Original Research Article

Post Covid Fungal Infection: Histopathological and Microbiological Correlation

Dr. Priyanka Vaghasiya[1*], Dr. Jignasa Bhalodia[2]

[1]3rd year resident doctor, [2]Professor and Head
Department of Pathology, GMERS Medical College, Sola, Ahmedabad, Gujarat
[*]Corresponding author email: **pd.vaghasiya46@gmail.com**

International Archives of Integrated Medicine, Vol. 8, Issue 8, August, 2021.
Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 15-08-2021 **Accepted on:** 25-08-2021
Source of support: Nil **Conflict of interest:** None declared.

How to cite this article: Dr. Priyanka Vaghasiya, Dr. Jignasa Bhalodia. Post Covid Fungal Infection: Histopathological and Microbiological Correlation. IAIM, 2021; 8(8): 53-61.

Abstract

Introduction: Mucormycosis is a life-threatening infection caused by saprophytic fungi belonging to the genera Mucor, Rhizopus and Absidia which belong to the order Mucorales and class Zygomycetes.Covid-19 is a life-threatening, infectious disease in which decreased CD4 and CD8positive cell counts, indicating susceptibility to fungal co-infections. Extensive use of steroids in Covid-19 management or associated with diabetes mallitus can also suppress immunity, allowing opportunistic fungal infections to colonise.

Materials and methods: A Retrospective study of 50 patients with invasive fungal infection who presented to the ENT department and who were either coronavirus-positive or had recovered from coronavirus infection, were included in the study. Tissue samples from all suspected site were received in formalin for histological examination and in without formalin were used for KOH smear and culture.

Result: A total of 50 patients presented. Out of 50 patient 43 (86%) cases were found to be positive based on direct microscopy, culture and histopathology. Among these 31 (62 %) cases were found to be positive by direct microscopy - KOH, 40 (80%) by culture and 43(86 %) by histopathology. Among 43 cases, 4 cases which was negative by KOH but positive by histopathology considering histopathology as a gold standard. Mucormycosis was seen in 23 patients, candidiasis in 6 patient, aspergillosis in 3 patient and mixed infection of mucormycosis with candidiasis in 6 patients, with aspergillosis in 3 patients and with both candidiasis and aspergillosis in 3 patients.

Conclusion: Covid 19 associated with invasive mucormycosis sinusitis is dangerous. Uncontrolled diabetes and over-zealous use of steroids are two of the main factors aggravating the illness. If infected, early surgical intervention and intravenous anti-fungal treatment should be sought for

management, as a good prognosis and less fulminant disease course can be achieved in cases of post-coronavirus mucormycosis.

Key words

Covid 19, Diabetes, Mucormycosis, Steroid.

Introduction

Mucormycosis infection of the sinuses is a form of life-threatening invasive fungal sinusitis that typically affects immunocompromised individuals with an impaired neutrophilic response.

Patients can include those with uncontrolled diabetes mellitus, acquired immunodeficiency syndrome, iatrogenic immunosuppression and hematological malignancies, and those who have undergone organ transplantation [1].

Systemic immune alterations of Covid-19 infection itself may lead to secondary infections, which are increasingly being recognized in view of their impact on morbidity and mortality [1, 2, 3].

Rhinocerebral mucormycosis is a life-threatening infection caused by saprophytic fungi belonging to the genera Mucor, Rhizopus and Absidia. All of these belong to the order Mucorales and class Zygomycetes [2, 3].

Inoculation by inhalation of fungal spores reach the nasal cavity, germination is favored by low oxygen concentration, high glucose, acidic medium and high iron levels. They germinate into hyphae.

Due to the metabolic hypoxic conditions, the Polymorphonuclear cells are less effective at removing these hyphae, as it is often found in patients with mucormycosis associated with Diabetes mellitus, thereby favoring the establishment of infection.

Extension of the disease into the maxillary and ethmoid sinus can lead to orbital involvement. Through the superior orbital fissure, ophthalmic vein and cribriform plate along the perivascular channels can occur the intracranial spread [3, 5].

