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Original Research Article

Rhino-orbital Aspergillosis' a rising concern during COVID-19 pandemic: A clinical study from Kolar district, South India

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ABSTRACT

Purpose: To describe and determine the proportion of Orbital Aspergillosis in suspected cases of Rhino-orbital infections and compare its severity and progression to Mucormycosis.**Materials and Methods:** This observational study was conducted over five months (April 2021-September 2021) in a notified nodal tertiary care center of a district for Black Fungus during the COVID-19 pandemic. Seventy-seven patients admitted to our hospital with a suspected diagnosis of fungal Rhino-orbital infections were included in this study. Socio-demographic history, clinical spectrum, laboratory and radiological evaluation, and outcomes of patients are compared. Data were presented using descriptive and inferential statistics.**Results:** Out of 77 patients with a mean age of 50.48±12.39 years admitted with rhino orbital infections, Aspergillosis was seen in 17(22.07%), Mucor infection was in 22(28.57%), Rhizopus infection in 12(15.5%), Candida infection in 14(18.1%) and Bacterial infection was in 12(15.76%). Males were more commonly affected. Patients initially presented with facial pain and periorbital swelling, rapidly progressing to proptosis, ptosis, restriction of extraocular movements, and finally, leading to no perception of light.**Conclusion:** We conclude that post-COVID-19 Orbital Aspergillosis is no more a rare entity and should be suspected in patients, especially if the patient is male and involved in agricultural work. This disease must be diagnosed early and treated promptly to avoid life-threatening complications.This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.For reprints contact: reprint@ipinnovative.com

1. Introduction

In the past, Rhino-orbital infections were rare and usually seen in immune-suppressed and immune-compromised individuals due to deficient phagocytic capability and a drop in T lymphocyte levels. Its incidence suddenly increased during the COVID-19 era due to the unregulated use of steroids.¹⁻³

Excessive use of corticosteroids helped to accelerate the growth of fungal hyphae, which is one of the known critical determinants of the progression of the disease and pathogenicity.⁴

This unregulated use of steroids led to a rampant rise in fungal infections in COVID-19 era and India witnessed an epidemic of Mucormycosis; amongst this chaos, some cases of Rhino-orbital Aspergillosis were also seen.³

Fungal rhino-orbital infections are most commonly caused by Mucorales, Aspergillus and Candida species. This study talks about Aspergillus which is a filamentous spore-producing fungus found on dead and decaying vegetative matter, which is ubiquitous in the atmosphere.¹ Its spores enter our body through the inhalational route (through nose and mouth), germinate, and produce hyphae that extend into the paranasal sinuses and orbit.¹

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These fungi produce a spectrum of events depending upon the individual's immune status. In atopic individuals, it causes allergic fungal rhinosinusitis, fungal balls, and invasive fungal sinusitis in immune-compromised patients.^{5,6} They present with headache, localized pain, nasal discharge, sinusitis, orbital cellulitis, diplopia, unilateral blindness, eye pain, protrusion, and vision diminution.^{5,7,8}

This study explores and analyzes the trend, clinical spectrum, risk of acquiring, and outcome of Rhino-orbital Aspergillosis compared to Rhino-orbital Mucormycosis during the COVID-19 pandemic.

2. Materials and Methods

2.1. Study setting and design

This observational retrospective study was conducted from 1st April 2021 to 1st September 2021 in a tertiary care hospital in Kolar, South India. This hospital was a government-notified nodal center for diagnosing and managing "Black Fungus" during the second wave of the COVID-19 pandemic.

2.2. Inclusion criteria

Patients admitted to our hospital with a probable diagnosis of Rhino-orbital infection based on a clinical presentation from 1st April 2021 to 1st September 2021 were included in the study.

2.3. Exclusion criteria

Cases with no ocular involvement and old cases of invasive fungal infections before 1st April 2021 were excluded from the study.

2.4. Study population and sample size

Seventy-seven patients admitted to the hospital during the period with fungal Rhino-orbital infections were included in the study using non-probability sampling.

2.5. Data collection

Detailed history, including socio-demographic profile, occupation, history of fever, COVID-19 infection, steroid or immune-suppressants use, chronic disease, and oxygen mask use were collected and ascertained based on medical records.

