Short communication

Recent surge of mucormycosis in COVID-19 patients: clinicians' perspective from systems genomics

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Abstract
Mucormycosis has been largely associated with COVID-19 patients. With the growing number of cases, there is an immediate need to understand the treatment regimen for COVID-19 which could predispose to mucormycosis infection. The authors have highlighted the points from clinicians' perspective.

Keywords: comorbidities, COVID-19, mucormycosis, sequencing, systems genomics

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Introduction

Over the last 2-3 months, mucormycosis has been making strides among COVID-19 patients with underlying comorbidities and those patients who were treated with steroids for the cytokine storm. Uncontrolled diabetes and diabetics who have undergone organ transplantation were among the commonest responsible comorbid factors. With conditions such as onset of fever, hyperglycemic without ketoacidosis, histopathological examinations set a precedent for early diagnosis and treatment (Revannavar et al. 2021). Mucormycosis belongs to *Rhizopus oryzae* (most common) and family Mucoraceae, order Mucorales. While the most common etiologic agent causing mucormycosis in COVID-19 patients is *Rhizopus oryzae*, mucormycosis involving nose and sinuses [88.9 %] was the most common clinical entity followed by involvement of rhino-orbital area [56.7 %] (Kumar et al. 2021, Singh et al. 2021). An increased number of cases of rhino-orbital mucormycosis was diagnosed among patients infected with COVID-19. Diabetes with corticosteroid treatment serves as an independent factor to understand pathophysiological location of mucormycosis. Prevalence of mucormycosis was increasing and a large number of patients were at risk of this deadly infection (Ibrahim et al. 2012). The incidence of mucormycosis is not limited to immunocompromised patients alone (Bassetti and Bouza 2017). Several patients with diabetes, lung, renal and liver ailments developed pulmonary fungal infections (Wauters et al. 2012, Lin et al. 2017). In these cases, infections from *Aspergillus* spp. were highly prevalent followed by Mucorales infections as has been pointed out by Neofytos et al. (2013). In a recent report, 11717 cases have been reported in India, which is predominantly seen in males [78.9 %], both in patients with active [59.4 %] or recovered [40.6 %] COVID-19 infection (Live Mint 2021). The cases have been mostly reported from Gujarat [2859], Maharashtra [2770], Andhra Pradesh [768], Madhya Pradesh [752]

followed by Telangana [744], India. Pre-existing diabetes mellitus [DM] was observed in 80 % of cases and concomitant diabetic ketoacidosis [DKA] was noticed in 14.9 %. DKA was seen in 76.3 % of total cases who were also treated with corticosteroids for COVID-19 infection. *Aspergillus* and *Candida* (opportunistic fungus) infections in COVID-19 patients are surmounted by the additional diagnostics *viz.*, galactomannan/histopathology, direct microscopic examination, and qRT-PCR-based assays (Torelli et al. 2011). Though there is no known line of treatment or protocol for this, Song et al. (2020) recently provided a flow diagram in the management of candidiasis/ aspergillosis/ cryptococcosis in COVID 19 patients. We bring the following perspectives on the disease manifestation.

