Comparative Evaluation of COVID-19 Associated Mucormycosis (CAM) and Non-COVID-19-associated Mucormycosis (non-CAM)

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ABSTRACT

Objective: To compare COVID-19 associated mucormycosis cases (CAM) with non-COVID-19 associated mucormycosis (non-CAM) cases followed as in-patients.

Study Design: Observational Study.

Place and Duration of Study: Department of Infectious Diseases and Clinical Microbiology, Adana City Training and Research Hospital, Health Sciences University (HSU), Adana, Turkey, between January 2018 and March 2022.

Methodology: Patients with a diagnosis of mucormycosis (proven and probable) were dichotomised as COVID-19 associated mucormycosis and non-COVID-19 associated mucormycosis cases. Both groups were compared for underlying malignancy, chemotherapy, antifungal therapy related side effects and overall survival.

Results: Of the 35 cases enrolled in the study, 17 (48.6%) had CAM and 18 (51.4%) had non-CAM. A statistically significant difference was detected between non-CAM and CAM cases in terms of haematological malignancy, receiving chemotherapy, and antifungal therapy-related side effects (p=0.019, p=0.019, and p=0.027 respectively). Steroid use was found as a risk factor for the diabetic CAM cases (p<0.0001). The difference between the CAM and non-CAM cases in terms of overall survival was not statistically significant (p=0.088).

Conclusion: Because of the ongoing COVID-19 pandemic and the increasing number of critical patients, treatment of COVID-19 should be performed cautiously in patients who have the risk of developing CAM, particularly those with diabetes and immunosuppression (haematologic malignancy, receiving steroid or chemotherapy, *etc*.) and these patients should be monitored closely.

Key Words: *Mucormycosis, COVID-19, Mucormycosis associated with COVID-19, Diabetes mellitus, Turkey.*

How to cite this article: Oruc E, Gulen TA, Turunc T, Ekici NY, Unal N. Comparative Evaluation of COVID-19 Associated Mucormycosis (CAM) and Non-COVID-19-associated Mucormycosis (non-CAM). *J Coll Physicians Surg Pak* 2023; **33(02)**:153-157.

INTRODUCTION

Mucormycosis is a rare, rapidly-progressive fungal infection associated with angio-invasion and has a mortality rate of 40-80% unless diagnosed.[1] Mucormycosis is classified into six clinical categories as rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and other localisations depending on the clinical presentation and the anatomic localisations.[2]

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Received: September 06, 2022; Revised: December 03, 2022; Accepted: December 29, 2022
DOI: https://doi.org/10.29271/jcpsp.2023.02.153

Uncontrolled diabetes mellitus (with or without ketoacidosis), neutropenia, haematological malignancies, organ transplantation, the use of immunosuppressant drugs usages such as corticosteroids, excessive iron load (desferrioxamine use, *etc*.), and impaired skin integrity (due to trauma, burnt, *etc*.) are among the risk factors for mucormycosis.[3-5] Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (*SARS-CoV-2*), which is a new coronavirus that has been first identified in 2019 in China, has led to a worldwide pandemic resulting in 510,270,667 confirmed cases and 6,223,526 confirmed deaths to date.[6] In India, cases of invasive mucormycosis, also known as black fungus infection, increasing in number up to 9000 have been reported synchronously with the rising second wave of COVID-19.[7] During *SARS-CoV-2* pandemic, steroids have been prescribed by clinicians at an amount and for a duration quite exceeding those recommended by the World Health Organisation (WHO). As a consequent, patients' immune system has been suppressed, blood glucose regulation has been impaired, and patients have

become more susceptible to mucor molds regardless of the presence of diabetic conditions.[8] Such increment in the incidence of COVID-19 associated mucormycosis (CAM) has become an urgent concern worldwide and made the pandemic scenario more complex. The clinicians were dealing with the treatment of patients who had COVID-19 and providing care for them during *SARS-CoV-2* pandemic; on the other hand, they had to endeavour to diagnose and treat mucormycosis infections occurring in susceptible cases due to the treatment of COVID-19. The characteristics of CAM cases with diabetes[9] and non-COVID-19 associated mucormycosis (non-CAM) cases with diabetes have been highlighted earlier.[9,10] The present study aimed to compare CAM with non-CAM cases followed as in patients in a tertiary care hospital.

