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THE CHALLENGING ISSUES, DIAGNOSIS AND TREATMENT OF MUCORMYCOSIS-A NARRATIVE REVIEW

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ABSTRACT: Mucormycosis is a new fungal disease that increased the morbidity and mortality rate in this present scenario. It's difficult to diagnose and cure due to proper scientific evidence is not yet being designed. The disease's prevalence appears to be rising. In high-income nations, hematological malignancies are the most prevalent underlying illness, while uncontrolled diabetes is usually linked to pulmonary mucormycosis in low-income nations. Mucormycetes can be detected or identified using histopathology and molecular tests, and they can be recommended as important add-on techniques to augment standard diagnostic techniques. Reversal of underlying predisposing factors, early delivery of active antifungal medications at the appropriate dosage, thorough excision of all diseased tissues and different adjuvant treatments are all part of a successful therapy strategy mucormycosis. Liposomal amphotericin B antifungal medications have been added to our antifungal arsenal, but amphotericin B remains the medication of choice for first antifungal therapy. Despite attempts to better understand the pathophysiology of mucormycosis, early diagnosis and intensive treatment, the disease's fatality rate remains high.

INTRODUCTION: With the world reeling from the effects of the novel coronavirus, a sub-microscopic, enigmatically animated viral particle, we now have to deal with another previously unknown opportunistic adversary, the so-called "Black fungus" infection, rationally called mucormycosis. There are species that do not belong to the plant or animal kingdoms. They can be present in the dirt, trees, rotting organic matter, water, air, and moist areas, as well as in humans and animals. They, along with bacteria, play an essential role in our environment by degrading organic matter into simplified forms for plant consumption [1]. Mucormycosis (black fungus) is a severe but uncommon fungal infection caused by micromycetes, a type of mold. Molds of the order Mucorales cause rhino-orbital-cerebral-mucor-mycosis (ROCM).

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A few subgroups are most often implicated in this virus, such as Rhizopus, Mucor, and Rhizomucor. These fungi are angioinvasive, meaning they infiltrate and damage the surrounding blood vessels, causing tissue necrosis and death. Molds can be seen all over the environment and their spores can be found in the air. They get trapped in

the nasal cavity and the sinuses that surround it [2]. They ensconce themselves inside the tissue until they've found a favorable setting. When the spores germinate, the hyphae (filamentous processes) outgrow and emit destructive juices that digest the host tissue while still feeding the rapidly developing fungi. They kill the surrounding host tissue as they emerge in the nasal cavity. The nasal cavity and sinuses' bones are broken. The hard tongue, nasal bones, and skull base bones are among them. In the nasal cavity and oral cavity, black masses can be seen. It can cause bulging of the eyes, discomfort, frozen eye motions, and blindness if it damages the orbit and enters the eye socket [3].

As it breaches the skull base and fills the cranial cavity, it blocks main arteries and venous lakes, resulting in life-threatening brain strokes and bleeds. Spores can migrate deep into the respiratory system and settle safely in the parenchyma of the lungs (alveoli and bronchioles). The fungi multiply quickly in this setting, killing lung tissue and jeopardizing blood oxygenation. It will then spread across the circulatory system, causing an existential dilemma [4]. Due to the extreme disease's rarity, comprehensive, recent systematic reviews are almost necessary to accomplish, and the majority of contemporary knowledge on epidemiology, identification, and care comes from case analysis and empirical series [5]. For the person having specific underlying diseases, such as hematopoietic related stem cells, relatively large epidemiological studies were conducted. Despite their inherent limitations, the document is another valuable basis of infection.

Mucormycosis still has a high mortality rate. Antifungal medications are used in conjunction with surgical intervention in the treatment of fungal infections. Isavuconazole is the sole novel medication that demonstrates efficacy against Mucorales; however, it does not anticipate providing substantial improvements over amphotericin B-based medicines or posaconazole as first-line treatment. Because early diagnosis leads to a better prognosis, several researchers are striving to find novel ways for identifying mucormycosis sooner [6]. This review will examine the numerous disciplines of study focused on diagnosis, as well as the modalities utilized as main or complementary therapy of this sometimes-deadly condition. Mucormycosis is an uncommon fungal illness that has recently become more prevalent among COVID-19 patients in India and other Asian populations. Unfortunately, depending on the severity of the illness, it can kill anywhere from 46 to 96 percent. You may bring it inside if you enjoy gardening or other outside hobbies. It may also be found inside, as seen by the black fungal overgrowth on damaged bread or the fuzzy white mold that develops on fruits and eventually turns dark grey. The black fungus can also be found in air conditioner condensation lines and drop pans. In a nutshell, it has always been present in our environment [7]. However, it should only impact persons whose immune systems are impaired, such as uncontrolled diabetics, steroid users, or cancer patients undergoing chemotherapy. Only a few cases have been documented in India in the previous ten years. Thousands of cases of black fungus have been recorded in people suffering from or recovering from COVID-19 in the last week [8].

