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Case report

Breaking the mold: Insights into the clinical management and outcomes of rhinocerebral mucormycosis in adults

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ABSTRACT

Background: Rhinocerebral mucormycosis is a rare, life-threatening fungal infection that affects the sinuses, nasal passages, and brain. Its management remains challenging owing to high mortality rates. Combination antifungal therapy is an area of ongoing research aimed at improving outcomes. We aimed to describe the clinical management and outcomes of patients with rhinocerebral mucormycosis who were treated with antifungal combination therapy.

Methods: This retrospective case series included 10 patients diagnosed with rhinocerebral mucormycosis at two academic medical centers between January 2008 and July 2023 who received initial antifungal therapy with liposomal amphotericin B (L-AmB), alone or in combination, within 24 h of diagnosis. Clinical data were extracted from the medical records.

Results: Most patients were males (70 %) with uncontrolled diabetes (71.4 %). L-AmB was used as the initial therapy in all patients, either as monotherapy (n = 4) or combination therapy (n = 6), followed by posaconazole maintenance. The combinations included L-AmB with posaconazole (n = 4), L-AmB with micafungin (n = 3), or both (n = 3). The overall mortality rate was 50 %. Survivors had high morbidity, with median 31-day hospitalizations and 50 % readmission rate.

Conclusions: Despite aggressive management, rhinocerebral mucormycosis has high mortality and morbidity rates. While combination antifungal therapy aims to improve cure rates, our case series showed higher mortality rates than monotherapy. Additional research is warranted to optimize management approaches for this devastating infection.

Introduction

Rhinocerebral mucormycosis is a rare and life-threatening fungal infection that primarily affects the sinuses, nasal passages, and the brain. It predominantly affects individuals with underlying conditions such as uncontrolled diabetes, immunocompromised status, hematological malignancies, and organ transplantation [1]. Its diagnosis can be challenging owing to its nonspecific clinical presentation and lack of specific diagnostic tests. Prompt diagnosis and aggressive treatment are imperative to improve patient outcomes [2]. Specifically, the core of treatment comprises surgical debridement to eliminate infected necrotic tissue, along with antifungal therapy.

Liposomal amphotericin B (L-AmB) is the recommended first-line treatment for mucormycosis. However, it carries a high risk of nephrotoxicity, which may increase with prolonged use [3]. As such, it poses challenges in the management of this infection that can rapidly progress to a potentially fatal outcome. Alternative treatment strategies have been employed in real-world clinical practice, without much description of their associated outcomes.

In animal models, some antifungal combinations have shown the

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potential to improve cure and survival rates without antagonism [4,5]. Moreover, the results of some patient series are promising [6,7]. However, the optimal approach for combination antifungal therapy remains to be determined. This study aimed to describe the clinical management of rhinocerebral mucormycosis using a case series approach, with a particular emphasis on the role of combination antifungal therapy in patient outcomes.

Methods

Study design

This retrospective case series included patients diagnosed with rhinocerebral mucormycosis at the University of New Mexico Health Sciences Center (UNM HSC) and Medical Information Mart for Intensive Care (MIMIC)-IV database between January 1, 2008, and July 31, 2023. This study was approved by the Human Research Review Committee of the UNM HSC. The requirement for informed consent was waived owing to the retrospective nature of the study.

Study population and data collection

Patients were identified by searching the diagnostic codes for mucormycosis and fungal sinusitis in the electronic medical records and MIMIC-IV database. Additionally, Theradoc clinical surveillance software was used to identify culture-positive mucormycosis cases in UNM HSC. Clinical data were extracted from medical records and the database. To assess the level of comorbidities at the time of mucormycosis diagnosis, we calculated the Charlson comorbidity index (CCI) for each patient.

Patients were included if they were $\geq$ 18 years of age and had a confirmed histopathological or microbiological diagnosis of rhinocerebral mucormycosis caused by fungi within the Mucorales order. Patients were excluded if they did not receive initial treatment with L-AmB (alone or in combination) within 24 h of diagnosis, were incarcerated, if a non-Mucorales mold was isolated, if the mucormycosis diagnosis was presumed and not confirmed, or if the site of infection was not rhinocerebral.

