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Post Covid-19 rhino-orbital fungal infections: A histopathological study of 20 cases

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Abstract
COVID-19 is associated with a significant incidence of secondary infections, both bacterial and fungal immune dysregulation. Additionally, the widespread use of steroids, monoclonal antibodies, broad spectrum antibiotics as part of the armamentarium against COVID-19 may lead to the development or exacerbation of pre-existing fungal diseases. As the infection spreads, it can manifest as headaches, proptosis, ophthalmoplegia, acute vision loss, and multiple cranial nerve palsies. Mucormycosis is a rare life threatening opportunistic fungal infection caused by fungi of Mucorales order belonging to the phycomycetes class. Rhino-orbital mucormycosis usually develops in the patients with diabetes, prolonged corticosteroid use, hematological malignancies, chronic renal failure, and other immunocompromised states.
Rhino-orbital infection begins when fungal spores are inhaled and invade the nasal mucosa and sinusitis develops as the fungus spreads to the paranasal sinuses. Orbital involvement occurs when the infection invades the orbital wall from the paranasal sinuses. Symptoms may include pain, chemosis, vision loss, ophthalmoplegia and proptosis. Ophthalmoplegia arises from infection of the muscles and orbital space or when the third, fourth and sixth cranial nerves are affected. Peripheral seventh cranial nerve paresis or paralysis and hypoesthesia of the face are often observed.
Here we are presenting histopathological study of 20 cases of post COVID-19 rhino-orbital fungal infection.

Keywords: rhino-orbital, Covid-19, fungus, mucormycosis

Introduction
COVID-19 pandemic is an outbreak of coronavirus disease that was first identified in December 2019. The severity of the disease ranges from asymptomatic infection to respiratory failure and death. Secondary fungal or bacterial infections or coinfections are important challenges increasing the patient's morbidity and mortality [1]. Mucormycosis, candidiasis and pulmonary aspergillosis have been common fungal infections that were reported as super-infections in COVID-19 patients.
Mucormycosis is a condition with fulminant course and high mortality risk. The most common predisposing factor is DM [Diabetes mellitus] (60-80%), though hematological diseases, neoplasias, chronic renal failure, antineoplastic agents, immunosuppressive therapy, corticosteroid use, protein-calorie malnutrition, organ and bone marrow transplantation, and other conditions resulting in immunosuppression such as AIDS also factor in its etiology. With orbital involvement, clinical symptoms and findings include periorbital edema, pain, proptosis, ophthalmoplegia and decreased vision [2].
Rhizopus oryzae species accounts for 60% of all forms of mucormycosis and 90% of rhino-orbital-cerebral cases. These pathogens are ubiquitous spore-forming saprophytes growing in decaying organic matter, especially the blood vessels, causing thrombosis, infarction, and eventual necrosis. The usual portal of entry is the nose; from there they proliferate, spreading to the paranasal sinuses and orbit by direct extension or intravascular dissemination. Mucormycosis follows a rapidly progressive course and if left untreated it is rapidly fatal [3].
Orbital involvement results from invasion of lacrimal duct spreading through the thin medial orbital wall. The Mucorales hyphae have a predilection for growth into arteries and the lymphatic system. The angio- invasion by hyphae produced a fibrin reaction and formation of mucor thrombi, which occlude the arteries leading to ischemia, infarction, and consequent formation of black necrotic eschar of the skin and mucosa that is characteristic of rhino orbital mucormycosis [3].

MRI is useful in identifying intra dural and intra cranial extent of the infection and demonstrate the perineural spread. Biopsy is necessary to confirm the diagnosis. Invasive hyphae can be seen as ribbonlike, 10 to 20 Micron wide, haphazardly branched organisms with little or no septation [3].

Despite advances in diagnosis and treatment, a high mortality rate of 30 to 70% still exists for this disease.

