RESEARCH

RHINO-ORBITAL MUCORMYCOSIS IN THE ELDERLY POPULATION AFTER COVID-19

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Abstract

Introduction: In this study, we aimed to retrospectively evaluate the characteristics of mucormycosis cases seen in our clinic during the COVID-19 pandemic, the management of their treatment and the SARS-CoV-2 variants that were dominant at that time.

Methods: The medical records of patients diagnosed with rhino-orbital mucormycosis between March 2020 and July 2022 were retrospectively evaluated.

Results: Nine patients were diagnosed with rhino-orbital mucormycosis. Of these patients, six were male and three were female, and the patients were between the ages of 65-75 (mean 69.2). After the diagnosis of mucormycosis, antifungal treatment was initiated with liposomal amphotericin-B. Eight patients underwent surgery within 48 hours, only one patient refused to undergo surgery.

Conclussions: Mucormycosis is a rapidly progressing opportunistic fungal infection. Therefore, the most basic criteria determining mortality is the early detection of about mucormycosis infection and to diagnose it as soon as possible, especially in patients with an underlying immunosuppressive condition. Once a diagnosis of mucormucosis has been established, risk factors, especially blood sugar regulation, should be corrected. Furthermore, systemic and local antifungal therapy shuold be initiated, and urgent debridement should be performed.

Keywords: COVID-19; Mucormycosis; Aged.

INTRODUCTION

On the 7th of January 2020, the WHO defined a new coronavirus (2019-nCoV) that had not been detected in humans previously. On the 11th of February 2020, the disease was named coronavirus disease-19 (COVID-19) and the virus Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2) (1,2).

Since it was detected, SARS-CoV-2, which caused the death of millions, has constantly mutated like any other RNA virus. Although many variants were detected after index virus identification in the first cases in December 2019, five were classified as variants of concern (VOC). On the 18th of December 2020, Alpha (B.1.1.7. United Kingdom), December 2020 Beta (B.1.351, South Africa), 11 th of January 2021 Gamma (S.1, Brazil), 11th of May 2021, Delta (B.1.617.2, India) and on the 26th of November 2021 Omicron (B1.1.529, in multiple countries) have been declared VOCs (3).

Mucormucosis is a rare opportunistic fungal infection (0.005 to 1.7 per million) that progresses rapidly (4). It is often caused by Rhizomucor, Mucor, and Lichthimia spp. Fungi that cause mucor infection can be found in soil and mold or suspended in air (5,6). Deterioration of the immune system, such as Diabetes Mellitus (DM), transplantation, haematological malignancies, neutropenia, iron overload, long-term steroid use, human immune defficiency virüs (HIV), skin trauma, chemotherapy or intravenous drug use, and inhaled saprophytic fungi can be found in the paranasal sinuses and colonise the nasal cavity (4,5,7). This affects the pterygopalatine fossa, eroding the paranasal sinus wall, and spreads to the brain and orbit (rhino-orbito cerebral mucormycosis) or is observed as pulmonary, cutaneous, gastrointestinal, or disseminated mucormucosis (5). These fungi cause vascular thrombosis and tissue necrosis owing to their invasive properties, and causes a black scar in the nasal cavity or hard palate, which is typical of mucormucosis (5,6).

Decreased numbers of routine doctor check-ups due to pandemics, the deterioration of the control of comorbid diseases by Covid 19 infection, high-dose steroids used due to severe COVİD-19 infection, and the need for intubation, increases the incidence of not only mucormycosis but also other opportunistic fungal infections such as candidiazis and aspergillozis (4,7). Mucormycosis infection is more dangerous than other opportunistic infections due is its ability to spread rapidly (4,7,8). A delay of even a few hours in the diagnoses of patients may cause the spread of the disease and even death. If the patient is intubated or unconscious, it is very difficult to diagnose this opportunistic infection, which progresses rapidly in the nasal passage.

In this study, we evaluated the characteristics of the mucormycosis cases referred to our clinic and the management of their treatment by evaluating the dominant SARS-CoV-2 variant periods.

