

Occurrence of Mucormycosis in Setting of Covid 19 - A Prospective Observational Study

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Abstract

Coronavirus disease 2019 (COVID-19), an infectious disease caused by newly discovered novel severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), affecting millions of people worldwide. During the coronavirus pandemic, A sudden surge of sino-nasal mucormycosis has been observed in post-Covid patients or Covid patients, especially in former group. A prospective observational study was undertaken in department of Radio-Diagnosis at Jawaharlal Nehru medical college, Sawangi, Wardha, India on 30 patients over a period of 45 days, who had either tested SARSCOV-2 positive with RTPCR or who had recovered from Covid-19 infection and underwent CECT Paranasal sinus study for clinical suspicion of rhinosinusitis or orbital cellulitis showing features of invasive sinusitis and its complications. All the patients showed involvement of one or more sinuses. Ethmoid sinus was the most commonly involved sinus in our study which was seen in 29 (96.6%) of patients, while bilateral involvement was slightly more in maxillary sinuses i.e 22 patients(73.3%) as compared to ethmoid sinus which was seen in 21 (70%) patients. Majority of the patients were affected on left sided sinuses i.e. 20 patients (66.6%), whereas 13(43.3%) patients were affected on right side. A total of 25 (83.3%) of patients showed involvement of nasal cavity, of which 16(64%) had bilateral nasal cavity involvement, while nasal cavity were not involved in 5 (16.7%) patients. Of these 30 patients, 16 (53.3%) patients developed orbital cellulitis, more on left side. Cavernous sinus thrombosis was seen in 2 patients. 19 (63.3%) patients underwent Sino-nasal surgery and were confirmed having mucormycosis on histopathological examination. Rest of the patients diagnosed with mucormycosis showed radiological and microbiological evidence of mucormycosis and were treated medically. We concluded early diagnosis of Sino-nasal mucormycosis and ROCM with help of early clinical suspicion and available imaging modalities is possible and should be practiced.

Key words: Coronavirus 2 (SARS-CoV-2), Mucormycosis, orbital sinusitis, CECT PNS.

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Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by newly discovered novel severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), affecting millions of people worldwide. There have been a variety of complications reported during and post COVID infection[1]. Mucormycosis occurs relatively commonly in patients with certain predisposing medical conditions such as immunosuppression and diabetic ketoacidosis. Mucormycosis infiltrates the vascular lamina, causing infarction and necrosis as well as inflammation[2]

During the ongoing coronavirus pandemic, A sudden surge of sino-nasal mucormycosis has been observed in post-Covid patients or Covid patients, especially in former group[3].

Fatality rates for severe Mucormycosis infections can be close to 100% despite various active treatments [4]. Mucormycosis is associated with high mortality (>50%) and disability rates. Early diagnosis and initiation of therapy significantly improves survival and decreases morbidity. Advances in clinical laboratory methods also may provide an earlier diagnosis. Recognition of risk factors is a key element for early clinical diagnosis of mucormycosis[5]

Multiple studies have shown that there is correlation of Covid-19 and Sino-nasal mucormycosis. In many cases orbital and intra-cranial complications were associated with mucormycosis in post Covid infection status.[6-7]

Because of the involvement of para-nasal sinuses and its rapid extension into orbital and intracranial spaces, Non-invasive imaging like CT / MRI are strongly recommended in suspected COVID-19 cases, for both early evaluation and follow-up.[8] In the present study, a total of 30 patients who presented with Sino-nasal mucormycosis or ROCM, who were

SARSCov2 positive and were admitted to the tertiary care were studied.

Materials and Methods:

Study design The present study is a prospective observational study. Which was undertaken in patients presenting to the outpatient department or referred from the inpatient department to the Department of Radio-Diagnosis at Jawaharlal Nehru medical college , Sawangi , Wardha, India

Site of study The study was conducted over a period of 45 days in months of April- May 2021.

Sample size- The patients presenting to the department of radio diagnosis and satisfying the inclusion criteria between the study duration were considered for the study. A total of 30 patients were studied in the present study.

Inclusion Criteria

- Patients with Clinical suspicion of Sino-nasal mucormycosis
- The patients who were either tested SARSCOV2 positive with RTPCR or who had recovered from Covid-19 infection and underwent CECT Paranasal sinus study for clinical suspicion of rhino-sinusitis or orbital cellulitis and showed features of invasive sinusitis and its complications, were included in the study.

