Abstract: Introduction: Since the emergence of COVID-19 pandemic, several articles have reported the co-existence of mucormycosis and COVID-19. This study aimed to distinguish the characteristics of COVID-19-associated rhinocerebral mucormycosis. Methods: In this case series, 18 patients with COVID-19-associated rhinocerebral mucormycosis and unique clinical manifestations and outcomes, who were referred to Amiralam Hospital, a tertiary otorhinolaryngology center, Tehran, Iran, during the COVID-19 era, were reported. Results: Eighteen patients with the mean age of 62.0 ± 11.6 (range: 42 – 83) years were studied (50% males). The mean time interval between diagnosis of COVID-19 and first manifestation of mucormycosis was 15.5 ± 9.7 days. The most common presenting symptom was facial paresthesia (72.2%). Fifty percent of patients developed frozen eye. Palatal necrosis was seen in 7 cases (38.8%). Remarkably, facial paralysis was observed in 5 (27.7%) patients. Another notable clinical picture was cavernous sinus thrombosis, seen in 7 patients. We also had two cases of carotid artery occlusion. Three patients, unfortunately, passed away. Conclusion: Rhinocerebral mucormycosis is one of the most important complications of COVID-19 patients, especially those with underlying diseases. It seems that the key to proper management of mucormycosis is early diagnosis and timely intervention, which could give a patient a chance to live more.

Keywords: COVID-19; Mycoses; mucormycosis; paranasal sinuses

Cite this article as: Samimiardestani S, Irani S, Hasibi M, Seyedahadi M, Bastaninejad S, Firouzifar M, Mohammad Ardehali M, Berijani S, Erfanian R, Kazemi MA, Etemadi-Aleagha A, Rahimi A, Karimi Yarandi K, Ahadi S. Distinguishing Characteristics of COVID-19-Associated Mucormycosis; a Case Series. Arch Acad Emerg Med. 2022; 10(1): e66. https://doi.org/10.22037/aaem.v10i1.1644.

1. Introduction
COVID-19 pandemic is a crisis associated with considerable mortality and morbidity. Several COVID-19-associated complications have been described in the literature. Bacterial and fungal co-infections are among major complications that may increase the mortality rate of COVID-19 cases [1]. Mucormycosis is a serious but rare fungal infection caused by mucormycetes. Patients with underlying diseases, especially diabetes mellitus and immunodeficiency are highly vulnerable to mucormycosis [2]. It rarely affects immunocompetent patients [3]. Rhinocerebral involvement is the classic manifestation of mucormycosis. The incidence rate of rhinocerebral mucormycosis is approximately 1.7 per 1,000,000 of normal population, and its mortality rate is estimated at 40% to 80% [4]. Rhinocerebral mucormycosis usually presents in an acute setting. It originates from the nasal cavity and
paranasal sinuses, and spreads to the adjacent structures including the palate, pharynx, orbits, and the brain [5, 6]. Infection can spread to the meninges or the brain through the nerves, ophthalmic artery, or cribiform plate [7]. Management includes antifungal therapy, surgical resection, and if possible, reversal of impaired immunity. During the COVID-19 pandemic, we observed a significant rise in rhinocerebral mucormycosis in our ear, nose, and throat (ENT) specialty referral center. In this study, we present clinical manifestations and outcomes of patients with COVID-19-associated mucormycosis (CAM).

2. Methods

2.1. Study design and setting

This case series study was performed at Amir Alam Hospital in Tehran, Iran, which is a referral center for ENT conditions. During a 9-month period, from August 2020 to June 2021, patients with a diagnosis of rhinocerebral mucormycosis, who had concomitant COVID-19 or were diagnosed with and/or treated for COVID-19 within the past three months were included in the study. The protocol of study was approved by Ethics Committee of Tehran University of Medical Sciences (Ethics code: IR.TUMS.AMIRALAM.REC.1401.019) and researchers adhered to the ethical considerations and confidentiality of patients’ information.

