Mucormycosis and Covid-19 : an overview

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ABSTRACT

Mucormycosis is a rare but life-threatening fungal infection. Its most documented cases have been reported as secondary complications of COVID-19, in patients with diabetes mellitus, neutropenia, or treatment with corticosteroids, especially among critically ill patients. Laboratory diagnosis of mucormycosis is slightly difficult cause of rapid course of disease and doubtful significance of isolates as contaminants. The clinical material from infected area, nasal discharge or sputum may rarely contain fungal elements and deeper tissue section is required. Histopathological examination of the tissues affected typically shows characteristic broad, hyaline, ribbon-like, irregular fungal hyphae with wide-angle branching, accompanied by tissue necrosis and angioinvasion of the fungi. keeping in view the devastating course of mucormycosis and its inherent resistance to variety of antifungal drugs , every institution should emphasize the diagnosis and treatment in Emergency Department, wherein KOH mount should be done in suspected patients showing warning signs and symptoms on arrival followed by surgical debridement as early as possible to reduce further morbidity and mortality.

Introduction :

Mucormycosis is an acute and potentially fatal fungal infection caused by fungi related to the mucoraceae family. These fungi are opportunistic organisms and can be found in fruit, soil, feces, and may be cultured from the nasal and oral mucosa of healthy humans[1] they used to be rather treated as contaminants in diagnostic microbiology laboratory but understanding about mucormycosis has entirely changed. These are now emerging pathogenic organisms invariably leading to fatal consequences especially when there are predisposing factors in a particular clinical setting. These cases are increasingly being reported in the recent covid pandemic. A complex interplay of factors that include diabetes mellitus, any previous respiratory pathology, immunosuppressive therapy, nosocomial infection sources and systemic immune alterations of covid-19 infection itself lead to secondary infections, having impact on morbidity and mortality.

Historical Perspective :

In 1885, Kurchenmeister described case of mucormycosis in a patient with neoplastic lung disease. In 1885, Paltauf described the term mycosis-mycorina which is first disseminated case of zygomycosis. In 1943, Gregory and colleagues in the series of three fatal cases associated with diabetes reported advanced rhino-cerebral mucormycosis, proptosis and opthalmoplegia.

Harris reported cure of mucormycosis in pediatric patient with the discovery of amphotericin in 1957 as a breakthrough therapeutic agent and mortality of this disease dramatically reversed during those days.[2]

Mycology :

Mucorales are group of lower fungi, hyphae are non-septate, sparsely-septate or pauci-septate, and they reproduce asexually within a sac called as sporangium or by means of conidial development. They also reproduce sexually by formation of single thick walled spore called as Zycospore. Based on zycospore, they are classified under phylum zygomycota. The sub-phylum mucormycotina contains the order of mucorales which is more clinically important includes genera Lictheimia (formerly Absidia), Mucor, Rhizomucor and Rhizopus.

Epidemiology :

The incidence rate of mucormycosis globally ranges from 0.005 to 1.7 per million population. In Indian population its prevalence is 0.14 per 1000, which is about 80 times higher than developed countries. The fatality rate of mucormycosis is 46% globally.

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Common Causative Agents of Mucormycosis
Order : MUCORALES
Rhizopus arrhizus (old name r. Oryzae)
R. Microspores var. Rhizopodiformis
Mucor racemosus
Rhimucor pusillus
Lichtheimia corymbifera (mycocladus corymbiferus or absidia corymbifera)
Apophysomytes species
Cunninghamella bertholletiae
Saksenaea species
Cokeromyces recurvatus
Syncephalastrum recemosum

However, factors like intracranial or orbital involvement, irreversible immune suppression increases fatality to as high as 50% to 80%. A high suspicion for this disease must be considered in patients who are immunocompromised.[4,5]

Pathogenesis and Pathology :

