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ORIGINAL ARTICLE

COVID Associated Invasive Aspergillosis

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Abstract To study the possible association between invasive fungal sinusitis (aspergillosis) and coronavirus disease. An observational study was conducted at a tertiary care centre over 6 months, involving all patients with aspergillosis of the paranasal sinuses suffering from or having a history of COVID-19 infection. 92 patients presented with aspergillosis, all had an association with COVID-19 disease. Maxillary sinus (100%) was the most common sinus affected. Intraorbital extension was seen in 34 cases, while intracranial extension was seen in 5 cases. Diabetes mellitus was present in 75 of 92 cases. All had a history of steroid use during their coronavirus treatment. New manifestations of COVID-19 are appearing over time. The association between coronavirus and aspergillosis of the paranasal sinuses must be given serious consideration. Uncontrolled diabetes and overzealous use of steroids are two main factors aggravating the illness, and both of these must be properly checked.

Keywords COVID associated aspergillosis · COVID-19 · Paranasal sinuses · Aspergillosis · Diabetes mellitus · Steroid

Introduction

Over the past year COVID-19 pandemic has caused turbulence in the world. The second wave has been catastrophic all over the world particularly in India. During the months of April and early May 2021, millions were affected and thousands were seeking hospital care [1]. Overwhelming number of patients needed oxygen therapy which put tremendous pressure on health infrastructure [2]. Recently, an association was observed between Otorhinolaryngology and coronavirus, a more dangerous and potentially deadly one: that of invasive fungal sinusitis resulting from mucormycosis [3]. Apart from this, another type of

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invasive fungal infection was also observed among COVID affected patients resulting from aspergillosis.

Aspergillus species are ubiquitous in nature, exposure and inhalation of their spores is a frequent event. When the spores are inoculated into anaerobic sinuses they may become pathogenic [3]. Tissue invasion is uncommon and occurs most frequently in the setting of immunosuppression associated with therapy for hematologic malignancies, hematopoietic cell transplantation, or solid organ transplantation. Neutropenia and glucocorticoid use are the most common predisposing factors. Histopathology, invasive aspergillosis is characterized by progression of the infection across tissue planes. One hallmark of infection is vascular invasion with subsequent infarction and tissue necrosis. The prognosis of invasive fungal sinusitis is potentially fatal, with an extremely high mortality rate, particularly in immunocompromised patients [4].

Clinically, the patients may present with nasal polyps, anterior and posterior nasal discharge, nasal obstruction, epistaxis, headache, anosmia, proptosis or snoring [5]. Aspergillus as a pathogen cannot actively penetrate undamaged and intact mucus membrane or skin as it lacks keratolytic enzymes. On the basis of this finding, paranasal sinus aspergillosis is grouped into invasive (acute fulminant, chronic invasive, granulomatous invasive) and non-invasive (fungus ball and allergic fungal rhinosinusitis) forms depending on invasion of the mucosal layer and destruction of the bone. Any type of paranasal aspergillosis may progress to more aggressive disease illustrating the importance of early recognition of this increasingly encountered disease [6, 7]. Intracranial spread of the infection occurs very rapidly due to close proximity of the sinuses with cranial cavity. It is a dreaded complication, as it is usually fatal if not treated promptly. Orbital involvement occurs by contiguous spread of the disease from paranasal sinuses, by expansion or bone erosion due to pressure effect of the polyps or fungal tissue invasion. It is considered to worsen the prognosis of sinonasal aspergillosis. Moreover, the superior orbital fissure and optic canal directly open into the middle cranial fossa, and are ready pathways for further intracranial spread of the infection [8].

Recently, there has been a change in the incidence of aspergillus infection of the sinuses, with more cases being diagnosed much more frequently. Over the last 6 months, our institute, a tertiary care teaching hospital, has observed a sudden upsurge in cases of invasive sinonasal aspergillosis, with much of the emergency operating theatres being occupied with patients undergoing radical surgical procedures for this condition.

