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Review Article

An insight of covid-19 and Mucormycosis

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ABSTRACT

Mucormycosis is an infrequent infectious disease engendered by Mucorales fungi that primarily affects COVID-19-positive patients in India. Corticosteroids are frequently used to treat COVID-19. Corticosteroids vanquish the body's immune response and raise blood sugar levels in diabetic COVID-positive patients and are often found with the Rhino-orbital cerebral Mucormycosis. Neutropenia, solid organ, and stem cell grafting, excessive intake of iron, and deferoxamine therapy are associated risk factors. The saprophytic fungus initially attacks the sinuses before spreading to the oral cavity, lungs, and eye orbit, causing an acute phase of inadequate blood supply to the tissue which finally led to Necrosis. If left untreated, it can result in temporary or permanent loss of vision, fever, headache, reddened and swollen skin near the nose or eyes, facial pain, and eventually death. Laboratory parameters, tissue biopsy, CT scan, and reverse transcriptase-polymerase chain reaction are few investigations. Amphotericin B and Micafungin are the commonest advisable anti-fungal medication. Surgical debridement or removal of contaminated tissue, particularly in infections of the rhino-orbito-cerebral, cutaneous, and gastrointestinal Mucormycosis, is required.

Keywords: Clinical Parameters, COVID-19, Mucormycosis, risk factors, laboratory

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INTRODUCTION

The fatal second wave of the COVID-19 is a global widespread of the disease and has had destructive repercussions over the healthcare system. The disease pattern of COVID-19's first wave can range from mild to life-threatening pneumonia including an increase of pro-inflammatory markers, like IL 1, IL 6, tumor necrosis-α, <CD4 interferon-gamma expression, and some CD4 and CD8 cells, which raise the vulnerability of the co-infections against the bacteria and fungi. [1, 2]. COVID-19 patients are susceptible to develop severe opportunistic infections (e.g., oropharyngeal-candidiasis, lung-aspergillosis, and candida infections of the blood circulation system, etc.) due to the accompanying comorbidities (e.g., uncontrolled diabetes mellitus), or immuno-compromised conditions (e.g., corticosteroid medication, prolong Intensive care unit stays). [3, 4]. Mucormycosis is one such opportunistic infection. It is frequently Fatal and is caused by a fungus called mucormycetes (about 5-15 microns in diameter) [5], found in the environment. Rhizopus, Mucor, Rhizomucor, Syncephalastrum, Cunninghamella bertholletiae, Apophysomyces, and Lichtheimia strain of the fungi are the usual molds that cause mucormycosis. [6]. these fungi are often found in soil and conjunction with organic decay matter (e.g., bread molds, vegetables, leaves, compost piles, and rotten wood) and evolve rapidly in vivo and culture. [7]. the evidence-based findings in (Table-1) pertain to COVID-19 patients admitted to the hospital with mucormycosis. Mucormycosis is also associated with diabetes, cancer, Stem cell, and Organ transplantation, Neutropenia (low white blood cell count), Iron overload, subcutaneous tissue injuries, and Deferoxamine therapy. [8]. According to the WHO's weekly update on COVID-19 in India (May 23, 2021), there are (26, 530, 132) infected individuals and (299, 266) cumulative deaths. [9]. The mortality rates varied according to the seriousness of the patient, the type of fungus,

and the affected body site. For example, (46%) mortality was observed in sinus-infected COVID-19 positive patients, (76%) in pulmonary infections, and (96%) mortality was observed in disseminated Mucormycosis. [6]. the infection is prevalent in Covid-19 patients, particularly diabetic patients, affected by corticosteroid therapy. The fungal infection has been identified worldwide, including states of India, like Karnataka, Uttarakhand, Telangana, M.P., and Bihar. (10) Infection occurs due to inhalation, inoculation, or ingestion of fungal spores from the environment, which can spread throughout the lungs, nasal sinuses, orbit, face, and central nervous system. Additionally, the fungus can spread through cuts, scrapes, puncture wounds, or other trauma of the skin. Most cases in the current pandemic are sporadic and healthcare-related, such as negative pressure rooms, water leakages, and unmaintained air filtration, unsterile medical devices, and building structures.[11-20].

