ORIGINAL ARTICLE
HEAD AND NECK SURGERY AND ONCOLOGY
DOI: 10.5152/B-ENT.2021.20429

Did COVID-19 increase rhinoorbitocerebral mucormycosis?: 9 consecutive cases on pandemic days

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Cite this article as: Bal KK, Alagoz S, Delibas V, Kuran G, Ozdas T, Yucel Ekici N. Did COVID-19 increase rhinoorbitocerebral mucormycosis?: 9 consecutive cases on pandemic days. B-ENT 2021; 17(3): 149-54.

ABSTRACT

Objective: Mucormycosis is an opportunistic infection caused by saprophytic fungi that can rapidly progress and cause death in patients who are characterized as immunosuppressive. In this study, we discus nine consecutive patients we encountered during the coronavirus disease 2019 (COVID-19) pandemic in the light of literature information.

Methods: Nine consecutive patients with rhino-orbitocerebral mucormycosis were included in the study. Preoperative examination, preoperative radiological imaging, postoperative examination, and postoperative radiological imaging results of the patients were retrospectively analyzed by scanning their medical files.

Results: All the patients who presented to us had facial swelling (100%). The gender distribution was five women (55%) and four men (45%). The age distribution was between 34 and 70 years, and the mean value was 58 years. The average ages of the deceased patients and survivors were 61 and 51 years, respectively.

Conclusion: Mucormycosis is a rare opportunistic infection that can rapidly progress, and if left untreated, can cause the death of the patient within a few days. Therefore, it should be diagnosed quickly and operated immediately by surgeons experienced in this field. The COVID-19 pandemic may disrupt the regulations existing in additional comorbid diseases and increase the susceptibility to mucormycosis.

Keywords: COVID-19, cranial nerve diseases, diabetes mellitus, mucormycosis, opportunistic infections

Introduction

Mucormycosis is an opportunistic infection caused by saprophytic fungi that can rapidly progress and cause death in patients who are characterized as immunosuppressive. It is divided into rhino-orbitocerebral (ROC), pulmonary, cutaneous, gastrointestinal, and disseminated according to its localization in the body. The most common causative agents are Rhizopus, Mucor, and Lictemia (absidia). The most common cause of ROC mucormycosis is *Rhizopus arrhizus* (formerly *Rhizopus oryzae*). The risk factors were diabetes mellitus (DM), transplant recipients, hematology malignancies, neutropenia, iron overload, voriconazole prophylaxis, long-term steroid use, skin trauma, chemotherapy, acquired immune deficiency syndrome, and intravenous drug use. These fungi are found in the soil, mildew, and suspended in the air. These fungi often enter the nasal cavity and sinuses of immunosuppressive patients through inhalation and colonize the structures here. The most common reservoir is the ptergopalatine fossa. The infection erodes the sinus walls and spreads to the orbit and brain. Fungi can cause nerve dysfunction by direct nerve invasion and vascular thrombosis owing to their angioinvasive feature. The Rhizopus species reproduce by using ketones of patients with diabetic ketoacidosis with ketoreductase enzymes. Acid blood pH and high glucose levels create the most suitable environment for them to reproduce. In addition, hyperglycemia disrupts neutrophil chemotaxis and reduces the effect of neutrophils, which are the most important defense cells in fungal phagocytosis (1, 2). Increased blood iron level also increases fungal growth; however, this is mostly isolated in patients with hematological malignancies or receiving deferasamine and often causes pulmonary mucormycosis. These fungi also cause vascular thrombosis and tissue necrosis owing to their angioinvasive properties. The most common symptom is facial/periorbital swelling, pain, or numbness. Its characteristic feature is black eschar in the nasal cavity and hard palate. Although there are studies on new methods in its diagnosis, classic methods are used more frequently. The emergency biopsy should be examined histologically and microbiologically. Microscopic morphology showed typically

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Received: March 10, 2021 **Accepted:** August 19, 2021 **Available Online Date:** October 18, 2021
Available online at www.b-ent.be

ribbon-like, irregularly shaped, non-septate, or sparsely septate hyphae and broad hyphae with right angled branching in the samples. There are three basic criteria in its treatment, which if applied can significantly reduce mortality. These include treatment of the underlying immunocompromised conditions, systemic antifugal therapy, and emergency surgical debridement (3). Our aim was to share the findings we detected in seriously fatal cases of ROC mucormycosis and to demonstrate ineffective control of chronic diseases during the COVID-19 pandemic can have important consequences.

