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Case report

# Disseminated mucormycosis in a patient with severe COVID-19 on venovenous extracorporeal membrane oxygenation: A case report

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ABSTRACT

*Background:* Since the global outbreak of coronavirus disease 2019 (COVID-19), there have been several reports of mucormycosis as a secondary complication. However, the disseminated type of mucormycosis is extremely rare.

*Case:* A 58-year-old male patient with COVID-19 started receiving venovenous extracorporeal membrane oxygenation because of severe respiratory failure. During hospitalization, intra-abdominal hemorrhage occurred and an emergency laparotomy was performed. Subsequently, the patient suffered septic shock, and part of the small intestines and the abdominal wall became necrotic. Finally, the patient died. At autopsy, he was diagnosed with disseminated mucormycosis.

*Conclusion:* Disseminated mucormycosis should be considered in patients with COVID-19 with refractory sepsis unresponsive to broad-spectrum antimicrobial therapy.

## Introduction

Mucormycosis is an infection caused by fungi belonging to the order Mucorales. Mucorales have low pathogenicity; therefore, pathogens of this order mainly cause opportunistic infections [1]. With increased survival of the patient population at risk of opportunistic infection, such as older adults, patients with diabetes, and patients with human immunodeficiency virus, the epidemiology of mucormycosis is changing. Increased incidence is detected, especially in patients with hematologic malignancies, as well as bone marrow transplant recipients [2]. In mucormycosis, the true incidence/prevalence may be higher than recorded because of undiagnosed cases, because of the difficulty of obtaining samples from deep tissues and the low sensitivity of diagnostic tests [3].

Risk factors for mucormycosis include diabetes mellitus, hematologic malignancies, transplantation, adrenal corticosteroid therapy, and neutropenia; however, a significant number of cases of patients without underlying diseases or risk factors has been reported [3,4]. The clinical mucormycotic infection types include nasal-oral-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated infection, where mucormycosis invades multiple organs. Nasal-oral-cerebral, pulmonary, and cutaneous types are more common, while gastrointestinal and disseminated types are less commonly reported [5,6]. Disseminated types of mucormycosis are vascularly invasive and can cause sepsis and necrosis of multiple organs. Patients with hematologic malignancies and transplants are at a higher risk of disseminated mucormycosis [3,6].

Since the novel coronavirus disease (COVID-19) outbreak, many cases of mucormycosis in patients with COVID-19 have been reported worldwide. Mucormycosis associated with COVID-19 is known as COVID-19-associated mucormycosis (CAM). Most CAM cases are of rhino-orbital-cerebral and pulmonary CAM. However, the disseminated type is rare [7,8].

Herein, we report a rare case of disseminated mucormycosis in a patient with severe COVID-19 on venovenous extracorporeal membrane oxygenation (VV-ECMO).

## Case

A 58-year-old man with no obesity or history of diabetes mellitus was admitted to another hospital with a diagnosis of COVID-19. The patient

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developed respiratory failure and mechanical ventilation was initiated; however, his respiratory condition worsened. Therefore, the patient was transferred to our hospital. Arterial blood gas analysis showed severe hypoxia (partial pressure of oxygen/fraction of inspired oxygen ratio = 67.3), and chest computed tomography (CT) showed bilateral ground-glass opacity. We diagnosed the patient with acute respiratory distress syndrome and, then, he initiated VV-ECMO. Additionally, methylprednisolone 70 mg (1 mg/kg/day) was administered for prevention of progressive fibrosis of the lung on day 7.

On day 9, after the patient was placed in a supine position, he developed shock and abdominal distension. Contrast-enhanced CT revealed intra-abdominal hemorrhage. Resuscitative endovascular balloon occlusion of the aorta and an emergency laparotomy were performed. The source of the bleeding was the artery on the dorsal side of the intestinal membrane. Bleeding control was difficult, and massive blood transfusions and a total of five laparotomies were performed over 5 days. In the second surgery, right hemicolectomy was performed for bleeding control. Furthermore, ileostomy was performed in the fifth surgery.

