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BLACK FUNGUS AND CORONAVIRUS

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ABSTRACT

The aim of the study was to determine the influence of the SarsCov2 virus on the spread of the black fungus, a dangerous and even deadly disease that spreads mainly in Asia. The etiology of this disease, symptoms and diagnosis, clinical significance, identification, relationships between this disease and diabetes and coronavirus infection are discussed. In addition, treatment and prevention options were analyzed, especially in patients with chromoblastomycosis, as well as prophylaxis. Patients with diabetic ketoacidosis have been shown to be at a higher risk of developing the black fungus known as Mucormycosis. Patients with a positive coronavirus test are also exposed to black fungus infection. The disease spreads through the respiratory tract, affecting people with weakened immune systems and those treated with steroids. Black fungus symptoms vary depending on where it resides, leading to a variety of facial and cerebral symptoms. It has been established that the fungus does not spread between humans or between humans and animals, but is usually found in people who are immunocompromised or are taking medications that reduce the body's ability to fight germs and diseases. Mucormycosis, in conditions of high humidity and high temperature, can prove fatal as the risk of transmission increases, especially in the event of the SarsCov 2 pandemic. In the near future, this fungus could pose a very real problem to human health worldwide.

Keywords: *black fungus, diabetes mellitus, invasiveness, immunity, prevention, treatment, SarsCov2*

INTRODUCTION

At a time when India is struggling with an increasing number of deaths caused by SARS-CoV-2 coronavirus infection, doctors warn against a so far rare fungal infection caused by the so-called black fungus. If left untreated, the disease can become dangerous and even lead to death. Mucormycosis, or "black fungus", is increasingly affecting COVID-19 patients. Experts are alarming that half of the patients who develop the infection die. Black fungus cases have been reported in hospitals in Delhi, Pune and Ahmedabad. In the state of Gujarat, about 300 cases have now been reported in four cities. New infections are coming so quickly that the governmental pandemic team in India has issued a special message warning of the disease. India is also not the only country with reported cases of the "black mushroom". Other cases have also been reported in several other countries, including the UK, US, France, Austria, Brazil and Mexico, but the number is much greater in India [Biswas 2021, Parakash & Chakrabarti, 2021]. Rhinocerebral (Sinus and Brain) *Mucormycosis* is an infection in the sinuses that can spread to the brain, commonly affecting people with uncontrolled diabetes and those who had kidney transplant. Pulmonary (Lung) *Mucormycosis* is common among people with cancer and also with organ transplant or a stem cell transplant. Cutaneous (Skin) *Mucormycosis* occurs after the fungi enter the body through a break in the skin, due to surgery, burn injuries or skin trauma, and have a weakened immune system. Gastrointestinal *Mucormycosis* is more visible among young children, especially premature and low birth weight infants less than 1 month of age, who have antibiotics, surgery, or medications that lower the body's ability to fight germs and sickness. Disseminated Mucormycosis happens when the infection spreads through the bloodstream to affect

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another part of the body, and most commonly affects the brain, spleen, heart, and skin [Petrikkos et al. 2012, Skiada et al. 2013, Binder et al. 2014, Danion et al. 2014, NORD 2018, Kumar 2021, Parakash & Chakrabarti, 2021]. Transmission of black fungus occurs through inhalation, inoculation, or ingestion of spores from the environment affecting the lung or sinus forms of the infection, as someone inhales the spores from the air. Mucormycosis is an uncommon angioinvasive disease, resultant of a fatal fungal infection that usually affects patients with altered immunity, caused by mold fungi of the genus *Rhizopus, Mucor, Rhizomucor, Cunninghamella* and *Absidia* of order- *Mucorales*, Class- *Zygomycetes* [Ibrahim & Kontoyiannis 2013, Parakash & Chakrabarti, 2021]. The facilitating environment for Mucorales spores to germinate in people with COVID-19 is low oxygen, high glucose, acidic medium, high iron levels and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators [Kumar et al., 2021]. The burden of black fungal diseases are acute, severe, eye infection, and chronic based on population and disease demographics. Black fungus infected patients are those who have had exposures that put them at risk for fungal eye infections, lasting for several days to several weeks after the fungi enter the eye, leading to eye pain, redness, blurred vision, sensitivity to light, excessive tears and discharge. Though surgery is vital to remove dead tissue, the therapy can use antifungal agents posaconazole (oral) and isavuconazole, but are expensive unlike the affordable Intravenous amphotericin B [GAFFI, 2020].

