Section: Pathology

Original Research Article

HISTOMORPHOLOGICAL PROFILE OF RHINOCEREBRAL MUCORMYCOSIS IN COVID-19 POSITIVE PATIENTS

Hidhaya Fathima K[1], Kamaleshwari.K[2], Joel Dhanapandian.S[3], Johnsy Merla J[4]

[1]Associate Professor, Department of Pathology, Tirunelveli Medical College, Tirunelveli, Tamilnadu, India.
Associate Professor, Department of Pathology, Tirunelveli Medical College, Tirunelveli, [2]Tamilnadu, India.
[3]Professor, Department of Neurosurgery, Tirunelveli Medical College, Tirunelveli, Tamilnadu, India.
[4]Associate Professor, Department of Pathology, Tirunelveli Medical College, Tirunelveli, Tamilnadu, India.

Received : 07/06/2025
Received in revised form : 03/08/2025
Accepted : 21/08/2025

Keywords:
Rhinocerebral mucormycosis, COVID-19, Histomorphology, Angioinvasion, Necrosis

Corresponding Author:
Dr. Johnsy Merla J,
Email: drjohnsymerla@gmail.com

DOI: 10.47009/jamp.2025.7.5.7

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (5); 29-32

ABSTRACT

Background: COVID-19-associated mucormycosis (CAM), particularly the rhinocerebral form, is a severe opportunistic fungal infection that occurs due to immune dysregulation and steroid use. Histopathological evaluation is crucial for early diagnosis, assessment of angioinvasion, and treatment guidance. This study aimed to examine the patterns of various histomorphological features of mucormycosis in COVID-19-positive patients. **Materials and Methods:** This retrospective study included 40 inpatients of Tirunelveli Medical College, during March –May 2021. Demographic data, predisposing conditions, and clinical features were collected from the medical records. H&E-stained tissue sections were evaluated for fungal load, hyphal morphology, inflammatory response, infarction type, angioinvasion, and necrosis. **Result:** The study included 40 patients (30 men and 10 women) aged 30–80 years old. Histopathology revealed suppurative inflammation with neutrophil predominance in 25 patients, with mild, moderate, and severe inflammation observed in seven, 22, and 11 patients, respectively. Vascular invasion with thrombi was observed in four patients, involving both arteries and veins, often associated with necrotic tissue and fungal hyphae within the vessel walls. Suppurative granulomas with giant cells were observed in two patients. Necrosis was mild in 11 patients, moderate in 26, and severe in 3. Infarction was mild in 14 patients, moderate in 22, and severe in 4. **Conclusion:** COVID-19-associated rhinocerebral mucormycosis showed mainly suppurative inflammation, variable necrosis, and occasional vascular invasion, with rare granulomatous changes. Larger studies are required to assess the prognostic significance of these findings.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a global pandemic and triggered a complex cascade of immunological and metabolic derangements, predisposing patients to secondary opportunistic infections. Among these, mucormycosis, a rare angioinvasive fungal infection caused by fungi of the order Mucorales, emerged as a significant and life-threatening complication during the second wave of COVID-19 in India and several other countries.[1]

Mucormycosis primarily affects immunocompromised individuals, including those with uncontrolled diabetes mellitus, haematological malignancies, solid organ transplant recipients, and those on prolonged corticosteroid therapy.[2] The rhino cerebral form, which involves the nasal cavity, paranasal sinuses, orbit, and brain, is the most common clinical manifestation of COVID-19-associated mucormycosis (CAM), accounting for the surge in patients during the pandemic.[3] The interaction between COVID-19-induced immune dysregulation, hypoxia, elevated ferritin levels, and the widespread use of immunosuppressive therapies, especially corticosteroids, has been postulated as a crucial factor contributing to this phenomenon.[4]

Histopathological examination remains a cornerstone in the diagnosis and evaluation of mucormycosis. It not only confirms the presence of

ISSN (O): 2687-5365; ISSN (P): 2753-6556

fungal elements but also provides insights into the pattern of tissue invasion, extent of vascular involvement, and host immune response. Classical histomorphological features include broad, ribbon-like, non-septate or pauci-septate hyphae with right-angle branching, tissue necrosis, angioinvasion, and perineural infiltration of the host tissue.[5] Identifying these features can significantly influence therapeutic decisions and prognosis.

