

## Case Report

# COVID-19 pneumonia and mucormycosis a new challenging duo-rhino-oculo-cerebral mucormycosis: a case report

Sudhir K. Atri<sup>1</sup>, Sanjay Fotedar<sup>1</sup>, Homdutt<sup>2\*</sup>, Vinay Malik<sup>3</sup>, Parul Punia<sup>4</sup>

<sup>1</sup>Department of Medicine, <sup>4</sup>Department of Microbiology, Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India

<sup>2</sup>Department of Medicine, Sanjay Gandhi Memorial Hospital, Magolpuri, Delhi, India

<sup>3</sup>Department of Radiology, Healthmap Diagnostics, Rohtak, Haryana, India

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### \*Correspondence:

Dr. Homdutt,

E-mail: [dr.homdutt@gmail.com](mailto:dr.homdutt@gmail.com)

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### ABSTRACT

The pandemic of corona virus disease 2019 (COVID-19) has posed challenge not only in management of the primary disease but the emerging complications associated with COVID-19 has further complicated the course of disease. The course of COVID-19 disease is associated with infectious and noninfectious complications former include secondary bacterial and fungal infection adding to mortality and morbidity. COVID-19 disease associated candidiasis and aspergillosis have been reported as super infections but with the steroid and supplemental oxygen as mainstay treatment modality mucormycosis is now complicating the course of disease and presently posing challenge in India with already overburdened health care service. Mucorales is a saphrophytic fungi causes rhinocerebral infection involving nasal passages, sinuses, oral cavity and brain. It is usually seen in immunocompromised host and in diabetics with poorly controlled blood sugar level. High degree of clinical suspicion is needed to suspect and diagnose mucormycosis. It is a fatal disease because of its angioinvasive pathogenesis and treatment is promptly initiated to salvage mortality and morbidity. Authors report a case of rhino-oculo-cerebral mucormycosis in a middle-aged diabetic patient with severe COVID-19 disease.

**Keywords:** COVID-19, Pneumonia, Mucormycosis, Rhino-oculo-cerebral mucormycosis

### INTRODUCTION

Corona virus disease 2019 (COVID-19) outbreak has involved the whole globe, despite global effort no definitive treatment has been described till now except managing symptoms and prevention. COVID-19 disease is a primary respiratory illness which is characterized by wide clinical spectrum ranging from asymptomatic/mild diseases to life threatening diseases and complicated by secondary events including infections and systemic spillover of inflammation. Viral diseases including influenza, Middle East respiratory syndrome-related coronavirus (MERS), severe acute respiratory syndrome (SARS) involving the respiratory system are associated with secondary infections, a well-documented

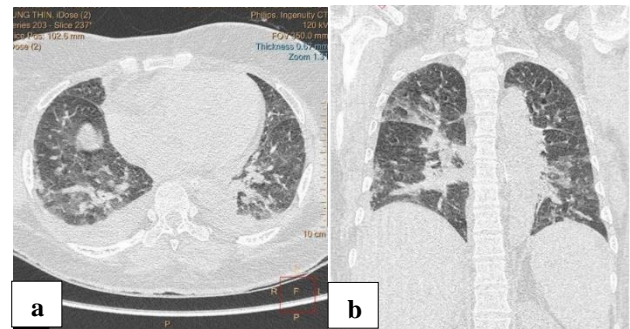
phenomenon. The secondary infections in COVID-19 disease still in exploratory phase as with time new complications are being documented and common in critically ill and hospitalized patients up to 30%.<sup>1,4</sup> Corticosteroids including dexamethasone and methyl prednisolone are the part of armamentarium used in management of COVID-19 disease, the mainstay treatment proposed to modulate the associated inflammation and reducing the progression of respiratory inflammatory cascade thereby preventing ventilatory failure. The steroid use is known for secondary effects including infections, immune system modulation, glycemic intolerance and precipitation of latent diabetes and many other physiological disturbances. Mucormycosis is a rare fungal disease but potentially fulminant, caused by mucorales of phylum zygomycota is now being

