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Review Article

The mucormycosis surge in COVID-19 pandemic: an analysis of associated risk factors and review of literature of reported cases

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ABSTRACT

COVID-19 patients are particularly susceptible to secondary infections, both bacterial and fungal, most likely due to immunological dysregulation. Secondary systemic mucormycosis was identified to be the significant cause of this epidemic among fungal infections. Post-COVID-19 complications are being reported all around the world, creating major pressure on healthcare services and the lives of the patients. PRISMA guidelines were used to conduct a literature review for articles published on COVID-19 associated Mucormycosis (CAM) between January 1, 2020, to May 18, 2021. The inclusion criteria were based on peer-reviewed studies in English covering cases with COVID-associated mucormycosis (CAM). Articles describing fungal coinfections that were not mucormycosis cases, non-COVID-19 cases, and studies with a lack of clarity were excluded from the review. The review includes 31 articles comprising of 21 Case Reports and 10 Case Series. Out of 104 cases, 76% were from India, 77.9% were males. Predisposing variables such as diabetes (71.15%), hypertension (37.5%), and ketoacidosis (10.6%) were found to be substantial contributors to the aggressive growth of opportunistic fungal infections such as mucormycosis. Rhino-orbital mucormycosis (n=47), followed by Rhino-orbital-cerebral mucormycosis (n=32), and Pulmonary mucormycosis (n=10) were commonly reported in the case studies and literature reviews which presented either following COVID-19 infection or a few weeks after active COVID-19 infection. Significant mortality (36.9%) was reported among patients. As per our observations, CAM could be a serious consequence of severe COVID-19, especially in people with uncontrolled diabetes.

Keywords: COVID-19, Mucormycosis, Diabetes mellitus, CAM, SARS Co-V2

INTRODUCTION

The novel SARS-CoV2 virus causes COVID -19 infection has been attributed to a wide range of disease patterns, from a mild cough to life-threatening pneumonia.[1] COVID-19 is linked to a high rate of secondary infections, both bacterial and fungal, most likely as a result of immunological dysregulation. Furthermore, the frequent use of steroids, broad-spectrum antibiotics, and monoclonal antibodies against COVID-19 may result in the formation or aggravation of a pre-existing fungal infection.[2]

Mucormycosis is a rare, opportunistic angio-invasive illness caused by a saprophytic Mucorales fungus. Fungal spores are easily aerosolized and can enter the human body by inhalation, local inoculation (such as a skin lesion), or gastrointestinal absorption. The establishment

of the fungi and progression of mucormycosis requires specific crucial phases regardless of the point of entrance.[3] This includes spore inoculation on host tissue; evading phagocytosis and germinating into angio-invasive hyphae. The Mucorales use certain host circumstances (e.g., hyperglycemia, ketoacidosis, iron overload, etc.) to boost their development and pathogenicity. In mice models of mucormycosis, increased iron concentrations promote fungal growth by limiting phagocyte function and lowering IFN-secretion.[4] The actual prevalence of mucormycosis in India is unknown due to a lack of population-based studies. Mucormycosis is estimated to be 70 times more prevalent in India than it is in the rest of the world.[5]

Increased awareness, advancements in diagnostic techniques, and the prevalence of predisposing variables are all attributing to an upward trend. Mucormycosis is most common in immunocompromised patients, such as those with haematological malignancies, transplant recipients, in people with uncontrolled diabetes mellitus, and, even more rarely, immunocompetent patients.[6] With the extensive use of broad-spectrum antibiotics and steroids, 8% of coronavirus-positive or recovered patients had secondary bacterial or fungal infections during hospitalization, according to a recent study.[7] COVID-19 is a life-threatening infectious disease in which patients has an overexpression of inflammatory cytokines and impaired cell-mediated immunity, as evidenced by a decrease in the number of cluster of differentiation 4 and 8 positive T-helper (CD4+ T and CD8+ T) cells, indicating susceptibility to fungal co-infection. India has a high prevalence rate of type 2 diabetes mellitus (8.9% of adults, 77 million patients), which is a well-known risk factor.[8]

Without early diagnosis and treatment, the illness may proceed quickly, with fatality rates of 50–80% reported from intra-orbital and cerebral complications. Care is frequently ineffective, resulting in infection spread and fatality, despite the prompt diagnosis, treatment of underlying illnesses, and intensive medical and surgical intervention.[7]

METHODS

For systematic reviews, the search method and analysis were carried out following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.9 Full-length publications were appraised for eligibility after the titles and abstracts of the retrieved papers were examined. No unpublished information was obtained.

Search strategy

Two investigators (S.P. and C.M.) have independently performed a systematic search of the literature across Google Scholar, PubMed, ScienceDirect, and Web of Science for 'COVID-19', 'SARS-CoV-2', 'Mucormycosis', 'Ophthalmic manifestations', 'Diabetes', 'Immunosuppressants', 'COVID associated mucormycosis' and 'intravenous liposomal Amphotericin-B'.

