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A retrospective analysis on mucormycosis in patients with hematological diseases: a single center experience from Turkey

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ABSTRACT

Aim: Mucormycosis is an acute, invasive, devastating and highly fatal fungal infection, affecting particularly immunocompromised patients; fortunately, it is rare. This study aimed to describe the attitude of mucormycosis in patients with a hematological disease, and to evaluate the risk factors associated with mortality.

Material and Method: We retrospectively assessed the demographic and clinical data of patients who were diagnosed with mucormycosis in Erciyes University Hematology and Bone Marrow Transplantation Center, between 2010 and 2020. The study was included 34 patients with a history of either hematological malignancy or hematopoietic stem cell transplantation.

Results: Twenty-seven patients had proven infection, and the others had possible infection. The most frequent underlying disease was acute leukemia. Seven-teen patients had a history of allogeneic transplantation, and frequency of mucormycosis was 3.5% among allogeneic transplant recipients. The most frequent site of infection was the rhino-orbital region (85.3%). Forty-seven percent of patients presented with acute orbital symptoms. Fifteen patients were on a mucor-active antifungal (posaconazole and liposomal Amphotericin B) prophylaxis or treatment at the time of diagnosis. All patients received liposomal Amphotericin B and seven patients received posaconazole additionally as initial therapy. Surgical debridement was performed in 91.1% of patients. The two-year mucor-related mortality rate was 44.1%. The survival curves were significantly lower in patients with concomitant fungal pneumonia, allogeneic transplantation and also in patients who were receiving mucor-active antifungal drugs at the time of diagnosis.

Conclusion: Mucormycosis remains a significant problem for hematology clinicians despite the expanding use of antifungal prophylaxis. Moreover, breakthrough infections indicate rising danger regarding resistant agents. We also highlight that, most of the patients receiving broad-spectrum antifungal prophylaxis are more fragile and more complicated patients, which put them at increased baseline risk for mucormycosis, and deserve more attention.

Keywords: Invasive fungal infection, mucormycosis, hematological malignancy, hematopoietic stem cell transplantation

INTRODUCTION

Invasive fungal infection (IFI) is a remarkable cause of morbidity and mortality in immunocompromised states. Particularly, mucormycosis is prominent among other species with a high fatality rate. Mucormycosis is a standard nomenclature used for invasive necrotizing infections caused by fungi belonging to the Mucorales order (old name Zygomycetes). The well-known members are Rhizopus, Rhizomucor, Mucor, Lichtheimia (Absidia), and Cunninghamella species (1). Since Mucorales are ubiquitous fungi and can release airborne spores, it is easy to be exposed anywhere. Although they are not resistant to intact human immunity, they can grow rapidly and cause devastating infections in immune-compromised patients.

The well-known risk factors of mucormycosis include diabetes mellitus, glucocorticoid treatment, penetrating trauma, or burns. Also, the patients with hematologic malignancy and hematopoietic stem cell transplantation (HSCT) are perfect hosts for mucormycosis.

In fact, the characteristics of infection vary depending on the factors such as geography, economy or features of the population studied. Hematologic malignancies are the most frequent underlying disease in Europe, whereas diabetes is more frequent reason in the Middle East, India, and Africa (2-5). In patients with hematological malignancy or HSCT, mucor frequency was reported between 2–8%, and the mortality rate could reach up to 65% (3,6-11).

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In this study, we aimed to evaluate the course of mucormycosis infection and associated risk factors in patients with hematological disease.

MATERIAL AND METHOD

The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 21.04.2021, Decision No: 2021/293). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study design

We retrospectively collected the data of mucormycosis in patients with a history of either hematological malignancy or HSCT. The study was conducted in Erciyes University Hematology and Bone Marrow Transplantation Center in Turkey, between 2010 and 2020.

Thirty-four patients with diagnosis of mucormycosis were included. All but one had deep tissue biopsy. Thus, the data was recorded regarding histopathologic and direct microscopic examination and cultures. Based on the 2019 criteria provided by the European Organization for Research and Treatment of Cancer/ Mycosis Study Group (EORTC/MSG), patients were categorized into three diagnosis subgroups: proven, probable, and possible mucormycosis (12).