Clinically, rhinocerebral mucormycosis can present with atypical signs and symptoms similar to complicated sinusitis, such as headache, nasal blockade, crusting, proptosis, facial pain and oedema, ptosis, chemosis, black eschar over nasal cavity and even ophthalmoplegia, with headache and fever and various neurological signs and symptoms if intracranial extension is present [1, 2].

Histological features include mycotic infiltration of blood vessels, vasculitis with thrombosis, tissue infarction, hemorrhage and acute neutrophilic infiltrate [1, 3, 4].

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 [3, 4].

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.

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 [1, 6].

Here, we present our recent and still ongoing experience of 50 cases of mucormycosis of the

sinuses seen over a time period of just three months, with these patients being, or having previously been, Covid-19 positive.

Materials and methods

A Retrospective study was undertaken at GMERS Medical College, Sola, Ahmedabad, India, over a period of three months, from May to June 2021.

Tissue samples from all suspected site were received in formalin for histopathological examination and in without formalin were used for KOH smear and fungal culture.

Once fungal hyphae demonstrated by KOH mount method, histological examination performed. The various types of fungi were confirmed by histopathological examination.

Histopathology: All histological tissue obtained in formalin were fixed with 10% neutral formaldehyde for 24 h, routinely dehydrated and embedded with paraffin, 4 μM sections were serially cut on albumin coated slides and stained by Hematoxylin and Eosin (H&E) and Periodic Acid Schiff (PAS) stain.

KOH Microscopy and Culture: Tissue was examined in 20% KOH. Culture was done on Sabouraud Dextrose Agar (SDA) with chloramphenicol and incubated at 25ºC and 37ºC respectively and were examined until 28 days.

Results

A total of 50 patients presented; 36 of these were male and 14 were female with ages ranging from 30 to 74 years (mean = 67 years). The majority of patients (88.0%) were aged over 40 years, with those aged 30–60 years (6.0%) being most affected (**Table – 1**).

Table – 1: Details of cases.

SR NO.	AGE	SEX	DIAGNOSIS	COVID STATUS ON ADMISSION	DIABETES	STEROID ADMINISTRATION	KOH	SITE
1	46	M	MUCORMYCOSIS	+VE Before 1 month	Yes	Yes	MUCORMYCOSIS	Right nasal cavity
2	68	F	MUCORMYCOSIS	+VE Before 1 month	Yes	Yes	MUCORMYCOSIS	Bilateral nasal cavity
3	60	F	CHRONIC SINUSITIS	+VE Before 15 days	Yes	Yes	MUCORMYCOSIS	Left nasal cavity, left maxilla
4	75	M	ASPERGILLOSIS	+VE Before 25 days	No	Yes	MUCORMYCOSIS	Right maxilla
5	53	F	ASPERGILLOSIS	+VE Before 1 month	Yes	Yes	MUCORMYCOSIS	Left sphenoid, maxilla
6	42	F	MUCORMYCOSIS	+VE Before 16 days	Yes	No	MUCORMYCOSIS	Left middle turbinate, maxilla
7	30	F	CHRONIC SINUSITIS	+VE Before 1 month	No	Yes	No growth	All sinuses
8	41	M	CANDIDIASIS	+VE Before 18 days	No	Yes	MUCORMYCOSIS	Left and right maxilla
9	74	M	MUCORMYCOSIS	+VE Before 2 month	Yes	Yes	MUCORMYCOSIS	Maxilla
10	45	M	MUCORMYCOSIS	+VE Before 6 days	Yes	Yes	MUCORMYCOSIS	Middle turbinate
11	31	F	ASPERGILLOSIS	+VE Before 12 days	No	No	No growth	
12	52	F	MUCORMYCOSIS	No H/O COVID	Yes	No	No growth	Left alveolus
13	60	M	MUCORMYCOS	+VE Before 10	No	Yes	MUCORM	Right and left