2.2. Managements

The diagnosis of mucormycosis was made based on the paranasal sinuses’ endoscopic findings and confirmed by positive fungal smear and culture, and histopathological documentation of fungal invasion in the paranasal sinuses and nasal cavity samples. Proper antifungal agent (Liposomal Amphotericin B at 3-5 mg/kg or conventional Amphotericin B at 1 mg/kg) was started during the first 24 to 48 hours of admission for all the patients. SARS-CoV-2 infection was confirmed using reverse transcription polymerase chain reaction (RT-PCR) and a spiral chest computed tomography (CT) scan was performed for all cases to assess lung involvement. Patients with active COVID-19 were transferred to the COVID-19 ward and received intravenous (IV) Remdesivir at 200 mg in the first day followed by 100 mg daily for the minimum duration of five days.

Soon after stabilization of patients’ general condition as well as the serum glucose and electrolyte levels, endoscopic debridement of the paranasal sinuses was performed. The extent of surgical debridement was determined based on the clinical and radiological findings, ranging from simple excision of the necrotic soft tissue and bone in the turbinates and nasal septum to a more extensive procedure including partial or radical maxillectomy and debridement of pterygopalatine fossa, alveolar ridge, and palatal resection even orbital exenteration or skull base surgery. Intravenous (IV) Amphotericin B was continued after surgery until a minimum total curative dose of the medication was achieved. The patients underwent weekly endoscopic examination during the admission and re-debridement was performed in the presence of any suspicious necrotic tissue.

2.3. Data gathering

We collected the following data for all cases: demographic data, predisposing factors, time interval between COVID-19 and the onset of mucormycosis, patient’s clinical manifestations and intra-operative and endoscopic findings, anatomical extension of the fungal infection, and patient's outcome (categorized as deceased, still hospitalized, or alive—meaning no more hospitalized).

2.4. Statistical analysis

Statistical analysis was done using SPSS version 23 and findings were reported as mean ± standard deviation or frequency (%).