A complex interplay of factors that include diabetes mellitus, any previous respiratory pathology, immunosuppressive therapy, nosocomial infection sources and systemic immune alterations of COVID-19 infection itself may lead to secondary infections, which are increasingly being recognised in view of their impact on morbidity and mortality [9]. Furthermore, as COVID-19 is a life-threatening, infectious disease, affected patients show an overexpression of inflammatory cytokines, and impaired cell-mediated immunity with decreased cluster of differentiation 4 and 8 positive T-helper (CD4 + T and CD8 + T) cell counts, indicating susceptibility to fungal co-infections [10]. Critically ill patients, especially those admitted to intensive care units and those who required mechanical ventilation, or who had a longer duration of hospital stays, even as long as 50 days, were more likely to develop fungal co-infections [11]. Extensive use of steroids in COVID-19 management can also suppress immunity, allowing opportunistic fungal infections to colonise. Hence, it is important to be aware that COVID-19 patients can develop further fungal infections during the middle and latter stages of this disease, especially severely ill individuals [12].

Here, we present our study on 92 cases of sinonasal aspergillosis of the sinuses observed over a time period of 6 months, with these patients being, or having previously been, COVID-19 positive.

Material and Methods

A prospective observational study was undertaken at Sawai Man Singh Medical College and Hospital, Jaipur, India, over a period of 6 months, from April to September 2021. All patients with invasive rhino-orbito-cerebral aspergillosis who had recovered from coronavirus infection were included in the study. All patients underwent surgical debridement, along with control of immunocompromised status and intravenous antifungal administration. The details of presentation, predisposing history, imaging findings, comorbidities, management details, and follow-up information were recorded and analysed.

Observation and Results

A total of 475 cases of COVID associated invasive fungal sinusitis were treated at the institute. Of these, 92 subjects were diagnosed with COVID associated aspergillosis, out of which 72 were male patients and the rest 20 were females. All cases identified were chronic invasive aspergillosis in our study. In all cases aspergillus was identified from nasal tissue except one where aspergillus was diagnosed from hard palate.

All patients had involvement of nose and one or more paranasal sinuses, 34 had orbital involvement, 5 had intracranial extensions and 1 had pulmonary involvement

Table 1 Involvement of paranasal and surrounding organs

Site	Ethmoids	Maxillary	Sphenoid	Frontal	Mandible	Maxilla	Palate	Orbit	CNS	Pulmonary
No. of cases (n) (%)	70 (76%)	92 (100%)	50 (54.3%)	10 (10.8%)	0 (0%)	10 (10.8%)	1 (1.08%)	34 (37%)	5 (5.4%)	1 (1.08%)

Table 2 Associated comorbid conditions

Comorbidities	No. of cases (n) (%)
Diabetes	75 (81.5%)
Hypertension	50 (54.3%)
Aplastic anemia	1 (1.08%)

Table 3 Distribution of species on culture

Culture—species	No. (%)
Aspergillus flavus	54 (58.6%)
Aspergillus niger	21 (22.8%)
Aspergillus nidulans	6 (6.5%)
Aspergillus fumigates	3 (3.2%)
Mixed	8 (8.6%)

(Table 1). Maxillary sinus was found diseased in all cases followed by ethmoidal sinuses. Involvement of sphenoid and frontal sinuses were less common.

All patients had one or more comorbidities. Out of 92 subjects 75 were diabetics. 60 of these were with uncontrolled diabetes with glycosylated hemoglobin levels more than 6.5% and the rest had controlled diabetes. 50 patients were hypertensive. One patient had aplastic anemia with significant neutropenia and was awaiting bone marrow transplant.78 patients had received oxygen supplementation (Table 2).

All 92 patients had a history of use of oral or intravenous steroids at the time of COVID-19 illness, but none were admitted in ICU at the time. All patients had recovered from COVID-19 at least 14 days before developing symptoms of fungal disease.

KOH staining and fungal culture showed various species of Aspergillus (Table 3). Most common species identified was *Aspergillus flavus* (54) followed by *Aspergillus niger* (21), *Aspergillus nidulans* (6), *Aspergillus fumigatus* (3) and rest were mixed along with either different aspergillus species or zygomycetes group of fungi like rhizopus or mucor (8).

All the patients were surgically debrided and treated with antifungals (amphotericin and azoles) and are being followed up. Intraoperatively the disease was cleared from involved areas, however contrary to findings in mucormycosis, necrotic tissue was much lesser and black necrotic tissue was not seen. Over a follow up of minimum 3 months there were no deaths.

Discussion

Since COVID-19 pandemic, various manifestations and complications have been documented. Invasive aspergillosis has also been currently reported in COVID-19 patients. It is one of the most common opportunistic infections found in patients with immune disorders [13]. Aspergillosis presents in different clinical forms according to the patient's immune status. The most common site of Aspergillosis is the lung which carries a higher mortality rate. Other clinical forms like sinonasal aspergillosis also can be severe and fatal [14]. It has been a debatable topic if some infectious disease, such as COVID-19, could be a risk factor for developing fungal infections. But there have been increasing reports of fungal infections such as candidiasis, aspergillosis, and mucormycosis in patients with COVID-19 patients especially among critically ill patients with severe COVID-19 [13, 15, 16].

