Case Series

Epidemic in pandemic: Fungal sinusitis in COVID-19

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Abstract

Objective: To describe the clinical pattern of invasive fungal sinusitis in COVID-19 and post-COVID-19 cases. **Methods:** All patients affected by COVID-19 or having a history of COVID-19 infection with an invasive fungal lesion (mucormycosis/aspergillosis) of the paranasal sinuses, orbit, palate, brain, lung, skin/cheek, and dental has been evaluated for possible description in tertiary care hospital in May 2021. **Results:** Twenty-four patients presented with clinical signs and symptoms of fungal infection with a history of COVID-19. Paranasal sinuses were involved in all patients. Palatal involvement was seen in seven cases. Intraorbital extension was seen in 13 cases. Intracerebral involvement was seen in three cases. Comorbid type 2 diabetes was seen in 20 patients. The use of steroids was noticed in 16 cases. Our observation revealed that uncontrolled diabetes, overuse of steroids, increased ferritin levels, and low hemoglobin percentage are the main factors aggravating mucormycosis.

Keywords: Amphotericin B, COVID-19, invasive mucormycosis, paranasal sinuses, steroids

Introduction

The coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was identified first in Wuhan, China. Till today, complete information on COVID-19 sequelae is not available.[1] COVID-19 pandemic has been associated with otorhinolaryngological features like anosmia in the earlier phase till the late-presenting mucormycosis as invasive fungal sinusitis.[2] It takes around 4 weeks for the hyphal invasion and symptoms to emerge and get noticed.[3] Uncontrolled diabetes, immunosuppression, acquired immunodeficiency syndrome (AIDS), and underlying malignancies are the important predisposing factors in developing invasive fungal sinusitis, i.e., Mucormycosis infection.[4] It is observed that *Mucoraceae* member, *Rhizopus oryzae* is the most common cause of this infection. The prime characteristic feature of mucormycosis is the angioinvasion resulting in thrombosis and tissue necrosis.[5]

On clinical examination, in most of the rhino mucormycosis, patients presented with similar regular complaints of sinusitis like nose block, crust formation, proptosis, facial edema and pain, and eye pain.[6] A black eschar may be noticed in the nasal cavity or over the hard palate.[7] When the infection spreads to intracranial, neurological signs and symptoms such as fever and headache manifest.[6] In histological findings, there will be mycotic infiltration of blood vessels, tissue infarction, hemorrhage, and neutrophil infiltration.[8] In 50%–80% population, there were intracranial and orbit complications developing due to delayed diagnosis. Even though promptly treated, mortality rates were gradually increasing because of the rapid progression of the disease.[9] In the second wave of the pandemic, there is a rapid shoot-up of invasive fungal sinusitis cases, primarily mucormycosis. In our tertiary care teaching

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hospital also, a similar surge in mucormycosis was observed. Here, we would like to present our sinonasal mucormycosis case experiences of the first 24 cases operated in 1 month. All 24 patients had a history of COVID-19. Our study raises awareness to the primary care family physicians in approaching and treating the mucormycosis patients as they are the bridging source to the patients and tertiary care institutes.

Cases

A series of cases that were reported at the All India Institute of Medical Sciences, Raipur, India in May 2021 was evaluated and described. A total of 24 patients got admitted with chief complaints of facial edema, nasal crusting, and orbital swelling. All cases were diagnosed as invasive fungal sinusitis specifically mucormycosis and supported by clinical, radiological findings along with potassium hydroxide (KOH) mount. All the patients had COVID-19-positive history and were somewhere currently in treatment. The patient's geographical data, comorbidities, COVID treatment history, COVID vaccination status, and clinical findings were tabulated [Tables 1 and 2].

Management of mucormycosis cases

Patients with signs and symptoms suggestive of mucormycosis are confirmed using KOH mount microscopy and culture [Figure 1]. Patients undergo diagnostic nasal endoscopy for the sampling of nasal discharge and crusts. Liposomal Amphotericin B is the antifungal of choice used at a 5–10 mg/kg body weight dose. The extent of the disease is evaluated using contrast-enhanced CT and MRI at the time of admission. The principle of early and aggressive surgical debridement within 1–2 weeks is followed. The ethmoid sinus is the most commonly involved sinus with the lesion extending to orbit, maxillary sinus, frontal sinus, sphenoid sinus, hard palate, frontal, parietal, and temporal lobe.

