Case Report

Dual Invasive Pulmonary Mycosis in a Post Covid-19 Patient: An Autopsy Diagnosis

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Abstract

Patients suffering from Covid19 associated lower respiratory tract infection are most often in an immunocompromised state and are indeed vulnerable to a host of bacterial and fungal infections. Among the fungi, common invaders include candidiasis, aspergillosis and mucormycosis. Aspergillosis is a relatively common fungal infection which has been widely reported to occur in patients suffering from or recently recovered Covid19 infection. The invasive form of this fungus, is, however, less commonly reported in literature. Invasive pulmonary mucormycosis is a relatively uncommon pulmonary fungal disease. Its early diagnosis is essential but difficult as it lacks an effective treatment protocol. Commonly affecting a primarily immunocompromised host, the diagnosis of both infecting fungi primarily rests upon detection of their hyphae and/or spores in the lung and vascular tissue. This report describes presence of invasive pulmonary mucor and aspergillosis detected at autopsy in a post covid 19 patient, who presented with a naso-orbital swelling and had a rather silent clinical course followed by sudden onset of a single episode of massive hemoptysis resulting in his death.

Keywords:

Invasive Fungal Infections, Pulmonary Aspergillosis – Invasive, Mucormycosis, Autopsy

Introduction

The year 2020 brought with it, the wave of a new viral infection, which is still a very much ongoing pandemic: the novel coronavirus SARS-CoV2, commonly known as Covid19 viral infection. This virus mainly affects the respiratory tract, and if not promptly managed, can most often lead to lung involvement, which may turn fatal.

It is also associated with a significant immunocompromise which leads to increased vulnerability to opportunistic infections. A variety of bacterial, viral and fungal infections have been known to opportunistically target immunocompromised patients. Both, Mucormycosis and aspergillosis are opportunistic fungal infections and have been known to cause secondary infections in patients suffering from or recently recovered from Covid19. While aspergillosis is known to affect Covid19 patients with acute respiratory

distress syndrome in the form of e COVID-19-associated invasive pulmonary aspergillosis (CAPA), mucor has been reported to cause rhino-orbito-cerebral Mucormycosis (ROCM) in patients just recovered from the virus [1].

Clinical diagnosis is difficult in dual pulmonary mycosis and relies mainly on histopathology and microscopy combined with culture from various clinical specimens.

Case Report

A 51-year-old male presented to a secondary care center with chief complaints of right naso-orbital swelling of 05 days duration. On enquiry, he had no history of associated nasal obstruction or discharge or anosmia. However, he gave a clinical history of having flu like symptoms and dyspnea approximately a month ago, for which he had reported to another medical center where he was evaluated for and diagnosed with SARS-Covid19 associated respiratory tract infection by RT PCR. A prognostic High Resolution Computer Tomography (HRCT) scan done at the same center was strongly suggestive of COVID – 19 associated pneumonia with a Corona virus disease 2019 Reporting and Data System (CORADS) score of 5 and a CT scan severity score of 23/27. He was managed as per the Covid19 treatment protocol and re-evaluated after resolution of symptoms radiologically. The CT severity score had subsided to 18/25. However, the patient began complaining of mild right orbital swelling for which he was evaluated with a Magnetic Resonance Imaging (MRI) study of paranasal sinuses for suspicion of mucormycosis. The subsequent MRI scan revealed features of sinusitis with erosion of anterior wall confirming nasal mucormycosis. He was managed with intravenous (IV) antifungals and was planned for surgical debridement for the same, but he refused to undergo the same at that center as he was symptomatically relieved.

However, following a week after being discharged from the center, he again presented with right naso-orbital swelling which did not subside even after an antibiotic course, and he presented with the same to the ENT OPD at this center.

On initial evaluation by the ENT specialist, right periorbital edema was noted and he was admitted for further evaluation and management as a case of “Post covid sequalae with suspected naso-orbital Mucormycosis”.

He was administered an initial prophylactic intravenous antifungal therapy, while he underwent CT scan of the paranasal sinuses for evaluation of the swelling. The scan was suggestive of Chronic sinusitis with features of Fugal sinusitis (Fig 1), and a biopsy was suggested for confirmation of the same. The patient also showed response to the prophylactic antifungal therapy in the form of reduction of the swelling. Due to the response, he was continued on the same treatment. Non-Contrast-enhanced CT (NCCT) chest was also done to evaluate the extent of post- covid sequalae, which showed bronchiectasis, cavitation and fibrosis in the right upper lobe with patchy ground glass opacities and fibrosis in all segments of lungs (Fig 2). Magnetic Resonance Imaging (MRI) studies confirmed the NCCT findings (Fig 3)

He also underwent ENT endoscopic examination which revealed a fragile mass in the right middle meatus associated with discharge with the right middle turbinate showing the presence of a greyish colored mass covered with discharge. A biopsy was obtained from the suspected areas and was submitted for fungal microbiological examination and histopathology. Wet mount Lactophenol Cotton Blue (LCB) stained slide from the same did not reveal any fungal elements. Culture for fungus did not show any growth. Biopsy revealed multiple tissue bits lined by pseudostratified columnar epithelium showing dense subepithelial mixed inflammatory infiltrate comprising of neutrophils, lymphocytes, eosinophils and plasma cells. No fungal elements were noted.

