Pulmonary mucormycosis after heart transplantation: an uncommon case report

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ABSTRACT

Background: Mucormycosis (MCR) is an uncommon but frequently deadly fungal infection that typically affects individuals with weakened immune systems. Pulmonary MCR, in particular, is most frequently observed in patients who have undergone stem cell or solid organ transplants. The incidence of MCR in solid organ transplant recipients is reported to be 0.07% within the first year. In almost 40% of these transplant patients, including the case we examined, the infection is diagnosed within the first 6 months after the transplant.

Case Presentation: We report a rare case of a 67-year-old man who developed pulmonary MCR within 6 months after undergoing a heart transplant. A bronchoscopy was conducted, and Reverse transcription polymerase chain reaction along with cultures of the broncho-alveolar samples tested positive for Mucorales. After consulting with experts from thoracic and vascular surgery, cardiology, pulmonology, and microbiology, and adhering to the expert guidelines, a semi-urgent source control procedure was recommended. This involved performing a thoracoscopic exploration of the right pleura, which was subsequently converted to a lateral thoracotomy, culminating in the resection of the right lower lobe.

Conclusion: Invasive MCR is a rare but serious fungal infection with a high risk of illness and death, particularly in people with underlying health issues or weakened immune systems. The clinical and imaging manifestations can vary among patients based on their immune status and how they contracted the infection. Despite these variations, it is vital to maintain a high level of suspicion for MCR, as early diagnosis and the rapid initiation of surgical and antifungal treatments are critical for improving survival chances.

Keywords: Case report, mucormycosis, pulmonary mucormycosis, heart transplantation.

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Background

Mucormycosis (MCR) is a rare opportunistic fungal infection, albeit often with lethal consequences. Transplant recipients, patients with hematologic malignancies, or poorly controlled diabetics are particularly susceptible to this group of infections [1]. Invasive MCR infections are only present in fewer than 1% of heart transplant recipients [3]. Inhalation of environmental spores of *Mucor* spp. can cause various forms of MCR. The most common predilection sites are rhino-orbital/cerebral (34%), cutaneous (22%), and pulmonary (20%) MCR; often with infarction and necrosis of affected tissues [6]. Over the past 15 years, the number of cases has risen alarmingly. The almost doubled incidence of MCR in many transplant centers has been associated with the introduction and extensive use of voriconazole prophylaxis in these vulnerable groups [4]. Early diagnosis of MCR remains critically important, although clinical and radiological tests often lack sensitivity and specificity. Diagnosis of MCR is based on PCR of fungal DNA, culturing the causative microorganism, and tissue histology. Currently, however, there are no specific serological tests for the diagnosis of MCR [8]. Urgent early surgical and medical interventions are crucial and sometimes lifesaving, although overall mortality remains very high. The cornerstones in the treatment of MCR are the management of underlying detrimental prognostic factors, e.g., neutropenia and hyperglycemia, early initiation of effective antifungal therapy, and in a considerable number of cases, surgical debridement of affected tissues [9].

We here present a case of a 67-year-old man who was diagnosed with pulmonary MCR within the first 6 months after heart transplantation.

Case Presentation

A 67-year-old patient presented in mid-March 2024 at the cardiology outpatient ward for a routine check-up following heart transplantation. He reported general malaise and illness. Bloodwork revealed a strongly elevated C-reactive

protein (CRP) level up to 250 mg/l (Ref. ≤5 mg/l). Chest-computed tomography (CT) showed pneumonia in the right lower lobe, for which empirical treatment with piperacillin-tazobactam (3 × 4 g/day) was initiated. An initial bronchoscopy showed intact endobronchial lumina with commensal flora. Due to biochemical and clinical deterioration, a repeat bronchoscopy was performed within a week and revealed clear infectious lesions in the right lower lobe. Reverse transcription polymerase chain reaction (RT-PCR) and cultures of the sampled broncho-alveolar material were positive for Mucorales. Empirical treatment with Amphotericin B (5 mg/kg) was initiated.