Definitions

Rhinocerebral mucormycosis was defined as the presence of Mucorales fungal infection involving the sinuses, oral cavity, or adjacent structures including the eyes and/or brain. Severe COVID-19 was defined as an oxygen saturation $<$ 94 % and requiring hospitalization within six months prior to the index encounter. Acute kidney injury (AKI) was defined as an increase in serum creatinine by $\geq$ 0.3 mg/dL within 48 h or an increase to $\geq$ 1.5 $\times$ from baseline within the last seven days of antifungal initiation. Drug-induced liver injury (DILI) was defined as alanine aminotransferase (ALT) $\geq$ 5 $\times$ the upper limit of normal (ULN) or ALT $\geq$ 3 $\times$ ULN and total bilirubin $\geq$ 2 $\times$ ULN occurring after antifungal initiation.

Statistical analysis

Statistical analyses were performed using R, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). Normally distributed variables were reported as mean (standard deviation [SD]) values, non-normally distributed variables were reported as median (interquartile range [IQR]) values, and frequencies and percentages were calculated. No statistical tests were performed.

Results

Ten patients with rhinocerebral mucormycosis were included in the study. Most patients were male (70 %), with a mean age of 51.7 years (SD 15.8) and a median CCI of 3 (IQR 2, 4). The most common comorbidity was diabetes (70 %), and many of these patients had uncontrolled disease (71.4 %), with a mean hemoglobin A1c level of 11.8 % (SD 3.74). Other underlying conditions included hematological malignancy (n = 3), neutropenia (n = 2), hematopoietic stem cell transplantation (n = 1), solid organ transplantation (n = 1), high-dose corticosteroids (n = 1), and COVID-19 (n = 1). Table 1 shows patient demographics and baseline characteristics.

The median time to presentation was seven days (IQR 4, 13.8), with facial edema being the most common symptom (70 %). The median time to diagnosis was 2.5 days (IQR 1, 4.8) and the median hospitalization was 31 days (IQR 17, 37.3). In 50 % of patients, the infection was limited to the sinuses, while 40 % had rhino-orbital-cerebral involvement, and 10 % had rhino-cerebral involvement. Of the discharged patients, 50 % had at least one hospital readmission and one (10 %) died during the 2-year follow-up period. One patient was discharged to hospice care and survival after discharge was unknown. Four patients (40 %) died before discharge.

Of the 80 % of patients who underwent endoscopic surgery, 62.5 % had open surgical debridement, and all confirmed cases of mucormycosis were diagnosed based on histopathological findings. Two patients were diagnosed using only tissue culture. *Rhizopus* species were the most common fungi identified (60 %), followed by *Rhizomucor* (30 %). The infection characteristics of the patients are presented in Table 2.

L-AmB was the first and most used antifungal agent (100 %), either as monotherapy or combination therapy, followed by posaconazole (80 %). The mean antifungal durations were 11 days (SD 12.9) and 374 days (SD 616.7), respectively. Two patients received L-AmB followed by an azole (20 %). Some patients received multiple forms of combination therapy. The most common combination was L-AmB and posaconazole (n = 4, 40 %), lasting 14.9 days (SD 18.9) on average. Three patients (30 %) received L-AmB and micafungin for 2.2 days (SD 2.5) and were later switched to L-AmB and azole. Three other patients (30 %) concomitantly received L-AmB, posaconazole, and micafungin for an average of 6.3 days (SD 18.8). Among the patients who received monotherapy, 25 %

Table 1
Demographic and baseline characteristics.

