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Mucormycosis – from the pathogens to the disease

U. Binder, E. Maurer and C. Lass-Flörl

Division of Hygiene and Medical Microbiology, Medical University Innsbruck, Innsbruck, Austria

Abstract

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 ketoacidotic patients.

Keywords: Angioinvasion, iron overload, ketoacidosis, mucorales, mucormycosis, risk factors, zygomycetes
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Corresponding author: U. Binder, Department of Hygiene, Microbiology and Social Medicine, Division of Hygiene and Medical Microbiology, Medical University Innsbruck, Fritz Pregl Str. 3/3, A-6020 Innsbruck, Tirol, Austria
E-mail: ulrike.binder@i-med.ac.at

Introduction

Invasive fungal infections caused by the members of *Mucorales* (mucormycosis) are relatively rare but have increased in the last years [1]. These aggressive and highly destructive infections occur predominantly in immunocompromised hosts, especially in patients with haematological malignancies or those receiving hematopoietic stem cell transplantation. Diabetic patients with ketoacidosis and patients with transfusional/dyserythropoetic iron overload are unique risk groups. The difficulties in diagnosis and subsequent antifungal treatment, partly due to a highly intrinsic resistance to many of the commonly used antifungal drugs [2,3], still leads to high mortality rates in certain patient groups [4].

Compared to other fungal pathogens, such as *Aspergillus fumigatus* or *Candida albicans*, only little is known so far on fungal properties leading to successful infection and host immune response to the various representatives of the Mucorales.

The Pathogens-Taxonomic Changes and Biological Characteristics

These pathogens display a highly diverse group, whose classification is in a constant state of flux. Until more than a decade ago, the phylum Zygomycota comprised the Mucorales, Entomophtorales and eight other orders which included fungi that were not considered to be human pathogens [5]. A comprehensive phylogenetic re-analysis of the kingdom Fungi, based on molecular methods [6], resulted in elimination of the polyphyletic phylum Zygomycota and placing the various taxa into the phylum Glomeromycota divided into four subphyla: Mucoromycotina, Entomophthoromycotina, Kickxellales and Zoopagomycotina (elevating the orders Mucorales and Entomophthorales to a subphylum status). Various gene regions have been used to separate lineages of the Glomeromycota, including ribosomal RNA subunits, elongations factors, α- and β-tubulins and mitochondrial small subunit ribosomal DNA [7–10]. This classification scheme might undergo further revision, but the

Mucoromycotina and Entomophthoromycotina are clearly separated into two different clades and are not related.

The changes in taxonomy were accompanied by a renaming of the disease caused by these aetiologic agents. The term 'zygomycosis', defined in 1976 by Ajello *et al.* [11], and describing any invasive fungal infection caused by species of the former phylum Zygomycota was replaced by either 'mucormycosis' or 'entomophthoromycosis' [9]. Due to the differences in morphology, ecology, epidemiology and the clinical pictures, the various causative agents are able to induce, 'mucormycosis' or 'entomophthoromycosis' is clinically a more specific name than 'zygomycosis'.

The Entomophthoromycotina, natural insect pathogens represented by the two genera Conidiobolus and Basidiobolus, are found in tropical and subtropical regions of the world, where they can cause chronic subcutaneous infections mostly in otherwise healthy patients [12].

The Mucoromycotina are found worldwide as common saprobes on decaying organic material or agricultural and forest soils. They are fast-growing organisms, characterized by large, ribbon-like hyphae with no or only few septae. Disease caused by representatives of the Mucoromycotina comprises severe and potentially life-threatening infections, particularly in the immunocompromised patient. The genera mainly involved in human disease (summarized in Table 1) are *Cunninghamella, Lichtheimia* (formerly *Absidia*), *Mucor, Rhizomucor, Rhizopus* and, depending on geographical distinction, *Apophysomyces* and *Saksenaea* [9,12,13]. The clinical characteristics will be further explained in the following chapters where we will focus on the Mucoromycotina as they play an increasing role in the clinical setting in the Western world.

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 [14–19]. 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) [20]. 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.* [19] reported an increase of mucormycosis in immunocompromised patients in the 1980s and 1990s.

