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A clinico-pathological study of COVID-19 associated rhino-orbital-cerebral mucormycosis

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Purpose: Known predisposing factors for mucormycosis are neutropenia and diabetes. Though COVID-19 is associated with hyperinflammatory response, a high surge in rhino-orbital-cerebral mucormycosis (ROCM) cases was observed during the second wave. The histopathological features reflect the background pathogenesis. This study analyzes the histopathological features and clinical presentation of COVID-19-associated ROCM. **Methods:** In this retrospective observational study, the clinical details of 89 proven ROCM patients treated during May–July 2021 were collected from the case records. Histopathological features were correlated with clinical staging groups and outcomes. The mean neutrophil-to-lymphocyte ratio (NLR) of clinical and outcome groups were compared. **Results:** The mean age was 54.71 ± 11.03 years, with male patients constituting a majority (78.7%). Uncontrolled diabetes mellitus was noted in 70.8% of patients, and 3.4% had normal range of blood sugar. The mean blood sugar was 298.08 ± 99.51 mg/dL. The mean duration of onset of symptoms of mucormycosis from the diagnosis of COVID-19 was 17.36 ± 7.392 (3–45) days. Poor outcome with disease progression or death occurred in 21.3% of patients. Clinical group II patients (44.9%) with ROCM stages 3c and above had poor outcomes ($P = 0.005$). Histopathological analysis showed minimal inflammation in 25.8%, neutrophil extracellular trap (NET) in 75.3%, and angio-invasion in 28.1% of patients. Minimal inflammation was associated with clinical group II ($P = 0.004$) and poor outcome ($P = 0.001$). Angio-invasion correlated with poor outcome ($P = 0.007$). Patients with severe clinical group and poor outcome had higher mean NLR with $P = 0.017$ and $P = 0.007$, respectively. **Conclusion:** Vision loss and cerebral involvement had poor outcomes. The histopathologic features such as inflammation and angio-invasion along with NLR aid as prognostic indicators in the management of ROCM. The role of NET in the pathogenesis of COVID-19-associated ROCM needs further studies.

Key words: Angio-invasion, COVID-19-associated ROCM, histopathology, inflammation, prognosis, stages of ROCM

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Mucormycosis is an opportunistic fungal disease with a high prevalence in India (140 per million) and a high case fatality rate (49%).[1,2] Neutropenia and diabetes-related neutrophilic dysfunction are considered as predisposing factors for mucormycosis.[3,4] COVID-19 infection is linked with hyper-inflammatory response.[5] However, a high surge in mucormycosis cases occurred during the second wave of COVID-19 pandemic in India. The histopathological features reflect the background pathogenesis.

This study correlates the histopathological changes and clinical presentation of rhino-orbito-cerebral mucormycosis (ROCM) patients in the background of COVID-19 pandemic and assesses whether the histopathological features help as prognostic aid in the management of COVID-19-associated ROCM.

Methods

After getting approval from the institutional ethical committee, 89 histopathologically proven ROCM patients treated at a tertiary care center during May–July 2021 were included in this retrospective, observational, cross-sectional study. The clinical features of 89 proven ROCM patients were obtained from the case records.[6] Socio-demographic details, diabetic status, COVID-19 status, NLR, primary symptoms, and signs were recorded.

Histopathological confirmation of specimens from functional endoscopic sinus surgery (FESS) with or without orbital decompression and neurosurgical abscess drainage was done at the Department of Pathology. The culture reports of the cases were recorded. Mucormycosis specimens from other sites such as cerebral abscess due to direct wound infection were excluded.