The term "Aspergillosis" is defined as an illness due to allergy, airway or lung invasion, cutaneous infection, or extrapulmonary dissemination caused by species of Aspergillus [17]. Out of more than 185 species of the Aspergillus, almost 95% of all infections are caused by *Aspergillus fumigatus*, *Aspergillus flavus* and *Aspergillus niger* [5]. *A. flavus* is found to be the most common species associated with both chronic invasive and granulomatous Aspergillus rhinosinusitis [18, 19]. This could be due to the presence of most *A. flavus* spores in the air, which are affected by the climatic conditions of this region [20]. Our study had also reported maximum cases with A.flavus. The maxillary sinus is most commonly affected of all sinuses which was also consistent with our study results [19].

COVID-19 patients especially those who were critically ill were susceptible to many other secondary bacterial and fungal infections. Increasing reports of secondary fungal infections caused by Aspergillus and Candida species have been reported [15, 16]. However, Aspergillus co-infection in patients with COVID-19 pneumonia can cause acute respiratory distress syndrome too. A study was done by Aia Mohamed et al. on thirty eight COVID-19 associated invasive pulmonary aspergillosis (CAPA) cases and the most common pathogen was *A. fumigatus* [13]. Sebastian et al. also conducted a review on three cases of COVID-19 associated with invasive fungal sinusitis, one of which was due

to Aspergillus, and the rest were zygomycosis (mucormycosis) [15]. Hosseinikargar et al. described a case of invasive Aspergillus rhinosinusitis in a critically ill COVID-19 patient affected by acute myeloid leukemia (AML) from northeastern Iran [21]. However, the aspergillus species could not be identified due to contamination and was missed.

There could be various possible explanations for association between COVID-19 and invasive fungal sinusitis, including the immunosuppression caused by COVID-19 infection and disease process, or the irrational use of steroids and broad spectrum antibiotics in the management of COVID-19, leading to the development or exacerbation of a pre-existing fungal disease. The National Institute of Health, according to the Randomised Evaluation of COVID-19 Therapy ('RECOVERY') Collaborative Group, recommends steroid use only in patients who are on a ventilator or require supplemental oxygen, but not in milder cases [22]. The guidelines specifically mention the risk of developing a secondary infection [23].

Among patients with COVID-19 associated fungal infections, the timely administration of antifungal therapy is paramount for a favorable outcome, particularly for aspergillosis. Accurate diagnosis of the disease can be determined by the existence of consistent clinical symptoms, specific radiological aspects and mycological data [20]. Both magnetic resonance imaging [MRI] and CT scan are of utmost importance to establish a diagnosis of invasive fungal sinusitis. Opacity of the sinus with or without destruction may be seen in the invasive form. Bone erosion and extrasinus extension are the classic CT findings highly suggestive of invasive fungal sinusitis found in later part of disease course (Fig. 1a–c) The most common early sign is severe unilateral nasal cavity mucosal and soft tissue edema [24]. Bone involvement and erosion is more delineated on CT, while soft tissue extensions, vascular invasion and cavernous sinus involvement are more appreciated on MRI [17] (Fig. 2a–c). Surgical debridement of abnormal tissue in the sinus is recommended for antifungal therapy to reach the infected area. Surgery may improve the control of fungal disease and patient survival.

According to updated guidelines released by The Infectious Diseases Society of America [IDSA] for the treatment of invasive aspergillosis in 2008, Voriconazole [broad-spectrum triazole] has now become the drug of choice for invasive aspergillosis [25]. This drug is better tolerated and has increased efficacy with improved survival [with a lower mortality rate], and is significantly less toxic than amphotericin