Pathophysiology

The saprophytic fungus grows rapidly in the raised blood sugar conditions and successfully allows surviving in the acidotic conditions by three mechanisms: (a) Hyper-glycation of iron-absorbing proteins with weaker iron absorbance, increased pronouncement of GRP 78, (b) the protein receptors of mammalian gives chances to bind Mucorales, (c) and the declined phagocytosis bonded with hyperglycemic state. Rhizopus-oryzae produces massive spores ingested by the host or by a host with a normal immune system. The ciliary mechanism propels the spores (which germinate into numerous hyphae) into the pharynx, where they invade the oral cavity, mucous membranes, and nose, throat, and paranasal sinuses. Due to the fungus's angio-invasive nature and a weakened immune system, the nasal turbinates become the first site of infection, resulting in sinusitis episodes. Within a few days, this can advance to the Pan sinus and the palate in the buccal cavity, orbit of the eye, and brain, causing the inadequate blood supply to the tissue and Necrosis. [29]. Sign of orbital involvement in Mucormycosis is explained in (Flowchart-1)

Types of mucormycosis

According to anatomical distribution and clinical demonstration, Mucormycosis is subdivided into six clinical constructs. 1. Rhino-orbito-cerebral mucormycosis, 2. Pulmonary mucormycosis, 3. Cutaneous mucormycosis, 4. Gastrointestinal mucormycosis, 5. Disseminated mucormycosis, and 6. Uncommon, which represent rare forms like endocarditis, osteomyelitis, peritonitis, and renal infection. [21]. (Table-2)

Diagnosis

A sterile specimen is taken from the infection area for culture or histological examination. [43, 44]. Physical examinations, in addition to medical history and symptoms, are significant. If the infection is found clinically enriched with mucormycosis, non-sterile sites, such as throat sputum, may be cultured. Although mucormycetes are very tough to confirm with the other filamentous fungi in any tissue, and there are presently some laboratory parameters available: serological tests, serum urea, creatinine, glucose levels, D-dimer, beta-D-glucan or Aspergillus galactomannan, RT-PCR] test is yet available for diagnosis [45], depending on the suspected area of the infection, radio imaging like CT scan for lungs, sinuses, or other sections of the body may be performed. [46]. Mucormycosis has a lousy prognosis, although fatality rates vary according to its type and severity. The cerebral rhino form is fatal in 30%–70% of cases, while disseminated mucormycosis is fatal in 90% of cases. [47]. Patients with AIDS have a nearly 100% mortality rate. [48]. Mucormycosis can result in neurological dysfunction, blindness, and blood clotting in the vessels of the brain or lung. [9].

Management

Mucormycosis is a fatal infection and in its initial stage, antifungal medication and surgical debridement of necrotizing soft tissue may lead to overcoming the illness. Doctors and scientists are continually discovering the most effective methods for preventing fungal infections. [50, 51]. Amphotericin B, Micafungin is typically provided intravenously, whereas Posaconazole and ravuconazole are typically supplied orally. Amphotericin B lipid formulations are frequently utilized as first-line therapy. [52]. additionally, surgical debridement or removal of contaminated tissue is required, particularly in rhino-orbito-cerebral, cutaneous, and gastrointestinal Mucormycosis infections. [53-55]. the recommended countermeasures are listed and should be followed, even if their effectiveness in preventing mucormycosis is not established well. [56, 57]. (Table-3)

Guidelines for identification of high-risk mucormycosis patients

To aid in the early detection and treatment of high-risk mucormycosis in COVID-19 patients, people with diabetes, or Immunosuppressed individuals, the patients and caregivers should be aware of and consult with a doctor, ENT, Ophthalmo l6 mm Neurologist, dentist, or surgeon. if they exhibit any of the symptoms listed below (Evidence-based Advisory). [60]. (Table-4)

CONCLUSION

This paper aims to increase awareness of the importance of early detection and treatment of various fungal infections, particularly Mucormycosis with a high mortality rate, in COVID-19 patients to lower the risk of death. Due to the significant death rate associated with this condition, more stress must be laid on a high index of suspicion, early diagnosis, and proper care to maximize patient survival. To give suitable customized treatment, it is essential to investigate the risk factors and various invasive fungal infections. Additional studies and reviews are necessary to comprehend the significance of opportunistic infections in COVID-19 patients fully. The frontline workers must emphasize the baseline assessment of these high-risk patients, followed by weekly examination till the discharge period, follow-up examination, depending on the patient's

condition, maybe follow up every two weeks till six weeks or once every month last up to three months.

