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Mucormycosis, Diabetes Mellitus and COVID-19 - An Emerging Concern

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ABSTRACT

Introduction: Mucormycosis is emerging, rapidly spreading situation. Mucormycosis is an opportunistic fungal infection seen in patients with Diabetes Mellitus. In the present scenario of co-existing SARS-CoV-2, the severity of this infection has grown manifold on account of co-existing hyperglycemia and steroid use. It can become a serious condition as it invades orbit and has potential of intracranial spread. We analyse co-infection of Mucormycosis, diabetes mellitus association with COVID-19. **Methods:** We carried out a comprehensive review of the literature using suitable keywords such as 'COVID-19', 'Mucormycosis' and Diabetes Mellitus' on the search engines of PubMed, Scopus, Google Scholar and Research Gate in the month of April 2021 to identify characteristics of these increasing co-infection (Mucormycosis and COVID-190 in patients with of diabetes mellitus during the COVID-19 pandemic. **Results:** Co-infection of Mucormycosis with COVID-19 in patient with Diabetes mellitus being treated with steroids for the SARS-CoV-2 viral infection is becoming evident, presenting diagnostic and treatment challenges. Manifestations, severity and organ involvement has been reported to be variable. Preliminary diagnosis and prompt initiation of management is paramount to treatment. The role of newer modalities for detection and novel antifungal agents for treatment can be considered significant for current scenario and future research. **Conclusion:** Emergence of co-infection is a serious health challenge for patients with COVID-19. A strict glycemic monitoring and control is mandated, especially when corticosteroids are utilized to combat the severity of SARS-CoV-2. A high index of suspicion, early intervention, health education, and infection prevention are paramount to avoid severe intracranial and orbital complications.

INTRODUCTION:

The ongoing coronavirus disease 2019 (covid-19) has seen various dilemmas and challenges. The disease has manifested in various forms and severity. The multiorgan involvement is also known. The recent occurrence of mucormycosis has created another challenge for managing the covid-19 patients. Various contributory factors have played the role for its occurrence.

Diabetes mellitus and co-infection

Diabetes mellitus and associated uncontrolled hyperglycemia has been known to be a classical risk factor supplementing immunosuppression for acquiring opportunistic infections, such as mucormycosis with potential morbidity and mortality. [1] the causative agents for the disease are fungal spores, which are rapidly spreading in nature, yet possess a low virulent potency in immunocompetent hosts. [2] thereby inferring that human are exposed to many airborne fungal spores, however, the immunocompromised hosts are at higher risk for acquiring a severe infection. [1, 2] co-infection with mucormycosis in diagnosed or undiagnosed hyperglycemic in covid-19 patients receiving corticosteroid therapy creates a perfect milieu for further fungal proliferation and fulminant infection in severe cases. [3] diabetes mellitus has an undeniable role in the pathogenesis of mucormycosis, as evident from the higher reported diabetics and co-infected individuals with mucormycosis. [4]. The favorable environment offered by hyperglycemia, ketosis and immunosuppression could be important attributable factors.

This document attempts to highlight the correlation between diabetes mellitus, covid-19 and mucormycosis, epidemiology, microbiological aspects, pathogenesis and clinical features, management, presentation, and severity of mucormycosis in the context of co-existing severe acute respiratory syndrome coronavirus 2 (sars-cov-2).

Epidemiology

The global incidence of mucormycosis cases have been on the rise since recent past. [3] the asian counties have specifically been facing an extreme surge. [4] of note, a great majority of diabetics have been found to be presenting with mucormycosis during the course of their illness. [4, 5] consequently, rhino-orbital-cerebral mucormycosis (rocm) has been known to be the most common form of the disease among diabetics, followed by pulmonary and

cutaneous ones. [5] suboptimal access to medical therapies, lack of awareness, poor compliance to anti-diabetics could be some of the contributing factors.

The most common cause implicated among the western countries has been hematological malignancies. [6] protracted neutropenia during acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes, or recipients of hematopoietic stem cell transplant have higher odds of invasive fungal infections, including mucormycosis. In this regard, pulmonary mucormycosis has been the commonest form among the developed countries. [5,6]

What is mucormycosis?

