Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Mucormycosis: A new threat to Coronavirus disease 2019 with special emphasis on India

Deganta Ghosh a,1, Sagardeep Dey a,1, Himanko Chakraborty a,1, Sneha Mukherjee a,1, Ankita Halder a,1, Akash Sarkar a,1, Pallab Chakraborty b,1, Rajdeep Ghosh c,1, Joy Sarkar a,6

a Department of Botany, Dinabandhu Andrews College, Garia, Kolkata, West Bengal, India, 700064
b Department of Botany, Acharya Prafulla Chandra College, New Barrakpur, Kolkata, West Bengal, India, 700131
c GSL Medical College and General Hospital, Rajahmundry, Andhra Pradesh, India, 533296

ARTICLE INFO
Keywords: Corticosteroid COVID-19 Diabetics Mucormycosis Rhizopus

ABSTRACT
The main reason for the growth of mucormycosis in people with Coronavirus disease-2019 (COVID-19) is mainly produced by Rhizopus spp. The infective mechanisms and issues recognized in Rhizopus spp. are the cell wall, germination proteins, and enzymes assisted to iron sequestration, GohP protein, and positive regulation of the GRP78 cell receptor. Mucormycosis is mainly caused by the Rhizopus spp. such as R. oryzae, R. microsporus, R. arrhizus, R. homothallicus, etc. that are gifted to numerous host defense mechanisms and attribute to the endothelium via specific receptors, GRP78 simplifying their endocytosis and angio-invasion. Factors such as hyperglycemia, elevated iron concentrations, and ketoacidosis have been shown to contribute to the pathogenesis in the tentative situation. The analytical data of ‘black fungus disease’ or ‘mucormycosis’, specify India reported for about 42.3% of published cases, followed by the USA about 16.9%, Iraq, Bangladesh, Iran, Paraguay, and 1 case each from Brazil, Mexico, Italy, UK, China, France, Uruguay, Turkey, and Austria. The COVID-19 infection is maybe a predisposing factor for mucormycosis and is related to a high mortality rate. Early recognition and restriction of hyperglycemia, liposomal amphotericin B, and surgical debridement are the bases in the successful managing of mucormycosis.

1. Introduction
Mucormycosis is an uncommon angio obtrusive disease principally perceived in immunocompromised patients which happens because of the growth of mucorales.1 The term ‘Mucormycosis’ was instituted by an American pathologist R. D. Baker and it can likewise be called Zygomycosis. Mucormycotina falls under the normal saprobes which are found in bad organic matter or soil. Infections are designated by instantaneous progression.2 The Mucorales are not demanding creatures, they develop at temperature ranges between 25 °C and 55 °C.3 Being ubiquitous organisms, Mucorales are dominant in commencing and accelerating the decay of organic materials. Since openness to spores of these growths is unavoidable, the uncommonness of the diseases is harmful and is a validation of an extremely basic inclination.4

The initially announced instance of mucormycosis traces back to 1885 when the German pathologist Paltauf depicted the primary case as Mycosis Mucorina.5 The pace of mucormycosis expanded mostly in immunocompromised individuals subsequently in the 1980s–1990s.6

Different types of mucormycosis that can be associated with COVID-19 infection are, rhino-cerebral mucormycosis, pulmonary mucormycosis, gastrointestinal mucormycosis, cutaneous mucormycosis, and miscellaneous. For the region of the head and neck, mucormycosis can be assorted into isolated nasal, rhino-orbital, or rhino-orbital-cerebral mucormycosis. In the case of sino-orbital mucormycosis, the mold mainly enters via the respiratory tract and is containing the nose and sinuses, into the orbital and intracranial structures with the possibility of further progression.5,6 Pulmonary mucormycosis is a lethal aggressive fungal infection. It typically infects immunocompromised patients. Transbronchial biopsies and Bronchial alveolar lavage (BAL) are usually explained as non-septated hyphae in the case of pulmonary mucormycosis.7 Mucormycosis in the gastrointestinal (GI) tract occurs due to the ingestion of the spores of the fungus. It is rarely reported in the COVID-19 patient.8 Patients with persistent skin maceration or skin barrier disruptions (catheter insertion, trauma, injections, burn) are

* Corresponding author.
E-mail address: jsarkar80@gmail.com (J. Sarkar).
1 These authors have contributed equally to this work.

https://doi.org/10.1016/j.cegh.2022.101013
Received 7 September 2021; Received in revised form 10 December 2021; Accepted 10 March 2022
Available online 19 March 2022
2213-3984/© 2022 The Authors. Published by Elsevier B.V. on behalf of INDIACLEN. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
suitable for increasing the risk of cutaneous mucormycosis. The fungus can invade into adjacent fat, fascia, muscle, and even bone, while hematogenous spread with secondary vascular invasion is fewer common. However, hematogenous dissemination with cutaneous mucormycosis has high fatality rates.

From the perspective of disease to the immunocompromised people, mucormycosis likewise create a high danger for the patient determined to have serious COVID-19 pneumonia. This happens because of the hospitalized status, previous comorbidities, and treatment regimens comprising of steroids and generally anti-toxins. The predominance of mucormycosis in India is approximately 0.14 cases per 1000 populace, about multiple times the pervasiveness in different countries. COVID-19 contamination has been related to parasitic diseases. Globally, the most well-known danger factor related to mucormycosis is diabetes mellitus. In the prevalence of the COVID-19 pandemic, it is believed that this drop in resistance could be set off to these instances of mucormycosis.
2. Mucormycosis as COVID-19’s deadly companion

The aggravation of COVID-19 in 2020 has effectively crushed the entire world in its first wave, where an enormous number of cases have been noticed including deaths and deterioration. The destruction proceeds in 2021 in the period of second-wave, more in the most exceedingly terrible structure. 1-3 The flood of COVID-19 in its subsequent wave has additionally left a path of infection and deaths, where the ‘black fungus disease’ or ‘mucormycosis’ went with. Mucormycosis is a rare but severe complication of COVID-19, which may lead to a threat to life. 4,5

Up to May of 2021, we have dissected around 59 instances of Coronavirus disease 2019 (COVID-19) associated mucormycosis reported worldwide. Table 1

| Reported Area | Total No. of case | Age/SEX | Underlying Disease | Disease Type | Verified COVID-19 | Medicine used for COVID-19 | Fungal culture | Clinical Outcomes | Reference |
|---------------|-------------------|---------|--------------------|--------------|-------------------|--------------------------|----------------|-------------------|-----------|
| India         | 25                | 23-78 M-22 F-3 | DM-24 (32-78) No-67 M | No All | Rhino-orbital: 23, 60 Rhino-orbital cerebral: 40, 38, 51, 45, 56, 78, 67, 56, 37 Rhino-sinistic: 43, 64, 49, 59 M, 59F Pulmonary: 55, 32, 43, 72 Sino-orbital: 38 Paranasal: 68 | Confirmed | Steroid-51, 37, 43, 56, 78, 49, 60, 55, 38, 64, 60, 59F, 72 Tolcizumab-51, 37, 60 Remdesivir-32 M, 51, 37, 43, 56, 49, 55, 62, 38, 67, 72, 38, 45 | Positive (Rhizopus spp.) | Expired-10 Recovered-13 Unchanged-2 | 5,22,26 |
| Bangladesh    | 3                 | No reported | Not reported | Not reported | Rhino-orbital: 33, 60 Rhino-orbital cerebral: 36, 48 Pulmonary: 44, 49, 56, 79 Rhino-sinistic: 41 Cutaneous: 68 No applied: 32F, 40, 23 | Not reported | Not reported | Not reported | Not reported | Not reported | Link 1 |
| USA           | 10                | 33-79 M-8 F-2 | DM-36, 48, 79, 68 | No-9 | Rhino-orbital: 33, 60 Rhino-orbital cerebral: 36, 48 Pulmonary: 44, 49, 56, 79 Rhino-sinistic: 41 Cutaneous: 68 No applied: 32F, 40, 23 | Confirmed | Steroid-36, 44, 48, 49, 60, 41, 79, 56, 68 Tolcizumab-33, 56 Remdesivir-36, 44, 48, 49, 60, 79 | Positive all (79 M & 44M Aspergillus sp.) | Expired-6 Recovered-3 Unchanged-1 | 12,24,30,37-32 |
| UK            | 1                 | 22 M-1 | No | No | Pulmonary | Confirmed | Not applied | Positive | Expired | 32 |
| Brazil        | 1                 | 86 M-1 | No | No | Gastrointestinal | Confirmed | Not applied | Positive (Rhizopus spp.) | Expired | 8 |
| Italy         | 1                 | 66 M-1 | No | No | Pulmonary | Confirmed | Not applied | Positive (Rhizopus spp.) | Expired | 34 |
| France        | 1                 | 55 M-1 | No | Yes | Pulmonary | Confirmed | Not applied | Positive (Aspergillus spp.) | Expired | 25 |
| Iran          | 4                 | 40-61 M-24 F-2 | DM-44, 54, 48, 36 | No-All | Rhino-orbital: 61, 54 Rhino-orbital cerebral: 40 Rhino-sinistic: 44 Rhino-cerebral | Confirmed | Steroid-40, 44, 54, 61 Tolcizumab-No Remdesivir-40, 54 | Positive (Rhizopus spp.) | Expired-2 Recovered-2 Unchanged-No | 24,36,37 |
| China         | 1                 | 32 F-1 | No | No | Rhino-orbital | Confirmed | Not applied | Positive (Rhizopus spp.) | Expired | 23 |
| Mexico        | 1                 | 24 F-1 | DM-No | No | Rhino-orbital | Confirmed | Not applied | Positive (Rhizopus spp.) | Expired | 38 |
| Austria       | 1                 | 53 M-1 | No | Yes | Pulmonary | Confirmed | Not applied | Positive (Rhizopus spp.) | Expired | 39 |
| Turkey        | 1                 | 56 F-1 | DM-56 | No | Rhino-orbital sinistic | Confirmed | Steroid-56 Tolcizumab-No Remdesivir-No | Positive (Rhizopus spp.) | Expired | 40 |
| Uruguay       | 1                 | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Recovered | 2 |
| Paraguay      | 2                 | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | 3 |
| Iraq          | 5                 | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | 4 |
| Chile         | 1                 | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | 5 |

