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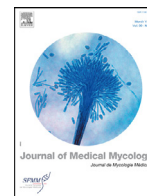
Case report

First report of COVID-19-associated rhino-orbito-cerebral mucormycosis in pediatric patients with type 1 diabetes mellitus

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A R T I C L E   I N F O

A B S T R A C T

Coronavirus disease 2019 (COVID-19) is a major public health problem worldwide. These patients are at increased risk of developing secondary infections due to a combination of virus- and drug-induced immuno-suppression. Recently, several countries have reported an emergence of COVID-19 associated mucormycosis (CAM), particularly among patients with uncontrolled diabetes, with India reporting an alarming increase in rhino-orbito-cerebral mucormycosis (ROCM) in post-COVID cases. Hyperglycemia and diabetic ketoacidosis (DKA) are the major underlying risk factors. So far, case reports and review articles have reported CAM only in adult patients. Here, we describe the first cases of COVID-19-associated ROCM in two pediatric patients with Type 1 diabetes mellitus (DM). Both the cases had asymptomatic infection with SARS-CoV-2 and developed ROCM during the course of treatment of DKA. None of them had exposure to systemic steroids. Imaging findings in both cases revealed involvement of orbit, paranasal sinuses, and brain with cavernous sinus thrombosis. The patients underwent craniotomy with evacuation of abscess. Microbiological and histopathological findings were consistent with the diagnosis of mycormycosis, with fungal culture growing *Rhizopus arrhizus*. Post-operatively, the patients received liposomal amphotericin B (LAMB) and systemic antibiotics. Retrobulbar injection of LAMB was given in an attempt to halt orbital disease progression. However, it wasn't successful and both of them had to undergo orbital exenteration eventually. ROCM is a rapidly progressive disease and prompt diagnosis with aggressive surgery and timely initiation of antifungal therapy can be life-saving. Physicians should have a high index of suspicion, so as to avoid a delayed diagnosis, particularly in post-COVID patients with uncontrolled diabetes.

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be a major public health problem worldwide. Recent reports suggest an increased incidence of secondary bacterial and fungal infections in COVID-19 patients [1]. While COVID-19 associated pulmonary aspergillosis (CAPA) has been extensively discussed, other invasive fungal diseases such as candidemia, trichosporonosis, fusariosis, histoplasmosis, cryptococcosis, coccidioidomycosis and currently, COVID-19 associated mucormycosis (CAM) have also been reported [2,3]. As India battles the second wave of COVID-19, an outbreak of mucormycosis has been observed across several Indian states. So far, India has

reported more than 47,000 cases of CAM with an overall case fatality rate of 36.5% [4]. On 20th May 2021, the Government of India declared mucormycosis a *notifiable disease* under Epidemic Diseases Act 1897 [5]. Several hospitals across the country have set up "Mucormycosis Ward" to tackle the rising number of cases. While uncontrolled diabetes mellitus (pre-existing and new-onset DM) continues to be the classical risk factor associated with mucormycosis, other predisposing factors such as diabetic ketoacidosis (DKA), hematological malignancy, hypertension, kidney disease and use of systemic corticosteroids have also been recognised [3]. COVID-19 itself is a diabetogenic state [6–8], which together with immune dysregulation, cytokine storm, thrombo-inflammation, microvascular coagulation and immune exhaustion may facilitate secondary fungal infections. Further, COVID-19-induced immunosuppression and use of systemic steroids and anti-Interleukin-6 agents (e.g. tocilizumab) in these susceptible hosts, along with high fungal spore counts in

Indian environment provide a fertile ground for invasive mould diseases. Mucormycosis is an angioinvasive infection and can manifest as rhino-orbito-cerebral (ROCM), pulmonary, gastrointestinal, cutaneous, renal, and disseminated forms [9]. ROCM is a rapidly progressive disease and unless diagnosed promptly and managed aggressively, can lead to fatal consequences. While case reports, systematic reviews and meta-analyses on CAM continue to emerge, the disease has not yet been reported in paediatric population. Here, we report the first two autochthonous cases of COVID-19-associated ROCM in pediatric patients with Type 1 DM.