The zygomycetes were first described class of fungi by whittaker. Among this class, the three most common orders of fungi reported to be involved in fungal infections in animals and humans include the mucorales, the entomophthorales and the mortierellales. [2] the entomophthoromycosis are known to cause loco-regional, slowly progressive infections in immunocompetent hosts; whereas the mucorales can lead to serious invasive and disseminating infections in immunocompromised patients. [1,2] the latter group commonly includes *mucor circinelloides, rhizopusarrhizus, rhizopus microspores, lichtheimia corymbifera and cunninghamella bertholletia*. [2] the most common type observed is *rhizopusoryzae*, accounting for approximately 60% of infections and causes majority of rocm. [5] their fungal spores have profound distribution over vegetable and agricultural waste, organic debris, compost, and soil. Microbiologically they are identified through their characteristic appearance of hyphae, septa, pigmentation and branching angle. [7] they spread through oro-nasal route, invade the mucosal barriers and lead to severe disseminated infections in predisposed individuals will compromised immunity. [8]

Why mucormycosis developing in patients with diabetes mellitus coinfection with covid-19?

Diabetes mellitus has been found to be one of the most common risk factors associated with mucormycosis. [1] furthermore, comorbid illnesses such as hematological malignancies, haemopoietic stem cell transplant, corticosteroid therapy, burns, sepsis, trauma etc. Have been correlated with severe fulminating mucor infections. [1] notably, trauma and natural disasters have been found to be contributing to disease in healthy individuals; nevertheless, healthcare associated serious fungal infections are continuously emerging. [2, 4]

Covid-19 viral pneumonia is associated with dysfunctional alveolar capillary membrane, endothelial damage, compromised cellular immunity and inflammatory tissue damage. [5] these cellular and biological immune response to these manifestations is already impaired in patients with diabetes mellitus with uncontrolled hyperglycemia and further accentuated in patients receiving corticosteroid therapy; acting as a morbid vicious triad. [9] this could be a plausible primary cause of higher incidence of mucormycosis in patients with diabetes mellitus and covid-19. Besides, in critically ill patients having reduced t-cell activities, hyperglycemia, acidemia, high ferritin levels and high inflammatory markers, the risk and severity for invasive fungal infections enhances manifold. [1,5].

The clinical spectrum varies depending upon the primary organ involvement. The most common being rhino-orbito-cerebral mucormycosis (rocm) [5]. Rocm involves nasal mucosal, sinuses, orbital disease, and central nervous system. [10] the presenting symptoms could be fever, headache, nasal/ sinus congestion, black discoloration of nasal/ oral mucosa/ lesions/ swelling over face. [3,5] the pulmonary mucormycosis remains the other manifestation and leads to inflammatory changes in the lung parenchyma leading to shortness of breath, cough, fever, and acute respiratory distress syndrome in severe cases. The gastrointestinal mucormycosis is rare in adults, though children and infants may present with nausea, vomiting, diarrhea, and acute abdomen. The cutaneous mucormycosis leads to erythema, skin lesions, ulcers with blackish discoloration. [11] though the disseminated mucormycosis is rare but fatal disease with multiple organ dysfunction. The pulmonary and disseminated infections have been reported to have the highest rate of mortality. [3] however, initial presentation with cns involvement represents a severe form of disease, often acting as a sole determinant of the sequelae and survival. [10] uncontrolled hyperglycemia plays the most important role as a risk factor for rocm, though its association is common with other types of mucormycosis as well. [10,11] the manifestations of the disease could be manifold and varying in nature. [12] the severity and fatality of infection is affected by the organ involvement, immune status of the patient, comorbid conditions, and prompt diagnosis/ management.

Investigations

The outcome of mucormycosis depends upon prompt diagnosis and initiation of treatment. The challenges in early diagnosis pertaining to non-specific clinical and radiological presentation has been well recognized. [13] moreover, diagnostic distinction of mucorales

from invasive aspergillosis is extremely important, as the plan of management and treatment strategies are different for both. Methods for microbiological detection of causative agent include mycological cultures, histopathological detection, and radiological assessment. Low grade sensitivity associated with these modalities prohibits prompt diagnosis and intervention. [14]. Moreover, serological tests are inconclusive for mucormycosis. [13,14] these factors have led to development of newer modalities for diagnosis and precise detection of mucorales. Advanced methods among those include quantitative polymerase chain reaction (qpcr) targeted against specified fungal components from the clinical specimen. [14,15] coth gene, an integral component of spore coating protein homolog has been uniquely identified in the organisms of mucorales order, causing fulminant mucormycosis. Successful detection of coth by pcr amplification of clinical samples such as plasma, urine and bal in mice infected with mucorales has been performed. [14] among humans, coth detection in urine samples from patients with histopathologically proven mucormycosis was successful. [14]. Recently, detection of mucorales specific dna by qpcr in bronchoalveolar lavage (bal) specimen has been found to have a good sensitivity and specificity, and lead to early diagnosis and management of disease. [15].

