

Rhino-Orbito-Cerebral Mycosis and COVID-19: From Bad to Worse?

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Abstract

Background: There has been an increase an alarming rise in invasive mycoses during COVID-19 pandemic, especially during the second wave. **Aims:** Compare the incidence of invasive mycoses in the last three years and study the risk factors, manifestations and outcomes of mycoses in the COVID era. **Methodology:** Multicentric study was conducted across 21 centres in a state of western India over 12-months. The clinico-radiological, laboratory and microbiological features, treatment and outcomes of patients were studied. We also analysed yearly incidence of rhino-orbito-cerebral mycosis. **Results:** There was more than five-times rise in the incidence of invasive mycoses compared to previous two-years. Of the 122 patients analysed, mucor, aspergillus and dual infection were seen in 86.9%, 4.1%, and 7.4% respectively. Fifty-nine percent had simultaneous mycosis and COVID-19 while rest had sequential infection. Common presenting features were headache (91%), facial pain (78.7%), diplopia (66.4%) and vision loss (56.6%). Rhino-orbito-sinusitis was present in 96.7%, meningitis in 6.6%, intracranial mass lesions in 15.6% and strokes in 14.8%. A total of 91.8% patients were diabetic, while 90.2% were treated with steroids during COVID-19 treatment. Mortality was 34.4%. **Conclusion:** Invasive fungal infections having high mortality and morbidity have increased burden on already overburdened healthcare system. Past illnesses, COVID-19 itself and its treatment and environmental factors seem responsible for the rise of fungal infection. Awareness and preventive strategies are the need of hours and larger studies are needed for better understanding of this deadly disease.

Keywords: Rhino-orbito-cerebral mycosis, invasive fungal infection, mucormycosis, COVID-19

INTRODUCTION

In the ongoing coronavirus 19 (COVID-19) pandemic, due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), different clinical manifestations have been described over time. Initially, it was thought to be a predominantly respiratory disease, but later prothrombotic and other extrapulmonary manifestations have been described. Initial central nervous system (CNS) manifestations described were encephalopathy and anosmia. Later ischemic cerebrovascular events and neuromuscular manifestations were described. Post COVID-19 manifestations described are Guillain-Barre syndrome (GBS), acute disseminated encephalomyelitis (ADEM), and mononeuropathies.

Secondary bacterial or fungal infections during or after COVID-19 are not uncommon.^[1] Most common invasive fungal infections with COVID-19 are pulmonary aspergillosis and rhino-orbito-cerebral syndrome due to mucor-mycosis. Multiple case-reports and case-series

describe the rhino-orbito-cerebral syndrome leading to variable involvement of nose, paranasal sinuses, orbit, and intracranial structures including vessels following COVID-19 infection.^[2-8]

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Submitted: 25-May-2021 **Revised:** 14-Jun-2021 **Accepted:** 24-Jun-2021

Published: 23-Aug-2021

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DOI: 10.4103/aian.aian_463_21

India is the second-most affected country due to COVID-19 infection.^[9] India also has the second largest population of diabetes mellitus which is a known risk factor for invasive fungal infections^[10] and the highest burden of mucor in the world (140 cases per million population).^[11] Thus, it is expected that India will have many cases of this disease.^[6] In a recent article by John *et al.*,^[5] 71% of cases of mucor-mycosis with COVID-19 were reported from India. Since the onset of the COVID-19 pandemic, especially during the second wave in India, we have seen a steep rise in rhino-orbito-cerebral mycosis in COVID-19 patients. In the following study, we describe our observations.

METHODOLOGY

This is a retrospective, observational, and multi-centre study conducted by Maharashtra Association of Neurology (MAN) in association with allied specialists who looked after our subjects. Our study was conducted between May 2020 and April 2021 over a 12-month period in Maharashtra which is a state in Western India which has so far reported the maximum number of COVID-19 patients in India. Consecutive cases of laboratory confirmed rhino-orbito-cerebral mycosis cases with or after COVID-19 infection in from 21 centres in Maharashtra, India were included.