Proven mucormycosis was defined as the disease with mycologic evidence; positive histopathologic and direct microscopic examination and/or positive specimen culture obtained from a sterile tissue biopsy.

Probable mucormycosis required the presence of mycologic evidence in the sample obtained by bronchial lavage, sinus aspiration or sputum, along with typical clinical and/or radiological features.

Patients with typical clinical and/or radiological features and disease progression compatible with mucormycosis, but without any mycological evidence, were defined as possible mucormycosis.

The date of diagnosis corresponded to the day of the biopsy.

The last 30 days preceding the diagnosis of mucormycosis were considered for iron chelation, antifungal prophylaxis, corticosteroid, and immunosuppressive treatment. In addition, steroid exposure was recorded if >8 mg/day of methylprednisolone (or equivalent) for more than 21 days.

Early clinical response was assessed in terms of resolution of symptoms and fever at on the 15th day of diagnosis.

Statistical Analysis

Statistical analysis were performed using the commercial statistical package SPSS (IBM SPSS Statistics 24). Statstical significant was considered as $p<0.05$. According to the normality of distrubution of variables 'Independent Sample-t' test (t-table value) and 'Mann-Whitney U' test (Z-table value) were used to compare the two independent groups. Relationships between categorical variables were compared using 'Fisher's exact test' (chi-square test), 'continuity correction' or 'Pearson-χ2 tests', as appropriate. Survival curves were constructed using 'Kaplan-Meier analysis' and 'Cox-Regression analysis' was performed for identifying factors effecting survival.

RESULTS

The study included 34 patients diagnosed with mucormycosis, of which 21 (61.8%) were male. The mean age was 45.6±15.3 (range 19–70) years. Acute leukemia was the most common underlying disease (20 patients, 58.8%). Fourteen (41.2%) patients were in remission in terms of underlying disease at the time of mucor diagnosis.

During the study period, a total of 457 allogeneic HSCT was performed in our center. The frequency of mucormycosis was 3.5% among these patients. Seventeen patients were allogeneic transplantation recipients, and 11 of them were from full-match sibling donors. Patient characteristics are displayed in **Table 1**.

The most frequent site of infection was rhino-orbital region (n:29, 85.3%), and three patients presented with pulmonary mucormycosis (**Table 2**). In addition to these pulmonary mucor patients, 13 patients had preexisting or concomitant pulmonary fungal infection confirmed with imaging, but not specified.

Table 2. Site of infection and symptoms

	N (%)
Site of infection	
Sino-orbital	29 (85.3)
Cerebral	1 (2.9)
Pulmonary	3 (8.8)
Gastrointestinal	1 (2.9)
Symptoms	
Periorbital swelling and pain	16 (47.0)
Facial pain	13 (38.2)
Fever	25 (73.5)
Headache	6 (17.6)
Oral-palatine lesion	5 (14.7)
Nasal congestion	3 (8.8)

Table 1. Characteristics of patients, survived and expired because of mucormycosis