Patients presenting with the limited disease are operated on via functional endoscopic sinus surgery. The extensive disease requires an external approach via lateral rhinotomy using Moore's incision with occasional lip split. Medial maxillectomy and turbinectomy are performed on the involved side. Patients with extraconal orbital involvement are managed using decompression of the medial wall of the orbit, whereas patients with radiologically and clinically confirmed intraconal disease and loss of vision are managed using orbital exenteration. A prosthodontist takes dental impressions before surgery for patients with palatal involvement. Infrastructure maxillectomy with obturator placement is the preferred procedure in cases with palatal involvement. Intracranial extension of mucormycosis needs debridement and craniotomy by neurosurgeons [Figures 2 and 3].

Liposomal amphotericin B is the antifungal of choice in the postoperative period, with the cumulative target dose being 2 to 3 g for complete treatment. Twice daily nasal douching and endoscopic suctioning are done as a part of postoperative cavity care. Patients undergoing craniotomy for intracranial extension are managed using mannitol, levetiracetam, and higher antibiotics.

Table 1: Demographic data

Demographic data	Distribution *n* (%)
Age (years)	
<30	0 (0)
31-40	2 (8.3)
41-50	6 (25)
51-60	8 (33.3)
61-70	6 (25)
71-80	2 (8.3)
Sex	
M	17 (70.8)
F	7 (29.2)
Socioeconomic status	
Low	22 (91.7)
Moderate	2 (8.3)
Comorbidities	
Type 2 DM	20 (83.3)
Hypertension	11 (45.8)
Multiple comorbidities	2 (8.3)

Table 2: Organ-related signs and symptoms in mucormycosis cases

Organs involved
1. Para nasal sinuses - 24
2. Orbit -- 13
3. Palate -- 07
4. Brain -- 03
5. Teeth & gum -- 04
6. Cheek skin -- 03

Symptoms
1. Nasal crusting -- 15
2. Nasal discharge -- 15
3. Facial edema/ swelling -- 22
4. Facial pain -- 22
5. Cheek numbness -- 14

Eye Symptoms & Signs
1. Normal vision -- 13
2. Partial loss of vision -- 04
3. Complete loss of vision -- 07
4. Normal eye movements -- 14
5. Restricted eye movements -- 10
6. Chemosis -- 09
7. Proptosis -- 15
8. Ptosis -- 15

Lung Involvement-fungus
1. Yes -- 01
2. No -- 23

Dental problems
1. Dental loosening -- 08
2. Dental pain -- 09
3. Palatal crusting -- 09
4. Palatal perforation -- 04

Artificial eye prosthesis is provided to patients undergoing orbital exenteration after healing and fibrosis of the orbital cavity. Out of 24 patients, three patients died in post-op in between the 3rd to 5th day because of septicemia and the remaining are in the recovery stage with treatment ongoing. A total of four COVID-19-positive mucormycosis patients have been operated on at our institute until now.

Discussion

The second wave of COVID-19 infections has seen an alarming rise of mucormycosis cases throughout the globe. A spectrum of clinical and radiological presentations of this previously rare fungal disease is being reported every day. Mucormycosis is an aggressive fungal infection belonging to

