Open Forum Infectious Diseases

NOVEL ID CASES

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

William Mundo,[1,2] Amber Berning,[3] Yiannis Koullias,[1,6] Daniel B. Chastain,[4] Neil Stone,[5] Carlos Franco-Paredes,[6,7] Andrés F. Henao-Martínez,[1,6] and Lilian Vargas Barahona[6]

[1]School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA, [2]School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA, [3]Department of Pathology, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA, [4]Department of Clinical and Administrative Pharmacy, University of Georgia College of Pharmacy, Albany, Georgia, USA, [5]Hospital for Tropical Diseases, University College London Hospitals, London, UK, [6]Division of Infectious Diseases, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA, and [7]Hospital Infantil de México, Federico Gómez, México City, México

Cryptococcus species are ubiquitous in the environment with a global distribution. While causing disease predominantly in immunocompromised hosts such as those with advanced HIV, HIV-uninfected patients are increasingly recognized as being 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 nontraditional risks factors for cryptococcal disease, such as lymphopenia and hypogammaglobulinemia, and the potential implications of pleurovenous catheters in *Cryptococcus* dissemination.

Keywords. acquired immunodeficiency/complications; chylothorax; cryptococcosis/complications; *Cryptococcus neoformans*/immunology; pleurovenous shunt complications.

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, as 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–immunoglobulin M (IgM) and hyper–immunoglobulin E (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 extraneurologic 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 nonpulmonary 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 nontraditional 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

Received 26 March 2021; editorial decision 13 May 2021; accepted 14 May 2021.

Correspondence: Andrés F. Henao-Martínez, MD, University of Colorado Denver, 12700 E. 19th Avenue, Mail Stop B168, Aurora, CO 80045 (andres.henaomartinez@cuanschutz.edu).

Open Forum Infectious Diseases®2021

© The Author(s) 2021. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

DOI: 10.1093/ofid/ofab258

previous 2 years due to a rapid accumulation of chylous pleural effusions. He underwent placement of a pleurovenous catheter 3 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 the abdomen and pelvis 1 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 an 18-kg (40-lb) weight gain since shunt placement and 1 week of dyspnea, abdominal distension, and increased edema in the upper and lower extremities. Vital signs were significant for a blood pressure of 95/61 mmHg, heart rate of 75 beats per minute, temperature of 36.3°C, respiratory rate of 16 breaths per minute, and oxygen saturation of 96% on 1 L 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 of 0.66 mg/dL (0.70–1.30 mg/dL), alkaline phosphatase of 272 U/L (39–117 U/L), alanine aminotransferase of 103 U/L (7–52 U/L), aspartate aminotransferase of 112 U/L (12–39 U/L), total protein of 3.5 g/dL (6.4–8.9 g/dL), and serum albumin of 1.9 g/dL (3.5–5.7 g/dL). His white blood cell (WCB) count was 4.2 k/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, 670–1822 mg/dL], 23 mg/dL [reference, 43–279 mg/dL], 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 3.5 L of pleural fluid and 5 L 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 5, peritoneal fluid culture grew yeast, later identified as *Cryptococcus neoformans*, via matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry. The patient was started on fluconazole 400 mg orally 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 >72 hours), and his pleurovenous shunt was removed due to suspected colonization. The tip of the shunt culture also grew *C. neoformans*. Despite these measures, the patient continued to deteriorate, and he was transitioned to comfort care measures and died 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 the pleura and pericardium with an associated lymphocytic infiltrate (Figure 3). There was no evidence of active sarcoidosis. There was no evidence of cryptococcal meningoencephalitis or cryptococcal pneumonia.

Patient Consent

The use of the clinical data was 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 [11]. Since the early 1900s, only 50 cryptococcal empyemas [12–20] and 65 cryptococcal peritonitis cases have been reported [21–31]. There may be underreporting cases of empyema and peritonitis due to difficulty in diagnosis.