Epidemiology: Rhizopus spp., Mucor spp. and Lichtheimia spp. are the most common mucormycosis agents. Apophysomyces and Saksenaea are some of the less common genera in Mucorales [9]. Mucormycosis (Rhizopus spp. And Lichtheimiaspp) has a wide range of causes in various regions [10]. Though Rhizopus is the common disease causative species in India, emerging species such as Rhizopus homothallic and uncommon agents like Mucor irregularities and Thamnostylum are causing the disease. The majority of cases of mucormycosis are caused by ingestion of fungal sporangiospores that have been expelled in the air also direct inoculation of organisms into gastrointestinal tract mucosa.

Mucormycosis is affected by seasonal fluctuations, with the majority of infections occurring between August and November. According to a recent study, patients with trauma were more likely to be infected with non-Rhizopus spp. Patients infected with Apophysomycesspp were all immune-competent, had largely acquired infection by trauma, and infection was primarily restricted to the body's internal organs [11]. In India, Apophysomyces variabilis and Saksenaeaerythrospora induce nosocomial infection has been recorded after intramuscular injections.

Infection with Cunninghamella has been linked to a worse prognosis. Mucormycosis has become more common in recent decades, owing to an increase in the number of severely immune-compromised people. Mucormycosis instances are now recorded worldwide; however, there seem to be disparities in epidemiology between industrialized and developing nations. The condition is still uncommon in affluent nations, and it is usually encountered in individuals with hematological malignancies (HM) [12]. Mucormycosis is more frequent in poorer nations, particularly India, and instances are mostly seen in individuals with uncontrolled diabetes mellitus (DM). Mucormycosis can manifest itself in a variety of ways, in healthy organs.

The most common clinical manifestation of HM is pulmonary illness. In India, the most common symptom was rhinoorbito cerebral manifestations linked with uncontrolled diabetes, and isolated renal mucormycosis has evolved as a novel clinical entity. Mucorales infections are known for progressing quickly. Mucor circularities is a newly identified opportunistic fungus that causes an infection with a radically different distribution and clinical appearance. It was initially detected in Chinese farmers. The infection is long-lasting, occurs in immune-competent persons, has no clear risk factors, and affects the skin and subcutaneous tissues, eventually leading to severe deformity. Data from two worldwide registries was recently used to study mucormycosis in children [13].

Diagnosis: In the last two decades, mucormycosis infection (formerly known as zygomycosis) (6) has increased, particularly in immunocompromised individuals. Mucormycosis was the third most prevalent infection in a study of fungal illness in patients with hematopoietic stem cell transplant (HSCT), following candidiasis and aspergillosis. Mucormycosis is still difficult to diagnose, despite its rising prevalence. Mucormycosis is typically difficult to distinguish from other frequent invasive mold infections, such as aspergillosis, both radiographically and clinically. The "gold standard" for the detection of mucormycosis infection is histopathology. On the other hand, it necessitates a high level of pathology competence, it is also impossible to identify the species. Mucormycosis-infected organisms from tissue samples that have been detected histopathologically generally do not grow in fungal cultures, but proper results only 50% of culture were positive, according to a recent study [14]. The inability to confirm mucormycosis that has been identified histopathologically and establish the specific treatment on species consequences. Mucorales are mainly only resistant to amphotericin antibiotics, and posaconazole is sometimes treated, in contrast to Aspergillus species, which are sensitive to voriconazole and echinocandins. Mucormycosis-infected organisms from tissue sample [15].

AS a result, improved approaches for confirming tissue level diagnosis and identifying species-specific infected species are required. Using PCR-based techniques to detect fungal infection is a unique technology that could improve mucormycosis infection and diagnosis. Previously published PCR and sequencing of Mucorales 18S ribosomal DNA to assess mucormycosis and distinguish the infecting organism in paraffin-embedded tissue samples. A retrospective cohort of patients treated for hematological malignancies with histopathologically established mucormycosis was evaluated at the molecular level [16].

