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Case Report

Rhinocerebral mucormycosis in COVID-19 patient with diabetes a deadly trio: Case series from the north-western part of India

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ABSTRACT

Coronavirus disease 2019 (COVID-19), may present with a myriad of clinical manifestations and complications. Patients with COVID-19 are at increased risk of pulmonary thromboembolism, acute cardiac injury, arrhythmias, acute stroke, and secondary infections. Mucormycosis is a catastrophic fungal infection characterized by vascular invasion, thrombosis, and necrosis of tissues. We report five cases of COVID-19 infection, who developed rhino-orbital mucormycosis, during the course of treatment. Early recognition of this life-threatening infection is the key to allow for optimal treatment and improved outcomes.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had been spread globally. While the pathophysiology of the SARS-CoV-2 is still under investigation, a myriad of symptomatic manifestations and complications of the disease continue to be identified [1]. COVID-19 may be associated with a variety of bacterial and fungal co-infections and may be associated with pre-existing morbidity or may develop as a hospital-acquired infection. The fungal co-infections associated with COVID-19 might be missed or misdiagnosed. COVID-19 patients, particularly those with diabetes, who are immunocompromised or severely ill, have a higher probability of suffering from invasive fungal infections [2].

Mucormycosis is a wide spectrum of subacute or acute, and devastating infections, caused by angiotropic fungi, and is associated with high morbidity and mortality. The vast majority of patients with invasive mucormycosis are immunocompromised either taking immunosuppressant drugs or have underlying comorbidities, like diabetes mellitus, hematologic malignancies, and trauma or are transplant recipients [3]. Rhinocerebral mucormycosis (RCM) is an opportunistic infection of the paranasal sinuses and brain. Globally incidence of mucormycosis is low and is most commonly found in India and the Middle East [4]. Outbreaks of mucormycosis, even in immunocompetent adults, have also been associated with major natural disasters [3]. We describe a case series of five patients of rhinocerebral mucormycosis associated with COVID-19 infection.

2. Case History

2.1. Materials and methods

This is a retrospective case series analysis of patients with reverse-transcriptase polymerase chain reaction (RT-PCR) confirmed COVID-19, who were diagnosed as rhinocerebral mucormycosis during the course of treatment presenting to a single tertiary-center in Northwest Rajasthan, India during months of the November–December 2020. Patients were diagnosed by characteristic clinical manifestation, imaging, and histopathological examination or culture of the sinonasal specimen. We evaluated the patients' demographic details, clinical presentation, laboratory and imaging findings, management, complications, and

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Table 1
Clinical profile, treatment and outcome of our case series and previously reported cases of mucormycosis with COVID-19 infection.