METHODOLOGY

Patients at the age of >18 years, who met the criteria for proven or probable mucormycosis based on the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/ MSG)[11], were followed between January 2018 and March 2022 as inpatients in the HSU Adana City Training and Research Hospital, were enrolled in this retrospective study. The protocol of the study was approved by the ethical committee of Adana City Training and Research Hospital, Health Sciences University (HSU), Adana, Turkey, (Approval No. 1927).

Patients' hospital records were retrospectively screened and those with data meeting the following EORTC/ MSG criteria were included in the study. The patients were then dichotomised according to the definition of CAM and non-CAM described below.[5] Patients younger than 18 years of age and patients who were diagnosed with mucormycosis in another centre and hospitalised in the hospital for treatment were excluded from the study.

Proven mucormycosis meant the presence of direct microscopic and/or culture-dependent microbiologic confirmation, or histopathologic confirmation in a clinically/radiologically suspected mucormycosis case. Probable mucormycosis meant the presence of supportive diagnostic nasal endoscopy findings and/or radiological findings supportive of mucormycosis in a clinically suspected mucormycosis case. COVID-19 associated Mucormycosis (CAM) meant positivity of *SARS-CoV-2* polymerase nucleic acid chain reaction (PCR) test at the time of or 12 weeks before the diagnosis of mucormycosis in combination with related symptoms. Non-COVID-19 associated mucormycosis (non-CAM) meant absence of the positivity of *SARS-CoV-2* polymerase nucleic acid chain reaction (PCR) test at the time of or 12 weeks before the diagnosis of mucormycosis in combination with absence of related symptoms.

Patients' demographic, radiological, histopathological and microbiological characteristics, comorbidities, and diagnostic and treatment methods were retrieved from electronic patient records and were recorded in the case report forms. Tissue biopsy materials obtained from clinically suspected mucor patients were first inoculated into SGA medium. Thereafter, the samples were kept in 10% potassium hydroxide for 15 minutes and then subjected to direct microscopic examination. Non-septate or pauciseptate hyphae structures with irregular ribbon--like appearance and 90-degree branching that vary in width was searched. The plates were incubated for 2-5 days both at 30°C and at 37°C. Mucorales tended to reproduce rapidly and filled the entire petri dish within a few days. After macromorphological and micromorphological evaluation of the fungi grown in the medium with lactopheneol cotton blue dye, matrix assisted laser desorption ionization time of flight (MALDI-TOF; Vitek MS BioMèrieux–IVD; Liyon, France) were used to identify the fungus.

Sections obtained from the clinical materials were stained with haematoxylin eosin and PAS. In the microscopic examination of stained preparations, and detection of non-septate hyphae branching at right angles was defined as mucor.

Descriptive statistics were presented as frequency, percentage, mean and standard deviation, median, minimum, and maximum. Categorical variables were analysed by Fisher's Exact test if the percentage of cells, where the expected value was <5, was greater than 20%, whereas, Pearson Chi-Square test was used if it was smaller than 20%. The assumption of normality was checked with the Shapiro-Wilk test. The difference between the numerical data of the two groups was analysed by independent samples t-test if the data were in accordance with the normal distribution. Analyses were done using SPSS 23.0 program. Level of statistical significance was considered to be $p<0.05$.

RESULTS

A total of 35 mucormycosis cases were evaluated. Of the cases, 23 (65.7%) were males, 12 (34.3%) were females and the mean age was 59.54±15.32 (22-84) years. According to the EORTC/ MSG criteria, 31 cases (88.6%) had proven mucormycosis and 4 cases (11.4%) had probable mucormycosis. Thirty-four cases were clinically classified as rhinocerebral (5 cases rhinoorbital, 5 cases nasal, and 24 cases rhinoorbitocerebral) and one was classified as disseminated mucormycosis. Diabetes mellitus 80% (n= 28) was the most common comorbidity. Among the cases with diabetes, 18 (64.2%) had ketoacidosis.

There was statistically significant difference between non-CAM and CAM cases in terms of haematological malignancy, receiving chemotherapy, and antifungal drug-related side effects $p=0.019$, $p=0.019$, and $p=0.027$ respectively). Steroid use was found to be a risk factor for the diabetic CAM cases ($p<0.001$). Comparison of demographic characteristics, site of clinical involvement and treatment outcomes between CAM and non-CAM patients is summarised in Table I.

