Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CASE REPORT

# Challenges in Management of Disseminated Mucormycotic Infection with Endocarditis in an Adult Patient Receiving Liver Transplantation

Yue Wu[1,2,*], Xinyu Yu[1,2,*], Yuntao Zhang[1,2], Junfang Liu[1,2], Ying Chen[1,2], Rongrong Wang[3], Wei Zhang[1,2]

[1]Department of Hepatobiliary and Pancreatic Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, People's Republic of China; [2]Liver Transplant Center, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, People's Republic of China; [3]Department of Clinical Pharmacy, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wei Zhang, Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, People's Republic of China, Email 1307018@zju.edu.cn; Rongrong Wang, Department of Clinical Pharmacy, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, People's Republic of China, Email 1513056@zju.edu.cn



**Abstract:** Mucormycosis is a rare fungal infection. With the recent advancements in diagnostic technologies, including molecular diagnostic techniques, such as PCR and metagenomic next-generation sequencing, the detection rates of mucormycosis have increased. However, its mortality rates remain alarmingly high. Although post-liver transplantation mucormycosis cases are infrequently reported (less than 1%), their mortality rate ranges from 60% to 90%, while mucormycotic endocarditis is even rarer. This article summarizes the clinical manifestations of mucormycosis in a post-liver transplantation adult patient and reviews the existing literature on mucormycotic endocarditis, with the aim of outlining its clinical features, diagnostic challenges, and therapeutic strategies.

**Keywords:** mucormycosis, endocarditis, liver transplantation, metagenomic next-generation sequencing, *Rhizomucor*, *Cunninghamella*

## Introduction

Mucormycosis is one of the most common causes of deep fungal infections, alongside candidiasis and aspergillosis.[1] It is an invasive fungal infection caused by ubiquitous filamentous fungi belonging to the order *Mucorales* and is characterized by an extremely high mortality rate. In recent years, the reported incidence of mucormycosis has risen, probably due to the growing population of high-risk individuals and advances in diagnostic techniques.[2] The risk factors for this disease include cirrhosis, neutropenia, prolonged corticosteroid use, malnutrition, poorly controlled diabetes, iron overload, hematologic malignancies, recent allogeneic stem cell or solid organ transplantation, severe burns, and major traumatic injuries. High-risk patients may develop mucormycosis following exposure to spores via inhalation or traumatic inoculation, as these spores are widespread in the environment, leading to either community-acquired or nosocomial infections.[3,4] Clinically, mucormycosis, like aspergillosis, exhibits angioinvasive growth, predisposing patients to thrombosis and emboli.[5] It is marked by extensive necrotic vasculitis that results in thrombus formation, progressive tissue infarction, and even systemic dissemination.[6] Its management typically requires aggressive surgical debridement and prolonged antifungal therapy.[7] Infective endocarditis (IE) demonstrates significant clinical burden, with 2019 incidence reported at 13.8 per 100,000 and overall mortality persisting at 30%.[8] The condition is predominantly caused by *Staphylococcus aureus*, streptococci (notably viridans group), and enterococci—collectively accounting for ~80% of cases. Major risk factors include underlying cardiac abnormalities (eg, rheumatic or congenital heart disease), prosthetic valves, intracardiac devices, and intravenous drug use. In contrast, fungal endocarditis comprises a distinct minority (1–3% of IE cases) yet carries disproportionate mortality exceeding 70%, with *Candida* species responsible for

Received: 14 April 2025
Accepted: 19 August 2025
Published: 5 September 2025

>50% of these infections and *Aspergillus* being less common.[9,10] Notably, key risk factors specific to this fulminant subtype include prosthetic valves, prior cardiac surgery, and immunosuppression.[10] Mucormycotic endocarditis is a scarcely reported disease with near-complete lethality.[6] Given the high mortality rate of mucormycosis, it is important to improve its detection rate through better diagnostic strategies and timely treatment and management. Gaining a clearer picture of the clinical manifestations, diagnostics, and management would help improve its diagnosis and management and potentially help improve its survival rate. This report describes the clinical manifestations and course of mucormycosis in a post-liver transplantation adult patient and reviews the existing literature on mucormycotic endocarditis.

## Case Presentation

A 51-year-old male (weight: 93 kg, height: 170 cm, BMI: 32.2 kg/m²) underwent liver transplantation at our hospital for acute-on-chronic liver failure. His medical history included hypertension, diabetes mellitus, and hepatitis B surface antigen positivity for over a decade. One month prior to surgery, he developed jaundice (scleral icterus and skin yellowing), abdominal distension, fatigue, decreased appetite, and dark tea-colored urine, with progressive worsening. Initial laboratory tests at a local county hospital revealed that his total bilirubin level was 338 μmol/L; direct bilirubin, 268.7 μmol/L; indirect bilirubin, 69.7 μmol/L; HBV-DNA, $10^9$ IU/mL; international normalized ratio, 2.32, and prothrombin time, 24.6 s. The patient received hepatoprotective therapy with glycyrrhizin-based medications (80 mg IV daily) and intravenous S-adenosylmethionine (1,000 mg/day), but his condition deteriorated despite this. Twelve days before the transplant procedure, he was transferred to our hospital. Chest CT showed no infiltrates, and the findings of electrocardiography and echocardiography were unremarkable. Treatment included tenofovir alafenamide (antiviral), hepatoprotective agents, choleretics, gastric protectants, laxatives, and ammonia-lowering therapy. During hospitalization, oliguria (25 mL/h) and increasing lactate levels (12 mmol/L) prompted admission to the intensive care unit 8 days before the procedure for continuous renal replacement therapy. The lactate levels improved temporarily, but hypotension and hypoxemia necessitated mechanical ventilation the next day. Blood cultures revealed the presence of Gram-negative bacilli, and chest radiography revealed bilateral pulmonary infiltrates. The patient was diagnosed with septic shock complicated by pulmonary infection. Following ICU admission, empiric therapy with meropenem (1 g every 8 hours) and micafungin (100 mg/day) was immediately initiated and maintained until liver transplantation. Vancomycin (500 mg every 8 hours) was additionally administered starting 4 days prior to the procedure. Serial monitoring demonstrated progressive normalization of serum lactate levels, resolution of shock, and reduction of inflammatory biomarkers (C-reactive protein and procalcitonin) to near-normal ranges. Preoperative arterial blood gas analysis indicated a $PaO_2/FiO_2$ ratio of 204 mmHg.

