ORIGINAL ARTICLE

FUNGAL RHINOSINUSITIS IN THE CO-MORBID COVID-19 POSITIVE PATIENTS- A RETROSPECTIVE ANALYSIS

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ABSTRACT

Objective: To determine the; Frequency of types of fungi and identify the commonest fungus implicated in fungal rhinosinusitis in covid-19 positive patients. Frequency of clinical types of fungal rhinosinusitis in covid-19 positive patients. Commonest co-morbidity and type of fungal rhinosinusitis associated with it.

Methods: This retrospective study was conducted at ENT Department Medical Teaching Institution, Hayatabad Medical complex, Peshawar during the period July 1, 2021 to Dec 31, 2022. Record of all the covisd-19 positive patients admitted to this department was examined. Those who have fungal rhinosinusitis were selected. The co morbidities in these patients such as diabetes, chronic renal failure and malignancies were recorded. Frequency of types of fungi, fungal rhinosinusitis and the commonest co-morbidity were determined. Chi-square test performed and p-value determined to determine significance of observed relationship of fungal rhinosinusitis with diabetes mellitus, renal failure and malignancies.

Results: A total of 86 patients, male: female ratio was 1.26:1. The ages ranged from 28-80 years with mean age of 56.13 ± 3.221 years. A total of 65(75.5%) patients were diabetic. Acute fulminant fungal rhinosinusitis was the commonest clinical type occurring in 40(46.5%) patients. Mucor was isolated from 56(65%). Chi square test and p value showed that the invasive fungal rhinosinusitis caused by mucor has significant association with diabetes in these patients (p=0.02).

Conclusion: Acute fulminant fungal rhinosinusitis caused by mucor is the commonest fungal infection in the co-morbid diabetic covid-19 positive patients. As this is a life-threatening disease, timely recognition and prompt treatment is important.

Keywords: Covid-19, Fungal Rhinosinusitis, Mucormycosis, Diabetes Mellitus, SARS-CoV-2

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INTRODUCTION

Covid-19 disease is an infectious disease caused by SARS CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). The virus was first identified in Wuhan, China in December 2019. The WHO declared it a 'Public health Emergency of international Concern' on January 30, 2020 and advised all countries to reduce exportations and take measures for the disease's containment including active surveillance, early detection and case management. In keeping with its rapid spread and associated morbidity and mortality, the WHO declared it a 'Pandemic' on March 11, 2020[1].

The portal of entry of virus is through the deposition of respiratory droplets and particles on exposed mucous membranes in the mouth, nose or eyes. The respiratory droplets released during exhalation carry virus and is a major source of rapid spread of the disease[2,3].

Though the commonest presentation of covid-19 disease is respiratory tract infection, breathing difficulties and a high incidence of smell and taste disturbances, there has been a surge in the cases fungal rhinosinusitis possibility due to impaired cell mediated immunity, immunosuppressive therapy and co-existent diabetes mellitus. Patients on long term steroid therapy and prolonged mechanical ventilator support may also be prone to develop these infections. The fungi involved can be Rhizopus, mucor, rhizomucor and aspergillus species[1,2].

The most commonly accepted classification divides fungal rhinosinusitis into invasive and non-invasive forms based on histopathological evidence of tissue invasion. The invasive form includes acute Invasive (fulminant) fungal rhinosinusitis, granulomatous invasive fungal rhinosinusitis and chronic invasive fungal rhinosinusitis. The non-invasive disease includes saprophytic fungal infestations, fungal ball and fungus related eosinophilic and including allergic fungal rhinosinusitis. It is the acute Invasive (fulminant) fungal rhinosinusitis that is commonly seen in immunocompromised patients and those with covid-19 disease [3]. Globally, the prevalence of Mucor mycosis varied from 0.005 to 1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000) in India compared to developed countries, in a recent estimate of year 2019–2020 [4].

Acute invasive fulminant rhinosinusitis (AIFR) is an Angio invasive & rapidly fatal infection. It is caused by Rhizopus oryzae of the order Mucorales and class zygomycetes and is responsible for nearly 90% of AFIR cases. Diabetes mellitus has been the most common factor linked with development of acute form of Mucor mycosis globally with an overall mortality of 60%. The presence of DM has been an independent risk factor (Odds ratio 2.69; 95% Confidence Interval 1.77–3.54; $P < 0.001$) in a large meta-analysis of 851 cases conducted in 2018[5,6,7].

