

Diabetes Mellitus and Glucocorticoid Use As Risk Factors for COVID-19 Associated Mucormycosis

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ABSTRACT

Background: A surge of cases of Coronavirus Disease 2019 (COVID-19)-Associated Mucormycosis (CAM) was recently observed.

Objective: To determine the contribution of diabetes and glucocorticoid therapy in predisposing to CAM.

Methods: Pubmed search until July 2nd, 2021. Search terms included mucormycosis, diabetes, glucocorticoids, corticosteroids, coronavirus disease 2019, mortality. Randomized trials, case series, retrospective, pre-print studies, meta-analysis, professional guidelines are reviewed. Pertinent *in vitro* and animal studies are also included.

Results: Diabetes mellitus was reported in 78-85% of cases of CAM worldwide, with the highest rates present in India. Diabetic Ketoacidosis (DKA) was observed in 3.5-41% of cases of CAM. Glucocorticoid therapy emerged as another predisposing factor occurring in 85% of cases of CAM. Injudicious use of glucocorticoids may be a contributing factor in a substantial proportion of subjects with CAM. Majority of patients develop symptoms of CAM between day 10 and 15 from the diagnosis of COVID-19. However, some cases of CAM may present up to 3 months after COVID-19 or following recovery from COVID-19. Mortality rates of CAM overall ranges from 34-48%. Surgical debridement may be associated with improved survival.

Conclusions: High index of suspicion for CAM should be present in patients with diabetes and those receiving corticosteroids. Effective glycemic control and judicious use of glucocorticoids should be implemented to decrease incidence of CAM.

Keywords:

Mucormycosis, COVID-19, Diabetes, Glucocorticoids, Corticosteroids, Dexamethasone, Mortality

Introduction

Shortly after the beginning of COVID-19, a surge of cases of CAM was observed worldwide. The largest number of cases of CAM was reported in a retrospective Indian study called Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC). COSMIC included 2,826 patients with rhino-orbital-cerebral mucormycosis (ROCM) who were managed by ophthalmologists from January 1st 2020 to May 26, 2021 in 22 Indian states. The median (range) age was 51 (12-88) years. In the COSMIC, systemic use of corticosteroids and diabetes emerged as the 2 most common predisposing factors for CAM, being present in 87% and 78% of patients, respectively [1]. The largest international series of patients with CAM was published by Pal et al. [2], who described 99 cases until May 14, 2021. Again, most of these cases were reported from India (72%), followed by the USA (10%), and Egypt (6%). Indeed, in pre-COVID-19 era, it was already known that the highest prevalence of mucormycosis was present in India, close to 0.14 cases per 1000 population, a prevalence that is approximately 80 times that in developed countries [3]. In all reported series of CAM,

there was a clear male preponderance. Thus, overall, 71-78% of patients with CAM were males [1,2,4]. The commonest causative species of mucormycosis was *Rhizopus* species (85% of isolated species) [2].

Pathogenesis of Mucormycosis and Its Relevance to COVID-19, Hyperglycemia and Diabetic Ketoacidosis

The main target of Mucorales, the fungus causing mucormycosis, is endothelial cells lining blood vessels [5]. Thus, this fungus invades endothelial cells after binding to a receptor located at the surface of endothelial cells called: glucose-related protein 78 (GRP78) [6]. Mucorales adhere to GRP78 receptors by expressing a spore Coat Homolog (CotH) protein [7]. Binding of the fungus CotH protein to the host receptor GRP78 leads to endocytosis of the organism and subsequent spread in the human body [5]. Free iron is essential for the survival of mucormycosis [8]. This is supported by the observation that iron starvation *in vitro* causes apoptosis of *Rhizopus oryzae* [9].

Importantly, COVID-19 infection is characterized by release of ferritin in the circulation as inflammatory marker [10]. As a result, ferritin loses part of its inner iron content leading to increased levels of free serum iron [10]. In addition, hyperglycemia may increase free iron by causing glycosylation of transferrin and ferritin thereby reduce iron binding [11]. Moreover, acidotic