Exclusion criteria

- Patients not giving consent for the study were excluded from the study

Data collection

The clinical details, co-morbidities details, imaging findings, were obtained and recorded using a semi structured questionnaire.

Data analysis

The data was collected and entered in MS excel and analyzed using OPEN EPI 3.2.1

software, the continuous variable were presented in proportion and percentages.

Ethical clearance was obtained from the institutional ethical committee with ethical certificate number

Imaging procedure

The patients in the present study, underwent contrast enhanced CT scan of paranasal sinuses and orbits.

CECT PNS of all patients were done using GE 16-slice scanner. With patient in supine position, axial CT images were obtained parallel to the hard palate from the roof of frontal sinus to the level of hard palate. Extended cranial and caudal sections were obtained wherever required. The images were obtained with a slice thickness of 3 mm and reconstructed to axial, coronal and parasagittal planes at an interval of 1 mm. Scanning parameters included a tube potential of 130 kV and an average tube current of 55 mA. Non-ionic Iodinated IV contrast (Ultravist 300 mg I/mL, at 1.5 cc/Kg) was administered to all patients.

The CECT findings suggesting invasive fungal sinusitis were soft tissue densities partially or completely opacifying sinus cavities or nodular mucosal thickening in sinus cavities with absence of fluid levels. The invasive features of the disease were seen in form of focal bony erosion or

destruction with infiltration into extrasinus soft tissues. Increased attenuation, bulk and streaking of extrasinus soft tissues and fat was suggestive of extra sinus infiltration, these features could be especially appreciated in pre and retro antral spaces. CECT findings suggestive of orbital cellulitis were increased bulk and attenuation of intra-orbital fat (either extra-conal, or both extra and intra-conal fat) and/or extra-ocular muscles. Involvement of cavernous sinus thrombosis was seen in form of non-enhancement of the cavernous sinus with flattening or bulging of lateral wall of cavernous sinus.

Results

In the present study, out of the total selected 30 patients, only two (6.6%) patients were SARS CoV2 positive at the time of presentation (proven with Covid-RT-PCR test done in our hospital laboratory) and remaining 28 (93.4%) patients had recent history of Covid disease, treated and recovered. Out of total of 30 patients, majority i.e. 20 (66.7%) were male and 10 (33.3%) were female patients. A total of 26 (86.6%) of the patients had comorbidities, 7 (23.3%) patients had both diabetes and hypertension and 12 (40%) had only diabetes, 7 patients (23.3%) had only hypertension. 4 patients (13.4%) had no co-morbidities.

Table 1: showing the frequency of the Co-morbidities in the study subjects table 1.

Comorbidities	Frequency
No comorbidities	4 (13.4%)
Diabetes Mellitus + Hypertension	7 (23.3%)
Only Diabetes Mellitus	12 (40%)
Only Hypertension	7 (23.3%)
Total	30(100%)

All the patients showed involvement of one or more sinuses at the time of presentation (Table 2). Ethmoid sinus was the most commonly involved sinus in our study which was seen in 29 (96.6%) of patients, while bilateral involvement was slightly more in maxillary sinuses i.e. 22 patients (73.3%) as

compared to ethmoid sinus which was seen in 21 (70%) patients. Majority of the patients were affected on left sided sinuses i.e. 20 patients (66.6%), whereas 13 (43.3%) patients were affected on right side. A total of 25 (83.3%) of patients showed involvement of nasal cavity, of which 16 (64%) had bilateral

nasal cavity involvement, while nasal cavity were not involved in 5 (16.7%) patients. (table 2)

Table 2: Showing the details of involvement of one or more sinuses at the time of presentation

SINUS	BILATERAL INVOLVEMENT	ONLY LEFT SIDE	ON RIGHT SIDE	NOT INVOLVED
Maxillary	22 (73.3%)	3 (10.0%)	3 (10%)	2(6.7%)
Ethmoid	21 (70%)	4 (13.3%)	4 (13.3%)	1 (3.4%).
Sphenoid	15 (50%)	6(20%)	2(6.7%)	7 (23.3%)
Frontal	9(30%)	7 (23.4%)	4 (13.3%)	10 (33.3%)
Nasal cavity	16 (53.3%)	5(16.7%)	4 (13.3%)	5 (16.7%)

Of these 30 patients, 16 (53.3%) patients developed orbital cellulitis, 56.25% had left sided (9/16 patients) involvement was more than right side which was 43.76 % (7/16) . Cavernous sinus thrombosis was seen only in 2 patients. 19 (63.3%) patients underwent Sino-nasal surgery and were confirmed having mucormycosis on histopathological examination. Rest of the patients diagnosed with mucormycosis showed radiological and microbiological evidence of mucormycosis and were treated medically.

