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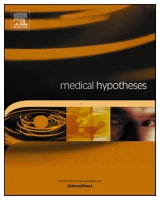
Medical Hypotheses 152 (2021) 110613

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy



Does COVID 19 generate a milieu for propagation of mucormycosis?

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ARTICLE INFO

Keywords:
ACE2
COVID 2019
Mucorales
Mucormycosis
SARS-CoV-2

ABSTRACT

Corona Virus Disease 2019 (COVID 2019), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a dreadful infectious disease which has emerged as one of the most significant medical emergency affecting everyone directly or indirectly. COVID 2019 is a multisystem disease and causes severe immunosuppression. Initially thought to affect mainly the respiratory system, it strikes all vital organ systems and cause defects in cardio-circulatory, respiratory system and gastrointestinal systems to name a few leading to copious biochemical alterations. Reports show there is thromoembolism, raised ferritin levels, lymphocytopenia, thrombocytopenia, lactic acidosis, acute diabetes like state and cytokine storm. Data regarding levels of neutrophils is equivocal. Further there is increased incidence regarding high incidents of mucormycosis in COVID 2019 positive subjects. In the present paper, we identified and correlated the virus mediated biochemical alterations as the potential ideal environment for propagation of mucorales; and thus concentrate on early diagnosis and treatment of mucormycosis in COVID 2019 cases.

Introduction

Rapid emergence from an epidemic outbreak in Wuhan, China to a pandemic [1] Corona Virus Disease 2019 (COVID 19) is possibly one of the biggest medical emergencies we have ever faced. The causative agent of COVID 19 later was identified as novel β-coronavirus, which has been formally named as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. COVID 19 is known to invade the host cell by its high affinity and binding through angiotensin converting enzyme-2 (ACE-2) receptors which is known to highly express on the pulmonary epithelial cells [3,4] explaining its primary association with pneumonia and deterioration of respiratory functions. As of now, it is established that there is multi-system tropism including respiratory system, gastrointestinal tract (GIT), cardiovascular system (CVS), liver, pancreas, nervous system, ocular system and others [4]. This may be explained due to the fact that the ACE-2 receptor is expressed not only in the lungs, but also in abundance in the epithelial cells of esophagus, the pancreas, absorptive enterocytes of the ileum and colon and cardiovascular and renal tissues [5].

Recent papers have reported rhino-orbital, gastrointestinal and pulmonary mucormycosis in COVID 2019 positive subjects [6–9] particularly in health care professionals. Mucormycosis is mainly an opportunistic fungal infection with grave outcome if not diagnosed and treated in time. Populations at a higher risk are mainly immunodeficient viz., patients with uncontrolled diabetes, neutropenic subjects, stem cell transplant (SCT), patients on chemotherapy or immunosuppressive drugs and chronic renal failure [7]. Recently, a surge of mucormycosis was noted in COVID 19 patients as aforementioned, even in health care givers. This paper discusses the relationship between COVID 19 and mucormycosis and a plausible underlying mechanism for such a peculiar link.

The hypothesis

Rather than race, gender or age, the underlying disease is more important in the development of the infection. We hereby hypothesize that the Corona Virus Disease 2019 creates a milieu for propagation of mucorales and subsequent mucormycosis.