A review of cases from 18 countries, Martin Hoenigl and colleagues found that the frequency of Covid-19 associated Mucor mycosis has been increasing since early 2021 particularly in uncontrolled diabetics and those with hyperglycemia and receiving systemic corticosteroid therapy. The rhino-orbito-cerebral Mucor mycosis is the most frequent form with 49% mortality. Those who survive are left with severe life changing morbidities such as loss of vision[8].

As fungal rhinosinusitis is a potentially life-threatening condition especially in co- morbid conditions like diabetes, renal failure and malignancies, early recognition and prompt treatment is therefore vital to save the lives of the patients or minimize the extent of life changing morbidities.

METHODS

Place and duration of study: ENT Department Medical Teaching Institution, Hayatabad Medical complex, Peshawar during the period July 1, 2021 to Dec 31, 2022.

Objective: To determine; The frequency of types of fungi and identify the commonest fungus implicated in fungal rhinosinusitis in covid-19 positive patients.

The frequency of clinical types of fungal rhinosinusitis in covid-19 positive patients.

The commonest co-morbidity and type of fungal rhinosinusitis associated with it.

Study Design, Sampling Size and Technique: This is a retrospective and analytical study. The record of patients admitted to this department during the study period was analyzed. Statistical analysis was carried out at 95% confidence interval and a margin of error of 5%.

Ethical approval was sought from the institutional ethical review board. The record of patients admitted to this department for treatment of fungal rhinosinusitis was included in the study after fulfilling the inclusion criteria. Record of these patients was examined. Recent or previous evidence (not exceeding 6 months) of covid-19 positivity was searched for. Positive PCR or rapid antigen test was considered as ample proof of covid-19 disease. Patients who had fungal rhinosinusitis as proven by fungal culture studies and biopsy were selected. Data regarding age, gender and demographic details was recorded. The co morbidities in these patients such as diabetes, chronic renal failure and malignancies were recorded. The type of treatment they were receiving when on ward or previously were noted. The findings of nasendoscopy and results of imaging studies were examined as an auxiliary proof of clinical disease. The extent of spread of disease was ignored for purpose of calculations. The frequencies of the type of fungi & fungal infection as well as the type of associated co-morbidity were analyzed to determine percentages.

Statistical Analysis:

The information obtained was recorded on a proforma. Descriptive statistics for variables like gender, age, diabetic status and co-morbid conditions was analyzed to determine the frequencies. Cross tables were used to find out the observed relationships of gender and ages of the patient with fungal rhinosinusitis and co-morbid. Chi-square test was performed and p-value determined to find out the significance of the observed relationship of fungal rhinosinusitis with co-morbidities like diabetes, renal failure and malignancies. The data was analyzed using IBM SPSS v 26.0 for windows.

RESULTS

A total of 86 patients were included in the study. There were 48 males and 38 females with M:F ratio of 1.26:1. The ages ranged from 28-80 years with mean age of 56.13 ± 3.221 years. The age group wise distribution of gender has been shown in Table 1. Out of these 65 (75.6%) were diabetics. The maximum number of diabetics 21 (24.41%) were in age group 51-60 years. Out of the total diabetic patients, 28 (43%) were on insulin and 37 (57%) were using oral hypoglycemics. The detail of diabetes in relation to age groups has been shown in Table 2. Table 3 depicts the details of other co-morbidities in the diabetic and non-diabetic patients. The type of treatment these patients were receiving or has received for diabetes, renal failure and malignancies is shown in Table 4. Mucor mycosis was the predominant fungal infection and occurred in 58 (65.1%) of patients. The clinical presentation was dominated by acute fungal rhinosinusitis (AFRS) and occurred in 48 (55.8%) of the patients. Table 5 & 6 give the details of the type of fungi and their clinical presentation and the various age groups. Mucor mycosis was the commonest presentation in diabetic patients. The clinical presentation of fungal disease in diabetics is given in Tables 7. Chi square test and p value showed that the invasive fungal rhinosinusitis caused by mucor has significant association with diabetes in these patients (p=0.02).

Table 1: Age groups and gender of the patients

		Gender of Patients		
	Count	Male	Female	Total
Age Groups	28-40 yr	7	3	10
	41-50 yr	8	12	20
	51-60 yr	12	16	28
	61-70 yr	10	7	17
	71-80 yr	11	0	11
Total		48	38	86

Table 2: Age groups and diabetic status of the patients

		Diabetic status		
Count		Diabetic	Non-Diabetic	Total
Age Groups	28-40 yr	8	2	10
	41-50 yr	15	5	20
	51-60 yr	21	7	28
	61-70 yr	13	4	17
	71-80 yr	8	3	11
Total		65	21	86

Table 3: The frequency of diabetes and other co-morbidities in patients.