Disseminated cryptococcosis manifesting with extrapulmonary and extraneurological presentations is increasingly recognized [32]. Cryptococcal empyema has been reported in patients with malignancy being treated with biological agents [15–17]. Peritonitis tends to occur in the setting of peritoneal dialysis with end-stage renal disease [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

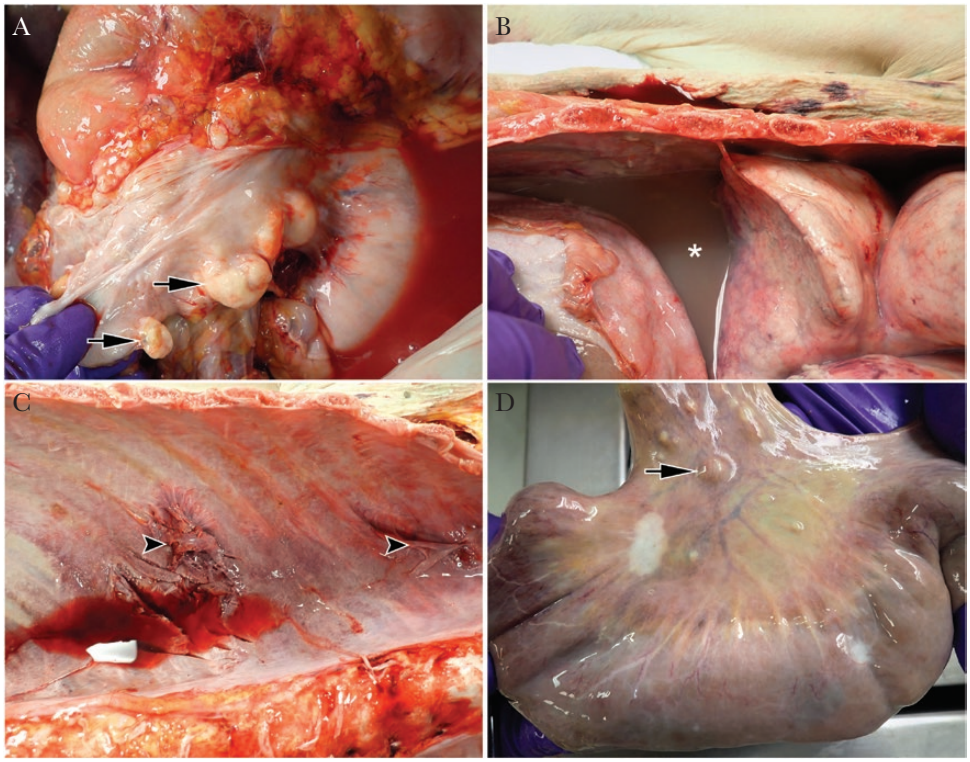

Figure 1. Gross anatomy description. A, Bowel mesentery with calcified lymphadenopathy (arrows); blood-tinged chyloperitoneum present in the background. B, Right pleural cavity with chylothorax (asterisk). C, Right pleural cavity after lung removal demonstrating pleural adhesions to the chest wall (arrowheads). D, Loop of bowel with calcified lymphadenopathy (arrow) and mesenteric plaque.