Liver transplantation was performed with a graft from a 48-year-old male brain death donor who died of hypertensive intracerebral hemorrhage. The procedure, a modified piggyback technique, lasted 7 h and 5 min, with a cold ischemia time of 3 h and 33 min and an anhepatic phase of 50 min. Intraoperative immunosuppression therapy included methylprednisolone (1000 mg) and basiliximab (20 mg). Tacrolimus (target trough: 3–5 ng/mL) was initiated on postoperative day (POD) 3. Preoperative serum metagenomic next-generation sequencing (mNGS) preliminarily detected mucormycetes, prompting immediate treatment with isavuconazole (200 mg IV) before entering the operating room. The diagnosis of mucormycosis was established based on the patient's history of suboptimal long-term glycemic control in diabetes mellitus, underlying chronic liver disease with progression to hepatic failure, and definitive evidence from serum mNGS testing.

Bradycardia (40–50 bpm) and hypotension occurred on POD 1, with the electrocardiogram showing high-grade atrioventricular block (Figure 1A). A temporary VVI pacemaker was implanted (Figure 1B). Formal serum mNGS results confirmed the presence of *Rhizomucor pusillus* (203 sequence reads) and *Cunninghamella elegans* (40 sequence reads). Necrotic eschar-like skin lesions were noted on the upper abdomen (Figure 2). Isavuconazole (200 mg/day after a 48-h loading dose of 200 mg/8 h) and amphotericin B colloidal dispersion were administered (2–4 mg/kg of body weight/day). The initial postoperative antimicrobial regimen comprised meropenem for Gram-negative coverage and vancomycin for Gram-positive coverage. On POD 7, antimicrobial therapy was de-escalated to cefoperazone-sulbactam based on sputum culture identification of *Ralstonia mannitolilytica* with susceptibility testing (MIC ≤4μg/mL). Subsequently, on POD 10, therapy was shifted to levofloxacin due to coagulopathy evidenced by elevated INR. Postoperative echocardiography was performed every other day, and serum troponin (TnI) and B-type natriuretic peptide (BNP) levels were monitored daily. Progressive elevation of TnI and BNP levels was observed (Figure 3). On POD 4,

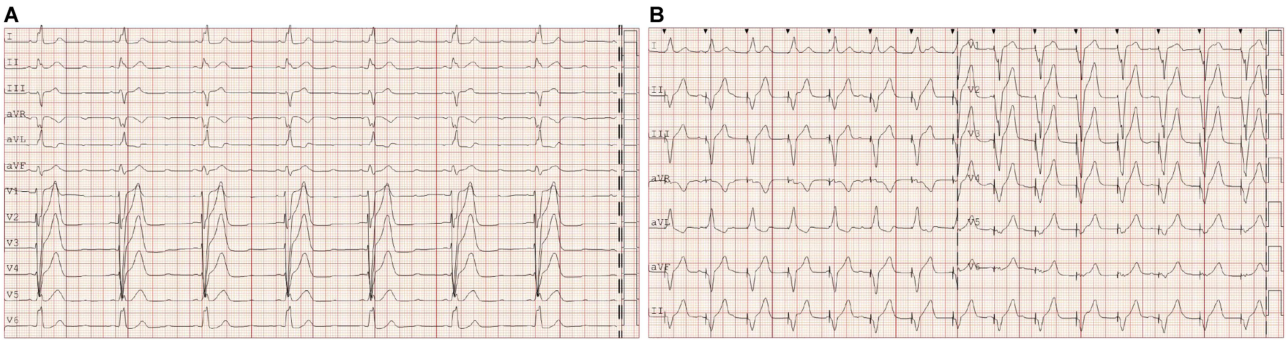


**Figure 1** Postoperative electrocardiogram findings. (**A**) High-grade atrioventricular block with 3:1 atrioventricular conduction and complete left bundle branch block. (**B**) Post pacemaker implantation ECG showing VVI pacing mode with a pacing rate of 90 beats per minute (bpm). The black triangles indicate the pacing spikes.

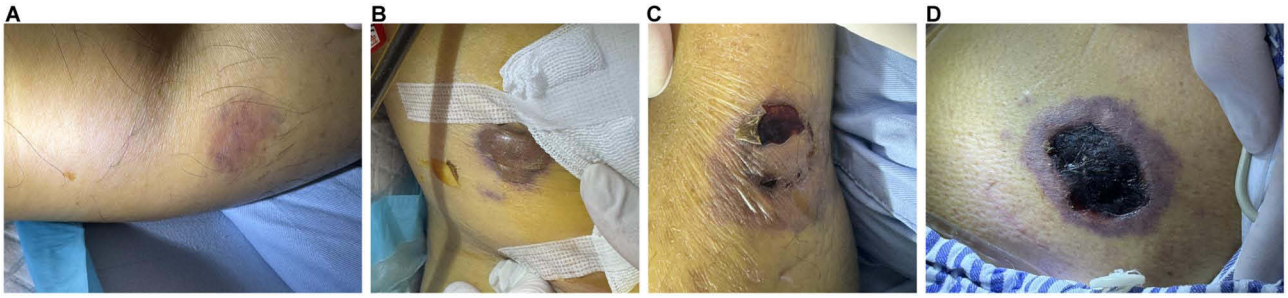


**Figure 2** Clinical manifestations of skin necrosis at different stages of progression. (**A**) Circular erythema; (**B**) Swelling/necrosis; (**C**) Dry ulcer; (**D**) Necrotic eschar.