3. Results

3.1. Baseline characteristics of studied cases

Eighteen patients with diagnosis of mucormycosis and COVID-19, including 9 males and 9 females, with the mean age of 62.0 ± 11.6 (range: 42 – 83) years were studied. Clinical presentation, treatment, extent of surgery, and outcome of studied patients are summarized in Table 1 and Figure 1. The mean time interval between COVID-19 diagnosis and first manifestation of mucormycosis was 15.6 ± 9.7 days (range from 0 to 43 days). Three patients received antifungal therapy and Remdesivir simultaneously. Twelve out of the 18 patients had received corticosteroids as an adjunct treatment for severe COVID-19. Fourteen patients were known cases of diabetes mellitus (DM), and three patients had new-onset DM. The most common presenting symptom was facial paresis (72.2%). Among our patients, 11 (61%) had ophthalmoplegia, 10 (55.5%) had visual impairment, and 4 patients (22%) had proptosis (Figure 2). Fifty percent of our patients developed frozen eye. Palatal necrosis was seen in 7 cases (38.8%). Remarkably, facial paralysis was observed in 5 patients (27.7%) and it was a presenting symptom in all of them. Interestingly, one of our patients, case No 14, had a 5-month-history of facial paralysis without any other mucormycosis manifestations a week after COVID-19 infection. Nasal obstruction was seen in 22% and dark nasal discharge was present in 16% of the patients. The presenting symptom of one patient was fever. One patient had teeth loosening due to hard palate involvement. Two patients presented with loss of consciousness. Another notable clinical picture was cav-
| No./sex/age | Predisposing factors | Steroid | Hospitalization | Interval (days) | Signs/symptoms | Imaging findings | Endoscopy findings | Extension of Disease | Surgery report | Outcome |
|-------------|----------------------|---------|----------------|----------------|---------------|----------------|-------------------|--------------------|---------------|---------|
| 1/64/F     | DM, Anemia           | Y       | Y              | 12             | Frozen eye, ophthalmoplegia, vision loss, proptosis, facial paralysis and paresthesia, loss of consciousness | Maxillary and ethmoidal sinusitis, PPF involvement, inflammation of orbital muscles, IOF& SOF, orbital apex, fat stranding of intraconal & extracranal fat, oval foramen, CST, carotid vasculitis, buccal abscess and gas bubble in ramus & body of mandible, inferior alveolar nerve involvement, skull base osteomyelitis | No evidence of necrosis | Buccal, masticator, and parapharyngeal space, orbital apex, PPF cavernous sinus | Antrostomy, ethmoidectomy, sphenoidotomy, buccal abscess drainage/3 times | Alive/9-month follow-up |
| 2/58/F     | DM, HTN, Anemia      | N       | Y              | 14             | Facial paralysis and paresthesia, ophthalmoplegia, nasal obstruction, proptosis | Sphenoid sinus dehiscence, CST, orbital cellulitis | Inferior turbinate necrosis | Masticator and parapharyngeal space | Antrostomy, ethmoidectomy, sphenoidotomy, Draf IIb, orbital exenteration/ 3 times | Alive/6-month follow-up |
| 3/52/F     | DM, HTN              | Y       | Y              | 10             | Fever, frozen eye, ophthalmoplegia, visual impairment, proptosis | CST | Middle turbinate necrosis | Medial and superior orbital wall, PPF, cribriform plate, parasellar area and cavernous sinus, orbital apex | Ethmoidectomy, antrostomy, PPF debridement, Draf IIb, ITF debridement, orbital decompression/ 2 times | Alive/6-month follow-up |
| 4/53/F     | DM                   | Y       | Y              | 21             | Cheek paresthesia, ophthalmoplegia | Orbital abscess, brain micro-abscess | Evidence of previous antrostomy and ethmoidectomy, no necrosis | Medial and inferior orbital wall, PPF, cribriform plate | Ethmoidectomy, antrostomy, orbital decompression and abscess drainage, bilateral PPF debridement / 2 times | Alive/9-month follow-up |
| 5/52/M     | DM, HTN              | N       | Y              | 12             | Simultaneous Frozen eye, vision loss, ophthalmoplegia, facial paralysis and paresthesia | Maxillary and ethmoidal sinusitis, CST | Evidence of previous sphenoidotomy and ethmoidectomy, nasal septum necrosis | CST, orbit, PPF | Ethmoidectomy, antrostomy, bilateral PPF debridement, ITF debridement, orbital decompression/ 3 times | Alive/8-month follow-up |
| No./sex/age | Predisposing factors | Steroid | Hospitalization | Interval (days) | Signs/symptoms | Imaging findings | Endoscopy findings | Extension of Disease | Surgery report | Outcome |
|-------------|----------------------|---------|-----------------|----------------|----------------|-----------------|-------------------|---------------------|---------------|---------|
| 6/68/M      | DM, HTN              | Y       | N               | 4              | Facial paralysis and paresthesia, nasal obstruction and dark nasal crust, palatal necrosis, blurred vision | Maxillary and ethmoidal sinusitis, nasal septum and Lt. middle turbinate necrosis | Lt. hard palate | Antrostomy, middle turbinate resection, PPF debridement, partial maxilllectomy, ITF debridement | Alive/7-month follow-up |
| 7/82/M      | DM                   | N       | Y               | 5              | Frozen eye, ophthalmoplegia, visual loss, dark nasal crust, palatal necrosis, cheek paresthesia | Maxillary sinusitis and erosion, PPF, sphenoid sinus, CST | Nasal septum and Rt. middle turbinate necrosis | PPF foramen rotundum, ITF | No debridement | Death   |
| 8/47/M      | DM                   | Y       | Y               | 30             | Nasal obstruction, Facial swelling | Maxillary & ethmoid sinus, PPF | Middle and inferior turbinate necrosis | PPF | Ethmoidectomy, antrostomy, PPF debridement/2 times | Alive/1-month follow-up |
| 9/68/M      | DM, HTN, IHD, Gout   | Y       | N               | 15 days        | Frozen eye, ophthalmoplegia, vision loss, facial paresthesia | Maxillary & ethmoid sinus & preantral space involvement, orbital apex, intracanal fat haziness | Superior, middle, and inferior turbinate necrosis | PPF, middle and inferior turbinate | Antrostomy, middle turbinate resection, PPF debridement, partial maxilllectomy, ITF debridement, retrobulbar amphotericin B injection/3 times | Alive/still hospitalized with good condition |
| 10/67/M     | DM, HTN              | Y       | Y               | 10             | Frozen eye, ophthalmoplegia, vision loss, facial paresthesia, palatal necrosis | Middle and inferior turbinate necrosis | PPF, superior, middle, and inferior turbinate | Antrostomy, middle turbinate resection, PPF debridement, partial maxilllectomy, palatal debridement | Death |
| 11/68/M     | DM, HTN, CKD         | N       | Y               | 43             | Facial paresthesia, tooth loosening, palatal necrosis | Evidence of previous antrostomy, ethmoidectomy and sphenoidotomy, palatal bone necrosis | PPF, middle and inferior turbinate | Antrostomy, middle turbinate resection, PPF debridement, partial maxilllectomy, palatal debridement | Alive/1-month follow-up |
| 12/80/F     | HTN                  | Y       | Y               | 20             | Necrosis of nasal septum and palate | Mucosal thickening in ethmoid, sphenoid & maxillary sinus, air bubbles in PPF & infratemporal & masticator space (necrotizing fasciitis), orbital apex, intraconal & extraconal space, IOF SOF | Middle and inferior turbinate necrosis, palatal bone necrosis | PPF, palatine bone | Antrostomy, middle turbinate resection, PPF debridement, partial maxilllectomy, palatal debridement | Death |
| No./sex/age | Predisposing factors | Steroid | Hospitalization | Interval (days) | Signs/symptoms | Imaging findings | Endoscopy findings | Extension of Disease | Surgery report | Outcome |
|-------------|----------------------|---------|----------------|----------------|----------------|----------------|-------------------|---------------------|--------------|---------|
| 13/54/M    | DM                   | Unclear | Y              | 15             | Frozen eye, ophthalmoplegia, vision loss, facial paresthesia | Necrosis in nasal endoscopy | PPF | Antrostomy, middle turbinate resection, PPF debridement, orbital debridement | Alive/2-month follow-up |
| 14/62/F    | DM                   | N       | N              | 7              | Facial paresthesia, Facial paralysis | No evidence of necrosis in diagnostic endoscopy | Middle turbinate, PPF, orbit | Antrostomy, ethmoidectomy, sphenoidectomy, middle turbinate resection, PFF & ITF debridement, debridement of orbital floor, buccal abscess drainage/3 times | Alive/-month follow-up |
| 15/40/F    | DM                   | Y       | Y              | 15             | Frozen eye, ophthalmoplegia, vision loss, proptosis, facial paresthesia | Evidence of previous antrostomy, ethmoidectomy and sphenoidectomy and new necrosis in posterior septum | PPF, ITF fossa, rotundum foramen | Antrostomy, ethmoidectomy, sphenoidectomy, middle turbinate resection, PPF debridement, debridement of medial and inferior orbital rim, drainage of orbital abscess, orbital exenteration/3 times | Alive/1-month follow-up |
| 16/57/F    | DM                   | Y       | Y              | 20             | Frozen eye, ophthalmoplegia, vision loss, proptosis, facial paresthesia, dark nasal crust, palatal necrosis | Necrosis in middle turbinate and nasal floor | Evidences of previous debridement in another center, PPE, septum and middle turbinate just inferior to cribriform plate | Antrostomy, ethmoidectomy, sphenoidectomy, middle turbinate resection, PPF debridement, debridement of medial and inferior orbital rim, drainage of orbital abscess, resection of anterior table of frontal sinus & ascending process of maxilla | Alive/2-month follow-up |
Table 1: Baseline characteristics, treatment, extent of surgery and outcome of patients with COVID-19-associated mucormycosis