Owing to the above microbiological and histopathological findings, the patient was started on prophylactic injectable antifungals with antibiotic cover and oral antihypertensives as well as antihistaminic agents along with Tab Paracetamol 500 mg SOS. The

clinical course of the patient remained predominantly silent following the above-mentioned management. However, within approximately a week of this management, the patient complained of sudden onset of non-specific uneasiness after a meal and immediately had a sudden episode of massive hemoptysis after which he collapsed. He was immediately shifted to the ICU and attempted resuscitation; but could not be revived after administering 45 mins of Cardiopulmonary Resuscitation (CPR).

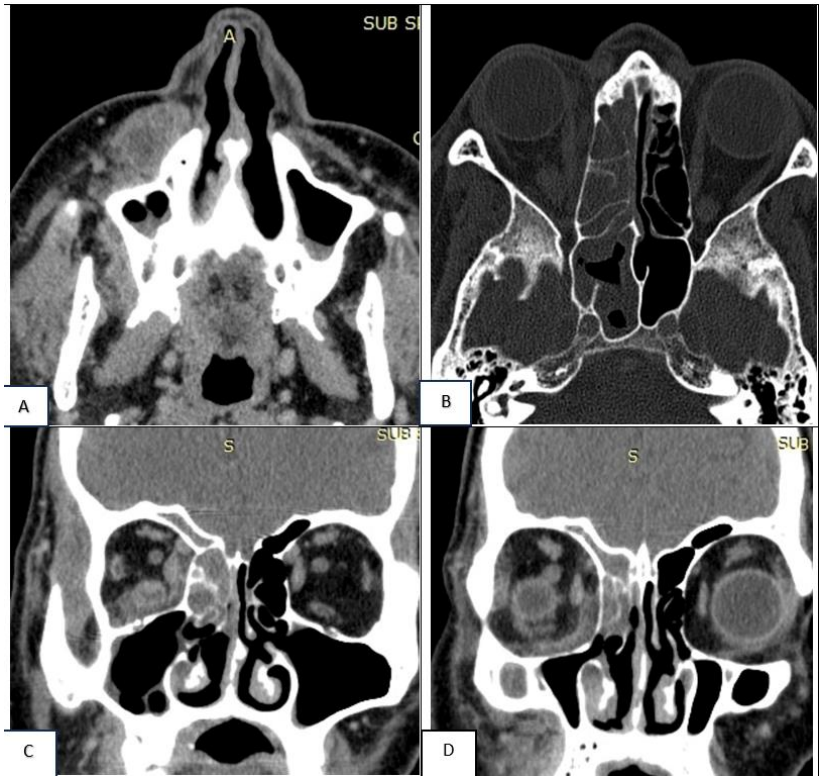

Figure 1: CT scan imaging of the paranasal sinuses shows Heterogenous soft tissue contents mass in the right buccal space (1A & 1B) with extension of the contents into the medial wall of right orbit as well as the ethmoidal air cells and the maxillary sinus (Fig 1C & 1D), suggestive of Chronic Fungal Sinusitis

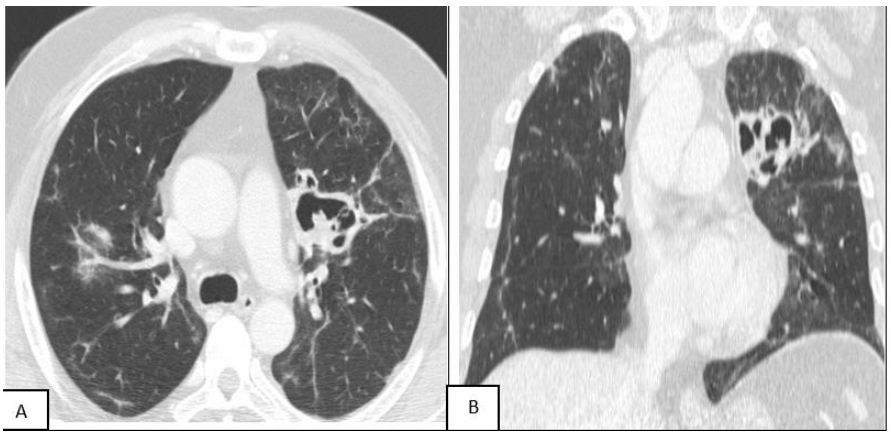

Figure 2: NCCT chest of the patient reveals bronchiectasis, cavitation and fibrosis in the right upper lobe with patchy ground glass opacities and fibrosis in all segments of lungs (2A & 2B) suggestive of post Covid19 sequalae.

