(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 4, Issue 5, Page No: 704-710
September-October 2021

IJMSCR

An Insight into The Unholy Trinity of Covid-19 Associated Mucormycosis and Diabetes Mellitus

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Background: Mucormycosis is an angioinvasive disease caused by the Rhizopus particularly affecting the immunocompromised individuals. Giant cell invasion, thrombosis and eosinophilic necrosis are the pathological hallmarks noted, which requires an antifungal therapy and surgical intervention. Aim: To understand the factors and mechanisms involved in the pathophysiology of Covid-19 Associated Mucormycosis and Diabetes Mellitus. Methods: The Pubmed and Google scholars were searched for studies, case reports and reviews with titles including mucormycosis, Covid-19 Associated Mucormycosis and Diabetes Mellitus and black fungus and its pathophysiology published until April 2021. Conclusion: The intersection of this trinity appears to be the predictor of diabetic emergencies which is aggravated by dehydration, hyperglycemia and acidosis creating a perfect storm for the penetration of Mucorales.All efforts should be made to promote the judicious use of corticosteroids and antifungals along with the proper maintenance of blood sugar levels in order to alleviate the burden of this fatal trinity.

Keywords: Mucormycosis, Covid-19, Diabetes Mellitus, Trinity

INTRODUCTION

Severe Acute Respiratory Syndrome Virus 2 (SARS-COV-2) accounting for over 2.8 million deaths per day worldwide, has been linked with an array of fungal infections.[1] Of late, several cases are being reported on Covid-19 Associated Mucormycosis (CAM).[2] In addition, Diabetes Mellitus (DM) is a focal point in accelerating CAM.[3]

Mucormycosis (MCR) is an angioinvasive disease caused by the mold fungi Rhizopus, particularly affecting the immunocompromised individuals. [4,5] Giant cell invasion, thrombosis and eosinophilic necrosis of the underlying tissue are the pathological hallmarks noted in CAM.[6,7] We aim to postulate a mechanistic description responsible for the deadly trinity of CAM and DM.

METHODS:

For this literature review, the Pubmed and Google scholars were searched for related titles published until April 2021. Terms used to identify and retrieve the relevant data include: MCR, CAM, DM and MCR, black fungus and its pathophysiology. Also, references noted in b

the retrieved articles were also accessed and reviewed. Studies, case reports and reviews that explored the novel advances in the mechanisms behind

the intersection of this trinity and its factors are reviewed and discussed in this article.

RESULTS:

Overview of the putative factors

Although, the causal link between this trinity remains unearthed, there are triggers aplenty found in its mechanism.

(i) Presence of DM with or without DKA

Increases the contraction of CAM and may precipitate DKA as ketonemia and ketoacidosis even in the absence of DM. Glucocorticoids-induced immune suppression and hyperglycemia decreases both the first and the second line defense mechanism paving a vulnerable path to MCR.[8]

(ii) Rampant use of immunity boosters

The rampant use of multivitamins containing iron and zinc as immunity boosters elevate the free-iron level via glycosylation of ferritin and transferrin, which decreases the binding of iron. Moreover, concomitant acidosis and increased cytokine levels also declines the ability of transferrin to chelate iron; enhancing the development of mucor. Further, the expression of glucose-regulator protein 78(GRP-78) of endothelium and mucorales adhesin spore coating homolog (Cot H) protein will enable angioinvasion, hematogenous dissemination and necrosis of the tissue.[9]

(iii)Irrational use of antifungals and antibiotics

Excessive antifungal (Voriconazole) usage as prophylaxis to prevent the secondary or opportunistic fungal infection in covid -19 affected individuals due to the reduction in CD-4+, CD-8+ and T-cells may reduce the lymphocytes which can be responsible for breakthrough MCR. CD-4+ and CD-8+ are mucorale-specific T-cells that produce cytokines such as IL-4, IL-10, IL-17 and IFN- γ. [10]

Likewise, the irrational use of broad-spectrum antibiotics in covid-19 patients can also predispose to acquire MCR.

