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Retrospective Study

Mucormycosis in COVID-19 Pandemic

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ABSTRACT

Background
Coronavirus disease-2019 (COVID-19) has been associated with a wide range of opportunistic fungal infections. Many countries have seen an unprecedented rise in cases of COVID-19-associated mucormycosis (CAM). The purpose of this study is to identify the correlation between the COVID-19 epidemic and mucormycosis. Our study also provides details on factors causing CAM.

Methods
A retrospective study from November 2020 to February 2022 includes four cases of COVID-19-associated rhino-orbital mucormycosis treated at Habib Thameur Hospital's ENT Department.

Results
The mean age of patients was 67.5-years, 75% were males, and the most frequent underlying conditions were diabetes mellitus (100%). The median time interval between the diagnosis of COVID-19 and the first evidence of mucormycosis infection was 15-days; two patients required hospitalization in a COVID unit, and two patients received oxygen therapy at home. All patients received corticosteroid therapy at a dose of 1 mg/kg/d for an average of 10-days. Treatment using antifungals and surgery was described in all the patients. Amphotericin B deoxycholate was used in 75% and lipid formulation in 25%. Two patients presented renal insufficiency due to amphotericin B; the doses were adapted with good evolution. In that report, the case fatality rate was 75%.

Conclusion
Mucormycosis is a fatal fungal infection that usually affects patients with altered immunity. Several cases of mucormycosis in people with COVID-19 have been increasingly reported worldwide. Diabetes mellitus (DM), steroid overdose, immunosuppression, and high iron levels, combined with other factors such as prolonged hospitalization, unhygienic conditions, and the use of ventilators, combine to create an ideal environment for contracting mucormycosis. Lastly, there is a need to create awareness about fungal diseases among clinicians in order to help identify early symptoms and restrict the spread of lethal fungal diseases. A collaborative team of otolaryngologists, ophthalmologists, anesthesiologists, and resuscitators will be required in hospitals to accelerate optimal management.

Keywords
Coronavirus; Mucormycosis; Fungal infection.

INTRODUCTION

Coronavirus disease-2019 (COVID-19) has been associated with a wide range of opportunistic bacterial and fungal infections. Many countries have seen an unprecedented rise in cases of COVID-19-associated mucormycosis (CAM).[1] Since the outbreak of the COVID-19 pandemic, the global prevalence of mucormycosis has varied from 0.005 to 1.7 per million people.[2] Although the first case of CAM was reported in Chile, most cases were reported in India. This opportunistic infection occurs within 12 to 18-days of recovery from COVID-19.[1]

The purpose of this study is to identify the correlation between the COVID-19 epidemic and mucormycosis. Our study provides details on factors causing COVID-associated mucormycosis. We also aimed to describe the frequency, presentations, and in-hospital outcomes of mucormycosis patients in the scope of COVID-19.

METHODS

A retrospective study was conducted from November 2020 to February 2022 with four cases of COVID-19-associated rhino-orbital mucormycosis managed in the ENT department of Habib Thameur Hospital. The patient's history, imaging findings, examination findings, steroid usage, and outcome were analyzed.

Exclusion Criteria

Patients with fungal infections other than mucormycosis or without a confirmed diagnosis of COVID-19.

RESULTS

We describe our experience in managing four consecutive COVID-19 patients admitted to our department who presented within the same month with associated mucormycosis (Table 1).

The mean age of patients was 67-years, 75% being males, and the most frequent underlying conditions were diabetes mellitus (DM) (100%). The median time interval between the diagnosis of COVID-19 and the first evidence of mucormycosis infection was 15-days; two patients required hospitalization in a COVID unit, and two patients received oxygen therapy at home. All patients received corticosteroid therapy at a dose of 1 mg/kg/d for an average of 10-days.

Blood sugar control and management of diabetic ketoacidosis (DKA) were challenging. Three patients had DKA with very high blood sugar above 20-25 mmol/l that required high doses of insulin therapy.

Four patients underwent endoscopic sinus surgery and debridement of all necrotic tissue from the nasal and sinus cavities. This procedure was repeated in all patients to debride any necrotic tissue that appeared (Table 2).

Table 1. *Characteristics of COVID-19-Associated Mucormycosis Cases, Medical and Surgical Interventions and Outcomes*

