ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 11 | November - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

FUNGAL RHINOSINUSITIS: A CLINICOPATHOLOGICAL STUDY

Histopathology

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ABSTRACT

Background: The diverse manifestations seen in both clinical and radiological aspects accompany fungal infection of mucous membranes in the nose and sinuses. This condition can have severe consequences, potentially leading to significant illness and even death. Consequently, it is crucial to maintain a high level of suspicion regarding fungal causes when dealing with patients experiencing rhinosinusitis. **Aim:** To establish its prevalence and contribute to the development of effective treatment guidelines. Additionally, to identify the various types of fungi responsible for causing rhinosinusitis. **Materials and Methods:** Our study with cross-sectional design was conducted on 450 patients of rhinosinusitis. Comprehensive clinical histories were extracted from medical records, while culture reports were collected whenever possible. To examine the specimens in detail, histopathological examinations were performed using staining techniques such as Hematoxylin and Eosin, as well as special stains like PAS and GMS stains. The collected data was subsequently analyzed to derive findings and conclusions. **Results:** A total of 247 cases of Fungal Rhinosinusitis (FRS) were diagnosed, out of which 79 cases were diagnosed in Chronic Rhinosinusitis (CRS) patients and 168 cases in Acute Rhinosinusitis (ARS), those with COVID-19. Most common age group affected was 41-50 years. Among CRS patients, 46 (58.2%) patients were diabetics, 76 (96.2%) had nasal obstruction, 75 (94.9%) had nasal discharge, 70 (88.6%) had headache, 66 (83.5%) had sneezing, 21 (26.6%) had facial pain and 17 (21.5%) had eye symptoms. Among 168 patients with ARS, 131 (78%) patients were diabetics, all the 168 (100%) patients had nasal obstruction, nasal discharge, head ache and sneezing, 133 (79.2%) patients had facial pain and 67 (39.9%) patients had eye symptoms. Irrespective of the type of FRS, Maxillary sinus was the most common sinus involved, and Mucormycosis was the most common fungus isolated on HPE. **Conclusion:** With the growing incidence of FRS in India, it becomes imperative to raise awareness among pathologists, microbiologists, and treating physicians regarding accurate diagnosis of FRS. The identification of fungi in these cases holds significant importance, not only for diagnosing chronic sinusitis, but also for guiding appropriate treatment strategies, particularly when dealing with infections caused by uncommon pathogens.

KEYWORDS

Fungal Rhinosinusitits, Mucormycosis, Paranasal sinuses, COVID-19

INTRODUCTION

Fungal Rhinosinusitis (FRS) has been recognized in the field of medicine for centuries, but in recent times, there has been a greater understanding of this condition. FRS encompasses a range of disease processes that differ in its clinical presentation, histological characteristics, and biological significance. It can manifest as acute (aggressive; with symptoms lasting less than 30 days), subacute (symptoms persisting for 30-90 days), or chronic (indolent; with symptoms lasting longer than 90 days).[1]

Chronic rhinosinusitis (CRS) is a prevalent condition affecting approximately 20% of the population in India, with an estimated 31 million people affected annually. It is defined as persistent inflammation of the mucosal lining of the nose and paranasal sinuses lasting for at least 12 weeks. On other hand, Acute rhinosinusitis (ARS) is nowadays being more prevalent with aggressive symptoms, after the COVID-19 pandemic.[2]

While fungal infections of the nose and paranasal sinuses are relatively rare, its incidence has been increasing in recent years. This rise can be attributed to factors such as international travel, opportunistic infections resulting from the use of potent cytotoxic drugs, steroids, and antibiotic therapy.[3] Multiple extrinsic and intrinsic factors contribute to this condition. Extrinsic causes include viral, bacterial, or fungal infections, or allergic conditions, including both IgE and non-IgE mediated reactions. Intrinsic factors involve genetic, autoimmune, or structural causes.[4]

The overall prevalence of FRS is 35.06%, with a prevalence of 30% among CRS cases. Patients who develop the invasive form of the disease, particularly those with compromised immune systems, experience high morbidity and mortality.[5] However, FRS can also occur in individuals with a healthy immune system. While the prevalence has increased, the etiology, pathogenesis, and natural progression of the disease remain unclear.[6,7]

