Clinical Phenotypes of COVID-19 Associated Mucormycos

Subjects: Infectious Diseases

Contributor: Maria Panagiota Almyroudi , Karolina Akinosoglou , Jordi Rello , Stijn Blot , George Dimopoulos

Mucormycosis is a rare infection caused the members of the order *Mucorales*. Its prevalence ranges from 0.005 to 1.7 per million people worldwide, while in India, it reaches 14 cases per 100,000 inhabitants . During the COVID-19 pandemic, a surge in mucormycosis cases has been observed, especially in India, where the Government of India portal reported 47,508 cases from 5 May 2021 to 3 August 2021. Characteristically, Samir Joshi et al. reported 160 cases of COVID-19-associated mucormycosis (CAM) from April to May 2021 in the Ear, Nose, Throat Department of BJGMC-SGH hospital in India, compared with 3–8 cases of mucormycosis detected each year from 2016 to 2020.

mucorales invasive fungal infections SARS-CoV-2

1. Clinical Presentation

CAM was diagnosed after a median of 17.4 days (Q1:14.4, Q3:21.8, IQR 7.5 days) post COVID-19 diagnosis but simultaneous manifestation with acute COVID-19 is also reported. Mucormycosis may be associated with neuroinflammation of the acute phase or be integrated in the post-COVID-19 syndrome [1]. However, the long period that is mediated between COVID-19 positivity and CAM diagnosis may actually reflect a delay in diagnosis, that may be associated with a higher mortality [2].

Mucormycosis most commonly affects the head and neck region. ROCM is the commonest form globally and was also the most frequent form associated with COVID-19. ROCM was diagnosed in 8082/8218 (98.3%) CAM patients and pulmonary infection in 98/8218 (1.2%), of whom 30.6% were in Europe. (**Table 1**). Mucormycosis of the gastrointestinal tract was found in 5/8218 (0.06%) CAM patients, cutaneous in 11/8218 (0.13%), disseminated in 11/8218 (0.13%) and renal in 1/8218 (0.01%) (**Table 1**). In Europe 3/40 (7.5%) of CAM patients had ROCM, 30/40 (75%) had pulmonary mucormycosis, 4/40 (10%) mucormycosis of the gastrointestinal tract and 3/40 (7.5%) disseminated (**Figure 1**).