			IS	days			YCOSIS	maxilla
14	67	M	CHRONIC SINUSITIS	+VE Before 6 days	No	Yes	No growth	All sinuses
15	67	M	CANDIDIASIS	+VE Before 16 days	No	Yes	No growth	Left maxilla
16	48	M	MUCORMYCOSIS+ CANDIDIASIS	No H/O COVID	Yes	No	MUCORMYCOSIS	Right and left maxilla, left ethmoid, left alveolus, left orbit, left frontal
17	42	M	MUCORMYCOSIS	+VE Before 26 days	No	No	MUCORMYCOSIS	Left maxilla
18	53	F	CHRONIC SINUSITIS	+VE Before 40 days	Yes	Yes	No growth	Right maxilla
19	54	M	MUCORMYCOSIS	No H/O COVID	Yes	No	MUCORMYCOSIS	Left maxilla, left inferior turbinate
20	52	M	MUCORMYCOSIS	+VE Before 1 month	No	Yes	MUCORMYCOSIS	Ethmoid, dental tissue
21	43	M	MUCORMYCOSIS + ASPERGILLOSIS	+VE Before 15 days	No	Yes	No growth	Left inferior turbinate
22	32	M	MUCORMYCOSIS	+VE Before 45 days	No	Yes	No growth	Right frontal
23	63	M	MUCORMYCOSIS	+VE Before 2.5 months	No	Yes	No growth	Left alveolus
24	67	M	MUCORMYCOSIS	No H/O COVID	Yes	No	MUCORMYCOSIS	Left maxilla
25	36	F	CANDIDIASIS	No H/O COVID	No	No	MUCORMYCOSIS	Right maxilla, Right uncinate
26	55	M	MUCORMYCOSIS	No H/O COVID	No	No	No growth	Right middle turbinate, Right maxilla
27	60	M	MUCORMYCOSIS	+VE Before 2.5 months	No	Yes	MUCORMYCOSIS	Left maxilla, Right uncinate
28	35	M	CHRONIC SINUSITIS	+VE Before 2 months	Yes	Yes	MUCORMYCOSIS	Left nasal cavity
29	48	M	ACUTE INFLAMMATION	No H/O COVID	Yes	Yes	No growth	Left nasal cavity
30	59	M	MIXED INFLAMMATION	+VE Before 1 month	Yes	No	MUCORMYCOSIS	Left nasal cavity
31	54	M	CANDIDIASIS	+VE Before 12 days	No	No	No growth	Right maxilla
32	50	M	MUCORMYCOSIS+ CANDIDIASIS	No H/O COVID	Yes	No	No growth	Left middle turbinate, left maxilla
33	34	M	CANDIDIASIS	+VE Before 10 days	No	Yes	MUCORMYCOSIS	Right inferior turbinate, right maxilla
34	58	F	MUCORMYCOSIS	+VE Before 6 days	No	Yes	No growth	Left maxilla, Left ethmoid
35	56	M	MUCORMYCOSIS+ASPERGILLUS+ CANDIDIASIS	+VE Before 16 days	No	Yes	No growth	Left maxilla
36	47	F	MUCORMYCOSIS	No H/O COVID	Yes	No	MUCORMYCOSIS	Right upper alveolus
37	72	M	MUCORMYCOSIS	+VE Before 26 days	No	No	MUCORMYCOSIS	Left & Right maxilla
38	58	M	MUCORMYCOSIS	+VE Before 40 days	Yes	Yes	No growth	Alveolus
39	70	M	MUCORMYCOS	No H/O COVID	Yes	No	MUCORM	Right septum,

