INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 7; Issue 07(A); July 2021; Page No.5859-5865
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr20211031

Research Article

THE CROSSING OF UNCONTROLLED DIABETES MELLITUS AND HORRIBLE COVID-19 UPSHOT THE HURRICANE FOR BLACK FUNGUS

Raghavendra Rao M.V[1], Aruna Kumari.B[2], Pallavi SP[3], Dilip Mathai[4], Tina Presilla[5], Mahendra Kumar verma[6], Ahmad Abdul Khabeer[7] and Vijay Kumar Chennamchetty[8]

[1]Scientist-Emeritus and Director of Central research laboratory, Department of Laboratory Medicine, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India #1
[2]Department of Respiratory Medicine, ESIC Medical College, Sanathnagar Hyderabad, T India
[3]Department of Sports Medicine, College of Physiotherapy, Apollo Institute of Medical Sciences & Research, Telangana state, Hyderabad, India
[4]Department of Medicine, Dean, Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana, India
[5]DVL, Apollo institute of Medical Sciences and Research, Hyderabad, TS, India
[6]American University School of Medicine Aruba, Caribbean islands,
[7]ENT, Gandhi Medical College, Hyderabad, TS, India
[8]Department of Pulmonology, Apollo institute of Medical Sciences and Research, Hyderabad, TS, India

ARTICLE INFO

Article History:
Received 06th April, 2021
Received in revised form 14th May, 2021
Accepted 23rd June, 2021
Published online 28th July, 2021

Key words:
Pulmonary mucormycosis, Leukemia, Neutropenia, Gastrointestinal mucormycosis, Rhino cerebral, Liposomal amphotericin B

ABSTRACT

India is the first diabetes country in the world. In the first wave mucormycocosis was negligible in incidence in comparison to second wave of COVID but "The black fungus has painted the country vermillion in the second round." Black fungus is a rare, but aggressive fungal infection. Black fungus is Mucormycosis. Black fungus cases are more in hot tropical countries because the environment is ideal for these spores present in the air to grow. Our breath makes the mask moist, which becomes a potentially sound place for the fungus to grow."Black fungus is the crossing of uncontrolled Diabetic mellitus and COVID-19 in the pandemic. COVID-associated aspergillosis (CAPA), and (COVID-19-associated mucormycosis) CAMCR cases are well registered. Physicians are suspicious about (COVID-19-associated mucormycosis) CAMCR especially if rhino-orbital or rhino-cerebral presentations are noted in severely ill patient with COVID-19 and Diabetes Mellitus.DM (Diabetes Mellitus) patients with COVID-19 develops Craniofacial pain without bump. Offensive smelling nasal extravasate with headache and foul halitosis in a diabetic and COVID-19 patient should be considered exceedingly distrustful of mucormycosis. Black fungus spreads to the eyes and causes blindness. In the brain causes headache and seizures.

INTRODUCTION

Uncontrolled diabetes mellitus is the major risk factors for mucormycosis (1) Organ transplantation in patients is the major risk factor for this infection (2). Lymphocytopenia has been identified as predicting death in this. (3) Indiscriminate use of Glucocorticosteroid is a risk factor for fungal infection (4) Mucormycosis is a rare, emerging fungal infection, with high morbidity and mortality. (5)

It is impossible to conduct large, randomized clinical trials, epidemiology, diagnosis, and treatment, originating from case reports (6). Relatively large epidemiological studies were performed either on a national level (7). In patients with selected underlying diseases, for example, hematopoietic stem cell transplantation (HSCT) (8). The major risk factors are neutropenia, uncontrolled diabetes (9). Invasive mucormycosis is the third most frequent invasive fungal infection (IFI) (10). Mucormycosis is associated with angio-invasion and high mortality (11). Diabetes mellitus, organ transplants, and corticosteroid therapy are the major sources (12) D.M is the most common risk factor (13,14).