Discussion

In the present study we found that Ethmoid sinus was the most commonly involved sinus, while bilateral involvement was slightly more in maxillary sinuses, Majority of the patients were affected on left sided sinuses. 83.3%of patients showed involvement of nasal cavity.

In a study by Moorty et al[9] all the 18 patients in the study presented with symptoms of maxillary sinusitis. Loss of vision was noted in 12 of the 18 patients (which was not statistically significant) and 7 of them underwent orbital exenteration .

In a study by Aranaiz et Al [10] the most common type of mucormycosis seen was rhino-cerebro-orbital mucormycosis (44–49%), followed by cutaneous (10–19%),

pulmonary (10–11%), disseminated (6–11%) and gastrointestinal (2–11%).

In study by Patel A et al¹¹ It had been shown that rhino-orbital mucormycosis was the foremost common (315/465, 67.7%) presentation followed by pulmonary (62/465, 13.3%), cutaneous (49/465, 10.5%). In another study done in Japan by Kazuhiro Nomura et al [12] The most commonly involved sinus was the maxillary sinus (86/104, 82.7%) followed by the sphenoid sinus (11/104, 10.6%).

In a study by Nehara HR et al [13] , 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.

Previously the incidence of fungal infection was seen during the SARS-CoV infection pandemic in the year 2003 and was reported to range from 14.8% to 27%. The present SARS-CoV virus responsible for corona pandemic shares similar species as SARS-CoV with similar biological and clinical characteristics. [14]

Initial cases reporting association of Covid-19 and rhino- orbital mucormycosis were published in September 2020 by Mehta - Pandey and Wethman-Ehrenreich separately. [14]. Since then many similar case or case series have been published reporting sino-nasal mucormycosis or ROCM in covid-19 infected cases.

According to Garg D, et al , in a case report of corona-virus associated pulmonary mucormycosis with systematic review of association of coronavirus with mucormycosis (involving lung, Sino-nasal or other organs), the authors identified multiple studies describing mucormycosis in association with COVID-19. The Corona virus may cause immune dysregulation and the treatment with immunomodulatory drugs could be the predisposing risk factor for emergence of the fungal infections [15].

A case series report of 10 patients by Mishra N et al. highlighted the possibility of a correlation between COVID-19 and rhino-orbito-cerebral mucormycosis infections. The authors propose that the increased susceptibility of corona infected patients to mucormycosis is due to secondary impairment of barrier defense, phagocytes and lymphocytes dysfunction and the use of immunosuppressive medications [16]

Multiple studies have suggested the association between diabetes mellitus and mucormycosis. In our study more than 50% cases were diabetics. Recent publication by Sharma et al¹⁴ reported case series of 23 Covid patients presenting with Sino-nasal mucormycosis. In their case series 21/ 23 patients had diabetes. Our findings match with the findings of Sharma et al showing association and rising incidence of mucormycosis and covid-19 disease patients, which also suggests that the covid-19 patients with diabetes have increased risk of fungal infections.

A systematic review conducted by John et al and Awadhesh Kumar Singh et al has

reported confirmed cases of mucormycosis in patients with Covid-19 infections. The study findings suggest a triad of mucormycosis, diabetes and steroid therapy in people with COVID-19 [17,18].

In their study Awadhesh kumar singh A K Singh et al suggests Diabetes and corticosteroid therapy as two triggering factors, amongst many triggering factors, causing precipitation of mucormycosis in patients with Covid-19. Endothelial damage and reduction in CD4+ and CD8+ level caused by Covid-19 , predisposes to secondary or opportunistic fungal infection. Also in diabetes high blood glucose concentration enhances fungal growth [17,18].

