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EC CLINICAL AND MEDICAL CASE REPORTS

Research Article

SARS-CoV-2 Associated Mucormycosis: Review of Epidemiology and Aetiology

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Received: August 16, 2021; **Published:** September 24, 2021

Abstract

Purpose: Mucormycosis, is a clinical condition characterized by infarction and necrosis of host tissues from invasion of the vasculature by hyphae. Even though mucormycosis was largely considered a rare condition, the current SARS-CoV-2 pandemic is coinciding with surge of SARS-CoV-2 associated mucormycosis. The aim of this paper is thus to provide a scientific overview of the epidemiology, aetiology and pathogenesis of SARS-CoV-2 associated mucormycosis.

Methods: Comprehensive search of online databases was done. Available evidence such as case reports/case series, qualitative and quantitative epidemiological studies as well as other relevant reference lists were systematically assessed.

Results: All eligible published articles and case reports were analysed. Accordingly, information gathered was categorized and discussed into three domains: patients characteristic in terms of sex and age, history and comorbidities and clinical manifestations.

Conclusion: Healthcare professionals are recommended to be cautious in management of SARS-CoV-2 with low dose steroids as well as be strict in controlling blood glycaemic level in diabetic patients and those who are at risk of developing diabetes. Healthcare professionals working in the designated SARS-CoV-2 scenery should be vigilant for the incidence of invasive SARS-CoV-2 associated mucormycosis for early diagnosis.

Keywords: *SARS-CoV-2 Associated Mucormycosis; COVID-19 Associated Mucormycosis; Mucormycosis; COVID-19; SARS-Cov-2*

Abbreviations

DM: Diabetes Mellitus; DKA: Diabetic Ketoacidosis; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus disease-2019; GRP78: Glucose Regulated Protein with the Molecular Weight of 78 kDa; CotH: Coating Homolog Protein

Introduction

Mucormycosis (formerly known as zygomycosis) is frequently a life-threatening infection which is predominantly observed in susceptible individuals, notably immunocompromised patients and those with poorly controlled diabetes, especially ketoacidosis [1]. This rare but at the same time serious angio-invasive infection is caused by a group of fungi called *mucormycetes* [2]. These organisms are ubiquitous in nature and they are commonly found in vegetation and in soil and their rapid growth as well as their ability to release large numbers of spores has made mucormycosis airborne [3]. The paranasal sinuses and the nasopharynx are the primary targets of the spores leading to subsequent raid of the orbit and intracranial cavity [4] as well as infections of the lungs and other parts of the body [5]. According to CDCD [6], rapid onset of tissue necrosis with or without fever which result in invasion of blood vessels and subsequent thrombosis are labelled as a classic clinical sign of this condition.

Irrespective of the ample exposure to these fungi in our everyday activities, mucormycosis has been a rare infection [7]. Worldwide, the incidence of mucormycosis is hard to estimate as it is a rare and usually a not reportable condition [8] but this phenomenon recently took a sudden turn with the emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

The incidence of SARS-CoV-2 associated mucormycosis is difficult to estimate as the risk varies widely in different populations. According to a systematic review done by *Awadhesh Kumar Singh et al.* [9], cases of SARS-CoV-2 associated mucormycosis, amongst people with SARS-CoV-2 and those who 've recovered from SARS-CoV-2, are commonly being reported from India. The country has being reporting thousands of cases [10] in stark contrast with the 19 cases that have been reported from the rest of the world so far [9]. Cases have been described in Europe, Americas, and Asia [9,11] but to the best of the authors' knowledge, there are no reports from Africa and Australia. The prevalence of mucormycosis in India, which is 70 times higher than the overall figure for the rest of the world, before the SARS-CoV-2 outbreak, can explain the surge in the incidence of SARS-CoV-2 associated mucormycosis [12].

Currently, there are many published studies and case reports that explore the association of mucormycosis with SARS-CoV-2.

Aim of the Study

The aim of this study however, is to rigorously analyse epidemiological data as well as determine the aetiology of this disease association through literature evaluation.

