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CASE REPORT

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COVID-19-Associated mucormycosis: Case series from a tertiary care hospital in South India

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Abstract

The pandemic coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is a global health problem. COVID-19 has given rise to a number of secondary bacterial or fungal infections. During the second wave of COVID-19, India experienced an epidemic of mucormycosis in COVID-19 patients. In this paper, we discuss the clinical features, investigations and management of four patients having COVID-19-associated mucormycosis (CAM), especially rhino-orbital mucormycosis (ROM) caused by *Rhizopus arrhizus* and *Mucor* species. We also compare the cases and their risk factors with previously reported CAM cases in India. Three patients had mucormycosis after recovering from COVID-19. They were successfully treated with surgical debridement and early initiation of anti-fungal therapy with systemic amphotericin B and other supportive measures such as broad-spectrum antibiotics, insulin infusion, antihypertensives and analgesics. The remaining patient had mucormycosis during COVID-19. He was admitted in the intensive care unit due to COVID-pneumonia and was on mechanical ventilation. In spite of all supportive measures, the patient succumbed to death due to cardiogenic shock. Three out of our four patients had diabetes mellitus. All patients were treated with systemic steroid during COVID-19 treatment. Diabetes mellitus and steroid treatment are the major risk factors for CAM. Early diagnosis of this life-threatening infection along with strict control of hyperglycemia is necessary for optimal treatment and better outcomes.

INTRODUCTION

The pandemic coronavirus disease 19 (COVID-19) caused by novel severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) has affected millions of people worldwide. COVID-19 has been associated with a number of opportunistic bacterial and fungal infections [1]. Recently, during the second wave of COVID-19, several cases of COVID-19-associated mucormycosis (CAM) have been reported from various parts of the world, particularly from India [2]. In May 2021, the Government of India declared mucormycosis as a notifiable disease in many states, under the Epidemic Diseases Act 1897 [3]. India has reported more than 47000 cases of CAM from May 2021 to July 2021 [4].

Mucormycosis is an opportunistic fungal infection caused by genus *Rhizopus, Mucor*, *Rhizomucor, Cunningamella, Licthemia, Syncephalastrum, Sakseneae,* and *Cokeromyces* of order Mucorales and class Zygomycetes. These are saprophytic fungi found in soil and the environment [5]. The clinical types of mucormycosis include pulmonary mucormycosis, gastrointestinal mucormycosis, cutaneous mucormycosis, rhino-orbito-cerebral mucormycosis and disseminated mucormycosis [6]. In this paper, we report four cases of rhino-orbital mucormycosis (ROM) presented to Government Medical College Kannur (GMCK), Pariyaram, Kerala, India during May to July 2021, with their clinical features, diagnosis, management and outcome. Additionally, we compare our cases with the previously reported cases in India and analyse the risk factors.

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Keywords: COVID-19; Mucormycosis; Rhino-orbital mucormycosis; Diabetes mellitus; Mucorales; *Rhizopus arrhizus*.

Abbreviations: Ampho B, amphotericin B; CAD, coronary artery disease; CKD, chronic kidney disease; F, female; HTN, hypertension; LPCB, lactophenol cottonblue; M, male; Posa, posaconazole; SDA, sabouraud dextrose agar; T2DM, type II diabetes mellitus; U/L, unilateral.

CASE PRESENTATION

Case 1

A 73-year-old male patient with type II diabetes mellitus (T2DM), hypertension (HTN), coronary artery disease (CAD) and chronic kidney disease (CKD), undergoing maintenance hemodialysis, was presented to the emergency department of GMCK, with complaints of swelling of the right eye for 1 week and loss of vision of right eye for 1 day. He was confirmed with COVID-19 twelve days before his presentation to GMCK and hospitalized elsewhere due to COVID-19 pneumonia, for which he was treated with systemic steroids, systemic broad-spectrum antibiotics, oxygen supplementation, insulin infusion and other supportive measures.

On examination, he was found afebrile and his vitals were stable. There was periorbital oedema and lid oedema on the right eye. Extraocular movements of the right eye were restricted. Bloodstains were present on the right nasal cavity. The patient was admitted (day 0). His laboratory investigations revealed leucocytosis (Total WBC count: 19000/µl [normal: 4300–10300/µl]) and deranged kidney functions (blood urea: 61 mg/dl [normal: 15–40 mg/dl], serum creatinine: 2.5 mg/dl [normal: 0.6–1.6 mg/dl]). Magnetic Resonance Imaging (MRI) of the brain and orbit revealed features of fungal invasive sinusitis (refer Fig. 1, Table 1). On day 3, the patient underwent right-sided endoscopic sinonasal debridement by Denker's approach with right-sided orbital exenteration. Tissue samples were sent for microbiological and histopathological examinations, which confirmed mucormycosis (see Table 2, Fig. 2a, b). Direct microscopy with 10% potassium hydroxide (KOH) mount showed broad aseptate fungal hyphae with wide-angle branching similar to that of Mucorales (see Fig. 3a). The patient was started on intravenous amphotericin B (70 mg/day) in 5% dextrose. Fungal culture revealed *Mucor* species (see Fig. 4a, b). The patient also received other supportive measures such as broad-spectrum antibiotics, insulin infusion, anti-hypertensives, analgesics and hemodialysis during the hospital stay. The patient was continued on intravenous amphotericin B for 28 days. The repeat fungal culture of nasal tissue was sterile. The patient was discharged after 31 days on oral posaconazole for 2 weeks. After 2 weeks of discharge from hospital, the patient presented with cerebrospinal fluid (CSF) rhinorrhea. The patient was kept under observation and managed conservatively with prophylactic antibiotic and bed rest in head up position. There were no signs of meningitis. The patient was discharged after 24 hours and he was advised to continue oral posaconazole for a total of 3 months with follow-up every 2 weeks. The patient was found stable during the follow-ups.