Furthermore, development of assays for detection oh coth and other genomic components in clinical specimen remains a subject of future exploration.

Management and preventive strategies

Initiation of treatment should commence as early as possible for favorable outcomes. A comprehensive plan of management based upon disease severity and consideration of comorbid illnesses should be made. Accordingly, pharmacological treatment or surgical intervention or both should be considered and performed. Antifungal therapy remains the cornerstone of pharmacological management. Early initiation of antifungal therapy has been significantly correlated with reduced mortality rates. [16]. Antifungal agents such as polyenes and triazoles have been widely utilized. [2,8]. Liposomal amphotericin-b (l-amb) is regarded as the most effective antifungal therapy against mucormycosis, thereby rendering it as a first line agent. [2,8,16] the most administered dose is 5mg/kg/day, continued for 3 weeks. [2]. Further dose escalation may be needed depending upon the severity of the disease and primary organ involvement, such as cns infections etc. [2,10] however, the optimal dose of l-amb has been a matter of discussion.

Triazoles have been utilized s second line agent or as a part of combination therapy. Among triazoles, posaconazole and isavuconazole have been found to have been effective against infection with mucorales; whereas fluconazole, itraconazole and voriconazole have been demonstrated to be active against aspergillus with insignificant action against mucorales. Posaconazole is available in oral as well as intravenous suspension formulation. It is regarded as a salvage treatment therapy, and it is prescribed as 200 mg twice a day. Therapeutic drug monitoring (tdm) is highly recommended with it. [17]. Isavuconazole is a useful alternative to l-amb when the latter is contraindicated. It may be prescribed as oral or iv formulation with a loading dose of 600 mg in divided doses for 2 days followed by 200 mg per day. It has an added advantage of improved pharmacokinetic properties such as better safety profile in the form of hepatic and renal functions, lesser cutaneous reactions, drug interactions and cardiovascular effects. [18] nevertheless, the minimum inhibitory concentration (mic) for isavuconazole is 2-4 times higher as compared to posaconazole. [17,18].

Combination therapy with different class of antifungals has recently been taken into consideration in view of broader spectrum and supra-additive effects, especially in patients with severe immune deficiency; however, adverse effects such as drug interactions, cost-effectiveness and toxicities must be recognized. [19] further research is warranted for an ideal polyene and triazole combination resulting in better clinical outcomes than either of the agents. Moreover, the role of antifungal stewardship in appropriate management of this disease cannot be denied. [20]

Surgical intervention

Surgical debridement of the infected, necrosed tissue is the mainstay of treatment for mucormycosis. [10, 21] in case of rocm, imaging studies such as ct, mri may aid in the assessment for the extent of resection. In the early disease stage, endoscopic debridement is a preferred modality as it may suffice for the beneficial outcome. However, extensive progression of infection may enforce open surgeries such as orbital exenteration, maxillectomy, and others which may not be limited to craniofacial resection as well. [10,21] surgical intervention in combination with systemic antifungal therapy may be favorable in patients with loco-regional spread of the infection. [21] postoperative outcomes have been unpredictable, and depend upon comorbid illnesses, disease severity, immune status, extent of resection and rate of recurrence. [22]

Adjuvant therapies

These are targeted to provide an adjunct to immunity, especially in patients with chronic immunosuppression, such as haematological malignancies, prolonged neutropenia and persistently raised inflammatory markers. The therapy includes, but is not limited to, haemopoietic growth factors, e.g. G-csf, white cell transfusion or if-gamma. [2] nivolumab is a novel monoclonal antibody, with a mechanism proposed to inhibit pd-1 pathway mediated cytokine production. [2] other adjuvant measures which could possibly expedite the innate immune function includes a strict glycemic control in patients with diabetes, anti-retroviral therapy in patients with hiv/ aids, use of iron chelating agents such as deferasirox, considering tapering down on corticosteroid therapy and reversal of chronic acidemia (in critically ill patients with renal or metabolic disorders) with soda bicarbonate, as acidemia has been found to contribute to fungal endothelial invasion and hamper the neutrophil activity. [5, 23] apart from the pharmacological measures, hyperbaric oxygen therapy (hbo) has been formulated to have significant potential benefits such as inhibition of fungal proliferation, reversal of acidosis, improved neutrophil function and hastening of wound healing in postsurgical group of patients.[2]. Continuation of treatment is advised until improvement in clinical, radiological and immune function. However, the actual duration should be individualized on case to case basis, as an optimal duration for treatment is still debatable.

