

SPECTRUM OF FUNGAL SINUSITIS IN POST-COVID-19 CASES, CORRELATING HISTOPATHOLOGICAL FINDINGS AND FUNGAL CULTURES IN A TERTIARY CARE CENTER

Sivaranjani S.C¹, Christy D. Ramya², V. Martina³, R. Poornakala⁴

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Corresponding Author:
Dr. R.Poornakala,
Email: drpks@gmail.com

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¹Assistant Professor, Department of Pathology, Tirunelveli medical College, Tamilnadu, India

²Assistant Professor, Department of Pathology, Thoothukudi medical College, Tamilnadu, India

³Associate Professor, Department of Pathology, Government Stanley Medical College, Tamilnadu, India

⁴Assistant Professor, Department of Microbiology, Tirunelveli medical College, Tamilnadu, India

Abstract

Background: Fungal sinusitis is a late complication of COVID 19 infection, particularly in immunocompromised individuals. Diagnosing mixed fungal infections in sinusitis is challenging because of overlapping symptoms and diagnostic limitations. This study is aimed to evaluate the correlation between fungal culture and histopathology for accurate diagnosis. **Materials and Methods:** This retrospective and descriptive study includes 81 patients of all ages and either sex diagnosed with fungal rhinosinusitis and a history of COVID-19 infection in the past. This study was conducted in the Department of Pathology and Microbiology at Government Thoothukudi Medical College over three months in 2021. Clinical and laboratory data were collected, and sinonasal samples were analysed using histopathological examination, potassium hydroxide (KOH) mount, and fungal culture. **Result:** The mean age of the participants was 53.61 years, with an almost equal gender distribution 50.6% in male, 49.4% in female. Most patients (87.7%) had no significant comorbidities, whereas diabetes was the most common risk factor, seen in 8.6% of patients. Functional endoscopic sinus surgery (FESS) was performed in 92.6% of the patients, and 96.3% were diagnosed with fungal sinusitis. Mucor group was the most common fungi detected (89.2%), followed by Aspergillus (4.1%) and rare fungi (1.4%). KOH tests showed 88.9% positivity, whereas cultures demonstrated a 90.1% positivity rate. Mixed infections of Mucor and Aspergillus was identified in 9.9% of the cases. Histopathology revealed a higher detection rate of mixed infections than cultures, with 6.8% of cases being histopathologically positive but culture-negative. **Conclusion:** The analysis of samples by both fungal cultures and histopathological examination is essential for the diagnosis of mixed fungal infections. Morphologically distinct findings such as angio invasion were observed in only in the histopathological examination of tissues especially in mucormycosis cases.

INTRODUCTION

The COVID-19 pandemic has brought many challenges on a global scale. One of its late complications is the development of fungal sinusitis. The substantial increase in fungal sinusitis cases after COVID-19 has made it a notifiable disease. In several states of India, more than 30,000 cases have been reported.^[1] The immunocompromised state of patients allows secondary fungal infections by predisposing them to various other respiratory infections through immune system dysregulation.^[2] Diagnostic methods begin with clinical evaluation, which involves recognising characteristic

manifestations such as headache, nasal discharge, obstruction, fever, and facial or eye pain. Radiographic imaging techniques help assess the extent of infection. Microbiological analysis plays a crucial role in the identifying the specific fungal species with microscopy and culture of sinonasal samples. Fungal sinusitis was confirmed using KOH mounts and fungal cultures. Histopathological examination of sinonasal specimens is essential for determining the invasiveness of fungal infections. Additionally, molecular methods can be used to confirm the causative agents.^[3] Fungal rhinosinusitis can be classified as invasive and non-invasive. Mucor belongs to the Zygomycetes family and is identified microscopically by its broad,

aseptate, wide angle branched fungal hyphae. Hyphal invasion of the tissues characterises the mucormycosis.^[4] The most common non-invasive lesions are caused by *Aspergillus* species, usually in the form of fungal balls. Microscopic examination reveals delicate, septate, acute-angle branched, narrow-based fungal hyphae with occasional fruiting bodies.^[5]

The primary factors facilitating fungal spore germination in COVID-19 patients include the ideal environment created by low oxygen levels (hypoxic state) and high glucose levels (due to diabetes and steroid therapy).^[6] The diagnosis of mixed fungal infections in fungal sinusitis presents challenges due to overlapping clinical presentations, variable imaging findings, difficulty in culturing the fungi and limitations in histopathological evaluation. This study aims to emphasize the simultaneous role of fungal culture and histopathological examination, as an essential tool for the accurate diagnosis of fungal infections especially in the mixed fungal infections and Dematiaceous fungus.