In recent years, health-care-associated mucormycosis is increasingly documented (15). Mucormycosis frequently infects the sinuses, brain, or lungs (16). Patients present with

Corresponding author:* **Raghavendra Rao M.V
Scientist-Emeritus and Director of Central research laboratory, Department of Laboratory Medicine, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India #1

nonspecific symptoms like cough, dyspnea, chest pain, and fever (17). Clinical diagnosis is difficult in pulmonary mucormycosis, and early diagnosis is needed for this life-threatening infection (18)

Chronological record of significant events

First case in humans reported in 1885 by Friedrich Küchenmeister (19) Fürbringer first described the disease in the lungs in 1876 (20) Gregory first observed the rhino-orbital cerebral mucormycosis in 1943. The order Mucorales contains many species, 38 are associated with human infections (21) mucormycosis in India were estimated to be about 70 times higher than in the rest of the world (22)

Due to its rapidly growing number of cases many Indian state governments have declared it an epidemic (23)

Diabetic ketoacidosis and mucormycosis

The tissues become relatively acidic in uncontrolled blood sugar patients. It is the ideal environment for fungus growth. Diabetes and obese people gravitable to develop more severe Covid-19 infections. Covid-19 virus can damage airway tissue and blood vessels, and increase susceptibility to fungal infection. Mucorales need iron for growth, and stay away from host phagocytic defence mechanisms. (24)

Mucorales have a ketone reductase system and allows them to bloom in hyperglycemic and acidotic conditions, may be due to the higher incidence of mucormycosis in patients with diabetic ketoacidosis (25) uncontrolled diabetes and indiscriminate use of drugs especially corticoids, causes decrease in immunity,"

Symptomatology

Pain under the eyes and redness around eyes, partial loss of vision, black lesions on nasal bridge and bleeding from nose (Epistaxis) toothache or loosening the teeth, fever, cough, headache, and bloody vomit. SOB, altered mental status. Unnatural headaches, sinus pain, forehead pain, and visual disturbances. Affects eyes and brain when enters through sinus. Biggest cause is poor control of diabetes. Patients with immunocompromised are at high risk. The infection starts from the nose, upper jaw and travels to the brain. Experts say that once it reaches brain, it is almost a death sentence. mortality rate of about 50%.

Glucocorticoids- and invasive black fungus infections

Glucocorticoid secretion is mainly regulated by corticotropin. Humans secrete 8-30 mg of cortisol and 1-4 mg of corticosterone in 24 hrs. cortisol has a diurnal rhythm of secretion with its peak at 4-8 AM.

High blood levels of glucocorticoids like cortisol bring about long -loop feedback inhibitions of the hypothalamic CRH release, the responsiveness of pituitary corticotroph cells to corticotropin-releasing hormone (CRH), and the synthesis and secretion of POMC and ACTH. Glucocorticoid administration decreases the firing frequency of hypothalamic neurons, inhibits CRH release, and lowers the secretions of POMC and ACTH Phagocytosis by the lung macrophages (asexual spores) is the first line of defence against inhaled mould in the lung, but some of the conidia fight phagocytosis, germinate to hyphae, and authorise an invasive infection. The neutrophils are finally destroyed by the oxidative cytotoxic components of polymorphonuclear leukocytes (PMNs).

The monocytes and macrophages, PMNs, and T lymphocytes help in intracellular killing (26)

Some more differentiated macrophages, activated by cytokines, engage acquired host resistance to fungus

1. Glucocorticoids exert many immunosuppressive effects.
2. Glucocorticoids activate cellular immunodeficiency.
3. They increase host susceptibility to fungal infections
4. Several immunosuppressive and anti-inflammatory effects of glucocorticoids may be exerted through inhibition of NFB, which regulates inflammatory responses and other transcription factors.
5. Glucocorticoids affect every cell involved in immune and inflammatory response.
6. Glucocorticoids affect mononuclear leukocytes, causing reversible lymphopenia and monocytopenia. Decreased proliferation and migration of lymphocytes
7. Glucocorticoids diminish the circulating CD4+ and, CD8+ T lymphocytes.
8. Injection of 400 mg of hydrocortisone, within 4 hours will reduce more than half of circulating lymphocytes
9. More than 40% of monocytes are reduced after administration of glucocorticoid,
10. Administration of glucocorticoids, to patients show defective delayed Type hypersensitivity and, tuberculin skin test results are very often false-negative
11. Glucocorticoids will block natural-killer-cell Cytotoxicity
12. Glucocorticoids administration produce dysfunction of Th1/Th2 ,T-helper cells and recommending Th2-cytokine response, that results in a crackdown of phagocyte cell function and produces fungal infections. (27)
13. Glucocorticoids decrease secretion of interleukin-2, interleukin-12, tumour necrosis factor (TNF), and interferon and increase interleukin-4, interleukin-5, and interleukin-10 Glucocorticoids inhibit NFB and activator protein 1 (AP1), the principal mediators of interleukin-1 transcriptional activation in monocytes and macrophages.(28) Glucocorticoids also suppress several PMN functions. (29)

What additional might cause black fungus?

