Section: Pathology

Original Research Article

INTEGRATING CLINICAL AND PATHOLOGICAL DATA IN MUCORMYCOSIS: A COMPREHENSIVE STUDY

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ABSTRACT

Background: Mucormycosis is an emerging dreadful opportunistic angio-invasive fungal infection occurring predominantly in immunocompromised individuals. Popularly known as "Black fungus", it gained popularity due to its association with SARSCOVID-19. The aim of the present study was to analyse various predisposing factors and histopathological features associated with mucormycosis and to draw a correlation between histopathology and radiological findings.

Materials and Methods: The present study was a two year retrospective study conducted in Department of Pathology, Kurnool medical college, Kurnool from January 2022 to December 2024. All the suspected cases of mucormycosis specimens sent to the Department of Pathology, Kurnool Medical College, for histopathological diagnosis were included in the present study. Formalin fixed paraffin embedded histological sections were studied microscopically. All the sections were stained with H & E stains and special stains like PAS (Periodic acid Schiff) and GMS (Gomori's Methenamine Silver). Clinical details of systemic hypertension, diabetes, and steroid and oxygen therapy were retrieved from case records.

Results: The present study includes 61 cases of mucormycosis, in which 47 were males and 14 were females with male to female ratio of 3.3:1. Maximum numbers of cases were observed in the age group of 51 to 60 years (37.7%). Youngest patient was of 15 days old male child and oldest age was 72 years. The most common symptom noted was facial pain. In the present study study, 47 cases (77%) were diabetic and Rhino-sinusoidal mucormycosis was the most typical presentation. Histologically, chronic inflammatory reaction with extensive areas of necrosis and granuloma formation was seen in most of the cases. The fungal elements have been appreciated and sensitivity of different stains to appreciate the fungal structures has been compared in the present study.

Conclusion: Histopathological features such as high fungal load, angio-invasion and extensive areas of necrosis play an important role in accurate diagnosis and assessing the prognosis. We also conclude that extra vigilance in immunosuppressed patients is essential to facilitate early diagnosis and optimizing prompt treatment.

Keywords: Mucormycosis, fungal hyphae, diabetes mellitus, steroid therapy.

INTRODUCTION

Mucormycosis is a life threatening opportunistic mycotic infection caused by saprophytic fungi belonging to class zygomycetes, which is subdivided into Mucorales and Entomophthorales in which Mucorales is responsible for an acute angioinvasive infection in immunocompromised patients.[1] According to literature, nearly 50% of mucormycosis patients have the medical history of diabetes mellitus, as a predisposing factor.[2] Zygomycosis is the third foremost cause of invasive fungal infection after candidiasis and aspergillosis. The fungus gains its entry through inhalation, ingestion, direct contact or

traumatic inoculation of spores. Mucor mycosis invades the tissues directly, causes necrosis and spreads from nasal and sinus mucosa rapidly into orbit followed by cavernous sinus and cranium1. If left undiagnosed, Mucor mycosis can be fatal.[2] Most commonly patients present with nasal blockage, facial pain, proptosis, oedema, headache, fever, ophthalmoplegia and neurological symptoms, in case of intracranial extension.[3] Histopathological examination shows extensive necrosis with long, aseptate fungal hyphae with right angle branching. The fungus is seen infiltrating into blood vessels causing infarction of tissues and haemorrhage.[4] Angioinvasion is the most common and important histological feature of invasive Mucor mycosis.[5] The global pandemic of COVID-19 caused by corona virus 2 showed a sudden escalation of cases with Mucormycosis particularly during the second wave.[6] Globally, the incidence of mucormycosis varies from 0.005 to 1.7 per million populations. The estimated prevalence of mucormycosis in India is 140 per million population.[7,8] Thus, individuals with uncontrolled diabetes, immuno-suppression, such as systemic corticosteroid therapy, chemotherapy, organ transplantation, malignancies, neutropenia, trauma and burns, were at high risk in acquiring Mucor mycosis.[9] Early diagnosis of mucormycosis is of essesntial to improve outcome and to reduce the need for or extent of surgical resection. The aim of the present study was to analyse various predisposing factors and histopathological features associated with mucormycosis and to draw a correlation between histopathology and radiological findings.