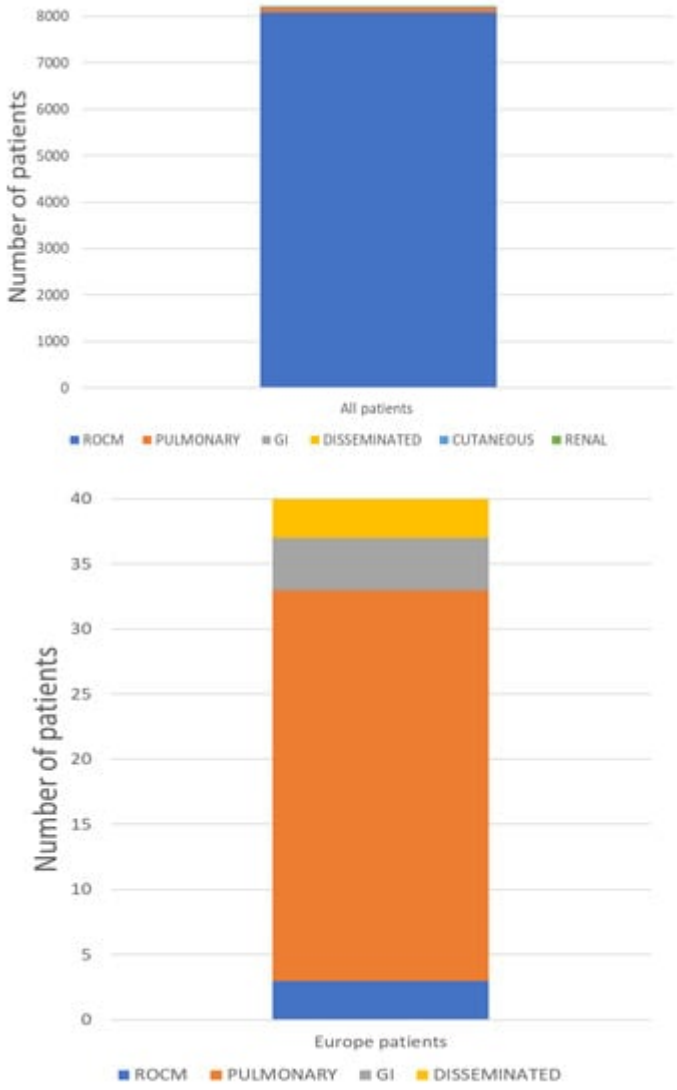

Figure 1. Clinical presentation of patients with CAM in total and in Europe.

Table 1. Incidence of CAM among hospitalized COVID-19 patients, type of infection, invasive or non-invasive mechanical ventilation, risk factors and all-cause mortality.

Study	Incidence of CAM (%)	Type of Infection (%)	Cerebral Involvement /ROCM pts, n (%)	IMV or NIV n (%)	DM (% of CAM pts)	Steroids Intake (% of CAM pts)	All-Cause Mortality (%)
Said Ahmed WM et al. [3]	NA	Maxillary osteomyelitis	0/14 (0%)	NA	64.2% DM 35.7% with temporary post-COVID-19 hyperglycemia	NA	NA
Murthy R et	NA	RO	0/111 (0%)	NA	NA	NA	NA

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al. [4]							
Walia S et al. [5]	NA	SN (100%), O (51.85%), C (9.44%), Cu (1.85%), P (0.18%).	51/529 (9.6%)	NA	97.96%	84.85%	9.25%
Vare AA et al. [6]	1.36%	ROCM	3/67 (5%)	18/67 (27%)	90%	84%	34%
Fouad YA et al. [2]	NA	O	0/26 (0%)	NA	96.2%	76.9%	46,2%
Soni K et al. [7]	NA	ROCM	29/145 (20%)	NA	86.2%	65%	18%
Metwally MI et al. [8]	NA	Head and neck	8/63 (12.7%)	NA	80.9%	82.5%	17.5%
Arora U et al. [9]	NA	RS (29%), RO (47.3%), ROCM (14.5%), O (1.3%), RO/palatal (5.3%), Cu (0.6%), P (1.3%), D (0.6%)	22/148 (14.9%)	NA	92.1%	65.8%	NA
Jindal G et al. [10]	NA	ROCM	9/15 (60%)	NA	100%	80%	6.6%
Syed-Abdul S et al. [11]	NA	NA	NA	NA	NA	NA	NA
Patel A et al. [12]	NA	RO (96.5%), P (3.4%)	0/28 (0%)	NA	NA	NA	NA
Pruthi H et al. [13]	NA	P	NA	0/5 (0%)	100%	NA	80%
Bansal SB et al. [14]	10.8%	RO (91%), P (9%)	NA	0/11 (0%)	64%, 36% developed transient hyperglycemia	100%	18.2%

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Dulski TM et al. [15]	NA	RO (10%), ROCM (30%), P (30%), D (20%), GI (10%)	3/4 (75%)	5/10 (50%)	80%	90%	60%
Meshram HS et al. [16]	4.4%	ROCM (91.8%), P (8.2%)	11/42 (26.2%)	0/61 (0%)	24.6%	44%	26.2%
Aggarwal SK et al. [17]	NA	ROCM	4/13 (30.8%)	NA	92.3%	92.3%	15.4%
Kulkarni R et al. [18]	2.1% (1 centre)	ROCM	12/102 (11.8%)	NA	81.6%	NA	51%.
Choksi T et al. [19]	NA	ROCM	6/73 (2%)	17/73 (23.3%)	74%	98%	36%
Kumar S et al. [20]	NA	ROCM	60/287 (21%)	NA	80%	NA	NA
Mehta R et al. [21]	NA	ROCM	0/17 (0%)	NA	100%	NA	NA
Panwar P et al. [22]	NA	ROCM	0/7 (0%)	NA	100%	42.8%	0%
Patel DD et al. [23]	NA	ROCM	21/96 (21.9%)	6/96 (6.3%)	71.8%	82.3%	NA
Vaid N et al. [24]	NA	ROCM	NA	NA	33.8%	100%	10.7%
Goddanti N et al. [25]	NA	ROCM	NA	NA	95.7%	79%	NA
Yadav T et al. [26]	NA	ROCM	25/50 (50%)	NA	86%	44%	NA
Meshram VB et al. [27]	NA	ROCM (90.9%), P (9%)	3/10 (30%)	0/11 (0%)	54.5%	100%	27%

