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The Mystery of Mischievous Mucormycosis, Life and Death Dilemma

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Abstract
Mucormycosis (also called zygomycosis) is a rare infection caused by organisms that belong to a group of fungi called Mucoromycotina in the order Mucorales. These fungi are typically found in the soil and associated with decaying organic matter, such as leaves, compost piles, or rotten wood. Saprophytic zygomycetes (Eg . Mucor, Rhizopus) are found in tissues of hosts. In persons with diabetes, extensive burns, leukemia, lymphoma, or other chronic illness or immunosuppression. Rhizopus species, Mucor species, and other zygomycetes invade proliferate in the walls of blood vessels, producing thrombosis. Of note, due to its relatively limited activity, itraconazole prophylaxis in immunosuppressed patients may select the fungi in phylum Zygomycota as the cause of infections. Rhino cerebral infections Usually occur during a DKA episode, disrupting host defense mechanisms, thereby permitting Rhizopus oryzae. The correction of acidosis inhibits such growth. The clinical characters are nasal stuffiness, epistaxis, and facial pain. Later, proptosis, chemosis, and ophthalmoplegia. Fever and confusion. Black necrotic eschar on the nasal turbinates or palate.

Keywords; *Mucormycosis, Pulmonary mucormycosis, Leukemia, Neutropenia, Necrotizing Fasciitis.*

Introduction

Gastrointestinal mucormycosis, Rhino cerebral, Liposomal amphotericin B Introduction Mucormycosis is a rare, emerging fungal infection with high morbidity and mortality. (1) It is impossible to conduct large, randomized clinical trials, epidemiology, diagnosis, and treatment, originate from case reports (2). Relatively large epidemiological studies were performed either on a national level (3). For example, in patients with selected underlying diseases, hematopoietic stem cell transplantation (HSCT) (4). The major risk factors are neutropenia, uncontrolled diabetes(5). Mucormycosis infections occur following inhalation, implantation, or ingestion of spores. Angioinvasion likely contributes to the organism's capacity to hematogenous disseminate to other target organs (6). Invasive mucormycosis is the third most frequent invasive fungal infection (IFI) (7). Humans acquire the infection predominantly by inhalation of sporangiospores. (8,9) *Rhizopus arrhizals* are the most common agent causing mucormycosis globally (10 Mucormycosis is associated with angio-invasion and high mortality (11). The infection is increasingly reported in diabetes mellitus, solid organ transplants, and corticosteroid therapy (12). Diabetes mellitus is the most common risk factor in the Asian continent. (13,14). In recent years, health-care-associated mucormycosis is increasingly documented (15). *Rhizopus arrhizals* is causes mucormycosis followed by Lichtheimia, Apophysomyces, Rhizomucor, Mucor, and Cunninghamella species (16,17). An ulcer or a dental extraction in the mouth can be the port of fungal invasion (18). Risk factors for invasive mucormycosis include long-term neutropenia, intravenous drug use, malnutrition, stem cell or solid organ transplantation, severe skin damages such as burns and surgical suture sites (19). Diagnosis is usually made by clinical suspicion and a histopathological examination (20).

History

About 250 million years ago, fungi became abundant in many areas, based on the fossil record. (21) Since fungi do not bio mineralize, they do not readily enter the fossil record. (22). One from the Ordovician has been dismissed because it lacks any distinctly fungal features and is held by many to be contaminated (23). The evolution of fungi has been going on since fungi diverged from other life around 1.5 billion years ago (24, 25). Lichen-like

fossils have been found in the Doushantuo Formation in southern China, dating back to 635–551 Ma (26)

How can fungus cripple your immune system?

Relatively little is known about the immune response to fungal agents. Cellular immunity appears to be the most important immunologic factor in resistance to fungal infections, although humoral antibody certainly may play a role. Th1-type responses are protective via the release of IFN-y. By constant Th2 responses (IL-4 and IL-10) typically correlate with disease exacerbation and pathology. The intense mononuclear reactions direct the importance of cellular reactions by the intense mononuclear infiltrate, and granulomatous reactions that occur in tissues infected with fungi and that fungal infection are frequently associated with depressed immune reactivity of the delayed-type (Opportunistic infections) (27). Mice inhalation of *Aspergillus fumigatus* leads to a rapid increase in philosophic numbers in the spleen, blood, and lung (28). This increase is IL-3 dependent.IL-3 is important for the recruitment of basophil into mediastinal lymph nodes following Nippostrongylusbrasiliensis infection. (29). Life-threatening fungal infections have risen sharply in recent years, owing to advances and medical care intensity that may blunt patients' immunity. These insights create a foundation for developing new immune-based strategies to prevent or enhance fungal diseases. (30) These nature experiments offer a unique opportunity to develop new knowledge in immunological research and devise immune-based therapeutic approaches for patients infected with fungal pathogens (31).