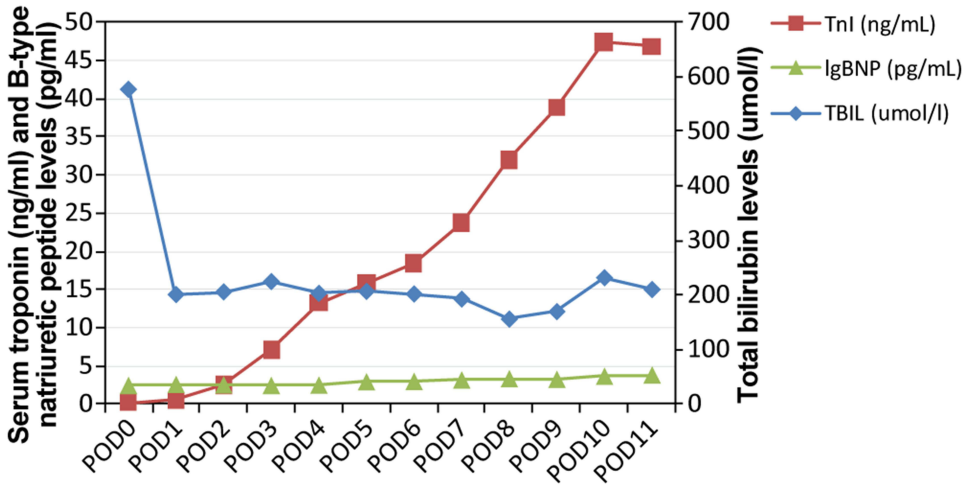


**Figure 3** Post-transplantation daily trends in serum troponin, B-type natriuretic peptide, and total bilirubin levels. Postoperative monitoring demonstrated serum total bilirubin levels fluctuating around 200 μmol/L, while serum troponin I and B-type natriuretic peptide (BNP) exhibited progressively increasing trends.

non-contrast CT scans of the head and chest, along with abdominal CT angiography, were performed. The scans revealed large areas of pulmonary exudates in the lungs and multiple wedge-shaped infarcts in the spleen and kidneys (Figure 4). Intravenous immunoglobulin (0.25 mg/kg of body weight/day) was administered to enhance humoral immunity.

On POD 7, echocardiography revealed apical wall motion abnormalities, which were accompanied by increased levels of TnI (23.8 ng/mL) and BNP (1439.5 pg/mL). Repeated serum mNGS detected *Cunninghamella bertholletiae* (841 sequence reads). Further, expansion of the cutaneous lesions was observed (Figure 2), and bedside biopsy of the abdominal eschar was performed. Coronary angiography showed 30% stenosis in the proximal left anterior descending artery (for which no intervention was administered).


https://doi.org/10.2147/IDR.S534279

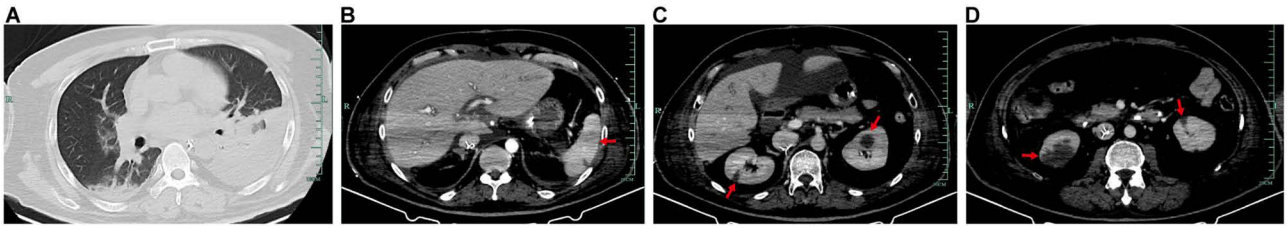


**Figure 4** Multiorgan CT findings showing disseminated mucormycosis. (**A**) Chest CT demonstrating multifocal consolidations in the lungs. (**B**) Splenic wedge-shaped infarct following vascular distribution (arrowhead). (**C** and **D**) Bilateral renal multiple wedge-shaped infarcts aligned with vascular territories (arrowhead).

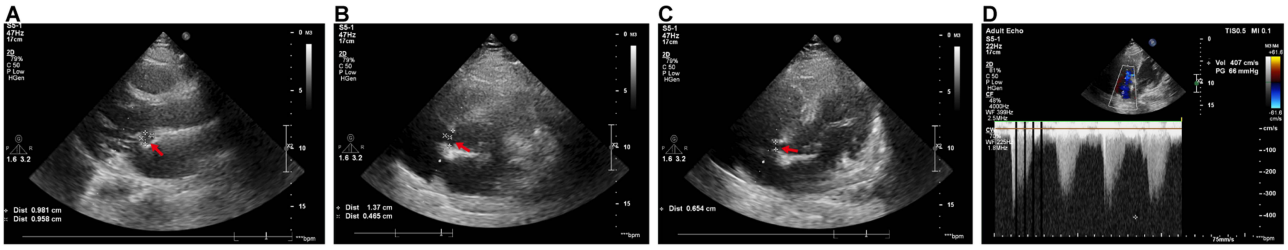


**Figure 5** Echocardiographic findings on postoperative day 7. (**A**) Sac-like structure protruding into the left atrium from the base of the anterior mitral leaflet, measuring 1.0×1.0 cm (arrowhead). (**B**) Echo discontinuity in the membranous ventricular septum with a sac-like structure extending into the right atrium (1.4 × 0.4 cm) (arrowhead). (**C**) Perforation of the membranous ventricular septum with a defect width of 0.65 cm (arrowhead). (**D**) Peak flow velocity of 4.1 m/s at the septal perforation site.

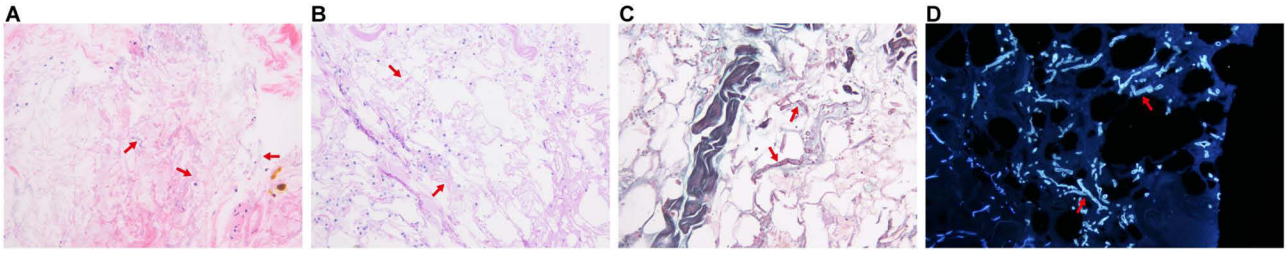


**Figure 6** Biopsy pathology images of eschar necrosis in the abdominal wall skin. (**A**) Hematoxylin and eosin staining, (**B**) periodic acid-Schiff staining, (**C**) Grocott's methenamine silver (GMS) staining, and (**D**) immunofluorescence staining demonstrating abundant broad, non-septate, right-angled branching hyphae (arrowhead).