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Zirpe K et al. [28]	NA	ROCM	20/84 (23.8%)	NA	64.3%	83.3%	15.5%
Alloush TK et al. [29]	NA	ROCM	9/14 (64.2%)	0/14 (0%)	92.8%	NA	21.4%
Pal P et al. [30]	NA	ROCM	3/10 (30%)	NA	70%	80%	30%
Danion F et al. [31]	NA	P(53%), GI (18%), ROCM (12%), D (18%)	NA	13/17 (76.5%)	47%	76.5%	88%
Nehara HR et al. [32]	NA	ROCM	18/105 (17.1%)	NA	78.1%	66.3%	19.05%
Pandiar D et al. [33]	NA	Oral	0/12 (0%)	NA	66,7%	NA	NA
Kumar S et al. [34]	NA	NA	NA	0/55 (0%)	83.6%	98.2%	16%
Bilgic A et al. [35]	2.5%	ROCM	NA	6/38 (16%)	50%	100%	5%
Guemas E et al. [36]	7.1%	P	NA	NA	20%	90%	50%
Kumar SG et al. [37]	NA	ROCM	44/101 (43.6%)	NA	94%	80.1%	17.8%
Mani S et al. [38]	NA	ROCM	4/89 (4.5%)	NA	96%	92%	3.4%
Dravid A et al. [39]	NA	ROCM (98.3%), D (1.7%)	26/58 (44.8%)	3/59 (5.1%)	89.8%	100%	25.4%
Naruka S et al. [40]	NA	ROCM	9/79 (11.4%)	NA	100%	NA	18.18%
Jain K et al. [41]	NA	ROCM	3/95 (3.2%)	NA	77%	100%	5.2%

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Bhanuprasad K et al. [42]	NA	ROCM	39 (29.5%)	3/132 (2.3%)	97.7%	55.3%	9.8%
Desai EJ et al. [43]	NA	ROCM	0/100 (0%)	NA	80%	NA	20%
Nasir\n et al. [44]	0.35%	P (60%), ROCM (40%)	4/4 (100%)	3/10 (30%)	70%	80%	70%
Gupta \s et al. [45]	NA	ROCM	4/56 (7.1%)	NA	85%	66%	16%
Joshi S et al. [46]	NA	ROCM	22/178 (12.4%)	5/178 (2.8%)	74.2%	52.8%	15%
Pradhan P et al. [47]	NA	ROCM	10/46 (21.7%)	NA	95.65%	89.1%	19.5%
Mehta RNM et al. [48]	NA	ROCM	33/215 (15.3%)	NA	91%	88%	12.1%
Riad A et al. [49]	NA	ROCM	7/7 (100%)	NA	85.7%	100%	0%
Guzmán-Castro S et al. [50]	0.04%	ROCM (83.3%), P(16.6%)	5/5 (100%)	2/6 (33.3%)	83.3%	100%	83.3%
Seidel D et al. [51]	2 centres: 0.67%, 0.58% ICU: 1.47%, 1.78%	P(84.6%), ROCM (7.7%), GI (7.7%)	1/1 (100%)	11/13 (84.6%)	23.07%	84.6%	53.8%
Gupta R et al. [52]	NA	ROCM	25/115 (21.7%)	13/115 (11.3%)	85.2%	100%	21.7%
Alfishawy M et al. [53]	NA	ROCM (95.2%), P (4.8%)	5/20 (25%)	NA	90%	100%	33.3%
Dave TV et al. [54]	NA	ROCM	19/58 (33%)	NA	74%	NA	34%