Discordance for understanding pathogenesis of mucormycosis: A discordant state in the form of diabetes, rampant use of corticosteroids in COVID-19 infection are well known causes for increased cases of mucormycosis. Glucose intolerance and inappropriate use of steroids could make the patient more vulnerable to mucormycosis. On the other hand, COVID-19-associated mucormycosis [CAM] cases presented with signs and symptoms compatible with rhino-orbital or rhino-cerebral syndromes in addition to other clinical forms of mucormycosis (Monte et al. 2020, John et al. 2021, Khatri et al. 2021). As per European Confederation of Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM), other allied diseased phenotypes such as diabetes and inappropriate corticosteroid use in addition to large spores of mucorales are known to be the plausible reasons (Garg et al. 2021, Rudramurthy et al. 2021). In addition, the patients with diabetes and hyperglycemia have antiviral immunity to SARS-CoV-2, which might favor secondary infections. On the other hand, Zinc supplementation is also known to be a contributor to mucormycosis. Recent studies by Muthu et al. (2021) have shown how *Rhizopus arrhizus* isolates obtained by CAM patients have comparative clinical profiles augmenting the role of Zinc in cases when compared to controls. However, more *in vitro* and *in vivo* validations or molecular docking complexes could be done to validate this study. Further, as per Klimko et al. (2019) there are differences in clinical signs and symptoms between aspergillosis and mucormycosis. They have also reported that, in comparison to aspergillosis, the number of pulmonary mucormycosis cases are less than rhino-nasal mucormycosis (Klimko et al. 2019). Further, patients with pulmonary mucormycosis experience localized pain syndrome, hemoptysis and pleural effusion which is established between aspergillosis and mucormycosis in onco-hematological patients (Klimko et al. 2019). Several species of *Rhizopus* and *Mucor* [genera] cause a fungal disease or mucormycosis and so this inherent discord between them could give us prospective leads on genetic susceptibility. Timely differentiation between aspergillosis and mucormycosis is highly vital for therapeutic interventions.

Host-pathogen sequences: Sequencing the genomes of the pathogen-host with the immunocompromised conditions prevailing from diabetic ketoacidosis, neutropenia, organ transplantation, and/or increased serum levels, adjunctive antifungal therapy will be useful. To better disseminate this understanding, metagenomic or metatranscriptomic analysis would allow us to know the inherent “known unknown” genes associated with the pathogenesis of mucormycosis and the host response to invading hyphae. This would also invite several promising therapeutic strategies in preclinical stages as identified and described *impromptu*.

Treatment regimen: Another link associated with this sequencing approach is to bring a treatment regimen [Dx and Rx] parenteral meropenem/oral oseltamivir with parenteral methylprednisolone although clinicians argue vivid use of methylene blue as a solution for mucormycosis, though treatment is still a challenge (Skiada et al. 2018). As plasma therapy is a bygone conclusion for COVID-19 patients, studies on extensive use of steroids/monoclonal antibodies/broad-spectrum antibiotics would bring exacerbation of a preexisting fungal disease and manifestations of it (Mehta

et al. 2020). As the treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy, Intravenous (IV) amphotericin B is the drug of choice for initial therapy. However, posaconazole or isavuconazole have been considered as a step-down therapy for amphotericin B responders, which can further serve as a salvage therapy for patients who don't respond to or cannot tolerate amphotericin B. This will also allow a precedent for physicians about the possibility of secondary invasive fungal infections in patients with COVID-19 infection.

Genetic susceptibility: Given the innate immunity protection against these infections, there could be a chance of primary immunodeficiencies [PIDs] associated with COVID-19 infection. Therefore, it is anticipated that SNPs in innate immunity genes, *toll*-like receptors [TLRs] and cytokines/chemokines might be associated with this infection (Lionakis et al. 2015). This not only impairs the immune response, exposing patients to higher risk of developing opportunistic infections leading to worse outcomes (Pasero et al. 2020).

Road ahead: From a clinical point of view, one should take a syndromic approach and we should ensure the nomenclature is simple and widely acceptable, like flu though it is caused by more than 50 different viruses. With a recent report showing patients with probable pulmonary Aspergillosis and possible mucormycosis, early diagnosis could be aspergillus galactomannan antigen obtained from serum whereas in case of pulmonary mucormycosis, there is a need to identify such hyphae/infection using cytology meeting the diagnostic criteria for probable COVID-19-associated pulmonary aspergillosis [CAPA] (Johnson et al. 2021). On the other hand, there is a combined risk of diabetes associated with these infections which may invite these IFI to be promoted through airway channels and diaphragm. As combined probable pulmonary aspergillosis and possible mucormycosis cases are increasing, there is a need for healthcare professionals to be aware of the complications and treatment regime. If the treatment regime is different for mucormycosis from that of aspergillosis, then there is a need for taxonomists to warrant a separate name. The taxonomists and clinicians must converge this line for a great beginning in taking up mucormycosis as a generic term.

Competing interests
The authors declare no competing interests.

Author contributions
All the authors contributed equally to this manuscript.

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