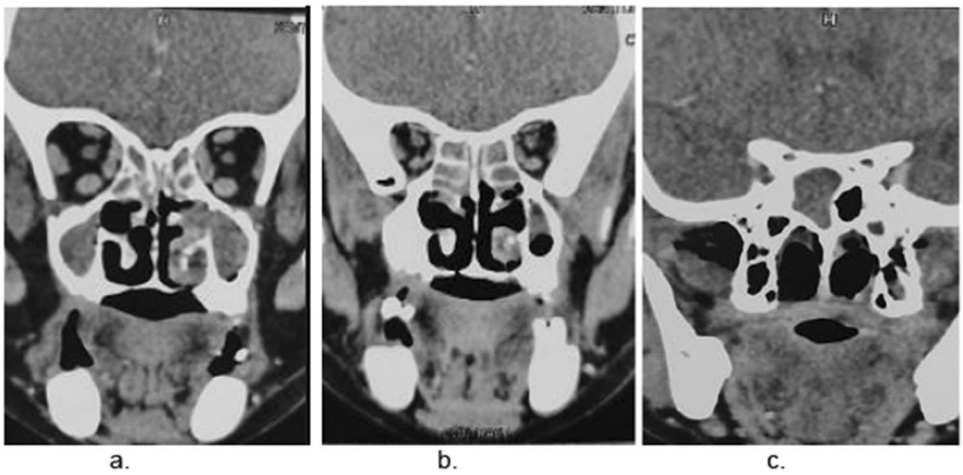

Fig. 1 **a–c** Coronal, non-contrast computed tomography scans of the paranasal sinuses, showing involvement of the sinuses

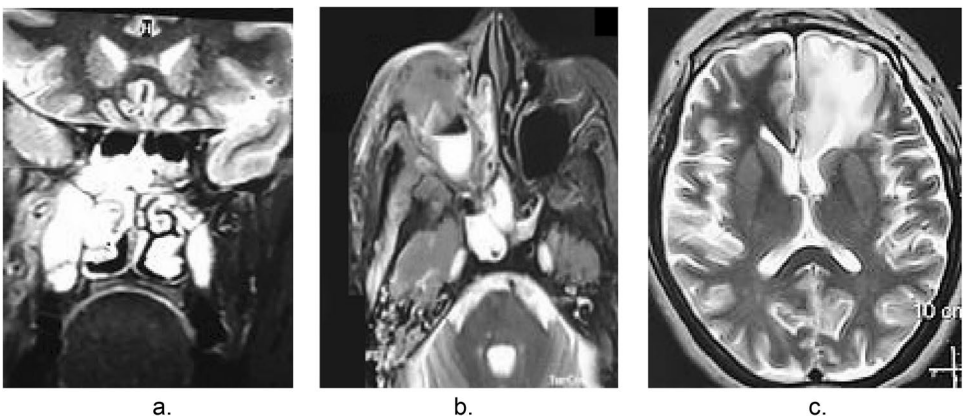

Fig. 2 **a–c** Coronal and axial Gadolinium enhanced magnetic resonance imaging scans of paranasal sinus, orbit and brain showing involvement of all sinuses along with extension into orbit and brain

B [26]. The recommended dosing regimen of voriconazole is 6 mg/kg IV every 12 h on day one followed by 4 mg/kg IV twice daily, and after, 200 mg orally twice daily. In case of intolerance to voriconazole, the IDSA suggests using a lipid formulation of amphotericin B at 5 mg/kg IV per day.

For the treatment of invasive aspergillosis of the sinuses, oral antifungal therapy should be continued for at least 4–6 months to prevent disease recurrence [27]. The duration of therapy depends on various factors such as the site of the infection, the patient's underlying disease and the need for further immunosuppression, and the response to therapy. Regular post-operative follow-up should be done in all the cases with CT scan and nasal endoscopy every 3–4 months. Early diagnosis of recurrent disease requires prolonged systemic antifungal chemotherapy.

We studied 92 cases of sinonasal aspergillosis over the period of 6 months. All patients were COVID-19 positive previously. All patients underwent surgical debridement. All were followed up for 6 months of study period except 5 patients who were lost to follow up. There were no mortalities.

The differential diagnosis of invasive aspergillosis includes mucormycosis, benign and malignant neoplasms, syphilis, tuberculosis, sarcoidosis, Wegener's granulomatosis, lymphoma, mucopyocele and allergic fungal sinusitis.

Conclusion

Invasive sinonasal aspergillosis in COVID-19 patients should be given serious consideration as it is a very fatal condition. Uncontrolled diabetes and injudicious use of steroids are the two main aggravating factors for the disease process. Therefore, these should be properly controlled. In conjunction with paraclinical factors (imaging characteristics, histological results, and mycological techniques), the clinical manifestation can lead to an early diagnosis and a better prognosis. Moreover, early surgical intervention and antifungal prophylaxis are both important for increasing survival in these patients.

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Declarations

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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