The incidence of hospital admissions of rhino-orbito-cerebral fungal infection for 2 years prior to the study period (May 2018 to Apr 2020) was calculated from electronic medical records (EMRs) of Deenanath Mangeshkar Hospital, Pune, India and was compared with incidence in the study period.

The fungal infection occurring within 60 days of onset of COVID-19 infection was considered post-COVID-19. Rhino-orbito-cerebral mycosis was defined as laboratory proven fungal infection of nose, paranasal sinuses, orbit, and/or intracranial structures due to mucor-mycosis or aspergillus or both. Diagnosis was achieved by potassium hydroxide (KOH); calcofluor stain of tissue obtained from scrapping from nose, palate, or paranasal sinus; histopathology of biopsied tissue; and/or fungal growth in cultures. Patient demographics, clinical laboratory, radiological and microbiological features, treatment, and outcomes were analyzed.

C-reactive-protein (CRP) was considered to be elevated if it was >6 mg/L; d-dimer was considered elevated if it was >500 ng/ml; ferritin was considered elevated if it was >350 ng/mL; and interleukin 6 (IL-6) was considered elevated if it was >7 pg/ml. COVID-19 severity was classified on the basis of computed tomography (CT) score as mild (0–8), moderate (9–15), and severe (>16).^[12]

The data were analyzed by a central team based in Deenanath Mangeshkar Hospital, Pune, India. The data were anonymized and waiver of written consent for patients was granted. The study protocol was approved by ethics committee of first hospital.

OBSERVATIONS AND RESULTS

Incidence of rhino-orbito-cerebral mycosis

As compared to the incidence of rhino-orbito-cerebral mycosis for 2-year period prior to study period, there was a rise in the incidence of the fungal infections during the study period. [Table 1].

A total of 122 patients were seen during the study period. The patient characteristics and their COVID-19 treatment details are presented in Table 2. The characteristics of mycosis are presented in Table 3.

Demographics

Mean age of patients in the study was 57.37 years with age-range between 17 and 85 years. There was a male preponderance with male to female ratio 3.52:1. Of 122 patients, 113 (92.6%) had developed fungal infection after Feb 2021.

Clinical manifestations, co-morbidities, investigations, and treatment during COVID-19

Patients suffering from COVID-19 had respiratory involvement in all, renal and hepatic impairment in 26 (21.3%) and 9 (7.4%), respectively. Of 122 patients, 78.7% were known diabetic on treatment while 13.1% were found to have hyperglycaemia during their admission for COVID-19. None of the subjects had prolonged immunosuppression, underlying malignancy, or organ transplantation as risk-factors for invasive fungal disease. Oxygen was used during the course of illness in 69.7%, non-invasive ventilation in 27.9% while invasive ventilation was required in 5.7%. Corticosteroids were used in 90.2%, remdesivir in 82.8%, and tocilizumab in 13.1% as a part of the treatment.

Clinical manifestations, investigations, treatment, and outcomes of rhino-orbito-cerebral mycosis

Of 122 patients, 72 (59%) patients developed fungal infection with COVID-19 while 50 (41%) developed it in post-COVID-19 period. The average duration between COVID-19 and onset of symptoms of CNS mycosis was 14.77 days (0–60 days).

The presenting symptoms of rhino-orbito-cerebral mycosis were headache in 91%, facial pain in 78.7%, diplopia in 66.4, unilateral visual loss in 56.6%, and focal deficit in 13.9%.

Clinically and radiologically rhino-orbito-sinusitis was present in 96.7%, meningitis in 6.6%, intracranial mass lesions in 15.6%, and strokes in 14.8% [Figure 1]. One patient each had temporal lobe and pterygopalatine fossa involvement, ventriculitis in one, and clivus and basisphenoid involvement. Concomitant lung involvement was seen in one.

Of the total 18 strokes, 5 had watershed infarcts (2 posterior watershed, 1 anterior watershed, 1 both anterior and posterior watershed, and 1 internal watershed infarct) in the same side as the sino-orbital involvement. Three had large-vessel disease with ipsilateral middle cerebral artery (MCA) infarct. Two presented with bilateral frontal infarcts. Two others presented with hemiparesis. Data were inadequate in remaining five patients.