Diabetes may escalate the probability of developing Black Fungus Infection Post COVID-19. Steroids and tocilizumab drugs decrease immunity. Individual more susceptible to opportunistic infection like mucormycosis," Professionals suggest that the indiscriminate use of steroids for Covid treatments could be linked to mucormycosis or other fungal infections.

Two extensively recommended steroids are dexamethasone and methylprednisolone. These are drugs that reduce the inflammation caused by the body's immune response for Covid patients.

Steroids and IL-6 inhibitors (tocilizumab) decrease immunity. COVID-19 also decreases immunity thus leading to further immune suppression.

How Fungus Can Debilitate Your Immune System?

“Thanks to our body’s defence mechanisms, which are

continuously and assiduously fighting these omnipresent organisms, This crisis has created immune defense mechanisms against fungi with the ultimate goal of therapeutic intervention. (30) Mice inhalation of A*spergillus fumigatus* leads to a rapid increase in philosophic numbers in the spleen and blood but also in the lung (31)

IL-3 is important for the recruitment of basophil into mediastinal lymph nodes following *Nippostrongylus basiliensis* infection. (32) The new insights create a foundation for the development of new immune-based strategies for prevention or enhanced clearance of fungal diseases. (33) Developing new knowledge in immunological research and for devising immune-based therapeutic approaches for patients infected with fungal pathogens (34).

Who is susceptible to black fungal infections?

1. Hypo immunity patients are more susceptible to infection.
2. Diabetes reduce immune response.
3. Hyperglycaemia in acidic environment particularly in diabetic ketoacidosis boost up the rapid growth
4. Steroids escalate blood sugar levels and decline the immune response of the body.
5. Patients on immunosuppressants
6. Patients suffering from malignancies
7. Patients with iron overdose
8. Malnourished, trauma, and burn people.

Mucormycosis in a Diabetic Patient

Rhizomucor pusillus is an opportunistic fungus that causes infections (mucormycosis) in patients with diabetes mellitus and immunodeficiency. Striking manifestations are sinus, pulmonary, and skin infections. Skin lesions consist of tender, erythematous, indurated, and necrotic plaques.

Nonspecific. In high-risk individuals, invasive fungal infection should be suspected if there is hemoptysis, pleuritic chest pain, unilateral facial pain or swelling, orbital swelling, or proptosis. Other presentations include tissue necrosis, often a late sign, is a hallmark of mucormycosis, resulting from angioinvasion and vascular thrombosis.

Cutaneous mucormycosis--Diabetic mellitus patients

The fungus enters through a cut, scrape, burn. Cutaneous mucormycosis is the third most common form of the disease, after pulmonary and rhino-cerebral. The predisposing factors of this infection are haematological malignancies, diabetes mellitus, and immunocompetent. (35) Further progression into deeper tissue affecting muscles, tendons or bone is possible (36) Cutaneous mucormycosis is seen in patients with large open wounds, and lesions (37)

Pulmonary mucormycosis

It is an uncommon but deadly fungal infection (38,39) It typically affects immunocompromised patients, such as recipients of stem cell or organ transplant. (40) Pulmonary mucormycosis affects immunosuppressed and diabetes mellitus patients (41) Pulmonary mucormycosis infection has a high mortality (40–76%) (42)

Rhino- orbital mucormycosis in Covid-19 patient

One case of severe covid pneumonia-presented after 5 days of ICU stay with Rhino orbital pulmonary mucor. Repeated debridement of ethmoidal sinus is going on. Patient is stable.

41 year old female patient presented to the emergency department with complaints of Shortness of gradual in onset,progresses from grade 2 to grade 4 within 2 weeks, fever, Cough, generalised body pains. RT PCR is positive for covid 19.

