Annals of Hematology (2023) 102:2933–2942
https://doi.org/10.1007/s00277-023-05349-5

ORIGINAL ARTICLE

Lack of surgical resection is associated with increased early mortality in hematological patients complicated with rhino-orbital-cerebral mucormycosis

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Received: 6 March 2023 / Accepted: 28 June 2023 / Published online: 8 July 2023

Abstract

Rhino-orbital-cerebral mucormycosis (ROCM), which is an acute fatal infectious disease with a high mortality rate, is increasingly being diagnosed in patients with hematological diseases worldwide. We aimed to investigate the clinical characteristics, treatment, and prognosis of hematological diseases complicated by ROCM. Our sample comprised a total of 60 ROCM patients with hematological diseases. The most common primary disease was acute lymphoblastic leukemia (ALL) (*n*=27, 45.0%), while 36 patients (60.0%) were diagnosed with a clear type of pathogen, all belonging to the Mucorales, most commonly *Rhizopus* (41.7%). Of the 32 patients (53.3%) who died, 19 (59.3%) died of mucormycosis, and 84.2% (*n*=16) of those died within 1 month. Forty-eight cases (80.0%) received antifungal treatment combined with surgical therapy, 12 of whom (25.0%) died of mucormycosis, amounting to a mortality rate that was significantly lower than in patients who received antifungal therapy alone (*n*=7, 58.3%) (*P*=0.012). The median neutrophil value of patients who underwent surgery was 0.58 (0.11–2.80) 10^3/μL, the median platelet value was 58.00 (17.00–93.00) 10^3/μL, and no surgery-related deaths were reported. Multivariate analysis showed that patient's advanced age (*P*=0.012, *OR*=1.035 (1.008–1.064)) and lack of surgical treatment (*P*=0.030, *OR*=4.971 (1.173–21.074)) were independent prognostic factors.

In this study, hematological diseases associated with ROCM have a high mortality rate. Lack of surgical treatment is an independent prognostic factor for death from mucormycosis. Surgery may therefore be considered in patients with hematological disease even if their neutrophil and platelet values are lower than normal.

Keywords Rhino-orbital-cerebral mucormycosis · Hematological diseases · Immunocompromised · Surgical treatment

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Introduction

Rhino-orbital-cerebral mucormycosis (ROCM) is a rare group of Mucor infections involving the rhino, orbital, and cerebral regions. It has a high morbidity and mortality rate [1] and often results in blindness, ocular necrosis, facial paralysis, and other sequelae, while also being physically and emotionally disabling [2–5]. The exact pathogenesis and mode of transmission of ROCM are unknown, but it is generally believed that the fungus first infects the nasal mucosa and then spreads to the sinuses; it may then spread to the orbit via the crinoid sinus, maxillary sinus, or nasolacrimal duct. If poorly controlled, it can eventually spread to the brain through the orbital vertex, orbital vessels, and crinoid plate [6]. If left untreated, this can have serious short-term consequences.

With the COVID-19 pandemic causing huge numbers of infections worldwide, ROCM has been increasingly diagnosed in recent years, especially in immunocompromised patients with hematological diseases, malignancies, or diabetes mellitus and in transplant recipients [7–9]. Currently, systematic reviews of ROCM in patients with diabetes and organ transplantation are common [10–13], whereas studies on hematological diseases combined with ROCM are relatively rare and tend to be case reports. Although recent studies have indicated higher survival rates in patients with leukemia and ROCM, ranging from 13% to 50% [6], such figures should not necessarily be seen as cause for optimism because of the often delayed diagnosis and rapid progression of the disease [14]. Moreover, due to immunodeficiency, severe granulocytopenia, and thrombocytopenia, there is usually no prospect of surgery, which makes debridement difficult and increases mortality [15]. To assist clinicians in the early identification of hematological diseases associated with ROCM and to determine the value of medical or surgical treatment and the optimal timing to develop effective, targeted treatment plans as early as possible, we analyzed the data of patients published from 2000 onwards to summarize the epidemiological distribution characteristics, clinical symptoms, treatment, and prognosis of ROCM. As illustrated in Fig. 1, we present a suggested pathway for the diagnosis and treatment of patients with hematological diseases complicated by ROCM based on the findings of this study.

Methods

Literature search and case selection criteria

The literature search was limited to cases or case series of ROCM in patients with hematological diseases (both cancer and non-cancer) reported in English. We searched the PubMed database for all mucormycosis cases from 2000 to 2022 using the following keywords: rhino-orbital-cerebral mucormycosis, mucormycosis, ROCM associated with hematological diseases, hematological diseases, leukemia, anemia, myeloma, lymphoma, and hematopoietic stem cell transplantation (HSCT). A total of 655 English-language articles were retrieved using keywords in the literature retrieval system. Of these, 611 were excluded because the site of infection and type of pathogen did not meet the definition of ROCM. Articles reported in languages other than English were also excluded. Finally, a total of 44 articles were included, including 60 cases that met the criteria (Fig. 2). Once this was established, we analyzed cases from published studies. This study did not require approval from an ethics committee.