states, such as DKA, cause release of iron from iron-binding proteins such as transferrin [12]. Collectively, COVID-19 infection, hyperglycemia and DKA may therefore potentiate fungus virulence by increasing free iron availability. The elegant *in vitro* and *in vivo* studies in mice by the group of Gebrenmarian et al. [5], have clarified why patients with DKA are particularly predisposed to mucormycosis by recording the following observations. First, elevated albeit physiologic concentrations of glucose, free iron, and ketoacids, as prevailing in DKA, enhance expression of both the fungus ligand CotH and its receptor GRP78 [5]. Second, the enhanced expression of GRP78 and CotH were mainly driven by beta-hydroxy butyrate (representative of ketone bodies in DKA) and iron and to a lesser extent by glucose. Third, increased expressions of CotH and GRP78 were specific to beta-hydroxy butyrate since acidosis caused by lactic acid or HCL did not have any effect [5]. Fourth, beta-hydroxy butyrate abolished the ability of human neutrophils to kill the *Rhizopus* in cell culture [5]. Meanwhile, correction of acidosis by sodium bicarbonate completely reversed the inhibitory effect of beta-hydroxy butyrate on neutrophil function, and decreased fungus virulence and mortality in mice [5].

Diabetes Mellitus As a Risk Factor for CAM

Diabetes mellitus was present in 78-85% of cases of CAM [1,2,4]. Approximately 90% of CAM cases occurred in type 2 diabetes and 10% in type 1 diabetes [4]. These statistics are expected since diabetes was historically the most frequent underlying disease in mucormycosis in general. For instance, in the pre-COVID-19 era, the meta-analysis of Jeong et al. [13], showed that diabetes was the most common condition associated with mucormycosis occurring 40% of cases (340 of 851). Furthermore, diabetes emerged as independent risk factor for RCOM, odds ratio 2.49 (95% CI 1.77-3.54; $P < 0.001$) [13]. The implication of diabetes in mucormycosis is particularly evident in low and middle-income countries [3,13]. Thus, in the international series reported by Hoengl et al. [4], diabetes was a more predominant risk factor for CAM in cases reported from India (40/42, 95.2%). Most patients had uncontrolled diabetes with a median value of hemoglobin A1c (HbA1c) of 9.6%. (range 4.8 to 17.1%) [1]. The proportions of CAM patients having DKA varies widely being 3.5% in the Indian study by Sen et al. [1], 29% in the series of Pal et al. [2], and highest 41% in the global series reported by of Hoengl et al. [4]. This wide variation may be attributed in part to differences in definition of DKA and possibly reporting bias knowing that these studies are all retrospective in design [1,2,4].

Glucocorticoid Usage As Risk Factor for CAM

Corticosteroids may facilitate mucormycosis infection by causing impairment of immunity, defective phagocytosis and worsening hyperglycemia [10]. Use of systemic glucocorticoids (oral or intravenous) was documented in 83-87% of patients with CAM [1,2]. In COSMIC, intravenous corticosteroids were given to 78% of patients for a median of 6 days [1]. Intravenous methylprednisolone (51%) and dexamethasone (48%) were the most commonly used agents [1]. Oral corticosteroids were used by 64% of patients for a median duration of 8 days [1]. In the international series reported by Pal et al. [2]. parenteral dexamethasone (dose and duration not mentioned) was the

commonest form of administered glucocorticoid.

Interestingly, in the landmark RECOVERY Study from the UK, dexamethasone therapy has been shown to decrease mortality in patients with COVID-19 [14]. However, this mortality benefit was limited to COVID-19 patients with hypoxia, whereas in milder cases not requiring oxygen there was a trend towards increase mortality with dexamethasone therapy [14]. It should be emphasized that in the RECOVERY trial, dexamethasone was used in small doses of 6 mg/d (equivalent to 32 mg/d of methylprednisolone, 40 mg/d of prednisone, or 160 mg/d of hydrocortisone) for up to 10 days [14]. The latter doses are clearly smaller than those implicated in predisposing to mucormycosis. Thus, a cumulative dose greater than 600 mg of prednisone (equivalent to approximately 90 mg of dexamethasone) has been found to predispose immunocompromised patients to mucormycosis [15]. Based on the above, corticosteroids should be used judiciously and only in hypoxic patients with COVID-19 who require oxygen support. Indeed, one factor that may have contributed to increased incidence of CAM in India was the inadvertent use of corticosteroids. Thus, data derived from COSMIC showed that despite the fact that 57% (1602 of 2826) of patients required oxygen support, much more subjects 87% received corticosteroids [1]. In addition, 80% (314 of 393) of hospitalized COVID-19 patients who did not need oxygen received corticosteroids [1]. Moreover, 21% (373 of 1775) of patients received glucocorticoids more than the recommended duration of 10 days [1]. Interestingly, tocilizumab, another immunosuppressive agent used in severe forms of COVID-19 does not appear to predispose to mucormycosis since only 2% of patients with CAM were using this drug [1].

