

Non Mucor Fungal Invasive Rhino Sinusitis with Ocular Signs in SARS Cov-2 Infection with Delta Variant (B.1.617.2) in India.

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Research Article

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Abstract

Objective: To highlight fungi other than mucoromycetes as causative agent of invasive rhinosinusitis with ocular signs in recovered or concurrent covid 19 patients and identifying the presenting features, risk factors, intervention and outcomes.

Method and analysis- Retrospective interventional study of seven patients with covid 19 who developed non mucor invasive rhinosinusitis with ocular involvement. Clinical presentation ,history and investigations analyzed. Management was by intravenous liposomal amphotericin B and functional endoscopic sinus surgery (FESS) with paranasal sinus debridement. Limited orbital debridement with or without transcutaneous retrobulbar liposomal amphotericin B(TRAMB) was done in patients with orbit involvement. Postoperative antifungal therapy was decided on basis of the causative fungi.

Results- Four cases of Aspergillus and one each of Fusarium, Culvularia and Penicillium was seen .All patients had prominent periocular swelling and edema with pain and nasal stuffiness. Orbit involvement on MRI was seen in four cases: Partial third nerve palsy was seen in two and cavernous sinus thrombosis was seen in one with aspergillosis. Proptosis was not witnessed in any case. History of Diabetes and use of steroids was seen in all. All patients had mild to moderate covid with oxygen supplementation needed in one. No mortality , vision loss or exenteration happened.

Conclusion: Secondary infection by Fungi other than mucoromycetes can be seen in covid 19. Timely surgical intervention and use of appropriate antifungals by correctly identifying causative fungi can lead to good prognosis.

Background

The severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) Delta variant (B.1.617.2), a variant of concern, was associated with the second wave of pandemic in India during March–May 2021[1]. Many of those who survived developed invasive fungal rhinosinusitis with ocular involvement. Though infections caused by mucoromycetes dominated , there were also instances of other fungal infections with apparently similar presentation[2] However first-line treatment of different fungi can be different and empirical treatments should be avoided as much as possible[3] The present article demonstrates the clinical features and outcome of patients presenting with possible invasive mycosis with rhino -sino -orbital disease which was later demonstrated to be due to fungi other than mucoromycetes in recovered or concurrent covid19.

Aim- To highlight fungi other than mucoromycetes as causative agent of invasive rhinosinusitis with ocular symptoms in covid 19 patients and identifying the presenting features ,risk factors ,intervention and outcomes.

Materials And Methods

Retrospective observational study of patients who presented between April and June 2021 with possible mycotic invasive rhinosinusitis and ocular signs in recovered or concurrent covid 19 infection. All Mucor mycosis cases were excluded. Mycosis other than mucoromycetes were included in this study. The demographic and clinical data were collected with the consent of the patients and with approval by the Institutional Review Board (159/IEC/IGIMS/2021). Tenets of Helsinki was adhered to. Each patient was subjected to a complete history taking, including ocular complaints and systemic illnesses along with their treatment. The diagnosis of COVID 19 was based on Real-time reverse transcriptase-polymerase chain reaction test (RT-PCR) on nasopharyngeal/oropharyngeal swabs. Different Laboratory tests were analyzed: Complete blood count (CBC), platelets, C-reactive protein (CRP), a lactate dehydrogenase (LDH), procalcitonin, D-dimer, serum ferritin and blood sugar. Magnetic resonance imaging (MRI) orbit, brain, and paranasal sinuses (PNS) with or without computed tomography (CT) was performed for assessing extent of the disease. High-resolution computed tomography thorax and COVID-19 reporting and data system (CORAD) score was used (RSNA consensus statement) to assess suspicion of chest involvement while CT severity score was used to categorize patients into mild (<8) moderate (9-15) and severe disease (>15) [4]. Deep seated tissue obtained with the help of deep nasal swab or sinus endoscopy was sent for KOH mount and fungal culture based on the clinical suspicion. Proven mycosis was decided on the basis of the former showing fungal hyphae in biopsy specimen with associated tissue necrosis or a positive culture result done on specific fungal culture media like Sabourauds dextrose agar. Isolated fungal colony were confirmed microscopically by performing Lactophenol cotton blue mount (LPCB) (Figs 1a-d). Possible mycosis was diagnosed if only the criteria for a host factor and a clinical criterion were met but mycological criteria were absent, which was mostly at the time of admission[5]