Characteristics	Total (n = 10)
Male, n (%)	7 (70)
Age, mean (SD)	51.7 (15.8)
Race, n (%)	
American Indian/Alaska Native	4 (40)
White	3 (30)
African American	1 (10)
Unknown	2 (20)
Not Hispanic/Latino, n (%)	7 (70)
BMI, n (%)	
Underweight (< 18.5)	1 (10)
Healthy weight (18.5 to < 25)	2 (20)
Overweight (25 to < 30)	3 (30)
Obese (≥ 30)	3 (30)
Unknown	1 (10)
Charlson comorbidity index, median (IQR)	3 (2, 4)
Comorbidities, n (%)	
Diabetes mellitus	7 (70)
Leukemia	3 (30)
Moderate to severe CKD	2 (20)
Congestive heart failure	1 (10)
Solid tumor	1 (10)
Mucormycosis risk factors, n (%)	
Uncontrolled diabetes	5 (50)
Hematologic malignancy	3 (30)
Neutropenia	2 (20)
COVID-19 pneumonia	1 (10)
Hematopoietic stem cell transplantation	1 (10)
Solid organ transplantation	1 (10)
High-dose corticosteroids	1 (10)

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; IQR, interquartile range; SD, standard deviation.

Table 2
Infection characteristics of the cohort.

Characteristics	Total (n = 10)
Hemoglobin A1c% on admission, mean (SD)	11.8 (3.7)
Time to presentation in days, median (IQR)	7 (4, 13.8)
Time to diagnosis in days, median (IQR)	2.5 (1, 4.8)
Admission symptoms[a], n (%)	
Facial edema	7 (70)
Visual disturbances	4 (40)
Nasal congestion or discharge, including epistaxis	3 (30)
Facial pain	3 (30)
Proptosis	3 (30)
Confusion	3 (30)
Headache	1 (10)
Other[b]	5 (50)
Infection sites, n (%)	
Rhinosinusitis	5 (50)
Rhino-orbital-cerebral	4 (40)
Rhino-cerebral	1 (10)
Mucorales species[c], n (%)	
Rhizopus species	6 (60)
Rhizomucor species	3 (30)
Procedure or intervention, n (%)	
Endoscopic sinus surgery	8 (80)
Open surgical debridement	6 (60)
Hospital length of stay in days, median (IQR)	31 (17, 37.2)
Survival on discharge, n (%)	6 (60)
Survival at 2-year follow up, n (%)	5 (50)
Hospital readmissions for index infection, n (%)	5 (50)
Infection recurrence, n (%)	2 (20)

Abbreviations: IQR, interquartile range; SD, standard deviation.
[a] Multiple admission symptoms may have been reported in one patient; therefore, these cells did not contribute to the total number of patients diagnosed with rhinocerebral mucormycosis.
[b] Other admission symptoms included fever in three patients, slurred speech in one patient, and eye pain in another patient.
[c] One patient did not have a positive culture; therefore, these cells did not add to the total number of patients diagnosed with rhinocerebral mucormycosis.

Table 3
Antifungal therapy characteristics.

Characteristics	Total (n = 10)
Initial L-AmB dose, n (%)	
5 mg/kg	8 (80)
> 5–9.9 mg/kg	2 (20)
≥ 10 mg/kg	0 (0)
Antifungal therapies, n (%)	
Monotherapy[a]	4 (40)
Dual therapy	3 (30)
Triple therapy	3 (30)
Monotherapy duration in days, mean (SD)	
L-AmB	11.1 (17.9)
Posaconazole	374.6 (616.7)
Isavuconazole	412.2 (707.8)
Timing of combination therapy start after diagnosis, n (%)	
≤ 3 days	3 (30)
> 3 days	3 (30)
Combination therapies[b], n (%)	
L-AmB + posaconazole	4 (40)
L-AmB + micafungin	3 (30)
L-AmB + isavuconazole	1 (10)
L-AmB + micafungin + posaconazole	3 (30)
Combination therapy duration in days, mean (SD)	
L-AmB + posaconazole	12.9 (18.9)
L-AmB + micafungin	2.2 (2.5)
L-AmB + isavuconazole[c]	6.1 (NA)
L-AmB + micafungin + posaconazole	6.3 (18.8)