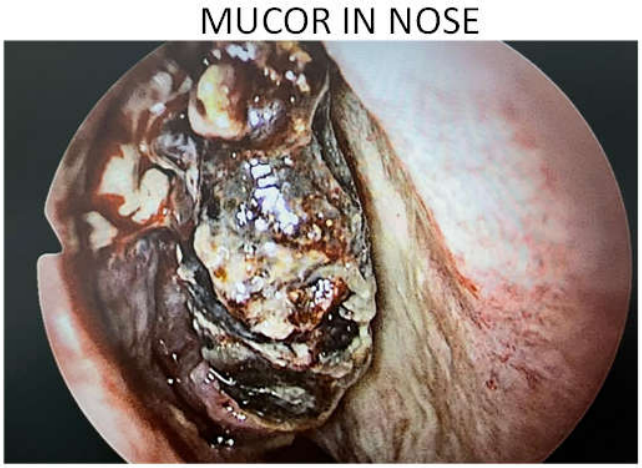
- She has been on antihypertensive medication for 10 years . Not a known diabetic
- On examination:Pt conscious,coherent,co-operative
- Vitals: Spo2:80% on room air, 92% with 15 litres of O2,BP-130/80,Respiratory rate 32 breaths per minute,temperature-102*F
- Lab parameters: D-dimer and ferritin are moderately elevated.CBP is normal.
- Medication given
- INJ.PIPTAZ 4.5 gm I.V TID-for 10 days
- INJ.SOLUMEDROL 125 mg IV BD-5 days
- INJ.CLEXANE 40 mg s/c BD-2 weeks
- INJ.PAN 40 IV OD-2 weeks
- TAB.TELMA 40 OD-2 weeks
- NIV support initiated and continued for 5 days
- GRBS was measured every 8 HRLY and Human Actrapid Insulin was given according to sliding scale.
- Inj.paracetamol 1 gram administered twice in the course whenever fever spikes of 104*F was observed.

Pt was improving .Shortness of breath is grade 2 and off niv ON DAY 5.Maintaining with 5 litres oxygen with mask. Complaining of retro orbital pain and a headache.ENT opinion was taken, rhino orbital mucor was suspected.MRI was suggestive of angioinvasive fungus and the case was posted for nasal endoscopy for debridement.

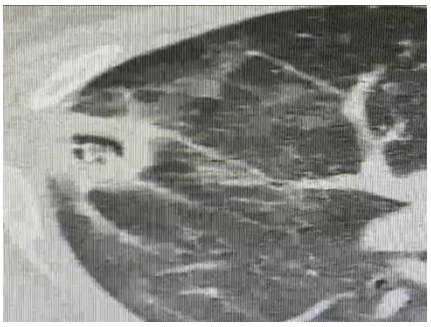
Debrided material showed inflammatory cells and broad branching Aseptate fungal hyphae consistent with fungal sinusitis(mucormycosis)

She Undergoing Medical Management with Liposomal Amphotericin B.

- Ct chest showing peripherally located cavitating fungal ball.
- Bronchoalveolar lavage did not reveal any fungal hyphae.



- Ct chest showing peripherally located cavitating fungal ball.



- Bronchoalvelar lavage did not reveal any fungal hyphae.

A perfect tempest in Covid-19-associated mucormycosis

Unchecked diabetes makes an appearance as a crucial element in acquiring black fungus infection or mucormycosis, which flares up in Covid-19 patients after convalescence to further complications. The fungi has potential to flourish and cause damage under filthy conditions, "Moisture in the environment, dirty domains and can be a big source of infection. Covid-19-associated mucormycosis showed 94% of patients had diabetes

Biotechnology for Molecular Diagnosis of Black fungus

1. Direct microscopy of clinical specimens and culture is strongly recommended for identification of mucormycosis.
2. Histopathology may allow differentiation of mucormycosis from aspergillosis
3. Microscopicy estimates morphology, branching and septation. For the species recognition direct microscopy is not useful
4. Grinding of specimens should therefore be avoided (43)
5. Standardized appraisals are available for the detection of fungus-specific antigens
6. CT lesions are expressive for invasive fungal disease
7. The 1,3-b-D-glucan is a common component of the cell wall of a wide variety of fungi but not of the Mucorales.
8. Detection of antigen and Mucorales-specific T cells.
9. Fungus T cells were detected by an enzyme-- linked immunospot (ELISpot) assay.
10. Molecular-based methods for direct detection -PCR that targets the 18S ribosomal DNA of Mucorales was evaluated on fresh tissue specimens
11. The semi-nested PCR as described was also evaluated on formalin-fixed paraffin-embedded tissue specimens (44)
12. Mucorales PCR was positive in 22 of 27 tissue specimens from patients with a haematological malignancy (45)
13. The failure to amplify specific DNA might result from fungal DNA concentrations below detection limits. (46)

Breakthrough Treatments of Black fungus in Covid-19-associated diabetes mellitus patients

Early intervention of monoclonal antibody treatment may reduce the risk of several illnesses and hospitalization for people with Covid-19 who are at high risk of developing serious illness. Invasive fungal diseases were reduced by posaconazole 200 mg three times daily. (47,48) The prospective SEIFEM-B 2010 registry on newly diagnosed acute myelogenous leukaemia (n = 515) compared posaconazole with itraconazole prophylaxis and no mucormycosis cases were diagnosed in either group (49) While fluconazole (50) and voriconazole (51) are not active against mucormycosis, itraconazole may yield some activity, but may be inferior to posaconazole (52)

