

# World Journal of *Virology*

*World J Virol* 2022 September 25; 11(5): 221-393



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**INDEXING/ABSTRACTING**

The WJV is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Yun-Xi Chen*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lai Wang*.

**NAME OF JOURNAL**

*World Journal of Virology*

**ISSN**

ISSN 2220-3249 (online)

**LAUNCH DATE**

February 12, 2012

**FREQUENCY**

Bimonthly

**EDITORS-IN-CHIEF**

Mahmoud El-Bendary, En-Qiang Chen

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2220-3249/editorialboard.htm>

**PUBLICATION DATE**

September 25, 2022

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<https://www.wjgnet.com/bpg/gerinfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/gerinfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Rhino-orbital-cerebral mucormycosis as a complication of coronavirus disease 2019

Raid M Al-Ani

### Specialty type:

Otorhinolaryngology

### Provenance and peer review:

Invited article; Externally peer reviewed.

### Peer-review model: Single blind

### Peer-review report's scientific quality classification

Grade A (Excellent): 0  
Grade B (Very good): 0  
Grade C (Good): C, C  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Apiratwarakul K, Thailand; Meena DS, India

**Received:** April 17, 2022

**Peer-review started:** April 17, 2022

**First decision:** May 12, 2022

**Revised:** May 13, 2022

**Accepted:** August 12, 2022

**Article in press:** August 12, 2022

**Published online:** September 25, 2022



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### Abstract

Coronavirus disease 2019 is a highly contagious respiratory disease caused by severe acute respiratory syndrome coronavirus 2. This disease as well as its various treatments like steroids, antivirals, and antibacterials can alter the immune state of the affected individuals and result in secondary infections such as mucormycosis. Mucormycosis is a well-known opportunistic fungal infection that affects immunocompromised subjects, particularly those with diabetes mellitus, prolonged antibiotic or steroid use, and patients with organ transplantation, neutropenia, and hematological malignancies. Rhino-orbital-cerebral mucormycosis is an aggressive disease owing to its ability to invade the blood vessels by fungal hyphae, leading to necrosis of the involved structures. Large cases were reported from India, indicating that this clinical entity shows a geographical variation. The affected patients are suffering on a clinical spectrum depending on the stage of the disease. Radiological assessment, including computerized tomography and magnetic resonance imaging, is necessary to evaluate the stage of the disease and choose the appropriate surgical treatment. A multidisciplinary approach is required to treat rhino-orbital-cerebral mucormycosis and includes local or intravenous antifungal drugs, debridement of the dead tissues, and appropriate management of any predisposing conditions. The disease has a very poor prognosis with a death rate of 50%. This review aimed to summarize the demographic and clinical risk factors, investigations, treatments, and outcomes of coronavirus disease 2019 patients with rhino-orbital-cerebral mucormycosis.

**Key Words:** Rhino-orbital-cerebral mucormycosis; Mucormycosis; Nose and paranasal sinuses; Orbit; Cerebrum; COVID-19

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**Core Tip:** Rhino-orbital-cerebral mucormycosis is an aggressive, opportunistic fungal infection. There is an increment in cases of this condition in the era of coronavirus disease 2019, particularly in India. It usually affects the severe or critical types of the COVID-19 and those with a history of diabetes mellitus, corticosteroid therapy, and mechanical ventilation. Early diagnosis with prompt treatment carries a better outcome. The treatment consists of intravenous or local amphotericin B, surgical debridement, and reversal of any immunocompromised conditions. However, this disease has a poor prognosis with a high rate of morbidity and mortality.

**Citation:** Al-Ani RM. Rhino-orbital-cerebral mucormycosis as a complication of coronavirus disease 2019. *World J Virol* 2022; 11(5): 293-299

**URL:** <https://www.wjgnet.com/2220-3249/full/v11/i5/293.htm>

**DOI:** <https://dx.doi.org/10.5501/wjv.v11.i5.293>

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a peculiar disease owing to having many characteristics. First, although the disease affects mainly the respiratory system, it can affect any part of the body. Therefore, there is a diversity of clinical manifestations. These manifestations are either classical (fever, cough, headache, dyspnea, and olfactory and gustatory abnormalities) or non-classical (gastrointestinal symptoms, dysphonia, facial palsy, etc). Second, long-standing features, either due to the disease itself or its treatment, such as anosmia, dysphonia, sudden sensorineural hearing loss, and mucormycosis are debilitating manifestations of the disease. Third, there is a geographical variation of the COVID-19 manifestations such as rhino-orbital-cerebral mucormycosis (ROCM) that affects mainly the Indian population. Fourth, the clinical features might be related to the pandemic wave and a variant of the virus as ROCM appeared in the second wave in India and was caused by the delta variant[1,2].