Case presentation

Case 1

An 11-year old male from Chitradurga district of Karnataka, presented to the Emergency Clinic of National Institute of Mental Health and Neurosciences (NIMHANS) in Bengaluru (Karnataka, India), with history of weight loss for six months, pain and swelling of left eye for eight days and high grade fever (>101°F) for three days. Ten days ago, he was admitted to a private hospital in Tumakuru (Karnataka) with fever and difficulty in breathing (day 0). He was subsequently diagnosed with Type 1 DM with concomitant DKA and past infection of COVID-19 (based on reactive SARS-CoV-2 IgG antibody test) (day 2). During the course of treatment, he developed left hemifacial pain and swelling of left eye (day 3). In view of suspected mucormycosis, he was referred to Bowring and Lady Curzon Medical College and Research Institute in Bengaluru, for further management (day 10). The clinical and radiological findings being suggestive of central nervous system (CNS) involvement, he was referred to NIMHANS for neurosurgical intervention. On admission to our facility (day 11), the patient was conscious and oriented with stable vitals and a Glasgow Coma Score (GCS) of 14/15 (E4M6V4). Neurological examination revealed 3rd, 4th and 6th cranial nerve (CN) palsy and complete ophthalmoplegia of left eye. The left-sided pupil was nonreactive with absent direct light reflex. Muscle tone, muscle power, and superficial

and deep tendon reflexes were preserved. There were no cerebellar or meningeal signs. Hematological findings (day 11) were within normal limits, except for a microcytic hypochromic picture and low hemoglobin level (8.2 g/dL; [normal range: 11−13 g/dL]). Biochemical investigations (day 12) revealed hypokalemia (Serum K^+ = 2.8 mmol/L; [normal range: 3.6−5.2 mmol/L]) and hyperglycemia (random blood glucose= 329 mg/dL; [normal: <200 mg/dL]). Coagulation profile, liver and renal function tests were within normal limits. Urinalysis was negative for ketone bodies. Contrast enhanced computed tomography (CECT) scan of brain revealed peripherally enhancing lesion of size 2.9×6.7 cm and 6.5×2.5 cm involving right and left frontal lobes, respectively with associated perilesional edema. The lesions extended posteriorly to involve nucleus accumbens, caudate and putaminal regions and were seen communicating inferiorly in the region of cribriform plate (Fig. 1A−C). There was evidence of bilateral sphenoidal, posterior ethmoidal and left maxillary sinusitis. Based on clinical and radiological findings, a diagnosis of bilateral frontal cerebral abscess of infective etiology was made. The patient underwent bifrontal craniotomy with cortisectomy in bilateral middle frontal gyrus (day 12). The abscess wall was friable with cavity containing frank greyish-white granular pus extending to the base of anterior cranial fossa. The abscess was evacuated and a subgaleal drain was left in situ.

Case 2

A 13-year old female from Bellary district of Karnataka, presented to the Emergency Clinic of NIMHANS with pain, swelling and diplopia in left eye for eight days. She was a known case of Type 1 DM, receiving a combination of regular and isophane insulin (Mixtard) for two years. Twenty days ago, she was admitted to Bellary District Hospital with vomiting, lethargy, confusion and hyperglycaemia (random blood glucose and HbA1c were 550 mg/dL and 8.72%, respectively, at presentation) and was diagnosed with DKA (day 0). Incidentally, she was tested positive for SARS-CoV-2 RNA by reverse transcription-polymerase chain reaction (RT-PCR), despite having no symptoms of

