Journal of Communicable Diseases
Special Issue - COVID-19 & Other Communicable Diseases, Pg. No. 245-252
Peer Reviewed & Open Access Journal

Case Report

Fungal Nasal Polyposis during COVID-19 Pandemic - A Review of 4 Cases

Gayathri Devi[1], Vijayashree Raghavan[2], Aarthi Kannan[3]

[1]Postgraduate Resident, [2]Professor & HoD, [3]MD & Professor, Department of Pathology, Chettinad Hospital & Research Institute, Tamil Nadu, India.
DOI: https://doi.org/10.24321/0019.5138.202237

I N F O

Corresponding Author:
Vijayashree Raghavan, Department of Pathology, Chettinad Hospital & Research Institute, Tamil Nadu, India.
E-mail Id:
drvjshree@gmail.com
Orcid Id:
https://orcid.org/0000-0002-7655-243X
How to cite this article:
Devi G, Raghavan V, Kannan A. Fungal Nasal Polyposis during COVID-19 Pandemic - A Review of 4 Cases. Special Issue - COVID-19 & Other Communicable Disease. 2022;245-252.

Date of Submission: 2021-10-29
Date of Acceptance: 2022-01-08

A B S T R A C T

Nasal polyps are usually associated with inflammation, allergy or mucoviscidosis. The global burden of patients with COVID-19 infection, including that in the Indian sub-continent,is still very high and they are at an increased risk of developing invasive fungal infections probably due to their immunocompromised state. Here, we review 4 cases of fungal nasal polyposis in patients with an ongoing or past history of COVID-19 infection with or without associated co-morbidities.

Keywords: COVID-19, Fungal Nasal Polyposis, Aspergillus, Mucormycosis

Introduction

Fungi are eukaryotes, which have a nucleus with a RNA-rich nucleolus and other cytoplasmic organelles. They are described within the eukaryotes by the absence of their flagella, thus making them immotile, spore production during asexual reproduction and the requirement of aerobic environment for their growth. Their cell wall contains chitin, glucan and glycoproteins. The cell wall composition differs among various fungal organisms which can be used to differentiate one from another.[1] The most common human infections include Rhizopus (most commonly R.oryzae & rhino-orbital cerebral mucormycosis), Rhizomucor and Mucor. A few less common infections include Cunninghamella, Absidia, Saksenea and Apophysomyces. The mode of transmission can be through inhalation or through direct inoculation. The most commonly affected sites of involvement include sino-nasal, orbital, CNS, pulmonary, systemic, cutaneous and gastrointestinal infection secondary to pre-existing ulcers in malnourished or it can disseminate in the absence of treatment.[2]

Nasal polyps are associated with inflammation, allergy, or mucoviscidosis and clinically, appear as soft exophytic masses extending laterally from the mucosa into the anterior part of the middle meatus. Fungal rhinosinusitis (FRS) describes a spectrum of diseases ranging from benign colonization of the nose and sinuses by fungal organisms to acute invasive and life-threatening inflammation extending to the orbit and brain.[3,4] The phylogenic classification of fingal organisms[5] is shown in Figure 1.

The extent of fungal infection depends on the immune status of the host with invasive lesions seen in immunocompromised status.[5] COVID-19 infection caused by SARS-COV-2 has been known to cause pulmonary andextra-pulmonary symptoms.There is also a higher chance of invasive fungal infections, especially in immunocompromised andseverely

ill patients.[6] This article describes the clinicopathological findings in sino-nasal polyposis during the COVID pandemic. The classification of fungal rhinosinusitis is depicted in Figure 2.

Materials and Methods

The clinical details of the cases have been collected from the medical records department of our hospital which are shown in Table 1. CT scan was done for case 2 and case 3, the images of which are shown in Figure 3. The histopathological diagnosis was determined from the morphology using routine haematoxylinandeosin stain and special stains such as Periodic acid Schiff stain and Gomori'smethenamine stain. The fungal species were histologically differentiated based on their microscopic appearance. The photo-micrographic plates are shown in Figures 4-7.

