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A RETROSPECTIVE STUDY ON DIAGNOSTIC TRIAD AND MULTIFACTORIAL CAUSATION OF FUNGAL RHINOSINUSITIS IN THE ERA OF COVID 19

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ABSTRACT

Background: The importance of this study is due to the outbreak of epidemic (AIFRS) in the COVID-19 pandemic, even in immunocompetent patients. **Methods:** A retrospective single-center study carried out in a tertiary care hospital, AKOLA. Study Conducted in patients with or without a history of COVID-19 who are clinically and radiologically suggestive of acute fungal rhino sinusitis. Data collected by interviewing the patient admitted to the ward during the period of July 2020 to July 2022 and from medical case records. All data analysis completed using a simple analytical method. **Results:** The total number of enrolled patients is 166 and we did our study in 150 patients as rest of them did not fit into the inclusion criteria. The epidemic emerged due to multifactorial causes, including medical and environmental factors (temperature and humidity). The most common cause was COVID-19 infection in the background of anemia, thrombocytosis, and lymphocytopenia. We had 98 histopathologically proven cases of mucormycosis and 9 cases of mixed fungal infection. And the sensitivity and specificity of HPE were 94.8% and 100%, respectively. **Conclusion:** We present a broad concept of the range of diseases (acute, granulomatous, and chronic invasive fungal rhino sinusitis) that have been linked to the host immune response during the COVID-19 pandemic. A high index of clinical suspicion and multidisciplinary approach will aid in the diagnosis of AIFRS and enable early management to reduce morbidity and mortality.

KEYWORDS

INTRODUCTION

Acute Invasive Fungal Rhino Sinusitis was a rare condition in medicine until the twentieth century; nevertheless, there has been a recent upsurge in instances. It could be attributed to advances in treatment modalities such as transplants, blood cancer, and lower mortality, as well as a rise in lifestyle diseases. In March 2020, the World Health Organisation classified COVID-19 illness a pandemic. Our institution followed the ICMR guidelines for management, and there were some reports of an increase in AIFRS, particularly among immune-compromised patients. However, during the second wave of COVID-19 infection, the frequency of AIFRS cases increased exponentially, even in immunocompetent patients. As part of their prescribed treatment, a significant number of patients had taken oxygen therapy, Remdesivir, and steroids. It was noted that the patient experienced a brief episode of hyperglycemia while infected with COVID-19.

Mucorales cause the majority of AIFRS (zygomycosis) in the sinonasal area. Mucorales comprises 261 species in 55 genera, 38 of which have been associated with human infection. The most common species all over the world is Rhizopus arrhizus (Oryzae). Currently, the most active medications against mucorales are amphotericin B, posaconazole, and isavuconazole. Amphotericin B was the most effective against all isolates except Cunninghamella and Apophysomyces. Terbinafine shown good efficacy except for Rhizopus oryzae, Mucor circinelloides, and Rhizomucor variabilis isolates.

Mortality will be significantly decreased with early identification and treatment. A non-invasive method for the early identification of mucormycosis is real-time semi-nested qPCR[27]. There is a restricted supply of it. The diagnostic triad—clinical, radiographic, and pathological evaluation—are easily available techniques of diagnosis. To study the pathology, radiology, clinical feature and multi-factorial causes of AIFRS was the primary goal.

MATERIALS AND METHODS

Study Site, Study Population, Sample Size,

The present retrospective study was conducted at Government Medical College, Akola, in Maharashtra, India. It is a tertiary care hospital that provides health care services to more than a district. For the current study, data was collected from the medical case records of patients who were admitted to the ENT ward from August 2020 to July 2022.

Selection Of Patients

Inclusion Criteria

- Patient attended in OPD or Causality with signs of acute rhino sinusitis

Exclusion Criteria

- Patients who were certified within 24 hours of hospital admission without a proper diagnosis

Data Collection

- Reviewing the case files and investigation reports of patients admitted during the study period.
- We have classified our patients clinically with DNE into 3 stages according to symptoms.
- Stage 1: Sino-nasal and dental symptoms
- Stage 2: orbital symptoms +/- Stage 1
- Stage 3: any CNS symptoms +/- Stage 2

- MRI and CT are used for radiological classification. Radiological staging [1]