Fig. 1. Pre-contrast (A) and post-contrast (B & C) axial and coronal CT images of Case 1 showing hypodense lesion with peripheral thin rim of enhancement in bilateral frontal lobes (white arrows). Fig. C reveals heterogeneous content within left ethmoid & maxillary sinuses (white asterix)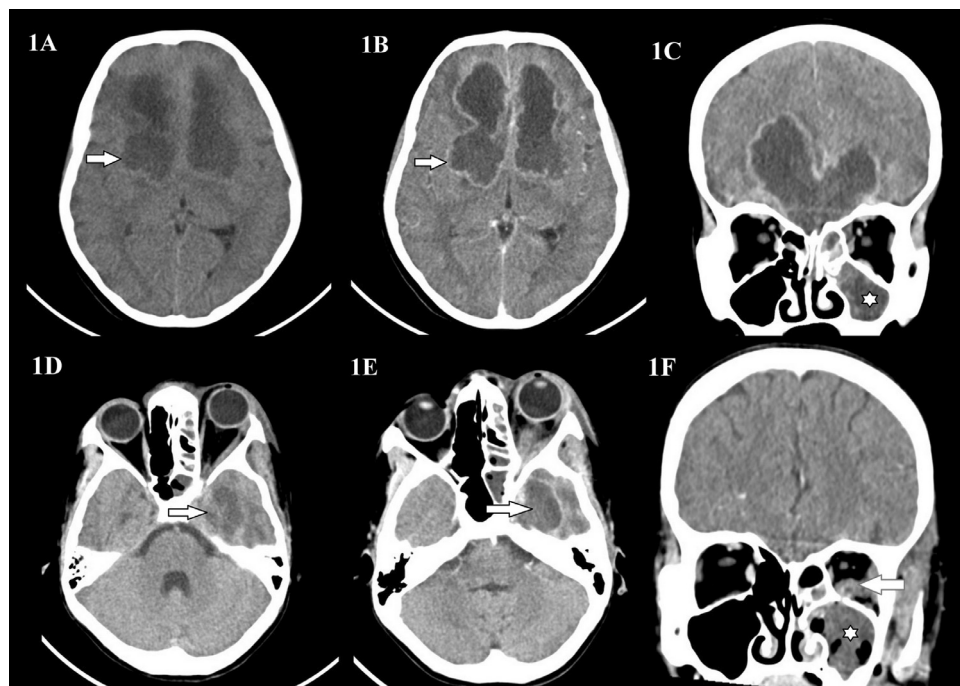. Pre-contrast (D) and post-contrast (E) axial CT images of Case 2 showing hypodense lesion with peripheral thin rim of enhancement in left temporal lobe (white arrow). Left orbital cellulitis is noted as thickened periorbital & preseptal soft tissue. Fig. F (coronal CT image of Case 2) demonstrates soft tissue within left maxillary sinus (asterix) & left orbital collection (white arrow).

COVID-19 (day 2). During the course of treatment, she developed fever with pain and swelling of left eye (day 12). CECT of brain and paranasal sinuses revealed features suggestive of ROCM (day 14). She was administered amphotericin B deoxycholate (liposomal formulation was unavailable) and referred to Bowring and Lady Curzon Medical College and Research Institute in Bengaluru, for further management (day 16). However, the clinical and radiological findings being suggestive of CNS infection, she was referred to NIMHANS for neurosurgical intervention (day 20). On admission to our facility (day 20), the patient was conscious and oriented with stable vitals and a Glasgow Coma Score (GCS) of 13/15 (E4M5V4). Neurological examination revealed complete ophthalmoplegia of left eye with nonreactive left pupil and absent direct light reflex. Muscle tone, muscle power, and superficial and deep tendon reflexes were preserved. There were no cerebellar or meningeal signs. Hematological and biochemical findings (day 20) were within normal limits. Random blood glucose and HbA1c were 83 mg/dL and 8.26%, respectively, on admission (day 20). Liver function tests revealed hypoalbuminemia (3 g/dL; [normal: 3.8−5.4 g/dL]) and low albumin/globulin ratio (1.00; [normal: 1.2−2.5]). Coagulation profile and renal function test did not show any derangement. Urinalysis was negative for ketone bodies. CECT of brain (day 20) revealed a hypodense lesion with peripheral thin rim of enhancement in left temporal lobe. Left orbital cellulitis was noted as thickened periorbital & preseptal soft tissue (Fig. 1D−F). Based on clinical and radiological findings, a diagnosis of left temporal brain abscess of infective etiology was made. The patient underwent left frontotemporal craniotomy with left temporal cortisectomy (day 21). The abscess wall was well-defined circumferentially, except medially where bone erosion was observed. The abscess cavity contained frank greyish-white granular pus, which was drained.