Case/ Author	Age/ sex	Comorbidity	Clinical manifestations	Imaging	HPE	Treatment	Outcome
Case 1	59/F	T2DM, HTN	Headache, ptosis, chemosis, mild proptosis, loss of vision, complete ophthalmoplegia, blackish discharge from nasal cavity, black crust on hard palate	Bilateral maxillary, ethmoid, left frontal and sphenoid sinusitis, cavernous sinus thrombosis.	LCB/KOH mount of nasal discharge showed aseptate filamentous fungal hyphae, suggestive of rhizopus and confirmed on culture	Liposomal amphotericin B, antibiotics, Inotropes, MV	Deceased
Case 2	52/ M	T2DM	Headache, diminished vision, mild proptosis, chemosis, mild restriction of ocular movement of right eye. blood tinged black discharge from nasal cavity	Right orbital cellulitis, right maxillary sinus, bilateral ethmoid & sphenoid sinusitis	LCB mount of nasal discharge revealed rhizopus arrhizus, cotton wool-like white growth on culture	Liposomal amphotericin B, antibiotics, posaconazole	Follow-up
Case 3	62/F	T2DM, HTN	Loss of vision, periorbital swelling, lid edema, black patches on lids of right eye, blood-tinged discharge from nasal cavity, black crust on hard palate	Pansinusitis, right orbital cellulitis, endophthalmitis, cavernous sinus thrombosis	KOH mount of nasal scraping revealed rhizopus	Liposomal amphotericin B, antibiotics	Hospitalized
Case 4	70/F	T2DM	Decreased vision, diplopia, lid edema, chemosis, mild proptosis, ophthalmoplegia of left eye, black crust in nasal cavity	Left orbital cellulitis, erosion of medial wall-floor of left orbit and pansinusistis (L > R)	LCB mount of nasal scraping and sabouraud dextrose agar culture revealed rhizopus arrhizus	Liposomal amphotericin B, antibiotics, supportive	Hospitalized
Case 5	68/F	T2DM	headache, facial swelling, ptosis, lid edema, loss of vision, proptosis and complete ophthalmoplegia of right eye, blood-tinged black discharge from nostrils & black crust on hard palate	Right pre and post septal orbital cellulitis with endo-ophthalmitis, right cavernous thrombosis, multiple lacunar infarcts and pansinusitis	LCB & KOH mount of nasal scraping and culture revealed rhizopus arrhizus	Liposomal amphotericin B, antibiotics, Inotropes, supportive	Deceased
Werthman et al.	33/F	HTN/ Asthma	Left-sided ptosis, proptosis, complete ophthalmoplegia and altered sensorium, DKA	Maxillary & ethmoidal sinusitis, MRI brain showed multiple areas of infarction and ischemia	Culture of nasal mucosal swab	Lateral canthotomy, sinus debridement & amphotericin B	Deceased
Mehta et al.	60/ M	DM	Proptosis, chemosis, periorbital edema, soft tissue necrosis of lids of right eye. Fixed dilated left eye	Right frontal, maxillary, & ethmoidal sinusitis. Retrobulbar soft tissue swelling mild proptosis on right side	Nasal biopsy from the middle turbinate, confirmed by culture	Amphotericin B, inotropes, MV	Deceased
Silvino et al.	86/ M	HTN	Diarrhea, melena, abdominal tenderness, and severe anemia	Two giant gastric ulcers with dirty debris & deep hemorrhagic base on greater and lesser curvature on EGD	Biopsy of gastric ulcer (HE stain)	PRBC transfusion, Inotropes, MV	Deceased Before DX

HPE, Histopathology examination; F, Female; M, Male; T2DM, Type 2 Diabetes mellitus; HTN, Hypertension; DKA, Diabetic ketoacidosis; L, Left; R, Right; LCB, Lactophenol cotton blue; KOH, Potassium hydroxide; MV, Mechanical ventilation; DM, Diabetes mellitus; EGD, Esophagogastroduodenoscopy; PRBC, Packed red blood cell; HE, Hematoxylin and eosin; Dx, Diagnosis; NA, Not available.

outcome (Table 1). Written informed consent was taken from each patient. This study was approved by Institutional Ethics and Research Board [No:F. 29(Acad)SPMC/2020/2322 dated December 07, 2020].

2.2. Case 1

A 59-year-old female, known diabetic admitted with COVID19 pneumonia. She was started on oxygen supplementation, intravenous meropenem, remdesivir, dexamethasone, subcutaneous enoxaparin, tablet azithromycin, basal-bolus insulin, and supportive care, as per institutional protocol. On day 6 she developed severe headache and drooping of the right eyelid. Examination revealed a diminished vision, chemosis, mild proptosis, complete ophthalmoplegia, blackish discharge from the nasal cavity, and black crust on the hard palate. CT paranasal sinus (PNS) revealed bilateral maxillary, ethmoid, left frontal and sphenoid sinusitis, and blocked right osteomeatal opening (Fig. 1a). MRI Brain and orbit revealed right cavernous sinus thrombosis. Lactophenol cotton blue (LCB) and KOH mount of nasal discharge revealed broad aseptate filamentous fungal hyphae suggestive of *Rhizopus*. Nasal discharge was cultured on sabouraud dextrose agar and *Rhizopus arrhizus* was grown. Intravenous liposomal amphotericin B (5mg/kg/day) was started and the steroid was discontinued. The patient continued to deteriorate, eventually required inotropes and mechanical ventilation. Due to persistent hypotension, we were unable to carry out debridement and despite all measures, she died on day 10 of admission.