TABLE 1. Classification of clinically relevant fungi formerly regarded as 'zygomycetes' [9,13]

Subphylum	Genus	Species most frequently isolated from patients
Mucormycotina	*Apophysomyces*	*A. variabilis*
	Cunninghamella	*C. bertholletiae*
	Lichtheimia (Absidia)	*L. corymbifera*
		L. ramosa
	Mucor	*M. circinelloides*
	Rhizopus	*R. arrhizus (oryzae)*
		R. microsporus
	Rhizomucor	*R. pusillus*
	Saksenaea	*S. vasiformis*
Entomophthoromycotina	*Basidiobolus*	*B. ranarum*
	Conidiobolus	*C. coronatus*

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 [21,22].

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 [22,23].

Clinical manifestations of pulmonary mucormycosis are very similar to those of pulmonary aspergillosis [15,24]. Chest radiographs from patients with pulmonary aspergillosis are indistinguishable from those with pulmonary mucormycosis. Interestingly, Camilos *et al.* [15,24] found independent predictors for pulmonary mucormycosis in a retrospective study reviewing clinical characteristics and CT features in 45 patients with cancer and either pulmonary aspergillosis or pulmonary mucormycosis. Appearance of more than ten nodules as well as the formation of micronodules were shown to be more

common in patients with pulmonary mucormycosis, and therefore regarded as significant predictors. Involvement of the sinuses was seen to occur only in patients who suffered from pulmonary mucormycosis. In general, fever and cough are the symptoms seen in most patients, together with pleuritic chest pain and dyspnoea. In case the pathogen is invading blood vessels, massive hemoptysis can occur, as well as a systemic dissemination of the disease.

Cutaneous mucormycosis can develop after inoculation of traumatic skin wounds or burns, or-in some rare cases, result from disseminated disease [19,25–27].

If primarily acquired by direct inoculation into wounds, acute inflammatory response is seen with the formation of abscesses, skin swelling and necrosis. Characteristically, the initially red lesions develop to black eschar. Further progression into deeper tissue effecting muscles, tendons or bone is possible and may also lead to disseminated disease [28]. In patients with large open wounds, lesions with areal hyphae, visible by eye, have been observed [29].

Gastrointestinal manifestation, caused by the uptake of contaminated food or beverages, is relatively uncommon [19]. In some cases, the use of contaminated herbal and homoeopathic medicines has been linked to gastrointestinal disease development [30,31]. The disease can affect any part of the alimentary system, but is mostly seen in the stomach [22,32]. Symptoms depend on the location of the disease and usually abdominal pain, distention together with nausea and vomiting are seen.

The disseminated form of mucormycosis may originate from any primary sites of infection. It has been reported in pulmonary, cerebral and cutaneous disease [19]. In most cases, the organ from which dissemination occurs is the lung, but the disease can also spread from the alimentary tract or wounds. Symptoms are of great variety, which make diagnosis even harder, but a metastatic skin lesion is certainly a sign to suspect disseminated mucormycosis.

Risk Factors

Although there have been some reports of Mucormycosis in immunocompetent people [19,22,32], it is still regarded an opportunistic disease and specific risk factors for mucormycosis in different patient populations have been identified. Mostly, the disease affects patients with haematological malignancies (HM) and prolonged severe neutropenia. Outstanding in comparison to other fungal infections is the high incidence amongst patients with poorly controlled diabetes, especially complicated by ketoacidosis (DKA), patients with iron overload or those who underwent major trauma [19,33–35].

Highest at risk for the development of mucormycosis are patients, who either have decreased amounts of mononuclear and polymorphonuclear phagocytes, that would inhibit germination of spores in healthy humans, or whose underlying disease disturbs the function of their phagocytotic cells. This includes patients with HM, patients who underwent hematopoetic stem cell transplantation and also patients who received high-dose corticosteroid treatment [36–38].

