Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Oral and Maxillofacial Surgery Cases 8 (2022) 100262

Contents lists available at ScienceDirect

Oral and Maxillofacial Surgery Cases

journal homepage: www.oralandmaxillofacialsurgerycases.com

Resurgence of mucormycosis during COVID-19 pandemic

Kamran Ali *, Shiraz Altigani Mohammed Salih

Oral Surgery, Qatar University College of Dental Medicine, Qatar

ARTICLE INFO

Keywords:
Corona virus
Immunosuppression
Mucormycosis

ABSTRACT

Objective: To explore the literature on corona-associated mucormycosis and explain its relevance to dentists and oral surgeons.
Methods: A literature search was carried out to identify reported cases on corona-associated mucormycosis since the start of COVID-19 pandemic.
Results: A review of literature identified 265 published papers on CAM between March 2020 and September 2021. Careful screening of abstracts and full texts revealed 29 studies reporting case series of CAM and, 27 case reports on CAM.
Conclusions: A multitude of factors may be responsible for the alarming rise in the incidence of corona-associated mycosis including reduced access to routine medical services during the pandemic, injudicious use of antibiotics, steroids and nutritional supplements. Risk factors contributing to corona-associated mucormycosis need to be recognized. Dentists and oral surgeons can contribute to early recognition of corona-associated mucormycosis involving the maxilla, and palate. Prioritizing research focus on optimal management of mucormycosis may reduce the morbidity and mortality associated with this debilitating infection.

1. Introduction

Mucormycosis is a fulminant, potentially fatal, opportunistic fungal infection. It affects immunocompromised patients, and its mortality rate has been reported to be as high as 80%. First described as *Phycomycosis* by Paltauf in 1885, the term mucormycosis was introduced by Baker in 1957 and still remains in use [1,2]. Currently, Mucorales fungi are the next most common mold pathogens after Aspergillus, leading to invasive fungal disease in susceptible patients.

Mucormycosis is primarily seen in patients with immunosuppression. Due to the increasing incidence of diabetes mellitus, cancer, and growing number of organ transplantations, the number of patients at risk for this deadly infection is increasing. Despite aggressive therapy including surgical debridement and adjunct antifungal therapy, morbidity and mortality following mucormycosis remains high. New strategies to prevent and treat mucormycosis are warranted. A better understanding of the pathogenesis and host response to mucormycosis may provide targets for novel therapeutic interventions in the future [3].

Based on clinical presentation and involvement of typical anatomic regions, mucormycosis is classified into five clinical types namely, (i) rhino-cerebral, (ii) pulmonary, (iii) cutaneous, (iv) gastrointestinal, and (v) disseminated. These categories of invasive mucormycosis tend to occur in patients with specific defects in host defense. For example, patients with diabetes mellitus (DM) complicated by ketoacidosis typically develop the rhinocerebral form of the disease, and much more rarely develop pulmonary or disseminated disease [4].

The rhino-orbito mucormycosis (ROM) is the most common type of mucormycosis [5,6]. The disease process starts with inhalation

* Corresponding author.
E-mail addresses: ali.kamran@qu.edu.qa (K. Ali), shiraz@qu.edu.qa (S.A.M. Salih).

https://doi.org/10.1016/j.omsc.2022.100262
Received 13 April 2022; Received in revised form 20 April 2022; Accepted 16 May 2022
Available online 23 May 2022

of the fungus into the paranasal sinuses. The fungus may spread to invade the palate, maxilla, orbit, or centrally to involve the brain. If untreated, infection usually spreads from the ethmoidal air sinuses to the orbits, resulting in the loss of extraocular muscle function and proptosis [7]. Classically, the clinical presentation has been described as an orbital cellulitis with proptosis, and neuropathies including loss of vision.

ROM frequently involves the palate and maxilla (Fig. 1). Necrotic exposure of the palatal bone may the first clinically visible manifestation of the disease and patients may initially present to dentists or oral and maxillofacial surgeons. Similarly, neuropathies involving the trigeminal or facial nerve may initially present to oral and maxillofacial surgeons (Fig. 2).