reported as complicating the course of COVID-19 disease. Globally the incidence varies in between 0.005 to 1.7 per million, in India reported as about 0.14/1000 higher than developed countries. Mucormycosis is associated with fatality rate of 40% globally with significant increase to 50-80% because of underlying immunocompromised state.<sup>1,5</sup> Mucormycosis is caused by filamentous fungi, an opportunistic pathogen seen in immunocompromised host and is responsible for life-threatening infection, usually presenting as acute infection with slowly progressive chronic state in some instances. Though seen in immunocompromised host but may also involve immunocompetent host also. The disease is seen with various clinical states as severe burns, diabetic ketoacidosis, and steroid therapy, PLHIV/AIDS, neutropenia, hemochromatosis, hematological malignancies and malnutrition. In the present scenario of COVID-19 pandemic association of mucormycosis has been described with steroid use the mainstay treatment of COVID-19.<sup>1,6</sup> Prompt diagnosis and initiation of treatment is important as the disease carries poor prognosis.

## CASE REPORT

A middle-aged woman 49 years of age diagnosed as case of COVID-19 pneumonia, reverse transcriptase polymerase chain reaction (RT-PCR) positive for COVID-19, was admitted in COVID care centre of our institute a tertiary care centre at North India. On examination patient was febrile, respiratory rate of 28/minute, dyspneic with room air oxygen saturation of 80%, hemodynamically stable with blood pressure 120/80 mmHg, investigations revealed total leucocyte count (TLC) 14000/mm<sup>3</sup>, differential leucocyte count (DLC) 75/20/02/03/0, electrocardiography (ECG) revealed sinus tachycardia, renal functions normal, liver function test shows mild derangement aspartate aminotransferase (AST)-50 IU, alanine transaminase (ALT) 56 IU with normal serum amylase level, fasting blood sugar 250 mg/dl, post prandial 240 mg/dl, HbA1c 8%, D-dimer-700 ng/ml (0-500 ng/ml), C-reactive protein (CRP)-15.25 ng/ml (1-6 ng/ml). High-resolution computed tomography (HRCT) thorax was planned which revealed multifocal areas of consolidative opacities and nonsegmental areas of ground glass attenuation in both lung parenchyma with peripheral predominance suggesting COVID organizing pneumonia with bilateral pleural effusion (Figure 1). Patient was also a known case of diabetes type-2 on oral hypoglycemic agents with no other significant medical history. Patient was managed according to set protocol with injection remdesivir 200 mg IV on first day as loading dose followed by 100 mg OD per day for 4 days, injection dexamethasone 6 mg intravenous twice daily besides O<sub>2</sub> supplementation by nonrebreathing mask at rate of 15 l/min, injection piperacillin plus tazobactam 4.5 gm intravenous 8 hourly and injection azithromycin 500 mg intravenous OD, injection enoxaparin 60 mg subcutaneously along with symptomatic treatment was given. Blood sugar level monitoring was done regularly and managed by regular insulin 6 units subcutaneously 8

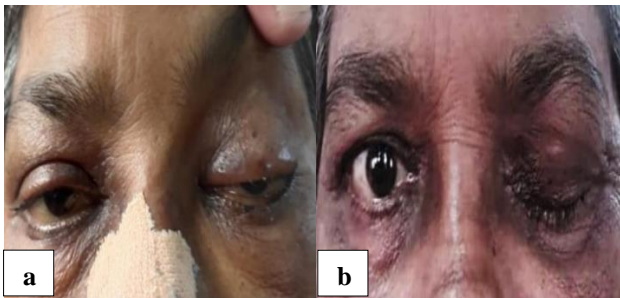
hourly and long-acting insulin-glargine 12 unit subcutaneously at night, fluctuating blood sugar levels were managed by adjusting the insulin dosage proportionately to blood sugar levels. Patient responded initially and oxygen requirement got down to 7 l/min, on 10<sup>th</sup> day patient complained of pain and swelling in both eyes with nasal stuffiness and decreased visual acuity of both eyes. On examination periorbital swelling was present along with edematous eye lids in left eye and bilateral conjunctival congestion was found (Figure 2a). Vision was reduced to finger counting in both eyes, decreased gaze in all directions with left maxillary sinus tenderness. Patient also developed weakness in right side of body with aphasia and drooping of upper eye lid of left eye and decreased level of consciousness on next day suggesting secondary event involving central nervous system with cranial nerve palsy. Multidisciplinary team opinion was sought, plain and contrast enhanced brain magnetic resonance imaging (MRI) scan including paranasal sinuses, B/L orbit was performed which revealed heterogeneous altered signal intensity soft tissue in the left maxillary sinus, extending in the left ethmoid, frontal and sphenoid sinuses with involvement of left nasal cavity, inflammatory mucosal thickening of nasal turbinates. Invasion of left pre-maxillary and post maxillary buccal space was noted (Figure 3a and b).



