoma, leukemia, solid organs or bone marrow transplant recipients, systemic lupus erythematosus, sarcoidosis, diabetes mellitus, rheumatoid arthritis, chronic treatments with corticosteroids, immunomodulators and anti-TNF- α agents.

The clinical picture of cryptococcosis differs depending on the patient's immune status. In immunocompetent patients, the infection is self-limited and minimally symptomatic; in the immunocompromised host, the disease can be severe and disseminated.

Clinical manifestations of pulmonary cryptococcosis varies from mild symptoms such as cough, expectoration, prolonged febrile syndrome, weight loss, and anorexia to disseminated cryptococcosis involving several organs. This is why it is necessary to test for CNS involvement in immunosuppressed patients. [6,7]

There are three types of radiological patterns in pulmonary cryptococcosis: (1) nodular mass, (2) consolidation and (3) reticulo-alveolar opacities. Nodules are the most frequent radiological finding in immunocompetent and immunosuppressed patients. These can be multiple, single, or cavitated with regular or irregular contours and may have confluent or be diffused in distribution. [8,9] Consolidations, reticular infiltrates, ground-glass opacities, a halo sign and mediastinal, or hilar adenopathy may also be found. Other less frequent findings are pleural effusion, cavitation and endobronchial lesions. After treatment of pulmonary cryptococcosis, bronchiectasis and fibrotic areas may appear. [10,11]

The yield from a pleural fluid culture for *Cryptococcus* is approximately 50%. Another method for diagnosis is the detection of Cryptococcal antigen in the pleural fluid. The title of antigenemia seems to be related to the route of dissemination—contiguous dissemination via subpleural pulmonary lesions is usually more common than bloodborne dissemination. [12]

In a review of patients with HIV and pulmonary cryptococcosis, 10% had pleural involvement and most cases were accompanied by disseminated cryptococcosis. There are only 50 reported cases of pleural cryptococcosis described in the literature. [3,12]

In a Young et al review, 14 of the 30 patients with pleural effusion due to *Cryptococcus* have a disease localized to the thorax and 16 have disseminated disease. Predisposing disease or immunosuppressive treatment were found in 17 patients. Cultures of pleural fluid for cryptococci were positive in 11 of 26 patients. (in the other 15 patients, the diagnosis was established by histopathological study of lung samples). [13]

The guidelines from the Infectious Diseases Society of America (IDSA) for cryptococcal disease recommend treatment of disseminated disease with CNS involvement or severe pulmonary involvement with two weeks of Liposomal Amphotericin and Flucytosine, continuing liposomal amphotericin B and flucytosine, then continuation with oral Fluconazole for maintenance and suppression. When available, therapy doubled with amphotericin Band fluconazole may also be considered as an alternative when there is lack of access to flucytosine. [15]

Conclusion

Pulmonary cryptococcosis is difficult to diagnose in non-AIDS immunosuppressed patients as the clinical and radiological manifestations are atypical. Pleural involvement is uncommon. Clinical suspicion and invasive methods are necessary to establish the diagnosis and appropriate treatment.

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