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NEW ALARMING DISEASE: FUNGAL DISEASE OUTBREAK HERE

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ABSTRACT

Is this deadly fungal disease linked with covid?

Is this infection spread to whom effect it?

You and your doctor can recognize the symptoms of a fungal disease early and may help prevent serious complications.

Keywords: Fungal Disease, Plant, Symbiotic

INTRODUCTION:

Mucormycosis is an angioinvasive fungal infection. It belongs to the mucorales order of fungi. Based on the clinical presentation it is classified as rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated or other, which includes uncommon rare forms, such as endocarditis, osteomyelitis, peritonitis, renal, etc. The disease was first described in 1876 when Fürbinger described in Germany a patient who died of cancer and in whom the right lung showed a hemorrhagic infarct with fungal hyphae and a few sporangia. In 1885, Arnold Paltauf published the first case of disseminated Mucormycosis, which he named “Mycosis mucorina”. His drawings of the etiologic agent showed the presence of sporangiophores and rhizoid-like structures, and this led to the conclusion that the infection was most probably caused by Lichtheimia corymbifera.

Over time, more cases were diagnosed, and the incidence of the disease has increased. Currently, Mucorales fungi are the next alarming disease and most common mold pathogens i.e.Aspergillus, leading to invasive fungal disease in patients with malignancies or transplantation. The incidence of mucormycosis has also increased significantly in patients with diabetes, which is the commonest underlying risk factor globally.

The epidemiology of mucormycosis is evolving as new immunomodulating agents are used in the treatment of cancer and autoimmune diseases, and as the modern diagnostic tools lead to the identification of previously uncommon genera/species such as the Apophysomyces or Saksenaea complex. (Anna Skiada, 2020)The aim of this article is to present an update on the epidemiology and the available diagnostic methods for this potentially lethal disease. Mucormycosis has become an increasingly common disease, representing the second most common infection caused by molds after Aspergillus among 109 cases of culture-proven cases in a large cancer center in which it represented 20% of all such case in which it represented 20% of all such cases. The increased incidence of diabetes, use of immunocompromising agents and the introduction of voriconazole prophylaxis or treatment among immunocompromised patients have been associated with the emergence of mucormycosis. (V.

SAEGEMAN, 2010)

Mucorales can gain entry to a susceptible host through inhalation, ingestion of contaminated food, or abraded skin. These routes result in rhino-orbito-cerebral, pulmonary, gastrointestinal, or cutaneous/wound infections. One of the characteristic features of mucormycosis is its angioinvasive property, resulting in vascular thromboses and ultimately tissue necrosis. Ketoacidosis and deferoxamine are known to predispose to mucormycosis, revealing the importance of hyperglycemia, iron, and acidifying ketone bodies in mucorales virulence. Angioinvasion was reported to be related to the interaction between a spore-coating protein family (CotH) on Rhizopus spp. surface and endothelium glucose regulator protein 78 (GRP78) expressed at the surface of endothelial cells. (Benoit Pilmis, 2018)

National and international status of Mucormycosis:

Country	Total Population (in millions)	Total Estimated Fungal Burden	Mucormycosis		Invasive Aspergillosis	
			Total Burden	Rate/100K	Total Burden	Rate/100K
Algeria	40.4	568,942	79	0.2	2865	7.1
Argentina	43.8	881,023	75	0.17	2536	5.8
Australia	23.57	693,708	21	0.06	560	3–29%
Belgium	11.1	233,000	31	0.58	675	6.08
Brazil	194.0	3,800,000	243	0.2	8664	4.47
Cameroon	24.2	1,126,332	5	0.2	1175	5.3
Canada	35.5	652,932	43	0.12	566	1.59
Chile	17.5	325,036	35	0.2	296	1.7
Colombia	49.3	760,808	99	0.2	2820	5.7
Czech Republic	10.5	176,073	22	0.2	297	2.8
Denmark	5.6	894,430	1	0.02	294	5.3
Dominican Republic	10.9	2,293,681	20	0.2	61	0.8
France	65.8	968,143	79	0.12	1185	1.8
Greece	10.8	194,067	7	0.06	1125	10.4
India	1300.0	NA	171,504	14	NA	NA
Ireland	6.4	117,384	13	0.2	445	7
Japan	127.0	2,370,314	254	0.2	1308	1
Jordan	6.3	119,153	1	0.02	84	1.34
Kazakhstan	17.7	300,824	16	0.09	511	2.8
Kenya	43.6	3,186,766	80	0.2	239	0.6
Korea	48.0	985,079	68	0.14	2150	4.48
Malawi	17.7	1,338,523	30	0.2	1186	6.7
Mexico	112.3	2,749,159	134	0.12	4510	4
Nigeria	155	17,983,517	300	0.2	928	0.6
Norway	5.2	839,087	7	0.1	278	5.3
Pakistan	184.5	3,280,554	25,830	14	10,949	5.9
Philippines	98.4	1,852,137	20	0.02	3085	3
Portugal	10.6	1,695,514	10	9.5	240	2.3
Qatar	1.9	33,448	23	1.23	11	0.6
Romania	19.7	436,230	7	0.04	1524	7.7

