A Case Series of Eight Mucormycosis Patients during SARS-CoV-2 –Pandemic

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Abstract

The outbreak of opportunistic fungal infections such as mucormycosis has been a critical issue following coronavirus disease 19 (COVID-19). Mucormycosis is happened by the fungal group Mucorales and commonly affects immunocompromised patients. To date, COVID-19-associated mucormycosis (CAM) is being reported in several countries. It should be noted that CAM has been started in patients approximately within two to three weeks after the onset of COVID-19. However, here, in one case, fungal symptoms appeared after just one week. In patients with mucormycosis due to this enigmatic infection, the sinuses were most commonly affected, followed by the orbit, nose, and finally the brain. All cases received glucocorticoids as a part of viral therapy. Diabetes mellitus (DM) was reported in all but one case in which COVID-19 was detected, without complications, and this may be the sole predisposing agent. Therefore, in this manuscript, we reported eight cases of COVID-19-induced mucormycosis. Although one case experienced evacuation of the right eye, others discharge with promising outcomes after receiving surgical debridement and proper anti-fungal treatment including, amphotericin B, caspofungin, and posaconazole.
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Keywords: COVID-19; Fugal Infection; Mucormycosis

Introduction

Coronavirus disease 2019 (COVID-19), attributed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was presented as a global pandemic by the World Health Organization (WHO) in March 2020 (1). The individuals are exhibiting mild to severe symptoms depending upon the extent of infection encountered by the virus and their immunity (2). The immune dysregulation associated with COVID-19 is encouraged and exasperated by concomitant medical conditions such as diabetes mellitus, and the widespread use of immunosuppressive agents such as steroids additionally broad-spectrum antibiotics (3). Changes in human microbiota have been recently observed in COVID-19 patients. Patients are often colonized or tainted by microorganisms responsible for secondary infections (co-infections or superinfections), often caused by bacteria and fungal pathogens (4) that have been identified as a fatal predictor (5). These diseases are actuated by a wider fungal group, called mucormycetes, and the contamination is named COVID-19-associated mucormycosis (CAM) (6).

Mucormycosis or black fungus is an opportunistic infection leading to the invasion of blood vessels by fungal hyphae, resulting in infarction and necrosis of a variety of end-organ host tissues. It is caused by fungi of the order Mucorales with acute incidence, rapid progression, and high fatality (7). Risk factors for mucormycosis include diabetes mellitus, hematological malignancies, solid organ transplantation, iron overload, neutropenia, and prolonged glucocorticoid use, all resulting in immune dysfunction. A prolonged stay on ventilators is another reason for developing fungal infections (8). Mucormycosis can be categorized as one of six shapes: rhino-orbital-cerebral mucormycosis (ROCM), pulmonary, cutaneous, gastrointestinal (GI), disseminated, and mucormycosis of uncommon sites (9). Mucormycosis may be a therapeutic crisis that requires prompt initiation of systemic antifungals and adjunctive

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surgery (1). The mucormycosis-associated mortality is 35–50% in afflicted individuals. Most of the cases have been reported from India, which coincidently has the second-highest number of diabetic people in the world. Besides that, France, Iran, Russia, Pakistan, Bangladesh, Mexico, Oman, Egypt, Argentina, the United States of America, etc. have reported cases of this fungus as well (6). Considering that the current pandemic continues to be a significant public health issue all-inclusive, there needs to be a heightened awareness about mucormycosis among patients with COVID-19, since both situations in combination may lead to noteworthy morbidity and mortality. In this case series, we present eight cases of mucormycosis from Imam Reza Hospital of Mashhad, Iran which has been infected with COVID-19 with or without other underlying disease.

