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Pattern of Fungal Infection in Post COVID-19 Patients: A Narrative Review

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ABSTRACT

COVID-19 is caused by the new Severe Acute Respiratory Coronavirus COV 2 (SARS-CoV-2) which was labelled a worldwide outbreak even by The World Health Organization on January 30, 2020. The pandemic has hit 213 nations and territories as of August 20, with about 22 256 219 confirmed cases worldwide. Patients with underlying illnesses have a poor prognosis for the disease, with comorbidities documented in a substantial percentage of hospitalised and severe cases. According to preliminary data, older people and people with pre-existing diseases including chronic obstructive pulmonary disease, cardiovascular disease, cancer and diabetes mellitus, are more vulnerable to extreme COVID-19 than others.

Coronavirus are a broad group of viruses that can cause a variety of lung diseases in human beings, from mild to severe. CoV-2, or severe acute respiratory syndrome, is an infective and pathogenic Coronavirus that first appeared towards the end of 2019 and has subsequently produced a pandemic of acute respiratory illness known as "Coronavirus disease 2019", which is a global health issues. Its complaints can vary from a simple cough to more extreme disorders like bronchitis, pneumonia, ARDS, MODS, and can be fatal. COVID-19 is known to have rapid and serious advancement in those with already existing health issues, often resulting to death. SARS-CoV-2 infected a huge number of people worldwide, causing cold, cough, chest pain, dyspnoea, and individuals with additional ailments are at the greatest chances of developing the disease. Mucormycosis, Aspergillosis, Cryptococcosis, candidiasis as comorbidities in COVID-19 sufferers are discussed in detail in the review.

Key words: COVID-19, Coronavirus, Fungal infection, Comorbidities

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INTRODUCTION

Physicians have detected an increase in the prevalence of Post COVID-19 sequelae as the fight against Coronavirus illness 2019 (COVID-19) continues in India. Secondary infections, which account for 10-30% of COVID-19 cases, arise mostly after severe illness and in ICU treated people. Secondary bacterial or fungal infections occur ten times more frequently in patients with severe illnesses than secondary viral infections. Invasive fungal infections such as invasive Mycoses, *Aspergillus* infections, Cryptococcosis and *Candida* infections are more common in COVID-19 sufferers, especially those who are extremely unwell or immune compromised.

Corona virus infection (COVID-19) is a disease due to infection of Coronavirus-2, which causes Severe Acute Respiratory Syndrome (SARS-CoV-2).

Secondary infections are very common following severe illness and in Intensive care COVID-19 patients, accounting for 10-30% of all cases. Secondary bacterial or fungal infections are 10 times more common in patients with severe illnesses than secondary viral infections. Since the 1918 influenza pandemic, opportunistic infections have been documented as a result of respiratory viral infections. Even though the large percentage of COVID-19 instances are mild or moderate, around 16% of individuals who are diagnosed to have COVID-19 require medical attention and oxygen therapy, and 5 percent of the total progress major illness and require ICU care. Infections with other respiratory viruses, such as influenza, can cause ARDS and Invasive Pulmonary Aspergillosis (IPA) affects up to nearly a third of critically sick people.

Even though the pathogenesis of COVID-19 is unknown, it's indeed possible that immunological dysfunction and pulmonary damage done by COVID-19 immunopathology enable *Aspergillus* super infection in a way that is different from other respiratory viruses [1].

This review is done to understand the pattern of fungal infections and its pathogenesis among post COVID-19 people.

LITERATURE REVIEW

Mucormycosis

Mucormycosis is caused by moulds of the *Mucorales* order. Thermotolerant organisms, such as the one identified in India's COVID-19 Associated Mucormycosis (CAM) patients, can induce opportunistic diseases, which can be deadly. Mucormycosis is perhaps the most dreaded illness of all infectious diseases "Schwartz made a daring statement [1]. "It's a very deadly and terrible fungal ailment, but it is still caused due to moulds which are all around us and that we breathe in all the time. This is not an issue if your immune system is operating normally; none the less, a variety of immune deficiencies might predispose someone to infection by inhaled spores. Hemi facial oedema, fever, discomfort, vision loss, headache and black lesions with dead tissue apparent are all symptoms [2]. Mucormycosis is swiftly lethal without severe therapies like as antifungal agents and excision of dead cells (that is painful, debilitating and aggressive).