All possible mycosis who presented at our hospital were initiated on liposomal amphotericin B (5 mg/kg/day, up to a maximum of 10 mg/kg/day for CNS infections) intravenously (IV) with renal monitoring [6]. Functional endoscopic sinus surgery (FESS) with PNS debridement and liposomal amphotericin B irrigation was done by Otolaryngologists in all cases who were RT-PCR negative for covid 19 and samples were sent for microscopic examination and fungal cultures . Limited orbital debridement with socket irrigation with

Amphotericin B was done in patients with radiological evidence of orbital involvement. In the interim waiting period, transcutaneous retrobulbar liposomal amphotericin B (TRAMB) (3.5 mg/mL) was administered to cases with ophthalmoplegia. Postoperatively, long-term antifungal treatment mostly with oral Posaconazole (loading dose 300 mg twice a day on the first day, maintenance dose 300 mg orally once a day, starting on the second day) was initiated based on microbiological report and availability of drug. Other drugs like oral voriconazole and itraconazole was also administered in few cases.

Results

Retrospective analysis of 160 hospital records of patients admitted with possible mycotic invasive rhinosinusitis was done. All cases had presented between April and June 2021. Ninety-six patients had associated ocular symptoms. Seven patients out of these were determined to be non mucor cases: Four cases of Aspergillus (aspergillosis) and one each of Fusarium (fusariosis), Curvularia (curvulariosis) and Penicillium (penicilliosis) associated invasive rhinosinusitis with ocular signs were seen. All patients had prominent periocular swelling and edema with pain and nasal stuffiness (Table 1). Both eyes (BE) were involved in three cases (patients 2, 5 and 6) (Fig 2). There was no acute loss of vision in any case. Ocular evaluation demonstrated partial third nerve palsy with normal pupillary reactions in cases 3 and 6 respectively (aspergillosis and penicilliosis). Proptosis was not witnessed in any case. Intracranial extension with cavernous sinus thrombosis was seen in one case with aspergillosis (patient 2). This patient had periocular swelling and edema but did not show any orbital finding of proptosis or ophthalmoplegia. RT-PCR for Covid 19 was positive in five cases while it was negative in two cases (patients 6 and 7). The geographic profile was limited to the Indian state of Bihar. Mean age at presentation was (47± 3years). All patients showed a history of past or recent onset diabetes mellitus and had been administered intravenous dexamethasone during the disease course. Mild to moderate Covid was seen in all except patient 4 who needed oxygen support with nasal prong (Aspergillosis). Haematological investigations done at time of presentation to us showed: Raised serum ferritin and CRP in all cases. Neutropenia was not present in any case. Lymphopenia was present only in case 6 (Penicilliosis) (Table 2). This was also the only patient who complained of toothache and had the shortest interval between onset of covid symptoms and those of invasive mycosis (6 days). There was no mortality or need for orbital exenteration in any case.

Aspergillus – was seen as septate hyphae, branched at 45 degree angle (patients 2, 3, 4 and 5) (Figs 1d, h). Diagnostic nasal endoscopy with biopsy from the affected side was inconclusive in three patients. However, FESS specimen showed presence of Aspergillus flavus in fungal culture. All patients were put on oral Posaconazole postoperatively. Along with FESS, limited orbital debridement and socket irrigation with liposomal Amphotericin B was also done in case 2. However this patient developed extensions into cavernous sinus after discharge and was later administered an initial loading dose of iv voriconazole 6mg/kg body weight on day one followed by a maintenance dose of 4mg/kg body weight for two weeks. Upon resolution of symptoms a dose regimen of 200mg bd was followed. Patient 3 with ophthalmoplegia was given TRAMB while awaiting FESS.

Fusarium- was seen as thin, septate, hyaline hyphae (patient 7) (fig1c, g). The patient presented seventeen days after onset of covid 19 symptoms. RTPCR report, was not accessible and she was diagnosed with Covid 19 on basis of HRCT report. Diagnostic nasal endoscopy with biopsy was confirmatory for Fusarium. She underwent FESS and sinus irrigation with Liposomal Amphotericin B. followed by oral Posaconazole, 800 mg/24 h in two divided doses for 12–16 weeks.

Curvularia- was seen as dematiaceous, dark pigmented filamentous fungi (patient1) (fig1a, e). The patient presented 15 days after the onset of symptoms of COVID-19. Diagnostic nasal endoscopy and biopsy confirmed the presence of Curvularia. The patient underwent FESS and sinus irrigation with liposomal amphotericin B. Postoperative regimen included liposomal amphotericin B and Itraconazole 200mg twice orally.