| No./sex/age | Predisposing factors | Steroid | Hospitalization | Interval (days) | Signs/symptoms | Imaging findings | Endoscopy findings | Extension of Disease | Surgery report | Outcome |
|-------------|---------------------|---------|-----------------|----------------|----------------|-----------------|-------------------|---------------------|---------------|---------|
| 17/59/F    | DM, HTN, IHD        | Y       | N               | 17             | Nasal obstruction, facial edema | Maxillary, ethmoid, and frontal opacification | Necrosis in middle turbinate | Maxilla, ethmoid, frontal, PPF | Resection of right middle turbinate, antrostomy, sphenoidotomy, anterior & posterior ethmoidectomy, frontal sinusotomy/2times | Alive/Still hospitalized with good condition |
| 18/83/M    | HTN, DM             | Y       | Y               | 20             | Palatal necrosis | Ethmoid and sphenoid opacification, bone erosion in medial wall of orbit, infraorbital space, greater wing of sphenoid | Not performed (directly referred to operation room) | Maxillary, ethmoid & sphenoid, palate and alveolar ridge, PPF inferior orbital fissure | Endoscopic maxillectomy, resection of pterygoid processes, ascending process of maxilla, inferior & medial wall of orbit, debridement of pterygoid muscles, palatal & alveolar ridge resection | Alive/Still hospitalized with good condition |