MATERIAL AND METHODS

The following databases: PubMed, ScienceDirect, Google Scholar, ProQuest, Semantic Scholar and Cochrane were searched using the following key terms: "antidiabetic compounds", "bioactive compounds" or "natural compounds", and "carbohydrates" "herbal carbohydrates", "Health" and "type 2 diabetes", "SarsCov2", "pathogenic fungi", black fungus "

Admission Criteria. It included research studies (in silico, in vitro and in vivo) using various research models such as human cell lines and laboratory animals that have reported that carbohydrates have health effects, including type 2 diabetes, also in languages other than English, so as not to limit the scope of work. In addition, a manual search was performed to locate previous research articles based on references to published narrative articles and systematic review articles.

Exclusion criteria. Studies that looked at other types of disease were excluded. Search results were limited to original scientific articles published between 2001 and 2021. Duplicate articles from different databases were searched and only one was kept. Data on the "black fungus", the effects and the place of their occurrence were extracted**.**

RESULTS

Symptoms and Diagnoses

General symptoms are one-sided facial swelling and numbness, headache, nasal or sinus congestion, black lesions on nasal bridge or upper inside of the mouth, fever, abdominal pain, nausea and gastrointestinal bleeding. Disseminated type occurs in those who are already sick from other medical conditions, posing more complications in detection of the symptoms are related to mucormycosis, at times those infections in the brain can lead to mental status changes or coma. Diagnosis and Testing considers medical history, symptoms, physical examinations, and laboratory tests while diagnosing those suspected of the infection [Kameshwaran, et al. 2021]. Collection of a sample of fluid from the respiratory system or may perform a tissue biopsy with a small sample of affected tissue is analysed in a laboratory for evidence of mucormycosis under a microscope or in a fungal culture. Coronavirus damages airway tissue and blood vessels, thereby increasing susceptibility to fungal infection. Immediate initiation of therapy is critical due to the infection nature such as acute, and fulminate. Depending upon the results such as presence of predisposing conditions, signs and symptoms of disease, observation of fungal elements, and smears of material [Branscomb 2002; Biswas et al. 2021]. General cleanliness includes visible dust, dirt, and

stains; evidence of fungal growth and damage such as visible mold and mildew, stains, mold odor, fungal growth on drywall surface or underneath wall coverings, fungal growth on building's interior support structures and building materials; and evidence of air intrusion from outdoors or from other adjacent spaces likely that of the status of window seals, seals surrounding plumbing pipe intrusions, and lack of self-closing doors are pertinent patient care areas and locations based on relevance to potential exposures, as per epidemiologic review of initial cases [USDHHS, 2020].

Clinical Significance

In order to understand the pathology of the black fungus that causes brain infections in East Asian patients, it is necessary to understand its natural ecological niche. From the relatively low degree of molecular variability of the black yeast *Exophiala dermatitidis*, a potential factor causing infections in East Asian patients, it can be concluded that this species is a new pathogen currently undergoing active speciation. It has been found to be an oligotrophic fungus under conditions of a hot, humid environment, such as e.g. in steam rooms. Strains of *Cladophialophora*, *Fonsecaea*, and *Ramichloridium*, known to humans as inducers of chromoblastomycosis, are often found on aggregated, rotten plant material. However, the molecular biodiversity of fungi in the environment is much higher than in humans, so it is difficult to precisely trace the etiological factors of the disease. This approach has been successful for *Cladophialophora carrionii*, whose muriform-like cells, a tissue form of chromoblastomycosis, are found in cactus drying spines. The performed phagocytosis tests can provide methods of distinguishing both pathogens and non-pathogens, since the killing rates of strict saprobes turned out to be significantly higher than in species known to be pathogens. Therapeutic options for patients with chromoblastomycosis were discussed, of which muriform cells, i.e. the tissue form of chromoblastomycosis, are found, for example, in drying spines of cacti [de Hoog et al. 2000, Song et al. 2017, Kameshwaran et al. 2021].