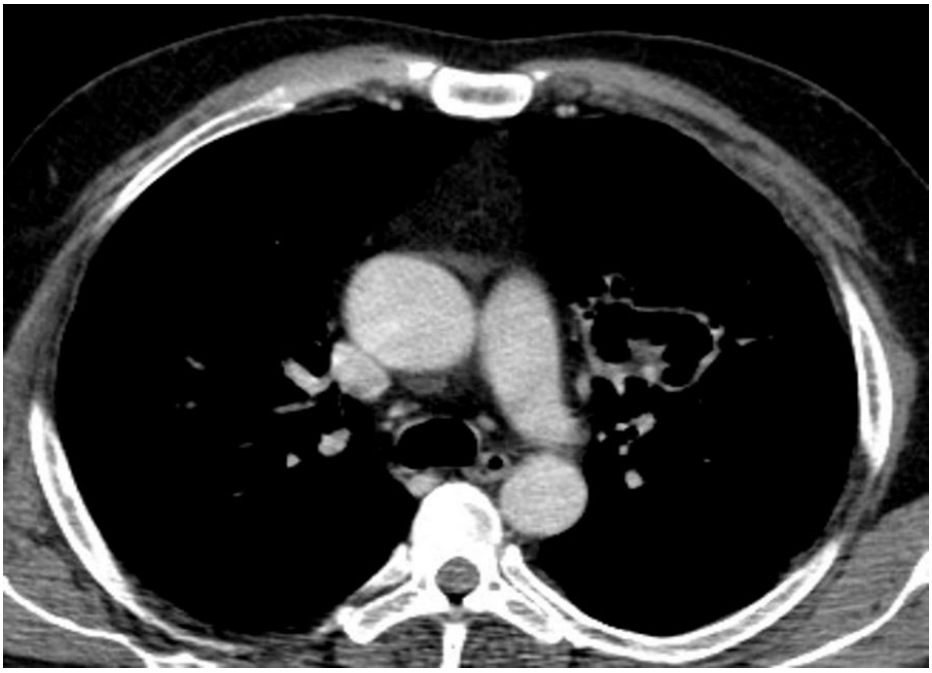

Figure 3: MRI chest of the patient reveals cavitation and fibrosis along the right upper lobe; confirming the presence of a cavitary lesion in the lung.

Autopsy of the patient was conducted the next day to ascertain the cause of the sudden onset massive hemoptysis leading to the death of the patient.

External examination of the body revealed no gross external abnormality. However, the mouth and bilateral nostrils showed presence of residual blood. The other orifices did not show presence of any abnormal discharge. No external features suggesting decomposition were noted.

A detailed internal examination of the body revealed the oropharynx, laryngopharynx and esophagus filled with blood and partially formed clots, with a distended stomach filled with partially formed clots. The thoracic cavity showed bilaterally distended, heavy lungs with their external surface appearing shiny and congested with areas of mottling present. The cut surfaces of both the lungs revealed numerous bronchiectactic cavities (Fig 4) of varying sizes with the largest measuring 1cm in its greatest dimension, along with presence of scattered areas of parenchymal bleed oozing fresh blood present bilaterally. The large airways were completely occluded with partially clotted blood. The pleural cavity also showed presence of hemorrhagic fluid. No other gross abnormality was noted in the respiratory and alimentary tract. The central nervous system (CNS), cardiovascular system, lymphoreticular system, endocrine system, soft tissue and skeletal system did not show any gross abnormalities. The gross autopsy findings were, therefore, suggestive of massive bilateral pulmonary hemorrhage with bronchiectasis.