Case 2

A 49-year-old male patient with T2DM and HTN was presented to ENT OPD with pain, swelling and numbness over the right side of the face for 1 week. He was confirmed with COVID-19 twenty days before his presentation to GMCK and was admitted elsewhere due to COVID-19 pneumonia. He was treated with systemic steroids, broad-spectrum antibiotics, oxygen supplementation, insulin infusion and antihypertensives.

On examination, he was afebrile and his vitals were stable. Examination of the right eye revealed lid oedema and chemosis. Extraocular movements of the right eye were mildly restricted. He was admitted (day 0). His blood investigations revealed elevated C-reactive protein (CRP: 34.4 mg/l [normal: 0–10 mg/dl]) and high blood glucose levels (random blood sugar: 418 mg/dl [normal: 80–140 mg/dl]). His MRI brain with orbit revealed features of sinusitis with right orbital extension (refer Fig. 1, Table 1). On day 2, the patient underwent right-sided functional endoscopic sinus surgery by Denker's approach with right-sided orbital decompression. Tissue samples were sent for microbiological and histopathological examinations which confirmed mucormycosis (see Table 2, Fig. 2c, d). KOH mount revealed broad aseptate fungal hyphae with wide-angle branching (see Fig. 3b). The patient was started on intravenous amphotericin B (70 mg/day) in 5% dextrose. On day 6, fungal culture revealed *Rhizopus* species (see Fig. 4c, d). The identification was confirmed by matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS). The isolate was identified as *Rhizopus arrhizus*. The patient received intravenous amphotericin B for a total period of 26 days. He also received other supportive measures such as broad-spectrum antibiotics, insulin infusion, antihypertensives and analgesics during the course of his hospital stay. The patient responded well to the treatment. Fungal culture of nasal tissue was performed again, which was sterile. He was discharged after 30 days on oral posaconazole for a course of 2 weeks. The patient was advised to continue oral posaconazole for a total of 3 months with follow-up every 2 weeks. The patient was found stable during the follow-ups.

Case 3

A 35-year-old male patient presented to the ENT department with complaints of pain and numbness on the left side of the face and left-sided nasal obstruction for 1 week. He was confirmed with COVID-19 twenty-four days before his presentation to GMCK and was admitted elsewhere due to COVID-19 pneumonia. He had history of high blood glucose during the COVID-19 infection. He was treated with systemic steroids, broad-spectrum antibiotics, oxygen supplementation, insulin supplementation and other supportive measures.

On examination, he was afebrile with stable vitals. Local examination revealed left-sided maxillary sinus tenderness and edematous middle turbinate. He was admitted (day 0). His laboratory investigations revealed elevated C-reactive protein (CRP: 12.9 mg/dl