CST: Cavernous Sinus Thrombosis, DM: Diabetes Mellitus, HTN: Hypertension, ICA: Internal Carotid Artery, IOF: Inferior Orbital Fissure, ITF: Infratemporal Fossa, Lt: left, PPF: Pterygopalatine Fossa, Rt: Right, SOF: Superior Orbital Fissure; IHD: Ischemic Heart Disease; CKD: Chronic Kidney Disease.

Figure 1: Percentage of different clinical presentations of patients with COVID-19-associated mucormycosis.
ernous sinus thrombosis, seen in 7 patients. We had two cases of carotid artery occlusion, without significant neurological manifestations (Figure 2).

### 3.2. Outcomes

Three patients passed away. One of them died before any surgical intervention due to rapid progression of the disease, and the other one died the day after the extensive debridement due to necrotizing fasciitis and intracranial involvement. The third patient had died due to cardiovascular problems unrelated to mucormycosis disease, a week after the debridement. Ultimately, 15 cases were discharged with prescription of oral Posaconazole with favorable condition and normal sinus endoscopy.

### 4. Discussion

Since the emergence of the COVID-19 pandemic, several publications have reported the co-existence of mucormycosis and COVID-19 disease. It seems that COVID-19 infection may predispose the susceptible patients at risk of developing mucormycosis, especially in patients with DM. Apart from increasing the risk of immunodeficiency, administration of corticosteroids in COVID-19 patients could result in hyperglycemia, which additionally makes the patients susceptible to mucormycosis. Moreover, alteration of the innate immunity due to COVID-19 infection and the microangiopathies causing endothelial damage during COVID-19, are other predisposing factors [8, 9]. As a tertiary ENT center, we recognized a significant rise in mucormycosis during the COVID-19 era.

Almost all signs and symptoms known to be associated with rhinocerebral mucormycosis were observed in our COVID-19-associated mucormycosis (CAM) patients. The rapid development of frozen eye was occasionally seen in mucormycosis patients before, but it seems more common in CAM patients. Moreover, facial paralysis is a notable manifestation in our patients. Half of our patients had frozen eye at presentation and one-third had facial paralysis, which was considerably different from our pre-COVID-19 experience. Bayram et al. reported a case series of CAM patients, in which the most common manifestation was proptosis and 63% of their patients had frozen eye. They did not report facial paralysis as a presenting manifestation of mucormycosis. In that case series, 63% of patients passed away [10].