Mucormycosis had a 55 percent overall death rate before its relationship with COVID-19, and disseminated Mucormycosis was approximately 96 percent lethal. The kind of mould, the site(s) of infection, and the patient's underlying ailment or prior history of illness, including COVID-19, do have an impact on the infection's prognosis. Mucormycosis is more likely to infect immune compromised people. Carcinoma, burns, bone marrow or organ transplantation and other trauma which induce skin tears, corticosteroid therapy, neutropenia, and uncontrolled diabetic ketoacidosis are all important risk factors. Immunodeficiencies, such as diabetes, are well-known for creating immunological imbalances that allow fungal infections to grow, as well as predisposing individuals to severe COVID-19. Furthermore, to prevent detection during early infection, the SARS-CoV-2 virus adopts various novel tactics that further depress the immune system. Mucormycosis symptoms vary depending as to where the fungi have been developing in the human.

Rhino orbital cerebral and pulmonary mucormycosis are the two most common kinds of mucormycosis in this situation. The clinical and imaging data, as well as the correlation of probable risk factors and the form of illness onset or progression, are used to make a diagnosis. Severe acute respiratory syndrome CoV-2 is unique because it induces nuclear factor-κB while blocking interferon-1, enabling SARS-CoV-2 to multiply uninhibited, without the need for a rallying call, while continuing to call for reinforcements. As a result, a huge proportion of immunological infiltrate (immune system cells and cytokine in fluid) is produced, with neutrophillic infiltration being the most notable diseases of SARS-CoV-2 infected patients. Proinflammatory infiltrate are present in these infiltrates. As they build up, cells start to act within their own inflammatory setting, resulting in the "cytokine storm" which is linked with serious COVID-19 [3].

Ultimately, infiltration combined with inhibited interferon induction, which generally inhibits the virus from propagating and causes excessive cell death, might cause respiratory failure. Destruction of the airway epithelial cells and also blockade of Interferon-1 pathway make people more vulnerable to fungal infection. Corticosteroids, such as dexamethasone, can also be used to decrease inflammation. Corticosteroid usage, on the other hand, seems to be a potential risk for mucormycosis, and also elevated blood glucose levels is a documented adverse impact. If you have a history of diabetes, your chances of developing Mucormycosis increase dramatically. Amphotericin B, among one of the therapies for treating mucormycosis, targets sterols, lipid prevalent both in humans and fungal cell membranes. Ergosterol, a constituent of fungal cellular membrane, is far more responsive to this anti-fungal drug than cholesterol, although infusion related toxicity, which is likely the result of proinflammatory cytokine release, limits amphotericin B dosage.

Moreover, corticosteroid usage during Amphotericin B therapy has been linked to metabolic abnormalities such as hypokalemia, complicating medical management during CAM.

Aspergillosis

In COVID-19 individuals with elevated risk characteristics, *Aspergillus* species might be a significant source of life-threatening illness. Glucocorticoid use, Chronic Obstructive Pulmonary Disease (COPD), Cystic Fibrosis (CF), prolonged neutropenia, inherited immune deficiencies, Solid Organ Transplant (SOT), Hemopoietic Malignancy (HM), allogeneic Hematopoietic Stem Cell Transplant (allo-HSCT), and other ailments are all significant risk factors for the patient populations [4].

Aspergillosis (fungal diseases caused by the fungi *Aspergillus*) in persons having severe COVID-19 is still a mystery to researchers. Scientists previously believed that Aspergillosis only affected persons with highly compromised immune systems. However, Aspergillosis is becoming more common in individuals who do not have a compromised immune system but are experiencing severe certain infections, like as influenza. COVID-19 Associated Pulmonary Aspergillosis has been reported in a few recent studies (CAPA).

Even if people with serious COVID-19 who might have decreasing pulmonary function or septic disorder do not have traditional risk indicators of *Aspergillous nigar* infection, clinicians should investigate the potential of aspergillosis.

Candidiasis

In patients with serious COVID-19 infection who are at higher likelihood to be treated with wide spectrum antibacterial agents, nutritional support, as well as invasive evaluations, and in patients with prolonged neutropenia and some other immunological system depreciation indicators, the infection rate with various species of candida may rise dramatically. Non culture

diagnostic methods like as Mannan and anti-Mannan IgG tests, BDG, and PCR based assays such as *C. Albicans* Germ Tube Antibody (CAGTA) are now being utilised in clinical practise as adjuncts to cultures in the diagnosis of invasive candidiasis [5].

