Review

COVID-19 and mucormycosis superinfection: Exploring the missing pathophysiological links

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ABSTRACT

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### Table 1

A tabulation of the outcomes of literature review of patients co-infected with COVID-19 and mucormycosis to date.

| Author        | Age and Sex | Patient Characteristics | Radiological findings | Laboratory parameters | Treatment | Prognosis |
|---------------|-------------|-------------------------|-----------------------|-----------------------|-----------|-----------|
| Pasero et al. | 66 y/o Male | Multiple organ dysfunction, (SOFA)² | CT scan: Opacification of the left maxillary sinus and sclerosis. The Thoracic scans: cavitary lesions in the upper lobe of left lung. | Second BAS test: cotton-candy colonies on (SDA)³ | Liposomal Amphotericin B, 5 mg kg⁻¹ IV. | Died |
| Johnsen et al. | 79 y/o Male | Co-morbs: DM, HTN. Developed hypoxic respiratory failure. | CT chest: extensive bilateral pneumonia and new development of bilateral upper lobe cavitations | KOH preparation, culture, and isolation from the BAL culture tested positive for Mucormycosis infection. | Changed to IV L-AmB 400 mg daily for suspected mucormycosis infection. | Patient remained on ventilator support, tolerated IV L-AmB treatment, and was discharged to a long-term acute care facility |
| Krishna et al. | 22 y/o Male | Co-morbs: Hypothyroidism, Recurrent episodes of vasoplegic shock and multi-organ dysfunction. | CTPA: segmental pulmonary embolism in the left lower lobe & peripheral consolidation in lower lobes and right upper lobe | Autopsy findings: hematogenous dissemination, necrotic vasculitis, and cerebral invasion | Discovery of mucormycosis was post-mortem hence no treatment was opted. | Died due to cardiac tamponade |
| Veisi et al. | 40 y/o Female | Bilateral visual loss and complete ophthalmoplegia of the right eye | Orbital CT and MRI scans confirmed Mucormycosis presence. | Histopathological examination of paranasal sinuses showed granulomatous inflammation; positive Mucormycosis | Systemic amphotericin B and daily endoscopic sinus debridement and irrigation with diluted amphotericin B | She died because of dissemination into CNS |
| Veisi et al. | 54 y/o Male | Co-morbs: DM. Vision loss, proptosis, orbital inflammation, and complete ophthalmoplegia on the left side | Facial motility difficult | Necrotizing granulomatous inflammation with hyphae. | Systemic amphotericin B and daily endoscopic sinus debridement and irrigation with diluted amphotericin B | 2 months later: discharged with oral posaconazole (800 mg/ day) |
| Maini et al. | 38 y/o Male | Bilateral visual loss and complete ophthalmoplegia on the left side | CT scan revealed unilateral opacifications of the left orbit and paranasal sinuses | Systemic amphotericin B and daily endoscopic sinus debridement and irrigation with diluted amphotericin B | Died due to cardiac arrest 7 months later |
| Baskar et al. | 28 y/o Male | Sudden vision loss and swelling of the right eyes. | CE CT⁺ scan of nose and paranasal sinuses with orbit: right intraconal and retrobulbar soft tissue density along with mucosal thickening in the right ethmoid sinus | Tissue biopsy: branched septate hyphae confirming mucormycosis. | IV Fluconazole & Amphotericin B, followed by surgical debridement | Recovered with minimal residual deformity |
| Arana et al. | 62 y/o Male | Co-morbs: DM, fever, headache, and left malar region swelling | CT scan: left maxillary sinusitis | Histopathological findings: aseptate broad based hyphae grown on SDA and stained with lactofuchsin | IV Fluconazole & Amphotericin B and anazole (initially isavuconazole and subsequently posaconazole). 6 surgical debridement procedures. Total left maxillectomy | Disease free at 2 month follow up. |
| Arana et al. | 48 y/o Male | Co-morbs: Hx of CKD, pain and an increase of lower right limb diameter | Unavailable | Culture from necrotic tissue showed Lichtheimia ramosa (musculoskeletal mucormycosis) | Liposomal Amphotericin B 5 mg/kg x24h together with isavuconazole (3 months) 200 mg/8 h for 24 days | Recovered after 3 months |
| Sai Krishna et al. | 34 y/o Male | Co-morbs: HTN¹ & DM. Continuous pain and swelling over the right side of the midface since 2 months. | CBCT: aggressive osteolytic lesions in the right maxilla | Biopsy, curettage and saucimerization: Fungal osteomyelitis. | IV liposomal Amphotericin B 5 mg/kg/day. Surgical resection via Weber Ferguson approach. | 2 months; no signs of disease. |
| Sai Krishna et al. | 50 y/o Male | Co-morbs: uncontrolled DM. Swelling over the right side of the midface since 2 months | 3D CT: mucormycosis of right maxilla and zygoma | Thick-walled septate fungal hyphae with right-angled branching in P.A.S. stain: mucormycosis of the right maxilla | IV liposomal Amphotericin B 250 mg | Recovered 2 months later. |
| Bellanger et al. | 55 y/o Male | Feverish, with worsened respiratory function. | Chest CT: non-specific bilateral ground glass opacities suggesting COVID 19 infection. | Tracheal aspirate and BAL³ positive in culture for both Aspergillus fumigatus and Rhinosporidium seeberi | Liposomal amphotericin B began at day 23 (5 mg/kg) | Died at day 40. |