Pathogenicity and Clinical Significance

Mucor spp. are among the fungi causing the group of infections referred to as zygomycosis. Although mucormycosis has often been used for this syndrome, zygomycosis is now the preferred term for this angio-invasive disease. Zygomycosis includes mucocutaneous and rhinocerebral infections, septic arthritis, dialysis-associated peritonitis, renal infections, gastritis, and pulmonary infections. Diabetic ketoacidosis and immunosuppression are the most frequent predisposing factors. Desferrioxamine treatment, renal failure, extensive burns, and intravenous drug use may predispose to zygomycosis development. Of note, due to its relatively limited activity, itraconazole prophylaxis in immunosuppressed patients may select the fungi in phylum Zygomycota as the cause of infections. Rhino cerebral infections Usually occur during a DKA episode, disrupting host defense mechanisms, thereby permitting Rhizopus oryzae. Such growth is inhibited by the correction of acidosis. Clinical characters are nasal stuffiness, epistaxis, and facial pain. Later, proptosis, chemosis, and ophthalmoplegia. Fever and confusion. Black necrotic eschar on the nasal turbinates or palate.

Complications

Multiple cranial nerve palsies. Visual loss. Frontal lobe abscess. And Carotid artery or jugular vein thrombosis causing hemiparesis. Pulmonary mucormycosis are common in Leukemia, Neutropenia, and patients on Chemotherapy. Cutaneous mucormycosis may lead to Necrotizing Fasciitis. Gastrointestinal mucormycosis produces GIT disturbances.

Microbiology Laboratory Investigations

Wet mount, Gram Stain, BHI broth, Fungal culture, Blood culture Biotechnology and Molecular Diagnosis of Mucormycosis. PCR, RFLP, DNA sequencing that targets the 18S ribosomal DNA of Mucorales, Antigen Detection & Specific T cells. Galactomannan and ß-D Glucan – If negative, likely invasive mucormycosis than IPA. Mucorales-specific T cells - enzyme-linked immunospot (ELISpot) assay, Sequencing of Internal Transcribed Spacer (ITS) of rRNA techniques.

Rapid detection of Susceptibility

Few data are available on the in vitro profile of Mucor spp. In an in vitro study comparing the in vitro activity of amphotericin B, ketoconazole, itraconazole, and voriconazole, amphotericin B yielded the lowest MICs against Mucor spp. Among the azoles, while the MICs of ketoconazole and itraconazole were comparable, voriconazole yielded considerably high MICs.Similar to the other genera belonging to the phylum Zygomycota, treatment of Mucor infections remains difficult. Due to its property to invade vascular tissues, infarction of the infected tissue is common, and mortality rates are very high. Early diagnosis is crucial, and surgical debridement or surgical resection, as well as antifungal therapy, are usually required. Amphotericin B is the most commonly used antifungal agent. Liposomal amphotericin B and other lipid-based amphotericin B formulations, such as amphotericin B colloidal dispersion, have also been used in some cases with zygomycosis. Response rates are, unfortunately, unsatisfactory. Reversal of immunosuppression is one of the most significant factors influencing the clinical outcome. Adjuvant therapy with cytokines, particularly the colony-stimulating factors, has anecdotally been associated with better clinical response. There are also a few data on the successful use of fluconazole and terbinafine in zygomycosis treatment, which require validation. Interestingly, fluconazole combined with trovafloxacin or ciprofloxacin proved to be effective in a murine model of pulmonary zygomycosis.

Animal Models to Study Mucormycosis

Various model hosts, ranging from mammalian species such as laboratory mice over other vertebrates to alternative invertebrate hosts, have been employed to analyze pathogenesis and the impact of potential risk factors on infection, to compare the virulence of mucoralean species and strains, and to determine the efficacy of antifungals. Mucormycosis is a rare but often fatal or debilitating infection caused by a diverse group of fungi. Animal models have been crucial in advancing our knowledge of mechanisms influencing mucormycosis's pathogenesis and evaluating therapeutic strategies (32). In general, mammalian species are considered the gold standard for studying human diseases due to similarities in anatomy and physiology. Various animal models have been developed in mice and rats to study type 1 and type 2

diabetes. (33) Indeed, various species, ranging from laboratory mice, rats, guinea pigs, and rabbits, to more exotic species like bank voles or Asian water buffalo calves can be infected experimentally with pathogenic micromycetes (34). Most studies, however, used mice or rabbits (35).