Candida auris is a newly discovered fungus that has the potential to cause catastrophic infection outbreaks in healthcare institutions. It has spread most often in lengthy care institutions that care for persons with serious medical problems in the United States. However, occurrences of *Candida auris* have now been documented in COVID-19 units of tertiary care providing hospitals from the beginning of the epidemic. During the COVID-19 pandemic, modifications in normal infection control methods, such as restricted supply of hand gloves and gown, or reusing of such items, or alterations in sanitization and disinfected practices, may have contributed to these outbreaks. Multiple states have lately identified recently *Candida auris* infections with no ties to confirmed instances or hospitals overseas, implying a rise in undetected transmission. Because treatment centres and public wellbeing agencies resources have now been redirected to cope to COVID-19, screening for *Candida auris* colonisation, a key aspect of containment efforts, has become increasingly restricted [6].

Invasive cryptococcosis

COVID-19 in cryptococcosis is most commonly shown as meningoencephalitis in individuals having Human Immunodeficiency Virus (HIV) infections and a CD_4+ T-lymphocyte counts of less than 200 cells/L, SOT, allogeneic haemopoetic stem cell, or various other immunological impairment. Because of the difficulties in diagnosing cryptococcosis and identifying *Cryptococcus* species such as *Cryptococcus* neoformans and *Cryptococcus gattii*, Cryptococcus infection is typically diagnosed by a blend of routine laboratory and clinical confirmations. Growth culture, molecular detection, serology, histopathology and direct microscopy are some of the approaches used to confirm the infection. For diagnosing cryptococcosis, a sample of cerebrospinal fluid can also be combined along with India ink and seen under the microscope for the prototype appearance of *Cryptococcus*, which generally consists of slender budding encapsulated yeasts. Samples of culture must be put onto sabouraud dextrose agar medium and incubated at 30°C for 7 days within aerobic environment, with regular observations [7].

Furthermore, cultures obtained from individuals on antifungal medication might require more time in order to grow. *Cryptococcus* colonies are mucoid and creamy in appearance. *Cryptococcus* capsular polysaccharides may be identified and analysed from bodily secretions like sera, CSF, BAL, and diseased tissue. The Enzyme Linked Immunoassay (EIA), Latex Agglutination Test (LAT), and lateral flow immunoassay are the three different types of Cryptococcal Antigen (CrAg) identification assays now accessible (LFA). These procedures are quick, accurate, and specific, but they haven't been validated for pulmonary samples like as broncho alveolar lavage, sputum and pleural fluid. When existing diagnostic methods are unable in establishing a diagnosis of cryptococcosis, a genomic detection of *Cryptococcus* is necessary. Multiplex PCR, probe based microarrays, isothermal amplification technique, DNA sequencing for identification, and Pan fungal PCR are some of the molecular technologies used. All individuals with cryptococcosis should have a Cerebro Spinal Fluid (CSF) and a lumbar puncture examination (along with antigen) once the diagnosis has been made. *Cryptococcus* has the ability to spread throughout central nervous system, leading to cryptococcal meningitis [8].

Invasive fungal infection are associated with a significant chances of death in individuals with pre-existing morbidities, ranging from 8.2 percentage up to 42 percentage depending upon the fungal illness. Neutropenia individuals, patients undergoing chemotherapy, particularly for haematological malignancies, patients undergoing extended corticosteroid treatment or solid organ [9] transplantation, biotherapy or HSCT allografts or patients with severe pulmonary illnesses are also at risk for invasive aspergillosis. *Pneumocystis jerovci* infection is an opportunistic infection that can affect lymphopenic individuals, HIV-positive patients, and patients with haematological malignancies, solid organ transplants, or chronic respiratory illnesses. Invasive mucormycosis is becoming more common in susceptible patients, such as those with haematological malignancies, diabetes or chronic lung diseases, solid organ transplants, as well as surface level injuries in burns patients or post local trauma (thanks to improved diagnostic tools) [10].

