



# Post Covid-19 Sinonasal Candidiasis: A Crisis Within the Pandemic

Sudhir Bhandari<sup>1</sup> · Saloni Agarwal<sup>2</sup> · Shruti Bhargava<sup>3</sup> · Sunil Samdhani<sup>2</sup> · Shashank Nath Singh<sup>2</sup> · Bharat Bhushan Sharma<sup>1</sup> · Bharti Malhotra<sup>4</sup> · Meenu Bagarhatta<sup>5</sup> · Shrikant Sharma<sup>1</sup> · Aruna Vyas<sup>4</sup> · Vishnu Sharma<sup>1</sup> · Mohnish Grover<sup>2</sup>

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**Abstract** The aim of this study was to find out the association of sinonasal candidiasis and Covid-19 infection. A prospective observational study was conducted at a tertiary care centre from April to September 2021, involving all patients with invasive candidiasis of the paranasal sinuses having a history of Covid-19 infection. A total of 18 patients of covid associated sinonasal candidiasis among the 475 cases of fungal rhinosinusitis were studied. All patients had involvement of nose and sinuses and 2 patients had orbital involvement with no loss of vision, while 3 had intracranial extensions and 1 had pulmonary involvement. Mandible was involved in 1 patient alone, while the maxilla and palate were involved in 5 patients. 15 patients were hypertensive, 12 diabetics and 1 had aplastic anaemia. Cultures showed that 8 patients had *C. parapsilosis*, 5 had *C. albicans*, 3 had *C. tropicalis* and 2 had mixed fungal infections. All patients underwent surgical debridement and antifungal administration. They were followed up for a minimum of 3 months. There was only one mortality (with aplastic anaemia), rest 17 were disease free at the time of writing this article. This is perhaps the first case series of post covid sinonasal candidiasis in the world. Invasive sinonasal candidiasis is a newer

sequela of COVID-19 infection. Uncontrolled diabetes and over-zealous use of steroids at the time of Covid-19 are few of the known risk factors. Early surgical intervention and anti-fungal treatment should be sought for management.

**Keywords** Sinonasal candidiasis · Invasive fungal infections · Covid-19 · Echinocandins

## Introduction

Covid-19 is a new entity among the spectrum of respiratory infections caused by SARS-CoV-2 or Severe Acute Respiratory Syndrome Corona Virus-2. The infection first detected in December 2019 in Wuhan, China spread worldwide within a short span and with every passing day had newer alterations in its pathophysiology, management, sequelae and complications [1]. We saw a gradual rise in fungal sinusitis associated with covid infection in the first peak of Covid-19 [2]. These co-infections rose to a sudden surge with the second peak of Covid-19 in May 2021 in India and led to an epidemic.

Invasive fungal sinusitis is a life-threatening infection that typically affects immunocompromised individuals with an impaired neutrophilic response. Patients can include those with uncontrolled diabetes mellitus, acquired immunodeficiency syndrome, iatrogenic immunosuppression and haematological malignancies, and those having undergone organ transplantation [3]. Covid associated mucormycosis has also been widely described and a study by Sharma et al. talked about this even in the first wave of Covid 19 [4]. Invasive rhino-orbito-cerebral candidiasis on the other hand, has not been described much. We attempt to throw light on this, with our experience of 18 cases of sinonasal candidiasis over a period of 6 months.

✉ Mohnish Grover  
drmohnish.aiims@gmail.com

<sup>1</sup> Department of Medicine, SMS Medical College and Hospital, Jaipur, India

<sup>2</sup> Department of ENT, SMS Medical College and Hospital, Jaipur, India

<sup>3</sup> Department of Pathology, SMS Medical College and Hospital, Jaipur, India

<sup>4</sup> Department of Microbiology, SMS Medical College and Hospital, Jaipur, India

<sup>5</sup> Department of Radiodiagnosis, SMS Medical College and Hospital, Jaipur, India

**Table 1** Fungal spp of Covid associated fungal infections

No of patients	Fungal class	Fungal species
16	Candida	C.albicans, C.tropicalis, C.parapsilosis
405	Mucorales	396-Mucor 9-Rhizopus
40	Aspergillus	A.niger, A.fumigatus, A.albus
12	Mixed growth	Mucor + aspergillus
2	Mixed growth	Mucor + candida
Total: 475		

## Materials 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 candidiasis who had recovered from coronavirus infection, and with any 2 of the following 3 screening procedures positive for invasive FRS-nasal/palatal biopsy, KOH mount and Gadolinium enhanced MRI scans with fat suppression and diffusion weighted imaging, 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.