The sudden upsurge in CAM patients has necessitated a detailed understanding of its histopathological spectrum, particularly in the context of SARS-CoV-2 infection. Limited data are available on how the COVID-19 milieu alters tissue response to Mucor infection. It is hypothesised that the underlying hypercoagulable state, lymphopenia, and endothelial damage induced by the virus may exacerbate the angioinvasive potential of mucorales.[6] Moreover, diabetic ketoacidosis, which is common in severe COVID-19 patients and a risk factor for mucormycosis, further enhances iron availability, supporting fungal proliferation.[7] While clinical and radiological assessments are crucial, definitive diagnosis and subtype characterisation rely on histomorphological confirmation. In addition, histopathology helps differentiate mucormycosis from other fungal infections, such as aspergillosis, which can coexist or mimic its presentation, particularly in COVID-19 immunocompromised patients.[8]

Aim

This study aimed to examine the patterns of various histomorphological features of mucormycosis in COVID-19-positive patients.

MATERIALS AND METHODS

This retrospective study included 40 inpatients of Tirunelveli Medical College, during March–May 2021.

Inclusion and exclusion criteria

Patients with invasive rhino-cerebral mucormycosis were included; patients with non-invasive fungal sinusitis, isolated cutaneous mucormycosis, or insufficient tissue for histopathological evaluation were excluded.

Methods

Demographic features, predisposing conditions, and clinical features were obtained from medical records. Tissue sections were reviewed with haematoxylin and eosin (H and E) stain. To confirm the presence of fungal elements and to aid in morphological characterisation, special stains were performed wherever required, and fungal load in the tissue was graded as mild, moderate, and severe. The morphology of the fungal hyphae, degree of neutrophilic and granulomatous response, type of infarction, angio invasion, and necrosis were graded, assessed and documented.

RESULTS

Among the 40 patients studied (30 males, 10 females) aged 30–80 years, histopathological examination most frequently showed suppurative inflammation with predominant neutrophils in 25 cases, while suppurating granulomas with mixed inflammatory cells were observed in 2 cases. The degree of inflammation was mild in seven patients, moderate in 22, and severe in 11. Vascular invasion with thrombus formation was observed in four cases. Necrosis was mild in 11 patients, moderate in 26, and severe in 3, whereas infarction was mild in 14 patients, moderate in 22, and severe in 4 patients (Table 1).

In cases with vascular invasion, both arteries and veins were affected, with fungal hyphae present within vessel walls or forming thrombi, often associated with necrosis of adjacent tissue.