Support for hypothesis

COVID 19 is a multi-organ disease involving almost all the vital

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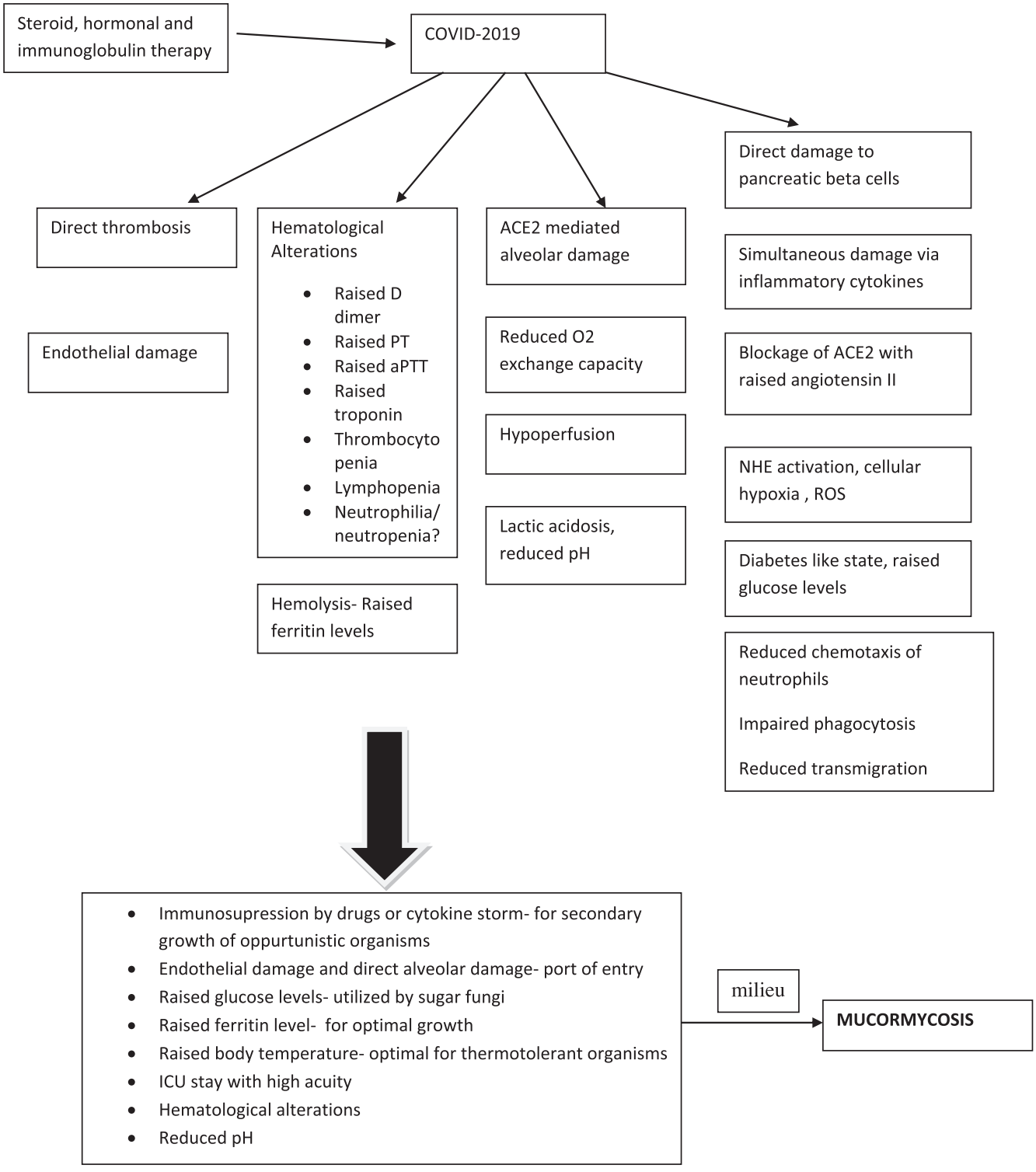
https://doi.org/10.1016/j.mehy.2021.110613
Received 20 January 2021; Received in revised form 11 May 2021; Accepted 24 May 2021
Available online 26 May 2021

Table 1
Showing Schematic representation of biochemical alterations underlying COVID 2019 creating suitable environment for growth and propagation of mucormycosis.



systems of the body. A higher incidence of vascular thrombosis has been reported in COVID-19 patients particularly in intensive care unit (ICU) admissions [10,11]. Kumar A *et al* hypothesized that virus binding mediated dysregulation of ACE-2 signaling in vascular endothelium is responsible for thrombosis in dermal micro-vessels and organ vasculature in COVID-19 [12]. Vascular thrombosis and coagulopathies which may be further complicated by various biochemical alterations seen in COVID 19 viz. raised levels of D dimer, prothombin time (PT), activated partial thromboplastin time (aPTT), troponin T levels particularly in the patients with cardiac injuries. In various retrospective studies, particularly from China, it has been found that D-dimer levels were pronounced in COVID 19 positive cases and the trend correlated with the severity of the disease [13,14]. Based on recent studies, Terpos *et al* opined that in a subgroup of patients DIC-related complications might have led to death independently of ARDS [1]. In hospitalized COVID-19 patients, venous thromboembolism (VTE) risk is an emerging issue seen due to prolonged

immobilization, dehydration, cytokine storm or presence of other cardiovascular risk factors. VTE may further be complicated by virus mediated endothelial cell activation/damage [1]. Management of non ambulatory subjects by hormones and immunoglobulins may lead to an increase in the viscosity of blood. Additionally, vascular endothelial damage could also be the effect of mechanical ventilation, central venous catheterization, and surgeries, all factors may cumulatively lead to a venous state including damage to elastic lamina of blood vessels supporting the propagation of mucorales.