Penicillium- was seen as hyaline, septate hyphae on microscopic examination (patient 6) (fig1b, f). The patient presented with teeth pain, orbital and facial pain and bilateral eye swelling. There was associated ophthalmoplegia in same eye. Diagnostic nasal endoscopy was not confirmatory. TRAMB and FESS with limited orbital debridement and socket irrigation with liposomal Amphotericin B was done on basis of MRI findings and clinical examination. Microscopic examination and culture of FESS specimen showed presence of Penicillium sp. Postoperatively oral Posaconazole was prescribed.

Discussion

The Delta variant (or B.1.617.2 strain) of the coronavirus was primarily responsible for the second wave of Covid-19 in India during March-April and had 50% more transmissibility than the Alpha variant or B.1.1.7 with more severe disease and deaths in the second wave.^{1, 7} The second wave also came across features like headache, localized pain, nasal discharge, sinusitis, orbital cellulitis and diminution of vision due to invasive fungal sinusitis occurring mainly after recovery of COVID-19 patients.² This was mostly attributed to Mucormycosis². Other fungi mostly aspergillus have also been reported as cause of invasive rhinosinusitis but in much less frequency. Though literature search did not yield much information on fungi other than mucoromycetes as causative agent for invasive rhino sinusitis with ocular signs in covid, it is

important to identify other causative fungi as presentation might be similar but management protocol may differ mainly in the use of appropriate antifungals. The conventional tests that identify a fungal pathogen and confirm a mycosis diagnosis have different limitations, such as the time required to obtain a result or the impossibility of determining the fungus at the species level.⁸ Though species identification was important we were able to do so only in aspergillus (*aspergillus flavus*). We however initiated antifungal treatment on the suspicion of possible mycosis without waiting for its confirmation which would have meant delay in initiating treatment and possible mortality. Another reason was that diagnostic nasal endoscopy with biopsy was deferred in patients who were not yet RTPCR negative due to apparent risk of transmission of the virus to the health personnel.

In this study we noted that *Fusarium*, *Aspergillus*, *Penicillium* and *Curvularia* associated invasive rhinosinusitis with ocular symptoms had similar presentation and risk factors. Case reports from pre covid times suggest that all of them can be associated with invasive rhino sino orbital disease^[3,9-11]. Most of our patients had history of moderate covid disease, home treatment with no supplemental oxygen requirement and recent onset diabetes. The incidence of mycosis was hypothesized to increase considerably as a result of widespread use of steroids, antibiotics and antimetabolites in the second wave [12-14]. However none of our patient gave history of the latter.

CT is modality of choice when patient history and physical examination are suspicious for fungal infection though MRI was predominantly used in our cases. They may be superior to CT for the evaluation of the orbital apex, cavernous sinus and to detect enhancement of the optic nerve and cerebral dura^[15]. Contrast Enhanced-MRI showed maxillary sinusitis in the form of significant mucosal thickening to be predominant in most cases though sphenoid was the predominant sinus involved in case1(*Curvularia*) and case 2 (*Aspergillo*sis). *Aspergillus* has a predilection for affecting the sphenoid sinus more than others, a finding which is poorly understood and may be related to low oxygen tension and a more acidotic environment within this sinus [15]. The disease's invasive nature and the sphenoid's proximity to critical structures of the skull base may explain the more aggressive clinical course in case 2^[16]. However other cases of aspergillo

sis showed predominant maxillary sinusitis. Diffuse involvement of all sinuses was seen in penicilliosis. Bilateral periocular swelling and edema with sign of orbital inflammation like ophthalmoplegia with partial 3th nerve palsy was seen in *Aspergillus* and *Penicillium* associated rhinosinusitis (case 3, 6). Periocular swelling and edema in rest led us to suspect orbit involvement with a diagnosis of possible invasive rhino sino orbital disease and start management accordingly (table 1). However, involvement of orbit was not present in imaging reports of all, which was delayed due to the prevailing overburdened hospital system (case1, 4, 5). Where orbit involvement was present, it was seen as hyperintensity of the retro bulbar space on MRI with contrast as seen in cases 2, 3, 6 and 7.

Periocular swelling and edema in cases 1, 4 and 5 may be a result of inflammatory reaction to the invasive fungal rhinosinusitis in the periocular tissue and not due to orbit involvement. There was no erythema or tenderness in any case, hence cellulitis was ruled out. Periocular swelling in our cases of invasive fungal rhinosinusitis did not always indicate orbital involvement. The partial third nerve palsy in cases 3 and 6 resolved gradually over time. Though many reports have suggested that cranial nerve palsy in the setting of COVID-19 infection may be associated with improved patient outcomes and temporary cranial nerve deficits compared to other neurological deficits, we couldn't find literature supporting this from case reports of cranial nerve palsy with secondary invasive fungal disease in Covid 19 [17].