Table No. 1: Radiological Staging Of Acute Invasive Fungal Rhinosinusitis

Stage 1 : Involvement of nasal mucosa	a) Limited to middle turbinate
	b) Involvement of inferior turbinate or ostium of NLD
	c) Involvement of septum
	d) Bilateral nasal mucosa involvement
Stage 2 : Involvement of paranasal sinuses	a) One sinus
	b) Two Ipsilateral sinuses
	c) > Two Ipsilateral sinus involvement and/or palate/oral
	d) B/L paranasal sinus involvement or involvement of zygoma or mandible or ITF
Stage3 : Involvement of orbit	a) Nasolacrimal duct , median orbit , vision unaffected .
	b) Diffuse orbital involvement (>1 quadrant or >2b structure) , vision unaffected
	c) Central retinal artery or ophthalmic artery occlusion or sup. Orbital fissure , inf. Orbital fissure involvement with vision loss

	d)	Bilateral orbital involvement
Stage 4 : Involvement of CNS	a)	Focal or partial cavernous sinus involvement and or involvement of cribriform plate
	b)	Diffuse cavernous sinus involvement and /or cavernous sinus thrombosis
	c)	Involvement beyond the cavernous , involving base skull , ICA occlusion brain infarct
	d)	Multifocal and diffuse CNS disease

Statistical Analysis
Continuous variables were presented as mean (± SD), and categorical variables were written as number (%).

Ethics Committee's Approval
Approval was obtained from the Institutional Ethical Committee's (IEC) of the Government Medical College, Akola. (reference outward no. Anat 292/23 dated 17/08/23)

RESULTS
We have conducted study on 150 patients, 106 of whom were male. The mean age is 52 years.

Multifactorial
Recent studies of AIFRS show multifactorial causation. In our study, of the 113 COVID-19-positive patients, 106 were receiving steroids as a component of their COVID-19 treatment regimen or as a result of other health issues. Thirteen patients had post-COVID-19 or recent-onset diabetes, while sixty patients had pre-COVID-19 DM. Two patients had undergone organ transplants and three patients were suffering from renal disease each had extensive and uncontrolled disease, along with one case each of AIDS, cancer, and hypothyroidism (Figure 1). 106 individuals underwent oxygen (humidified) therapy as part of their COVID-19 treatment. We noticed a correlation between a decrease in average environmental temperature of about 4 degrees Celsius, an average increase in humidity of 30% in the month of June, and an increased number of hospital admissions for AIFRS cases[2,3,4]. (Fig. 2a,2b)

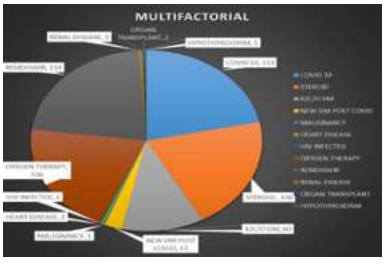

Figure No. 1: Diagramatic Representation Of Predisposing Factors

Figure No. 2a: Average Change In Temperature And Number Of Cases

Figure No. 2b Shows The Average Change In Humidity And The Number Of Cases.

Haematology
We found that anemia affected 79% of the participants in our study, with the majority falling into the mild group. Additionally, in addition to neutrophilia in 51% of patients and lymphocytopenia in 52% of patients, there was thrombocytosis in 29% of patients and a preponderance of high normal platelet counts in the remaining patients.

Pathology
Tissue collected during endoscopic sinus surgery, send to pathology in 10% neutral-buffered formalin. A final diagnosis of the lesion was made based on histopathological reports. We had 150 clinico-radiologically suspected AIFRS patients. In which 98 patients were histopathologically positive for mucormycosis (Figure 3), the pathology report shows very thick aseptate fungal hyphae branching either right angle or wide angle with acute neutrophilia in a background of lymphocytosis and plasma cells. In addition, patients with extensive disease reported many colonies of fungus hyphae with areas of necrosis and bony invasion. In which 12 patient's report were having foreign body giant cells and granuloma in the presence of fungal elements. And four patients had foreign body giant cells in the background of chronic inflammation.

On 40 individuals, no fungal elements were found, but there was fibrofatty collagenous tissue, congested arteries, and necrotic tissue on a backdrop of mixed inflammatory cells (lymphocytes, eosinophils, neutrophils, and plasma cells). In which six patients had foreign body giant cells and granuloma.

Additionally, nine individuals had mixed fungal infections (Aspergillus, Mucor). This included three patients with fungal-infused granuloma and foreign body giant cells, four patients exhibited chronic infiltration and necrosis with fungal components, while two had acute neutrophil infiltration. There were three reports of just aspergillus.

