Ezgi Erdal Karakaş https://orcid.org/0000-0003-3437-2294
Sibel Altunışık Toplu https://orcid.org/0000-0002-2915-4666
Sevgi Demiröz https://orcid.org/0000-0002-9836-6814
Mehmet Özcan https://orcid.org/0000-0003-0969-1373
Serdar Karakaş https://orcid.org/0000-0001-8314-7806
Sezai Yılmaz https://orcid.org/0000-0002-8044-0297

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Prolonged Antifungal Therapy and Survival in a Liver Transplant Recipient with Rhino-Orbitocerebral Mucormycosis: A Case Report

Rino-Orbito-Serebral Mukormikozlu Bir Karaciğer Nakli Alıcısında Uzun Süreli Antifungal Tedavi ve Sağkalım: Olgu Sunumu

Erdal Karakaş et al. Extended Therapy and Survival in Liver Transplant ROCM

Ezgi Erdal Karakaş[1*], Sibel Altunışık Toplu[1], Sevgi Demiröz[2], Mehmet Özcan[3], Serdar Karakaş[4], Sezai Yılmaz[4]

[1]İnönü University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Malatya, Türkiye
[2]İnönü University Faculty of Medicine, Department of Radiology, Malatya, Türkiye
[3]İnönü University Faculty of Medicine, Department of Pathology, Malatya, Türkiye
[4]İnönü University Faculty of Medicine, Liver Transplant Institute, Department of General Surgery, Malatya, Türkiye

Ezgi Erdal Karakaş MD, İnönü University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Malatya, Türkiye
e_ezgi_95@hotmail.com
0000-0003-3437-2294

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Abstract
Mucormycosis is a rare and rapidly progressive fungal infection associated with high mortality, particularly among immunocompromised individuals. Solid organ transplant recipients remain at risk not only during the early posttransplant period but also during episodes of intensified immunosuppression for rejection. We report the case of a 14-year-old female liver transplant recipient who developed rhino-orbitocerebral mucormycosis that was initially misdiagnosed as a dental abscess and orbital cellulitis. Early clinical suspicion, prompt histopathological confirmation, aggressive surgical management—including enucleation and partial maxillectomy—and prolonged antifungal therapy (liposomal amphotericin B followed by posaconazole) resulted in survival despite cerebral involvement. At 18 months posttransplantation, the patient remains alive and continues antifungal therapy, with radiologically stable residual lesions. This case highlights the importance of maintaining a high index of suspicion, ensuring early diagnostic confirmation, and implementing prolonged, individualized antifungal therapy to achieve favorable outcomes in liver transplant recipients with cerebral mucormycosis.
Keywords: Mucormycosis, liver transplantation, solid organ transplantation, antifungal therapy, cerebral involvement

Öz
Mukormikoz, özellikle immün yetmezliği olan hastalarda görülen, yüksek mortalite ile seyreden nadir ve fulminan bir fungal enfeksiyondur. Solid organ nakli alıcıları, yalnızca erken nakil sonrası dönemde değil, aynı zamanda rejeksiyon tedavisi sırasında uygulanan yoğun immünosupresyon dönemlerinde de risk altındadır. Bu yazıda, başlangıçta dental apse ve orbital selülit olarak yanlış değerlendirilen, rino-orbito-serebral mukormikoz gelişen 14 yaşında bir kadın karaciğer nakli alıcısının olgusu sunulmaktadır. Erken klinik şüphe, hızlı histopatolojik doğrulama, enükleasyon ve parsiyel maksillektomiyi içeren cerrahi debridman ile liposomal amfoterisin B'yi takiben posakonazol ile uygulanan uzun süreli antifungal tedavi, serebral tutulum varlığına rağmen sağkalım ile sonuçlanmıştır. Nakilden 18 ay sonra hasta, radyolojik olarak stabil rezidüel lezyonlar eşliğinde antifungal tedavi altında yaşamını sürdürmektedir. Bu olgu, serebral mukormikoz gelişen karaciğer nakli alıcılarında sağkalımın sağlanmasında yüksek klinik şüphe ve bireyselleştirilmiş, uzun süreli tedavinin önemini vurgulamaktadır.
Anahtar Kelimeler: Mukormikoz, karaciğer nakli, solid organ nakli, antifungal tedavi, serebral tutulum

Introduction

Infections remain among the most frequent complications after liver transplantation (LT) and continue to be a leading cause of posttransplant mortality. Opportunistic infections, particularly invasive fungal diseases, pose a significant threat to transplant recipients who require lifelong immunosuppressive therapy. Although these infections most commonly occur within the first few months after LT—when the intensity of immunosuppression is greatest—they may also develop later during periods of augmented immunosuppressive therapy for acute rejection. Therefore, transplant recipients remain vulnerable to opportunistic infections during both the early and late posttransplant periods.