METHOD

The medical records of patients diagnosed with rhino-orbital mucormycosis between March 2020 and July 2022 were evaluated retrospectively. Patients diagnosed with COVID-19 by PCR and whose mucormycosis diagnosis was confirmed by histopathological and direct microscopic methods were included in the study.

All patients diagnosed with mucormucosis were followed up by the Infectious Diseases, Ear Nose Throat (ENT), and Eye Diseases departments using a multidisciplinary approach. Demographic characteristics of these patients, initial symptoms and findings, PCR results for SARS-CoV-2, treatments they received, hospital stay duration, presence of DM and blood sugar levels, presence of other comorbid diseases, physical examination findings, imaging methods, and type of surgery were recorded for patients who underwent surgery. Paranasal sinus computed tomography (PNS-CT) and magnetic resonance imaging (MRI) were performed for all patients to evaluate eye involvement.

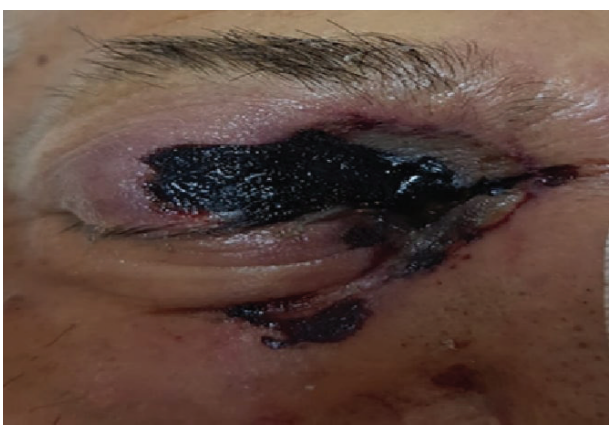
Approval for the study was granted by the University of Health Sciences Antalya Training and Research Hospital Local Ethics Committee (date: 2021, number: 333).

RESULTS:

All patients with mucormycosis were treated between June 2021 and November 2021. All patients were diagnosed with COVID-19 based on nasopharyngeal swab sample examination with SARS-CoV-2 real-time reverse transcription polymerase chain reaction (RTPCR), all of which resulted in delta variants. COVID-19 infection was defined as severe when SpO2 was <90% or the respiratory rate was >30 breaths/min at admisson or during hospitalisation(4). Nine patients were diagnosed with rinoorbital mucormucosis (Figure 1). Of these patients, six were male and three were female, and the patients were between the ages of 65–75 (mean 69.2). The patient information is presented in Table 1.

Seven patients had uncontrolled DM. The mean fasting blood glucose level of the patients was 283.27 mg/dL with a mean glycated haemoglobin (HbA1c) of 10.8% (±1.28). All patients were diagnosed by histopathological and microbiological examination of tissue samples taken from the nasal passage.

Figure 1. Rhinoorbital mucormucosis (orbita, eyelid and facial skin involvement)



The hospitalisation of patients diagnosed with mucormycosis was between 1–85 days. Once mucormycosis diagnosis was confirmed, patients were administered 5–10 mg/kg/day intravenous liposomal amphotericin B. Eight patients underwent surgery within 48 hours. Informed consent was obtained from all patients (first-degree relatives of the intubated patients) before surgery. One patient did not undergo surgery.

Medial maxillectomy and orbital exenteration were performed on the affected side in all the patients who underwent surgery. All patients underwent endoscopic sinus surgery, removal of non-viable tissues, and excision of the septum excised (Figures 2-3). Hard palate excision was performed in four patients. Postoperatively, the patients were followed-up with daily endoscopic examinations. Repeated debridement was performed in all patients during follow-up. The patients were followed up in the hospital for 20–95 days (mean 67.11 days) after the surgical intervention. Three patients were discharged from the hospital. The one patient who refused surgery died because of septic shock, and another five patients died while in the hospital due to cardiac or pulmonary causes. All the patients had unilateral eye involvement. In the patient that did not undergo surgery, the other eye was also involved 6 days after diagnosis (Figure 4).