Laboratory diagnosis and treatment (both cases)

The intra-operative pus aspirates from both the patients were sent for microbiological and histopathological examinations. Direct microscopy (20% potassium hydroxide mount) of pus in both cases revealed hyaline, broad, sparsely septate, ribbon-like fungal hyphae with right angle branching, resembling those of *Mucorales* (Fig. 2). Histopathological examination showed central microabscesses and suppurative granulomas comprising of lymphocytes, plasma cells, foamy macrophages and multinucleated giant cells with large areas of necrotic brain parenchyma containing broad, aseptate fungal hyphae, exhibiting branching resembling those of *Mucorales* (Fig. 3A−H). There was evidence of angioinvasion with vessel wall

Fig. 3. Photomicrograph showing suppurative granulomatous lesion with fungal hyphae morphologically resembling those of Mucorales. Fig. A−D show broad, ribbon-like, aseptate fungal hyphae with infrequent branching at right angles in tissue specimen from Case 1 [Fig. A (x100) & B (x200) show fungal hyphae in Hematoxylin & Eosin stain; Fig. C and D (x200) demonstrate fungal hyphae in Grocott Gomori Methanamine Silver and Periodic Acid Schiff stains, respectively]. Fig. E−H show broad, ribbon-like, aseptate fungal hyphae with infrequent branching at right angles in tissue specimen from Case 2 [Fig. E (x100) & F (x200) show fungal hyphae in Hematoxylin & Eosin stain; Fig. G and H (x200) demonstrate fungal hyphae in Grocott Gomori Methanamine Silver and Periodic Acid Schiff stains, respectively].

Fig. 2. Direct microscopy (20% KOH mount) of tissue specimen showing hyaline, broad, ribbon-like aseptate fungal hyphae with wide-angle branching resembling those of Mucorales (x400).
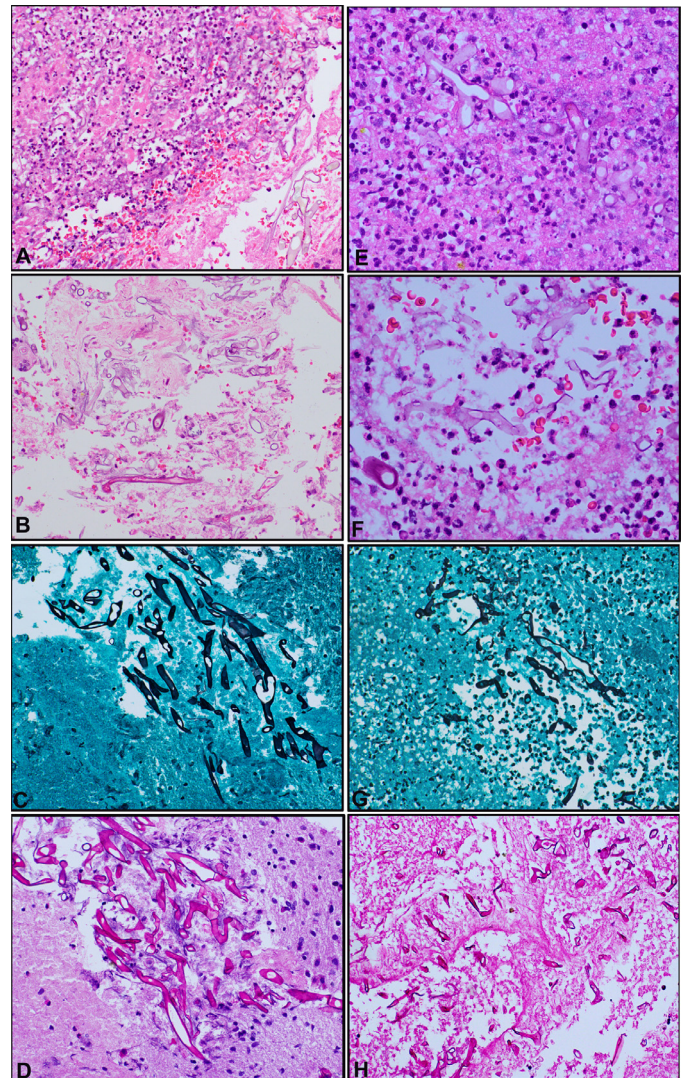
destruction in both the cases. The specimens were inoculated on routine bacteriological culture media and Sabouraud destrose agar (SDA) with and without cycloheximide and incubated at 25 °C and 37 °C. Bacterial cultures were sterile after 48 h of aerobic and anaerobic incubation. Fungal culture showed fast growing, cottony, fluffy mould, initially white and later becoming blackish-grey, filling up the tubes with no pigmentation on the reverse (Fig. 4A). Lactophenol cotton blue (LPCB) staining revealed long smooth-walled, non-septate sporangiophores arising from stolons opposite rhizoids, usually in groups of two or more. Sporangia were globose, greyish black and multi-spored. Columellae and apophysis together were globose and collapsing to an umbrella-like form after spore release. Sporangiospores were subglobose to ellipsoidal, with striations on the surface (Fig. 4B). A presumptive identification of *Rhizopus arrhizus* was made based on characteristic microscopic morphology. The identification was further confirmed by matrix assisted laser desorption ionization-
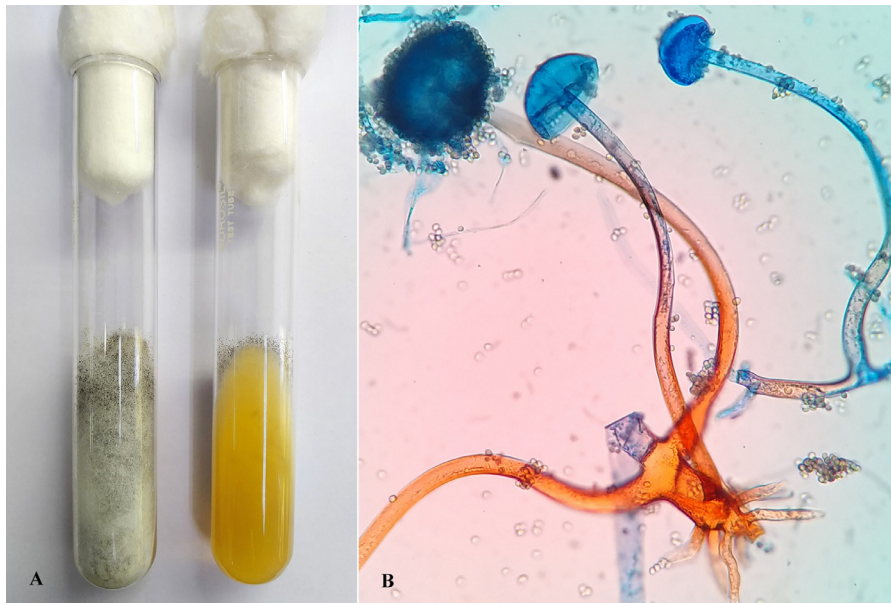
Fig. 4. Gross appearance and microscopic morphology of *Rhizopus arrhizus* isolated from tissue specimens. 4A Fungal culture on SDA showing cottony, fluffy mould, initially white and later becoming blackish-grey, filling up the tubes with no pigmentation on the reverse. 4B LPCB mount showing long, smooth-walled, non-septate sporangiophores arising from stolons opposite rhizoids, usually in groups of two or more. Sporangia are globose, greyish black and multi-spored. Columella and apophysis together are globose and collapsing to an umbrella-like form after spore release. Sporangiospores are subglobose to ellipsoidal (x400).