Initially, there was a swiftly favorable evolution under Amphotericin B, but after 2 weeks of therapy, there was the re-emergence of fever and clinical deterioration. Subsequent repeated chest-CT imaging showed a large cavitating mass (Figure 1). To cover potential bacterial surinfection, meropenem (2 g/24 hours in continuous IV infusion) was started, and vancomycin (500 mg/24 hours in continuous IV infusion, with a creatinine of 2.85) was also associated due to blood cultures positive for *Enterococcus faecium*. Following multidisciplinary consultation (thoracic and vascular surgery, cardiology, pulmonology, and microbiology), and in line with available expert guidelines, the decision was made to proceed with semi-urgent source control. Therefore, video-assisted thoracoscopy was planned.

A thoracoscopic exploration of the right pleura was performed, followed by conversion to a lateral thoracotomy and the performance of a right lower lobe resection with drainage of a large transdiaphragmatic abscess (Figure 2). Figure 3 shows the intraoperative findings of a large transdiaphragmatic abscess with a fistulous tract to the suprahepatic space. Extensive irrigation was carried out with warm saline and povidone-iodine for 30 minutes. A chest drain was left in place in the pleura, and a Blake drain (drain with multiple drainage routes) was positioned suprahepatically (intra-abdominally) through the diaphragmatic defect.

Postoperatively, there was a favorable clinical and biochemical evolution with the removal of drains guided by appearance and output. Antibiotic therapy could be de-escalated to amoxiclav (4 × 1 g/day) and metronidazole (3 ×