Case presentation

A 29-years- old male patient was admitted to Imam Reza Medical Center with pain and diminished vision in his right eye on March 2021. He experienced these symptoms three weeks after getting affected with COVID-19. No past medical or drug history was detailed by the patient. During the treatment of COVID-19, he received dexamethasone, naproxen, famotidine, and montelukast. On physical examination, proptosis, malaise, and ophthalmoplegia were obvious. There was no nasal discharge. The laboratory examination results on admission date were: leukocytes, 8.8 *103 / mL (neutrophils, 65%); hemoglobin, 9.2 g/dl; C-reactive protein (CRP), 0 mg/L; erythrocyte sedimentation rate (ESR), 5 mm/h. CT scan revealed the involvement of the brain and findings were highly assumed for invasive fungal rhino sinusitis and orbital involvement. The patient received the following medical interventions for two weeks: clindamycin (600 mg every eight hours), liposomal amphotericin B vial 400 mg daily (5 mg/kg), caspofungin (loading dose: 70 mg then 50 mg daily), and ceftriaxone. After the improvement of the patient's symptoms, he was discharged from the hospital with personal consent and provided he continued appropriate treatment. One month later, the patient returned to the hospital due to insufficient adherence to his therapy and was treated for the second time with liposomal amphotericin B with suitable outcomes.

The second case was a 43-year-old man that was diagnosed with COVID-19 on May 2021. The patient suffered from diabetes that was controlled with metformin 500 mg daily. There were no allergic reactions or drug sensitivity. He underwent high-dose glucocorticoid therapy with no approved indication (normal serum oxygen saturation). During hospitalization, the patient's sugar level went out of control and the glycemic profile remained uncontrolled despite use of oral and parenteral anti-diabetic agents. After three weeks, he was referred to Imam Reza Medical Center with the complaint of bilateral blurred vision, right facial paralysis, hyposmia, headache, malaise, and sinus pain. Blood sugars at admission were 346 mg/dl with hemoglobin A1C 5 %. Leukocytes, 7.8 *103 /mL (neutrophils, 65%); hemoglobin, 10.8 g/dl; CRP, 21 mg/L; ESR, 31 mm/h were laboratory results. All examinations were normal but just in the nasal examination, there was paleness in the right septum and right concha necrosis was recognized. On the other hand, there was no necrosis, paleness, or hypoesthesia in the palate. CT scan revealed evidence of opacities and consolidation in the right paranasal sinuses and bilateral maxillary with bone disintegration in the medial wall of the right maxillary and demineralization in the left maxillary medial wall. Muscle biopsies revealed necrotic tissue with non-septate fungal hyphae suggestive of mucormycosis. The patient received liposomal amphotericin B 350 mg daily (5 mg/kg). After that, due to the lack of liposomal amphotericin B patient received posaconazole IV 300 mg twice daily for two doses, then 300 mg once daily. Finally, in the post-treatment biopsies, no evidence of fungal invasion was identified and the patient was discharged with oral posaconazole for twelve days.

The third case was a 66-year-old male with a history of shortness of breath for seven days, on June 2021. Diagnosis of COVID-19 was affirmed as reverse transcription-positive by polymerase chain reaction (RT-PCR). The patient had no previous history of any debilitating conditions. He had no history of tobacco smoking or alcohol consumption. He was monitored in the ward for 10 days. Remdesivir and dexamethasone were administrated for 7 days. After ten days, the patient was discharged from the hospital with oral prednisolone in good general condition. After 7 days, the patient complained of two white sores on the palate. Physical examination ascertained, necrotic eschars on the palate and nasal turbinate. Afterward, nasal endoscopy was performed. Severe involvement and necrosis of the nasal floor, palate mucosa, right nasal septum mucosa, and middle nasal concha as well as left ethmoid sinuses were observed. Laboratory tests at admission were as followed: fasting blood sugar (FBS), 99 mg/dl; hemoglobin A1C, 6.7%; leukocytes, 9.2 *103 /mL (neutrophils, 85.1%); hemoglobin, 13.7 g/dl; CRP, 0 mg/L; ESR, 1 mm/h. Surgical debridement of infected tissues has been performed and reported acute necrotizing inflammation with mucormycosis. In this manner, treatment with liposomal amphotericin B 350 mg daily (5 mg/kg) was begun. Concurrently, the patient underwent daily endoscopic paranasal sinuses debridement and irrigation

with normal saline. After each debridement, the patient was treated with clindamycin 600 mg every 8 hours for 48 hours. On the tenth day of treatment, patient experienced decreased oxygen saturation of arterial blood, suspecting pulmonary embolism, pneumonia, or pulmonary involvement of mucormycosis, and caspofungin (loading dose:70 mg then 50 mg daily) was added to the treatment. Pulmonary mucormycosis was ruled out through bronchoscopy. Also, pneumonia and pulmonary embolism were excluded. However, as the patient's clinical course improved, caspofungin continued. During his treatment course, the patient developed hypokalemia and acute kidney injury, additional hydration with normal saline was recommended before amphotericin B administration and therapy with oral potassium chloride syrup. He was discharged after 6 weeks of hospitalization after taking amphotericin B liposomal for 42 days, and caspofungin for 28 days, with desirable healing. At the time of discharge posaconazole 200 mg twice a day was administrated for twelve days.