Refractory shock and escalating lactate levels on POD 8 necessitated maximal vasopressor support (with norepinephrine). Repeated serum mNGS confirmed persistence of *R. pusillus* (52 sequence reads). Echocardiography demonstrated ventricular septal fistula (into the right atrium) and mitral valve perforation on POD 10 (Figure 5). The patient died of progressive hemodynamic collapse on POD 11. Postmortem skin biopsy pathological examination confirmed broad, non-septate hyphae consistent with mucormycosis in the deep dermis and subcutaneous fat layers (Figure 6).

## Discussion

The present report describes a rare case of post-liver transplantation mucormycosis in a patient characterized by persistence of *Cunninghamella* and *Rhizomucor* species, cardiac involvement, progressively worsening necrotic lesions and eschar formation, and systemic spread, all of which contributed to a poor prognosis that eventually led to death on the 11$^{th}$ day after the procedure. The observations here highlight the importance of employing molecular diagnostic technologies such as mNGS for accurate detection and early initiation of antifungal treatment.

Mucormycosis is most commonly caused by *Rhizopus, Mucor*, and *Lichtheimia* (formerly *Absidia*) species.[11] While *Cunninghamella* (formerly classified under *Absidia*) is less frequent, it is associated with exceptionally high mortality.[12] In this case, repeated serum mNGS detected *Cunninghamella* and *Rhizomucor*, which explains the patient's poor prognosis. Mucormycosis progresses rapidly and is notoriously challenging to diagnose, contributing to its dismal survival rates.[13] Serological diagnosis is particularly difficult compared to the diagnosis of other fungal infections, and

historically, a definitive diagnosis was often achieved only postmortem via histopathological assessment.[1,14] In the present case, too, the causative pathogen was identified later on in the disease course through mNGS, and the diagnosis was confirmed only through postmortem skin biopsy analysis. These findings highlight the current challenges in the timely diagnosis and treatment of mucormycosis.

The diagnosis of mucormycosis relies on early recognition of host risk factors, clinical signs, imaging observations, histopathological manifestations, and molecular diagnostics.[15] The 2019 ECMM/MSGERC guidelines[16] emphasize the application of imaging, histopathology, and culture for diagnosis, but these methods are limited by low culture yield and delayed histopathological presentation. For example, Mucorales lack 1,3-β-D-glucan in their cell walls,[11] as a result of which serum galactomannan and β-D-glucan assays usually yield false-negative results.[17] Further, while histopathological examination often reveals characteristic broad, pauci-septate hyphae, cultures frequently remain negative.[18] Instead, fluorescence microscopy and molecular diagnostic techniques (eg, PCR and mNGS) may offer enhanced diagnostic accuracy,[19,20] as observed in the present case, underscoring the critical role of mNGS in early detection, particularly in high-risk perioperative settings. Additionally, high-resolution CT may show angioinvasive features (eg, nodules, halo/reverse halo signs, cavities, and wedge-shaped infarcts).[6] Specifically, the reverse halo sign—a focal ground-glass opacity encircled by consolidation—is an early indicator of pulmonary mucormycosis.[21,22] Disseminated disease, often hematogenously seeded from the lungs, may involve the heart, brain, or kidneys.[23] In this patient, CT imaging revealed wedge-shaped hypodense lesions in the kidneys and spleen aligned with vascular distributions, suggestive of Mucorales-related intravascular fungal embolism leading to renal and splenic infarctions. These radiological findings indicated disseminated systemic mucormycosis.

Mucormycosis is classified based on anatomical involvement into rhinocerebral, pulmonary, cutaneous, gastrointestinal, and disseminated forms, as well as rare forms such as endocarditis, osteomyelitis, peritonitis, and renal infections.[6] Cutaneous mucormycosis typically arises from traumatic inoculation of fungal spores into disrupted skin (eg, surgery, burns, and trauma), potentially leading to systemic dissemination.[24,25] Skin lesions in primary cutaneous mucormycosis include abscesses, necrotic eschars, dry ulcers at the inoculation site. In contrast, diffuse erythema is a nonspecific sign of disseminated disease resulting from hematogenous spread, typically originating from pulmonary or rhinocerebral foci in immunocompromised hosts.[26,27] In the present case, initial circular erythema progressed to necrosis and eschar formation, with lesions expanding in both number and severity. Thus, such cutaneous changes—particularly isolated, round erythematous, or necrotic lesions in post-transplant patients—should raise suspicion of mucormycosis and prompt immediate skin biopsy or mNGS to confirm the diagnosis and initiate aggressive antifungal therapy with or without surgical debridement.[20]

As reported by F. Lanternier et al[28] infection site significantly impacted survival, with mortality rates of 22% (cutaneous), 25% (rhinocerebral), 48% (pulmonary), and 79% (disseminated). Pulmonary mucormycosis, the most common form in solid organ transplant recipients,[29,30] often extends to the chest wall, vasculature, or mediastinum.[31,32] Cardiac involvement (endocarditis or myocarditis) is rare but carries near-universal mortality.[6] Mucormycotic endocarditis manifests catastrophically as heart failure, valvular perforation, intracardiac masses, or sudden cardiac arrest. Without radical surgical excision and prolonged antifungal therapy, mortality approaches 100%.[20] A literature review identified 21 reported cases of cardiac mucormycosis between 1994 and 2023[17,32–51] and found only 4 survivors,[38,39,42,51] one of whom experienced relapse[39] (Table 1). The affected patients, including a blood type-incompatible liver transplant recipient, were found across all age groups and were reported to be universally immunocompromised as a result of immunosuppressive drug therapy.[48] The clinical manifestations of cardiac mucormycosis include intracardiac mass or vegetations, myocardial infarction, congestive heart failure, conduction system disease, valvular incompetence, and pericarditis.[52] Among the cases identified in the literature review, 2 presented with fatal complete atrioventricular block,[33,45] 5 exhibited coronary artery embolism (4 of whom manifested STEMI),[32,44,46,47,50] 10 demonstrated intracardiac masses or valvular vegetations, and 4 patients displayed myocarditis-associated symptoms.[17,34,35,37] In the present case, an adult patient undergoing liver transplantation with a donation after brain death (DBD) graft for hepatic failure developed postoperative high-grade atrioventricular block and endocarditis complicated by perforation of the membranous ventricular septum and mitral valve. The clinical course culminated in fatal cardiac failure with cardiogenic shock. Diagnosis was predominantly confirmed histologically, often postmortem (50% of cases in our review, as observed in the current case too), highlighting the challenges with early detection and