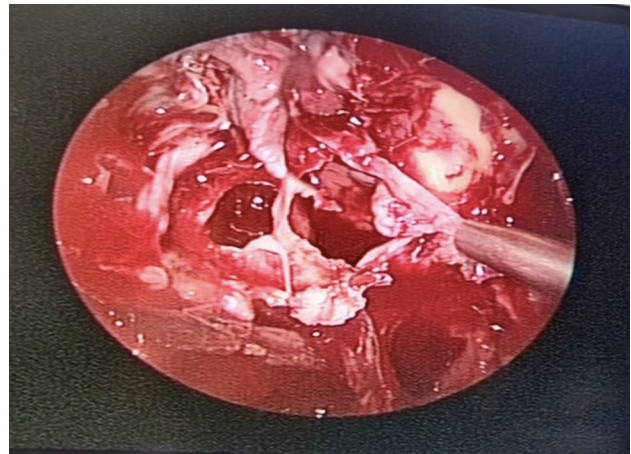
## Results

Of the 800 patients screened for FRS post Covid-19, a total of 475 cases of covid associated invasive fungal sinusitis were treated at the institute. Of these, 405 had mucor, 40 had aspergillus, 16 had candida and 12 had mucor with aspergillus, 2 had mucor with candida in covid associated invasive FRS (Table 2). Of the total 18 patients with invasive sinonasal candidiasis, 5 were females and 13 males. Age group was between 5 years to 68 years (mean 50.1 years). All patients had involvement of nose and one or more paranasal sinuses, 2 had orbital involvement (but with no loss of vision), 3 had intracranial extensions and 1 had pulmonary involvement (Tables 1, 2).

All patients had one or more comorbidities: 15 patients were hypertensive, 12 diabetics and 1 had aplastic anaemia. The patient with aplastic anaemia had significant

**Table 3** Distribution of species on culture

Culture-Species	No. (in %)
<i>C. parapsilosis</i>	8 (44.4)
<i>C. albicans</i>	5 (27.8)
<i>C. tropicalis</i>	3 (16.6)
Mixed fungal species	2 (11.1)

**Fig. 1** Endoscopic image showing post covid sinonasal candidial infection involving left posterior ethmoid sinuses

neutropenia and was awaiting bone marrow transplant. 14 patients had received oxygen supplementation and oral or intravenous steroids at the time of covid-19 illness, but none were admitted in ICU.

KOH staining and fungal culture showed various species of Candida. 8 patients had *C. parapsilosis*, 5 had *C. albicans*, 3 had *C. tropicalis* and 2 had mixed fungal infections (Table 3).

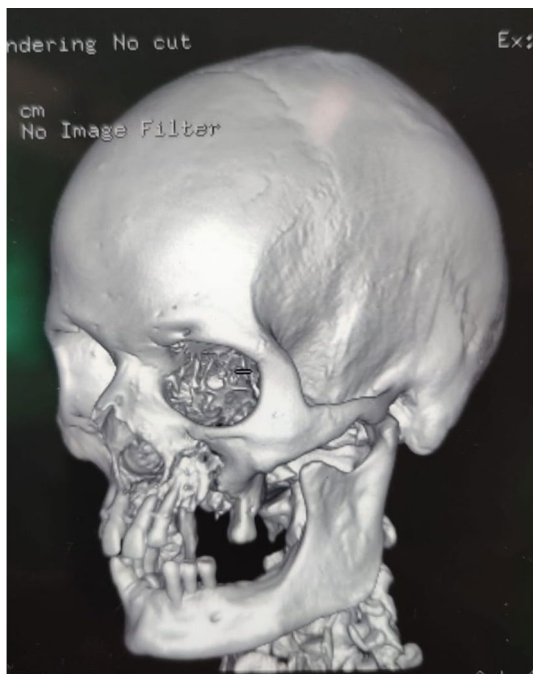
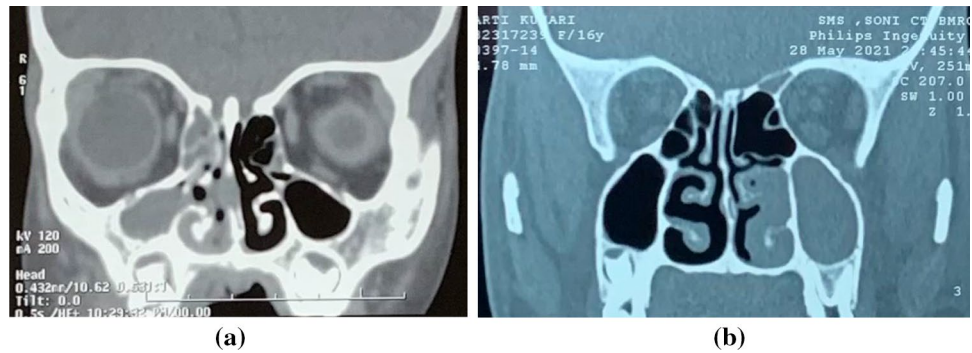
All 18 patients had recovered from covid-19 at least 14 days before developing symptoms of fungal disease.