Thrombocytopenia, lymphocytopenia and leucopenia were unequivocally reported in COVID 19 patients [13–16] however, equivocal findings were noted regarding neutrophils count [2,17,18]. Ubiquitous presence of ACE2 on the surface of lymphocytes is the cause of direct injury by SARS-CoV-2 by lysis [19]. Other factors responsible for lymphocytes damage are a)'cytokine storm' promoting apoptosis of lymphocytes by markedly raised levels of interleukins (mainly IL-6, IL-7, IL-2, interferon gamma inducible factor, granulocyte colony stimulating factor), tumor necrosis factor alpha; b) cytokine mediated atrophy of lymphoid tissue, and c) inhibition of lymphocyte proliferation mediated by lactic acidosis [20–24]. Resultant lymphocytopenia thus causes a breach in immune health of COVID 19 positive patients. Lactic acidosis could also be the resultant of is direct damage to the type II alveolar cells causing reduced oxygen exchange capacity, leading to hypoperfusion, finally switching to anaerobic glycolysis and raised lactic acid levels. The end result is marked reduction in the pH. Systemic steroids are administered in COVID 2019 which leads to immuno-suppression leaving the subjects at a higher risk to develop opportunistic infections. Lactic acidosis, reduced pH and immuno-suppression are known risk facts of mucorales.

ACE-2 mediated pancreatic beta cells damage and higher plasma glucose levels were seen in previous studies and have known to cause 'acute diabetes' like state [25,26]. Simultaneous damage to beta cells may be exaggerated via inflammatory cytokines [27]. Glucose regulation may further be affected through the sodium and hydrogen ion exchanger (NHE) and lactate pathways [28]. Virus mediated blockage of ACE-2 leads to raised levels of angiotensin II which also activates NHE causing cellular hypoxia and generation of reactive oxygen species (ROS) [4]. Endothelial damage, insulin resistance and raised glucose levels could be the end result. Diabetes like state may also reduce the chemotactic activity, impaired phagocytotic efficiency and transmigration of neutrophils through endothelial cells. Another finding of particular interest is raised ferritin levels in COVID 2019 patients due to increased hemolysis [16,29] a source of nutrition for mucorales. Acidosis further leads to an elevated level of serum iron which is a good source of nutrition for mucorales.

Thus, COVID 19 causes systemic manifestations and the consequences create a milieu for mucorales, which is schematically shown in Table 1.

Discussion and conclusion

Mucormycosis is an uncommon but lethal fungal disease. The causative opportunistic fungus bears unique properties. They are aseptate and fast growers. *Rhizopus oryzae* is known to grow at the rate of 3 mm/h at 36 °C which is much higher as compared to other fungi [30] and thus could be the first to grow when the optimal conditions are provided as in the present scenario, the COVID-2019. These are thermotolerant i.e., they are efficiently able to survive at temperature above 37 °C, thus, they can survive the raised body temperature seen in most infection diseases including COVID-2019. Further, the known risk factors for mucormycosis are provided by SARS-CoV-2 infection, including raised ferritin, immunosuppressed condition, diabetes like state, and endothelial damage. The mucorales grow fast and utilize simple carbohydrates. Diabetes like state with raised glucose levels may act as a good source of nutrition for the organism. Garrett's theory of succession for sugar decomposition by fungi may be applicable, the fungus act in sequence. Initial are the sugar fungi succeeded by cellulolytic, ligninolytic and finally the secondary sugar fungi [31]. Clinical signs such as nasal obstruction, periorbital/ buccal swelling, and any degree of blackish discoloration should alarm the clinician for emergency biopsy and prompt treatment.

In conclusion, COVID-19 hit the globe in ways which were not foreseen by anyone and brought a plethora of complications along with it. On top of instigating pulmonary collapse and other systemic complications, SARS-COV2 causes an array of biochemical reactions in the body that lead to immunosuppression and increased proclivity for opportunistic infections especially mucormycosis. In the present paper, we propose a novel hypothesis for the occurrence of mucormycosis with scientific evidence that explains dysregulation of ACE-2 expression not only in lungs but also in bounty in esophagus, pancreas, ileum, colon, cardiovascular and renal tissues and how this leads to a cascade of pathways that craft a suitable microenvironment for opportunistic infections like mucormycosis. With this proposition based on the incidental findings in the literature, we feign that COVID affected individuals are at a higher than normal risk of contracting opportunistic infections especially mucormycosis and should be taken into account while devising the treatment plan.

Funding

There was no funding involved with this project.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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