İstanbul Med J 2021; 22(4): 245-9
DOI: 10.4274/imj.galenos.2021.65872

Mucormycosis in Hematologic Malignancies: Clinical Follow-Up and Treatment Results

Hematolojik Malignitelerde Mukormikozis: Klinik Takip ve Tedavi Sonuçları

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ABSTRACT

Introduction: Mucormycosis is an aggressive-progressive invasive fungal infection caused by mold fungi in the division of mucorales of the zygomycetes class with high mortality, and is the most common fungal infection in patients with hematologic malignancies.

Methods: This study retrospectively evaluated patients with mucormycosis diagnosis between January 2015 and December 2019, including demographic features, hematologic diseases and comorbidities, radiological evaluations, symptoms and signs, treatments, and outcomes.

Results: Maxillofacial 9/19 (47.37%) of patients and 10/19 (59.9%) rhinoorbital mucor. Hematologic malignancy was observed in 15 (78.95%) patients, whereas others had additional pre-disposing factors, such as diabetes mellitus and chronic renal failure. The most common find-ings were persistent fever, mucopurulent nasal flux, and periorbital edema. Endoscopic sinus surgery + medication was administered in 12/19 (62.2%) patients and antifungal therapy in 7/19 (37.8%). In addition, 15/19 (79.95%) patients died and 4/19 recovered with sequela.

Conclusion: The first large-scale mucormycosis study from our country will guide in determining the treatment algorithm. Effective and early surgery and antifungal application reduce mortality in mucormycosis by early diagnosis and multidisciplinary approach, without bone destruction in the paranasal sinus computed tomography with recurrent fever and earlystage sinusitis finding by performing a biopsy.

Keywords: Fungal infection, mucormycosis, hematology

ÖZ

Amaç: Mukormikoz, yüksek mortaliteye sahip zigomiset sınıfının mucorales bölümünde yer alan, küf mantarlarının neden olduğu agresif ilerleyen invaziv bir mantar enfeksiyonudur. Hematolojik maligniteli hastalarda en sık görülen mantar enfeksiyonu olarak karşımıza çıkmaktadır.

Yöntemler: Çalışmamızda Ocak 2015-Aralık 2019 tarihleri arasında mukormikoz tanısı alan hastalar retrospektif olarak değerlendirildi. Hastaların demografik özellikleri, hematolojik hastalıkları ve komorbiditeleri, radyolojik değerlendirmeleri, semptom ve bulguları, tedavileri ve sonuçları değerlendirildi.

Bulgular: Olgularımız 9/19 (%47,37) maksillofasiyal ve 10/19 (%59,9) rinoorbital mukor hastalarıydı. Hastaların 15'inde (%78,95) sadece hematolojik malignite varken, diğerlerinde diabetes mellitus ve kronik böbrek yetmezliği gibi ek predispozan faktörler vardı. En sık görülen bulgular inatçı ateş, mukopürülan burun akısı ve periorbital ödemdi. Hastaların 12/19'u (%62,2) endoskopik sinüs cerrahisi + antifungal tedavi ve 7/19'u (%37,8) sadece antifungal tedavi gördü. Hastaların 15/19'u (%79,95) öldü ve bunların 4/19'u sekel ile iyileşti.

Sonuç: Ülkemizden ilk büyük ölçekli mukormikoz çalışması, tedavi algoritmasının belirlenmesi açısından yol gösterici olacaktır. Erken tanı ve multidisipliner yaklaşımla, etkili ve erken cerrahi ve antifungal uygulama ve biyopsi ile, mukormikozda mortalitenin, tekrarlayan ateş ile paranazal sinüs bilgisayarlı tomografide kemik destrüksiyonu olmaksızın, azaltılabileceğini düşünmekteyiz.

Keywords: Fungal enfeksiyon, mukormikoz, hematoloji

Introduction

Mucormycosis is an aggressive-progressive invasive fungal infection caused by mold fungi in the division of mucorales of the zygomycetes class (1,2), which is the most common fungal infection after Aspergillus spp. in patients with stem cell and solid organ transplantation (3,4). The true incidence of the disease is unknown; however, its incidence in the United States is 1.7/1000000 per year with approximately 500 cases per year (5). The incidence of autopsies performed in the risky patient

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Cite this article as/Atıf: Sarı ND, Serin I, Kırgezen T, Doğu MH. Mucormycosis in Hematologic Malignancies: Clinical Follow-Up and Treatment Results. İstanbul Med J 2021; 22(4): 245-9.

Received/Geliş Tarihi: 02.02.2021
Accepted/Kabul Tarihi: 21.06.2021

group was 8-13%, as it is responsible for 10% of the invasive mold-fungal infections in the high-risk patient group (6,7).