Methods

Nine patients who presented with ROC mucormycosis between 10.03.2020-10.12.2020 were included in the study. Preoperative examination; preoperative radiological imaging; pre, intra, and postoperative photographs; postoperative examination; and postoperative radiological imaging results of the patients were retrospectively analyzed by scanning their files. Preoperative paranasal sinus computed tomography (CT) and contrast-enhanced cerebral magnetic resonance imaging (MRI) were performed in all the patients. All the patients were examined by the ophthalmologist to test visual acuity. All the patients were examined by preoperative radiology and neurology physicians for intracranial dissemination. Antibiotic and antifungal treatments were administered to all the patients according to the opinion of the infectious diseases physician. The patients consulted with physicians of internal medicine, oncology, cardiology, and nephrology, as necessary according to their comorbidities. The comorbidities included DM, chronic renal failure (CRF), breast cancer (BC), hypertension (HT), cardiac failure (CF). The age, sex, cranial neuropathies, hemoglobin A1c, and surgery types of the patients were recorded. The surgeries performed included lateral rhinotomy (LR), left maxillectomy, right maxillectomy, hard palate excision (HPE), septum excision (SE), orbital exenteration (OR), and functional endoscopic sinus surgery (FESS). Tissue and fungal cultures and samples for pathology were quickly taken from patients with suspected mucormycosis. Patients who were recognized by direct microscopy began emergency surgery and antifungal therapy. Growth status in the medium was followed for the definitive result. The diagnosis of all the patients was made as a result of growth in the microbiological culture samples. Extensive radical surgical procedures such as total maxillectomy, FESS, HPE, LR, SE, and OR were performed on patients who agreed to have the procedures. Although all the patients received liposomal amphotericin B (Ampho-B), various antibiotic combinations (such as vancomycin, meropenem, and linezolid) were administered. COVID-19 swab PCR was obtained from all the patients at admission and/or preoperatively. Written consents from the patients and approval of the University of Health Sciences Adana City Training and Research Hospital Clinical Research Ethics Committee were obtained for our study (meeting number: 74, decision number: 1234, date: 13/01/2021)

Main Points:

- All the nine patients with mucormycosis who presented to us had facial swelling (100%). The gender distribution was five women (55%) and four men (45%). They were between 34 and 70 years with the mean age being 58 years.
- Diabetes mellitus was the most common comorbidity (77%).
- Hemoglobin A1c result was available in all the patients with diabetes, and the mean value was 12.3.
- Surgical procedures performed in patients undergoing surgery were lateral rhinotomy (100%), maxillectomy (100%), and orbital exentration (77%) on the affected side (two patients did not want the procedure), palate excision (100%), septum excision (100%), and functional endoscopic sinus surgery (100%).
- We think that the cases of mucormycosis have increased owing to ineffective control of their diseases because of disruption of doctor visits with the pandemic.