MATERIALS AND METHODS

This retrospective, descriptive study included 81 patients from the Department of Pathology and Microbiology at Government Thoothukudi Medical College over three months in 2021.

Inclusion Criteria

Patients of all ages and either sex diagnosed with fungal rhinosinusitis and a history of post-COVID-19 infection were included in the study.

Exclusion Criteria

Non-COVID-19 patients with fungal rhinosinusitis were excluded.

Methods

Clinical and laboratory data were obtained from hospital records, and sinonasal samples received in the Department of Pathology and Microbiology were analysed using histopathological examination, potassium hydroxide (KOH) mount, and fungal culture.

Statistical Analysis: Data are presented as mean, standard deviation, frequency, and percentage. Categorical variables were compared using Pearson's chi-square test. Significance was defined as P values less than 0.05 using a two-tailed test. Data analysis was performed using IBM SPSS version 21.0.

RESULTS

The average age was 53.61 years (± 10.39 years). The gender distribution was almost equal, with 50.6% male and 49.4% female patients. Most patients (87.7%) had no other comorbid conditions, while diabetes was the most common risk factor which coexisted in 8.6% of patients.

The main surgical procedure performed was functional endoscopic sinus surgery (FESS), which was performed in 92.6% of the patients. A total of

96.3% of the patients were diagnosed with fungal sinusitis.

Analysis of tissue samples showed that *Mucor* was the most common type of fungus, occurring in 69.1% of patients [Figure 1].

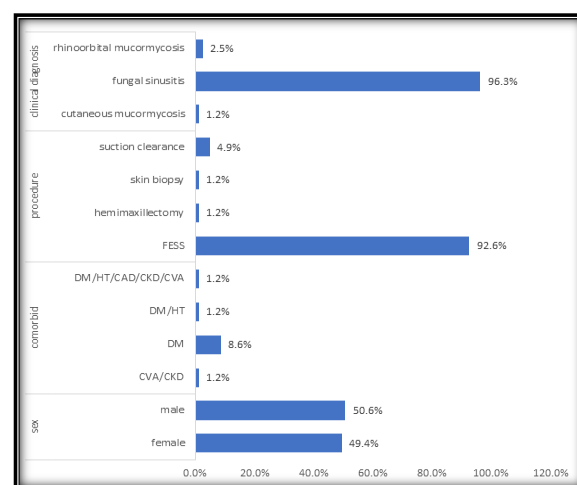


Figure 1: Demographic, comorbidities, and procedures in post-covid-19 fungal sinusitis patients

Mixed infections with *Mucor* and *Aspergillus* were found in 9.9% of patients. Angioinvasion, where the fungus invades blood vessels, was observed in 34.6% of patients, whereas bony invasion, where the fungus invades bone, was observed in 2.5% of patients.

Fungal infections were confirmed by the following laboratory tests- KOH tests were positive in 88.9% of patients, and cultures were positive in 90.1% of patients. Culture of the samples showed *Mucor* group to be the most common fungi (89.2%), followed by *Aspergillus* group (4.1%) and rare dematiaceous fungi such as *Alternaria*, *Bipolaris*, and *Penicillium* (1.4% each) [Figure 2].

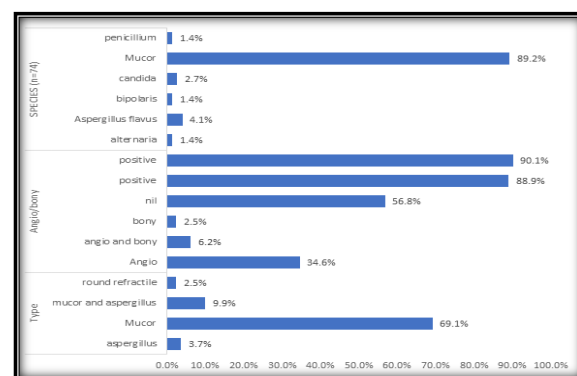


Figure 2: Fungal type, tissue invasion, and microbiological findings in post-covid-19 fungal sinusitis

Mucor species were the most commonly detected species in both culture (76.7%) and histopathology (69.1%). KOH positivity (88.9%) also aligned with culture results, confirming its diagnostic value. Histopathological examination revealed fungi, but cultures were negative (6.8%) [Table 1]. Mixed fungal infections of *Mucor* and *Aspergillus* was

reported in 9.9% of cases histopathologically while the KOH and fungal cultures showed only Mucor positivity in those cases. In certain cases which reported nil fungal elements in histopathology, culture showed positive for rare dematiaceous infections like *Alternaria*, *Bipolaris* and *Candida*.

