Disseminated Cryptococcal Disease in a Patient with Chronic Chylothorax and a Pleurovenous Catheter: A Case Report with Autopsy Findings

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Abstract

*Cryptococcus* species are ubiquitous in the environment with a global distribution. Whilst causing disease predominantly in immunocompromised hosts such as those with advanced HIV, HIV-uninfected patients are increasingly recognized to be affected. The most common forms of infection are cryptococcal pneumonia and meningitis. HIV-uninfected patients and extrapulmonary infections have worse outcomes, likely due to delayed diagnosis and treatment. *Cryptococcus* infections involving chylothorax or chyloabdomen have rarely been reported in humans. We describe a case of fulminant disseminated cryptococcosis with fungemia, peritonitis, and empyema in a patient with chronic chylothorax treated with an indwelling pleurovenous shunt. Key autopsy findings included cryptococcal organisms identified on calcified lymphadenopathy, pleural adhesions, and pericardium. We discuss the importance of identifying patients with non-traditional risks factors for cryptococcal disease, such as lymphopenia and hypogammaglobulinemia, and the potential implications of pleurovenous catheters in *Cryptococcus* dissemination.

**Key Words:** *Cryptococcus neoformans*/immunology, Cryptococcosis/complications, chylothorax, pleurovenous shunt complications, acquired immunodeficiency/complications.
Introduction

Cryptococcosis is an opportunistic fungal infection caused by the globally distributed encapsulated yeast Cryptococcus neoformans or Cryptococcus gattii, affecting mainly immunocompromised patients.\(^1,2\) Cryptococcosis can also infect immunocompetent hosts, evidenced by outbreaks in otherwise healthy individuals in North America and Canada.\(^3,4\) Cryptococcosis is associated with meningitis in patients with HIV/AIDS; however, clinicians have recognized its growing importance in HIV-uninfected patients, particularly in high-income countries.\(^4,5\)

Immunocompromised hosts at risk of Cryptococcus infection include patients with sarcoidosis, systemic lupus erythematosus, malignancy, cirrhosis, and recipients of solid-organ transplantation. Less commonly, conditions with functional hypogammaglobulinemia such as Hyper-IgM and IgE syndromes are also associated with Cryptococcosis.\(^6,7\) Protein-losing enteropathy—excessive loss of serum proteins into the gastrointestinal tract—leads to chronic hypogammaglobulinemia and body cavity effusions, which can also increase the risk of cryptococcosis.

The clinical and epidemiological characteristics of cryptococcal infection in HIV-uninfected individuals are highly heterogeneous, often causing delays in diagnosis and treatment of a disease with high morbidity and mortality, particularly given the protean extrapulmonary and extra-neurologic manifestations.\(^8,9\) There is also a lack of evidence-based recommendations for cryptococcosis treatment in non-HIV-associated cases. The majority of randomized clinical trials for cryptococcosis have been in the setting of HIV-associated cryptococcal meningitis, leading to a knowledge gap in the management of non-HIV cases\(^10\), and in particular, non-neurological and non-pulmonary manifestations.

We describe the case of a patient with chronic chylothorax and chylous ascites requiring a pleurovenous shunt, who developed fatal disseminated cryptococcosis with fungemia, empyema, pleural catheter infection, and peritonitis. Key autopsy findings are presented. We will describe uncommon risk factors and outcomes in previous cases with Cryptococcus empyema and peritonitis.
We aim to discuss the importance of recognizing lymphopenia and hypogammaglobulinemia as non-traditional risk factors for Cryptococcosis.

Case Description

A 66-year-old white, non-Hispanic man with a history of chronic chylothorax, chylous ascites, and protein-losing enteropathy from lymphangiectasia presented with dyspnea, abdominal distension, and diffuse edema. He had a history of unconfirmed sarcoidosis but was not on any treatment. He had no history of abdominal surgeries or liver disease. He had required therapeutic thoracentesis every other week in the previous two years due to a rapid accumulation of chylous pleural effusions. He underwent placement of a pleurovenous catheter three months before presentation to relieve symptoms and decrease the need for frequent percutaneous drainage of fluid. He moved from an urban center in Missouri to Denver, Colorado, where he routinely cleaned a fountain in his backyard that attracted multiple species of birds. Computerized tomography of abdomen and pelvis one year prior showed a large right pleural effusion with nonspecific ground-glass opacities in the posterior left lower lobe and extensive calcified lymph nodes.