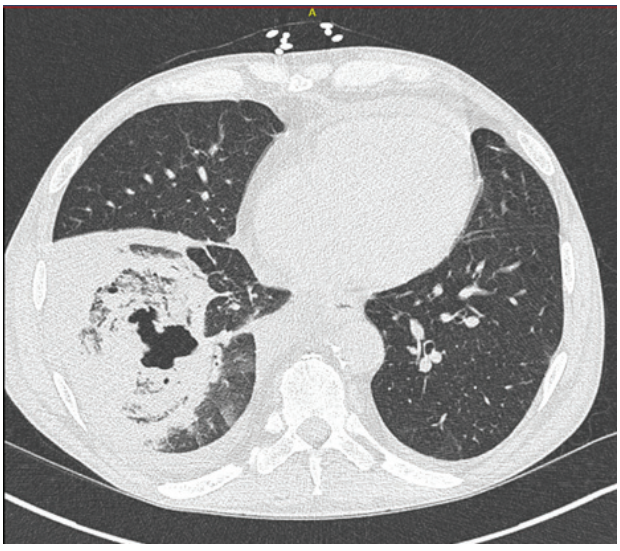

Figure 1. *CT chest: evolving cavitating mass.*

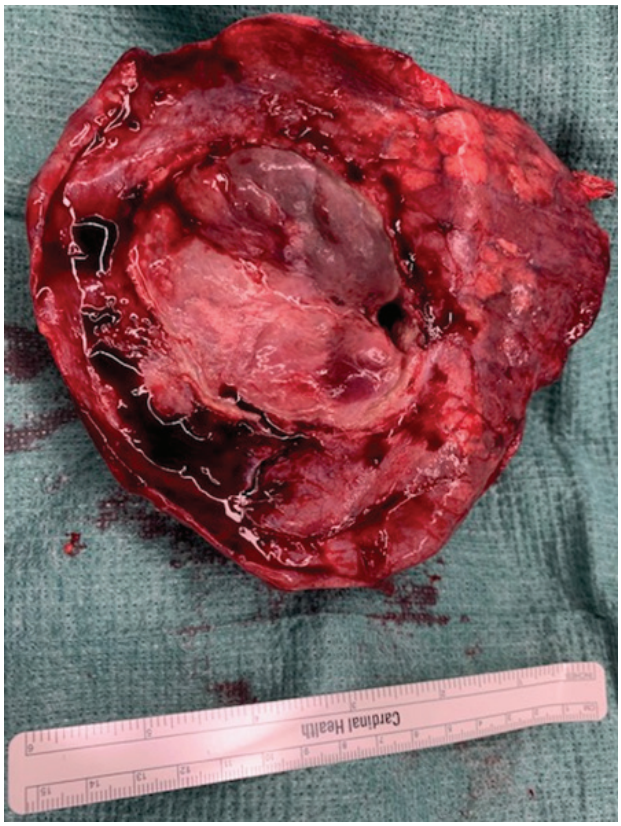

Figure 2. *Right lower lobe resection.*

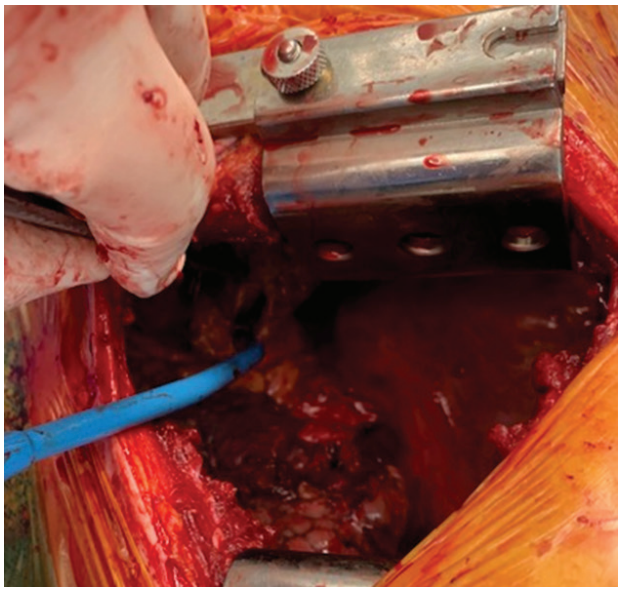

Figure 3. *Fistulous tract from chest cavity to the suprahepatic space.*

500 mg/day) based on the intraoperative cultures, which were positive for *Rhizopus microsporus*, *Enterococcus faecium*, and *Veillonella*. For the next 3 weeks, the patient was doing well, still recovering but without any abdominal complaints. Several bronchoscopies have been performed in the context of mucopurulent sputum and have shown good healing of the sutures after resection. Unfortunately, the patient died due to *Pseudomonas* sepsis at the intensive care department.

In September 2023, the man underwent a heart transplantation due to underlying end-stage ischemic cardiomyopathy with terminal heart failure. Postoperatively, immunosuppressive medications were administered according to protocol, including grafalon, mycophenolic acid (Cellcept) (2 × 1,000 mg/day), tacrolimus (Prograft) 2 × 2 mg, and solu-Medrol 3 × 125 mg IV at day 1, followed by a tapering dose of 20 mg daily.

There was a Cytomegalovirus (CMV) mismatch (the donor was CMV positive while the recipient was negative), leading to the prophylactic intravenous administration of Megalotect until serial PCR tests were negative three times in a row.

However, the initial hospitalization course for heart transplantation became more complicated due to the development of acute cholecystitis (acute severe pain in the right hypochondrium with positive Murphy's sign and ultrasonographic findings of sludge with small gallstones and gallbladder wall thickening) 2 weeks postoperatively. An urgent laparoscopic cholecystectomy was performed. Postoperatively, there was a deterioration in the patient's overall condition with diffuse pain complaints. High-resolution CT showed no pneumonia, but abdominal ultrasound revealed a heterogenous fluid collection at the site of the gallbladder bed. Two successful ultrasound-guided punctures were performed (due to recurrent collection). Persistent bile leakage after drain placement necessitated an endoscopic retrograde cholangiopancreatography, which showed an incomplete clipping of the cystic duct. Extended drainage with removal of the drain after 3 weeks led to favorable clinical and biochemical evolution until discharge.

The question remains whether the development of right lower lobe MCR with fistulisation from/towards the right hepatic region is related to prolonged biliary drainage after cholecystectomy.