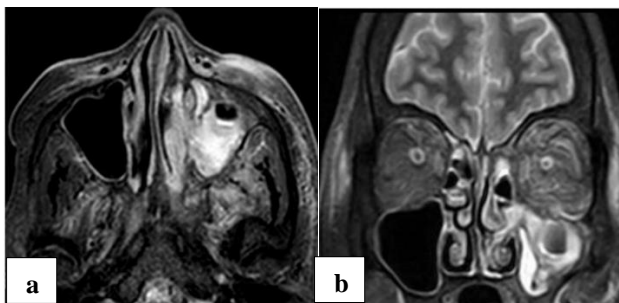
**Figure 1: HRCT chest (a) axial and (b) coronal reveals multifocal consolidative opacities and nonsegmental areas of ground glass attenuations in both lung parenchyma with peripheral predominance and mild pleural effusion.**

Enhanced soft tissue seen involving the medial extraconal compartment of both orbit and left orbital apex. Mild enhancing left perioptic soft tissue thickening was seen with diffusion restriction and low ADC value in left optic nerve. Enhancing asymmetric soft tissue thickening involving left cavernous sinus with convex margin and loss of T2 flow void signal in the left internal carotid artery suggesting cavernous sinus thrombosis and vascular invasion (Figure 4a and b). Multifocal patchy areas of altered signal intensity showing restricted diffusion in left frontoparietal region representing areas of acute infarct was noted (Figure 5). Findings were consistent with fungal infection involving left nasal cavity, maxillary sinus, ethmoid sinus, frontal sinus, bilateral orbit and intracranial extension with cavernous sinus thrombosis. Patient was

put on liposomal amphotericin B 5 mg/kg body weight per day with injection vancomycin 1 gm twice daily, injection meropenam 1gm thrice daily and Functional endoscopic sinus surgery was done as emergency procedure and the findings were consistent with the imaging studies, necrotic debris was found in left maxillary, ethmoid and frontal sinus along with slough and polypoid mass lesion in left maxillary sinus and involvement of left nasal cavity. Removal of the collections and partial debridement of maxillary sinus was done and sent for potassium hydroxide (KOH) mount and culture which revealed mucorales fungus, KOH mount showing hyaline, broad, aseptate ribbon like hyphae with nodal rhizoids, on SDA culture growth was observed within 48 hours, with cottony, greyish colony with black sporulation (Figure 6). Anticoagulation was continued after FES and tablet ecosprin 150 mg along with mannitol 100 mg intravenous was added along with symptomatic treatment, keeping close watch on vitals and coagulation profile. FES was repeated again after 5 days and debridement of left maxillary sinus was repeated and tablet posaconazole was added as add on therapy 300 mg twice on day one followed by 300 mg once a day. Patient responded to the medical and surgical management; sinus tenderness regressed along with periorbital swelling with partial improvement in vision of right eye (Figure 2b).

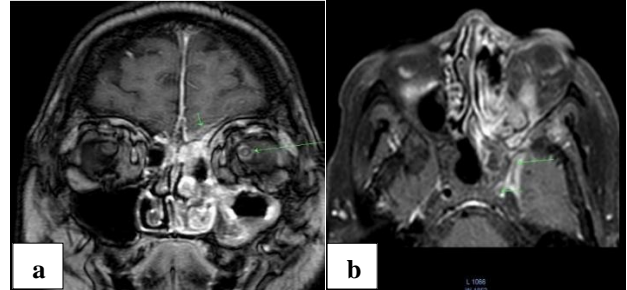


**Figure 2:** (a) On presentation, bilateral orbital swelling with drooping of upper eyelid of left eye, and (b) after four weeks, swelling and chemosis relieved with drooping of upper eyelid of left eye.