Table 1: Yearly incidence of rhino-orbito-cerebral mycosis

	May 2018-April 2020	May 2020-April 2021
Invasive CNS fungal infections (mucor and aspergillus)	26	30
Total in-patient admissions	130945	53034
Incidence of invasive CNS fungal infections	0.99276/10,000 admissions/year	5.6567/10,000 admissions/year

CNS - central nervous system

Table 2: Patient characteristics and COVID-19 treatment

		Number (n=122)	Percentage
Age (years)		57.37 +/- 11.76 (17-85)	
Gender	Male	95	77.9
	Female	27	22.1
Onset of invasive fungal infection after COVID-19 (days)	During COVID-19 (0-14 days)	72	59
	After COVID-19 (>14 days)	50	41
COVID-19 severity on CT chest* (n=106)	Mean duration	14.77 +/- 10.1 days (0-60)	
Medical illness	Mild (1-8)	28	26.4
	Moderate (9-15)	56	52.8
	Severe (>15)	22	20.8
Laboratory abnormalities	Diabetes mellitus	96	78.7
	Diabetes after COVID-19	16	13.1
	Hypertension	54	44.3
	Chronic kidney disease	15	12.3
	Chronic liver disease	3	2.5
Treatment for COVID-19	Elevated CRP (mg/dL) (n=105)	100	95.2
	Elevated d-Dimer (ng/mL) (n=94)	67	71.3
	Elevated ferritin (ng/mL) (n=58)	43	74.1
	Elevated IL-6 (pg/mL) (n=56)	52	92.9
Treatment for COVID-19	Oxygen	85	69.7
	Non-invasive ventilation	34	27.9
	Invasive ventilation	7	5.7
	Corticosteroids	110	90.2
	Remdesivir	101	82.8
	Tocilizumab	16	13.1

COVID19 - coronavirus 19; CT - computed tomography; CRP - C-reactive-protein; IL-6 - interleukin-6

During admission for management of fungal infection, the highest average sugar was 362 mg/dL with a range of 112–659 and 66.6% patients had ketosis. The diagnosis was achieved by demonstrating fungal elements by stains in 82%, histopathology of biopsied tissue in 86.9%, and culture in 21.3% [Figure 2]. The causative fungi were mucor in 106 (86.9%), aspergillus in 5 (4.1%), and both mucor and aspergillus in 9 (7.4%) while fungus was not classifiable in 2 (1.6%).

All patients were treated with amphotericin B while oral posaconazole was used in 18.9%. Commonest surgical intervention performed was functional endoscopic sinus surgery (FESS) in 87.7% and orbital debulking in 21.3%. One patient had developed right middle cerebral artery–anterior cerebral artery watershed infarct which was treated with intravenous thrombolysis with tissue plasminogen activator following which she underwent mechanical thrombectomy. Post-procedure she developed intracranial haemorrhage and succumbed to the damage. Two subjects required temporal lobectomy. In an attempt to preserve the eye and vision, six

subjects received retro-orbital injection amphotericin B for orbital fungus invasion. Out of these, two went on to require exenteration of the eye while vitrectomy was performed in another subject.

Amongst 122 patients, 42 (34.4%) died in-hospital during treatment while 74 (60.7%) were discharged from hospital, often with residual morbidity. Five (4.1%) patients were lost to follow-up with incomplete treatment while one patient was still ongoing treatment at the time of this manuscript writing,

DISCUSSION

In this large study of the rhino-orbito-cerebral fungal infection with COVID-19, we describe clinical and radiological features, risk factors, and outcome of patients.