Case	1	2	3	4
Age	72	62	65	69
Sex	Male	Male	Male	Female
Days since COVID-19 symptoms started	12-days	22-days	8-days	18-days
COVID-19 strain	Not done	Not done	Not done	Delta variant
Indication for admission	Mucormycosis	Mucormycosis	Mucormycosis	Mucormycosis
Prior steroidtherapy	1 mg/kg/d	1 mg/kg/d	1 mg/kg/d	1 mg/kg/d
Known/new DM	Known	Known	Known	New
Diabeticketoacidosis (DKA)	Yes	Yes	No	Yes
Comorbidities	High blood pressure	Morbidobesity	High blood pressure	Renalfailure
Symptom/clinicalfindings	-Headache -Left eye pain -Left periorbital swelling+chemosis -Palatal eschar -Confusion	-Right facial numbness -Right periorbital swelling+chemosis -Ophthlamoplegia -Palatal eschar	-Left facial numbness -Nasal fullness -Left periorbital swelling -Ophthalmoplegia	-Nasal fullness -Left eye chemosis+ophthalmoplegia -Leftcheekinduration
Extension of mucormycosis	Rhino-orbital	Rhino-orbital	Rhino-orbital	Rhino-orbital
Nasal endoscopy	Necrosis of entire left-side mucosa extending into contralateral side	Dusky necrotic mucosa involving the septum	Necrosis of entire left-side mucosa extending into contralateral side	Congestedmucosa No necrosis
Tissue bacterial	No growth	*Klebsiella Pneumoniae*	No growth	No growth
Surgical intervention	Yes	Yes	Yes	Yes
Orbital exenteration	No	No	No	No
Initial therapy	IV amphotericin B deoxycholate 0.7 mg/kg	IV amphotericin B deoxycholate 0.7 mg/kg	IV amphotericin B deoxycholate 0.5 mg/kg	IV AmBisome 5 mg/kg×3 weeks
Outcome	Died	Died	Died	Discharged after 7-weeks

Table 2. *Description of Radiological Findings of the Described Patients with COVID–19–Associated Mucormycosis and Surgical Interventions*

Patient	Description of Radiological Findings	Surgical Intervention
Patient 1	**Contrast CT:** Total opacification of left maxillary sinus with central hyperdensities and opacification of left ethmoid air cells. There was associated subcutaneous thickening of left periorbital and pre-maxillary regions with mild left-eye proptosis.	Debridement included medial maxillectomy with ethmoidectomy.
Patient 2	**Contrast CT:** Complete opacification in right maxillary sinus with mild mucosal thickening in right ethmoid, sphenoid and frontal sinuses. Periorbital edema and soft tissue infiltration anterior to right maxillary and cheek area. Mild right-eyeproptosis	Debridement of all necrotic mucosa, including all right-sided sinuses and nasal septum.
Patient 3	**Contrast CT:** Complete opacification and mucosal thickening of left maxillary, ethmoid and frontal sinuses with bone refraction. Soft tissue infiltration of left periorbital area and left-eye proptosis. Soft tissue infiltration in sphenopalatine and nasopharynx.	Debridement of all necrotic tissue involving all left paranasal sinuses and posterior nasal septum.
Patient 4	**Contrast CT:** Dense opacification of left nasal cavity, frontal and ethmoid sinuses. Mucosal thickening in both maxillary sinuses with bone remodeling. Prominent left ophthalmic vein and intraorbital fat stranding. Left-eyeproptosis.	Debridement of all necrotic tissue involving all left paranasal sinuses.

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Amphotericin B deoxycholate was used at 75% and liposomal amphotericin at 25%. Two patients presented renal insufficiency due to amphotericin B; the doses were adapted with good evolution.

The duration of intravenous treatment differed between patients according to the severity of the disease. The average treatment duration was 7-weeks, except in the case of a patient who died earlier.

One patient with rhino-orbital mucormycosis survived, and the rest died of advanced mucormycosis involvement. They had a very extensive disease. The case fatality rate was 75%.

DISCUSSION

The coronavirus disease has become a global threat since its emergence at the end of 2019.[2] Moreover, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection could present with secondary infection by other viruses, bacteria, or fungi. Among them is mucormycosis, which is a rare but aggressive fungal disease, and mainly since the outbreak of COVID-19, more and more cases of CAM have been reported.[3]

Up to 8% of COVID-19 cases are complicated by secondary bacterial and invasive fungal infections.[4] The use of broad-spectrum antibiotics and steroids increased the risk of such complications.[5]

Since the outbreak of the COVID-19 pandemic, the global prevalence of mucormycosis has varied from 0.005 to 1.7 per million.[1]

Patients can present with facial pain or swelling, headaches, paresthesia, or visual loss. On clinical examination, periorbital swelling, proptosis, chemosis, ophthalmoplegia, and facial nerve palsy might be found. Later, signs like palatal necrosis or nasal septum eschar may develop.[5,6] The most common presentations reported by our patients were headache, periorbital pain, proptosis, and chemosis.[7]

Facial pain and oedema are the most common symptoms. Additionally, these patients could have the presentation of fever, conjunctival chemosis, eyelid edema, deteriorating visual acuity, ophthalmoplegia, diplopia, proptosis, periorbital pain, headache, cranial nerve palsy ear pain, nasal blockage, black nasal crusts, nasal discharge, epistaxis, periocular hypoesthesia, palatal eschar, loose teeth, and facial deviation. Computed tomography (CT) or magnetic resonance imaging (MRI) can show sinusitis, erosions of the nasal septum, sinus wall, and hard palate, panophthalmitis, orbital infiltration involving the optic nerve, skull base involvement, and cerebral sinus thrombosis with secondary vasculitis.[5,8] Although the diagnosis of CAM is based on the identification of organisms in tissue by histopathology with culture confirmation, it should also require clinicians' high index of suspicion, recognition of host factors, prompt assessment of clinical manifestations, and further image investigations using CT or MRI.[9]

First-line treatment with high-dose liposomal amphotericin B is recommended.[10] Liposomal amphotericin B (5 mg/kg/day), diluted in 200 cc 5% dextrose over a 2 to 3-hour infusion, is the preferred regimen, and a higher dose of 10 mg/kg/day may be given in cases of orbital-cerebral involvement.[6,8] The management of mucormycosis is multidisciplinary, including glycemic control and surgical debridement, depending on the extent of involvement.

