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Coronavirus Disease Associated Mucormycosis (CAM) - A Novel Threat: A Review of Literature

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Abstract

SARS-CoV-2 has been postulated as the causative organism for coronavirus disease 2019 and thereby also leading to Severe Acute Respiratory Distress Syndrome and a serious health threat to humanity. The high number of COVID-19 cases around the world is overwhelming hospitals thereby pushing global death toll to over 3706,752 which coerced clinicians, epidemiologists and health experts from around the world in a desperate need to find newer treatment options like corticosteroids. Severe coronavirus disease is currently managed by systemic glucocorticoids. In the Pretext of COVID-19 disease being managed by systemic glucocorticoids, COVID 19 associated pulmonary aspergillosis is increasingly recognized as a complication, mucormycosis is coming forward as a problem. In this paper, we are reviewing the existing literature on CAM (Coronavirus Associated Mucormycosis) with regard to its pathogenesis, clinical features and treatment options.

Mucormycosis (CAM) is an extremely rare clinical entity and only handfuls of cases are reported till date. This particular paper will throw light on COVID-19 Associated Mucormycosis, its implications on steroid use and also its therapeutic options in detail so as to understand this clinical entity and its social and health implications it has on the society.

Keywords: Coronavirus; Mucormycosis; Steroids; Pandemic; Mucorales

Abbreviations

CAM: Coronavirus Associated Mucormycosis; AMB: Amphotericin B

Introduction

History teaches us of the incident Late December 2019, where the outbreak of a mysterious pneumonia characterized by symptoms of fever, dry cough and fatigue, also presenting with severe gastrointestinal symptoms in a seafood market in Wuhan, China. A previously unknown coronavirus now named as the 2019 novel coronavirus which has caused a formidable outbreak in numerous cities in China and exploded globally. The treatment for corona COVID-19 is still a mystery but some clues are emerging in this regard [1].

Virology

Coronavirus is an envelope, positive single stranded RNA virus. It belongs to Orthocoronavirus subfamily with the characteristic "crown-like" spikes on their surfaces. The exact prequel to origin, location and natural reservoir of 2019 Coronavirus remains unclear, but it is postulated that the virus is zoonotic and the bats may be the culprit and reason attributed to sequence identity to the variant of bat-COV. The infectious doses for 2019-nCoV are not certain but a high viral load of up to 108 copies/ml in a patient's sputum has been found [1-3].

Clinical manifestation

COVID-19 has a mean incubation period of 5.2 days. Symptoms begin with certain nonspecific syndromes including fever, fatigue and dry cough. Multiple systems involved include respiratory (cough, sore throat, shortness of breath, hemoptysis, rhinorrhea and chest pain), gastrointestinal (nausea, diarrhea, and vomiting), musculoskeletal (muscle ache) and neurologic (confusion or headache). The common signs and symptoms are cough (76% to 82%), fever (83% to 98%) and shortness of breath (31% to 55%). Patients harboring fatal disease develop Acute Respiratory Distress Syndrome (ARDS) and tend to worsen in a short period of time and die of multiple organ failure. Theoretically lungs' being the major involved organ, the further mechanics and behavior of the virus is unknown [3].

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The definitions of reported COVID-19 include,

1). any one of the following

a. Febrile illness

b. Acute respiratory infection

2) Laboratory conditions with any of the following:

Nasopharyngeal swab, sputum or lower respiratory tract aspirate etc. were isolated and identified as 2019-nCOV.

Clinical specimens that indicate positivity by RT-PCR. Epidemiologic conditions with any of the following 14 days much before onset of symptoms.

3) Clinical, radiological or pathological evidence of pneumonia.

History of evidence of contacting patients with fever or respiratory symptoms or even travelling.

Confirmatory laboratory diagnosis [3] usually relies on the principles of a real time RTPCR assay to detect viral RNA by targeting a consensus E region of pan beta COV or even other more specific regions such as RdRp and/or N region. Chest X-ray, computed tomography usually reveals bilateral pneumonia with multiple mottling and ground glass opacity.

Treatment

Currently there is no certified treatment for COVID-19. The main strategies are symptomatic and supportive care mentioned as maintaining oxygen saturation, keeping vital signs and blood pressure and treating complications and blood pressure and treating complications such as secondary infections or organ failure.