On initial presentation, he reported 18 kg (40 lb.) weight gain since shunt placement and one week of dyspnea, abdominal distension, and increased edema in upper and lower extremities. Vital signs were significant for a blood pressure of 95/61 mmHg, heart rate of 75 beats per min, temperature of 36.3 degrees Celsius, respiratory rate of 16 breaths per min, and oxygen saturation of 96% on 1 liter of oxygen by nasal cannula. He was in no distress and had evident temporal wasting. The cardiac exam was unremarkable. Breath sounds were decreased on the right base with faint wheezes bilaterally. The abdomen was distended with a palpable fluid wave. He had bilateral upper and lower extremity edema. He was alert and oriented with no focal neurological deficits. Laboratory studies were notable for sodium of 147 mmol/L (133 – 145 mmol/L), creatinine 0.66 mg/dL (0.70 - 1.30 mg/dL), alkaline phosphatase 272 U/L (39 - 117 U/L), alanine aminotransferase 103 U/L (7 - 52 U/L), aspartate aminotransferase 112 U/L (12 - 39 U/L), total protein 3.5 g/dL (6.4 - 8.9 g/dL) and serum albumin of 1.9 g/dL (3.5 - 5.7 g/dL). White blood cell (WCB) count was 4.2k/L with an absolute lymphocyte
count of 100 cells/L. Fourth-generation HIV 1/2 antibody/p24 antigen, Hepatitis C virus (HCV) antibody and HCV quantitative RNA were negative. Hypogammaglobulinemia was noted with low levels of immunoglobulins G and M (416 mg/dl [reference 670-1,822], 23 mg/dl [reference 43-279], respectively), whereas immunoglobulin A levels were normal. Ultrasound of the abdomen showed normal liver echotexture and moderate ascites.

The patient underwent right thoracentesis and paracentesis, removing 3.5L of pleural fluid and 5L of ascitic fluid. The shunt was found to be patent. Peritoneal fluid was cloudy, with 38 WBCs (80% monocytes) and triglycerides of 124 mg/dL. Direct gram stain showed no organisms. On day five, peritoneal fluid culture grew yeast, later identified as Cryptococcus neoformans, via a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry. The patient was started on fluconazole 400 mg PO daily for fungal peritonitis. Further workup was pursued to assess disseminated cryptococcosis and repeat pleural, peritoneal fluid, and blood cultures grew Cryptococcus neoformans.

After repeating therapeutic thoracentesis and paracentesis, the patient became hypotensive, did not respond to volume resuscitation, and ultimately developed shock. He was started on intravenous liposomal amphotericin B and flucytosine. Lumbar puncture was deferred due to coagulopathy, intact mental status, and already established disseminated disease. Despite standard of care antifungals, blood cultures continued to grow C. neoformans (for over 72 hours), and pleurovenous shunt was removed due to suspected colonization. Tip of shunt culture also grew C. neoformans. Despite these measures, the patient continued to deteriorate, and he was transitioned to comfort care measures and passed within 24 hours. Autopsy findings were notable for chylothorax from chronic lymphatic and thoracic duct obstruction (Figure 1), cryptococcosis infecting diffuse calcified lymphadenopathy (Figure 2), and cryptococcal organisms in pleura and pericardium with an associated lymphocytic infiltrate (Figure 3). There was no evidence of cryptococcal meningoencephalitis or cryptococcal pneumonia.
Patient Consent Statement

The use of the clinical data has been performed under an approved protocol by the Colorado Multiple Institutional Review Board (COMIRB Protocol 15-1340) and an exemption of informed consent was granted. All identifying details of the patient have been removed in accordance with our institutional policy (COMIRB) and Oxford University Press publishing policy.