Inclusion and exclusion criteria

Inclusion criteria

Considering articles for review in the English language. Covering COVID Associated Mucormycosis (CAM) cases published between January, 2020, to May, 2021. Patients with confirmed COVID-19 cases (either active or recovered) were involved in the study. Case reports, case series, and cross-sectional studies associated with mucormycosis were involved in the study.

Exclusion criteria

Articles with other fungal infections that were not mucormycosis were excluded from the study. Patients without confirmed COVID-19 diagnosis were excluded from the study.

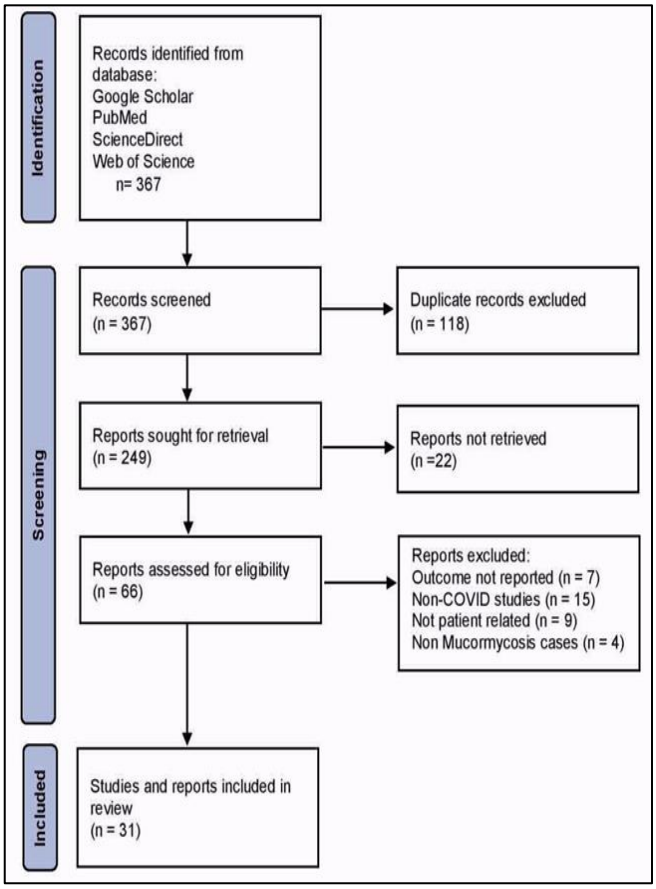

Figure 1: Flow diagram of the study selection process.

Data extraction

Two investigators (S.P. and C.M.) independently performed data collection. The literature review included

31 records, in which 14 articles from India and 17 articles worldwide were included. The review consisted of 21 case reports and 10 case series. Selected studies were reviewed and data extracted in terms of country of study, patients symptomatology, history of COVID-19 (active or recovered), associated predisposing comorbidities, presence of diabetes mellitus, diabetic ketoacidosis, corticosteroid use, use of Remdesivir, use of intravenous liposomal Amphotericin-B and other antifungal agents, surgical intervention, type of mucormycosis, investigation (laboratory blood test, radiological test, CT scan, MRI, histological finding, fungal culture report, etc.), treatment outcome in term of alive, dead or lost in follow-up.

Statistics

The socio-demographic data along with other variables were represented in percentage. The age of patients in the case series was shown as mean age in years.

RESULTS

The literature review included 31 records out of 367 articles that were searched for this paper using PRISMA guidelines as seen in the flow diagram of Figure 1.

Table 1 depicts the characteristics of CAM patients. 79 and 11 proven mucormycosis cases were reported from India and the United States of America respectively, out of the 104 confirmed CAM cases. Until May 18, 2021, 10 instances have also been recorded from Iran, 02 from Brazil, 01 from Italy, and 01 from Mexico. The median age was 54 years with the range being 24 years to 86 years. 81/104 (77.9%) were male and 23/104 (22.1%) were female. All reported cases have been diagnosed as a case of COVID-19 disease by RTPCR or other confirmatory tests. In our review, the most common medical comorbid illnesses were diabetes mellitus 74/104 (71.15%), 39/104 (37.5%) cases hypertension, 11/104 (10.6%) cases had diabetic ketoacidosis, followed by 9/104 (6.7%) had renal disorders, 6/104 (5.77%) had respiratory disorders, and 5/104 (4.8%) had cardiovascular disorders.

Table 2 gives a summary of the case reports and series and their interpretation. The most common presentation was rhino-orbital mucormycosis 45/104 (43.27%), followed by 32/104 (30.77%) had Rhino-orbital-cerebral mucormycosis, 10/104 (9.62%) presented with pulmonary mucormycosis.