Histopathological sections stained with Hematoxylin and Eosin (H and E) and periodic acid-Schiff (PAS) were evaluated. Based on the presence of hyaline (non-pigmented) broad (5–20-μm wide, ribbon-like), pauciseptate, or aseptate hyphae

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showing right-angled or obtuse-angled branching, the diagnosis of mucor was histopathologically confirmed [Fig. 1a].[3,7] The histopathological parameters, namely fungal load, areas of necrosis, inflammatory response, and angio-invasion, were analyzed and graded by one observer.[4,8,9] Fungal load was graded as low or high based on the number of foci per slide, the number of hyphae per foci, and the presence or absence of sheet-like dense clusters of fungi or endospore formation.[8] The slides showing ≥5 foci per slide, ≥5 hyphae per foci, and presence of dense clusters of fungi and endospore formation were graded as high load [Fig. 1b]. Areas of necrosis were graded as small or large based on the proportion of necrotic areas to total material submitted for histopathological examination.[4,8] Slides showing ≥50% were graded as large areas of necrosis.

Inflammatory response was graded as minimal, moderate, or marked based on the presence or absence of neutrophilic infiltration surrounding necrosis and/or hyphae.[4,8,9] The intense neutrophilic response around necrosis and/or hyphae was graded as marked inflammatory response [Fig. 1c]. The absence or minimal neutrophilic infiltration or lympho plasmocytic response around necrosis and hyphae were graded as minimal inflammatory response. Moderate neutrophilic infiltration in viable tissue or around necrosis and not around hyphae was graded as moderate inflammatory response. The presence or absence of nuclear debris (chromatin material) forming extracellular network surrounding necrosis or fungal hyphae (NET) was also noted [Fig. 1d].[9] Angio-invasion of fungi was graded as presence or absence.[4,8] The infiltration of hyphae in the walls of the blood vessel was considered as presence of angio-invasion [Fig. 1e]. Suspicious angio-invasion with hyphae inside the small spaces amidst necrosis as well as hyphae surrounded by hemorrhage was also considered as presence of angio-invasion [Fig. 1f].

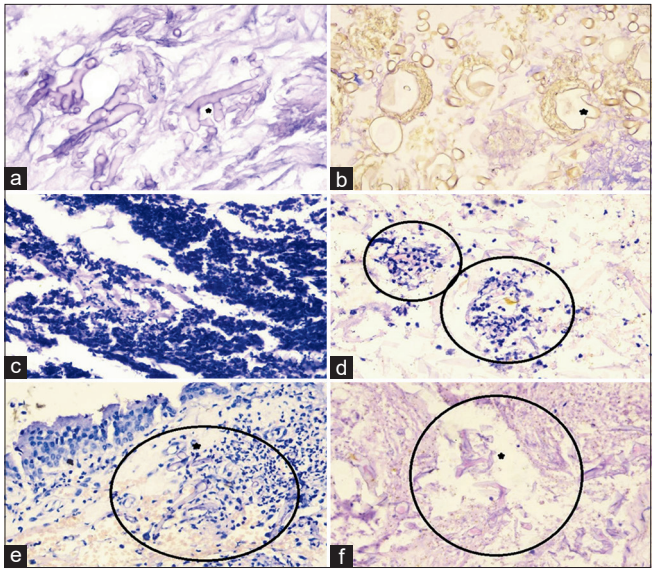

Figure 1: Histopathological pictures (a) PAS, 40 × broad, branching hyphae (black asterisk); (b) H and E 40×, endospores with columella (black asterisk); (c) H and E 10×, marked neutrophilic inflammation, (d) H and E 40×, neutrophil extracellular trap (black circle), Angioinvasion – H and E 40×; (e) Hyphae in the vessel wall; (f) Hyphae in space surrounded by erythrocytes (black circle, asterisk)

Based on the clinical symptoms, signs, diagnostic endoscopic assessment, and radiological findings, the histopathologically confirmed 89 ROCM patients were staged as follows.[10] Patients with involvement of the nasal mucosa were graded as stage 1, with involvement of paranasal sinuses as stage 2, with involvement of orbit as stage 3, and with involvement of the central nervous system (CNS) as stage 4. Further, stage 1 was graded based on the involvement of middle turbinate as 1a, inferior turbinate/ostium of nasolacrimal duct as 1b, nasal septum as 1c, and bilateral nasal mucosa as 1d. Stage 2 was graded based on the involvement of one para-nasal sinus as 2a, two ipsilateral sinuses as 2b, more than two ipsilateral sinuses and/or palate/oral cavity as 2c, and bilateral para-nasal sinuses or involvement of the mandible/zygoma as 2d [Fig. 2a].