2.3. Case 2

A 52-years-old male, known case of diabetes mellitus and COVID-19 presented with headache, diminished vision, and redness of the right eye. He was on oral prednisolone for COVID-19 and on a sliding scale regular human insulin for diabetes. On examination he was afebrile, his vitals were stable, and there was mild proptosis, chemosis, diminished vision, mild restriction of ocular movement of the right eye, and blood-tinged black discharge from the nasal cavity. Laboratory investigation revealed, neutrophilic leucocytosis, hyperglycemia (RBS 350 mg/dl) with ketosis without acidosis. MRI Orbit and PNS revealed mild right pre-orbital soft tissue swelling with retro-bulbar fat standing and mucosal thickening in the right maxillary sinus, bilateral ethmoid, and sphenoid sinuses. Histopathological examination of nasal discharge revealed *Rhizopus*. Clinical material was inoculated on sabouraud dextrose agar at 25 °C and 37 °C aerobically. After 2–3 days, cotton wool-like white growth appeared which became dark on further incubation. LCB mount of cultured growth revealed thick-walled, aseptate refractile hyphae, suggestive of *Rhizopus arrhizus* (Fig. 1b). The patient was treated with intravenous fluids, basal-bolus insulin, intravenous meropenem, vancomycin, and liposomal amphotericin B (5 mg/kg/day). The patient recovered over 4 weeks and discharged on oral posaconazole.