Results

All nine patients with mucormycosis who presented to us had facial swelling (100%). The gender distribution was five women (55%) and four men (45%) with ages between 34 and 70 years and a mean value of 58 years. The average ages of the deceased and the survivors were 51 years. DM was the most common comorbidity (77%). In two patients without DM, one had a history of only BC and chemoradiotherapy, and the other patient had HT and CRF. The hemoglobin A1c result was available for all patients with DM, and the mean value was 12.3. Four (44%) patients had right eye involvement, four (44%) had left eye involvement, and one (12%) had bilateral eyes involvement. Most of the patients were hospitalized on suspicion of mucormycosis, and one patient was consulted on the 10th day and another on the third day. Of the nine patients, only one did not agree to the surgery voluntarily (case 8). Two patients did not agree to have OR (cases 3 and 4). Eight of the nine patients were diagnosed with mucormycosis, biopsies were taken on the day of our consultation, and five patients were operated on the first day. As only one patient was consulted on the second day, the 2nd day could be operated on and two patients died in the intensive care unit before they could be operated upon. One patient did not agree to the operation (case 8). Surgical procedures performed in patients undergoing surgery were LR (100%), maxillectomy (100%), and OR (77%) on the affected side (two patients did not agree), HPE (100%), SE (100%), and FESS (100%). Once mucormycosis was diagnosed, the hospital stay was between one and 70 days. All the patients received Ampho-B (100%) and meropenem (100%) as antifungal and antibiotics. Linezolid was administered to one patient, and vancomycin was administered to another. Two (22%) patients survived and seven (78%) patients died. In all (100%) the patients, second, third, fourth, and sixth nerve paralysis was present, and three (33%) patients had additional facial (seventh) nerve paralysis. Interestingly, hypoglossal nerve paralysis developed in one (11%) patient (case 9). All the patients were consulted preoperatively for eye diseases, and all had loss of vision and direct light reflex in the affected eye. All of them had ophthalmoplegia. All the patients who agreed to have the surgery and whose general condition were relatively good were operated upon. Patients who did not undergo surgery were those who refused the surgery and/or were in septic shock. Patient information is presented in Table 1. All images of the patients are shown in Figures 1 to 5.