Methods

This paper is a narrative review of the published literature on the epidemiology and aetiology of SARS-CoV-2 contributing to the development of mucormycosis.

Search strategy

To evaluate all available published information concerning SARS-CoV-2 associated mucormycosis, a literature search was made across the following platforms, that is, Google Scholar, Web of Sciences, Opengrey, PubMed/Medline, Wiley online library and Sciences direct. For comprehensive data extraction 'COVID-19' OR 'SARS-CoV-2' AND 'Mucormycosis' OR 'Rhino-orbital mucormycosis' OR 'Mucormycetes' OR 'Zygomycosis' were used as search terms with suitable [Boolean] operators in titles and/or abstracts of articles. In order not to miss, relevant articles from the bibliographical list of available studies that meet the eligibility criteria as well as cited references of relevant reviews were retrieved and screened for potentially eligible articles.

All articles that directly associate mucormycosis with SARS-CoV-2 were included in this study. While studies that have other possible alternative explanations or patients having fungal infections other than mucormycosis were excluded.

Data extraction

Retrieved papers titles and/or abstracts were independently scanned to exclude duplicate studies and studies that fail to meet the aforementioned eligibility criteria. Eligible studies were further assessed in full-text in order to assess the totality of evidence available in the medical literature, case reports/case series, epidemiological and other relevant data. For further assessment, efforts were made to find relevant information about patients' number, characteristic, presence of comorbidities and history and severity of SARS-CoV-2. The time lag between SARS-CoV-2 to a diagnosis of mucormycosis, clinical manifestation of mucormycosis and isolated fungal species were evaluated. Treatment modalities for SARS-CoV-2 with immunomodulating drugs and the utilization of corticosteroids were also reviewed. Finally, reported patient outcomes were analysed.

Result

Cases of SARS-CoV-2 associated mucormycosis are rigorously being reported from different parts of the world. According to Martin Hoenigl., *et al.* [11], more of the cases are being reported from India while few cases are reported from different centers in USA, Pakistan, France, Iran, Mexico, and Russia. There are also unpublished single case reports in Austria, Bangladesh, Brazil, Chile, Czech Republic, Germany, Italy, Kuwait, Lebanon, Turkey, and the United Kingdom. As of June 2021, there are also three SARS-CoV-2 patients in Oman [10], diagnosed with this condition.

Prevalence of SARS-CoV-2 associated mucormycosis is disproportionally high in males when compared with females [9,11,13-16]. Also, older population is predominantly affected by this condition with median age ranging from 52 - 55 years. Table 1 summarizes the characteristics of the patients. Diabetes Mellitus (DM) and Diabetic Ketoacidosis (DKA) were documented as common predisposing risk factors other than SARS-CoV-2. Rimesh Pal., *et al.* in their systematic review of 99 cases, reported that DM (85%) and glucocorticoid (85%) as the most common risk factors. Correspondingly, Martin Hoenigl*., et al.* [11], described overenthusiastic use of corticosteroid in the management of SARS-CoV-2 in 75% case with majority of the patients (more than 80%) having pre-existing DM; and DKA in 40.9% of the cases. All-cause mortality of SARS-CoV-2 associated mucormycosis was identified as 48.8%, 30.7% and 34% according to Martin Hoenigl*., et al.* [11], Awadhesh Kumar., *et al.* [9], and Rimesh Pal*., et al.* [13] respectively.