Russia	142.9	3,082,907	232	0.16	3238	2.27
Serbia	7.1	156,825	23	0.33	619	8.8
Spain	47.0	8,144,605	20	0.04	1293	2.75
Thailand	65.1	1,254,562	130	0.2	941	1.4
Ukraine	45.5	999,152	90	0.1975	1233	2.7067
United Kingdom	63.18	241,525–662,987	57	0.09	2901–2912	4.59–4.61
USA	NA	NA	36	0.3	301	2.4
Republic of Uzbekistan	30.7	536,978	27	0.08	1521	4.8

NA: data not available.

(Chakrabarti, 2019)

The true incidence/prevalence may be more in mucormycosis, as many of the cases remain undiagnosed due to difficulty in collecting the sample from deep tissue and low sensitivity of diagnostic tests. The Leading International Fungal Education (LIFE) portal has estimated the burden of serious fungal infections globally. According to their estimate, the annual prevalence of mucormycosis might be around 10,000 cases in the world barring India. After the inclusion of Indian data, the estimate of mucormycosis rose to 910,000 cases globally. The estimated incidences per million populations in different continents were: Europe (from 0.2 cases in Denmark to 95 cases in Portugal), USA (3.0 cases), Canada (1.2 cases) and Australia (0.6 cases). A computational-based approach estimated the prevalence of mucormycosis at 140 cases per million populations in India, with the prevalence ranging between 137,807 cases to 208,177 with the mean of 171,504 and a mean attributable mortality at 65,500 (38.2%) per year. (Chakrabarti, 2019)

Is this Fungal diseases can affect anyone.

Fungal infections are often caused by fungi that are common in the environment. Most fungi are not

dangerous, but some types can be harmful to health. Mild fungal skin diseases can look like a rash and are very common. Fungal diseases in the lungs are often similar to other illnesses such as the flu or tuberculosis. Some fungal diseases like fungal meningitis and bloodstream infections are less common than skin and lung infections but can be deadly. According to the centre for disease control and prevention report, these fungi found everywhere, but the habitat of this fungi is outdoor, i.e. soil, on the plant, indoor on surface air, on the human skin surface and inside the body. There are many fungi Like mold, mushroom, yeast, and fungi, but few of them are affected sick of people and create serious complication. They cause a severe type of infection like asthma, allergy, rashes or skin disease, lung infection and many more. Many types of fungal disease caused by different fungi, i.e. blastomycosis.

Distinctive Features of the Immunopathogenesis of Mucormycosis

Medically important members of the order Mucorales share many features with other filamentous fungi such as portals of the host for infection (airways and disrupted mucocutaneous barriers), the main lines of innate host defences (phagocytes, specific ligands in fungal spores such as pathogen-associated molecular patterns (PAMPs) and immune cells such as Toll-like receptors (TLRs)), as well as histopathological and clinical features [19, 20]. However, Rhizopus oryzae and other selected Mucorales possess unique virulence characteristics and exert distinctive host–pathogen interactions compared to other fungi facilitating, thus, host evasion and disease progression [21].

There are several lines of in vitro evidence showing that R. oryzae and other members of the Mucorales have reduced susceptibility to innate host defence as compared to other more common fungi, such as Aspergillus fumigatus or Candida albicans [22, 23]. Moreover, differential interspecies susceptibility patterns to host responses exist within the order Mucorales [24, 26]. Namely, members of the genus Rhizopus suffer less hyphal damage and stimulate an impaired oxidative burst in human phagocytes as compared to Lichtheimia (Absidia) spp. [24], and Cunninghamella bertholletiae shows, in vitro, increased resistance to phagocyte-induced hyphal damage and, in vivo, increased virulence in an experimental neutropenic pulmonary mucormycosis model in comparison with Rhizopus spp.