time of flight mass spectrometry (MALDI-TOF MS) (VITEK® MS, bio-Mérieux, Marcy l'Etoile, France) using VITEK® MS Mould Kit (contains ethanol, formic acid and acetonitrile for protein extraction from moulds) and VITEK® MS V3.2 Knowledge Base- Clinical Use database. Using a score value of 2.0 as the cut-off for identification, both the mold isolates were identified as *Rhizopus arrhizus* with 99.9% confidence. A diagnosis of rhino-orbito-cerebral mucormycosis (ROCM) Stage 4 (cerebral involvement with cavernous sinus thrombosis and frontal lobe infarction) was made in both the cases. Post-operatively, both the patients received retrobulbar injection of liposomal amphotericin B (LAMB) 1 ml of 3.5 mg/ml every 48 h. Aditionally, intravenous (i.v) LAMB (10 mg/kg/day) in 5% dextrose over one hour for six weeks, ceftriaxone 1 gm i.v twice a day for three days, amikacin 375 mg i.v once a day for three days and metronidazole 250 mg i.v thrice a day for three days were also administered. Human Actrapid (short-acting human insulin; 40 IU/ml) was administered subcutaneously as per sliding scale along with strict glycemic monitoring. The patients were observed in neurosurgery recovery ward for 48 h and then, shifted to Bowring and Lady Curzon Medical College and Research Institute, where they underwent orbital exenteration with resection of the involved sinuses.