In our review, out of 104 CAM cases, 36/104 (34.62%) of the patients were treated with injection Remdesivir, 95/104 (91.8%) patients received intravenous corticosteroids during COVID-19 treatment, while 99/104 (95.19%) cases received intravenous liposomal Amphotericin-B for treatment of mucormycosis. A combination of antifungal agents was used in 34/104 (32.7%) cases, the most common combination used was Posaconazole 21/104 (20.2%) along with intravenous liposomal Amphotericin-B. Combined medical and surgical management was performed in 85/104 (81.73%) of the cases. In our study overall mortality was reported to be 36.9%.

Table 1: Characteristics of the 104 patients with COVID associated mucormycosis (CAM).

Variable (n=104)		N (%)
Country where the cases were reported	India	79 (76)
	United States of America	11 (10.6)
	Iran	10 (9.6)
	Brazil	2 (1.9)
	Italy	1(0.95)
	Mexico	1 (0.95)
Sex	Male	81 (77.9)
	Female	23 (22.1)
Underlying factors	Diabetes	74 (71.15)
	Hypertension	39 (37.5)
	Diabetic Ketoacidosis	11 (10.6)
	Renal Disorders	9 (8.65)
	Respiratory Disorders	6 (5.77)
	Cardiovascular Disorders	5 (4.8)
Management	Remdesivir	36 (34.62)
	Corticosteroids	95 (71.8)
	Liposomal Amphoterin-B	99 (95.19)
	Other Antifungal agents	34 (32.7)
	Combined medical and surgical management	85 (81.73)
Outcome	Alive	63 (61.1)
	Death	38 (36.9)
	Not known	3 (2.9)

DISCUSSION

Patients who require critical care due to COVID-19 pneumonia have risk factors and underlying conditions that make them susceptible to invasive fungal infections. Uncontrolled Diabetes mellitus, particularly diabetic ketoacidosis, is a prevalent predisposing condition.[10]

Out of the 104 confirmed mucormycosis cases, 79 were reported from India, 11 cases were from the United States of America, 10 cases were reported from Iran and 2 from Brazil, 1 case from Italy, and 1 was reported from Mexico till 18 May 2021. In our study maximum cases were reported from India (76%).

Table 2: Summary of the review of 31 literature (or 104 cases) in COVID Associated Mucormycosis.

Authors	Country	Age in years	Sex	Study Design	Comorbid Illness	Clinical Presentation	Treatment for COVID-19	Specific treatments	Investigations	COVID-19 testing	Type of involvement in CAM	Outcome
Chennamchetty et al[19]	India	72	Male	Case report	Hypertension, Steroid-induced Diabetes Mellitus, Hypothyroidism	COVID-19 pneumonia, Severe ARDS, hemoptysis	Inj. Remdesivir, methylprednisolone, Convalescent plasma, Antibiotics	Liposomal Amphotericin-B, Tab. Posaconazole at discharge	PET CT scan, CT guided biopsy of a nodule in right upper lobe, blood culture	COVID +	Pulmonary	Alive
Dronamraju et al[20]	India	50	Male	Case report	Recent history of COVID-19 Pneumonia	Headache, Diminished vision in the right eye, Swelling of the right eyelid, Nasal blockage, h/o fever, tenderness over sinuses	Supportive antibiotics	Liposomal Amphotericin B	MRI brain, CT scan brain, Nasal swab culture	COVID-19 RTPCR +	Rhinocerebral	Death
Garg et al[21]	India	55	Male	Case report and systematic review	Diabetes mellitus, Hypertension, Ischemic cardiomyopathy, End-stage renal disease, h/o dialysis	Fever, Dry cough, Progressive breathlessness	Inj. Meropenem, Inj. Remdesivir Dexamethasone,	Liposomal Amphotericin –B	Chest X-ray, CT CHEST, SDA culture of pleural effusion, LCB mount, MALDI TDF, S. galactomannan	COVID-19 RTPCR +	Pulmonary	Alive

Continued.

