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Cell & Cellular Life Sciences Journal
ISSN: 2578-4811

The Mycelial Mire-Mucormycosis

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Mini Review

Volume 6 Issue 2

Received Date: July 29, 2021

Published Date: August 27, 2021

DOI: 10.23880/cclsj-16000162

Abstract

Mucormycosis is an infrequent, angio-invasive, fatal fungal infection incriminating immunocompromised individuals. Mucormycosis commonly arises due to infection with rapidly progressive, pauci-septate moulds or fungal species such as Rhizopus, Mucor, Lichtheimia (Absidia) or Entomophthorales. Mucormycosis is a significant, secondary fungal infection associated with SARS-CoV-2 infection wherein pulmonary mucormycosis and rhinocerebral mucormycosis are commonly engendered. Especially, a triad of mucormycosis, diabetes mellitus and prolonged corticosteroid therapy is exemplified in subjects with COVID-19. Elevated plasma glucose, reduced pH, free iron and ketones along with decreased white blood cell phagocytic activity amplifies propagation of mucor. Mucormycosis commences with inhalation or ingestion of environmental spores which are subsequently phagocytosed within polymorphonuclear cells. Mucormycosis appears within the nasal cavity, paranasal sinuses, orbit, central nervous system (CNS), pulmonary parenchyma, gastrointestinal tract (GIT), cutaneous surfaces, jaw bones, joints, cardiac muscle, renal parenchyma and mediastinum. Infiltration with giant cells, vascular thrombosis and eosinophilic necrosis of encompassing soft tissue is pathognomonic of mucormycosis. Serological assessment with enzyme linked immunosorbent assay (ELIZA), immunoblot or immunodiffusion assays and molecular assays as polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP) or DNA sequencing techniques are optimal for diagnosing mucormycosis. Appropriate therapy of mucormycosis is contingent to antecedent commencement of antifungal agents, treatment of comorbid conditions and debridement of infected tissue.

Keywords: Mire-Mucormycosis; DNA; Fungal Species; SARS-CoV-2

Preface

Phycomycosis or Zygomycosis was initially scripted by Paltauf in 1885 and subsequently designated as Mucormycosis by Baker in 1957 as an aggressive infection engendered by *Rhizopus spp* [1,2]. Mucormycosis is an infrequently discerned, fatal fungal infection incriminating individuals with incompetent immunity. An angio-invasive fungal infection, mucormycosis is engendered by diverse, specific, filamentous fungi of order Mucorales. Diverse species of mucomycosis generating filamentous fungi of order Mucorales can be isolated from the soil, bread, decomposing vegetables, fruits, plants, animal matter or dust. Mucormycosis induced severe infections are accompanied with enhanced mortality. Rhizopus is a common species associated with mucormycosis along with Mucor and Lichtheimia (Absidia). Mucormycosis is also associated with non angio-invasive, non-disseminating moulds of the order Entomophthorales. Mucormycosis is exemplified by a variety of rapidly progressive, pauci-septate moulds or fungal species wherein pathogenesis or precise disease mechanism may not be identical. Also, fungal dissemination to diverse organs may induce various categories of mucormycosis which constitute a brisk, angio-invasive disease of worldwide geographic distribution, circumvention and regulation of mucormycosis is contingent

to preliminary disease discernment and maintenance of competent immune system. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with several opportunistic bacterial and fungal infections wherein Aspergillosis and Candida are prominent fungal pathogens inducing co-infection in COVID-19. Mucormycosis is a significant, secondary fungal infection associated with SARS-CoV-2 infection. Commonly, pulmonary mucormycosis and rhinocerebral mucormycosis are associated with COVID-19. As the immune status of individuals infected with SARS-CoV-2 is compromised, proportionate occurrence of mucormycosis is enhanced. Adoption of glucocorticoids to treat SARS-CoV-2 may enhance possible occurrence of secondary infections. Additionally, concurrent immunomodulatory drugs, immune dysregulation and viral infection may compute possibility of secondary infections.