(iv)Role of the hospital environment and oxygen humidifiers

Pathogens can persist in headers and bed bars, taps, bed side table and other hospital surfaces for several months causing the risk of infections. Furthermore, in the absence of disposable oxygen humidifiers, potential nosocomial pathogens can reach deep into the lungs immediately after inhalation via the generation of aerosol particles.[11]

(v) Others

Other risk factors for invasive MCR includes malnutrition, intravenous (IV) drug use, long term neutropenia, solid organ or stem cell transplantation and severe skin damages such as surgical suture site infection and burns. Additionally, the administration of non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressants, monoclonal antibody (Ab) and SARS-COV-2 may also lead to MCR.[12]

Even though, neutropenic patients accelerate the risk for MCR; acquired immune deficiency syndrome (AIDS) patients are not placed in the risk category. Hence, exhibits the critical role of neutrophils in hindering the fungal spore proliferation.[13]

Potential Virulent factors

Rhizopus species possess an active ketone reducatase system that favors its growth in glucose-rich and acidic medium as seen in ketoacidotic states along with the ability to secrete various lytic enzymes like aspartic proteinases.[14]

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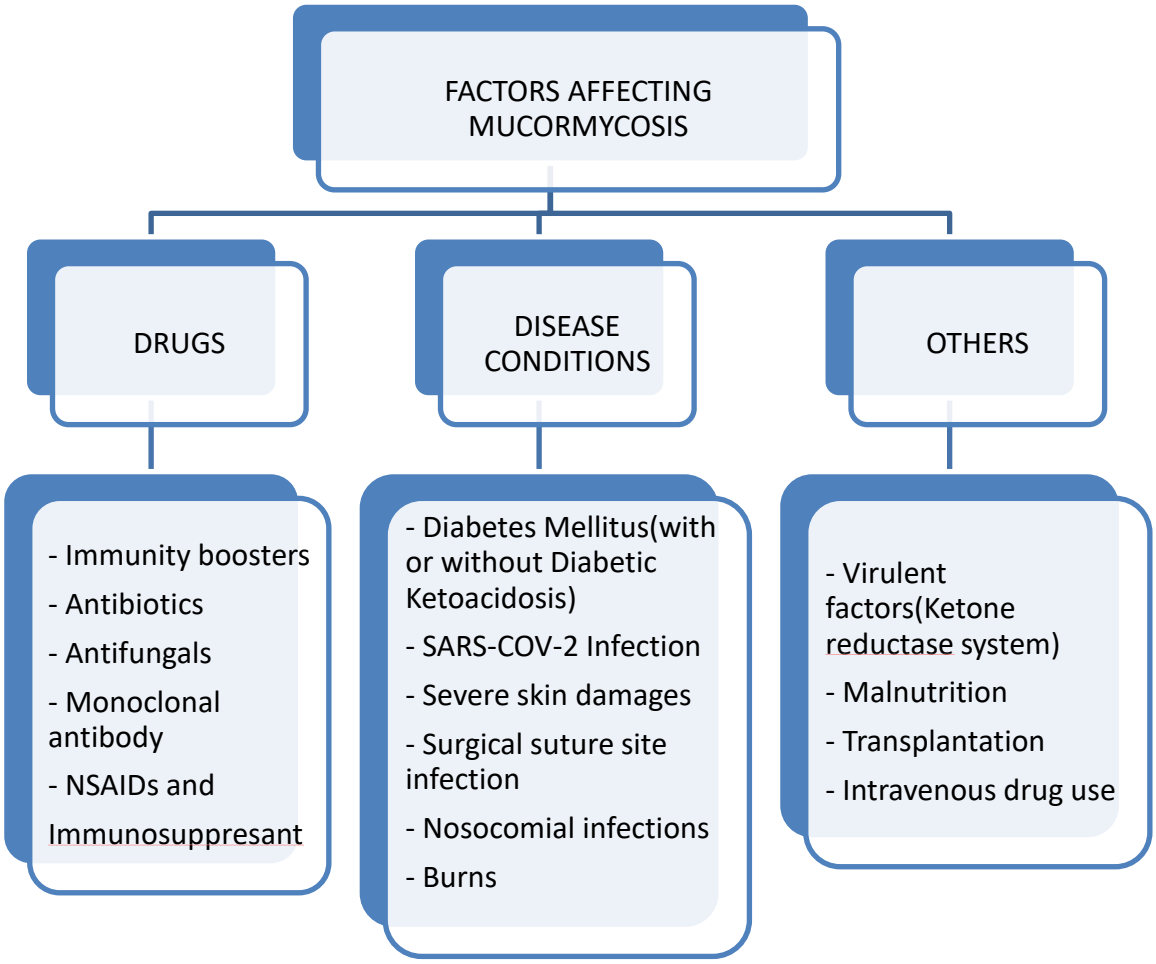