Remdesivir was an experimental drug, no longer used as per WHO. It is identified as a Novelty as anti-nucleotide analogue prodrug developed by Gilead sciences, INC. Convalescent therapies like plasma from recovered COVID-19 patients. This form of therapy is no longer advised as it offers no benefit. Antiviral drugs Lopinavir/ Ritonavir and Ribavirin are used in the treatment but their clinical efficacy is yet to be seen. Vaccines for COVID-19 are introduced in the general population as a sign of relief for the world but efficacy of vaccines is yet to be seen. Steroids are used in severe coronavirus disease and an improved mortality is seen and widespread use of steroids is implemented weighing the benefits and risks on a patient-to-patient basis [4].

Patients with severe COVID-19 may develop a systemic inflammatory response leading to lung injury and multisystem organ dysfunction. It has been proposed in concept the potent anti-inflammatory effects of corticosteroids may prevent or mitigate these deleterious effects. The randomized evaluation in COVID-19 therapy (RECOVERY) trial [5], a randomized, multicentric open label in hospitalized patients with COVID-19 showed that the mortality from COVID-19 was lower among patients randomized to receive dexamethasone compared to those receiving the standard of care. The efficacy and safety of combination therapy of corticosteroids with an antiviral agent targeting Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) for the treatment has never been rigorously studied among clinical trials. However, for theoretical reasons this combination therapy is devoted to be beneficial in patients with severe disease.

Review of Literature

The pandemic of Coronavirus Disease 2019 (COVID-19) remains to be a significant problem worldwide. While several treatment options have been researched, however systemic steroids [4] have shown proven benefit in the management of COVID-19 infection and proving improved survival. Unfortunately, the widespread use of steroids is leading to secondary bacterial or fungal infections. Pulmonary aspergillosis [6-8] complicates the course of COVID-19 but mucormycosis is a relatively new and rare clinical entity. Mucormycosis is a life-threatening infection that occurs in patients who are immunocompromised like patients who are on systemic glucocorticoids as a part of therapeutic option of severe COVID-19 infections, diabetes, ketoacidosis, neutropenia [8], organ transplantation and increased levels of serum iron [9]. Despite aggressive therapy, that includes the concept of disfiguring surgical debridement and adjunctive antifungal therapy, the overall mortality rate is noted to be high. Newer strategies developed to prevent and treat mucormycosis are urgently needed. Understanding the pathophysiology and pathogenesis of mucormycosis and the ability of the host to respond to it will ultimately provide targets leading to novel therapeutic interventions. In this paper, we have reviewed the current knowledge about virulence traits being used by the common etiological agent of mucormycosis-*Rhizopus oryzae* [10]. Patients presenting with elevated serum levels of available iron are somehow susceptible to mucormycosis and these infections are found to be highly angioinvasive, due emphasis should be placed on the ability of the organism to acquire iron from this host and on its interactions with endothelial cells lining blood vessels. A number of promising therapeutic strategies are still in the pipeline [3].

Mucormycosis is an infection caused by fungi belonging to the order Mucorales [4]. *Rhizopus oryzae* is the most common organism seen to be isolated from patients with mucormycosis and is definitely responsible for approximately 70% of all cases of mucormycosis. The major risk factors for mucormycosis [1] thereby include uncontrolled diabetes mellitus, which may present with complications like ketoacidosis and other forms of metabolic acidosis, treatment with steroids, organ and or bone marrow transplantation [8], burns, trauma, malignant hematological disorders and dexamethasone therapy in patients receiving hemodialysis. Because of widespread use of systemic steroids [4] in COVID-19 infected patients are dramatically increasing. Unfortunately, despite of surgical debridement and adjunctive antifungal therapy, overall mortality rate continues to remain >50% and almost approaching 100% [11] among patients with disseminated disease on those with persistent neutropenia [8]. Definitely newer strategies to prevent and treat mucormycosis are urgently required and can be facilitated through clear understanding of the progression of the disease [1].

Experimental and Clinical data demonstrates that those individuals who lack phagocytes or have impaired phagocytic function are seen to have a higher risk of mucormycosis. For example, severely neutropenic patients who are always at increasing risk of developing mucormycosis in contrast to those patients suffering with AIDS who do not appear to be at increased risk for developing mucormycosis. These findings ascertain those neutrophils, but not only T-lymphocytes are crucial towards inhibiting fungal spores. In addition to those host factors that predispose patients to mucormycosis, Mucorales possess virulence factors that cause the organism to cause the disease. One such trait is leading to acquiring

