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Case Report

Invasive hepatic mucormycosis: A case report and review of the literature☆

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ABSTRACT

Mucormycosis generally develops under immunocompromised conditions, including hematological malignancies and solid organ or hematopoietic stem cell transplantation. Although mucormycosis usually affects the lungs and paranasal sinuses, sporadic cases of invasive mucormycosis of the liver have been reported. We hereby report a patient with myelofibrosis who developed hepatic mucormycosis diagnosed by post-mortem examination. An extensive literature review identified 13 reported cases of hepatic mucormycosis, including ours, without lung involvement. Most of the underlying diseases or conditions were hematological malignancies and solid organ transplantation. Three cases had splenic lesions and four had gastrointestinal lesions, suggesting the possibility of translocation to the liver and/or spleen from the gastrointestinal tracts. Hepatic mucormycosis should be recognized as one of the presentations of invasive mucormycosis, especially when hepatic nodules are found in immunocompromised patients such as those with hematological malignancy or recipients of solid organ transplantation.

1. Introduction

Mucormycosis has been well recognized as a life-threating invasive fungal infection most commonly occurring in immunocompromised patients [1]. Underlying conditions commonly associated with mucormycosis include prolonged neutropenia, hematological malignancies, solid organ or hematopoietic stem cell transplantation, and diabetes mellitus. The prognosis of mucormycosis remains poor, especially in patients with hematological malignancies. A recent French study analyzing the registry data showed that the 90-day mortality rate of mucormycosis was 60% in patients with hematological malignancies [2]. Mucormycosis usually affects the lungs and paranasal sinuses. However, any other organs could also be involved. We encountered a case of hepatic mucormycosis presenting as multiple nodular lesions in the liver without respiratory organ involvements, which developed during the clinical course of myelofibrosis with neutropenia and corticosteroid treatment. Since only sporadic cases of hepatic mucormycosis have been reported, we here report the clinical course of our case along with an extensive review of the cases reported in the literature in order to clarify the clinical characteristics of hepatic mucormycosis.

2. Case report

A 75-year-old man had received steroid therapy (prednisolone, 20 mg per day) and multiple red blood cell transfusions over 18 months in order to relieve his symptoms associated with primary myelofibrosis. Although his serum ferritin level increased to more than 2000 ng/ml due to red blood cell transfusions, he was free from impaired glucose tolerance. In addition, he suffered from persistent severe neutropenia (less than 0.5×10^9/L). He was admitted to the

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hospital because of high-grade fever and pneumonia, for which cefepime followed by meropenem was ineffective. Although both serum galactomannan and (1,3)-β-D-glucan (β-D-glucan) were negative, intravenous voriconazole (VRCZ) at a daily dose of 6 mg/kg was empirically initiated at Day 10 after admission, which reduced his fever. VRCZ was given for 2 weeks. However, he subsequently developed high-grade fever again at Day 24 after admission, which was accompanied by right upper abdominal pain. Laboratory data demonstrated mild liver dysfunction (AST 71 U/L and ALT 72 U/L) and markedly elevated C-reactive protein (19.19 mg/dL) and procalcitonin (99.99 ng/ml) values in addition to the preexisting neutropenia (0.3×10^9/L). Both serum galactomannan and β-D-glucan remained negative. A computed tomography (CT) scan showed multiple low-density lesions in the liver and one isolated low-density lesion in the spleen, but no new lesions in the lungs (Fig. 1). Neither CT scan nor magnetic resonance imaging was performed to evaluate the lesions in the brain or paranasal sinuses. Repeated blood cultures failed to grow any pathogens. Based on these findings suggestive of fungal infection, VRCZ was switched to liposomal amphotericin B (3 mg/kg/day). Although liposomal amphotericin B administration was continued, the patient succumbed two weeks after the onset of abdominal pain. A postmortem examination revealed multiple yellowish or whitish nodules of up to 2 cm in diameter in the liver (Fig. 2). In addition, a single nodule of 4.5 cm was also observed in the spleen. Histological examinations of these nodular lesions in the liver revealed coagulative necrosis and perivascular or vascular invasion, including invasion into the portal vein, hepatic artery and central vein, by irregularly broad pauciseptate hyphae, indicative of fungi which belong to species of subphylum Mucoromycotina (Fig. 3). Similar findings were also observed in the splenic lesions. Lesions of mucormycosis were not identified in the lungs, gastrointestinal tract, or any organs other than the liver and spleen. Molecular methods using polymerase chain reaction were attempted to identify the specific pathogen in the formalin-fixed and paraffin-embedded tissue sample. However, definite results could not be obtained. Based on these findings, mucormycosis involving the liver and spleen was histologically diagnosed.