	Total n=34 n (%)	Expired n=15 n (%)	Survived n=19 n (%)	P*
Age mean, years ± SD (min-max)	45.6 ±15.3 (19-70)	42.4 ±16.1 (19-68)	48.1±14.6 (26-70)	p=0.295
Gender Male	21 (61.8)	7 (46.7)	14 (73.7)	χ2=1.573 p=0.210
Status of underlying disease				χ2=0.015 p=0.901
Active	20 (58.8)	9 (60.0)	11 (57.9)	
Remission	14 (41.2)	6 (40.0)	8 (42.1)	
Underlying disease				
AML	20 (58.8)	9 (60.0)	11 (57.9)	
ALL	4 (11.8)	2 (13.3)	2 (10.5)	
Lymphoma	3 (8.8)	1 (6.6)	210.5)	
MDS	1 (2.9)	0	1 (5.2)	
Aplastic anemia	1 (2.9)	1 (6.6)	0	
Other	5 (14.7)	2 (13.3)	3 (15.7)	
Transplantation history				χ2=3.135 p=0.077
No	16 (47.1)	4 (26.7)	12(63.2)	
Yes	18 (52.9)	11 (73.3)	7 (36.8)	
Auto- HSCT	1 (5.6)	1 (9.1)	0	
Allo- HSCT	17 (94.4)	10 (90.9)	7 (100)	
Full-match	11 (64.7)	6 (60.0)	5 (71.4)	
Haplo identical	6 (35.2)	4(40.0)	2 (28.6)	
GVHD				p=0.783
No	7 (38.9)	4 (36.4)	3 (42.9)	
Yes	11 (61.1)	7 (63.6)	4 (57.1)	
Comorbidity[1]				p=0.451
No	24(70.6)	12 (80.0)	12 (63.2)	
Yes	10 (29.4)	3 (20.0)	7 (36.8)	
Antifungal prophylaxis[2]				p=0.257
No	8 (23.5)	2 (13.3)	6 (31.6)	
Yes	26 (76.5)	13 (86.7)	13 (68.4)	
Posaconazole	11 (42.3)	6 (46.2)	5 (38.5)	χ2=1.958 p=0.581
Voriconazole	5 (19.2)	2 (15.4)	3 (23.1)	
Fluconazole	6 (23.1)	2 (15.4)	4 (30.7)	
L-AmB	4 (15.4)	3 (23.0)	1 (7.7)	
Steroid use[2]				χ2=0.377 p=0.539
No	19 (55.9)	7 (46.7)	12 (63.2)	
Yes	15 (44.1)	8 (53.3)	7 (36.8)	
Immunosuppressive[2]				p=0.718
No	24 (70.6)	10 (66.7)	14 (73.7)	
Yes	10 (29.4)	5 (33.3)	5 (26.3)	
Chelator[2]				p=0.889
No	26 (76.5)	11 (73.3)	15 (78.9)	
Yes	8(76.5)	4 (26.7)	4 (21.1)	
Deferoxamine	1 (2.9)	-	1 (25.0)	p=1.000
Deferosirox	7 (20.5)	4 (100.0)	3 (75.0)	
Mucormycosis relapse				p=0.902
No	26 (76.5)	11 (73.3)	15 (78.9)	
Yes	8 (23.5)	4 (26.7)	4 (21.1)	
Concomitant fungal pneumonia				χ2=5.670 p=0.017
No	18 (52.9)	4 (26.7)	14 (73.7)	
Yes	16 (47.1)	11 (73.3)	5 (26.3)	
Early response				p=0,000
No	8 (23.5)	8 (53.3)	0	
Yes	26 (76.5)	7 (46.7)	19 (100)	
Hospitalization[2]				p=0.128
Yes	24 (70.6)	13 (86.7)	11 (57.9)	
No	10 (29.4)	2 (13.3)	8 (42.1)	

[1]Diabetes mellitus, chronical lung disease, or rheumatismal disease, [2]at the time of symptom onset, *Relationships between categorical variables were compared using the 'Fisher's exact test' (chi-square test), 'continuity correction' or 'Pearson-χ2 tests', as appropriate

According to the EORTC criteria, 27 (79.4%) patients had proven infection, and the others had possible infection. There were no cases labeled as probable infection. Histopathology was diagnostic in 79.4% of subjects, culture was positive in 38.2% (n:13), and Rhizopus sp. was the most frequent species (n:7/13). Eight out of 13 patients with culture growth were on posaconazole prophylaxis (**Figure 1**). Twenty-six (76.5%) patients were on antifungal prophylaxis or treatment at the time of diagnosis, and 20 of them received mold-active antifungals.

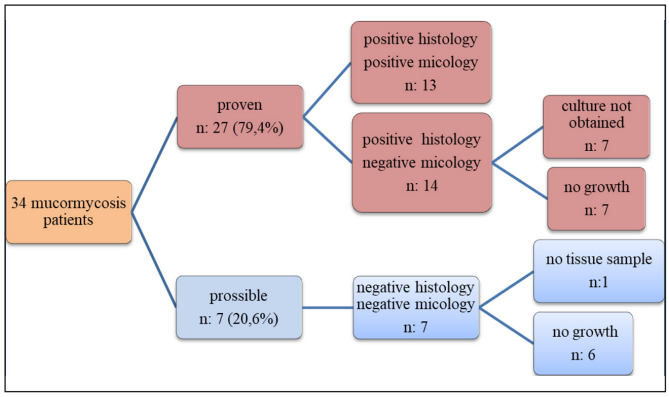

Figure 1. Distribution of patients according to EORTC criteria and diagnostic tools.
EORTC: European Organization for Research and Treatment of Cancer (2019)