Authors	Country	Age in years	Sex	Study Design	Comorbid Illness	Clinical Presentation	Treatment for COVID-19	Specific treatments	Investigations	COVID-19 testing	Type of involvement in CAM	Outcome
Honavar et al[22]	India	60.5±12 (mean) n=3	Male-3	Retrospective interventional study	Diabetes mellitus (common), Hypertension, Coronary artery disease	Ophthalmoplegia, Ptosis, Chemosis	Methylprednisolone, Prednisolone, Dexamethasone	FESS, Amphotericin-B, Inj. Posaconazole	Culture for Mucor (66.67%), Histopathology (66.67%),	COVID +	Rhino-orbital-3	Alive-3
Maini et al[23]	India	38	Male	Case Report	No h/o Diabetes, or any debilitating disorder before treatment.	Fever, Cough, Breathlessness, Malaise, Proptosis, Chemosis	Inj. Remdesivir, Methylprednisolone, Dexamethasone	Inj. Pipracillin+ Tazobactum, Metronidazole, Fluconazole, Inj. Amphotericin-B, Tobramycin, Surgical debridement of necrotic tissue	Complete Blood Count, Blood Sugar estimation, Histopathology, IL-6, CRP, D-dimer, MRI brain and orbit	COVID-19 RTPCR +	Rhino-orbital-cerebral	Alive
Mehta et al[1]	India	60	Male	Case Report	Diabetes mellitus, Lung disease,	Severe breathlessness, Pyrexia, Tachypnea, Generalized malaise, Non-healing ulcer on the right foot, Bilateral lid edema	Inj. Meropenem, oral Oseltamivir, methylprednisolone, Dexamethasone, Inj. insulin, Inj. Tocilizumab	Inj. Amphotericin-B, inj. Vancomycin	Chest CT scan, MRI brain, nasal and paranasal sinuses, SDA culture for mucormycosis,	COVID 19 RTPCR +	Rhino-orbital	Death
Mishra et al[24]	India	59 (mean) ±14.63 n=10	Male- 9 Female-1	Retrospective Analysis	Diabetes mellitus-8, Hypertension-3, Ischemic heart disease, Chronic kidney	Right eye pain, Chemosis, Loss of vision, Epistaxis, Bleeding gums	Steroids, Inj. Remdesivir, Inj. Tocilizumab	FESS, Orbital exenteration, Local debridement, Inj. Amphotericin B, Inj.	Histopathological examination, fungal smear, CT PNS, CT Brain	COVID-19+	Rhino-orbital-cerebral -10	Alive-5 Death-4 Lost in the follow-

Continued.

Authors	Country	Age in years	Sex	Study Design	Comorbid Illness	Clinical Presentation	Treatment for COVID-19	Specific treatments	Investigations	COVID-19 testing	Type of involvement in CAM	Outcome
					disease- 2, Chronic liver disease, Hypothyroidism- 2, No comorbidity-1			Posaconazole, Endoscopic maxillectomy, ethmoidectomy,				up- 1
Moorthy et al[8]	India	54.6 (mean) ±10.4 n=18	Male- 15 Female- 3	Retrospective multicentre observational study	Uncontrolled diabetes- 16 Non-diabetic- 2, Steroid- 16	Maxillary sinusitis, Loss of vision	COVID-19 symptomatic management	Inj. Amphotericin-B, Orbital exenteration- 7, FESS- 17, Maxillectomy- 11	Routine blood examination, X-ray Chest, CT scan, MRI, fungal culture	COVID-19 RTPCR + Previous h/o infection- 15, on admission- 3	Rhino-orbital- 9, Rhino-orbital-cerebral- 9	Alive- 11, Death- 6, Unknown- 1
Revannavar et al[25]	India	Middle-aged	Female	Case report	Diabetes mellitus	Ptosis, Facial pain, Ophthalmoplegia	Aspirin, Inj. Amphotericin-B,	FESS, Insulin therapy	CBC, LFT, KFT, S. Electrolytes, CRP, D-dimer, S. ferritin, S. procalcitonin, CT Paranasal sinus, MRI brain, Histopathology	RTPCR +	Rhino-orbital	Alive
Saldanha et al[26]	India	32	Female	Case report	Uncontrolled diabetes mellitus	Left eye Ptosis, Left facial pain	Supportive antibiotics	Amphotericin B, Endonasal Surgery	Nasal endoscopy, CT scan nose, and paranasal sinus, MRI, Nasal swab	CBNAAT for covid-19+, COVID 19	Rhino-orbital cerebral	Alive

Continued.

Authors	Country	Age in years	Sex	Study Design	Comorbid Illness	Clinical Presentation	Treatment for COVID-19	Specific treatments	Investigations	COVID-19 testing	Type of involvement in CAM	Outcome
									for culture, KOH wet mount			
Sarkar et al[27]	India	45.5 (mean) ±14.04 n=10	Male- 8, Female- 2	Case Series	Diabetic ketoacidosis (At presentation- 4, DKA (During hospitalization)- 5, None- 1	Viral Pneumonia, Severe ARDS, Pansinusitis	. Dexamethasone, Inj. Remdesivir- 4, Ventilator support- 9, Monoclonal antibodies, Broad-spectrum antibiotics	Inj. Amphotericin-B, FESS, Surgical debridement, Maxillectomy- 4 Exenteration- 1	MRI, CT scan, KOH wet mount, Tissue biopsy, Fungal culture	COVID-19 RTPCR +	Rhino-orbital- 9 Rhino-orbital-cerebral- 1	Alive- 6 Death- 4
Sharma et al[7]	India	Age- N.A. n=23	Male- 15, Female- 8	Prospective observational study	Uncontrolled diabetes mellitus- 12, Controlled diabetes- 9, Hypertension- 14, Renal failure- 1	Ethmoidal and maxillary sinusitis	Steroids, Broad spectrum antibiotics	Inj. Amphotericin-B, Surgical debridement - 21	MRI, CT Scan	COVID-19 RTPCR + h/o previous infection- 19 currently infected - 4	Rhino-orbital- 10 Rhino-orbital-cerebral- 2 Hard palate- 9	Alive

Continued.