Author	Study design	SARS – CoV-2 associated mucormycosis patients (n)	Sex/Age	Comorbidities	Time lag between SARS – CoV-2 to mucormycosis diagnosis	Treatment modalities for SARS – CoV-2	Clinical manifestations of SARS – CoV-2 associated mucormycosis	Patient outcome
Rimesh Pal., *et al*. [13], June, 2021	Systematic review	99	Male 78%	DM (85%)	15 days	Glucocorticoid (85%)	Rhino-orbital mucormycosis (42%), Rhino-orbito-cerebral mucormycosis (24%) Pulmonary mucormycosis (10%)	Mortality rate (34%)
Awadhesh Kumar., *et al*. [9], May 2021 ref	Systematic review	101	Males 78.9%	DM (80%), DKA (14.9%)		Corticosteroid (76.3%)	Nose and sinuses (88.9%), Rhino-orbital (56.7%)	Mortality rate (30.7%)
Farzad., *et al*. [14], June 2021	Descriptive multicentre study	15	Male 66%, Median age 52 yrs	DM (86%)	Median of seven days, (range: 1–37 days)	Intravenous corticosteroid therapy (46.6%)		Mortality rate (47%)
Martin Hoenigl., *et al*. [11], May 2021	Analysis of cases	80	Male 77.5%Median age 55yrs	DM (82.5%), DKA (40.9%), Hypertension (18.8%), Chronic kidney diseases (6.3%), Hematological malignancies (6.3%), Elevated HbA1c, Renal disease,	Median of ten days, (range: 0-90 days)	Corticosteroids (75%), Systemic corticosteroids prior to diagnosis of mucormycosis (80%), Tocilizumab (n=6)	Rhino-orbital cerebral mucormycosis (73.75), Pulmonary disease (22.5%),	Mortality rate (48.8%) Loss of vision (46%) Surgical resection (n=46)

Atul Patel., *et al*. [16], September 2021	Multi-center retro-spective study	187	Male 80.2% Mean56.9 yrs	DM (20.9%), Hematologic malignancy, Solid organ transplan-tation	18 (IQR 11–27 days)	Glucocorti-coid Tocilizumab (2.7%)	Rhino-orbital region (58.2%), Rhino-orbital-cerebral, Pulmo-nary	Mortal-ity rate (44%)
Teny M. John., *et al*. [15], April 2021	Lit-erature review	43	Male 83%, Media55 yrs	DM (n=33), DKA (n=8) Renal failure (n=7)	Mean of 22 days (SD of 24)	Systemic cor-ticosteroids (n=36), Tocilizumab	Rhino-orbital-cerebral (n=11), Rhino-orbital (n=17), Rhino-cerebral (n=3), Sinusitis (n=3), Pneumo-nia (n=3)	Mortal-ity rate (49%)
Anagha Rajeev Joshi., *et al*. [18], June 2021	Descrip-tive retro-spective study	25	Male 64%, Mean 55.2 yrs	DM (88%), HIV (n=2)	-	Corticoste-roids (100%), Immunomod-ulating drugs (n=6)	Rhino-orbito-cerebral mucormy-cosis	Mortal-ity rate (56%), Surgical debride-ment (40%)
DM: Diabe-tes Mel-litus; DKA: Diabetic Ketoaci-dosis								

Table 1: *Published studies of SARS-CoV-2 associated mucormycosis as of July 2020.*

Time interval between diagnosis of SARS-CoV-2 and first manifestation of mucormycosis was marked in many studies. Mucormycosis was recognized at the time of SARS-CoV-2 diagnosis in some cases while in others it took as long as 90 days [11]. *Rhizopus* species were among the most commonly isolated species [17] leading to different clinical manifestations. Rhino-orbital mucormycosis was consistently reported as the most common manifestation, followed by rhino-orbito-cerebral mucormycosis [13,15]. Few cases of pulmonary and gastrointestinal mucormycosis were also seen [9,13].

Discussion

The numerous factors involved in nature of SARS-CoV-2 associated mucormycosis make the diagnosis and management of this condition very challenging. Nevertheless, the presence of DM with or without DKA, massive steroid use as well as SARS-CoV-2 itself are some of the major risk factors to the development of this life threating fungal infection. SARS-CoV-2, an infective inflammatory disease, is pathophysiologically involved in the marked reduction of CD4 and CD8 levels, endothelial damage, altered iron metabolism and increased iron overload, among others, increased level of cytokines especially interleukin-6 [19]. This heightened inflammatory state involving a cytokine storm and hyper ferritinemia [20] is a predisposition to opportunistic fungal infections. Moreover, the iron overload in the body may lead to death of pancreatic beta cells and insulin resistance by increasing oxidative stress [21] instigating incidence of type 2 diabetes mellitus [22]. Availability of free unbound iron in our system is of particular interest for fungal species with high affinity for iron. Like all fungi with specific uptake mechanisms to sequester iron, siderophores, mucormycosis grow abundantly in iron-rich media [23].