Doctors look at your medical history, symptoms, physical examinations, and laboratory testing when diagnosing mucormycosis. If your doctor suspects you have mucormycosis in your lungs or sinuses, he or she may take a sample of your respiratory system fluid to submit to a lab [17]. A tissue biopsy, in which a tiny sample of afflicted tissue is evaluated in a laboratory for signs of mucormycosis under a microscope or in a fungal culture, may be performed by your healthcare practitioner. Depending on the location of the suspected infection, imaging tests such as a CT scan of your lungs, sinuses, or other sections of your body may be required [18].

Clinical Diagnosis: A high index of suspicions, knowledge of host cell proteins, and early clinical examination are all important symptoms required to diagnose mucormycosis. Diplopia is a condition in which a person has two eyes a neutropenic patient with diabetes or pleuritic discomfort [19]. The presence of a host might indicate the presence of an infection, which should lead to treatment. The employment of imaging modalities as soon as

possible and subsequent acquisition samples for histology, microbiological, and other tests and cutting-edge molecular techniques. As previously stated, Mucorales infection's most typical clinical manifestations. Rhinocerebral, pulmonary, soft tissue, and disseminated infections are some of the most common; almost every organ, however, can be impacted by illness [20]. Mucormycosis is characterized by tissue necrosis; however, the end results of syndrome-based diagnostic techniques lack high specificity. On the other hand, aspergillus also can cause similar symptoms in affected patients. Furthermore, in tuberculosis-endemic nations, the two illnesses may coexist, as in the case of a diabetic patient. Nonetheless, there are specific characteristics that should raise your suspicion of invasive pulmonary mucormycosis. A history of past voriconazole prophylaxis onset in an impaired patient undergoing treatment for fungal infection and antifungal medications active against other infection [21].

Microscopic Examination: The pillars of diagnosing mucormycosis are microscopically direct and indirect histopathological and culture of diverse clinical specimens. Microscopic examination of clinical samples, ideally it provides for a quick presumptive diagnosis of mucormycosis infection. Mucorales hyphae range in width from 10 and above meters, are pauci-septate, and have an uneven, looks like a ribbon structure with wide-angle (90o) bifurcations being common [22]. On hematoxylin and eosin sections, fungal components are plainly visible; methenamine Gomori's silver staining for analyzing the external structure in greater level. Inflammation, such as neutrophilic or granulomatous, dominates tissue histology, notably in immune-compromised people. The presence of significant infarcts and angioinvasion characterizes invasive illness. A perineural invasion may be seen when nerve structures are implicated. When compared to non-neutropenic individuals, neutropenic individuals have a more widespread angioinvasion [23].

Serology: The effectiveness of an enzyme-linked immunospot (ELISpot) test was used to identify Mucorales specific T lymphocytes in three hematological patients who developed invasive mucormycosis. Mucorales-specific T lymphocytes were not seen in any of the controls. Further research on particular thymus cells is to be conducted [24, 25].

Molecular Analysis: Molecular-based techniques such as PCR (Polymerase Chain Reaction) and RFLP (Restriction Fragment Length Polymorphism analyses (RFLP) based methods necessitate the specific type of antigen produced by the fungal infection. All of the assays listed above can be used to detect and identify the Mucorales. The internal transcribed spacer genes are the focus of the bulk of molecular experiments [26]. Several investigations have been conducted utilizing paraffin-embedded samples, with varying results.

The detection accuracy of the investigations varied, with the smallest drawback being its low proportion of patients tested. Because the efficacy of the infection analysis has not been properly investigated and clinically evaluated, they cannot be recommended as a single, stand-alone technique in routine clinical diagnostics. Recent attempts to diagnose diseases using molecular markers in blood and serum have generated encouraging clinical results. Compared to culture, serum for molecular diagnostics resulted in an earlier diagnosis and overall verified culture-proven instances. Due to this, molecular-type of detection tests could be advised as useful supplements to traditional diagnostic techniques [27].

The Mucorales-related fungal disease has always been on the rise, with substantial morbidity and death linked within it. The absence of a non-invasive, fast, and accurate screening test has been a major stumbling block in treatment [28]. A key unmet need in modern mycology is the development of an early identification of mucormycosis using a culture-independent biomarker. Immunofluorescence to confirm the histologic prognosis of intrusive mold infection, PCR on formalin-fixed paraffin-embedded (FFPE) methods from serum/blood have mostly been developed.