The diagnosis of FRS relies on a high level of suspicion based on clinical indicators, as the patient's history and physical examination alone are seldom conclusive. Clinical presentation can offer clues to the specific subcategories of FRS, but definitive diagnosis relies on direct microscopic examination, culture, and histopathology of the sinus tissue or material obtained. Histopathology is crucial for distinguishing between invasive and non-invasive types of the disease and for classification purposes. Direct microscopy and culture aid in determining the underlying cause.[8]

Therefore, a comprehensive examination with correlation to culture results is essential. Early diagnosis and accurate classification of FRS can guide treatment protocols, prevent unnecessary surgical procedures, and promote effective treatment. The classification and diagnostic criteria of FRS should facilitate clinical trials aimed at establishing appropriate treatment approaches.[9] Thus, our study was undertaken to study histopathological features that contribute to the diagnosis of FRS. The study objectives were to determine the prevalence of FRS, and to identify the different types of fungi causing Rhinosinusitis, also by correlating the presence of fungus in tissue with culture wherever possible.

MATERIALS AND METHODS

Our study with cross-sectional design was carried out in the Department of Pathology, Karnataka Institute of Medical Sciences, Hubballi. The biopsy specimens from nose and paranasal sinuses received from the Department of ENT at the study centre were examined. A total of 450 specimens fixed in 10% formalin fixative, processed for histopathology and diagnosed as FRS on histology were collected over a period of 3 years, from December 2020 to December 2022.

Our study included biopsy specimens from nose and paranasal sinuses of the patients with chronic inflammatory disease of sinuses, with no response to medical treatment and patients undergoing functional endoscopic sinus surgery and also from the patients with recurrent sinusitis (>4 episodes/year). Due to COVID-19 pandemic, there was an acute surge of FRS cases during the study period, and hence these cases were also included in the study. Inadequate samples and specimens from nasopharynx were excluded from the study. Patients

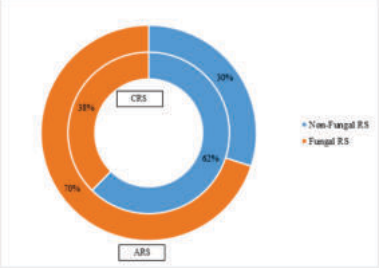
with malignancy of nose and paranasal sinuses were not included.

All consecutive cases satisfying inclusion criteria were recruited for the study after taking informed consent. A pre-designed proforma which is internally validated was used to collect the information on all the needed variables. The detailed clinical history was collected from clinical records and culture reports were collected wherever available from microbiology department. The tissues received were processed, embedded in paraffin wax and sectioned. Sections were stained by routine Hematoxylin and Eosin stain and special stains like Periodic acid-Schiff (PAS) and Gomori's methenamine silver (GMS) stains.[10,11] The data was collected in a specially designed proforma for the study. It was transferred to a master chart which was then be subjected to statistical analysis.

The information collected regarding all the selected cases was recorded in Microsoft excel. Continuous data was represented in terms of means and standard deviations, and the categorical data in frequencies and proportions. Statistical Software SPSS version 26 was used to analyze the data and interpret the findings.

RESULTS

On analyzing 450 cases of rhinosinusitis (210 CRS and 240 ARS cases), the prevalence of FRS was estimated to be 54.8% (247 out of 450). Among those 247 FRS cases, 79 (37.61%) cases were diagnosed as CRS (Non-COVID) patients and 168 (70.0%) cases as ARS (COVID) cases. Due to the outbreak of COVID-19 pandemic, there was an acute increase in the incidence of FRS cases [Table/Fig-1].



[Table/Fig-1]: Distribution Of FRS Among The Study Subjects

Among both CRS and ARS cases, commonest age group with FRS was 41-50 years. Also majority of the subjects were males, and Diabetes Mellitus (DM) was the most common co-morbidity observed in the study, followed by Hypertension (HTN) [Table/Fig-2].