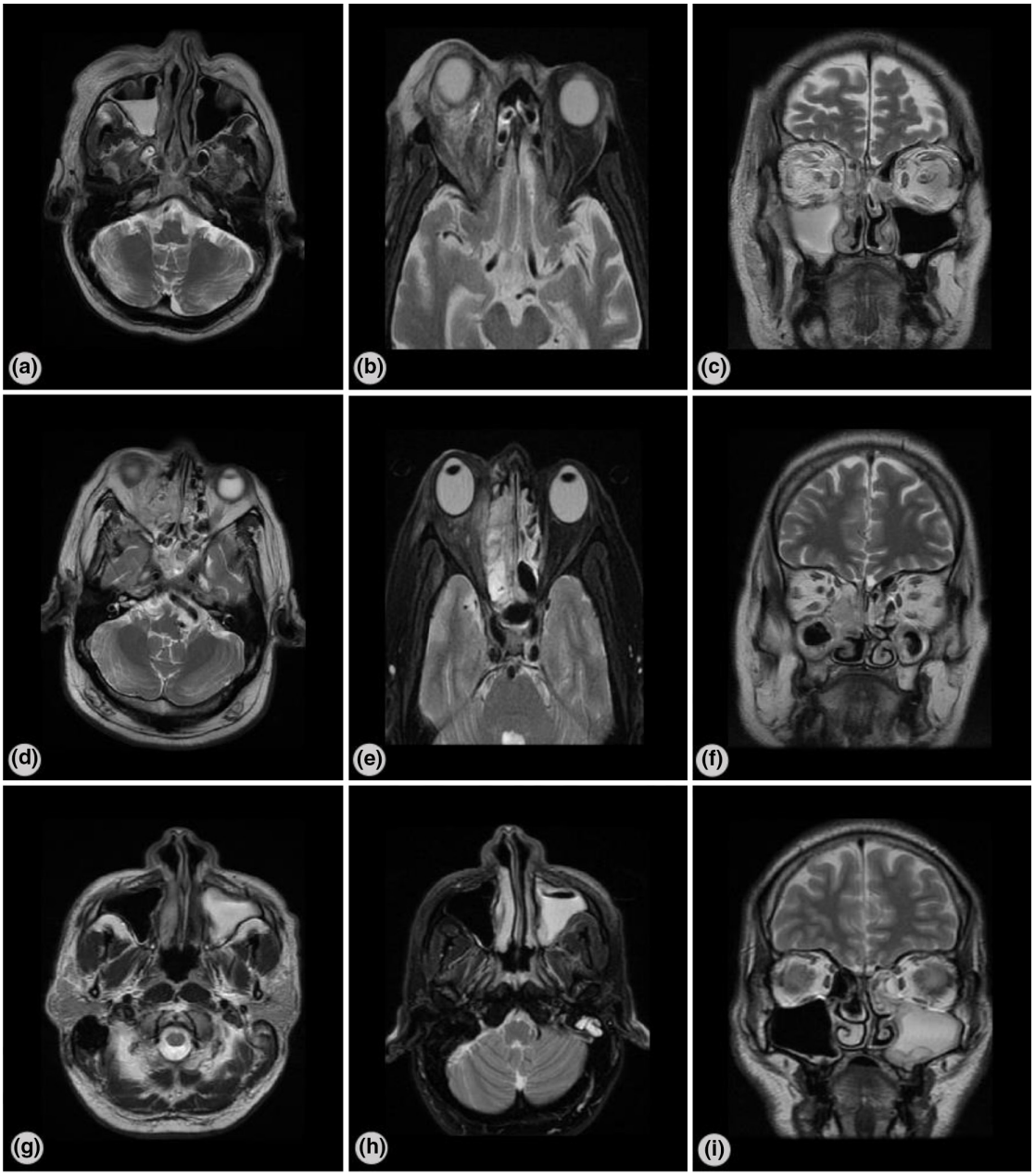

Fig. 1. MRI brain and orbit of cases 1, 2 and 3. *Case 1* : [1A,1C] Axial and coronal T2W MRI showing mucosal thickening in right maxillary and bilateral ethmoidal sinuses. [1B] T2 fat sat axial MRI showing inflammatory changes of right orbital soft tissue extending to orbital apex, pre-septal/ peri-orbital region with proptosis of right globe suggestive of right maxillary and ethmoidal sinusitis with orbital extension. *Case 2* : [1D,1F] Axial and coronal T2W MRI showing hetero intense mucosal thickening in bilateral ethmoid, maxillary and sphenoid sinuses. [1E] T2 fat sat axial MRI showing mild right eye proptosis with right orbital soft tissue inflammatory changes- suggestive of orbital extension. *Case 3* : [1G,1I] Axial and coronal T2W MRI showing mucosal thickening of maxillary and ethmoidal sinuses with complete opacification of the left maxillary sinus. [1H] T2 fat sat axial MRI showing left maxillary sinusitis with retro antral soft tissue inflammatory changes involving masticator space and pterygopalatine fossa suggestive of invasive sinusitis.

[normal: 0–10 mg/dl]). His MRI brain and orbit revealed features of sinusitis (see Fig. 1, Table 1). On day 2, the patient underwent left-sided endoscopic sinonasal debridement by Denker's approach. Tissue samples sent for microbiological and histopathological examinations confirmed mucormycosis (refer Table 2, Fig. 2e, f). KOH mount showed broad aseptate fungal hyphae with wide-angle branching. The patient was started on intravenous amphotericin B (70 mg/day) in 5% dextrose. On day 6, fungal culture revealed *Rhizopus* species (see Fig. 4e), which was confirmed by MALDI-TOF MS as *Rhizopus arrhizus*. The patient received intravenous amphotericin B for 33 days along with broad-spectrum antibiotics and analgesics. The patient responded well to

Table 1. Summary of patient characteristics, clinical features, radiological findings, treatment and outcome in the four cases of rhino-orbital mucormycosis (ROM) presented to Government Medical College Kannur, Pariyaram, Kerala, India, during the period May 2021 to July 2021

Case	Age/Sex	Co-morbidities	Clinical features	Radiological findings (MRI brain and orbit)	Treatment	Outcome
Case 1	73/M	T2DM, HTN, CAD CKD	Periorbital oedema, Loss of vision	Features of fungal invasive sinusitis involving right maxillary, ethmoid sinuses with right orbital extension and severe proptosis of the eyeball.	Surgery + Ampho B (28 days)+Posa (2 weeks)	Survived
Case 2	49/M	T2DM HTN	U/L facial pain, numbness, swelling and chemosis of the right eye.	Sinusitis involving bilateral maxillary, ethmoidal, frontal and sphenoid sinuses with extension into the right orbit.	Surgery + Ampho B (26 days)+Posa (2 weeks)	Survived
Case 3	35/M	–	U/L facial pain and numbness, U/L nasal obstruction	Mucosal thickening of left maxillary and ethmoidal sinuses with minimal extension into the left pterygoid region.	Surgery + Ampho B (33 days)+Posa (2 weeks)	Survived
Case 4	49/M	T2DM HTN, CKD	Periorbital oedema and chemosis	Not done	Not done	Deceased