DISCUSSION

Mucormycosis is a rapidly progressing opportunistic fungal infection (4,8,9). If there is no rapid intervention, it could reach the orbit and brain, causing death.

Although mucormycosis develops after severe COVID-19 infection, it has been reported that people who have mild illness also develop mucormycosis. The average time between COVID-19 infection and the development of mucormycosis is 15 days (6,7). However, mucormycosis infections have also been reported 42–90 days post COVID-19 infection

Table 1. Patients' informations with mucormucosis.

	Age/ Sex	Comorbidity	Vari-ant	Hba1c	Side	Corticosteroid treatment	Anti-fun-gal	Anti viral	ICU	Hos	Surgery	Mor-tality
1	73/M	DM (type 2)	Delta	13,7	Left	Dexamethasone 8 mg for 7 days	L-Amp B	Fav	Entube	62	MM+OE+ESC	Ex
2	68/F	DM (type 2), HT, Obesity	Delta	14,7	Right	Dexamethasone 6 mg for 9 days	L-Amp B	Fav	Entube	75	HPR+M-M+ESC+OE+SE	Alive
3	75/M	DM (type 1)	Delta	10,8	Left	Dexamethasone 6 mg for 10 days	L-Amp B	Fav	None	69	MM+ESC+OE+SE	Ex
4	65/F	CKF, Drug abuse	Delta	5,7	Right	Methylprednisolone 250 mg for 2 days and 80 mg for 5 days	L-Amp B	Fav	None	95	HPR+M-M+ESC+OE+SE	Alive
5	67/M	DM (type 2), HT	Delta	12,6	Right	Dexamethasone 6 mg for 10 days	L-Amp B	Fav	Entube	80	HPR+M-M+ESC+OE+SE	Ex
6	72/M	Pancreas Ca, CT, RT	Delta	4,6	Left	Methylprednisolone 100 mg for 3 days and 60 mg for 7 days	L-Amp B	Fav	None	45	MM+ESC+OE+SE	Alive
7	65/F	DM (type 2), HT	Delta	13,2	Right	Dexamethasone 6 mg for 10 days	L-Amp B	Fav	Entube	20	None	Ex
8	72/M	DM (type 2), HT	Delta	11,8	Right	Dexamethasone 6 mg for 7 days	L-Amp B	Fav	Entube	82	MM+ESC+OE+SE	Ex
9	66/F	DM (type 2), HT	Delta	10,7	Left	Dexamethasone 6 mg for 10	L-Amp B	Fav	Entube	76	HPR+M-M+ESC+OE+SE	Ex

(DM: Diabetes Mellitus, CKF: Chronic Kidney Failure, Hos: hospitalisation time, L-Amp B (Liposomal Amphotericin-B).

Fav (Favipiravir), MM: medial maxillectomy, OE: Orbital exenteration, ESC: Endoscopic Sinus Surgery, HPR: Hard Palate Resection, SE: Septum Excision)