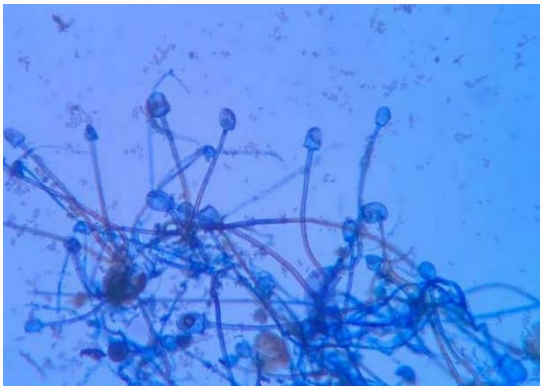

Figure 1: Microscopic view of *Rhizopus oryzae* showing non-septate hyphae.

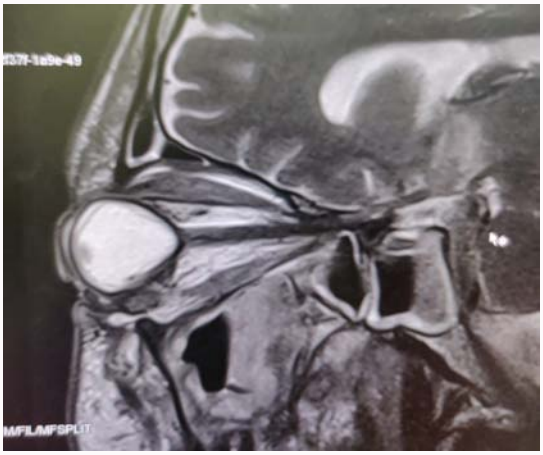

Figure 2: MRI reveals non-enhancing areas within thickened mucosa of left maxillary sinus suggestive of mucormycosis.

iron from the host. Iron is considered an essential element required for cell growth and the development contributing too many vital processes of the cell. *Rhizopus* is also known to secrete Rhizoferrin, a siderophore which belongs to the polycarboxylate family. This siderophore supplies Rhizopus with enough iron through the receptor mediated energy dependant process [3].

The most common signs and symptoms were fever, rhinorrhea and headache, while the most ominous symptom was loss of vision. The Clinical Hallmark associated with invasive mucormycosis is tissue necrosis resulting from angioinvasion [12] and also subsequent thrombosis. In most cases, the infection is almost rapidly progressive and therefore resulting in death unless the risk factors [13] are corrected and the treatment with antifungal agents associated surgical debridement is instituted. Based on the clinical presentation and anatomical site, invasive mucormycosis [14] is considered as one of the following 6 major clinical forms.

1) Pulmonary [7,15]
2) Rhino cerebral [12,16]
3) Gastrointestinal [17]
4) Cutaneous
5) Disseminated [18,19]
6) Uncommon rare forms [20]

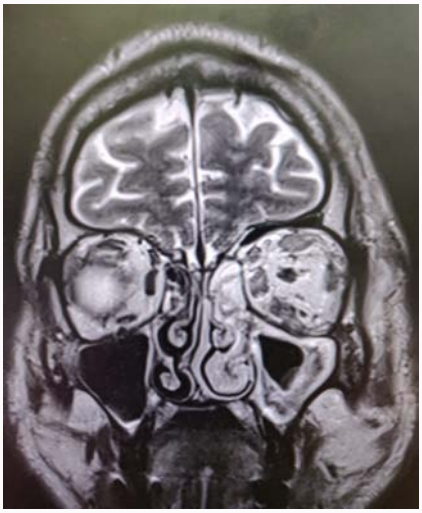

Figure 3: MRI shows mucosal thickening left maxillary sinus suggestive of mucormycosis.

The most common reported sites of invasive mucormycosis have been the lungs [7,19] (24%), sinuses (39%), skin (19%).

Diagnosis

The prerequisites attributed for diagnosis are associated with high index of recognition and suspicion of host factors and early assessment of clinical manifestations. Diplopia associated in a patient with diabetes [21] or pleuritic pain in neutropenic patient may also be a sign of this infection and should force us to resort to the prompt use of imaging modalities and subsequent acquisition of samples for testing by microbiology, histology, and advanced molecular methods. The list of signs & symptoms that may be seen as red flags include cranial nerve palsy, diplopia, proptosis, sinus pain, periorbital [18] swelling, orbital apex syndrome and ulcers of the palate. Radiologically, multiple nodules causing pleural effusion are more common in mucormycosis [16,22]. Microscopic culture examinations of various clinical specimens are cornerstones of diagnosing mucormycosis.