However, methylprednisolone was discontinued from day 11 because of the development of intra-abdominal hemorrhage. Then, a 30 mg/day methylprednisolone administration was initiated on day 21. On day 24, the patient developed septic shock. Broad-spectrum antimicrobials (meropenem and vancomycin) and antifungals (micafungin) were administered; however, there were no signs of improvement, and the iliac stoma and abdominal wall became necrotic. Although surgical debridement of the necrotic area was performed on the 30th day, the necrotic area expanded further on the 41st day. The patient died on the 46th day due to multiple organ failure. Histopathological examination of the resected segment of the ileum revealed filamentous fungi (Fig. 1), and mucormycosis was suspected.

A pathological autopsy revealed Mucor species, predominantly in the ileum, transverse colon, abdominal wall, skin, liver, spleen, and lower pole of the right kidney. These results led to the diagnosis of disseminated mucormycosis.

## Discussion

To our knowledge, this is the first report of disseminated mucormycosis in a patient with COVID-19 receiving VV-ECMO. Previous studies have reported that disseminated mucormycosis accounts for approximately 13 % of total mucormycosis cases [6]. Disseminated mucormycosis reportedly accounts for 1 % of CAM [9]. The most common dissemination sites are the lungs, followed by the central nervous system, sinuses, liver, and kidney [10]; however, the site of dissemination is not clear in most cases [6]. In this case, the pathological autopsy revealed that the site of dissemination was neither the nasal cavity nor the lung. Mucor species were detected in necrotic tissues, including the liver, right kidney, and intravenous thrombus, where surgical resection was performed. This suggests that the portal of entry may be the site of intraperitoneal hemorrhage or the abdominal wall, and that multiple surgeries for intraperitoneal hemorrhage may have affected the invasion of mucor species.

Diabetes mellitus with poor glycemic control and steroid use have been identified as risk factors for CAM [8,9]. Although diabetes mellitus is, according to one study, one of the most common causes of CAM, steroid treatment in COVID-19 may induce further hyperglycemia and immunosuppression, which increases the risk of developing CAM. Severe COVID-19 promotes the secretion of stress hormones and cytokines, which increase insulin resistance [11]. In this case, the patient had no history of diabetes mellitus. However, the patient was administered dexamethasone for 10 days, followed by methylprednisolone. Long-term use of corticosteroids may have been associated with the development of mucormycosis. Mucormycosis complications should be considered when long-term steroid administration is used.

Disseminated mucormycosis has a high mortality rate because it is difficult to diagnose, with few indicators of suspected infection. The nasal-oral-cerebral type may show a black necrotic eschar, and the pulmonary type may show a halo sign or reverse halo sign on CT [1,4]. However, there are no clinical findings that are characteristic of disseminated mucormycosis. A definitive diagnosis is only made after direct detection of Mucorales using histological biopsy [1].