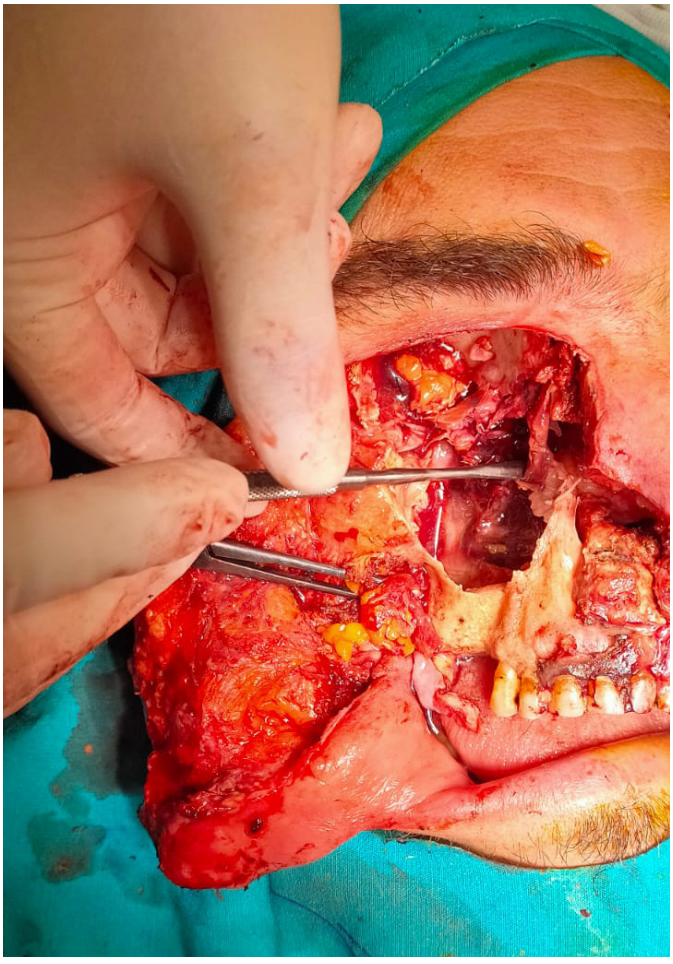

Figure 1. Maxillectomy and orbital exenteration

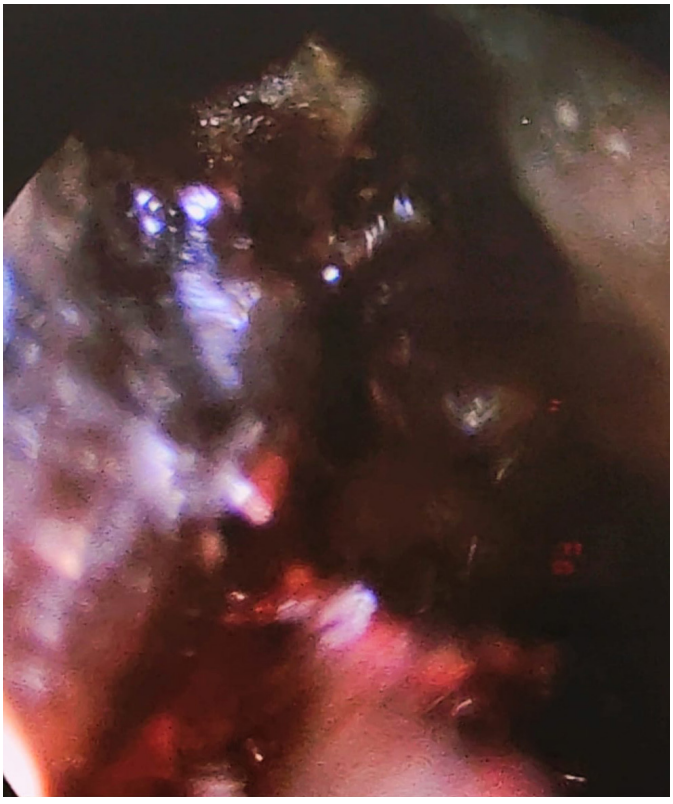

Figure 2. Necrotic tissues in the nasal cavity

Figure 3. Hypoglossus paralysis

Figure 4. Necrotic areas on hard palate

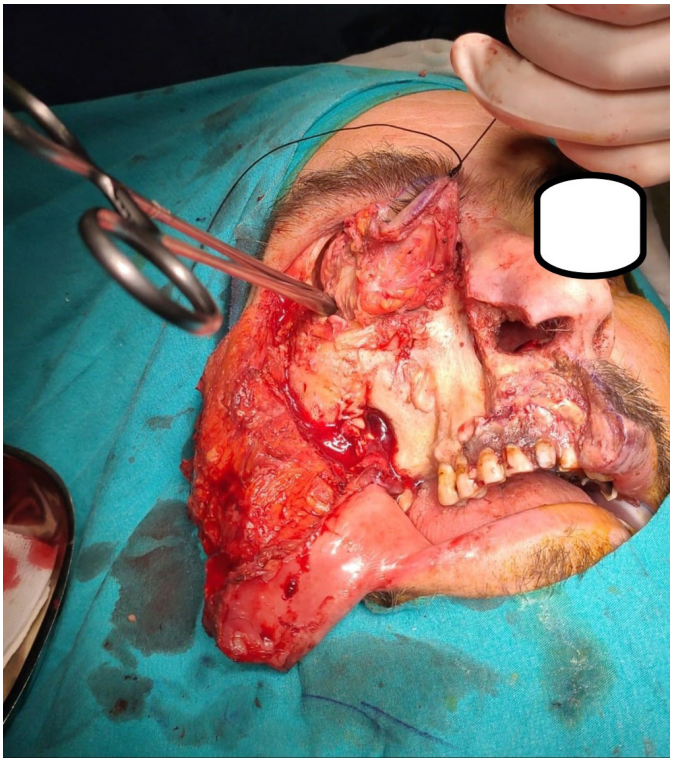

Figure 5. Intraoperative view

Discussion

Mucormycosis has mostly been described in debilitated patients who are immuncompromised or have metabolic problems. We focused on ROC mucormycosis, which can be divided into different types according to the area of involvement. As the Rhizopus species responsible most frequently for ROC have an active ketone reductase enzyme, they use hyperglycemia and ketones in diabetic patients and grow in a favorable environment. In addition, the activity and chemotaxis of neutrophil cells, important in defense against fungi, decrease during hyperglycemia. In these patients, the number of neutrophils in their blood increases, but their effects are reduced. Moreover, pulmonary mucormycosis is the most common form in patients with hematological malignancies and excess iron. The pterygopalatine fossa is thought to be the region where colonization is most common. Therefore, debridement performed in this area or washing with Ampho-B can give good results in terms of local control. This shows that effective treatment is a combination of surgical debridement and appropriate antifungals. If not treated effectively or not treated at all, the patient usually dies within two weeks (1).

The diagnosis of mucormycosis is made following histological and microbiological examinations of the biopsy taken from the necrotic focus as a standard, typically ribbon-like, irregularly circumscribed, non-septate or less septate, wide hyphae and right-angle branching hyphae. However, in recent studies, matrix-assisted laser desorption ionization time of flight mass spectrometry technique, in which mucor can be diagnosed at the species level by PCR amplification and sequencing has come to the fore. With this technique, the mucor proteins are compared with the proteins in the data, enabling diagnosis at the level of species. This study indicated that mortality was high if six days had passed after the onset of symptoms. The incidence of mucor has also been observed to increase in the late fall and winter months in countries such as Turkey, similar to our study (2).

In a diagnostic study, it has been shown that the diagnosis can be made by mucor DNA circulating in the blood or cerebrospinal fluid. Therefore, the underlying immunocompromised condition can be diagnosed early, and treatment can be corrected; and if required, surgical and antifungal treatments can be administered earlier, which will reduce the mortality and morbidity. Mucor DNA can be detected in suspicious and at-risk patients before their