



Understanding the Spectrum of Invasive Fungal Sinusitis in the Aftermath of Covid-19: Insights into Clinical and Mycological Variability

¹Deepalakshmi Tanthry, MBBS, DLO, DNB ENT, Associate Professor, Department of Otorhinolaryngology, A. J. Institute of Medical Science and Research Centre, Mangaluru, Karnataka, India

²Meghana Udaya Acharya, MBBS, MS (ENT), Postgraduate, Department of Otorhinolaryngology, A. J. Institute of Medical Science and Research, Mangaluru, Karnataka, India

³Gururaj Tanthry, MBBS, MD, FCA, DM/M.Ch, Professor, Department of Anaesthesia, A. J. Institute of Medical Science and Research, Mangaluru, Karnataka, India

Corresponding Author: Meghana Udaya Acharya, MBBS, MS (ENT), Postgraduate, Department of Otorhinolaryngology, A. J. Institute of Medical Science and Research, Mangaluru, Karnataka, India

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Abstract

Introduction: Fungal rhinosinusitis (FRS), once considered a rare entity, has seen a steep rise in incidence in recent times. FRS signifies varied spectrum of disease ranging from the mild form of superficial colonization, allergic manifestations to life threatening extensive invasive disease. The COVID-19 pandemic has been attributed to rise in invasive fungal sinusitis cases, which raises public health concerns. Our aim was to gain insight into various clinical manifestations and fundamental causes of FRS.

Materials and methods: This retrospective, observational study included all patients with clinical and radiological signs of rhinosinusitis and

histopathological confirmation of fungal rhinosinusitis. The study population was treated by surgical debridement and antifungal therapy following surgery. Evaluations were conducted on the demographic information, risk factors, clinical presentations, treatment regimen, and its results.

Results: A total of 10 male patients with a mean age of 43.66 ± 5.95 years were included in our study. Common associated co-morbidity was diabetes mellitus. Post-operative specimen sent for HPE revealed infection with *Aspergillus* species in 2 patients, *Candida* species in 1 patient and *Mucormycosis* in 7 patients. All patients were disease-free during the follow-up period after combined surgical and antifungal treatment.

Conclusion: With increasing incidence of fungal rhinosinusitis in the post covid-19 era, it is crucial to obtain timely diagnosis and prompt treatment with antifungal therapy and surgical debridement for better outcomes and higher survival rates.

Keywords: Chronic rhinosinusitis, COVID-19, Fungal sinusitis, Mucormycosis, Paranasal Sinus Diseases, Rhinosinusitis, Sinusitis

Introduction

In the environment around us, fungi are omnipresent. Direct contact, ingestion or inhalation can all result in transmission of fungal diseases. Invasive fungal rhinosinusitis (IFRS) is a potentially lethal infection that primarily affects the immunocompromised. Histologically, it is described as existence of fungal hyphae in blood vessels, bone, mucosa, or submucosa [1]. Traditionally regarded to be a rare entity, observations concerning it have emerged more widespread globally in recent decades. Due to increased risk of IFRS in COVID-19 patients, fungal infections have grown increasingly noteworthy in the context of public health as a consequence of the pandemic [2].

Recent research has shown that individuals with uncontrolled diabetes mellitus, acquired immunodeficiency syndrome, hematologic malignancies, etc. tend to be at higher risk of contracting IFRS. In recent decades, there has been a discernible upsurge in the number of cases diagnosed with sinus Mucormycosis infections [3].

IFRS may be associated with bizarre signs and symptoms that mimic pan-sinusitis. Pathologies spectrum widely in diversity, encompassing conditions such as orbital angioinvasive illness, rhino-orbital-cerebral disease, rhino-maxillary diseases, and sinonasal disorders. IFRS cause severe intra-cranial and extra-

cranial problems because the pathogenic fungus spread precisely through osseous structures, skull base foramina, and along arteries and nerves. The results of IFRS are detrimental, with a documented mortality rate of 20%-80% [2].