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Selarka L et al. [55]	1.8%	ROCM	9/47 (19.1%)	20/47 (42.6%)	76.6%	100%	23.4%
Avatef Fazeli M et al. [56]	NA	ROCM	0/12 (0%)	1/12 (8.3%)	83.33%	75%	66.7%
Mishra Y et al. [57]	3.36%	ROCM	0/32 (0%)	NA	87.5%	93%	12.5%
Sen M et al. [58]	NA	ROCM	539/2826 (19.1%)	114/1602 (7.1)	78%	87%	14%
Pakdel F et al. [59]	NA	ROCM	7/15 (46%)	1/15 (6.7%)	86%	46.6%	47%
Y M. Reddy et al. [60]	NA	RO	0/6 (0%)	NA	100%	66.7%	100%
R. Arora et al. [61]	NA	ROCM	6/60 (10%)	NA	98.3%	63.3%	NA
D.P Gupta et al. [62]	NA	ROCM	NA	NA	100%	NA	5.7%
M.Gautam et al. [63]	NA	ROCM	NA	NA	100%	66.7%	0%
R.M.Mehta et al. [64]	NA	P	NA	4/5 (80%)	80%	100%	80%
Y.M.Reddy et al. [65]	NA	ROCM	NA	NA	100%	80.6%	35.5%
S.P.Singh et al. [66]	NA	RO	0/6 (0%)	0/6 (0%)	100%	66.7%	16.7%
M.Hada et al. [67]	NA	ROCM	54/270 (20%)	NA	92.2%	72%	NA
M. Kumar H et al. [68]	NA	ROCM (85.7%), P (14.3%)	15/24 (62.5%)	6/28 (21.4%)	75%	70.4%	73.9%
S. Bhandari et al. [69]	NA	NA	NA	NA	86.8%	84.3%	NA

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M Chouhan et al. [70]	NA	ROCM	9/41 (21.9%)	NA	97.6%	87.8%	9.8%
Y. Singh et al. [71]	NA	ROCM (92.3%), P (7.7%)	2/12 (16.7%)	10/13 (76.9%)	61.5%	84.6%	69.2%
S M Desai et al. [72]	NA	ROCM	3/50 (6%)	NA	82%	84%	30%
A. Kumari et al. [73]	NA	ROCM	4/20 (20%) [58]	NA	80%	80%	30%
S. Mitra et al. [74]	NA	ROCM	NA	[90] NA	100%	78.1%	NA
A Ramaswami et al. [75]	NA [48]	ROCM	17/70 (24.3%)	NA	70%	70%	NA
A.R. Joshi et al. [76]	NA	ROCM	7/25 (28%) [18]	12/25 (48%)	88%	100%	56%
A. Patel et al. [77]	7 centers: 0.27% (general wards)	ROCM (86.1%), P (8.6%), renal (0.5%), other (e.g., Cu, GI) (2.7%), D (2.1%)	44/161 (27.3%)	NA	60.4%	78.1%	44.1%
S Sharma et al. [78]	NA	ROCM	2/23 (8.7%)	NA	[91] 91.3%	100%	NA
R. Kant et al. [79] [13]	NA	ROCM (96%), P (4%)	11/96 (11.5%)	NA	95%	81%	13%
C. Eker et al. [80]	NA	ROCM	9/15 (60%)	NA	100%	NA	33.3%
A.K. Pandit et al. [81]	NA	ROCM	[91] 30/56 (53.6%)	NA	85.7%	53.6%	30.6%
S.F. Youssif et al. [82]	7.6%	ROCM	32/33 (97%)	NA	63.6%	NA	90.9%

Early recognition of CAM is crucial, as delay in therapy is associated with higher mortality [16]. A high index of suspicion should be maintained when clinical symptoms and radiological features appear in a patient with predisposing factors. According to criteria proposed by the European Confederation of Medical Mycology and the

