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ORIGINAL RESEARCH

Distinguishing Characteristics of COVID-19-Associated Mucormycosis; a Case Series

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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

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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]. Mucromycosis 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

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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 cribriform 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 table1 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 paresthesia (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-

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
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 & extraconal 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	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

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
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 maxillectomy, 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, intraconal fat haziness	Superior, middle, and inferior turbinate necrosis	PPF, middle and inferior turbinate	Antrostomy, middle turbinate resection, PPF debridement, partial maxillectomy, 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 maxillectomy, 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 maxillectomy, 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 maxillectomy, palatal debridement	Death

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
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	PPF, IOF, foramen rotundum, vidian canal, cavernous sinus, buccal and preantral space, ICA C1-C7 thrombosis	No evidence of necrosis in diagnostic endoscopy	Middle turbinate, PPF, orbit	Antrostomy, ethmoidectomy, sphenoidectomy, middle turbinate resection, PPF & 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	Ethmoid, sphenoid & maxillary sinus, cribriform plate, PPF, IOF, foramen rotundum, vidian canal, buccal and preantral space, orbital apex, cavernous sinus, ICA	Evidence of previous antrostomy, ethmoidectomy and sphenoidotomy 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	Maxillary, ethmoid, sphenoid, PPF, IOF, fat stranding of pre-antral fat, orbital apex, rotundum foramen, vidian canal, fat stranding of buccal, masticator & parapharyngeal space	Necrosis in middle turbinate and nasal floor	Evidences of previous debridement in another center, PPF, 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	Predisp-osing factors	Steroid	Hospi taliza-tion	Interv al (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 hospital-ized 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 hospital-ized 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.

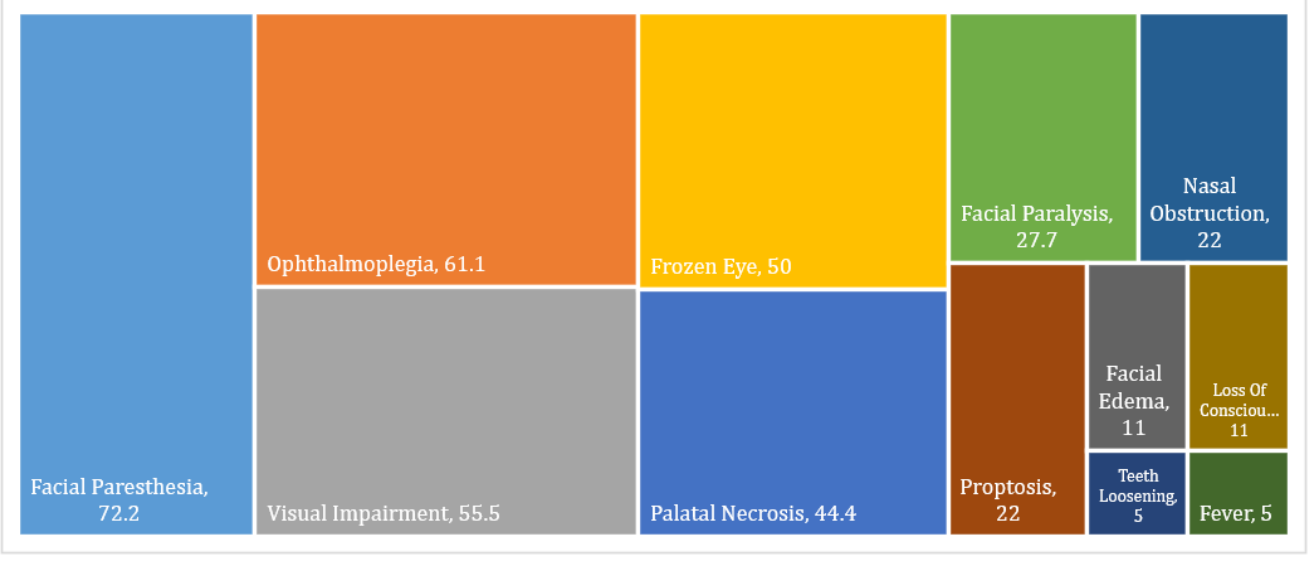

Figure 1: Percentage of different clinical presentations of patients with COVID-19-associated mucormycosis.

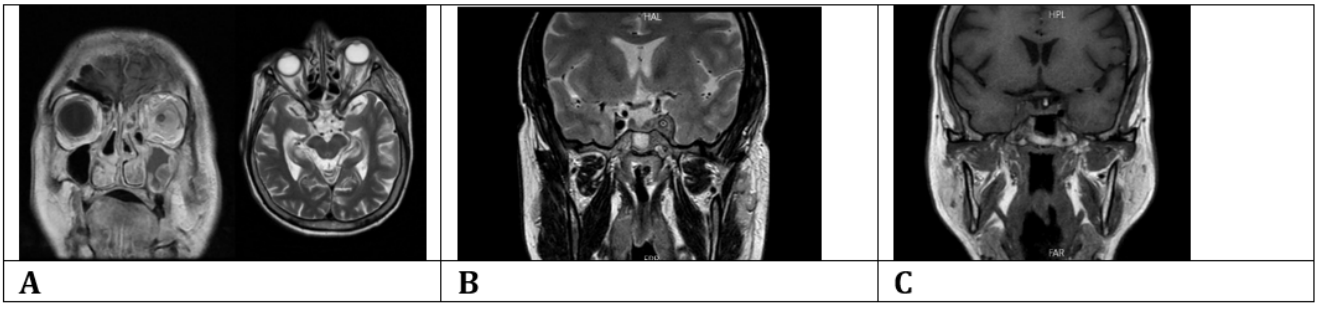

Figure 2: Magnetic resonance imaging (MRI) without contrast of patient No.1, shows orbital cellulitis, maxillary and ethmoidal sinusitis (A); Left cavernous sinus thrombosis and internal carotid occlusion in patient No 15 (B); Right Cavernous sinus thrombosis and internal carotid occlusion in patient No 14 (C).

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. It seems that steroid administration is a double-edged sword for management 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

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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 of the manuscript. Mehrdad Hasibi contributed in conceptualization and performing the infectious consultations. Maral Seyedahadi contributed in conceptualization and neurologic consultations. Shahin Bastaninejad contributed in conceptualization and collaborated in endoscopic surgeries. Mohammadreza Firouzifar contributed in conceptualization and collaborated in endoscopic surgeries. Sina Berijani and Samira Ahadi, otolaryngology residents, contributed in conceptualisation, data collection, collaboration in endoscopic surgeries and writing the original draft. Mojtaba Mohammadi Ardehali 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-Aleagha 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 Amiralam Hospital. Also, all the patients' records are protected and confidential.

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