All cases underwent paranasal tomography, with additional magnetic resonance imaging (MRI) of the cranium and orbita performed in the patients considered to have cranial and orbital involvement. An appearance suggestive of mucormycosis was detected in 12 (34.3%) of the cases that underwent cranial MRI

and in 15 (78.9%) of the cases that underwent orbital MRI. Radiological findings of the cases are demonstrated in Table II.

Endoscopic sinus surgery was performed in 74.3% (n=26) of the cases, and all cases received systemic antifungal therapy (Liposomal amfotericin B, 5 mg/kg IV). Sixteen cases had undergone orbital exenteration. It was detected that only three cases were healed without sequel, while two cases were healed with loss of vision and one case was healed with hemiplegia and loss of vision.

Table I: Characteristics of CAM and non-COVID-19 associated mucormycosis patients.

	CAM= 17 N (%)	Non-CAM=18 N (%)	p 1,2,2
Mean age (year)	62.12±14.26	57.11±16.29	0.342[1]
Gender (Female/Male)	(23.5%) 4/13 (76.5%)	(44.4%) 8/10 (55.6%)	0.289[2]
Diabetes mellitus (DM)*	16 (94.1%)	12 (66.6%)	0.088[3]
Diabetic ketoacidosis (DKA)	9 (52.9%)	9 (%50)	0.862[2]
Haematologic disease**	0	6 (33%)	0.019[3]
Kidney transplantation	1 (%)	0	0.486[3]
Steroid use	17 (100%)	0	<0.0001[2]
Chemotherapy use	0	6 (33%)	0.019[3]
Site of involvement			0.252[3]
Nasal	4 (23.5%)	1(5.6%)	
Rhinocerebral***	13 (76.5%)	16 (88.8%)	
Disseminated		1 (5.6%)	
Pathologic diagnosis	16 (94.1%)	15 (83.3%)	0.603[3]
Growth in the culture			0.589[3]
No growth	1 (7.7%)	2 (20%)	
Mucor spp	9 (69.2%)	5 (50%)	
Rhizopus oryzae	3 (23.1%)	3 (30%)	
Surgical intervention			
Exentration	8 (47.1%)	8 (44.4%)	0.877[2]
Antifungal drug side effect	9 (52.9%)	16 (88.9%)	0.027[3]
Result			0.088[3]
Exitus	12 (70.6%)	17 (94.4%)	
Healing/healing with sequel	5 (29.4%)	1 (5.6%)	

**3 cases of acute myeloid leukemia, 1 case of aplastic anemia, and 1 case of plasma-cell cancer; **3 cases of chronic kidney disease and 1 case of chronic renal failure; ***Rhinoorbitocerebral involvement in 24 and rhinoorbital involvement in five case; [1]Independent t test, [2]Pearson Chi square test, [3]Fisher's Exact test were used.*

Table II: Radiological findings.

Radiological imaging and pathological findings	N (%)
Computed tomography of the paranasal sinuses (94.3%)	
Edema of the sinus mucosa	32 (97%)
Orbital MRI (54.3%)	15 (78.9%)
Inflammation of the periorbital muscle	7 (20%)
Cranial MRI (71.4%)	
Brain infarction	7 (20%)
Brain abscess	2 (5.7%)
Cavernous sinus involvement	2 (5.7%)
Internal carotid artery occlusion	1(2.9%)

DISCUSSION

COVID-19 caused numerous cases and deaths occurring during the first wave in 2020. In addition, during the next wave of COVID-19, mucormycosis, called as black fungus disease, caused worldwide concern. The majority of the cases occurred during the second wave of the active *SARS-CoV-2* outbreak in India and Indian Central Government announced a mucormycosis outbreak in May 2021.[8] Subsequently, cases have been reported from many countries across the world.[3,12,13]

In this study of mucormycosis afflicted patients, the gender and mean age comparison showed no statistically significant difference between the two groups. Similar to the study by Eker *et al.*,[10] this study determined that CAM cases were seen more frequently in older males compared to non-CAM cases.

In literature, the majority of cases presented with rhino-orbito-cerebral (ROC) mucormycosis; pulmonary mucormycosis was the most common clinical involvement in the cases reported from European countries such as France, England, and Italy,[14-16] which was different from the large case series reported from India.[17,18] The number of CAM cases in the present study were higher than that reported from Europe, with similar patient characteristics to the case series reported from India. This can be explained by suboptional blood glucose control in diabetic population in Turkey as compared to Europe, as well as by missing cases of pulmonary and gastrointestinal mucormycosis since it is more difficult to diagnose them.