The pathogen as an asexual spore-forming fungus can infect the oral and nasal cavities through inhalation. In the presence of a normal immune system, the spores are usually removed by phagocytic leukocytes. The pathogen can transform into hyphae-form in individuals with predisposing factors such as uncontrolled DM (particularly in the presence of ketoacidosis), malignancy (such as lymphoma and leukemia), renal failure, organ transplantation, advanced rheumatologic disorders using immunosuppressive agents (such as prolonged use of corticosteroids), AIDS, extensive burn, and chronic sinusitis. In ketoacidosis, low serum ph diminishes the phagocytic effect of macrophages, chemotactic and oxidative burst of neutrophils. Commonly found mucormycetes, rhizopus arrhizus has several virulence factors like angioinvasive growth at or above body temperatures along with active ketone reductase system and hydroxamate siderophores. Rhizopus species have an active ketone reductase system and thrive in high glucose and acidotic conditions. The normal serum inhibits rhizopus whereas serum from patients of diabetic ketoacidosis stimulates its growth. It has also been observed that patient on dialysis and iron overload, who has been treated with deferoxamine, an iron chelator are susceptible to mucormycosis. Mucorales use this chelator as a siderophore to obtain more iron which stimulates the growth of fungus. The risk factors include neutropenia, high-dose systemic steroids, protein-calorie malnutrition, solid organ or marrow transplant, immunodeficiency, leukemia and intravenous drug abusers. Covid-19 is a life-threatening, infectious disease, affected patients show an overexpression of inflammatory cytokines, and impaired cell-mediated immunity with decreased cluster of differentiation 4 and 8 positive T-helper (CD4 + T and CD8 + T) cell counts, indicating susceptibility to fungal co-infections.[1,6] In these conditions, leukocytes have less efficacy on the hyphae forms of fungi and the pathogen may proliferate more easily. The organism have predilection for elastic lamina, invades the vessel walls of the infected region and results in thrombosis, ischemia, and necrosis. The infection can directly spread into the paranasal sinuses and then invade into orbital and intracranial spaces by direct spread or via the bloodstream. This form is rhino-orbito-cerebral mucormycosis and is the most common type of human mucormycosis, presented with nasal stuffiness, foul smell, epistaxis, nasal discharge, unilateral facial edema, diplopia, proptosis pain and redness around eyes, loss or vision, restriction of eye movements palatal or palpebral fistula, blackish discoloration over bridges of nose / palate, prolonged fever, headache, toothache, altered mental status. The cutaneous, pulmonary, gastrointestinal, and disseminated form of mucormycosis are uncommon presentations of this infection.

Diagnosis :

Laboratory diagnosis of mucormycosis is slightly difficult cause of rapid and fulminating course of disease and doubtful significance of isolates as contaminants. The clinical material from infected area, nasal discharge or sputum may rarely contain fungal elements and deeper tissue section is required. 1, 3-beta-D-glucan in blood serum is of

Table 1 : **Characteristics of Covishield, Covaxin and Sputnik V***

Preferred specimen collection according to site of infection	
Rhino-oculo-cerebral mucormycosis	Scraping or exudate from nares, hard palatal lesion, sinus material, endoscopic collection of debrided tissue and biopsy from extracted tooth socket area
Cutaneous	Aspirations collected with sterile needle and syringe from undrained abscess , needle tissue from both centre and edge of the lesion
Pulmonary	Sputum Broncheo-alveolar lavage Lung biopsy-collected by bronchoscope Fluoroscope guided trans-thoracic needle aspiration or open lung biopsy
Gastrointestinal	Endoscopic biopsy of the lesions
Renal	Biopsy of the lesions

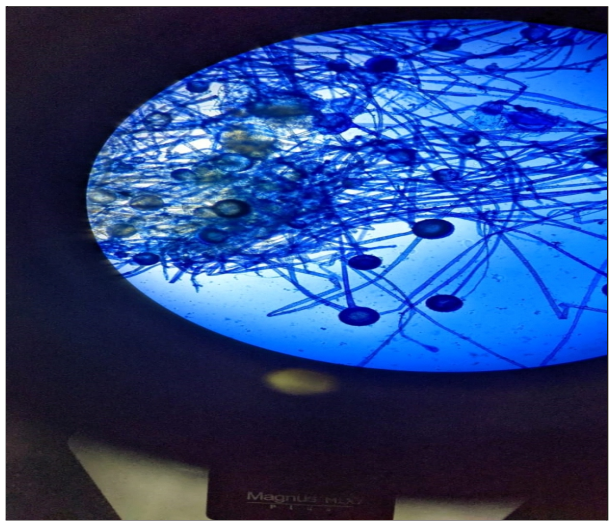
little or no significance as in other systemic mycosis. However, certain investigational studies have demonstrated that polymerase chain reaction and matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry can be used to identify causative species from culture specimens.[7]