Discussion and Literature Review

Fungi are widespread in the environment and play a crucial role in the ecosystem and biodiversity because they are essential for nutrient cycling and waste recycling. It is estimated that there are 1.5 million different species of fungi, of which only about 300 are known to cause diseases in humans [1].

MCR is caused by fungi belonging to the order Mucorales (Rhizopus (in our patient), Mucor, and Lichtheimia (formerly Absidia), which account for >90% of all cases of MCR [2].

Pulmonary MCR is most commonly seen in immunosuppressed patients, mainly in those with stem cell transplants or solid organ transplants. The reported incidence of MCR in recipients of solid organ transplants is 0.07% after 1 year. In nearly 40% of such transplant patients, as in our case, the diagnosis was made within the first 6 months post-transplantation [11].

In recent years, there has been an increase in the number of cases, attributed to the use of voriconazole prophylaxis [5]. However, it is not known whether this association really has an epidemiological link or if it is rather a result of the evolution of transplantation methods and immunosuppression strategies. The existence of voriconazole in both oral and injectable forms allows for prolonged antifungal treatment in patients with significant immunosuppression. One might hypothesize that patients, by not developing aspergillosis during the post transplantation period, can later develop MCR in the context of ongoing immunosuppression and exposure to high-dose corticosteroids. Conversely, it is possible that metabolic factors associated with transfusions and prolonged treatment with high doses of corticosteroids (i.e., iron overload and hyperglycemia) could independently promote the development of MCR, irrespective of exposure to voriconazole, in these chronically immunosuppressed patients [6].

Patients typically present with fever, dyspnea, cough, and sometimes massive hemoptysis. On chest CT imaging, pulmonary MCR may show a "reverse halo sign" (a central area of ground-glass necrosis encircled by consolidation), but it is more commonly identified by nonspecific pleural effusions and pulmonary nodules, complicating the noninvasive diagnosis of MCR [10].

MCR is the most angioinvasive among all fungal diseases, characterized by extensive tissue invasion and tissue destruction [7]. Historically, approaches to managing MCR have been tailored individually for each case. However, a recent guideline from the European Confederation of Medical Mycology recommends high-dose liposomal amphotericin B as the first-line treatment, with IV isavuconazole or posaconazole as second-line therapies. Early surgical debridement is recommended, both to manage the infection source and to confirm the diagnosis [8].

In this case, the patient received amphotericin B high dose according to the recommendations. Due to clinical deterioration, meropenem and vancomycin were added to cover potential secondary infection. Surgical debridement was performed as soon as possible. What distinguishes this case is the patient's medical background. The hospitalization following the heart transplant had already been prolonged due to acute cholecystitis, which later resulted in the formation of a collection caused by a bile leak. It is still unclear whether the formation of a right lower lobe

MCR that connects to the right hepatic area is associated with extended biliary drainage following cholecystectomy.

Conclusion

Invasive MCR is an uncommon yet severe fungal infection that carries a significant risk of morbidity and mortality (40%-80%), especially in individuals with pre-existing health conditions or compromised immune systems. Clinical and imaging findings may differ among patients, depending on their immune health and how the infection was contracted. Nonetheless, maintaining a high index of suspicion for the infection is crucial, as prompt detection and swift commencement of surgical and antifungal treatments are essential for enhancing survival rates. Previous cases of pulmonary MCR in post-heart transplant patients have been documented; however, there is still a lack of robust evidence for direct management, especially concerning immunosuppression.

List of Abbreviations

CMV	Cytomegalovirus
CRP	C-reactive protein
CT	Computed tomography
MCR	Mucormycosis
RT-PCR	Reverse transcription polymerase chain reaction

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written informed consent was obtained from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of case

1	Patient (sex, age)	67 years, male
2	Final diagnosis	Pulmonary MCR
3	Symptoms	General malaise and illness
4	Medications	Thoracoscopic exploration: right lower lobe resection
5	Clinical procedure	Surgery
6	Specialty	Cardiology