Authors	Country	Age in years	Sex	Study Design	Comorbid Illness	Clinical Presentation	Treatment for COVID-19	Specific treatments	Investigations	COVID-19 testing	Type of involvement in CAM	Outcome
Shirke et al[28]	India	63	Male	Case series	Diabetes mellitus	Maxillary pain, Dental abscess, Fever	Inj. Amoxicillin, Inj. Paracetamol	Liposomal Amphotericin B, dental extraction, Surgical debridement of necrotic tissue	Facial CT Scan, HRCT chest, Culture for fungus	COVID-19 RTPCR +	Osteomyelitis of maxilla secondary to Mucormycosis	Alive
		45	Male	Case series	Hemolytic anemia	Right periorbital swelling, Palate swelling	Inj. Remdesivir, Inj. Heparin	inj. Posaconazole, Liposomal Amphotericin B, Surgical debridement	Facial CT Scan, fungal culture	COVID 19 RTPCR +	Rhino-orbital	Death
Sebastian et al[10]	India	61 (mean ±2.16 n=3	Male - 3	Case series	Diabetes Mellitus- 3, Hypertension, Coronary artery disease- 1, Renal disease- 2, Peptic Ulcer- 1	COVID-19 pneumonia with ARDS, Periorbital swelling, Blackening of the middle turbinate, Shock, Renal Failure, Altered Sensorium, Septicemia, Proptosis, Hematemesis	Mechanical ventilation, vasopressors, renal replacement therapy, broad-spectrum antibiotics, steroids, insulin	Antifungals not given	CT Scan Thorax and paranasal sinuses, KOH test, RTPCR Fungal culture not done	COVID-19 RTPCR +	Pulmonary, Rhino-orbital	Death
Junior et al[13]	Brazil	86	Male	Case report	Hypertension	Cough, Diarrhea, Dyspnea, Fever, Mild abdominal tenderness	Inj. Ceftriaxone, tab Azithromycin, Tab Oseltamivir, Hydrocortisone	Blood transfusion, Omeprazole	CT chest, Esophagogastroduodenoscopy, Pathological examination	COVID-19 RTPCR +	Gastrointestinal	Death

Continued.

Authors	Country	Age in years	Sex	Study Design	Comorbid Illness	Clinical Presentation	Treatment for COVID-19	Specific treatments	Investigations	COVID-19 testing	Type of involvement in CAM	Outcome
Rabelo et al[29]	Brazil	50	Female	Case Report	Diabetes mellitus	Headache due to COVID-19, painful hard palate lesion,	Antibiotics, NSAIDs	Amphotericin-B, Hydrocortisone, Surgical debridement, antihistamine therapy,	Incisional biopsy, CT scan, Histopathology, PAS test	COVID-19 RTPCR +	Gastrointestinal	Alive
Karimi-Galougahi et al[30]	Iran	61	Female	Case report	Diabetes mellitus	Hemifacial pain, Rhinorrhea, Chemosis, Diabetic Ketoacidosis, Acute sinusitis	Inj. Remdesivir, Interferon-alpha, Systemic corticosteroid	Insulin therapy, Systemic antifungals, FESS, Exenteration	CT paranasal sinuses, MRI orbits, Sino-nasal endoscopy	COVID-19 RTPCR +	Rhino-orbital	Not known
Rezaie et al[31]	Iran	53.75 (mean) ±19.75 n=7	Male-6, Female-1	Case presentation & review article	Uncontrolled diabetes mellitus-3, Hypertension-4,Bronchial asthma- 1, Pancreatitis- 1, Hyperlipidemia- 1	Severe ARDS	Oxygen supplementation with mechanical ventilation, systemic corticosteroids,	Antifungal monotherapy (43%), Combined antifungal therapy (28.57%), surgical intervention (in 4 patients)	Blood culture, KOH examination, Ct scan paranasal sinus	COVID-19 RTPCR +	Rhino-orbital-cerebral- 2 Others- 5	Death-7
Veisi et al[32]	Iran	40	Female	Case report	No h/o ARDS, immune system disorders, or any chronic conditions	Blepharoptosis, Ophthalmoplegia, Proptosis,	Supplemental oxygen, Remdesivir, Levofloxacin, Dexamethasone, Meropenem, Vancomycin,	Refused surgery. The patient was on regular paranasal sinus debridement	CT scan orbit, MRI, Histopathology, H&E staining test	RTPCR +	Rhino-orbital-cerebral	Death
		54	Male	Case report	Diabetes mellitus	Blepharoptosis, Proptosis, Chemosis, Mild conjunctival infection	Supplemental oxygen, Remdesivir, Levofloxacin, Piperacillin-Tazobactum,	FESS, Amphotericin-B, Insulin therapy, Dexamethasone,	CT Scan, MRI, Histopathology	RTPCR +	Rhino-orbital	Alive

Continued.