3. Review of the literature on hepatic mucormycosis

Basically using the PubMed online database, we searched the English-language literature published from 2000 to 2017 for the terms “hepatic mucormycosis” and “liver mucormycosis”, and identified 105 reports. Among these reports, we selected the patients with mucormycosis involving the liver, but excluded cases of hepatic mucormycosis with disseminated systemic infection or

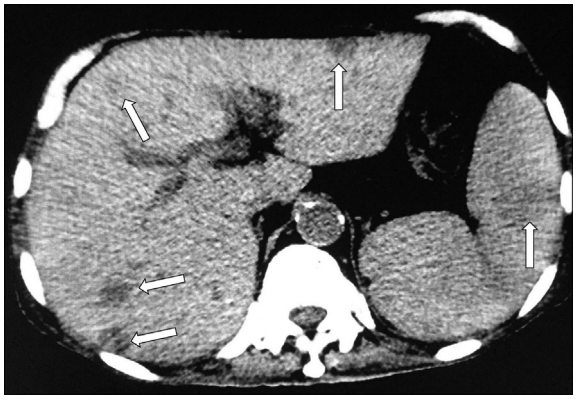

Fig. 1. Computed tomography scan image of the abdomen. Arrows indicate the multiple low-density nodular lesions in the liver and a single lesion in the spleen.

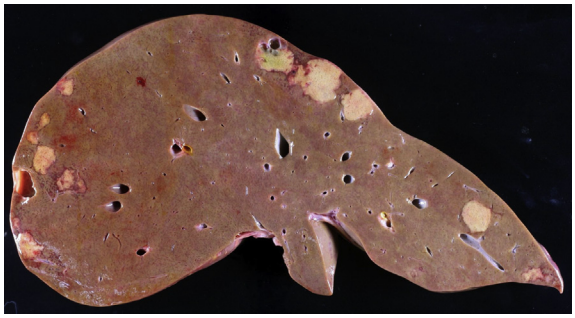

Fig. 2. Macroscopic findings of the liver by autopsy. Multiple yellowish or whitish nodules were observed in the liver.

respiratory organ involvements. Consequently, we identified 13 cases of hepatic mucormycosis [3–15]. Among the cases, species were documented only in two cases (Rhizopus oryzae in Case 5; Absidia corymbifera in Case 7). The characteristics of the 14 cases, including our present case, are summarized in Table 1. The median age was 48 years with a wide range from 2 to 75 years. All patients had underlying immunocompromised conditions, with the most common being acute leukemia or other hematological malignancies (Cases 6–13, and our present case) followed by liver or kidney transplantation (Cases 1–3). At the onset of mucormycosis, most cases of hematological malignancies had neutropenia, and half of them were placed on systemic corticosteroids.

Half of the cases had multiple lesions (57%) in the liver. Four cases, including ours, had concurrent splenic lesions. Although the data were limited, there was clear evidence of gastrointestinal tract lesions in 4 cases. In one of these cases, Case 4, the onset of gastrointestinal lesions preceded the onset of hepatic lesions. Treatments for mucormycosis varied: the most commonly used agent was amphotericin B or liposomal amphotericin B followed by posaconazole. Surgery or drainage was applied in 7 cases in combination with an anti-fungal agent, while Case 3 underwent surgery alone. The outcome was death in half of the cases, while the other patients successfully recovered.