Discussion

We describe a case of fulminant disseminated cryptococcosis in the setting of a chronic lymphangiectasia and protein-losing enteropathy complicated by lymphopenia, hypogammaglobulinemia, chylothorax and chylous ascites requiring a pleurovenous shunt placement. Cryptococcal empyema and peritonitis are rare and potentially fatal conditions if not diagnosed early and treated promptly.\textsuperscript{11} Since the early 1900s, only 50 cryptococcal empyemas\textsuperscript{12-20} and 65 cryptococcal peritonitis cases have been reported.\textsuperscript{21-31} There may be underreporting cases of empyema and peritonitis due to the difficulties in diagnosis.

Disseminated cryptococcosis manifesting with extrapulmonary and extra-neurological presentations is increasingly recognized\textsuperscript{32}. Cryptococcal empyema has been reported in patients with malignancy being treated with biological agents.\textsuperscript{15-17} Peritonitis tends to occur in the setting of peritoneal dialysis with end-stage renal disease.\textsuperscript{22, 24} Patients presenting with peritonitis or empyema who are suspected to be immunocompromised should be evaluated for cryptococcal infection to prevent dissemination.

The underlying chylothorax with repeated large-volume thoracentesis and protein-losing enteropathy resulting in malnutrition likely contributed to the longstanding and profound lymphopenia in this patient, representing a significant risk factor for cryptococcal infection. The patient did have a negative 4\textsuperscript{th} generation HIV $\frac{1}{2}$ antibody p24 antigen test. Lymphocyte loss from chronic chylothorax fluid removal and protein losing-enteropathy leads to a net immunosuppressed state.\textsuperscript{23, 33, 34}
The role of hypogammaglobulinemia in our patient also played an essential role in increasing the risk of infection. In vitro studies have demonstrated that human IgM and IgG change the morphology of *C. neoformans* and that IgM inhibits titaian-like cell formation, which can reduce virulence and the risk of disseminated disease. Previous reports have described an association between hypogammaglobulinemia and increased risk for cryptococcal disease, including in HIV infected patients. Hypogammaglobulinemia—as a surrogate marker for immunodeficiency and nutritional status—can be a clinically helpful marker risk for cryptococcosis in HIV-uninfected patients.

*Cryptococcus* has also been reported often as a life-threatening complication of sarcoidosis. However, the autopsy findings did not confirm the diagnosis of sarcoidosis. There are clinical-pathological overlap findings between sarcoidosis and *Cryptococcus* infection, including lymphadenopathy and granuloma formation. Sarcoidosis can be a risk factor in up to 2.9% of cryptococcosis infections. Glucocorticoids, which are often used to treat sarcoidosis, further increase immunosuppression and the subsequent risk of cryptococcosis. The autopsy revealed a high burden of disease involving lymph nodes diffusely, pleura, and pericardium with a modest lymphocytic infiltrate. Interestingly the patient did not manifest pericarditis clinically. It is also notable there was no central nervous system involvement despite persistent cryptococcemia. The fungal burden rather than an exuberant inflammatory response were more likely to be responsible for disease pathogenesis.

A pleurovenous shunt is a relatively non-invasive procedure used to treat patients with intractable pleural effusions. It allows for external manual compression for fluid drainage, but shunt failure, pulmonary edema, post-shunt coagulopathy, deep vein thrombosis, and bacterial infection remain commonly reported complications. There are no reports of pleurovenous shunts being complicated by fungal diseases or being a risk factor for dissemination. We hypothesize that a pleurovenous shunt...
dissemination mechanism mediated the translocation of yeast from the pleural cavity to the bloodstream and peritoneum.