https://doi.org/10.2147/IDR.S534279



**Table 1** Epidemiological Features, Clinical Presentations, Pathogen Identification, Diagnostic Strategies, and Treatment Protocols in Cardiac Mucormycosis Patients

| Case Number [Reference] | Publication Year, Nation | Age/ Sex | Underlying Disease (Immune Status) | Clinical Features of Cardiac Disorders | Other Involved Organs | Mucor Species | Means of Diagnosis | Surgical Approach | Medication | Prognosis |
|---|---|---|---|---|---|---|---|---|---|---|
| 1[33] | 1994, United Kingdom | 71/F | DM, CRF, SLE | Complete heart-block, Supraventricular and Ventricular arrhythmias | / | Mucormycosis | Autopsy (an abscess in the muscular septum) | / | / | Death |
| 2[32] | 1999, Germany | 35/M | AML | STEMI | Lung, spleen, kidney | *Cunninghamella bertholletiae* | Sputum culture; Autopsy | / | AMB (total dose 225 mg), VORI | Death |
| 3[34] | 2002, America | 48/F | LDRT | Endocarditis (congestive heart failure) | Lung, brain, liver, spleen, pancreas, gastrointestinal tract, skin | *Cunninghamella bertholletiae* | Autopsy | / | / | Death |
| 4[35] | 2004, Switzerland | 40/F | AA (undergone a medullary cell transplantation) | Acute fulminant myocarditis | Lungs, liver, kidneys, brain, skin | Mucormycosis | Autopsy | / | / | Death |
| 5[36] | 2004, America | 32/M | Primary red cell aplasia | Aortic valve vegetation | / | *Cunninghamella bertholletiae* | Excised tissue culture | Aortic valve replacement and debridement of the proximal ascending aorta | AMB | Death |
| 6[37] | 2006, Türkiye | 13/M | AA | Heart insufficiency manifested with sepsis | / | Mucormycosis | Autopsy | / | AMB (1 mg/kg) | Death |
| 7[38] | 2007, Croatia | 37/M | UC | Right atrial mass | Lung | Mucormycosis | Excised tissue pathology | Surgical excision | LAMB (5 mg/kg, total dose 1.8g) | Survived |
| 8[39] | 2008, India | 2/F | T-cell immunodeficiency | Mitral valve vegetations | Cerebral embolism | Mucormycosis | Excised mass histopathology | Surgical excision | AMB (total dose 45 mg/kg), FLU (5 mg/kg/d) | Survived (recurrence) |
| 9[40] | 2008, Netherlands | 80/F | Essential thrombocytosis, implanted permanent pacemaker | Right atrium large mass attached to the pacemaker lead, Tricuspid stenosis | Lung | *Mucor spp* | Valve tissue culture | Surgical removal of the entire pacemaker system | LAMB (7 mg/kg) | Death |
| 10[41] | 2009, Japan | 71/F | MDS | Left atrial mass | Cerebral embolism | Mucormycosis | Autopsy | / | / | Death |
| 11[42] | 2010, America | 6/F | T-ALL | Right ventricular mass | Lung, the right pulmonary artery | *Absidia corymbifera* | Blood culture; Excised tissue pathology | Resection of the vegetations, radical resection of all involved cardiac tissues (secondary surgery) | LAMB (5–10 mg/kg) and POS (200mg twice a day) | Survived |
| 12[43] | 2013, America | 60/F | GVHD after BMT for MDS | Left ventricular (multi-chambered) mass | / | *Cunninghamella* | Excised tissue pathology | Debridement of the chambers | / | Death |
| 13[44] | 2016, Australia | 26/F | BLTx | Anterior-STEMI (hyphal occlusion of the left anterior descending artery) | / | Mucormycosis | Autopsy | / | / | Death |
| 14[45] | 2018, Japan | 74/F | Overlapping dermatomyositis and SS, DILI | Complete atrioventricular block | Lung, kidneys, spleen | Mucormycosis | Autopsy | / | / | Death |
| 15[51] | 2019, America | 62/M | DM, AML | Intracardiac mass extending between the right atrium and right ventricle | Lung | Mucormycosis | Lung biopsy | / | LAMB, POS | Survived (dyspnea) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 16[46] | 2020, America | 57/M | BLTx | PEA, Infero-lateral wall STEMI (coronary artery thrombosis) | Lung, aorta, skin | *Apophysomyces elegans* | Autopsy | / | / | Death |
| 17[17] | 2020, Japan | 64/M | Amiodarone-induced interstitial pneumonia, (GC therapy) | Fulminant myocarditis | Lung, brain, thyroid, subcutaneous tissue | Mucormycosis | Autopsy | / | / | Death |
| 18[47] | 2020, Germany | 20/M | Allo-SCT due to pro-B ALL | Mitral valve insufficiency, a thickened anterior valve leaflet and tendinous chord ruptures | / | *Rhizomucor miehei* | Autopsy | / | ISA | Death |
| 19[48] | 2022, Japan | 47/M | ABOi-LDLT | Bigeminy and atrial-ventricular block, cardiac arterial occlusion | Lung, brain, thyroid, liver, gastrointestinal tract, kidneys | *Cunninghamella bertholletiae* | PCR and culture of the excised lung segment | Right lung segmentectomy | AMB (5mg/kg) | Death |
| 20[49] | 2022, Japan | 49/F | B-ALL | Large mural thrombus in the left ventricle | Lung, liver, kidney, spleen | *Cunninghamella bertholletiae* | Autopsy | / | / | Death |
| 21[50] | 2023, Japan | 63/F | AML (M5a) | STEMI (inferior wall), Cardiac arrest | Lung | Mucormycosis | Autopsy | / | / | Death |