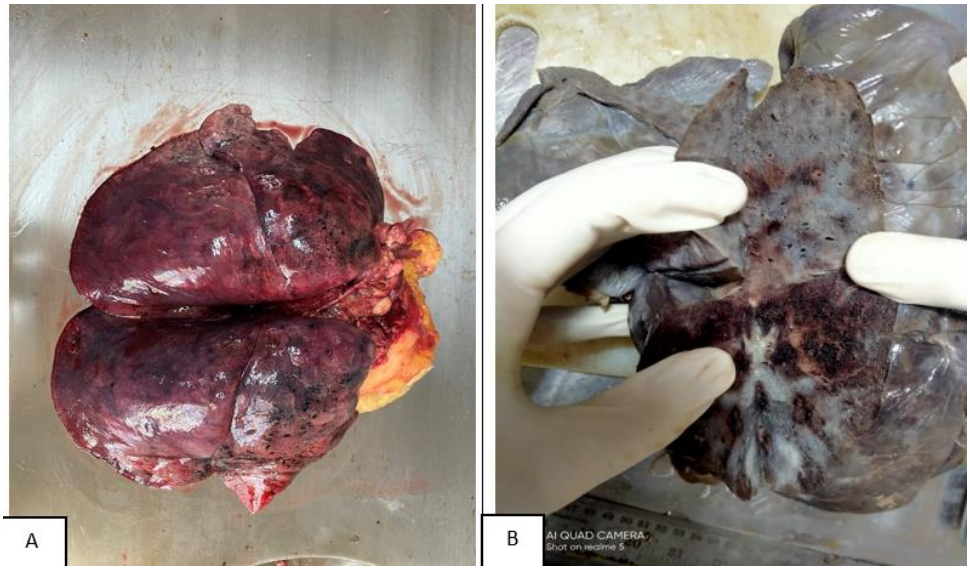

Figure 4: Gross appearance of the lungs reveal boggy, hemorrhagic lungs (4a) with presence of congestion and bronchiectactic cavities (4b) along the lung parenchyma

Microbiological cultures sampled from the CSF, pericardial fluid, peritoneal fluid, pleural fluid and heart blood did not show any growth after 48 hours of inoculation.

Microscopic evaluation of the lungs revealed extensive bronchiectasis with associated interstitial fibrosis of the lungs bilaterally, with presence of large areas of interstitial and intra-alveolar hemorrhage (Fig 5). The bronchiectactic cavities also showed presence of broad, aseptate, irregular fungal hyphae with sporangia, which appeared to invade into the adjacent lung parenchyma as well as the pulmonary vasculature (Fig 6). Additionally, the same microscopic field of the lung also showed presence of thin, septate hyphae with acute angle branching, associated with presence of fruiting bodies, indicating a dual fungal infection of mucormycosis and aspergillosis. This was confirmed on evaluation of the same tissue with special stain Grocott, which highlighted the two different types of fungal hyphae present within the lung cavities (Fig 7).

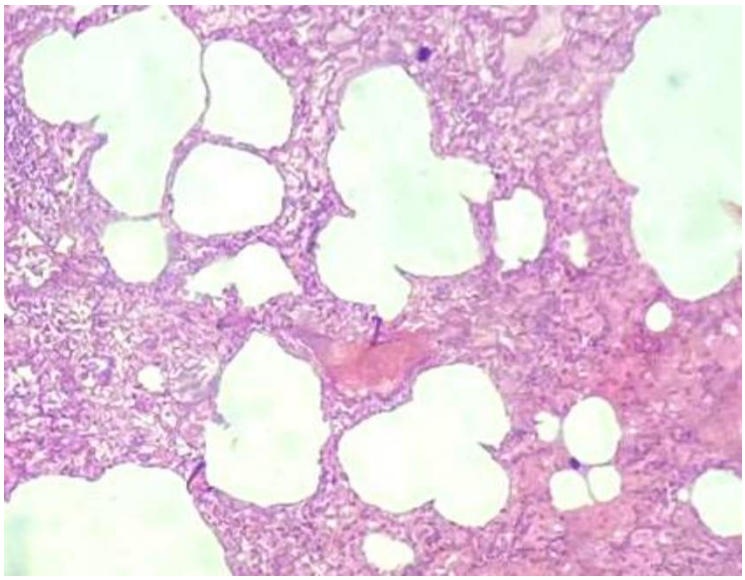

Figure 5: Microscopy of the lung reveals presence of bronchiectasis within the lung parenchyma.