Increased plasma glucose level in SARS-CoV-2 patients has been pronounced among diabetes, pre-diabetes, and/or obese patients [24]. The hyperglycemic state coupled with increased level of iron and ketone bodies which is a hallmark feature of DKA has resulted in overexpression of a mammalian Glucose Regulated Protein with the molecular weight of 78 kDa (GRP78) receptors on the host cell surface [25]. According to animal studies done on mice's, this host receptor that mediates invasion and damage of human endothelial cells is highly expressed in sinus, lungs, and brain of mice with DKA when compared with normal mice [26]. Also, a case-control study revealed that serum level of GRP78 was significantly higher in SARS-CoV-2 (+) patients when compared with SARS-CoV-2 (−) pneumonia and the control group [27].

According to recent findings, *Rhizopus* species have the ability to interacts with GRP78 on nasal epithelial cells via its spore coat protein homologs (CotH3) to invade and damage the nasal epithelial cells potentially leading to frequently lethal rhinoorbital/cerebral mucormycosis [28]. As a result of this, SARS-CoV-2 patients with the above-mentioned potential risks are uniquely susceptible to mucormycosis. Also, patients with compromised phagocytes/neutrophils either in number or function are at higher risk when compared to individuals with deficiency with certain types of leukocytes, especially T lymphocytes, as they are especially involved in the inhibition of fungal spore proliferation [29].

Steroids are used in the management of severe and critically ill SARS-CoV-2 patients. They counteract the body's immune system and reduce inflammation in the lungs as well as serve to alleviate multisystem organ dysfunction [30,31]. The reduced immunity due to corticosteroid intake when coupled with uncontrolled blood sugar levels and the possible subsequent DKA precipitation, all provide a fertile media for the germination of mucor spores [16,32]. Moreover, steroid use reduces the phagocytic activity of WBC, making patients suffering from the likes of diabetes exceptionally susceptible to mucormycosis [9]. It is of interest that elevated blood glucose level, low pH or acidic media, availability of free unbound iron, impairment in phagocytic activity of WBC, heightened expression of GRP-78 of endothelium cells along with fungal ligand spore CotH protein, leads to angio-invasion and tissue necrosis.

Conclusion and Recommendations

In conclusion, the plausible emergence of SARS-CoV-2 associated mucormycosis in immunocompromised patients, the lethal nature of the disease, the specificity and consistency of the association observed worldwide, and the suggested possible biological mechanism, makes this condition a critical medical emergency in this pandemic. In addition, the underlying predisposing medical conditions of SARS-CoV-2 affected person, nature of fungus, and affected site of the body highly contribute to the overall complications of mucormycosis. As a result of this, mucormycosis (even with aggressive treatment) has a very high mortality rate and poor prognosis. It is, however, important to note that this presented evidence is based on the currently available information in the medical literature; thus, conclusions and recommendations may change with more updated evidences and studies in the ongoing pandemic.

All global health systems should be aware of this fungal co-infection and should increase clinical suspicion of mucormycosis in SARS-CoV-2 patients to minimize its public health impact. Healthcare professionals should adhere to recommended low dose and short duration of steroid use coupled with strict monitoring and control of blood glycaemic level in diabetic patients. Efforts should be made to bring rapid corrections of the underlying predisposing conditions and facilitate an early diagnosis and initiation of appropriate treatment of mucormycosis. Finally, as this viral breakthrough, SARS-CoV-2, is inevitable, we recommend healthcare professionals to be vigilant to any fungal infections that are bound to arise leveraging this clinical condition.

Ethics Approval and Consent for Publication

Not applicable.

Authors' Contribution

Both authors made a significant contribution throughout the review process to write up of the manuscript. Both authors did the literature search and analysis of literature. Authors gave final approval of the last version to be published.

Availability of Data

Data used for this report are all available on this article.

Funding Support

No funding was used to carry out this investigation.

Conflict of Interest

The authors declare that they have no competing interests.

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Volume 4 Issue 10 October 2021