Invasive mucormycosis is a rare but highly aggressive fungal infection associated with a reported mortality rate of 40%–50%[1,2]. The principal pathogenic genera include Rhizopus, Mucor, Lichtheimia, Syncephalastrum, Saksenaea, Cunninghamella, Rhizomucor, and Apophysomyces[3]. The disease is characterized by angioinvasion leading to vascular thrombosis, hemorrhagic necrosis, and tissue infarction. It may spread contiguously to adjacent anatomical structures or disseminate hematogenously to distant organs[4]. Established risk factors include hematologic malignancies, prolonged neutropenia, uncontrolled diabetes mellitus, solid organ transplantation, extended corticosteroid use, and human immunodeficiency virus infection[5]. Although most cases occur within 3–6 months after transplantation, mucormycosis in liver transplant recipients has frequently been reported as early as the first posttransplant month[5].

Prompt diagnosis and early intervention are critical determinants of outcome. The cornerstone of management consists of reversal of predisposing factors whenever feasible, aggressive surgical debridement, and early initiation of appropriate antifungal therapy. Rhino-orbitocerebral mucormycosis (ROCM) represents a rapidly progressive and life-threatening manifestation, particularly in immunocompromised individuals such as solid organ transplant (SOT) recipients. The present case is notable for the unusually early onset of ROCM following LT. This report emphasizes the need for heightened clinical vigilance for atypical presentations in immunosuppressed patients, as early recognition and coordinated multidisciplinary management are essential to improving survival.

Case Report

A 14-year-old girl with intrahepatic cholestasis underwent living-donor orthotopic LT in October 2023. The procedure was uneventful, and she had no significant comorbidities. Postoperatively, she was monitored in the intensive care unit, where her clinical course remained stable. Standard immunosuppressive therapy consisting of tacrolimus, mycophenolate mofetil, and prednisolone was administered.

On postoperative day 33, she developed a dental abscess and was referred to our clinic one week later. At admission, she was febrile (38 °C) and in moderate clinical condition. Her heart rate was 89 beats/min, and blood pressure was 122/70 mmHg. Physical examination revealed marked swelling, erythema, and warmth in the right periorbital region. The right eyelid was severely edematous, completely closed, and tender on palpation. A hemorrhagic superficial erosion was also observed on the right nasal ala, raising suspicion for mucormycosis. The remainder of the systemic examination was unremarkable. Laboratory investigations showed leukocytosis with a white blood cell count of 21,850/mm³ (89% neutrophils), elevated C-reactive protein (16.2 mg/dL; reference range: 0–0.5 mg/dL), and procalcitonin of 0.53 ng/mL. Based on the presumptive diagnoses of orbital cellulitis and mucormycosis, empiric intravenous therapy with piperacillin–tazobactam (4.5 g four times daily), teicoplanin (400 mg twice as a loading dose, followed by 400 mg once daily), and liposomal amphotericin B (5 mg/kg/day) was initiated.

For further evaluation of orbital involvement, the ophthalmology team performed cranial and orbital magnetic resonance imaging, and the otolaryngology team obtained paranasal computed tomography. On postoperative day 41, imaging demonstrated right orbital proptosis; soft tissue densities extending into the periorbital region and temporal fossa; thickening of the extraocular muscles; heterogeneity of the intraconal fat; and a focal lesion in the right lateral pons. A biopsy of the nasal mucosa revealed gray–brown necrotic tissue fragments measuring 0.2–1.0 cm. Histopathological examination using periodic acid–Schiff and Grocott Methenamine Silver staining demonstrated broad, aseptate, ribbon-like hyphae, consistent with mucormycosis (Figure 1).

