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**Pleural involvement in cryptococcal infection**

Georgakopoulou VE *et al*. Pleural involvement in cryptococcal infection

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**Abstract**

Pleural involvement of cryptococcal infection is uncommon and is more commonly observed in immunocompromised hosts than in immunocompetent ones. Pleural involvement in cryptococcal infections can manifest with or without pleural effusion. The presence of *Cryptococcus spp.* in the effusion or pleura is required for the diagnosis of cryptococcal pleural infection, which is commonly determined by pleural biopsy, fluid culture, and/or detection of cryptococcal antigen in the pleura or pleural fluid.

**Key Words:** Cryptococcosis; Pleural effusion; Pleural diseases; Fungal lung diseases; Pleural Cavity; Cryptococcus neoformans

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**Core Tip:** The importance of pleural involvement in cryptococcal infections is often overlooked. When biopsy results are inconclusive, further testing for invasive granulomatous infections, such as pulmonary cryptococcosis, should be done. When indicated, a sensitive cryptococcal antigen assay and fungal culture should be used to evaluate pleural effusion specimens. Even if the cryptococcal antigen test is negative, clinicians should investigate pleural cryptococcosis in cases of pleural nodules without pleural effusion, especially in the context of immunosuppression.

**TO THE EDITOR**

We read with interest a case report by Wu *et al*[1], who described a case of a 29-year-old male, immunocompetent host with cryptococcal pneumonia accompanied by pleural effusion. In that case, chest imaging showed scattered numerous cavities in the superior segment of the left lower lobe with a rough cavity wall and a cavity and pleural effusion in the anterior segment of the left lower lobe[1].

*Cryptococcus* is an invasive fungus that causes cryptococcosis, a disease that is common in immunocompromised people and rare in healthy individuals. *Cryptococcus neoformans* and *Cryptococcus gatti* are the two *Cryptococcus* species most frequently associated with human cryptococcal infections. The organism is found globally. The most common kind of exposure involves a history of contact with soil contaminated with bird droppings. The fungus capsule contains the polysaccharides glucuronoxylomannan and glucuronoxylomannogalactan, which are the major components that contribute to the fungus's virulence[2]. Immune suppression is the most important underlying mechanism in the development of cryptococcal infection. Disorders like acquired immune deficiency syndrome (AIDS), diabetes mellitus, and chronic liver and renal disease, prolonged administration of steroids, use of immunosuppressive agents, such as monoclonal antibodies, and solid organ transplantation are commonly associated with the development of cryptococcal disease[3].

*Cryptococcus* species spread by inhalation, and despite the fact that the virus most commonly enters the body through the lungs, meningoencephalitis is the most prevalent clinical manifestation of the infection[4]. According to several studies, in pulmonary cryptococcosis, pulmonary nodules are the most prevalent computed tomography findings of pulmonary cryptococcosis in immunocompetent hosts, with multiple nodules being more common than solitary lesions. The majority of them are poorly defined and inhomogeneous, with air-bubble signs seen. Consolidation, ground glass opacities, and masses are also described. The halo, air bronchogram, and cavity signs can also be seen. In these individuals, the pulmonary lesions are mostly seen in the lower lung lobes and the lung periphery[5,6]. In immunocompromised patients, the most common imaging findings are multiple nodules, which are usually larger than those in normal hosts, pulmonary cavitations, and single or multiple consolidations. Adenopathy and pleural effusions, which are sometimes small and unilateral, are usually observed in cases of extensive lung infection[7].

Pleural involvement of cryptococcal infection is rarely observed and is more commonly seen in immunocompromised hosts than in immunocompetent ones[8]. Pleural effusion associated with cryptococcal infection in an immunocompetent host was described for the first time in 1941[9]. Since then, approximately 50 cases of pleural effusion related to cryptococcal infection due to *Cryptococcus neoformans,* in the context of both lung and disseminated disease, have been described[10]. A total of 32 cases out of 50 had only pulmonary cryptococcosis, and 18 out of 50 patients were related to disseminated disease. Eight patients experienced severe pulmonary cryptococcosis, requiring, in some cases, surgical management with decortication and lobectomy. The immunosuppressive risk factors identified in these 50 cases were solid organ transplantation, AIDS, hematological malignancies, administration of corticosteroids, diabetes mellitus, chronic obstructive pulmonary disease, bronchial asthma, liver cirrhosis, and end-stage renal disease. Interestingly, 14 patients were immunocompetent. The majority of pulmonary nodules were observed in the lower lobes and in a subpleural distribution. Of note, 26 patients had only pleural effusion on computed tomography imaging[11,12].

The diagnosis of cryptococcal pleural infection requires proof of the presence of *Cryptococcus spp.* in the effusion or pleura and is typically established by examination of pleural biopsy, fluid culture, and/or detection of cryptococcal antigen (CrAg) in the pleura or pleural fluid[13]. Detecting *Cryptococcus neoformans* by histopathological examination is the gold standard for confirming the diagnosis. The detection rates of *Cryptococcus neoformans* with Gomori-methenamine silver stain and periodic acid-Schiff stain are 100%. The morphology present in tissue with *Cryptococcus neoformans* infection using Gomori-methenamine silver and periodic acid-Schiff (PAS) staining reveals arrow-based budding yeasts (4-10 μm) with a thick capsule, while the morphology present in tissue with histoplasmosis reveals small yeasts (2-4 μm) with narrow-based budding grouped in clusters inside macrophages[14].

 The classic approach for diagnosing *Cryptococcus* *neoformans* is Indian ink staining, in which the refractile mucinous capsule around the pathogen is delineated, resulting in a distinctive "starry night" appearance. The sensitivity and specificity of India ink stains, on the other hand, are very heterogeneous and usually operator-dependent[15]. Polymerase chain reaction (PCR) analysis of pleura tissue has also been used for the identification of *Cryptococcus* *neoformans* in cryptococcocal pleuritis[16].