M: Male, F: Female, DM: Diabetes mellitus, DKA: Diabetic ketoacidosis, T1DM: Type 1 diabetes mellitus, T2DM: Type 2 diabetes mellitus, COVID-19: Coronavirus disease 2019.
and around 1336 deaths in Maharashtra, and about 708 deaths in Gujarat, brought about by this dark organism (Link 6). Telangana and Madhya Pradesh have been seen with 2638 and 2370 sequentially, where Madhya Pradesh has seen the expiration of 167 individuals. Besides, 1947 cases and 351 deaths in Delhi have been accounted for, close by Haryana with 1764 cases and 268 deaths. Uttar Pradesh, Karnataka, and Rajasthan are confronting the deficiency of liposomal amphotericin B, guaranteeing with around 2477, 3906, and 3621 cases distributively, brought about by the verse growth of mucormycosis (Link 7; Link 9). The ongoing report uncovers the passageway of the dark parasite in West Bengal and Punjab with 179 and 158 cases approximately, where 11 deaths of individuals have been reported from West Bengal. Assam and Himachal Pradesh count with the least number of cases and may rise in the upcoming days (Fig. 2). The abrupt acceleration of dark organisms close by COVID-19 leads to the issues for the deficiency of liposomal amphotericin B in numerous states including Goa, Odisha, Kerala, and more. The ‘black fungus disease’ or ‘mucormycosis’ have been announced as an ‘epidemic’ by Rajasthan, Gujarat, and Odisha (Link 6; Link 7; Link 8; Link 9). However, various cases are expanding day by day which may lead towards another disturbance alongside COVID-19.21,22

A sudden escalation of mucormycosis is being reported in cases with COVID-19.22 Many cases reveal the affection of mucormycosis even while undergoing treatment for COVID-19 (Table 2).

In general, from the referenced cases on mucormycosis related COVID-19 in India, the most effective type of mucormycosis, that is, the sort which holds the more detrimental rate is Rhino-orbital cerebral mucormycosis with about 36%, alongside Rhino-sinusitis mucormycosis with 24%. The Rhino-orbital mucormycosis and Pulmonary mucormycosis holds about 20% and 16% respectively, while the Parasal type holds the least number of cases with 4% of viability.46–48 (Fig. 3). Trigger off mucormycosis may prompt a deadly rise and could be fatal.

3. *Rhizopus*, the key player for COVID-19 associated mucormycosis

Mucormycosis is drivinglogically throughout the world, especially in India. The ruling fungal genera Mucorales, especially the *Rhizopus* species is the most well-known growths found in the patients of mucormycosis in both diabetic and non-diabetic COVID-19 patients. *Rhizopus* species appears differently concerning some others from the Mucorales family.21 Since it is aseptate and making sporangiophores, it is remarkably quick in making and spreading sorts of molds with blackish and a bit of the caramel or brownish sporangia49 (Fig. 4). Different aspiratory mucormycosis was perceived by going to the parasites with septate hyphae and sporangiophores through direct microscopy or despite fluorescent brighteners from clinical models like sputum, Bronchoalveolar Lavage Fluid (BALF), and so on also, by using the Lactophenol cotton blue (LCB) association in microscopy, the septate hyphal arrangement and the strain of hyphae were analyzed to see the microorganism.48–51 To confirm the assurance, non-pigmented hyphae showing tissue assault should show up in tissue sections stained with hematoxylin and eosin (HE) staining, Periodic Acid Schiff (PAS), or Grocott-methenamine-silver (GMS).43,52 The most notable species that cause mucormycosis after COVID-19 in India comprises *Rhizopus oryzae*, *Rhizopus microsporus*, *Rhizopus arrhizus*, *Rhizopus homothallius*, and some different equally species. These developments now and again impact the immunocompetent, yet rather immunocompromised patients.21

In patients with seriously controlled diabetes mellitus, the persistently expanded blood glucose levels will provoke the debilitated neutrophil measure.52 The parasites increase section through internal breath into the!paranasal sinuses and may finally spread to be the sphenoïd sinus and immense sinus. However most instances of mucormycosis are sporadic, and a sudden outburst of mucormycosis is ought to be lethal.53

3.1. Clinical expressions of the disease

Alongside COVID-19, the major cause for the increasing rate of mucormycosis triggered by *Rhizopus* spp. has been integrated with the upliftment of prevalence of diabetes mellitus (DM) and diabetic ketoacidosis (DKA). Infectious diseases hold up to 12% of all deaths in people with diabetes mellitus.54–56 DM is a classical fear element for mucormycosis, associated with high ailment and mortality rate in COVID-19, while DKA also stands as an ideal risk factor.27,57 In recent studies, euglycemic DKA is also being reported in COVID-19 patients.24 The pervasiveness of type 1 DM and DKA in COVID-19 were much higher compared to the type 2 DM and DKA in the general population.28 In addition, the utilization of immunosuppressive treatment like glucocorticoids and tocilizumab results in systemic immune adoptions by the infection that paved the way for mucormycosis contamination in patients during COVID-19.29

Mucormycosis would also be fatal for the patients who are seriously immunocompromised, likewise in cancer patients or AIDS patients.21 The infection of mucormycosis targets the region of the nose, sinuses, orbit, central nervous system (CNS), lung (pulmonary), gastrointestinal tract (GIT), skin, jawbones, joints, heart, kidney, mediastinum (invasive type), and abdominal portion.17,60 It is signaled by the appearance of hyphal invasion of sinus tissue in between a period of fewer than four weeks.51,62 Fever, headache, coughing, shortness of breath, bloody vomit and, altered mental state are all the primary symptoms of the disease. Moreover, congestion with the nasal release (blackish/bloody), confined pain on the cheekbone, partial facial pain with swelling, blackish discoloration above the bridge of nose or palate, loosening of teeth, diminished or double vision, skin lesion is the severe symptoms for the distinctive types of mucormycosis.9,21

In the first instance, the expression of rhino-cerebral mucormycosis is compatible with either sinusitis or periorbital cellulitis and includes eye or facial pain with numbness, followed by the onset of conjunctival suffusion, blury vision, and soft tissue swelling.63–67 Fever is inconsistent and might be absent in up to half of cases; white blood cell counts are typically uplifted, as far as the patient has functioning bone marrow.64,67 Histological features include mycotic invasion of blood vessels, vasculitis with thrombosis, tissue localized necrosis, hemorrhage, and intense neutrophil infiltrate.68

The clinical indications of pulmonary mucormycosis include cough with chest pain and dyspnea.69 This facilitates the result of inhalation or lymphatic spread. Patients with DKA can also thrive the disease, even though contamination in the patients is less conventional and less volatile than the infectious track that is typically seen in the patients with neutropenia.70,71 Otherwise, it also arises in the leukemic patients undergoing chemotherapy.4