Sixteen patients (47.0%) presented with acute orbital symptoms such as swelling, erythema, and pain in the periorbital region. The other common presenting symptoms were facial swelling and pain mainly localized at the maxillary area, palatine ulcer with necrosis, headache, and nasal congestion (**Table 2**). The median time from the onset of symptom to treatment was 2.5 days (min-max 1–7days).

Twenty-four patients (70,6%) developed infections during hospitalization, and 11 of them were transplant recipients. Twenty out of 34 patients (58,8%) were diagnosed in Autumn. The seasonal variation is demonstrated in (**Figure 2**).

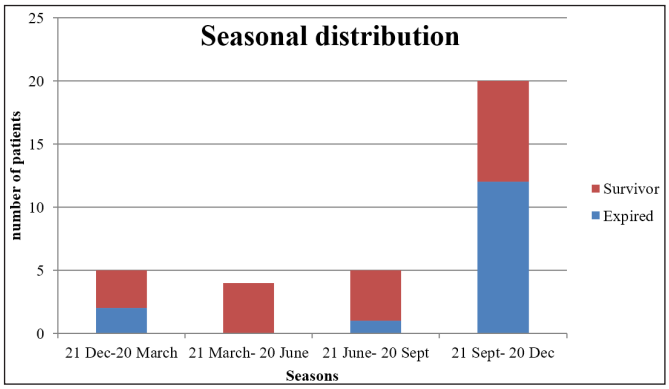

Figure 2. Distribution of patients according to seasonal variation

Twenty-three patients had a platelet level lower than 50×10^3 cell/mcL, 11 had absolute neutrophil count lower than 500 cell/mcL, and 14 had lymphocytes lower than 400 cell/mcL at diagnosis. However, there was no significant association between mortality and cytopenias (**Table 3**).

The median time to mucor diagnosis from transplantation was 0.35 years (min-max: 0.01–5.8), and from diagnosis of malignancy was 1.34 years (min-max: 0.25–8.55).

All patients received liposomal amphotericin B (L-AmB) at a dose of 5–10 mg/kg, and seven patients received additional posaconazole as initial therapy. However, posaconazole did not provide any significant advantage in terms of mortality or survival time. Thirty-one (91.1%) patients received surgical intervention in addition to medical treatment.Early clinical response was achieved in 26 (76.5%) patients on the 15th day. The remaining eight (23.5%) patients expired within 21 days due to mucormycosis infection; six were HSCT recipients. The median treatment duration was 39 days (min-max 4–117 days).

Sixteen patients received maintenance treatment with posaconazole (median 30 days, min-max 10–150 days). Mucor infection relapsed in eight patients (34.7% in responsive patients) after an average of 95.7 (±23.8) days from the first diagnosis (min-max 72–140 days), and six of them were on posaconazole maintenance (mean time to relapse, 95.7 (±23.8).