Pleural fluid cultures for *Cryptococcus neoformans* are frequently negative, most likely due to the small number of fungi present[11]. CrAg test is considered an effective non-invasive diagnostic tool, with its role in serum and cerebrospinal fluid being well accepted with high sensitivity and specificity[12]. Additionally, this test has a low incidence of false-positive reactions, making it valuable in diagnosing cryptococcosis when cultures of pleural fluid are negative[11]. Moreover, it has been reported that pleural effusion CrAg has higher sensitivity than serum CrAg test in patients with pleural effusion as the only clinical presentation of cryptococcal infection[17]. However, the diagnosis of cryptococcal pleural effusion in the case by Wu *et al*[1] was made by positive serum CrAg, positive India ink staining of bronchoalveolar lavage fluid, and positive PAS staining for *Cryptococcus* of lung tissue obtained by percutaneous lung biopsy, while neither pleural aspiration nor pleural biopsy was reported[1].

In recent years, molecular identification and strain typing methods have been used to analyze *Cryptococcus*. The identification methods include DNA-DNA hybridization and nested, multiplex and real-time PCR. Regarding *Cryptococcus* typing, the following techniques have demonstrated the best ability to differentiate between fungal serotypes and molecular types: Serotyping, random amplified polymorphic DNA, multilocus enzyme electrophoresis, restriction fragment length polymorphism, electrophoretic karyotyping, PCR-fingerprinting, amplified fragment length polymorphism, multilocus microsatellite typing, single locus and multilocus sequence typing, matrix-assisted laser desorption/ionization time of flight mass spectrometry, and whole genome sequencing. These typing methods have contributed in revealing the phylogenetic pattern, the origin of numerous lineages and their scattering patterns, the distribution of genetic variation among geographic regions and ecosystems, and precise mutations during infections[18,19]. In addition, the cloning of *URA5* gene, *TRP1* gene, and recombinant DNA is helpful to study the taxonomic status, phylogenetic origin, and epidemiological investigation of *Cryptococcus neoformans*[20-22].

The patient in case by Wo *et al*[1] was initially treated with a daily dose of 400 mg of fluconazole, but he had not a satisfactory clinical outcome a week later and the therapy was modified to voriconazole 200 mg twice daily. Complete resolution of the lesions was observed after 8 wk of therapy. In non-immunocompromised patients with pulmonary cryptococcal infection, it is recommended the administration of fluconazole 400 mg daily and switching to itraconazole (200 mg twice per day orally), voriconazole (200 mg twice per day orally), or posaconazole (400 mg twice per day orally) in cases with no clinical improvement, no fluconazole availability, or contraindication[23].

Cryptococcal pleural effusions are usually located in the right hemithorax. They vary in size from minimal to massive and are almost always related to parenchymal lesions ranging from subpleural nodules to interstitial infiltrates or pulmonary lesions. The character of the fluid is usually bloody or serosanguinous[11]. Pleural fluid total cell counts range from 169/mm3 to 12000/mm3, with lymphocytes predominating in most cases, but neutrophils and eosinophils have also been reported[16]. The fluid is traditionally exudative; however, cases of transudative fluid have also been described, bringing awareness of this diagnosis in immunocompromised patients regardless of the transudative pleural effusion[24].

It is worth-mentioning that cryptococcal pleural effusion may have high levels of adenosine deaminase (ADA), making the discrimination between this fungal infection and tuberculosis difficult. Yoshino *et al*[25] described a case of cryptococcal pleuritis, diagnosed by the isolation of *Cryptococcus neoformans* in the culture of the pleural effusion, containing a high level of ADA in a patient with AIDS. Wee *et al*[10] also reported a case of a patient with acute myeloid leukemia and a cryptococcal pleural effusion with increased pleural fluid ADA level[4]. Previous research has shown that ADA levels in the pleural fluid > 40 IU/L demonstrate a high sensitivity (81%-100%) and a high specificity (83%-100%) for diagnosing tuberculosis pleuritis[26]. ADA is an enzyme present in most cells, notably lymphocytes, that catalyzes the conversion of adenosine to inosine. As a result, it is hypothesized that ADA levels would be higher in lymphocyte-rich pleural effusions, such as those seen in cryptococcal infections[25].Some studies found that an increased level of ADA was rarely observed in nontuberculous lymphocytic pleural effusions and that a level of ADA greater than 40 IU/L ruled out tuberculosis; however, cases of cryptococcosis were not included in these studies[27]. ADA test has high negative predictive value and is an excellent test to rule out tuberculosis[28]. Some studies demonstrate that an ADA level > 45 to 60 units/L has a sensitivity of 100% and a specificity up to 97% for tuberculous pleural effusion[29,30].

In addition, pleural involvement in cryptococcal infections includes pleural infection without pleural effusion. Of interest, pleural cryptococcosis without pleural effusion has been described only in one case in the literature. The authors described this extremely uncommon entity in a patient suffering from rectal carcinoma under chemotherapy and mentioned as a possible explanation for this finding that lung cryptococcosis, developed in the peripheral lung parenchyma during chemotherapy, had a rupture into the pleural cavity space[31].

Pleural involvement in cryptococcal infections is under-appreciated. When biopsy results are inconclusive, further testing for invasive granulomatous infections, such as pulmonary cryptococcosis, should be conducted. Where needed, pleural effusion should be evaluated using a sensitive CrAg assay as well as fungal culture. Furthermore, clinicians should consider pleural cryptococcosis in cases of pleural nodules without pleural effusion, especially in the context of immunosuppression, even if the CrAg test is negative.

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