Demographic features and incidence

Mean age of our cohort was 57.37 and with males >75% which matches with published non-COVID-19 mucor studies as well as post-COVID-19 rhino-orbito-cerebral mucor case series.^[4-8,13-15]

Table 3: Characteristics of rhino-orbito-cerebral fungal infection

		Number (n=122)	Percentage
Fungal symptoms	Headache	111	91
	Facial pain	96	78.7
	Focal neurological deficits	17	13.9
	Diplopia	81	66.4
	Loss of vision	69	56.6
Fungal syndromes	Rhino-orbital-sinusitis	118	96.7
	Stroke	18	14.8
	Mass lesion	19	15.6
	Meningitis	8	6.6
Laboratory abnormalities	Highest sugars (mg/dL)	362 +/- 111 (112-659)	
	Ketosis (n=60)	40	66.6
Diagnostic modality	Stains	100	82
	Histopathology	106	86.9
	Culture	26	21.3
Type of fungus	Mucor	106	86.9
	Aspergillus	5	4.1
	Both mucor and aspergillus	9	7.4
	Not classified	2	1.6
Anti- fungal treatment	Amphotericin B	119	97.5
	Triazoles	23	18.9
Surgery	FESS	107	87.7
	Orbital decompression	26	21.3
	Ommaya reservoir	1	0.8
	Temporal lobectomy	2	1.6
Outcome	Survived	74	60.7
	In-hospital death	42	34.4
	Lost to follow-up	5	4.1
	Treatment ongoing	1	0.8

FESS - functional endoscopic sinus surgery

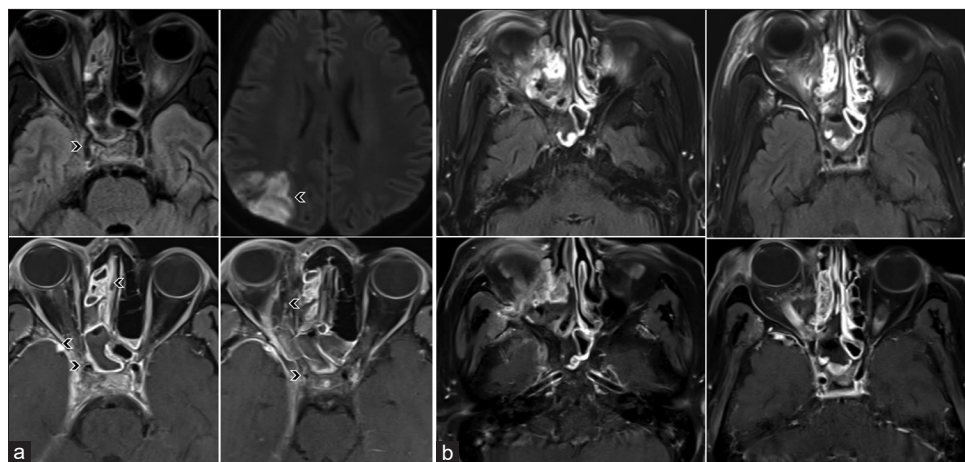


Figure 1: MRIs of brain and orbit with contrast to two patients with rhino-sino-orbital mucor. (a) Showing soft tissue along the cavernous sinus (right > left), partially encasing, and narrowing the cavernous portion of right ICA and ICA–MCA junction. DWI axial image shows a wedge shaper right parietal infarct. Also evident is an increase in the heterogeneously enhancing mucosal thickening involving right nasal cavity with thinning (attenuation) of the bony portions of nasal septum, right superior, and middle turbinates. Dural enhancement is seen along the right anterior temporal lobe. Ill-defined enhancing soft tissue is seen within the orbit with heterogeneously enhancing bulky extra-ocular muscles. Mild increase in intra-orbital and intra-conal fat stranding is seen. (b) Displaying heterogeneously enhancing mucosal thickening is noted involving the right nasal cavity. There is soft tissue in the basi-sphenoid area and mass effect is also seen on the optic nerve at the optic canal level with enhancement of the optic nerve sheath. Adjacent dural enhancement is seen along the right anterior temporal lobe. There is infiltration of the orbit with enhancement of its structures and evidence of proptosis. Mild enhancement and oedema are seen involving the masticatory muscles.)