The fourth case was a 60-year-old woman with a history of well-controlled non-insulin-dependent diabetes mellitus (DM) and hypertension that was affected by COVID-19, confirmed by RT-PCR and the chest CT scan. She was managed by remdesivir, empiric antibiotic therapy, dexamethasone, and a high-flow nasal cannula for breathing support. On the 14th day, the patient complained of right orbital pain, unilateral eyelid swelling, purulent discharge, facial pain and paresthesia, and facial numbness on the right side together with progressive vision loss. She was transferred to Imam Reza Hospital with suspicion of mucormycosis. The laboratory examination results were the following: FBS, 121 mg/dl; hemoglobin A1C, 5.6%; leukocytes, 9.1 *103 /mL (neutrophils, 70%); hemoglobin, 9 g/dl; CRP, 6 mg/L; ESR, 20 mm/h. A CT scan showed opacifications in the bilateral maxillary, sphenoidal, and ethmoidal sinuses together with right orbital tissue involvement, bone devastation of sinus walls, obtrusive to paranasal sinuses with secondary involvement of the right orbit, right-sided proptosis, expanded mucosal thickness in all paranasal sinuses. Histopathological assessment of the mucosa revealed broad aseptate hyphae with right-angled branching consistent with fungal hyphae similar to mucormycosis. With the diagnosis of a sino-orbital mucormycosis, debridement of the necrotic tissues was performed. Additionally, amphotericin B 400 mg daily (5 mg/kg) was prescribed for the patient. On the next day, the patient had fever for several times. Blood culture was ordered, and empirical treatment with vancomycin (1 gram twice daily) and cefepime (2 grams three times a day) was started. After 72 hours, the blood culture was positive for Enterobacter which was sensitive to ceftriaxone, amikacin, gentamicin, and ciprofloxacin. Hence, anti-microbial treatment was narrowed and vancomycin and cefepime were replaced by ceftriaxone (1gram IV twice daily). Brain magnetic resonance imaging (MRI) was normal and brain involvement of mucormycosis was ruled out. Since noticeable clinical improvement was not accomplished, the dose of amphotericin B was increased to 600 mg daily, and caspofungin (loading dose: 70 mg then 50 mg daily) was added to her regimen.

The fifth case was a 65-year-old man with known prior DM, hypertension, and Ischemic heart disease (cardiac pacemaker implantation) who was diagnosed with COVID-19 seventeen days before admission on May 2021. The infection was defined based on lung CT scan. The patient's medication history was as follows: metformin, nitroglycerin, aspirin, glibenclamide, atorvastatin, losartan, prednisolone, valsartan/amlodipine, and bisoprolol. Before admission, the patient was treated with dexamethasone and oral prednisolone. He endured hypoesthesia on the right side of the face and right cheek with retro-orbital pain, developing blindness in the right eye. Right frontal cerebral pain, hyposmia, and palate dysesthesia were also evident in the patient. In the eye examination, there was no response to light, brief proptosis and ptosis, pupil fixation, and restricted movement in all directions. Normal left eye movements and mid-size and reactive pupil was reported. In the nasal examination, evidence of necrosis in both lateral nasal cavities was seen. The laboratory data were: FBS, 171 mg/dl; hemoglobin A1C, 13.7 %; leukocytes, 10.3 *103 /mL (neutrophils, 70%); hemoglobin, 11 g/dl; CRP, 10 mg/L; ESR, 4 mm/h. Chest X-Ray was normal. PNS (peripheral nervous system) CT scan revealed diffuse turbidity in the ethmoid, maxillary, and bilateral sphenoid sinuses and nasal cavities. No evidence was found in favor of bone invasion and destruction. The patient underwent debridement for two times and a biopsy was taken from the patient for pathology. Microscopic examination reveals sections of the respiratory mucosa with foci of coagulation necrosis with fungal hyphae with irregular walls. Necrotic mucosa with fungal hyphae compatible with mucormycosis. The patient underwent six FES and in the latter, there was no evidence of fungal invasion and no fungal element was detected. The patient received liposomal amphotericin B 350 mg daily (5 mg/kg). Due to liposomal amphotericin B shortage, the patient received multiple posaconazole injections of 300 mg twice daily for two doses, then 300 mg once daily. Eventually, the patient was discharged after two months and placed on posaconazole suspension for twelve days.

