Case report

Disseminated mucormycosis: An unusual case of ascites with bone marrow invasion

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\textbf{ABSTRACT}

Mucormycosis is a fatal invasive illness most frequently seen in immunocompromised hosts with uncontrolled diabetes, hematological malignancies, organ transplantation, or long-term steroid treatment. It has a poorer outcome than other fungal diseases due to its rapid spread and resistance to antifungal agents. We report a rare case of disseminated mucormycosis including the bone marrow, peritoneum, lung, and lymph nodes in an apparently immunocompetent 58-year-old gentleman who presented with two months of ascites and weight loss. After a thorough analysis, we found aseptate fungal hyphae in the bone marrow and ascitic fluid. In addition, a cottony white, woolly growth indicative of mucor species was seen in the ascitic fluid culture. CT scans of the chest and abdomen indicate characteristics consistent with mucor invasion. We began the patient on tablet posaconazole, but he died on the fifth day. The atypical presentation in an apparently immunocompetent patient and broad dissemination with rare bone marrow involvement emphasizes the disease’s invasiveness.

\textbf{Introduction}

Mucormycosis is an invasive deadly fungal illness caused by the species belonging to the genus Mucor, Rhizomucor, Rhizopus, order Mucorales, and class Zygomycetes \cite{1}. Classification of mucormycosis includes rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, etc. In 1876 Fürbinger first described mucormycosis in the autopsy of a German cancer patient, where he found fungal hyphae with few sporangia in the right lung \cite{2}. Mucormycosis has a worse outcome among fungal diseases as it tends to disseminate rapidly and has less response to antifungal agents \cite{3}. In the case of invasive fungal infection, bone marrow dissemination of mucormycosis is rare. However, only a handful of cases of peritonitis have been reported worldwide \cite{4}. We report an unusual dissemination of mucormycosis involving bone marrow, peritoneum, lung, and lymph nodes.

\textbf{Case summary}

A non-diabetic, non-alcoholic 58-year-old gentleman with a previous history of mild COVID-19 infection presented to us with ascites and weight loss for two months. Initially, he got admitted to a local hospital where he was labeled decompensated liver cirrhosis and discharged with conservative management. However, his health deteriorated; he was moved to another tertiary facility, where comprehensive blood tests and laparoscopic exploration revealed numerous tubercles in the parietal peritoneum and liver; multiple biopsy samples were collected. While waiting for the histopathology report, antitubercular treatment was started empirically. Histopathology indicated a lymphoproliferative disease, whilst immunohistochemistry showed an inflammatory lesion. A biopsy of the liver revealed mild chronic hepatitis. Consultation with a hematologist revealed insufficient evidence of lymphoproliferative disease. At that time, the ascitic fluid study showed straw color, exudative, serum ascites to albumin gradient (SAAG) was 10.2 g/L, and negative for nucleic acid amplification test (Xpert MTB/RIF) and malignant cells. In addition, the ascitic fluid culture showed the growth of pseudomonas spp. He was treated with broad-spectrum antibiotics; antitubercular medication was discontinued. But his health deteriorated, so he was transferred to Bangabandhu Sheikh Mujib Medical University.

When we received the patient in June 2021, he was profoundly anorexic, losing 15 kg of body weight and substantial abdominal...
distension. He had moderate anemia, lymphadenopathies involving cervical and axillary regions, gross ascites with hepatomegaly, and a just palpable spleen, but no palmar erythema, encephalopathy, and jaundice. As the patient's vitals were deteriorating, we restarted antitubercular therapy empirically. We sent for blood and ascitic fluid for study. His complete blood counts revealed hemoglobin 10.6 g/dl, ESR 50 mm in the 1st hour, white blood cells 11,000/mm³ with neutrophil 88%, platelets 230,000/mm³, peripheral blood film microcytic hypochromic with target cells, schistocyte, spherocyte, agglutination. Hb electrophoresis showed the Hb E trait. His full liver function tests were normal. His fasting blood sugar was 4.8 mmol/L, and his Hb1Ac was 5.7%. Ascitic fluid results were: WBC 500 cells/mm³ (neutrophils 45%, lymphocyte 55%), total protein 39 g/L, ADA 23.6 U/L; serum ascites to albumin gradient 16.61 g/L. Ascitic fluid for gram stain & culture, AFB stain, and nucleic acid amplification test (Xpert MTB/RIF) showed no organism. Viral markers, HBsAg, Anti HCV, Anti HBcAb, and Anti-HIV Ab(1 +2) were negative. D-Dimer 0.86 µg/ml, LDH 355 U/L, C-reactive protein 9.1 mg/L, S. ceruloplasmin:21 mg/dl, ANA was negative, S. CA-19.9 18.5 U/ml, S. CEA 1.51 ng/ml. Abdominal computed tomography revealed hepatosplenomegaly, moderate ascites, and abdominal lymphadenopathy. Chest computed tomography showed mediastinal and bilateral axillary lymphadenopathy with bilateral pulmonary inflammatory lesion with few ground-glass opacities and fibrosis in both lower lobes (Fig. 1a). Echocardiography showed no valvular or pericardial abnormality. Upper gastrointestinal endoscopy was normal. The bone marrow study showed the presence of aseptate hyphae (Fig. 1b), although the bone marrow culture study didn’t show any organism growth.