			IS				YCOSIS	right ethmoid
40	60	F	MUCORMYCOSIS	+VE Before 1 month	No	Yes	MUCORMYCOSIS	Right maxilla
41	63	M	MUCOR+ ASPERGILLOSIS+ CANDIDIASIS	+VE Before 1 month	Yes	Yes	MUCORMYCOSIS	Right ethmoid, maxilla
42	45	M	MUCORMYCOSIS + CANDIDIASIS	+VE Before 1 month	Yes	Yes	MUCORMYCOSIS + ASPERGILLOUS	Right & left maxilla
43	65	M	MUCORMYCOSIS	+VE Before 3 months	Yes	Yes	No growth	Left maxilla, alveolus
44	40	F	CHRONIC SINUSITIS	+VE Before 15 days	No	Yes	No growth	Right ethmoid
45	48	M	MUCORMYCOSIS	+VE Before 1 month	No	Yes	MUCORMYCOSIS	Maxilla
46	58	M	MUCORMYCOSIS + CANDIDIASIS	+VE Before 2 months	No	Yes	MUCORMYCOSIS	Right & left maxilla
47	62	M	MUCORMYCOSIS + CADIDIASIS + ASPERGILLUS	+VE Before 1 months	No	Yes	ASPERGILLOUS	Left inferior turbinate, Left ethmoid, left maxilla
48	39	F	MUCORMYCOSIS + CANDIDIASIS	+VE Before 2 months	Yes	Yes	No growth	Right sphenoid
49	53	M	CANDIDIASIS	+VE Before 1 months	No	Yes	No growth	Left & right orbit
50	59	M	MUCORMYCOSIS + CANDIDIASIS	+VE Before 1 month	Yes	No	No growth	Right maxilla

Table - 2: Results of 50 clinically suspected cases of chronic fungal rhinosinusitis by different methods.

Total cases=50	**Direct microscopy=KOH**	**Culture**	**Histopathology**
Positive	31	40	43
Negative	19	10	07

Table - 3: Incidence of sinus affected.

Sinus affected	**Case No.(%)**
Maxillary	30
Ethmoid	10
Frontal	05
Sphenoid	03
Turbinate and uncinate process	17
Alveolus	07

Table – 4: Stages of presentation and status of co-morbidities.

Sr No.	**Stage**	**Involvement**	**Comorbid condition**	**No. of patients**
1.	**Stage-1**	Nose and PNS	With diabetes mellitus With Covid 19 infection With no history of diabetes mellitus and Covid 19 infection	19 03

2.	**Stage-2**	Nose and PNS with orbital extension	With diabetes mellitus With Covid 19 infection With no history of diabetes mellitus and Covid 19 infection	01 00
3.	**Stage-3**	Nose and PNS with intracranial extension	With diabetes mellitus With Covid 19 infection With no history of diabetes mellitus and Covid 19 infection	00 00

Figure - 1a and 1b: Hematoxylin and eosin staining showing angioinvasion by broad aseptate fungal hyphae.