Discussion

We report the first two autochthonous cases of COVID-19-associated ROCM in pediatric patients with Type 1 DM. Both the patients had history of uncontrolled DM and asymptomatic infection with SARS-CoV-2. While published literature describes several cases of CAM, particularly in adult patients with undiagnosed or uncontrolled DM, the disease has not yet been reported in pediatric population. Type 1 DM constitutes 5−10% of all cases of diabetes. The incidence is increasing worldwide with nearly 75,000 new cases being diagnosed every year [10]. A recent cross-sectional study revealed that 47% of Indians were unaware of their diabetes status and only a quarter of the diagnosed cases achieved glycemic control with treatment [11]. According to The Diabetes Atlas 2017 data, India is the home to an estimated 128,500 children and adolescents with Type 1 DM [10]. The Karnataka state Type 1 DM registry reported an incidence of 3.7/

100,000 in boys and 4.0/100,000 in girls over a period of 13 years [12]. However, in absence of a national diabetes registry, the actual figures might be higher than estimated.

There appears to be a bi-directional relationship between DM and COVID-19. It is now well established that COVID-19 patients with diabetes exhibit a greater incidence of DKA and hyperosmolar hyperglycemic state, necessitating unusually high doses of insulin [8,13]. According to a meta-analysis of eight studies, COVID-19 accounted for 14.4% of newly diagnosed diabetes in hospitalised patients [6]. The diabetogenic effect of COVID-19 is attributed to SARS-CoV-2- and pro-inflammatory cytokine-mediated damage to the pancreatic beta cells, together with impairment of insulin receptor signalling and high degree of peripheral insulin resistance [13]. Moreover, COVID-19 causes immunosuppression through impairment of CD4+/CD8+ T-cells and antigen presenting dendritic cells and thus, may favor secondary fungal infections [3,14].

Mucormycosis is an angioinvasive disease caused by saprophytic fungi belonging to the order *Mucorales*. They are ubiquitous, present abundantly in Indian soils and environment. India accounts for the highest number of mucormycosis cases in the world. As per recent data, the prevalence of mucormycosis in India is about 0.14 cases per 1000 population, which is nearly 80 times higher than developed countries [9]. Several pathogenic *Mucorales* like *Rhizopus, Apophysomyces, Mucor, Rhizomucor, Lichtheimia* and *Cunninghamella* have been isolated from Indian soil and air samples. A total of 11 genera and 27 species have been implicated in mucormycosis [15]. *Rhizopus arrhizus* is the most common causative agent of mucormycosis both in India as well as globally [9]. However, other species such as, *Rhizopus microsporus* and *Rhizopus homothallicus* are increasingly being reported from India [16]. In the present report, *Rhizopus arrhizus* was the causative agent of ROCM. Based on the anatomical site involved, mucormycosis can manifest in several clinical forms: ROCM is the commonest type in India (45−74%), followed by cutaneous (10−31%), pulmonary (3−22%), renal (0.5−9%), gastrointestinal (2−8%), and disseminated infections (0.5−9%) [9]. Overall, rhino-orbital and ROCM are the most common presentations of CAM in India (89%), followed by pulmonary and disseminated forms (10%) [4,17]. Mucormycosis is sometimes referred to as *diabetes-defining illness*. Diabetes mellitus is

the commonest predisposing factor for ROCM. According to a recent estimate, 77% of ROCM cases occur in diabetics [16]. A recent analysis of 80 cases of CAM from 18 countries revealed that diabetes was the predominant risk factor in Indian cases (95.2% versus 68.4% among cases from other countries), with uncontrolled or poorly controlled diabetes (80.3%) being the commonest presentation and DKA identified in 41% of the patients [18]. In another systematic review of 101 cases of CAM, it was observed that 81% of the cases were from India and hyperglycemia at presentation was the predominant risk factor in 83% of the cases (15% had concomitant DKA), with history of corticisteroid treatment for COVID-19 in 76.3% [3]. While systemic steroids have been shown to offer survival benefit in COVID-19, their immunosuppressive action together with underlying diabetes and the complex cascade of SARS-CoV-2-induced immunological events, lead to an inflammatory state which might favour invasive fungal infections [1,18]. In the present series, both the patients had COVID-19 with uncontrolled diabetes and concomitant DKA. However, none of them had received systemic steroids for the treatment of COVID-19.