[Table/Fig-2]: Characteristics Of The Study Subjects

		FUNGAL RHINOSINUSITIS			
		CRS / NON-COVID (N=79)		ARS / COVID (N=168)	
		N	%	N	%
Age group	≤30 years	10	12.6%	10	6.0%
	31-40 years	14	17.7%	37	22.0%
	41-50 years	26	32.9%	51	30.4%
	51-60 years	15	19.0%	37	22.0%
	>60 years	14	17.7%	33	19.6%
Gender	Male	56	70.9%	114	67.9%
	Female	23	29.1%	54	32.1%
Co-morbidities*	DM	46	58.2%	131	78.0%
	HTN	41	51.9%	60	35.7%
	HIV/HBsAg	2	2.5%	2	1.2%

* Multiple selections

Nasal discharge (96.2%) was the commonest presentation among the subjects with CRS, followed by nasal obstruction (94.9%), and headache (88.6%). On the contrary, all the subjects with ARS presented with nasal obstruction, discharge, headache and sneezing. However, maxillary sinus was commonly involved in either cases [Table/Fig-3].

[Table/Fig-3]: Presentation Among The Study Subjects

		FUNGAL RHINOSINUSITIS			
		CRS / NON-COVID (N=79)		ARS / COVID (N=168)	
		N	%	N	%
Clinical presentation*	Nasal obstruction	75	94.9%	168	100.0%
	Nasal Discharge	76	96.2%	168	100.0%
	Headache	70	88.6%	168	100.0%
	Sneezing	66	83.5%	168	100.0%
	Facial pain & swelling	21	26.6%	133	79.2%
	Eye symptoms	17	21.5%	67	39.9%
Paranasal sinus involvement*	Frontal	18	22.8%	42	25.0%
	Sphenoid	20	25.3%	82	48.8%
	Ethmoid	28	35.4%	71	42.3%
	Maxillary	70	88.6%	132	78.6%

* Multiple selections

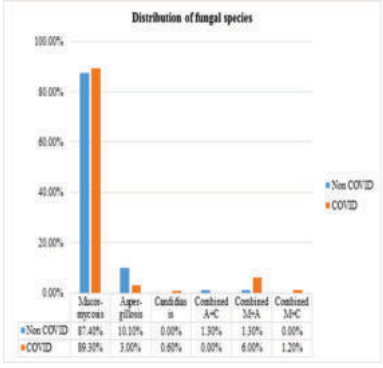
All were subjected to microscopic examination, where lymphocytes (84.8%) were in majority of CRS cases, while neutrophils (90.5%) were abundant in ARS. However, in both, necrosis was observed in majority followed by hemorrhage. Radiologically, polyps (59.5%) were commonest in CRS cases, while palatal involvement (24.4%) in ARS cases [Table/Fig-4].

[Table/Fig-4]: Investigation Findings Among The Study Subjects

Microscopic examination		FUNGAL RHINOSINUSITIS			
		CRS / NON-COVID (N=79)		ARS / COVID (N=168)	
		N	%	N	%
Inflammatory Cells*	Neutrophils	11	13.9%	152	90.5%
	Lymphocytes	67	84.8%	57	33.9%
	Histiocytes	28	35.4%	53	31.5%
	Plasma cells	23	29.1%	39	23.2%
	Eosinophilis	11	13.9%	0	0.0%
	Giant cells	12	15.2%	9	5.4%
	Epithelioid cell granuloma	5	6.3%	1	0.6%
Tissue reaction*	Metaplasia	10	12.7%	3	1.8%
	Ulcer	16	20.3%	6	3.6%
	Haemorrhage	38	48.1%	104	62.3%
	Necrosis	55	69.6%	136	84.5%
Radiological examination*	Polyps	47	59.5%	5	3.0%
	Palatal involvement	5	6.3%	41	24.4%
	Orbital extension	2	2.5%	36	21.4%
	Brain/Skull base involvement	0	0.0%	13	7.7%

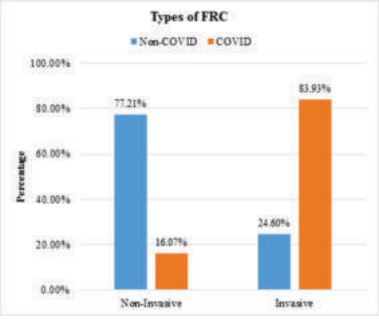
* Multiple selections

On histopathological examination, Mucormycosis was the most common type of fungi identified in both the groups i.e., 87.40% among CRS, and 89.30% among ARS cases. The next common agent was Aspergillosis (10.10%) in CRS cases, whereas combination of Mucormycosis and Aspergillosis (6.00%) in ARS cases [Table/Fig-5].