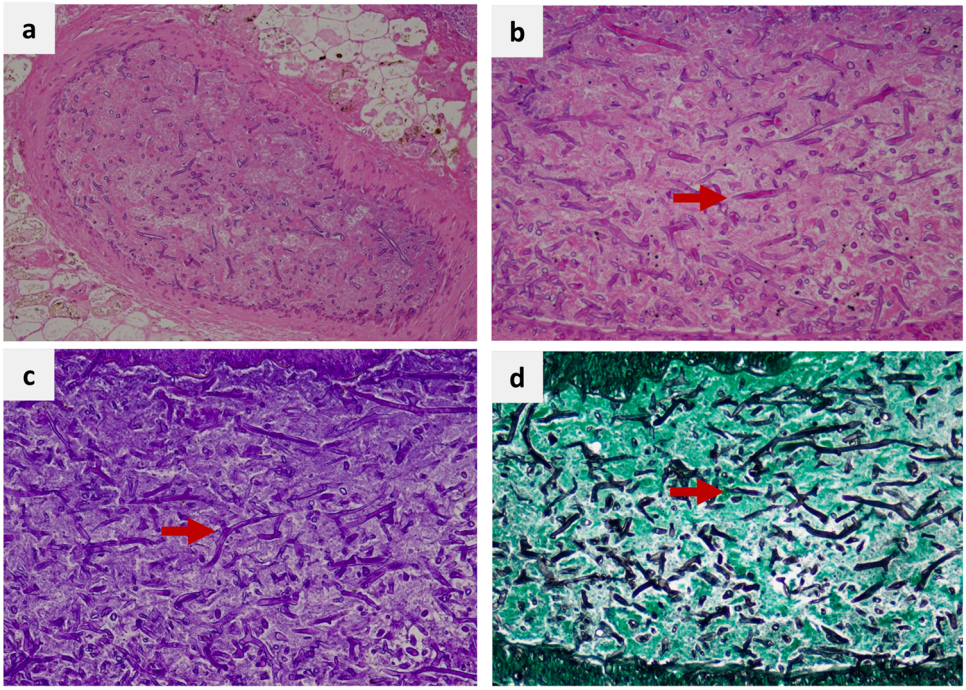


**Fig. 1.** Mucor embolization of blood vessels in the section of the necrotic ileum. Small artery embolized thrombus containing many mycelia (a). Mucormycosis was suspected because of the wide, irregular, and ribbon-like mycelia in each section (arrow) stained with hematoxylin-eosin (b), periodic acid-Schiff (c), and Grocott–Gomori's methenamine silver (d).

Nonpigmented mycelia with few septations must be identified in tissue sections stained with hematoxylin–eosin, periodate acid-Schiff stain, or Grocott–Gomori's methenamine-silver stain [1,4]. The mycelium of Mucorales is characterized by its wide and irregular (ribbon-like) shape [1]. Fungal biomarkers, such as serum 1,3-β-D glucan and blood cultures, are usually negative. A previous study reported that Mucorales was grown on culture in approximately 79 % of cases; thus, morphological evaluation of cultured isolates was observed to aid genera/species identification of the Mucorales pathogens in only approximately 53 % of cases [6]. In this case, the patient suffered from septic shock based on clinical and laboratory findings; however, broad-spectrum antimicrobial therapy did not provide any improvement. Mucormycosis was not suspected, and a definitive diagnosis was made by pathological autopsy. If mucormycosis had been suspected earlier, the progression of necrosis may have been controlled.

The standard treatment for mucormycosis is surgical debridement of the necrotic tissue and administration of amphotericin B. The newer azoles, isavuconazole and posaconazole, can be used as salvage therapy after initial treatment with amphotericin B [1,12]. Antifungal drugs, except those listed above, are ineffective against mucormycosis. In this case, micafungin was also administered because of the elevated β-D-glucan levels; however, there was no effective result. Probably, it was a false positive result. The administration of amphotericin B, in addition to early debridement of the necrotic area, may have been effective. Although evidence for secondary prophylactic administration is lacking [1], it may be considered in patients at a high risk of CAM, such as those with poorly controlled diabetes or those on long-term steroids.

## Conclusion

Disseminated mucormycosis can occur in patients with COVID-19 on VV-ECMO. Disseminated mucormycosis should be considered in patients with COVID-19 with refractory sepsis who are unresponsive to broad-spectrum antimicrobial and antifungal therapies.

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## Ethical approval

Ethics approval has been obtained.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## CRediT authorship contribution statement

**Hazuki Ito:** Conceptualization, Date curation, Writing – original draft, Writing – review & editing. **Ryuichiro Kakizaki:** Term, Conceptualization, Writing – original draft, Writing – review & editing. **Keisuke Harada:** Resources, Data curation, Writing – original draft. **Daisuke Kyuno:** Investigation, Visualization. **Terufumi Kubo:** Investigation, Visualization. **Naofumi Bunya:** Resources, Data curation. **Takehiko Kasai:** Resources, Data curation. **Shuji Uemura:** Supervision. **Eichi Narimatsu:** Project administration.

## Competing interests

There are no conflicts of interest to declare.

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