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Tablel 1 Analytical findings of COVID-19 patients with Mucormycosis

Reference	Database	Manifestation and Risk factors	Laboratory parameters	Treatment and Outcome
Hai at S.W et al (24) (2021)	Research Gate	24/F with COVID-19, Diabetes, obesity, Respiratory failure with saturation level 80%; Left lid swelling and hypoesthesia; left proptosis with hyperemic conjunctiva and an opaque cornea	Glucose: 509mg/dl Tracheal Secretion culture. *pneumoniae, E cloacae.* Serum Urea: 25.7mg/dl Serum creatinine: 1.07 mg/dl D- Dimer: 3.12 µg/mL	Antibiotic therapy: Amoxicillin-clavulanate Antifungal therapy: Amphotericin B Oxygen support: Ambient air
Ruan Q et al (2020) (25)	PMC	25/F; Chronic liver disease with grade II hepatic encephalopathy, Acute kidney disease.	TTP blood culture: 14 *(C.auris)* D Dimer: 1,068 µg/mL S. Urea:150mg/dl S. Creatinine:28.7 mg/dl	Therapy for SARS-CoV-2: Azithromycin; hydroxychloroquine. Antibiotic Therapy: Piperacillin/tazobactam; Meropenem, teicoplanin; Anti-fungal therapy: Amoxycillin/clavulanate Oxygen support: Ambient air
Chowdhary A et al (2020) (26)	PubMed	86/F, Diabetes Mellitus, Chronic liver disease, ischemic heart disease	TTP blood culture: 10 *(C.auris)* D Dimer: 980 µg/mL S. Urea: 58 mg/dl S. Creatinine:21.2 mg/dl	Therapy for SARS-CoV-2: Remdesivir, Azithromycin; hydroxychloroquine; Antibiotic therapy: Piperacillin/tazobactam, Meropenem, Antifungal Therapy: Micafungin Oxygen support: High-flow oxygen
Chowdhary A et al (2020) (27)	PMC	69/M; Diabetes, Hypertension, Asthma	TTP blood culture: 14 *(C.auris)* D Dimer: 760 µg/mL S. Urea: 34 mg/dl S. Creatinine:1.8 mg/dl	Therapy for SARS-CoV-2: Azithromycin; favipiravir; tocilizumab; convalescent plasma. Antibiotic therapy: Cefixime, Meropenem. Antifungal therapy: Micafungin Oxygen support: Invasive mechanical ventilation
Cortegiani A et al (2020)(28)	PMC	66/M; Diabetes, Hypertension	TTP blood culture: 14 and 17 *(C.auris)* D Dimer: 3,024 µg/mL S. Urea: 54 mg/dl S. Creatinine:2.3 mg/dl	Therapy for SARS-CoV-2: Azithromycin, hydroxychloroquine, convalescent plasma, tocilizumab, and Remdesivir Oxygen Support: Invasive mechanical ventilation Antibiotic therapy: piperacillin/tazobactam, teicoplanin. Antifungal therapy: Micafungin, Amphotericin B