MATERIALS AND METHODS

Study Design: The present study was a two year retrospective study conducted in Department of Pathology, Kurnool medical college, Kurnool. All the suspected cases of mucormycosis specimens sent to the Department of Pathology, Kurnool Medical College, for histopathological examination from January 2022 to December 2024 were included in the present study. Ethical clearance was obtained from Institutional ethical committee. Formalin fixed paraffin embedded histological sections were studied microscopically. All the sections were stained with H & E stains and special stains like PAS (Periodic acid Schiff) and GMS (Gomori's Methenamine Silver). Clinical details of systemic hypertension, diabetes, and steroid and oxygen therapy were retrieved from case records.

Inclusion Criteria

All clinically suspected cases of mucormycosis who have undergone surgical debridement or any other surgical procedures were included in the present study

Exclusion Criteria

1. Inadequate biopsy samples.
2. Cases with inadequate clinical and radiological data.

Statistical Analysis: The frequency of microscopic lesions and their degree of association with PIH cases of varying severity was determined. Statistical analysis was done using χ 2 test; p value of <0.05 was considered significant.

RESULTS

The present study includes 61 cases of mucormycosis, in which 47 were males and 14 were females with male to female ratio of 3.3:1 [Figure 1].

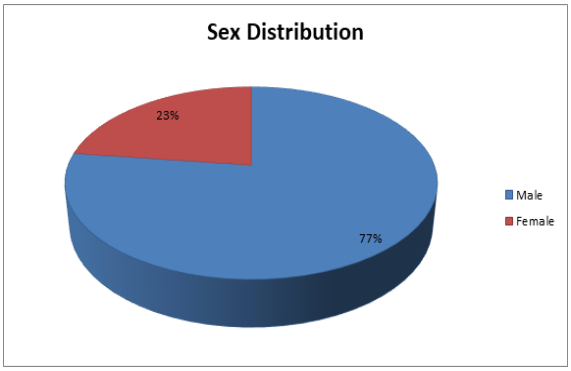

Figure 1: Sex distrubiton among 61 cases of mucormycosis

Age distribution of cases: Most of the cases were seen in the age group of 51 to 60 years (37.7%). Youngest patient was of 15 days old male child and oldest age was 72 years [Figure 2].

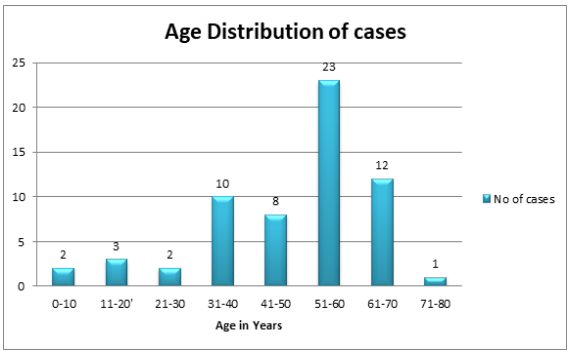

Figure 2: Age distribution of mucormycosis cases.

Clinical Presentation in mucormycosis: In the present study, the most common symptom observed was facial pain (85.2%) followed by headache (55.7%) and nasal blockage (26.2%).

Table 1: Clinical Presentation in mucormycosis

Clinical Presentation	No of cases
Facial pain	52
Periorbital swelling	03
Headache	34
Black/ blood stained nasal discharge	16

Decreased vision	04
Facial numbness	03
Nasal blockage	43
Ptosis	01
Breathlessness	02
Hemoptysis	02
Eizures	08

Co-morbidities seen in mucormycosis cases: In the present study study, most common coexsisting condition associated with mucormycosis is Diabetes mellitus accounting for 77% of total cases. [Table 2]

Table 2: Co-morbidities associated with mucormycosis.