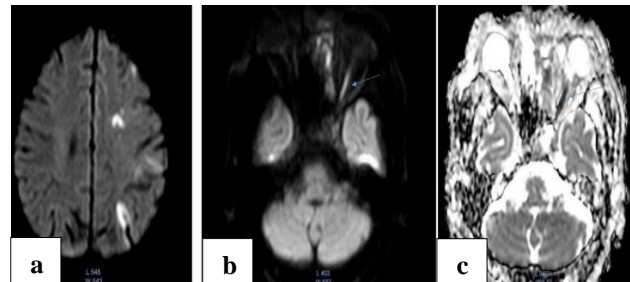


**Figure 3:** T2W FS MRI PNS (a) axial section reveals heterogeneous altered signal intensity soft tissue lesion involving the maxillary sinus infiltrating the periantral buccal space, and (b) coronal section reveals heterogeneous altered signal intensity involving the left maxillary, ethmoid, and left nasal cavity with hypointense areas within.

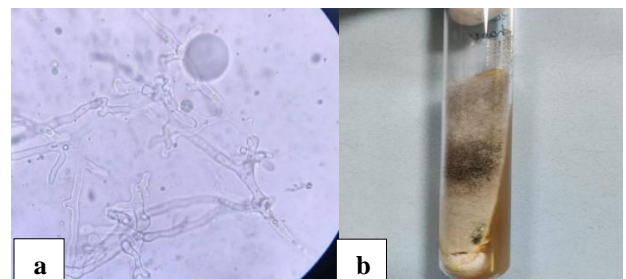
Patient started accepting semisolid to solid food after three weeks of amphotericin therapy and oxygen requirement was weaned off and became ambulatory with partial improvement in motor function of right side of body, discharged after completion of four weeks of amphotericin with plan to continue posaconazole till first follow up.



**Figure 4:** (a) Postcontrast fat suppressed T1W coronal image reveals heterogeneously enhancing soft tissue signal intensity involving the left maxillary, left ethmoid sinus, left nasal cavity with extension, in medial extra-conal compartment of b/l orbital, enhancing soft tissue thickening along left anterior frontal convexity (small arrow); and (b) axial section reveals involvement of left orbital apex, left cavernous sinus thrombosis (large arrow), and angioinvasion with left cavernous ICA thrombosis.



**Figure 5:** DWI images reveals (a) multifocal areas of acute infarcts in the left fronto-parietal region; (b) and (c) restricted diffusion in left optic nerve (arrow) and corresponding ADC map reveals low ADC value suggesting left optic nerve involvement.



**Figure 6:** (a) KOH mount showing hyaline, broad, pauciseptate ribbon like hyphae with nodal rhizoids of rhizopus species; (b) on SDA culture, growth was observed within 48 hours, with cottony, greyish colony with black sporulation.



## DISCUSSION

Mucormycosis a potentially fatal and acute infection caused by filamentous fungi belonging to Mucoraceae, clinically classified according the anatomical site involved rather than the causative agent. Clinical presentation can be nasal, rhino-orbital or more severe form rhino-orbital-cerebral. It can also present as cutaneous, pulmonary, gastrointestinal and disseminated disease. Genus *Rhizopus* accounting for majority of cases. Immunocompetent host is rarely affected, immunocompromised host is at risk and seen in hosts with diabetes mellitus with poor glycemic control, immunosuppressant use, neutropenia, hematological malignancies, hemodialysis, extensive burns and with high glucocorticoid use. In immunocompetent host the asexual spores, infective form of fungus is phagocytosed by leucocytes, at instances when immune system is compromised these spores escape phagocytosis, get transformed into hyphae and result in invasive fungal disease. The disease progression is characterized by invasion of vessel wall, thrombosis, ischemia and necrosis of the infected tissue/organ. It usually involves nasal cavity sometimes sinuses are directly involved and then orbital structures and subsequently intracranial cavity with contiguous and blood born infection.<sup>1,2,6,9</sup>