Authors	Country	Age in years	Sex	Study Design	Comorbid Illness	Clinical Presentation	Treatment for COVID-19	Specific treatments	Investigations	COVID-19 testing	Type of involvement in CAM	Outcome
							Vancomycin,	Posaconazole				
Pasero et al[33]	Italy	66	Male	Case report	Hypertension, Urinary tract infection	Hypoxia	Inj. Hydroxychloroquine, Lopinavir+ Ritonavir, Mechanical ventilation, Piperacillin+ Tazobactum, Levofloxacin	Amphotericin-B, inj. Isovuconazole, Thoracentesis	CBC, Bronchial aspirate, SDA, CT scan,	COVID +	Pulmonary	Death
Waizel-Haiat et al[12]	Mexico	24	Female	Case report	Obesity, Diabetes mellitus	Respiratory Failure, Left eyelid edema, Ptosis, Pallor hard palate	Inj. Imipenem/ Linezolid	Amphotericin-B	CT scan orbit, paranasal sinuses, and chest, CBC, LFT, KFT, D-dimer, Tracheal secretion culture, fungal culture	COVID-19 RTPCR +	Rhino-orbital	Death
Alekseyev et al[34]	U.S.A.	41	Male	Case report	Diabetes mellitus I, Hypertension	Dry cough, Loss of taste, Nasal pain	Steroids, Hydroxychloroquine,	Insulin therapy, Cefepime, Amphotericin-B, Surgical debridement, Heparin	X-ray chest, CT scan, MRI, LFT, KFT, S. electrolytes, S. ferritin, G6PD, fungal culture	COVID-19 RTPCR +	Rhino-cerebral	Alive

Continued.

Authors	Country	Age in years	Sex	Study Design	Comorbid Illness	Clinical Presentation	Treatment for COVID-19	Specific treatments	Investigations	COVID-19 testing	Type of involvement in CAM	Outcome
Kanwar et al[35]	U.S.A.	56	Male	Case report	End-stage renal disease, h/o hemodialysis	Fatigue, shortness of breath, Hemoptysis	Methylprednisolone, Inj. Tocilizumab, Convalescent plasma, Inj. Vancomycin, Inj. piperacillin-Tazobactum	Inj. Liposomal Amphotericin B,	Chest Xray, CT Chest, USG Guided Thoracocentesis, Sputum culture on SDA slant, Histopathological examination of parietal pleura, PAS staining,	COVID-19 RTPCR +	Pulmonary	Death
Cockerham et al[36]	U.S.A.	35	Male	Case report	MRSA, Uncontrolled Diabetes Mellitus I, Diabetic nephropathy	Diabetic ketoacidosis, headache, altered mental status, left eye pain	Ampicillin+ Sulbactum, Remdesivir, Dexamethasone	Amphotericin-B, Surgical debridement of necrotic tissue	ESR, CRP, D-dimer, CT scan orbits, MRI orbits, nasal endoscopy	COVID +	Rhino-orbital-cerebral	Alive
Dallalzadeh et al[37]	U.S.A.	36	Male	Case Report	Diabetes mellitus	Left facial swelling ,sinusitis, ,Diabetic ketoacidosis	Oral antibiotics, Corticosteroids, Inj. Remdesivir	Lateral canthotomy and cantholysis, Endoscopic sinus debridement, Inj. Amphotericin, inj. Isavuconazole, inj. micafungin	Ophthalmic examination, fundoscopic exam, MRI Face and brain, chest X-ray, fungal culture	COVID-19 RTPCR +	Rhino-orbital	Death

Continued.