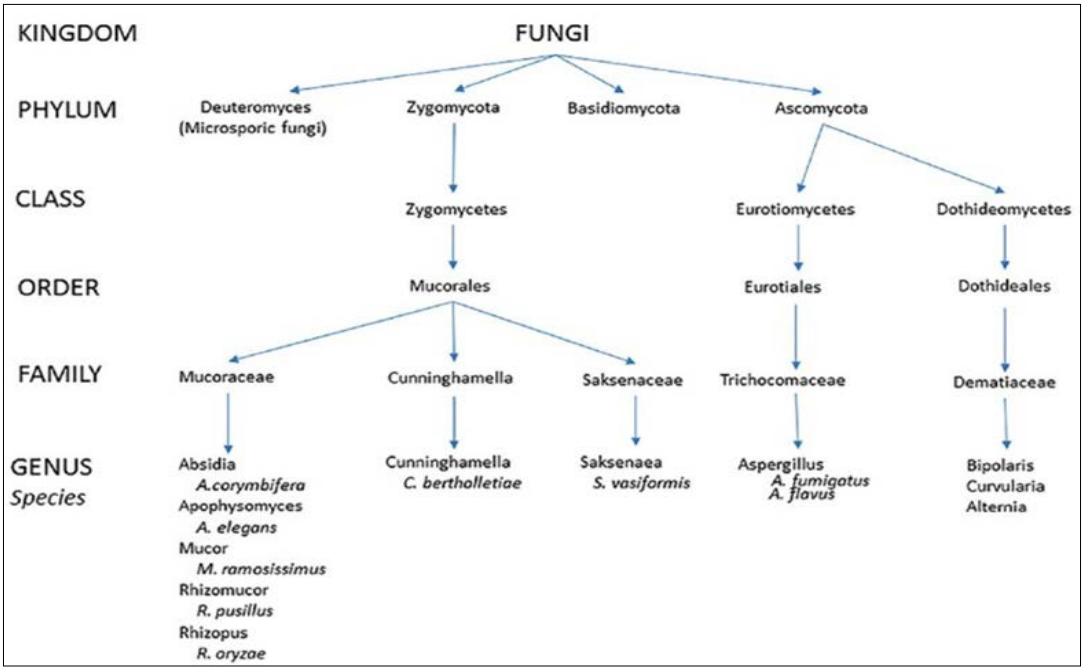

Figure 1. Phylogenic Classification of Fungal Organisms

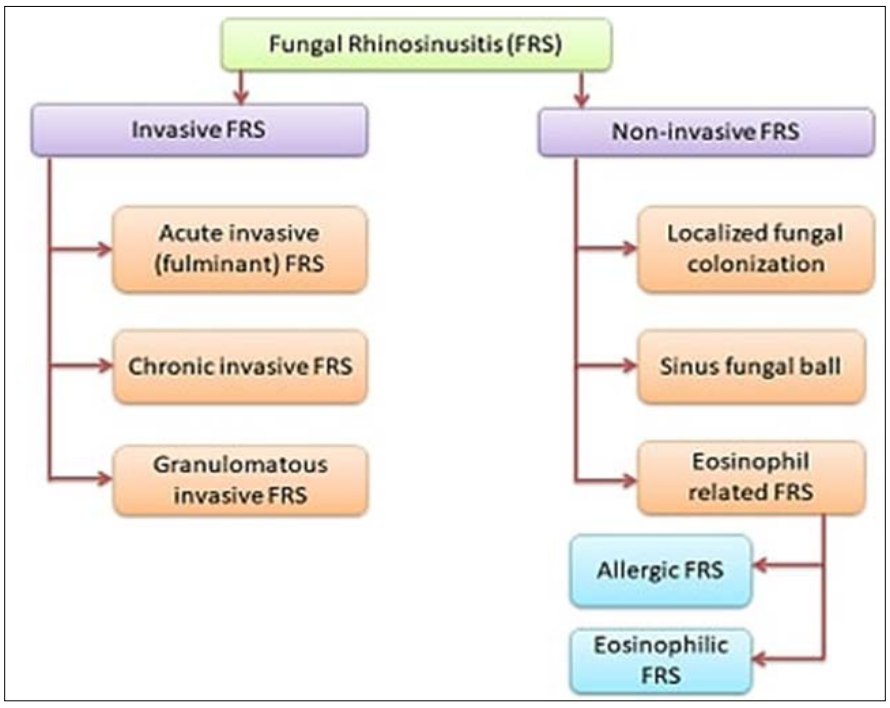

Figure 2. Types of Fungal Rhinosinusitis

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202237

Table 1.Clinical Details of the Patients

S. No.	Chief Complaints	Past History	COVID Status
1.	Right facial pain, headache, foul-smelling discharge from the right side of the nose for 4 months	Not a known case of diabetes mellitus, hypertension, tuberculosis, bronchial asthma, epilepsy or thyroid disorder	Post COVID
2.	Growth in the right nasal cavity & right nasal blockage for 14 days	Not a known case of diabetes mellitus, hypertension, tuberculosis, bronchial asthma, epilepsy or thyroid disorder	COVID positive
3.	Right side nasal blockage, headache, increased perception of smell, mouth breathing for 1 month	Not a known case of diabetes mellitus, hypertension, tuberculosis, bronchial asthma, epilepsy or thyroid disorder	COVID positive
4.	Left facial swelling, headache, running nose for 2 months	Known case of Type II DM for 10 years on regular treatment. Not a known case of hypertension, tuberculosis, bronchial asthma, epilepsy or thyroid disorder	Post COVID