		Diabetic Status		
Count		Diabetic	Non-Diabetic	Total
Other Co-Morbidities	Head and Neck Ca	7	4	11
	Breast & other Ca	7	1	8
	Renal failure	5	2	7
	None of these	46	14	60
Total		65	21	86

Ca: carcinoma

Table 4: The type of treatment of diabetes and other co-morbidities.

		Treatment of diabetes			Comorbidities Treatment		
		Insulin	Oral hy	None	Post CRT	Dialysis	None
Diabetic Status	Diabetic	21	34	10	14	5	46
	Non-Diabetic	7	3	11	5	2	14
Other Co-Morbidities	Head and Neck Ca	2	7	2	11	0	0
	Breast & other Ca	1	2	5	8	0	0
	Renal failure	6	1	0	0	7	0
	None of these	19	27	14	0	0	60

Post CRT: post chemotherapy, Oral hy: oral hypoglycemic drugs, Ca: carcinoma

Table 5: The frequency of fungal types and their clinical presentation

		Type of Rhinosinusitis				
		AFRS	Chr Granulomat	Mycetoma	Non-Invasive	Total
Type of Fungus	Mucor mycosis	43	11	1	1	56
	Aspergillosis	4	11	2	0	17
	Candidiasis	0	1	2	8	11
	Histoplasmosis	1	1	0	0	2
Total		48	24	5	9	86

Mucor: Mucor mycosis, asperg: aspergillosis, candid: candidiasis, histop: histoplasmosis, AFRS: acute fulminant fungal rhinosinusitis, Chr granulomat: chronic granulomatous fungal rhinosinusitis, Non-Invasive: Non-Invasive fungal rhinosinusitis

Table 6: Fungal rhinosinusitis and its relationship to various age groups.

		Type of rhinosinusitis				
		AFRS	Chr Granulomat	Mycetoma	Non-Invasive	Total
Age Groups	28-40 yr	9	0	1	0	10
	41-50 yr	11	8	0	1	20
	51-60 yr	17	6	1	4	28
	61-70 yr	7	8	1	1	17
	71-80 yr	4	2	2	3	11
Total		48	24	5	9	86

AFRS: acute fulminant fungal rhinosinusitis, chr granulomat: chronic granulomatous fungal rhinosinusitis, Non-Invasive: Non-Invasive fungal rhinosinusitis

Table 7: Types of fungi and the types of fungal rhinosinusitis in the diabetic patients.

			Type of fungus			
			Mucor	Asperg	Candid	Histopl
Types	AFRS	Diabetic	37	3	0	0
		Non-Diabetic	6	1	0	1
	Chr Granulomat	Diabetic	4	10	1	1
		Non-Diabetic	7	1	0	0
	Mycetoma	Diabetic	0	2	1	0
		Non-Diabetic	1	0	1	0
	Non-Invasive	Diabetic	0	0	6	0
		Non-Diabetic	1	0	2	0

Mucor: Mucor mycosis, asperg: aspergillosis, candid: candidiasis, histop: histoplasmosis, AFRS: acute fulminant fungal rhinosinusitis, chr granulomat: chronic granulomatous fungal rhinosinusitis
Non-Invasive: Non-Invasive fungal rhinosinusitis

DISCUSSION

Covid-19 disease has diverse symptomatology ranging from asymptomatic to severe disease & multiple organs failure. Lately, the increase in number of fungal rhinosinusitis has been alarming. These infections are either fatal or leave the patients with life changing morbidities for the rest of their lives. Since SARS-CoV-2 infected patients have elevated inflammatory cytokines and compromised cell-mediated immunity, as evidenced by lower counts of the cluster of differentiation of 4 and 8 positive T-helper (CD4+ T and CD8+ T) cells, suggesting vulnerability to fungal co-infections[9,10].

The results of this study reveal that a total of 65(75.5%) patients were diabetic. Acute fulminant fungal rhinosinusitis was the commonest clinical type occurring in 40(46.5%) patients. Mucor species were isolated from 56(65%) of these cases. Our findings are supported are supported by Lao M and colleagues who observed that acute fulminant fungal rhinosinusitis (AFRS) was an overwhelming infection that occurred in the severely immunocompromised patients. Patients with uncontrolled diabetes mellitus, undergoing hemodialysis or had malignancies were also at high risk[11,12].

Recently, many reports of increasing incidence of acute invasive fulminant fungal rhinosinusitis (AIFRS) after or during SARS-CoV-2 infection have been published. In an Egyptian study conducted in 2022 by Abide K and colleagues found diabetes in 98.4% of their patients with covid-19 associated fungal rhinosinusitis[13].