Aspergillus, a type of mold, was commonly seen in ICU admitted patients causing pulmonary involvement in many studies in both waves. However, there were only few reports of invasive aspergillus rhinosinusitis with associated ocular signs. In our study, out of 96 patients of possible rhino -sino -orbital mycosis we saw aspergillo

sis in 4 patients with one developing intracranial extension on follow-up. A study by Noha Ahmed El-Kholy on Invasive Fungal Sinusitis in Post COVID-19 patients saw mucor species in 77.8% and *Aspergillus fumigatus* in 30.6% [18]. *Aspergillus* invasive rhino sinusitis with ocular involvement has been reported in pre covid era too^[16]. However one of the reasons of predominance of mucoromycetes in covid 19 patient could be that India has a large population of people with diabetes mellitus where it is predominantly seen^[19]. Conversely, *Aspergillus* species are more common in other immunocompromised individuals in whom neutropenia is the dominant condition—especially persons with hematologic malignancies, hematopoietic stem cell transplant recipients, and solid-organ transplant recipients^[20]. Neutropenia though was not present in any patient at presentation in our cases.

Azoles such as voriconazole are the optimal choice if *Aspergillus* is proven on culture though Amphotericin is also active in many *Aspergillus* isolates^[21]. In addition, the newer azoles, Posaconazole and Isavuconazole, are promising secondary choices because they can be delivered orally and thus an excellent choice for prolonged, outpatient management [22] *Fusarium*. *Fusarium* has been mentioned in literature as the second most frequent mold after *Aspergillus* to be involved in fungal infections especially among immunocompromised patients^[23]. However covid 19 associated secondary infection has been dominated by molds like mucoromycetes. Even before covid 19 pandemic, the epidemiology of fungal infections among the immunocompromised patient population had been noted to have changed with the use of antifungal prophylaxis^[24]. This change included a drop in the incidence of yeast infections, namely *Candida albicans*, and an increase in mold infections^[24]. Successful treatment is highly dependent on the particular *Fusarium* species involved in the infection which could not be ascertained in our case. However, our patient responded well to management by FESS and postop Posaconazole. For management of fusariosis high dose intravenous amphotericin B formulation is recommended as the first line

of therapy in patients. Voriconazole is also effective in treating fusariosis. Intolerance, contraindication, or failure of the Amphotericin B formulation warrants the use of voriconazole as an alternative agent, and Posaconazole is licensed as salvage therapy against invasive fusariosis.[25]

Penicillium is a mold and is usually considered a contaminant or colonizer which can occasionally cause a life-threatening infection [24]. Our patient had raised markers of inflammation with new onset diabetes and the only patient in our series to have lymphopenia at time of presentation to us. The reason of this could be that the time from onset of covid 19 to symptoms of mucor was shortest with 6 days when the patient had probably not yet fully recovered from covid infection which is more associated with lymphopenia. According to one report, a shorter time duration between onset of covid 19 and symptoms of mucor mycosis entails a more severe disease which may have been the case here too [27]. The patient developed symptoms of invasive rhino sinusitis with orbital involvement as seen by partial 3rd nerve palsy and MRI report. We couldn't identify the species here but few are highly susceptible to miconazole, itraconazole, ketoconazole, and 5-fluorocytosine. Amphotericin B showed intermediate antifungal activity, while fluconazole was the least active [28].

Curvularia -There are few reports of Curvularia associated fungal sinusitis though invasive disease with CNS involvement has also been reported. A case series on human Curvularia infections by M. G. Rinaldi noted that none of the patients suffered from known immunologic disorders or underlying debilitating diseases, however our patient had preexisting diabetes mellitus[29]. All patients had been treated by surgical management of sinus disease with variable use of antifungals and good outcomes similar to ours. The in vitro antifungal susceptibility of clinical isolates of *Curvularia* was tested against 9 drugs using a reference microdilution method. The most active drugs were the echinocandins, amphotericin B, and posaconazole, whereas voriconazole and itraconazole showed poor activity[30].