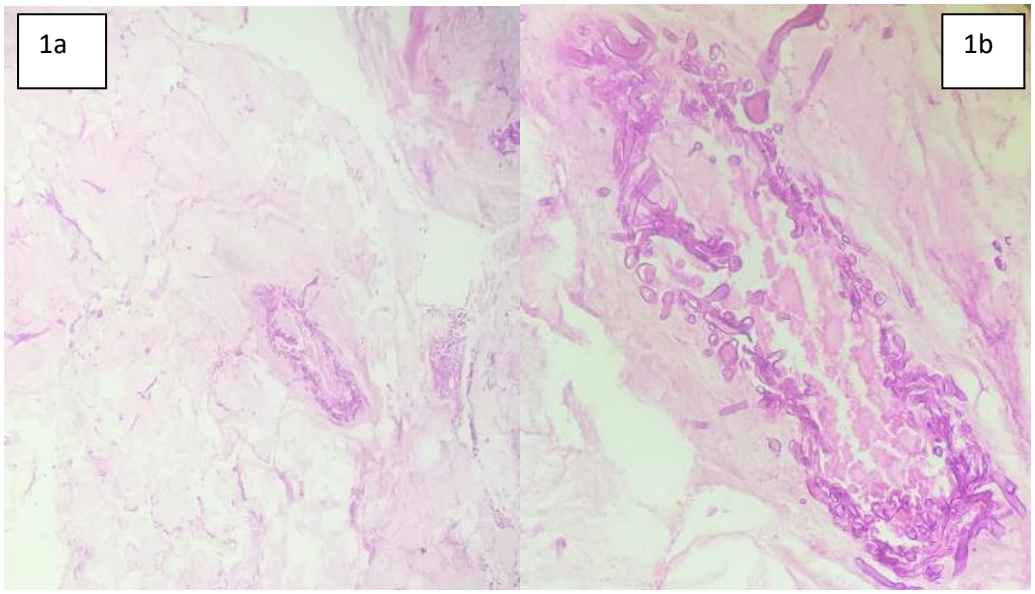
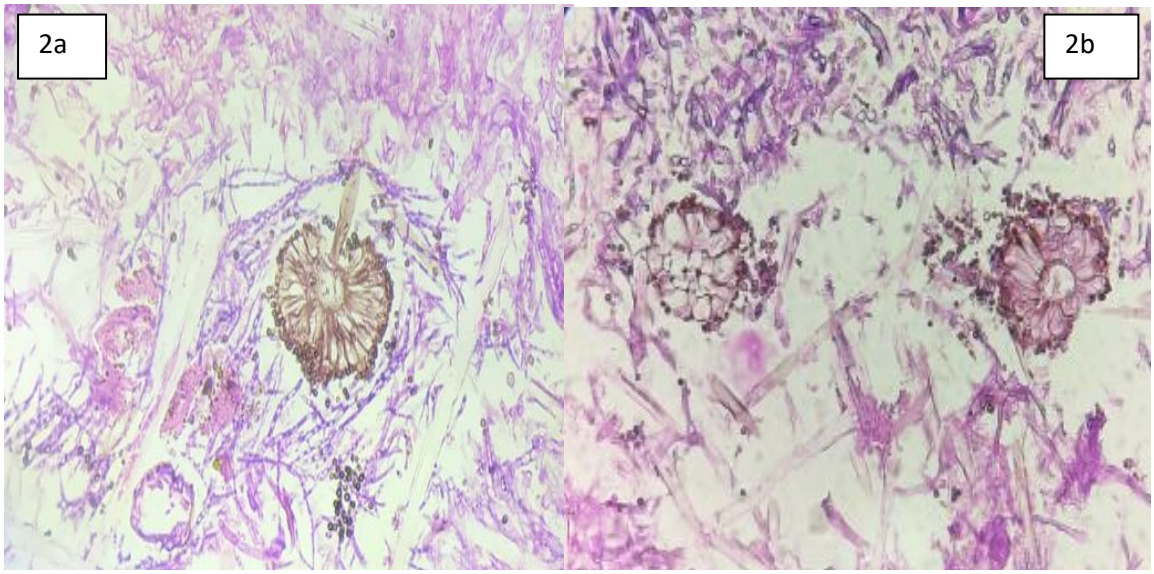


Figure - 2: Hematoxylin and eosin staining showing (2a)- thin septate fungal hyphae with fruititing body of aspergillus fungus, (2b)- Broad aseptate fungal hyphae with fruititing body of mucormycosis.



Four (04) of the patients were coronavirus-positive at the time of presentation but had been infected for more than 14 days; the remaining 46 had been infected earlier and had recovered. 34 patients received steroids for management of their covid infection either previously or after diagnosis was confirmed upon admission (**Table – 1**).

Out of 50 patient 43 (86%) cases were found to be positive based on direct microscopy, culture and histopathology. Among these 31 (62 %) cases were found to be positive by direct microscopy-KOH, 40 (80%) by culture and 43(86 %) by histopathology (**Table - 1, 2**), 4 case which was negative by KOH but positive by histopathology (**Table – 1**) considering histopathology as a gold standard.

30 patients had a primary disease infection involving the maxillary group of sinus air cells. The turbinate and uncinate process was affected in 17 cases, The ethmoid sinus was affected in 10 of 50 cases. Sphenoid and frontal and alveolus involvement was less common (**Table – 1**).

Mucormycosis was seen in 23 patients, aspergillosis in 3 patient and mixed infection ofmucormycosis with candidiasis in 6 patients, with aspergillosis in 3 patients and with both candidiasis and aspergillosis in 3 patients.

Nose and PNS were involved in 45 cases. In 5 cases, there was Orbital involvement along with Nose and PNS while no cases had intracranial extension from cases which we received for the histopathology processing (**Table – 3**).

The most common co-morbidity with covid 19 was the diabetes mellitus. Other co morbidity in our case was prolonged steroid use. In stage 1, 22 patients had DM and 34 patients were on prolonged steroid use. In stage 2, 01 patients had DM with diabetic ketoacidosis (**Table - 1, 4**).