Patel et al., conducted a multicenter retrospective study in India to investigate the CAM patients. Among 287 mucormycosis patients, 187 (65.2%) had CAM. The prevalence of CAM was 0.27% among hospitalized COVID-19 patients. They noted a 2.1-fold rise in mucormycosis during the study period. The most common underlying disease was uncontrolled diabetes among CAM patients. COVID-19 was the only underlying disease in 32.6% of CAM patients. The mortality rate was 45.7% and was similar in CAM and non-CAM patients [11]. Similarly, in our series, DM was the most common predisposing factor among CAM patients: 13 patients had diabetes and 2 had new-onset diabetes after steroid administration. Note that 10 patients had a history of steroid administration for treatment of COVID-19 [12]. In a multicenter series from Iran, 15 patients with CAM were reported. Median age of patients was 52 years and 66% were male. The median time interval between diagnosis of mucormycosis and COVID-19 was 7 days, and 86% of patients had diabetes mellitus, while 46.6% received intravenous corticosteroid. Orbital exenteration was performed in five patients (33%), while seven (47%) died from mucormycosis [13].

Another unique finding in our cases was cavernous venous sinus thrombosis (CVST). More than half of our patients developed CVST and amazingly all of them survived. To the best of our knowledge, there is no report of CVST among CAM patients in the previous literature. Although, there are reports of CVST among COVID-19 patients [14-16].

Another noteworthy finding in our CAM patients was internal carotid artery (ICA) occlusion. There are several reports...
about ICA occlusion among COVID-19 patients as well as mucormycosis patients, independently [17-21]. But there were no reports of ICA among CAM patients, to the best of our knowledge.

Different studies have reported the mortality rate of mucormycosis between 40-80%, depending on the underlying conditions and extent of infection [22]. We had a significantly lower mortality rate of 16% in our study. It could be attributable to a high clinical suspicion, rapid diagnosis and intervention owing to being a referral center for otolaryngology patients. CAM indeed needs multidisciplinary management and thorough and serial examination.

COVID-19-associated mucormycosis is a rising condition during the pandemic, and may be associated with less usual presentations; clinicians should be made aware of this unusual presentation and incidence. It seems that the key to proper management of mucormycosis is early diagnosis and timely intervention, which could give the patient a better chance of survival.

5. Conclusion

Rhinocerebral mucormycosis is one of the most important complications of COVID-19 patients, especially those with underlying diseases. It seems that the key to proper management of mucormycosis is early diagnosis and timely intervention, which could give a patient a chance to live more.

6. Declarations

6.1. Acknowledgments

The authors would like to sincerely thank the residents and fellowship students in ENT ward and operation room and anesthesiology technologists who helped in performing the surgeries of high-risk patients, peri-operation followings, and gathering the data. Also, we should express our sincere thanks to Dr. Hojjat Salmasian for English editing the manuscript.

6.2. Authors’ contributions

Seyedhadi Samimi contributed in conceptualization, data collection, and collaborated in endoscopic surgeries. Shirin Irani contributed in study design, data collection, data interpretation, and collaborated in endoscopic surgeries and writing the original draft. Mohjaba Mohammadi Ardeshi contributed in conceptualization and collaborated in endoscopic surgeries. Reza Erfanian contributed in conceptualization and collaborated in endoscopic surgeries. Mohammad Ali Kazemi contributed in conceptualization and radiologic consultations. Afshar Etemadi-Alegha contributed in conceptualization and collaborated in anesthesia. Abolfazl Rahimi contributed in conceptualization and ophthalmologic consultation. Kourosh Karimi Yarandi contributed in conceptualization and neurosurgical consultation. All authors read and approved the final manuscript. Shirin Irani had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

6.3. Funding and supports

This project did not have any sources of financial support.

6.4. Conflict of interest

The authors declare no conflict of interest in this study.

6.5. Data availability

The Authors guarantee that data of the study are available and will be provided if anyone needs them.

6.6. Ethical considerations

This study was approved by the ethical committee of Amirlam Hospital. Also, all the patients’ records are protected and confidential.

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