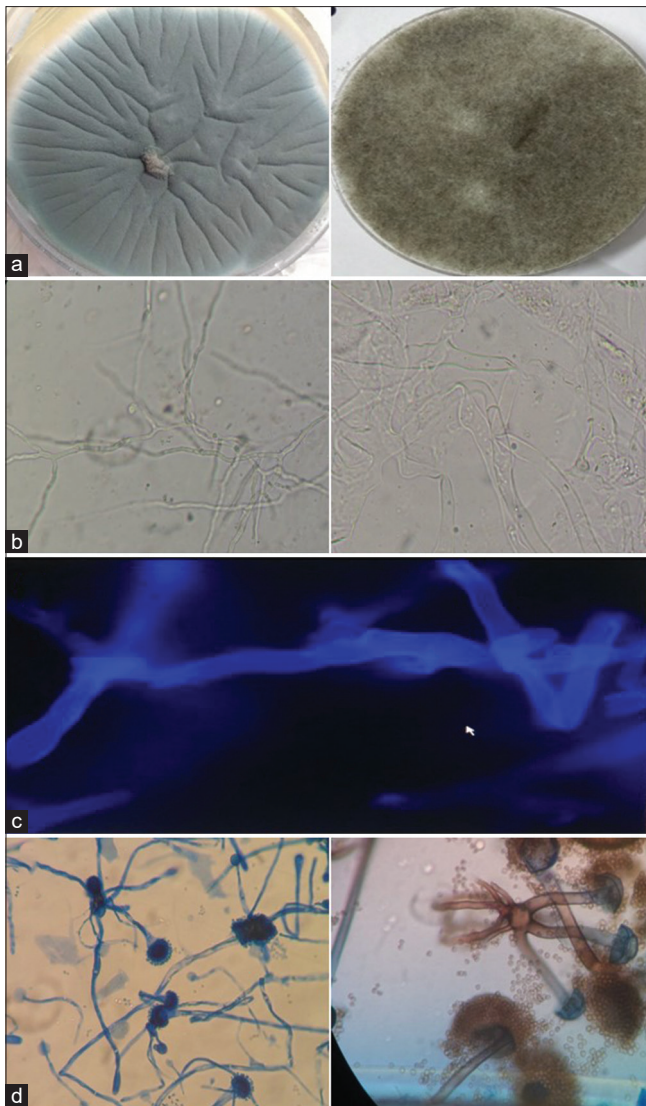


Figure 2: Microbiological features of the rhino-orbito-cerebral mycosis. (a. Growth on Sabouraud's agar: Velvety smoky green growth of *Aspergillus fumigatus* and cottony black growth of mucorales. b. KOH preparation: Narrow hyaline septate acutely branching fungal hyphae of aspergillus and hyaline broad aseptate right angled branching fungal hyphae of mucorales. c. Calcofluor preparation: fluorescent broad aseptate right angled branching fungal hyphae of mucorales. d. Lactophenol Cotton Blue (LPCB preparation): from the growth of *Aspergillus fumigatus* showing characteristic sporulation and from the growth of mucorales identified as *Rhizopus* species showing sporangia filled with endospores.)

The true incidence of rhino-orbito-cerebral mycosis in COVID-19 is not known. However, our hospital-based data show that the number of admissions with fungal infections has increased more than five-folds compared to the previous 2 years. Cases were reported from 11 districts from the state of Maharashtra which had witnessed highest number of COVID-19 cases in India so far.^[16] Since the cases were collected by neurologists in the respective centers, there may be a selection bias. In the study, 92.6% cases were seen during the second-wave of COVID-19 pandemic which started Feb

2021 onwards in India.^[17] A national registry urgently needs to be formulated to know the exact incidence as well as burden of the disease.

Characteristic of fungal infection

Relation to COVID-19

Since the secondary infections occur after immune dysregulation and/or metabolic derangements, these would occur few days after the onset of COVID-19 infection. Of 122 patients, 41% patients had the fungal infection after COVID-19 and the mean interval between COVID-19 and mycosis was 15 days, whereas 59% patients developed the fungal infection during the same admission when they were hospitalized for treatment of COVID-19. In the review by John *et al.*,^[5] 39% patients had concurrent mucormycosis with COVID-19 while 61% had sequential mucormycosis after COVID-19.

Clinical features

The clinical features in our series match with other previous reports.^[6,11] Since the patients were seen by neurologists, head and face pain, diplopia, and vision loss were more common than nasal discharge. We did not have any patients with dental involvement.