Timing of CAM in Relation to Diagnosis of COVID-19

Most cases of CAM occur concomitantly or shortly after diagnosis of COVID-19 [1]. The median time interval between COVID-19 diagnosis and first evidence of CAM diagnosis was 10-15 days [2,4]. However, few cases of CAM may occur up to 3 months after COVID-19 diagnosis [1,16]. Indeed, in the COSMIC, 44% of patients presented with CAM following recovery from COVID-19 [1]. This observation emphasizes the need for continued vigilance with respect to any symptoms or signs suggestive of CAM for up to 3 months after COVID-19 even after recovery from COVID-19.

Prognosis of CAM

Case series generally reported mortality rates of CAM ranging from 34% to 48.8% [1,4]. However, the lowest mortality rates (14-37%) were recorded in patients with ROCM, whereas the highest rates (81%) were observed in the subgroup of patients with more invasive forms of mucormycosis including pulmonary, gastro-intestinal, and disseminated mucormycosis [1,4]. Median survival time from the day of diagnosis of mucormycosis was 75 days (95% CI, 132.2-136.8) for patients with ROCM versus only 9 days (95% CI, 2.3-15.7) for patients with pulmonary mucormycosis [4]. Adjunctive surgery, used in 81% of patients, was associated with better survival in the series reported by Pal et al. ($P < 0.001$) [2]. Similarly, in the series reported by Hongil et al. [4], mortality rates were lower in patients with ROCM who had adjunctive surgical treatment (4/28, 13.8%) versus patients treated by antifungals alone (5/8, 62.5%), ($P = 0.01$). In the latter series, surgery did not impact

the survival in patients with Central Nervous System (CNS) involvement [4]. Meanwhile, in COSMIC, there was evidence of improved survival in patients with ROCM invading the CNS who underwent surgical debridement of paranasal sinuses [1].

Clinical Implications

Since diabetes proved to be a common denominator in CAM, aggressive control of hyperglycemia is essential in patients with COVID-19. In cases complicated by DKA, rapid correction of acidosis is crucial given the role of ketoacidosis in aggravating mucormycosis infection [5]. Inadvertent use of glucocorticoids should be avoided in COVID-19 and limited to patients with hypoxia [14]. In fact, the roles of optimum glycemic control and appropriate use of glucocorticoids in decreasing incidence of CAM were supported by the absence of CAM cases in a large Indian series of 5,428 patients hospitalized with COVID-19 [17]. This achievement was accomplished by the implementation of strict protocols of glycemic control and use of low-dose corticosteroids [17]. Antifungal therapy should be rapidly initiated after consultation with the infectious disease service. In fact, delay in amphotericin therapy was shown to increase mortality among patients with hematologic malignancy affected by mucormycosis [18]. Surgical debridement should be considered for treatment of CAM since available retrospective data suggest that it may improve survival [1,2,4]. High index of suspicion for CAM should remain in effect for up to 3 months after diagnosis of COVID-19, particularly in patients with diabetes, DKA, and those using glucocorticoids.

Conclusions and Current Needs

Mucormycosis has been increasingly observed in association with COVID-19. Diabetes mellitus, with and without DKA, and use of corticosteroids emerged as the most common risk factors occurring in 78-87% of patients with CAM. Physicians should be aware of symptoms and signs of CAM to ensure timely diagnosis and treatment. In addition to strict glycemic control, judicious use of glucocorticoids, and hygienic hospital measures should be implemented [17]. Further studies are needed to determine the optimum prevention and treatment of CAM. Table 1 summarizes main measures for management of MAC based on available data.

Table 1: Measures for prevention and treatment of Coronavirus Disease 2019 (COVID-19)-Associated Mucormycosis (CAM).

S. No.	Measures
1	Maintain a high index of suspicion regarding CAM, particularly in patients with diabetes or receiving glucocorticoids.
2	Be aware that CAM may occur up to 3 months after onset of COVID-19.
3	Maintain hygienic hospital atmosphere to avoid contamination by the fungus [17].
4	Strict control of hyperglycemia, with optimum blood glucose 140-180 mg/dl in hospitalized patients [19].
5	Rapid control of diabetic ketoacidosis.
6	Follow guidelines regarding corticosteroid indications, doses and duration of treatment [14].

7	Early administration of anti-fungal therapy in case of suspicion of CAM.
8	Surgical debridement when indicated in addition to anti-fungal therapy.

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