Clinical Therapeutics/Volume ▮, Number ▮, 2018

Recent Advances in the Pathogenesis of Mucormycoses

George Petrikkos, MD, PhD[1,2]; and Constantinos Tsioutis, MD, PhD[1]

[1]School of Medicine, European University Cyprus, Nicosia, Cyprus; and [2]Infectious Diseases Research Laboratory, Fourth Dept of Internal Medicine, University General Hospital Attikon, Medical School, National and Kapodistrian University of Athens, Athens, Greece

ABSTRACT

Purpose: The purposes of this review are to describe the pathogenesis of mucormycosis and to address recent research advances in understanding the mechanisms of fungal invasion and dissemination.

Methods: Studies and reviews published in the PubMed and ClinicalTrials.gov databases until December 2017 that explored or reported recent advances in the understanding of the pathogenesis of mucormycosis were reviewed.

Findings: To cause disease, fungal spores need to evade the innate immune system and germinate, leading to angioinvasion and tissue destruction. Recent studies have found that Mucorales are able to downregulate several host defense mechanisms and have identified the specific receptors through which Mucorales attach to the endothelium, facilitating their endocytosis and subsequent angioinvasion. In addition, certain conditions found to act through various mechanisms and pathways in experimental and animal studies, such as hyperglycemia, elevated iron concentrations, and acidosis (particularly diabetic ketoacidosis), increase the virulence of the fungi and enhance their attachment to the endothelium, rendering patients with uncontrolled diabetes and patients with iron overload susceptible to mucormycosis. The role and various antifungal functions of platelets and natural killer cells are highlighted, and the potential contribution of alternative therapies, such as manipulating the innate immune host defenses with granulocyte transfusions or administration of growth factors and using the antifungal effects of calcineurin inhibitors, are presented. Finally, directions and possible implications for future research are provided.

Implications: This article provides a comprehensive overview of research advances in the pathogenesis of infections caused by Mucorales and helps future studies develop effective treatment strategies and improve patient outcomes. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key words: diabetes, iron, mycormycosis, neutropenia, pathogenesis, Zygomycetes.

INTRODUCTION

Mucorales are fast-growing thermotolerant fungi that are ubiquitous in the environment. They have a worldwide distribution and are commonly found in decaying organic material or agricultural and forest soils.[1] Mucormycosis, the infectious disease caused by fungi in the subphylum Mucormycotina of the phylum Zygomycota,[2] has gained interest during the past few decades because of its increasing incidence in immunosuppressed populations. It is the second most common mold infection and the third most common invasive fungal infection in patients with hematologic malignant tumors and organ transplantations.[3,4] Among Mucorales, the most common causative agents of mucormycosis and the ones that have been studied the most are the *Rhizopus, Mucor,* and *Lichtheimia* species.[4,5] Although Mucorales share common and unique characteristics, fungi-specific differences in pathogenesis, virulence, and susceptibility to host immunity have been recorded, resulting in the observed differences in epidemiology, site of infection, disease severity, and outcomes.[6–8]

Mucorales are considered opportunistic pathogens, requiring a breach in the immune system and occurring most frequently in patients with neutropenia, hematopoietic and solid organ transplantation, iron overload, uncontrolled diabetes mellitus (particularly

Accepted for publication March 13, 2018.
https://doi.org/10.1016/j.clinthera.2018.03.009
0149-2918/$ - see front matter

in the presence of diabetic ketoacidosis [DKA]), or malnutrition or as breakthrough infections after prolonged exposure to antifungals.[1,9–11] However, they are also encountered in immunocompetent persons with skin lesions, traumatic injuries, and burn injury.[3,12,13]

Clinical forms of mucormycosis can be classified according to anatomical site of infection as follows: rhinocerebral or rhinoorbital, pulmonary, cutaneous, gastrointestinal, disseminated, or other (uncommon) presentations, such as endocarditis, osteomyelitis, peritonitis, and renal infection.[1] For all invasive clinical presentations, the pathogenetic hallmark of disease is rapid and aggressive invasion of blood vessels, resulting in vessel thrombosis, tissue necrosis, and hematogenous dissemination of the fungus.[1,3]

High degree of suspicion, early diagnosis, and aggressive treatment are required to achieve optimal survival.[1,8] Still, even in cases treated with extensive (and often amputating) surgical debridement and high-dose liposomal amphotericin B, overall mortality remains high and may even exceed 90% in certain populations.[1,14] Factors associated with increased mortality rates include prolonged neutropenia, site of infection and disseminated disease,[14] delayed treatment,[15] infection due to *Cunninghamella* species,[10] and increasing age.[9]

Although the risk factors, clinical presentation, and outcomes of mucormycosis have been described, the pathogenetic basis of the disease is only recently becoming clear. The present review focuses on the pathogenesis of disease caused by Mucorales species and aims to provide a brief overview of selected research advances in understanding the underlying mechanisms of mucormycosis and their clinical importance.

METHODS

For this literature review, the PubMed and Clinical Trials.gov databases were searched for related titles published until December 2017. Terms used to identify and retrieve relevant articles included combinations of *mucormycosis*, *Zygomycetes*, and *pathogenesis*. In addition, references noted in relevant articles were also accessed and reviewed. Studies and reviews that explored recent advances in the understanding of the pathogenesis of mucormycosis were reviewed and are discussed in this article.

OVERVIEW OF THE PATHOGENESIS OF MUCORMYCOSIS

Several characteristics of Mucorales have been identified that contribute to their aggressive nature of disease: innate thermotolerance[2]; rapid growth[2]; ability to bind on endothelial cell surfaces[2]; ability to obtain iron from the host organism[2]; down-regulation of host-defense genes implicated in pathogen recognition, immune defense, and tissue repair [16]; inhibition of interferon(IFY)-γ expression[17]; and an evolutionary duplication of systems implicated in energy use and virulence, as revealed in whole genome sequencing of *Rhizopus oryzae*.[18] An additional factor that significantly contributes to the poor prognosis of these infections is the inherent resistance of Mucorales to most available antifungals, with amphotericin B, posaconazole, and isavuconazole considered the most potent antifungals in vitro.[19]

Fungal spores are easily aerosolized and may enter the human organism through inhalation, local inoculation (eg. skin lesion), or ingestion through the gastrointestinal tract. Regardless of the point of entry, establishment of the fungi and development of mucormycosis requires certain critical steps,[2,4,16,20,21] including inoculation of spores into host tissue (eg, skin or alveoli, depending on the site of entry); evading phagocytosis by macrophages and neutrophils and germinating into hyphae (the angioinvasive form of the fungus); increasing their growth and virulence by taking advantage of individual host conditions (eg, hyperglycemia, ketoacidosis, iron overload, functional or quantitative neutropenia); attaching to the endothelium through specific unique receptors, subsequently inducing endocytosis and causing endothelial damage; causing clinically apparent disease through hemorrhage, thrombosis, and tissue necrosis; and finally entering the circulation and disseminating hematogenously, leading to systematic disease and multiorgan involvement.

LATEST DEVELOPMENTS IN PATHOGENESIS OF MUCORMYCOSIS

Phagocytes

The second and most important line of host defense against invading fungi is composed of mononuclear cells, macrophages, and neutrophils. This innate immunity barrier is basically 2-fold: tissue macrophages