Patients who are at an intense danger of creating cutaneous mucormycosis are those with interruption of the typical defensive cutaneous hindrance. Typically, the factors of mucormycosis are incapable of nauseating intact skin. In immunocompromised and diabetic patients, the cutaneous lesions may also rise due to catheter insertion and insulin injection sites.72–74 Infected surgical dressings have also been incriminated as a source of cutaneous mucormycosis.75,76 Mucormycosis in the gastrointestinal tract is rare. It mainly hinders malnourished patients (especially infants or children) and is thought to arise from the ingestion of fungi.77–80 The most frequently involved sites include the stomach, ileum, and colon. The symptoms are varied and based on the site affected. Fever and hematocritia may also arise, along with lenient abdominal pain and distention related to nausea and vomiting are the best fitted well-known manifestations.81–83
Fig. 2. An illustrative presentation on the number of cases of Coronavirus disease 2019 (COVID-19) associated mucormycosis reported in the different States of India (till September of 2021). (a) The colors provided in the different geographical area represents the variation in the number of cases. (b) A schematic presentation on the number of deaths in different States of India due to mucormycosis. (c) Up-to-date state-wise statistical indication of COVID-19 cases along with mucormycosis cases of India\textsuperscript{21,22} (Link 6; Link 7; Link 8).
Table 2
A precise of cases reported in India on Coronavirus disease 2019 (COVID-19) associated mucormycosis.

| Case No. | Age/Sex | Reported Area | Occurrence of fungal colonies during microscopy | Causative Agent | Disease Type | Underlying Disease | Infected internal body parts | Symptoms | Clinical outcomes | Reference |
|----------|---------|---------------|-----------------------------------------------|-----------------|--------------|--------------------|-----------------------------|----------|------------------|----------|
| Case-1   | 32/F    | Mangalore     | Positive                                      | Rhizopus spp.   | Paranasal Mucormycosis | Diabetes mellitus, left eye complete ptosis, facial problem | Orbit al apex syndrome | Recovered but no improvement in vision | Expired  |
| Case-2   | 60/M    | Mumbai        | Positive                                      | Rhizopus spp.   | Rhino-orbital Mucormycosis | Diabetes mellitus, Lung disease | Sinus and orbit | Rapidly lost eye vision orbital swelling, headache, nosebleed | Expired  |
| Case-3   | 38/M    | Mumbai        | Positive                                      | Rhizopus oryzae | Sino-orbital Mucormycosis | Diabetes mellitus | Sinus and orbit | Swelling and pain in the left eye | Recovered |
| Case-4   | 72/M    | Hyderabad     | Positive                                      | Rhizopus oryzae | Pulmonary Mucormycosis | Diabetes mellitus | Lungs | Streaky hemoptysis | The patient is not improving |
| Case-5   | 40/F    | Mangalore     | Positive                                      | Rhizopus spp.   | Rhino orbital cerebral Mucormycosis | Diabetes mellitus | Sinus, orbit, and CNS | Swelling of the left eye and facial pain, rhinitis | Recovered |
| Case-6   | 38/M    | Bangalore     | Positive                                      | Rhizopus oryzae | Rhino orbital cerebral Mucormycosis | Diabetes mellitus | Orbit, sinus | Right eye pain and chemosis | Expired  |
| Case-7   | 51/F    | Mumbai        | Positive                                      | Rhizopus oryzae | Rhino orbital cerebral Mucormycosis | Diabetes, Hypothyroidism | Eye, sinus, and CNS | Left side facial pain, nose block, periorbital pain, and headache | Recovered |
| Case-8   | 45/M    | Puducherry    | Positive                                      | Rhizopus oryzae | Rhino orbital cerebral Mucormycosis | Diabetes mellitus, Hypertension, CKD | Eye damage, sinus, and CNS | Impairment of right eye vision | Recovered |
| Case-9   | 56/M    | Bangalore     | Positive                                      | Rhizopus oryzae | Rhino orbital cerebral Mucormycosis | CKD, diabetes, hypertension, hyperthyroidism | Eye conjunctiva, brain | Right eye swelling | Expired  |
| Case-10  | 78/M    | Bangalore     | Positive                                      | Rhizopus oryzae | Rhino orbital cerebral Mucormycosis | Diabetes and hypertension | Sinus, orbit, and CNS | Holocranial headache | Expired  |
| Case-11  | 43/M    | Bangalore     | Positive                                      | Rhizopus oryzae | Rhino-sinusitis Mucormycosis | Diabetes mellitus, CLD | Sinus, nasal passages, oral cavity, and brain | Dryness and cresting in the nasal cavity | Recovered |
| Case-12  | 60/M    | Delhi         | Positive                                      | Rhizopus arrhizus | Rhino-sinusitis Mucormycosis | Diabetes mellitus, deranged kidney function | Sinus and brain | Periorbital swelling, chemosis, restricted eye movement | Expired  |
| Case-13  | 64/M    | Delhi         | Positive                                      | Rhizopus microsporus | Rhino-sinusitis Mucormycosis | Diabetes mellitus, renal function failure | Sinus, nasal passages, oral cavity, and brain | Proptosis of the eye with Periorbital discoloration, blackening of the middle turbinate. | Expired  |
| Case-14  | 67/M    | Not Reported  | Positive                                      | Rhizopus oryzae | Rhino orbital cerebral Mucormycosis | Hypertension | Cornia, conjunctiva, eyelids, optic nerve damage | High fever, dizziness, blurred vision | Recovered |
| Case-15  | 49/M    | Not Reported  | Positive                                      | Rhizopus homothallicus | Rhino-sinusitis Mucormycosis | Diabetes mellitus, problem in breathing | Sinus, brain, and nasal passages | High fever, facial swelling | Recovered |
| Case-16  | 23/M    | Not Reported  | Positive                                      | Rhizopus oryzae | Rhino-orbital Mucormycosis | Diabetes mellitus, hypertension | Sinus and orbit | High fever, headache, periorbital pain, facial pain | Expired  |
| Case-17  | 59/F    | Delhi         | Positive                                      | Rhizopus arrhizus | Rhino-sinusitis Mucormycosis | Diabetes | Sinus and brain | High fever, facial swelling, blackening of turbinate | Recovered |
| Case-18  | 62/M    | Positive      |                                              |                 |                          |                          | | | Expired  | (continued on next page)
4. Molecular mechanism: the panoramic story of COVID-19 associated mucormycosis

4.1. Exposition: Preface of the story

The attendance of Diabetes mellitus (DM), whether with or without Diabetic ketoacidosis (DKA), enhances the chance of acquiring mucormycosis, and DM is frequently linked to enhanced COVID-19 intensity. Meanwhile, corticosteroid use is regularly linked with uncontrolled hyperglycemia and the commencement of DKA. Acidosis causes a low pH, which is ideal for mucor spores to grow. Furthermore, use of steroid decreases the phagocytic nature of WBC (both first and second-line defensive mechanisms), impairs bronchoalveolar macrophage ingestion, migration, and phagolysosome fusion, and makes a diabetic patient more prone to mucormycosis.

4.2. Crisis period of the story

According to a well-known and established hypothesis about the pathogenesis of DM, elevated levels of glucose in the muscle, and adipose tissue induce cellular hypoxia, endoplasmic reticulum (ER) stress, enhanced discharge of reactive oxygen species (ROS), free fatty acids (FFA), and cytokine production. Interleukin-1 (IL-1β) and tumor necrosis factor (TNF) are released by hypertrophic cells in adipose tissue, along with different chemokines. TNF-α recruits M1 macrophages, and
its activation produces more pro-inflammatory cytokines (most notably IL-1β) that cause chronic inflammation and the employment of additional M1 macrophages. FFA is also detected by TLR in the tissue cells, initiating JNK-AP-1 and IKK-NFkB signalling. The utterance and discharge of pro-inflammatory cytokines are enhanced consequently, which promotes the native inflammatory state. In diabetes individuals, M1 macrophages infiltrate the tissue, producing a pro-inflammatory M1 macrophage response rather than a regulating M2 macrophage response. Because M2 macrophages seem to be better able to trigger and then destroy fungal cells, penetration of diabetic tissue with M1 macrophages could provide to Rhizopus spp. impedance to phagocytosis.

