

Case Report

Rhino-ocular and rhino-oculo-cerebral mucormycosis; two extremes of clinical spectrum complicating COVID-19 disease: two case reports

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ABSTRACT

Corona virus disease 2019 is associated with wide spectrum of clinical features and secondary events complicating the natural course of disease, including infectious and noninfectious complications. As pandemic is evolving wide range of secondary infections including bacterial and fungal infections complicating the clinical course of COVID-19 disease are being reported, authors report two cases of rhino-orbital and rhino-orbito-cerebral mucormycosis in a patient of COVID-19 pneumonia. Mucormycosis is caused by saprophytic fungi involving nasal passages, sinuses, oral cavity and brain commonly. It is usually seen immunocompromised host and in diabetics with poorly controlled blood sugar level at times normal host though rare. High index of clinical suspicion is needed to suspect and diagnose mucormycosis to maximize the survival as disease is highly fatal because of its angio-invasive pathology.

Keywords: Rhino-orbital, Rhino-orbital-cerebral mucormycosis, Clinical spectrum, COVID-19

INTRODUCTION

COVID-19, a now global pandemic and in spite of extensive efforts no definitive treatment has been proposed till now, except prevention and symptomatic management. COVID pneumonia is clinically characterized by wide clinical spectrum varying from mild illness to life threatening state.¹ Secondary infections are known to be associated with viral diseases including influenza, MERS, SARS involving respiratory system and the clinical course of COVID-19 disease too is complicated by secondary infections, particularly in hospitalized and critically ill patients. Corticosteroids used in COVID-19 disease, to modulate the inflammation and reduce the progression of immune mediated injury and to prevent respiratory failure but is associated with secondary events including immune system modulation, glycemic intolerance and precipitation of latent diabetes and infections. Secondary bacterial and fungal infections develop during the course of COVID-19 disease either primarily or as hospital acquired infections or with use of immunomodulators. Mucormycosis is a rare but

potentially fulminant disease is now being reported complicating the course of COVID-19 disease, worldwide incidence varies in between 0.005 to 1.7 per million, with 0.14/1000 in India which is higher than developed countries. The fatality rate associated with Mucormycosis is 40% globally which significantly increases to 50-80% in immunocompromised host.^{2,3} Early diagnosis and prompt initiation of treatment is of utmost importance as the disease is highly aggressive.

CASE REPORT

Case 1

A 29 year adult diagnosed as case of COVID-19 pneumonia, RTPCR positive for COVID -19, was admitted in our Institute. On examination patient was febrile, dyspneic with room air saturation of 80% hemodynamically stable, investigations revealed total leukocyte count (TLC) 14000, DLC 75/15/6/4 (neutrophil/ lymphocyte/ eosinophil/ basophil), renal function test (RFT), normal liver function test (LFT)

shows mild derangement, D-dimer 650 ng/ml. HRCT chest revealed patchy ground glass appearance with peripheral predominance with CT score of 22/25 (Figure 1 A) with no remarkable history of any medical illness including diabetes mellitus. Patient was managed according to set protocol with injection remdesivir 200 mg iv on first day followed by 100 mg OD per day for 4 days, injection dexamethasone, O₂ supplementation by non-rebreather mask (NRM) mask at rate of 15 litre/min, and broad spectrum antibiotics. On 3rd day of admission blood sugar level was 300mg/dl, managed by regimen of regular and long acting insulin with proper blood sugar monitoring. During the stay in hospital on 8th day patient complained of decreased visual acuity, pain in left eye with nasal stuffiness, periorbital swelling, congestion and lid swelling along with vision reduced to finger counting in left eye was noted (Figure 2 A). CT scan PNS and orbit revealed the findings consistent with fungal infection of bilateral maxillary, ethmoid and frontal sinuses and extension into bilateral orbit and left premaxillary buccal space with sparing of intracranial cavity (Figure 1 A and B). Liposomal amphotericin B along with higher antibiotics were introduced, functional endoscopic sinus surgery (FESS) revealed extensive involvement of left nasal cavity, debridement of maxillary sinus was done and sent for KOH mount and culture, which revealed broad, pauci-septate ribbon, hyaline like hyphae of rhizopus species and culture characteristic growth of fungus (Figure 3 A and B). FESS was repeated after 5 days with debridement and tablet posaconazole 300mg was added. Patient was discharged after 4 weeks on completion of amphotericin B and tab posaconazole continued as per protocol (Figure 2 B).