Diagnosis criteria for ROCM and data extraction

The original case description met the definition of invasive fungal infection [16], and Mucorales was detected from rhino/orbital/cerebral by histological analysis or culture. If patients presented with symptoms of rhino/orbital/cerebral infection and Mucorales was detected by peripheral blood/tissue polymerase chain reaction (PCR) or metagenomic next-generation sequencing (mNGS), the diagnosis was also considered to be established. Year of publication, sex, age, type of hematological disease, method of treatment of hematological disease, prevention of infection, site of mucormycosis, clinical symptoms of mucormycosis, method of diagnosis, type of pathogen, method of treatment, and outcome were extracted from each case.

Statistical and data analysis

Measured data are expressed as median (IQR), and counts are expressed as *n* (%). The association between potential risk factors and mortality was determined using a rank-sum test or chi-squared test in order to perform univariate analyses. Logistic regression analysis was used for multivariate analysis of variables found to be significant in the univariate analysis. The significance level was set at a P value of less than 0.05. Statistical analysis was performed using SPSS version 26.0.

Results

Demography and medical history

A total of 60 cases of hematological disorders with ROCM published since 2000 were included, with basic patient information shown in Table 1. Among these, 37 were males

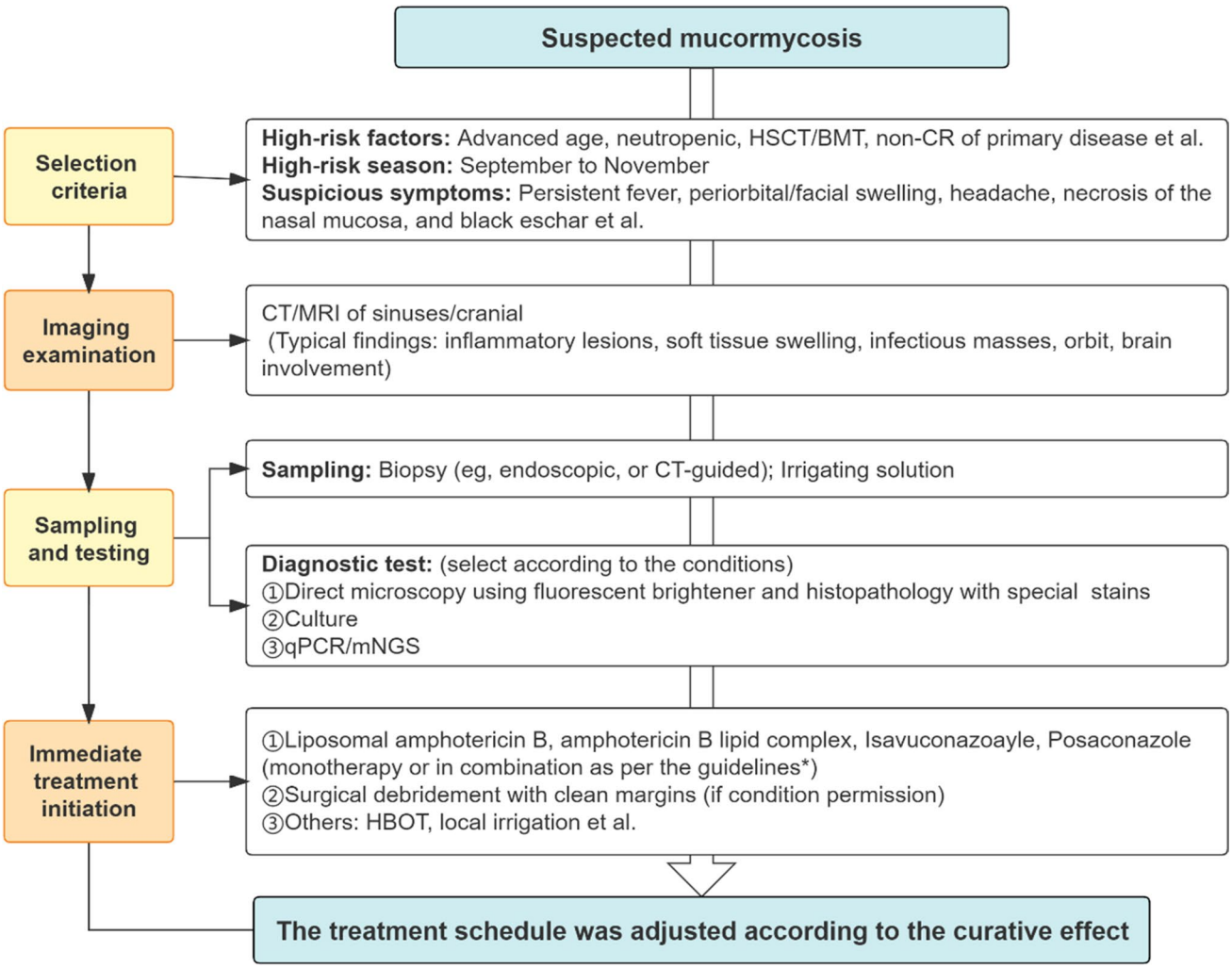

Fig. 1 Diagnostic and treatment pathway for hematological patients with ROCM (Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium [1]*)