Several cellular level injuries like endothelial damage, endothelitis, lymphopenia, thrombosis, and a drop-down in the degree of CD4+, CD8+, and T-cells levels are frequently caused by COVID-19 which is ultimately putting the patient at risk of secondary or opportunistic fungal infection. The fasting condition induced by a lack of insulin causes the catabolism of amino acids and triacylglycerols (TAGs), deposited in adipose tissue to become active as an energy source in diabetic patients. In serum, due to limited lipolysis, the concentrations of free fatty acids and glycerol, are much higher whereas the concentration of alanine is much higher due to muscle catabolism. Excess glucagon and insulin insufficiency stimulates gluconeogenesis, which uses those alanines and glycerol as substrates. Glucagon also advances the transformation of free fatty acids to ketones in the mitochondria. Insulin inhibits the transfer of the derivatives of free fatty acid to the matrix of mitochondria in normal conditions, but ketogenesis continues in the deficiency of insulin. Numerous ketone bodies are produced by virtue of TAG metabolism, influencing serum pH and causing the malfunction of numerous serum enzymes. Few instances, such as hemoglobin and transferrin, remain protonated and unable to transport Fe³⁺ at a pH of 6.88–7.3, resulting in a higher amount of Fe³⁺ accessible in serum in diabetic patients.

Numerous ketone bodies are produced by virtue of TAG metabolism, influencing serum pH and causing the malfunction of numerous serum enzymes. Few instances, such as hemoglobin and transferrin, remain protonated and unable to transport Fe³⁺ at a pH of 6.88–7.3, resulting in a higher amount of Fe³⁺ accessible in serum in diabetic patients. Rhizopus has a ketone reductase enzyme that enables the fungus to develop in this acidic condition apart from using the free Fe³⁺ in these patients. The acidosis produced by Rhizopus spp. affects other host enzymes, which hold a direct impression on chemotaxis and phagocytosis. Reduced iron levels have also been shown to promote the M1 pro-inflammatory LPS-induced response, suggesting that additional mechanism contributes to the dissemination of an adverse feedback to fungal allowance.
4.3. Rising period of the story

Free iron is another excellent resource for mucormycosis. According to several studies, iron plays a major function in *Rhizopus* and it is taken from the host via two methods, either siderophores (iron chelators) or high-affinity iron permeases.10,86 Fungi battle with the host for the free iron in the siderophore system. Intrinsically and extrinsically siderophores are the two major types of fungi siderophores. Speaking of *Rhizopus*, both forms of siderophores are utilized. The major intrinsic siderophore, found in *Rhizopus*, is Rhizoferin. It absorbs iron from outside the cell environment via a receptor-conciliated and energy-relent method. Thirteen potential siderophore permeases are found after the genome-sequencing investigation of *R. oryzae* which could act as receptors for different siderophores. According to numerous protein crystallography experiments, rhizoferin has a diaminobutane backbone connected to two citric acid residues with an R, R arrangement encircling a chiral centre.

Another consideration for a better phagocytic response is reactive oxygen species (ROS). Owing to insulin resistance, hyperglycemia persists in people with diabetes, and in an attempt to lower glucose levels, glucose metabolism and secondary lipolysis are elevated via oxidative phosphorylation. Low pH in patients with diabetic ketoacidosis (DKA) makes more vulnerability to mucormycosis as a result of the summed-up oxidative climate which influences glutathione to remodel through the GSH/GSSG compound cycle. Advanced glycation end products (AGEs) and ROS produced by enhanced glucose metabolism cumulate in organs and tissues, causing typical micro and macrovascular changes in diabetic patients directing to an enlarged vulnerability to a *Rhizopus* infection.100,101 Due to inadequacy of the cofactor NADPH, down-regulation of the major antioxidant system of glutathione (GSH/GSSG), which is the prime requirement for the reconstruction of reduced glutathione, ultimately reduces the ability of the patient to control the oxidative stress. The polyol route for glucose metabolism consumes NADPH quickly, resulting in a deficit of NADPH. Oxidative stress triggers inflammation through the NF-kB and TLR receptors, resulting in a long-term chronic inflammatory state.37,101

4.4. The climax of the story: The interaction between GRP78 and CotH3

In transformed fibroblasts, the production rate of a particular protein was increased when the reduction of glucose was caused. Later on, that particular protein was discovered as glucose-regulated proteins (GRPs). GRP78 or glucose-regulated protein has a molecular weight of 78-kDa, it was first identified as a heat shock protein that has a role in stress-related responses.102 It is also known as immunoglobulin-binding protein (BiP) or HSP72 and is mostly found in the lumen of the endoplasmic reticulum (ER) and produced in mammalian cells. The HSP72 gene, which is found on chromosome 9q34, encodes GRP78. GRP78 is mostly found in the ER, although it has also been found in the cytoplasm, mitochondria, nucleus, plasma membrane, and secreted, even though it is primarily responsible for engaging endogenous cytoprotective mechanisms.103 The nucleotide-binding domain (NBD) or ATPase and substrate-binding domain (SBD) or protein/peptide-binding domains are the two main functional domains of GRP78.104,105 The function of this protein is controlled by the allosteric ATPase cycle in which the binding with ATP and hydrolyzation of ATP is performed by NBD whereas the SBD performs the job of bindings with poly-peptides.106,107 GRP78 has long been believed to be a molecular chaperone having a place with the HSP70 family that directs the unfolded protein reaction (UPR) to control ER stress and assumes a critical part in protein collapsing and quality control, just as misformed protein degradation.108,109

GRP78 expression has recently gained importance due to its transcription to the cell membrane’s surface (csGRP78) during ER stress.110 where it serves as a receptor and regulator in cell indicating by forming complexes with extracellular ligands and proteins attached to the cell surface.111-113 Recent Research reveals that hyperglycemia behaves like a stress trigger in ER which simultaneously initiates the overexpression of the GRP78 protein, based on the glucose concentration. MTJ-1 chaperone-mediated mechanism helps to translocate these GRP78 proteins from the ER to the cell surface.114 Likewise, overexpression of csGRP78 has been found to play a crucial role as an entrance receptor for various pathogens, including the Ebola virus, Dengue virus, Coxsackievirus, and the new SARS-CoV2 virus, and other viruses and *Rhizopus* spp. as well.115-117

*Rhizopus* spp. interact with various receptors of epithelial cells of alveolar and nasal origin. When *Rhizopus* spp. infect nasal epithelial cells, csGRP78 is overexpressed, but not in alveolar epithelial cells. In addition, it was discovered that Rhizossp. interrelate with alveolar epithelial cells by binding to integrin-1 rather than csGRP78. Subcellular factors, like iron, glucose, and DKA trigger the excessive production of csGRP78 only in nasal epithelial cells and subsequently enhance the pathogenicity of *Rhizopus* spp.117

Following the discovery of GRP78 as a required receptor for the invasion of the species of Mucorales,115 the hunt for a possible ligand led to the discovery of CotH in Mucorales.116 As a result, in a wide spectrum of Mucorales species, the utterance of the CotH1, CotH2, and CotH3 genes has been identified. Nonetheless, research data has suggested that CotH3 is mostly produced in *R. oryzae* germinations and has a better ability to attach and so penetrate endothelium and nasal epithelial cells in the DKA environment.35,116,118,119 On the other hand, CotH7 is the primary ligand that interrelates with integrin-1 of alveolar epithelial cells in the pulmonary mucormycosis, and it is not closely linked to CotH3 (50% amino acid identity).118

In Mucorales, csGRP78 binds particularly with spore-coating homolog proteins (CotHh), facilitating invasion and injury to endothelial cells.115,116,118,119 By nature, CotHh protein is a type of protein kinase and a member of a vast family of spore coating proteins. It has diversified functions. It is essential for protein assembly in the inner layer of the spore-coat. During sporulation, this protein is produced and shows its activity. ATP-dependent autophosphorylation and successive phosphorylation of serine residues of CotG and CotB proteins regulate its activity. The half-life of CotH is only four to 5 h. Its concentration drops quickly when the structural gene’s transcription is turned off. Recent findings show its essential role in spore germination of many human pathogens like spore-producing fungi such as *Rhizopus oryzae* and the expression of many bacterial strains like *Bacillus anthracis*.116,120,121

The appearance and interaction of GRP78 and CotH leads to increased fungal interference and consequent endothelial injury in vitro.91,117 As the iron chelation fused with pH reversal by sodium bicarbonate protects endothelial cells from *Rhizopus*-mediated invasion and injury,81 it emerges that BHB-related acidosis has a straight effect on both GRP78 and CotH expression and an indirect effect by compromising transferrin’s ability to chelate iron. Important, host cells with higher BHB, produced as a result of DKA, have lower blood pH, higher accessible serum iron, higher GRP78 expression in focussed organs (e.g., lungs and sinuses), and are more susceptible to mucormycosis.91,115