M, male; F, female; T2DM, type II diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; CAD, coronary artery disease; U/L, unilateral; Ampho B, amphotericin B; Posa, posaconazole.

the treatment. Fungal culture of nasal tissue was performed again, which was sterile. He was discharged after 40 days on oral posaconazole for 2 weeks. The patient was advised to continue oral posaconazole for a total of 3 months with follow-up every 2 weeks. The patient was found stable during the follow-ups.

Case 4

A 49-year-old male patient was admitted (day 0) in the intensive care unit (ICU) with bilateral COVID-19 pneumonia and was put on mechanical ventilation. On day 6, he developed swelling around the left eye. He was a known case of T2DM and CKD (undergoing maintenance hemodialysis). He was receiving systemic broad-spectrum antibiotics, systemic steroids, insulin supplementation and other supportive measures. Examination revealed periorbital swelling and chemosis of the left eye. No proptosis, loss of consciousness, headache and vomiting was noted. Nasal cavity was normal. Nasal secretion was sent for fungal culture. His laboratory investigations revealed elevated C-reactive protein (CRP: 16 mg/dl: [normal: 0–10 mg/dl]), elevated D-Dimer (D-Dimer: 3.96 µg/ml [normal: <0.50]) and deranged kidney functions (blood urea: 211 mg/dl [normal: 15–40 mg/dl], serum creatinine: 9.6 mg/dl [normal: 0.6–1.6 mg/dl]). Due to poor general condition of the patient, we could not perform radiological investigations and collect tissue samples for histopathological examination. On day 7, the patient succumbed to death due to cardiogenic shock in spite of all measures. Fungal culture of nasal secretions revealed *Rhizopus* species (see Fig. 4f). It was confirmed as *Rhizopus arrhizus* by MALDI-TOF MS. Antifungal therapy could not be initiated in this patient.

DISCUSSION

The major risk factors for mucormycosis include diabetes mellitus (DM), haematological malignancies, organ transplant, neutropenia, iron overload and steroid therapy [7, 8]. In COVID-19 patients, presence of DM and SARS-COV-2 infection may cause mucormycosis. DM can cause mucormycosis by the following ways: (**I**) DM is a chronic inflammatory state causing endothelial dysfunction. High blood glucose increases the expression of glucose regulatory protein 78 (GRP78) receptor in human endothelial cells. GRP78 serves as a receptor for vascular invasion by Mucorales [9]. The endothelial invasion by Mucorales is mediated by spore cot protein homologs (CotH) which act as a ligand for GRP78 [10]. (**II**) High blood glucose causes glycosylation of transferrin and ferritin which results in reduction in iron-binding capacity and increases free iron. Free iron supports the growth of Mucorales. The acidosis in diabetic keto acidosis (DKA) decreases the binding of iron to transferrin and increases free iron in circulation [11]. High glucose and high iron content seen in DKA also causes overexpression of GRP78 which results in further endothelial invasion by Mucorales [12].

COVID-19 can cause mucormycosis by the following ways: (**I**) SARS-COV-2 infection causes endothelial dysfunction due to direct viral invasion and host inflammatory responses [13]. Endothelial damage promotes the invasion of Mucorales. (**II**) COVID-19 often causes immunosuppression by impairment of CD4 +cells, CD8 +cells, and antigen-presenting dendritic cells, which results in secondary or opportunistic fungal infections like mucormycosis [11]. (**III**) High doses of corticosteroids, used in managing COVID-19 patients, cause high blood glucose levels and immunosuppression by impairing neutrophil migration and phagolysosomal fusion, which makes COVID-19 patients vulnerable to secondary infections like mucormycosis [14].

Table 2. Microbiological and histopathological findings in the four cases of rhino-orbital mucormycosis (ROM) presented to Government Medical College Kannur, Pariyaram, Kerala, India, during the period May 2021 to July 2021

CCases	Direct microscopy with KOH mount	Fungal culture (SDA medium with chloramphenicol at 25 °C ad 37 °C)	LPCB staining	Organism	Bacterial culture	Histopathological examination
Case 1	Broad aseptate fungal hyphae with wide-angle branching.	Rapidly growing cotton candy-like colonies, initially white later turning to grey colour. No pigment was present on the reverse of the SDA tubes (see Fig. 5)	Fungal hyphae with branched sporangiophores bearing terminal spherical sporangia. The sporangia are thin-walled with large columella and without apophyses. Rhizoids were not seen (see Fig. 4a, b).	*Mucor* species	*Klebsiella pnemoniae* and *Pseudomonas aeruginosa*.	Tissue with broad aseptate fungal hyphae invading vessel.
Case 2	Broad aseptate fungal hyphae with wide-angle branching	Rapidly growing cotton candy-like colonies, initially white later turning to grey colour. No pigment was present on the reverse of the SDA tubes	Broad aseptate fungal hyphae with root-like structure 'rhizoid' at under point where sporangiophore develops. Sporangiophores are erect, unbranched, single, or groups of 2–3. Sporangiophores end in round sporangium containing columella at the tip (see Fig. 4c, d).	*Rhizopus arrhizus*	Sterile	Fungal colonies containing broad aseptate hyphae invading tissue and vessels.
Case 3	Same as case 2	Same as case 2	Same as case 2	*Rhizopus arrhizus*	Sterile	Tissue contains broad aseptate irregular fungal hyphae.
Case 4	Same as case 2	Same as case 2	Same as case 2	*Rhizopus arrhizus*	Not done	Not done