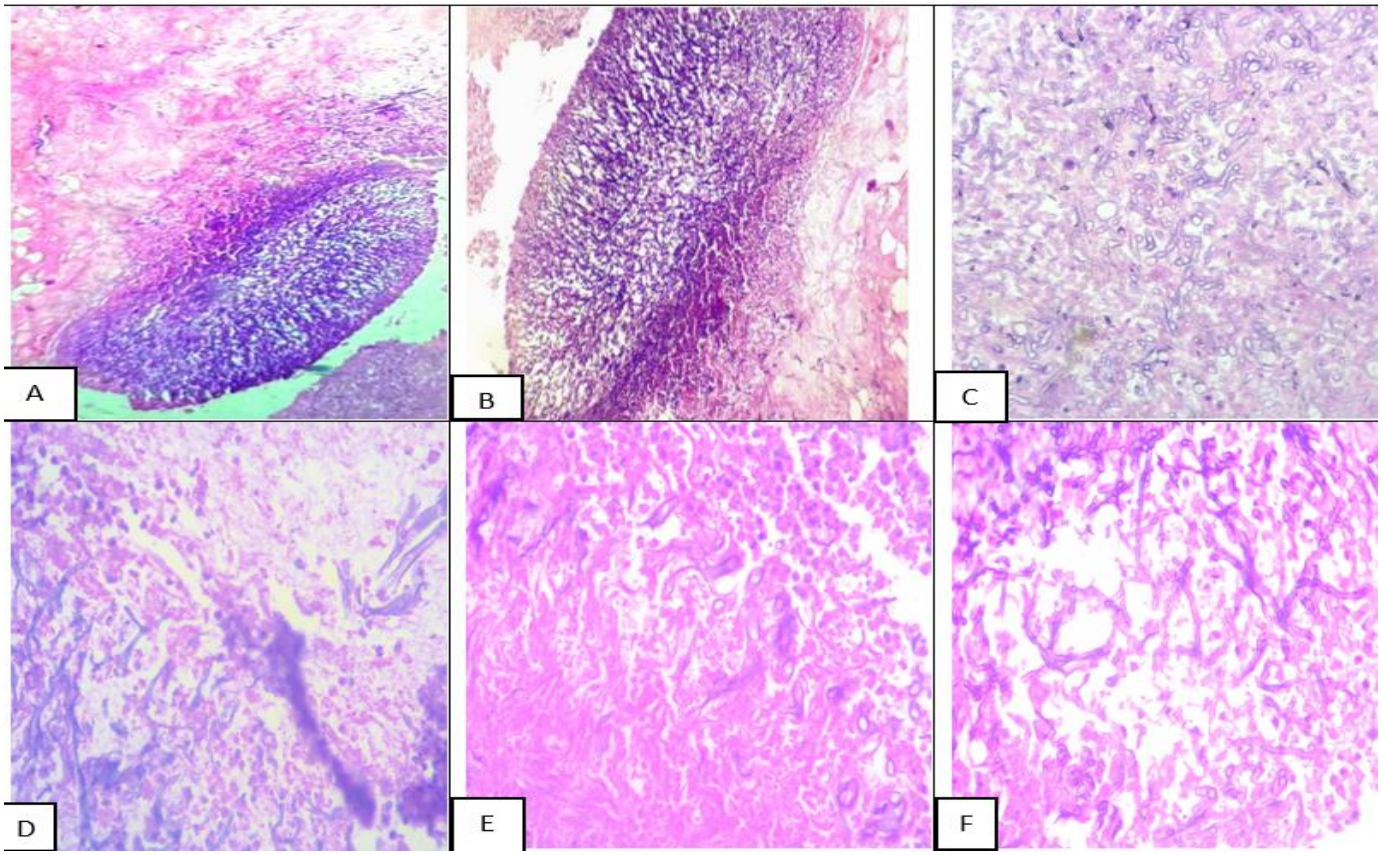

Figure 6: Microscopic evaluation of the lung parenchyma further reveals presence of fungal hyphae, forming an umbrella like lesion invading into the bronchial wall (6A – 100x, 6B – 400x). High power view (1000x) of the same reveals presence of two types of hyphae composed of thin, septate hyphae with acute angle branching, associated with presence of fruiting bodies (6C; 6F) as well as broad, aseptate, irregular fungal hyphae (6D; 6E), indicating a dual fungal infection of mucormycosis and aspergillosis.