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A. Sekaran, et al. [83]	NA	ROCM	6/30 (20%)	8/30 (26.7%)	100%	90%	16.7%
R. R. Shabana et al. [84] [93]	NA	ROCM	4/30 (13.3%)	1/30 (3.3%)	90%	66.6%	20%
A. K Patel et al. [85]	NA	ROCM (92.2%), P (7.8%)	5/59 (8.5%)	NA [94]	75%	90.6%	4.7%
H. D.D. Martins et al. [86]	NA	ROCM	0/6 (0%) [58]	NA	83.3%	NA	16.7%
S. Iqtadar et al. [87]	NA	ROCM	NA	0/7 (0%)	71.4%	100%	14.3%
A. Al Balushi et al. [88] [91]	NA	ROCM	3/10 (30%)	6/10 (60%) [31]	100%	30%	60%
R. Soman et al. [89] [36]	NA	ROCM (78.6%), P (21.4%)	5/22 (22.7%)	NA	[31] NA	NA	25%

simultaneously tested positive for Aspergillus. This cluster of cases was possibly attributed to environmental exposure, due to construction work near the hospital [36].

C: Cerebral, Cu: Cutaneous, DM: Diabetes Mellitus, D: Disseminated, GI: gastrointestinal, IMV: Invasive Mechanical Ventilation, NA: Not Available, NIV: Non-invasive ventilation, O: Orbital, P: Pulmonary, RO: Rhino Orbital, ROCM: Rhino-Orbital-Cerebral Mucormycosis, RS: Rhino-sinus, SN: Sinonasal.

Few studies in the literature report on the species isolated, reflecting the difficulties encountered with culture-based identification and the infrequent use of PCR. Rhizopus sp. were the most common species isolated. In a study including 203 cases of mucormycosis with positive cultures during the second wave of the pandemic in India, Rhizopus oryzae, followed by R. microspores, were most frequently identified [95].

Mixed infections with Aspergillus and Candida are detected both in pulmonary and rhino-orbital-cerebral form. Eighteen studies in the literature (12 from India, 3 from Europe, 2 from Pakistan and 1 from Egypt) refer to Aspergillus possible co-infection, with Aspergillus being isolated in 89/863 (10.3%) CAM patients. Danion et al., reported 5 mixed fungal infections with Aspergillus in 17 (29%) CAM cases, of which 2 exhibited pulmonary involvement, 1 ROCM, 1 disseminated and 1 GI disease. All patients were mechanically ventilated and COVID-19-associated pulmonary aspergillosis (CAPA) was diagnosed at a median of 2 days before CAM. Four out of five patients with CAM and CAPA received L-Amphotericin B (one was diagnosed after death) and 5/5 died [31]. In Toulouse, France, eight cases of concomitant infection with Mucor and Aspergillus were detected in the ICU and were attributed to construction work that was undertaken near the hospital. All patients had pulmonary involvement, 3/8 were treated with L-Amphotericin B, 4/8 with a combination of L-Amphotericin B and Posaconazole and/or isavuconazole and 1/8 with isavuconazole. Four out of eight (50%) patients died [36]. Aspergillus fumigatus,

Aspergillus niger and Aspergillus nidulans have been isolated [44], while mixed mold infections with Candida are also described in the literature [40][41]. Nidhya Ganesan et al. reported that among 60 biopsy samples from suspected rhino-maxillary/rhino-orbital mucormycosis post COVID-19, mucorales was isolated in 58 (96.67%) samples, aspergillus along with mucorales in 12 (20%) and a combination of mucorales and candida in 8 (13.33%) [96].

Neither 1,3-beta-D-glucan assay and galactomannan are positive in mucormycosis but can aid in the diagnosis of invasive pulmonary aspergillosis, which is recognized as a severe superinfection of COVID-19 pneumonia resulting in higher mortality. A positive serum or BAL galactomannan in a patient with compatible clinical presentation and imaging findings is indicative of invasive aspergillosis [97]. BAL galactomannan was measured in the study of R.H. Mehta et al. and was found positive (≥1) in 4/5 cases of COVID-19-associated pulmonary mucormycosis. In two cases, Aspergillus fumigatus was isolated in fungal culture, while in three cases, Aspergillus was identified in histopathological analysis [64]. Ultimately, mixed infection should be actively searched and isavuconazole is a potential empirical choice if mixed infection is suspected.

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