Novel antifungal agents

The unpredictable treatment outcomes with existing pharmacological and interventional therapies have insisted upon the ongoing research for novel antifungal therapies active against mucormycosis. The examples include, but are not limited to, vt-1161 also called as osteoconazole, apx001a and haemofungin. [2,17] recently, a newer field of exploration as to inhibit the egfr signaling for prevention of mucormycosis growth has gained interest. [24] further future research on human volunteers for in vivo activity is essential to establish the clinical role.

Challenges for clinicians in diagnosing and managing

The clinical and radiological diagnosis of mucormycosis is challenging. The factors contributing have been enumerated as:

(a) Mucormycosis is an uncommon disease with limited data on intervention and management. [25]

(b) There are a multitude of host factors promoting variable degree of various organ involvement. [26, 27]

(c) Non-specific clinical signs and symptoms overlapping with a variety of infectious diseases [27]

(d) Limited diagnostic tools with tissue culture/ histology; lean access to pcr labs in tertiary hospitals [5, 27]

(e) Low yield of respiratory specimen (bal/ sputum) for culture [14,27]

(f) Co-existing sars-cov-2 during the ongoing pandemic, with symptoms pertaining to immune deficits and surge of inflammatory markers broadly overlapping in both the spectrums. [28]

(g) The overwhelming presentation of mucormycosis in the scenario of covid-19 with exhaustion of healthcare system. [29, 30]

Situation in India: precipitating triggers

There has been a significant hike in the number of new mucormycosis cases over last few months across all over the world, especially in India. Certain undeniable contributary factors in the context of covid-19 pandemic second wave include a typical triad of uncontrolled hyperglycemia, steroid use and covid-19 infection over and above the misuse of pulse dose of corticosteroids, especially when repeated illicitly in case of persistently high inflammatory markers. [27, 31] moreover, in relatively healthy patients practicing home-based isolation, limited access to medical therapy on top of use corticosteroids have led to uncontrolled hyperglycemia with worsening immune status, making them vulnerable to opportunistic infection like such. [43, 47]

Futhermore, among the hospitalized patients, reduced t-cell functions, high ferritin levels with high iron load, hypoxemia, acidemia and ketosis aids to fungal growth and severe mocor infection. High levels of circulating inflammatory markers and acedia lead to reduced iron chelation, resulting in higher free iron levels, which further promotes fungal growth. [32]

The recent surge in the number of cases with covid-19 has demonstrated the diverse organ involvement by concomitant mocor infection; such as orbital compartment [33, 44, 46], rhino-orbital-cerebral system [34, 42], gastrointestinal system [35], pulmonary [36], involvement of craniofacial skeleton [37], paranasal sinuses [38], as fulminant fungal infection [39] [42], in underlying haematological malignancy [40] and even in oral cavity[41, 42] the impious coexistence of diabetes mellitus and covid-19 as a contributory factor to this recent surge in manifold manifestations of mucormycosis has been unanimously deciphered by several authors.[27,43]. Recent literature has confirmed the predominant impact of hyperglycemia and acidemia along with inflammatory endothelial dysfunction causing increased affinity and endothelial damage by mucor spore proteins (coth) leading to tissue invasion. [43-47]. In this regard it is important to recognize the ongoing critical situation of hyperglycemia, collateral sars-cov-2 and mucormycosis; accordingly prudent diagnostic and management techniques must be imbibed and implemented. [48]

CONCLUSION AND FUTURE DIRECTIONS:

The global burden of mucormycosis is exhausting the healthcare resources. The precise prevalence of the disease is difficult to predict owing to difficulties in diagnosis, under-reporting of new cases and majority of cases falling into the category of subclinical presentation due to concomitant infection with sars-cov-2.

Recent surge in the number of covid-19 cases with mucormycosis and concomitant hyperglycemia have been alarming. The present scenario has made it imperative to undertake immediate actions to prevent further deterioration of health condition. Screening of diabetics with regular healthcare checkups, timely initiation of antidiabetics and monitoring of clinical signs and symptoms is highly recommended.

Among the hospitalized patients strict glycemic monitoring, awareness and prudent utilization of corticosteroids is the absolute necessity. Prompt diagnosis and timely intervention for suspected cases, especially in high risk population is the need of the hour. Development and research for advanced diagnostic modalities and novel antifungal agents is highly emphasized in order to combat the disease in a proficient manner during upcoming years.

Contribution of authors:

- Khushboo Pandey: this author helped in review of literature and writing of the manuscript.
- Vibha Mehta: this author helped in review of literature and writing of the manuscript.
- Rakesh Garg: this author helped in literature search, writing and editing of the manuscript.
- Vijay Jain: this author helped in review of literature and editing of the manuscript the manuscript.

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