Optimal management of mucormycosis is complicated due to lack of well-defined predictors of clinical response to interventions and high risk of morbidity. Mucormycosis is more commonly reported from countries with poor socio-economic profile and has not received adequate focus in contemporary clinical research. Diagnosis of mucormycosis is based on clinical assessment, and relevant laboratory investigations [8]. Imaging techniques can provide useful information regarding the extent of specific organ involvement but are not conclusive. Histopathology, microbial identification with polymerase-chain reaction (PCR) tests are the key investigations to establish a definitive diagnosis [9].

Current management options focus on control of risk factors and a combination of anti-fungal therapy and surgical debridement of infected tissues. Owing to its broad-spectrum antifungal activity, traditionally amphotericin B has been the antifungal agent of choice for the treatment of mucormycosis [8–12]. Other options include posaconazole and isavuconazole [13]. Adjunctive measures to manage mucormycosis include irrigation of infected tissues with Amphotericin B, hyperbaric oxygen therapy and iron chelators. However, lack of robust evidence precludes their routine use in the management of mucormycosis.

The aim of this paper is to review current evidence on Corona-associated mucormycosis (CAM) following the start of COVID-19 pandemic.

2. Review of literature on corona-associated mucormycosis

This paper is based on a review of published literature and did not involve collection of new data. Therefore, the study was exempt from ethics approval. Images used in this paper were obtained after an informed consent from patients.

A review of literature identified 265 published papers on CAM between March 2020 and September 2021. Careful screening of abstracts and full texts revealed 29 studies reporting case series of CAM and, 27 case reports on CAM. Table 1 summarizes the key features of CAM reported in case series. M of studies from reporting CAM were from India.

Data from a total of 3856 patients included in 29 studies showed that at least 3000 (~80%) had pre-existing DM. Other underlying conditions included hypertension, ischemic heart disease, chronic kidney disease, and steroid therapy as depicted in Table 1.

In addition, 27 case reports on CAM were also published during this period. The case reports mirror patterns observed in studies included in Table 1 and majority of the reported cases were in adult males. DM was the most common underlying health condition and the clinical presentation included ROM; RCM while pulmonary involvement was observed in seven cases.

An alarming rise in the incidence of mucormycosis has been witnessed globally following the COVID-19 pandemic. Opportunistic fungal infections such as Aspergillosis, Candidiasis and mucormycosis are being reported increasingly in patients with COVID-19 [14]. Similarly, a 26.7% rise in the incidence of invasive fungal diseases has been reported in a multicenter cohort of COVID-19 intensive care patients in the UK, including a 12.6% incidence of invasive yeast infections [15]. Recent evidence also suggests that the fungal infections in COVID-19 positive patients may actually be under-reported [16].

CAM is an emerging public health concern. Based on the published literature. Hoenigl et al. analyzed 80 cases of CAM, with over 50% cases only from India [15]. Similarly, seven countries in the American continent have reported 16 cases of CAM up to June 9, 2021 [17,18].

Based on the published literature, India contributed to approximately 71% of global cases of CAM from December 2019 to start of

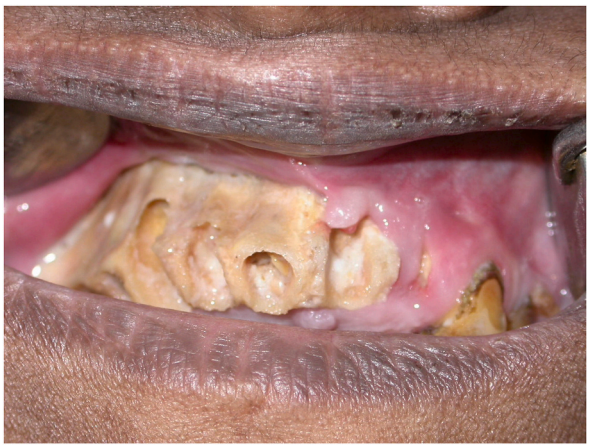

Fig. 1. Maxillary necrosis following mucormycosis.