The imaging spectrum of IFRS is broad. Early diagnosis and course of treatment depends on the knowledge of anatomy of surrounding structures as well as familiarity with both intra- and extra-sinonasal imaging characteristics—for instance, loss of contrast enhancement in the region that is affected hint at fungal invasion induced ischemia of the tissues [2].

With the goal to foresee positive results, it is of paramount importance to identify the fungi, assess the host immune system, and diagnose the disease promptly employing radiological, microbiological, histopathological examination. The aforementioned is recommended followed by immediate surgical intervention and medical management with antifungal therapy [4]. Prompt diagnosis and treatment avert rapid progression and catastrophic consequences [2]. Nevertheless, timely detection of IFRS may prove to be challenging because of its infrequency and ambiguous signs and symptoms.

The emphasis of this study is to deliver insights into an array of clinical manifestations, mycological causes, and treatment approaches in the aftermath of COVID-19 pandemic.

Materials and Methods

Study Design

Retrospective, observational study done from October 2022 to October 2023, in Department of Otorhinolaryngology in a tertiary care center in Mangaluru, India.

Ethical Clearance

This study was conducted in accordance with 1964 Helsinki declaration and its later amendments.

Study Participants and Data Collection

This study included all patients presenting to our Out-Patient Department (OPD) with clinical and radiological features of rhinosinusitis along with confirmed histopathological evidence of fungal rhinosinusitis. Data regarding patient's age, gender, presenting complaints, past history, comorbidities, imaging outcomes, surgical procedure, histopathological examination (HPE) reports and follow-up was collected, documented, and analyzed.

Treatment Protocol

The initial approach to treatment was surgical debridement. Prophylactic antibiotics were given. Informed consent was obtained from patients for surgical procedure as well as comprehensive evaluation of specimen. Depending on radiological results and the paranasal sinuses involved, patients underwent septal surgery, functional endoscopic sinus surgery (FESS) or Caldwell Luc operation under general anesthesia (GA).

10% buffered formalin was used as preservative solution to send intra-operative specimen for HPE. Fixation, dehydration, clearing, and impregnation were carried out according to accepted standards. Employing a microtome, tissues were sliced into thin sections, mounted on slides, and stained with hematoxylin and eosin.

Antifungal therapy was initiated upon histological diagnosis of fungal sinusitis. For cases of Mucormycosis, conventional amphotericin B injection was administered once daily for 3 weeks. One day prior to initiating, serum electrolytes, renal function tests, and bicarbonates were assessed. Patient was pre-medicated with 2ml intravenous injection of pheniramine maleate

and 100mg intravenous injection of hydrocortisone 30 minutes prior to infusion. Adequate prehydration of patient was ensured by administration of 500ml normal saline (NS) added with 1 ampule of potassium chloride over a period of 1 hour. 100mg amphotericin B injection was added in 500ml of 5% Dextrose. Intravenous infusion was started immediately after dilution. Initially 10ml was administered over 20 minutes to check for any adverse reactions before continuing at a rate of 125 ml/hour. Post infusion, patient was rehydrated with 500ml of NS intravenously. Urine output, bicarbonates, blood glucose levels and renal function tests were regularly monitored in addition to cardiac monitoring. Following 3 weeks of Amphotericin B therapy, patient was put on oral antifungal agents for the next 6 weeks. Itraconazole or Voriconazole were oral antifungal medications used. The prescribed dosage was 200mg twice daily for six-weeks.

Follow-Up

All patients were followed up for a period of 3 months following the surgery. Every follow-up visit (at 1 week, 1 month and at 3 months after procedure) included clinical examination and nasal endoscopy to evaluate symptomatic improvement and clinical outcomes.

A brief description of 5 cases is mentioned below.