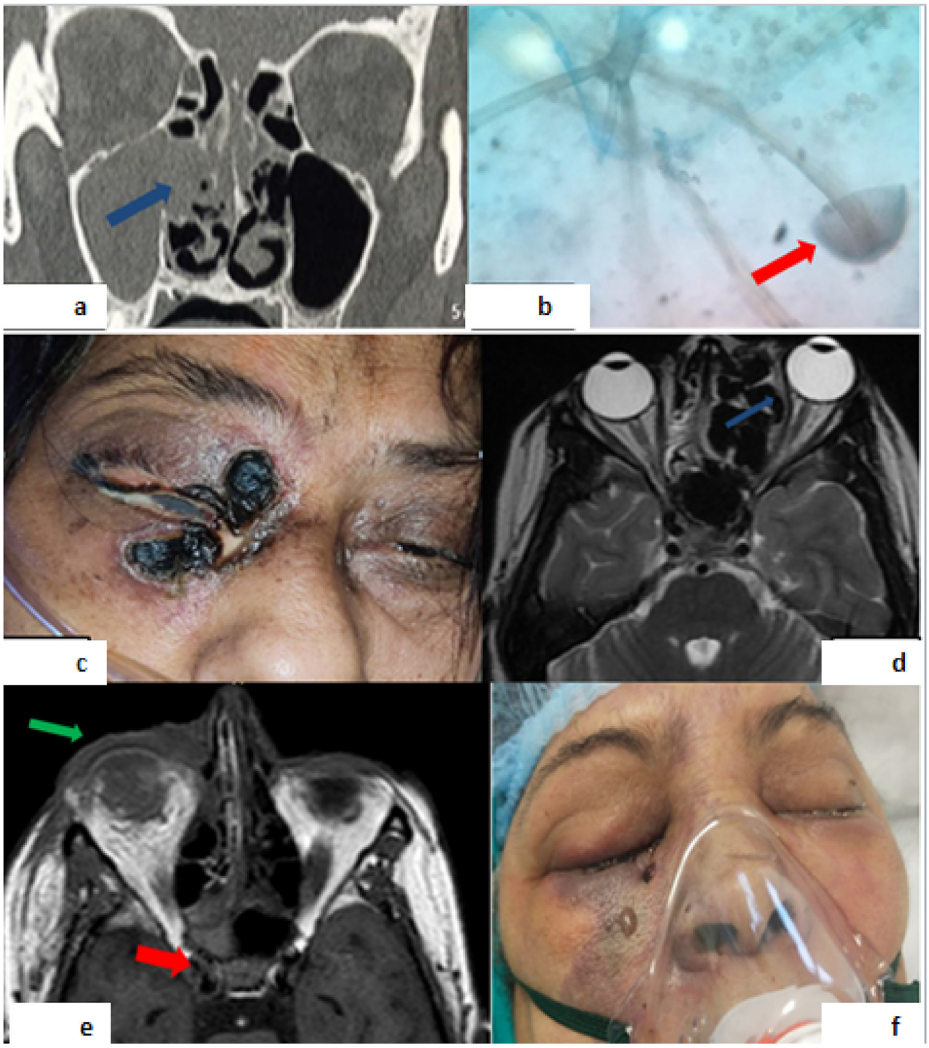

Fig. 1. Fig. 1a. CT scan showing mucoperiosteal thickening in bilateral maxillary, ethmoid, left frontal sinuses, and blocked right osteomeatal opening (blue arrow). Fig. 1b. Lactophenol cotton blue mount of nasal discharge showing broad aseptate hyphae with sporangiospore (red arrow) of rhizopus. Fig. 1c. Image of Case 3 showing right periorbital swelling, black patch on right lids. Fig. 1d. T2W MRI showing hypointense lesion causing expansion of nasal cavity, erosion of ethmoid sinus and medial wall of left orbit (blue arrow) causing mass effect on left medial rectus muscle and proptosis of left eye ball. Fig. 1e. Mild proptosis (green arrow), pre-orbital soft tissue swelling and altered shape of right orbit, thickening and peri-neural fat stranding of right optic nerve, and bulky right cavernous sinus (red arrow) suggestive of right pre and post septal orbital cellulitis, endo-ophthalmitis, and right cavernous thrombosis. Fig. 1f. Image of Case 5 showing bilateral facial and eye (right > left) swelling with necrosis of surrounding skin.

2.4. Case 3

A 62-years-old female with a history of COVID-19 pneumonia 1 month back presented with progressive painless swelling and loss of vision of the right eye, right facial swelling, and black patch on the right eye, and hard palate over 2 weeks. She was a known case of type 2 diabetes for 12 years, on insulin glargine and oral antidiabetic drugs. On examination she was afebrile, her vitals were stable, and there was right periorbital swelling, black patches on the right upper and lower lid, black blood-tinged discharge from the right eye and nasal cavity, and black crust on the hard palate (Fig. 1c). On investigation, there was neutrophilic leucocytosis, raised creatinine (creatinine 1.62 mg/dl), hyperglycemia, and ketoacidosis (pH 7.25). MRI Brain and orbit revealed right pre and post-septal orbital cellulitis, endophthalmitis, cavernous sinus thrombosis, and pan-sinusitis. KOH mount of nasal scraping revealed *Rhizopus.* She was started on intravenous fluids, insulin infusion, intravenous meropenem, linezolid, and liposomal amphotericin B (5mg/kg/day). She continuously deteriorated over the next 3 days, so she was shifted to another center, where she underwent debridement and is still under treatment but lost her right eye completely.

2.5. Case 4

A 70-years-old female known case of type 2 diabetes for 15 years was on home isolation for COVID-19 infection. She presented with progressive painless swelling, decreased vision, and double vision in the left eye on day 7 of illness. She was on intravenous remdesivir, dexamethasone, antibiotics, and subcutaneous insulin at home. On examination she was afebrile, her vitals were stable, and there was lid edema, chemosis, mild proptosis, fixed dilated pupil, and mild restriction of extraocular movement of the left eye with black crust in the nasal cavity. Laboratory investigation revealed leucocytosis and hyperglycemia without ketoacidosis. MRI orbit and PNS showed left orbital cellulitis, erosion of medial wall-floor of the left orbit, and pansinusitis (left > right) (Fig. 1d). Histopathological examination (LCB mount) of nasal scraping revealed mucormycosis, and *Rhizopus arrhizus* was grown on sabouraud dextrose agar culture. The surgical opinion was taken and debridement was advised, but the relative refused. She is still hospitalized and on intravenous liposomal amphotericin B, antibiotics, basal-bolus insulin, and supportive treatment, and her condition is stable.

2.6. Case 5

A 68-years-female known case of diabetes and COVID-19 pneumonia, shifted to post-COVID ICU after a negative RT-PCR report. On day 5, she developed a headache, right eye swelling, and drooping of the right upper eyelid. On examination, there was lid edema, loss of vision, proptosis, and complete ophthalmoplegia of the right eye, and blood-tinged black discharge from the nostril. MRI revealed right pre and post-septal orbital cellulitis with endo-ophthalmitis, right cavernous thrombosis, multiple lacunar infarct, and pansinusitis (Fig. 1e). Histopathological examination of nasal scraping revealed mucormycosis, and

Rhizopus arrhizus was grown on sabouraud dextrose agar culture. She was started on intravenous liposomal amphotericin B and broad-spectrum antibiotics and steroid was tapered. She progressively deteriorated, required inotropes and infection also spread to her left eye (Fig. 1f). Debridement could not be done due to hemodynamic instability and the patient succumbed on day 8 despite all measures.