After finding fungal hyphae from bone marrow, we stopped antitubercular therapy. We immediately sent another set of ascitic fluid for fungal stain and culture. In a Sabouraud dextrose agar, the culture of the ascitic fluid showed a cottony white, woolly growth at 48 h. Microscopic examination from culture growth of fungus in SDA agar with lactophenol cotton blue stain showed aseptate irregular hyphae where globule-shaped sporangia were filled with round spores (Fig. 1c). Morphology of organisms in ascitic fluid and bone marrow specimens were consistent with the mucor species.

Tablet posaconazole was started to treat mucormycosis because liposomal amphotericin B was expensive for the patient. It is to be noted that liposomal amphotericin B is supplied free of cost only in the treatment of visceral leishmaniasis by the government of Bangladesh. However, the patient passed away on the fifth day of antifungal therapy. Unfortunately, we couldn’t perform an autopsy on the patient as his family refused.

**Discussion**

Mucormycosis is most frequently found in immunocompromised hosts, such as those with uncontrolled diabetes, acquired immunodeficiency syndrome (AIDS), primarily hematological malignancies, organ transplantation, long-term steroid treatment, and prolonged neutropenia, malnutrition, severe burns, intravenous drug abuse [5]. Although uncommon, few instances have been observed in immunocompetent individuals [6].

Mucorales are fungi with fibrous mycelium that can grow rapidly. Mucorales have aseptate, thin-walled hyphae. Their right-angled branching enables rapid proliferation within the host tissue, ultimately resulting in blood vessel invasion, thrombosis, and necrosis [5,7].

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Fig. 1. a) Multiaxial CT chest parenchymal view showing ground-glass opacity and fibrosis, b) microscopic study of bone marrow showing aseptate hyphae, c) microscopic study from culture growth of fungus in SDA agar with lactophenol cotton blue staining.
However, we didn’t have any direct evidence of vascular invasion in our patient. Invasive mucormycosis is classified according to its site of involvement: 1) rhinocerebral (39%), 2) pulmonary (24%), 3) disseminated (23%), 4) cutaneous (19%), 5) gastrointestinal, and 6) others; including peritonitis, osteomyelitis, endocarditis, and renal infection [8]. The highest mortality rate is approximately 66% for patients with malignancies, compared to 44% among diabetic patients.

The lack of a specific clinical pattern makes the diagnosis of disseminated mucormycosis tricky [6]. Our patient was apparently immunocompetent and had a rapid onset of ascites and weight with a virulent disease course, which impeded a proper diagnosis. Yoon et al. described several cases of mucormycosis peritonitis; among them, peritoneal dialysis-related mucormycosis was the predominant cause. Few peritonitis cases were preceded by gastrointestinal mucormycosis; two had intestinal perforation [4]. Although peritonitis in mucormycosis has a relatively slow progression, patients who received delayed treatment had high mortality, near 100%, but successful treatment has been reported [9]. Our patient didn’t have any peritoneal dialysis history, so there might be possible gastrointestinal mucormycosis, ultimately peritonitis. Foods contaminated with molds, such as fermented milk and dried bread products, can cause bowel wall invasion and, eventually, blood vessels, leading to intestinal perforation, peritonitis, sepsis, and death[10,11]. However, most food-borne gastrointestinal mucormycosis is involved in immunocompromised people.

Dissemination of mucormycosis can occur hematogenously [12]. The lung’s most common organ is where frequent infiltration, consolidation, nodules, effusion, and hilar or mediastinal lymphadenopathy are seen in CT film [13]. Our patient had mediastinal lymphadenopathy and fibrosis with few ground-glass opacities, which might be explained by disseminated mucormycosis. One other rare dissemination was in the bone marrow involvement. We found aseptate hyphae during bone marrow examination. However, the culture from the bone marrow specimen did not show any growth of mucor species. One possible explanation, according to Badiee et al., is that; it is challenging to grow Mucorales or not show any growth of mucor species. One possible explanation, according to Badiee et al., is that; it is challenging to grow Mucorales or not show any growth of mucor species.

Amphotericin B liposomal is strongly recommended as the first-line treatment for mucormycosis. However, moderate strength is advised for intravenous isavuconazole and intravenous or delayed-release tablet posaconazole as a first-line treatment. Both of these triazoles are suggested as salvage treatments [15]. However, isavuconazole is administered successfully in a small number of patients with mucormycosis [16]. Mucormycosis necessitates surgical treatment for local control [17]. Surgical therapies and systemic antifungal therapy result in higher cure and survival rates. However, disseminated disease may encompass multiple sites of infection where surgical treatment may be ineffective [15].