Stage 3 ROCM with involvement of the medial orbit, nasolacrimal duct without affecting vision was graded as 3a and that with diffuse orbital involvement without affecting vision was graded as 3b [Fig. 2b]. Central retinal artery occlusion or involvement of orbital apex, superior orbital fissure, inferior orbital fissure with loss of vision was graded as stage 3c [Fig. 2c]. Bilateral orbital involvement with loss of vision was graded as stage 3d [Fig. 2d]. Stage 4 ROCM was graded based on the involvement of focal cavernous sinus as 4a; diffuse cavernous sinus as 4b; skull base, internal carotid artery occlusion, and brain infarction as 4c; and diffuse CNS involvement as 4d.

For analyzing the histopathologic features and clinical presentation, clinical groups I and II were formed. Patients in stages 1, 2, 3a, and 3b were included in clinical group I, and patients in stages 3c, 3d, and 4 were included in clinical group II. The outcome was classified as outcome group I, which included patients with regressed or stable residual disease, and outcome group II, which included patients with disease progression or death.

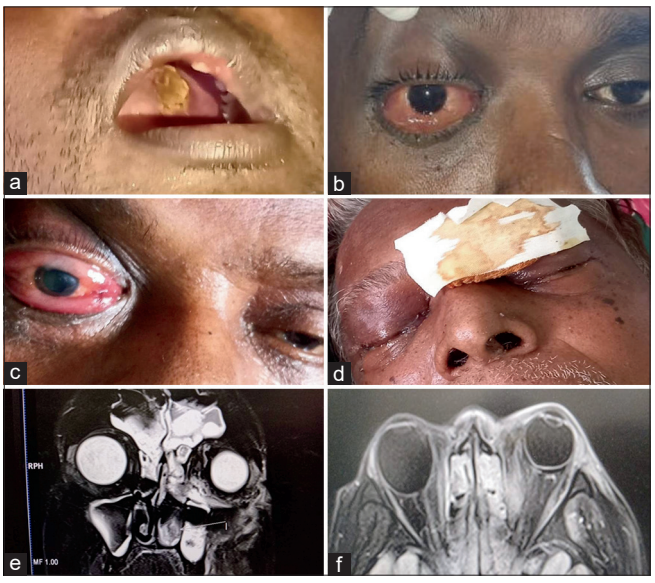

Figure 2: Clinical Pictures (a) palatal eschar; (b) Stage 3b with right periocular edema, chemosis, and proptosis; (c) Stage 3c with right chemosis and dilated pupil; (d) Stage 3d with bilateral periocular edema and proptosis. MRI images Coronal and Axial T2 weighted;(e) black turbinate sign (white arrow); (f) guitar pick sign

Statistical analysis was done by encoding the data in SPSS trial version 28. Data were represented as mean ± standard deviation for continuous variables (age and NLR) and frequency with proportion for the categorical variables (histopathological grading, clinical groups, outcome groups, etc.). Chi-square test was used to compare the frequency between the groups. Independent samples *t* test was used to compare the means between two groups. $P < 0.005$ was considered statistically significant.