(61.6%) with a median age of 30 (IQR, 12–58) years, of whom 21 were minors (35.0%). The most common primary disease was acute lymphoblastic leukemia (ALL) (*n*=27, 45.0%), followed by acute myeloid leukemia (AML) (*n*=14, 23.3%) and lymphoma (*n*=6, 10.0%). There were 14 patients (23.3%) with other underlying diseases, primarily diabetes (*n*=5, 8.3%), trisomy 21 syndrome (*n*=2, 3.3%), and renal failure (*n*=2, 3.3%). Of the 13 patients (21.7%) who reported the time of infection, 6 (46.2%) were infected between September and November as a seasonal peak.

Treatment options for the primary disease included chemotherapy (*n*=35, 58.3%), long-term immunosuppressive therapy (*n*=11, 18.3%), HSCT (*n*=9, 15.0%) etc. Regarding the status of the primary disease, 31 patients (51.7%) were newly diagnosed, and 20 (33.3%) were relapsed. After treatment of the primary disease, complete remission (CR) was achieved in 10 patients (16.7%).

There were 26 patients (43.3%) who received antifungal prophylaxis/treatment prior to ROCM, including fluconazole, voriconazole, AmB, micafungin, caspofungin, and posaconazole. Of the 10 patients (16.7%) who used AmB or posaconazole for antifungal prophylaxis/treatment and then received the treatment dose or drug adjusted, 8 (80.0%) survived.

Sites and symptoms of mucormycosis

The types of infection by site at the time of diagnosis in our review are shown in Fig. 3a. Overall, ROCM was the most common type (*n*=22, 36.6%). There were 17 cases (28.3%) complicated by oral infection, 8 (13.3%) with pulmonary fungal infection, and 3 (5.0%) with oral and pulmonary infections.

In addition to fever, patients with ROCM presented with periorbital swelling (23.3%, *n*=14), facial swelling (21.7%, *n*=13),