This patient's dissemination pathway begun with the immunocompromised state due to the secondary defects in humoral and cellular immunity. Lymphangiectasia associated with protein-losing enteropathy causes chylothorax via enteric lymphatic vessel leakage. The patient received a pleurovenous shunt to remove fluid from the thorax into the central venous system via the inferior vena cava. Before receiving the shunt, the patient likely had latent Cryptococcus infection in his pleura and lymph nodes, as evidenced by the multiple calcified lymph nodes with Cryptococcus on autopsy findings and prior imaging. The infection reactivated through acquired immunodeficiency and allowed the organism to spread through the lymphatic system to the pleural space. Once it caused empyema, the shunt facilitated dissemination to the central venous system reaching the blood and the peritoneum, causing fungemia and peritonitis, respectively. The host relies on pulmonary innate immune cells such as phagocytic macrophages, dendritic cells, and neutrophils as a first-line defense against Cryptococcus. However, the Cryptococcus capsule's antiphagocytic properties prevent elimination and raise questions about a biofilm that enables shunt infection. It is unclear why the central nervous system (CNS) was spared from infection in this case.

This case is novel as it is a co-existing empyema and peritonitis presenting in a patient with a pleurovenous shunt serving as the facilitator for dissemination. Chylothorax or chyloabdomen associated with Cryptococcus have only been reported in animals such as cats and dogs. Immunosuppressed patients with chronic indwelling pleurovenous shunts in place may need to be assessed for their risk of disseminated cryptococcosis.
Guideline-directed management of severe pulmonary or disseminated Cryptococcus in immunocompromised and immunocompetent patients is identical to CNS cryptococcosis treatment. Due to severe disease with Cryptococcosis and dissemination, our patient was treated with a standard regimen for CNS involvement with amphotericin B plus 5-flucytosine for the induction phase.

However, our patient failed initial treatment due to the burden of disease, unusual location of the infection, and medication toxicity complications. Therapy for our patient also became difficult as the pleurovenous shunt might have promoted the dissemination and increased the initial fungal burden.

This case highlights the importance of considering non-traditional immunosuppressive risk factors, as mortality in non-HIV immunocompromised hosts continues to remain high. Focusing only on commonly reported risk factors can lead to a delayed or missed diagnosis.

Conclusion

This case demonstrates that disseminated cryptococcal infection with a high disease burden involving pleura, peritoneum, pericardium, and bloodstream can occur in patients with non-traditional immunodeficiency conditions. We believe lymphopenia, hypogammaglobulinemia, malnutrition, and the presence of a pleurovenous shunt proved to be relevant in this case and contributed to dissemination with multiorgan involvement. We recommend a low threshold for Cryptococcus screening in patients with these risk factors. Mortality from cryptococcosis is higher in HIV-uninfected patients than in HIV-infected patients, likely due to delayed diagnosis. Early diagnosis and prompt treatment in patients with a suspected disseminated cryptococcal disease might reduce morbidity and mortality.
Potential Conflicts of Interest

No conflicts of interest.

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Figure 1. Gross anatomy description. A) Bowel mesentery with calcified lymphadenopathy (arrows); blood-tinged chyloperitoneum present in the background; B) Right pleural cavity with chylothorax (asterisk).

C) Right pleural cavity after lung removal demonstrating pleural adhesions to the chest wall (arrowheads).

D) Loop of bowel with calcified lymphadenopathy (arrow) and mesenteric plaque

Figure 2. Histopathology slides of the calcified lymph node. A) Lymph node with a collection of cryptococcal organisms and rim of residual lymphoid tissue; 40x B) Cryptococcal organisms in a partially necrotic background; 400x; C) Grocott methenamine silver (GMS) stain highlighting cryptococcal organisms; 100x; D) GMS stain highlighting cryptococcal organisms; 400x

Figure 3. Chest wall and pericardium histopathology findings. A) Chest wall with pleural adhesions (arrows) and associated inflammation; 40x; B) Adhesion demonstrating cryptococcal organisms and lymphocytic inflammation; 400x; C) GMS stain highlighting cryptococcal organisms in pleural adhesion; 400x; D) Pericardium with cryptococcal organisms and mild chronic inflammation; 400x
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