Direct microscopy of clinical specimens, with the use of optical brighteners such as Blankophon and Calcofluon White permits rapid presumptive diagnosis. Hyphae of Mucorales have variable width approx. (6 to 25 micrometer) and are non-septate or pauci-septate and also show irregular ribbon like appearance. The angle of branching is changing and includes wide angle (90 degrees) bifurcations. Fungal elements can be easily seen on hematoxylin and periodic acid Schiff, eosin section, or Grocott-Gomori's methenamine silver staining are used to highlight fungal hyphae and hence to evaluate morphology in more detail. Tissue histology is characterized by inflammation which may be neutrophilic or granulomatous, however the inflammation may be absent in immunocompromised patients [11,23]. All Mucorale which grow rapidly (3 to 7 days) on fungal culture media like potato dextrose agar and Sabouraud agar incubated at 25 to 30 degrees. A specific mouse monoclonal anti-Rhizomucor [19] -antibody employed for immunohistochemical analysis remains investigational. Elisa, immunoblots and immunodiffusion tests are evaluated with variable success. Mucorales specific T-cells were detected by an enzyme-linked immunospot (ELISpot) assay; however these diagnostic methods being still in the pipeline are subject to investigational studies. Molecular assays include conventional PCR

and RFLP analysis. Presently molecular based diagnostic assays have been ascertained to be recommended as a valuable add on tools that complement conventional diagnostic procedures [24].

The management of mucormycosis is based on the principles of multiple interventions occurring simultaneously or with different timing and/or intensity. The basic principles of mucormycosis treatment include intense attempts and risk stratification for severity of the disease but for early clinical and laboratory diagnosis, timely initiation of effective anti-fungal therapy (monotherapy [14] or combination) adjunct with aggressive surgical debridement of necrotic lesions and/or reversal of immunosuppression-discontinuation of steroid therapy remains the mainstay of therapy. Early diagnosis and prompt therapeutic intervention can prevent progressive tissue invasion and may also reduce the need for extensive surgery thereby improving survival [18].

Anti-fungal agents - only amphotericin B and its lipid formulation and very recently Isavuconazole have been renamed as first line therapy. On the contrary, Posaconazole [7,25] has been mainly studied as adjunct therapy. It should be noted though, that no validated Minimum Inhibitory Concentration (MIC) breakpoints are known for any of these agents. AMB is still considered the drug of choice for primary treatment of mucormycosis [13,26]. The efficacy attributed to AMB has been shown in both laboratory (*in vivo* and *vitro*) and clinical studies. Lipid formulations of amphotericin B (Liposomal AMB [26], LAMB and AMB Lipid complex ABLC) are considered to have better therapeutic index than the conventional Amphotericin B deoxycholate and are reserved as the first line therapy of mucormycosis. The optimal dosage for AMB formulations against mucormycosis is still undetermined [21]. The standard daily dose of LAMB and ABLC as suggested by current guidelines is 5 mg/kg/day. Triazides also act by depleting ergosterol from the fungal cell membrane [27].

Posaconazole and Isavuconazole are the antifungal agents which have good efficacy against mucormycosis. Despite the unknown solid clinical data therapy of mucormycosis in heavily immunocompromised patients along with a combination of antifungals [25] has become an increasingly common practice. The pros of such therapeutic approaches are seen to have synergistic effect and broader coverage and the cons are possible antagonistic, drug interactions, toxicity and cost [28].

Surgical resection [14] of necrotic tissues is the mainstay principle of the mucormycosis therapy [21]. Surgical treatment accompanied with antifungal therapy has shown to significantly improve survival, as compared to antifungal therapy alone. In certain cases of localized disease surgery may be curative. In patients associated with rhino-orbital mucormycosis, magnetic resonance imaging has a role in staging the respectability of the lesions. Similarly, surgical removal of infected tissues is of utmost importance [25]. It should be noted that an endoscopic approach is preferred over an open surgery in the patients with early, limited disease or associated with significant medical comorbidities. Open surgeries are generally preferred over extensive disease and include maxillectomy, orbital extension and include maxillectomy, orbital exenteration and/or craniofacial resection [14]. No survival benefit has been seen for such radical approach, especially in patients associated with limited life expectancy [7].