Figure: 1

Factors affecting Mucormycosis

Pathophysiology

Considering the reports on immunity, humoral immunity offers greater protection against fungal infections than cellular immunity. The latter is associated with TH1-type that offers primary protection and viral infection via IFN- gamma secretion. A delayed immune activity (cellular) and a poor immune surveillance were reported during the chronic inflammatory conditions including cancer and DM. Therefore, novel SARS-COV-2 infection not only impairs the cellular but also the humoral immunity upsurging the overall risk.[15]

Mucosis enter the blood vessel triggering thrombosis to cause ischemic cascade resulting in self-induced tissue damage. Characteristics of Mucorales that aggravate the disease the state includes: innate thermotolerance, rapid growth, immune defence, down regulation of host-defence genes, tissue repair, ability to obtain iron from host, inhibition of IFY- γ expression and inherent resistance to most of the available antifungal therapy. They are capable to downregulate several hosts defence mechanisms and have identified specific receptors to attach themselves to the endothelium. This facilitates endocytosis followed by angioinvasion by various steps such as inoculation of spores into host tissue, evading phagocytosis, germination to hyphae, accelerating the growth and virulence, endothelial attachment, endocytosis and endothelial damage, thrombosis and tissue necrosis, heterogeneous dissemination, initiation of systematic diseases and multi-organ involvement.

The initial two steps can directly result in chemotaxis of neutrophils by exerting their oxidative cytotoxic effect to cause direct damage by producing TN-α, IFN-γ and IL-1b. These cytokines activate and recruit other immune cells as any delay in this process destructs the tissue and disseminates the disease. Platelet aggregation and clot formation can prevent the

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hematogenous fungal dissemination via the expression of CD-154 and platelet toll-like receptors that facilitates platelet binding and cellular activation. This directly activates the intercellular adhesion mol-1 and vascular cell adhesion mol-2 pathways inducing the binding and maturation of dendritic cells. Therefore, the delay in IFN-γ response prolongs the hyperinflammatory state, thereby reducing the CD4+ and CD8+ cell counts. This exacerbates the cytokine storm in diabetics.[10] Covid infection will induce damage to pancreatic islets causing acute DM and DKA resulting in the diabetogenic state in covid-19 via the cytokine storm and the high expression of angiotensin converting enzyme 2 inhibitors (ACE-2-I) in pancreatic islets accelerating the insulin resistance. Moreover, steroid usage can also exacerbate the glucose homeostasis causing DM in MCR.[16]

When SARS-COV-2 enters and binds to the ACE-2 receptors, they cause direct injury to beta cells leading to insulin deficiency. It also down regulates the ACE-2 impeding the insulin secretion by paving way for unopposed angiotensin-2. This stimulates the secretion of aldosterone, hence the risk for hypokalemia. In uncontrolled sugar disease, fungal proliferation takes place declining the chemotaxis and the phagocytic efficiency. If the condition turns out to be DKA, then the probability of MCR doubles as the Rhizopus oryzae produces keto reductase which allows them to utilize the ketone bodies from the affected individual.

Later, it disrupts transferrin from being bound to iron by eliminating the cardinal host defense processes; thereby contributing to flourish the fungal development.[17] As a result, reactive oxygen species (ROS) may generate elevating the ferritin and intracellular iron level to cause hyper-ferritenemic syndrome via the iron overload. In the presence of ferrioxamine, mucorales induces the ferrioxamine receptors like Fob1 and Fob2 facilitating the iron uptake only from ferrioxamine.

On the other hand, the iron chelator deferoxamine has two mechanisms to release iron intracellularly. In the initial process, it strips ferric iron from transferrin and attaches on the fungal mold to transport iron intercellularly. The second mechanism involves high-affinity iron permease (FTR1) in Rhizopus that act as a cytoplasmic membrane permease to facilitate intracellular heme uptake through degradation with heme oxygenase. Studies also elicit the role of GRP-78 in enhancing the fungal endocytosis. It is a heat shock protein found in the endothelial surface of the host and acts as a receptor that mediates the penetration which results in endothelial dysfunction. The Cot H proteins found exclusively on mucorale surface binds to it and promotes fungal adhesion, angioinvasion and dissemination.[18]