Disease prevalence is high in patients with uncontrolled diabetes mellitus (DM), especially in undeveloped countries; however, it was reported in patients with hematologic malignancy and organ transplantation (8,9). In recent years, mucormycosis cases were reported under posaconazole prophylaxis, and was published that voriconazole prophylaxis causes a mucormycosis predisposition (10-13).

Turkey has very few numbers of reported mucormycosis incidences and publications with hematologic malignancy at the level of case reports, without case series. This study aimed to retrospectively evaluate patients with hematologic malignancies and mucormycosis, who were followed and treated in our hospital.

Methods

Our single-center retrospective study examined mucormycosis cases over the age of 18 years with hematologic malignancy between January 2015 and December 2019 with the approval of the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethical Committee (approval number: 2204, date: 21.02.2020). Informed consent was obtained from all participants. The diagnosis was made based on the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) (14) diagnostic criteria. Demographic features, additional comorbidities, laboratory, clinical, and treatment results of the cases were evaluated through the hospital registration system.

Statistical Analysis

This study contains descriptive data of the patient group. STATA software version 12.0 was used to analyze patient data. Data results were given as mean, standard deviation, or median and interquartile range according to their suitability. Informed consent was obtained from patients for clinical information and result utilization.

Results

Out of 19 patients who met the study criteria, 12 were female and 7 were male, and the median age was 58 years (range: 23-84). Apart from hematologic malignancy, predisposing conditions were determined as DM, chelation therapy (using deferoxamine), and additional immunosuppressive therapy. According to the EORTC/MSG criteria, 12/19 (63.16%) were evaluated as definite and 7/19 (36.84%) were possible mucormycosis. The cases had hematologic malignancy in 12/19 (63.16%) and multiple predisposing factors in 7/19 (36.85%). Case diagnoses were evaluated as follows: Acute myeloid leukemia (AML) (n=6), myelodysplastic syndrome (MDS) (n=6), acute lymphocytic leukemia (n=4), and lymphoma (n=3).

Paranasal sinus computed tomography (CT), which was the first choice in radiological imaging, was evaluated as rhinosinusal (RS) with isolated sinus involvement and rhinoorbital (RO) with orbital involvement. RO was classified in 9/19 (42.1%) of cases and RS in 10/19 (57.9%). In addition to the cases evaluated as RO (n=10), orbital magnetic resonance imaging (MRI) was performed. Of these cases, 62.2% were operated on and histopathologically confirmed. The demographic and clinical characteristics of the cases were evaluated in the study as presented in Table 1. The most common symptoms and signs was high fever in 17 patients (89.47%), mucopurulent nasal discharge in 15 patients (78.95%), percent sensitivity in 12 (63.16%), periorbital edema in 11 (57.90%), redness in 9 (47.37%), paralysis in 8 (42.11%), palate necrosis in 5 (26.32%), proptosis (21.05%) in 4, and exophthalmos (15.79%) in 3.

Our study calculated the annual disease incidence over 10000 applications/year and is 0.02-0.3/10000 between 2015 and 2019, as shared in Figure 1.

Mycological cultures were made in 7 cases, but in 2 Mucor spp. reproduction was detected, without possible typing. However, histopathological confirmation was provided in all patients who are operated on.

Considering the most common symptoms and signs, 17 patients (89.47%) had a high fever, 15 (78.95%) had mucopurulent nasal discharge, 12 (63.16%) had face sensitivity, 11 (57.90%) had periorbital edema, 9

Table 1. Demographic characteristics, clinical forms, hematologic diseases, and therapeutic outcomes of patients

	n (%)
Age, median (range)	58 (23-84)
Genter (male/female)	7/12
Hemotologic diseases/comorbidities	
AML	5 (26.32)
ALL	4 (33.33)
Lymphoma	2 (10.53)
AA	2 (10.53)
MDS	2 (10.53)
MM + DM* + CRF*	1 (5.26)
AML + DM*	1 (5.26)
MDS + DM* + CRF*	2 (10.53)
Antifungal use	**11 (57.89)**
Fluconazole	4 (33.33)
Posaconazole	3 (15.79)
Voriconazole	4 (33.33)
Anatomical localization	
Maxillofacial	9 (42.1)
Rhinoorbital	10 (57.9)
Treatment	
Endoscopic sinus surgery + medication	12 (62.2)
Only medication	7 (37.8)
Outcome	
Death	15 (79.95)
Mucor	12 (63.15)
Myocardial infarction	2 (10.53)
Hemorrhage	1 (5.26)
Recovery	4 (33.33)

AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia, AA: Aplastic anemia, MDS: Myelodysplastic syndrome, MM: Multiple myeloma, DM*: Diabetes mellitus, CRF*: Chronic renal failure

(47.37%) had redness, 8 (42.11%) had paralysis, 5 (26.32%) had palate necrosis, 4 (21.05%) had proptosis, and 3 (15.79%) had exophthalmos. Symptoms and findings of patients are demonstrated in Table 2.