Results

This study included 89 patients with ages ranging from 32 to 77 years, with 70 males and 19 females [Fig. 3]. The overall, male, and female mean age (in years) were 54.71 ± 11.03, 54.41 ± 11.19, and 55.79 ± 10.81, respectively. The age distribution showed maximum number of patients (33.7%) in the age group of 51–60 [Fig. 4]. Among 89 patients, three patients had normal range of blood sugar, 74 patients were known diabetic on treatment, and the rest were newly diagnosed diabetics. Uncontrolled diabetes mellitus was associated with 70.8% and diabetic keto-acidosis in 4.5% of patients [Table 1]. The mean blood sugar was 298.08 ± 99.51 (98–560) mg/dL. Concurrent infection with SARS-CoV-2 occurred in seven (7.9%) patients. The mean duration of onset of symptoms of mucormycosis from the diagnosis of COVID-19 was 17.36 ± 7.392 (3–45) days. Around 47.2% of patients had onset of symptoms of mucormycosis 14 days after the diagnosis of COVID-19 [Table 1] [Fig. 5]. Eighty-two patients had received systemic corticosteroid treatment for COVID-19. The predominant primary symptom was orbital/facial pain (29.2%) [Table 2], and the most frequent primary sign was periocular/facial edema (27%). Loss of vision was the presenting sign in 22.5% of patients [Table 3]. All patients underwent diagnostic nasal endoscopic examination and functional endoscopic sinus surgery with debridement of necrotic tissues.

The histopathological examination of specimens received from 89 patients revealed 93.3% with high fungal load.

Table 1: Diabetic and COVID-19 status

Parameter	*n*=89 (%)
Diabetes Mellites	
Known DM	74 (83.1)
Newly diagnosed DM	12 (13.5)
Nil	3 (3.4)
Control of Diabetes Mellitus	
Controlled with Oral Hypoglycemic agents	13 (14.6)
Controlled with Insulin	10 (11.2)
Uncontrolled	63 (70.8)
Not Diabetic	3 (3.4)
Diabetic Ketoacidosis	
Present	4 (4.5)
Duration of onset of mucor after COVID-19 in days	
Lowest through 5	3 (3.4)
6 to 10	4 (4.5)
11 to 14	40 (44.9)
15 to 28	37 (41.6)
29 through highest	5 (5.6)

Table 2: Frequency distribution of primary symptom in patients

Type of the symptom	*n* (%)
Orbital/Facial pain	26 (29.2)
Orbital/Facial swelling	21 (23.6)
Headache	23 (25.8)
Loss of vision	5 (5.6)
Drooping of eyelid	3 (3.4)
Nasal block	3 (3.4)
Nasal discharge	6 (6.8)
Loose tooth	1 (1.1)
Fever	1 (1.1)
Total	89 (100)