Treatment

Mucormycosis is a serious infection and needs to be treated with prescription antifungal medicines. Early recognition, diagnosis, and prompt administration of appropriate antifungal treatment are important for improving patients' outcomes with mucormycosis. 2 Amphotericin B, posaconazole, and isavuconazole are active against most mucormycetes. Lipid formulations of amphotericin B are often used as first-line treatment (36). Medications active against Aspergillus such as voriconazole are not active against mucormycetes. There is some evidence suggesting that pre-exposure to voriconazole may be associated with an increased incidence of mucormycosis in some patients (37,38). In addition, surgical debridement or resection of infected tissue is often necessary, particularly for rhino cerebral, cutaneous, and gastrointestinal infections (39). Control of the underlying immunocompromising condition should be attempted when possible. 2 The efficacy of other treatments such as hyperbaric oxygen therapy is uncertain but has been useful in certain situations (40).

About frontiers of Mucor research

Mucormycosis is a rare but often fatal or debilitating infection caused by a diverse group of fungi. Animal models have been crucial in advancing our knowledge of mechanisms influencing the pathogenesis of mucormycosis and to evaluate therapeutic strategies. Recent therapeutic advances have the potential to improve outcomes of mucormycosis. Lipid formulations of amphotericin B (LFAB) have evolved as the cornerstone of primary therapy for mucormycosis. Posaconazole may be useful as salvage therapy, but it cannot be recommended as primary therapy for mucormycosis based on available data. Combination polyene-posaconazole therapy was of no benefit in preclinical studies. Adjunctive therapy with recombinant cytokines, hyperbaric oxygen, and/or granulocyte transfusions can be considered for selected patients (41)

A shortened version of large work

The first is usually man or animals, and that of the other two is spores in the soil. The infections run a slow course. The tissue reaction is often granulomatous but may be negligible. Diagnosis by direct microscopy (often biopsies) and the naked eye and microscopically features of the organism in culture. Treatment is slow even when successful, and prevention is by avoidance (if possible) rather than by immunization. The systemic infections share these features and also have others in which they resemble pulmonary tuberculosis. They are acquired by inhalation; the lung's initial focus is commonly asymptomatic, and the infected person develops a delayed type of hypersensitivity reaction demonstrable in a tuberculin-type skin test with fungal antigen. There may be calcification or cavitation of the focus and possibly subsequent reactivation of the disease, and finally, if it disseminates, the infection carries a serious prognosis. Laboratory diagnosis of the mycoses particularly careful collection of specimens as they are often contaminated with faster-growing organisms, fungal, and bacterial. For microscopy, the associated tissue cells need to be cleared, i.e., rendered transparent, with KOH or dimethyl sulphoxide, and except yeasts, wet unstained preparations are more revealing than dry, stained smears. Sections of biopsies stained by methenamine-silver techniques may be extremely valuable. Cultures essential for the identification of most fungi and proves useful in guiding treatment. Serological and skin tests may help but need experienced interpretation. (42)

An opinion arrived at through a process of reasoning

Fungal infections cause mild as well as very serious human diseases. The fungus was adjacent to sinuses and with severe acidosis due to uncontrolled diabetes or late terminal disease stages. The organisms are normally saprophytic and Phycomycetes, usually Absida, Rhizopus, or Mucor. The infection develops into cellulitis, with the organism showing a predilection for blood vessels as an Aspergillus does when invading the lungs. Sinus infections spread rapidly to the orbit and brain, and most cases have been fatal. The phycomycetous are common free-living fungi with non-septate hyphae and reproduce asexually by producing large spores within a sporangium that develops at the end of aerial hyphae. They grow and sporulate rapidly. Wounds very rarely become infected with filamentous fungi. (43) Though mucormycosis exhibits several syndromes with isolated gastrointestinal system, skin, kidney, and central nervous system, the commonest and most devastating manifestations are rhino-orbital cerebral and pulmonary syndromes. (44) These fungi have a ketone reductase enzyme that permits a high-glucose environment (45). Concomitant sinusitis and voriconazole prophylaxes are significantly associated with the development of pulmonary mucormycosis (46). Cavitary lesions with the “air crescent sign” are rare (47). The high mortality observed in pulmonary mucormycosis may be related to delays in the diagnosis, poor host response (e.g., neutropenia), and limited available therapy. (48)

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