Figure No. 3: Diagrammatic Representation Of HPE Slide Reports

Table No. 2: Sensitivity And Specificity Of Histopathological Examination For Identifying Fungal Elements.

HPE report	Has disease	No disease	
Positive for fungal elements	110	0	PPV- 100
Negative for fungal elements	6	34	NPV-85
	Sensitivity 94.8	Specificity 100	
Simple statistic equations used PPV positive predictive value NPV negative predictive value			

Table No. 3 Clinical Staging

Stages	Number of patients
Stage 1	111
Stage 2	34
Stage 3	5

Table No. 4 Radiological Staging[1]

Stage	Number of patients
Stage 1: Involvement of nasal mucosa	A-0 B-0 C-0 D-0
Stage 2: Involvement of Paranasal Sinuses	A-8 B-32 C-22 D-29
Stage3: Involvement of Orbit	A-24 B-7 C-2 D-0
Stage 4: Involvement of CNS	A-7 B-1 C-6 D-12

DISCUSSION

Based on the results of the DNE and clinical examination, we clinically categorized the patients into three stages at the time of admission. Table No. 3 shows that there are 111 patients in the stage 1, 34 in the stage 2, and 5 in the stage 3 categories. Remarkably, 36 patients with severe disease on MRI but with minimal disease at the time of admission (Table 4). It implies that early care during this "golden period" would lower the death rate. We have observed nearly 100% mortality in patients who present with additional metabolic derangements together with intracranial illness symptoms.

There were 137 MRIs indicative of AIFRS, with 31 HPE reports negative for fungal illness. Those 31 MRIs were thoroughly examined, and we discovered that 30 patients had few symptoms following the COVID-19 infection, indicating that in the early stages of the disease, the specificity of the MRI appears to be low but the sensitivity is high. We treated ten patients with CECT suggesting AIFRS, six of whom had HPE-positive AIFRS and clinically severe illness. CECT of two patients revealed a typical retro orbital lump as part of inflammation.

Table No. 5: HPE Report Of Different Types Of Fungal Elements On The Slide

	Fungus present on HPE slide	Fungus absent on HPE slide	Mixed fungal elements on HPE slide
Mucormycosis	98	0	9
FBG with granuloma	12	6	3
FBG with chronic inflammation	4		4
Isolated aspergillus	3		

FBG – foreign body giant cell

Twelve of the 98 individuals in our research who tested positive for mucormycosis also had granulomas and foreign body giant cells. These results point to A. flavus-caused granulomatous invasive FRS, and four patients had foreign body giant cells in the background of persistent inflammation. It suggests A. fumigatuos-induced chronic invasive FRS with mucoral superadded infection[7]. Forty patients reported being negative for AIFRS; six of them exhibited granuloma and foreign body giant cells without any fungal components. Nine patients reported mixed fungus infection, with three having granulomatous fungal rhino sinusitis with superadded mucormycosis, four having chronic fungal rhino sinusitis with superadded mucormycosis, and the remaining two having acute invasive fungal rhino sinusitis caused by both aspergillus and mucor species (Table 5).

According to table no. 2, the current study's histopathology-based fungal hyphae identification has 100% specificity and 94.8 percent sensitivity. 100% is the positive predictive value and 85% is the negative predictive value. Despite null HPE results, six patients had clinical and radiological signs of acute invasive fungal rhinosinusitis (turbinate necrosis), which was treated as AIFRS. A few of them were diagnosed with culture and sensitivity.

In our study, the majority of patients had anemia. We have classified anemia according to the National cancer Institute. Mild: hemoglobin 10.0 g/dL to the lower limit of normal, Moderate: hemoglobin 8.0 to 10.0 /dL, Severe: hemoglobin 6.5 to 7.9 /dL, Life-threatening: hemoglobin less than 6.5 g/dL[9] . Most patients were healthy with mild normocytic normochromic anemia, even though we had 10% of patients with severe anemia, and two patients were in the life-threatening category with bone marrow suppression. Anemia is a common manifestation of COVID-19[12]. Anemia is due to an increase in pro-inflammatory cytokines and a subsequent increase in hepcidin levels, as hepcidin reroutes iron to the inflammatory process. And inflammation leads to inappropriate erythropoietin (EPO) levels and a decreased response to erythropoietin. There is also a chance of decreased RBC survival. These all contribute to normocytic normochromic anemia.