COVID-19 can impair the immune status of the patients. This process is aggravated more in patients with a history of other immunocompromised conditions like diabetes mellitus (DM) or those who are on long-term steroids or antibiotic therapy. Furthermore, COVID-19 subjects are more prone to get superadded infections in certain patients with low pulmonary reserve or who need mechanical ventilation[3]. It was reported that secondary bacterial and fungal infections in hospitalized patients were approaching the rate of 8%[3,4]. Moreover, fungal infections were occurring more in a severe or critical COVID-19 stage[5].

One of the fungal-related COVID-19 infections is mucormycosis. It occurs mainly in the region of the head and neck, and the most common site is rhino-orbital-cerebral. It is an aggressive disease and carries a high death rate (approximately 50%) even if it is treated early[6]. The aim of this narrative review was to summarize the demographic and clinical characteristics, diagnostic tools, treatments, and outcomes in patients with ROCM-related COVID-19.

## EPIDEMIOLOGY

### Geographical distribution

In the pre-COVID-19 period, the incidence of mucormycosis in India (0.14/1000 population) was 80 times higher than what was reported in the world (0.005-1.7/million population)[7]. This means that India is the highest-burden country on the healthcare services regarding mucormycosis[8]. Despite India being the second country regarding the number of COVID-19 patients (43088118) (WHO Coronavirus COVID-19 Dashboard on 5-5-2022, <https://covid19.who.int/table>), most of the large case series of ROCM-related COVID-19 came from India[1,2,9]. Small case series or reported cases came from other countries like Turkey[10], Egypt[11], Iran[12,13], Honduras[14], and Peru[15]. This indicates that mucormycosis is an endemic disease in India in pre- and during COVID-19 periods.

### Age

ROCM-related COVID-19 could affect any age. The median age is mostly in the sixth decade[1].

### Gender distribution

Males are two to three times more affected than females[1,9].

## CAUSATIVE AGENTS

Mucormycosis, previously known as zygomycosis, is a group of diseases caused by a fungal infection. The causative agent belongs to the order *Mucorales*. The *Rhizopus* specie is the commonest type[7] followed by, in descending order, *Mucor*, *Cunninghamella*, *Apophysomyces*, *Lichtheimia* (formerly *Absidia*), *Saksenaia*, *Rhizomucor*, and other species[10]. These fungi release a huge amount of spores into the surrounding air. Even though all human beings inhale these fungi, only individuals with impaired immunity from DM, organ transplantation, prolonged use of steroids or antibiotics, cytotoxic drugs, and malignancies are affected by the disease[16]. The disease is characterized by rapid progression from the nose to the orbit and then to the brain owing to the direct invasion of the blood vessels, which results in tissue necrosis[10].

## PREDISPOSING FACTORS

Patients with any medical condition or those who use certain drugs such as steroids, which affect the immune system, are capable of initiating opportunistic infections like mucormycosis[17]. A history of DM and corticosteroid therapy are among the commonest predisposing factors of ROCM-related COVID-19[1,9,18]. Around 70% of patients with this disease have a history of DM.

## PATHOPHYSIOLOGY

The correlation between COVID-19 and ROCM is well established in the literature[1,10]. There are several mechanisms by which COVID-19 enhances the possibility of mucormycosis. First of all, there is a dramatic reduction in T cells, including CD4+ and CD8+, particularly in the severe form of COVID-19. As a result, the immunocompromised condition will develop that might predispose to mucormycosis [19].

Second, in the severe COVID-19 state, there is a sudden rise in certain inflammatory markers like IL-6, IL-10, IL-2R, and TNF-alpha that results in a "cytokine storm"[19]. This storm increases ferritin levels and decreases iron export. Therefore, iron deposits inside cells. The high level of iron causes tissue necrosis and the free iron passes to the blood. The high environmental level of iron is a good medium for mucormycosis because the iron is essential for the growth of the fungi and spreading in the body [20].