Case 2

A 50 years old female diabetic patient on oral hypoglycaemic agent (OHA) was diagnosed as case of COVID pneumonia with RTPCR report positive, managed as per standard protocol. On 12th of admission patient complained diminished vision left eye and pain, examination revealed; vision reduced to light perception, B/L proptosis, and conjunctival congestion and maxillary sinus tenderness. MRI PNS and brain with contrast was performed which revealed heterogeneously enhancing altered signal intensity lesion with non-enhancing hypointense areas involving bilateral maxillary, ethmoid, frontal and sphenoid sinuses with invasion of intra and extra-conal compartment of bilateral orbit. Involvement of bilateral optic nerves, extra ocular muscles, orbital apex and left cavernous sinus was noted. Infiltration of left ocular globe with deformed and ruptured left globe was seen. Intracranial extension in left anterior frontal lobe and mild enhancing extradural soft tissue thickening in right frontal lobe noted. Attenuated caliber and luminal irregularity of bilateral cavernous segment of ICA, suggestive of angio-invasion. Mild enhancing asymmetric soft tissue thickening in left cavernous sinus with cavernous sinus thrombosis noted. Non enhancing left inferior nasal turbinate (black turbinate sign) also noted.

Extension of lesion in bilateral retro-maxillary and left oro-maxillary buccal space noted. Involvement of bilateral infra-temporal fossa, bilateral masticator space was seen with bilateral pterygo-palatine fossa and pterygo-maxillary fissures (Figure 4 A and B). Patient was put on injection vancomycin, meropenem and liposomal amphotericin B 5 mg/kg body weight started, multidisciplinary team planned FESS with debridement of involved sinuses and orbital exenteration of left orbit because of extensive involvement. FESS was repeated on alternate days for three consecutive days and orbital exenteration was done on 5th day of admission at our center after stabilization of the vitals (Figure 5). Blood sugar was managed by combination of short acting insulin and long acting insulin, tablet posaconazole 300 mg OD was added as add-on drug. D-dimer level were above upper normal decision was taken to start Anticoagulation with enoxaparin 0.6mg twice daily subcutaneously and subsequently shifted to tablet Apixaban 10mg twice daily through Ryle's tube with regular monitoring of INR, Ryle's tube feeding initiated and symptomatic treatment continued. Patient was discharged after completion of four weeks of liposomal amphotericin B therapy with advice to continue posaconazole and sinus irrigation weekly.

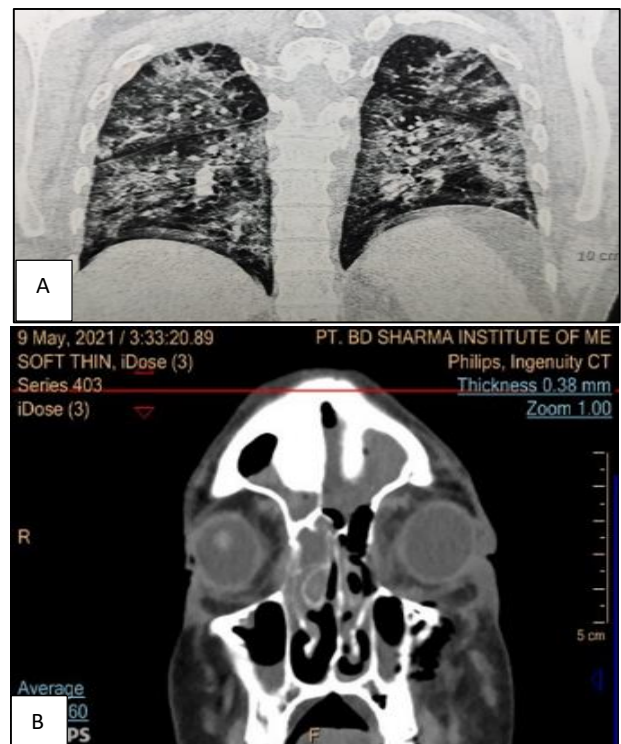


Figure 1 (A and B): Computed tomography (CT) of chest coronal section interlobular and irregular thickening with reticular patterns, multifocal alveolar and consolidative opacities in both lung fields and Coronal section NCCT PNS revealing soft tissue attenuation in B/L maxillary, ethmoid, and frontal sinuses with air locule and extension to medial extra-conal compartments of B/L orbit and left premaxillary space.