Disease Characteristics

Mucormycosis is commonly discerned in immunocompromised individuals associated with comorbid conditions such as uncontrolled diabetes mellitus, diabetic ketoacidosis, haematological or adjunctive malignancies, organ or bone marrow transplant, prolonged neutropenia, administration of immunosuppressive drugs or corticosteroids, iron overload or hemochromatosis, deferoxamine therapy, severe burns, acquired immunodeficiency syndrome (AIDS), intravenous drug abusers, malnutrition and occurrence of open wounds following trauma [3,4]. The ubiquitous Mucorales are preponderantly contemplated to be saprobic soil organisms. The fungi frequently emerge as soil associated protected spores within the tropical areas. Fungal spores are amenable to aerial dissemination, particularly during dry, arid summer season. Fungi may also be isolated from decaying plant or animal matter or deteriorating vegetables and fruits which are carbohydrate rich substances essential for fungal propagation and survival [3,4]. Generally, mucoromycota or the anamorphic Mucoralean fungi reproduce through non-motile sporangiospores retrieved from diverse sporangia. Alternatively, Mucoralean fungi may appear as parasites of plants, animals or various fungi thereby configuring different disease forms [3,4]. Frequently isolated fungal species from Mucormycosis are Apophysomyces, Cunninghamella, Lichtheimia (Absidia), Mucor, Rhizopus, Rhizomucor and Saksenaea of Order Mucorales and Class Zygomycetes. Rhizopus Oryzae is the commonest, universal species and accounts for around 90% of rhino-orbital-cerebral (ROCM) variant of mucormycosis [3,4]. Aforesaid fungi articulate spores which flourish in dry, humid or arid conditions. With aerial transmission, mild to severe infection may occur, particularly in immunocompromised individuals [3,4]. Extensive employment of corticosteroids is associated with occurrence of opportunistic fungal infection such as aspergillosis and mucormycosis. Especially, a triad of mucormycosis, diabetes mellitus and prolonged corticosteroids is observed in subjects with COVID-19. Controlling hyperglycaemia and antecedent commencement of appropriate antifungal therapy may be beneficial [3,4]. On account of delayed or inadequate detection, nearly half (50%) of instances of mucormycosis are discerned at autopsy [3,4].

Disease Pathogenesis

Mucorales species display differentiating characteristics such as structure, magnitude and shape of sporangia along with colour and condition of spores or mycelium [5,6]. Mucoralean fungi depict abundant, rapidly proliferating mycelium and associated anamorph articulations. The mycelium is non septate, pauci septate or irregularly septate. Anamorphic sporangiospores may generate sporangia with multiple spores. Fungal structures such as chlamydospores, arthrospores or yeast cells are infrequent. Sporangia are composed of variously outlined columella [5,6]. Certain species exhibit appendages which ensure conversion between filamentous, multicellular fungi and yeast-like fungi. Mucorales spores germinate in an environment of hypoxia, elevated glucose levels as with diabetes, new-onset hyperglycaemia or steroid-induced hyperglycaemia, acidic medium generated by metabolic acidosis or diabetic ketoacidosis, elevated ferritin levels and decimated phagocytic activity of white blood cells (WBC) appearing due to immunosuppression engendered by SARS-CoV-2, steroids or concurrent comorbidities with prolonged hospitalization [5,6]. Diabetes mellitus with uncontrolled hyperglycaemia, diabetic ketoacidosis and corticosteroids enhance possible emergence of mucormycosis. Reduced pH with consequent acidosis augments germination of mucor spores. Also, corticosteroids decimate phagocytic activity of white blood cells with impaired migration of broncho-alveolar macrophages, ingestion and phagolysosome fusion, thereby inciting the appearance of mucormycosis in diabetics [5,6]. Elevated plasma glucose, reduced pH, free iron and ketones along with decreased white blood cell phagocytic activity amplifies propagation of mucor. Additionally, expression of glucose-regulator protein 78 (GRP78) situated upon endothelial cells and fungal ligand spore coating homolog (CotH) protein is enhanced, thereby promoting angio-invasion, haematogenous dissemination and tissue necrosis [5,6]. Diverse virulence factors are associated with fungal species of order Mucorales such as:

- An iron rich environment which is conducive to propagation of Mucoralean fungi as iron is necessitated for cellular growth, reproduction and vital cellular functions. Acidosis or elevated cytokines in SARS-CoV-2 infection, especially interleukin-6 (IL-6), amplifies free iron by augmenting ferritin levels due to enhanced synthesis and decreased iron transport. Besides, the

ability of transferrin to chelate iron is reduced. Elevated serum iron levels predisposes to mucomycosis. Iron uptake is essential for enhancing fungal growth, evolution and pathogenicity [6,7].