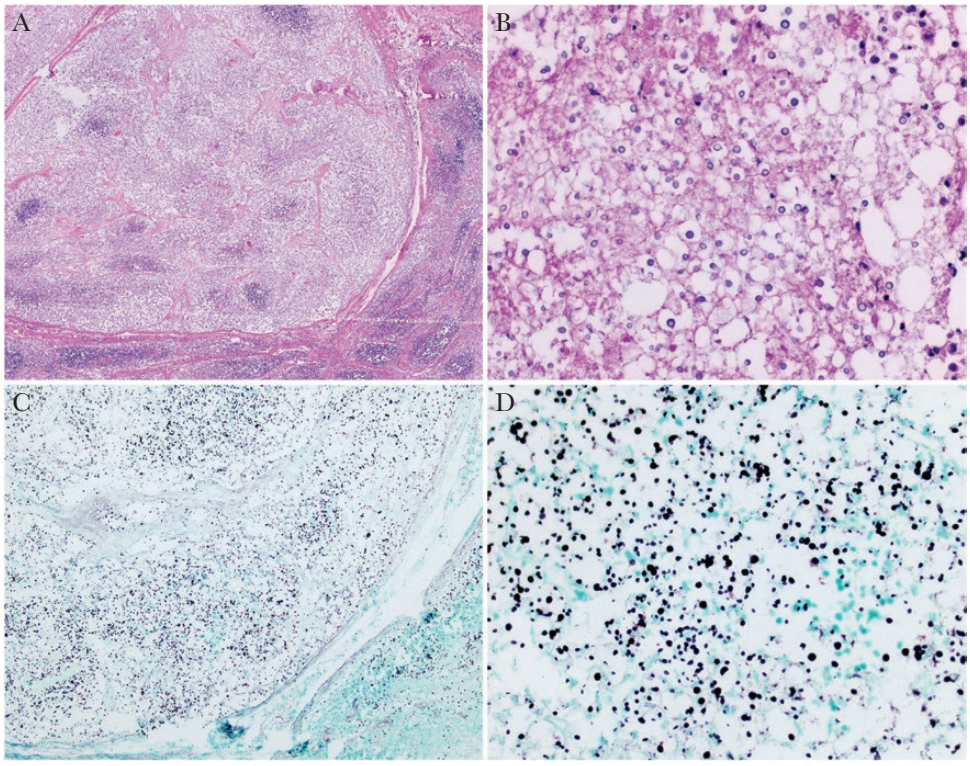

Figure 2. Histopathology slides of the calcified lymph node. A, Lymph node with a collection of cryptococcal organisms and rim of residual lymphoid tissue (40×). B, Cryptococcal organisms in a partially necrotic background (400×). C, Grocott methenamine silver (GMS) stain highlighting cryptococcal organisms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