symptoms occur. In this study, DM was the most common cause, and mortality was from ROC (41%) (3). Mucor DNA can be detected 68 days before the symptoms begin. Repeated surgeries in ROC are useful in providing local control and achieving good results. We also performed revision surgery in case 7. Liposomal amphotericin B is used as the standard and most effective and safest antifungal. Posacanazol and isavucanozol are also used as line 2 therapy or in combination. There are some authors who believe that hyperbaric oxygen therapy is beneficial because mucors are supposed to reproduce in an oxygenated environment (4), most frequently seen in patients between the ages of 46 and 60 years. The most common agent is *R. arrhizus (oryzae)* (5). The most common tomography finding is thickening of the sinus mucosa (6). Some authors report that clinical examination is as valuable as MRI during postoperative follow-up. Some also recommend control biopsies. As a result, mortality has dropped from 85% to 35% in the past 50 years (7).

Although there is no consensus on the duration of antifungal therapy, Ampho B should be given intravenously for at least six weeks on average. Nasal passage and surgical area can also be washed with Ampho B. In addition, some authorities may recommend low-dose heparin and anti-inflammatory drugs because of vascular thrombosis and inflammation (8). We used oxapar because our last two patients were positive for COVID-19 PCR. Therefore, we performed the operation with protective equipment. The painkillers we used also had anti-inflammatory properties. The color of the nasal drainage was mostly whitish, and the black eschar is characteristic. Although fever is not always seen, it is fluctuative. Some studies report that isavuconazole and posacanozol can be used as a second agent in the salvage treatment of patients who do not respond to amphotericin B (9). In a study where a combination of medical and surgical treatment was performed, it was indicated that increased surveillance from 57% to 78% compared with only medical treatment and sinus mucosal thickening and orbital invasion were observed in all the patients (10, 11). As some of our patients were neutropenic, we believe that granulocyte colony-stimulating factors can be used to regenerate host defense and strengthen leukocytosis. If the disease is limited to the rhino-orbital area and if there is no cerebral length, debridement antifungal therapy and lavage are very effective on surveillance. Although OR is not a standard approach, we performed OR in patients who we thought had developed permanent blindness on preoperative imaging and ophthalmology consultations, and we saw eye involvement during surgery. Ampho B treatment can be given as outpatient or continued for one year with posaconazole in patients who have stabilized in