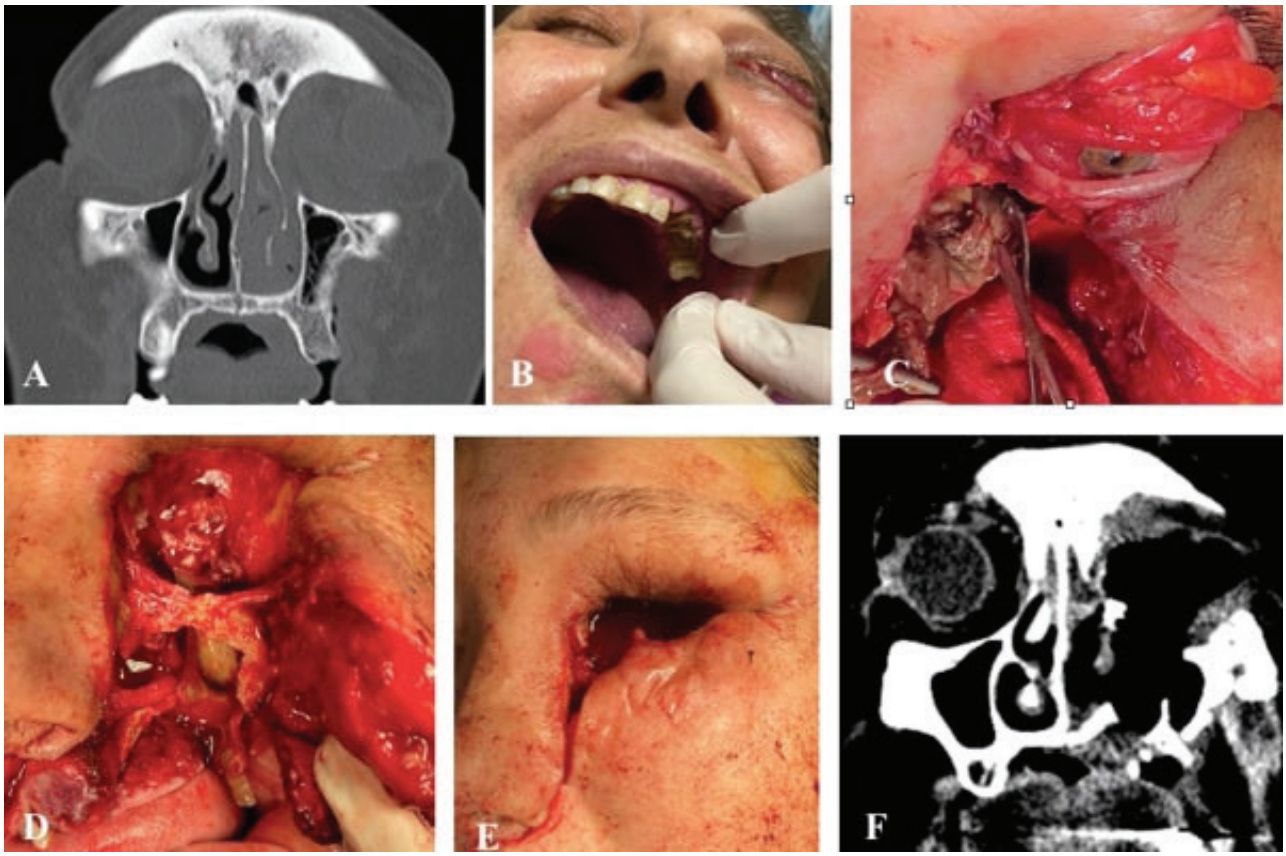
(7). Therefore, if mucormucosis is suspected, a rapid biopsy should be performed, and after histopathological and microbiological diagnoses, treatment should be started as soon as possible. Particular care should be taken in patients who are entubated, are in intensive care units, or have other predisposing factors.

The diagnosis of mucormycosis is typically made by histological and microbiological examination of the biopsy taken from the necrotic focus, with the appearance of strip-like, irregularly circumscribed, non-septate or less divided, wide hyphae, and vertically angled hyphae (4,8,10). However, it should not be forgotten that once biopsied lesions are detected, the disease has already begun. For this reason, studies aiming to detect mucor DNA in the blood and cerebrospinal fluid (CSF) are ongoing, so that diagnosis can be established before lesions occur (5).

Although there are many predisposing factors for the development of mucormycosis, DM is the most important factor determining morbidity and mortality (7,10). The acidic environment created by hyperglycaemia and ketoacidosis disrupts neutrophil chemotaxis, reduces neutrophil effects, and impairs fungal phagocytosis.