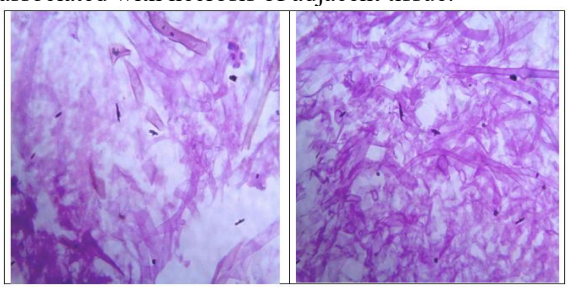

Figure 1. Fungal hyphae

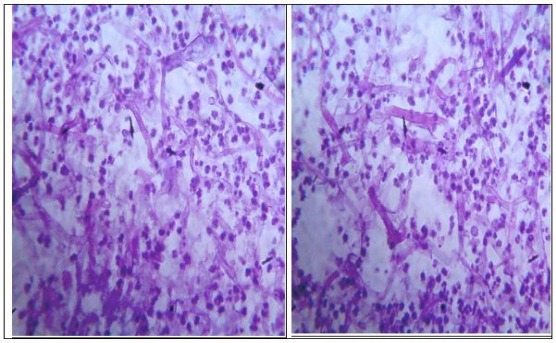

Figure 2. Neutrophilic response

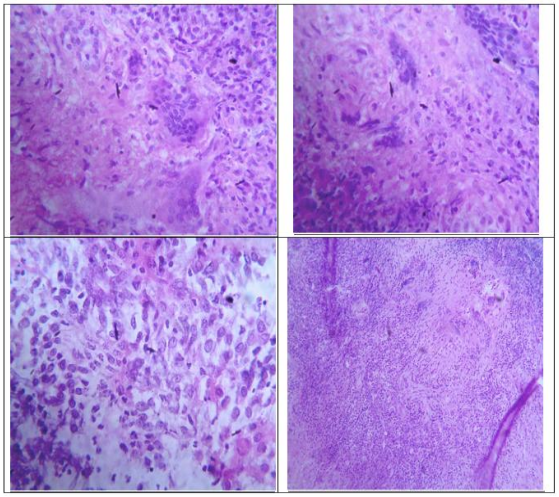

Figure 3. Granulomatous response

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 1: Histopathological features

		Frequency
Age range in years		30-80
Sex distribution	Male	30
	Female	10
Type of inflammation	Suppurative (predominantly neutrophils)	25
	Suppurating granuloma (neutrophils, lymphocytes, foreign body giant cells)	2
Degree of inflammation	Mild	7
	Moderate	22
	Severe	11
Vascular invasion	Vascular invasion with thrombi	4
Necrosis	Mild	11
	Moderate	26
	Severe	3
Infarction	Mild	14
	Moderate	22
	Severe	4

DISCUSSION

The term zygomycosis historically referred to infections caused by fungi in the class Zygomycetes, but mucormycosis is now the preferred term for infections due to Mucorales. Rhino-orbito-cerebral mucormycosis encompasses disease progression from the nasal and sinus mucosa to orbital tissues and, in advanced stages, to the central nervous system.

In our study of 40 patients (30 males and 10 females) aged between 30 and 80 years, histopathological examination revealed suppurative inflammation with a predominance of neutrophils in 25 biopsies and suppurating granulomas containing neutrophils, lymphocytes, and foreign body giant cells in 2 biopsies. The degree of inflammation was mild in seven patients, moderate in 22 patients, and severe in 11 patients. Vascular invasion with thrombus formation was identified in four cases, involving both arteries and veins. Necrosis was mild in 11 patients, moderate in 26 patients, and severe in three patients. Infarction was mild in 14 patients, moderate in 22 patients, and severe in four patients. The fungal density is highest within necrotic areas, underscoring the need to sample necrotic foci comprehensively to prevent underdiagnosis. Dovgan et al. observed severe systemic responses in five patients with fungal infections, including fever up to 39.1°C, blood pressure elevations up to 170/108 mmHg, and creatinine increases of up to 137% from baseline during Amphotericin B therapy. Suppurative inflammation was observed in 62.5% of the cases, and vascular invasion with thrombi was observed in 10% of the biopsies.[9]

Patel et al. analysed 236 biopsy specimens from post-COVID-19 patients, with 211 (89%) confirming invasive fungal infections. Suppurative and mixed inflammatory infiltrates were observed in most cases, and granulomatous inflammation with multinucleated giant cells was observed in 21% of cases. Angioinvasion was identified in 82 (38.56%) patients, with evidence of fungal elements within the vessel walls, thrombus formation, and surrounding necrosis.[10] Ivanov et al. studied 261 patients with COVID-associated mucormycosis (CAM) and confirmed extensive angioinvasion and tissue necrosis as key pathological features. Intracranial extension was observed in 24.5% of cases, and aggressive vascular invasion with thrombus formation was frequently noted, reflecting the characteristic angioinvasive behaviour of the Mucorales.[11]