[Table/Fig-5]: Fungal Species Identified On HPE Among The Study Subjects

On further evaluation, FRS was found to be more invasive among ARS cases, in comparison with CRS cases, which was statistically found to be significant ($p < 0.001$). Thereby implying the severity of FRS with invasive nature among ARS cases with COVID [Table/Fig-6]



[Table/Fig-6]: Types Of FRC Among The Study Subjects

The clinical and radiological images of the cases studied are as shown in Fig-7(a-d)

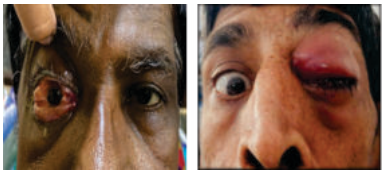


Figure 7 a,b - Case Of Invasive Fungal Rhinosinusitis Showing Orbital Involvement

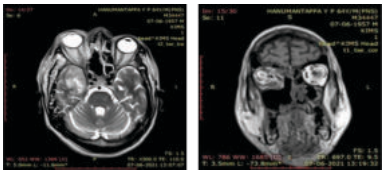
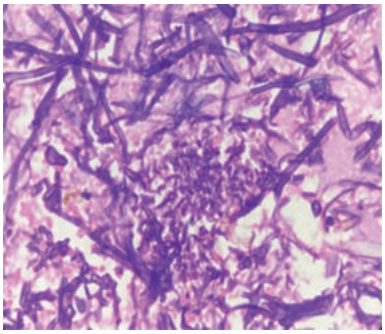
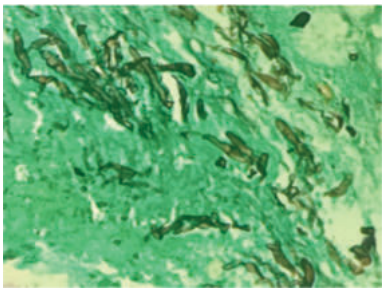


Figure 7 c,d –MRI Brain And PNS Showing Left Maxillary, Ethmoid And Bilateral Frontal And Sphenoid Sinusitis With Infiltration Into Right Orbit, Periorbital , Preantral Soft Tissue, And Right Masticator Space.

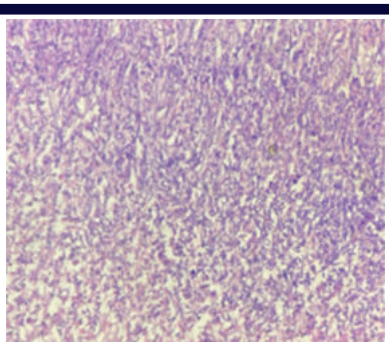
All the specimens sent for histopathological examination [Table/Fig-8(a-h)], were also stained with special stains like GMS and PAS, which was observed to be positive in all cases. Although KOH mount yielded 41.8% and 38.1% positive results among CRS and ARS cases respectively, the final confirmation of positive cases from the fungal culture was estimated to be 40.5% and 36.3% among CRS and ARS cases respectively.