Material and Methods

The present study is an observational study carried out in the department of pathology, at a rural based tertiary care centre on 20 rhino-orbital biopsy samples received from patients who had been affected with COVID 19 infection. The case selection was based on inclusion and exclusion criteria. Only rhino-orbital biopsy samples including exenterated eyeballs from post COVID 19 cases were included in the study while those biopsies received from cases with no prior COVID 19 infection and Sino-nasal biopsies without orbital involvement were excluded. Pertinent data like age, sex, RTPCR positivity, comorbidities, Remdesivir use, corticosteroid use and oxygen [O2] supplementation were collected from the patients. The received biopsy samples were fixed in 10% formalin, processed in automatic tissue processor and paraffin blocks were prepared. Tissue sections of 4- 6µ were cut and stained with hematoxylin and eosin stain [H&E] stain.

Observations and result

A total of 180 Sino-nasal and rhino-orbital biopsy samples from patients affected with COVID 19 infection in recent past were studied in the department of pathology at a tertiary care centre. Out of these 180 biopsy samples [Chart:1], 110 [61%] samples were positive for fungal infections histopathologically and 70 were negative. Out of these 110 positive samples, sinonasal biopsies were 90 [81.8%] and the rest 20 [18.2%] samples were naso-orbital [exenterated eyeballs] [Fig. A, B, C] samples which were included in the study. Along with the exenterated eyeballs, nasal scraping samples from 17 out of 20 patients were sent for KOH preparation for early detection of fungal infection, 5 patients came out to be positive for fungal hyphae while 7 patients were negative.

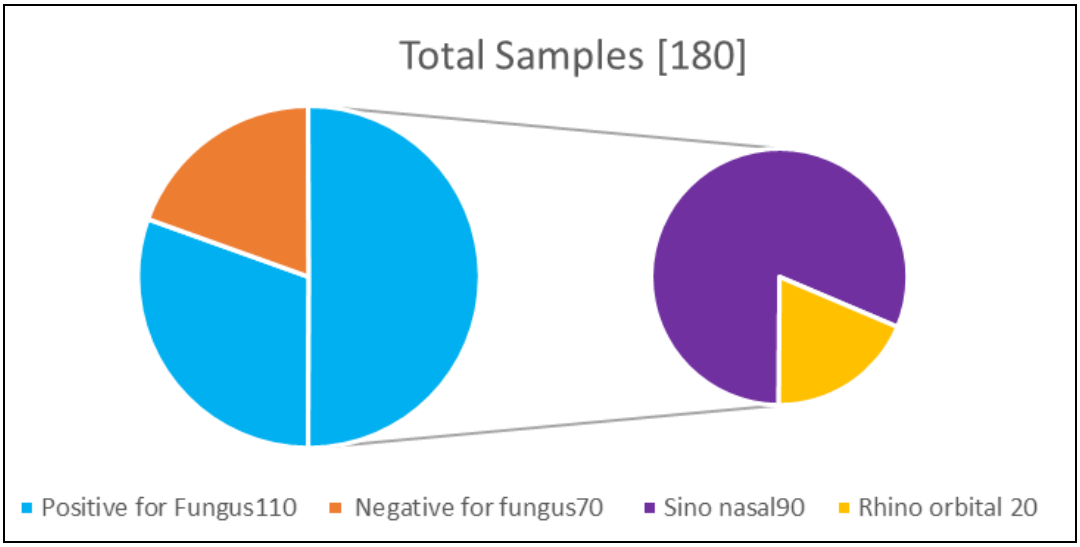

Chart 1: Showing distribution of number of biopsies received from post COVID-19 patients for histopathological examination

Age of the patients [Table 1] in our study was ranging from 28 years to 85 years. Most common age group involved was 61 to 70 years. Out of the 20 cases of post-COVID 19 rhino-orbital fungal infections, 10 cases were males while 10 cases were females with male to female ratio of M:F=1:1 with right eye involvement seen in 8 [40%] patients and left eye involvement in 12 [60%] patients.

Table 1: Age wise distribution of 20 cases of rhino-orbital fungal infection.