- High-affinity iron permease (FTR1) is a pre-requisite for iron uptake and transport within diverse fungal species. Decimation of genetic expression reduces virulence of organisms such as Rhizopus Oryzae [6,7].
- Rhizoferrin is a siderophore secreted by Rhizopus and appears as a component of polycarboxylate family. Essentially, rhizoferrin provides iron through a receptor-mediated, energy-dependent process [6,7]. Certain Mucoralean fungi utilize xenosiderophores such as deferoxamine to efficaciously obtain iron from the host [7].
- Calcineurin is a calcium and calmodulin-dependent serine/threonine protein phosphate which is an essential virulence factor of Mucorales pathogenicity and required for metamorphosing yeast-like fungi into hyphae. Calcineurin is concomitant to protein kinase A which is a significant factor of fungal pathogenesis [6,7].
- Spore coat protein is a universal virulence factor localized upon spores of Mucorales. The protein is crucial for fungal invasion during emergence of mucormycosis, for disruption and deterioration of immune cells and functions as a specific ligand for GRP78 receptor [6,7].

Fungal Propagation and Transference

Mode of fungal transmission is contingent to site and severity of infection. Mucormycosis preponderantly appears due to inhalation of fungal spores or sporangiospores by immunocompromised individuals. Rhinocerebral mucormycosis predominantly disseminates due to inhalation of fungal spores or droplet spread whereas cutaneous mucormycosis is transmitted through personal proximity [5,7]. Additionally, fungal transmission occurs with spore ingestion or inoculation of conidia from wounds or traumatic apertures [8,9]. Nosocomial infection is exceptional and occurs due to contaminated bandages, medical devices and equipment for ventilation [8,9]. Mucormycosis commences with inhalation or ingestion of environmental spores which are subsequently phagocytosed within polymorphonuclear cells. Evolution and persistence of fungi is facilitated by inadequate phagocytic activity of immune cells [8,9]. Hyperglycaemia and acidosis influence chemotaxis and immune cell induced phagocytic demolition of fungi. Rhizopus or associated fungi secrete ketone reductase which propagates fungi in acidic and glucose-rich environments, as encountered with ketoacidosis. Also, serum iron in soluble ferrous form enhances propagation and survival of fungal species [8,9]. Enhanced fungal virulence augments innate resistance of fungal species to human phagocytes. Subsequently, with haematogenous dissemination, fungi invade vascular articulations in order to engender thrombosis and tissue necrosis. Host-pathogen interaction induces extensive angio-invasion with occurrence of ischemic necrosis and tissue injury [8,9]. Rhizopus Oryzae and associated species transgress endothelial cells and extracellular matrix followed by binding of the organism to host endothelium. Subsequent endocytosis of the organism disrupts endothelial cells. Currently, it is posited that glucose-regulated protein (GRP78) functions as a receptor which mediates fungal penetration and cellular injury [8,9].

Clinical Elucidation

Characteristically, mucormycosis is associated with diverse clinical manifestations contingent to site of infection, disease severity and mode of transmission of diverse fungal species. Mucormycosis appears within the nasal cavity, paranasal sinuses, orbit, central nervous system (CNS), pulmonary parenchyma, gastrointestinal tract (GIT), cutaneous surfaces, jaw bones, joints, cardiac muscle, renal parenchyma and mediastinum. The infection may initiate a rapidly progressive, medical emergency [9,10]. Mucormycosis may be clinically segregated as:

- Black, necrotic nasal turbinate possibly due to dried, crusted blood.
- Unilateral, haemorrhagic nasal discharge and facial pain.
- Soft peri-orbital or peri-nasal swelling with discoloration and induration.
- Ptosis of eyelid, proptosis of eyeball or complete ophthalmoplegia.
- Multiple cranial nerve palsies unrelated to definitive lesions [11].