SDA, Sabouraud Dextrose Agar; LPCB, Lactophenol cotton blue.

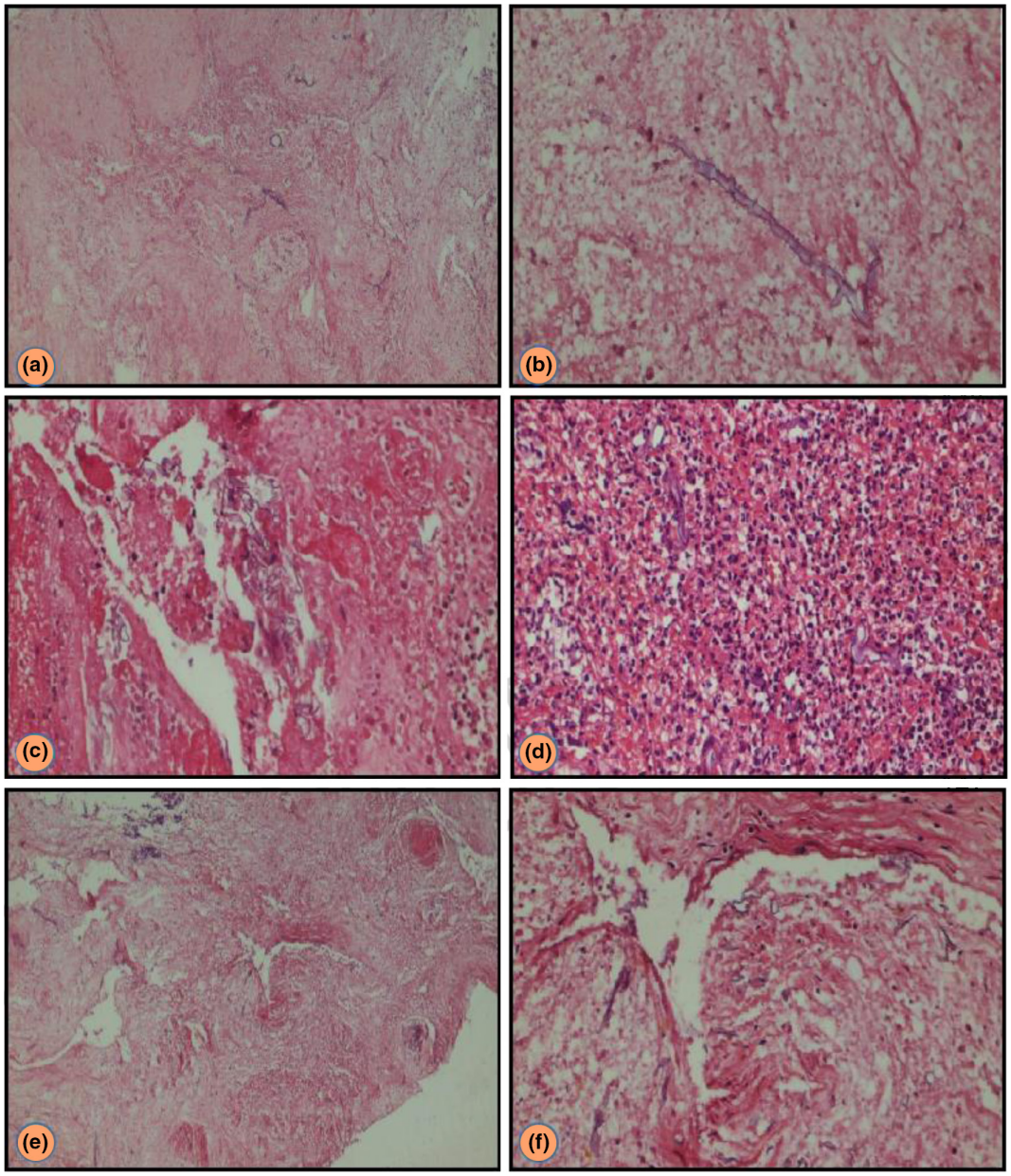

Fig. 2. Histopathology of tissue specimens of cases with Haematoxylin and Eosin staining showing broad aseptate hyphae with wide-angle branching (a, b), necrotic tissue showing broad aseptate fungal hyphae (c, e, f), broad fungal hyphae with acute inflammatory background (d). [*Case-1*: Fig. 2a, b; *Case 2*: Fig. 2c, d; *Case 3*: Fig. 2e, f].