**Abbreviations**: DM, diabetes mellitus; CRF, chronic renal failure; SLE, systemic lupus erythematosus; AML, acute myelogenous leukemia; LDRT, living donor renal transplantation; AA, Aplastic anaemia; UC, Ulcerative colitis; MDS, myelodysplastic syndrome; T-ALL, T-cell acute lymphoblastic leukemia; GVHD, graft-versus-host disease; BMT, bone marrow transplantation; BLTx, bilateral lung transplantation; SS, Sjögren syndrome; DILI, drug-induced liver injury; GC, glucocorticoids; Allo-SCT, allogeneic stem cell transplantation; ALL, acute lymphoblastic leukemia; ABOi-LDLT, ABO-incompatible living donor liver transplantation; B-ALL, B-cell acute lymphoblastic leukemia; STEMI, ST-segment elevation myocardial infarction; PEA, pulseless electrical activity; PCR, polymerase chain reaction; AMB, amphotericin B; VORI, voriconazole; LAMB, liposomal amphotericin B; FLU, fluconazole; POS, posaconazole; ISA, isavuconazole.

https://doi.org/10.2147/IDR.S534279

rapid progression. The International Society for Cardiovascular Infectious Diseases (ISCVID) updated infective endocarditis diagnostic criteria to reflect advances in microbiology, diagnostics, epidemiology, and management. The 2023 Duke-ISCVID criteria now include PCR and metagenomic sequencing as major microbiological criteria.[53] In the reviewed literature, all 6 patients with confirmed *Cunninghamella* infection died,[32,34,43,48,49] as observed in the present case. Moreover, species identification was not possible in 11 cases of *Mucorales* infection. *Cunninghamella* infection portends a dismal prognosis, with survival rates below 30%. All previously reported cases of disseminated *Cunninghamella* disease were fatal.[54] Disseminated multiorgan involvement was documented in 15 cases, with the origin of the disease identified as pulmonary mucormycosis with cardiac invasion in one case[32] and mycotic endocarditis secondary to catheter-related infection in another case.[38] Cardiac involvement typically reflects disseminated disease, arising via hematogenous spread or direct pulmonary invasion. Autopsy findings in such cases reveal fungal thrombi, invasive necrosis of the myocardium, and infarction. In this case, high-grade atrioventricular block on POD 1 corresponded to echocardiographic findings of septal perforation near the atrioventricular node and His bundle. Overall, the observations in the present case corroborate the findings of other studies on cases of mucormycosis with cardiac involvement and highlight the challenges with diagnosis.

Management of mucormycosis requires risk stratification, rapid antifungal therapy, surgical debridement, and reversal/elimination of predisposing factors.[55] First-line agents include lipid-based amphotericin B (5–10 mg/kg of body weight/day), with isavuconazole and posaconazole recommended as preferred options for salvage therapy. Although lipid-based amphotericin B has a lower incidence of nephrotoxicity, its higher cost leads to the more frequent use of conventional amphotericin B in Asian and African countries. The optimal duration of treatment for mucormycosis remains unclear, typically requiring weeks to months, and there is limited high-quality evidence supporting combination antifungal therapy. In our review of mucormycosis with cardiac involvement, all 4 surviving patients[38,39,42,51] received timely antifungal therapy with amphotericin B. In our case, although mucormycosis was detected via serum mNGS and treated with isavuconazole combined with amphotericin B colloidal dispersion, the dosage was suboptimal (3–5 mg/kg of body weight/day). The 2019 ECMM/MSGERC guidelines[16] recommend that surgical intervention be strongly considered when mucormycosis is suspected, provided surgical conditions are feasible. Notably, 3 patients (from our review) who achieved clinical improvement or were cured underwent prompt surgical debridement[38,39,42] (including one case with incomplete initial radical resection that required secondary debridement due to recurrent infection).[42] However, cardiac manifestations typically emerge when disseminated infection is already established, precluding surgical intervention, which was observed in most patients in the reviewed literature. In the present case, too, the patient rapidly developed high-grade atrioventricular block that was suggestive of fungal invasion of the membranous portion of the interventricular septum. In addition, the patient exhibited clinical manifestations of disseminated infection involving skin, kidneys, spleen, and lungs. These presentations rendered the patient ineligible for surgical intervention. Consequently, the infection remained uncontrolled. Retrospectively, serum mNGS testing should have been performed earlier when the patient was transferred to the ICU in the preoperative period due to shock and respiratory failure, as this would have enabled earlier initiation of therapy and slowed disease progression.

## Conclusions

Despite its relative rarity, mucormycosis poses a significant threat to immunocompromised patients due to its persistently high mortality rates. The nonspecific clinical manifestations and signs of mucormycosis present substantial diagnostic and therapeutic challenges. With advancements in liver transplantation techniques and perioperative management, an increasing number of patients with end-stage liver disease are undergoing transplantation, necessitating heightened vigilance for mucormycosis in this population. Direct microscopy, fungal culture, and histopathology remain the cornerstone of diagnosis but face several limitations in terms of timely diagnosis. Instead, novel molecular diagnostic technologies offer a complementary approach to facilitate early detection and prompt initiation of therapy. Effective management of mucormycosis requires multidisciplinary collaboration, and timely administration of targeted antifungal therapy is critical to reducing mortality.

## Data Sharing Statement

Data supporting this study can be obtained from the designated corresponding author Wei Zhang at 1307018@zju.edu.cn upon request. Other co-corresponding authors do not manage data requests.

## Ethics Approval

This study complied with the guidelines of the Chinese Ethics Committee and the Declaration of Helsinki and was approved by the Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine. All organs were donated voluntarily with written informed consent, and the donations were conducted in accordance with the Declaration of Istanbul. Since January 1, 2015, organ procurement from executed prisoners had been completely ceased in China, and no organs from executed prisoners were used in any case involved in this study.

## Consent for Publication

We confirm that all authors have approved the submission of this manuscript for publication and the consent of the patient's family was obtained for publication of the data and images. Ethical approval for publication of anonymized case details was granted by the Institutional Review Board of the First Affiliated Hospital, Zhejiang University School of Medicine.

## Acknowledgments

We sincerely thank our colleagues at the transplant center for their contribution to this study and their thoughtful comments, which greatly enhanced our work.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This project was supported by the Central Government Guidance Funds for Local Scientific and Technological Development (2024ZY01023).

## Disclosure

The authors have no conflicts of interest to declare in this work.