Stroke is an uncommon complication of the rhino-orbito-cerebral mycosis.^[18] The fungi causing rhino-orbito-cerebral syndrome are typically angio-invasive. The disease is known to start in nose from where it spreads to paranasal sinuses and orbits. If untreated, it spreads to superior orbital fissure and cavernous sinus. In cavernous sinus, it can invade internal carotid artery leading to occlusion, ischemic stroke, aneurysm formation, and rupture.^[19] In our series, there were 14.8% cases of ischemic strokes. The unusually high numbers of strokes may be due to selection bias as all patients were seen by neurologists. COVID-19 is a prothrombotic state where strokes are known to occur which can be an additional contributory factor.^[18]

Fungal syndromes

The CNS fungal syndromes vary depending on the type of the fungus. Smaller yeasts and pseudo-mycetes present with meningitis, encephalitis, and micro-abscesses while larger septate and non-septate fungi more often cause abscess/mass lesion, stroke, rhino-orbito-cerebral syndrome, and skull base syndrome.^[20] In our series, rhino-orbito-sinusitis was the most common syndrome in 96.7% followed by stroke, mass lesion, and meningitis.

Diagnostic modalities

Both CT and magnetic resonance imaging (MRI) show the extent of involvement very well, and MRI is best for soft tissue whereas CT is the modality recommended to see bone involvement.^[14] The study should image paranasal sinuses, orbit, and intracranial structures. Due to fear of spread of COVID-19 infection, many institutes limited the use of MRI in patients with COVID-19 only after they were deemed to be non-infectious. In our study, both modalities were used as per clinical scenario and dependent on the need of the surgical specialists.

Nasal swabs, nasal scrapings, aspirated fluids, histopathology specimens, and in rare cases, brain biopsy were obtained to demonstrate and isolate the fungus. Documenting invasion of fungus in the tissue on histopathology removed any doubt of contamination. Unlike aspergillus, where special serum tests such as galactomannan and beta-D-glucan are available, there are no such tests available for mucor, so we have to completely rely on documentation of fungus on the mucosa or in the tissue.

Fungus identification

Amongst cases of rhino-orbito-cerebral mycosis in COVID-19 or non-COVID-19 cases, mucor is the most common infection described.^[13] Mucormycosis are acute to subacute infections caused by the angio-invasive fungi in the order of mucorales. The most common manifestations are rhino-orbital cerebral and pulmonary syndromes.^[21] In our series, 86.9% patients had mucor as the sole causative agent.

Aspergillus is known to cause pulmonary aspergillosis in COVID-19 patients^[22] as well as rhino-orbito-cerebral syndrome in non-COVID-19.^[23] To the best of our knowledge, there are no case reports of rhino-orbito-cerebral aspergillosis with COVID-19. The dual infection caused by mucor and aspergillus has also been described in non-COVID-19 patients,^[24] but not in COVID-19. Both aspergillus and dual infections have been seen in our series in 4.1% and 7.4% patients, respectively.

Treatment of rhino-orbito-cerebral mycosis

The treatment of this type of fungal infection involves anti-fungal drugs, surgical debridement, and correction of metabolic abnormalities.^[14]

Some important points to remember are that the dose of liposomal amphotericin B needs to be escalated to 10 mg/kg/day in patients with cerebral involvement. Liposomal preparation increases the cost and many times, it is out of reach for the families in the present resource-limited times. So, in our country, we may have to adapt to using conventional amphotericin B with stringent renal monitoring. Amphotericin B has to be given for a minimum period of four weeks and the decision to use for even longer periods is based on resolution of disease both clinically and on imaging. Posaconazole and isavuconazole are oral triazole agents found useful in mucor which are well tolerated and can be used in patients with renal impairment, patients who develop amphotericin B toxicity, and in patients whose disease progresses on amphotericin B as well as maintenance therapy. There is no recommendation to use posaconazole routinely as a prophylaxis.^[14] Isavuconazole was found to be equally effective when compared with amphotericin B in an open label study.^[25] In our study, all patients were treated with amphotericin B while 18.9% were treated with triazoles.