On histopathology, the fungal hyphae of mucormycosis seen were broad, ribbon like, irregular and aseptate with branching at right angle, fungal hyphae of aspergillus were thin, septate with branching at acute angle. Submucosal infiltration was present. Both hyphae were evident with Hematoxylin and Eosin stain and PAS stain. Mucor and aspergillus sporangium with sporangiophore were evident on haematoxyline and eosin stain (**Figure - 2a, b**). Angioinvasion was demonstrated by H & E stain (**Figure - 1a, b**).

Discussion

The Covid-19 infection caused by the novel SARS-CoV-2 has been associated with a wide range of disease patterns, ranging from a mild cough to life-threatening pneumonia [13]. A myriad of manifestations and complications have been documented, and new ones are emerging and being reported on with each passing day as we learn more about this novel Covid-19 pandemic Mucormycosis or zygomycosis, also called phycomycosis, initially described in 1885 by Paltauf, is an uncommon and aggressive fungal infection that usually affects patients with alteration of their immunological system [15]. It is a lethal fungal disease, with rhinocerebral presentation being its most common form [16]. Although it has a low incidence rate, varying from 0.005 to 1.7 per million population, many cases have been seen recently, amounting to a significant increase in its incidence in the wake of the ongoing coronavirus pandemic.

Like SARS-CoV and Middle East respiratory syndrome, SARS-CoV-2 is also responsible for lower respiratory tract infection and can cause acute respiratory distress syndrome.[17] Besides the diffuse alveolar damage with severe inflammatory exudation, Covid-19 patients always have immunosuppression with a decrease in CD4+ T and CD8+ T cells.

During the SARS-CoV infection spread in 2003, the incidence of fungal infection was 14.8–27 per cent, and it was the main cause of death for severe acute respiratory syndrome patients, accounting for 25–73.7 per cent in all causes of death.23–25 Studies have shown that SARS-CoV

and SARS-CoV-2 belong to the same species, and have similar prevalence rates and biological and clinical characteristics. Based on our experience in 2003, it is important that physicians pay critical attention to the high probability of increased incidence of fungal infections in Covid-19 affected or recovered patients, similar to the finding observed in mucormycosis cases here.

Previously, few such incidental case reports have been published, but a firm association between Covid-19 and increased fungal infections can now be clearly seen. Mehta and Pandey reported a single case of a 60-year-old male with rhino-orbital mucormycosis associated with Covid-19 in September 2020 [13]. Another such case report was published by Werthman-Ehrenreich in the same month [14].

White et al. studied 135 adults with Covid-19 infection, and reported an incidence of 26.7 per cent for invasive fungal infections [1]. Song, et al. studied the association between Covid-19 and invasive fungal sinusitis in April 2020, and concluded that a large number of patients affected by or recovered from Covid-19 are at increased risk of developing invasive fungal diseases, and gave a management algorithm for such cases [1]. In a recent review, 8 per cent of coronavirus-positive or recovered patients had secondary bacterial or fungal infections during hospital admission, with widespread use of broad-spectrum antibiotics and steroids [1].

Due to the angioinvasive nature of the disease, skull base osteomyelitis and bone involvement is usually not seen or seen only late in the disease [2]. Only few case reports of chronic mucormycosis involving bone are available [2]. However in our series 15 patients presenting with acute mucormycosis went on to develop chronic infection with bone involvement following the initial treatment. The involved bones showed expansion, sclerosis, erosions and irregular lytic destruction. Also many of our patients showed destructive bony changes in the acute phase of the disease suggesting early bone involvement can also occurs.

Yohai, et al. reviewed 145 case reports of ROCM, 60% of them had diabetes, and analysed their ophthalmic and nonophthalmic signs and symptoms occurring at any time during the course of disease. Similarly Ferry and Abedi reported 16 cases of ROCM; 13 (81%) of them had diabetes. We have compared our observations with these two available series where the majority of the patients had diabetes [3].