## References

1. Kappe R, Seeliger HP. Serodiagnosis of deep-seated fungal infections. *Curr Top Med Mycol*. 1993;5:247–280.
2. Bitar D, Van Cauteren D, Lanternier F, et al. Increasing incidence of zygomycosis (mucormycosis), France, 1997–2006. *Emerg Infect Dis*. 2009;15(9):1395–1401. doi:10.3201/eid1509.090334
3. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis*. 2005;41(5):634–653. doi:10.1086/432579
4. Hartnett KP, Jackson BR, Perkins KM, et al. A guide to investigating suspected outbreaks of mucormycosis in healthcare. *J Fungi*. 2019;5(3).
5. Van Steenweghen S, Maertens J, Boogaerts M, et al. Mucormycosis, a threatening opportunistic mycotic infection. *Acta Clin Belg*. 1999;54(2):99–102. doi:10.1080/17843286.1999.11754215
6. Serris A, Danion F, Lanternier F. Disease entities in mucormycosis. *J Fungi*. 2019;5(1). doi:10.3390/jof5010023
7. Ibrahim AS, Spellberg B, Walsh TJ, et al. Pathogenesis of mucormycosis. *Clin Infect Dis*. 2012;54(Suppl 1):S16–22. doi:10.1093/cid/cir865
8. M L, Kim JB, Sastry BKS, et al. Infective endocarditis. *Lancet*. 2024;404(10450):377–392. doi:10.1016/S0140-6736(24)01098-5
9. Ambrosioni J, Hernández-Meneses M, Durante-Mangoni E, et al. Epidemiological changes and improvement in outcomes of infective endocarditis in Europe in the Twenty-First Century: an International Collaboration on Endocarditis (ICE) Prospective Cohort Study (2000–2012). *Infect Dis Ther*. 2023;12(4):1083–1101. doi:10.1007/s40121-023-00763-8
10. Thompson GR, Jenks JD, Baddley JW, et al. Fungal endocarditis: pathophysiology, epidemiology, clinical presentation, diagnosis, and management. *Clin Microbiol Rev*. 2023;36(3):e0001923. doi:10.1128/cmr.00019-23
11. Alqarihi A, Kontoyiannis DP, Ibrahim AS. Mucormycosis in 2023: an update on pathogenesis and management. *Front Cell Infect Microbiol*. 2023;13:1254919. doi:10.3389/fcimb.2023.1254919

12. Jeong W, Keighley C, Wolfe R, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. *Clin Microbiol Infect*. 2019;25(1):26–34. doi:10.1016/j.cmi.2018.07.011
13. Chavda VP, Apostolopoulos V. Mucormycosis - An opportunistic infection in the aged immunocompromised individual: a reason for concern in COVID-19. *Maturitas*. 2021;154:58–61. doi:10.1016/j.maturitas.2021.07.009
14. Sosnowska-Sienkiewicz P, Błaszczyk K, Kubisiak-Rzepczyk H, et al. How to treat a child with a concurrent diagnosis of leukemia and generalized mucormycosis? Case report. *Front Med Lausanne*. 2022;9:844880. doi:10.3389/fmed.2022.844880
15. Walsh TJ, Gamaletsou MN, McGinnis MR, et al. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). *Clin Infect Dis*. 2012;54(Suppl 1):S55–60. doi:10.1093/cid/cir868
16. Cornely OA, Alastruey-Izquierdo A, Arenz D, 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 Study Group Education and Research Consortium. *Lancet Infect Dis*. 2019;19(12):e405–e21. doi:10.1016/S1473-3099(19)30312-3
17. Fujisawa Y, Hara S, Zoshima T, et al. Fulminant myocarditis and pulmonary cavity lesion induced by disseminated mucormycosis in a chronic hemodialysis patient: report of an autopsied case. *Pathol Int*. 2020;70(8):557–562. doi:10.1111/pin.12943
18. Dadwal SS, Kontoyiannis DP. Recent advances in the molecular diagnosis of mucormycosis. *Expert Rev Mol Diagn*. 2018;18(10):845–854. doi:10.1080/14737159.2018.1522250
19. Millon L, Scherer E, Rocchi S, et al. Molecular strategies to diagnose mucormycosis. *J Fungi*. 2019;5(1). doi:10.3390/jof5010024
20. Millon L, Caillot D, Berceanu A, et al. Evaluation of serum mucorales Polymerase Chain Reaction (PCR) for the diagnosis of mucormycoses: the MODIMUCOR prospective trial. *Clin Infect Dis*. 2022;75(5):777–785. doi:10.1093/cid/ciab1066
21. Legouge C, Caillot D, Chrétien ML, et al. The reversed halo sign: pathognomonic pattern of pulmonary mucormycosis in leukemic patients with neutropenia? *Clin Infect Dis*. 2014;58(5):672–678. doi:10.1093/cid/cit929
22. Wahba H, Truong MT, Lei X, et al. Reversed halo sign in invasive pulmonary fungal infections. *Clin Infect Dis*. 2008;46(11):1733–1737. doi:10.1086/587991
23. Nadeem AM, Wahla AS, Al-Tarifi A. Invasive mediastinal mucormycosis with pulmonary and cardiac involvement in an adult with chronic granulomatous disease: case report and review of the literature. *Eur J Case Rep Intern Med*. 2021;8(5):002435. doi:10.12890/2021_002435
24. Neblett Fanfair R, Benedict K, Bos J, et al. Necrotizing cutaneous mucormycosis after a tornado in Joplin, Missouri, in 2011. *N Engl J Med*. 2012;367(23):2214–2225. doi:10.1056/NEJMoa1204781
25. Warkentien T, Rodriguez C, Lloyd B, et al. Invasive mold infections following combat-related injuries. *Clin Infect Dis*. 2012;55(11):1441–1449. doi:10.1093/cid/cis749
26. Skiada A, Petrikkos G. Cutaneous zygomycosis. *Clin Microbiol Infect*. 2009;15(Suppl 5):41–45. doi:10.1111/j.1469-0691.2009.02979.x
27. Petrikkos G, Skiada A, Lortholary O, et al. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis*. 2012;54(Suppl 1):S23–34. doi:10.1093/cid/cir866
28. Lanternier F, Dannaoui E, Morizot G, et al. A global analysis of mucormycosis in France: the RetroZygo Study (2005–2007). *Clin Infect Dis*. 2012;54(Suppl 1):S35–43. doi:10.1093/cid/cir880
29. Sun HY, Aguado JM, Bonatti H, et al. Pulmonary zygomycosis in solid organ transplant recipients in the current era. *Am J Transplant*. 2009;9 (9):2166–2171. doi:10.1111/j.1600-6143.2009.02754.x
30. Park BJ, Pappas PG, Wannemuehler KA, et al. Invasive non-aspergillus mold infections in transplant recipients, United States, 2001–2006. *Emerg Infect Dis*. 2011;17(10):1855–1864. doi:10.3201/eid1710.110087
31. Krishnappa D, Naganur S, Palanisamy D, et al. Cardiac mucormycosis: a case report. *Eur Heart J Case Rep*. 2019;3(3).
32. Naumann R, Kerkmann ML, Schuler U, et al. Cunninghamella bertholletiae infection mimicking myocardial infarction. *Clin Infect Dis*. 1999;29 (6):1580–1581. doi:10.1086/313537
33. Balaguer JM, Soto E, Perry D, et al. Postoperative intramyocardial abscess caused by mucormycosis. *Ann Thorac Surg*. 1994;58(6):1760–1762. doi:10.1016/0003-4975(94)91684-5
34. Zhang R, Zhang JW, Szerlip HM. Endocarditis and hemorrhagic stroke caused by Cunninghamella bertholletiae infection after kidney transplantation. *Am J Kidney Dis*. 2002;40(4):842–846. doi:10.1053/ajkd.2002.35698
35. Basti A, Taylor S, Tschopp M, et al. Fatal fulminant myocarditis caused by disseminated mucormycosis. *Heart*. 2004;90(10):e60. doi:10.1136/hrt.2004.038273
36. Mehta NN, Romanelli J, Sutton MG. Native aortic valve vegetative endocarditis with Cunninghamella. *Eur J Echocardiogr*. 2004;5(2):156–158. doi:10.1016/j.euje.2003.09.001
37. Saşmaz I, Leblebisatan G, Antmen B, et al. Cardiac mucormycosis in a child with severe aplastic anemia: a case report. *Pediatr Hematol Oncol*. 2006;23(5):433–437. doi:10.1080/08880010600692138
38. Gubarev N, Separovic J, Gasparovic V, et al. Successful treatment of mucormycosis endocarditis complicated by pulmonary involvement. *Thorac Cardiovasc Surg*. 2007;55(4):257–258. doi:10.1055/s-2006-924502
39. Shah S, Suresh PV, Maheshwari S, et al. Cardiac mucormycosis with T-cell immunodeficiency. *Indian Pediatr*. 2009;46(3):257–259.
40. Metallidis S, Chrysanthidis T, Kazakos E, et al. A fatal case of pacemaker lead endocarditis caused by Mucor spp. *Int J Infect Dis*. 2008;12(6): e151–2. doi:10.1016/j.ijid.2008.03.034
41. Chinen K, Matsumoto H, Fujioka Y. Cardiac mucormycosis presenting as a "fungus ball" in the left atrium. *Intern Med*. 2009;48(19):1781–1782. doi:10.2169/internalmedicine.48.2611
42. Mitchell ME, McManus M, Dietz J, et al. Absidia corymbifera endocarditis: survival after treatment of disseminated mucormycosis with radical resection of tricuspid valve and right ventricular free wall. *J Thorac Cardiovasc Surg*. 2010;139(4):e71–2. doi:10.1016/j.jtcvs.2008.07.073
43. Dwarakanath S, Kumar V, Blackburn J, et al. A rare case of multi-chambered fungal endocarditis from a virulent Cunninghamella infection. *Eur Heart J*. 2014;35(6):343. doi:10.1093/eurheartj/eht444
44. Ferreira D, Davies A, Thiruchelvam T, et al. Acute myocardial infarction in disseminated mucormycosis infection. *Eur Heart J*. 2017;38(11):838. doi:10.1093/eurheartj/ehw517
45. Nawata T, Kubo M, Kobayashi S, et al. Mucormycete Infiltration in the Cardiac Conduction System. *Can J Cardiol*. 2018;34(1):92.e9–92.e10. doi:10.1016/j.cjca.2017.10.002