Third, there is a higher prevalence of DM and diabetic ketoacidosis in patients with COVID-19 in comparison with the general population[21]. There are two causes of new-onset DM due to COVID-19; the use of steroids and the disease itself are similar to the severe acute respiratory syndrome coronavirus 1[22]. Also, there are two reasons for the diabetogenic nature of COVID-19: expression of angiotensin-converting enzyme 2 receptors in the pan-creatic islets as well as increased insulin resistance due to the cytokine storm[23]. There is more iron released into the circulation because the excessive glucose occupies the iron-binding site of ferritin and transferrin in patients with hyperglycemia and diabetic ketoacidosis allowing more iron to reach the blood. The high tissue iron level is a favorable medium for the growth of the fungi[24].

Lastly, endotheliitis as a sequel of COVID-19 might increase the risk of mucormycosis[25]. Damage to the endothelial tissue enhances angio-invasion and dissemination of mucormycosis. Besides, low pH in COVID-19 induces hyperglycemia, and high iron concentration contributes to the expression of two receptors: glucose regulatory protein 78 of endothelium cells and fungal ligand spore coating homolog protein. These mediate the adhesion and penetration of *Mucorales* into the tissues[26].

## CLINICAL FEATURES

The onset of the ROCM from the time of COVID-19 diagnosis ranged from 0 to 90 d with 56% of the cases presenting within 14 d[1]. Hence, it is necessary to advise the liable patients with this disease to look for any of the warning symptoms (nasal stuffiness or obstruction, bad odor smell, epistaxis, mucopurulent or blood-stained nasal discharge, pain in the teeth, sinuses, or orbit, worsening headache, facial pain, diplopia, proptosis, fever, facial paresthesia or anesthesia, facial palsy, sudden loss of vision, sudden ptosis, altered conscious level, and focal seizures) to catch the diagnosis early[27]. These symptoms occur almost always on one side. Fever could be a warning sign during or following the course of COVID-19 if the cause of the fever is not obvious or not detected. In such cases, a nasal examination is important to detect if there is a possibility of an early stage of mucormycosis or not.

Thereafter, a thorough examination is essential and should include endoscopic nasal, ophthalmological, and neurological examinations. In a large case series of 2826 patients with this disease, the authors reported the following signs: periocular/facial edema (33%); loss of vision (21%); ptosis (12%);



proptosis (11%); nasal discharge (10%); nasal ulcer/eschar (5.7%); diplopia/ocular movement restriction (3%); periocular/facial discoloration (2.3%); periocular hypoesthesia (1.3%); oral or palatal ulcer/eschar (0.6%); facial palsy (0.2%); and altered sensorium (0.1%)[1].

## STAGING SYSTEM

Adopting a staging system is crucial in the management of ROCM-related COVID-19. Owing to the huge number of cases found in India, the Indian ophthalmologist Honavar create a very useful staging system[27]. It is a simple system and depends on anatomical location from the starting point in the nose, then to the paranasal sinuses, orbit, and intracranial structures. In addition, the system considers the severity of each site. Furthermore, this system contains the specific symptoms and signs and useful investigations for each stage. As a next step, it is logical to check its validity, suggest the best option of treatment for each stage, and estimate the treatment outcomes.

## DIAGNOSIS

A high index of clinical suspicion is crucial for early diagnosis. Involved tissue biopsy and potassium hydroxide mount fungal staining is the cornerstone of the diagnosis. Culture and sensitivity are used to determine the fungal species. However, it is necessary to start with amphotericin B until the laboratory result is achieved. Radiological imaging in the form of computerized tomography and magnetic resonance imaging of the nose and paranasal sinuses is used to support the diagnosis and to evaluate the stage of the disease[1].

## TREATMENT

It is of utmost importance in the management of ROCM-related COVID-19 to use a multidisciplinary team including a specialist doctor in infectious diseases, internal medicine, intensive care, otolaryngology, ophthalmology, neuromedicine, and/or neurosurgery[2].

In general, the treatment consists of three steps: intravenous or local antifungals therapy; appropriate surgical debridement; and reversal of the immunosuppressive conditions[28].