The human body is influenced by physical activity and diet. The latter must be nutritionally balanced, contain the right type and amount of carbohydrates. Increasing or reducing the amount of carbohydrate above the desired amount can affect both physiological and metabolic processes. Increasing the amount of simple carbohydrates can cause obesity, a disease that puts people at even greater risk of disorders such as cardiovascular disease. Carbohydrate consumption also contributes to the growing epidemic of non-insulin dependent diabetes (type 2 diabetes). However, foods high in non-starch polysaccharides and foods with a low glycemic index protect against diabetes. Increased sugar consumption also contributes to the development of tooth decay [Kameshwaranet al. 2021]. Carbohydrate malabsorption can manifest as constipation, diarrhea, gas and stomach pain. It may occur as a result of congenital or acquired defects in the metabolism of enzymes or the intestinal mucosa. Celiac disease and Crohn's disease are examples of secondary malabsorption. Bacterial overgrowth of the small intestine (SIBO) can occur as a result of gastric bypass or gastric bypass disorders (chronic diabetes, scleroderma), causing impairment of the absorption interface and severe absorption disorders. Lactose intolerance, on the other hand, is a primary lactase deficiency. Lactase is an enzyme that breaks down lactose, disaccharide, into glucose, and galactose in the brush border of enterocytes into monosaccharides. Lactase deficiency is the most common enzyme deficiency in the world [Song et al. 2017, Wang et al. 2020]. The most frequently used method for diagnosing carbohydrate malabsorption is the hydrogen exhalation test. With incomplete absorption, undigested carbohydrates enter the colon, where there are hydrogen-producing bacteria. The hydrogen level (H2) is measured on the first expiration. Unmetabolized carbohydrates have an osmotic effect in the digestive tract and contribute to the symptoms of diarrhea and flatulence. Treatment of most carbohydrate malabsorption disorders involves avoiding the accompanying mono- or disaccharides [Hammer & Hammer 2012, Raithel et al. 2013].

1. Identification

Although Exophiala are environmental fungi, their presence in clinical specimens should not be disregarded as an impurity [Woo et al. 2013]. Black fungi have been known for decades, but they are

among the most difficult to identify groups of fungi, therefore diagnostic ambiguities have often occurred in the past [de Hoog et al. 2000]. Due to the advancement of molecular techniques and the availability of the DNA sequences of various gene loci in sequence databases such as GenBank, it was possible to identify Exophial down to the species level. Initially, it was intended to recover Candida species from this patient's samples. However, we did observe the appearance of unusual dark colonies on the SDA plates. The darkness of the color grew as the culture grew old and appeared as a "black mushroom" within a few days. To obtain a pure culture, black fungal colonies were grafted onto the SDA in the second round, which were then Gram stained. In two, two black fungal isolates were found, and the mouthwash samples were named [Binder et al. 2014, Seneviratne et al. 2015, Kumar 2021].

Seneviratne et al. [2015] described the first case of isolation of the species *E. dermatitidis* from the human oral cavity. E. dermatitidis is considered a new systemic pathogen in Southeast Asia [de Hoog et al. 2000]. Fatal brain infections and disseminated black fungi have previously been reported in China, with *E. dermatitidis* being one of the causative agents [Li et al., 2011]. Previously, isolation of this species from the oral cavity in humans has never been reported. These Authors described a case of two strains of *E. dermatitidis* isolated from the obturator of a patient with NPC during IMRT. They also performed a comprehensive molecular analysis of the isolates and characterized their phenotypic behavior in terms of antifungal susceptibility. They also obtained pioneering data on virulence attributes such as biofilm formation, hemolysin and proteinase determination. One of these *E. dermatitidis* isolates was resistant to caspofungin and amphotericin B, the two best antifungal drugs on the market for systemic fungal infections. This discovery justified further clinical trials on the dangerous fungal pathogen, especially in the growing immunocompromised population, including patients with NPC [Li et al., 2011, Rodrigues & Albuquerque, 2018].