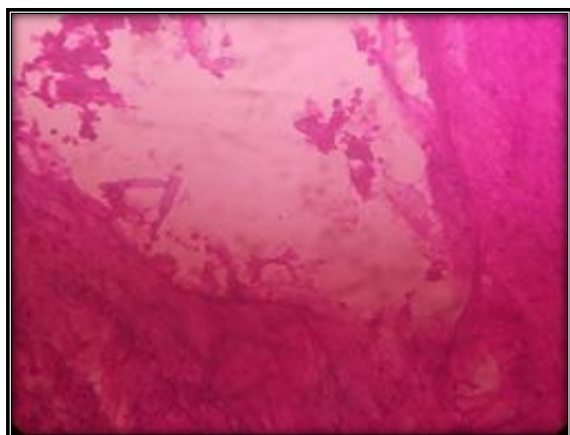


Figure 3: Mucor exhibiting angioinvasion

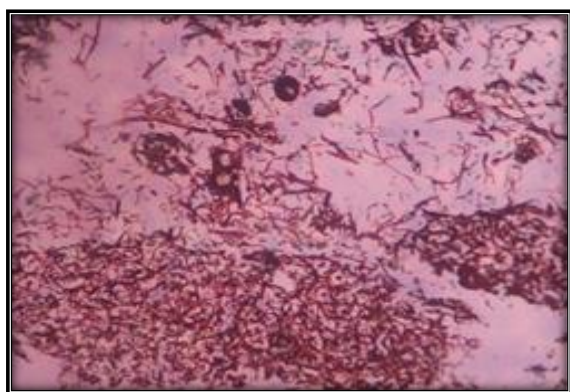


Figure 4: Gomori methanamine silver stain demonstrating mucor (broad based), aspergillus (slender with fruiting bodies)



Figure 5 Broad hyphae with fruiting body in KOH mount

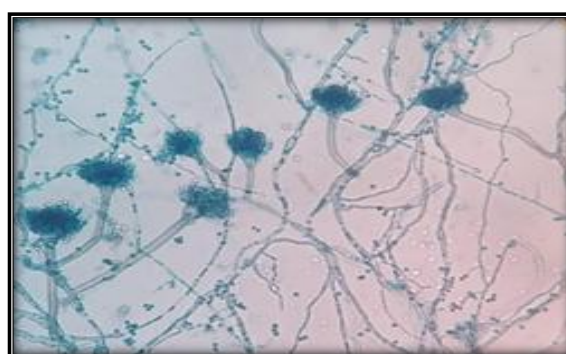


Figure 6: Aspergillus species in Lactophenol Cotton Blue mount

Table 1: Correlation between fungal culture and histopathological examination for diagnosing mixed fungal infections.

		KOH		Culture	
		Negative	Positive	Negative	Positive
Histopathological Type	Aspergillus(3)	1 (11.1%)	2 (2.8%)	1 (12.5%)	2 (2.7%)
	Mucor(56)	0	56 (77.8%)	0	56 (76.7%)
	Mucor and aspergillus(8)	0	8 (only for mucor) (11.1%)	0	8(only for mucor) (11%)
	Round refractile(2)	0	2 (2.8%)	0	2 (2.7%)
	Nil(12)	8 (88.9%)	4 (5.6%)	7 (87.5%)	5 (6.8%)

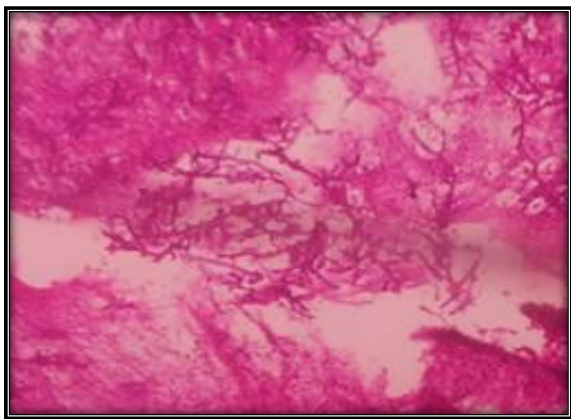


Figure 7: Dense sheets and clusters of mucor surrounded by necrotic tissue

DISCUSSION

COVID-19 is the worst pandemic of the 21st century, leading to a significant global death toll. In addition to its acute respiratory complications, it can also result in secondary infections, such as rhinocerebral mucormycosis, particularly in immunocompromised individuals, causing morbidity, facial disfigurement, and mortality. Mucormycosis is an opportunistic infection that is classified as rhino-orbital, rhino-orbital-cerebral, pulmonary, cutaneous, disseminated, or gastrointestinal. It enters the body through the respiratory tract and has a remarkable ability to invade the blood vessels and bones. Once the fungus invades the arteries, it forms thrombi within the blood vessels, leading to reduced blood supply and coagulative necrosis of the bone and soft tissue. Angioinvasion and bony invasion are pathological hallmarks of mucormycosis.