**Abbreviations.**

1. Syndrome with sequential organ failure assessment (SOFA).
2. Sabouraud dextrose agar (SDA).
3. CTPA: CT pulmonary angiography.
4. Functional Endoscopic Sinus Surgery (FESS).
1. Introduction

From its detrimental effects on various organs such as the liver to its potential long-term neurological effects, coronavirus-2019 (COVID-19) has continued to ravage healthcare systems across the world [1,2]. With the advent and distribution of vaccinations worldwide, at a historic pace, the world is slowly paving the way for a return to normalcy. However, the pandemic continues to reveal new challenges. One of these is superinfection with mucormycosis, an opportunistic fungal infection. Pre-pandemic, its prevalence has been primarily observed in immunocompromised patients, such as those with uncontrolled diabetes mellitus, neutropenia, hematological malignancies, and similar conditions [1]. Herein, we chronicle the relationship between COVID-19 and mucormycosis, collating the available sparse literature and positing future directions.

Untreated, the “black fungus” mucormycosis is rapidly fatal. Mucormycosis is caused by various fungi species from the Mucorales order [3]. As Mucorales spores exist widely in nature, it is possible for them to be present in the nasal mucosa of healthy people as a commensal organism [4]. If the patient develops a state of immunosuppression, however, this is when it may germinate pathologically within the paranasal sinuses and spread to nearby structures such as the orbit and, even worse, intracranially [5]. In Europe most cases have been identified with Rhizopus spp. (34 %), Mucor spp. (19 %), and Lichtheimia spp. (19 %) [3]. Its etiology, however, varies based on geography. For example, many cases in Australia were non-Rhizopus species infecting immunocompetent patients through trauma, yet these were limited to local infections. On the other hand, necrotizing fasciitis due to infection from intramuscular injections have been reported in India, and these cases were due to much rarer species of the Mucorales order.

The global incidence of mucormycosis has risen over the past few decades, yet these rising statistics have been virtually restricted to developing countries like India. In the United States and Europe, the prevalence is 0.01–0.02 per 100,000 population [3]. Meanwhile, India sees a prevalence of 14 per 100,000. In adults, the mortality rate ranges from 20 % to 100 % due to comorbidities, site of infection, treatment availability, and other factors such as quality healthcare systems. In children, the rate is 33.3 %. Historically, the rarity of mucormycosis has been the major obstacle in research [3]. This has prevented large studies and clinical trials that would typically elucidate information on its epidemiology, diagnosis, and treatment. It is treated with amphotericin-B, a last-line antifungal reserved for serious, systemic fungal infections. The only new antifungal drug with activity against Mucorales is isavuconazole; however, it offers little benefit over amphotericin-B and is replete with severe side effects.

2. Pathophysiology

COVID-19 has been shown to enter the cell via the ACE2 and TMPRSS-2 receptors. While ACE2-R is a ubiquitous receptor in the body, it has higher rates of expression in respiratory, renal, and gastrointestinal epithelium. TMPRSS-2 receptors are similar; they are present on many epithelia but especially on that of respiratory and gastrointestinal [1,2]. It has a propensity for attacking lymphocytes by binding to ACE2 receptors on these cells, inducing lymphopenia, reducing CD4+ and CD8+ T-cell counts and consequently reducing immunity levels. This damage is compounded with the raised interleukin levels (IL-2, IL-6, IL-7, interferon gamma inducible factor, granulocyte colony stimulating factor), effectively achieving a state of cytokine storm [4,6]. This causes atrophy of lymphoid tissue, weakening the defense system reserve pool, and preventing future production and proliferation of protective lymphocytes.