Treatment of invasive fungal rhinosinusitis with ocular involvement includes systemic antifungal agents, reversal of immune dysfunction, and optimal surgical resection of necrotic tissues, if present. Theoretically, surgical therapy reduces a significant portion of the fungal burden and the remainder of the invasive fungi can be reached by systematic antifungal therapy[31]. However in many hospitals like ours where FESS was delayed till patient became RTPCR negative for covid 19, antifungals and TRAMB were administered for disease control in the interim period.

Conclusion

The advent of the unprecedented covid 19 pandemic in multiple waves due to various mutations and its association with variable secondary fungal infections also involving ocular tissue makes it imperative that we gain knowledge about the presentations of different fungi and their management for optimum outcomes. Timely initiation of appropriate antifungal therapy and surgical management limits spread of the disease and saves eyes and lives.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose."

Author Contributions

Study conception and design was of Drs Anita Ambasta and Rakhi Kusumesh. Material preparation and data collection was done by Drs Kamlesh Rajpal, Shailesh kumar and Vivek Singh. The first draft of the manuscript was written by Dr Anita Ambasta and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript."

Ethics Approval- *This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Indira Gandhi Institute of Medical Sciences (159/IEC/IGIMS/2021).*

Consent to participate

The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 2a, 2b and 2c."

Conflict of interest- None

Financial interest- None

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Tables

Table 1-Patient characteristics in 7 non mucor rhinosinusitis with ocular signs in COVID-19

	Patient 1	Patient2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Fungi identified	Curvularia	Aspergillus	Aspergillus	Aspergillus	Aspergillus	Penicillium	Fusarium
Age	47	52	66	57	34	33	45
EYE	LE	BL	LE	LE	BL	BL	LE
Sex	M	M	F	F	M	M	F
Day of onset ^a	15	20	18	27	21	6	17
CT severity score	7	10	12	21	16	NA	NA
Periocular swelling	Present	Present	Present	Present	Present	Present	Present
Ophthalmoplegia	-	-	Present	-	-	Present	-
Vision	No loss	No loss	No loss	No loss	No loss	No loss	No loss
Oxygen support	None	None	None	Needed	None	None	None
Diabetes	Past history	New onset	Past history	Past history	New onset	New onset	New onset
PNS involved ^b	Sphenoid	Sphenoid	maxilla	Maxilla	maxilla	Diffuse	Maxilla
FESS ^c	Done	Done	Done	Done	Done	Done	Done
TRAMB ^d	-	-	Given	-	-	Given	-
Antifungal	L.AMPB ^f Itraconazole	L.AMPB Voriconazole	L.AMPB Posaconazole	L.AMPB Posaconazole	L.AMPB Posaconazole	L.AMPB Posaconazole	L.AMPB Posaconazole

^aDay of mycosis detection after onset of covid symptoms

^bParanasal sinus

^cFunctional Endoscopic Sinus Surgery

^dTranscutaneous retrobulbar liposomal amphotericin B

^fLiposomal Amphotericin B

Table 2- Biochemical characteristics in 7 non mucor rhinosinusitis with ocular signs in COVID-19

^aNA= Not Admissible.

Normal range of parameters:

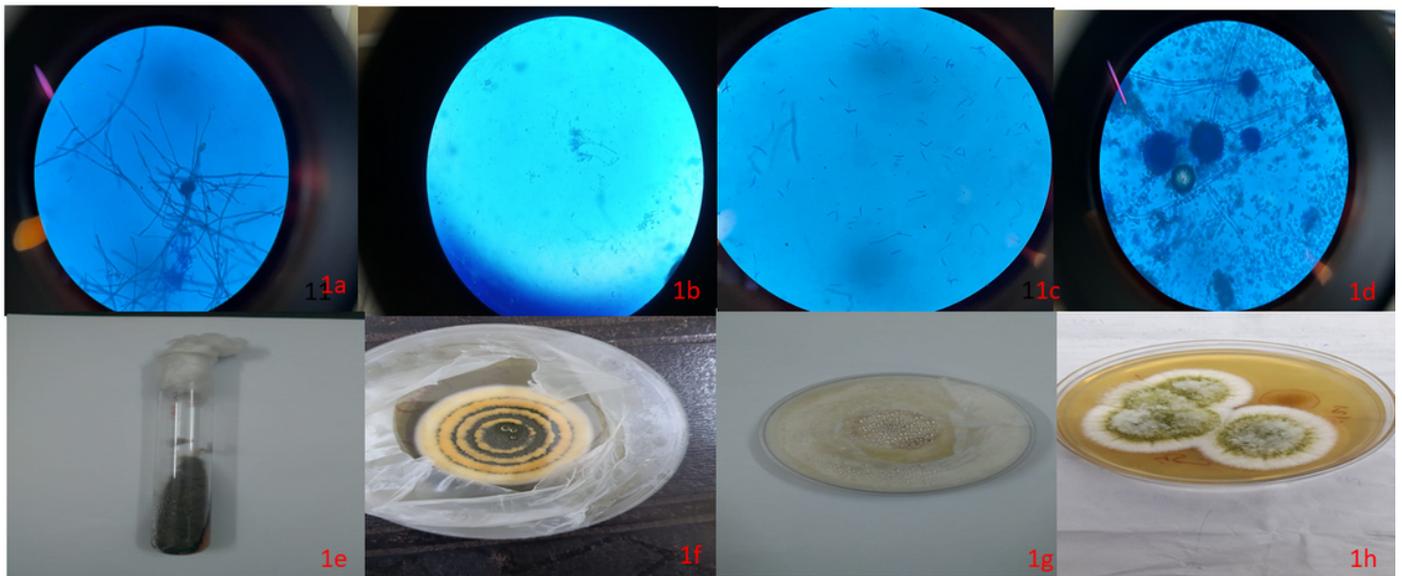
^b Ferritin -20 to 250 ng/mL for adult males. 10 to 120 ng/mL for adult females. ^c D dimer-less than 0.50.