Thus, the extraordinary affectability of DKA patients to mucormycosis is clarified by the special communications of GRP78 and CotH proteins, just as their expanded articulation under hyperglycemia and ketoacidosis. Treatment with anti-GRP78 or anti-CotH antibodies protects DKA and neutropenic mice against mucormycosis, emphasizing the relevance of GRP78/CotH protein interactions in the progress of mucormycosis.115,116,122 The discovery that reversing ketoacidosis in *Rhizopus*-infected animals by administering sodium bicarbonate (instead of insulin) enhances survival is also potentially clinically relevant.91 Reversal of accelerated fungal expansion, reconstruction of immune function, and terminating of fungal invasion of host tissues are thought to be the causes of this protection. The activity of GRP78/CotH interactions in the neutropenic host, the other main patient category prone to mucormycosis, is currently unknown.122,123
4.5. Falling action of the story

The processes that increase the interaction of invading fungus with endothelial/epithelial cells are beginning to gain a toehold, and they represent a key stage in the pathogenesis of diabetes-associated mucormycosis. Thus, the DKA environment, high glucose, iron, and Rhizobius butyrate (BHB) as the vital ketone body promote fungal development by promoting CotH3 expression. The surface translocation of the GRP78 protein, which copes with endoplasmic reticulum stress occurred by hyperglycemia and an acid milieu, assists a tissue stage favorable to Rhizopus spp. establishment. Iron is released from sequestrated protein transferrin by glycosylation mechanisms in the same tissue. As a result, high glucose concentrations, free iron availability, and aperic microenvironment boost CotH expression on the fungal cell surface facilitating GRP78/CotH3 contact for endothelial/epithelial invasion and fungal spread. The fungus must interrelate with its basement membrane after infecting the apparent nasal epithelium because the spores and stem cells from germ tubes adhere to extracellular matrix constituents. The scrutiny of Rhizopus spp. sticking to plates coated with collagen IV and laminin supports this theory.

4.6. Resolution: The final consequences

Meanwhile, endothelial cells keep on creating GRP78 in all cubicles, and the hypha can connect with these proteins on the basal side where the existence of reticulin filaments is surpassed, permitting it to secure and outdo this region to later collaborate with GRP78 communicated on endothelial cells’ luminal surface. When fungi become actualized in the lumen of blood vessels, they activate the extrinsic coagulation pathway, which causes cell injury and, as a result, the thrombus formed. This causes ischemia and prolonged hypoxia, resulting in tissue infarction and necrosis (Fig. 5). Finally, the microenvironment has changed and the disease has been established on the body.

5. Proposed modes of investigation for COVID-19 associated mucormycosis

To date, there are no pathognomonic hematologic changes. Elevated white blood cell counts and acute-phase reactant levels indicate the abnormalities that are found reflect underlying predisposing conditions (e.g., diabetic ketoacidosis) and general indications of fungal infection. Blood cultures are virtually always negative. Plain orbit or sinus radiography is not a reliable investigation for this disease. Computed Tomography (CT) analysis indicates the extent of orbital involvement and progression of the disease. Magnetic resonance imaging (MRI) is also helpful by showing T2-weighted MR images, which demonstrate intracerebral extension while on the other hand, contrast-enhanced MRI scans provide us a demonstration of the perineural spread of disease.

Angiography or surgical exploration is necessary for areas of anatomic complexity. Biopsy with histopathologic examination remains the most sensitive and specific modality for definitive diagnosis. Microscopic investigation shows that aseptate hyphal elements of the species belong to the order Mucorales are wide (ranging from 6 to 30 μm), thick-walled, ribbon-like, and showing branch at right angles. Whereas the hyphae of Aspergillus and, Fusarium are comparatively thinner, highly septate and showing branch at acute angles (Fig. 6). The width of the fungus and its ribbon-like shape are the most distinctive characteristics for identifying mucormycosis.

Schiff or hematoxylin and eosin staining can be used to better visualize the Mucorales; they do not stain as well as methenamine silver.

Histopathology is used to identify the Mucorales, but species identification is limited to culturing. Imaging techniques are used to investigate the condition’s advancement and severity. For example, fungal sinusitis that is different from bacterial sinusitis is the most usual finding on CT or MRI scans of the head and sinuses of a patient with rhino-orbital mucormycosis. MRI is more sensitive (by approximately 80%) than CT in the detection of orbital and CNS disease.

Nasal endoscopy is an excellent diagnostic method for determining the presence of mucormycosis, while the MRI findings are very useful and significant to show the spread of mucormycosis in different regions as a supportive example to make it clinically significant but these findings will be varying according to the case-by-case basis (Fig. 7).

The polymerase chain reaction (PCR) is used as a current diagnostic tool in the research of mucormycosis, however, it has not yet been licensed by the U.S. Food and Drug Administration (FDA) for this purpose and it is a rare find.

6. Current therapeutics for COVID-19 associated mucormycosis

As significant trouble, the prevalent COVID-19 spreads worldwide. While various treatment options are estimated, at that time systemic glucocorticoids are shown to enhance the survival rate of COVID-19. Glucocorticoids are not too expensive, available widely, and are shown to decrease fatality in COVID-19 patients with hypoxemia. Unfortunately, the extensive use of glucocorticoids can develop secondary fungal infections like mucormycosis.

If systemic glucocorticoids are shown to enhance the survival rate of COVID-19, they are not too expensive, available widely, and are shown to decrease fatality in COVID-19 patients with hypoxemia. Unfortunately, the extensive use of glucocorticoids can develop secondary fungal infections like mucormycosis.

The medical diagnosis of mucormycosis requires treatment quickly, as the fungal invasion advances rapidly. The polymerase chain reaction (PCR) is used as a current diagnostic tool in the research of mucormycosis, however, it has not yet been licensed by the U.S. Food and Drug Administration (FDA) for this purpose and it is a rare find.

Surgical debridement (FESS or Functional Endoscopic Sinus Surgery is a minimally invasive technique used to restore sinus ventilation and normal function and/or orbital exenteration) not only decreases the burden of the disease but also permits better percolation of intravenous medical drugs. It reduces further disease spreading and permits to allow intraoperative diagnosis of necrotic tissue with applicable characteristics to provide the sample for microbiological and histopathological confirmation. But prompt initiation of medication therapy and instant reversal of underlying risk factors are always the better alternatives to surgical debridement because it is crucial to maintain a high index of suspicion in patients who are at risk for mucormycosis at all times.

Antifungals can also play an important role along with surgical debridement. The guidelines, accepted globally in 2019 for the management and diagnosis of mucormycosis by Mycoses Study Group Education and Research Consortium (MSGERC) and the European Confederation of Medical Mycology (ECMM) strongly prescribe surgical treatment if possible with the addition of systemic treatment of antifungals.

Liposomal Amphotericin B, Posaconazole and Amphotericin B lipid complex oral suspension can be treated as first-line antifungal agent monotherapy and Isavuconazole can be assisted like salvage therapy. Irrigation of sinuses and orbit with(1 mg/ml) Amphotericin B improves the local drug concentration and is shown to enhance outcomes. Intra-orbital and Retrolubar injection in respect to Amphotericin B are also given in those patients who have no ability for surgical debridement (the dose of anesthesia along with retrobulbar injection is 1 ml of three 3.5 mg/ml). The recent guideline of MSGERC and ECMM for mucormycosis management recommends liposomal amphotericin B (L-AMB), the dose is 5–10 mg/kg every day. Adults and children are often administered to treat mucormycosis at start-up doses of 1 mg/kg daily for Amphotericin B deoxycholate (d-AMB) and 5 mg/kg daily for L-AMB and Amphotericin B lipid complex (ABLC). The dose of 5 mg/kg is used to recommend when the implication of the nervous system is absent. Amphotericin B has potential renal toxicity so that the dosage should be adjusted between 0.5 mg/kg/day and 1.5 mg/kg/day by the condition of the patient as well as disease. Hyperbaric oxygen (HBO) therapy should also be used in case of aggressive infection.