Age Groups	No of cases:	Percentage [%]
21-30 Years	01	5%
31-40 Years	02	10%
41-50 Years	05	25%
51-60 Years	03	15%
61-70 Years	06	30%
71-80 Years	02	10%
81-90 Years	01	05%
Total	20	100%

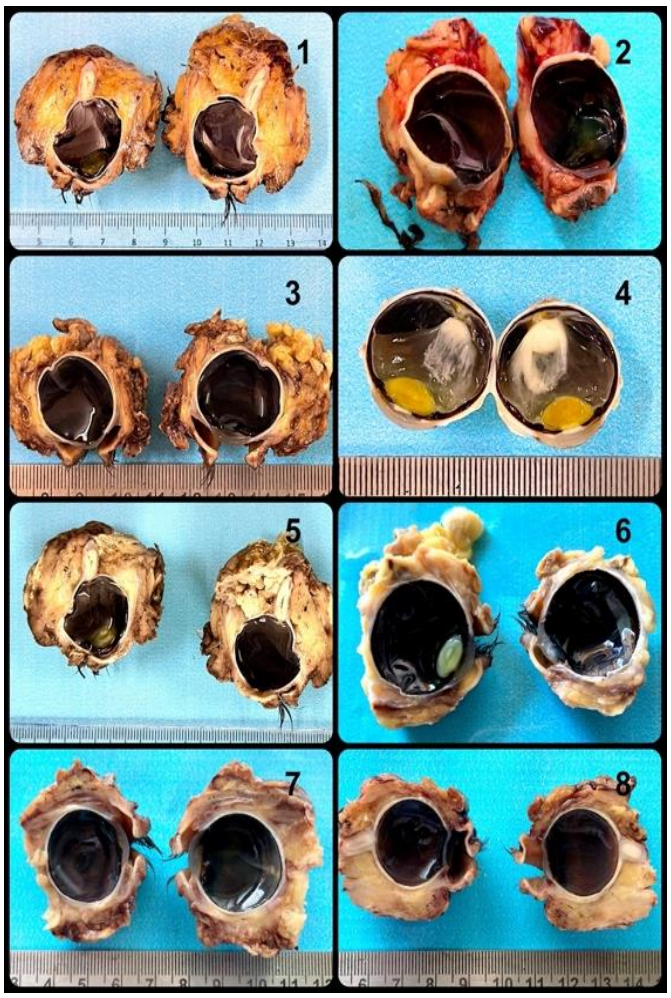

Fig A: Shows cut sections from 8 exenterated eyeballs along with periorbital tissue [Except Number 4].

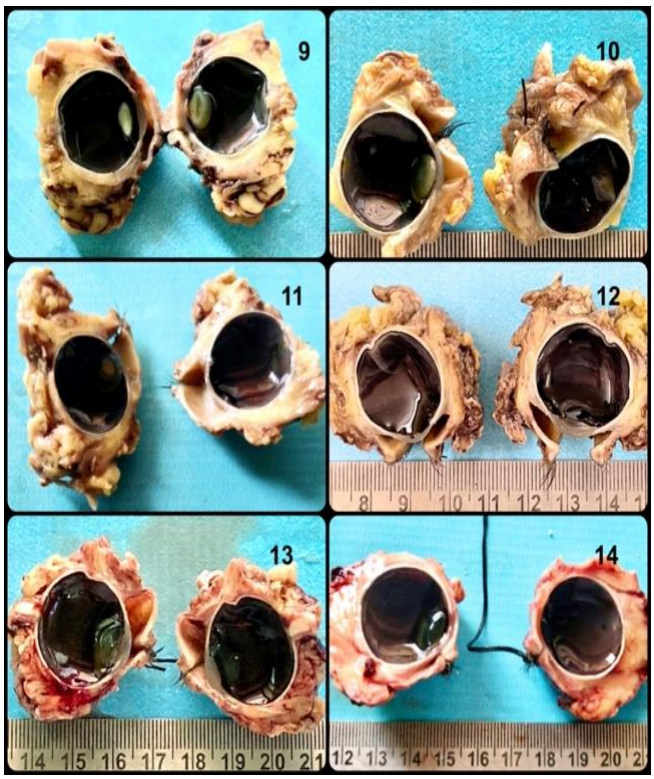

Fig B: Shows cut sections from another 6 exenterated eyeballs along with periorbital tissue.