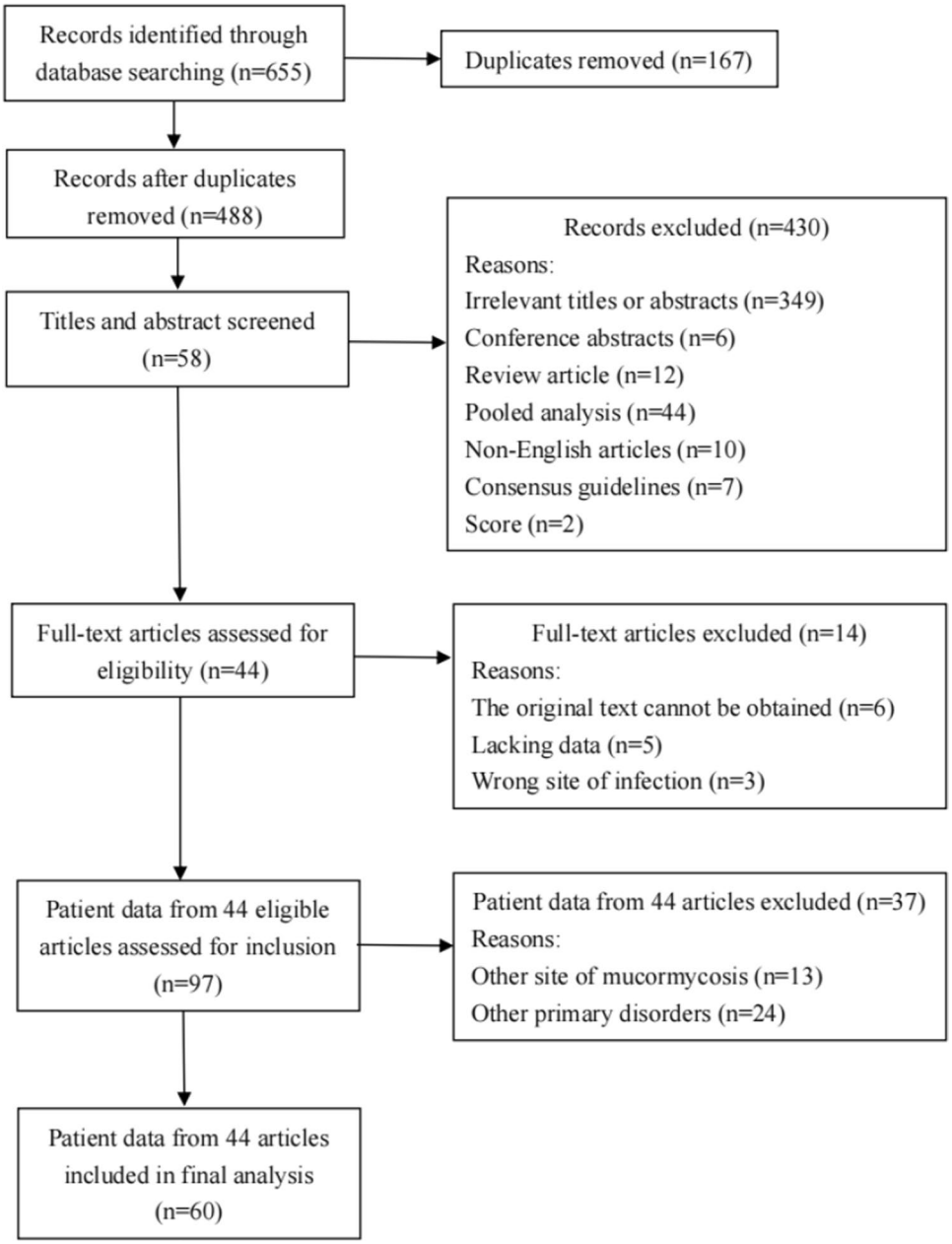

Fig. 2 The flow diagram of the selection of the cases

headache (15.0%, *n*=9), and other symptoms. Moreover, necrosis of the nasal mucosa and black eschar were seen in 48.3% (*n*=28) of patients with rhino infection (*n*=58, 96.7%), a typical clinical manifestation of mucormycosis (Fig. 3b).

Imaging examination

A total of 43 patients (71.7%) had imaging results—33 (55.0%) of these patients underwent computed tomography (CT), 16 (26.7%) underwent magnetic resonance imaging (MRI), and 6 (10.0%) underwent both tests. All imaging tests showed inflammation in the paranasal sinuses. In 27 patients (45.0%), the site of infection of the ROCM was completely identified.

Microbiologic and histopathologic findings

Histopathological examination was performed in 24 patients (40.0%), fungal culture was performed in 13 patients (21.7%), and both methods were used simultaneously to diagnose 12 patients (20.0%). In addition to traditional diagnostic methods, mNGS (*n*=2, 3.3%) and PCR (*n*=7, 11.7%) were used. The median time from the onset of clinical symptoms to the diagnosis of mucormycosis was 7 (IQR,4–10) days. Pathogenic zygomycetes were identified to species

Table 1 Demographic and clinical characteristics of patients

Characteristic	Median (IQR) or *n* (%) (*N*=60)
Age, years	30 (12–58)
Male	37 (61.67)
Primary disease	
ALL	27 (45.00)
AML	14 (23.33)
Lymphoma	6 (10.00)
AA	4 (6.67)
MDS	2 (3.33)
CML	2 (3.33)
CLL	2 (3.33)
Other*	3 (5.00)
Treatment of primary disease	
Chemotherapy	35 (58.33)
Long-term immunosuppressive therapy	11 (18.33)
HSCT	9 (15.00)
Supportive treatment	4 (6.67)
Immunochemotherapy	1 (1.67)
Disease status	
New diagnosed	31 (51.67)
Relapsed	20 (33.33)
Unknown	9 (15.00)
Primary disease efficacy	
CR	10 (16.67)
Non-CR	27 (45.00)
Unknown	23 (38.33)
Antifungal prophylaxis/treatment	26 (43.33)

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *AA* aplastic anemia, MDS myelodysplastic syndrome, *CML* chronic myeloid leukemia, *CLL* chronic lymphocytic leukemia, *HSCT* hematopoietic stem cell transplantation, *CR* complete remission

*Other: 1 case of acute biphenotypic leukemia, 1 case of unclassified leukemia, 1 case of multiple myeloma

level in 35 patients (58.3%) (Table 2). The most common pathogen was *Rhizopus* species (*n*=15, 25.0%), followed by *Mucor* species (*n*=8, 13.3%), and *Lichtheimia* species (*n*=5, 8.3%).

Therapy and prognosis

Treatment

Of all the available treatment strategies, antifungal therapy, surgery, local irrigation, and hyperbaric oxygen therapy (HBOT) were used (Table 3).

Excluding the 3 patients (5.0%) with unknown antifungal use, 57 patients (95.0%) received antifungal therapy, while 48 patients (80.0%) received both antifungal and surgical therapy.