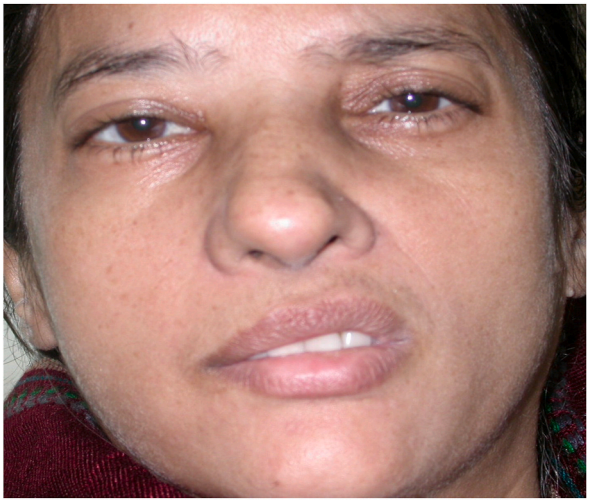

Fig. 2. Facial nerve paralysis following Mucormycosis.

Table 1
Corona-associated mucormycosis (CAM) cases reported between March 2020 to September 2021.

Author; Year & Location	Number of cases (N)	Mean Age (Years)	Gender	Clinical Presentation
Fouad et al. ., 2020, Egypt	6	51.2	M = 6	ROCM
Arora et al., 2021, India	60	57	M = 45; F = 15	ROCM
Ashour et al., 2021, Egypt	8	53.63	M = 5, F = 3	AIFS
Bayram et al., 2020, Turkey	11	73.1	M = 9; F = 2	ROM
Bhanuprasad et al., 2021, India	164	50.52	M = 101; F = 36	ROCM
Desil et al., 2021, India	100	56	M = 64; F = 36	ROM
Deve et al., 2021, India	58	55	M = 44; F 14	ROCM
Dubey et al., 2021, India	55	53;	M = 35, F = 20	ROCM
Elhamamsy et al., 2021 Multiple countries	3	67	M = 3	ROCM
Gupta et al. ., 2020, India	56	53	M = 41, F = 15	ROCM
Mishra et al., 2021, India	32	58.28	M = 17; F 15	ROM = 19; SM = 13
Mitra et al. ., 2021,India	32	57	M = 23; F = 9	ROCM
Moorthy et al. ., 2020, India	16	54.6	M = 15, F = 1	ROCM
Nair et al., 2021, India	127	35.9	Not reported	ROM
Nehara et al., 2021, India	5	59	M = 1; F = 4	ROM
Pakdel et al., 2020, Iran	15	52	M = 10; F = 5	ROM
Pradhan et al. ., 2021, India	46	48.80	M = 40, F = 6	ROM = 33; RCM = 10; Mandibular = 1; SM = 2
Ramaswami et al., 2021, India	70	44.5	M = 42; F = 28	ROM
Ravani et al., 2021, India	31	56.3	M = 20, F = 11	ROM
Roa et al., 2021, India	28	49.1	M = 22; F = 8	PNS and maxillary involvement
Saidha et al., 2021, India	6	39	M = 4; F = 2	PNS involvement
Sarkar et al., 2021,India	10	67	M = 8; F = 2	OM
Selarka et al. ., 2021, India	47	55	M = 35; F = 15	Maxillary and PNS involvement
Sen et al., 2020, India	6	60.5	M = 6	ROM
Sen et al., 2021, India	2826	51.9	M = 1993; F = 833	ROCM
Sharma et al., 2020, India	23	Not reported	M = 15; F = 8	SM
Singh et al., 2021, India	13	38	M = 10; F = 3	ROM = 8; RC = 2; PNS = 2; Pulmonary = 1
Veisi et al. ., 2021, Iran	2	40	M = 1; F = 1	ROM

Abbreviations: Orbital mucormycosis (OM); Rhino-orbito mucormycosis (ROM); Sinonasal mucormycosis (SM); Sino-orbital mucormycosis (SOM); Acute invasive fungal rhino-orbital-cerebral sinusitis (AIFS); Paranasal sinus (PNS).

April 2021, with majority of the cases occurring during the second wave [19]. Mucormycosis (Black fungus) during the second wave of COVID-19 has been described as an epidemic within a pandemic More than 31,000 cases have already been reported so far across India and more than 2100 people have died as a result of the disease. Majority of cases from India have been reported from the state of Maharashtra followed by Rajasthan, Gujarat, Madhya Pradesh, Haryana, Delhi, and Punjab. Cases of mucormycosis have more than doubled in India in late 2020 compared to the corresponding months of 2019 which suggests a direct correlation between COVID-19 and mucormycosis. Cases have been reported from every state of India and it is now included in the list of "notifiable" diseases [20]. Mucormycosis in India was predominantly seen in males and included both in individuals with active infection as well as those who had recovered from COVID-19. Mucormycosis involving nose and sinuses was most common followed by rhino-orbital involvement

[21].