The sixth patient was a 59-year-old addicted woman who was hospitalized in Imam Reza Medical Center due to

COVID-19 on August 2021. The diagnosis was confirmed by RT-PCR test. The patient had been diagnosed with type 2 diabetes mellitus and hypertension 10 years ago and she was being treated with insulin, losartan, amlodipine, and metoprolol. During the hospitalization, remdesivir and dexamethasone were administered. Three days later, the blood sugar started to rise and reached 350 mg/dl. It should be mentioned that before the COVID-19 treatment, the HbA1c was 5.3%. On day 7, she experienced severe headache, and edema evident on both sides of the face, but she was discharged after 10 days. One month later, the patient returned with a progression in pain and edema. All other examinations were normal. Routine blood tests yielded the following results: leukocytes, 10.3 *103 / mL (neutrophils, 67%); hemoglobin, 9.1 g/dl; CRP, 93 mg/L; ESR, 89 mm/h. The blood and urine cultures were negative. Bilateral sensory and also brain examination were normal. CT scan revealed evidence of opacities and consolidation in sinuses with bone destruction of sinus walls. Muscle biopsies revealed necrotic tissue indicative of mucormycosis. Liposomal amphotericin B 3oo mg daily (5mg/kg) was initiated and continued for two weeks. In the absence of liposomal formulation, she received conventional amphotericin 60 mg daily (1 mg/kg). Moreover, the patient underwent daily endoscopic paranasal sinuses debridement. During the treatment, she expanded hypokalemia and hypomagnesemia with 2.5 mmol/L and 0.82 mg/dl, respectively. These disturbances were managed with oral potassium chloride syrup and parenteral magnesium sulfate. The patient underwent three FES and in the last two, there was no evidence of fungal elements and discharged from the hospital with a posaconazole prescription with a good general appearance.

The seventh patient was a 60-year-old woman who was hospitalized for 20 days due to COVID-19 disease last month on August 2021. The diagnosis was estimated based on lung CT scan with 80% involvement and the patient was placed on remdesivir and dexamethasone. Since the patient was suffering from right upper limb thrombosis, heparin was started. Her medical history revealed that she had DM and hypertension which were managed with insulin and losartan. The patient also underwent cholecystectomy and hysterectomy. Four days after discharge, the patient was re-admitted to the hospital because of eyelid swelling, and proptosis on the left side together with blurred vision. Laboratory workup exhibited leukocytes, 10 *103 /mL (neutrophils, 72%); hemoglobin, 13.1 g/dl; CRP, 18 mg/L; ESR, 56 mm/h with FBS 93 mg/dl, and hemoglobin bA1C 5.3 %. On day three, she developed intermittent loss of consciousness and delirium but CNS and other examinations were normal. Blood culture was requested and after 72 hours, was positive for gram-negative bacilli. Furthermore, urine culture was positive for E.coli and ESBL sensitive to amikacin, imipenem, and nitrofurantoin. Imipenem was initiated at 500 mg every 6 hours. CT scan displayed left orbital tissue involvement. According to orbital mucormycosis, three retrobulbar injections of amphotericin B have been performed with no side effects aside from the debridement of the necrotic tissues. There were no adverse effects. Liposomal amphotericin B 350 mg daily (5 mg/kg) IV was injected into the patient. Because of liposomal amphotericin deficiency, she was given conventional amphotericin 75 mg daily (1 mg/kg) for three days and posaconazole 300 mg twice daily for 2 doses, then 300 mg once daily for six days during the course of therapy. During management, hypokalemia occurred with potassium 2.5 mmol/L and was controlled with oral potassium chloride syrup. The patient underwent four FES and in the last two, there was no evidence of fungal involvement and discharged from the hospital without unconsciousness with posaconazole administration.