Case 1

A 38-year-old male presented with one-week-history of diffuse headache, left-sided nasal obstruction and bilateral maxillary region pain. Despite using oral hypoglycemics for Type 2 DM for last three years, patient's HbA1c values were significantly elevated. Computed tomography (CT) image of paranasal sinuses (PNS) was indicative of chronic sinusitis (Figure 1). The patient was planned for surgical debridement via FESS. There were signs of Mucormycosis infection in

the samples from left middle meatus that was sent for histopathological analysis. According to the protocol, Amphotericin B therapy was initiated. After 3 weeks of treatment, patient had persistence of nasal obstruction. A nasal endoscopy was performed and left maxillary sinus mucosa debridement was done under local anesthesia. Histopathological study of the specimen showed spores of Candida (Figure 2). There was no evidence of Mucormycosis in the tissue. A follow-up CT scan was conducted (Figure 3) and Oral Voriconazole was prescribed for six weeks.

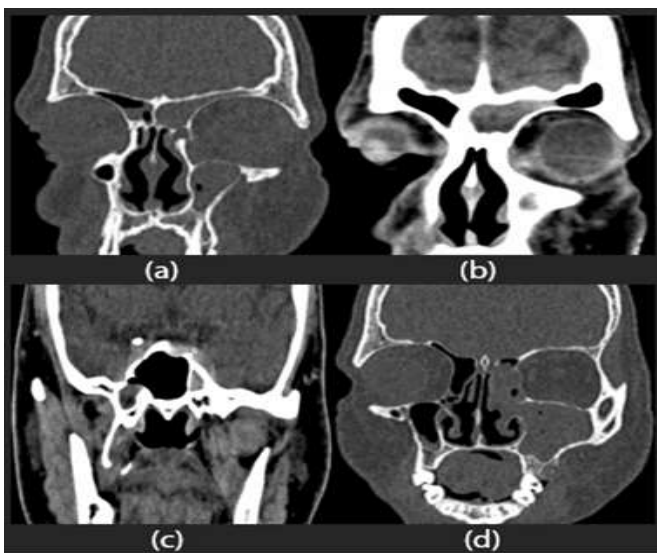


Figure 1: (a), (b), (c) - Soft tissue density with hyperdense areas observed in the bilateral maxillary, ethmoid, frontal, and sphenoid sinuses on CT-PNS; (d) Mild expansion of left maxillary sinus with occlusion of osteomeatal complex and no evident bony erosion or expansion into the intracranial and orbital spaces.

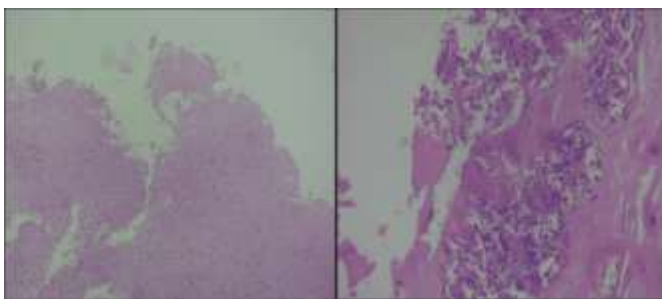


Figure 2: Sections from debrided maxillary sinus

mucosa specimen showing fragments of squamous epithelium with dense chronic inflammatory debris along with spores of Candida.



Figure 3: (a), (b), (c) - Post operative CT scan showing mild mucosal thickening in left frontal, bilateral maxillary, ethmoid and left sphenoid sinuses; (d) Thinning with focal breach in inferior wall of left maxillary sinus.