Figure 3.CT Images of Case 2 (A) showing Bilateral Nasal Polyposis with Maxillary Thickening and Case 3 (B) showing Right Antrochoanal Polyp

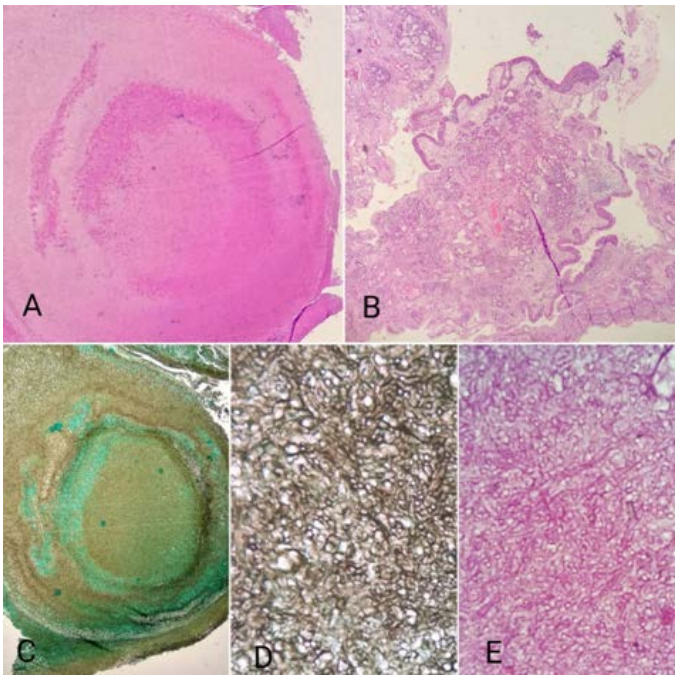

Figure 4.A&B; H & E: Sections show polypoidal tissue lined by pseudostratified ciliated columnar epithelium with squamous metaplasia. Stroma shows chronic inflammatory infiltrates, dilated submucosal glands & fibrosis; C-E: Few fragments show fungal organisms with septate hyphae, acute angle branching & conidiospores

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202237

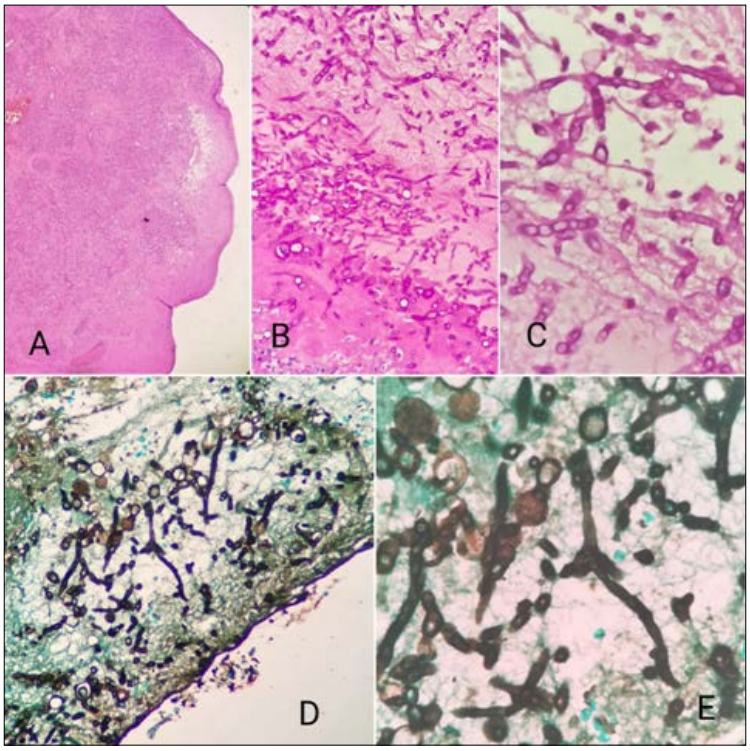

Figure 5.A: Sections show polypoidal tissue lined by pseudostratified ciliated columnar epithelium with squamous metaplasia. Stroma shows oedema, haemorrhage, congested blood vessels infiltrated by acute & chronic inflammatory infiltrates. B-E: One of the fragments show long filamentous hyphae with septae & acute angle branching. Conidial spores were also seen