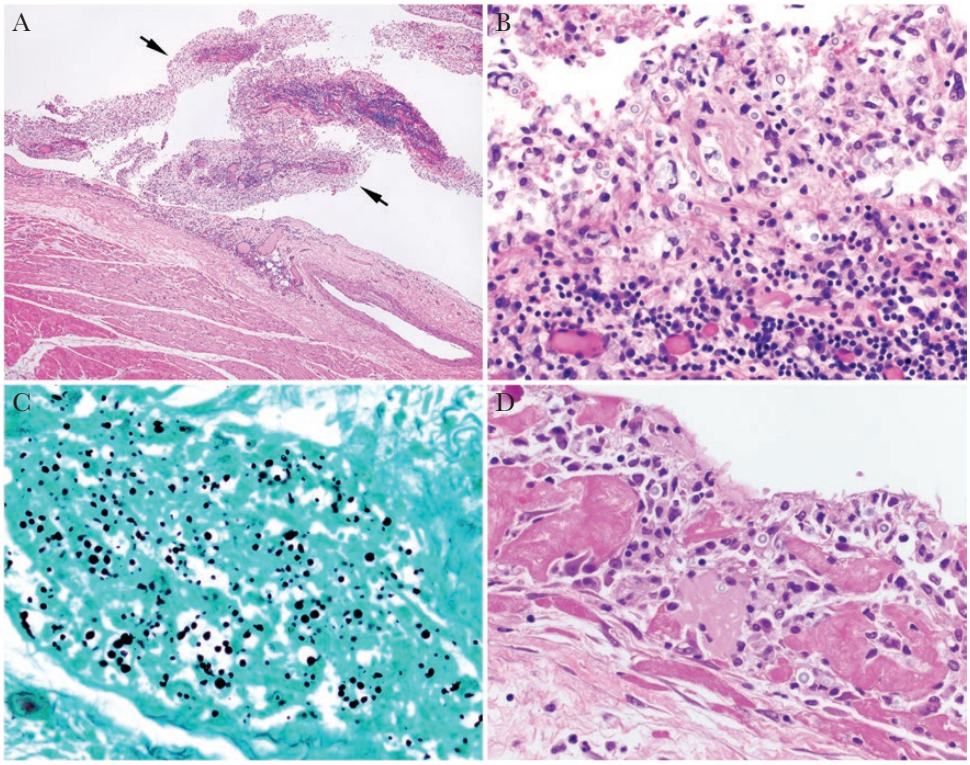

Figure 3. Chest wall and pericardium histopathology findings. A, Chest wall with pleural adhesions (arrows) and associated inflammation (40×). B, Adhesion demonstrating cryptococcal organisms and lymphocytic inflammation (400×). C, GMS stain highlighting cryptococcal organisms in pleural adhesion (400×).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

risk factor for cryptococcal infection. The patient did have a negative fourth-generation HIV 1/2 antibody p24 antigen test. Lymphocyte loss from chronic chylothorax fluid removal and protein-losing enteropathy leads to a net immunosuppressed state [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 immunoglobulin G (IgG) change the morphology of *C. neoformans* and that IgM inhibits titian-like cell formation, which can reduce virulence and the risk of disseminated disease [35]. Previous reports have described an association between hypogammaglobulinemia and increased risk for cryptococcal disease, including in HIV-infected patients [6, 36–38]. 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 often been reported as a life-threatening complication of sarcoidosis [39, 40]. 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 [41]. 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 the lymph nodes (diffusely), pleura, and pericardium with a modest lymphocytic infiltrate. Interestingly the patient did not manifest pericarditis clinically. It is also notable that there was no central nervous system involvement despite persistent cryptococcemia. The fungal burden rather than an exuberant inflammatory response was more likely to be responsible for disease pathogenesis.

A pleurovenous shunt is a relatively noninvasive procedure used to treat patients with intractable pleural effusions. It allows for external manual compression for fluid drainage [42], but shunt failure, pulmonary edema, postshunt coagulopathy, deep vein thrombosis, and bacterial infection remain commonly reported complications [43]. 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 began 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 [23]. 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 C*ryptococcus*. However, the C*ryptococcus* 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 demonstrates coexisting empyema and peritonitis in a patient with a pleurovenous shunt serving as the facilitator for dissemination. Chylothorax or chyloabdomen associated with *Cryptococcus* has only been reported in animals such as cats and dogs [44, 45]. Immunosuppressed patients with chronic indwelling pleurovenous shunts in place may need to be assessed for risk of disseminated cryptococcosis.

Guideline-directed management of severe pulmonary or disseminated *Cryptococcus* in immunocompromised and immunocompetent patients is identical to CNS cryptococcosis treatment [10]. 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 nontraditional immunosuppressive risk factors, as mortality in non-HIV immunocompromised hosts remains high [46]. Focusing only on commonly reported risk factors can lead to a delayed or missed diagnosis.

CONCLUSIONS

This case demonstrates that disseminated cryptococcal infection with a high disease burden involving the pleura, peritoneum, pericardium, and bloodstream can occur in patients with nontraditional immunodeficiency conditions. We believe that 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.

