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Mini Review

A Short Review on Mucormycosis and its Risk in COVID-19 Patients

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ABSTRACT

A life-threatening fungal infection known as mucormycosis occurs in immune compromised patients like patients having diabetic ketoacidosis, neutropenia, organ transplantation, increased serum levels of available iron etc. Mucormycosis is an emerging fungal infection worldwide, with devastating disease symptoms and diverse clinical manifestations. The most important underlying risk factors are immunosuppression, poorly controlled diabetes, iron overload and major trauma. The aetiological agents involved in the disease have been re-classified due to changes in taxonomy and nomenclature, which also led to appropriately naming the disease 'mucormycosis'. This article shortly explains the new nomenclature, clinical manifestations and risk factors and focuses on putative virulence traits associated with mucormycosis, mainly in the group of diabetic ketoacidosis patients.

A wide range of bacterial and fungal infection is seen in the patients with Coronavirus Disease 2019 (COVID-19). The use of steroids, monoclonal antibodies, broad-spectrum antibiotics may lead to the development of a preexisting fungal disease. Investigating pathogenesis and host response to invading hyphae of mucormycosis eventually will provide targets for novel therapeutic interventions. Physicians should be aware of the risk of resulting invasive fungal infections in patients with COVID-19 infection and diagnose the infections in such patients at earlier. The global mortality rate is high regardless of aggressive therapy, which consist of disfiguring surgical debridement and adjunctive toxic antifungal therapy.

Newer attempts to prevent and treat mucormycosis are crucial. Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has been sweeping across the globe.

Keywords: Mucormycosis; Diagnosis; Treatment; SARS-CoV-2; Corona virus 2019; Bacterial; Fungal infection

INTRODUCTION

A century ago, the 1918 influenza pandemic changed the world, when one third of the world's population became infected and >50 million people died. By examining lung tissue samples preserved in paraffin blocks, Morens, et al. [1], and colleagues from the National Institute of Allergy and Infectious Diseases found 80 years later that in fact the majority of deaths in the 1918 influenza pandemic resulted not from viral pneumonia, but from secondary bacterial pneumonia caused by common upper respiratory tract bacteria.

Present day another devastating worldwide pandemic we are facing, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) with to date>24 million individuals infected and a mortality rate>3%. Although superinfections were rarely reported in the beginning of the current pandemic, they are now on the rise, particularly reports about secondary fungal disease. SARS-CoV-2-Associated Pulmonary Aspergillosis (CAPA) has been the predominant fungal disease, adding insult to injury in Coronavirus Disease 2019 (COVID-19) patients with Acute Respiratory Distress Syndrome (ARDS), and although the pathogenesis is incompletely understood, there are several immunological mechanisms that may contribute to the development of CAPA and other fungal diseases. SARS-CoV-2 invasion results in the release of Danger-Associated Molecular Patterns (DAMPs) that act as endogenous signals that exacerbate

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the immune and inflammatory response leading to lung injury [2,3].

Besides, the diffuse alveolar damage with severe inflammatory exudation, COVID-19 patients always have immunosuppression with a decrease in CD4 T and CD8 T cells [4]. Critically ill patients, especially the patients who were admitted to the Intensive Care Unit (ICU) and required mechanical ventilation, or had a longer duration of hospital stays, even as long as 50 days, were more likely to develop fungal co-infections [5].

Hence, it is important to notice that COVID-19 patients can develop further fungal infections during the middle and latter stages of this disease, especially severely ill ones [6]. The Coronavirus Disease 2019 (COVID-19) infection caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) may be associated with a wide range of disease patterns, ranging from mild to life-threatening pneumonia. A wide range of bacterial and fungal co-infections may exist and may be associated with preexisting morbidity (diabetes mellitus, lung disease) or may develop as a hospital-acquired infection such as ventilator-associated pneumonia. India has a high prevalence rate of type 2 diabetes mellitus (8.9% of adults, 77 million patients), which is a well-known risk factor [7].

LITERATURE REVIEW

Mucormycosis in COVID-19 patients

Mucormycosis is an infection caused by fungi belonging to the order Mucorales [8]. *Rhizopus oryzae* is the most common organism isolated from patients with mucormycosis and is responsible for 70% of all cases of mucormycosis [9-11].