46. Naik CA, Mathai SK, Sandkovsky US, et al. Acute myocardial infarction secondary to mucormycosis after lung transplantation. *IDCases*. 2021;23:e01019. doi:10.1016/j.idcr.2020.e01019
47. Hagemann JB, Furitsch M, Wais V, et al. First case of fatal Rhizomucor miehei endocarditis in an immunocompromised patient. *Diagn Microbiol Infect Dis*. 2020;98(2):115106. doi:10.1016/j.diagmicrobio.2020.115106
48. Mita A, Hirano S, Uehara T, et al. Fatal disseminated mucormycosis due to Cunninghamella bertholletiae infection after ABO-incompatible living donor liver transplantation: a case report. *Surg Case Rep*. 2022;8(1):164. doi:10.1186/s40792-022-01516-4
49. Shintaku M, Yamada E, Ohta M, et al. Disseminated Cunninghamella bertholletiae mucormycosis with protracted clinical course and formation of a large intra-ventricular mural thrombus. *Int J Clin Exp Pathol*. 2022;15(5):233–237.
50. Kitazawa S, Kitazawa R. Acute myocardial infarction caused by coronary mucormycotic embolism. *IDCases*. 2023;31:e01686. doi:10.1016/j.idcr.2023.e01686
51. Soliman M, Harding C, El Haddad H, et al. Disseminated mucormycosis with extensive cardiac involvement. *Cureus*. 2019;11(5):e4760. doi:10.7759/cureus.4760
52. Jackman JD, Simonsen RL. The clinical manifestations of cardiac mucormycosis. *Chest*. 1992;101(6):1733–1736. doi:10.1378/chest.101.6.1733
53. Fowler VG, Durack DT, Selton-Suty C, et al. The 2023 Duke-International Society for cardiovascular infectious diseases criteria for infective endocarditis: updating the modified Duke Criteria. *Clin Infect Dis*. 2023;77(4):518–526. doi:10.1093/cid/ciad271
54. Hsieh TT, Tseng HK, Sun PL, et al. Disseminated zygomycosis caused by Cunninghamella bertholletiae in patient with hematological malignancy and review of published case reports. *Mycopathologia*. 2013;175(1–2):99–106. doi:10.1007/s11046-012-9595-y
55. Sipsas NV, Gamaletsou MN, Anastasopoulou A, et al. Therapy of mucormycosis. *J Fungi*. 2018;4(3).