During the fifth postoperative week, the patient developed right periorbital swelling accompanied by altered mental status. Magnetic resonance imaging (MRI) demonstrated restricted diffusion in the right lateral pons, suggestive of a mycotic embolism. Imaging also revealed involvement of the right periorbital, maxillary, and temporal soft tissues, along with signal abnormalities in the optic nerve and extraocular muscles.

By the sixth postoperative week, follow-up MRI showed abscess formation within the pontine lesion, bilateral dural enhancement, and progressive involvement of the optic nerve and rectus muscles (Figure 2).

At postoperative week 9, partial regression of the pontine lesion was observed; however, new extension into the cavernous sinus, optic canal, and cavernous segment of the internal carotid artery was noted. By the seventh postoperative month, MRI demonstrated further progression along the temporal muscle and trigeminal nerve. The pontine lesion measured approximately 8 × 25 mm, and the right globe was absent following surgical intervention (Figure 3). At 16 months, follow-up MRI revealed radiologically stable residual lesions without evidence of further progression.

On postoperative day 55, the patient underwent endoscopic sinus surgery, right eye enucleation, and partial maxillectomy performed by the ophthalmology and otolaryngology teams. Liposomal amphotericin B therapy was continued for approximately 20 days, along with antibacterial agents, until clinical stabilization was achieved; antibacterial therapy was subsequently discontinued. Due to persistent cranial involvement, liposomal amphotericin B was maintained until discharge. On postoperative day 140, the patient was discharged on oral posaconazole (300 mg/day). Because radiological evidence of residual cranial infection persisted, antifungal therapy was continued. At 18 months posttransplantation, she remains under regular outpatient follow-up and continues long-term antifungal treatment.

Discussion

Mucormycosis is a rare opportunistic fungal infection most commonly caused by *Rhizopus*, *Rhizomucor*, and *Cunninghamella* species. In SOT recipients, the reported incidence ranges from 0.4% to 16%, whereas in liver transplant recipients, the incidence is generally lower (0%–2%)[6,7]. Although invasive mold infections typically occur later after transplantation, mucormycosis can also develop during the early posttransplant period[8]. The mean time to onset has been reported as approximately 2.7 months after

transplantation. However, a 2024 tertiary-center case series of invasive fungal infections in SOT recipients documented mucormycosis in a kidney transplant recipient as early as postoperative day 61[8,9].

Several risk factors predispose liver transplant recipients to mucormycosis, including high-dose corticosteroid therapy, neutropenia, renal failure, prior antifungal prophylaxis with voriconazole or caspofungin, cholestasis, multiple blood transfusions, bacterial coinfections, and retransplantation[10,11]. In SOT recipients, the most frequently involved sites are the paranasal sinuses (39%), lungs (24%), skin (19%), central nervous system (9%), and gastrointestinal tract (7%)[12]. Rhino-orbital or rhinomaxillary mucormycosis typically originates in the nasal cavity and extends to the paranasal sinuses, ethmoid air cells, and sphenoid sinuses. Therefore, in transplant recipients presenting with fever, maxillary swelling, or radiologic evidence of sinus opacification, mucormycosis should be strongly considered.

The present case is notable for the unusually early development of ROCM following LT. Although mucormycosis has traditionally been described in the late posttransplant period, this case highlights the need for heightened clinical suspicion even during the early phase, particularly when patients present with atypical features such as dental abscess or orbital cellulitis.

Cerebral mucormycosis usually occurs via contiguous spread from the paranasal sinuses to the orbit and brain and is associated with high mortality. Retroorbital fungal foci causing pain have rarely been reported[13], and such extension frequently results in cavernous sinus thrombosis and death. Notably, our patient survived despite cerebral involvement, which is typically associated with a poor prognosis. Mortality rates remain substantial, with 90-day survival reported at only 50%–60% despite aggressive surgical and antifungal therapy[14]. The favorable outcome in our patient may be attributed to early clinical suspicion, prompt diagnostic confirmation, timely initiation of appropriate antifungal therapy, and aggressive surgical intervention.