The Relationship between the Disease and Diabetes

Severantes et al. [2015], Kumar [2021] and others [Club Nova et al. 2009, Binder et al. 2014, Wang et al. 2018, Li et al. 2019] believe that mucormycosis may be associated with the use of steroids such as dexamethasone, which are used to treat severe COVID-19. Steroids reduce lung inflammation in the case of SARS-CoV-2 coronavirus infection, but they also lower immunity and raise blood sugar levels in both diabetics and non-diabetic patients. It is believed that this large decline in immunity may put people at risk of developing mucormycosis. People with diabetes, also those who use steroids, take oxygen for a long time, and patients with a severe course of COVID-19 are most at risk of developing the infection. Vigilance should also be maintained in patients after chemotherapy and taking long-term immunosuppressants [Seneviratne et al. 2015, Kumar 2021].

Carbohydrates, and especially oligosaccharides, polysaccharides and glycoconjugates, are the most important part of the bioactive ingredients of natural products used in diagnostics, therapy, food additives, as well as in various biomaterials [DeFronze 1999, Club Nova et al. 2009, Wang et al. 2018]. The greatest endocrine disease related to metabolic disorders and carbohydrate metabolism characterized by elevated fasting blood glucose is diabetes mellitus (DM). While the cause of elevated blood glucose may be related to either too little or too much insulin, the complications of chronically high serum glucose are devastating to humans. Untreated DM can lead to serious complications. The significant morbidity and mortality of diabetes mellitus is due to macrovascular complications [Wang et al. 2018, Bolla et al. 2019]. DM is becoming a devastating scourge, and despite the increase in the number of new drugs to treat and prevent the disease, its prevalence is increasing. For this purpose, nutritional therapies are being considered, including the use of alternative systems of medicinal plants and herbal foods [Mahomoodally et al. 2012; Wang et al. 2018, Bolla et al. 2019].

Together with dietary raw materials, plant preparations have been and still are the basis of disease management, even after the introduction of insulin [Mahomoodally et al. 2012]. Activities such as: manipulating carbohydrate metabolism through various mechanisms, preventing and restoring β-cell integrity and function, or insulin-releasing activity, improve glucose utilization by medicinal plants and

inhibit the activity of digestive enzymes and provide a good opportunity to transform them into therapeutic ingredients nutritional [Sawicka & Gupta 2018,]. Recently, there is more and more work on the potential of medicinal herbs and food plants with antidiabetic activity to inhibit α-amylase and α-glucosidase, which leads to significant progress in understanding the activity of α-amylase and α-glucosidase, and thus to the development of new pharmacological agents [Anonymous 2019, Ratanakiri, et al. 2020]. A-amylase is believed to inhibit the gastrointestinal and metabolic effects, which may help not only in the treatment of postprandial hyperglycemia. Recently, the production and sale of α-amylase and α-glucosidase inhibitors that block digestion and absorption of ingested carbohydrates (mainly starch) have been promoted as a means of rapid weight loss. Patients are demanding new natural dietary supplements known as 'carbohydrate or starch blockers' and suggest that diets may eat carbohydrate-rich foods without experiencing weight gain or increased caloric intake [Bolla et al. 2019, Mahomoodally et al. 2012]. Today, many traditional and exotic species of herbs and foods are used in folk medicine to treat a variety of ailments, including chronic diseases such as DM [Mahomoodally et al. 2012, Sawicka & Gupta 2019]. Many kinds of extracts from various exotic as well as traditional species of herbs and food plants are registered as decoctions or "extracts" and commonly used as nutritional supplements [Anonymous 2019, Li et al. 2019, Rattanakiat et al. 2020]. Nevertheless, there is a need for its constant, constant supplementation or renewal. Carbohydrate analysis is essential to understanding structure-function relationships.