Rhizopus arrhizus is ubiquitous in Indian environment. Infection is acquired by susceptible hosts through inhalation of airborne sporangiospores, followed by colonization of nasal and sinus mucosa progressing to invasive sinopulmonary disease. Neutrophils and macrophages act as the first line of defence against fungal infections. In presence of DKA and hyperglycemic milieu, the phagocytic and chemotactic abilities of leukocytes are impaired [19]. Moreover, acidosis causes glycosylation of transferrin and ferritin and reduces iron binding, resulting in elevated levels of free iron. *Mucorales* possess high affinity permeases and siderophores which help in iron accusation necessary for their growth [20]. CNS penetration occurs either by hematogenous route (30%) or by direct contiguous spread (70%) from the paranasal sinuses [21]. Infection of sphenoid and ethmoid sinuses is particularly associated with high risk of cavernous sinus thrombosis and carotid artery invasion with embolization to frontal and parietal lobes. *Mucorales* are angioinvasive and endothelial invasion is mediated by spore coat protein homologs (CotH) which serve as ligand for glucose-regulated protein 78 (GRP78) receptors present on endothelial cells. Expression of GRP78 is increased by iron and hyperglycemia, which futher enhance endothelial invasion and damage [20,21]. Fungal hyphae invade the arterial lumen, leading to vascular occlusion, thrombosis and infarction with resultant hypoxia and tissue necrosis. ROCM proceeds through four stages- Stage 1: involvement of nasal mucosa, Stage 2: involvement of paranasal sinuses, Stage 3: orbital involvement, and Stage 4: involvement of CNS [22]. In the present series, both the patients had Stage 4 ROCM with cerebral involvement, cavernous sinus thrombosis and frontal lobe infarction, in addition to the characteristic "red flag signs of ROCM" proposed by Corzo-Leon et al., which include cranial nerve palsy, diplopia, sinus pain, ptosis, proptosis, periorbital swelling, and orbital apex syndrome [23]. Both of them developed mucormycosis during the course of treatment of DKA. Though our first case had COVID-19 in the unknown past (positive SARS-CoV-2 IgG antibody test), there are reports of mucormycosis developing as late as 90 days after COVID-19 diagnosis [17]. The second case had an interval of 10 days between COVID-19 diagnosis and the first evidence of mucormycosis. A multicenter epidemiologic study revealed that the median time to CAM diagnosis was 18 days, with majority of the patients developing late CAM (mucormycosis was diagnosed ≥8 days after COVID-19 diagnosis) [24]. Similar findings were reported by Pal et al. (median interval= 15 days) [17] and Muthu et al. (median interval= 19.5 days) [4]. This suggests that stringent caution should be exercised and a high index of suspicion for CAM should be kept for the first three weeks following the diagnosis of COVID-19.

Diagnosis of CAM is challenging. The hallmark of mucormycosis is tissue necrosis. However, clinical approach to diagnosis lacks sensitivity. Other angioinvasive fungi like *Aspergillus* and *Fusarium* may exhibit similar clinical and radiological manifestations. A lack of clinical suspicion, difficulty in isolating the causative fungus and absence of fungal biomarkers [(1→3)-β-D-Glucan and galactomannan], further add to the diagnostic dilemma. A definitive diagnosis of ROCM requires demonstration of fungal hyphae in tissue specimens by microscopy (direct and histopathology) and isolating the causative agent in culture. Direct microscopy (KOH mount and Calcofluor White staining) allows rapid presumptive diagnosis of mucormycosis, which is particularly essential for initiating early effective treatment. Histopathological examination of tissue can provide additional information on angioinvasion, infarcts and perineural invasion. It also helps in the diagnosis of culture negative cases and distinguishing a true fungal pathogen from a culture contaminant, which is particularly important for saprophytic fungi [25]. In our cases, both direct microscopy and histopathology were consistent with the diagnosis of mucormycosis. Isolation of the fungus in culture is imperative for speciation and antifungal susceptibility testing (AFST). Though speciation based on morphological features is satisfactory in most cases, it requires expertise and may be associated with failures. Molecular techniques targeting the internal transcribed spacer region provide reliable and accurate identification, but are available only in reference laboratories. Recently, detection of *Mucorales* DNA in blood has shown promising results for rapid non-invasive diagnosis and could be used as screening test in patients with "red flag signs" of ROCM. A new pan-Mucorales real-time (qPCR) commercial kit (Mucorgenius®, PathoNostics, Maastricht, The Netherlands) has been validated for detection of four main clinically relevant genera, i.e., *Mucor-Rhizopus* spp., *Lichtheimia* spp., *Rhizomucor* spp. and *Cunninghamella* spp., with an overall sensitivity of 75% in serial blood samples from patients with mucormycosis, often preceding a positive culture result by several days to weeks [26,27]. MALDI-TOF MS has emerged as a promising tool and the recent database (VITEK® MS V3.2 Knowledge Base) has been expanded to cover most species of pathogenic *Mucorales* [28]. In our case, VITEK® MS identified both the mould isolates as *Rhizopus arrhizus* with 99.9% confidence and a score value of >2.0, suggesting an excellent correlation. AFST is important for guiding optimal antifungal therapy, as some *Mucorales* exhibit high minimum inhibitory concentrations (MICs) against certain antifungals, e.g. *Cunninghamella* spp. against amphotericin B and *Mucor circinelloides* against posaconazole [29].