Authors	Country	Age in years	Sex	Study Design	Comorbid Illness	Clinical Presentation	Treatment for COVID-19	Specific treatments	Investigations	COVID-19 testing	Type of involvement in CAM	Outcome
		48	Male	Case Report	Diabetes mellitus, COVID19 Pneumonitis, Diabetic ketoacidosis	periorbital edema, purulent discharge	Inj. Remdesivir, Convalescent plasma. Dexamethasone	Inj. Amphotericin B, Inj. Isovuconazole	CT Scan face and brain, fungus culture of purulent discharge	COVID +	Rhino-orbital-cerebral	Alive
Johnson et al[38]	U.S.A.	79	Male	Case report	Diabetes mellitus, Hypertension	Fever, rigors, dry cough, shortness of breath	Inj. Ceftriaxone, Inj. Azithromycin, Inj. Remdesivir, inj. Dexamethasone, Vancomycin, inj. Norepinephrine	inj. Voriconazole, iv L-Amphotericin B ,inj. Insulin	Chest X-ray, CT chest, Microscopic examination of BAL specimen, KOH Microscopic examination, a culture of BAL specimen	Covid-19 RTPCR +	Pulmonary mucormycosis	Alive
Khan et al[39]	U.S.A.	44	Female	Case report	Hypertension,	ARDS	Inj. Remdesivir, Methylprednisolone, Mechanical ventilation,	Insulin therapy, Voriconazole, Piperacillin+ Tazobactum, Micafungin	CBC, CRP, S. Electrolytes, D-dimer, LFT, S. ferritin, Tracheal aspirate culture, Bronchoscopy	COVID +	Pulmonary	Death
Khatri et al[40]	U.S.A.	68	Male	Case report	h/o Heart transplant, Diabetes mellitus, Hypertension, Chronic, kidney disease	Cough, Diarrhea, Fever, Sternal wound discharge	Inj. Remdesivir , plasma infusion ,inj. Vancomycin, Inj. Meropenem ,inj.	Iv Amphotericin B, Inj. Posaconazole, Debridement of the thoracic cavity	Chest CT scan, fungal culture	COVID 19 RTPCR +	Cutaneous	Death

Continued.

Authors	Country	Age in years	Sex	Study Design	Comorbid Illness	Clinical Presentation	Treatment for COVID-19	Specific treatments	Investigations	COVID-19 testing	Type of involvement in CAM	Outcome
							cyclosporine, methylprednisolone, hemodialysis					
Mekonnen et al[41]	U.S.A.	60	Male	Case report	Uncontrolled diabetes mellitus, Hypertension, Asthma, Hyperlipidemia	Dyspnea, Hypoxia	Inj. Remdesivir, iv Vancomycin, Inj. Cefepime, Inj. Dexamethasone, plasma	Inj. Amphotericin B, Inj. Caspofungin, Retrobulbar inj. amphotericin B, Inj. Posaconazole	CT brain, orbit, and neck	COVID-19 RTPCR +	Rhino-orbital	Death
Placik et al[42]	U.S.A.	49	Male	Case report	No medical history	Fever, Cough, Dyspnea,	Oxygen supplementation, Ceftriaxone, Azithromycin, Enoxaparin, Dexamethasone, Inj. Remdesivir, Tocilizumab	Amphotericin-B, Mechanical ventilation	X-ray chest, CBC, CRP, LDH, Serum ferritin, D-dimer, fungal culture	COVID-19 RTPCR +	Pulmonary	Death
Werthman et al[43]	U.S.A.	33	Female	Case report	Hypertension, Asthma, Diabetic ketoacidosis	Altered mental status, Cough, Dyspnea, Vomiting, Left eye ptosis	Inj. vancomycin, Inj. Piperacillin+ Tazobactam, Inj. Remdesivir Plasma	Inj. Amphotericin-B, sinus debridement	Chest X-ray, CT head, face and orbit, Culture for fungus, MRI brain	COVID 19 RTPCR +	Rhino-orbital cerebral	Death

The youngest patient was 24 years and the eldest was 86 years. According to a previous study,11 India has the highest burden of mucormycosis cases in the world with an estimated prevalence of 140 cases per million population.[13] 75.7% were male and 24.3% were female.[12] All reported cases in our review were COVID-19 positive. Some patients had an active infection, while others had recovered or were in the recovery phase. The diagnosis was established mainly by radiological features, histopathological examination, microbiological, and culture for fungus.

In our systemic review analysis 72/104 (69.9%) cases had diabetes mellitus (DM II) and 11/104 (10.6%) cases had diabetic ketoacidosis (DKA), 30/104 (29.1%) cases hypertension (HTN), 7/104 (6.7%) had a renal failure (RF) 4/104 (3.8%) had coronary artery disease (CAD), 2/104 (1.9%) had a history of dialysis, and 2/104 (1.9%) had chronic liver disease (CLD). In our review, the clinical presentation of mucormycosis was consistent with the picture of mucormycosis in DM II where the predominant clinical presentation was rhino-orbital or rhino-cerebral disease predominates and DM II is the most common risk factor for mucormycosis and is associated with increased morbidity and mortality in COVID19.[11]