Current situation: COVID-19 and Fungal Co-infection (Mucormycosis)

Saprophytic fungi normally habituating fruits, starch containing material, soil and manure can also colonize oral mucosa, paranasal sinuses, nasal mucosa and pharyngeal mucosa asymptomatic patients. Fungal isolates belonging to class Zygomycetes and order Mucorales causes one very specific kind of infection which is referred as ‘Mucormycosis’. Arnold Paltauf in 1885 has firstly described this infection which is done by opportunistic fungal organisms mainly Rhizopus, Mucor and Lichtheimia in major cases ; along with hematologic malignancy it also manifests in medical situation like ketoacidosis, organ transplant, increased serum ions, malnutrition, diabetes mellitus and immunocompetency (Pandilwar P. K. et. al. 2020). The epidemiology of is highly dependent on patient’s medical condition. Most common form of mucormycosis is Rhino-orbito-cerebral mucormycosis; other form of mucormycosis are pulmonary, gastrointestinal, cutaneous, and disseminated mucormycosis ; The major risk factor for mucormycosis is Haematological conditions

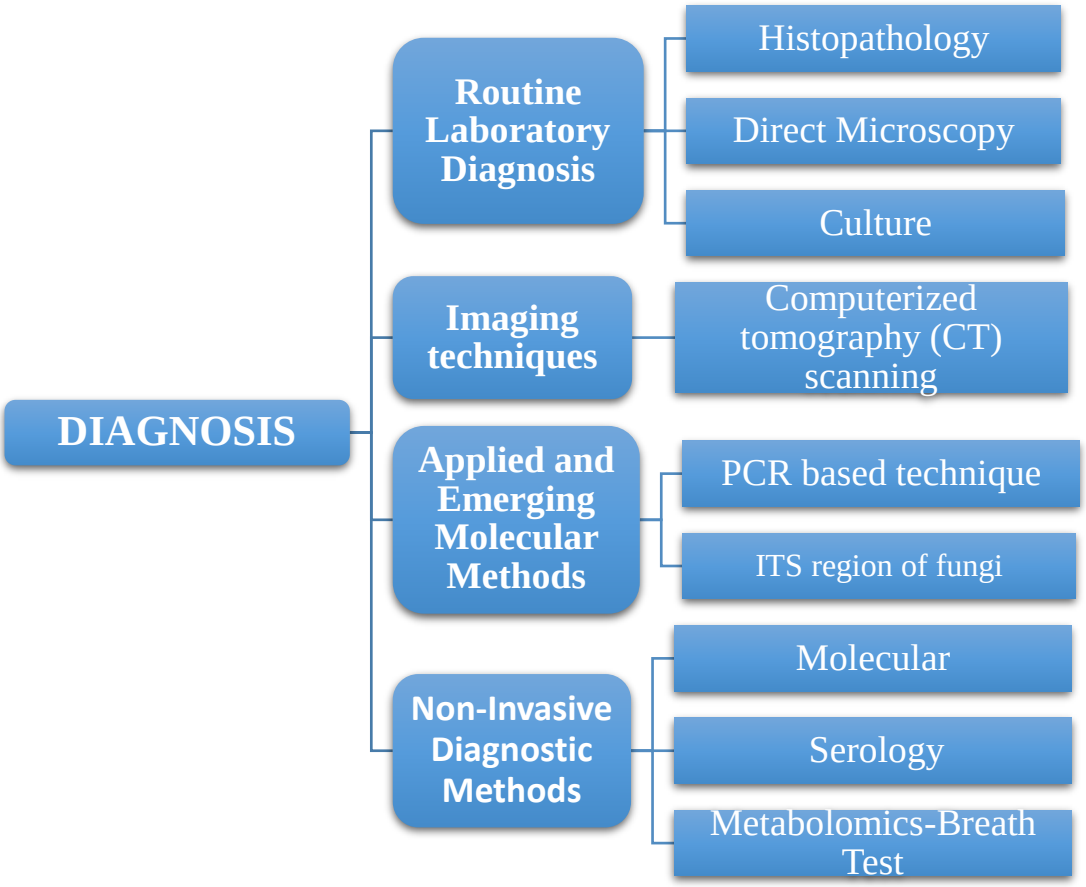
like malignancy, leukamea , myelodysplastic syndrome and sideroblastic anaemia. (Prabhu R. M. & Patel R. 2004). In last few months world is facing worst health problems and crisis for the first time after The Influenza pandemic (1918), World Health Organization (WHO) has declared pandemic of Corona Virus Disease 2019 (COVID-19) because of its rapid spread globally (Pemán J. et. al.2020). COVID-19 (Corona virus disease 2019) disease which is caused by SARS-CoV-2 (Corona virus) is firstly documented in December 2019 at China and it has been now became a pandemic world -wide, the epidemiology of this disease is under investigation in field of medicine (Werthman-Ehrenreich A. 2020). Till date (January 15, 2021) it has caused infection in 93,240,925 individuals and has caused death of 1,997,095 infected patients (Johns Hopkins University; Corona virus Resource Center [accessed 15.01.21]).Heavily infected COVID-19 patients have higher anti-inflammatory (IL-4, IL-10) and pro-inflammatory cytokine levels and less number of CD4 and CD8 levels which serves as a very prominent situation favorable for fungal infection to occur. Heavily infected COVID-19 patients have higher anti-inflammatory (IL-4, IL-10) and pro-inflammatory cytokine levels and less number of CD4 and CD8 levels which serves as a very prominent situation favorable for fungal infection to occur. In addition to this SARS- CoV-2 virus mainly attacks Lung tissues and also causes large bilateral lesions in intestine; this situation promotes growth of fungus belonging to Mucorales order which can mainly transmit through air borne route of gastro-intestinal route and establishment of infection stronger (Pemán J. et. al.2020). Number of study which have been implemented on ICU patients infected by Covid-19 having acute respiratory distress syndrome (ARDS) showing the fungal infection as a co-infection , which can be one of the responsible reason for morbidity and mortality of COVID-19 infected patients (Gangneux J. P. et. al. 2020).