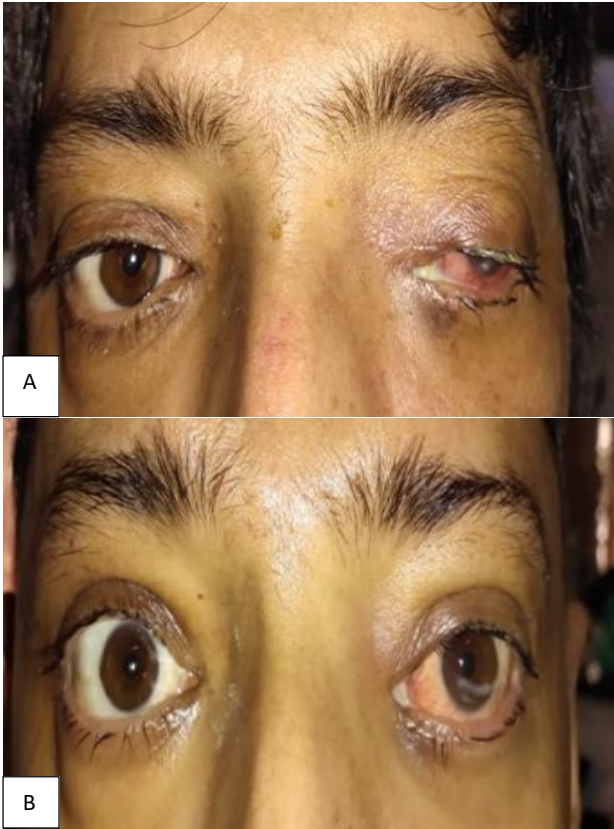


Figure 2 (A and B): Peri-orbital swelling, chemosis with lid edema and regression of the signs.

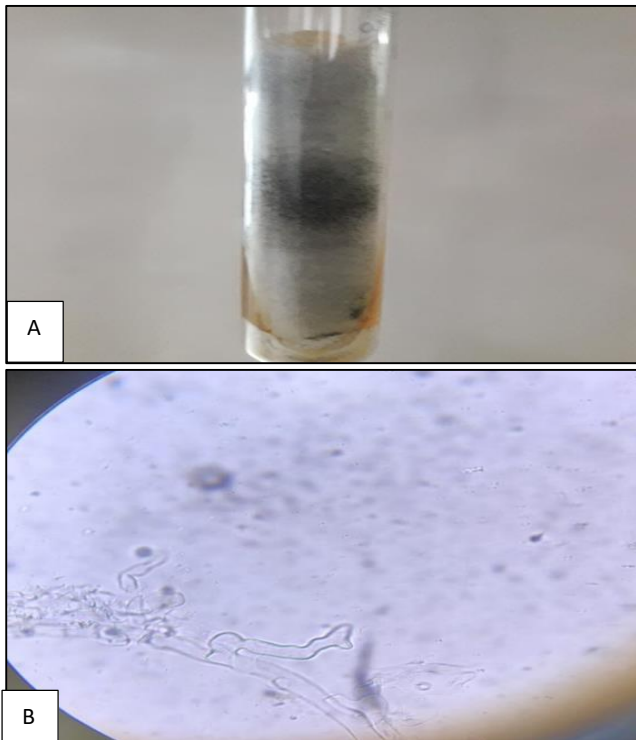


Figure 3 (A and B): SDA tube showing the characteristic greyish cottony growth with black sporulation, and broad, hyaline pauci-septate hyphae on KOH mount.