Case 2

An elderly male, aged 51, presented with left-sided nasal obstruction, cough, and post-nasal drip lasting three months, worsened by stress such as vigorous nose blowing and resolved spontaneously. He did not have any co-morbidities. An episode of abrupt onset bleeding from left nasal cavity is what alarmed the patient and brought him to the hospital. Anterior rhinoscopy exhibited his nasal septum was deviated to left and nasal endoscopy revealed blood-stained discharge in left middle meatus. CT-PNS findings raised the suspicion of polyp with calcifications or fungal ball (Figure 4). Patient was operated and left FESS along with Caldwell

Luc procedure was done to remove the mass from left maxillary sinus. The tissue's histopathology exhibited edematous stroma, congested blood vessels, seromucinous glands, and widespread lymphoplasmocytic infiltrates and eosinophils in sub-epithelium. Sheets of fungal hyphae and spores were seen in surrounding areas. Fungal hyphae were detected by Periodic Acid-Schiff (PAS) staining, and *Aspergillus fumigatus* growth was observed in fungal culture. Patient was prescribed six-week regimen of oral Voriconazole.

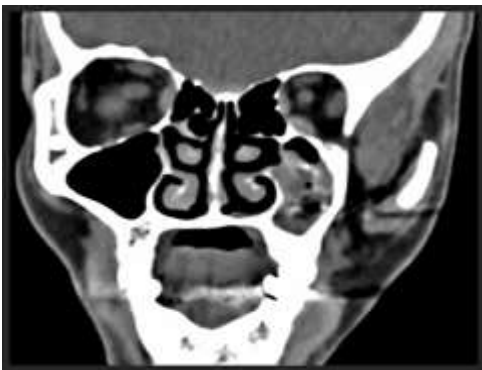


Figure 4: Soft tissue density with hyperdense areas within the left maxillary sinus. The frontal, ethmoid, sphenoid, and right maxillary sinuses displayed normal anatomical configuration.

Case 3

A 47-year-old man complained of 2-month history of right-sided nasal obstruction and 1-week history of right maxillary pain. He was diagnosed with hypertension five years prior, and was taking medicine for it regularly. A contrast-enhanced CT (CECT) scan of PNS showed results that suggested the likelihood of fungal infection of PNS (Figure 5). The procedure of bilateral FESS was performed and right maxillary sinus mucosa demonstrated histopathologically confirmed fungal sinusitis, morphologically favoring Mucormycosis. This stipulated the commencement of antifungal therapy with Amphotericin B for 3 weeks followed by Voriconazole for the next 6 weeks.

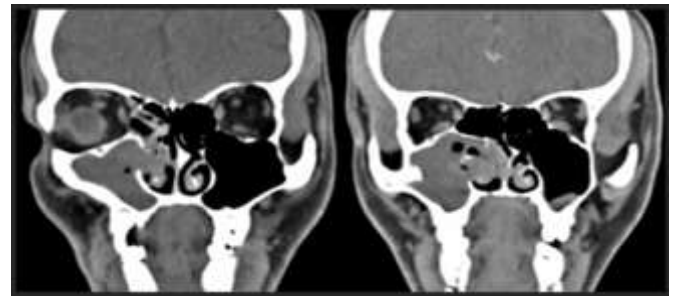


Figure 5: Non-enhancing soft tissue density lesion within the right maxillary sinus causing widening of maxillary ostium and extending into nasal cavity and ethmoid sinus on the right side detected on a CECT scan of the PNS. Nominal erosion of right inferior turbinate is also seen.

Case 4

A 42-year-old gentleman reported of diffuse headache of 3 days duration, which aggravated on bending forwards and was associated with pain behind left eye. Furthermore, he had experienced two episodes of blood-tinged sputum in three days, as well as postnasal drip. The patient was diagnosed to have type 2 diabetes mellitus one year prior, and has been on anti-diabetic medications ever since resulting in his blood glucose levels being within the normal range. Clinically, the patient had deviated nasal septum (DNS) to left and frontal sinus tenderness could be elicited on left side. The CT-PNS data confirmed soft tissue density in left osteomeatal complex (OMC) and frontoethmoidal recess, in addition to pansinusitis and DNS to left. The surgical approach included septal surgery and FESS. Although fungal culture yielded no growth, histopathological examination of the tissue sample provided findings that appeared morphologically congruent with *Aspergillus* (Figure 6) and consistent with fungal sinusitis. Given the aforementioned, patient was subsequently administered Itraconazole as per protocol.