4. Discussion

Our case of histologically diagnosed mucormycosis presented with high-grade fever and abdominal pain in the presence of neutropenia and systemic corticosteroid treatment, and the mucormycosis affected only the liver and spleen. The onset was acute and the outcome was dismal. Mucormycosis, which is one of the critical invasive fungal infections, has been well recognized as an infection that usually occurs under immunocompromised states such as hematological malignancies, solid organ or hematopoietic stem cell transplantation, and diabetes mellitus [1]. Mucormycosis commonly involves the paranasal sinuses and lungs and is thus considered an airborne infection. Previous studies demonstrated that the lungs and paranasal sinuses accounted for over 60% of the involved sites of mucormycosis [16,17]. Therefore, our experience with the present case of hepatic mucormycosis without respiratory organ involvement prompted us to review the literature on hepatic mucormycosis.

Based on our extensive search of the literature, only 14 cases of hepatic mucormyocosis, including our present case, fulfilled our selection criteria. The underlying conditions of hepatic mucormycosis cases are basically the same as those of mucormycosis in general. These include hematological malignancies, solid organ transplantation, neutropenia, and systemic corticosteroid administration. It was of note that splenic and gastrointestinal tract lesions were also identified in some of these cases. In particular, it

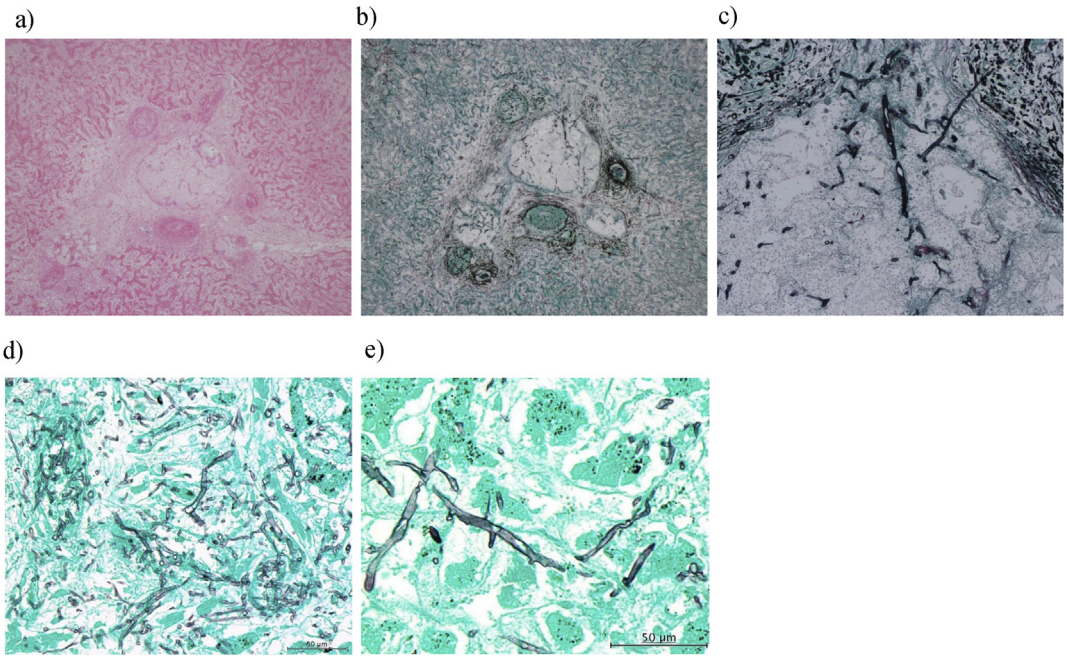

Fig. 3. Histological findings of the liver. a) Hematoxylin-eosin staining showed the coagulative necrosis in both portal triad and cords of hepatocytes. b) Grocott's methenamine silver staining of the same site of a) showed extensive proliferation of pauciseptate hyphae. c) High power view of b) showed invasion of paucisepate hyphae into the lumen of the portal vein. d) Another site of a–c) showed invasive proliferation of hyphae with penetration into the liver cell cords and small vessels. e) High power view of Grocott's methenamine silver staining showed irregularly contoured thin cell-walled pauciseptate hyphae which branch predominantly at right angles. (original magnifications: a and b: ×100, b and c: ×200, d: ×400).