The above two risk factors of mucormycosis (i.e., COVID-19 and DM) have a bidirectional relationship. On one hand, DM can cause severe COVID-19 due to impairment of immune responses which results in poor ability to fight against infection. On the other hand, COVID-19 complicates DM in the following two ways, (**I**) COVID-19 causes poor glycaemic control having insulin resistance and impaired insulin secretion which lead to DKA [15]. (**II**) The SARS-COV-2 enters into host cells using angiotensin-converting enzyme 2 (ACE 2) receptors [12]. ACE 2 receptors present in the pancreas allow the entry of SARS-COV-2 into beta cells. The damage of beta cells promotes DM [16].

In our case series, three of the four patients had prolonged history of DM. The remaining patient had hyperglycemia during the COVID-19 infection period. However, none of them had DKA. All the patients received steroids for treatment. However, we could not assess the dose and duration of used steroids, since most of the patients in our study were treated for COVID-19 elsewhere and those hospital records were unavailable. Our case series supports the study conducted by Patel *et al.* [17] that DM and corticosteroids are the prime factors predisposing CAM. A review of 101 cases of CAM reported from all over the world revealed

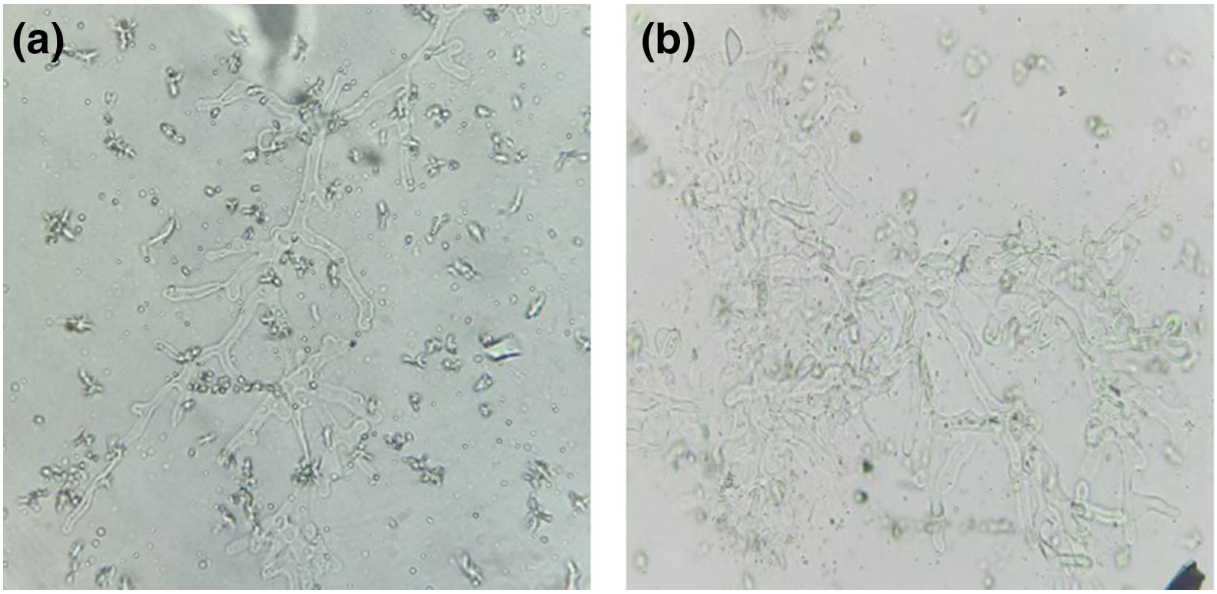

Fig. 3. Direct (×400) microscopy (with 10% KOH mount) of tissue specimens showing broad aseptate fungal hyphae with wide angle branching similar to Mucorales. (Fig. 3a, b are the KOH mount of case 1 and case 2, respectively).

that 81.2% of the cases were from India. The study also showed that the most important risk factor for CAM was hyperglycemia at presentation (due to pre-existing diabetes mellitus or new-onset diabetes mellitus). Pre-existing DM was present in 80% of the cases with DKA in 15% of the cases [11].

All CAM cases in our hospital were of the type rhino-orbital mucormycosis (ROM). A recent survey of CAM cases in India by Muthu *et al.* [4] also revealed that rhino-orbital mucormycosis (ROM) and rhino-orbito-cerebral (ROCM) mucormycosis were the most common presentations of CAM (89%). ROCM results in fatal complications in a few days, if the disease is left untreated.