As a part of hospital protocol, complete ophthalmic evaluation was done in all subjects, including visual acuity, torch light examination, extraocular movements, pupillary reaction, and posterior segment evaluation using Indirect ophthalmoscopy + 20D lens.

Microbiological and radiological evaluations, which were conducted to confirm the diagnosis, were collected.

2.6. Statistical analysis

Data was entered into the Microsoft office 2019 version and analyzed using Epi Info for Windows 7.2 (CDC, Atlanta, Georgia). Descriptive analysis was carried out by calculating the mean for continuous variables and frequency and proportion for categorical variables. Inferential analysis of different fungal infections was done using Kruskal Wallis Test, and a p-value less than 0.05 is considered significant.

2.7. Ethics approval and confidentiality

The institutional ethics review committee approved this study. The patient's identity and privacy were concealed, and confidentiality of data was ensured during the study.

3. Results

77 patients fulfilled the inclusion criteria and were enrolled in the study, it was noted that majority of adults lying in the age spectrum of 41-50 years presented with rhino-orbital infections with a mean age of 50.48 ± 12.39 years. Table 1 and Figure 1 depict that 64 males and 13 females were affected with the disease suggesting increased risk in males.

Table 1: Age distribution of patients diagnosed with rhino-orbital infections (n=77)

Age group	Males	Females	Total
<30 years	1	0	1
31-40 years	19	1	20
41-50 years	16	5	21
51-60 years	14	3	17
61-70 years	10	3	13
71-80 years	4	1	5
Total	64	13	77

Mean age 50.48 ± 12.39

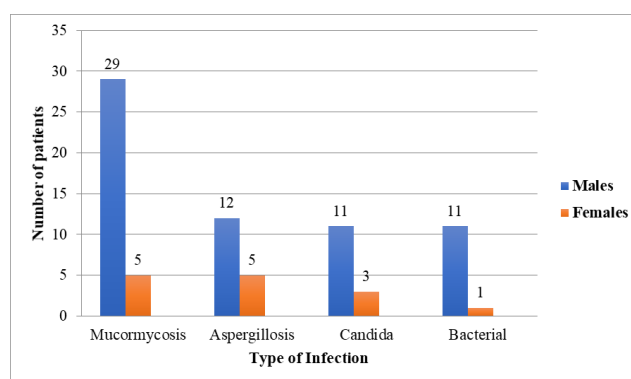


Figure 1: Gender distribution across the rhino-orbital infections

COVID 19 infection was seen to be the predominant risk factor in mucormycosis (76.47%), candida infection (71.42%) and bacterial agent (91.66%) whereas in aspergillosis type 2 diabetes (88.23%) was considered as a

more prevalent risk factor than COVID 19 (58.8%) as shown in Table 2.

We found out that the proportion of each etiological agent causing rhino-orbital infection; *Aspergillus* infection was 17(22.07%), *Mucor* infection 22(28.57%), *Rhizopus* 12(15.5%), *Candida* 14(18.1%), and bacteria was 12(15.76%) with the most common clinical presentation being facial pain and periorbital swelling.

Etiological agent was identified with the help of 10% KOH mount, Gram staining, histopathological examination of the tissue biopsy and radiological imaging. In case of fungus, positive test for KOH mount was suggestive of presence of fungal elements which was confirmed with histopathological examination revealing septate and aseptate fungal hyphae as shown in Figure 2 A,B, in bacterial causes Gram staining will reveal the type of bacteria and it is confirmed by tissue biopsy. Radiological imaging like CT scan and MRI were helpful in determining the extent and the course of invasion.

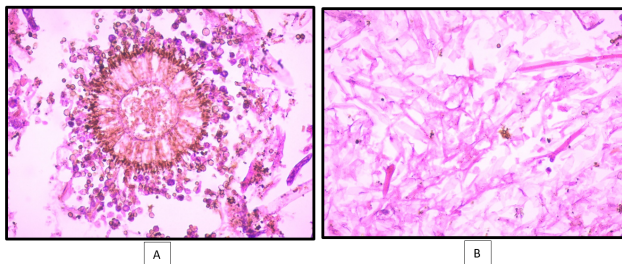


Figure 2: A, B): Histopathological section of Aspergillosis showing fruiting body and Mucormycosis showing aseptate hyphae respectively

Orbital Aspergillosis, being a fungal infection was seen most commonly in patients who were agricultural labourers by profession (35.29%), followed by household work (29.41%) and some others were drivers by profession (17.64%).