was evident that the onset of gastrointestinal tract lesions preceded hepatic lesion development in one case (Case 4). Based on the evidence of fungal involvement of the liver, spleen, and/or gastrointestinal tract with sparing the respiratory organ in these cases, the fungal infection could be thought to originate from the gastrointestinal tract and subsequently invaded the liver and spleen through the vasculatures [14]. Indeed, the findings of a recent Japanese study on autopsy cases of mucormycosis showed that the gastrointestinal tract and the liver were the most commonly involved sites among the 40 cases of gastrointestinal mucormycosis, which appears to reinforce our hypothesis [17]. Failure to detect the lesions in the gastrointestinal tracts in some of the cases, including our case, could be explained by the tiny lesions which could not be detected by biopsy or autopsy or the resolution of the lesion by antifungal agents. Therefore, mucormycosis is an airborne infection that invades the respiratory organs, but could also invade the gastrointestinal tract, resulting in the subsequent development of hepatic and splenic lesions.

There is little evidence to support the superiority of any treatment option for mucormycosis over any of the other available approaches. Nonetheless, antifungal agents, surgery, and control of the underlying condition contributing to the immunosuppressive states are strongly recommended for the management of mucormycosis [18]. There are several potentially effective agents for mucormycosis, including posaconazole, high doses of amphotericin B or its liposomal formulation, or combination treatments of these agents. Indeed, amphotericin B/liposomal amphotericin B and/or posaconazole have been used in most of the reported cases of hepatic mucormycosis. Because of the small number of cases, it is difficult to draw any definite conclusions regarding the efficacy of these treatments. However, it was found that half of the cases recovered from hepatic mucormycosis with anti-fungal agents alone or in

Table 1
Characteristics of reported cases of hepatic mucormycosis.

Case	Age	Sex	Underlying conditions			Hepatic lesion pattern	Splenic lesion	GI tract lesion	Treatment	Outcome
			Disease, treatment	Neutropenia	Steroid					
1[3]	2	Male	Liver transplantation	No	Yes	Single	No	None	AMPH-B, surgery	Dead
2[4]	23	Female	Liver transplantation	N.D.	Yes	Single	No	None	L-AMB, PCZ	Recovered
3[5]	50	Female	Kidney transplantation, DM	No	Yes	Single	No	None	Surgery	Dead
4[6]	50	Male	Renal failure, hemodialysis	N.D.	No	Single	No	Yes	PCZ	Recovered
5[7]	14	Male	Papillon-Lefevre syndrome	No	No	Multiple	No	None	L-AMB, drainage	Recovered
6[8]	48	Female	Acute leukemia	Yes	Yes	Multiple	No	Yes	AMPH-B, surgery	Dead
7[9]	4	Male	Acute leukemia	Yes	No	Single	No	Yes	L-AMB, PCZ, surgery	Recovered
8[10]	58	Male	Acute leukemia, DM	N.D.	No	Single	No	None	L-AMB, PCZ, surgery	Dead
9[11]	21	Male	Acute leukemia	Yes	Yes	Multiple	No	None	L-AMB, surgery	Recovered
10[12]	71	Male	Chronic lymphocytic leukemia	N.D.	N.D.	Multiple	Yes	None	N.D.	Dead
11[13]	58	Female	Acute leukemia	Yes	No	Multiple	No	None	AMPH-B, PCZ, drainage	Recovered
12[14]	12	Male	Acute leukemia	Yes	Yes	Multiple	Yes	Yes	None	Dead
13[15]	42	Male	Malignant lymphoma	No	No	Multiple	Yes	None	AMPH-B	Recovered
Present case	75	Male	Myelofibrosis	Yes	Yes	Multiple	Yes	None	L-AMB	Dead

GI, gastrointestinal; N.D., not described; DM, diabetes mellitus; AMPH-B, amphotericin B; L-AMB, liposormal amphotericin B; PCZ, posaconazole.

combination with surgical intervention or drainage. Therefore, we deem that the prognosis of hepatic mucormycosis would not be as dismal as that of disseminated or pulmonary mucormycosis, both of which have been reported to have a mortality over 70% [2,16,19].

We conclude that hepatic mucormycosis should be recognized as a cause of nodular lesions in the liver, especially when developing in immunocompromised patients with hematological malignancies and solid organ transplant recipients. An accumulation of more cases is warranted to further elucidate the clinical characteristics and optimal treatment for hepatic mucormycosis.

Conflict of interest

Authors declare that there is nothing to disclose.