The eighth patient was a 45-year-old woman with a history of DM and improved anemia who concede to Imam Reza Medical Center due to COVID-19. Three weeks ago, her COVID-19 infection had been proven by CT involvement on September 2021 and received parenteral remdesivir and dexamethasone. She was also on insulin therapy with hemoglobin bA1c 5.7 %. Therapeutic heparin had been given to the patient since the patient was involved in bilateral lower limb thrombosis. One week later, the patient alluded to the medical center with a headache, right orbital pain, and edema with purulent nasal discharges. Routine blood evaluation tests yielded the subsequent information: FBS, 131 mg/dl; hemoglobin A1C, 6.1%; leukocytes, 16.6 *103 /mL (neutrophils, 92%); hemoglobin, 9.1 g/dl; CRP, 82 mg/L; ESR, 55 mm/h. Although, the blood cultures consequences were negative. But the empiric treatment with ampicillin-sulbactam 3 grams every six hours IV had been introduced. The sensory and also brain assessments were normal. PNS CT scan represented turbidity in the ethmoid sinuses with bone destruction and also right orbital involvement. Muscle biopsies demonstrated necrotic tissue expressing mucormycosis. Liposomal amphotericin B 3oo mg daily (5 mg/kg) was imported into the therapy. In addition, the patient sustained daily endoscopic ethmoid sinuses debridement. Because of the lack of clinical recovery, the dose of amphotericin B was increased gradually to 500 mg daily and caspofungin (loading dose:70 mg then 50 mg daily) was added after three weeks of therapy. During the hospitalization, she experienced hypokalemia (2.7 mmol/L), which was well managed with potassium chloride injection. With no evidence of fungal elements in the last biopsy, the patient was discharged from the hospital with acceptable condition. The patients' information is summarized in Table 1.

Table 1. clinical characteristics and laboratory findings of eight patients with mucormycosis after COVID-19.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age/gender	29/Male	43/Male	66/Male	60/Female	65/Male	59/Female	60/Female	45/Female
Comorbidities	None	DM	None	DM, HTN	DM, HTN, IHD	DM, HTN	DM, HTN, Hysterectomy, Cholecystectomy	DM, Anemia
Symptoms of COVID-19	Cough , weakness, and dyspnea	Dyspnea , fever, and cough	Dyspnea	Fever, weakness, cough, and dyspnea	Cough, dyspnea	Headache, cough, anorexia, and dyspnea	Headache, fever, and dyspnea	Dyspnea, fever, and weakness
COVID-19 diagnosis	Lung CT	RT-PCR	RT-PCR	Lung CT/RT-PCR	Lung CT	RT-PCR	Lung CT	Lung CT