Since the disease carries high mortality, early surgical treatment in the form of debridement of necrosed tissue is a crucial step in treatment.^[13,14] FESS was the most frequently performed surgical procedure in our series. Another advantage of early surgery is the get tissue for diagnostic purpose. Emergency orbital exenteration achieved the “clean margin” goal and

proved life-saving. Neurosurgeons were deployed to deal with base of the skull disease and drainage of intra-cranial abscesses and collections. We tried to keep our practices as per European Confederation guidelines and recommendations discussed in the key articles.^[14]

Outcomes

The reported mortality due to invasive fungal infections is roughly 50% in non-COVID-19 patients^[13,14] as well as in COVID-19 patients.^[5] The mortality from COVID-19 related invasive fungal infections in our series was 34.4% in contrast to 50% in the literature. However, our mean duration of follow-up is 30 days. We plan to continue to monitor our patients regularly to look for relapses and complications. Early diagnosis, timely surgical intervention, and adequate anti-fungal therapy could have led to reduced mortality. An important point to note is that 4.1% of our patients were lost to follow-up solely due to financial reasons suggests the fact that the disease poses major challenge to already burdened health care system.

Risk factors for rhino-orbito-cerebral mycosis in COVID-19

Past illnesses

Uncontrolled diabetes mellitus (DM) is a well-known risk factor for invasive fungal infection. Hematologic cancers and solid organ or hematopoietic stem cell transplants are other risk factors. COVID-19 is more severe in patients with co-morbidities, DM being one of these. In our series, pre-existing DM and new onset DM were seen in 78.7% and 13.1% patients, respectively. Only 8.2% patients were non-diabetic. Other chronic illness and factors that are already known risk factors for mycosis such as underlying malignancies, organ transplantation, or taking immunosuppressant drugs were not seen in our series.

COVID-19 itself

COVID-19 infection leads to significant immune dysregulation which predisposes to secondary infections.^[1,5] New onset DM is well known in COVID-19 due to the use of steroids and pancreatic injury by SARS-CoV-2 virus.^[26] Elevated levels of ferritin are often seen in COVID-19 and result in intracellular iron overload which is subsequently released into circulation.^[5] High iron is an important factor for the growth of mucor.^[27] Of the available data in our study, 74.1% patients had high ferritin levels. Whether additional factors like severity of COVID-19 or length of hospital stay are risk factors for mycosis needs to be studied.

COVID-19 treatment

Following the RECOVERY trial, dexamethasone has become an important drug in COVID-19 management.^[28] Corticosteroids use, however, is a known risk factor for invasive fungal infection. In our series, 90.2% patients received steroids. Data need to be generated to see if there is a ‘threshold’ dose or duration of steroid use or whether one steroid is more risky than other. In our series, 13.1% received tocilizumab which is IL-6 inhibitor and causes significant immunosuppression and a known risk factor for invasive fungal infection.^[29] There have

been no reports of remdesivir increasing the risk of developing infections.

Other risk factors

Since pulmonary and rhino-orbito-cerebral forms of fungal infections are most common in COVID-19, ventilators or oxygen delivery systems may pose risk factors. There are no data on the use of these devices and subsequent fungal infections. However, healthcare associated mucormycosis is well known and can occur after surgeries, use of catheters, and adhesive tapes.^[30] Environmental factors, alteration in host immunity, and alteration in fungus behaviour may be additional risk factors.

Points to ponder

The sudden surge of cases was unexpected for healthcare facilities. Since the literature about the syndrome is limited to case reports and small case series, there are many points to ponder.

Why mucormycosis is more common than other fungi?

Amongst all fungal infections, mucormycosis is most commonly reported in COVID-19.^[4,5] The unique setting of prolonged hyperglycaemia, immune dysregulation, and iron overload would make a COVID-19 patient more susceptible for mucor infection. Specific defects in immune system after COVID-19 need to be studied to understand the pathophysiology of this syndrome.

Why India is more affected than other countries?

Although cases have been described from other countries, India so far has reported highest numbers of cases of this unique syndrome. As described in the Introduction, India has the second highest cases of COVID-19 as well as highest prevalence of mucor which makes the country more vulnerable for the infection.^[9,11]

Why is it more common in the second wave?