Mucormycosis occurring in immunocompromised individuals is categorized in decreasing order of frequency as

Rhinocerebral Mucormycosis

Which is a frequently discerned, acute fungal infection with emergent chronicity on account of rapid, aggressive fungal propagation? The condition is engendered by filamentous fungi of order Mucorales. The organism incriminates brain, nasal passages and paranasal sinuses. Variable prevalence of rhinocerebral mucormycosis is contingent to diverse categories of high-risk populations [9,10]. Disease progression and expansion of infection is contingent to disease severity, host immunity, duration of infection and contributory virulence factors [10]. Rhino-orbital-cerebral mucormycosis (ROCM) is subdivided into limited sino-nasal disease with sino-nasal tissue invasion, limited rhino-orbital disease which progresses into orbits and rhino-orbital-cerebral disease which incriminates the central nervous system. The variant is frequently delineated in individuals with uncontrolled diabetes mellitus and

diabetic ketoacidosis [10,12]. Infection commences with vascular invasion and endothelial injury within the nasal cavity with consequent ischaemia or tissue necrosis and gradually ingresses the paranasal sinuses [10,12]. Fungi adhere to superficial sinus surfaces and the humid nasal cavity facilitates fungal propagation and invasion. Initially, a fungal ball is configured within the maxillary sinus wherein concomitant bone erosion is absent [10,12]. Infiltration of brain or orbits occurs due to fungal invasion of sphenopalatine and internal maxillary arteries. Preliminary symptoms are non-specific thereby delaying disease discernment. Commonly, lethargy and one-sided headache is followed by facial pain, numbness, nasal discharge, sinusitis, convulsions, altered mental condition and altered gait. Intracranial mucormycosis is associated with a fatality of around 90% [10,12].

Pulmonary Mucormycosis

It is engendered by Rhizopus spp, Mucor or Rhizomucor spp and constitutes an estimated one fourth (25%) of mucormycosis infections. The variant is associated with proportionate mortality of around 40% to 70%, especially in rapidly progressive instances with localized infiltration and angioinvasion [10,12]. Pyrexia, haemoptysis and tissue infarction may ensue. Pulmonary mucormycosis is observed in subjects with neutropenia, bone marrow or organ transplant and haematological malignancies. Fungal inhabitation predominantly discerned in transplant induced immunocompromised individuals or haematological malignancies may terminate in life-threatening, opportunistic infections [10,12]. Fungal organisms are inhaled, ingress pulmonary spaces and adhere to endothelial cells with consequent tissue injury. Proportion of tissue injury and propagation of infection is contingent to immune competency of incriminated individual and contributory conditions [10,12]. Intrapulmonary imaging with assessment of lobar and segmental consolidation is recommended for appropriate discernment. Singular or multiple pulmonary nodules may be observed [10,12]. Infection induced enhanced mortality occurs due to multifocal pneumonia, bilateral pulmonary consolidation, delayed disease discernment, inadequate host immune response and unsatisfactory therapy [10,12].

Cutaneous Mucormycosis

It appears as a localized infection or disseminated disease. Cutaneous mucormycosis is predominantly engendered by common soil saprophytes such as *Apophysomyces spp* and *Saksenaea spp*. Fungal pathogens invade the integument due to trauma, surgical procedures and superficial cuts or abrasions. Cutaneous contamination may also ensue due to natural disaster, inoculation from soil or diverse sources of fungal contagion. Infection may disseminate briskly to intrinsic subcutaneous tissue, fascia or bone. Cutaneous mucormycosis can be categorized as primary mucormycosis and secondary mucormycosis [10,12].