Co-morbidities	No of cases	Percentage
Diabetes mellitus	47	77%
Tuberculosis	02	3.3%
CKD on dialysis	03	4.9%
Malignancy	02	3.3%
Steroid therapy	04	6.5%
HIV	03	4.9%

Site predilection of mucormycosis: Rhino-sinusoidal mucormycosis was the most typical presentation noted in the present study. Interestingly, in the present study one case of mucormycosis was seen in sebaceous horn and one case of mucormycosis was seen in the small intestine of 15 month old male child.

Table 3: Site predilection of mucormycosis

Site	No of cases	Percentage
Orbital	01	1.7%
Palatal	06	9.8%
Rhinoorbital	02	3.3%
Rhinosinusoidal	38	62.2%
Cerebral	09	14.7%
Intestinal	02	3.3%
Pulmonary	02	3.3%
Sebaceous horn	01	1.7%

Spectrum of histomorphological features in mucormycosis: Among the 61 histopathological specimens studied, we observed a wide array of findings like chronic suppuration (86.8%), necrosis (98.3%), granulomas (47.5%), giant cell reaction (36.1%), presence of fungal elements (96.7%), angioinvasion (8.2%). Most of the cases displayed chronic inflammatory reaction with neutrophils, lymphocytes and plasma cells with few of them showing giant cell response [Figure 6]. The tissue exhibited variable degree of necrosis in almost all the cases. The fungal elements were seen in most of the cases (96.7%). Among them, broad, aseptate fungal hyphae with wide angled branching suggestive of mucormycosis [Figure 3] were noted in the necrotic debris in 59 cases (96.7%) and mixed fungal infections with mucor and aspergillus were identified in other 2 cases (3.3%). Most of the fungal elements have been identified in routine haematoxylin and eosin stain (88.5%), where as in 7 cases, fungal elements could not be identified on routine H and E staining, but have been picked up by special stains like periodic acid Schiff (PAS) [Figure 4], Gomori Methenamine Silver (GMS) staining [Figure 5]. The special stains were performed in all the samples received and the rate of detection of fungal elements was found to be more in special stains. Few of the cases displayed angioinvasion (8.2%) with fungal hyphae in the lumen of the blood vessel and in the nerve respectively. Among the cases which showed angioinvasion, 2 cases were detected in routine Hematoxylin & Eosin stain and 2 cases in PAS stain and 1 case in GMS stain.

Table 4: Histomophological features seen in mucormycosis

Histomorphological features		No of cases	Percentage
Chronic Suppuration		53	86.8%
Necrosis	≥ 50%	34	57.3%
	≤ 50%	25	40.9%
Granulomas		29	47.5%
Giant cell reaction		22	36.1%
Angioinvasion		05	8.2%
Presence of other fungi		02	3.3%
Presence of fungal elements on H and E staining		54	88.5%
Presence of fungal elements on special stains		59	96.7%

Association of Necrosis with Mucormycosis: The grading of necrosis was done by viewing the amount of necrosis present under low power light microscopy in 10 low power fields.
Mild <30% necrosis/10 low power field,
Moderate 30%-50% necrosis/10 low power field and Severe >50% necrosis/10 low power field.
Among 59 cases of mucormycosis with necrosis, mild necrosis was seen in8 cases (13.1%), moderate necrosis in 17cases (27.9%) and 34 cases (55.7%) had severe necrosis.

Table 5: Mucormycosis and its association with Inflammation and Necrosis

Necrosis	No of cases	Percentage
Mild	08	13.1%
Moderate	17	27.9%
Severe	34	55.7%

Correlation between Radiological stage of mucormycosis and uncontrolled diabetes: Staging of mucormycosis patients based on radiological findings was done summarised in [Table 6]. Out of 61 cases, 4.9% cases were grouped in stage1 they showed involvement of nasal mucosa only. 62.2% cases belonged to stage 2 showed involvement of paranasal sinus along with nasal mucosa. 3.27% cases were grouped in stage 3 showed paranasal sinus and orbital involvement. Rest 14.7% cases were grouped in stage 4 showed paranasal sinus, orbital and central nervous system (CNS) involvement. Uncontrolled Diabetes which includes diabetic ketoacidosis also was statistically correlated with the radiological stages of the disease. This correlation showed that an acidotic state aids in the spread of the infection.