The optimal duration of antifungal therapy for mucormycosis remains undefined. Current guidelines recommend continuation of treatment until complete resolution of clinical symptoms and radiologic abnormalities, with regular reassessment[14]. Decisions regarding treatment discontinuation should be individualized and generally require evidence of complete surgical debridement, adequate clinical response, and absence of fungal elements on follow-up evaluation. In our patient, antifungal therapy was ongoing at 18 months posttransplantation. To our knowledge, this represents only the second reported case of ROCM in a liver transplant recipient successfully managed with combined antifungal therapy and radical surgical intervention[14]. Recent studies continue to demonstrate that although mucormycosis in SOT recipients is uncommon, it is associated with considerable mortality, underscoring the critical importance of early recognition and combined surgical–antifungal management strategies[15,16].

Conclusion

ROCM is a rare, acute, and aggressive infection that predominantly affects immunocompromised patients, including those with diabetes, malignancy, or solid organ transplantation. Its angioinvasive nature is associated with high morbidity and mortality. Optimal management is based on three key principles: early and radical surgical debridement, control of predisposing factors, and prompt initiation of effective antifungal therapy.

Invasive fungal infections following LT require a high index of suspicion, early imaging, rapid mycological confirmation, and timely multidisciplinary intervention. This case underscores that even in immunosuppressed patients presenting with nonspecific symptoms, early recognition and aggressive management are critical for improving survival. Furthermore, it highlights the importance of individualized, prolonged antifungal therapy in achieving favorable outcomes in liver transplant recipients with cerebral mucormycosis.

Ethics

Informed Consent:

Footnotes

Authorship Contributions

Surgical and Medical Practices:
Concept:
Design:
Data Collection or Processing:
Analysis or Interpretation:
Literature Search:
Writing:

Conflict of Interest: The author(s) declare no conflict of interest.

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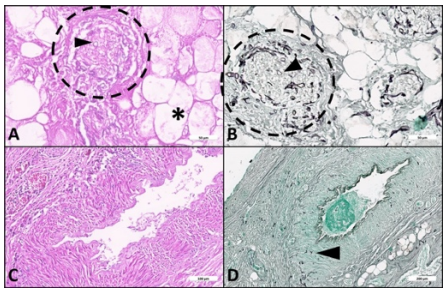

A, B, C, D KÜÇÜK OLSUN

Figure 1. Histopathological findings of nasal mucormycosis. (a) Ischemic mucosa and submucosal tissue demonstrating broad, ribbon-like fungal hyphae (arrowhead), also observed within an intravascular space (circled) (H&E stain; ×200). (b) GMS stain of the region shown in panel a highlighting fungal hyphae in both intravascular (circled) and perivascular areas (×200). (c) A large submucosal vascular structure exhibiting perivascular ischemic changes without clearly identifiable fungal elements (H&E stain; ×100). (d) GMS staining of the region shown in panel c revealing distinctly visible fungal hyphae (arrowhead) (×50).
GMS, Grocott Methenamine Silver; H&E, hematoxylin and eosin.

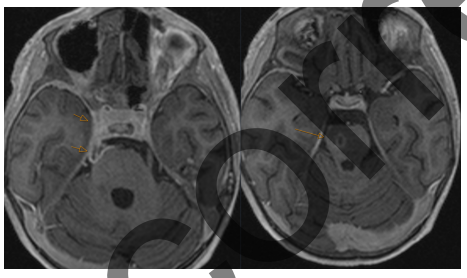

Figure 2. Contrast-enhanced T1-weighted fat-saturated magnetic resonance images obtained two days apart demonstrating progressive right orbital proptosis and extension of the mucormycosis lesion into the cavernous sinus (arrow).

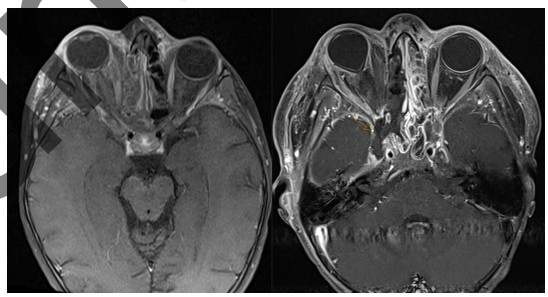

Figure 3. Follow-up contrast-enhanced T1-weighted fat-saturated magnetic resonance image obtained after right eye enucleation demonstrating linear enhancement along the trigeminal nerve (left image) and a peripherally enhancing abscess within the pons, consistent with disseminated mucormycosis.