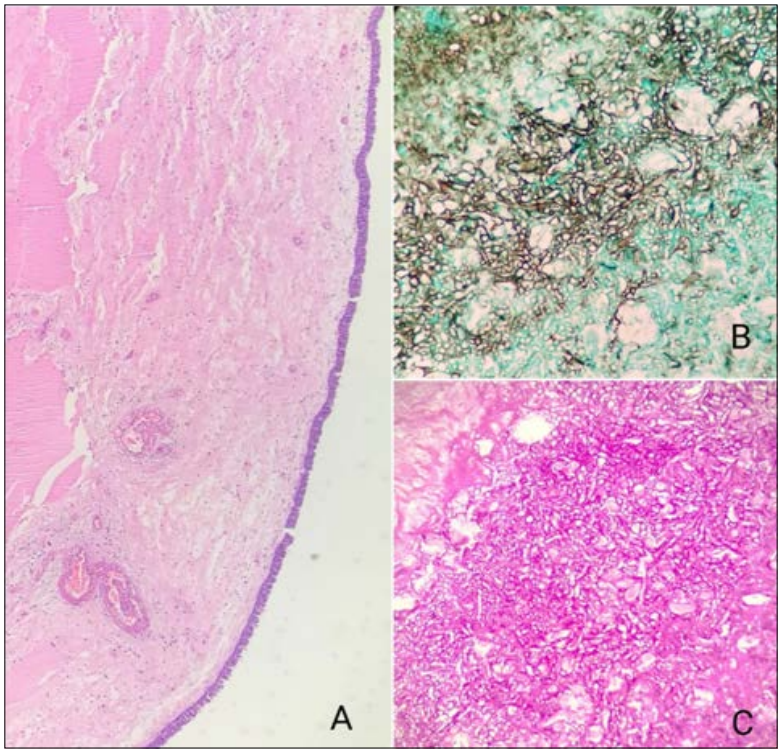

Figure 6.A: Sections show polypoidal tissue lined by pseudostratified ciliated columnar epithelium with focal squamous metaplasia. Stroma is oedematous with dilated blood vessels, few submucosal glands & acute chronic inflammatory infiltrates. B & C: Sections show septate acute angle branching fungal hyphae, conidiospores & fruiting bodies