Initiation of antifungal therapy within the first 5 d of the diagnosis improves the survival rate to 83%, which is much larger than the survival rate of 49% if the antifungal treatment started at  $\geq 6$  d[29]. Amphotericin B is considered the drug of choice as a monotherapy, while posaconazole or isavuconazole can be used as a salvage antifungal drug. A combination of amphotericin B and posaconazole can be used in refractory cases of mucormycosis[4]. In the largest case series in the world from India of 2826 patients with ROCM-related COVID-19, intravenous amphotericin B was used in 73% and intraorbital injection of amphotericin B in 22% of the patients. The study showed a satisfactory result with the use of amphotericin B[1]. Also, in another study from India of 58 patients, parenteral amphotericin B and surgical debridement were used in all patients[9]. In a case report study from Peru, isavuconazole was used, owing to the unavailability of amphotericin B, in a 66-year-old woman with this disease. The study revealed that the isavuconazole was effective and without adverse effects over 10 mo[15].

Of note, antifungal therapies have several shortcomings such as adverse effects related to infusion, optimal dosage, and nephrotoxicity. Nowadays, nanomedicine is an alternative promising solution, in which the intravenous route of the amphotericin B is shifted to other routes like through the mouth, local, and pulmonary routes. This system is under further development[30].

Surgical debridement has two advantages. It reduces the fungal load as well as provides sufficient tissue for histopathological evaluation. The process of debridement continues until the appearance of normal tissue that bleeds profusely. Removal of the palate, endoscopic nasal approach, and orbital decompression or exenteration are undertaken depending on the stage of the disease[28].

Correction of the hyperglycemic state, hypoxia, acidosis, and electrolyte disturbances are essential. We must take the opinion of relevant specialists concerning decreasing or discontinuing immunosuppressive or antibiotic therapy. Furthermore, the use of granulocyte colony-stimulating factors might increase the white cell count and improve host immunity[28].

## PREVENTION

A golden rule in medicine is that "prevention is better than treatment." This is particularly true in serious diseases like mucormycosis. Many measures should be taken to avoid such a sinister pathology:



judicious and supervised use of systemic corticosteroids in compliance with the current preferred practice guidelines; judicious and supervised use of tocilizumab in compliance with the current preferred practice guidelines; strict monitoring and control of DM; aggressive aseptic precautions while administering oxygen (sterile water for the humidifier, daily change of the sterilized humidifier and the tubes); personal and environmental hygiene: use of betadine as a mouth gargle, barrier mask covering the mouth and nose, and consideration of prophylactic oral posaconazole in high-risk subjects (> 3 wk of mechanical ventilation, > 3 wk of supplemental oxygen, > 3 wk of systemic corticosteroids, poorly or uncontrolled DM with or without ketoacidosis, history of chronic rhinosinusitis, and immunocompromised conditions)[27].

## PROGNOSIS

Although ROCM-related COVID-19 is a relatively uncommon condition, it is an aggressive disease with a high rate of morbidity and mortality[17]. One of the disaster complications is a loss of vision. In a large retrospective observational study from India of 2826 COVID-19 patients, there were 289 (16%) cases that ended with orbital exenteration[1]. The death rate is approaching 50%[18]. A recent study from Egypt reported a mortality rate of 21.4% (3/14)[31], which was considered low if one compares it with the mortality rate from India (31% to 49%)[32,33]. The fatality rate might range from 30% to 90% in patients with cerebral involvement[34]. It is of utmost importance to consider the staging system of the ROCM-related COVID-19 adopted by Honavar to determine the severity of the disease and survival rate[27]. It was reported in the literature that the delay in starting treatment even 6 d increases the 1-mo fatality from 35% to 66%[35]. Comorbidities and the immunosuppressive state of the patients will increase the aggressiveness of the disease and increase the morbidity and mortality rates. Early diagnosis and prompt treatment improve the outcomes.

## CONCLUSION

ROCM-related COVID-19 is an opportunistic serious fungal infection. The commonest causative agents are from the *Rhizopus* specie. It occurs as one of the complications of COVID-19, particularly in diabetic patients and those on corticosteroid therapy or mechanical ventilation. The disease affects mostly the Indian population. Angio-invasion with tissue destruction is the hallmark of the disease. A high index of clinical suspicion, early diagnosis, intravenous or local amphotericin B, and surgical debridement lead to better outcomes. However, it carries a high rate of morbidity and mortality.

## FOOTNOTES

**Author contributions:** Raid M Al-Ani performed all aspects of this manuscript's generation.

**Conflict-of-interest statement:** The author declares that there is no conflict of interest.

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**Country/Territory of origin:** Iraq

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**S-Editor:** Ma YJ

**L-Editor:** Filipodia

**P-Editor:** Ma YJ

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