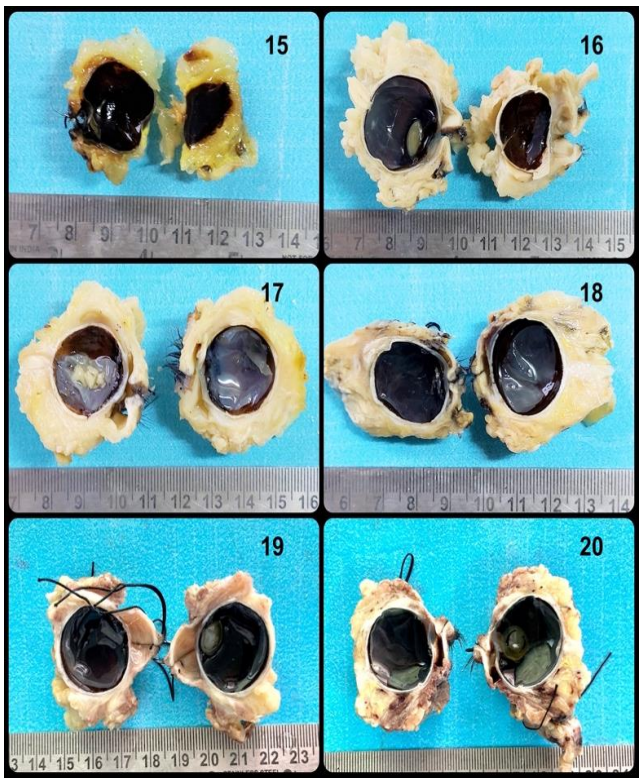

Fig C: Shows cut sections from another 6 exenterated eyeballs along with periorbital tissue.

In the present study of 20 patients of rhino-orbital fungal infection, the most common complaint [Table 2] was swelling of the affected eye seen in 16 patients followed by ptosis in 13 patients, proptosis in 11, pain in the eye in 10, headache in 9, facial pain in 6, facial swelling in 2 cases and toothache in single patient.

Table 2: Distribution of complaints in 20 patients of rhino-orbital fungal infection

Complaints of the patients	Out of 20 patients.
Swelling in the eye	16
Ptosis,	13
Proptosis	11
Pain in the eye	10
Headache	09
Facial pain	06
Swelling of the face	02
Toothache	01

In our study [Table 3] of 20 patients of rhino-orbital fungal infection, 14 patients were having DM and 9 patients were having associated HT. 15 patients were RTPCR positive, 11 patients received oxygen therapy, 8 patients received steroids and 5 patients received intravenous Remdesivir.

Table 3: Distribution of treatment modality and associated comorbidities seen in the 20 patients of rhino-orbital fungal infection

Treatment & Comorbidities	Out of 20 cases
Diabetes Mellitus [DM]	14
Hypertension [HT]	9
RTPCR COVID Positive	15
Intravenous Remdesivir	5
Oxygen therapy	11
Received steroids	8

Microscopically, [Table 4] [Fig. D, E] necrosis was the most common finding seen associated with fungal hyphae in 15 cases followed by granuloma formation and fibrofatty invasion in the periorbital tissue seen in 11 cases. 5 patients showed muscle and nerve invasion of fungal hyphae followed by vascular invasion with fungal emboli in 4 cases and abscess formation in 2 cases.

Table 4: Distribution of histopathological features seen in the biopsy samples of 20 patients of rhino-orbital fungal infection:

Histological features associated with fungal hyphae in the tissue.	Out of 20 patients.
Necrosis	15
Abscess	2
Granuloma	11
Muscle invasion	5
Vascular invasion with embolus	4
Nerve invasion	5
Fibrofatty invasion	11