Abbreviations: L-AmB, liposomal amphotericin B; NA, not applicable; SD, standard deviation.
[a] Monotherapy refers to the administration of a single antifungal agent. This may also represent cases of sequential therapy.
[b] Some patients received multiple forms of combination therapy and therefore, may be represented more than once.
[c] Standard deviation was not calculated because only one patient received this combination.

died (n = 1), whereas dual therapy (n = 2) and triple therapy (n = 2) had the same death rate of 66.7 %. The antifungal treatment strategies for the cohort are presented in Table 3.

Eight patients received an initial dose of 5 mg/kg L-AmB, one 7.5 mg/kg, and another 8 mg/kg. Dosages were adjusted for four patients; one increased from 5 to 7 mg/kg on day four of treatment, another from 5 to 8.5 mg/kg on day two, then decreased to 6.3 mg/kg on day three and increased to 7.4 mg/kg on day six. Patient three had a dose increase from 5 to 10 mg/kg on day three, followed by a decrease to 5 mg/kg on day four. Patient four had a dose increase from 5 to 10 mg/kg on day two, then decreased to 6 mg/kg on day eight.

Three patients developed additional complications including osteomyelitis (n = 1/10), stroke (n = 1/10), and seizures (n = 1/10). Four patients had L-AmB-associated AKI and one had DILI due to isavuconazole.

Discussion

This case series highlights the difficulties in managing rhinocerebral mucormycosis for which standardized treatment approaches are currently lacking. Our cohort showed a 50 % mortality rate, which is consistent with previous reports [8,9]. Additionally, our patients experienced significant morbidity, including prolonged hospitalization (median 31 days, IQR 17, 37.3) and a 50 % mucormycosis-related readmission rate. Diabetes, prevalent in 70 % of patients and often uncontrolled (mean A1c 11.8 %, SD 3.7), emerged as a significant risk factor.

Uncontrolled diabetes is a well-known risk factor for mucormycosis. In 2021, the International Diabetes Federation estimated that 573 million adults were living with diabetes worldwide, with a projected increase of 210 million by 2045 [10]. As the incidence of diabetes increases, the population most susceptible to mucormycosis continues to rise. The described incidences of mucormycosis and diabetes are mixed overall, with reported higher rates in India, the United States, Iran, and Mexico [11].

Diabetes pathogenesis promotes mucormycosis through altered innate and adaptive immune responses. Elevated glucose levels impact critical defense mechanisms involving neutrophils, dendritic cells, and natural killer cells [12]. Additionally, impaired wound healing and heightened iron and acidosis further contribute to Mucorales growth in uncontrolled diabetes [13,14].

Notably, early and aggressive surgical debridement of necrotic and infected tissues has been associated with improved survival and is considered critical for the treatment of this infection. In a retrospective case series of 90 patients with rhinocerebral mucormycosis who underwent solid organ transplantation, surgical intervention was associated with an 88 % reduction in mortality [15]. Most of our patients underwent endoscopic surgery, open surgical debridement, or both. Among the five deceased patients, one did not undergo any surgical intervention.

L-AmB was used as the primary antifungal at an initial dose of least 5 mg/kg. Although guidelines suggest doses of up to 10 mg/kg (i.e., high-dose) for central nervous system (CNS) infections [16], our cohort did not use high-dose treatment despite evidence of CNS spread in five patients. The AmbiZygo study reported improved response rates in patients receiving high-dose L-AmB and surgical intervention in the first month of treatment [8]. Notably, higher L-AmB doses have been correlated with increased nephrotoxicity rates with no proportional systemic concentration elevation [8,17]. Although guidelines advise L-AmB dose reduction for renal toxicity, they caution against doses below 5 mg/kg [16]. Among our cohort, one individual with AKI had a dose reduction, while three others had unclear reasons for the dose change. Dose reduction and lack of high-dose L-AmB use may have been out of caution in preventing nephrotoxicity and because of provider discomfort with

higher doses for extended periods. The duration of L-AmB administration was highly variable and has been poorly defined in current guidelines [16].