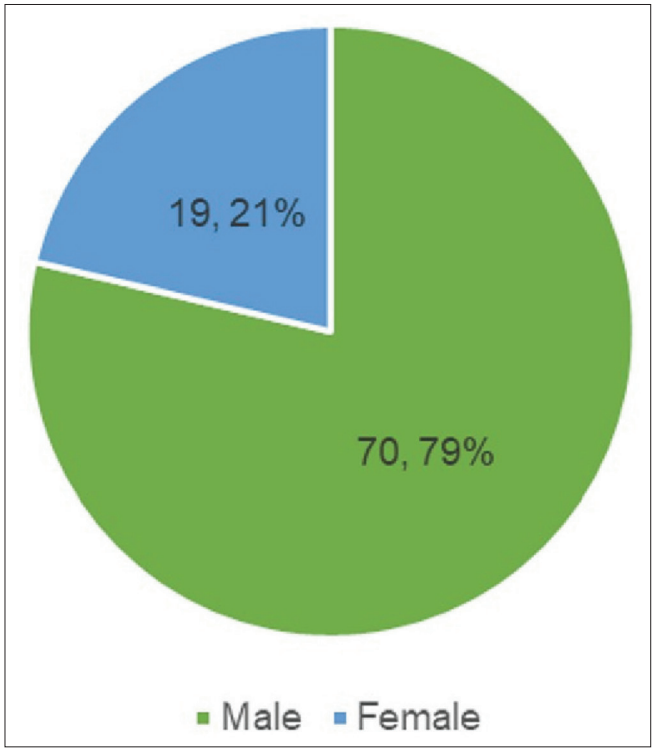

Figure 3: Gender distribution

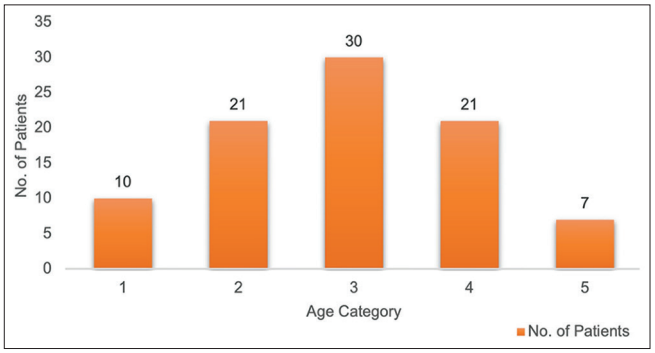

Figure 4: Age distribution: Category 1 - Lowest through 40, Category 2-41 to 50, Category 3-51 to 60, Category 4-61 to 70, Category 5-71 and higher

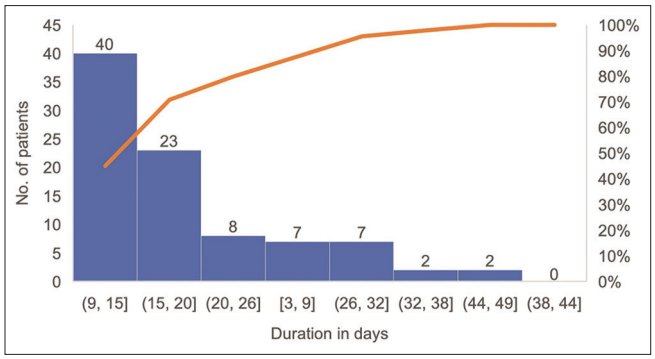

Figure 5: Duration of onset of symptoms of mucormycosis from the diagnosis of COVID-19. A Pareto chart with the distribution of the duration plotted in the descending order of frequency and a cumulative line on a secondary axis as a percentage of the total

Twenty-five cases showed dense clusters, and nine cases showed endospores. Large areas of necrosis and hemorrhage were seen in 78.7% of patients. Grading of neutrophilic inflammation showed minimal response in 25.8%, moderate response in 27%, and marked response in 47.2% of patients. The nuclear chromatin extracellular trap of neutrophils (NET) was present in 75.3% of patients. Among 89 patients, 25 (four with frank and 21 with suspicious) showed the presence of angio-invasion [Table 4]. Culture reports were positive for mucormycosis in 19 patients, negative for mucormycosis in 64 patients, and were not available in 6 patients. All 19 culture-positive Mucormycosis cases were non-pigmented.

The categorization of patients in different stages of ROCM showed that 39.32% of patients had stage 3c ROCM [Table 5]. Radiological features such as diffuse involvement of paranasal sinuses, erosion of medial orbital wall, diffuse involvement of the orbit, and extension through cavernous sinuses were observed. Black turbinate sign with non-enhancement of nasal turbinate and Guitar pick sign with conical deformation of posterior globe were also noted [Fig. 2e and f]. Among 89 patients, 49 (55.1%) were clinical group I with stages ≤3b and 40 (44.9%) were clinical group II with stages ≥3c. Patients with sino-nasal mucormycosis were treated with systemic liposomal amphotericin B (5 mg/kg/day) in 100 mL of 5% dextrose along with debridement of necrotic fungal debris. Patients with rhino-orbital mucormycosis were treated with a transcutaneous retro-orbital injection of amphotericin-B (TRAMB) (1 mL of 3.5 mg/mL) and orbital decompression. In cerebral involvement, neurosurgical drainage of fungal debris was also done. Systemic amphotericin-B was given for 2–8 weeks based on severity. Patients with clinical improvement were discharged and advised oral posaconazole 300 mg/day twice a day on the first day and once a day for 6 weeks. Patients with disease progression were referred to a higher center. All patients were followed up for a minimum period of 4 weeks after discharge or referral. In this study, 21.3% of patients had poor outcomes (outcome group II). Death occurred in three (two in stage 4d and one in stage 3d) patients. Comparison of clinical groups with outcome groups showed statistically significant association ($P = 0.005$) between clinical group II (stages ≥3c) with poor outcome group II [Table 6].