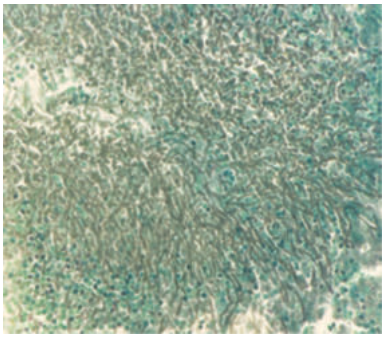
8a: (H&E; 40x) - Mucormycosis - Aspetate, Irregular, Broad, Ribbon Like, Obtuse Angle Branching Fungal Hyphae



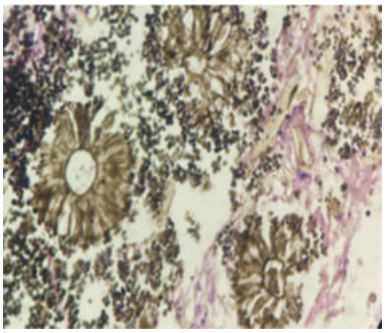
8b: (GMS, 40x) – Mucormycosis - Aspetate, Irregular, Broad, Ribbon Like, Obtuse Angle Branching Fungal Hyphae



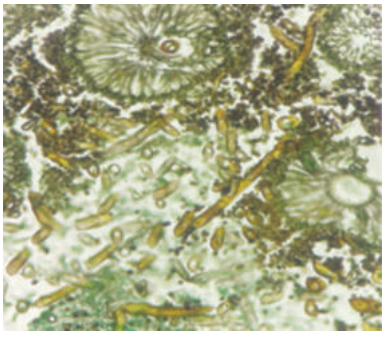
8c: (H&E, 40x) - Aspergillus - Septate, Acute Angle Dichotomous Branching Fungal Hyphae



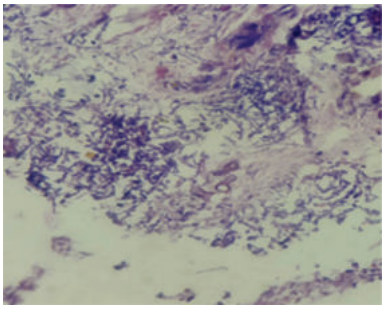
8d: (GMS, 40x) - Aspergillus - Septate, Acute Angle Dichotomous Branching Fungal Hyphae



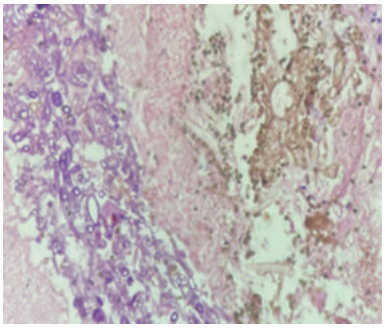
8e: (H&E, 40x) - Fruiting Body Of Aspergillus



8f: (GMS, 40x) - Fruiting Body Of Aspergillus



8g: (H&E, 40x) - Combined Mucor + Candida Infection



8h: (GMS, 40x) - Combined Mucor + Aspergillus Infection
[Table/Fig-8]: Histopathological Examination Of Specimens

DISCUSSION

On studying 450 cases of Rhinosinusitis, 247 (54.8%) cases were diagnosed as FRS. Out of which, 79 (37.61%) cases were CRS (Non-COVID) and 168 (70%) cases were ARS (COVID) cases. These FRS cases were analyzed and correlated clinicopathologically.

FRS previously considered as rare, is now being commonly recognized and is being reported with increasing frequency worldwide. In India, the disease was reported earlier only from Northern region of the country, but now it is increasingly being recognized from other parts as well. Other studies from North and South Indian regions of the country have also reported similar incidence ranging from 21.0% to 46.7%. Due to the outbreak of COVID-19 pandemic, there was an acute increase in the incidence of FRS cases in our study.

In our study, most common age group affected in both CRS and ARS cases, was 41-50 years and majority were males. This can be compared with the findings in previous studies such as Swain B et al[12] (31-50 years), and Das A et al[13] (30-50 years), where we can notice the concordance. Also male preponderance was evident in most of the previous literatures.

Majority of subjects with either CRS or ARS in our study were diabetics, followed by hypertensives. This sort of similarity was observed in many studies such as Han DH et al[13], Shah H et al[14], Ravindra P et al[15] and Suresh S et al[16], where the most common systemic disorder associated with FRS reported was Diabetes Mellitus. The rapid flare up of FRS cases during COVID-19 in our study might be due extensive steroid use for COVID-19 management which may exacerbate diabetes and immunosuppression leading to fungal disease.