In our study, out of 104 confirmed cases of mucormycosis, 74/104 (71.8%) cases received corticosteroid during COVID-19 treatment. In a previous study on 101 mucormycosis cases (95 confirmed and 6 suspected cases) in COVID-19, 80% of cases had DM II and 76.3% received a course of intravenous corticosteroids.[11] Similarly, in a systemic review, 41 confirmed reported cases in people with COVID-19, 93% cases were reported with DM II, while 88% were received intravenous corticosteroids.[14] Whereas a study conducted before the COVID-19 pandemic, a nationwide multicentre study of 388 cases of diagnosed/suspected mucormycosis in India, finds that 57% had uncontrolled DM II and 18% had DKA.[5,14] Corticosteroid use is a key factor for opportunistic mycoses, including mucormycosis, and frequent use of corticosteroid causes hyperglycemia.[11] A previous study reported that COVID 19 positive patients are highly susceptible to mucormycosis who are under high steroid doses or in immunosuppressive therapy.[15]

In addition to hyperglycemia, altered iron metabolism occurs in severe COVID 19 cases. There is a hyperferritinemic state; high ferritin is a marker of severe systemic disease. High ferritin level leads to excess intracellular iron that generates reactive oxygen species resulting in tissue damage. Cytokines, especially Interleukin-6 (IL-6), due to severe infection and DKA, stimulates ferritin synthesis; downregulates iron export resulting in intracellular iron overload, further exacerbating the process. Therefore, iron overload and excess free iron seen in acidemic states are one risk factor for mucormycosis.[11]

In our review, 55.3% of cases had rhino-orbital mucormycosis (ROM), 9.62% cases had pulmonary mucormycosis (PM), 31.0% had rhino-orbital-cerebral mucormycosis (ROCM), 1.9% had gastrointestinal mucormycosis (GM), and 0.9% had cutaneous mucormycosis (CM). Whereas in another study, 88.9% had nose and sinus involvement followed by 56.7% had rhino-orbital mucormycosis, 22.2% had rhino-orbital-cerebral mucormycosis.[14] In another study in India before the COVID-19 pandemic, of 465 cases of mucormycosis 67.7% patients had shown rhino-orbital mucormycosis as the most common presentation, followed by 13.3% as pulmonary and 10.5% exhibiting cutaneous type mucormycosis.[6]

Hyperglycemia and ketoacidosis enhance the expression of endothelial receptor glucose-regulated protein (GRP 78) and the mucorales spore coat protein homologs (CotH), which causes increased susceptibility of diabetic ketoacidosis patients to mucormycosis.[11,16]

In our review, intravenous liposomal Amphotericin-B has been used in 82.5% of cases of mucormycosis. It was found that a combination of antifungal agents was used in 19.4% of participants, and the most common combination used was Posaconazole 15.5% along with intravenous liposomal Amphotericin-B.

In our review, the combined medical and surgical management was performed in 79.6% of the cases. The overall mortality in our review was 36.9%. Whereas in another study,14 30.7% overall mortality was reported.

The presence of multiple comorbid conditions in COVID-19 positive patients, additional immunosuppression caused by glucocorticoids predisposing patients to invasive fungal infection. The current guideline for the management of mucormycosis suggests intravenous liposomal Amphotericin B at 5-10 mg/kg per day and up to 10 mg/kg per day in cases of central nervous system involvement.[17]

Control of hyperglycemia, judicious use of steroids, early diagnosis and treatment with intravenous liposomal Amphotericin-B, as well as surgical debridement, are all necessary for a successful outcome.[18]

Limitations

The sample size of the patients in the review was small and a large group is needed to draw adequate conclusions. We could not rule out publication bias as our study is based on reported cases. Duration of hospital stay, total duration of therapy, and duration of follow-ups were not uniformly documented in the published materials. Mucormycosis attributable mortality was not estimated due to a lack of acceptable and sufficient controls in the study. As a result of which, we could not exactly predict the associated risk factor leading to the development of CAM in COVID-19 positive patients.

Further, in absence of a denominator, we were unable to calculate the exact incidence of COVID-associated mucormycosis.

CONCLUSION

The diagnosis of mucormycosis is still challenging and very dynamic. In our study, we found that most cases were reported from India. All patients had a history of COVID-19 infection, and most patients were diabetic and received corticosteroid therapy during treatment of COVID-19, which suggests rationale use of the drug during the pandemic. Combined antifungal and surgical treatment may be associated with an increased survival rate. In the future, all clinicians should be aware of the possibility of fungal infections such as mucormycosis developing in COVID-19 patients, particularly those with comorbidities and who are on immunosuppressive drugs. Early diagnosis and intravenous liposomal Amphotericin therapy, as well as surgical intervention, are vital for a better outcome of the disease. To gain a better understanding of the novel viral infection and the associated coinfections, global scientific collaboration and publication of new findings are critical.

Future considerations

The findings from the review study implicate the requirements to consider necessary updates in the management of CAM that can be shared among healthcare professionals to provide and promote a holistic treatment model globally. The efficiency of early diagnosis and treatment can be inculcated in future research and policymaking to ensure adequate accessible information to minimize the impact of the disease.

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