Fungal signs and symptoms	Pain and diminished vision in right eye	Bilateral blurred vision, right facial paralysis, hyposmia, headache, malaise and sinus pain	Two white sores on the palate	Right orbital pain and proptosis, unilateral eyelid swelling, purulent discharge, facial pain and paresthesia, and facial numbness on the right side with vision loss	Hypoesthesia on the right side of the face, orbital pain, blindness in the right eye, right frontal cerebral pain, hyposmia, palate dysesthesia, no response to light, brief proptosis and ptosis, pupil fixation and restricted movement in all directions	Severe headache, and edema evident on both sides of the face	Eyelid swelling, proptosis on the left side with blurred vision	Right orbital pain and edema with purulent nasal discharges
Time of fungal symptoms onset after COVID-19 affection (days)	21	21	17	14	17	7	24	14
Serum studies at admission	Leukocytes, 8.8 *103 /mL (neutrophils, 65%); hemoglobin, 9.2 g/dl; CRP, 0 mg/l; ESR, 5 mm/h.	Leukocytes, 7.8 *103 /mL (neutrophils, 65%); hemoglobin, 10.8 g/dl; CRP, 21 mg/l; ESR, 31 mm/h	Leukocytes, 9.2 *103 /mL (neutrophils, 85.1%); hemoglobin, 13.7 g/dl; CRP, 0 mg/l; ESR, 1 mm/h.	Leukocytes, 9.1 *103 /mL (neutrophils, 70%); hemoglobin, 9 g/dl; CRP, 6 mg/l; ESR, 20 mm/h.	Leukocytes, 10.3 *103 /mL (neutrophils, 70%); hemoglobin, 11 g/dl; CRP, 10 mg/l; ESR, 4 mm/h.	Leukocytes, 10.3 *103 /mL (neutrophils, 67%); hemoglobin, 9.1 g/dl; CRP, 93 mg/l; ESR, 89 mm/h.	Leukocytes, 10 *103 /mL (neutrophils, 72%); hemoglobin, 13.1 g/dl; CRP, 18 mg/l; ESR, 56 mm/h	Leukocytes, 16.6 *103 / mL (neutrophils, 92%); hemoglobin, 9.1 g/dl; CRP, 82 mg/l; ESR, 55 mm/h.
FBS (mg/dl)/ HbA1C (%)	-	346/5	99/6.7	121/5.6	171/13.7	350/5.3	93/5.3	131/6.1
Involvement site	Brain, sinuses, nasal, and right orbits	Right paranasal and bilateral maxillary sinuses	Nasal and ethmoid sinuses	Right orbit, bilateral maxillary, sphenoidal, ethmoidal, and paranasal sinuses	Ethmoid, maxillary, and bilateral sphenoid sinuses, right orbit, and nasal cavity	All sinuses	Left orbit	Ethmoid sinuses, and right orbital
Medical treatment	Amphotericin B plus caspofungin for 14 days with subsequent posaconazole therapy	Amphotericin B for 35 days with subsequent posaconazole therapy	Amphotericin B for 42 days plus caspofungin for 28 days with subsequent posaconazole therapy	Amphotericin B for 90 days plus caspofungin for 35 days with subsequent posaconazole therapy	Amphotericin B for 42 days with subsequent posaconazole therapy	Amphotericin B for 30 days with subsequent posaconazole therapy	Amphotericin B for 40 days plus caspofungin for 21 days with subsequent posaconazole therapy	Amphotericin B for 45 days with subsequent posaconazole therapy
Drug-induced adverse effects	-	-	Acute kidney injury, hypokalemia	-	-	Hypokalemia, hypomagnesemia	Hypokalemia	Hypokalemia
Clinical outcome	Discharge after two courses of therapy in a good condition	Discharge in a good condition	Discharge in a good condition with continue oral therapy at home	The right eye was evacuated on the advice of an ophthalmologist	Discharge in a good condition with continue oral therapy at home	Discharge in a good condition	Discharge in a good condition	Discharge in a good condition