Another important risk factor for mucormycosis is steroid use. While steroids were not recommended in the treatment of COVID-19 during the first months of the pandemic, with the publication of many study results reporting the benefit of using corticosteroids to supress the systemic inflamatory over-response in severe COVID-19 patients, the Ministry of Health of our country launched a

Figure 2. A-B: Left rhinoorbital mucormucosis PNS CT and examination findings **C-E:** Subtotal maxillectomy and orbital exenteration intraoperative images **F:** Postoperative paranasal sinus CT



new COVID-19 guideline on the 2nd August 2020, instructing that "For those in need of oxygen, 6 mg/day dexamethasone (or equivalent glucocorticoids, such as 40 mg/day prednisolone or 32 mg/day methylprednisolone) can be used for 10 days" (11). It is believed that dysregulated and exessive cytokine storm may be a major cause of many metabolic problems seriously threatening the lives of COVID-19 patients, causing respiratory distress, multiple organ failure, or thromboembolic disease (12). In terms of recovery, it has been reported that steroid use was effective in reducing mortality in patients that were in need of oxygen (13). However, this high-dose steroid not only raises blood sugar in diabetic COVID-19 patients but also impairs neutrophil functions, which are the most important weapons of the immune system in fungal infections, and paves the way for opportunistic infections, especially mucormycosis (8,12).

Studies have shown that 78% of patients diagnosed with mucormycosis have a history of DM, and 85% have a history of high-dose glucocorticoid use (11). Glycaemic control is difficult to achieve when administering steroid therapy, especially in patients with diabetes and COVID-19.

In our study, only seven patients were diagnosed with DM. As all patients had severe COVID-19, they received corticosteroid therapy in the intensive care unit. There was no blood sugar level deterioration

Figure 3. A-C: Preoperative T2 sequence MRI inages of a patient with rhinoorbital mucormucosis Black arrow: Eye Involvement Star : Necrotic Tissues **D:** Intraoperative view of the patient after orbital exenteration and subtotal maxillectomy **E:** Post-operative image of the patient who was intubated due to COVID-19