In line with the WHO recommendations, guideline from the Ministry of Health in Turkey also recommends the use of corticosteroid therapy in COVID-19 to suppress hyper-inflammation.[19] The presence of diabetes mellitus in combination with steroid therapy increases the risk of mucormycosis by means of contributing to immunosuppression and hyperglycemia.[20] In the present study, COVID-19 cases with uncontrolled diabetes, who received steroids for the treatment of COVID-19 were complicated with mucormycosis. Steroid therapy in diabetic patients with COVID-19 should be used only in cases recommended by the guidelines, and these patients should be followed closely also after discharge from the hospital for blood glucose regulation and development of mucormycosis.

Haematological malignancy and chemotherapy are among the predisposing factors for the development of ROC mucormycosis particularly in non-diabetic patients.[16] The rates of chemotherapy and haematological malignancy were statistically significantly higher in non-CAM cases (p=0.019 and p=0.019, respectively). In this patient group, mucormycosis must be considered in the differential diagnosis since prompt diagnosis and treatment is associated with reduced mortality and morbidity.

The prevalence of ROC in non-CAM diabetes cases was reported to be 88% by Nithyanandam *et al.*, 51% by Jeong *et al.*, and 64% by Vaughan *et al.*[21-23] In two case series from Turkey, the most common clinical form was rhino-cerebral form (94-96%).[2,24] ROCM was detected in 88.9% of the non-CAM cases. Although ROC involvement in CAM cases shows variation between studies, it is seen at a rate of 74-86%.[3,13] Consistent with the literature, ROC was the most common type of involvement in our CAM cases with a prevalence rate of 76.5%. The groups showed no statistically significant difference (p=0.656) regarding the site of involvement, with ROC being the most common site in both groups. Since mucormycosis is an aggressive infection that usually spreads over the orbital or cranial area from the paranasal sinuses, radiological imaging is critical in the diagnosis. Appropriate scanning should be performed in the shortest time to detect the margin and the extension of the

disease. Paranasal CT revealed thickening and oedema of the sinus mucosa in 33 (97%) of the cases, which is consistent with mucormycosis. MRI can be used as a guide to detect intradural and intracranial infection, cavernous sinus involvement, and carotid artery thrombosis in the cavernous sinus. MRI is more sensitive than CT in visualising the orbital soft tissues.[14] An appearance suggestive of mucormycosis was detected in 34.3% by cranial MRI and in 78.9% by orbital MRI.

Early diagnosis, treatment of the predisposing situation, surgical removal of the infected tissue, and appropriate antifungal therapy is critical in the treatment of this fatal disease. Liposomal amphotericin B (LAmB), which is recommended as the first-line therapy, is an antifungal agent that can be used at high doses and shows good penetration to the brain with lower side effects.[23] It was detected that all cases in the present study had received parenteral LAmB therapy at a daily dose of 5 mg/kg. Of the cases, 71.4% developed side effects associated with LAmB therapy. The frequency of side effects was statistically significantly higher in the non-CAM cases (p=0.027). The present authors believe this to be due to the fact that non-CAM cases of haematological malignancy patients receiving chemotherapy constitute the vast majority. The most common side effects were acute renal failure and hypokalemia. Every patient who is receiving LAmB therapy requires close monitoring.

Tissue necrosis reduces the penetration of antifungal therapy into the infected area, and therefore the most critical step in treatment is the removal of necrotic tissue by surgical debridement. Besides, surgical debridement prevents the extension of infection to the other organs. In a meta-analysis, it was demonstrated that mortality remarkably decreased with the combination of surgery and antifungal therapy as compared to antifungal therapy alone.[25] In the present study, surgical debridement using endoscopic sinus surgery was performed in 26 (74.3%), and exenteration of the orbit was performed in 16 (45.7%) of the patients. The mortality rate was 82.9%. Survival rates showed no statistically significant difference between the cases (p=0.088). In the present study, the mortality of CAM cases was found to be lower than the mortality of non-CAM cases similar to the study of Eker *et al.*[10] This can be explained by the fact that the transient immunosuppression of the patients can be corrected with adequate supportive treatment and high doses of liposomal amphotericin-B. Only three cases were healed without a sequel, while 2 cases were healed with loss of vision, and one case was healed with hemiplegia and loss of vision.