Flow chart-1 Orbital manifestation of Mucormycosis

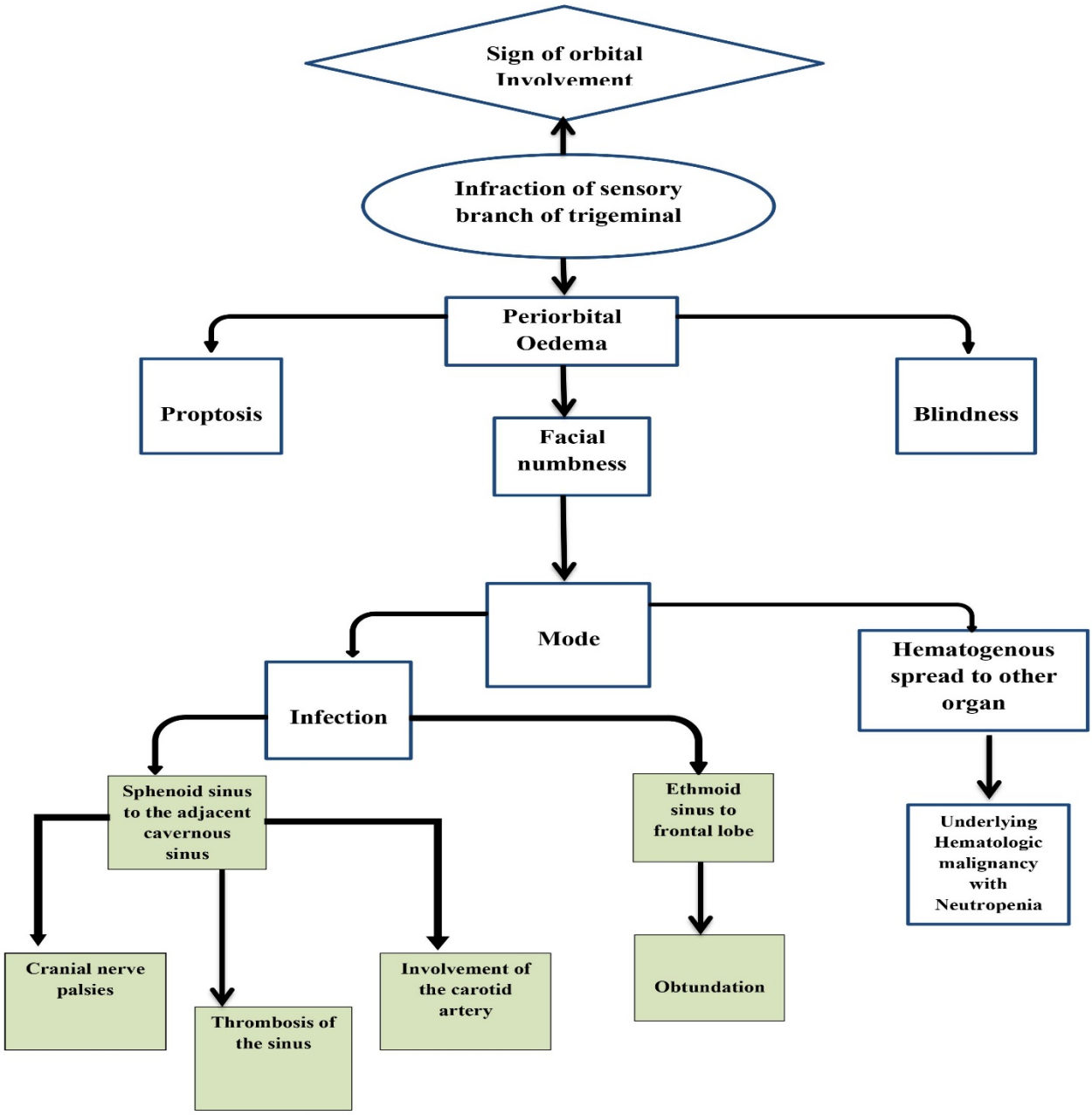


Table-2 Preventive measures

1	To raise public awareness about the condition. (58)
2	Avoid direct contact with floodwaters and water-damaged buildings following storms and other natural disasters.(59)
3	Avoid activities that require prolonged exposure to soil or dust.
4	When handling materials, wear gloves.
5	Use of soap and water for thorough cleaning of the skin Injuries.
6	Farmers and gardeners should be reminded to take precautions.
7	Utilization of High-efficiency particulate air (>90%) (HEPA) (BIII) (57)
8	Periodic air sampling of critical care units to check for spores.(58)
9	Directed room airflow, so that air from patient rooms flows into the corridor (BIII) (57)
10	Ascertain the sterility of humidifiers used during oxygen therapy. (58)
11	Barriers for the dust in patient care area.
12	Isolated rooms, with sealed windows and electrical points (BIII) (57)
13	Patients who have recovered should be recommended to remain inside until their natural strength and immunity have restored. (58)

Rating of Recommendations: B = Moderate; Rating of Evidence: III = Expert opinion; HEPA: high-efficiency particulate air

Table-3 Overview of varieties of Mucormycosis seen in COVID-19positive patients.