^dC reactive protein - below 3.0 mg/L.

^f Lymphocyte -18-45% of total white blood cells.

^gNeutrophil- 40% to 60% of total white blood cells. ^h Total leucocyte count - 4,500 to 11,000 WBCs per microliter.

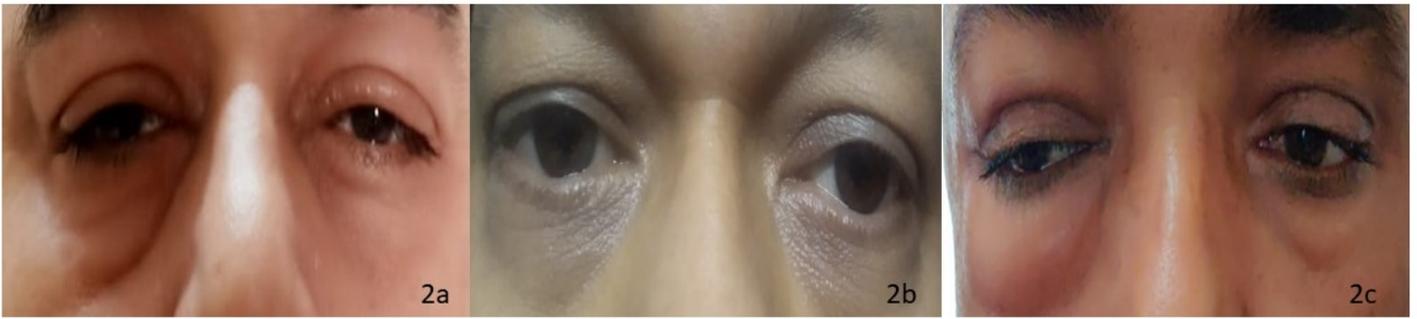
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Mean± SD
Fungi	Curvalaria sp	Aspergillus flavus	Aspergillus flavus	Aspergillus Flavus	Aspergillus flavus	Penicillium sp	Fusarium sp	
Ferritin ^b	390	735	412	222	NA ^a	269	NA	405.6±200.72
D DIMER ^c	2.3	1.31	1.51	0.97	0.28	0.41	NA	1.13±0.75
CRP ^d	120	50	24	15	20	NA	36	44.16±35
LYMPHOCYTES ^f	16	30	13	9	10	18	18	16.28±1.41
NEUTROPHIL ^g	76	64	81	78	84	76	76	76.4±6.26
TLC ^h	8630	9400	10400	12670	13020	4100	10540	9822±2986



Microscopic image showing(1a) Curvalaria (1b) Penicillium(1c) Fusarium (1d)Aspergillus
Fungal culture isolate(1e) Curvalaria(1f)Penicillium(1g) Fusarium(1h)Aspergillus

Figure 1

Microscopic images in lactophenol cotton blue mount (LPCB) and fungal cultures of isolates



(2a) patient 2, aspergillosis (2b) patient 5, aspergillosis (2c) patient 6, penicilliosis

Figure 2

Bilateral periocular swelling in non mucor fungal invasive rhino sinusitis

Table 1-Patient characteristics in 7 non mucor rhinosinusitis with ocular signs in COVID-19