On comparing the histopathological features with clinical and outcome groups, the inflammatory response had a significant

Table 3: Frequency distribution of primary sign in patients

Type of Primary Sign	*n* (%)
Periocular/facial edema	24 (27)
Loss of Vision	20 (22.5)
Proptosis	13 (14.6)
Ocular movement restriction	11 (12.4)
Nasal Discharge	11 (12.4)
Ptosis	4 (4.5)
Altered Sensorium	4 (4.5)
Palatal ulcer	2 (2.2)
Total	89 (100)

Table 4: Histopathological features of specimens

Features	*n* (%)
Fungal Load	
Low	6 (6.7)
High	83 (93.3)
Areas of Necrosis	
Small	19 (21.3)
Large	70 (78.7)
Inflammation	
Minimal	23 (25.8)
Moderate	24 (27)
Marked	42 (47.2)
NET	
Absent	22 (24.7)
Present	67 (75.3)
Angio-invasion	
Present	25 (28.1)
Absent	64 (71.9)

Table 5: Frequency distribution of stages of ROCM

Stages of ROCM	*n* (%)
1b	1 (1.12)
1c	1 (1.12)
1d	1 (1.12)
2a	2 (2.25)
2b	10 (11.24)
2c	6 (6.74)
2d	14 (15.74)
3a	5 (5.62)
3b	9 (10.11)
3c	35 (39.32)
3d	1 (1.12)
4c	1 (1.12)
4d	3 (3.37)
Total	89 (100)

Table 6: Significance of factors related to invasive clinical presentation and poor outcome

Variables	Invasive Clinical Presentation	Poor Outcome
Fungal load	*P*=0.554	*P*=0.186
Areas of Necrosis	*P*=0.187	*P*=0.194
Minimal Inflammation	*P*=0.004*	*P*=0.001*
Angio invasion	*P*=0.190	*P*=0.007*
NETosis	*P*=0.956	*P*=0.676
Mean NLR	*P*=0.017*	*P*=0.007*
Clinical Group II with Vision loss and Cerebral involvement		*P*=0.005*

*indicates *P*<0.05 and statistically significant

association with clinical groups (P = 0.004) [Table 6]. The inflammatory response and angio-invasion had a statistically significant association with outcome groups with P values of 0.001 and 0.007, respectively [Table 6]. Marked inflammation correlates with less clinical severity and good outcome.

The mean neutrophil-lymphocyte ratio was 5.25 ± 4.16 (0.72–20.0) [n = 79]. In the remaining 10 patients, the NLR details were not available. Patients with severe clinical stage and poor outcomes had higher mean NLR with P values of 0.017 and 0.007, respectively [Table 6]. The mean WBC count was 11,497 cells/mm^3 (range: 3600–19,500 cells/mm^3). Only one patient had lower WBC count (<4000 cells/mm^3) but with neutrophilic predominance. WBC count was high (>11,000 cells/mm^3) in 42 cases and normal (4000–11,000 cells/mm^3) in 36 cases.