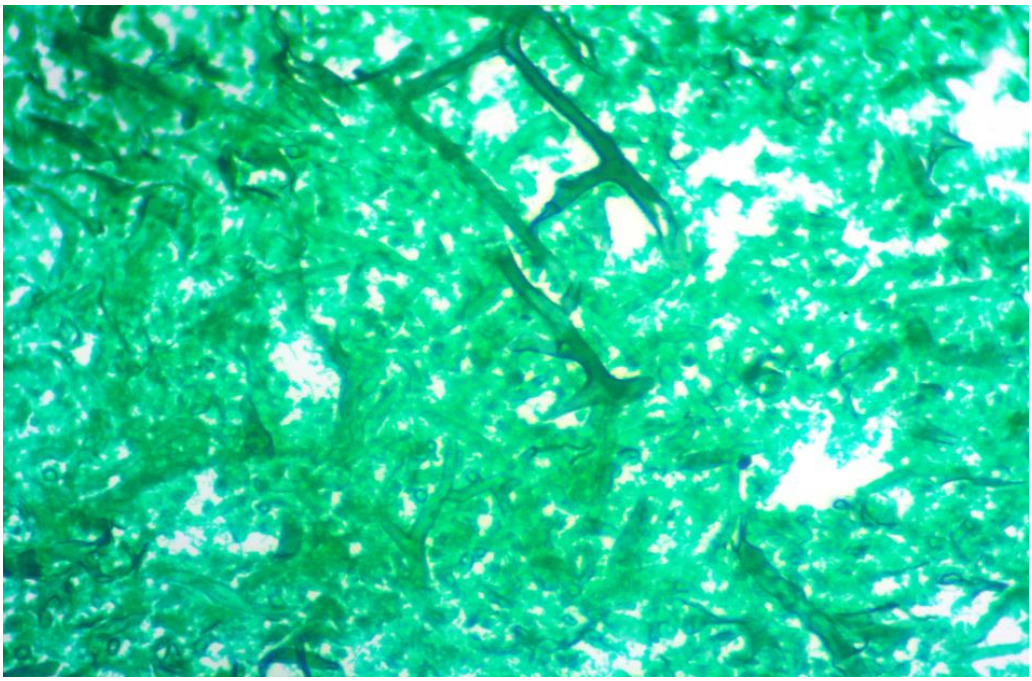

Figure 7: Grocott stain from the fungal colony shows two types of fungal hyphae composed of thin, septate hyphae with acute angle branching, associated with presence of fruiting bodies as well as broad, aseptate, irregular fungal hyphae, confirming a dual fungal infection of mucormycosis and aspergillosis.

The rest of the cardiorespiratory system showed a normal histomorphology. All the other organs sampled from the CNS, alimentary canal, genitourinary system, lymphoreticular system as well as soft tissue and skeletal system showed a normal histomorphology. The overall microscopic evaluation, therefore, indicated extensive bronchiectasis with massive interstitial and intra-alveolar bleed with disseminated mucormycosis and aspergillosis.

The overall gross and microscopic autopsy features ascertained the cause of death to be massive bilateral pulmonary hemorrhage leading to hypovolemic shock in the background of extensive bronchiectasis and bilateral pulmonary angioinvasive dual fungal infection with mucor and aspergillus in a case of recovered Covid19 pneumonia with diabetes mellitus.

Discussion

The incidence of invasive pulmonary fungal infections has increased in the recent years. And the surge of the Covid19 pandemic has only added fuel to the fire. The incidence of invasive pulmonary aspergillosis has risen since the Covid19 pandemic hit the country with its second wave, while invasive pulmonary mucormycosis is relatively known to be uncommon.

The aspergillus species of fungi are widespread and can be commonly isolated from indoor as well as outdoor environments, including hospitals. Aspergillus fumigatus is said to be the major culprit associated with pulmonary disease(2).

Invasive pulmonary aspergillosis (IPA) was first described by Rankin in 1953, in a window cleaner who presented with a thigh mass(3). It is a severe disease associated not only with immunocompromised patients but also those presenting with critical COPD or its exacerbation. Its presentation encompasses a varied clinical syndrome composed of Chronic Necrotizing Aspergillosis

(CNA), aspergilloma and Allergic Bronchopulmonary Aspergillosis (ABPA). While aspergilloma and ABPA are non-invasive forms of pulmonary aspergillosis, CNA is locally invasive and commonly accompanies patients with either mild immunodeficiency or chronic lung disease. Infection is known to occur through inhalation of the aspergillus conidia, therefore lungs are the most commonly affected organs. Less commonly, it may invade other regions such as the sinuses, the gastrointestinal tract or the skin. Skin invasion has been reported to occur through infected intravenous catheters, prolonged skin contact with adhesive tapes or secondary infection of burns(2).

Mucormycosis encompasses a group of fungal infections caused by fungi belonging to the Mucoraceae family, which are ubiquitous saprophytes(4,5). Rhizopus oryzae is the most common cause of infection from the Mucoraceae family, and is also known to have a predilection for vasoinvasion; followed by Mucor sp. and Lichthemia sp., while Cunninghamella bertholethiae appears to be the most virulent(6). These organisms have wide ecologic distribution, rapid growth and thermal tolerance, which promote human pathogenesis(7). Human infection is mainly known to occur by inhalation of the fungal spores. There is no evidence of human-to-human transmission reported so far(4,8).

Pulmonary mucormycosis is a life-threatening infection predominantly affecting immunocompromised hosts. It may develop as a result of inhalation of spores or by hematogenous or lymphatic spread. Portal of entry for Mucorales is the respiratory tract where the fungi can easily invade arteries, veins, and lymphatics and produce fatal thrombosis and infarction(4). The first case of pulmonary mucormycosis reported in 1876 by Fur Bringer(7).