Posaconazole prophylaxis was given to 3/19 (15.79%) cases, whereas 4/19 (21.05%) were taking voriconazole 2x4 mg/kg/day with high-possible invasive fungal infection. Liposomal amphotericin B (L-AMB) 1x5-6 mg/kg/day was administered to all patients diagnosed with mucor and 2 patients, without previously posaconazole prophylaxis treatment, received posaconazole and L-AMB combination therapy. The mean anti-fungal application time was 55.63 (3-260) days, 102.5 (20-260) days for survivors, 49.27 (3-100) for non-survivors. Posaconazole and L-AMB combination was administered in 2 of the surviving cases. The overall mortality rate was 79.95% and mortality attributed to mucor was 63.15% (3 patients died due to different reasons).

Discussion

Mucormycosis is an angioinvasive fungal infection with hematologic malignancy, especially in patients receiving chemotherapy and/or immunosuppressive therapy, causing sudden onset and high mortality. The causative spores of fungi are found mostly in soil, rotten fruits and vegetables, and moldy foods. Spores settle on the sinuses through inhalation or on the mucous membrane by contact cause invasion, vascular occlusion, and diffuse tissue necrosis in the vascular endothelium in cases with dysfunctional phagocytosis and neutrophil functions. Host defense determines the disease spread; therefore, in addition to hematologic malignancy, they are at high risk situations due to the following: diabetic ketoacidosis, intense and long-term corticosteroid use, premature birth, human immune deficiency virus, and patients who underwent solid organ transplantation. Therefore, despite the systemic antifungal usage and aggressive surgical debridement, mortality is very high (15-17), which was rarely reported in healthy people after iatrogenic injuries and after natural disasters such as volcano eruption and proboscis (18-21).

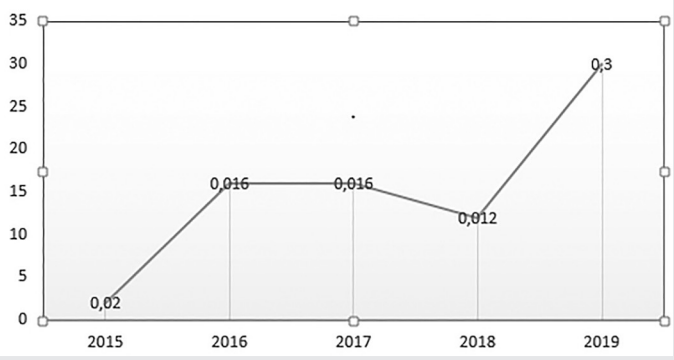

Figure 1. 10000 applications/year incidence between 2015 and 2019

*Demonstrates the change in the incidence of mucormycosis in patients diagnosed with hematological malignancies in our center between 2015 and 2019

Table 2. Symptoms and findings of patients

Symptoms/findings n (%)
Fever 17 (89.47)
Mucopurulent discharge 15 (78.95)
Facial sensitivity 12 (63.16)
Periorbital edema 11 (57.90)
Redness 9 (47.37)
Paralysis 8 (42.11)
Palate necrosis 5 (26.32)
Propitozis 4 (21.05)
Exophthalmos 3 (15.79)

Its clinical course was known for a long time; however, its epidemiology remains undetermined. Patients with hematological malignancy and organ transplantation are at the forefront in developed countries; however, uncontrolled DM ranks first in developing countries, such as Iran and India (8,22-25). A study from Turkey by Kursun et al. (26) determined DM as 50% and hematologic malignancy as 18% in series of 28 cases. The study of Arda et al. (27) reported hematologic malignancies as 50% and DM as 25%. A meta-analysis that included 851 cases by Jeong et al. (28) revealed that DM was 40%, hematological malignancy was 33%, and organ transplantation was 14% as predisposing.

The annual incidence was 0.47/10000 in the study from Lebanon; however, another study for DM was reported as 10.31/10000 (29,30), whereas Our study calculated the annual incidence as 0.073/10000 years for patients with hematological malignancies (Figure 1).

The annual incidence was 0.47/10000 in the study from Lebanon, with DM as 10.31/10000, whereas our study calculated it as 0.073/10000 per year for patients with DM.