Conclusion

We are learning more about the new and long-term manifestations of the Covid-19 infection. Uncontrolled diabetes and over-zealous use of steroids in Covid 19 management can also suppress immunity, allowing opportunistic fungal infections to colonise which might aggravating the illness, and both of these must be properly checked.

Its association with invasive mucormycosis sinusitis is dangerous and must be given serious consideration. Histopathological examination must be needed for diagnosing it properly.

If infected, early surgical intervention and intravenous anti-fungal treatment should be sought for management, as a good prognosis and less fulminant disease course can be achieved in cases of post-coronavirus mucormycosis.

References

1. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. J Laryngol Otol., 2021; 1–6. https://doi.org/10.1017/S0022215121000992
2. Jacob Therakathu, Shailesh Prabhu, Aparna Irodi, Sniya Valsa Sudhakar, Vikas K. Yadav, V. Rupa. Imaging features of rhinocerebral mucromycosis: A study of 43 patients. The Egyptian

Journal of Radiology and Nuclear Medicine, 2018; 49: 447–452.
3. V. P. Singh, Chetan Bansal, Madhuri Kaintura. Sinonasal Mucormycosis: A to Z. Indian J Otolaryngol Head Neck Surg., November 2019; 71(Suppl 3): S1962–S1971.
4. A Bhansali, S Bhadada, A Sharma, V Suresh, A Gupta, P Singh, A Chakarbarti, R J Dash. Presentation and outcome of rhino-orbital-cerebral mucormycosis in patients with diabetes. Post Graduate Medical Journal, 2004; 80: 670-674.
5. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. J Laryngol Otol., 2021; 1–6. https://doi.org/10.1017/S0022215121000992
6. Aditya Moorthy, Rohith Gaikwad, Shreya Krishna, Raghuraj Hegde, K. K. Tripathi, Preeti G. Kale, P. Subramanya Rao, Deepak Haldipur, Krishnamurthy Bonanthaya. SARS-CoV-2, Uncontrolled Diabetes and Corticosteroids - An Unholy Trinity in Invasive Fungal Infections of the Maxillofacial Region? A Retrospective, Multi-centric Analysis. J Maxillofac Oral Surg., 2021; 20(3): 1-8.
7. Katja Evert, Thomas Dienemann, Christoph Brochhausen. Autopsy findings after long-term treatment of COVID-19 patients with microbiological correlation. Virchows Arch., 2021; 479(1): 97-108.
8. Stefania Caramaschi, Meghan E. Kapp, Sara E. Miller. Histopathological findings and clinicopathologic correlation in COVID-19: a systematic review. Mod Pathol., 2021; 34(9): 1614-16633.
9. Brian Hanley, Kikkeri N Naresh, Candice Roufosse. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. Lancet Microbe, 2020; 1: e245–53.
10. Ajay Kumar Singh, et al. Fungal Rhinosinusitis: Microbiological and Histopathological Perspective, Journal of Clinical and Diagnostic Research, 2017 Jul; Vol-11(7): DC10-DC12.
11. Yanling Feng,, Dong Zeng, Lvyin Hu, Yuexiang Yang. Case report: histopathology and molecular pathology analysis on enteric tissue of a COVID-19 patient. Diagnostic Pathology, 2021; 16: 40.
12. Dora Y. Ho, Margaret Lin, Joanna Schaenman. Yield of diagnostic procedures for invasive fungal infections in neutropenic febrile patients with chest computed tomography abnormalities. Mycoses, 2011 January; 54(1): 59–70.
13. Mehta S, Pandey A. Rhino-orbital mucormycosis associated with COVID-19. Cureus, 2020; 12: e10726.
14. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. Am J Emerg Med., 2021; 42: 264 e5- 264 e8.
15. Paltauf A. Mycosis mucorina. Virchows Arch Pathol Anat Physiol Klin Med., 1885; 102: 543–64.
16. Arnáiz-García ME, Alonso-Peña D, González-Vela Mdel C, García-Palomo JD, Sanz-Giménez-Rico JR, Arnáiz-García AM. Cutaneous mucormycosis: report of five cases and review of the literature. J Plast Reconstr Aesthet Surg., 2009; 62: e434–41.
17. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol., 2020; 92: 568–76.