A prospective observational clinical study investigated clinical manifestations of rhino-orbital mucormycosis (ROM) in COVID-19 positive patients. Among 32,814 patients hospitalized with the diagnosis of COVID, 11 cases of mucormycosis were observed. The mean time-interval between COVID-19 diagnosis and ROM diagnosis was 14.4 ± 4.3 days. Seven patients (63.6%) had orbital apex syndrome, and four patients (36.4%) presented with orbital cellulitis [22].

3. Pathogenesis of mucormycosis in COVID-19 patients

A multitude of factors may be responsible for a sharp rise in the incidence of CAM. Injudicious use of steroids, antibiotics and nutritional supplements as self-medications increased during the COVID-19 pandemic. These trends were particularly common in countries where public has access to prescription medicines over the counter. Imprudent use of these medications may lead to immunosuppression and the dysbiosis of microbiota, rendering the high-risk groups even more vulnerable to mycotic disease [23]. Moreover, COVID-19 pandemic has impacted adversely on healthcare services globally and access to routine medical services for patients with chronic diseases has been compromised. Poor access to medical care, and inadequate monitoring of diseases such as DM may have contributed to the rising incidence of CAM.

Immune response to mucorales involves generation of oxidative free radicals and the cationic peptides such as, defensins. Tissue hypoxia secondary to COVID-19 provides a favorable environment for germination of mucorale spores and compromises phagocytic potential [23]. COVID19-mediated immune-dysregulation not only leads to a deficient innate immune response, but also leads to reduced activity of T lymphocytes [24]. High levels of pro-inflammatory cytokines developing as a result of COVID-19, promote fungal colonization and infection [18]. Furthermore, hyperglycemia and acidosis, as encountered in uncontrolled diabetics, also lead to reduced oxygen-dependent and oxygen-independent phagocytosis [4]. Finally, endothelial damage in COVID-19 may provide an additional pathway to promote mucorale adhesion and tissue penetration [25].

4. Conclusions and recommendations

CAM represents a double whammy and carries a poor prognosis overall. Prevention of CAM is the most fundamental strategy and hinges on vaccination, social distancing measures and reduction of risk factors such as immunosuppression secondary to DM, steroids and other immunosuppressive medications. Unlike COVID-19, mucormycosis has existed for well over a century. However, mucormycosis has not received adequate focus in clinical research and continues to show significant morbidity and high mortality in susceptible patients. Rapid advancements in medical research following the COVID-19 pandemic have enabled production of vaccines and other adjunctive therapies [26]. Mucormycosis has received a renewed focus during the COVID-19 pandemic due to high mortality rates in many countries, especially India. Whilst unfortunate, the recognition of CAM should be used as an opportunity to dedicate more resources to fund research for developing evidence-based clinical care protocols and therapies for mucormycosis. Dentists can also play their part in recognition of CAM as they may be the first members of the healthcare teams to identification of oral manifestations of COVID-19 including dry mouth, dysgeusia, oral ulcerations and opportunistic infections [27]. Additionally, involvement of the palate, maxilla may be the first signs of mucormycosis and patients may initially present to dentists and maxillofacial surgeons, providing early opportunities for diagnosis and prompt management.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Funding

Open access funding was provided by the Qatar National Library.

Credit author statement

Shiraz Altighani carried out the literature search. K Ali was responsible for drafting of the manuscript.

Declaration of competing interest

None of the authors have any conflict of interest to declare.