In immunosuppressed patients with a previous diagnosis of mucormycosis (n = 3) surgery with secondary antifungal prophylaxis put stop to recurrence (53) The use of sodium bicarbonate (with insulin) to reverse ketoacidosis, might be associated with the disease due to reversal of the ability of Mucorales. (54) Corticosteroids and other immunosuppressive drugs should be tapered quickly and to the lowest possible dose. (55)

Amphotericin B is the most active drug, except for some Cunninghamella and Apophysomyces isolates. Posaconazole and isavuconazole are also active, while itraconazole and terbinafine show some activity against certain strains. There seems to be some correlation between the degree of susceptibility of Mucorales isolates to amphotericin B and outcomes (56,57)

The need of New Antifungal Agents

1. new formulations of antifungals, like liposomal amphotericin B, amphotericin B lipid complex, amphotericin B colloidal dispersion, amphotericin B into a lipid nanosphere formulation, Iitraconazole, and β-cyclodextrin Iitraconazole or
2. combination therapies of one or more antifungal compounds, for example, amphotericin B + flucytosine, fluconazole + flucytosine, amphotericin B + fluconazole, caspofungin + liposomal amphotericin B, and caspofungin + fluconazole

Exposure elements

1. Specific risk factors for mucormycosis are patients with haematological malignancies (HM) and prolonged severe neutropenia.
2. Poorly controlled diabetes, especially complicated by ketoacidosis (DKA) Patients with iron overload (58)
3. Patients have decreased amounts of mononuclear and polymorph nuclear phagocytes. Patients whose underlying disease disturbs the function of their phagocytic cells.
4. Patients who underwent hemato-poetic stem cell transplantation and also patients who received high-dose corticosteroid treatment (59)
5. In DKA patients, elevated levels of free iron in serum are caused by a release of iron from binding proteins such as transferrin, which is due to a decreased pH level. (60,61)
6. The dysfunction of glucose and iron metabolism, and regulation of this, was shown to result in decreased phagocytic function and intracellular killing of R. oryzae (62)
7. Therapy with the iron chelator deferoxamine (DFO) further enhances the risk for angioinvasive mucormycosis the reason for which was subsequently proven to be the ability of DFO to act as a xenosiderophore after free iron was bound. In contrast, other iron chelators, such as deferasirox and defer prone, were shown not to be used as xeno siderophores by Rhizopus (63,64)
8. Therefore, these iron chelators do not increase the risk for development of mucormycosis. The breakdown of the skin-barrier and/or soft tissue injuries, caused by

local trauma or burns, is another risk factor for mucormycosis. Cutaneous mucormycosis or soft tissue infections have been linked to the use of contaminated bandages, needles or wooden tongue depressors in the clinical setting (65,66)

Also, infections have been acquired by insect and spider bites or surgical interventions. Importantly, cutaneous mucormycosis has been found in otherwise healthy humans (67)

Restriction

1. Early interpretations with adequate treatment along with surgical operation can boost up recovery.
2. Prediction may enhance with quick diagnosis.
3. Prompt management can enhance recovery and survival rates. Mucormycosis is often a post-mortem diagnosis.
4. Early diagnosis and treatment are crucial.
5. Increased awareness, will Control the fungal infections
6. Early diagnosis, controlling diabetes and using corticosteroids cautiously.
7. Antifungal treatment.

An opinion arrived at through a process of reasoning

The Covid-19 pandemic harmed our memories. Causalities with diabetic ketoacidosis (DKA) and Covid-19, are exclusively activate to mucormycosis, an angioinvasive fungal infection with high mortality. The disease affects the heart, eyes and the brain.

Many people with the disease had lost their sense of smell, affect the nervous system strokes and other neurological complications. Cutaneous mucormycosis, Pulmonary mucormycosis and Rhino- orbital mucormycosis in Covid-19 patient cases increased excessively. Doctors, Virologists, mycologists, scientists, Pulmonologists and dermatologists believe mucormycosis, which has an overall mortality rate of 50%, may be being triggered by the use of steroids, a life-saving treatment for severe and critically ill Covid-19 patients.