Table 1. Nine consecutive mucor cases

		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
1.	Facial swelling/ dysesthesia or pain	+	+	+	+	+	+	+	+	+
2.	Infraorbital or skin necrosis	+	-	+	-	-	-	-	-	-
3.	Hard palate necrosis	+	+	+	+	+	+	+	+	+
4.	Nasal discharge/black eschar	+	+	+	-	+	+	+	+	+
5.	Cranial nerve palsy	2/3/ 4/6	2/3/ 4/6	2/3/ 4/6	2/3/ 4/6	2/3/ 4/6	2/3/ 4/6	2/3/ 4/6/7	2/3/ 4/6/7	2/3/4/ 6/7/12
6.	Histopathology	Aseptate hyphae	Aseptate hyphae	Aseptate hyphae	Aseptate hyphae	Aseptate hyphae	Aseptate hyphae	Aseptate hyphae	Aseptate hyphae	Aseptate hyphae
7.	Culture	Mucor spp	Mucor spp	-	-	-	Mucor spp	Mucor spp	Mucor spp	Mucor spp
8.	CT , MRI	+	+	+	+	+	+	+	+	+
9.	Preoperative nasal biopsy	+	+	+	+	+	+	+	+	+
10.	Surgery	-	-	LR, LM, HPE SE, FESS	LR, LM, HPE SE, FESS	LR, RM, HPE, SE, OE, FESS	LR, LM, HPE, SE, OE, FESS	LR, RM, HPE, SE, OE, FESS	-	LR, LM, HPE, SE, OE, FESS
11.	Comorbidities	DM, CRF	BC	DM, CRF	HT, CRF	DM, CF	DM, CRF	DM	DM	DM
13.	Hba1c	10	-	13.5	-	13.9	14.1	11.3	12.4	11.4
14.	Mucor occurred on the day of hospitalization	10	1	3	1	1	1	1	1	1
15.	Sick Side	Right	Bilateral	Left	Left	Right	Left	Right	Left	Left
16.	Age/sex (Male: m, Female: f)	70/m	64/f	62/f	65/f	50/f	70/m	50/m	59/f	34/m
17.	Number of days after it was noticed and the patient was operated upon	-	-	1	2	1	1	1	-	1
18.	Length of hospital stay	1	1	5	5	17	70	55	1	2
19.	Antifungal and antibiotic	Ampho B Meropenem	Ampho B Meropenem	Ampho B Meropenem	Ampho B Meropenem Linezolid	Ampho B Meropenem	Ampho B Meropenem	Ampho B Meropenem Vancomycin	Ampho B Meropenem	Ampho B Meropenem
20.	Exitus(ex)/alive	ex	ex	ex	ex	ex	alive	alive	ex	ex
21.	Total vision loss/total ophthalmoplegia in the affected eye present: + absent: – direct light reflex present:+, absent: -	+ -	+ -	+ -	+ -	+ -	+ -	+ -	+ -	+ -
22.	Preoperative COVID-19 swap PCR results (positive: +, negative: –)	-	-	-	-	-	- +	-	+	

CRF: Chronic renal failure; BC: Breast cancer; HT: Hypertension; CF: Cardiac failure; LR: Lateral rhinotomy, LM: Left maxillectomy; RM: Right maxillectomy; HPE: Hard palate excision; SE: Septum excision; OR: Orbital exenteration; FESS: Functional endoscopic sinus surgery

the clinic and survive the acute period. Every patient should be seen by ophthalmology, oculoplastic surgeon, ENT, infectious diseases, neurosurgery, and pharmacologist. The COVID-19 pandemic may disrupt the control of comorbid diseases and increase the susceptibility to mucormycosis. Mucormycosis is a rare opportunistic infection that can rapidly progress, and if left untreated, can cause the death of the patient within a few days. Therefore, it should be diagnosed quickly and operated upon immediately by surgeons experienced in this field. We think that the cases of mucormycosis have increased because of ineffective control of their diseases owing to the disruption of doctor visits during the pandemic. ROC is an emergency that requires an appropriate suspicion and rapid diagnosis. Disruption of routine doctor visits during the pandemic may play a role in the prevalence of this disease.