Nasal discharge was the most common clinical presentation, followed by nasal obstruction and headache in our study, irrespective of the onset of condition. Even in a prospective study by Prateek et al[17], the most common presentations in cases of FRS were nasal obstruction (100.0%) and nasal discharge (100.0%) followed by headache (71.4%). The common presenting symptoms in another study by Ravindra P et al[15], were nasal obstruction (100%), headache (83%), nasal discharge (66%), which is in accordance to our study.

Maxillary sinus was most commonly affected in our study. Some of the patients presented with involvement of multiple sinuses. This mimics the presentation in previous studies by Ravindra P et al[15] and Suresh S et al[16], in which maxillary sinus involvement was abundantly noticed.

Based on histopathological examination in our study, among the 79 CRS cases, Mucormycosis (87.4%) was the common fungal species identified followed by Aspergillosis (10.1%). Even among 168 ARS study population, Mucormycosis (89.3%) was the commonest fungal species, followed by combined Mucor and Aspergillosis (6.0%). In a study by Suresh S et al[16], Mucormycosis (50%) was the most common organism isolated followed by Aspergillus species (43%) which correlated with our study. On the contrary, other studies such as Prateek et al[17] (67.7%), Kartikeyan P et al[18] (78.7%), Jain et al[19] (70%) and Han DH et al[13] (92%) showed Aspergillus as most commonly isolated fungal species. This sort of difference in the findings could be attributed to the fact that Aspergillus species predominate among hematologic malignancy patients, whereas Mucor predominate among poorly controlled diabetes patients. The more number of Mucormycosis cases in our study could be thus attributed to poorly controlled diabetes mellitus.

All the specimens sent for histopathological examination were stained with Hematoxylin and Eosin and also with special stains like GMS and PAS. Among the study population, all the patients were positive with GMS and PAS stains. Among the CRS cases, 33 (41.8%) had positive KOH mount results and culture was positive in 32 (40.5%) cases. Whereas among the ARS cases, 64 (38.1%) had positive KOH mount results and 61 (36.3%) had positive culture reports. In a previous study conducted on 50 FRS cases by M.T. Hedayati et al, fungal elements were detected by Calcoflour White (CFW) in 66.0% and KOH in 34.0% cases. Another study by Jain et al[19], reported that 150 of the 161 (93%) patients with clinically suspected FRS, showed evidence of fungal infections as indicated by either direct microscopy and/or culture. Of the 161 specimens from these individuals, 110 (68.2%) and 84 (52.1%) were positive for fungi by KOH and culture, respectively. Overall, our study showed special stains like GMS and PAS were 100% positive for fungus in comparison to KOH and Culture. The low positivity rate of KOH and Culture in the present study could also be due to a major portion of study population with limited availability of KOH and culture data.

CONCLUSION

Fungal Rhinosinusitis (FRS) is a disease that has a significant impact on the quality of life. Identifying the underlying cause can be challenging due to the highly diverse nature of the disease. The sinonasal mycotic infection was observed in 37.6% of CRS/Non-COVID and 70.0% of ARS/COVID in our study. This represents a substantial increase in the affected population, which has doubled or tripled during the COVID-19 pandemic.

Fortunately, advancements in diagnostic techniques such as histopathological examination of sinus specimens, CT scans, and Diagnostic Nasal Endoscopy have made the diagnosis of FRS more easy and reliable nowadays. The high prevalence of fungal rhinosinusitis in our study may be attributed to the increased occurrence of type 2 diabetes mellitus and the COVID-19 outbreak in our country. It is worth noting that the extensive use of steroids and broad-spectrum antibiotics for COVID-19 management may contribute to the development or worsening of fungal diseases.

Fungal infections of the sinonasal mucosa present with a wide range of clinical and radiological features and can have severe consequences, including high morbidity and mortality. Therefore, it is crucial to maintain a high level of suspicion for possible fungal causes mostly Mucormycosis and Aspergillosis in patients with CRS.

Since each variant of FRS is associated with distinct geographical and host-related risk factors, as well as different causative agents, it is essential to be aware of the prevalent fungal agents. Regular monitoring of fungal infections is necessary to study their patterns and identify any emerging trends. This monitoring is crucial for effective management and prevention strategies.

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