References

1. Ibrahim AS, Edwards JE, Filler SG. Zygomycosis. In: Dismukes WE, Pappas PG, Sobel JD, editors. *Clinical mycology*. New York, NY: Oxford University Press; 2003. pp. 241–51.
2. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2002;34:909–17.
3. Lewis RE, Georgiadou SP, Sampsonas F, Chamilos G, Kontoyiannis DP. Risk factors for early mortality in haematological malignancy patients with pulmonary mucormycosis. Mycoses 2013. doi: 10.1111/ myc.12101.
4. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet 2003; 362: 1828–1838.
5. Pandey A, Bansal V, Asthana AK, Trivedi V, Madan M, Das A ,2011, Maxillary osteomyelitis by mucormycosis: report of four cases. Int J Infect Dis 15(1):e66–e69
6. Roden MM, Zaoutis TE, Buchanan WL *et al*. . Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005; 41: 634–653.
7. Arastehfar A, Carvalho A, Van de Veerdonk FL, Jenks JD, Koehler P, Krause R, Cornely OA, Perlin DS, Lass-Florl C, Hoenigl M ,2020, COVID-19 associated pulmonary aspergillosis (CAPA)- from immunology to treatment. J Fungi 6(2):91.
8. Kontoyiannis DP, Azie N, Franks B, Horn DL. Prospective Antifungal Therapy (PATH) Alliance(®): focus on mucormycosis. Mycoses. 2014;57: 240–24
9. Richardson M., Richardson M.D., Warnock D.W. Fourth Edition. Wiley-Blackwell Publishing, Inc.; Chichester, UK: 2012. Fungal Infection: Diagnosis and Management
10. Chayakulkeeree M, Ghannoum MA, Perfect JR: Zygomycosis: the re-emerging fungal infection. Eur J Microbiol Infect Dis. 2006, 25: 215-229.
11. Roden, M.M.; Zaoutis, T.E.; Buchanan, W.L.; Knudsen, T.A.; Sarkisova, T.A.; Schaufele, R.L.; Sein, M.; Sein, T.; Chiou, C.C.; Chu, J.H.; *et al*. Epidemiology and outcome of zygomycosis: A review of 929 reported cases. Clin. Infect. Dis. 2005, 41, 634–653.
12. Jeong, W.; Keighley, C.; Wolfe, R.; Lee, W.L.; Slavin, M.A.; Kong, D.C.M.; Chen, S.C.A. The epidemiology and clinical manifestations of mucormycosis: A systematic review and meta-analysis of case reports. Clin. Microbiol. Infect. 2019, 25, 26–34
13. Prakash, H.; Ghosh, A.K.; Rudramurthy, S.M.; Singh, P.; Xess, I.; Savio, J.; Pamidimukkala, U.; Jillwin, J.; Varma, S.; Das, A.; *et al*. A prospective multicenter study on mucormycosis in India: Epidemiology, diagnosis, and treatment. Med. Mycol. 2018.
14. Chakrabarti, A.; Das, A.; Mandal, J.; Shivaprakash, M.R.; George, V.K.; Tarai, B.; Rao, P.; Panda, N.; Verma, S.C.; Sakhuja, V. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. Med. Mycol. 2006, 44, 335–342.
15. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Ralph ZJ ,2020,Invasive fungal diseases during COVID-19: we should be prepared. J De Mycol Med 30:100971
16. Nancy F Crum-Cianflone; MD MPH. "Mucormycosis". eMedicine. Retrieved May 19, 2008.
17. A. Serris, F. Danion, and F. Lanternier, “Disease entities in mucormycosis,” *Journal of Fungi*, vol. 5, no. 1, p. 23, 2019.
18. B. Nam, T. J. Kim, K. S. Lee, T. S. Kim, J. Han, and M. J. Chung, *European Radiology*, vol. 28, no. 2, pp. 788–795, 2018
19. Chander, Jagdish (2018). "26.Mucormycosis". *Textbook of Medical Mycology* (4th ed.). New Delhi: Jaypee Brothers Medical Publishers Ltd. pp. 534–596.
20. Yamin, Hasan S.; Alastal, Amro Y.; Bakri, Izzedin (January 2017). "Pulmonary Mucormycosis Over 130 Years: A Case Report and Literature Review". *Turkish Thoracic Journal*. **18** (1): 1–5.
21. Slavin, M.; Van Hal, S.; Sorrell, T.; Lee, A.; Marriott, D.; Daveson, K.; Kennedy, K.; Hajkowicz, K.; Halliday, C.;
22. Athan, E.; *et al*. Invasive infections due to filamentous fungi other than Aspergillus: Epidemiology and determinants of mortality. Clin. Microbiol. Infect. 2015, 21, 490