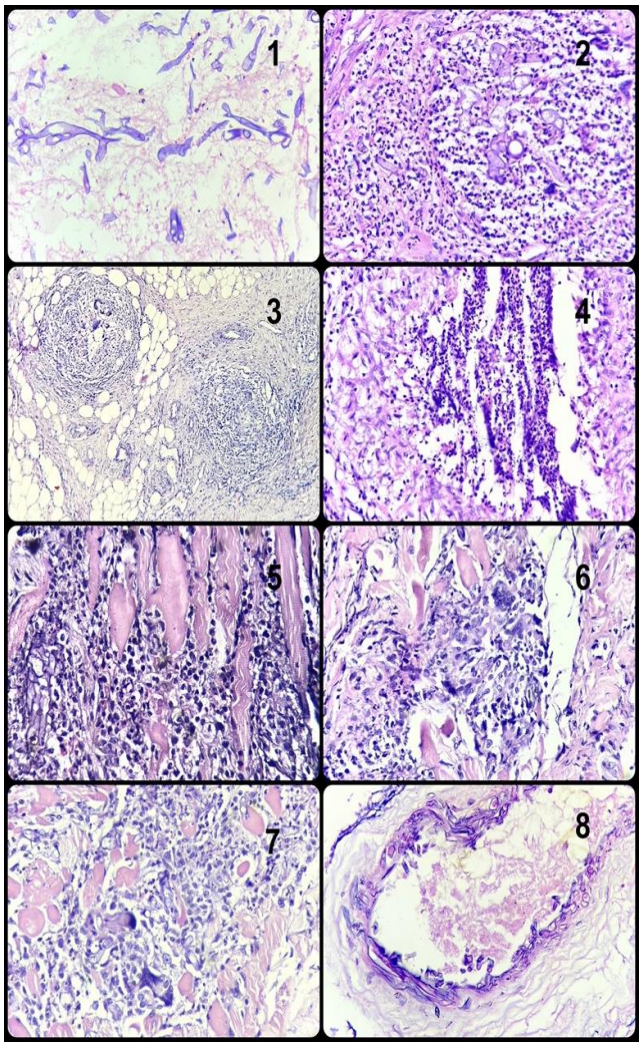

Fig D: Photomicrographs showing: [1]: Broad aseptate fungal hyphae with right angle branching in the background of necrosis. [H&E: 40X] [2]: Fungal hyphae surrounded by plenty of neutrophils [Abscess formation] [H&E: 40X]. [3]: Granuloma formation surrounding fungal hyphae. [H&E: 10X] [4]: Granuloma showing suppuration in the center surrounded by epitheloid cells, lymphocytes. [H&E: 40X] [5]: Muscle invasion and destruction by fungal hyphae and lymphocytes. [H&E: 40X] [6, 7]: Muscle invasion and destruction by fungal hyphae with granuloma formation [H&E: 40X]. [8]: Vascular invasion by fungal hyphae. [H&E: 40X]