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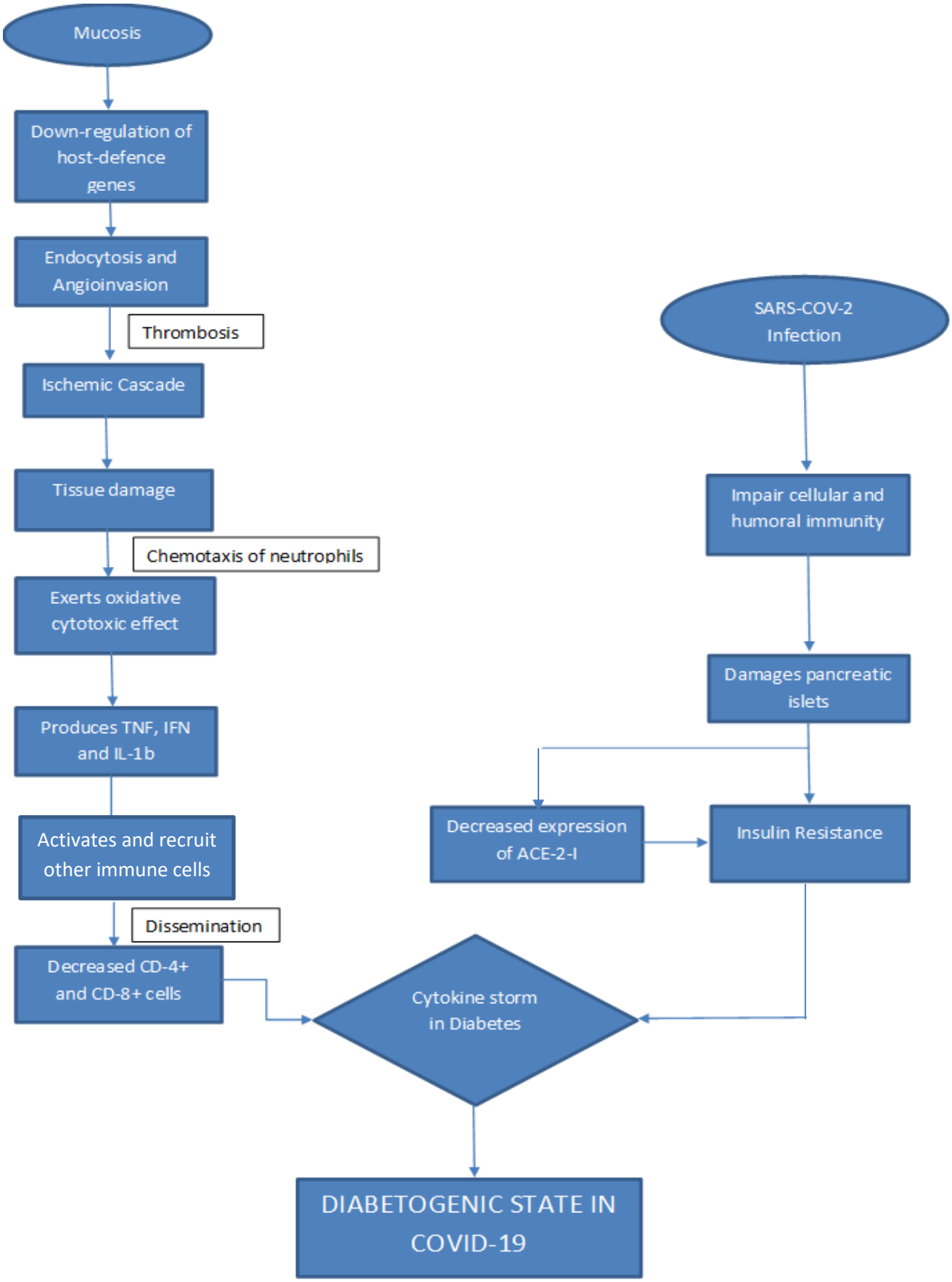

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Management

Emperical broad spectrum antifungals were used to manage the crisis of MCR. Primary therapy with liposomal Amphotericin B 5mg/kg/day diluted in 5% or 10% dextrose till a favourable outcome is obtained followed by oral Posaconazole 300mg/day is the treatment of choice.

If no signs of improvement, then it is advised to double the dose of Amphotericin B. Also, Aspirin can be administered when the patient is diagnosed with acute cerebral infarct.[19] In DKA, cautious administration of IV fluids, potassium correction and insulin therapy are provided to the patient.[20]

CONCLUSION

In the setting of the rampaging pandemic, MCR appears to be the intersection of covid infection and uncontrolled DM. Therefore, all efforts should be made to promote the judicious use of corticosteroids and antifungals along with the proper maintenance of blood sugar levels in order to alleviate the burden of this fatal trinity. The possible potential virulence factors and interventions to complement the existing therapeutic strategies will have a profound impact for individuals affected with the devastating infection.

ACKNOWLEDGEMENT

We express our gratitude to the Department of Pharmacy Practice, JKK Nattraja College of Pharmacy.

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