We have noticed a deterioration of anemia after starting Amphotericin B treatment, and it reversed after the completion of treatment. Amphotericin B causes a normochromic, normocytic anemia thought to be mediated by direct marrow toxicity or suppression of erythropoietin production[22]. It was noticed that posaconazole aggravated anemia. Anemia was linked to thrombocytosis in a large proportion of cases. When platelets detect pathogens, their interactions cause platelet activation and the secretion of a variety of peptides, forming a first-line defense against infection. Activated platelets also release chemokine and express ligands to activate leukocytes and trigger both the innate and adaptive immune responses[15]. It is also thought to be a part of the COVID-19 hypercoagulable state, where thrombuses form either a bed for fungus or protect it to multiplying. In a sizable portion of patients, it is also linked to lymphocytopenia and neutrophilia. As we know, a 60% risk of developing an AFIRS infection is reported if neutropenia persists for 3 weeks, and this rises to 100% when the neutrophil count is $<0.10 \times 10^9$/L.[19] In the present study, a cytokine storm resulted in a high neutrophil-lymphocyte ratio during COVID-19 infection[20], indicating overproduction of defective neutrophils. COVID-19 can also deplete lymphocytes. Lymphocytopenia may increase the likelihood of developing a AIFRS. Treatment with tocilizumab, an IL-6 receptor antagonist, increased the number of circulatory lymphocytes[16], reversed the count of lymphocytes, and improved adaptive immunity[17].

According to this study, COVID-19 infection, steroid therapy, pre- and post-COVID-19 diabetes mellitus, humidified oxygen therapy, cancer, renal illness, and organ transplantation are the factors that lead to the development of AIFRS. As we previously covered, immuno-suppression brought on by anemia and COVID-19-induced cytokine storms results in AIFRS. Moreover, hyperglycemia, including post-COVID-19 DM and ketoacidosis, impairs neutrophil function and releases free iron[8,21]. Both encourage the growth of AIFRS[18,24]. SARS-CoV-2 virus enters cells through the ACE 2 receptor and interacts with the renin-angiotensin-aldosterone system, which leads to the accumulation of angiotensin 2 and, consequently, the dysfunction of beta cells in pancreases[26]. And treatment with steroids as a part of COVID 19 management, which induces hyperglycemia. In contrast, several patients with dermatological diseases and arthritis receiving routinely monitored steroid treatment did not develop any COVID-19 complications or sequelae, including AIFRS, in our study. This implies that steroids alone are not the problem. The pathophysiological mechanism of AIFRS infection in organ transplant patients with or without COVID-19 infection is due to immunosuppression. AIFRS was seen in patients who received humidified oxygen during their immunocompromised stage. Divergent viewpoints existed on the same. To prevent nosocomial infections, we recommend using distilled water in a disposable oxygen humidifier, properly sanitizing the gas cylinder, and decontaminating the hospital setting. Hematological malignancy and longstanding neutropenia are sinister causes for the development of AIFRS-19.

According to our research, the month of June showed an accentuation of AIFRS together with a relative drop in the average environmental temperature of almost 4 degrees Celsius and an average 30% rise in humidity[2,3,4] (Fig. 2a,2b). It is almost similar to the Al-Ajam et al. study[25], in which a series of 16 cases of invasive rhinocerebral, cutaneous, and pulmonary mucormycosis were identified. He showed that the onset of symptoms clustered at the end of a dry period, which consistently extended from late May to October, i.e., early summer to the end of autumn, in 12 out of 16 patients, with a statistically significant seasonal variation ($p = 0.007$) that coincided with increasing rain levels. We suggest immunocompromised patients take more precaution during this period.

CONCLUSION

Hyperglycemia, ketoacidosis, neutropenia, and immunosuppression are known to cause AIFRS. We were able to elicit a connection between AIFRS and COVID-19 infection: COVID-19-induced hyperglycemia and anemia are associated with thrombocytosis, neutrophil cytokine storms, and lymphocytopenia. Our work demonstrates a link between poorly managed humidified oxygen therapy and environmental changes that have resulted in AIFRS. The sensitivity of histopathological examination for fungal elements is 94.8%, with a negative predictive value of 85%. This is less than what have we expected. Here, we present a broad concept of the range of diseases (acute, granulomatous, and chronic invasive fungal rhino sinusitis) that have been linked to the host immune response during the COVID-19 pandemic. A high index of clinical suspicion and multidisciplinary approach will aid in the diagnosis of AIFRS and enable early management to reduce morbidity and mortality.

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