Table 6: Correlation between Radiological stage of mucormycosis and uncontrolled diabetes.

Staging based on radiological findings	Uncontrolled Diabetes mellitus		Total
	Present	Absent	
Stage I nasal mucosa	02	01	03
Stage II PNS with mucosa	29	09	38
Stage III Orbit with PNS	02	-	02
Stage IV CNS with orbit or PNS	08	01	09
Total	41	11	52

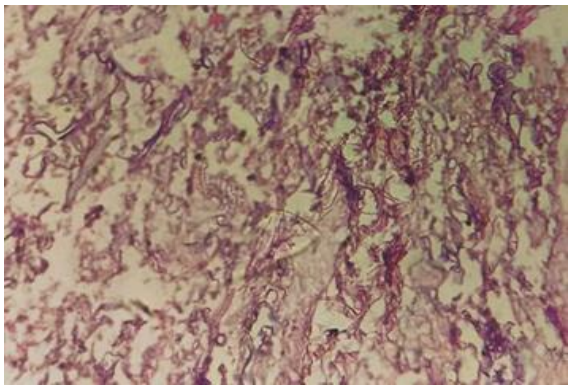

Figure 3: Showing aseptate, broad, large fungal hyphae branching at right angles (H&E, 40X)

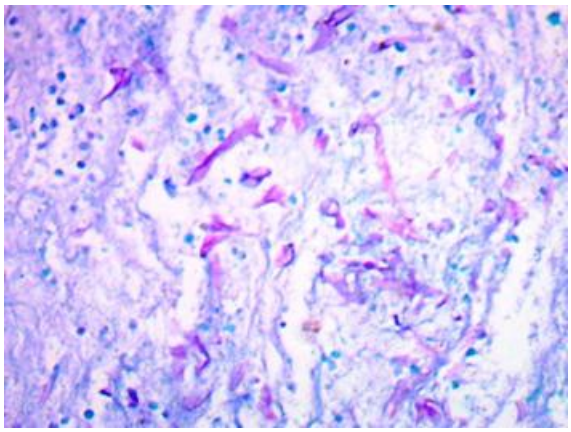

Figure 4: Showing aseptate, broad, large fungal hyphae branching at right angles (PAS, 40X)

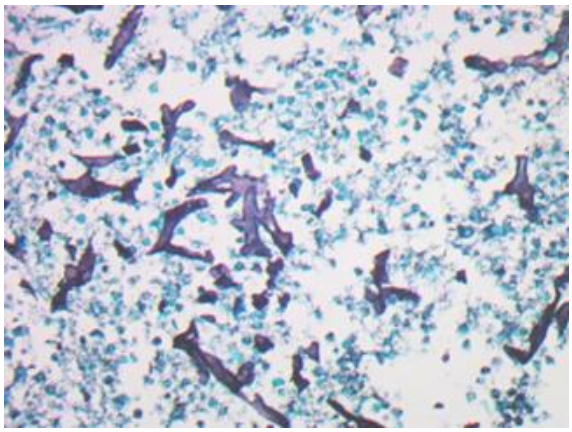

Figure 5: Showing aseptate, broad, large fungal hyphae branching at right angles (GMS, 40X)

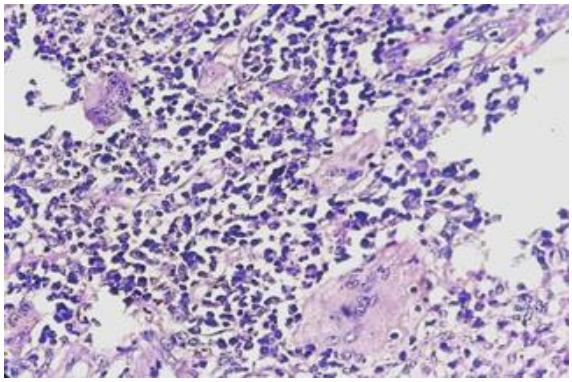

Figure 6: Showing giant cell reaction associated with mucormycosis (H&E, 40X)