Surgical strategies primarily consist of 20 debridement (33.3%), 12 sinusotomy (20.0%), 13 total or partial maxillectomy (21.7%), 5 orbital resection (8.3%), and 3 enucleation (5.0%). The median duration of surgery was 7 (IQR, 5–12) days. In the 9 patients (15.0%) with marked data, the preoperative neutrophil level was 0.58 (IQR, 0.11–2.80) 10^3/μL, and the platelet level was 58.00 (IQR, 17.00–93.00) 10^3/μL—all below the normal range.

Local irrigation was performed at the site of infection in 9 patients (15.0%). The irrigation solution was amphotericin B (AmB) (deoxycholate) in 4 patients (6.7%), amphotericin B liposomes (L-AmB) in 1 patient (1.7%), and normal saline in 1 patient (1.7%). A gelatin sponge containing L-AmB was applied in 1 patient (1.7%), and for 2 patients (3.3%) this treatment was not specified.

Prognosis

In terms of prognosis, it was found that 32 patients (53.3%) died. Nineteen of these (59.4%) died of mucormycosis, of

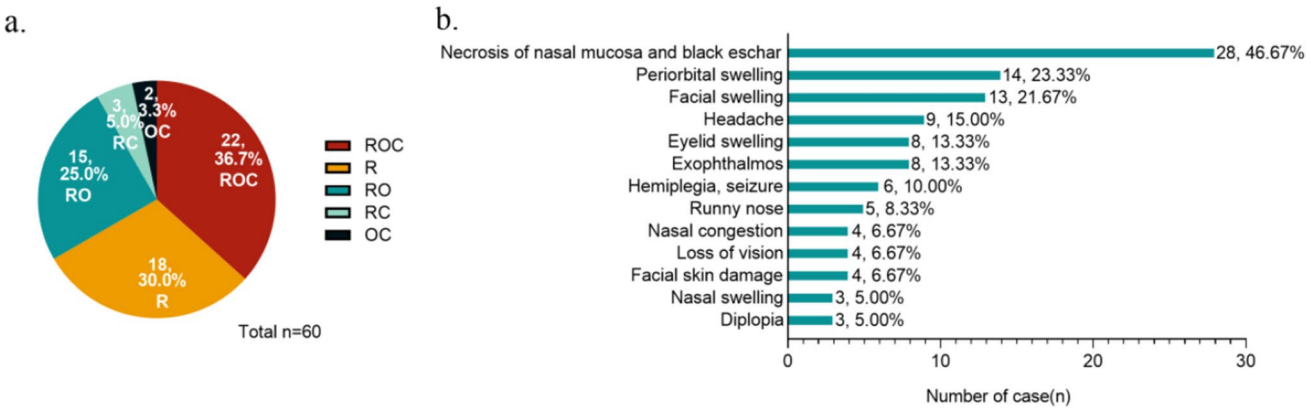

Fig. 3 **a** Sites of mucormycosis (ROC, rhino-orbital-cerebral; R, rhinal; RO, rhino-orbital; RC, rhino-cerebral; OC, orbital-cerebral) **b** Clinical symptoms (fever is excluded)

Table 2 Various pathogenic fungus and their fatality rate

Organisms identified	*n* (%)	Fatality rate *n* (%)
Mucorales	35 (58.33)	18 (51.43)
Mucoraceae	27 (45.00)	14 (51.85)
Mucor	8 (13.33)	5 (62.50)
Unidentified[*] *strain*	7 (11.67)	4 (57.14)
M. racemosus	1 (1.67)	1 (100.00)
Rhizopus	15 (25.00)	8 (53.33)
R. oryzae	6 (10.00)	5 (83.33)
Unidentified strain	5 (8.33)	2 (40.00)
R. arrhizus	3 (5.00)	1 (33.33)
R. genus	1 (1.67)	0 (0)
Rhizomucor	3 (5.00)	1 (33.33)
Actinomucor	1 (1.67)	0 (0)
Actinomucor elegans	1 (1.67)	0 (0)
Cunninghamellaceae	3 (5.00)	2 (66.67)
Cunninghamella	3 (5.00)	2 (66.67)
C. bertholletiae	2 (3.33)	1 (50.00)
Unidentified strain	1 (1.67)	1 (100.00)
Lichtheimiaceae	5 (8.33)	2 (40.00)
Lichtheimia	5 (8.33)	2 (40.00)
L. corymbifera	3 (5.00)	1 (33.33)
L. ornata	1 (1.67)	1 (100)
L. ramosa	1 (1.67)	0 (0)
Mucorales (Unidentified strain)	25 (41.67)	14 (58.33)

[*]Unspecified, the diagnostic modality is not indicated

whom 84.2% (n=16) died within 1 month (Fig. 4a). Nine (28.1%) patients died of progression or recurrence of the primary disease, 3 (9.4%) died of other types of infection, and 1 (3.1%) death could not be explained. The 1-month mortality of mucormycosis was 27.0±5.8% (n=16), the 3-month mortality of mucormycosis was 30.6±6.0% (n=18), and the 6-month mortality of mucormycosis was 32.5±6.2% (n=19). The median time from diagnosis to death for patients who died of mucormycosis was 20 (IQR, 14–29) days (Fig. 4b). Only 1 (1.7%) of the 19 patients who died of mucormycosis had achieved CR of the primary disease, 13 patients (21.7%) were non-CR, and the primary disease efficacy was not assessed in 5 patients (8.3%).