For the hyperglycemic patient, the early treatment of liposomal amphotericin B and if necessary surgical treatment is needed.
(caption on next page)
COVID-19. and necessarily use of glucocorticoids to treat the severity of suppressed condition of the patient, presence of acute hyperglycemia, than non-COVID patients with mucormycosis because of the immuno

Hence, the mortality of COVID-19 associated mucormycosis may higher -

Fig. 5. Diagram pictured the planned mechanisms for the immunopathogenesis of COVID-19 assisted mucormycosis in the immunocompromised diabetic individual[25,27,124] (Created with BioRender.com). (a) In COVID-19 severity, (b) uncontrolled diabetes mellitus and overdrive of Corticosteroid drugs increases the vulnerability to Mucorales infection due to diabetic ketoacidosis (DKA) and hyperglycemia. (c) An elevation in the glucose level of the adipose tissue induces endoplasmic reticulum (ER) stress, cellular hypoxia, enhanced discharge of free fatty acids (FFA), reactive oxygen species (ROS), and generate cytokine storm. (d) A diversified range of the cytokines like interleukin-1 (IL-1β), tumor necrosis factor (TNF), and various types of chemokines are released to the cellular hypoxic environment. (e) These cytokines especially TNF-α recruits the pro-inflammatory M1 macrophages and (f) inhibits the activity of anti-inflammatory M2 macrophages. (g) The activated M1 macrophage again discharges more pro-inflammatory cytokines like IL-1β, FFA and generates ROS. (h) These FFA are also detected by TLR-4 in the tissue cells, initiating JNK-AP-1 and IKK-NFkB (nuclear factor-kappa B) signalling. (i) Simultaneously, diabetic ketoacidosis (DKA) causes a low pH environment which ultimately enhances the cellular H+ ion level. (j) Due to the activity of hyperglycemia, iron-scavenging proteins like ferritin and transferrin show increased glycosylation in the blood vessel, which lowers their iron affinity. (k) Furthermore, in the attendance of an acidic condition promoted by the creation of ketone bodies (e.g., β-hydroxybutyrate [BHB]), the low pH environment in the blood vessels substantially restricts transferrin’s ability to chelate iron. (l) As a result, the accessibility of free iron in the blood vessel is stimulated whereas (m) the counts of IFN-γ, CD4+, CD8+, and T-cell are sharply declined. (n) A combination of free iron, glucose, and BHB triggers epithelial fungal adhesion and tissular hyphal growth or opportunistic fungal infection. (o) This combination causes a stress response in ER, which drives to overexpression of the GRP78 protein. (p) The MTJ-1 chaperone aids in the translocation of GRP78 proteins from ER to the cell surface. (q) Fungi battle with the host for the presence of iron in the siderophore system. (r) High glucose concentrations, free iron availability, and an acid microenvironment boost CoH expression on the fungal cell surface, facilitating GRP78/CoH3 contact for epithelial/endothelial invasion and fungal spread. (s) The connection between GRP78 and CoH is additionally aided by ROS, FFA, and cytokines. (t) Meanwhile, endothelial cells pursue to generate GRP78 in all partitions, and the hypha can connect with these proteins on the basal side and become internalized in the lumen of blood vessels. (u) They produce cell damage, thrombus formation, ischemia, prolonged hypoxia, tissue infarction, and finally necrosis by activating the external coagulation pathway.

Fig. 6. Compound microscopic view of different types of fungal species. (a–b) Compound microscopic view of Aspergillus sp. showing perpendicular hyphal branching pattern under ca. ×100 and ca. × 450 magnification, respectively. (c–d) Compound microscopic view of Paasartum sp. showing conidia with conidiospores and dichotomous hyphal branching pattern under ca. ×100 and ca. × 450 magnification, respectively. (e–f) Compound microscopic view of Rhizopus sp. showing perpendicular hyphal branching pattern under ca. ×100 and ca. × 450 magnification, respectively.

Hyperglycemia is annoyed with COVID-19 effective therapy, namely glucocorticoids. Multi-organ dysfunction and co-existing Acute Respiratory Distress Syndrome (ARDS) prevent timely testing and diagnostic imaging.[25,34] The hospitals are overburdened by patients of COVID-19, and diagnostics after those surgeries can be curtailed significantly.[34] Hence, the mortality of COVID-19 associated mucormycosis may higher than non-COVID patients with mucormycosis because of the immuno-suppressed condition of the patient, presence of acute hyperglycemia, and necessarily use of glucocorticoids to treat the severity of COVID-19.[39,146,147] Thus, in moderate COVID-19 cases (absence of hyperglycemia), the huge dose of glucocorticoid utilization must be avoided. Hence, the judicial considerable use of glucocorticoids in COVID-19 cases is necessary because this aggravates the hyperglycemia condition and advances the formation of diabetes ketoacidosis. Apart from this, in COVID-19 treatment, there is also an increment of D-Dimer as a product of cross-linked fibrin (inappropriate blood clot or thrombus formation).

To treat the inappropriate formation of thrombus, the immunomodulatory drug tocilizumab is using, which also unluckily, promotes the mucormycosis infection.[69] Therefore, the use of drugs like tocilizumab which are targeting the immune pathways is discouraged without any transparent benefit.[25,148] Moreover, the virus causes the dysregulation of the immune system and as a result, using consistent immunomodulatory medical drugs like tocilizumab can further raise this dreadful infection in the patients of COVID-19 disease.[25,148,149] So, it is necessary to use judicially under intense monitoring of the patient to detect an early fungal infestation.[138]

7. Conclusion

The recurrence of mucormycosis, opportunistic microorganisms has
expanded altogether in the previous twenty years. This study gives an overview of comparative cases of different countries, along with the implications of the disease. The rise in mucormycosis emerges to be the result of certain factors including diabetes, uncontrolled use of glucocorticoids (which raises blood glucose, free iron that advances the probable fungal infection), and COVID-19 infection (cytokine storm, neutropenia, endothelial cell surface injury). The involvement between the fungal species of *Rhizopus* and the endothelial cells has also been featured. The mechanism concerning the pathogenesis of the disease has been comprehended and would initiate a vital role in future elevation. Recent tentative regimens for the treatment of mucormycosis comprises featured. The mechanism concerning the pathogenesis of the disease has been comprehended and would initiate a vital role in future elevation. Recent tentative regimens for the treatment of mucormycosis comprises the usage of Amphotericin B and Isavucnazol. The administration of therapeutic substances should be closely managed to obtain a therapeutic impact at the moderate possible dose and for the shortest possible duration under keen observation. In the future, an improved establishment of the criteria regarding the diagnosis for COVID-19 associated mucormycosis is required including the radiological patterns of COVID-19 and the difficulty of isolating *Rhizopus* spp. Finally, rapid diagnosis and surgical debridement are considered to be the keystone for this life-threatening disease.

Authors’ contributions

Conceptualization: [Joy Sarkar]; Methodology: [Joy Sarkar]; Formal analysis and investigation: [Joy Sarkar]; Writing – original draft preparation: [Deganta Ghosh], [Sagardeep Dey], [Himank Chakraborty], [Ankita Halder], [Akash Sarkar], [Sneha Mukherjee], [Pallab Chakraborty], [Rajdeep Ghosh]; Writing – review and editing: [Joy Sarkar]; Funding acquisition: [N/A]; Resources: [N/A]; Supervision: [Joy Sarkar].

Declaration of competing interest

On behalf of all listed authors, the corresponding author declares that there is not any sort of financial and non-financial conflict of interest in the subject materials mentioned in this manuscript.

Acknowledgment

The authors like to acknowledge Mr. Debangan Chowdhury and Ms. Shreemoyee Palmal for providing us the microscopic images of *Apergillus* sp. The authors like to thank Mr. Prithu Bhattacharyya for supplying us one of the microscopic images of *Rhizopus* sp. We also like to acknowledge BioRender.com for making the way suitable to get Fig. 5.