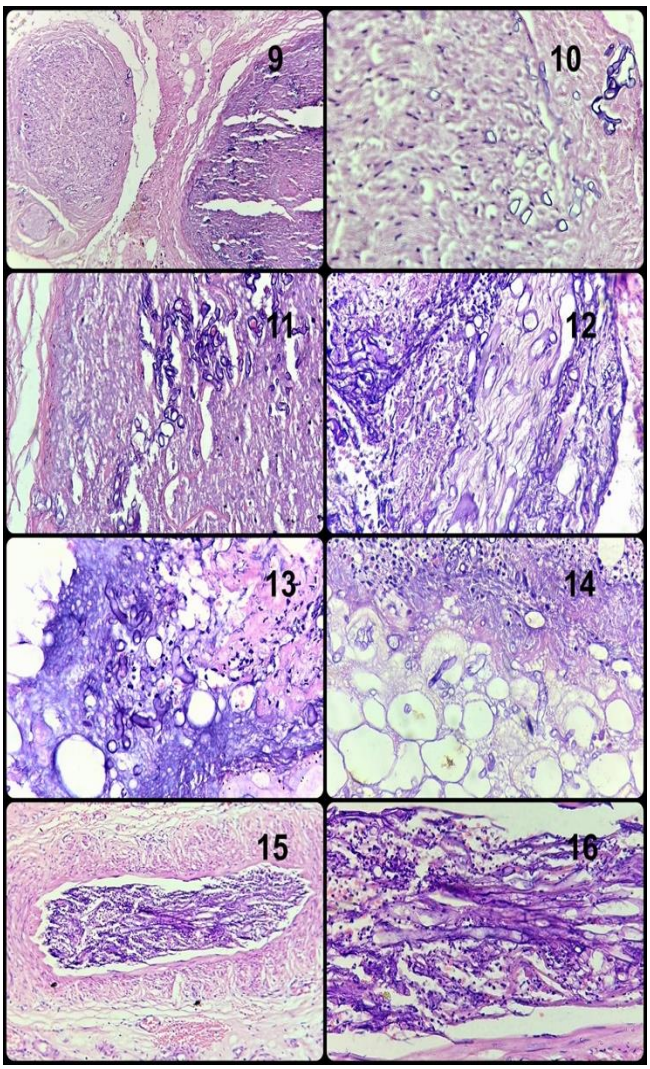

Fig E: Photomicrographs showing: [9]: Neural invasion of the fungal hyphae. [H&E: 10X] [10,11,12]: Neural invasion of the fungal hyphae. [H&E: 40X] [13,14]: Fungal hyphae invading the periorbital fibrofatty tissue. [H&E: 40X] [15]: Fungal emboli. [H&E: 10X] [16]: Fungal emboli. [H&E: 40X]

Discussion

COVID-19 infection caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) may be associated with a wide range of disease patterns. A wide range of bacterial and fungal coinfections may exist and may be associated with preexisting morbidity (diabetes mellitus, lung disease) or may develop as a hospital-acquired infection such as ventilator associated pneumonia [4].

Orbital involvement in the high mortality infections like mucormycosis may necessitate the decision to perform exenteration [2].

Mucormycosis, also known as zygomycosis or phycomycosis was first described by Paultaff in 1885. The fungus belongs to the phycomycetes class whose most common genera are mucor, rhizopus, absidia and basidiobolus. Mucormycosis is categorized as rhino-cerebral, pulmonary, cutaneous, gastrointestinal, or disseminated, depending on organ involvement; the most common form is rhino-cerebral [5].

It was deduced that the fungus received nourishment from elevated glucose levels in the body supporting the prevalence of mucormycosis in patients with poorly controlled diabetes [6].

Orbital involvement results from invasion off the nasal lacrimal duct spreading through the thin medial orbital wall. This usually presents with proptosis and medial rectus thickening. The initial symptoms of rhino orbital cerebral mucormycosis are consistent with those of sinusitis and periorbital cellulitis. This may include eye and/or Facial pain and facial numbness, followed by blurry vision. Other symptoms include multiple cranial nerve palsies, Unilateral periorbital facial pain, orbital inflammation, eyelid edema, blepharo prop ptosis, proptosis, acute ocular motility changes, internal or external of ophthalmoplegia, headache and acute vision loss. In immunocompetent patients, the nose and/or Maxillary sinuses appear to be the predominant source of infection of the respiratory tract. The earliest sign of infection is facial edema followed by proptosis, chemosis, and extraocular muscle paresis. Other manifestations include perinasal cellulitis, paresthesia, periorbital edema, mucopurulent rhinorrhea, and nasal crusting. A study reporting the epidemiology of zygomycosis shows that the mean age of patients affected was 38.8 years with male preponderance [65%] [3].

Yohai et al. reported ophthalmoplegia in 67% patients, vision impairment in 65%, proptosis in 64%, periorbital edema in 43% and periorbital pain in 11% of their patients. In the same study, 22% of patients had facial paralysis and 20% had facial hypoesthesia. Among 4 patients in the study, 2 had severe vision loss, proptosis and frozen orbit, and restricted eye movement was observed in another patient. Facial nerve involvement and facial hypoesthesia were found in 3 patients [2].

The histological stains that identify the mucor structures include hematoxylin and eosin, Periodic acid Schiff (PAS), and Gomorrah methamine silver (GMS). Histopathological examinations disclose relatively broad nonseptate hyphae with right angle branches, necrotizing granulomatous inflammation and the vasculitis together with the presence of mucor hyphae within the vascular wall and the lumen [1].

Conclusion

Physicians should be aware of the possibility of invasive secondary fungal infections in patients with COVID-19 infection especially in patients with pre-existing risk factor [4]. COVID-19 patients undergoing corticosteroid therapy have a risk of a rhino-orbital or rhino-orbito-cerebral mucormycosis, particularly when another risk factors such as diabetes is present. In these patients, vision changes, orbital pain, and orbital inflammation should be promptly evaluated, otherwise, the propagation of the infection into the intra cranial space may be fatal [1].

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