Risk factors for mortality in mucormycosis

When risk factors were compared between patients who died of mucormycosis and those who survived or died of other causes, such as progression of the primary disease or another type of infection. The median age (P=0.009), lack of surgical treatment (P=0.012) were statistical differences for patients dying from mucormycosis (Table 4). Multivariate analysis showed that patient's advanced age (P=0.012, OR=1.035 (1.008–1.064)) and lack of surgical treatment (P=0.030, OR=4.971 (1.173–21.074)) were independent prognostic factors (Table 5).

Discussion

ROCM is an acute fatal infectious disease characterized by rapid invasion of blood vessels, soft tissues, and bone and which has a high mortality. Notably, this type of infection lacks early typical clinical manifestations and often results in delayed diagnosis, which is not conducive to timely treatment of patients. In our review, the 3-month mortality of ROCM in hematological diseases was found to be 59.4%, which was higher than the 27.8% mortality observed when ROCM did not limit the primary disease [17]. This indicates a high mortality rate in hematological patients with ROCM.

Furthermore, our review showed that the most common hematological disease in ROCM was acute leukemia 27 (45.0%)—a finding that supports the results of previous studies [18]. In addition to leukemia, there are a few reports of lymphoma or myeloma also being associated with ROCM. This reminds us that we should be alert to the possibility of ROCM when the relevant clinical manifestations of the above diseases are present. We also found that 6 (46.2%) of the 11 patients with a clear duration of infection occurred between September and November. This is consistent with most previous studies reporting a peak of ROCM (August to November) [19–21], which can aid in the early detection of the disease [19]. RAST in vitro testing of atopic patient sera demonstrated a peak in the fall season in Candida and Mucor [22]. A study of seasonal fungal biota in dog fur demonstrated a summer peak in Rhizopus and an autumn peak for Mucorales [23]. Possible correlation with the seasonality of Mucorales growth still requires a larger assessment to define if this is a local or worldwide phenomenon.

Another notable finding was that the clinical symptoms of ROCM are not specific. During the early stages of mucormycosis, the clinical symptoms and radiographic features may be indistinguishable from those of rhinosinusitis [24]. Studies have shown that mucormycosis invading the cavernous sinus and the internal carotid artery can cause thrombosis, yet the cerebra-spinal fluid mostly remains normal and non-specific [18]. Moreover, there is currently no biomarker to identify the disease [14]. However, a more characteristic clinical manifestation of mucormycosis is the presence of a black necrotizing eschar on the skin mucosa [25]. In this review, 48.3% of patients (28/58) with rhino infection had nasal mucosal necrosis and black eschar. The paranasal sinuses are the main site for definitive diagnosis of infection. In our data, the sinuses were involved in all patients who underwent imaging. Thus, we advise that early imaging of the paranasal sinuses should be performed in patients with suspected ROCM, to clarify

Table 3 Prognosis of different treatment approaches for mucormycosis

	Died of mucormycosis (n=19)	Died of others* or survival (n=41)	Total (n=60)
Medication	19 (100.00)	41 (100.00)	60 (100.00)
Monotherapy	10 (52.63)	17 (41.46)	27 (45.00)
Mono AmB	6 (31.58)	4 (9.76)	10 (16.67)
Mono L-AmB	3 (15.79)	10 (24.39)	13 (21.67)
AmB derivatives replaced with L-AmB	1 (5.26)	3 (7.32)	4 (6.67)
Combination regimen	8 (42.11)	22 (53.66)	30 (50.00)
AmB combined with posaconazole	2 (10.53)	4 (9.76)	6 (10.00)
AmB combined with voriconazole	0 (0)	3 (7.32)	3 (5.00)
L-AmB combined with posaconazole	3 (15.79)	9 (21.95)	12 (20.00)
AmB combined with other antifungal drugs*	3 (15.79)	6 (14.63)	9 (15.00)
Unspecified*	1 (5.26)	2 (4.88)	3 (5.00)
Surgical operation	12 (63.16)	36 (87.80)	48 (80.00)
Debridement	3 (15.79)	17 (41.46)	20 (33.33)
Sinusectomy	3 (15.79)	9 (21.95)	12 (20.00)
Total or partial maxillectomy	5 (26.32)	8 (19.51)	13 (21.67)
Orbital resection	2 (10.53)	3 (7.32)	5 (8.33)
Enucleation	1 (5.26)	2 (4.88)	3 (5.00)
HBOT	0 (0)	6 (14.63)	6 (10.00)
Local irrigation	1 (5.26)	8 (19.51)	9 (15.00)