We hypothesise that fungus super-infections linked with universal COVID-19 might well be overlooked and misinterpreted depending on the retrospective examination of influenza and severe acute respiratory syndrome information from throughout the world. COVID-19 patients also demonstrated upregulation of inflammatory markers like cytokines as well as an altered cell mediated immune response by lower CD_8+T cell and CD_4+T cell levels, demonstrating vulnerability to fungal co-infection as a very dangerous to life infectious illness. Furthermore, COVID-19 sufferers having a weak immune system such as extended neutropenia, HSCT, glucocorticoid usage, hereditary or later in life developed immune compromised condition, or tumour, are much more susceptible to developing fungal super infection. Latest diagnostic data (galactomannan, culture, direct microscopic examination, PCR based tests, histopathology, MALDI-TOF technologies, (1,3)-D-glucan, so on) and therapeutic approaches for extensive mycosis are presented here. In COVID-19 patients, we believe it's also essential to evaluate potential precipitating factors, kinds of invasive mycosis, strengths and limits of diagnostic tools, healthcare institutions, and the requirement for standardized or tailored therapy [11].

DISCUSSION

The link between the invasive mucormycosis sinusitis and the SARS-CoV-2 virus is harmful thus it must be taken more seriously. Uncontrollably high blood sugar and overuse of corticosteroids are the most prominent causes of disease aggravation, and must all be managed. In instances where the patient had prior infection with COVID-19 and now currently also having mucormycosis infection, timely intravenous anti-fungal therapy and adequate surgical intervention must be attempted, as a favourable outcome and less severe critical or fulminate illness course can be attained. There is still much more to gain knowledge about the triple threat that has arose as a result of the pandemic, but it will be critical in the future to constantly watch blood sugar levels as well as meticulously discuss whatever underlying health issues the individual has prior to actually starting steroid treatment for COVID-19 infection [12].

In order to properly manage Mucormycosis and reduce mortality, doctors must remain vigilant and raise knowledge across the public health care system. Numerous healthcare systems in our nation have established Mucormycosis Out Patient Divisions (OPD) to track every COVID-19 healed individuals during 10 days to 6 weeks, as during that time period they are especially more susceptible to the infections by fungus. In the event of any symptoms, patients must visit as soon as possible the closest urban primary health centre or even the appropriate OPDs in healthcare institutions. For the timely and prompt detection and care of Mucormycosis infection, the ICMR recommends a multidisciplinary team approach involving medical and dental professionals [13].

CONCLUSION

In this perspective, we believe that a comprehensive set of instruments should be proposed in order to successfully define the epidemiology of invasive fungal infections throughout this devastating pandemic:

- Adoption of detection technologies on a local level to improve early diagnosis and patient management by allowing for fast specialised antifungal therapy. An effective syndromic genomic technique (QPCR for *Pneumocystis jiroveci*, *Mucorales* and *Aspergillus*) might be used alongside culture for pulmonary specimens together in two-step process. If any of these tests are positive, blood bioindicators would be used to verify the findings, such as blood QPCR and/or serum galactomannan, and/or serum beta-D-glucan, and/or cryptococcal antigenemia for *Mucorales* or *Aspergillus*, depending upon the positive results.
- Nationwide multicentre investigations involving collaborative consortia of ICU and Mycology professionals to explore the possibility of fungal super infection during COVID-19.
- Participation in national and worldwide registries, such as the European confederation of medical mycology's.

Collectively aim:

- To understand better the occurrence and dynamics of fungal illnesses during COVID-19, especially during in the Intensive care unit stay.
- To enhance diagnosis by presenting a syndrome molecular method for fungal pulmonary illness in acute respiratory distress syndrome patients who may be distributed amongst all hospitals who receive COVID-19 cases.
- To improve prompt COVID-19 care delivery by actual time assessment in order to offer a focused treatment as soon as feasible. Aspergillosis, pneumocystosis, and mucormycosis all have distinct first line therapies, and empirical therapies would be resisted as and when feasible. Preventive interventions including such antifungal drugs and chemoprophylaxis and environmental measures might well be considered based on the epidemiological data provided, with the goal of lowering morbidity and death.

The following aspects must be addressed in order to prevent COVID-associated invasive fungal infections

- In order to improve glycaemic control in diabetics
- Systemic corticosteroids should be used as needed
- Antibiotic, antifungal, and other immune modulators should not be used until absolutely essential

Countries might experience a rise in fungal infections as a result of the delta variant's expansion, not just in India but across the world. It is critical for health care workers to be more aware and prepared, particularly when dealing with high risk patients. Controlling these fungal diseases will need faster diagnosis, improved treatment options, and more research.

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