- Primary infection occurs where the organism is directly inoculated and lesions are composed of indurated, swollen, scaly, eventually erythematous plaques, tender nodules or purpuric lesions. Primary, nosocomial infection associated erythema and tenderness may rapidly progress to tissue necrosis [10,12].
- Secondary mucormycosis is frequently delineated and appears with the dissemination of fungi from diverse locations, usually rhinocerebral mucormycosis. Secondary infection commences with sinusitis along with configuration of necrotic eschar. Additionally, pyrexia, periorbital cellulitis, oedema or proptosis may be followed by intracranial involvement [10,12]. Upper and lower extremities, scalp, face, dorsal region, thorax, breast, neck or groin are commonly implicated in cutaneous mucormycosis [12].

Gastrointestinal Mucormycosis

It is an exceptional variant comprising of around~ 11% instances of mucormycosis and usually appears in malnourished subjects. Commonly, the stomach, colon, ileum, duodenum or jejunum are implicated with mild disease although infection may be fatal. Fungal infection commences with the ingestion of food infested with spores, ultimately incriminating the gastrointestinal tract. Aggressive antifungal and medical therapy may be adopted as cogent treatment strategy along with pertinent surgical intervention [8,9].

Disseminated Mucormycosis

It is the least frequent variant of mucormycosis usually observed within immunocompromised or neutropenic subjects with haematological neoplasms, post-transplant individuals or candidates treated with deferoxamine. The systemic variant arising due to invasive infection is accompanied by significant mortality of nearly ~90%. Fungal dissemination is preponderantly associated with mucormycosis and occurs due to invasion of vascular endothelial cells [8,9]. Infection may be mild or severe and incriminates organs such as pulmonary parenchyma, pancreas, brain or spleen [8,9]. Disseminated mucormycosis may manifest nonspecific clinical symptoms which delays appropriate disease discernment and enhances fungal invasion. Direct fungal inoculation is a common mode of disease transmission wherein fungi can infect cutaneous surfaces, subcutaneous tissue, adipose tissue or skeletal muscles. Severe instances are associated with infection within deep seated organs. Localized infection may emerge upon multiple sites [8,9].

Histological Elucidation

On microscopy, infiltration with giant cells, vascular thrombosis and eosinophilic necrosis of encompassing soft tissue is pathognomonic of mucormycosis [7,8]. Microscopic examination of order Mucorales demonstrates non-septate or pauci-septate fungal hyphae of variable width. Direct examination of incriminated tissue depicts rapidly evolving, diffusely disseminated moulds with emergence of aerial hyphae upon fungal culture, denominated as "lid lifters". Broad, ribbon-like, irregularly branching at right angles, pauci-septate hyphae of 5 microns to 15 microns diameter may be delineated [7,8]. Periodic acid Schiff's (PAS) or Grocott-Gromori' methenamine silver stain may be employed to morphologically highlight fungal hyphae. Emergence of rhizoids may be employed for identifying organisms of diverse species, categorized as

- Mucor genus depicts an absence of rhizoids
- Rhizopus genus is accompanied by nodal rhizoids
- Rhizomucor and Absidia / Lichtheimia exhibit intermodal rhizoids [7,8].

SARS-CoV-2 infection engenders endothelial inflammation, endothelial damage, vascular thrombosis, lymphopenia along with decimation of T helper lymphocytes (CD4+) and cytotoxic T lymphocytes (CD8+) accompanied by appearance of secondary or opportunistic fungal infections. Necrotic tissue may function as a nidus which contributes to fungal propagation [7,8]. Invasive fungal infection with significant angioinvasion is accompanied by elevated quantities of phagocytic cells like neutrophils and granulocytes [7,8]. Microbiological evaluation can be adopted for demarcating fungal hyphae from diverse fungal species contingent to hyphal diameter, presence or absence of septate hyphae, branching angle as with right angle or acutely branching hyphae and pigmentation of the organism. Mucormycosis requires a segregation from invasive mould infections such as invasive aspergillosis [7,8]. Nevertheless, singular histopathological examination may be inadequate for cogent differentiation of certain species [8].