References

1. Sugar AM. Mucormycosis. Clin Infect Dis. 1992;14(1):126–129. https://doi.org/10.1093/clinids/14.Supplement_1.S126.
2. Nishanth G, Anitha N, Arvindhha Babu N, Malathi L. Mucormycosis - a review. Eur J Med Res. 2020;7(3):1786–1791.
3. Kwon-Chung KJ. Taxonomy of fungi causing mucormycosis and entomophthoramycosis (zygomycosis) and nomenclature of the disease: molecular mycologic perspectives. Clin Infect Dis. 2012;54(12):18–15. https://doi.org/10.1093/cid/cis864.
4. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi. 2019;5(1). https://doi.org/10.3390/jf5010026.
5. Maini A, Tomar G, Khanna D, Kini Y, Mehta H, Bhagyasree V, Sino-orbital mucormycosis in a COVID-19 patient: a case report. Int J Surg Case Rep. 2021;82(1). https://doi.org/10.1016/j.ijscr.2021.105957.
6. Mohammadi R, Nazeri M, Amin Sayedayn SM, Ehteram H. A successful treatment of rhinocerebral mucormycosis due to Rhizopus Oryzae. J Res Med Sci. 2021;4(19):73.
7. Fernandez JF, Maselli DJ, Simpson T, Restrepo MI. Pulmonary mucormycosis: what is the best strategy for therapy? Respir Care. 2013;58(5):60–63. https://doi.org/10.4187/respcare.02106.
8. Do Monte ES, Dos Santos MLE, Ribiero IB, et al. Rare and fatal gastrointestinal mucormycosis (Zygomycosis) in a COVID-19 patient: a case report. Clin Endosc. 2020;53(6):746–749. https://doi.org/10.5946/CE.2020.180.
9. Spellberg B, Edwards J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev. 2005;18(3):556–569. https://doi.org/10.1128/CMR.18.3.556-569.2005.
10. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41(5):634–653. https://doi.org/10.1086/422579.
11. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 2012;54(1):23–34. https://doi.org/10.1093/cid/cir866.
12. Khatri A, Chang KM, Berlinrut I, Wallach F. Mucormycosis after Coronavirus disease 2019 infection in a heart transplant recipient - case report and review of literature. J Med Mycol. 2021;32(1). https://doi.org/10.1016/j.jmm.2021.101125.
13. Bhatt K, Agoli A, Patel M H, et al. High mortality co-infections of COVID-19 patients: mucormycosis and other fungal infections. Discoveries. 2021;9(1). https://doi.org/10.15190/d.2021.5.
14. Khan N, Gutierrez CG, Martinez DV, Proud KC. A case report of COVID-19 associated pulmonary mucormycosis. Arch Clin Cases. 2020;5(3):46–51. https://doi.org/10.22551/2020.28.0703.10172.
15. Revannavar SM, Supriya P, Samaga L, Vineeth K. COVID-19 triggering mucormycosis in a susceptible patient: a new phenomenon in the developing world? BMJ Case Rep. 2021;2021;2021. https://doi.org/10.1136/bcr-2021-241663.
16. Das S, Sarkar S, Das A, Das S, Chakraborty P, Sarkar J. A comprehensive review of various categories of face masks resistant to Covid-19. Clin Epidemiol Global Health. 2021;12:1000835. https://doi.org/10.1016/j.jcgh.2021.100835.
17. Sharma S, Grover M, Bhargava S, Sandhani S, Kataria T. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. J Laryngol Otol. 2021;135(5):442–447. https://doi.org/10.1017/S0022215121000992.
Saldanha M, Reddy R, Vincent MJ. Title of the article: paranasal mucormycosis in India. J Otolaryngol Head Neck Surg. Published online 2021;10:212-114.

Sarkar S, Gokhale T, Choudhury S, Deb A. COVID-19 and orbital mucormycosis. Indian J Ophthalmol. 2021;69(4):1002-1004. https://doi.org/10.1007/s41143-020-00236-9.

Chakrabarti A, Singh R. Mucormycosis in India: unique features. Mycoses. 2014;57 (3):85-90. https://doi.org/10.1111/myco.12245.

Diwakar A, Dewsn RK, Chowdhury A, Ramdhmani H, Khanna G, Gaur SN. Zygomycosis - a case report and overview of the disease in India. Mycoses 2007;50 (4):247-254. https://doi.org/10.1111/j.1365-3179.2007.01882.x.

Meis JF, Chakrabarti A. Changing epidemiology of an emerging infection: Zygomycosis. Mycoses. 2009;52(5):10-14. https://doi.org/10.1111/j.1469-3780.2009.02973.x.

Pate A, Kaur H, Xess I, et al. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Infect Dis. 2020;67(7):944. https://doi.org/10.1093/cid/ciaa1298. Published online.

Skadi a, Lass-Floren C, Klimko N, Ibrahim A, Roilides E, Petrikos G. Challenges in the diagnosis and treatment of mucormycosis. Med Mycol. 2018;56(1):93-101. https://doi.org/10.1093/mmy/myx101.

Kr PK. Mucormycosis: a black fungus- post covid complications. J Reg Biol Med. 2021;3(4):1-8. https://doi.org/10.37191/Mapsci-2582-385X-3(4)-078.

Dadhwal SS, Kontoyiannis DP. Recent advances in the molecular diagnosis of mucormycosis. Expert Rev Mol Diagn. 2018;18(10):845-854. https://doi.org/10.1080/14737159.2018.1522250.

Song G, Liang G, Liu W. Fungal Co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China. Mycopathologia. 2020;189:1-4. https://doi.org/10.1007/s11046-020-00154-7.

Zhou C, Byard RW. An analysis of the morbidity and mortality of diabetes mellitus in a forensic context. J Forensic Sci. 2018;63(3):1149-1154. https://doi.org/10.1111/1556-4029.13674.

Wang Y, Bell TM, Berenson K, et al. Economic costs of diabetes in the U.S. in 2017. Diabetes Care. 2018;41(5):917-928. https://doi.org/10.2337/db17-1800.

John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe covid-19 converge: the perfect storm for mucormycosis. J Fungi. 2021;7(4):298. https://doi.org/10.3390/j fungi7040298.

Morales-Franco B, Nava-Villallona M, Medina-Guerrero EO, et al. Host-Pathogen molecular factors contribute to the pathogenesis of rhizopus spp in diabetes mellitus. Curr Med Res Opin. 2021;1-12. https://doi.org/10.1080/07020714.2021.1903044. Published online.

Goldman N, Fink D, Cai J, Lee YN, Davies Z. High prevalence of COVID-19-associated diabetic ketoacidosis versus COVID-19 associated vasculopathy. Diabetes Metab Syndr: Clin Res Rev. 2021:10:289-28. https://doi.org/10.1016/j.dsx.2020.108291.

Oriol P, Hermans MP. Euglycemic diabetic ketoacidosis in a patient with type 1 diabetes and SARS-CoV-2 pneumonia: case report and review of the literature. Acta Clin Belg. Int J Clin Lab Med. 2021;1-5. https://doi.org/10.1055/a-1784286. Published online.

Lanternier F, Dananou E, Morizot G, et al. A global analysis of mucormycosis in France: the RetroZygo study (2005-2007). Clin Infect Dis. 2012;54(1):S35-S43. https://doi.org/10.1086/660007.

Ferguson BJ. Definition and role of fungal rhinoinitis. Otolaryngol Clin. 2000;33(2):227-235. https://doi.org/10.1016/S0030-6665(00)00002-X.

Chakrabarti A, Denning DW, Ferguson BJ, et al. Fungal rhinoinitis: a categorization and definitional schema addressing current controversies. Laryngoscope. 2009;119(9):1801-1818. https://doi.org/10.1002/lary.20905.

Dhiwakar M, Thakar A, Babu S. Improving outcomes in rhinocerebral mucormycosis - early diagnostic pointers and prognostic factors. J Laryngol Otol. 2003;117(11):861-865. https://doi.org/10.1017/S002221510325542485.

Talpy VM, Goldschmidt-Reuven A, Balkon M, et al. Rhinocerebral and rhino-orbital mucormycosis - a case report and overview of the disease in India. Clin Microbiol Infect. 2002;8(2):127-22. https://doi.org/10.1046/j.1469-3095.2002.00783.x.

Peterson KL, Wang M, Canalis RF, Abemayor E. Rhinocerebral mucormycosis: evolution of the disease and treatment options. Laryngoscope. 1997;107(7):855-862. https://doi.org/10.1097/00005537-199707000-00004.

Thajeb P, Thajeb T, Dai D. Fatal strokes in patients with rhino-orbito-cerebral mucormycosis and associated vasculopathy. J Fungi. 2021;7(5):80. https://doi.org/10.37191/Mapsci-2582-385X-3(4)-098.

Khor BS, Lee MH, Leu HS, Liu JW. Rhinocerebral mucormycosis in Taiwan. J Microbiol Immunol Infect. 2016;49(5):593-597. https://doi.org/10.1016/j.jmii.2016.09.005.

Cools A, Keppens S, Vermeulen K, et al. Aspergillus fumigatus villosum in a human kidney transplant recipient. Scand J Infect Dis. 2005;37(10):825-828. https://doi.org/10.1080/03035890500251068.