3. Discussion

We retrospectively analysed five cases of rhinocerebral mucormycosis with COVID-19 infection. The patients were diagnosed with a combination of clinical, radiological, and histopathological findings. Patients with COVID-19 are at increased risk of secondary fungal infection due to the complex interplay of multiple risk factors, including pre-existing diseases (diabetes mellitus), use of immunosuppressive drugs, hospital-acquired infections, and systemic immune alterations by COVID-19 itself [5]. In this case series, all the patients had a history of diabetes mellitus and were treated with intravenous steroid for COVID-19 infection. Persistent hyperglycemia of diabetes is thought to responsible for impaired chemotaxis and phagocytosis of neutrophils. Besides this, acidosis in diabetic ketoacidosis impairs the binding of iron to transferrin, increasing free iron that promotes fungal multiplication [4]. Steroid-induced immunosuppression in COVID-19 patients and immune dysregulation associated with COVID-19 infection, with reduced numbers of T lymphocytes, CD8+T, and CD4+T cells, may alter innate immunity that may permit invasive secondary fungal infections [6].

The most common causative species are *Rhizopus* and *Mucor*. Infection of humans occurs by aerosolized fungal spores deposited on the nasal mucosa, with subsequent invasion and progression to the paranasal sinuses, orbits, and brain. Vascular invasion is a characteristic feature and eventually causes infarction, hemorrhage, and tissue necrosis [7]. These patients usually present with unilateral facial swelling, proptosis, and palatal perforation [8]. In this series the causative species was *Rhizopus* in all patients. All patients presented with headache, unilateral facial swelling, proptosis, ophthalmoplegia, and diminished vision. Three patients had palatal involvement and three patients had cerebral involvement.

Diagnosis of rhinocerebral mucormycosis is established by characteristic clinical manifestations, radiological findings, histopathological examination and culture of affected tissue or nasal discharge. Broad-based aseptate hyphae with irregular right-angled branching are characteristic microscopic features. CT/MRI of paranasal sinuses, orbit, and brain should be done to determine the extent of the disease. Imaging findings include the maxillary, ethmoid, or sphenoid sinusitis with orbital or intracranial extension, bony erosions, and cavernous sinus thrombosis [8]. Diagnosis should be suspected in high-risk individuals, if there is unilateral orbital swelling, proptosis, facial pain, or swelling [1]. In this series all patients had bilateral sinusitis and unilateral orbital cellulitis, three patients had unilateral cavernous sinus thrombosis and one patient had multiple lacunar infarcts. Histopathological examination of nasal discharge revealed broad aseptate filamentous fungal hyphae suggestive of *Rhizopus*. Nasal discharge was cultured on sabouraud dextrose agar and *Rhizopus arrhizus* was grown in four cases.

Management of rhinocerebral mucormycosis consists of surgical drainage of PNS and debridement of orbital or cerebral disease, combined with intravenous antifungal drugs. First-line antifungal treatment consists of intravenous liposomal amphotericin-B (5–10 mg/kg/day) and second-line antifungals such as intravenous or oral posaconazole can be used as salvage therapy, with a course of at least 6 weeks duration usually required. Strict glycemic control is also a key aspect of treatment. Mortality rates for rhinocerebral mucormycosis range from 40 to 80% depending on underlying conditions [8]. Early diagnosis and prompt treatment are crucial, as a delay of even 6 days is associated with a doubling of mortality [1]. Following confirmation of the diagnosis all patients were treated with intravenous amphotericin B and one patient underwent debridement. Out of five patients, two are still hospitalized, and one improved and under follow-up, and two died with a mortality rate of 40%.

A handful of cases of mucormycosis with COVID19 have been previously reported [1,9,10] (Table 1). To the best of our knowledge, this is the first case series of mucormycosis in COVID-19 patients from India. It is impossible to make out whether COVID-19 infection is contributory to mucormycosis or merely coincidental.

To conclude, COVID-19 is frequently associated with secondary infections, both bacterial and fungal possibly due to immune dysregulation. Besides this, the widespread use of broad-spectrum antibiotics, steroids, or monoclonal antibodies in the management of COVID-19 may lead to the development or exacerbation of pre-existing fungal diseases. The clinician should be aware of the possibility of invasive fungal infections in patients with COVID-19, especially in patients with risk factors, and should enable early diagnosis and treatment to reduce morbidity and mortality.

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Conflicts of interest

There are no conflicts of interest.

CRediT authorship contribution statement

Hardeva Ram Nehara: Manuscript preparation, Methodology. **Inder Puri:** Data curation, Data collection, Writing – original draft, preparation. **Vipin Singhal:** Visualization, Investigation. **Sunil IH:** Investigation, Supervision. **Bhagirath Ram Bishnoi:** Investigation, Validation. **Pramendra Sirohi:** Writing – review & editing.

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