Sample Collection :

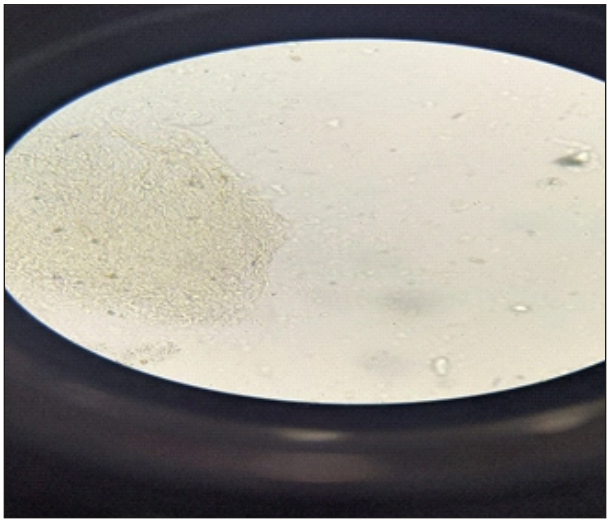
Specimens should be collected aseptically in sterile container which should be transported to laboratory within four hours. Dry swabs should not be used for sample collection.

A) Direct Examination :

The microscopic examination of nasal discharge or biopsy material in KOH mount shows characteristic broad, non-septate, ribbon like hyphae with wide-angle or right angle branching at irregular intervals. The hyphal elements of mucormycetes is recognized as non-septate thick-walled (10-20 mm across) hyphae, with wide-angle branching. Mucormycetes are well seen in calcofluor white stain and H & E stain. Due to absence of cross-walls, fluids from hyphae are free to escape and during handling hyphae collapse and crinkle giving ribbon-like appearance. These features distinguish from slender hyphae of Aspergillus, Fusarium and Scedosporium species which have regular dichotomous branching and frequent septation. Therefore, it is recommended not to homogenize tissue material and specimen must be directly inoculated on to culture media to keep viability of fungal cells.



MICROSCOPIC APPEARANCE OF MUCOR SP. (LCB *400)



BROAD, RIBBON-LIKE NON-SEPTATE HYPHAE WITH WIDE ANGLE BRANCHING SEEN IN WET MOUNT (KOH*400)

WHITE MYCELIAL GROWTH OF MUCOR SPP IN 72 HOURS ON SDA

B) Fungal Culture :

The mucormycetes can be easily grown on conventional media like SDA with antibiotics at both temperatures i.e 25° and 37° Celsius. Although mucormycetes are not fastidious fungi they still fail to grow sometimes during primary isolation as sparsely septate fungi, while handling lose the viability as cytoplasm oozes out. The rapidly growing mycelial colonies are floccose, dense and hairy like appearance. They are described as fibrous or cotton candy growth which is very vigorous hence some of mucormycetes of order mucorales are called as 'lid-lifters' as they press upon petri dish from below.[1]

Treatment :

Mucormycosis is a life threatening condition, can become fatal in short span if specific diagnosis isn't established in time thereby delaying of proper antifungal therapy. Small focal lesions can be surgically resected before lesion progress to involve the critical structures or distant organs. Concomitant approaches to treat mucormycosis include -

A) Rapid correction of underlying predisposing factor of host like diabetic ketoacidosis

B) Surgical debridement of necrotizing tissue

C) Antifungal therapy

D) Adjunctive therapy such as hyperbaric oxygen[1]

Antifungal Therapy :