References

[1] Bitar D, Van Cauteren D, Lanternier F, Dannaoui E, Che D, Dromer F, et al. Increasing incidence of zygomycosis (mucormycosis), France, 1997–2006. Emerg Infect Dis 2009;15:1395–401.
[2] 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). Clin Infect Dis 2012;54(Suppl. 1):S35–43.
[3] Marco del Pont J, De Cicco L, Gallo G, Llera J, De Santibanez E, D'Agostino D. Hepatic arterial thrombosis due to Mucor species in a child following orthotopic liver transplantation. Transpl Infect Dis 2000;2:33–5.
[4] Abboud CS, Bergamasco MD, Baia CE, Lallee MP, Zan AS, Zamorano MM, et al. Case report of hepatic mucormycosis after liver transplantation: successful treatment with liposomal amphotericin B followed by posaconazole sequential therapy. Transplant Proc 2012;44:2501–2.
[5] Mekeel KL, Hemming AW, Reed AI, Matsumoto T, Fujita S, Schain DC, et al. Hepatic mucormycosis in a renal transplant recipient. Transplantation 2005;79:1636.
[6] Mezhir JJ, Mullane KM, Zarling J, Satoskar R, Pai RK, Roggin KK. Successful nonoperative management of gastrointestinal mucormycosis: novel therapy for invasive disease. Surg Infect (Larchmt) 2009;10:447–51.
[7] Dalgic B, Bukulmez A, Sari S. Pyogenic liver abscess and peritonitis due to Rhizopus oryzae in a child with Papillon-Lefevre syndrome. Eur J Pediatr 2011;170:803–5.
[8] Suh IW, Park CS, Lee MS, Lee JH, Chang MS, Woo JH, et al. Hepatic and small bowel mucormycosis after chemotherapy in a patient with acute lymphocytic leukemia. J Kor Med Sci 2000;15:351–4.
[9] Luer S, Berger S, Diepold M, Duppenthaler A, von Gunten M, Muhlethaler K, et al. Treatment of intestinal and hepatic mucormycosis in an immunocompromized child. Pediatr Blood Cancer 2009;52:872–4.
[10] Su H, Thompson 3rd GR, Cohen SH. Hepatic mucormycosis with abscess formation. Diagn Microbiol Infect Dis 2012;73:192–4.
[11] Khan AA, Kumaran V, Jain D, Siraj F, Aggarwal S. Hepatic mucormycosis in a patient of acute lymphoblastic leukemia: a case report with literature review. Indian J Hematol Blood Transfus 2013;29:96–8.
[12] Trenker C, Dohse M, Metzelder SK, Rexin P, Mariss J, Goerg C. 71-year-old patient with chronic lymphocytic leukemia (CLL) and hypoechoic nodular spleen and liver lesions with fatal outcome: presentation of mucormycosis in B-mode imaging and contrast-enhanced ultrasound (CEUS). Ultrasound Int Open 2016;2:E100–1.
[13] Bernardo RM, Gurung A, Jain D, Malinis MF. Therapeutic challenges of hepatic mucormycosis in hematologic malignancy: a case report and review of the literature. Am J Case Rep 2016;17:484–9.
[14] Yang C, Friess SH, Dehner LP. Hepatic mucormycosis mimicking veno-occlusive disease: report of a case and review of the literature. Pediatr Dev Pathol 2016;19:150–3.
[15] Yasmeen S, Waqas O, Munir J, Sultan F, Hameed A. Hepatosplenic mucormycosis post autologous stem cell transplant. Pak J Med Sci 2017;33:776–8.
[16] Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005;41:634–53.
[17] Suzuki Y, Kume H, Togano T, Ohto H. Epidemiology of zygomycosis: analysis of national data from pathological autopsy cases in Japan. Med Mycol J 2017;58:E89–95.
[18] Tissot F, Agrawal S, Pagano L, Petrikkos G, Groll AH, Skiada A, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica 2017;102:433–44.
[19] Spellberg B, Kontoyiannis DP, Fredricks D, Morris MI, Perfect JR, Chin-Hong PV, et al. Risk factors for mortality in patients with mucormycosis. Med Mycol 2012;50:611–8.