Treatment

Treatment with prescription for antifungal medicine requires surgery to cut away the infected tissue. There is no vaccine to prevent mucormycosis and it is quite difficult to avoid the omnipresent fungi in the environment. Early detection can prevent loss of eyesight, nose or jaw through clinical intervention, while those with weakened immune systems may reduce the chance of developing the infection by avoiding areas with a lot of dust like construction or excavation sites, direct contact with water-damaged buildings, flood water after hurricanes, natural disasters, and activities involving close contact to soil, often associated with decaying organic material such as fruit and vegetables. Upon establishing the diagnosis, immediately correct hypoxia, acidosis, hyperglycemia, and electrolyte imbalance; while discontinuing steroids, anti-metabolites, and immunosuppressive drugs. Surgery should be undertaken, with amphotericin B therapy, continued until remission is achieved with Liposomal amphotericin B [Branscomb, 2002]. Mucormycosis is a highly lethal fungal infection in immunocompromised and a severe one in renal transplant recipients. Surgical debridement combined with antifungals, especially liposomal amphotericin B and posaconazole, can significantly improve a patient's overall survival [Ibrahim & Kontoyiannis 2013, Katragkou et al. 2014, Song et al., 2017].

None can be spared

Thousands of mucormycosis cases have been reported following India's second wave of COVID-19 cases. This fatal, neglected disease has finally been highlighted all over the world [Cornely et al. 2019, Millon et al. 2019, Biswas 2021, Kumar 2021, Parakash & Chakrabarti 2021]. Among physicians, lack of personal protective equipment is the most commonly cited cause of thier death. Exemption of elederly physicians from front-line work can save some lives. Mucormycosis burdens the immunocompromised patients, using drugs that suppress the immune system such as corticosteroids. However the mortality can be delayed with newly developed pathogenesis medications requiring injection of antifungal agents, surgical intervention and timely dosage of antifungal therapy. However, the treatment differs in species and effects on the human body varying widely between developed and developing nations. While it is less common and seen only in patients with haematological malignancies(HM) in developed regions; it is common in patients with uncontrolled diabetes mellitus or trauma in developing countries [Kumar, 2021]. Fatality rate with mucormycosis is as high as 90%, rapid dissemination of mucormycosis is an extraordinary phenomenon and even a delay of 12 h in the diagnosis could be fatal. 50% of cases of mucormycosis have been diagnosed only in the post-mortem autopsy series, where its temporal

associations in relation to comorbidities, association with drugs being used in COVID-19 and overall characteristics of patients had a cumulative outcome [Kumar et al., 2021]. Patients with leukemia or lymphoma suffering from the pulmonary form usually die from the infection due to GI tract infection [Wang et al. 2020]. The overall mortality is high, as death results in 2 weeks if untreated or unsuccessfully treated [Branscomb, 2002]. Fungal diseases are clinically silent in their early stages and can mimic other infections. Hospitals in underdeveloped countries have little or no diagnostic capability for complex test formats, expense, inadequate laboratory infrastructure and a lack of training are all barriers to black fungus diagnostic testing [Song et al. 2017, GAFFI, 2020]. Seneviratne et al. [2015], Bongomin et al. [2017], Rodrigues & Albuquerque [2018] showed that black fungus isolates are resistant to caspofungin, the main antifungal agent in systemic candidiasis. Since little is known about the black fungus in clinical settings, it is important that clinicians stay abreast of new discoveries in this field.

CONCLUSION

Controlling black fungal infections require more awareness towards better tests to diagnose them at the early stage, focus on controlling diabetes and using corticosteroids wisely. Patients will need access to timely surgery and antifungal treatment. Many biotic and abiotic factors can influence the treatment of mucormycosis, including: underlying health condition related to infection (e.g., diabetes, haematological cancer, etc.), location and extent of infection, time to appropriate diagnosis and treatment initiation, age, general health status and other factors.

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