Mucorales are inherently resistant to many antifungal drugs used to treat systemic mycoses including Ketoconazole, Fluconazole, Voriconazole, Flucytosine (5-FC) and the Echinocandins. Variable susceptibility to itraconazole and the squalene-epoxidase inhibitor terbinafine is seen. There were no standard guidelines defined by any of the organizations as it is available in case of Candidiasis, Cryptococcusis and Aspergillosis. However, as also supported by joint clinical guidelines by The European Society Of Clinical Microbiology and Infectious Diseases and European Confederation Of Medical Mycology (2013) based on the consensus derived from experiences of clinicians, the treatment of mucormycosis has been with the use of conventional Amphotericin - B Deoxycholate administered at maximal tolerated dose of 1.0 - 1.5 mg/kg/day. Unfortunately high dose of amphotericin-B are not tolerated for longer days, especially with patients with preexisting renal dysfunction (diabetic patients, those taking concomitant nephrotoxic drugs and transplant recipients). Liposomal Amphotericin-B (L-AMB) is to be given in higher

doses of 5-10 mg/kg/day in patients with renal compromise. Duration of both can be ranging from 14 to 21 days depending on severity till clinical resolution and radiological stabilization, after 14 days of therapy. Amphotericin monitoring chart including cumulative dosage and electrolyte imbalance and correction should be followed while patient is on treatment. Patient is shifted on maintenance therapy with orally available azole derivative - Posaconazole when clinically stable (600mg per day in divided doses) preferably given with high-fat food to maximize the drug absorption. Steady state plasma concentrations of Posaconazole are not reached until after about one week of therapy, therefore patient should receive several days of Amphotericin B formulation when the patient is started on Posaconazole therapy. Cytokines such as interferon-? and granulocyte - macrophage colony stimulating factors (GM-CSF) have also been used to treat mucormycosis.[8,9]

Prevention :

Covid-19 is associated with increased incidence of secondary infections probably due to immune dysregulation. Additionally, the use of steroids / monoclonal antibodies / broad-spectrum antibiotics as a part of fighting force against covid-19 may lead to development / exacerbation of fungal diseases especially patients with preexisting risk factors. The use of therapeutic agents including steroids should be monitored to achieve the therapeutic effect at lowest dose for the crucial time period. Environmental cleanliness should be maintained to have no exposure to dead or decaying organic matter. Strict glucose monitoring in patients with steroid therapy should be done to control hyperglycemia. The warning signs and symptoms-pain and redness around the eyes and nose, fever, headache, coughing, shortness of breath, altered mental status, should not be ignored. [10,11]Keeping in view the rapid and devastating course of mucormycosis, every institution should resort on to its local mandatory protocol in Emergency Department, wherein KOH mount should be done in suspected patients on arrival followed by surgical debridement as early as possible to reduce further morbidity and mortality.

References :

1. Jagdish Chander, textbook of medical mycology, 4th edition
2. Mandell, douglas and benett's, principles and practice of infectious diseases, volume 2
3. Rippon, medical mycology , 3rd edition
4. Aastha maini, gaurav tomar, deepak khanna, yogesh kini, hardik mehta , v. Bhagyashree , sino-orbital mucormycosis in a covid-19 patient :a case report , international journal of surgery case reports 82(2021)105957
5. J.chander, m.kaur, n.singhla, r.punia, s. Singhla,a.attri ,j.guarro , mucormycosis :a battle with deadly enemy over a five-year period in india , j.fungi 4(2)(2018)46
6. Sharma s, grover m, bhargava s, samdani s, kataria t . Post coronavirus disease mucormycosis :a deadly addition to the pandemic spectrum . J laryngol otol 2021; 1-6.
7. Ge Song, G. Liang, W. liu, Fungal Co-Infections Associated With Global COVID-19 Pandemic: A Clinical And Diagnostic Perspective From China,http://doi.org/10.1007/s11046-020-00462-9
8. Cornerly oa, arikan-akdagli s, dannaoui e, et al. ESMCID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin microbial infect.2014; 20 suppl 3:5-26. Doi:10.1111/1469-0691.12371
9. Management protocol for mucormycosis, by multidisplinary mucor management team, 16.05.2021, AIIMS,Rishikesh
10. Mehta s, pandey a (september 30, 2020) rhino-orbital mucormycosis associated with covid-19. Curues12(9): e10726.doi10.7759/cureus.10726
11. Global guideline for the diagnosis and management of mucormycosis: an initiative of the european confederation of medical mycology in cooperation with the mycoses study group education and research consortium. Lancet infect dis. 2019 dec; 19(12):e405-e421. Doi:10.1016/s1473-3099(19)30312-3.