This also accounts for diabetic patients, especially those whose disease is poorly controlled. In DKA patients, elevated levels of free iron in serum are caused by a release of iron from binding proteins such as transferrin, which is due to a decreased pH level. The dysfunction of glucose and iron metabolism, and regulation of this, was shown to result in decreased phagocytic function and intracellular killing of *R. oryzae* [39–42]. Additionally, chemotaxis of neutrophils was shown to be impaired in murine models to whom high amounts of iron were given, but could be prevented by applying the iron chelator deferasirox [43].

Therapy with the iron chelator deferoxamine (DFO) further enhances the risk for angioinvasive mucormycosis [44], the reason for which was subsequently proven to be the ability of DFO to act as a xenosiderophore after free iron was bound. In contrast, other iron chelators, such as deferasirox and deferiprone, were shown not to be used as xenosiderophores by *Rhizopus* [43,45,46]. Therefore, these iron chelators do not increase the risk for development of mucormycosis.

The breakdown of the skin-barrier and/or soft tissue injuries, caused by local trauma or burns, is another risk factor for mucormycosis. Cutaneous mucormycosis or soft tissue infections have been linked to the use of contaminated bandages, needles or wooden tongue depressors in the clinical setting [47,48]. Also, infections have been acquired by insect and spider bites or surgical interventions. Importantly, cutaneous mucormycosis has been found in otherwise healthy humans [49–53].

Some cases have been reported where patients suffered from cutaneous mucormycosis who survived natural disaster such as tornadoes, hurricanes, tsunamis or volcanic eruptions, adding the occurrence of 'natural disasters' to the list of putative risk factors for mucormycosis [18,54–56].

Another predisposing factor of mucormycosis is the use of voriconazole in high risk patients, either for prophylaxis or treatment of other fungal infections. Voriconazole has been shown to be inactive against Mucorales *in vitro*. Mostly, patients who underwent hematopoetic stem cell transplantation were at risk for so called breakthrough infections under voriconazole therapy [57–59]. A surveillance study comparing patients with mucormycosis to patients with invasive aspergillosis (IA), showed that many risk factors for these different fungal

infections were overlapping. However, two risk factors seemed to be more specific for mucormycosis than for IA. One of which was the occurrence of mucormycosis as a breakthrough infection in patients who were given voriconazole as prophylaxis [17].

Neonatal prematurity or malnourishment are risk factors associated mainly with gastrointestinal mucormycosis [60].

Virulence Traits

To understand mucormycosis in more detail, it is of importance to obtain detailed knowledge about putative virulence traits of the causing agents, as well as to understand their interaction with the host immune system. For other fungal pathogens such as *A. fumigatus* some potential virulence factors have been discussed, but not many studies have been carried out on the members of the Mucoromycotina.

The small conidial size of *A. fumigatus* is often regarded as a putative virulence factor because the size allows conidia to enter the host via respiration. Spore size of the Mucoromycotina is variable, depending on the species 3–11 μm, but in general bigger than those of *A. fumigatus* for example. Still, they can be inhaled and cause disease in the human lungs.

Obviously, the clinically relevant species of the Mucoromycotina are thermotolerant and therefore able to grow at 37°C, some even at higher temperatures. Nevertheless, in a recent article by Schwartze *et al.* [61] the growth speed of clinically relevant *Lichtheimia* spp. strains was compared to *Lichtheimia* species of which no human cases where reported so far. In part, slower growth at 37°C of some *Lichtheimia* species, such as *L. hyalopsora*, might explain low virulence potential of these strains, while for other slow growing Mucorales where shown to be fully virulent. Therefore, no clear correlation between growth speed at host temperature and differences in virulence potential was detected.

On the secretion of proteases, which might contribute to an easier invasion of host tissue and increase host damage, not much is know yet, except that some representatives of the Mucoromycotina have a lot more genes encoding for lytic enzymes than other fungal pathogens [39,62,63].