Conclusion

The peculiar nature of our patient’s presentation, the absence of any recognized immunocompromised condition, the quick deterioration, the involvement of a wide variety of organs, and the delay in diagnosis contributed to our patient’s death. Studies related to this emerging fatal fungal infection are limited, retrospective & based on institutions with specific populations at risk. We suggest that high clinical vigilance, quick laboratory diagnosis, and prompt treatment are essential for improving this devastating natural history of mucormycosis.

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CRediT authorship contribution statement

Chowdhury Adnan Sami: Directly involved in patient care, data collection, writing. Hasan Mostafa Rashed: Writing, literature review. Abed Hussain Khan: Attending physician, literature review. Lovely Barai: Microbiological & biochemical assessment. Shohael Mahmud Afrat: Attending physician, writing, literature review.

Ethical approval

This study was granted ethics committee approval at Bangabandhu Sheikh Mujib Medical University.

Consent

Informed written consent was taken from the patient’s family for publication, and it is available to the author.

Conflict of interest

We declare no known conflict of interest.

References

[1] Walther G, Wagner L, Kurzai O. Updates on the taxonomy of mucorales with an emphasis on clinically important taxa, (n.d.). [https://doi.org/10.3390/jbf0100010].
[2] Führinger P. Beobachtungen über Lunghymose beim Menschen. Arch Pathol Anat 1876;66:330–65. [https://doi.org/10.1107/0F01878266].
[3] Katragkou A, Walsh TJ, Rolides E. Why is mucormycosis more difficult to cure than more common mycoses? Clin Microbiol Infect Publ Eur Soc Clin Microbiol Infect Dis 2014;20(Suppl. 6):S74–81. [https://doi.org/10.1111/1469-0691.12466].
[4] Yoon S, Kim H, Moon H-W, Huh H, Hur M, Yun Y-M, et al. A case of peritonitis and disseminated mucormycosis caused by mucor circinelloides in a patient with nodal marginal zone B-cell lymphoma. Lab Med Online 2020;10:250–4. [https://doi.org/10.2343/0fme.2020.10.3250].
[5] Sugar Alan M. Mucormycosis. Clin Infect Dis 1992;14(Suppl. 1):S126–9. [https://doi.org/10.1093/cid/14.Supplement_1.S126].
[6] Gupta KL, Joshi K, Pereira B&G, Singh B&K. Disseminated mucormycosis presenting with acute renal failure. Postgrad Med J 1987;63:297–9. [https://doi.org/10.1136/pgmj.63.738.297].
[7] Fraser JL, Hall GS, Procop GW. Histologic features of zygomycosis: emphasis on perineural invasion and fungal morphology. Arch Pathol Lab Med 2001;125:375–8. [https://doi.org/10.5888/ajcp.2001.125.05:0111].
[8] Goodman NL, Rinaldi MG, Balows A, Hausler WJ, Herrmann KL, Isenberg HD, et al. Agents of mucormycosis. Man Clin Microbiol 1991:674–92. [https://eurekamag.com/research/029/940/029940134.php].
[9] Sarrami AH, Setareh M, Izadinejad M, Afshar-Moghaddam N, Baradaran-Mahdavi MM, Meidani M. Fatal disseminated mucormycosis in an immunocompetent patient: a case report and literature review. Int J Prev Med 2013;4:668–71.
[10] Benedict K, Chiller TM, Mody RK. Invasive fungal infections acquired from contaminated food or nutritional supplements: a review of the literature. Foodborne Pathog Dis 2016;13(7):343–9. [https://doi.org/10.1136/fpd.2015.2108].
[11] Virk SS, Singh RP, Arora AS, Grewal JS, Puri H. Gastric mucormycosis—an unusual cause of massive upper gastrointestinal bleed. Indian J Gastroenterol 2004;23:146–7.
[12] Liu MF, Chen FF, Hsiao TR, Liu CC. Disseminated mucormycosis simulating cerebrovascular disease and pulmonary alveolar haemorrhage in a patient with systemic lupus erythematosus. Clin Rheumatol 2000;19:311–4. [https://doi.org/10.1007/s100670000052].
[13] McAdams HP, Rosado de Christenson M, Strollo DC, Pate EF. Pulmonary mucormycosis: radiologic findings in 32 cases. Am J Roentgenol 1997;168:1541–8. [https://doi.org/10.2214/ajr.168.6.9168721].
[14] Badiee P, Arastefar A, Jafarian H. Comparison of histopathological analysis, culture and polymerase chain reaction assays to detect mucormycosis in biopsy and blood specimens. Iran J Microbiol 2013;5(4):406–10. [https://doi.org/10.5859/2001-125-0375-HFOZ].
[15] Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dananouei E, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses
[16] Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane EM, Perfect JR, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis 2016;16. https://doi.org/10.1016/S1473-3099 (16)00071-2.

[17] Lanternier F, Dannaoui E, Morizot G, Elie C, Garcia-Hermoso D, Huerre M, et al. A global analysis of mucormycosis in France: the RetroZygo study (2005–2007), (n.d.). (https://doi.org/10.1093/cid/cir880).