CASE REPORT

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Covid-19 Associated Fungal Pneumonia: A Case Series

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Abstract

Fungal pneumonias are difficult to diagnose and are likely underestimated. Aspergillus and Candida infections in COVID-19 patients will require early detection by a comprehensive diagnostic intervention {histopathology, direct microscopic examination, culture, (1,3)-β D-glucan, galactomannan, and PCR-based assays} to ensure effective treatments. Particularly in the setting of COVID-19, where the clinical picture, and radiological findings of fungal pneumonia resemble those of severe COVID-19; blood tests lack sensitivity and, most importantly, sampling of the primary site of infection is rarely performed, due to the risk of COVID-19 transmission through bronchoscopy with bronchoalveolar lavage. We performed Fiber-optic bronchoscopy and collected samples in all 5 cases of this series, and confirmed the diagnosis of CAPA which made it possible to start treatment timely.

Key words: Covid-19, fungal pneumonia, aspergillosis, BAL galactomanan, corticosteroids.

Introduction

Invasive fungal infections have been increasingly reported in patients with coronavirus disease-2019 (COVID-19), primarily invasive candidiasis and pulmonary aspergillosis[1,2].

Aspergillosis, like mucormycosis, has classically been seen primarily in immunocompromised patients; however, it has been increasingly observed in patients admitted to intensive care units, patients with severe influenza, and now COVID-19, termed COVID associated pulmonary aspergillosis (CAPA)[3].

These infections may reflect impaired mucosal barrier and a dysfunctional immune response in severe viral infections and the use of immunosuppressive medications like corticosteroids and interleukin (IL-6) inhibitors like tocilizumab[4,5].

Of note, CAPA incidence rates reported to date have varied widely, ranging from 4%[6] to 35%[7] in mechanically ventilated critically ill patients. Factors that may contribute to the differing incidence rates are 3-fold. First, fungal diseases and specifically CAPA are difficult to diagnose and are likely underestimated, particularly in the setting of COVID-19 associated ARDS, where the clinical picture and radiological findings of CAPA resemble those of severe COVID-19[8,9]; blood tests lack sensitivity due to the primarily airway invasive growth of aspergillus in nonneutropenic patients[10]; and, most importantly, sampling of the primary site of infection is rarely performed, due to the risk of COVID-19 transmission through bronchoscopies with bronchoalveolar lavage (BAL) or autopsies (due to the overlap of imaging findings between CAPA and COVID-19, post-mortem fine needle biopsies alone may not be sufficient to detect focal CAPA[11], which are both aerosol-creating procedures[12]. Random diagnosis of CAPA, without specifically and creatively searching for it, is therefore virtually impossible in this setting, and diagnosis requires specific expertise and awareness, which is rare given that fungi are neglected pathogens[13,14].

We found 5 cases of post-covid associated pulmonary aspergillosis.

Case 1

A 67-year-old male, a coal mine worker and chronic smoker with no other associated comorbid condition, tested positive for COVID-19 by RT-PCR on 10/5/21 and tested negative on 27/5/21. During hospital stay he was given symptomatic treatment for COVID-19 alongwith oral steroids. Patient was requiring oxygen support at 5 l/min. CT scan of the patient was done on 27/5/21 which showed interstitial, peripheral pleural and interlobular septal thickening. Patchy areas of ground glass opacification were noted. Para-septal and centriacinar emphysematous changes were seen in both lungs.

Fiber-optic bronchoscopy (FOB) was done on 27/5/21 and it came out to be positive for fungal stain with occasional budding yeast cells in broncho-alveolar lavage (BAL) fluid. Fungal culture was positive for *Aspergillus flavus*, *Candida tropicalis* and mucor species in BAL fluid. Repeat CT scan was done which showed area of consolidation with internal cavity communicating with bronchi in B/L lower lobes. CT severity index was 14/25. Repeat FOB was done on 7/6/21