Treatment Options: Mucormycosis is best treated with a multimodal strategy that includes reversing or stopping fundamental elements that predispose (if feasible), earliest administration of reactive fungal medicines in the right dosage, full excision of diseased organs, and the utilization of different

adjuvant treatments. Diabetic patients who are uncontrollable diabetes are suspects of having mucormycosis infection must have their metabolic abnormalities corrected as soon as possible. In this context, experimental research indicates that using bicarbonate with sodium in order to recover from ketoacidosis, regardless of how moderate or extreme the acidosis is, may be linked to a better illness prognosis owing to the ability to reverse the abilities [29]. Corticosteroids and other immuno suppressive medications should be discontinued as soon as feasible and at least low dose achievable.

Earlier detection is critical to begin therapeutical measures as soon as possible in order to prevent increasing invasions of tissue and its deadly consequences, reduce the impact of detection of corrective treatments, and improve the result and enduring [30]. Most antifungals, including voriconazole, are resistant against Mucorales fungus in vitro except for some Cunninghamella and Apophysomyces strains. Itraconazole and related derivatives are having effectiveness in some new strains, as do posaconazole and isavuconazole. There appears to be a link between Mucorales isolates sensitivity to amphotericin B and their outcomes [31]. Mucorales have numerous similarities to certain other molds, including invasion portals, intrinsic resistance mechanisms, and histological and therapeutic abilities.

Other types of Mucorales, such as Lichtheimia and Mortierella spp., have unique virulence characteristics that allow infecting them people with diabetic ketoacidosis or any kinds of acidic involvements, as well as impose unique host-pathogen interactions [32]. Mucormycosis is also characterized by widespread angioinvasion, which results in vascular thrombosis and tissue destruction.

Angioinvasion causes the organism to spread hematogenously, whilst necrosis of the afflicted tissues inhibits immune secretion cells and medications from reaching the infected areas. In comparison to some other fungus, such as Aspergillus and R. oryzae, possess a lower vulnerability to innate host defense, making them more difficult to cure and, as a result, associated with higher mortality [33]. Recently ECIL (European conference on infections in Leukemia) proposed the guidelines that lipid formulated (Liposomal) amphotericin B as a first-degree option for mucormycosis antifungal treatment. Besides, infections of the brainstem and related organs (peripheral nervous system) 5 to 10 mg/kg/day is advisable for the usage of Liposomal amphotericin B. At week four, the overall response rate was 36 percent, and at week five, it was 45 percent. Renal function impairment was observed in 40% of patients, as evidenced by a doubling of blood creatinine levels.

Although the study was prospective, it was not controlled; therefore, the findings ought to be used to guide future research [34]. The ideal dosage for medicine against fungal infections is still a point of contention, also in some antifungal medicines such as Triazoles, posaconazole, and isavuconazole. Posaconazole is recommended as a salvage or maintenance therapy by ECIL-6, but the ESCMID/ECMM recommendations prescribe it as a first-degree antifungal drug at a dosage of 200 mg orally. Posaconazole's introduction of intravenous and tablet formulations has resulted in higher medication solubility and sensitization [35].

Triazole (Isavuconazole) is a newly discovered having antifungal action against Mucorales and other fungal species. Because these antifungal activity outcomes were equivalent, isavuconazole drugs were recommended as first-line therapy for mucormycosis instead of amphotericin B. Although the findings are promising, the study has certain limitations, including limited sample size and lack of a control system, which also be considered [36]. Posaconazole combined with amphotericin B as proposed by ECIL-6 is another salvage therapy option. There is no evidence that using two antifungals as first-line therapy is effective. Using a propensity score analysis, the effects of monotherapy vs combination therapy were investigated in a recent trial with hematologic malignancies, but negative results were noted in most of the combination treatments [37].

In contrast, this retrospective analysis shows patients treated with a combination of amphotericin B and caspofungin revealed a survival advantage. In conjunction with a polyene, patients who received iron chelated deferasirox drug in conjunction with a polyene had a higher chance of

survival in preclinical studies. However, individuals who received deferasirox had a higher death rate in a random clinical trial 38. Deferasirox's efficacy as an adjuvant treatment in diabetic patients has been demonstrated in multiple studies, but it has yet to be proven in clinical studies. The length of active antifungal therapy has yet to be defined. Posaconazole and isavuconazole are two active drugs with oral formulations that are favoured. Other adjuvant treatments include the use of O2 (Oxygen) to create a higher oxygen level in cell surface also the simultaneous injection in cytokine level with antifungal medication. Moreover, previous preclinical evidence suggests that macrophage cell colony-stimulating molecules boost the immunity signals against certain Mucorales, potentially aiding treatment. However, because there is no clinical data on their usage, these treatments should be taken with care [39].