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202237

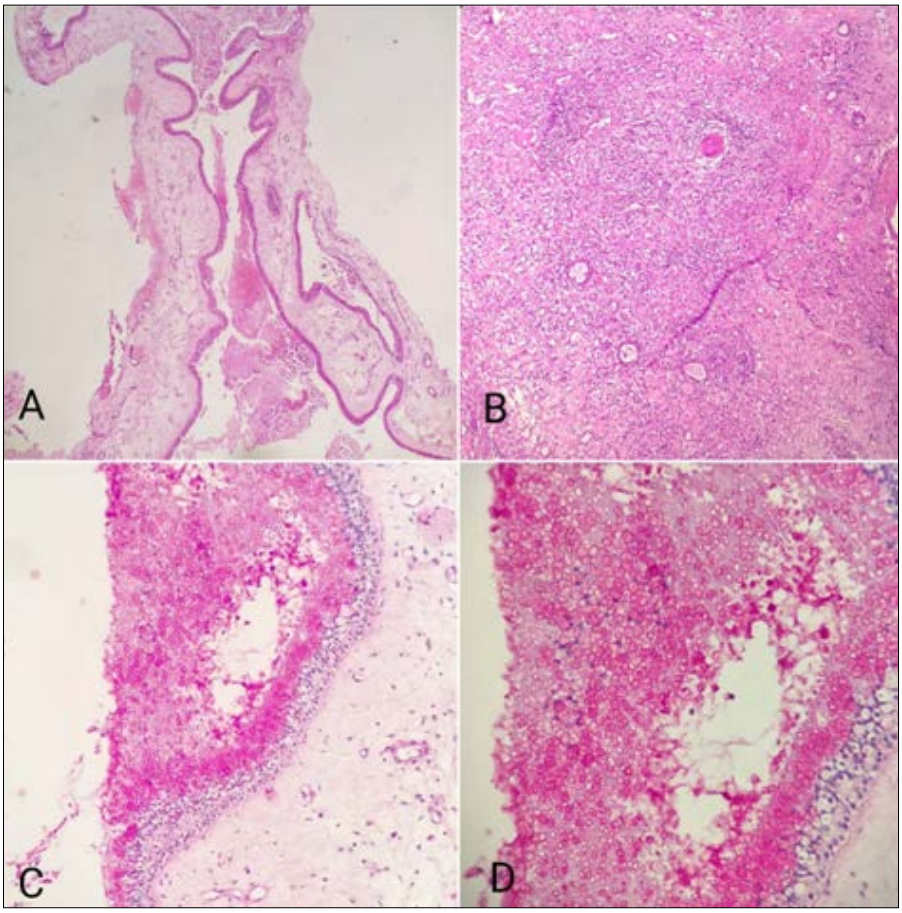

Figure 7.A& B: Sections show polypoidal tissue lined by pseudostratified ciliated columnar epithelium with focal squamous metaplasia & erosion. Stroma shows dense inflammatory infiltrates, occasional giant cells, oedema and areas of necrosis; C & D: Sections show broad-based right-angled fungal hyphae

Discussion

Our study included 4 patients, all of them were middle-aged female patients, 2 of them were COVID-19 positive and 2 were in the post-COVID status, during our study period. They presented with complaints such as nasal blockage, growth in the nasal cavity, foul-smelling nasal discharge, facial pain and headache. They did not receive any corticosteroid therapy for the COVID-19 infection, since the severity of infection was of milder degree. 3 out of 4 patients had Aspergillus infection while one of the patients had Mucormycosis infection who was a known case of type 2 diabetes mellitus and was on medication.

Mucorales and Aspergillus are present ubiquitously in the soil, dust, unfiltered air and decaying plants and humans are exposed daily to these fungal organisms.

Mucormycosis is an extremely rare fungal infection that can occur in an apparently healthy individual. In a recent estimate, the prevalence of mucormycosis in the global population ranges from 0.005 to 1.7/million, while in the Indian population, it is nearly 80 times higher. Even though mucormycosis occurs in immunocompromised individuals such as patients who have undergone organ transplantation or in haematological malignancies, diabetes mellitus still is considered a high-risk factor for developing mucormycosis. India, being the second largest population with diabetes mellitus worldwide, has increased number of mucormycosis cases also. Our study included a case of mucormycosis who is a known case of diabetes mellitus on treatment and she has had COVID infection a few weeks ago suggesting that her underlying immunocompromised state due to diabetes and COVID infection might have predisposed her to develop mucormycoses infection.[7,8]

The pathogenic mechanism involves mononuclear cells, macrophages and neutrophils. The fungal spores are phagocytosed by the tissue macrophages cells by producing perforin, reactive oxygen metabolites, antimicrobial enzymes and few cationic peptides, while a few spores that escape this phagocytic function develop into hyphal forms resulting in neutrophil chemotaxis with an oxidative cytotoxic effect.

They also attract other immune cells by releasing pro-inflammatory cytokines like interlukin-1 beta (IL-1b), tumour necrosis factor (TNF-α) and interferon-gamma (IFN). Because of this overexpression of inflammatory

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202237

cytokines, reduced CD4+ T and CD8 + T cell counts because of impaired cell-mediated immunity thus resulting in severe lymphopenia. The dissemination of the infection resulting in tissue damage occurs because of failure of this initial inflammatory response.[9]

On the other hand, Gupta A et al.[10] has suggested that the increased incidence of mucormycosis infection in the COVID-19 patients who did not have a previous history of diabetes mellitus, can be because of the affinity of SARS-CoV-2 to the ACE2 receptors could have directly damaged the beta cells in the pancreas or indirectly by damaging the blood vessels of the beta cells resulting in endothelitis which is an understudied subject in COVID-19-associated mucormycosis. The innate immune system plays a vital role in fighting the fungal infection by releasing oxygen free radicals to destroy their hyphae in a healthy individual. In a COVID affected individual, the innate immune system is affected, so there will be a precocious release of these cells from the marrow, as the site of origin of neutrophils is in the bone marrow, more immature forms of these neutrophils will be released which makes them incompetent to fight these fungal infections.