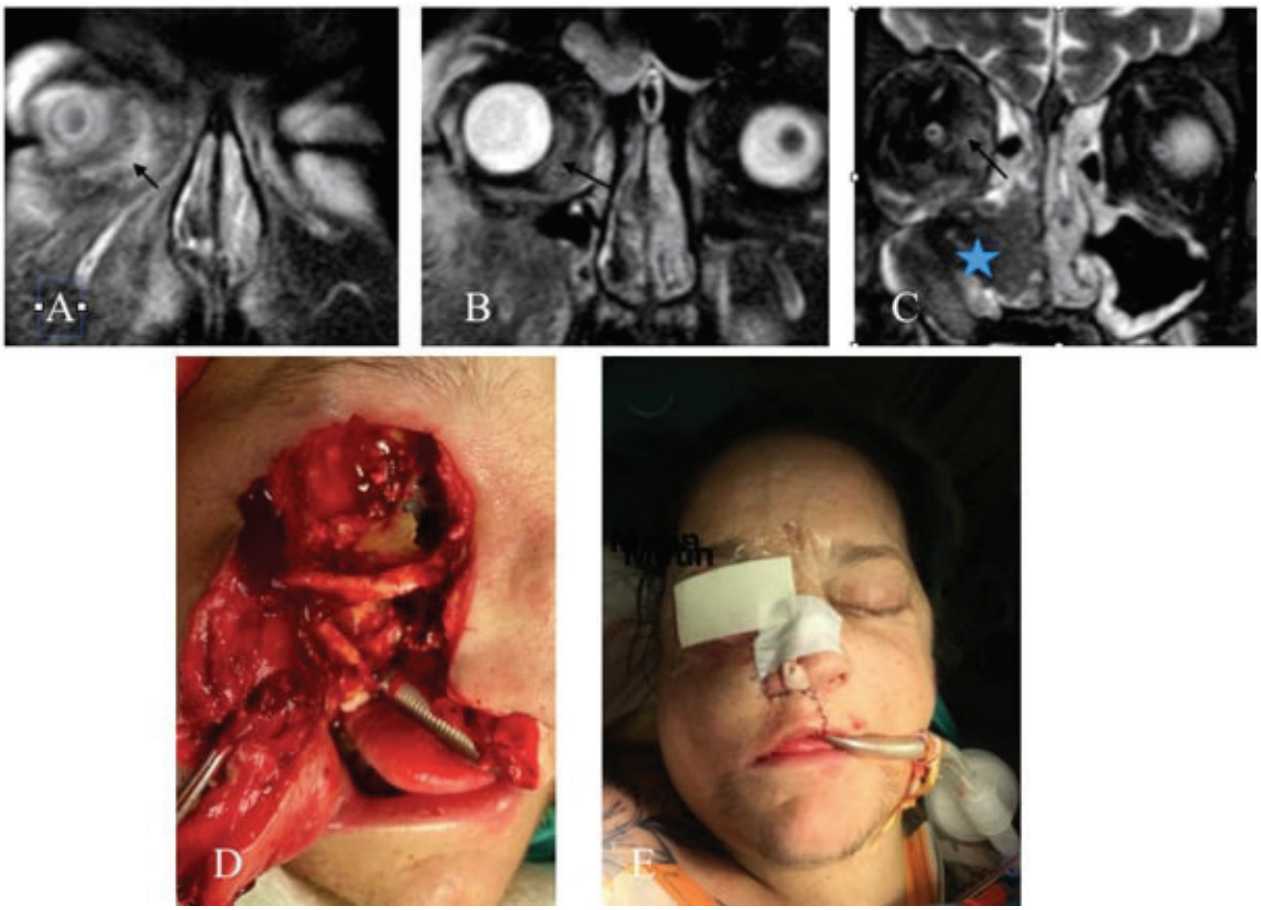
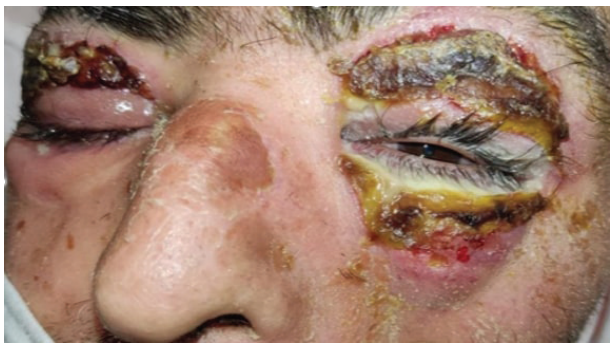


Figure 4. Bilateral eye involvement in the patient who did not accept surgery



in the two patients who did not have DM. However, one of these patients had a history of chronic renal failure and drug abuse, whereas the other had a history of chemoradiotherapy for pancreatic cancer.

In our study, all patients with mucormucosis who were diagnosed with COVID-19 were found to have delta variants. We attribute this situation to the fact that the delta variant causes more severe clinical effects than previous variants and to the increased use of corticosteroids at the intensive care unit. Therefore, opportunistic infections should be carefully considered when initiating corticosteroid treatment in patients with diabetes.

Mucormycosis is a rapidly progressing opportunistic fungal infection. Therefore, the most important criterion determining mortality in treatment is the early suspicion and diagnosis of mucormycosis infection, especially in patients with an underlying immunosuppressive state (4,8). Once mucormycosis has been diagnosed, comorbid risk factors, especially blood sugar regulation, should be corrected, and systemic and local antifungal therapy should begin. Furthermore immediate surgical debridement should also be performed. One year of treatment with posaconazole can be prescribed to patients whose condition stabilises after liposomal amphotericin B administration and surgical debridement.