Acknowledgments

Financial support. No funding was received. No funding agencies had any role in the preparation, review, or approval of this manuscript. Its contents are the authors' sole responsibility and do not necessarily represent the official institution's views.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Maziarz EK, Perfect JR. Cryptococcosis. Infect Dis Clin North Am **2016**; 30:179–206.
2. May RC, Stone NR, Wiesner DL, et al. *Cryptococcus*: from environmental saprophyte to global pathogen. Nat Rev Microbiol **2016**; 14:106–17.
3. Harris JR, Lockhart SR, Sondermeyer G, et al. *Cryptococcus gattii* infections in multiple states outside the US Pacific Northwest. Emerg Infect Dis **2013**; 19:1620–6.
4. Mirza SA, Phelan M, Rimland D, et al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992–2000. Clin Infect Dis **2003**; 36:789–94.
5. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. Clin Infect Dis **2000**; 30:S5–S14.
6. Neto R, Guimarães MC, Moya MJ, et al. Hypogammaglobulinemia as risk factor for *Cryptococcus neoformans* infection: report of 2 cases [in Portuguese]. Rev Soc Bras Med Trop **2000**; 33:603–8.
7. Winkelstein JA, Marino MC, Ochs H, et al. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine **2003**; 82:373–84.
8. Marr KA, Sun Y, Spec A, et al. A multicenter, longitudinal cohort study of cryptococcosis in human immunodeficiency virus–negative people in the United States. Clin Infect Dis **2019**; 70:252–61.
9. Pappas PG. Cryptococcal infections in non-HIV-infected patients. Trans Am Clin Climatol Assoc **2013**; 124:61–79.
10. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. Clin Infect Dis **2000**; 30:710–8.
11. Setianingrum F, Rautemaa-Richardson R, Denning DW. Pulmonary cryptococcosis: a review of pathobiology and clinical aspects. Med Mycol **2018**; 57:133–50.
12. Chang W-C, Tzao C, Hsu H-H, et al. Isolated cryptococcal thoracic empyema with osteomyelitis of the rib in an immunocompetent host. J Infect **2005**; 51:e117–9.
13. Jasper FWC, Jade LLT, Iris WSL, et al. Fatal empyema thoracis caused by *Schizophyllum commune* with cross-reactive cryptococcal antigenemia. J Clin Microbiol **2014**; 52:683–7.
14. Koehler AB, Vijayvargiya P, Ding W. Probable invasive pulmonary cryptococcosis and possible cryptococcal empyema in CLL treated with frontline ibrutinib. Mayo Clin Proceed **2019**; 94:915–7.
15. Kohli A, Sachdeva A, Pickering EM. Cryptococcal empyema treated with tube thoracostomy and intrapleural fibrinolysis. Monaldi Arch Chest Dis **2020**; 90.
16. Mulanovich VE, Dismukes WE, Markowitz N. Cryptococcal empyema: case report and review. Clin Infect Dis **1995**; 20:1396–8.
17. Swan CD, Gottlieb T. *Cryptococcus neoformans* empyema in a patient receiving ibrutinib for diffuse large B-cell lymphoma and a review of the literature. BMJ Case Rep **2018**; 2018:bcr2018224786.
18. Tenholder MF, Ewald FW Jr, Khankhanian NK, Crosby JH. Complex cryptococcal empyema. Chest **1992**; 101:586–8.
19. Wahab JA, Hanifah MJ, Choo KE. Bruton's agammaglobulinaemia in a child presenting with cryptococcal empyema thoracis and periauricular pyogenic abscess. Singapore Med J **1995**; 36:686–9.
20. Zitun M, Elmassry M, El Nawaa SEN, et al. A rare case of cryptococcal empyema in an immunocompetent patient. Chest **2020**; 158:A1257.
21. Cole SL, Ledford DK, Lockey RF, et al. Primary gastrointestinal lymphangiectasia presenting as cryptococcal meningitis. Ann Allergy Asthma Immunol **2007**; 98:490–2.