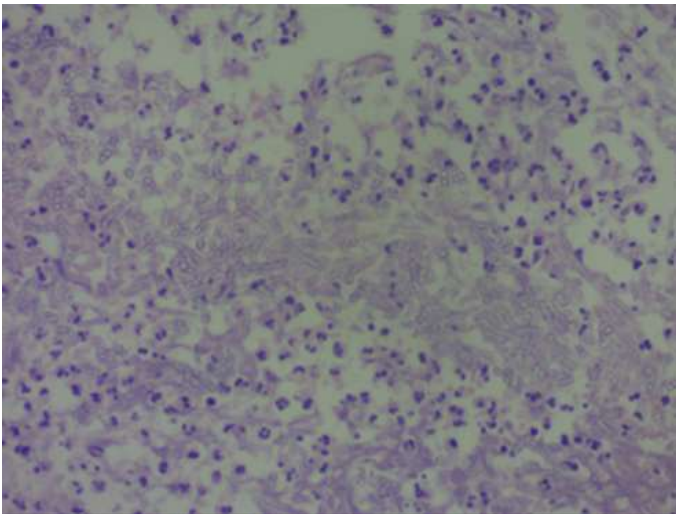


Figure 6: Section shows edematous respiratory mucosa infiltrated by large number of inflammatory cells consisting of predominantly lymphocytes, plasma cells and occasional eosinophils. Fungal balls seen consisting of septate fungi at acute angles, morphologically consistent with Aspergillus.

Case 5

A male patient aged 48 years experienced right-sided frontal headache and right nasal discharge over a span of 3 weeks. He was a known case of uncontrolled Type 2 DM and hypothyroidism since 1 year and under medications for the same. Anterior rhinoscopy revealed DNS to left. Plain CT imaging of PNS displayed mucosal thickening in left maxillary sinus and diffuse soft tissue density in right maxillary sinus extending into right OMC. The treatment strategy was FESS with corrective septal surgery. Sample from right-side maxillary sinus was sent to histopathologist for assessment. The sections studied exhibited fungal organisms morphologically favouring Mucormycosis (Figure 7). This prompted the initiation of three-week course of Amphotericin B. During the post-operative period, patient continued to have left-sided nasal obstruction. One month after surgery, a follow-up CT-PNS scan indicated mild soft tissue density in bilateral

maxillary sinus. Revision FESS was done and mucosa from both maxillary sinuses was sent for histopathological analysis. As stated in the report, respiratory mucosa with necrotic granulation tissue was seen with no obvious fungal elements. Itraconazole tablets were administered as a continuation of antifungal treatment.

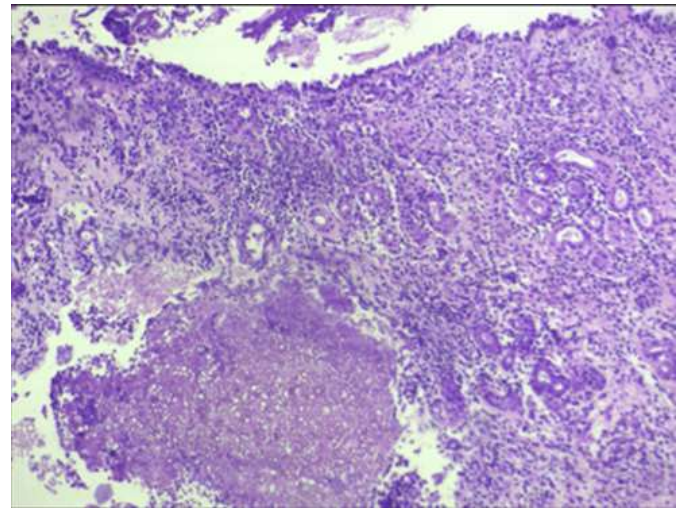


Figure 7: Section show fragments of tissue lined by respiratory epithelium with underlying dense mixed inflammatory infiltrate composed of neutrophils, lymphocytes and plasma cells with entangled mass of fungal organisms having broad aseptate hyphae with right angle branching morphologically favouring Mucormycosis.