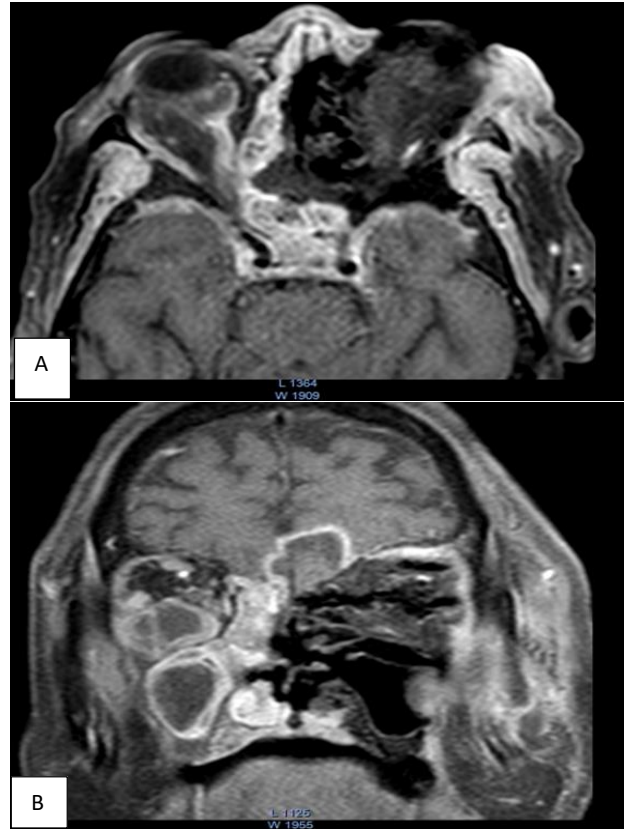


Figure 4 (A and B): Post contrast T1W FS MRI orbit and PNS axial and coronal sections revealing heterogeneously enhancing lesion with non-enhancing hypo intense areas involving B/L maxillary, ethmoid and sphenoid sinuses with invasion of intra and extra-conal compartment of V/L orbit, involvement of bilateral optic nerves, extra ocular muscles, orbit apex, left cavernous sinus with involvement of left ocular globe and intracranial extension. Attenuated caliber and luminal irregularity of B/L ICA and left cavernous sinus thrombosis noted. Non enhancing left inferior nasal turbinate (black turbinate sign) also present.



Figure 5: Post murcormycosis exenteration status of left eye with skin excoriation and edema in right eye.

DISCUSSION

COVID-19 disease is associated with clinical spectrum of mild to severe clinical manifestations, management includes symptomatic care, remedial measures, oxygen and corticosteroids. The use of steroids and immunomodulation associated with COVID-19 disease itself, predispose the patient to invasive fungal disease with mucormycosis as challenging secondary infection.³ Mucormycosis is a fatal infection, acute in onset caused by filamentous fungi of family mucoraceae and usually categorized anatomically depending upon site involved. Involvement of head and neck region can present clinically as nasal, rhino-orbital or more severe form rhino-orbital-cerebral. These fungi are usually opportunistic pathogens found in, soil, vegetation, faces and can be cultured from oral and nasal mucosa. Oral and nasal cavity get infected by inhalation of asexual spore in immunocompetent host these spores are taken care by phagocytic leucocytes, if the host is immunocompromised or has some co-morbidity spores get transformed into hyphae and disease process sets in.^{4,5} Proliferation of the pathogen results in invasion of vessel wall causing ischemia due to thrombosis and finally results in the necrosis of the tissue/organ involved. Infection of the sinuses can be due to direct spread and then by invasion of the orbit and intracranial structures or by hematogenous route. Rhino-orbital-cerebral mucormycosis is the commonest clinical presentation in human host; other forms include pulmonary, cutaneous, gastrointestinal and disseminated, not seen commonly.³