JeicanII et al. in their study, have compared the histopathological and ultramicroscopic features of chronic rhinosinusitis with nasal polyp(CRSwNP) and COVID-19 samples in 25 patients. They found out that features like inflammatory infiltrate predominantly composed of eosinophils, thickening of the basement membrane with fibrotic and edematous stroma are more commonly identified in the CRSwNP group than in the COVID-19 samples. In addition to these features, COVID-19 samples in their study have also shown a viral cytopathic like feature with lymphocyte predominant inflammatory infiltrate. In our study, all four cases showed squamous metaplasia of the lining epithelium, acute and chronic inflammatory infiltrate predominantly composed of lymphocytes, neutrophils and a few plasma cells. One of our cases showed stromal oedema with giant cell reaction to the fungal hyphae. But we did not observe any viral cytopathic like feature in our case study.[11]

The characteristic histopathological features of mucormycosis infection will be giant cell invasion, thrombus formation and necrosis of the damaged tissue. Our case also showed similar histopathological features. The possible aetiological agents triggering polyps are identified as allergy, infections due to bacterial, fungal andviral organisms andenvironmental pollution[12,13] Fungal colonization with evidence of invasion is important for suitable management. In our cases, the fungal invasion was seen as superficial fungal infections. No definite invasion was noted. Even though our case did not show any of the invasive features, the special stains showed the characteristic morphology of mucormycosis such as the broad-based fungal hyphae and right-angled branching of the fungal hyphae. COVID-19 infection may cause secondary infections related to immunosuppression.

"Fungal ball" occur in immunocompromised patients. They are defined as a densely matted ball of extra-mucosal fungal hyphae thatneither shows evidence of invasion nor elicit a granulomatous reaction in the surrounding stroma. The most commonly encountered organism are the Aspergillus species, though different fungal species can produce a fungal ball. Microbiological cultures can be done but they are considered unreliable with decreased positive rates probably because of the poor viability of the fungal organisms. One of our patients showed fungal ball histologically, andpresented with complaints of facial pain, right nasal blockage and foul-smelling nasal discharge. It commonly affects the maxillary sinus and three of our cases presented with maxillary sinus polyp and one of them presented as bilateral antrochoanal polyp.[14]

Both Mucormycosis and Aspergillosis are lethal fungal infections even after medical and surgical management with the mortality rate over 50%.[15] Both mucormycosis and Aspergillus infections can even co-exist in some patients and their combined incidence ranges from 1.88% to 25%. Singh AV et al. in their study has included 10 consecutive cases with dual/ mixed COVID associated mucor-aspergillosis (CAMA) with all the patients having a positive diabetic history. These patients were also having certain other increased associating risk factors such as corticosteroid therapy and living under unhygienic environments.[16]

Singh S et al. has shown that even allergic fungal rhinosinusitis (AFRS) has been associated with vision loss in a series of four cases during this COVID-19 pandemic because of delayed surgical management because of COVID restrictions such as travel restriction. Usually, AFRS is a slowly progressive disease causing paranasal sinus expansion which may even lead to bony erosion of the skull base. The pressure can cause damage to the optic nerve or it can inhibit the blood supply resulting in complete/ partial blindness.[17] But our patients did not show any such serious complications caused by the fungal organisms.

Few studies have reported that aspergillus plays an important role in worsening the prognosis of the COVID-19 patients. Agrawal S et al, in their case report, have suggested that aspergillus infection as the possible etiological agent as the cause of death in a young 20-year-old pregnant female with COVID-19 infection who had no other clinical history of immunosuppression despite active management which shows the fatal sequelae of the fungal infection even when there is no immunosuppression.[18]

SelarkaL et al. in their prospective, observational study

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202237

included COVID affected patients with mucormycosis from three tertiary care hospitals to observe their clinical presentation, risk factors, diagnosis and prognostic outcomes. Out of 2567 patients, 47 had mucormycosis infection and majority of them had other co-morbid conditions like hypertension and diabetes mellitus and a minority of the patients had sinusitis. Their study has shown that hyperglycemia, severe pneumonia, ventilator support and not receiving the COVID-19 vaccination as important predisposing factors.[19]

Bhanuprasad K et al.[20] has analysed the risk factors for developing mucormycosis in a prospective cohort study including 132 patients with rhino-orbito-cerebral mucormycosis (ROCM) and a control group of 32 patients who had negative RT-PCR results for COVID-19 but had ROCM. Both groups had diabetic patients either as uncontrolled diabetes mellitus or newly diagnosed diabetes mellitus. Also, patients have undergone corticosteroid therapy even in milder infections. They have shown that steroid use has been significantly associated with COVID-MUCOR. In conclusion, they have shown that conventional risk factors such as diabetes mellitus, use of industrial-grade oxygen and recent injudicious use of corticosteroids which in itself can cause hyperglycaemia resulting in dysfunction of the phagocytes has resulted in a surge of mucormycosis infection during COVID pandemic in Indian population.

Singh K et al.[7] has done a study in a recent estimate, using data from PubMed and google scholar including 101 cases of COVID-19 patients with mucormycosis infection, out of which 82 cases were from the Indian population and 19 were belonging to rest of the world. About 80% of these cases were associated with diabetes mellitus and approximately 15% of the cases were having diabetic ketoacidosis. Mortality rate was observed in approximately 30% of the cases.