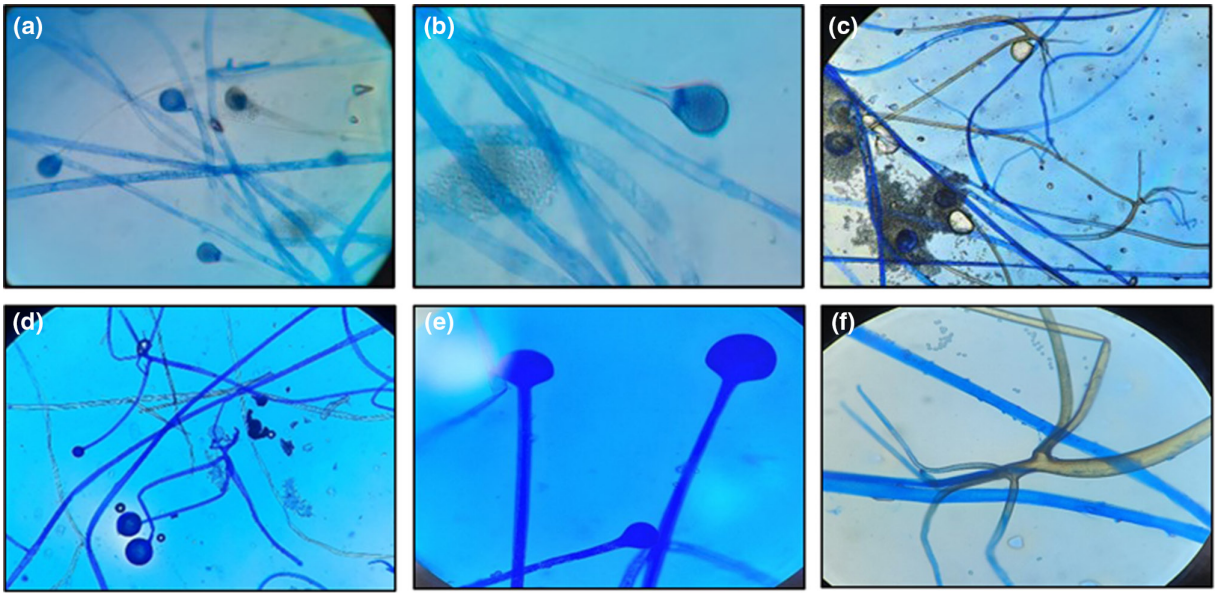

Fig. 4. LPCB staining of cases. *Case 1*: [5A] Aseptate fungal hyphae with sporangiophores ending in terminal sporangia. Rhizoids are absent (×100). [5B] Sporangia filled with sporangiospores (×400). *Case 2*: [5C,5D] Long aseptate sporangiophores originating from stolon opposite to rhizoids (×100). *Case 3*: [5E] Aseptate erect sporangiophores ending in terminal sporangium (×400). *Case 4*: [5F] 'Rhizoids' – root-like structure at under points where sporangiophore develop (×400). All our figures are available in Figshare [1].

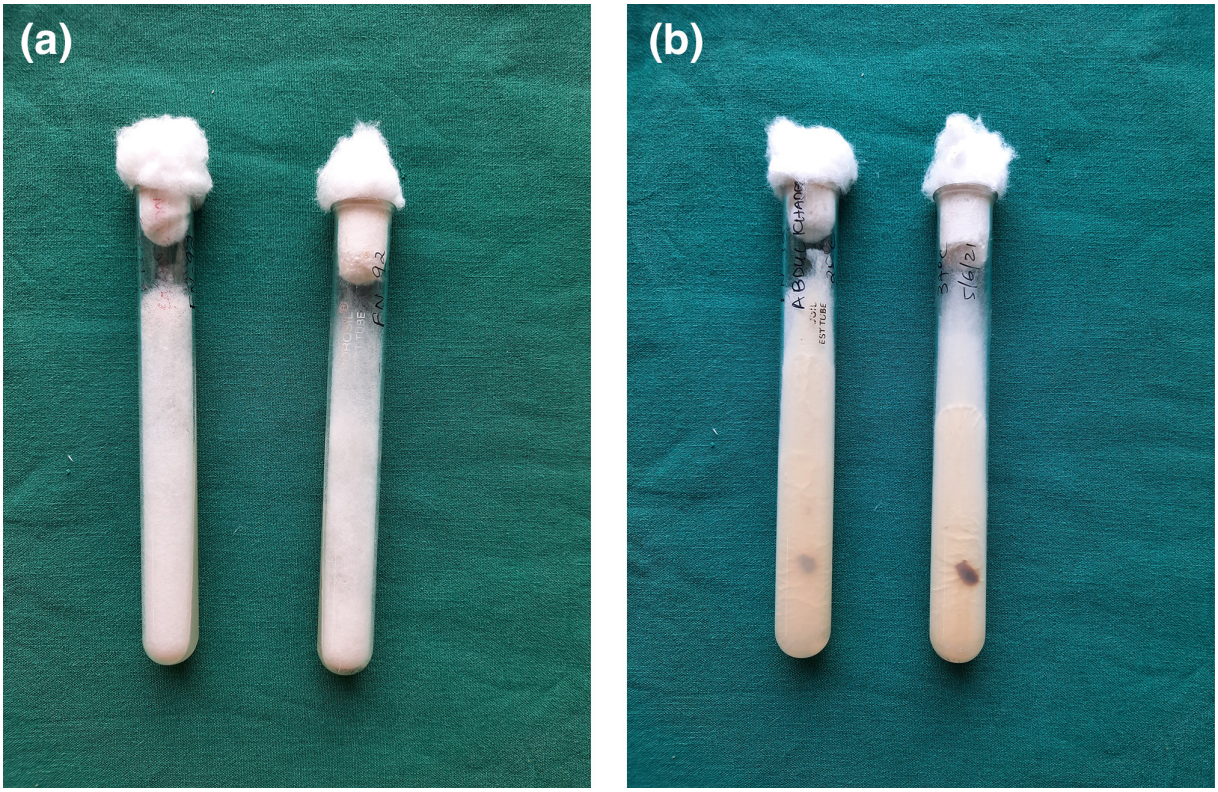

Fig. 5. Fungal culture showing white cotton-candy like growth on SDA medium incubated at 25 °C and 37 °C. The left and right figures show the obverse and reverse sides of the tubes, respectively. No pigmentation is seen on the reverse sides of the tubes.