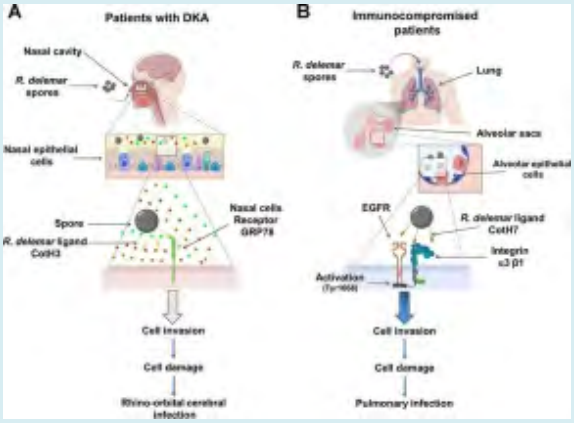

Figure 1: Mucormycosis demonstrating mechanism of cellular injury in rhinocerebral and pulmonary mucormycosis as encountered with diabetic ketoacidosis and immune compromise [13].

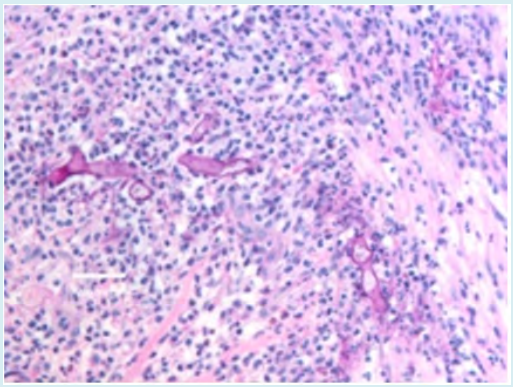

Figure 2: Mucormycosis exhibiting broad, aseptate, ribbon-like fungal hyphae disseminated in an inflammatory infiltrate of neutrophils and macrophages [14].

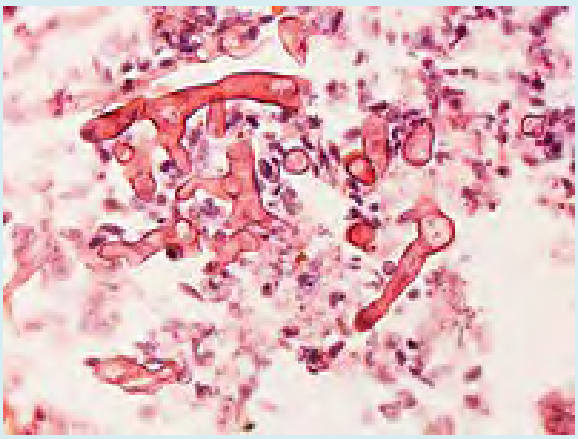

Figure 3: Mucormycosis delineating broad, pauci-septate hyphae disseminated in clusters of acute inflammatory cells [15].

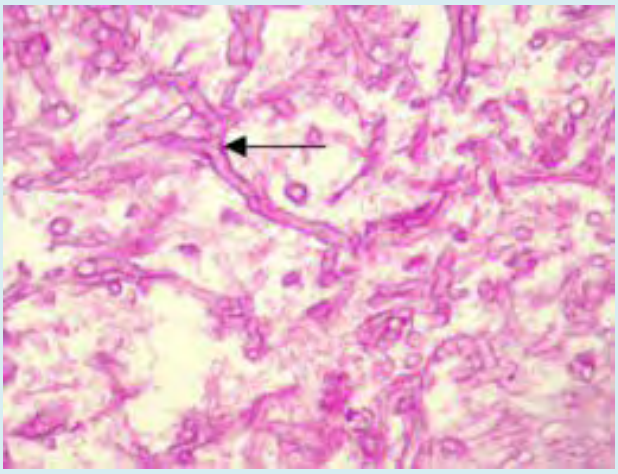

Figure 4: Mucormycosis exemplifying ribbon-like fungal hyphae surrounded by moderate exudate of acute and chronic inflammatory cells [16].