Invasive mucormycosis has been associated with COVID-19 patients suffering from trauma, diabetes, glucocorticoid use, prolonged neutropenia, etc.[21] Aspergillosis is also implicated in life-threatening infection if there is immunosuppression with COVID-19 infection.[22,23] Though all our cases had superficial infections, those with COVID & diabetes mellitus had mucormycosis. Many studies have shown a higher incidence of mucormycosis in COVID-19 patients with diabetes mellitus. The more likely causes for developing mucormycosis are hyperglycaemia, widespread use of steroids for COVID-19 infection (which alone can cause increased blood sugar levels and high risk for developing opportunistic infections) and iron overload resulting in dysfunction of the phagocytes.[20] Since this increases the risk of invasiveness, proper follow-up & treatment is required. Though there were no studies related to the increased infections due to cloth masks, all these cases had used cloth masks andwhether that predisposed them to fungal infection, is not known.

Conclusion

This case study highlights the importance of clinical history andhistopathological examination of sino-nasal polyps. Though all these patients had similar symptoms of nasal block andallergic rhinitis, the presence of COVID infection andimmunosuppressed states should not be underscored and proper follow up is needed in these cases.

Sources of Funding: None

Conflict of Interest: None

References

1. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. ClinMicrobiol Rev. 2000 Apr;13(2):236-301. [PubMed] [Google Scholar]
2. Lee AS, Lee PWY, Allworth A, Smith T, Sullivan TJ. Orbital mycoses in an adult subtropical population. Eye. 2020 Sep;34(9):1640-7. [PubMed] [Google Scholar]
3. Malik TL, Pal MB. Prevalence of fungal infection in nasal polyps. Pakistan J Med Heal Sci. 2014;8(4):1077-81. [Google Scholar]
4. Benninger MS, Ferguson BJ, Hadley JA, Hamilos DL, Jacobs M, Kennedy DW, Lanza DC, Marple BF, Osguthorpe JD, Stankiewicz JA, Anon J, Denneny J, Emanuel I, Levine H. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol Neck Surg. 2003 Sep;129(3):S1-32. [PubMed] [Google Scholar]
5. Gavito-Higuera J, Mullins C, Ramos-Duran L, Sandoval H, Akle N, Figueroa R. Sinonasalfungal infections and complications: apictorial review. J Clin Imaging Sci. 2016 Jun;6:23.[PubMed] [Google Scholar]
6. Song G, Liang G, Liu W. Fungal co-infections associated with global COVID-19 pandemic: aclinical and diagnostic perspective from China. Mycopathologia. 2020 Aug;185(4):599-606. [PubMed] [Google Scholar]
7. Kumar A, Singh R, Joshi SR, Misra A. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19 . The COVID-19 resource centre is hosted on Elsevier Connect, the company' s public news and information.
8. Bhalla A, Manjari M, Kahlon SK, Kumar P, Kalra N. Cytokeratin 5/6 expression in benign and malignant breast lesions. Indian J PatholMicrobiol. 2010 Oct-Dec;53(4):676-80. [PubMed] [Google Scholar]
9. Chamilos G, Lewis RE, Lamaris G, Walsh TJ, Kontoyiannis DP. Zygomycetes hyphae trigger an early, robust proinflammatory response in humanpolymorphonuclear neutrophils through toll-like receptor 2 induction but display relative resistance to oxidative damage.