Table 3. Laboratory tests for mucormycosis patients at the time of diagnosis

	Expired (n=15)		Survived (n=19)		p/z*
	x̄±S.S.	Median [Min-Max]	x̄±S.S.	Median [Min-Max]	
D-Dimer (ng/ml)	2559.90±3235.67	1850.0 [269.0-11360.0]	2604.74±2631.70	1080.0 [390.0-8730.0]	Z=-0.092 p=0.927
LDH (U/L)	563.87±1013.89	256.0 [127.0-4157.0]	270.26±94.58	254.0 [130.0-433.0]	Z=-0.347 p=0.729
Fibrinogen (mg/L)	516.75±186.54	555.5 [227.0-768.0]	408.56±156.00	415.5 [175.0-827.0]	t=1.716 p=0.097
C-RP (mg/L)	102.71±111.25	50.0 [4.0-328.0]	66.47±81.26	37.0 [1.0-285.0]	Z=-1.012 p=0.311
Ferritin (µg/L)	2364.41±1508.21	1790.0 [694.0-5096.0]	2565.79±1854.29	2130.0 [473.0-9029.0]	Z=-0.122 p=0.903
Iron (µg/dl)	159.08±94.01	148.0 [40.0-340.0]	180.63±95.32	170.0 [19.0-396.0]	t=0.632 p=0.532
T Sat (%)	0.88±0.61	0.81 (0.08-2.49)	0.66 ±0.20	0.75 (0.38-0.90)	P=0.229
Neutropil (10^3/µg)	2.40±2.85	0.8 [0.0-7.7]	2.48±2.18	2.1 [0.0-6.4]	Z=-0.434 p=0.664
Lymphocyte (10^3/µg)	0.99±1.68	0.5 [0.1-6.8]	1.15±2.09	0.7 [0.1-9.4]	Z=-0.382 p=0.702
Platelets (10^3/µg)	64.73±84.66	15.0 [5.0-262.0]	64.06±75.14	31.0 [9.0-230.0]	Z=-0.706 p=0.480

*According to the normality of distribution of variables 'Independent Sample-t' test (t-table value) and 'Mann-Whitney U' test (Z-table value) were used to compare the two independent groups. LDH: Lactate dehydrogenase, C-RP: C reactive protein, T Sat: transferrin saturation

Two-year mucor related mortality rate was 44.1%. The Median follow-up was 4.2 months (min-max 0–24.0), and mean survival time was 13.85 months (95% CI, 10.0–17.7%). The mucor-related mortality was not different in the analysis of subgroups based on gender, underlying disease, antifungal prophylaxis or graft versus host disease (GVHD) (p>0.05). The mortality was higher in patients with transplantation history (61.1% vs 25.0%) but it was not statistically significant. Likewise, there was no significant difference between expired and survived patients in terms of inflammatory markers, iron parameters or blood counts (p>0.05) (**Table 3**). The Mortality was significantly higher in patients with concomitant fungal pneumonia ($\chi 2=5.670$; p=0.017) and with no early clinical response (p=0.000) (**Table 1**). The survival curves were significantly lower in patients with concomitant fungal pneumonia and allogeneic transplantation and also in patients who were receiving mucor-active antifungal drugs (posaconazole and L-AmB) for prophylaxis or treatment of the previous infection (**Figure 3**).

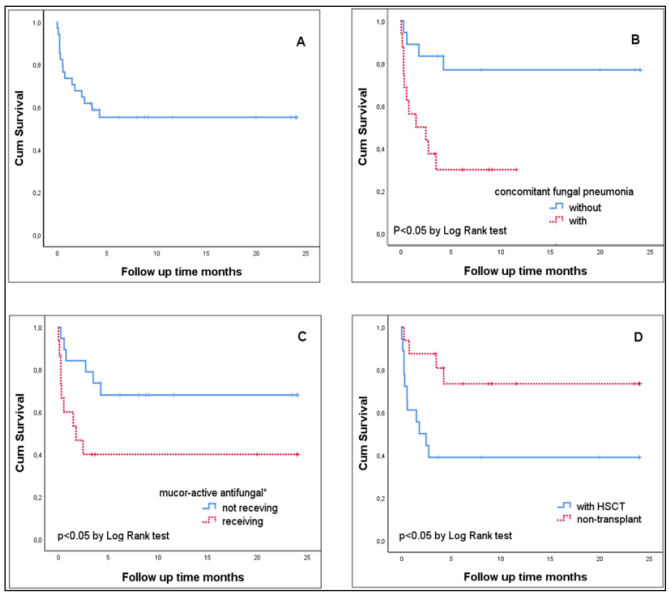

Figure 3. 2-year survival curves for the patients with mucormycosis, overall survival (A), for patients with or without concomitant fungal pneumonia (B), for patients receiving antifungal prophylaxis/ treatment or not at the time of mucor diagnosis (C), for patients with or without HSCT history (D) (Kaplan–Meier analysis)

HSCT: hematopoietic stem cell transplantation, *Posaconazole or liposomal Amphotericin B

DISCUSSION

Although effective prophylaxis and treatment options are developing for fungal agents, we still have limited solutions for mucormycosis. Moreover, the effect of broad-spectrum antifungal prophylaxis on the risk of mucor infection is a matter of debate. Some studies highlight the increasing use of mold-active antifungals (in particular voriconazole) as responsible for the higher rate of mucormycosis (1,9,13-17). On the contrary, Abidi et al. (18) reported similar results between the groups with or without voriconazole exposure. They emphasized that the enlargement of the risk population is responsible for the rising number of cases.