Another virulence factor is iron acquisition [44], as iron is an essential element for fungal cell growth and development. This was shown to play a major role in virulence of *A. fumigatus* [64]. Low iron concentrations in the host environment, achieved by bound iron to proteins, such as transferrin, ferritin and lactoferrin, is an effective defence strategy against invading microorganisms. This strategy seems to be highly effective against Mucorales, as they were shown to be extremely restricted in growth in normal serum unless exogenous iron is added [37,65]. Some pathogens are able to overcome this limitation by special iron uptake systems. In the case of *A. fumigatus* these are reductive iron assimilation or the production and secretion of siderophores [64]. Contrary to *A. fumigatus*, *R. oryzae* lacks genes for non ribosomal peptides, the enzymes that produce hydroxamate siderophores, the most common group of fungal siderophores [62]. It therefore fully depends on rhizoferrin, which is less efficient, reductive iron assimilation by rFTR1 and possibly iron acquisition through degradation of heme by heme oxygenase. Sequence analysis of the *Rhizopus*-genome revealed two putative genes encoding heme oxygenases in *Rhizopus* [39,66]. The fact, that the expression of high affinity iron permease rFTR1 is required for full virulence of *Rhizopus* in a DKA mouse model, additionally underlines the correlation of iron uptake and virulence [44,66]. Nevertheless, iron homeostasis is not fully characterized in any of the Mucorales yet. Clinically, the link between iron metabolism in both fungus and host is of high relevance, because iron overload *per se* is one major risk factor in mucormycosis as described in the paragraph on risk factors for mucormycosis [63,67].

One hallmark of mucormycosis is angioinvasion, and the ability of a fungal pathogen to invade host cells is a putative virulence factor. Recently, the glucose regulated protein 78 (GRP78) has been identified to enable invasion of the pathogen via an endocytotic mechanism. This endothelial cell receptor exclusively interacts with Mucorales and not other fungal pathogens such as *A. fumigatus* or *C. albicans* [68,69]. While GRP78 was shown to be necessary for invasion of endothelial cells, a receptor involved in-or the mechanism of-adhesion to endothelial cells was not determined so far [69]. These findings were successfully linked to DKA by showing that iron availability and high glucose levels affect the receptor function. In contrast, chelating iron with phenanthroline prevented endothelial invasion and subsequently host cell damage. Additionally, high iron and glucose levels, as they occur in DKA patients, induce expression of GRP78 both *in vitro* and in DKA mice [69].

Another aspect contributing to virulence of a pathogen is its capability to evade recognition and elimination by the host immune system. Phagocytosis of spores was shown to be less efficient in comparison with conidia of *A. fumigatus*, which might partly be attributed to their size and is, similar to damage and killing by phagocytes, species dependent [70]. Whether reduced killing of this group of pathogens is due to differences in recognition patterns is not fully understood yet. Nevertheless, a difference in PAMP (pathogen associated molecular patterns) recognition between *R. oryzae* and *A. fumigatus* has been shown. Whereas recognition of *A. fumigatus* is mediated by toll-like receptor 2 (TLR 2) and TLR 4, only TLR 2 seems to

be involved in recognition of *R. oryzae* [71,72]. This discrepancy might be attributed to differences in cell wall composition between *Aspergilli* and the Mucorales. This needs to be further investigated, because cell wall composition is not fully deciphered for all pathogenic Mucorales yet [62,73]. Also, variations in cytokine release in response to members of the Mucorales compared to *Aspergillus* have been detected. *Rhizopus*, for example, causes a more pronounced proinflammatory response with elevated IL-6 release and TNF-α secretion [74,75]. In general, differential regulation of genes involved in immune response to *R. oryzae* was shown to be less pronounced than in response to *A. fumigatus* conidia, that induced a fourfold greater number of differentially expressed genes in human monocytes [36,73,76].

Concluding Remarks

The key points of mucormycosis, such as the rapid growth of the various pathogens causing disease, their high affinity to blood vessels, plus the unique susceptibility of DKA patients to this disease have long been known, but the molecular mechanisms involved are still partly deciphered so far. The identification of one receptor (GRP78) and its necessity for virulence and regulation by both iron and hyperglycaemia has been a break-through in mucormycosis research. Hopefully, in the next years additional members of the Mucorales will have their genomes sequenced and annotated, which will help to decipher virulence traits and to better understand the host-pathogen interaction.

Transparency Declaration

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