HBOT, hyperbaric oxygen therapy

*Other antifungal drugs, voriconazole, ketoconazole, isaconazole, or itraconazole

*Others, All patients except those who died of mucormycosis

*Unspecified, the type of antifungal drug used is not specified

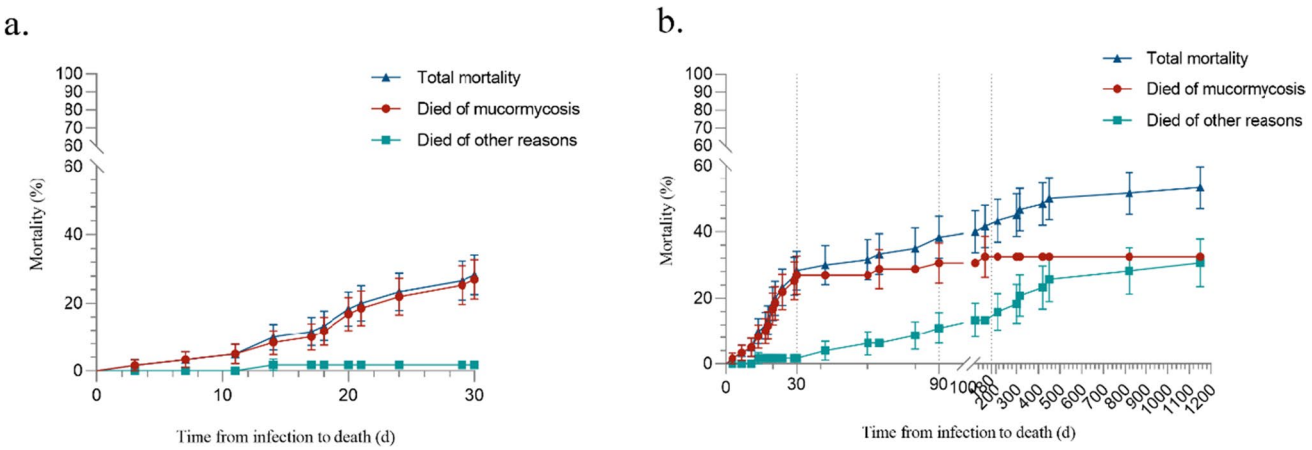

Fig. 4 **a** Mortality of 1-month post ROCM **b** Mortality of 6-months post ROCM

whether further pathological histological examination is needed to help us make an early diagnosis. Our review shows that the most common pathogen was Rhizopus species (41.7%), which is consistent with the findings of other studies [18, 19]. Koehler et al. also developed and validated the European QUALity (EQUAL) score for mucormycosis management in hematology, they can be used as guidance tool for clinicians to evaluate the specific position of the patient on the mucormycosis management path [26].

Given that delayed treatment is associated with increased mortality, it is important to start treatment as soon as possible [27]. Even when treatment is started promptly, though, there remains the question of whether combination therapy or monotherapy is more effective. In our review, the mortality rate of mucormycosis in

Table 4 Univariate analysis of risk factors for death from mucormycosis

	Died of mucormycosis (*n*=19)	Others[1*] (*n*=41)	*P*
Age	51 (27–63)	22 (10–45)	0.009
Primary disease			0.405
ALL	6 (31.58)	21 (51.22)	
AML	6 (31.58)	8 (19.51)	
Lymphoma	3 (15.79)	3 (7.32)	
Others[2*]	4 (21.05)	9 (21.95)	
Primary disease status			0.228
Newly diagnosed	7 (36.84)	24 (58.54)	
Relapsed	9 (47.37)	11 (26.83)	
Unknown	3 (15.79)	6 (14.63)	
Primary disease efficacy			0.051
CR	1 (5.26)	9 (21.95)	
Non-CR	13 (68.42)	14 (34.15)	
Unknown	5 (26.32)	18 (43.90)	
During transplantation			0.126
Yes	5 (26.32)	4 (9.76)	
No	14 (73.68)	37 (90.24)	
Mucormycosis lesions			1.000
Monofocal mucormycosis[*]	2 (10.53)	5 (12.20)	
Multifocal mucormycosis[*]	17 (89.47)	36 (87.80)	
Mucormycosis invades the brain			0.578
Yes	10 (52.63)	17 (41.46)	
No	9 (47.37)	24 (58.54)	
Mode of medication			0.400
Monotherapy	10 (52.63)	17 (41.46)	
Combination regimen	8 (42.11)	22 (53.66)	
Surgical operation			0.012
Yes	12 (63.16)	36 (87.80)	
No	7 (36.84)	5 (12.20)	