Discussion

Mucorales spores are ubiquitous in the environment. A healthy host with intact mucosa and innate immunity is usually resistant to the development of the disease. Neutrophils and macrophages play a major defensive role and inhibit the germination of spores. Neutrophils also have the ability to produce NETs to eliminate fungal hyphae. The Mucorales species are thermotolerant and have a rapid growing capacity utilizing high carbohydrate sources and iron.[3,4] The most common mucormycetes, Rhizopus arrhizus, have many virulence factors such as dormant spore formation, angio-invasive nature, and production of destructive enzymes.[3,4] The Mucorales invade the blood vessel wall by specific receptor mediated endocytosis.[11] Mucormycetes have a predilection for elastic lamina of large and small arteries, causing thrombosis and infarction. Thus, angio-invasion, tissue necrosis, and hemorrhage with acute and chronic inflammation are the primary histopathological features of mucormycosis.[3,11,12]

This study analyzed the clinical and histopathological features of 89 proven COVID-19-associated ROCM. The mean age (54.71 years) and male preponderance of patients in this study were like those in other studies.[10] Uncontrolled diabetes mellitus was the major predisposing factor.[10,13,14] Interestingly, COVID-19-associated ROCM also occurred in patients with normal range of blood sugar as well as in newly diagnosed diabetics.[15] Both concurrent COVID-19 infection and recovered COVID-19 were associated with ROCM.[10,16] Orbital or facial pain with swelling were the red-alert features in COVID-19 patients. Orbital involvement with loss of vision and central nervous system involvement resulted in poor outcomes.[10,17] Death in ROCM was associated with diabetic ketoacidosis and cerebral involvement.[18] Similar to COVID-19, high neutrophil-lymphocyte ratios were associated with severe ROCM and poor outcomes.[19]

Histopathological features, namely fungal load and areas of necrosis, had less correlation with clinical stages and outcome because of the ubiquitous nature of the fungi and as specimens were from sino-nasal debridement. All specimens from cerebral abscess of stage 4 ROCM had high fungal load and large areas of necrosis. Angio-invasion was associated with poor outcomes like in other studies.[8] Also, in this study, moderate or marked neutrophilic inflammation was associated with a less severe clinical stage and favorable outcome. Out of four patients with diabetic keto-acidosis, three cases had minimal inflammation and one case had moderate inflammation. NETs were seen in 30 out of 40 patients in the severe clinical group.

The genesis or worsening of hyperglycemia occurs in patients with COVID-19 due to direct injury to human islet cells, leading to β-cell damage and reduced endogenous insulin secretion. Elevated cytokines such as IL-6 can lead to worsening of insulin resistance.[20] Drugs used in the management of COVID-19, such as glucocorticoids and remdesivir, can further worsen glucose control and predispose to ROCM. Ketoacidosis-induced free-iron availability favors the growth and dissemination of mucormycosis.

COVID-19 infection is complicated by a hyper-inflammatory state and hyperferritenimic state due to cytokine storm.[5,20,21] IL-6 is a potent inducer of energy-dependent NET formation. NET causes endothelial injury and promotes venous thrombosis.[22,23] Hyperglycemia also activates the neutrophils to release NET and subsequently causes thrombosis.[24] All these interrelated factors disturb the common commensal of nasal mucosa, mucormycetes resulting in extensive dissemination, and clinical presentation of rhino-orbital-cerebral mucormycosis.

Conclusion

The management of COVID-19-associated ROCM necessitates a multidisciplinary approach. Detailed histopathological evaluation helps in assessing the progression and prognosis of ROCM. The salient features of this study are as follows. Orbital involvement with loss of vision and central nervous system involvement are poor prognostic clinical features of COVID-19-associated ROCM. Angio-invasion and minimal neutrophilic inflammation are poor prognostic histopathological features. High neutrophil-lymphocyte ratios in complete blood count and diabetic ketoacidosis are associated with poor prognosis.

This study confirms that COVID-19 and uncontrolled diabetes had complex interactions that resulted in the sudden surge of ROCM. Inflammation and NETosis were unique in COVID-positive Mucormycosis. The role of NET in the pathogenesis of COVID-19-associated ROCM needs further studies.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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