In a retrospective study in India in 2022 involving 124 covid-19 positive patients with acute fulminant fungal rhinosinusitis, Baghel SS and colleagues found that 92.1 % of patients had mucor, 16.9% had aspergillus and 12% had both of them. Among the co-morbidities, 83% had diabetes, hypertension in 30.6%, heart disease in 6.5%, liver disease in 4%, renal disease in 12.9% and receiving immunosuppressive therapy (4%). They further stated that of the total, 20 patients were COVID-19 positive at the time of presentation while the remaining had recovered from an earlier proven infection. During management of COVID-19, 72.6% of these patients also received corticosteroids[14].

Early diagnosis and timely institution of treatment in acute fulminant rhinosinusitis is helpful in reducing morbidity and mortality. Clinical suspicion and imaging studies are of immense importance. Vadher PR in India studied the extent of spread of fungal rhinosinusitis by imaging studies. Their study

included 200 patients. Co-morbidities like DM (39.5%), Hypertension (4.5%), both (10.5%) and hematological abnormalities (0.5%) were present in the study population. Mucor was the commonest fungus in 49% of patients and diabetes was the commonest co-morbidity in 40%. The authors noted a significant relationship between the spread of disease and the number and severity of co-morbidities present[15].

Various studies in the literature support a strong association of acute invasive fungal rhinosinusitis with diabetes. Lao M and colleagues, in China, while studying invasive fungal disease in type 2 DM observed that inpatient mortality was 23.3%. Glycosylated hemoglobin level was higher in non survivors than survivors. They concluded that prolonged hyperglycemia was associated with unfavorable outcomes[11].Ismaiel WF and colleagues retrospectively studied 56 patients with acute invasive fungal rhinosinusitis and found a significant difference in occurrence of disease in post covid period than 2017-2018. This happened especially in those with immunocompromised status, diabetes, renal disease and liver dysfunction[16]. A meta-analysis of 14 studies involving 206 cases of covid-19 related cases conducted by Donovan MR and colleagues found diabetes as the most common co-morbidity in 73.3% of the patients with invasive fungal rhinosinusitis. Recent or prolonged steroid use was observed in 65% of the patients[17].

In Nephrology Department of the Postgraduate Training Institute, Karachi, Pakistan while studying the mortality rate of covid-19 positive hemodialysis and diabetic patients in the 1st and 2nd waves of pandemic, Rahim S & colleagues observed 1.46 and 1.54 times higher overall death rates respectively for the 1st and 2nd waves when compared with similar duration of the pre-covid era. For similar period of both waves, deaths due to diabetes were the highest of all other co-morbidities ($p = 0.04$)[18].

Advantages of the study: Fungal rhinosinusitis can occur during or after recovery from covid-19 disease. The presence of co-morbid conditions like diabetes, renal failure & hem dialysis, malignancy, chemo-radiotherapy and immunosupression due to other causes predisposes the patients for acquiring the disease. As the acute fulminant type of invasive fungal rhinosinusitis is the commonest type occurring in the co-morbid patients, this study will help create awareness among the clinicians to make a early diagnosis and impress upon them the importance timely institution of treatment of not only the disease itself but the co-morbidities as well.

LIMITATIONS

This is a retrospective analysis of patients with covid-19 disease who were admitted with fungal rhinosinusitis. A prospective study with this aspect could give more information about the epidemiology and risk factors leading to this condition. Besides the sample size being small, this study was tertiary care hospital-based where only the complicated cases were referred from districts headquarter hospitals. A true picture of the situation is therefore less likely to be obtained.

CONCLUSION

Acute fulminant fungal rhinosinusitis caused by mucor is the commonest fungal infection in the co-morbid diabetic covid-19 positive patients. As this is a life-threatening disease, timely recognition and prompt treatment is, therefore, important to save the life of the patients and minimize the disabling morbidities associated with it.

CONFLICT OF INTEREST:

We, the authors, have no conflicts of interest to declare in relation to this article.

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AUTHOR'S CONTRIBUTIONS

SK: Principal author. Conception of idea, acquisition of data, analysis of data, critical analysis of content, drafting the article and final approval for publication

KA: Corresponding author. Conception of idea, acquisition of data, analysis of data, critical analysis of content, drafting the article.

AYM: Co-author. Acquisition of data, analysis of data, drafting the article.

WS, MI, AN: Acquisition of data, analysis of data, critical analysis of content.