In the study by Mani et al., histopathological analysis of 89 patients revealed a high fungal load in 93.3% of cases, with large necrotic and haemorrhagic areas in 78.7% of cases. Angioinvasion was noted in 28% (25 cases) of patients, and marked neutrophilic inflammation was observed in 47.2% of patients, with a statistically significant correlation between intense inflammation and better outcomes (p=0.001).[12] Agarwal et al. examined 31 patients (20 males and 11 females; age range 23–76 years) with COVID-19–associated mucormycosis and found histopathological features of broad aseptate branching hyphae in all cases, predominantly at 90° angles (96.7%). Macrophage and neutrophil infiltration was observed in 93.5% of cases, with granulation tissue in 61.3% of cases. Angioinvasion was observed in 77.4% of cases, and necrotic changes were common in the middle turbinate, maxillary, and sphenoid sinuses.[13]

Mukkamil Ahmed et al. studied 260 histopathological samples from COVID-19–positive patients with suspected mucormycosis and reported chronic suppuration in 93.8% of cases, necrosis in 68.8% (with >50% tissue involvement in 59.2% of these), granulomas in 27.3%, and giant cell reaction in 21.5%. Angioinvasion and perineural invasion were observed in 9.2% and 0.8% of the patients, respectively. Fungal elements were present in 68.1% of samples, predominantly broad, aseptate hyphae suggestive of mucormycosis.[14] Bahal et al. reported 9 confirmed COVID-19–associated mucormycosis cases (39–67 years; near-equal gender), with diabetes in 77.7% and hypertension in 33.3%. Paranasal sinus involvement occurred in 88.9% (maxillary in all), mixed fungal infection in 33.3%, necrosis up to 70% in diabetics, angioinvasion in 33.3%, soft tissue invasion in 44.4%, thrombosis in 22.2%, and granulomatous inflammation in 33.3% of the cases.[15]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Ganesan et al. studied 60 post-COVID mucormycosis patients over 3 months, with a mean age of 51.68 ± 10.7 years and a male predominance of 83.3%. All patients were diabetic, and 88% had elevated HbA1C levels. Histopathological examination showed tissue necrosis in 71.7% of cases, predominantly of the mixed suppurative type of inflammation (73.3%), followed by acute (21.7%) and chronic (5%) inflammation. Severe neutrophilic infiltration was observed in 83.3% of cases, and granulomatous inflammation was observed in 23.3% of cases, mainly in rhino-maxillary specimens. Fungal morphology was dominated by Mucorales (96.7%), with co-infection by Aspergillus in 20% and Candida in 13.3% of cases. Tissue invasion was identified in 85% of specimens, angioinvasion in 71.7%, bony invasion in 10%, and perineural invasion in 8.3% of specimens.[16]

Our findings are consistent with previous reports showing predominant suppurative inflammation, frequent necrosis, and occasional granulomatous responses. Although the angioinvasion rates were lower than those in several studies, the overall inflammatory and necrotic patterns were comparable, with variations likely due to the patient profile, biopsy timing, and sampling sites.

CONCLUSION

Our study demonstrated that COVID-19-associated rhinocerebral mucormycosis most commonly showed suppurative inflammation with marked neutrophilic infiltration, varying degrees of necrosis and infarction, and occasional vascular invasion with thrombus formation. Granulomatous inflammation and giant cell reactions were infrequent. Future studies with larger sample sizes and correlations with clinical outcomes are needed to better understand the prognostic significance of these histopathological patterns.