Diabetic patients diagnosed as case of mucormycosis often have history of poor glycemic control with prolonged blood sugar elevation leading to impaired neutrophil function. Ketoacidosis seen in poorly controlled diabetes also contributes to impaired host defenses against infectious agents with acidic pH and elevated blood sugar levels by impairing defense mechanisms. Acidic pH is responsible for dissociation of iron-protein complexes thus iron becoming available for fungal growth. Rhino-cerebral being commonest presentation in diabetics.<sup>2,4</sup>

In the present scenario of COVID-19 pandemic there is complex interplay of the primary disease and preexisting diseases of the host including diabetes, pulmonary and any other systemic illness and secondary infections. COVID-19 disease itself alters the immune system, innate immunity is altered by affecting the T-lymphocytes, CD4+T-cell and CD8+T-cell thereby predisposing to secondary infections both bacterial and fungal. The management and research activities going on all over globe regarding the pathophysiological disturbances, the challenges of management and associated complications including secondary infections.

The steroids used as primary armamentarium in management of COVID-19 disease are known for their secondary effects. In India as per guidelines methyl prednisolone and dexamethasone are being used for 10 days sometimes the duration is extended in patients with extensive pulmonary involvement. Steroids themselves can result in unmasking the prediabetic to diabetic state and impaired blood sugar levels in both diabetics and nondiabetics thus predisposing to secondary infections.<sup>2,4,5</sup>

In the present case, host had history of type-2 diabetes mellitus with no history of any other medical illness, redness of left eye was noted on 10th day of admission which led to suspicion of secondary infection. In the background of COVID-19, steroid and raised blood sugar level fungal infection was suspected which further proved radiologically and by culture. It is very important to keep close watch on secondary events particularly secondary infections even in nondiabetic patients as in present case.

Diagnosis of mucormycosis is usually made on basis clinical features, meticulous systemic examination, imaging modalities too play crucial role and finally by histopathology and culture. Imaging studies, CT scan and MRI play important role in diagnosis and accessing the severity of spread. Depending upon the site and extent of involvement the imaging studies may reveal opacification and erosion of sinus walls, altered tissue signal of the orbital structures, focal intracranial lesions include filling defects of cavernous sinus and focal mass lesion with meningeal signs. Clinically mucormycosis is diagnosed when black necrotic tissue is detected in tissue/organ involved and then confirmed histopathologically. The stains used are periodic acid Schiff (PAS), hematoxylin and eosin and gomori methamine silver (GMS) for detection of fungal structures. Histopathological features reveal nonseptate hyphae which branch at right angles, inflammation usually necrotizing granulomatous and vasculitis along with invasion of vessel wall and lumen by mucor hyphae. Management of mucormycosis confirmed/suspected requires multidisciplinary team management between intensivist, ophthalmologist, oromaxillofacial and neurosurgeon. Surgical debridement to clear the margins is crucial to stop the spread, orbital clearance including enucleation of eye ball, CNS salvage. Equally important is medical management with amphotericin-B preferably liposomal preparation being less toxic is the main stay of treatment. Extensive disease may contemplate second line therapy, combination of amphotericin B with echinocandins result in better efficacy. Second line therapy also includes posaconazole and isavuconazole. Patients intolerant to amphotericin B, posaconazole is given and this drug can be used as add on therapy also.<sup>6-8</sup>

## CONCLUSION

COVID-19 is disease that modulates the immune system and predisposes the host to secondary infections; high degree of clinical suspicion especially in the current pandemic is needed to diagnose this fatal secondary infection at earliest so as to initiate the treatment before the vital structures are involved so as to decrease the mortality and morbidity. Health care professionals involved in COVID care should not ignore the development of new signs and symptoms during the management of COVID-19 disease. Daily evaluation of COVID-19 patients must include the monitoring of vision, ocular movements, pupillary function, sinus discharge, tenderness and any change in sensorium so as to pick up any secondary

infection at earliest. The management protocols need to be reassessed and surveillance for secondary infections and multidisciplinary approach to be included for maximizing the survival rates and there should be judicious use of immunosuppressants with stress on watchful monitoring.

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