KOH mount serves as a rapid screening test to detect the presence of fungi and, in some cases, allows morphological categorisation of fungal filaments. Further culture on Sabouraud dextrose agar with antibiotics, Potato Dextrose agar helps confirm the presence of fungi, although mixed or overlapping fungal infections may be missed in cultures since the fungal balls of *Aspergillus* are difficult to grow in cultures. Histopathological evaluation of tissue samples from clinically suspected fungal sinusitis cases remains the gold standard for diagnosing not only mucormycosis but also other fungal infections, such as aspergillosis. Mucor family is identified by its aseptate, broad, wide angle branched, ribbon-like fungal hyphae, whereas slender filaments with septations and acute angle branching characterise *Aspergillus* family.

Histopathology detected mixed fungal infections in 9.9% of cases, whereas culture detected only Mucor family in those cases. Additionally, 6.8% of the cases were positive on histopathology but negative on culture. This finding is aligned with that of Guarner et al., who emphasised that histopathological examination remains vital because of its ability to detect tissue invasion that cultures may fail to identify. The discrepancy in detection rates shows the

importance of combining diagnostic modalities.^[7] Higher rates of positivity have been reported in studies by Ganesan et al., where mucorales were predominant.^[8] Agrahari et al. found that discrepancies between KOH and culture results could arise from non-viable fungal elements or inadequate sampling.^[9]

The KOH positivity rate of 88.9% and culture positivity of 90.1% in our findings confirm the diagnostic value of these methods, similar to the findings of Guarner et al. regarding the importance of KOH preparations in identifying fungal elements. These rates suggest effective detection of fungal infections, consistent with Mishra et al. and Dhafiri et al., who reported that KOH preparations are critical in dermatological practice, often serving as the first line of investigation alongside culture methods.^[10,11] Our results show that histopathology is important for detecting invasive fungal infections, particularly angioinvasion (34.6%) and bone invasion (2.5%). This finding is aligned with that of Zirpe et al., who found that angioinvasion was prevalent in their cohort of patients with COVID-19-associated mucormycosis (56.3%). The emphasis on identifying angioinvasion is critical, as it has been associated with worse outcomes in fungal infections.^[12]

The ability to identify mixed infections more effectively through histopathology, as indicated in our findings, shows the complexities discussed by Paul et al. regarding co-infections of mucormycosis and *Aspergillus*. Their findings underscore the challenges of diagnosing these mixed infections, which can complicate treatment strategies.^[13] Walke et al. also showed an increasing incidence of dual infections in post-COVID-19 patients,^[14] which aligned with our emphasis on the need for both histopathological and culture diagnostics.

We found limitations of fungal culture in detecting polymicrobial infections, where one fungus may dominate. This limitation was also reported by Guarner et al., who discussed the need for histopathological assessments in addition to culture results to improve diagnostic accuracy.^[7] The findings from Ghosh et al. found similar challenges in differentiating fungi based solely on culture results, emphasising the value of histopathology in elucidating complex infections.^[15]

Our findings suggest that early diagnosis using histopathology and culture improves treatment and reduces complications. Manchanda et al. reported the vital nature of prompt medical management in invasive fungal infections associated with COVID-19.^[16] Krammer et al. also reported that rapid diagnostic techniques, including KOH preparations, can lead to timely interventions that are critical for patient survival.^[17]

CONCLUSION

Histopathological examination and fungal culture goes hand in hand balancing the pros and cons of

these diagnostic methodologies in accurate diagnosis of fungal sinusitis, especially the mixed infections. These findings reinforce the importance of integrating histopathology into diagnostic algorithms for fungal sinusitis to ensure more accurate and timely clinical decision-making. The identification of vascular and bony invasion determines the prognosis of patients. The presence of karyorrhectic debris indicates the aggressiveness of the infection. Future studies should explore molecular diagnostic techniques, such as PCR-based fungal identification, and their roles in improving the detection of mixed infections.

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