Diagnosis:

Mucormycosis diagnosis is based on the recognition of signature signs, a thorough history of the patient, a rigorous clinical assessment and a number of specialised examinations. Early detection of mucormycosis remains difficult, creating a bottleneck in the creation of advanced, successful clinical trials and is a significant unmet need. This is significant because the outcome of mucormycosis is clearly affected by delayed care (Chamilos Get al.2008).

Its enigmatic clinical appearance and regular occult distribution, the absence of sensitive non-cultural diagnostic tools (e.g. antigen and molecular detection platforms), and the fact that the culture of samples collected from non-sterile locations (e.g. sputum) is neither sensitive nor precise are major problems in the diagnosis of mucormycosis (Tarrand JJ et al.2003 and Torres-Narbona M et al. 2008)

Some of the diagnostic tools for mucormycosis based on microbiology and molecular techniques are presented in fig 1.



[Fig: 1 Diagnostic tool for Mucormycosis]

Routine Laboratory Diagnosis:

In clinical practice, laboratory diagnosis of mucormycosis includes histopathology, direct examination of wet mounts and culture.

Histopathology:

A conclusive diagnosis is based on the demonstration of fungal hyphae typical for mucormycetes in biopsies of infected tissues, or bronchoalveolar lavage (BAL) in patients with mucormycosis. Histopathology is a very valuable diagnostic method as it distinguishes the presence of the fungus as a pathogen in the specimen (Ribes, J.A et al.2000)

Direct Microscopy:

Direct microscopy of wet KOH mounts can be used for rapid presumptive diagnosis of mucormycosis. It can be added to all materials sent to the clinical laboratory, preferably utilising fluorescent brighteners such as Blankophor and Calcofluor White along with KOH, which improve the visualisation of the distinctive fungal hyphae, requiring a fluorescent microscope in this case. (Walsh, T.J et al. 2012) Fresh

material direct microscopy is an economical, yet invaluable, method of rapidly giant microscopy. However, these approaches do not classify a fungus at the stage of the genus or species. (Cornely, O.A et al. 2019)

Culture:

Specimen culture is important for the diagnosis of mucormycosis as it facilitates the detection of the stage of genus and organisms, and consequently the testing of antifungal susceptibility. Mucorales are thermotolerant and can develop rapidly at temperatures of 37 ° C. They grow on virtually any carbohydrate substrate, colonies typically appear within 24-48 h, and colony and microscopic morphology and growth temperature are dependent on recognition.

Flight mass spectrometry matrix aided laser desorption ionisation time (MALDI-TOF) detection of cultured Mucorales is a promising approach for those laboratories that are sufficiently equipped but require further confirmation data. (Walsh, T.J et al. 2012)

Imaging techniques

To assess the precise site and magnitude of an infection, imaging methods such as computerised tomography (CT) scanning may be used. A device and x-rays are used during CT scanning to produce a film that displays cross-sectional images of some tissue structures. The lungs, sinuses, facial muscles, or other parts of the body can be scanned by a CT scan. A CT scan of the lungs will show a reverse halo sign in individuals with pulmonary mucormycosis. This diagnostic hint is a region that resembles ground glass on the film of tissue death (necrosis). It is indicative of an infection of mucormycosis. (Legouge, C.et al.2014)

Applied and Emerging Molecular Methods

As a helpful tool to validate the infection and classify the strains involved, molecular approaches have advanced. There are, thus, methods developed on the one hand to reliably classify strains at the species level that have already grown in cultures and, on the other hand, methods for detecting mucormycetes in tissues.