ROCM is associated with high morbidity and mortality, as it is a rapidly progressive disease and patients seek medical care late in the disease process. Also, low affordability makes many patients quit antifungal therapy. The mortality rate in ROCM approaches 60% despite treatment and amongst survivors, 46% have permanent loss of vision [18]. However, the mortality rate in CAM (36.5%) has been reported to be much lower than the previous Indian data on non-COVID-19 mucormycosis (52%) [4]. Improving the survival rate requires rapid diagnostic and therapeutic interventions with a multidisciplinary holistic approach. Aggressive surgical debridement of infected tissues, early initiation of appropriate antifungal therapy and achieving adequate glycemic control are cornerstone in the management of mucormycosis. Surgical debridement with healthy margins is essential for optimal drug delivery to the site of infection. However, prognosis of CNS disease is dismal with no significant survival benefit despite surgical intervention [18,21]. A recent analysis showed that median survival time for COVID-19 associated ROCM patients with proven CNS involvement (Stage 4) was 26 days from the day of diagnosis, with a higher survival rate among those without CNS involvement [18]. Liposomal amphotericin B in a dose of 10 mg/kg/day i.v for 6 weeks constitutes the first-line treatment for CNS mucormycosis. Other alternative regimens include posaconazole i.v/delayed release tablet (300 mg BID on day 1, then 300 mg/day for 6 months) and i.v/oral isavuconazole (200 mg TID on day 1 and day 2, then 200 mg/day for 6 months) [30]. If resource-limited settings where LAMB, posaconazole and isavuconazole are not available or

affordable, oral itraconazole in a dose of 200 mg TID for 3–6 weeks is recommended [31]. Retrobulbar injection of amphotericin B has emerged as a promising non-surgical option prior to orbital exenteration in ROCM cases. Though several case reports have documented its success in halting orbital disease progression and preserving the globe [32], it wasn't successful in our cases and both of them had to undergo orbital exenteration as a life-saving procedure.

Conclusion

ROCM is a catastrophic consequence in the context of COVID-19 in India, particularly in those with uncontrolled diabetes. While excessive use of systemic steroids for the treatment of COVID-19 has been linked to increased incidence of CAM in adults, its occurrence in pediatric diabetic patients with no history of steroid exposure indicates that hyperglycaemic state is the major predisposing factor for the disease. However, much remains to be understood regarding the complex association between mucormycosis and COVID-19. Despite the availability of improved diagnostics and effective antifungals, ROCM remains a highly lethal and disabling disease. The situation is further complicated by scarcity of LAMB and high price of antifungal drugs. The domestic production of antifungal drugs needs to be scaled-up to meet the growing demands. All efforts should be made to correct the underlying metabolic derangements. A high index of suspicion together with an early diagnosis and prompt management can improve survival in such cases.

Ethics approval

Not applicable

Consent to participate

Written informed consent was obtained from parents of the patients.

Authors' contributions

Conceptualization: JD, AS, NS, VHB; Data curation: JD, AS, EM, NS; Formal analysis: JD, AS, VHB, NS, SKK, MDB, NBN, DS; Validation: All authors; Visualization: All authors; Roles/Writing - original draft: JD, AS, EM, NS; Writing - review & editing: JD, AS, EM, NS

All authors have reviewed and approved the final version of the manuscript

Declaration of Competing Interest

All Authors declare to have no conflict of interest/competing interest to disclose with this manuscript.

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