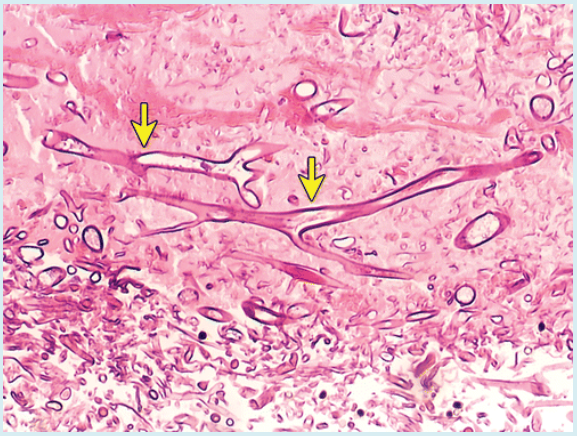

Figure 5: Mucormycosis enunciating broad, irregularly branching fungal hyphae intermingled with scant inflammation [17].

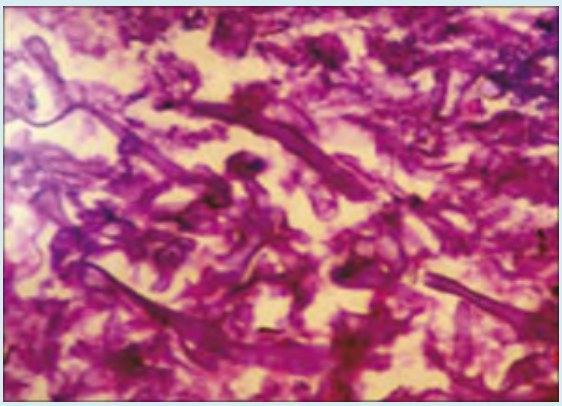

Figure 6: Mucormycosis depicting entangled, broad, ribbon-like, irregularly branching fungal hyphae [18].

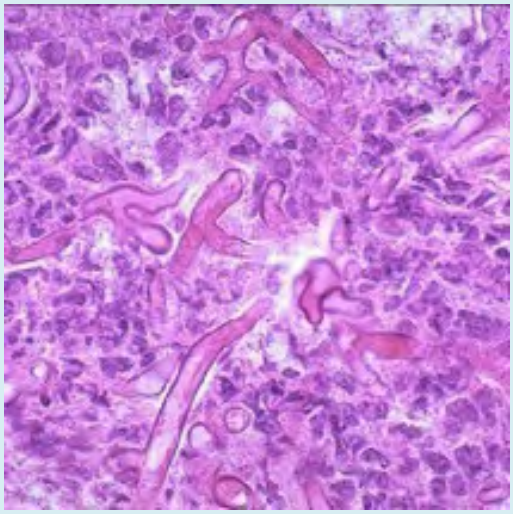

Figure 7: Mucormycosis exhibiting entangled, broad, ribbon-like fungal hyphae surrounded by accumulation of inflammatory cell [19].

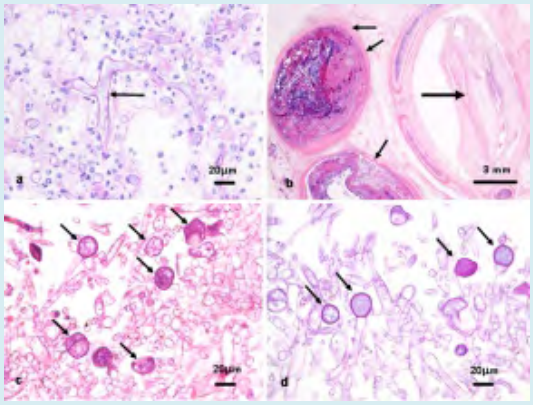

Figure 8: Mucormycosis demonstrating aggregates of fungal spores and hyphae which are broad, ribbon-like and irregularly branched with an encompassing acute inflammatory exudate [20].