The defensive mechanisms in a normal host are mediated by macrophages that inhibit germination of fungal spores and neutrophils that kill hyphal elements by oxidative bursts. Additionally, Potenza et al.(9), in their brief report of mucormycosis in hematologically compromised patients, have described the role of Mucorales-specific T cells (CD4+ and CD8+), which damage Mucorales hyphae by producing cytokines such as IL-4, IL-10, IL-17 and IFN- gamma. Immunocompromised states present with defective macrophage function, which weaken the host immune response against these opportunistic fungi. Also, Covid19 infection alters the immune system by compromising the CD4+ and CD8+ T lymphocytes, producing lymphopenia, which makes the patient highly vulnerable to opportunistic infections(10).

Additionally, Covid19 is also known to produce a hyper-inflammatory state resulting in dysfunction of numerous pro-inflammatory cytokines, dendritic cells, neutrophils and monocytes along with lymphopenia causing massive pulmonary parenchymal damage associated with pulmonary fibrosis and limited repair through enhanced pathological fibroblasts. The significant damage to the lung parenchyma, exposing the substratum, possibly worsened by the additional inflammatory immune response to the presence of fungal pathogens but also inflammatory fungal toxins, could provide the opportunity for fungi to become pathogenic. Potential increased fungal tissue adherence permits invasion of the already compromised or even repairing tissue containing high levels of fibrin/fibrinogen. Also, hypoxia, common in severe Covid19 cases, possibly modulates host immune response to fungi and has been shown to limit cytokine release from and maturation of dendritic cells stimulated with A. fumigatus. Increased platelet counts, common in Covid19 patients with severe disease, associated with vascular complications may increase risk of co-infections(11).

The high mortality rate of the pulmonary mycoses is attributed to delays in diagnosis, an unbalanced immune system and a poor host response, along with the complexity of the treatment(10). The sequalae include angioinvasion and direct tissue injury of the respiratory tract, direct extension from the lungs into the great vessels, invasion from the paranasal sinuses into the orbit and brain and hematogenous dissemination into the CNS(4).

Our case presented with direct tissue injury to the respiratory tract in the form of bronchial wall invasion as well as angioinvasion with an underlying diabetes mellitus.

Clinically, the patient may commonly present with non-specific symptoms such as fever, dyspnea, cough and pleuritic chest pain. Other uncommon clinical features include progressive subcutaneous emphysema, Pancoast's syndrome, Horner's syndrome and bronchial perforation. Fungal angioinvasion results in thrombosis, with consequent infarction and necrosis of the lung parenchyma, causing cavitation which may manifest as hemoptysis, which often takes a fatal turn if a major blood vessel is involved(4). Although there is no recent data available in literature, a review of 255 patients of pulmonary mucormycosis done by Tedder et al in 1994 has documented hemoptysis as a presenting feature in 16% patients while it was fatal in 13% patients(12). Additionally, rupture of an involved vessel into the diseased bronchus leads to massive hemorrhage within the large airways, which results in asphyxia(5). Although IPA is one of the most common causes of hemoptysis in neutropenic patients(2), Hou et al(13), in their study of IPA in 690 patients found cough to be the most common presenting symptom.

Radiologically, CT scan and CT combined with high resolution imaging (HRCT) is considered the modality of choice for the evaluation and determining the extent of respiratory involvement by mucor and aspergillus respectively.

Table 1 differentiates the clinical and radiological features between both the fungi (1).

Table 1: Difference between the clinical and radiological features of Pulmonary Aspergillosis and Mucormycosis.

Features	**Pulmonary Aspergillosis**	**Pulmonary Mucormycosis**
1. Age(1)	5^{th} –6^{th} decade	5^{th} –6^{th} decade
2. Gender(1)	Male predominant	Male predominant
3. Lifestyle(1,2)	More common in those suffering from COPD	More common in smokers
4. Involvement of other sites:(1)		
• Paranasal sinuses	+	+++
• Central Nervous System	+	+++
5. Risk factors:(1)		
• Diabetes	++	+++
• Chronic Lung disease	+++	+
• Hematological disease	+	+++
• Neutropenia	+	+++
• Systemic Corticosteroid therapy	+++	+
• Post influenza	+++	-
• Post SARS Cov2 infection	++++	+
6. Radiological features:(1)		
• Consolidation	+	++
• Cavitation	+	++
• Halo Sign	++	+
• Reverse Halo sign	+	++
7. Fungal culture positivity(1)	++	+
8. Drug of choice(1)	Voriconazole	Amphotericin B
9. Mortality(15,16)	Approx 60%	Approx 80%

Diagnosis of pulmonary fungal infection is based on histopathology and direct microscopy along with culture of various clinical

specimens. Sputum and BAL cytology are often unpredictable and may be negative. Sputum in such patients may be either white, yellow, blood tinged or even grossly bloody, and is often misleading as a diagnostic modality. Histopathologically, mucor appears as broad, aseptate hyphae with right angle branching and can be distinguished from Aspergillus which have regular and septate hyphae with an acute angle branching(4). Apart from Hematoxylin and Eosin (H&E) stains, the fungi also stain well with Grocott-Gomori methenamine silver stain(2,6).

