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"Black Fungus Unveiled": Exploring the Menace and Medication

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Abstract: *In recent years, there has been significant progress in treating mucormycosis. Beginning therapy as early as possible is crucial to achieve better outcomes. Therefore, maintaining a high level of suspicion and performing biopsies on possible lesions aggressively is essential. Whenever feasible, surgical removal of infected or necrotic tissue should be performed as the data supports its need. Lipid formulations of amphotericin B are now the standard treatment for mucormycosis as they are superior in safety and efficacy. Posaconazole may be useful as salvage therapy, but there is insufficient data to recommend it as the primary therapy. Preclinical and limited retrospective clinical data suggest that the combination of lipid formulations of amphotericin and echinocandin improves survival during mucormycosis. Therefore, additional studies are required to explore the potential of iron acquisition abrogation as an adjunctive treatment of mucormycosis. Combination polyene-posaconazole therapy was not beneficial in preclinical studies. For selected patients, adjunctive therapy with recombinant cytokines, hyperbaric oxygen, and/or granulocyte transfusions can be considered. Large-scale, prospective, randomized clinical trials are necessary to define optimal management strategies for mucormycosis.[1]*

Keywords: Celosia argentea, emulgel, medicinal plants, gelling agent, co-surfactant, surfactant

I. INTRODUCTION

History

Amphotericin B is an antifungal substance that was first extracted in 1955 from Streptomyces nodosus, a bacterium found in the soil of the Orinoco River region of Venezuela. It was discovered by researchers at the Squibb Institute for Medical Research who were looking for ways to combat fungal infections. Although two antifungal substances were extracted from the soil culture, Amphotericin B proved to be more effective. For many years, it was the only effective therapy for invasive fungal disease until the development of the azole antifungals in the early 1980s. [2]

Diagnosis

Mucorales are a type of fungi that can be found everywhere and are particularly common in soil and decomposing organic matter. [3,4]. A diagnosis of mucormycosis is often misdiagnosed as invasive aspergillosis among haematology patients. In haematology patients, an antemortem diagnosis of mucormycosis is only made in 23-50% of cases. [5,6]

Treatment

Potassium iodide, miconazole, cotrimoxazole, ketoconazole, itraconazole, amphotericin B, terbinafine, hyperbaric oxygen, and surgical debridement have been used in various combinations with variable success.[7]. Early diagnosis, removal of predisposing factors, timely antifungal therapy with surgical removal of all infected tissues, and adjunctive therapies are four major factors to eradicate Mucormycosis.[8]. If possible, the best treatment for mucormycosis is the removal of infected tissues. However, this is easier in some cases, such as rhino-cerebral or cutaneous infections, but it is impossible to operate in many cases, such as pulmonary disease or if the virus invades the cerebral area."[9]. A study has shown that early surgical removal of infected sinuses in rhino-cerebral mucormycosis can prevent the infection from spreading to the eyes, resulting in higher cure rates of up to 85%. Additionally, if surgery is performed with antifungal agents, the mortality rate can be reduced from 70% to 14%.[8].

Epidemiology

In India, Rhizopus species are the most common cause of mucormycosis, but emerging species like Apophysomyces elegans, A. variabilis, and Rhizopus homothallicus, as well as uncommon agents such as Mucor irregularis and Thamnostylum lucknowense are also being reported. [10,11]. Mucormycosis is a fungal infection that is mainly caused

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by breathing in fungal sporangiospores present in the air or by direct inoculation of the organism through damaged skin or gastrointestinal tract mucosa. The incidence of mucormycosis is influenced by seasonal variations, with most cases being reported between August and November.[12]. According to a recent study on the epidemiology of mucormycosis in Australia, trauma patients tend to be infected more frequently with uncommon, non-Rhizopus species. Patients infected with Apophysomyces or Saksenaea are typically immunocompetent, contracted the infection through trauma and had their infection localized to the skin, soft tissues, and bones.[13].