All the patients were surgically debrided and treated with antifungals (echinocandins and azoles) and are being followed up. Intraoperatively the disease was cleared from involved areas, however contrary to findings in mucormycosis, there was no necrotic tissue and the vascularity was more than usual (Fig. 1). Over a follow up of minimum 3 months there was only one mortality. He was having aplastic anaemia with significant neutropenia and cerebral involvement.

**Table 2** Involvement of paranasal and surrounding organs

Site	Ethmoids	Maxillary	Sphenoid	Frontal	Mandible	Maxilla	Palate	Orbit	CNS	Pulmonary
No. of cases	18	12	2	1	1	5	5	2	3	1

**Fig. 2** CT scan bone window of paranasal sinuses with involvement of (a) right ethmoids and maxillary sinus and (b) left inferior and middle turbinates with anterior ethmoids and maxillary sinus and thinning of palate



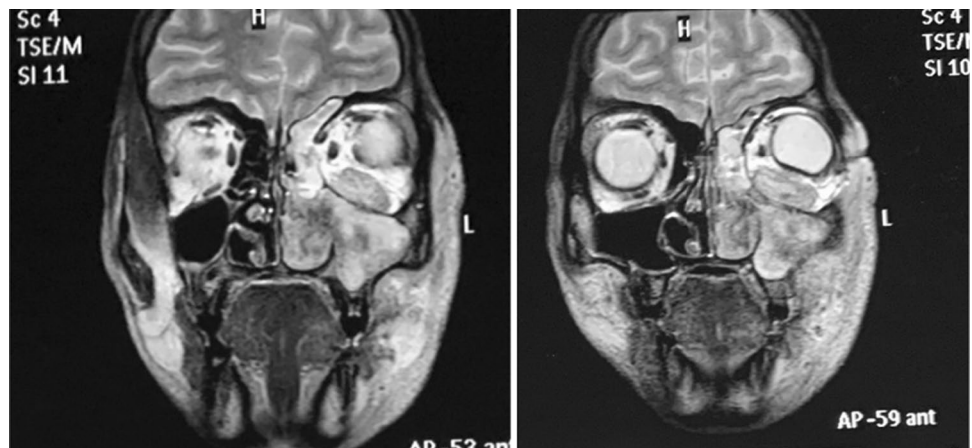
**Fig. 3** Computes Tomography Scan of face in 3 dimension showing erosion of left mandible and maxilla in case of post covid sinusitis

**Discussion**

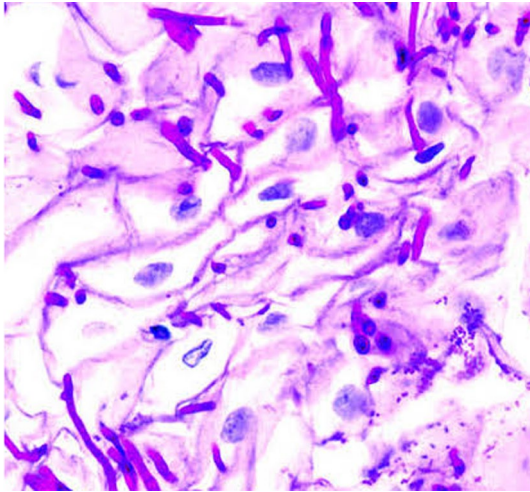
Covid associated mucormycosis is a known entity, however other species of fungus can also be involved in opportunistic infections after Covid-19. This study deals with such patients of sinonasal candidiasis and is perhaps the first case series in published English literature. Similar to the SARS-CoV and Middle East Respiratory Syndrome (MERS), SARS-CoV-2 may also cause lower respiratory tract infection and lead to acute respiratory distress syndrome (ARDS) [5]. Previous research has demonstrated similarities in prevalence and biological and clinical characteristics of SARS-CoV and SARS-CoV-2 which belong to the same species [6]. During the widespread SARS-CoV infection of 2003, the incidence of fungal infection was 14.8–27%, and it was the main cause of death for severe ARDS patients that is 25–73.7% of all deaths [7, 8].

Prevalence of FRS prior to Covid-19 era was reported at 0.11% of population [9], but post the onset of Covid-19 pandemic, very limited data is available on the prevalence of FRS with Covid-19 [10]. A study reported an incidence of 26.7% for invasive fungal infections among 135 adults with Covid-19 infection [11]. Song et al. concluded that most patients affected by or recovered from Covid-19 are at

**Fig. 4** MRI T1-weighted images with Turbo spin Echo indicating left ethmoid and maxillary involvement with intra-orbital extension and involvement of extra-ocular muscles and peripheral tissue inflammation viewed as hyperintensities







**Fig. 5** Candida species on PAS staining showing budding

increased risk of developing invasive fungal diseases when he studied the association between Covid-19 and invasive fungal sinusitis in April 2020, and devised his management algorithm [12]. A recent review showed that 8% of coronavirus-positive or recovered patients had secondary bacterial or fungal infections during hospital admission, under the cover of widespread use of broad spectrum antibiotics and steroids [13]. The second peak of covid-19 with delta strain in 2021 in India, led to a myriad of manifestations and complications and a rarely encountered entity of invasive sinonasal candidiasis.