The small sample size and retrospective study design are the main limitations of the present study. However, it is the first study on this subject covering different patient groups from Turkey with the largest sample size to date.

CONCLUSION

Mucormycosis is an angioinvasive fungal infection with increasing incidence also in COVID-19 cases. Unnecessary corticosteroid use is the main risk factor for mucormycosis, especially in diabetic patients during the COVID-19 pandemic. Mortality can be reduced by early diagnosis and treatment achieved by clinical suspicion. In order to suppress hyper-inflammation in COVID-19 patients, it would be reasonable to use the corticosteroids in the patient groups defined in the guidelines and to monitor the patients who are likely to develop CAM cautiously and closely.

ETHICAL APPROVAL:
The protocol of the study was approved by the ethics committee of Adana City Training and Research Hospital, Health Sciences University (HSU), Adana, Turkey (Approval No. 1927).

PATIENTS' CONSENT:
In keeping with the policies for a retrospective review, the informed consent requirement was waived.

COMPETING INTEREST:
The authors declare no competing interest.

AUTHORS' CONTRIBUTION:
EO: Conception and design of work. The acquisition, analysis, and interpretation of data. Drafting the work and reviewing it critically for important intellectual content. Revision of the manuscript.
TAG: Data curation, literature reviewing, and statistical analysis.
TT: Data curation, literature reviewing, and visualisation.
NYE: Data curation and literature review.
NU: Literature reviewing and drafted the manuscript.
All authors contributed to the study conception and design. All authors have read and approved the final version of the manuscript.

REFERENCES

1. Miller MA, Molina KC, Gutman JA, Scherger S, Lum JM, Mossad SB, *et al*. Mucormycosis in hematopoietic cell transplant recipients and in patients with haematological malignancies in the era of new antifungal agents. *Open Forum Infect Dis* 2020; **8(2)**:ofaa646. doi: 10.1093/ofid/ ofaa646.
2. Kursun E, Turunc T, Demiroglu YZ, Alışkan HE, Arslan H Evaluation of 28 cases of mucormycosis. *Mycoses* 2015; **58(2)**:82-7. doi: 10.1111/myc.12278.
3. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, *et al*. The emergence of COVID-19 associated mucormycosis: A review of cases from 18 countries. *Lancet Microbe* 2022; **3(7)**:e543-e552. doi: 10.1016/S2666-5247(21)00237-8.
4. Demiroğlu YZ, Turunc T, Erkan AN, Alkan O, Alışkan HE, Çolakoğlu S, *et al*. Rhinocerebral Mucormycosis Treated with Posaconazole: A Case Report. *Klimik Dergisi* 2010; **23(3)**:130-3. doi: 10.5152/kd.2010.34.
5. Honavar SG. Code mucor: Guidelines for the diagnosis, staging and management of rhino-orbito-cerebral mucormycosis in the setting of COVID-19. *Indian J Ophthalmol* 2021; **69(6)**:361-65. doi: 10.4103/ijo.IJO_1165_21.
6. WHO coronavirus (COVID-19) Dashboard WHO coronavirus (COVID-19) dashboard with vaccination data. Available from: http://COVID19.who.int/).
7. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in

COVID-19: A systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr* 2021; **5(4)**:10214. doi: 10.1016/j.dsx.2021.05.019.