Drugs used in the treatment of Mucormycosis

Amphotericin B and its lipid formulations target ergosterol in fungal walls, destabilizing cells. They are FDA-approved for treating mucormycosis.[14]. It has been found that AMB lipid formulations (including liposomal AMB, LAMB, and the AMB lipid complex, ABLC) are more effective than conventional AMB, with improved therapeutic indexes. However, in vitro studies have shown that AMB activity against Mucorales varies greatly. Recent in vivo and in vitro studies suggest that to effectively treat mucormycosis, surgical debridement, and antifungal treatments should be considered. The optimal dosage of these drugs depends on the specific disease areas and the patient's condition. When the infection involves the brain or occurs in solid organ transplant recipients, a high dose of LAMB and ABLC (10 mg/kg/day) is considered therapeutic. Depending on the response to the first line of treatment, the continuation of LAMB/ABLC treatment at a high dose is often recommended when the disease is stable or there is only a partial response to the drugs. However, in the case of progressive disease, treatment with LAMB or ABLC in combination with posaconazole is recommended. [15,16].

Recent complications of black fungus with COVID-19 patients: -

The coronavirus has been linked to various bacterial and fungal infections that can take advantage of a weakened immune system.[17]. After the outbreak in China in December 2019, COVID-19 has been linked to various modifications related to pathophysiology, diagnosis, and complications. This may lead to a wide range of disease forms, including rhino, orbital, and cerebral mucormycosis. Several cases of such disease manifestations have been reported during COVID-19 illness. Patients with iatrogenic immunosuppression, haematological malignancies, diabetes mellitus, and acquired immunodeficiency syndrome are at risk. In COVID-19 patients, hypoxic conditions can occur due to endothelial barrier disruption and impaired oxygen diffusion capacity.[18].

Antifungal agents against mucormycosis: -

Researchers are working on a promising treatment for mucormycosis. In mice with disseminated mucormycosis, survival rates were enhanced by combinations of echinocandin and lipid polyenes.[19].

Important antifungal drugs for the treatment of mucormycosis and their possible mode of action are presented in Table 1.[20,21].

II. CONCLUSION

Mucormycosis is a fungal infection that can be fatal for people with weakened immune systems. It is more common in individuals who are on hemodialysis, taking high-dose glucocorticoids, have significant burns, or have uncontrolled diabetes mellitus**.** The mortality rate of this illness is more than 40%, and it can even reach 100% in patients who have disseminated illness, brain infection, or persistent neutropenia. A comprehensive review of global efforts towards the discovery and development of therapeutic agents for treating mucormycosis is provided in this article. The review focuses specifically on the mechanism of action of various therapeutics, including new antifungal agents being investigated as part of the global response to control and combat this lethal infection. As indicated in the review, various antifungal agents can be promising for treating this life-threatening disease. However, large-scale clinical investigations are strongly suggested to address these issues.[22].

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Table 1. Important antifungal drugs for the treatment of Mucormycosis and their possible mode of action. [20,21]

S. No	Antifungal Drug	Target*	Mode of action
1	AmB	Ergosterol in the fungal cytoplasmic membrane	"Ion channel formation, ergosterol sequestration, and induction of reactive oxygen species are the processes that are being referred to in the text."
2	Itraconazole	lanosterol 14-α-demethylase	Inhibits the biosynthesis of ergosterol
3	Posaconazole	lanosterol 14-α-demethylase	Inhibits the biosynthesis of ergosterol
4	Isavuconazole	lanosterol 14-α-demethylase	Inhibits the biosynthesis of ergosterol
5	Echinocandins	*β*-(1,3)-D-glucan synthase	Inhibition of biosynthesis of *β*-(1,3)-D-glucan
6	Oteseconazole (VT-1161)	lanosterol 14α-demethylase	Inhibits the synthesis of ergosterol
7	Terbinafine	Squalene epoxidase	Inhibits the synthesis of ergosterol
8	Rapamycin	FKBP12	FKBP12-dependent inhibition of a TOR kinaseInhibits calcineurin phosphatase activity
9	Tacrolimus (FK506)	FKBP12	FKBP12-dependant inhibition of PP2B
10	Manogepix and prodrug fosmanogepix	Inositol acyltransferases (Gwt1)	Prevents the maturation of GPI-anchored proteins
11	Jawsamycin	Catalytic subunit Spt14/Gpi3 of the fungal UDP-glycosyltransferase	Inhibits the biosynthesis of GPI-anchored proteins
12	Fluvastatin and other statin	Hydroxymethylglutaryl-CoA (HMG-CoA) reductase enzyme	Inhibits the biosynthetic pathway of sterols
13	Anti-CotH3 antibodies	16-mer peptide region of the CotH3 of Mucorales	Bind to glucose-regulated protein 78 (GRP78) on endothelial cells.

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