DISCUSSION

As the COVID-19 pandemic spread globally, Mucormycosis emerged as a significant concern with mortality rates ranging from 31-50%.[2] Hypoxia, hyperglycemia, acidic conditions (metabolic and diabetic ketoacidosis), increased iron levels, and decreased phagocytic activity of white blood cells owing to immunosuppression are the primary causes for Mucormycosis.[6] In the present study, out of 61 cases of Mucormycosis, we noted male predominance with male to female ratio of 3.3:1, similar to studies done by Sreelakshmi et al,[10] and Arora et al.[11] The possible contributing factor was increased outdoor exposure to fungal spores in males and estrogenic protective role in females.[12] The clinical presentations of mucormycosis are rhino-orbital-cerebral, pulmonary, intestinal, cutaneous and disseminated. Diagnosis is made by clinical suspicion and histopathological examination. Weak host defenses are the major risk factors for invasive fungal diseases. Pulmonary mucormycosis is a relatively rare, which is difficult to diagnose early and lacks effective treatment according to Guarner J et al and Kim JH et al.[13,14] In the present study we noted predisposing factors such as diabetes (86.8%), including diabetic ketoacidosis as most common, which is similar to S Patil et al,[15] who observed diabetes (76.6%). Pakdel et al, Fouad et al, Ponce-Rosas et al,[16-18] also made similar observations of diabetes as predisposing factor. Thus, the basis of high Mucormycosis prevalence in India may be due to latent, poorly monitored and uncontrolled diabetes, new onset diabetes.[19] Diabetic ketoacidosis helps in multiplication of fungal elements by increasing the free iron concentration and reducing circulating antifungal agents.[20] The mainstay of diagnosis is the histopathological examination of the tissues as it differentiates from other fungal infections. Mucormycosis appears as large non septate pale staining fungal hyphae branching at wide angles. This is important for early initiation of therapy and favorable prognostic outcomes as studies have shown that delay in initiating treatment by only 6 days had increased twofold mortality rate.[21] In the present study we noted extensive areas of necrosis in 98.3% cases and granulomatous inflammation in 47.5%. Angio-invasion was observed in 8.1% of the study population which correlate with studies done by Kavita et al,[19] Ashina Goel et al,[22] and Sree Lakshmi et al.[10] Hemorrhage and infarction noted may be due to the angio-invasive nature of the fungal hyphae causing destruction of vessel wall and luminal invasion.[23] Thus, the present study emphasizes that histopathological examination can help in the early diagnosis, effective treatment of Mucormycosis and thereby predicting the prognosis of the patient.

In the present study one evisceration specimen was sent to Department of Pathology for histopathological examination with clinical history of blindness in one eye with extensive tissue destruction. Clinically the provisional diagnosis was Mucormycosis. However on histopathological examination, only extensive necrosis was seen, No fungal hyphae were seen in H and E stain as well as in special stains. Same contents were also sent to Microbiology Department simultaneously for culture sensitivity but no growth was seen for initial 10 days. After 10 days, a small growth was seen and the organism identified was Curvularia species which belongs to genus Ascomycetes which generally cause indolent keratitis when left untreated can progress to endopthalmitis leading to globe rupture.

CONCLUSION

Mucormycosis is a rare but potentially life-threatening fungal infection that warrants consideration in patients with uncontrolled diabetes and corticosteroid use. Early detection via histomorphological assessment supported by special stains plays a critical role in averting adverse clinical consequences. Awareness of unsual and rare fungal pathogens is crucial and should be included in the differential diagnosis for accurate diagnosis inorder to reduce morbidity and mortality.

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