Results

A total of 10 patients were included in our investigation of which all were male with a mean age of 43.66 ± 5.95 years. The most common reported symptoms were nasal obstruction (70%) followed by headache and facial pain (50%). Nasal discharge, post nasal drip and nasal bleed were other reported symptoms. The duration of these symptoms was acute (<1 month) in 60% and chronic (>1 month) in 40 % cases.

The commonly associated comorbidity was Type 2 DM (60%). On the basis of HbA1c values, 40% patients had uncontrolled DM and 20% had controlled DM. Other comorbidities in study population included hypertension (20%) and hypothyroidism (10%).

CT-PNS showed evidence of sinusitis in majority of individuals (80%). A possibility of fungal sinusitis was seen in CT findings of only 2 patients. All 10 patients were treated by surgical debridement and antifungal therapy.

HPE revealed Mucormycosis infection in 7 specimens followed by presence of Aspergillus in 2 specimens and Candida in 1 specimen. Amphotericin B was started for all patients of Mucormycosis followed by oral antifungal drugs. Majority of the patients (~70%) had clinical improvement following 3 weeks of Amphotericin B and were put on oral antifungals for the next 6 weeks. ~30% patients had persistence of symptoms during follow-up visit after 1 month for which a repeat surgical intervention was done and antifungal treatment was continued based on HPE reports. Oral Itraconazole or Voriconazole was started for patients with Aspergillus or Candida infection.

All the cases on follow up by clinical examination and diagnostic endoscopy did not show any features suggestive of invasive fungal sinusitis at the end of 3 months.

Discussion

Of the various infectious processes, a particular subcategory that an otorhinolaryngology surgeon ought to be knowledgeable about is mycological infections, considering that they can be observed in head and neck surgery, rhinology, and otology [5]. Usually, the inhaled fungi comprise of a normal component of sinonasal microbiota. Eventually, these fungal organisms are killed

by immune mechanisms operating in the body. The immune system mechanisms are disturbed in immunocompromised individuals, following prolonged usage of antibiotics, humid environment, etc. increasing the likelihood of fungal infections. Therefore, fungi become pathogenic only under favorable environmental conditions.

In diverse ecological settings, occurrence of fungal diseases has risen dramatically since the year 2000. An estimated annual incidence of invasive fungal infection is 6 for every 100,000 individuals [6].

COVID-19 virus is the underlying cause of infection known as severe acute respiratory syndrome corona virus 2 (SARSCoV-2) [7]. Kerala notified the first case in India in January 2020. Considerable immunological dysregulation brought on by infection by COVID 19 virus increases predilection to subsequent infections. The rapid rise in number of cases of Mucormycosis during the global outbreak was largely ascribed to the ubiquitous existence of fungi in surroundings in tandem with high prevalence of diabetes and other immunocompromised conditions in the general population. Abnormalities in iron metabolism, widespread utilization of corticosteroids and antibacterial medications were the explanations proposed for striking increase in incidence following the pandemic [7, 8, 9].