Out of 17 patients with Orbital Aspergillosis, 12 were males (70.58%) and remaining females, suggesting that males are more commonly affected. The most common risk factor was type 2 Diabetes mellitus 88.23% followed by COVID-19 infection at 58.8%, followed by cigarette smoking which was 47.05%.

Table 3 depicts the incidence and association of Rhino-orbital Aspergillosis across other fungal infections among total Rhino-orbital cases, and the difference was statistically significant (Kruskal Wallis test, $H = 23.0769$, $P < 0.05$).

Most patients presented with facial pain, periorbital swelling and tenderness which rapidly progressed to proptosis, ptosis, restriction of extraocular movements and ultimately no perception of light and cerebral invasion.

All 17 cases of Orbital Aspergillosis showed paranasal spread, 2 cases had adjacent nasal spread, 10(58.8%) had bilateral involvement, and 3 had bone erosion (17.64%).

In comparison to this, Mucormycosis showed bilateral invasion in 12 (36.36%) cases, 3 (9.09%) cases showed bone erosion, and 1 (3.03%) showed intra-cranial spread.

In this study, it was seen that most cases were infected with *Aspergillus fumigatus* species, i.e., 8(47.05%).

Three patients affected with Aspergillosis presented with coinfection; 1 with mucor, the other with rhizopus and candida; the patient who presented coinfection with mucor was taken up for exenteration as the disease progressed rapidly.

In 6(35.29%) patients, orbital decompression was done, and in the other three patients, the affected bone was removed during endoscopic debridement. One patient with Aspergillosis was subjected to surgical debridement twice to avoid spreading the infection to the brain, showing the invasive nature of the fungi.

In this study, 10 patients died, of which one patient had Orbital Aspergillosis, 4 proven for mucormycosis, 1 by bacterial infection and 2 confirmed cases of candida, and the other 2 patients had KOH positive but no culture reports for the same. The patient with orbital aspergillosis died within a week of diagnosis of aspergillosis showing the increased mortality and morbidity rate of the disease.

4. Discussion

Orbital fungal infections are not only vision-threatening but also have high mortality rates.⁹ The incidence of invasive mold infections is higher in developing countries due to many economically deprived sections with poor hygiene, poor sanitation, inadequate air quality precautions, and poor hospital care practices.¹⁰

In this study, we have compared Rhino-orbital Aspergillosis with mucormycosis as Aspergillosis is more invasive and virulent, and its highly variable clinical features lead to misdiagnosis and inappropriate management.⁹

Orbital Aspergillosis is a fungal infection caused most commonly by species such as *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus niger*; it was seen that 47.05% were infected with *Aspergillus fumigatus* in this study which was at par with other studies.¹¹ Some studies suggest that *Aspergillus flavus* is more common in developing countries like India.¹¹

Orbital Aspergillosis was 22.07% of the total suspected rhino-orbital fungal infections. The proportion of Aspergillosis with that of other fungal infections was found to be statistically significant as per the Kruskal Wallis test in this study.

The mean age of Orbital Aspergillosis was 50.48 ± 12.39 years in our study, which may or may not be immune-compromised, unlike previous case reports, which stated prevalence increases at 60 years.¹² Most of them presented with periorbital pain and swelling as their presenting complaint. As the disease progressed the ocular signs of

Table 2: Risk factors and clinical presentation across different causes of Rhino-orbital infections (n=77)

Causative agent	Mean±SD* Age in years	Male: Female ratio	T2DM*	COVID-19 Infection	Steroid use history	Clinical presentation (n)
Mucormycosis (n=34)	50.65±10.24	5.8:1	58.8%	76.47%	50%	Facial pain and periorbital swelling (13)
Aspergillosis (n=17)	50.70±14.64	2.4:1	88.23%	58.8%	17.64%	Facial pain and periorbital swelling (7)
Candida (n=14)	48.57±14.56	3.6:1	28.57%	71.42%	71.42%	Facial pain and periorbital swelling (7)
Bacteria (n=12)	51.66±12.22	11:1	58.33%	91.66%	33.33%	Headache (5)