Furthermore, there is lactic acidosis, which destroys type II alveolar cells—the regenerative lung cells—leading to a plethora of respiratory difficulties that exacerbate acid-base levels. Eventually, this causes hypoxemia and hypoperfusion. Therefore, tissues depend on anaerobic metabolism that worsens the already present acidic conditions. Coupled with the urgent need to treat the cytokine storm via immunosuppressive steroids, all of this promotes an optimal environment for the fungus to thrive [7]. Finally, two other conditions fuel Mucorales growth in the infected body: raised ferritin levels due to increased hemolysis (iron is toxic to phagocytes) and a raised body temperature (they are thermotolerant organisms) [8]. The fungus receives its nutrition from ACE-2 mediated damage to pancreatic beta cells that results in and elevated plasma glucose levels [9,10]. In fact, this explains why mucormycosis is more prevalent in those with diabetes: it thrives when there is an abundance of sugar. In a study in Mexico reviewing mucormycosis cases, diabetes was an underlying comorbidity in up to 72 % of patients [3]. As mucormycosis invades blood vessels via endothelial damage, the insulin resistance and raised glucose levels result in proliferation of the fungus and progressive weakening of an already shattered immune system. These catastrophic consequences can only mean the eventual deterioration of the patient. While Mucorales can be a commensal organism in immunocompetent patients, the severe cases of COVID-19 infection are often immunocompromised and are hospitalised for longer, with some even requiring long-term mechanical ventilation. This ventilation further makes them susceptible to infections like mucormycosis.

3. Literature review

We perused the PubMed, MEDLINE, and SCOPUS databases using the medical subject headings (MeSH) “Coronavirus disease 2019”, “COVID-19” AND “Mucormycosis.” Articles in languages other than English were excluded. Case reports, case series, correspondence articles, and editorials were included in the present review. A total of 12 cases were retrieved, comprising 11 males and 1 female. The mean age of onset was 48 ± 17 years. Notably, the mortality rate hovered at a soaring 33.3 %, further invoking the notion of early intervention in afflicted patients. These outcomes are depicted in Table 1.

The studies in the table describe patient outcomes of a Mucormycosis
infection in the context of COVID-19. The key takeaway is clear: mortality and morbidity are very high. COVID-19 complications have been a major focus and thus repeatedly described in numerous published studies since its initial outbreak; the potential havoc that a COVID-19 regimen that does not overly suppress the immune system while also optimal strategy would be to find an equilibrium between a testament Mucormycosis and its deleterious effects and often fatal outcome. The major focus and thus repeatedly described in numerous published trials are designed

4. Conclusion

As there is currently no standard protocol that is being implemented to treat Mucormycosis in COVID-19 patients, there is undoubtedly an overwhelming need to formulate one. Moreover, the results of the current study have ramifications beyond a COVID-19 and Mucormycosis superinfection. While COVID-19 has been shown to produce an immunosuppressed state on its own, the need for a standard protocol is further necessitated when considering COVID-19 patients with concurrent immunosuppressive conditions, as they are even more susceptible to Mucormycosis and its deleterious effects and often fatal outcome. The optimal strategy would be to find an equilibrium between a testament regimen that does not overly suppress the immune system while also resolving the ongoing cytokines storm characteristic of severe COVID-19.

Given these evolving challenges, it is imperative that large scale trials are designed—not just to discern the interplay between COVID-19 and Mucormycosis, but also other immunosuppressive states that can portend significant morbidity and mortality.

5. Limitations

The article has some limitations. For instance, having a prior diagnosis of diabetes mellitus is a well-established predisposing factor for developing a mucormycosis infection. The causality between COVID-19 and mucormycosis cannot be reliably drawn. Nevertheless, there is a conspicuous correlation between the two that cannot be discounted. Finally, while Mucormycosis infection can be seen worldwide, it has a higher prevalence in the more underdeveloped regions of the world. Thus, published cases are much more likely to come from these regions.

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