It is our hypothesis that the new SARS-CoV-2 strain alters immune regulation in such a way that it predisposes the high-risk group to these invasive mycoses (mucor and aspergillus) specifically. A point to note is that this suppression of immunity is different from AIDS patients, lymphoproliferative disorders, or those are on immunosuppressive therapies after transplants. This is because there has been reporting of neither opportunistic viral infection such as JC virus and cytomegalovirus nor protozoa such as toxoplasma and not even the yeast fungus, cryptococcus.

What to expect in future?

It is difficult to predict how prevalent would the fungal infection be in COVID-19 patients. Although the literature about this syndrome is limited, a large number of cases have been seen in many states in India. Since the second-wave of COVID-19 is still ongoing in India, the mycosis cases will continue to be seen. It is indeed a new epidemic in the ongoing pandemic.

What needs to be done?

Research needs to be undertaken to understand the basic cause

behind the susceptibility to invasive fungal infections due to moulds after COVID-19. Areas that need to be addressed are the form of immune dysregulation after COVID-19 and whether it is more severe with the newer strain that has appeared in the second wave. Additionally, it would be worth studying whether SARS-COV2 promotes invasive fungi to grow in the host which it infects. Larger multi-centric studies and meta-analysis to document clinical features, treatment strategies, and prognostic indicators are necessary. Awareness about this disease amongst physicians dealing with patients of COVID-19 needs to improve and preventive strategies need to be devised.

Limitations

Since this was a retrospective study involving data about two different infections in the same subjects many times spanning over two different hospital admissions, there were some missing data. Since the COVID-19 treatment often happened in another hospital, details about that treatment were at times hard to trace.

CONCLUSIONS

In the second-wave of COVID-19 pandemic in India, there has been a sharp rise in fungal infections. In this largest till date reported study of rhino-orbito-cerebral mycosis, mucor was the most common causative agent followed by aspergillus. Clinical manifestations of mycosis in COVID-19 patients were broadly the same as seen in non-COVID-19 host, except possibly high numbers of strokes. At present, we recommend a similar diagnostic and therapeutic approach to tackle the fungal infections. A high degree of suspicion for invasive fungal infections in this COVID-19 pandemic is necessary and one must suspect these even on appearance of non-specific symptoms such as headache facial/eye pain and nasal blockade. Early diagnosis cannot be any more rewarding in any other illness than these fungal infections as it would amount to saving the eye, sparing the patient from having a morbid brain surgery or even saving a life.

Several factors are responsible for this wrath [Figure 3]. Host factors include poorly controlled DM, ketosis, and other co-morbidities such as chronic kidney disease and

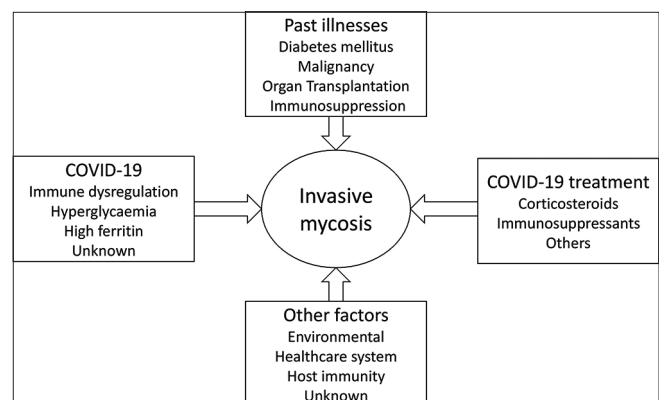


Figure 3: Suggested causative factors for invasive mycosis in COVID-19

immunosuppressive therapies. SARS-CoV-2 factors are new onset hyperglycaemia, rise in ferritin, and creating a state of immune dysregulation while the use of steroids and tocilizumab is treatment factors. Research needs to be undertaken to study new predisposing factors in post-COVID hosts, and the difference in the way new strain of SARS-COV2 affects immunity and whether it carries the ability to promote fungal infection in any way.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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