The definitive diagnosis is made by histopathological examination; however, imaging methods help determine the invasion and complications rather than the disease diagnosis. CT demonstrated bone destruction and MRI provides more information in the intracranial and orbital structure invasion evaluation (31). McDonogh et al. (32) emphasize the need to suspect mucormycosis when symptoms of sinusitis are seen clinically and radiologically in patients with immune deficiency or DM. Mucosal sinus CT should be taken in all our patients to detect mucosal thickening in the early stages. Bone destruction is an early sign for mucor (n=10), thus an orbital and facial MRI was taken to determine the orbital spread. RO was observed in 9/19 (42.1%) cases and RS in 10/19 (57.9%).

Mucormycosis begins with necrosis in the palate or sinuses reaching the orbital and brain tissues (33). Patients usually present with facial paralysis and headache, fever, and signs related to soft tissue inflammations. Depending on the necrosis, black creams on the palate and nose are observed. Symptoms and findings detected in our study were resistant fever (89.47%), mucopurulent nasal discharge (78.95%), and facial area pain (67.2%) in both groups. Palate necrosis was seen in 26.32% in RS localization, neurological symptoms were seen in RO localization; paralysis in 47.37%, proptosis in 21.05%, and exophthalmos in 15.79%.

For a definitive diagnosis, a deep biopsy sample is taken from the suspicious nasal and/or oral mucosal lesions and fresh tissue samples are examined by histopathological and microbiological methods; septum-free, randomly-branching hyphae should be seen and macroscopic and

microscopic examination of colonies that were grown in Sabouraud dextrose agar media should be done (34). The review of Jeong et al. (28) achieved a histopathological diagnosis of 88%.

The underlying disease must be corrected to use systemic antifungal therapy in mucormycosis treatment, removal of necrotic tissues due to invasion and thrombosis, and host defense recovery. Operation decision in patients with hematologic malignancy becomes difficult due to factors, such as thrombocytopenia, anemia, and coagulation pathologies. Therefore, earlier antifungal therapy initiation is vital. A study by Chamilos et al. (35) retrospectively evaluated 70 patients with hematologic malignancies, which revealed a two-fold increase in mortality 12 weeks after diagnosis in patients in which anti-fungal therapy was started after the 6th day following the mucor diagnosis. In our study, all patients received L-AMB after a paranasal sinus CT. The average time of operation of patients was 4.4 (1-15) days after CT.

Statistical comparison was not made due to a small case group. Our overall mortality rate was 15/19 (79.95%); however, three of our cases died due to non-mucormycosis reasons. Mortality attributed to mucor was calculated as 63.15%. According to published studies, the mortality rate varies between 30% and 69%. The survivor evaluation revealed that most of them were RS located, with the time of operation at 2.2 (1-18) days after the paranasal sinus CT, and the average duration of antifungal therapy was 102.5 (90-120) days. Survivors used 62.8% (35-92) L-AMB and were cured with a posaconazole (800 mg PO/day) tablet within 172.6 (75-354) days.

Posaconazole is an azole with anti-mucor activity. Suspension form absorption is directly related to food and its consumption is recommended with a fatty or high-calorie meal. In our country, the first approved suspension form for invasive fungal infection prophylaxis during MDS and AML induction therapy was firstly used in our cases. In our series (n=5), patients who developed mucor under prophylaxis (15.79%) were using posaconazole (3x200 mg/day), but three of these cases were used for <10 days.

This retrospectively planned study was unable to evaluate the effective dose at a blood concentration level of the drug. Different studies reported that breakthrough infections develop under posaconazole prophylaxis and inappropriate usage of the recommended prophylactic medication (36-38). Posaconazole tablet was used after discharge in patients using L-AMB at the hospital. Posaconazole tablets were preferred due to their high efficacy, good tolerability, and low drug interaction.

Study Limitations

The most important limitation of the study was the small patient group. The difference in the time to surgery was an important obstacle to make a comparison between patients.

Conclusion

In our country, published case-based reports are limited and we believe that it is the first large-scale mucormycosis study conducted in a group of patients with hematologic malignancies, which will shed light on the future treatment algorithm determination. In this study, effective surgery and antifungal application reduce mucormycosis mortality by performing an early diagnosis with a multidisciplinary approach and biopsy sampling with persistent fever before bone destruction in the paranasal sinus CT and before further development.

Acknowledgments: We respectfully remember all the colleagues we lost in the COVID-19 fight.

Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2204, date: 21.02.2020).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - T.K., Concept - N.D.S., T.K.; Design - N.D.S., I.S.; Data Collection or Processing - N.D.S., T.K.; Analysis or Interpretation - I.S.; Literature Search - N.D.S., M.H.D.; Writing - M.H.D, I.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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