Debridement should be performed at an early stage, before the infection spreads to the surrounding tissues, especially the skull base. In cases where cerebral involvement occurs, local control cannot be achieved and morbidity increases considerably. It is important to achieve local control of infections with repeated debridement. Washing the cavity with amphotericin B during debridement yielded more successful results in the local control of the infection (5,8). Although nasal and paranasal debridement is safely performed in rhino-orbital mucormycosis, there is no consensus regarding orbital involvement. Orbital orbital exenteration can be performed in collaboration with an ophthalmologist in patients with orbital involvement or permanent vision loss. However, recommending exenteration in patients without total vision loss causes some type of surgical avoidance. However, based on our clinical experience, if the infection extends out of the sinuses and reaches the orbit, exenteration is important for both local disease control and early recurrence detection after surgery.

CONCLUSION

Disease severity in COVID-19 may vary according to the variant. It should be noted that the risk of developing mucormucosis will increase in patients with comorbid diseases, especially in cases of severe COVID-19 or intensive care hospitalisations, which may increase the need for high-dose steroid use. Clinical suspicion plays an important role in the diagnosis of mucormucosis. Treatment should be performed quickly and care should be taken to perform the widest surgical debridement required.

Conflict of Interest: The authors declare that they have no conflict of interest.

REFERENCES

1. World Health Organization. Interim Guidance Diagnostic Testing for SARS-CoV-2, 2020. [Internet]. https://apps.who.int/iris/handle/10665/334254. Accessed: 11.10.2020.
2. Bhimraj A, Morgan RL, Hirsch Shumaker A et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with Coronavirus Disease 2019 (COVID-19). Clin Infect Dis 2020; 10: 1-13. (PMID: 36063397)
3. Kumar M, Sarma DK, Shubham S et al. Mucormycosis in COVID-19 Pandemic: Risk Factors and Linkages. Curr Res Microb Sci. 2021; 2: 100057. (PMID: 34396355).
4. Fazeli MA, Rezaei L, Javadirad E et al. Increased Incidence of Rhino-Orbital Mucormycosis in an Educational Therapeutic Hospital During the COVID-19 Pandemic in Western Iran: An Observational Study. Mycoses. 2021; 64 (11) : 1366-1377. (PMID: 34252988).
5. Bal KK, Alagoz S, Delibas V et al. Did COVID-19 Increase Rhinoorbitocerebral Mucormycosis?: 9 Consecutive Cases on Pandemic Days. B-ENT 2021; 17 (3): 149-154. (DOI: 10.5152/B-ENT.2021.20429).
6. Pal R, Singh B, Bhadada SK et al. COVID-19-Associated Mucormycosis: An Updated Systematic Review of Literatüre. Mycoses 2021; 64 (12): 1452-1459. (PMID: 34133798).
7. Singh AK, Singh R, Joshi SR et al. Mucormycosis in COVID-19: A Systematic Review of Cases Reported Worldwide and in India. Diabetes Metab Syndr 2021; 15 (4): 102146 (PMID: 34192610)

8. Sharma S, Grover M, Bhargava S et al. Post Coronavirus Disease Mucormycosis: a Deadly Addition to the Pandemic Spectrum. J Laryngol Otol 2021; 135 (5): 442-447. (PMID: 33827722).

9. Dallalzadeh LO, Ozzello DJ, Liu CY et al. Secondary Infection with Rhino-Orbital Cerebral Mucormycosis Associated with COVID-19. Orbit 2022; 41 (5): 616-619. (PMID: 33752571)

10. Bhattacharyya A, Sarma P, Sharma DJ et al. Rhino-Orbital-Cerebral-Mucormycosis in COVID-19: A Systematic Review. Indian J Pharmacol 2021; 53 (4): 317-327. (PMID: 34414911).

11. World Health Organization. Clinical management of COVID-19 interim guidance. 2020. [Internet]. Available from: http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/publications-and-technical-guidance/2020/clinical-management-of-covid-19-interim-guidance. Accessed:27.05.2020

12. Al-Tawfig JA, Alhumaid S, Alshukairi AN et al. COVID-19 and Mucormycosis Superinfection: the Perfect Storm. Infection 2021; 49 (5): 833-853. (PMID: 34302291).

13. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021; 384 (8): 693-704. (PMID: 32678530)