Atallah B, El Nekidy W, Mallah SI, et al. Thrombotic events following tocilizumab therapy in COVID-19 patients. J Fungi. 2020;6(1):62. https://doi.org/10.3390/j fungi6010062.

Thajeb P, Thajeb T, Dai D. Fatal strokes in patients with rhino-orbito-cerebral mucormycosis and associated vasculopathy. J Fungi. 2021;7(5):80. https://doi.org/10.37191/Mapsci-2582-385X-3(4)-098.

Kerr OA, Bong C, Wallis C, Timman MJ. Persistent cutaneous mucormycosis masquerading as pyoderma gangrenosum. Br J Dermatol. 2004;150(6):1212-1213. https://doi.org/10.1111/j.1365-2133.2004.07582.x.

Quinio D, Karam A, Leroy JP, et al. Zygomycosis caused by Cunninghamella bertholletiae in a kidney transplant recipient. Med Mycol. 2020;58(8):881-885. https://doi.org/10.1080/13693780103103691.
Clinical Epidemiology and Global Health 15 (2022) 101013
15
101 de Melo LGP, Nunes SOV, Anderson G, et al. Shared metabolic and immune-regulatory defects
and mood disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2017;78:34-50. https://doi.org/10.1016/j.pnpbp.2017.04.027.
102 Wang M, Wey S, Zhang Y, Ye R, Lee AS. Role of the unfolded protein response regulator GRP78/Bip in
development, cancer, and neurological disorders. Antioxidants Redox Signal. 2005;11(9):2307–2316. https://doi.org/10.1089/ars.2005.11.2307.
103 Casas C. GRP78 at the centre of the stage in cancer and neuroprotection. Front Neuosci. 2017;11(177):1–15. https://doi.org/10.3389/fnneuro.2017.00177.
104 Ting J, Lee AS. Human GRP78/Bip and the unfolded protein response and its pseudogene: structure, conservation, and regulation. DNA. 1998;7(4):
275–286. https://doi.org/10.1080/10645039875818889.
105 Yang J, Nune M, Zong Y, Zhou L, Liu Q. Close and allosteric opening of the polysaccharide-binding site in a human Hsp90 alpha chaperone BIP. Structure. 2015;23(12):
2191–2203. https://doi.org/10.1016/j.str.2015.10.012.
106 Hughes SJ, Antoschenko T, Chen Y, Li Pizarro JC, Park HW. Probing the ATP site of GRP78 with an unnatural amino analog. PLoS One. 2011(5), e10154862. https://doi.org/10.1371/journal.pone.0101548.
107 Hendershot LM, Valentine VA, Lee AS, Morris SW, Shapiro DN. Localization of the gene encoding human hsp/bip/grp78, the endoplasmic reticulum cognate of the hsp70 family, to chromosome 9q34. Genomics. 1994;20(2):281–284. https://doi.org/10.1006/geno.1994.1166.
108 Roller C, Maddalo D. The molecular chaperone GRP78/Bip in the development of chemoresistance: mechanism and possible treatment. Front Pharmacol. 2013;4(10):
1–5. https://doi.org/10.3389/fphar.2013.00030.
109 Kwon JW, Jung I, Lee D. Glucose-regulated protein 78 in the aqueous humor in diabetic macular edema patients. Medicine. 2018;97(45), e12757. https://doi.org/10.1097/md.0000000000012757.
110 Sun FC, Wei S, Li CW, Chang YS, Chao CC, Lai YK. Localization of GRP78 to mitochondria under the unfolded protein response. Biochem J. 2006;396(1):31–39. https://doi.org/10.1042/BJ20051916.
111 Ni M, Zhang Y, Lee AS. Beyond the endoplasmic reticulum: atypical GRP78 in cell virology, signaling and cancer. Front Oncol. 2011;1(4):181–188. https://doi.org/10.3389/fonc.2011.00169.
112 Gonzalez-Gronow M, Selim MA, Papas J, Pizzo SV. GRP78: a multifunctional receptor on the cell surface. Antioxidants Redox Signal. 2009;11(9):2299–2306. https://doi.org/10.1089/ars.2009.2568.
113 Crane ED, Al-Hashimi AA, Chen J, et al. Anti-GRP78 autoantibodies induce endothelial cell activation and accelerate the development of atherosclerotic lesions. J Clin Investig. 2013;128(24), e93963. https://doi.org/10.1172/JCI93963.
114 Van Krieken R, Bhattacharyya S, Westwood J, et al. Cell surface expression of 78-kDa glucose-regulated protein (GRP78) mediates diabetic nephropathy. J Biol Chem. 2019;294:
19277–19276. https://doi.org/10.1074/jbc.R118.006939.
115 Liu M, Spellberg B, Phan QT, et al. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. J Clin Invest. 2012;120(6):
1914–1924. https://doi.org/10.1172/JCI41614.
116 Gebremariam T, Liu M, Luo G, et al. CotH3 mediates fungal invasion of host cells during mucormycosis. J Clin Invest. 2014;124(1):237–250. https://doi.org/10.1172/JCI71349.
117 Ha DP, Van Krieken R, Carlos AJ, Lee AS. The stress-inducible molecular chaperone GRP78 as potential therapeutic target for coronavirus infection. J Infect. 2020;81(3):
452–482. https://doi.org/10.1016/j.jinf.2020.06.017.
118 Alqarshi A, Gebremariam T, Gu Y, et al. GRP78 and integrins play different roles in host cell invasion during mucormycosis. mBio. 2020;11(3). https://doi.org/10.1099/mbo1.0.00872-0. e00872-0.
119 Shumilov E, Bacher U, Perske C, et al. In situ validation of the endothelial cell receptor GRP78 in a case of rhinocerebral mucormycosis. Antimicrob Agents Chemother. 2009;53:
2191–2203. https://doi.org/10.1128/AAC.01372-08.
120 Istitaco R, Sirec T, Gigli R, et al. Flexibility of the programme of space coat formation in Bacillus subtilis: bypass of Cse1 requirement by over-production of CotH. PLoS One. 2013(9), e74499. https://doi.org/10.1371/journal.
pone.0074499.
121 Nguyen KB, Sreelatha A, Durrant ES, et al. Phosphorylation of space coat proteins by a family of atypical protein kinases. Proc Natl Acad Sci USA. 2016;113(25):
E3482–E3491. https://doi.org/10.1073/pnas.1605917113.
122 Gebremariam T, Alkhazraji S, Soliman SSM, et al. Anti-CotH3 antibodies protect mice from mucormycosis by prevention of invasion and augmenting eopsonophagocytosis. Sci Adv. 2019;5(6), eaaw1327. https://doi.org/10.1126/sciadv.aaw1327.
123 Li J, Lee A. Stress induction of GRP78/Bip and its role in cancer. Curr Med Mol. 2006;6(1):45–54. https://doi.org/10.1007/s10590-005-1041-y.
124 Baldin C, Ibrahim AS. Molecular mechanisms of mucormycosis—the bitter and the sweet. PLoS Pathog. 2017;13(5), e1006408.
125 Boelaert JR, De Locht M, Van Cauter J, et al. Mucormycosis during deferoxamine therapy is a siderophore-mediated infection: in vitro and in vivo animal studies. J Med Microbiol. 2007;56(5), 541–546. https://doi.org/10.1099/jmm.0.62324-0.
126 Bouchra JP, Oumezzine NA, Lisitzky JC, Larcher G, Tronchin G, Chabasse D. Attachment of spores of the human pathogenic fungus Rhizopus oryzae to human red blood cell membrane carbohydrates. J Biol Chem. 2018;293(34):
39847–39857. https://doi.org/10.1074/jbc.M118.007984.
127 Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards JJ, Ibrahim AS. Recent advances in the management of mucormycosis: from bench to bedside. Clin Infect Dis. 2009;49:
(4), 672–677. https://doi.org/10.1086/599105.
128 Negad A, Prabhu S, Irodi A, Stadler SV, Yadav VK, Rupa V. Imaging features of rhinocerebral mucormycosis: a study of 43 patients. Egypt J Radiol Nucl Med. 2018;49(2):
447–452. https://doi.org/10.1016/j.ejrm.2018.01.001.
129 Guerner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. Clin Microbiol Rev. 2012;25(4):247–280. https://doi.org/10.1128/CMR.00353-10.
130 Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. Clin Microbiol Rev. 2012;25(4):247–280. https://doi.org/10.1128/CMR.00353-10.