Numerous disorders of PNS have been attributed to fungi and they are all typified by growth of fungi with pathogenic potential in mucosal lining or secretions of the sinuses. Clinically speaking, fungal rhinosinusitis (FRS) is categorized based on appearance or lack of fungal components in mucosa lining the PNS as well as the response of host to presence of fungal elements [10]. FRS represents range of disorders rather than being a

single entity. The ability of hyphae of fungi to penetrate the tissues across epithelial layer determines whether they are invasive or non-invasive. As the term implies, invasive fungal rhinosinusitis may lead to substantial invasion of tissues via mucous membrane, bones, nerves, blood vessels and adjacent structures. In addition to this variation in FRS pathophysiology, there also exists a variance in the disease's chronicity, consequently classifying it further into acute (symptoms lasting for <4 weeks) and chronic (symptoms for >4 weeks). FRS has been divided into six major subcategories. Non-Invasive Fungal Rhinosinusitis which includes Allergic fungal rhinosinusitis, Fungal Ball and Saprophytic fungal infestation; Invasive Fungal Rhinosinusitis comprising of Acute invasive fungal rhinosinusitis, Chronic invasive fungal rhinosinusitis and Chronic Granulomatous invasive fungal rhinosinusitis [5].

Acute IFRS had been defined as invasion of mucosa, sub mucosa, blood vessels or bone of the PNS in the backdrop of symptoms of sinusitis lasting for duration of less than one month [5, 11]. Although acute IFRS is infrequent, it is a disorder which requires to be detected and managed immediately considering it can have potentially fatal consequences if left untreated. It is commonly seen in patients with immunocompromised conditions. Possible clinical features include nasal obstruction, fever, facial discomfort or pain and rhinorrhea. Yet, typical signs of rhinosinusitis may sometimes not be noticed even in cases of advanced acute IFRS. In addition to making prompt detection more perplexing, the invasive symptoms that occur can manifest abruptly and exacerbate in a span of few hours. These symptoms, which includes numbness, edema and erythema of face, headache, loss of vision or diplopia, proptosis and neurological deficits, are primarily caused

due to invasion of surrounding structures. Deficits in cranial nerves III, IV, and VI could indicate that the cavernous sinus is involved [5].

On the other hand, chronic IFRS has insidious onset and progresses gradually over time. It can manifest as mass in the PNS or nasal cavity leading to unilateral nasal obstruction, blood-stained nasal discharge, cacosmia or proptosis. Additional sites of invasion include anterior cranial fossa, which may result in neurological problems, or the maxillary sinus. These can often be misdiagnosed as carcinoma.

The most commonly reported symptom according to our findings was nasal obstruction which was followed by headache and facial pain. Majority of these symptoms were of acute presentation lasting for less than four weeks.

According to research conducted by Kursun et al on acute IFRS in non-COVID patients, diabetes mellitus was the most prevalent co-morbidity [11]. DM also happened to be the most frequent associated condition in previous researches done before the COVID-19 outbreak. Study conducted by Turner et al. in 2013 reported that 47.8% of patients had diabetes followed by hematologic malignancies in 39.0% and corticosteroid use in 27.6% of patients [11]. This is consistent with the findings of our research, which showed that diabetes mellitus and hypertension were the most common related disorders.

If IFRS is suspected in a patient, the first step is to obtain a panel of blood tests to help determine the underlying cause predisposing to IFRS. Akin to other types of fungal rhinosinusitis, a computed tomography with contrast enhancement (CECT) scan is the primary radiological investigation which is vital for diagnosis. Apart from radiological signs that are distinctive to

fungal sinusitis, namely calcification and loss of bony limits of the sinuses, additional signs related to fungal sinusitis include the ones observed in bacterial sinusitis like air fluid levels or mucoperiosteal thickening of more than 8 mm ^[12]. The initial results of CT scan in acute IFRS are not distinctive and are usually characterized by asymmetrical thickening of mucosa. As the condition advances, scan will show additional bony destruction and invasion into surrounding tissues. It has been demonstrated that the most distinctive indication for acute IFRS affecting maxillary sinus is invasion of the fat around maxillary antrum ^[5]. Bony erosion and hyper attenuation are the hallmark features in chronic IFRS. Frequently, additional imaging is needed, for instance a contrast-enhanced MRI (CE-MRI). It has been found that this is more sensitive than CT in detecting acute IFRS. A CE- MRI may also detect invasion into deeper tissues and involvement of meninges or cavernous sinus. CT scan readings of most of our patients showed non-specific signs of sinusitis without any evidence of bony destruction. Only 2 patients had findings suspicious of fungal sinusitis.