Adjuvant therapy [28] the increased oxygen pressure attained with Hyperbaric Oxygen (HBO) treatment also improves the functionality of neutrophils. Furthermore, HBO therapy promotes the AMB [13] action by reversing acidosis. Finally high oxygen pressure that inhibits fungal growth and improves the rate of wound healing, thus treatment along with HBO has been proposed as an adjunct to surgical and antifungal therapy for mucormycosis. Immuno-augmentation strategies such as administration of granulocyte colony stimulating factor or interferon gamma have been proposed as an adjunct therapy. The above-mentioned adjunct therapies are based on limited data and case reports [23]. The adjunct therapies have been tested with unclear success. Statins have shown *in vitro* and *in vivo* activity against *Rhizopus* species although reliable clinical data is lacking. The combination of IFN-gamma and nivolumab, a monoclonal antibody which decreases Programmed Death-1(PD-1) and its expression on T cells [25]. Interferon gamma restores the monocyte function and has been used as rescue therapy with life threatening fungal infections. While nivolumab binds to PD-1, which blocks interaction with its ligands and therefore improves the efficacy of PD-1 pathway mediated inhibition of T-cell proliferation and cytokine production, these therapies are still under clinical trials with unknown success [29].

There is no standard duration of treatment for mucormycosis [14]. Decisions are made on an individual basis and with the principle, antifungal therapy of mucormycosis is still continuing till resolution of all clinical, laboratory and imaging signs and symptoms of infection and reversal of immunosuppression. Oral formulation of newer azoles with associated activity against Mucorales such as posaconazole and isovuconazole [30] are denoted to have an important role in bridging the initial IV treatment of mucormycosis towards long term treatment. In selected patients, positron emission tomography/computed tomography scan may have a role in securing the distinction between radiographic signs of active disease and inactive scars, therefore enabling treatment discontinuation [9,13].

Management of mucormycosis is dependent on recognizing disease patterns and also on early diagnosis [15,30]. Ideally, every large hospital should possess a facility that can function as a high-level isolation unit. An isolation unit will ensure that the healthcare staff and the hospital are fully equipped to deal with infectious disease outbreaks. Unfortunately, similar facilities do not exist in several hospitals, especially in third world countries. In such a scenario, healthcare setups need to convert their existing general structure towards a distinction of infectious disease component of the facility [27].

The investigational agent VT-1161 is a novel inhibitor of the fungal CYP51 which has *in vitro* activity against Mucorales, [14] including *Rhizopus oryzae* and *Cunninghaemella*. However, this agent is seen to be still under clinical trial phase. Another novel agent hemofungin-inhibits *in vitro* growth of several fungi including *Rhizopus* [19].

Discussion

COVID-19 pandemic has claimed many lives around the world. Systemic glucocorticoids are the drugs that have shown survival benefit in severe COVID-19 infection, nevertheless glucocorticoids can cause increased risk of secondary infections such as mucormycosis. More so the immune dysregulation attributed to the virus and also concurrent use of immunomodulatory drugs [29] such as tocilizumab will further increase the risk of mucormycosis. The overzealous use of systemic glucocorticoids has caused a sudden surge of opportunistic fungal infections like mucormycosis [13]. One alarming observation

is considered to be the development of mucormycosis in patients with COVID-19 with absence of traditional risk factors like diabetes mellitus, transplantation or hematological malignancies warrants the need for judicious use of systemic glucocorticoids. Furthermore, the drugs attribute to targeting immune pathways such as tocilizumab in the absence of clear benefit should be discouraged [29] research now [21].

Bacterial co-infections were dominant in all COVID-19 patients, Streptococcus pneumonia was the most common, followed by *Klebsiella pneumoniae* and *Haemophilus influenzae* [20]. Doctors caring for critically ill COVID-19 patients must be aware of invasive mucormycosis due to the overzealous use of systemic glucocorticoids that can complicate the course of COVID-19.

An associated high degree of clinical suspicion is a must to diagnose mucormycosis [24]. Early diagnosis and timely management are estimated to be necessary to improve outcomes in mucormycosis in patients with COVID-19 infections.

Conclusion

Systemic glucocorticoids are an effective drug and have shown survival benefit in severe COVID-19 infection but their overzealous use can have devastating consequences such as invasive mucormycosis.

Judicious use of systemic glucocorticoids cannot be stressed enough in this paper.

The concurrent use of systemic glucocorticoids and immunomodulatory drugs like tocilizumab could possibly increase the risk of mucormycosis and should be at the back of every clinician's mind who is involved in the treatment of COVID-19 infection.

Mucormycosis is still considered a life-threatening condition and requires a high degree of clinical suspicion for its diagnosis. Early diagnosis has a better outcome for patient survival.

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