Extra sinus extension to orbit and brain causing Rhinocerebral mucormycosis begins from infected nasal and sinus mucosa. Commonest route to orbital extension is through nasolacrimal duct, ethmoid orifices or dehiscent medial orbital wall[19]. Intracranial extension can occur along perivascular channels and through cribriform plate and orbital apex [20,21].

The involvement of Sino-nasal region by mucormycosis and its extra-sinus extension can be diagnosed well and in early stages by non-invasive radiological investigations like CT or MRI scans [19]. The CT and MRI shows mucosal thickening with absence of air-fluid level in the infected sinuses. Destruction of bony sinus walls are well appreciated on CT. Features of ipsilateral cavernous sinus thrombosis and partial or complete occlusion of internal carotid artery can also be evaluated by imaging [19,20]. Extrasinus invasion like orbital involvement, pre and retro antral , infratemporal invasion, perineural invasion and intracranial complications like venous sinus or arterial thrombosis are better evaluated on MRI, as it provides better soft tissue resolution.



[Figure 1-a]

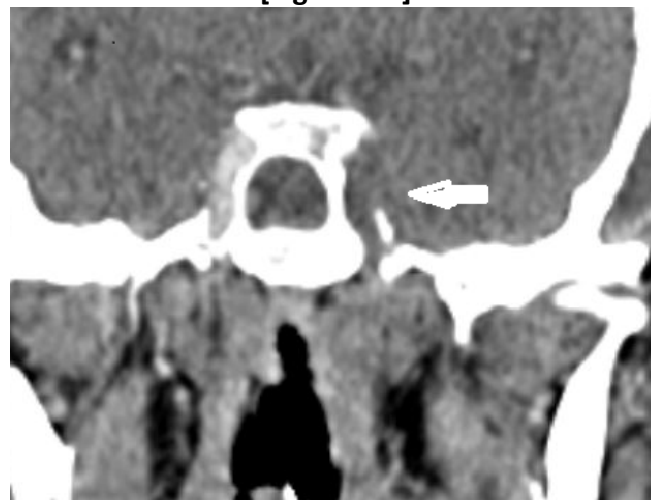


Figure-1[b]

Figure 1: Contrast enhanced computed tomography images of left cavernous sinus thrombosis- (a) axial and (b) coronal images, showing a bulky left cavernous sinus with a convex lateral margin and post contrast filling defect in cavernous sinus (arrows). The right cavernous sinus shows normal post contrast enhancement

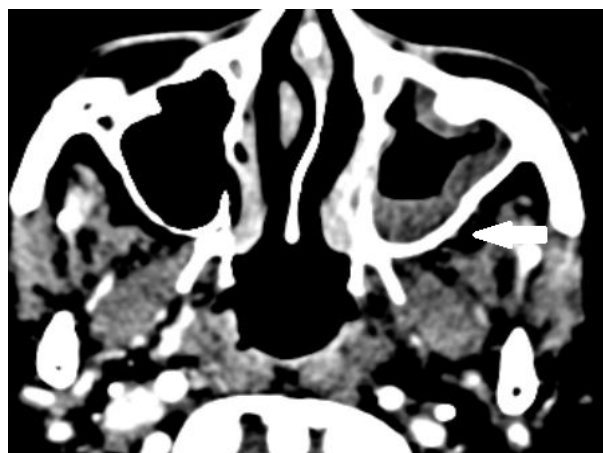


Figure 2: Left maxillary fungal sinusitis- Unenhanced axial computed tomography image showing mucosal thickening in left maxillary sinus (arrow) which was proved on KoH study to be mucormycosis.



Figure 3 -a



Figure 3-b

Figure 3: Right invasive mucormycosis . (a) Axial computed tomography Bone window image showing destruction of maxillary bone on right side (white arrow). (b) Coronal computed tomography Bone window image showing destruction of medial wall of opacified right maxillary sinus (white matter).



Figure 4: Left orbital cellulitis- Contrast enhanced computed tomography axial image showing increased bulk and attenuation of medial extraconal fat in left orbital cavity.

Conclusion

Early diagnosis of Sino-nasal mucormycosis and ROCM with help of early clinical suspicion and available imaging modalities is possible and should be practiced, especially in setting of predisposing factors like Covid disease infection and diabetes mellitus, which can help clinicians to take timely decisions and interventions, helping to reduce the morbidity and mortality.

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