Due to its affordability and easy availability in majority of institutions, histopathological detection of invasive fungal forms in tissue is the frequently employed diagnostic procedure for final diagnosis of IFRS. Two most widely used special stains for fungi are Grocott-Gomori's methenamine-silver (GMS) and periodic acid-Schiff (PAS). Since it explicitly depicts angioinvasion, IFRS is exclusively documented in HPE. Chronic IFRS has a weaker inflammatory response and fewer inflammatory cells which distinguishes it from acute IFRS ^[5]. However, a noteworthy shortcoming is lack of sensitivity in terms of identifying the fungi. A few plausible causes for this could be the specimen's sparse

fungal growth, potential loss of fungal elements while processing, and interobserver variability ^[7]. Fungal cultures show no growth in nearly 30% of patients with acute IFRS ^[13]. Both acute and chronic IFRS are frequently caused by species of *Aspergillus* and organisms in the *Zygomycetes* order. Based on our analysis, *Mucor* accounted for 70% of causative agents, followed by *Aspergillus* species accounting for 20% and *Candida* species for 10%.

Three components comprise the treatment of IFRS: antifungal therapy, surgical debridement, and reversal of the pre-disposing state ^[5]. Surgery is widely acknowledged as an essential component of treatment. It is primarily done by endoscopic sinus surgery to obtain tissue specimen for establishing a diagnosis. Additionally, as thorough surgical debridement boosts survival, necrotic tissue should be debrided concurrently. It has been found that commencing systemic antifungal medications early increases survival. Amphotericin B is the cornerstone of antifungal treatment since it effectively combats *Aspergillus* and *Mucorales*. Adjuvant drugs like Itraconazole have demonstrated poor efficacy and hence should not be used as first-line treatments for *Mucormycosis*. Ravuconazole and posaconazole have demonstrated in vitro action against *Mucormycosis*, rendering them an effective therapeutic option. For first-line management of *Mucormycosis*, the combination of isavuconazole or Voriconazole with relatively effective antifungal therapy has been reported to be helpful in patients admitted to the Intensive Care Unit (ICU) and can be used as a maintenance therapy ^[14]. Echinocandins are the drug of choice for treatment of *Candida* infection. Posaconazole, Voriconazole, isavuconazole, fluconazole and Liposomal Amphotericin B are the second-line alternatives that can be used ^[10].

First line of treatment of Aspergillus infection is triazoles, specifically Voriconazole, isavuconazole or posaconazole for invasive infections [15]. The literature also offers some proof for the implementation of hyperbaric oxygen as an adjuvant in treatment of FRS since it releases oxygen free radicals [5].

Patients in our study who had histopathologically confirmed Mucormycosis were started on conventional amphotericin B. Liposomal amphotericin B was more expensive and therefore not preferred despite the fact that it is less nephrotoxic. 70% cases responded to Amphotericin B and showed improvement. 30% patients had persistence of nasal obstruction which required additional surgical intervention followed by biopsy, however a repeat HPE did not show any evidence of Mucormycosis and hence oral antifungals were continued with regular follow-up until resolution of symptoms. Furthermore, we noticed that patients' responses to Voriconazole and Itraconazole were similar. All patients were disease-free after 3 months of surgery.

Conclusion

In post-COVID-19 period, fungal rhinosinusitis is becoming increasingly prevalent. It happens to be one of the most frequent unrecognized reasons for mortality among patients. A multidisciplinary approach is essential given that diagnosing invasive fungal infections can be challenging for clinicians. To improve prognosis and increase chances of survival, complex diagnostic work-up which includes clinical, radiological and microbiological assessment is critical for accurate diagnosis and immediate treatment.

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