The mode of infection occurs through inhalation of fungal spores. From nasal mucosa, it spreads to turbinate bones, paranasal sinuses, orbit, palate and brain. A typical characteristic feature of the disease is its rapid progression into tissue necrosis due to invasion of blood vessels [6].

All our CAM patients were males. Muthu *et al.* [4] also observed that majority of CAM patients in India are males. Three of our patients had mucormycosis in post-COVID-19 period (12–24 days of detecting COVID-19). One patient developed mucormycosis during active COVID-19 (sixth day). The diagnosis period in our cases is similar to the study by Muthu *et al.* [4] which shows mucormycosis was diagnosed after a mean of 19.5 days from COVID-19 diagnosis.

In our cases, mucormycosis was diagnosed by a combination of clinical, radiological, microbiological and histopathological findings. Corzo-Leon *et al.* [18], proposed 'red flag signs' for diagnosis of ROCM in diabetic patients. They include cranial nerve palsy, diplopia, sinus pain, proptosis, periorbital oedema, orbital apex syndrome and ulcers on the palate. The most common presentation in our case series was unilateral facial pain, numbness and periorbital oedema. Loss of vision at presentation was found in one patient. Radiological investigation of ROCM consists of CT/MRI of paranasal sinuses, orbit and brain. The radiological findings in our cases include maxillary, ethmoid and sphenoid sinusitis. Orbital extension was present in two of our cases.

A definitive diagnosis of mucormycosis is generally obtained by demonstration of fungus by direct microscopy (KOH mount or histopathology) and isolation of fungus in culture. Direct microscopy by KOH mount of nasal tissue facilitates in early diagnosis of mucormycosis which helps the treating clinicians to start anti-fungal treatment promptly. HPE of tissue specimens also demonstrates fungal hyphae and gives additional information about inflammatory changes, infarction, angioinvasion and perineural invasion. In our cases, KOH revealed broad aseptate fungal hyphae with wide angle branching. Nasal tissue was cultured in SDA and incubated at 25°C and 37°C. Fungal culture revealed white cotton candy like colonies, which initially were white in colour and later turned to grey, filling the tubes. LPCB mount from the colonies revealed *Rhizopus* species in three patients and *Mucor* species in one patient. The confirmation of *Rhizopus* was done by MALDI-TOF MS. *Rhizopus arrhizus* was identified with 99.9% confidence and score value greater than two. Our observation is similar to Muthu *et al.* [4] which also reported *Rhizopus arrhizus* as the most common fungi causing CAM in India.

Management of CAM consists of early diagnosis, treatment of underlying risk factors, timely surgical excision of infected tissue and quick initiation of systemic antifungal agents. The antifungal agents available for treating mucormycosis include intravenous (i.v) amphotericin B, oral/i.v posaconazole and oral/i.v isavuconazole [19]. Three of our patients were managed with surgical debridement and i.v amphotericin B, along with other supportive measures. Extensive disease was present in one case, in which orbital exenteration was done. All the above three patients survived. However, the fourth patient succumbed to death. He had severe COVID-19 pneumonia and hence we could not take him for investigations and treatment. An analysis by Pal *et al.* [20] on CAM cases of India reported that surgery and anti-fungal therapy was performed in 81% of patients. They also observed that after treatment the survival rate was 66% and mortality rate was 34%.

India contributes a major part to the global burden of DM [21]. Investigations of the reasons behind the high surge of CAM in India would be an interesting research problem. A surveillance study conducted by Rudramurthy *et al*. [22] on fungal spore burden in hospital air of a tertiary care hospital, reported that high spore count was found in the hospital air. The outbreak of CAM in India may be due to joint action of COVID-19, high burden of uncontrolled DM, inappropriate corticosteroid therapy along with high fungal spore count in Indian hospital environments.

CONCLUSION

Mucormycosis is a hazardous complication of COVID-19, especially in India. We studied four cases of ROM, reported in our hospital and compared them with other CAM cases in India. Majority of CAM were caused by *Rhizopus arrhizus*. Our study supports DM and use of steroids as the major risk factors contributing to CAM. Strict control of blood glucose and judicious use of steroids in COVID-19 patients is recommended to reduce the burden of mucormycosis. Early diagnosis and management are necessary for better outcomes in mucormycosis.

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Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
Consent for publication of the clinical details and clinical images of the cases, without revealing patient identity, was obtained from patients/ relatives of patients.

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