23. lan Schwartz, Arunaloke Chakrabarti (June 2, 2021). "'Black fungus' is creating a whole other health emergency for Covid-stricken India". *The Guardian*. Retrieved June 3, 2021.
24. Delhi/Jaipur/LucknowMay 19, Dev Ankur Wadhawan Pankaj Jain Samarth Shrivastava Kumar Kunal New; May 19, 2021UPDATED; Ist, 2021 17:51. "Rajasthan declares black fungus an epidemic; cases pile up in several states | 10 points". *India Today*. Retrieved May 20, 2021.
25. Ibrahim AS. Host-iron assimilation: pathogenesis and novel therapies of mucormycosis. Mycoses 2014;57(Suppl 3):13-7.
26. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev 2000;13:236-301.
27. Large JPG. Aspergillus fumigatus and aspergillosis. Clin Microbiol Rev 1999; 12: 310–50.
28. Clemons KV, Calich VL, Burger E, *et al*. Pathogenesis I: interactions of host cells and fungi. Med Mycol 2000; 38: 99–111
29. Kovalovsky D, Refojo D, Holsboer F, Arzt E. Molecular mechanisms and Th1/Th2 pathways in corticosteroid regulation of cytokine production. J Neuroimmunol 2000; 109: 23–29.
30. Boss B, Neeck G, Engelhardt B, Riedel W. Influence of corticosteroids on neutrophils, lymphocytes, their subsets, and T-cell activity markers in patients with active rheumatoid arthritis, compared to healthy controls. Ann N Y Acad Sci 1999; 876: 198–200
31. Akash verma, Marcel Wuthrich, George Deepe and Bruce Klein; Adaptive immunity to fungi,a subject collection from fungal Human fungal pathogens ,Gold spring harbor perspective in medicine, pp 93
32. Poddighi D, Mathias CB, Freyschmidt EJ, Kombi D,*et al*.2014.Basophils are rapidly mobilized following initial aeroallergen encounter in naive mice and provide a priming source of IL-1 in adaptive immune responses. J. Biol Regul. Homeost. Agents 28,91-103.
33. Kim S, Prout M, *et al*.2010.Cutting edge basophils are transiently recruited into the draining lymph nodes
34. Akashverma, Marcel Wutrich, *et al*.Adaptive immunity to fungi cite the article as cold spring Harb Perspect.Med Doi.10.1101.esh perspect.ao 19612.
35. Michail S, Lionakis, li G, Netea and Steven M, Mendelian genetics of human susceptibility to fungal infection, cold spring Harb prospect.Med DOI 10.1101/csh Perspect.a019638Miha
36. Skiada A, Petrikkos G. Cutaneous mucormycosis. Skinmed, 2013; 11: 155–159; quiz 159-60.
37. Geisen M, Fodor P, Eich G, Zollinger A, Dzemali O, Blumenthal S. Disseminated cutaneous mucormycosis in a patient on high-dose steroid therapy for severe ARDS. Intensive Care Med 2011;
38. 1895– 1896. 29. Chawla R, Sehgal S, Kumar SR, Mishra B. A rare case of mucormycosis of median sternotomy wound caused by Rhizopus arrhizus. Indian J Med Microbiol 2007; 25: 419–421.
39. Hamillos G, Samonis G, kontoyiannis DP. Pulmonary mucormycosis. *Semin Respir Crit Care Med.* 2011; 32(6):693–702.
40. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, *et al*. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis.* 2005;41(5):634–653.
41. Spellberg B, Kontoyiannis DP, Fredricks D, Morris MI, Perfect JR, Chin-Hong PV, *et al*. Risk factors for mortality in patients with mucormycosis. *Med Mycol.* 2012;50(6):611–618.
42. Lee FY, Mossad SB, Adal KA. Pulmonary mucormycosis: the last 30 years. *Arch Intern Med.* 1999;159(12):1301–1309.
43. Smith JA, Kauffman CA. Pulmonary fungal infections. *Respirology.* 2012;17(6):913–926.
44. Larone DH. Medically important fungi: a guide to identification. Washington DC: ASM Press, 2011.
45. Hammond SP, Bialek R, Milner DA, Petschnigg EM, Baden LR, Marty FM. Molecular methods to improve diagnosis and identification of mucormycosis. J Clin Microbiol 2011;
46. 2151–2153. 49. Bialek R, Konrad F, Kern J *et al*. PCR based identification and discrimination of agents of mucormycosis and aspergillosis in paraffin wax embedded tissue. J Clin Pathol 2005; 58: 1180–1184.
47. Bialek R, Konrad F, Kern J *et al*. PCR based identification and discrimination of agents of mucormycosis and aspergillosis in paraffin wax embedded tissue. J Clin Pathol 2005; 58: 1180–1184.
48. Cornely OA, Maertens J, Winston DJ *et al*. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007; 356: 348–359.
49. Ullmann AJ, Lipton JH, Vesole DH *et al*. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007; 356: 335–347.
50. Pagano L, Caira M, Candoni A *et al*. Evaluation of the practice of antifungal prophylaxis use in patients with newly diagnosed acute myeloid leukemia: results from the SEIFEM 2010-B registry. Clin Infect Dis 2012; 55: 1515–1521.
51. Singh J, Rimek D, Kappe R. In vitro susceptibility of 15 strains of zygomycetes to nine antifungal agents as determined by the NCCLS M38-A microdilution method. Mycoses 2005; 48: 246–250.
52. Guinea J, Pelaez T, Recio S, Torres-Narbona M, Bouza E. In vitro antifungal activities of isavuconazole (BAL4815), voriconazole, and fluconazole against 1,007 isolates of zygomycete, Candida, Aspergillus, Fusarium, and Scedosporium species. Antimicrob Agents Chemother 2008; 52: 1396–1400.
53. Rambach G, Oberhauser H, Speth C, Lass-Florl C. Susceptibility of Candida species and various moulds to antimycotic drugs: use of epidemiological cutoff values according to EUCAST and CLSI in an 8-year survey. Med Mycol 2011; 49: 856–863.
54. Nosari A, Ravini M, Cairoli R *et al*. Surgical resection of persistent pulmonary fungus nodules and secondary prophylaxis are effective in preventing fungal relapse in patients receiving chemotherapy or bone marrow transplantation for leukemia. Bone Marrow Transplant 2007; 39: 631–635.
55. Gebremariam T, Lin L, Liu M *et al*. Bicarbonate correction of ketoacidosis alters host-pathogen interactions and alleviates mucormycosis. J Clin Invest. 2016; 126: 2280–2294.
56. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic