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and samples were sent for KOH stain, fungal culture and sensitivity, pyogenic culture and sensitivity, galactomannan antigen, AFB stain, and CBNAAT. Results were as follows: BAL KOH: negative; BAL galactomannan: negative; BAL AFB stain: negative; BAL CBNAAT: negative; BAL fungal culture: *Candida tropicalis*. Results of his blood investigations were: Total leucocyte count: 15,860/microlitre with 89.1% neutrophils, 7.20% lymphocytes and 3% monocytes; haemoglobin: 11 gm/dl; blood urea: 42 mg/dl; serum creatinine: 0.60 mg/dl; total bilirubin: 0.30 mg/dl; aspartate transaminase: 30 U/L; alanine transaminase: 44 U/L; serum sodium: 137 meq/l; serum potassium: 4.20 meq/l; prothrombin time: 19.5 sec; INR: 1.46; APTT: 33.6; D-dimer: 2012; C-reactive protein: 2.4 ng/ml; procalcitonin: 0.11 ng/ml; serum galactomannan antigen: positive; serum β- d-glucan: positive (574 pg/ml); HbA_1c: 6.6; interleukin 6: 29.46 pg/ml; HIV, HBs antigen, HCV: negative; serum ferritin: 593.6ng/ml. Based on clinical, radiological and microbiological investigations, diagnosis of covid-associated pulmonary mucormycosis with covid-associated pulmonary aspergillosis with pneumoconiosis with chronic obstructive pulmonary disease was made and patient was started on broad spectrum antibiotics alongwith injection amphotericin B and symptomatic treatment. He was discharged on 21/6/21 on oral posaconazole for 14 days. Patient was reviewed on follow-up where he showed clinical and radiological improvement. He was advised to continue with inhaled medications.