Abbreviation: Coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Computed tomography (CT), C-reactive protein (CRP), 0 mg/l; erythrocyte sedimentation rate (ESR), diabetes mellitus (DM), Hypertension (HTN), Reverse transcription-polymerase chain reaction (PCR), Fasting blood sugar (FBS), Hemoglobin A1C (HbA1C), magnetic resonance imaging (MRI).

Discussion

AMucormycosis is a serious fungal infection produced by a group of molds called mucormycetes (10). Although these fungi are set up everywhere soil, dirt, and decaying vegetation are the sole source (10, 11). Generally, mucormycosis is caused by the inhalation of spores and begins with acute sinusitis. These fungi are angioinvasive and result in thrombosis and necrotic tissues (11). Mucormycosis is a rare infection in healthy individuals, while it is observed in patients with predisposing factors like uncontrolled diabetes, hematologic cancer and other immunocompromised conditions. Hypoxia, broad-spectrum antibiotics, and corticosteroid use are other reasons for debilitating the immune system and facilitating fungal invasion (12). Moreover, a systematic review exhibited that hypertension and cardiac disease were reported in nearly one-third and one-tenth of cases respectively (11). Studies suggest that all genders and ages are in danger of this life-threatening disease, with a higher incidence in older adults (5). Recent data declared a growing outbreak of mucormycosis in COVID-19 patients contributing to treatment failure (13). This co-infection first happened in India with a high mortality rate and subsequent progress in other regions (14) both underdeveloped and advanced countries. Besides, steroid use induced high blood glucose levels in COVID-19 patients facilitating mucormycosis infection by diminishing the levels of T cells resulting in cytokine storm and impairment of cellular functions (15). The most common sites of infections were accounted to be in the sinuses (39%), lungs (24%), and skin tissue (19%) where dissemination occurred in 23% of these cases (7). Rhino-orbital-cerebral mucormycosis is the most common presentation with DM as the most concurrent underlying disease. The documents also showed the most significant underlying cause in Iran was DM (10). The misdiagnosis of mucormycosis is one of the reasons for high mortality (13). Initial symptoms resemble bacterial sinusitis. Symptoms such as facial pain and numbness, fever, and headaches, often accompanied by nerve palsy, nasal discharge, nasal ulceration, hemiplegia, eschars, and mental deterioration. The infection can cause necrosis of the palate, turbinates, and other nasal structures. On the other hand, orbital involvement can lead to pain, visual loss, proptosis, discharge, and edema (16, 17). The infection can spread from the sinuses via the orbital area to the brain (18). Clinical suspicion along with radiological investigations are diagnosis approaches (16). In detail, MRI and CT scans of the affected regions can guide detection showing opacification and infiltrates (8, 13). As well endoscopy and biopsy of affected sinuses and necrotic tissues are required to confirm a diagnosis (11). Increased incidences CAM further complicate COVID-19 disease management. The management of COVID-19-associated mucormycosis includes a combination of antifungal therapy and, in severe cases, surgical removal of involved tissues. Surgical treatment is associated with better survival rates due to extend drug penetration into the tissues (15). The antifungal therapeutics may be prescribed for several weeks to months until a resolution of symptoms (8). Polyenes (amphotericin derivatives) and triazoles (isavuconazole and posaconazole) are the main antifungal medicines against mucormycosis. Posaconazole is given as salvage treatment to the patient with intolerance to amphotericin B. The recommended beginning dose of liposomal formulation is 5 mg/kg daily. The dose may enhance up to 10 mg/kg daily to control the co-infection more efficiently with a focus on brain involvement (13, 15). Studies have shown that amphotericin B is well-tolerated and can be administered safely to patients (19). Conventional amphotericin B (1–1.5 mg/kg) may be used if liposomal formulations of amphotericin B are not available or when renal involvement of mucoromycosis occurs, because of better penetration to kidneys. However, the liposomal formulations of amphotericin B are the treatment of choice, particularly because of lower nephrotoxicity, as high dose is administered in mucormycosis. A combination of amphotericin B with posaconazole or echinocandins, and also posaconazole with echinocandins has been proposed in some studies. It was cited that combination therapy using amphotericin B and caspofungin is more effective than monotherapy against rhino-orbital-cerebral mucormycosis. Patients responding to amphoterin B, posaconazole, can be ordered for step-down therapy whereas in salvage therapy, patients not responding are given posaconazole with a dose of 300 mg/kg every 12 h, followed by 300 mg every 24 h afterward (15). Despite adequate medical and surgical options, the fatality rate is high and in some conditions, orbital extraction may aid in illness improvement (16). Without early treatment and identification, this ailment may lead to lethal complications. Therefore, clinical guidelines should be noticed for the urgent diagnosis, appropriate use of antibiotics, and glucocorticoid to be put on controlling DM and other risk agents in COVID-19 cases (20).

In this case report, we report eight CAM from Iran, in all age groups. This survey identified DM and corticosteroid use as the most frequent predisposing factors. Since one of the patients had no immune dysfunction except steroid use, it can be concluded that both immunocompetent and immunocompromised patients may be affected by mucormycosis infection. The patients had various symptoms but fever, cough, dyspnea, and weakness were the most common clinical symptoms among patients with fungal co-infections and COVID-19. The onset of mucormycosis symptoms were reported within seven days after COVID-19 beginning in one case, while in others the symptoms appeared at least after 14 days. Owing to the clinical manifestations, and risk factors, mucormycosis was established after confirmation with images and endoscopic tissue biopsies. When the blood vessel necrosis occurs in the ophthalmic artery it might lead to blindness which happened in one case. All patients were administrated systemic antifungal treatment with the surgical intervention and discharged in good condition. Some patients underwent conventional amphotericin B or posaconazole as monotherapy due to lack of liposomal Amphotericin-B. In addition, glycemic control was achieved helping in the early recovery of the patient.

In conclusion, mucormycosis is likely a fungal complication of COVID-19. Proper schedule including early diagnosis and management of CAM with suitable antifungal particularly amphotericin B, with or without caspofungin, and posaconazole beside surgical debridement can facilitate improvement. In addition, consideration should be given to control patients' blood sugar properly and avoiding inappropriate indications and doses of glucocorticoids.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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