At least 15 distinct candidial spp. are known to cause human diseases, but the majority of invasive infections are caused by *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei* [14–16]. *C. albicans* has been encountered most commonly worldwide. Non-albicans candidemia is rare [16]. In India, *C. parapsilosis* and/or *C. tropicalis* are much more frequently encountered than *C. glabrata* [17, 18]. In our study, we found 8 cases of *C. parapsilosis*, 5 of *C. albicans* and 2 of *C. tropicalis*. *Candida spp.* are common commensals in the skin, gut microbiota in almost 60% of healthy individuals [19]. Further, any break in the cutaneous and gastrointestinal barriers, increased or abnormal colonization and a combined local or generalized defect in host defences promote an invasive disease [19]. Three major conditions predispose to human invasive candidial infections i.e. long-term and/or repeated use of broad-spectrum antibiotics (as this depletes commensals in the gut which release anti-Candida spp. protective factors from the mucosa), breach of the gastrointestinal and cutaneous barriers by cytotoxic chemotherapy-induced mucositis and the third factor is iatrogenic immunosuppression, such as chemotherapy-induced neutropenia or corticosteroid therapy [14, 15].

Besides the diffuse alveolar damage with severe inflammatory exudation, Covid-19 patients always have

immunosuppression following a decrease in CD4 T and CD8 T cells, indicating their susceptibility to fungal co-infections [12, 20]. Neutropenia has been well-established as a risk factor for development of the invasive infection and a cause of mortality in humans [21, 22]. In contrast to mucosal candidiasis, during invasive *Candida spp.* infection immunity relies on myeloid phagocytes (neutrophils, monocytes, macrophages and dendritic cells) and not on lymphocytes [21, 23, 24]. Extensive use of steroids in Covid-19 management can also suppress immunity, allowing opportunistic fungal infections to colonise [4], as reiterated in our study. Clinically, invasive sinonasal candidiasis presents similar to complicated sinusitis, with atypical signs and symptoms like nasal (nasal blockade, crusting, proptosis, facial pain), orbital (oedema, ptosis, chemosis, and even ophthalmoplegia with headache and fever) and neurological, if intracranial extension is present [25, 26]. We echo the same findings in our study. Non-contrast computed tomography scan of the paranasal sinuses is usually the first investigation of choice (Figs. 2 and 3), while gadolinium-enhanced magnetic resonance imaging (Fig. 4) is resorted to when extrasinus extension is suspected [4]. Histological features in candidiasis is (Fig. 5) common to all fungal infections—mycotic infiltration of blood vessels, vasculitis with thrombosis, tissue infarction, haemorrhage and acute neutrophilic infiltrate [27]. Since no clinical signs or symptoms are specific for invasive candidiasis, clinicians have to rely on fungal cultures, histopathological examination and empirical evidence in the setting of ICU, each of which have a low sensitivity [28–30]. Thus, timely diagnosis of invasive candidiasis is the key to ensure a favourable outcome. In fact, a delay of 1–2 days in initiation of effective antifungal therapy has been associated with a doubling of mortality [28, 29].

Based on the guidelines by Infectious Diseases Society of America (IDSA) 2016 and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 2018, a protocol of initiation therapy with echinocandins and a step down with azoles is being followed for invasive candidiasis [31–33]. In our institute, we used echinocandins and azoles in all these patients. Nasal endoscopy at every fortnight with MRI scans at 3 months for prognosis, followed by continuation or stepdown of antifungals was done.

## Conclusion

Newer and long-term manifestations of the Covid-19 infection are cropping up. Its association with invasive candidiasis in the current setting is dangerous and should be duly given serious consideration. Uncontrolled diabetes, overzealous use of steroids, ventilator assisted respiration, central venous catheter, prolonged ICU admissions in association with COVID-19 infection, are few of the main factors

aggravating the illness, and must be properly checked. Early surgical intervention, control of immunocompromised status and intravenous antifungal treatment should be the aim of management in such cases.

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**Data Availability** Not Applicable.

**Code Availability** Not Applicable.

#### Declarations

**Conflicts of interest** The authors have no conflicts of interest to declare relevant to the content of this article.

**Ethics Approval** Not Applicable.

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

**Consent for Publication** The participant has consented to the submission of the case report to the journal.

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