Antimicrob Agents Chemother. 2008 Feb;52(2):722-4. [PubMed] [Google Scholar]
10. Gupta A, Sharma A, Chakrabarti A. The emergence of post-COVID-19 mucormycosis in India: can we prevent it? Indian J Ophthalmol. 2021;69(7):1645-7.[Google Scholar]
11. Jeican II, Gheban D, Barbu-Tudoran L, Inișca P, Albu C, Ilieș M, Albu S, Vică ML, Matei HV, Tripon S, Lazăr M, Aluaș M, Siserman CV, Muntean M, Trombitas V, Iuga CA, Opincariu I, Junie LM. Respiratory nasal mucosa in chronic rhinosinusitis with nasal polyps versus COVID-19: Histopathology, electron microscopy analysis and assessing of tissue interleukin-33. J Clin Med. 2021;10(18):1-29. [PubMed] [Google Scholar]
12. Bachert C, Wagenmann M, Rudack C, Höpken K, Hillebrandt M, Wang D, van Cauwenberge P. The role of cytokines in infectious sinusitis and nasal polyposis. Allergy. 1998 Jan;53(1):2-13. [PubMed] [Google Scholar]
13. Razmpa E, Khajavi M, Hadipour-Jahromi M, Kordbacheh P. The prevalence of fungal infections in nasal polyposis. Acta Med Iran. 2007;45(1):46-50. [Google Scholar]
14. Deutsch PG, Whittaker J, Prasad S. Invasive and non-invasive fungal rhinosinusitis - a review and update of the evidence. Medicina (Kaunas). 2019 Jun;55(7):319. [PubMed] [Google Scholar]
15. Johnson AK, Ghazarian Z, Cendrowski KD, Persichino JG. Pulmonary aspergillosis and mucormycosis in a patient with COVID-19. Med Mycol Case Rep. 2021 Jun;32:64-7. [PubMed] [Google Scholar]
16. Singh V, Prasad A, Panda PK, Totaganti M, Tyagi A, Thaduri A, Rao S, Bairwa M, Singh AK. Mixed invasive molds among COVID-19 patients. medRxiv [Preprint]. 2021[cited2021 Aug 10].Available from: https://www.medrxiv.org/content/10.1101/2021.08.09.21261555v1. [Google Scholar]
17. Singh A, Kumar R, Kanodia A, Sagar P, Verma H, Kumar R. Management of allergic fungal rhinosinusitis associated with vision loss during COVID-19 era. Indian J Otolaryngol Head Neck Surg. 2021 Oct;1-6. [PubMed] [Google Scholar]
18. Agrawal S, Phulware RH. COVID-19 associated pulmonary aspergillosis (CAPA) in a pregnant woman. Autops Case Rep. 2021 Aug;11:e2021313. [PubMed] [Google Scholar]
19. Selarka L, Sharma S, Saini D, Sharma S, Batra A, Waghmare VT, Dileep P, Patel S, Shah M, Parikh T, Darji P, Patel A, Goswami G, Shah A, Shah S, Lathiya H, Shah M, Sharma P, Chopra S, Gupta A, Jain N, Khan E, Sharma VK, Sharma AK, Chan ACY, Ong JJ.Mucormycosis and COVID-19: an epidemic within a pandemic in India. Mycoses. 2021 Oct;64(10):1253-60. [PubMed] [Google Scholar]
20. Bhanuprasad K, Manesh A, Devasagayam E, Varghese L, Cherian LM, Kurien R, Karthik R, Deodhar D, Vanjare H, Peter J, Michael JS, Thomas M, Samuel P, Varghese GM.Risk factors associated with the mucormycosis epidemic during the COVID-19 pandemic. Int J Infect Dis. 2021 Oct;111:267-70. [PubMed] [Google Scholar]
21. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, Hoenigl M, Jensen HE, Lagrou K, Lewis RE, Mellinghoff SC, Mer M, Pana ZD, Seidel D, Sheppard DC, Wahba R, Akova M, Alanio A, Al-Hatmi AMS, Arikan-Akdagli S, Badali H, Ben-Ami R, Bonifaz A, Bretagne S, Castagnola E, Chayakulkeeree M, Colombo AL, Corzo-León DE, Drgona L, Groll AH, Guinea J, Heussel CP, Ibrahim AS, Kanj SS, Klimko N, Lackner M, Lamoth F, Lanternier F, Lass-Floerl C, Lee DG, Lehrnbecher T, Lmimouni BE, Mares M, Maschmeyer G, Meis JF, Meletiadis J, Morrissey CO, Nucci M, Oladele R, Pagano L, Pasqualotto A, Patel A, Racil Z, Richardson M, Roilides E, Ruhnke M, Seyedmousavi S, Sidharthan N, Singh N, Sinko J, Skiada A, Slavin M, Soman R, Spellberg B, Steinbach W, Tan BH, Ullmann AJ, Vehreschild JJ, Vehreschild MJGT, Walsh TJ, White PL, Wiederhold NP, Zaoutis T, Chakrabarti A; Mucormycosis ECMM MSG Global Guideline Writing Group.Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019 Dec;19(12):e405-21. [PubMed] [Google Scholar]
22. Miceli MH, Churay T, Braun T, Kauffman CA, Couriel DR. Risk factors and outcomes of invasive fungal infections in allogeneic hematopoietic cell transplant recipients. Mycopathologia. 2017 Jun;182(5-6):495-504. [PubMed] [Google Scholar]
23. Poli P, Timpano S, Goffredo M, Padoan R, Badolato R. Asymptomatic case of COVID-19 in an infant with cystic fibrosis. J Cyst Fibros. 2020 May;19(3):e18.[PubMed] [Google Scholar]

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202237