REFERENCES

1. Song G, Liang G, Liu W. Fungal co-infections associated with global COVID-19 pandemic: A clinical and diagnostic perspective from China. Mycopathologia 2020;185:599–606. https://doi.org/10.1007/s11046-020-00462-9.
2. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005;41:634–53. https://doi.org/10.1086/432579.
3. Mehta S, Pandey A. Rhino-orbital mucormycosis associated with COVID-19. Cureus 2020. https://doi.org/10.7759/cureus.10726.
4. Papamanoli A, Kalogeropoulos AP, Hotelling J, Yoo J, Grewal P, Predun W, et al. Association of serum ferritin levels and methylprednisolone treatment with outcomes in nonintubated patients with severe COVID-19 pneumonia. JAMA Netw Open 2021;4:e2127172. https://doi.org/10.1001/jamanetworkopen.2021.27172.
5. Prabhu RM, Patel R. Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect 2004;10 Suppl 1:31–47. https://doi.org/10.1111/j.1470-9465.2004.00843.x.
6. John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: The perfect storm for mucormycosis. J Fungi (Basel) 2021;7:298. https://doi.org/10.3390/jof7040298.
7. Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clin Infect Dis 2012;54 Suppl1:S16-22. https://doi.org/10.1093/cid/cir865.
8. Kwon-Chung KJ, Sugui JA. Aspergillus fumigatus--what makes the species a ubiquitous human fungal pathogen? PLoS Pathog 2013;9:e1003743. https://doi.org/10.1371/journal.ppat.1003743.
9. Dovgan EV, Andreev VA, Borovoy VN, Kuzmina EV, Andreeva IV, Kovalenko TN, et al. Rhino-cerebral mucormycosis in patients with COVID-19: clinical cases and treatment in a regional hospital. Clinical Microbiology and Antimicrobial Chemotherapy 2024;26:113–20. https://doi.org/10.36488/cmac.2024.1.113-120
10. Patel K Dr, Patel M Dr, Padsala S Dr, Chaudhary P Dr, Patel M Dr, Dabhi H Dr. A retrospective analysis of histopathological findings in rhinoorbital fungal infection in post-COVID-19 patients. GLOBAL JOURNAL FOR RESEARCH ANALYSIS 2023:92–5. https://doi.org/10.36106/gjra/7608897.
11. Ivanov SY, Polyakov KA, Popova SV, Svistushkin VM, Kochetkov PA, Eremeeva KV, et al. Post-COVID-19 mucormycosis of the maxillofacial area. Head and Neck Russian Journal 2023;11. https://doi.org/10.25792/hn.2023.11.4.50-56.
12. Mani S, Thirunavukkarasu A. A clinico-pathological study of COVID-19-associated rhino-orbital-cerebral mucormycosis. Indian J Ophthalmol2022;70:1013–8. https://doi.org/10.4103/ijo.IJO_2366_21.
13. Agarwal V, Susan A, Varghese J, Bhatia D, Singla S, Varghese A, et al. The spectrum of radiological findings of rhino-orbital cerebral mucormycosis with endoscopic and histopathological features in patients with COVID-19: A descriptive study. Niger J Med 2022;31:691. https://doi.org/10.4103/njm.njm_121_22.
14. Ahmed SM, Divyarani MN, Roopa AN, Sowmya SM, Mohammed R, Baig R, et al. Histomorphological study of mucormycosis in COVID-19 patients. Int J Health Sci 2023;7:2875–86. https://doi.org/10.53730/ijhs.v7ns1.14596.
15. Bahal N, Piyush AR, Kala PS, Dogra S, Thapliyal N. Rhinocerebral mucormycosis: A clinicopathological analysis of COVID-19-associated mucormycosis. J Family Med Prim Care 2024;13:3257–63. https://doi.org/10.4103/jfmpc.jfmpc_42_24.
16. Ganesan N, Sivanandam S. Histomorphological features of mucormycosis with rise and fall of COVID-19 pandemic. Pathol Res Pract 2022;236:153981. https://doi.org/10.1016/j.prp.2022.153981.

ISSN (O): 2687-5365; ISSN (P): 2753-6556