the Mucorales family, found in immunocompromised diabetics.[10] It is a rare syndrome, with rhinoorbital disease being the most common presentation. Few cases of mucormycosis surfaced in 2019. The sudden surge in mucormycosis cases in the second wave of COVID-19 suggests a strong correlation between COVID-19 and mucormycosis [Table 3]. COVID-19 infection is known to cause lymphopenia with a decrease in both CD4, CD8 T cells leading to suppressed immunity.[11] The misinterpretation of the hallmark randomised evaluation of COVID-19 therapy (RECOVERY) trial to rampant use of steroids caused further immunosuppression. Steroids cause impaired leukocyte migration due to decreased production of cytokines and chemokines. Various opportunistic infections such as candidiasis are commonly seen even with the use of topical steroids.[12] Mucormycosis requires an iron-rich environment. It is prevalent in patients treated with desferrioxamine, an iron chelator.[13] An inflammatory reaction to COVID 19 causes a rise in acute phase reactants such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin. Patients with diabetic ketoacidosis have a low-blood pH causing proton-mediated displacement of ferric ions from serum carrier molecules contributing to the iron-rich environment and reduced immunity.[14] In our case series, all cases had elevated ferritin levels, and the majority of them were diabetic. Multiple interplays of factors with preexisting comorbidities such as COVID-19 infection, injudicious use of steroids and antibiotics, high ferritin levels, decreased hemoglobin levels, uncontrolled diabetes, and reduced immunity are being identified for the rise in mucormycosis cases. Patients affected by COVID-19 and those who required oxygen therapy or were admitted to intensive care units for longer durations were also more prone to develop the fungal disease. In the present study, it was observed that 23 patients did not take the COVID-19 vaccine. Diabetic control and screening of early symptoms of Mucormycosis are necessary for COVID-19 patients. Early diagnosis using

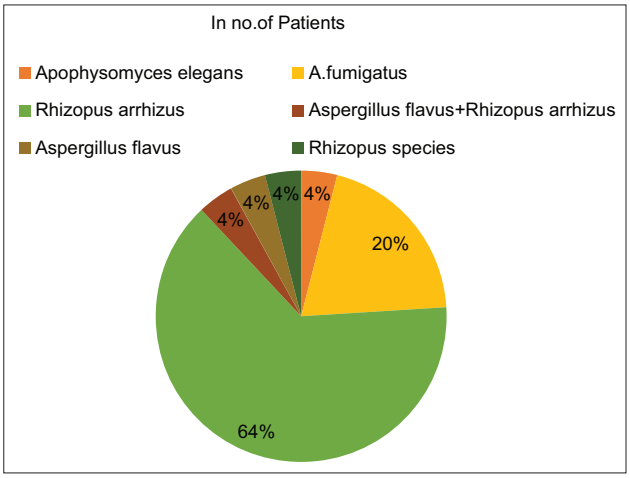

Figure 1: Part a: variants of mucormycosis

Table 3: COVID-19 and fungal infection risk factors

Parameters	Numbers (%)
COVID symptoms	
URTI (cough, cold, sore throat, nose block)	8 (33.3)
Shortness of breath	15 (62.5)
Asymptomatic	1 (4.2)
Oxygen support	14 (58.3)
Use of steroids	16 (66.7)
Use of REMDESIVIR	11 (45.8)
Duration of hospital stay	
<5 days	1 (4.2)
6-10 days	6 (25)
11-15 days	6 (25)
>15 days	9 (37.5)
Days between post COVID and symptoms of fungal infection	
<5	4 (16.7)
5-10	6 (25)
11-15	3 (12.5)
16-20	3 (12.5)
21-25	1 (4.2)
26-30	2 (8.3)
>1 month	5 (20.8)

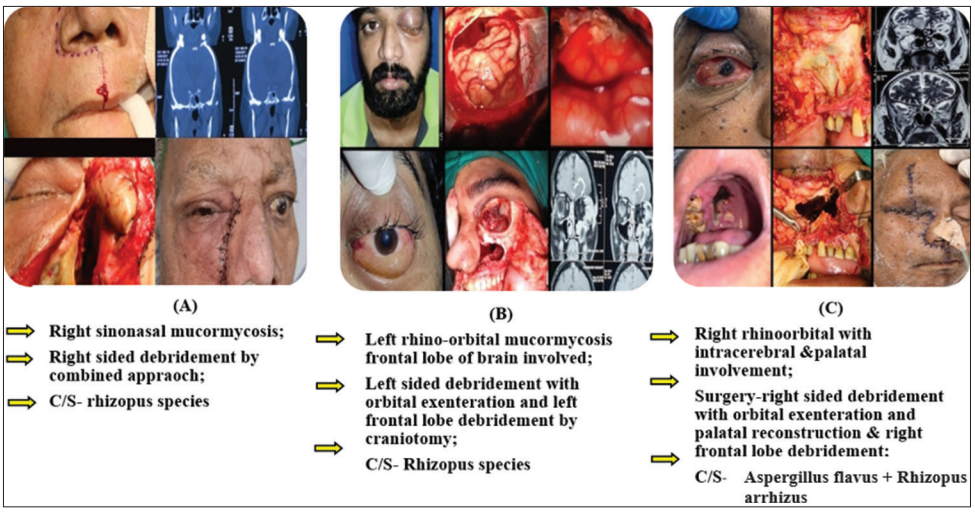

Figure 2: Part A–C: sinonasal, rhino-orbital, intracerebral, and palatal mucormycosis