ITS region:

For fungi in general, the ITS region is the most commonly sequenced DNA region. ITS sequencing is an effective tool and has generally been the most helpful method for species-level molecular systematics, and also within species, and it is recommended as a first-line method for identifying Mucorales specimens. (Cornely, O.A et al. 2019)

PCR based method:

The causative species of the infection can be identified by this examination. PRC is a test tool to recognise and render copies of unique deoxyribonucleic acid segments (DNA). Several methods have been developed for the identification in tissues, including PCR-based techniques such as nested PCR, real-time PCR (qPCR), nested PCR in combination with RFLP, PCR in combination with electrospray

ionisation mass spectrometry (PCR/ESI-MS) and PCR/high-resolution melt analysis. The test can identify small quantities of DNA including genetic material in infectious species such as fungi (HRMA). Many of these techniques have reportedly been successfully applied, and on fresh or deep-frozen samples they perform better. (Alanio, A. et al. 2015)

Non-Invasive Diagnostic Methods:

Molecular:

Invasive treatments may not be appropriate to some classes of patients (haematological malignancies with thrombocytopenia, ICU patients, etc.) in the samples used in any of the above-mentioned processes. Considering the angioinvasive aspect of the infection, blood cultures remain negative. In fact, only a handful of cases have been described so far with a positive blood culture. Fungal DNA does circulate in the blood, however. There is also a lot of current research based on non-invasive approaches such as qPCR for the identification in blood (plasma or serum) or urine of circulating mucoral DNA. A extremely reliable technique for the detection of invasive mucormycosis in immunocompromised patients has been shown to be Serum Mucorales PCR. (Springer, J.et al.2016)

Blood qPCR methods are fast (about 3 h turnaround time). They are highly specific, although their specificity is lower than in tissues. In addition, they are able to detect immunocompromised mucormycosisin patients faster than the traditional approaches of mycology or imaging. Therefore, they are useful for high-risk patient screening and surveillance and may improve longevity. Baldin et al. have shown that the spore-coating protein homolog CotH genes, which are unique to Mucorales, have provided promising results in a mouse model in the search for new particular targets, with urine being the favoured sample type relative to plasma or BAL. This procedure had 90 percent sensitivity in cases of reported mucormycosis and was 100 percent specific. (Baldin, C.et al.2018)

Serology:

With varied success, enzyme-linked immunosorbent assays, immunoblots, and immunodiffusion tests have been evaluated. In three hematologic patients who developed intrusive mucormycosis, Mucorales specific T cells were identified by an enzyme-linked immunospot assay (ELISpot).

Burnha-Maurish et al. tested the monoclonal antibody (2DA6) in the ELISA sandwich for new serological test targets and found it to be strongly reactive with distilled Mucor spp. fucomannan. A lateral flow immunoassay (LFIA) for the identification of Mucorales cell wall fucomannan was subsequently developed in clinical samples and shown that LFIA was more easy to use than ELISA and had the ability to be used on BAL, serum, urine and tissue as a point-of-care procedure. The test was capable of identifying R easily and correctly. Oh, L. Delemar. With corymbifera, M. And C. circinelloides. Bertholletiae, in murine models early after infection (within 3–4 days of infection). (Orne, C et al.2018

Metabolomics-Breath Test

Koshy et al. analysed breath volatile metabolite profiles in an experimental murine model of invasive mucormycosis (IM), using the three Mucorales organisms that most often cause human IM-

Rhizopusarrhizus var. Yeah, arrhizus, R. Var arrhizus. R. and Delemar. Thermal desorption gas chromatography/tandem mass spectrometry (GC-MS) microsporus. The results revealed that the three species of Mucorales had different breath profiles of the volatile metabolite sesquiterpene that could be used in vivo to classify these infections. These profiles separated the infections from each other and from aspergillosis, so this approach has the ability to non-invasively diagnose fungal infection, and perhaps track therapy response. It may also be used in a high-risk population, such as patients with neutropenia due to leukaemia therapy or those undergoing hematopoietic cell transplantation, in addition to Aspergillus galactomannan, to screen for mould infections (Koshy, S. et al. 2017). This approach seems to be very attractive and promising, but requires more appraisal

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