In current practice all patients with acute leukemia and HSCT receive antifungal prophylaxis during chemotherapy and neutropenic period, or posttransplant period, in some degree. In our cohort, more than three quarters of patients were receiving a mold-active antifungal at the time of mucor diagnosis. Eleven patients developed mucormycosis under posaconazole prophylaxis, and four patients were under L-AmB (3 mg/kg) treatment for fungal pneumonia. These patients displayed worse survival curves (**Figure 3**).

Invasive breakthrough fungal infections and also mucormycosis have been associated with a higher mortality rate reaching 70% in hematologic cancer patients (1, 19). Recently, a retrospective study from the USA reported 103 breakthrough mucor infections in patients with hematologic malignancy, and 16 of them were either under mucor-active antifungal treatment or prophylaxis such as posaconazole, isavuconazole and AmB. The mortality was significantly higher in these patients than those on other mold-active antifungals (20).

These findings could indicate resistant infections. On the other hand, most of these patients receiving broad-spectrum antifungal prophylaxis are more fragile and are complicated with a hematologic malignancy or bone marrow transplantation, which put them at increased baseline risk for mucormycosis.

The distribution of clinical manifestations has been variably reported in the literature due to the divergent factors such as risk population, geography, and social aspects. Pulmonary disease is the most common presentation in mucor patients with hematological malignancy based on reports from France, Israel, and Germany (3,21,22). Other studies from India, South America, the Middle East, and Africa display rhino-orbito-cerebral disease predominance (5,2-25). In the present cohort, the rhino-orbital region was the most frequent site of infection by a wide margin; however, 13 out of 29 rhino-orbital diseases had concomitant pulmonary fungal infection unspecified. In clinical practice, our patients with a prediagnosis of fungal pneumonia receive mold-active antifungal treatment empirically, primarily targeting aspergillus infection. To differentiate pulmonary IFI, isolation of agents through a proper biopsy is not possible in the majority of the patients. Moreover, overlap infections may easily be overlooked. So, the low proportion of pulmonary presentation can be deceptive for our population.

The rhino-orbito-cerebral infection usually starts in the nasal sinus and spreads to the palate, orbits, skull base, and brain. Accordingly, headache, facial pain, and nasal discharge are the most frequently reported symptoms for presentation (26,27). In our study, the most frequent symptom was unilateral orbital swelling, and the following was facial pain. In fact, fever was also present in most of the patients. However, it can be complicated with some factors such as neutropenia, other infections, and drug reactions which are quite common for our inpatients. Orbital or facial complaints should be considered alarming symptoms and deserve more attention.

There are some challenges in diagnosis. The reference method is a direct macroscopic and microscopic examination and culturing of biopsy fragments. Histopathologic identification of fungal elements compatible with Mucorales is crucial because it can reveal the fungus as a pathogen. Also, histopathology can define angioinvasive necrotic inflammation. However, culture is negative in a large proportion of the patients. This fungus is very fragile in nature, therefore sampling and transport issues are critical. In addition, culture possesses the possibility of contamination during sampling or laboratory process (28, 29). Samples using bronchial lavage and sinus aspiration are not valuable since diagnosis requires sterile tissue biopsy from the affected organ. However, proper tissue biopsy can be difficult due to localizations or thrombocytopenia. At this point, the management of thrombocytopenia requires extra attention. Furthermore, in the cases that have been already under mold-active antifungals, growth could be suppressed, or fungus may present atypical morphological features(30).