The major risk factors for mucormycosis include uncontrolled diabetes mellitus in ketoacidosis, other forms of metabolic acidosis, treatment with corticosteroids, organ or bone marrow transplantation, neutropenia, trauma and burns, malignant hematologic disorders, and deferoxamine therapy in patients receiving hemodialysis [12-14]. Because of the increasing prevalence of diabetes mellitus, cancer, and organ transplantation in the aging US population, the number of patients at risk for this deadly infection is dramatically increasing [15].

Host defense against mucormycosis clinical and experimental data clearly demonstrate that individuals who lack phagocytes or have impaired phagocytic function are at higher risk of mucormycosis. For example, severely neutropenic patients are at increased risk for developing mucormycosis. In contrast, patients with AIDS do not seem to be at increased risk for developing mucormycosis [16].

These findings suggest that neutrophils, but not necessarily T lymphocytes, are critical for inhibiting fungal spore proliferation. Furthermore, both mononuclear and polymorphonuclear phagocytes of normal hosts kill Mucorales by the generation of oxidative metabolites and the cationic peptides, defensins [17-19]. A recent study showed exposure of neutrophils to *Rhizopus oryzae* hyphae results in upregulation in Toll-like receptor 2 expression and in a robust proinflammatory gene expression with rapid induction of NF-jB pathway-related genes [20].

In the presence of hyperglycemia and low pH, which is found in patients with Diabetic Ketoacidosis (DKA), phagocytes are dysfunctional and have impaired chemotaxis and defective intracellular killing by both oxidative and nonoxidative mechanisms [21]. Mucorales are present in soil and decaying matter, in immunocompetent people, the spores of Mucorales that reach the respiratory tract adhere to the nasal mucus and are eliminated either by swallowing or sneezing, if there is any wound in the mucous membranes, the polymorphonuclear neutrophils phagocytose and destroy the fungal structures. Neutrophils are the host defense against these infections; therefore, individuals with neutropenia or neutrophil dysfunction are at the highest risk. This is seen clinically in leukemia patients and bone marrow transplant patients, who are at the highest risk.

Rhizopus arrhizus studies have demonstrated that the ketone bodies present in these patients are metabolized by a ketone reductase, which allows them to survive in conditions with an acid medium; thus, the fungi become hyphal forms in host tissues and then invade blood vessels. This extensive angioinvasion results in vessel thrombosis and tissue necrosis. Diabetes patients usually present with clinically uncontrolled diabetes and the increased amounts of circulating glucose, providing excellent conditions for the rapid development of filamentous structures that first bind to blood vessels and then penetrate them, completely clogging them in a few days and causing extensive areas of ischemic necrosis.

Also, metabolic acidosis prevents chemotaxis of polymorphonuclear leukocytes, causes decreased phagocytic activity, and reduces local inflammatory response in a patient whose immune system is already compromised from one or more additional diseases [22,23].

Epidemiology

The global popularity of COVID-19 and the possibility of fungal co-infections As the human-to-human transmitted disease, Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2), has been an emergency global public health events [24,25].

Till May 18, 2020, the COVID-19 has rapidly spread to 212 countries and caused nearly 5 million laboratory-confirmed cases and more than 310,000 deaths globally. Like SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERSCoV), SARS-CoV-2 is responsible for lower respiratory infection and can cause Acute Respiratory Distress Syndromes (ARDS) [26].

Coronavirus Disease 2019 (COVID-19) has become a pandemic. As of April 2, 2020, a total of 896,450 laboratory confirmed cases have been reported. The death toll from COVID-19 has soared quickly: 45,526 deaths have been reported globally, including 24,692 deaths in only a week (March 26, 2020, through April 2, 2020) [27].

The infection clinical manifestations tissue necrosis due to invasion of blood vessels and subsequent thrombosis are the hallmarks of invasive mucormycosis. Furthermore, infections with Mucorales are, in most cases, characterized by rapid progression. Mortality rates vary, depending on the site of infection and the condition of the host. Nevertheless, rates of death are estimated to range between 40% and 70%, even with antifungal therapy [28-33].