Mortality rates can be as high as 50-80%, which is consistent with the mortality rate in our series (75%).[7] Mortality in mucormycosis depends on co-morbidities and the extent of involvement and is higher in cases of intracranial involvement.[7,11]

RISK FACTORS

Factors associated with the increase in mucormycosis cases in COVID-19 patients include DM, steroid overdose, high iron levels, and immunosuppression, combined with other possible factors such as unhygienic conditions, prolonged hospitalization, use of ventilators, and leaky humidifiers in oxygen cylinders.[5,12] A review of the literature revealed 29 studies reporting case series of CAM. Data from a total of 3856 patients included in those studies showed that at least 3000 (~80%) had pre-existing DM. Other underlying conditions included hypertension, ischemic heart disease, chronic kidney disease, and steroid therapy.[7]

Uncontrolled DM was the most common underlying condition that contributed to CAM.[3,6,13] Additionally, other immune-compromised conditions, including neutropenia, end-stage kidney disease, hematologic malignancy, solid organ transplant recipients, and the use of corticosteroids, have been reported.[14]

Among our patients, three were known to have DM, mainly uncontrolled, and the other one was newly diagnosed. Most patients had haemoglobin A1c (HbA1c) levels of approximately 11%. DM inhibits the activity of natural killer cells and T-cells. High blood sugar impairs neutrophil activity required to kill organisms and decreases phagocytic activity. In DKA, these organisms can use ketones to grow.[6,8]

The binding of iron to transferrin is impaired in an environment with a pH below 7.4, so more iron is available for fungal metabolism, which plays a major role in its virulence.[15] All our patients were diabetic and presented with rhino-orbital mucormycosis without cerebral extension. Those with poor glycemic control and DKA had a more unfavorable outcome and died.

Poorly controlled diabetes is a good breeding ground for mucormycosis.[7,9] The SARS-CoV-2 virus can infiltrate pancreatic beta cells, leading to necroptosis and consequent metabolic derangement.[8]

In addition, COVID-19 disease is associated with an increase in pro-inflammatory markers, such as interleukin (IL)-1 and IL-6, and treatment with IL-6 receptor antagonists could lead to an increased risk of fungal infections.[16] COVID-19 may affect the immune system, leading to lymphopenia, dysregulation of CD4 interferon-gamma expression, and reduced numbers of T-lymphocytes, $CD4^+$ T-cells, and $CD8^+$ T-cells, impairing innate immunity.[4,17]

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An acidic pH in serum reduces the ability of transferrin to bind iron, and unbound iron in serum encourages the growth of R. oryzae (a causative agent of mucomycosis).[11] Clinical model data have demonstrated that the presence of elevated serum iron predisposes the host to mucormycosis due to the critical role of the ability of Mucorales to acquire host iron as a virulence factor.[13]

Rhizopus invades the epithelium *via* fungal spore coat proteins (CotH) and binds to the host receptor (GRP78) on nasal epithelial cells.[12] The use of corticosteroids in the treatment of patients with COVID-19 may stimulate the expression of CotH3 and GRP78 by the nasal epithelium, thus facilitating invasion by fungal cells.[7,8]

Finally, the recent surge in COVID-19 cases was associated with an unprecedented shortage of oxygen availability, resulting in the use of industrial-grade oxygen in some parts of the country. Although exposure to impure oxygen was thought to be a possible risk factor,[17] Patients in our study required oxygen or ventilatory support, suggesting that it was unlikely to be a significant factor.

To prevent mucormycosis in patients with COVID-19, it is necessary to reduce the duration of corticosteroid therapy and ensure optimal control of blood sugar levels.[5,9]

CONCLUSION

Mucormycosis is an aggressive, opportunistic infection with high morbidity and mortality. Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported worldwide.

Diabetes mellitus, steroid overdose, immunosuppression, and high iron levels, combined with other factors such as the use of ventilators, unhygienic conditions, and prolonged hospitalization, combine to create an ideal environment for contracting mucormycosis.

Lastly, there is a need to create awareness about fungal diseases among clinicians in order to help identify early symptoms and restrict the spread of lethal fungal diseases.

A collaborative team of otolaryngologists, ophthalmologists, anesthesiologists, and resuscitators will be required in hospitals to accelerate optimal management.

FINANCE STATEMENT

Not applicable.

DECLARATIONS ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not Applicable.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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