Investigative Assay

Mucormycosis can be diagnosed contingent to appropriate recognition of host factors and assessment of diverse clinical manifestations. Preliminary discernment may prevent severe disease and subsequent, disease- associated mortality [10,12]. Fungi specific beta (β) glucan and Aspergillus galactomannan assays are non-reactive [10,12]. Serological assessment with enzyme linked immunosorbent assay (ELIZA), immunoblot and immunodiffusion assays may be performed for determining mucormycosis. Mucorales-specific antibodies can be detected by enzyme linked immunospot assay, which are especially beneficial for discerning invasive mucormycosis [10,12]. Molecular assays such as polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP) and DNA sequencing techniques are optimal for diagnosing Mucorales [10,12]. Whole blood or serum samples may be subjected to an internal transcribed spacer or 18S rRNA genetic assay. Additionally, nuclear ribosomal internal transcribed spacer (ITS) or 28S ribosomal RNA sequencing may be employed [10,12].

Therapeutic Options

Preliminary intervention is mandated in immunocompromised individuals on account of extensive mortality associated with mucormycosis [10,12]. Optimal therapy of mucormycosis is contingent to antecedent commencement of antifungal agents, treatment of comorbid conditions and debridement of infected tissue. Correction of iron overload, hyperglycaemia or metabolic acidosis and discontinuation of immunosuppressive drugs is necessitated [10,12]. Associated metabolic abnormalities require rapid correction. Tapering of corticosteroids and cessation of immunosuppressive drugs is beneficial. Therapeutic benefit of mucormycosis is achieved by antecedent diagnosis with expeditious initiation of medical management [10,12]. Mucorales may be resistant to majority of antifungal agents such as Voriconazole although intravenous Amphotericin B is efficacious in treating maximal varieties of Mucorales spp [10,12]. Drugs such as Posaconazole, Isavuconazole, Itraconazole and Terbinafine demonstrate variable efficacy against Mucorales spp. Hyperbaric oxygen and cytokines may be advantageously employed along with antifungal agents [10,12]. Surgical debridement is an essential manoeuver and surgical eradication is recommended for extermination of necrotic tissues and encompassing, infected healthy tissues. Generally, surgery is necessitated for treating rhinocerebral mucormycosis, soft tissue infection or a singular, localized pulmonary lesion [10,12]. Additionally, preventive measures such as utilization of masks in endemic or spore-rich areas, healthy diet and appropriate lifestyle is recommended to prevent severe infection [10,12].

References

1. Paltauf A (1885) Mycosis mucorina. Virchows Arch Pathol Anat Physiol Klin Med 102: 543-564.
2. Baker RD (1957) Mucormycosis-a new disease? J Am Med Assoc 163(10): 805-808.
3. Hernandez JL, Buckley CJ (2021) Mucormycosis. Stat Pearls International Treasure Island, Florida.
4. Camara LCR, Emmanuel IGM, Rene RG, Erick JRR, Ana SAC, et al. (2014) Clinical features and outcome of mucormycosis. Interdisciplinary perspectives on infectious diseases.
5. Skiada A, Lass FC, Klimko N, Ibrahim A, Roilides E, et al. (2018) Challenges in the diagnosis and treatment of mucormycosis. Medical mycology 56(1): 93-101.
6. Reid G, Lynch JP, Michael CF, Nina MC (2020) Mucormycosis. Semin Respir Crit Care Med 41(1): 99-114.
7. Hassan MIA, Voigt K (2019) Pathogenicity patterns of mucormycosis: epidemiology, interaction with immune cells and virulence factors. Med Mycol 57 (2): S245-S256.
8. Ana DCP, Esperanza CW, Ivett M, Jorge OC, Oliverio W (2017) Cutaneous mucormycosis. Anais brasileiros de dermatologia 92(3): 304-311.
9. Anna S, Ioannis P, Maria DA (2020) Epidemiology and Diagnosis of Mucormycosis: An Update. Journal of fungi (Basel, Switzerland) 6(4): 265.
10. Singh AK, Singh R, Shashank RJ, Anoop M (2021) Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 15(4): 102146.
11. Smith HW, Kirchner JA (1950) Cerebral mucor-mycosis: a report of 3 cases. Arch Otolaryngol 68: 715-726.
12. Ashraf SI, Brad S, Thomas JW, Dimitrios PK (2012) Pathogenesis of mucormycosis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 54(1): S16-22.
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