The challenge associated with diagnosis of mucormycosis is not only a reason for high mortality rates, but also makes it difficult to determine the exact incidence of the disease. Furthermore, studies show differences in capture periods, populations, and definition of proven/probable cases. A recent study carried out in France over a 10 year period, showed, that the annual population-based incidence rate increased by 7.4% per year (from 0.7 to 1.2 cases/million persons in 2006). The specific annual incidence rate rose by 24% per year in patients with haematological malignancies, which increased from 0.02 to 0.2 cases/million over time. Similar, Roden, et al. [11], reported an increase of mucormycosis in immune compromised patients in the 1980s and 1990s.

Classification of mucormycosis is performed according to the anatomic site of infection, reflecting in part the portals of entry in the human body. Spores enter the body either *via* the respiratory tract, through injured skin or *via* the percutaneous route (e.g., transmission of spores by contaminated needles or catheters), or *via* ingestion of contaminated food. Disease may present as rhino-orbital-cerebral, pulmonary, cutaneous/subcutanous, gastrointestinal or disseminated form.

Rhino-orbital-cerebral disease defines an infection that originates in the paranasal sinuses, following inspiration of spores, and possible extension to the brain. Sequentially, nose, sinuses, eyes and brain are affected. Symptoms at early stage of disease might be sinus pain, nasal congestion, fever, soft tissue swelling and headache. Nasal ulceration might occur as well. Progression of disease, which usually is rapid if not treated, results in extension to neighbouring tissues, thrombosis and further necrosis, causing painful black eschar on the palate or nasal mucosa. Extension to the eyes is possibly, leading to blurred vision or even complete loss of vision. From the eyes the disease can progress towards the central nervous system resulting in altered consciousness, cranial neuropathies or cerebral abscesses [34].

Treatment

The standard management of mucormycosis requires early diagnosis, a reversal of risk factors and underlying illness, surgical debridement, and prompt administration of intravenous antifungals-usually amphotericin B. This entails the prompt management of hyperglycemia, acidosis, and cessation of immunosuppressive agents when possible.

Amphotericin B is considered first-line therapy for mucormycosis. The lipid formulation of amphotericin B is administered in high doses intravenously once a day as initial therapy. The initial starting dose is 5 mg/kg IV daily, with a maximum dose of 10 mg/kg IV. Treatment duration depends upon the patient's clinical picture.

DISCUSSION

Surgical debridement of infected tissue should be urgently performed to limit the further spread of infection. Aggressive surgical debridement of necrotic tissue should take place immediately. This may involve radical facial resections, partial pneumonectomy, colectomy, etc., in accordance with the site of disease. Similar to necrotizing fasciitis, this requires very aggressive surgical management and often carried dramatic morbidity. Unless the immune status can be restored, the outcomes are unfortunately very poor even with the most aggressive therapies and drastic surgical intervention.

Posaconazole or isavuconazole has some evidence as second-line therapy in mucormycosis. For salvage treatment, posaconazole 200 mg IV four times daily is recommended. The guidelines do not support the combination of amphotericin and posaconazole. Other adjuncts include hyperbaric oxygen. The increased oxygen pressure improves the ability of neutrophils to kill the organism and facilitates wound healing.

CONCLUSION

The logical extension of the observations of the roles of key virulence factors is to develop therapeutic strategies that will translate to interventional clinical trials. Such clinical trials require considerable time and effort in study design, implementation, and analysis. The possible benefits of interventions that would complement existing therapies would be profound for patients with mucormycosis. COVID-19 is associated with a significant incidence of secondary infections, both bacterial and fungal probably due to immune dysregulation. The widespread use of steroids/monoclonal antibodies/broad-spectrum antibiotics as part of the armamentarium against COVID-19 may lead to the development/exacerbation of preexisting fungal diseases. Physicians should be aware of the possibility of invasive secondary fungal infections in patients with COVID-19 infection especially in patients with preexisting risk factors and should enable early diagnosis and treatment with the subsequent reduction of mortality and morbidity. The use of therapeutic agents should be monitored to achieve a therapeutic effect at the lowest dose and shortest durations. The use of broad-spectrum antibiotics, especially in the absence of infection, should be re-evaluated.

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