Finally, VT-1161, a fungal CYP51 inhibitor with selective action against R. oryzae, Lichtheimia, and Cunninghamella, shows in vitro action against Mucorales, including R. oryzae, Lichtheimia, and Cunninghamella [40]. When administered therapeutically or prophylactically, VT-1161 was demonstrated to the higher life of neutropenic with R. Oryzae [41]. While more research is needed to determine the efficiency of VT-1161 to act against other Mucorales molecules. This ergosterol synthesis inhibits the useful addition to our arsenal against mucormycosis.

Challenges in Treatment: Antifungal therapy takes many weeks, making it difficult for hospitals to accommodate patients with mucormycosis, who must be placed in different hospital wards. Surgery must also be done with caution since extensive mucormycosis surgery might negatively affect patients, especially viral infected patients. Experts say that maintaining appropriate hygiene is especially crucial for diabetes patients since the risk of opportunistic infection is particularly high in them.

They also recommended that persons who use oxygen concentrators clean their humidifiers on a regular basis [42]. Every year, millions of patients in India are admitted to hospitals with diabetes, steroid use, or cancer, but no one contracts this like the Covid-19 virus. Millions of people worldwide get infected with COVID, become diabetic, are put on steroids, and their immune systems are weakened, yet they do not contract black fungus [43]. The primary reason behind the fungal infection is an unsanitary and filthy method of supplying oxygen to patients in many parts of India, compounded with the indiscriminate use of steroids in the treatment. To begin with, medical oxygen is a highly refined form that is more than 99.5 percent pure after many compressions, filtration, and purification stages. The cylinders used to store, transport, and consume liquid oxygen are thoroughly cleaned and disinfected. Second, oxygen requires humidification, especially when given to patients at a high flow rate [44].

This is accomplished by passing it through a sterile water-filled container. The water itself must be sterilized and replaced regularly in accordance with the procedure. If the water is not sterile, it might cause infection with the black fungus (This is especially true if high-flow oxygen is administered over an extended length of time.) On the other hand, if oxygen is provided without being humidified, the mucosal membrane will dry out and the inner lining of the lungs will be damaged. It will also thicken the sputum or discharge, making it difficult to remove. Both of these have caused a slew of problems for infected individuals [45]. Next, the administration of steroids in the therapy of COVID-19 must occur at the appropriate moment. Steroids are only beneficial in treating COVID's symptoms, not the virus itself. If administered early, while the virus is multiplying, it is risky and damaging.

This will lower bodily immunity and allow viruses to replicate more easily. Giving steroids to a diabetic patients prematurely or needlessly would boost their blood sugar to dangerously high levels, increasing their chance of COVID severity and exposing them to the harmful effects of mucormycosis [46].

Finally, while increasing the manufacturing of medicine (Amphotericin B) to treat black fungus is a wonderful idea, we must keep in mind that this illness kills between 46 and 96 percent of persons once infected. The harsh reality is that Amphotericin B is extremely poisonous. To minimize this new adversary, the true solution is to

impose quality control and compliance for manufacturing, storage (in cylinders), and distribution (sterile water, clean oxygen system) and avoid indiscriminate use of steroids. A decent shower, not an expensive perfume, is the answer to terrible body odor [47].

CONCLUSION: Mucormycosis, although its rarity, is a significant burden on immune-compromised people due to its high death rate. The introduction of new immunosuppressive drugs with effective has been linked to an increase in the disease's prevalence. Diabetics, particularly in poorer nations, are vulnerable to this potentially fatal condition. There has been various research on its pathophysiology; however, there are still a lot of unanswered concerns. Mucormycosis is still difficult to diagnose and cure. The clinical presentation is ambiguous, and it is sometimes too late to offer effective treatment once it is determined that the patient has mucormycosis. AS a result, early detection is critical and it is the primary focus of current research.

The foundations of diagnosing mucormycosis are direct inspection, culture, and histopathology, although time consumptive and high insensitive. New methods with perfect molecular techniques provide an option that leads to early detection and a proper therapeutical approach towards the treatment. Mucormycosis is treated with a multimodal approach that includes reversing underlying risk factors, administering antifungal medications, surgical intervention, and numerous adjuvant therapy.

Antifungal medication should be started as soon as possible and dosed appropriately. The most often used antibiotics are amphotericin B and posaconazole. Isavuconazole is a novel triazole that has efficacy against mucormycosis agents, although it does not appear to give a better likelihood of survival than earlier therapies. Proper targeted immunological therapy and immunologic and metabolomic characterization of the host may all develop in the near future, for the best prognosis and treatment of this deadly disease.

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