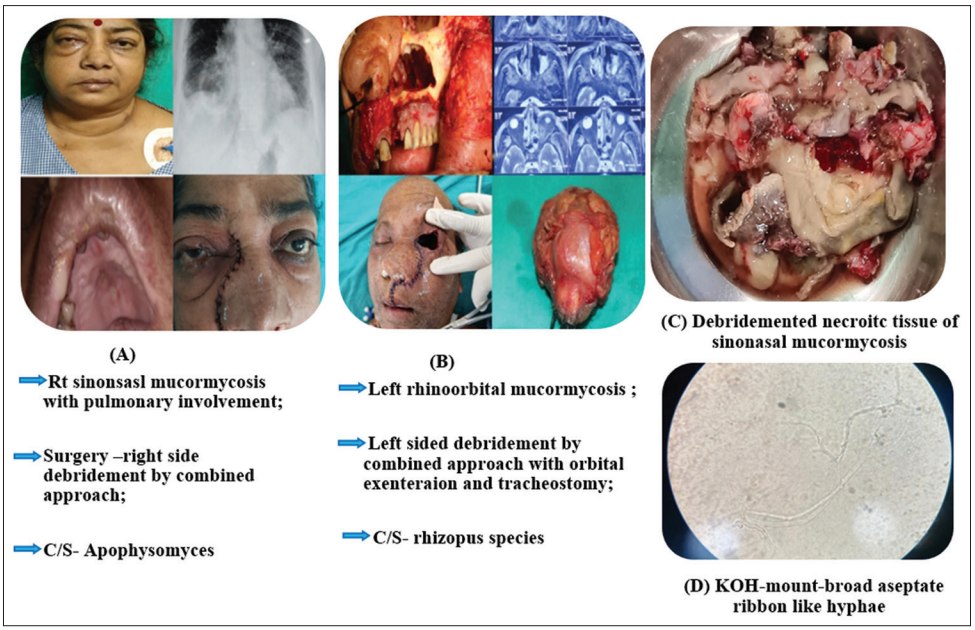

Figure 3: Part A–D: pulmonary involvement, rhino-orbital, necrotic tissues, and aseptate hyphae

fungal KOH mounts, nasal endoscopies, imaging is crucial in managing COVID-19-associated mucormycosis. Aggressive surgical debridement, antifungals, and diabetic control are vital in reducing mortality and morbidity among the patients. Early suspicion based on clinical history and examination is essential for the primary care physicians keeping in mind the increasing incidence and grave prognosis of the untreated disease. A high suspicion will facilitate early referral of patients to centers providing surgical and medical management thereby reducing mortality and morbidity of the disease.

Conclusion

We propose that COVID-19 is associated with multiple secondary fungal infections because of immune dysregulation, widespread use of steroids, high glycemic index, prolonged hospital stay in intensive care units, and increased ferritin levels. These factors are highly aggravating the illness. Treating clinicians must be aware of all these factors and should opt for early surgical interventions along with antifungal medications for a good prognosis. Thus, declining mortality and morbidity rates. The use of drugs should be carefully monitored to achieve therapeutic efficacy at lower doses for shorter durations. Unnecessary use of antibiotics, specifically in the absence of infection, should be re-evaluated to reduce unwanted secondary infections. Mucormycosis was previously a rare disease, but the recent spike in the cases has made it an important differential for the primary care physician. Patients presenting with sinonasal and ocular complaints and a history of COVID-19 and diabetes mellitus should undergo further workup and evaluation on the lines of COVID-19-associated mucormycosis along with symptomatic management. This research article highlights that sinusitis and routine nasal complaints should not be ignored as there might be chances of mucormycosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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