References

[1] Paltauf A. XXV. Mycosis mucorina. In: Archiv für pathologische Anatomie und Physiologie und für klinische Medicin Band 102; 2021.
[2] Baker RD. Mucormycosis—a new disease? J Am Med Assoc 1957;163(10).
[3] Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clin Infect Dis 2012;54(SUPPL. 1).
[4] Spellberg B, Edwards J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management, vol. 18. Clinical Microbiology Reviews; 2005.
[5] Tsagkovits A, Ioannidis D, Rokade A. The microscope drape method to reduce aerosolisation during endoscopic sinus and skull base surgery in the COVID era. How i do it. Eur Arch Oto-Rhino-Laryngol 2021;278(2).
[6] Garlapati K, Chavva S, Vaddeswarupu RM, Surampudi J. Fulminant mucormycosis involving paranasal sinuses: a rare case report. Case reports in dentistry. 2014. 2014.

[7] Rapidis AD. Orbitomaxillary mucormycosis (zygomycosis) and the surgical approach to treatment: perspectives from a maxillofacial surgeon, vol. 15. Clinical Microbiology and Infection; 2009.
[8] Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: an update. Journal of Fungi 2020;6.
[9] Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect 2014;20(S3).
[10] Lanternier F, Poiree S, Elie C, Garcia-Hermoso D, Bakouboula P, Sitbon K, et al. Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis. J Antimicrob Chemother 2015;70(11).
[11] Blyth CC, Gilroy NM, Guy SD, Chambers ST, Cheong EY, Gottlieb T, et al. Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and haemopoietic stem cell transplantation. Intern Med J 2014;44. 2014.
[12] Tissot F, Agrawal S, Pagano L, Petrikkos G, Groll AH, Skiada A, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica 2017;102(3).
[13] Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis 2016;16(7).
[14] Pemán J, Ruiz-Gaitán A, García-Vidal C, Salavert M, Ramírez P, Puchades F, et al. Revista Iberoamericana de Micología Fungal co-infection in COVID-19 patients: should we be concerned? Rev Iberoam De Micol 2020;37(2).
[15] Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, et al. The emergence of COVID-19 associated mucormycosis: analysis of cases from 18 countries. SSRN Electron J 2021:1–33.
[16] Song G, Liang G, Liu W. Fungal Co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China, vol. 185. Mycopathologia; 2020.
[17] Nucci M, Engelhardt M, Hamed K. Mucormycosis in South America: a review of 143 reported cases, vol. 62. Mycoses; 2019.
[18] Farias LABG, Damasceno LS, Bandeira SP, Barreto FK de A, Leitão TDMJS, Cavalcanti LP de G. COVID-19 associated mucormycosis (CAM): should Brazil be on alert?, vol. 54. Revista da Sociedade Brasileira de Medicina Tropical; 2021.
[19] Gambhir RS, Aggarwal A, Bhardwaj A, Kaur A, Sohi RK, Mehta S. Covid-19 and mucormycosis (Black Fungus): an epidemic within the pandemic. Rocz Panstw Zakl Hig 2021;72(3).
[20] Rocha ICN, Hasan MM, Goyal S, Patel T, Jain S, Ghosh A, et al. COVID-19 and mucormycosis syndemic: double health threat to a collapsing healthcare system in India. Trop Med Int Health 2021;26(9).
[21] Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metabol Syndr: Clin Res Rev 2021;15(4).
[22] Bayram N, Ozsaygılı C, Sav H, Tekin Y, Gundogan M, Pangal E, et al. Susceptibility of severe COVID-19 patients to rhino-orbital mucormycosis fungal infection in different clinical manifestations. Jpn J Ophthalmol 2021;65(4).
[23] Rodriguez-Morales AJ, Sah R, Millan-Oñate J, Gonzalez A, Montenegro-Idrogo JJ, Scherger S, et al. COVID-19 associated mucormycosis: the urgent need to reconsider the indiscriminate use of immunosuppressive drugs, vol. 8. Therapeutic Advances in Infectious Disease; 2021.
[24] Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: we should be prepared. J Mycol Med 2020;30.
[25] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in covid-19. N Engl J Med 2020;383(2).
[26] Holman W, Holman W, McIntosh S, Painter W, Painter G, Bush J, et al. Accelerated first-in-human clinical trial of EIDD-2801/MK-4482 (molnupiravir), a ribonucleoside analog with potent antiviral activity against SARS-CoV-2, vol. 22. Trials; 2021.
[27] Coll Y, Elmahgoub F. Could dentists be the first to diagnose COVID-19 due to oral manifestations?, vol. 22. Evidence-based dentistry; 2021.