*T2DM Type 2 Diabetes mellitus, SD: Standard deviation

Table 3: Association of Rhino-orbital aspergillosis with other fungal infections

Infection type	N	Mean Rank	H statistics (Kruskar Wallis test)	P value
Candida	5	9	23.0769	0.00012*
Mucor	5	23.5		
Aspergillosis	5	13.5		
Penicillium	5	3.5		
Rhizopus	5	19		

*P<0.05 statistically significant

the disease varied; while some showed proptosis, ptosis and complete ophthalmoplegia some others showed retinal involvement like central retinal artery occlusion and orbital apex syndrome as shown in Figures 3 and 4.

**Figure 3:** Patient with orbital aspergillosis**Figure 4:** Patient with orbital mucormycosis

Males were commonly affected (68.75%) as they were exposed more to the external environment than females. Agriculturist was seen to be the most common occupation in this study who were more at risk for

being exposed to the fungal spores.¹⁰ It was seen that 58.8% of patients developed Rhino-orbital Aspergillosis with a history of COVID-19 infection, which is 10% more than the previous studies.⁶ 88.23% were known cases of type 2 Diabetes mellitus, suggesting that an immune-compromised state increases the risk of infection. Studies also suggest that uncontrolled diabetics cause poor humoral immunity and neutrophilic dysfunction leading to rhino-orbital infections.¹³ An environment of low oxygen tension, hyperglycemia, and ketosis provides an excellent medium for the fungus to thrive.¹⁴

The symptoms correlated to the findings of case reports of Green et al. in 1969, Yu et al. in 1980, Spoor et al. in 1982, and Austin et al. in 1983, where all the patients presented with pain as their initial complaint.¹² Symptoms and signs were similar to that of Rhino-orbital Mucormycosis. However, the progression of the disease and severity was seen to be more aggressive in Aspergillosis than mucormycosis, as all cases had paranasal sinus spread, 11.76% had adjacent nasal spread, 58.8% had bilateral involvement, and 17.64% had bone erosion.

One patient with Rhino-orbital Aspergillosis was subjected to surgical debridement two times to avoid spreading the infection to the brain, showing the invasive nature of the fungi.

Two patients showed coinfection with Mucorales, and one showed coinfection with candida. Patients with coinfection with Mucorales presented with more aggressive progression than candida.

Treatment was directed at limiting the progression of infection with a combination of surgical debridement,

antifungal therapy, and reversal of immune-compromising factors, when possible.¹⁵

All patients were treated with Intravenous Amphotericin B once fungal elements were confirmed by microbiological examination. In case of an extensive spread of infection, endoscopic debridement was done. Nine patients were subjected to radical surgery, and one was to orbital exenteration to remove the affected bone and the necrotic tissue to prevent the progression of the disease.

Patients responded well to surgical debridement and Inj Liposomal Amphotericin and were downregulated with Posaconazole oral medications.⁶ Antifungal medication was given for up to six weeks to recover.²

Despite the growing interest in the role of invasive Aspergillosis in COVID-19 patients, existing evidence comes from case series; hence, in the present study, a new risk factor is identified, and Aspergillosis has been a challenging diagnosis and risk factor for COVID-19 individuals.

We conclude that during the COVID-19 era, Mucormycosis and Aspergillosis have become a concern. This study shows that males and being in agricultural work are at risk for developing Rhino-orbital infections. Like Mucormycosis, Aspergillosis is also highly invasive and must be diagnosed and treated with utmost urgency. This disease requires a multidisciplinary approach as it is associated with not only Rhino-orbital infections but also pulmonary and other systemic illnesses.

Limitations of this study are that it is a retrospective study; a prospective study would have been more appropriate in comparing the progression and severity of the disease. However, we attempted this report on our experience handling Rhino-orbital Aspergillosis and Mucormycosis during the COVID-19 pandemic from this region, which was not reported earlier.

5. Source of Funding

None.

6. Conflict of Interest

None.

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