There is no reliable, standardized laboratory technique for mucormycosis for now. Serological tests and molecular methods are under investigation but have limited utility in identifying mucormycosis (4,31,32). Thus, the absence of culture positivity or histological evidence should not exclude the diagnosis if the clinical picture is significantly suggestive. The present study included seven patients diagnosed with possible mucormycosis according to EORTC criteria. In five of these patients, the biopsy was performed under L-AmB. There was no mycological or histological evidence in these patients, despite a highly suggestive clinical course for mucormycosis. These patients had rhino-orbital infections, and endoscopic examination was feasible; thus, the specific necrotic lesion could be observed directly. However, for pulmonary or disseminated disease to prove mucormycosis can be a real challenge, and maybe some of the patients with these features are overlooked.

In this high-risk population, not only an early-aggressive diagnostic approach, but also prompt initiation of mucor-effective antifungal treatment and maintaining enough long is life-saving. In a retrospective study on treatment, Camilos et al. (33) reported that delaying treatment resulted in a 2-fold increase in mortality rate. The breakpoint (between early and delayed treatment) was the 6th day of onset of symptoms. Regarding the median time from initial symptom to initiation of treatment, Axell-House et al. (20) reported six days, and Lanternier et al. (3) said two weeks in all and one week specifically in HSCT recipients. This period was shorter in our study (median 2.5 days), nevertheless this advantage did not improve the outcomes. We should point out that, we did not report fever as an initial symptom because most patients were complicated with another infection

About 80% of our patients were inpatient at the onset of symptoms; thus, empirical treatment could be started soon upon biopsy. Although the result is not statistically significant, mortality was higher in hospital-acquired infections than community gained (54% and 20%, respectively). Most of these inpatients had active underlying disease and were on chemotherapy.

There are some restricted studies on treatment and most of the data are coming from retrospective analyzes. L-AmB is still the most effective agent and combination with surgical debridement is highly suggested because of survival advantage (3,23,31,34,35).

In present study, mucor-related mortality was lower than previous reports for patients with hematologic malignancy (44.1%) (2,3,10,11,15). In many reports, localization of infection is an important determiner in mortality and mortality is higher in pulmonary disease (3,5,23). The difference between localizations was not significant in our cohort, probably due to less number of patients with involvement other than rhinoorbital region. However, mortality was significantly higher in patients with concomitant fungal pneumonia. These pulmonary infections were not able to specified, and maybe some of them were mucor infections.

The lesser number of patients is the main limitation of our study. Moreover, most of the patients suffered from a magnitude of complex risk factors such as cytopenia, antibiotics, antifungals, chemotherapy, and immunosuppressors. So it was not easy to assess the contribution of these factors with the outcomes.

In conclusion, we attempted to determine the attitude of mucormycosis in patients with hematologic malignancies and bone marrow transplantation. This study is noteworthy regarding the study period and the