Recently, more reliable diagnostic modalities have been introduced for patients with suspected IPA, which have their foundation in detection of the Aspergillus antigens in body fluids using ELISA, double-sandwich ELISA and PCR with improved sensitivity and specificity(2,14).

Management of both the pulmonary fungi differs in its modalities.

Management of pulmonary mucormycosis includes medical as well as surgical intervention. The European Confederation of Medical Mycology Mucormycosis Guidelines strongly suggest an early surgical treatment to remove infected tissue. This can either be done through local debridement or a complete resection, along with a systemic antifungal treatment(14). Liposomal Amphotericin B remains the mainstay of medical management.

Management of IPA is still a challenge inspite of introduction of newer antifungal agents and the high mortality rates are a harsh proof. Therapy should be considered as soon as there is a clinical suspicion of IPA, and while a workup is under way.

Table 2 mentions the medical management plan of various types of pulmonary aspergillosis.

Table 2: Management plan of various types of pulmonary aspergillosis.

Pulmonary Aspergillosis	**1st line therapy**	**2nd line therapy**
1. IPA	Voriconazole	Alternative therapy: liposomal amphotericin B Continuation therapy: voriconazole or itraconazole Salvage therapy: Echinocandin or Posaconazole
2. Chronic Necrotizing Aspergillosis	Voriconazole	Alternative therapy: Itraconazole Severe cases: Intravenous voriconazole or liposomal amphotericin B Consider surgical resection
3. Aspergilloma	Observation	Bronchial artery embolization Surgical resection Consider itraconazole
4. Allergic bronchopulmonary aspergillosis	Corticosteroids	Itraconazole or voriconazole as steroid-sparing agents

Surgical resection has generally a limited role in the management of patients with IPA, but it becomes important in cases with invasion of bone, burn wounds, epidural abscesses and vitreal disease(2).

A detailed literature review of dual pulmonary mycosis occurring in post covid patients revealed only three such cases reported previously, all of which were diagnosed clinically. There hasn't been a previous report of autopsy diagnosis of a dual invasive pulmonary fungal infection in a post covid19 patient reported in literature. Table 3 gives the details of the previously reported cases of dual invasive pulmonary fungal infections reported in literature till date.

Table 3: Cases of dual/mixed pulmonary fungal infections reported in literature till date.

Author	Country/Year	Pt age	Pt sex	Comorbidity	Covid19 status	Radiology	Isolated fungi	Diagnosis on	Patient outcome
Khan et al(17)	USA 2020	44	Female	Diabetes	Active	Cavitation	Mucor, Aspergillus and Candida	Tracheal aspirate and BAL	Died
Johnson et al(18)	USA 2021	79	Male	Diabetes Hypertension	Recovered	Cavitation	Mucor, Aspergillus	BAL	Was alive (on ventilator support) at the time of publication
Bellanger et al(19)	France 2021	77	Male	Lymphoma (Autologous HCT)	Recovered	NR	Mucor, Aspergillus	Tracheal aspirate and BAL	Died
Rai et al(1)	India 2021	56	Male	Diabetes	Recovered	Cavitation with Reverse Halo Sign	Mucor, Aspergillus	BAL fluid-PC	Died
Present case	India 2023	51	Male	Diabetes	Recovered	Bronchiectasis, cavitation and fibrosis in the right upper lobe with patchy ground glass opacities and fibrosis in all segments of lungs	Mucor, Aspergillus	Autopsy – lung cavities	Died

Conclusion

Invasive pulmonary mycosis is a fatal infection if not diagnosed and managed on time. SARS-CoV-2 infection is known to cause severe immunosuppression that compromises the host response and increases the risk of opportunistic infections, including those caused by molds and aspergillus leading to higher risk of negative outcomes in the case of delayed diagnosis and inadequate treatment. Strategies for early detection of these infections that could be adopted include a high suspicion in all post Covid19 patients presenting with even minor symptoms, an early radiological and histopathological intervention in such patients, and administration of prompt aggressive medical and surgical management which may eventually turn out significant and may improve the patient outcome.

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