Ethics Committee Approval: University of Health Sciences Adana City Training and Research Hospital, (Approval No : 1234).

Informed Consent: Written consent was obtained from all patients participating in the study for the surgical procedure and the study. In addition, verbal and written consent was obtained from three patients whose photographs were used.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – K.K.B., S.A., V.D., G.K., T.O., N.Y.E.; Design – K.K.B., S.A., V.D., G.K., T.O., N.Y.E.; Supervision – K.K.B., S.A., V.D., G.K., T.O., N.Y.E.; Resources – K.K.B., S.A., V.D., G.K., T.O., N.Y.E.; Materials – K.K.B., S.A., V.D., G.K., T.O., N.Y.E.; Data Collection and/or Processing K.K.B., S.A., V.D., G.K., T.O., N.Y.E.; Analysis and/or Interpretation – K.K.B., S.A., V.D., G.K., T.O., N.Y.E.; Literature Search – K.K.B., S.A., V.D., G.K., T.O., N.Y.E.; Writing Manuscript – K.K.B., S.A., V.D., G.K., T.O., N.Y.E.; Critical Review – K.K.B., S.A., V.D., G.K., T.O., N.Y.E.

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

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

References

1. Pathak VK, Saxena R, Awasthi S, Gaur S, Singh SK. Rhinoorbitocerebral mucormycosis with maggots in a neglected diabetic patient. Indian J Otolaryngol Head Neck Surg 2018; 70: 156-8. [Crossref]
2. Sağıroğlu P, Koç AN, Atalay MA, Gelmez GA, Canoz O, Sariguzel FM. Mucormycosis experience through the eyes of the laboratory. Infect Dis (Lond) 2019; 51: 730-7. [Crossref]
3. Serris A, Danion F, Lanternier F. Disease Entities in Mucormycosis. J Fungi (Basel) 2019; 14; 5: 23. [Crossref]
4. Danion F, Aguilar C, Catherinot E, Alanio A, DeWolf S, Lortholary O, et al. Mucormycosis: new developments into a persistently devastating infection. Semin Respir Crit Care Med 2015; 36: 692-705. [Crossref]
5. Chander J, Kaur M, Singla N, Punia RPS, Singhal SK, Attri AK et al. Mucormycosis: battle with the deadly enemy over a five-year period in India. J Fungi (Basel) 2018; 4: 46. [Crossref]
6. Kursun E, Turunc T, Demiroglu YZ, Aliskan HE, Arslan AH. Evaluation of 28 cases of mucormycosis.Mycoses. 2015; 58: 82-7. [Crossref]
7. Moro JGM, Calleja JMLA, García MB, Carretero JLC, Rodriguez JG. Rhinoorbitocerebral mucormycosis: a case report and literature review. Med Oral Patol Oral Cir Bucal 2008; 13: E792-5.
8. Sachdeva K. Rhino-oculo cerebral mucormycosis with multiple cranial nerve palsy in diabetic patient: review of six cases. Indian J Otolaryngol Head Neck Surg 2013; 65: 375-9. [Crossref]
9. Galletti B, Freni F, Meduri A, Oliverio GW, Signorino GA, Perroni P. Rhino-orbito-cerebral mucormycosis in diabetic disease. J Craniofac Surg 2020; 31: e321-4. [Crossref]
10. Hassan FA, Aljahli M, Molani F, Almomen A. Rhino-orbito-cerebral mucormycosis in patients with uncontrolled diabetes: A case series. Int J Surg Case Rep 2020; 73: 324-7. [Crossref]
11. Jiang N, Zhao G, Yang S, et al. A retrospective analysis of eleven cases of invasive rhino-orbito-cerebral mucormycosis presented with orbital apex syndrome initially. BMC Ophthalmol 2016; 16:10. [Crossref]