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *CR* complete remission

[1*]Others, All patients except those who died of mucormycosis

[2*]Others, 4 cases of aplastic anemia, 2 cases of myelodysplastic syndrome, 2 cases of chronic myeloid leukemia, 2 cases of chronic lymphocytic leukemia, 1 case of acute biphenotypic leukemia, 1 case of unclassified leukemia, 1 case of multiple myeloma

[*]Monofocal mucormycosis, Mucormycosis was present in only 1 site; Multifocal mucormycosis, Mucormycosis was present in ≥ 2 sites

Table 5 Multivariate analysis of risk factors for death from mucormycosis

Risk factors	*P*	*OR*	*95%CI*
Age	0.012	1.035	1.008~1.064
Lack of surgical treatment	0.030	4.971	1.173~21.074

patients treated with AmB (including liposomes) in combination with posaconazole (26.7%) was lower than in patients treated with either monotherapy (37.0%) (*P*=0.400)—which was also found to be the case in Caitlin et al.'s [28] research. It should be noted that although AmB or posaconazole was given for antifungal prophylaxis/treatment, the breakthrough of Mucorales still occurred. Fortunately, however, by adjusting the treatment dose or drug, 8 (80.0%) patients were able to survive while the other 2 (20.0%) died from the progression of the primary disease, and the Salmanton-Garc ı´ a et al's research has found that: Posaconazole new formulations were effective in terms of treatment response and associated mortality of IM [29]. Suggesting that active treatment should be given after Mucorales breakthrough. The study by Marty et al. states that patients with L-AmB intolerance could also be given Isavuconazole —— an effective and well-tolerated antifungal agent that can be safely administered orally or intravenously [30].

Due to the presence of varying degrees of necrotic tissue, surgical debridement appears to be a critical factor in controlling and ultimately curing ROCM [17, 31, 32]. Our study showed that the mortality rate of mucormycosis was much higher in patients who did not undergo combined surgery (58.3%) than in those who did undergo surgery (25.0%) (*P*=0.012). Operative time has also been associated with survival [14, 32]. In our sample, the median operative time was 7 (IQR, 5–12) days. Patients who underwent surgery after 7 days of infection had higher mortality from mucormycosis (26.3%) than those who underwent surgery within 7 days (0). However, severe thrombocytopenia and granulocytopenia may affect the performance of surgery. In this review, the median neutrophil and platelet levels in patients who underwent surgery were 0.58 (0.11–2.80)10^3/μL and 58.00 (17.00–93.00)10^3/μL, respectively. No deaths related to surgery were reported in our case series. On balance, then, we recommend that surgery be considered even in patients whose neutrophil and platelet levels are lower than normal.

In our review, the 1-year mortality rate of patients with hematological diseases complicated by ROCM was 53.3% (*n*=32), of whom 59.4% (n=19) died of mucormycosis. However, of these deaths, 84.2% occurred within 1 month. Univariate analysis showed that advanced age (*P*=0.009) and lack of surgical treatment (*P*=0.012) were associated with death. After conducting a multivariate analysis, we found that patient's advanced age (*P*=0.012, *OR*=1.035 (1.008–1.064)) and lack of surgical treatment (*P*=0.030, *OR*=4.971 (1.173–21.074)) were independent risk factors for death from mucormycosis. This suggests that, if

conditions allow, hematological diseases with ROCM should also be treated surgically when possible.

When standard treatment fails and the central and axial nervous system is involved, the introduction of HBOT can be used as an adjunct to avoid the devastating effects of this infection [33]. Animal studies have shown that hyperbaric oxygen can inhibit the inflammatory response by down-regulating cytokines [34, 35], indicating that HBOT can also improve the effectiveness of some antimicrobial drugs [36]. Although only 6 patients received HBOT in this trial, it is notable that all 6 of them survived. This reminds us that the use of HBOT in hematological patients with ROCM warrants further investigation, especially in patients who are not suitable for surgery.

In spite of the key contributions made by this study, it should also be acknowledged that it suffers from some limitations. Indeed, the data that we analyzed were taken from published case reports, but the value of surgical treatment and the range of surgical safety in terms of neutrophil and platelet levels must be further validated by prospective studies. Having said this, we can still say that the results have some value in guiding clinical practice.

Hematological diseases associated with ROCM have a high mortality rate. To this end, it is found that antifungal therapy combined with early surgery is an effective treatment strategy for patients with hematological disease.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-023-05349-5.

Author contributions WT, SH, JW, and JW designed and supervised the work, interpreted the results, and approved the final version; XC, JX, XW find and filter documents; JA, JZ, XL analyzed data, XC and JX wrote and revised the manuscript; all authors read and approved the final manuscript.

Data availability We declare that the data supporting the conclusions of this article are fully described within the article.

Declarations

Ethics approval and consent to participate We have analyzed cases obtained from studies that were published. Therefore, this study did not require approval from the ethical committee.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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