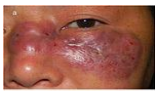
Type	Frequency	Diagnostic signs	Progression	Risk Factors
Rhino-orbital cerebral Mucormycosis	Frequent type (34%) (22)	Unilateral facial swelling, headache, nasal / sinus congestion/pain, blackish lesions over the nasal bridge or on upper pallet, Seropurulent nasal discharge with fever. Ptosis, proptosis with disfunctioning of extraocular muscle maybe with visual disturbance. (30, 31) 	Necrotic black lesion on the hard palate, nasal turbinate with black pus libration from the affected area, fifth or seventh nerve palsy, ophthalmoplegia, and loss of eyesight are diagnostic indications for higher center involvement. (30)	Diabetes (145(33%) out of 337), renal transplant, neutropenic cancer patients, hematopoietic stem cell transplant, or solid organ transplant.(32)
Pulmonary Mucormycosis (PM)	Common (20%) (22)	**Non-specific signs**: Cold infection with cough, chest pain, Dyspnea and fever,. **Specific Sign**: Reverse halo sign (19-94%) (33) **Chest radiograph**: lobar and segmental consolidation; multifocal pneumonia pattern with bilateral consolidation (34); alone or Multifarious nodules or masses. (35)	1) Consolidation and masses; involve both lungs; Pulmonary Necrosis; Delays in treatment are accompanied with a high mortality rate.	Diabetes mellitus, hematologic malignancy, profound Neutropenia, solid organ and stem cell transplant.
Cutaneous Mucormycosis (17,18)	Commonest (22%) (22)	**Transmission**: Skin trauma (69%) (36) and burn (9%) (37) Patients by direct inoculation. **Typical sign**: Necrotic eschar characterized by pus, abscess formation, warmth, excessive redness or swelling around a wound, and Necrosis. **Investigation**: Biopsy and culture	An erythematous, indurated, and painful cellulitis rapidly gives rise to an ulcer occupied with a black eschar and Necrosis.	Hematological malignancies; Uncontrolled diabetic patients and individuals with immunosuppression
Gastrointestinal Mucormycosis	Less common in adults but commonest in neonates (38-41)	**Non-specific sign**: Enteralgia and distention accompanied with nausea, vomiting, fever, hematochezia, intra-abdominal abscess, massive gastric bleeds, etc. **Investigation**: Biopsy or endoscopy; although tough to make clinical diagnosis with necrotizing enterocolitis.	Study over the 72 patients affected with gastro-intestinal Mucormycosis, the infection was primarily limited to the stomach, intestine, colon, and ileum. (74%) liver and (22%) (22)	Diabetes, corticosteroid intake, organ or stem cell transplant, and raised serum iron availability due to acidosis or deferoxamine administration (6)
Disseminated Mucormycosis	Rare (13%) (22)	The infection spread through the bloodstream and affects the lung and brain (common), spleen, heart, skin, and other organs can also be affected. Mortality rate= (95-100%) but evidence reported successful treatment (42)	It can invade cutaneous, subcutaneous, fat, muscle-skeletal tissues, and deep organs.	Patient with Neutropenic, hematologic malignancies, post transplants or on deferoxamine therapy.

Table-4 identification of high-risk Mucormycosis patients

Early Detection	Uncontrolled diabetes, diabetic ketoacidosis, and diabetics patients receiving corticosteroids or tocilizumab
	Patients on immunosuppressant's or anticancer medication, as well as those suffering from chronic severe sickness
	High doses of steroids dependent patient or tocilizumab over an extended period
	Incidence involving severe COVID cases
	Patients receiving oxygen through nasal prongs, mask, or ventilator
Danger Signs	Nasal discharge or mucous that is abnormally dark, or bleeding from the nose
	Nasal obstruction
	Headache or discomfort in the eyes
	Swelling encircling the eyes, diplopia, eye redness, vision loss, difficulty closing or opening the eye.
	Unilateral Numbness or tingling feels over the face, difficulty in chewing or opening the mouth.
	Toothache, loosening of teeth, jaw involvement
	Chest pain, pleural effusion, hemoptysis, worsening of respiratory symptoms
Regular self-Assessment	Full face inspection in day light for swelling over all part of face.
	Touch examine over the skin for change in color, hardness, and pain.
	Oral and nasal evaluation by the torch to find out discoloration and swelling inside the buccal cavity and inside the nasal area.