Secondary infections complicate the course of COVID-19, including bacterial and fungal because of complex interplay between the primary disease, the host factors and steroids and the supplemental oxygen.² Immune modulation has been described with COVID-19 disease resulting in reduction in number of T lymphocytes (CD4+T cell and CD8+T cell) and markedly elevated levels of TNF-alpha, IL-2, IL-6, IL-10. Corticosteroids used in COVID-19 disease are also implicated for secondary fungal infection as associated with altered glycemic status even in non-diabetic patients, as one of our case was non-diabetic who received short course of dexamethasone developed rhino-orbital mucormycosis. Genus *Rhizopus* accounting for majority of cases, mucormycosis is usually not seen in immunocompetent host, immunocompromised people are at risk and also host with conditions as diabetes mellitus with poor glycemic control, immunosuppressant use, neutropenia, hematological malignancies, hemodialysis, extensive burns and with high glucocorticoid use.^{6,7} The two case reports present the two clinical extremes of the mucormycosis complicating the COVID-19 disease, at one end patient was young non-diabetic, suspected and diagnosed early, treatment promptly initiated and the left eye was salvaged. On the contrary second diabetic age more than 50 years had more extensive disease when suspected and the left eye needed evisceration and partial loss of vision in right eye. Mucormycosis is characterized

by rapid progression and prognosis is decided by multiple factors including age, co-morbid conditions, and early diagnosis and initiation of treatment.

Clinically if detected early the prognosis and survival rates can be improved by early introduction of anti-fungal drugs and surgical intervention. The clinical presentation varies depending upon the stage and extent of involvement, nasal inflammation with swelling, stuffiness and discharge, maxillary tenderness may be the early features followed by the symptoms depending upon the extent of spread to the orbit and CNS. Orbital involvement is characterized by pain, loss of vision, proptosis, drooping of eye lids and ophthalmoplegia both internal and external and vision loss due to optic nerve involvement or the invasion of retinal vessels.^{4,5} CNS, intracranial infection is due to contagious spread from orbit and sinuses or by blood stream characterized by involvement of cavernous sinus resulting in thrombosis and cranial nerve involvement and focal mass lesions, infarction and meningeal signs. Imaging studies depending upon the region or organ involve reveal filling defects, opacification and erosion of sinus walls, altered signal intensities of orbital components with erosion of walls and focal mass lesions, intracranial focal mass lesions, infarction, filling defects of cavernous sinus and meningeal signal alteration. Diagnosis suspected clinically and on imaging studies is confirmed by histopathology and detection of necrotic tissue with characteristic blackish appearance in the involved organ.^{3,7}

Early diagnosis and treatment play vital role in management of COVID-19 associated complications. The routine physical evaluation of hospitalized patients of COVID-19 disease should include daily monitoring of vision, ocular mobility, pupillary function and sinus tenderness particularly in the patients with diabetes and those receiving steroids. Imaging studies to be planned at earliest depending upon clinical findings, CT and MRI scan plays important in role in detecting the involvement of sinuses, bony wall erosion, orbit and intracranial structures. On histopathology the mucormycosis is confirmed by periodic-acid-Schiff (PAS), hematoxylin and eosin and Gomori-methenamine-silver (GMS) staining with culture in SDA medium and direct microscopy adding on to diagnostic aspect.³

CONCLUSION

Rhino-orbito-cerebral mucormycosis is fatal infection and with CNS involvement mortality rises up to 50%-80%, early diagnosis and multidisciplinary team approach forms the corner stone of management. Surgical intervention includes extensive debridement ensuring clear margins with close coordination between oro-maxillary-facial, neurosurgeon and ophthalmologist equally important the medical management and critical care support. Amphotericin B is accepted as drug of choice, liposomal form being less toxic and renal

functions need to be monitored during the therapy because of nephrotoxicity. Combination therapy which includes echinocandins and amphotericin B is considered in extensive disease as second line therapy. Posaconazole, triazoles and isavuconazole are also second line antifungal drugs, posaconazole being used as add on drug and in step-down phase in current epidemic in India. Anticoagulation is now being equally recommended to be used in moderate to severe case. The use of anticoagulation is associated with positive outcome by decreasing both severity and incidence of thrombosis and improving the outcome. Sepsis induced coagulopathy (SIC) scoring system and D-dimer level are being currently used for induction of anticoagulation in COVID-19 disease though specific and final guidelines not proposed yet.

High index of clinical suspicion for secondary events including secondary infections, fungal infections in particular in COVID-19 disease is important to decrease the morbidity and mortality. Patients with comorbidities as diabetes in particular and with corticosteroid used as treatment modality need to be evaluated daily so that any secondary infection is detected and managed as early as possible.

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