All patients who were discharged alive received azoles for maintenance therapy. Delayed-release posaconazole tablets were the predominant azole (80 %) used alone and in combination therapy, likely owing to their inclusion in the UNM HSC drug formulary, whereas non-formulary isavuconazole was used in only three patients. The total duration of treatment varied significantly from six months to lifelong.

Combination antifungal therapy is an ongoing area of clinical debate. Global guidelines [16] acknowledge the available literature surrounding combination therapy with a polyene backbone plus echinocandin and/or azoles but do not provide recommendations for or against this strategy. Animal studies and a few small retrospective cohorts have compared monotherapy to dual antifungal therapy, showing conflicting effects on survival [4,5,8,18,19]. Data on triple therapy are exceedingly sparse and do not suggest any benefits over monotherapy [20]. In our cohort, three patients received dual therapy and three received triple therapy. Four patients who received combination therapy died; two received dual therapy, and two received triple therapy.

Our data suggest that monotherapy was beneficial compared with combination therapy, with an overall lower mortality rate (25 % vs. 66.7 %, respectively). However, it is difficult to ascertain the true mortality benefit with such a small sample size, lack of statistical tests performed, and possible biases (e.g., survivor bias) in the data. Additionally, it is possible that patients who received combination therapy were sicker or had more advanced disease, prompting the use of combination or salvage therapy.

Poor outcomes with high mortality and morbidity rates highlight the need for standardized management strategies for rhinocerebral mucormycosis. This case series underscores the need for improved management approaches to mitigate high mortality rates. Specifically, the differences between monotherapy and combination therapies warrant further investigation. The ongoing discourse on combination therapies featuring polyene-based variations reinforces the need for additional research to delineate optimal strategies.

Our study has several limitations. First, its retrospective design limited our ability to establish causality or evaluate the efficacy of different treatment strategies. Second, because we did not perform statistical analysis owing to the small sample size, we were unable to determine the best antifungal combination therapy for rhinocerebral mucormycosis. Third, the specific population may limit generalizability, despite a multicenter approach and the inclusion of patients from two institutions. Finally, we acknowledge the influence of formulary considerations on antifungal choices, which may limit the diversity of treatments and the applicability of findings to institutions with different formularies.

Conclusion

In this case series, rhinocerebral mucormycosis was predominant in males with diabetes, with a mortality rate of 50 % and significant morbidity. Variations in antifungal treatment and duration highlight the absence of standardized infection management. Patients with rhinocerebral mucormycosis, irrespective of surgical debridement and antifungal therapy, are prone to hospital readmission and death, emphasizing the critical need for further research to refine therapeutic approaches.

Ethical approval

This study was approved by the University of New Mexico Health Sciences Center.

Consent

Consent was waived due to the retrospective nature of the study. Additionally, some of the patients in this case series we obtained from a deidentified database. Therefore, it would be impossible and unethical for the investigators to re-indentify these patients for the purposes of obtaining consent.

CRediT authorship contribution statement

Nicole L. Hlavacek: Writing – review & editing, Writing – original draft, Data curation. **Michael L. Bernauer:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Nestor R. Sosa:** Writing – review & editing, Writing – original draft. **M Gabriela Cabanilla:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation, Conceptualization. **Elizabeth A. Shald:** Writing – review & editing, Writing – original draft, Data curation.

Declarations of interest

None.

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None.

Author contribution

MGC conceived the original idea and supervised the project. MGC, EAS, NLH and NRS wrote the manuscript. MGC and MLB provided the initial patient datasets, collected data from the MIMIC-IV database, and provided advice on the study methods and design. EAS and NLH collected data from the UNM HSC electronic health records. MLB performed the statistical analyses. All authors discussed the results, reviewed, edited, and provided critical feedback on the manuscript, and approved the final draft.

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