number of patients for a single-center experience. Since mucormycosis is a rare infection, the accumulation of experiences will constitute the data pool. We want to emphasize the limited utility of the prophylactic approach. Early suspicion and prompt initiation of the treatment remains the key in this precarious population.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 21.04.2021, Decision No: 2021/293).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Kontoyiannis DP, Lewis RE, editors. Agents of Mucormycosis and Entomophthoramycosis. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 7th ed. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia: Churchill Livingstone Elsevier; 2010.
2. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi 2019; 5: 26.
3. 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: S35-S43.
4. Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: an update. J Fungi 2020;6:265.
5. Stemler J, Hamed K, Salmanton-García J, et al. Mucormycosis in the Middle East and North Africa: Analysis of the FungiScope® registry and cases from the literature. Mycoses 2020; 63: 1060-8.
6. Cuenca-Estrella M, Bernal-Martinez L, Isla G, Gomez-Lopez A, Alcazar-Fuoli L, Buitrago M. Incidence of zygomycosis in transplant recipients. Clin Microbiol Infect 2009;15: 37-40.
7. Roques M, Chretien ML, Favennec C, et al. Evolution of procalcitonin, C-reactive protein and fibrinogen levels in neutropenic leukaemia patients with invasive pulmonary aspergillosis or mucormycosis. Mycoses 2016; 59: 383-90.
8. Hoenigl M, Strenger V, Buzina W, et al. European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) host factors and invasive fungal infections in patients with haematological malignancies. J Antimicrob cChemother 2012; 67: 2029-33.
9. Kontoyiannis DP, Marr KA, Park BJ et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis 2010; 50: 1091-100.
10. 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: 1855.
11. Roden MM, Zaoutis TE, Buchanan WL et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005; 41: 634-53.
12. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis 2020; 71: 1367-76.
13. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. Clin Infect Dis 2008; 47: 1041-50.
14. Wingard JR. The changing face of invasive fungal infections in hematopoietic cell transplant recipients. Curr Opin Oncol 2005; 17: 89-92.
15. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis 2005; 191: 1350-60.
16. Maertens J. Evaluating prophylaxis of invasive fungal infections in patients with haematologic malignancies. Eur J Haematol 2007; 78: 275-82.
17. Siwek GT, Dodgson KJ, de Margarida MS, et al. Invasive zygomycosis in hematopoietic stem cell transplant recipients receiving voriconazole prophylaxis. Clin Infect Dis 2004; 39: 584-7.
18. Abidi MZ, Sohail MR, Cummins N, et al. Stability in the cumulative incidence, severity and mortality of 101 cases of invasive mucormycosis in high-risk patients from 1995 to 2011: a comparison of eras immediately before and after the availability of voriconazole and echinocandin-amphotericin combination therapies. Mycoses 2014; 57: 687-98.
19. Rausch CR, DiPippo AJ, Bose P, Kontoyiannis DP. Breakthrough fungal infections in patients with leukemia receiving isavuconazole. Clin Infect Dis 2018; 67: 1610-3.
20. Axell-House DB, Wurster S, Jiang Y et al. Breakthrough mucormycosis developing on mucorales-active antifungals portrays a poor prognosis in patients with hematologic cancer. J Fungi 2021; 7: 217.
21. Hardak E, Fuchs E, Geffen Y, Zuckerman T, Oren I. Clinical spectrum, diagnosis and outcome of rare fungal infections in patients with hematological malignancies: experience of 15-year period from a single tertiary medical center. Mycopathologia 2020; 185: 347-55.
22. Koehler P, Mellinghoff SC, Stemler J, et al. Quantifying guideline adherence in mucormycosis management using the EQUAL score. Mycoses 2020; 63: 343-51.
23. Prakash H, Ghosh AK, Rudramurthy SM, et al. A prospective multicenter study on mucormycosis in India: Epidemiology, diagnosis, and treatment. Medical Mycology 2019; 57: 395-402.
24. Nucci M, Engelhardt M, Hamed K. Mucormycosis in South America: a review of 143 reported cases. Mycoses 2019; 62: 730-8.
25. Dolatabadi S, Ahmadi B, Rezaei-Matehkolaei, A et al. Mucormycosis in Iran: a six-year retrospective experience. J Mycologie Medicale 2018; 28: 269-73.
26. Vaughan C, Bartolo A, Vallabh N, Leong SC. A meta-analysis of survival factors in rhino-orbital-cerebral mucormycosis—has anything changed in the past 20 years? Clin Otolaryngol 2018; 43: 1454-64.
27. Ketenci I, Ünlü Y, Kaya H, et al. Rhinocerebral mucormycosis: experience in 14 patients. J Laryngol Otol 2011; 125: e3.
28. Skiada A, Lass-Floerl C, Klimko N, Ibrahim A, Roilides E, Petrikkos G. Challenges in the diagnosis and treatment of mucormycosis. Medical Mycology 2018; 56: S93-S101.

29. Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. Clin Microbiol Rev 2011; 24: 247-80.
30. Walsh TJ, Gamaletsou MN, McGinnis MR, Hayden RT, Kontoyiannis DP. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). Clin Infect Dis 2012; 54: S55-S60.
31. 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: e405-e21.
32. Vehreschild JJ, Koehler P, Lamoth F et al. Future challenges and chances in the diagnosis and management of invasive mould infections in cancer patients. Medical Mycology 2021; 59: 93-101.
33. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B–based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis 2008; 47: 503-9.
34. Tissot F, Agrawal S, Pagano L, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica 2017; 102: 433.
35. Skiada A, Pagano L, Groll A et al. Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. Clin Microbiol Infect 2011; 17: 1859-67