22. Mansoor GA, Ornt DB. Cryptococcal peritonitis in peritoneal dialysis patients: a case report. Clin Nephrol **1994**; 41:230–2.
23. Naranjo-Saltos F, Hallo A, Hallo C, et al. Gastrointestinal cryptococcosis associated with intestinal lymphangiectasia. Case Rep Med **2020**; 2020:7870154.
24. Smith JW, Arnold WC. Cryptococcal peritonitis in patients on peritoneal dialysis. Am J Kidney Dis **1988**; 11:430–3.
25. Barnett AE, Brust KB. Cirrhosis, gastrointestinal bleed, and cryptococcal peritonitis. Proc (Bayl Univ Med Cent) **2020**; 33:195–8.
26. Saif MW, Raj M. Cryptococcal peritonitis complicating hepatic failure: case report and review of the literature. J Appl Res **2006**; 6:43–50.
27. Saeed MA, Al Khuwaitir TS. Spontaneous cryptococcal peritonitis successfully treated with fluconazole. Afro-Egypt J Infect Endemic Dis **2015**; 5:131–3.
28. Srivastava VK, Siddiqui AH. Cryptococcal peritonitis in a patient with liver cirrhosis: case report. Int J Life Sci Scienti Res **2017**; 3:970–2.
29. Barnett AE, Brust KB. Cirrhosis, gastrointestinal bleed, and cryptococcal peritonitis. Proc. (Bayl Univ Med Cent) **2020**;33:195–8. doi: 10.1080/08998280.2020.1723361.
30. Stiefel P, Pamies E, Miranda M, et al. Cryptococcal peritonitis: report of a case and review of the literature. Hepato-gastroenterol **1999**; 46:1618–22.
31. El-Kersh K, Rawasia WF, Chaddha U, Guardiola J. Rarity revisited: cryptococcal peritonitis. Case Rep **2013**; 2013:bcr2013009099.
32. Lin Y-Y, Shiau S, Fang C-T. Risk factors for invasive *Cryptococcus neoformans* diseases: a case-control study. PLoS One **2015**; 10:e0119090.
33. Wasmuth-Pietzuch A, Hansmann M, Bartmann P, Heep A. Congenital chylothorax: lymphopenia and high risk of neonatal infections. Acta Paediatr **2004**; 93:220–4.
34. Nishida T, Sakakibara H. Association between underweight and low lymphocyte count as an indicator of malnutrition in Japanese women. J Womens Health (Larchmt) **2010**; 19:1377–83.
35. Trevijano-Contador N, Pianalto KM, Nichols CB, et al. Human IgM inhibits the formation of titan-like cells in *Cryptococcus neoformans*. Infect Immun **2020**; 88:e00046-20.
36. Lao M, Li C, Li J, et al. Opportunistic invasive fungal disease in patients with type 2 diabetes mellitus from Southern China: clinical features and associated factors. J Diabetes Investig **2020**; 11:731–44.
37. Henao-Martínez AF, Gross L, McNair B, et al. Risk factors for cryptococcal meningitis: a single United States center experience. Mycopathologia **2016**; 181:807–14.
38. Yan X, Zong F, Kong H, et al. Pulmonary fungal diseases in immunocompetent hosts: a single-center retrospective analysis of 35 subjects. Mycopathologia **2016**; 181:513–21.
39. Posteraro P, Vacca K, Celi M, et al. Fatal fulminant cryptococcemia complicating sarcoidosis: is it to be expected? Med Mycol Case Rep **2018**; 22:42–4.
40. Leonhard SE, Fritz D, van de Beek D, Brouwer MC. Cryptococcal meningitis complicating sarcoidosis. Medicine **2016**; 95:e4587.
41. Bernard C, Maucort-Boulch D, Varron L, et al. Cryptococcosis in sarcoidosis: cryptOsarc, a comparative study of 18 cases. QJM **2013**; 106:523–39.
42. Artemiou O, Marta G-M, Klepetko W, et al. Pleurovenous shunting in the treatment of nonmalignant pleural effusion. Ann Thoracic Surg **2003**; 76:231–3.
43. Perera E, Bhatt S, Dogra VS. Complications of Denver shunt. J Clin Imaging Sci **2011**; 1:6.
44. Meadows RL, MacWilliams PS, Dzata G, Meinen J. Chylothorax associated with cryptococcal mediastinal granuloma in a cat. Vet Clin Pathol **1993**; 22:109–16.
45. Hatch A, Jandrey KE, Tenwolde MC, Kent MS. Incidence of chyloabdomen diagnosis in dogs and cats and corresponding clinical signs, clinicopathologic test results, and outcomes: 53 cases (1984–2014). J Am Vet Med Assoc **2018**; 253:886–92.
46. Motoa G, Pate A, Chastain D, et al. Increased cryptococcal meningitis mortality among HIV negative, non-transplant patients: a single US center cohort study. Ther Adv Infect Dis **2020**; 7:2049936120940881.