8. Hagen A. COVID-19-Associated Mucormycosis: Triple threat of the pandemic. asm.org/articles/2021/july/COVID-19-associated-mucormycosis-triple-threat-of 15 july 2021.
9. Bayram N, Ozsaygılı C, Sav H, Tekin Y, Gundogan M, Pangal E, *et al.* Susceptibility of severe COVID-19 patients to rhino-orbital mucormycosis fungal infection in different clinical manifestations. *JPN J Ophthalmol* 2021; **65(4)**:515-25. doi: 10.1007/s10384-021-00845-5.
10. Eker C, Tarkan O, Surmelioglu O, Dagkiran M, Tanrisever I, Yucel Karakaya SP, *et al*. Alternating pattern of rhino-orbital-cerebral mucormycosis with COVID-19 in diabetic patients. *Eur Arch Otorhinolaryngol* 2022; **29**:1–8. doi: 10.1007/s00405-022-07526-0.
11. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, *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(6)**:1367-76. doi: 10.1093/cid/ciz1008.
12. Dilek A, Ozaras R, Ozkaya S, Sunbul M, Sen E, Leblebicioglu H. COVID-19-associated mucormycosis: Case report and systematic review. *Travel Medicine and Infectious Disease* 2021; **4**:102148. doi: 10.1016/j.tmaid.2021.102148.
13. Pal R, Singh B, Bhadada SK, Banerjee M, Bhogal RS, Hage N, *et al*. COVID-19- associated mucormycosis: An updated systematic review of literature. *Mycoses* 2021; **64(12)**: 1452–9. doi: 10.1111/myc.13338.
14. Patel A, Agarwal R, Rudramurthy SM. Multicentre epidemiologic study of Coronavirus disease-associated mucormycosis. *India. Emerg Infect Dis* 2021; **27(9)**: 2349-59. doi: 10.3201/eid2709.210934.
15. Selarka L,Sharma S, Saini D, Shevkani M, Xess I, Sharma R, *et al*. Mucormycosis and COVID-19: An epidemic within a pandemic in India. *Mycoses* 2021; **64(10)**:1253-60. doi: 10.1111/myc.13353.
16. Bellanger AP, Navellou JC, Lepiller Q, Brion A, Brunel AS, Millon L, *et al*. Mixed mold infection with Aspergillus fumigatus and Rhizopus microsporus in a severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) patient. *Infect Dis* 2021; **51(7)**:633-5. doi: 10.1016/j.idnow. 2021.01.010.
17. Hanley B, Naresh KN, Roufosse C, Nicholson AG, Weir J, Cooke GS, *et al*. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: A post-mortem study. *Lancet Microbe* 2020; **1(6)**:e245-e253. doi: 10.1016/S2666-5247(20)30115-4.
18. Pasero D, Sanna S, Liperi C, Piredda D, Branca GP, Casadio L, *et al*. A challenging complication following *SARS-CoV-2* infection: A case of pulmonary mucormycosis. *Infection* 2020; **49(5)**:1055-60. doi: 10.1007/s15010-020-01561-x.
19. T.C. Saglik Bakanligi Halk Sagligi Genel Mudurlugu. COVID-19, Antisitokin antiinflamatuar tedaviler, koagulopati yönetimi rehberi. 7 Kasım 2020. Available from: COVID19.saglik.gov.tr/Eklenti/39296/0/COVID-19rehberianti sitokin antiinflamatuartedavilerkoagulopatiyonetimipdf.pdf.
20. Ahmadikia K, Hashemi SJ, Khodavaisy S, Getso MI, Alijani N, Badali H, *et al*. The double-edged sword of systemic corticosteroid therapy in viral pneumonia: A case report and comparative review of influenza-associated mucormycosis *versus* COVID-19 associated mucormycosis. *Mycoses* 2021; **64**:798e808. doi: 10.1111/myc.13256.
21. Nithyanandam S, Jacob MS, Battu RR, Sánchez-Nuño YA, Davila-Villa P, Anaya-Ambriz EJ, al. Rhino-orbito-cerebral mucormycosis. A retrospective analysis of clinical features and treatment outcomes. *Indian J Ophthalmol* 2003; **51**: 231-6.
22. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, *et al*. The epidemiology and clinical manifestations of mucormycosis: A systematic review and meta-analysis of case reports. *Clin Microbiol Infect* 2019; **25**:26-34. doi: 10.1016/j.cmi.2018.07.011.
23. Narayanan S, Chua J V, Baddley JW. Coronavirus disease 2019–associated mucormycosis: risk factors and mechanisms of disease. *Clin Infect Dis* 2021; **74**: 1279-1283. doi: 10.1093/cid/ciab726.
24. Kömür S, İnal AS, Kurtaran B, Ulu A, Uğuz A, Aksu HS, et al. Mucormycosis: A 10-year experience at a tertiary care center in Turkey. *Turk J Med Sci* 2016; **46(1)**:58-62. doi: 10.3906/sag-1409-137.
25. Skiada A, Pagano L, Groll A, Zimmerli S, Dupont B, Lagrou K, *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**: 1859-86. doi: 10.1111/j.1469-0691.2010.03456.x.