malignancy who have zygomycosis. Clin Infect Dis. 2008; 47: 503–509.

57. A. Salas V, Pastor FJ, Calvo E *et al*. Efficacy of posaconazole in a murine model of disseminated infection caused by Apophysomyces variabilis. J Antimicrob Chemother. 2012; 67: 1712–1715.
58. B. Perkhofer S, Lechner V, Lass-Florl C. In vitro activity of isavuconazole against Aspergillus species and zygomycetes according to the methodology of the European Committee on Antimicrobial Susceptibility Testing. Antimicrob Agents Chemother. 2009; 53: 1645–1647.
59. Neofytos D, Horn D, Anaissie E *et al*. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis 2009; 48: 265–273.
60. Petrikkos G, Drogari-Apiranthitou M. Zygomycosis in immunocom-promised non-haematological patients. Mediterr J Hematol Infect Dis 2011; 3: e2011012.
61. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoy- iannis DP. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis 2012; 54 (Suppl 1): S23–S34.
62. Roilides E, Kontoyiannis DP, Walsh TJ. Host defenses against zygomycetes. Clin Infect Dis 2012; 54 (Suppl 1): S61–S66.
63. Artis WM, Fountain JA, Delcher HK, Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferring and iron availability. Diabetes 1982; 31: 1109–1114.
64. Dabritz J, Attarbaschi A, Tintelnot K *et al*. Mucormycosis in paediatric patients: demographics, risk factors and outcome of 12 contemporary cases. Mycoses 2011; 54: e785–e788.
65. Ibrahim AS. Host cell invasion in mucormycosis: role of iron. Curr Opin Microbiol 2011; 14: 406–411.
66. Reed C, Ibrahim A, Edwards JE Jr, Walot I, Spellberg B. Deferasirox, an iron-chelating agent, as salvage therapy for rhinocerebral mucormycosis. Antimicrob Agents Chemother 2006; 50: 3968–3969.
67. Spellberg B, Andes D, Perez M *et al*. Safety and outcomes of open-label deferasirox iron chelation therapy for mucormycosis. Antimicrob Agents Chemother 2009; 53: 3122–3125.
68. Rammaert B, Lanternier F, Zahar JR *et al*. Healthcare-associated mucormycosis. Clin Infect Dis 2012; 54 (suppl 1): S44–S54.

How to cite this article:

Raghavendra Rao M.V *et al* (2021) 'The Crossing of Uncontrolled Diabetes Mellitus And Horrible COVID-19 Upshot The Hurricane For Black Fungus', *International Journal of Current Medical and Pharmaceutical Research,* 07(07), pp 5859-5865.

****