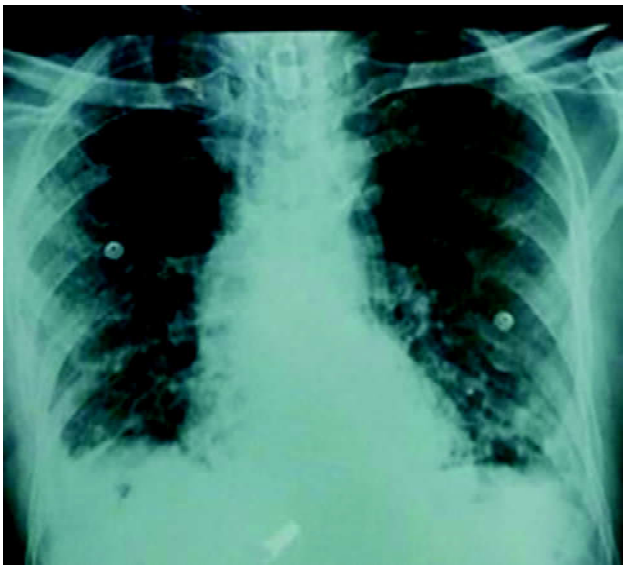

Fig. 1: *Chest X-ray.*

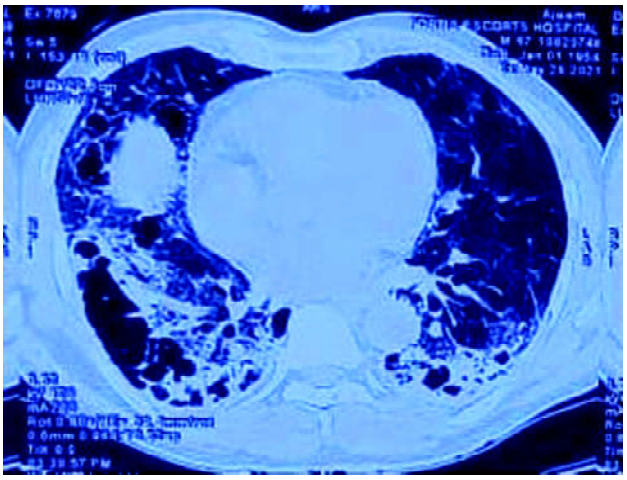

Fig. 2: *CT chest.*

Case 2

A 45-year-old male, sweet maker, nonsmoker, with no history of any chronic illness, tested positive for COVID-19 by RT-PCR on 29/4/21 and tested negative on 27/5/21. Patient was initially requiring high flow oxygen support. He was given symptomatic treatment for COVID-19 along with steroids and injection remdesivir. CT scan was done on 29/05/21 which showed multifocal areas of ground glass attenuation with interstitial thickening, cavitatory nodules, and fibroatelectatic lesions in both lung fields with subcentrimetric mediastinal lymphadenopathy. There was improvement in his oxygen requirement to 2 l/min. Fiberoptic bronchoscopy was done on 4/06/21. BAL for fungal stain showed septate hyphae, acute angle with branching. No yeast cells/psedo-hyphae seen. BAL AFB was negative. A repeat CT scan was done on 4/06/21 which showed resolution of interstitial thickening and fibroatelectatic lesions, but there was formation of a cavity with air crescent sign in the right upper lobe, and another small cavity in the left lower lobe. Repeat fiber-optic bronchoscopy was done on 9/06/21 and BAL fluid was collected from the right upper lobe and posterior basal segment of the left lower lobe.

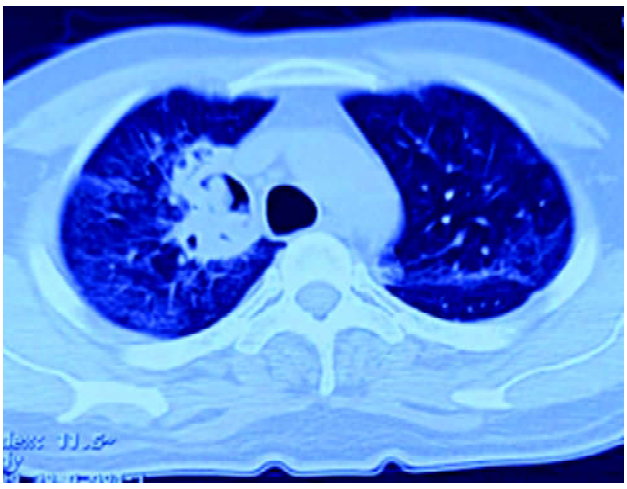

Fig. 3: *CT chest.*

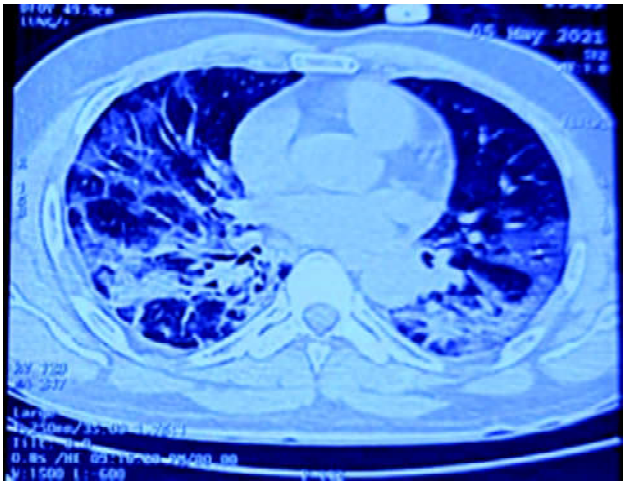

Fig. 4: *CT chest.*

BAL CBNAAT was also positive with very low *Mycobacterium tuberculosis* load and rifampicin resistance was absent. BAL KOH stain: negative; BAL galactomannan: positive; BAL AFB stain: negative; BAL fungal culture: no growth after 3 weeks of incubation. Results of his blood investigations were: total leucocyte count: 6,100 /micro l; haemoglobin: 10.6 gm/dl; blood urea: 16 mg/dl; serum creatinine: 0.60 mg/dl; total bilirubin: 1.04 mg/dl; aspartate transaminase: 42 U/L; alanine transaminase: 44 U/L; serum sodium: 131 meq/l; serum potassium: 4.20 meq/l; prothrombin time: 13.1 sec; INR: 0.97; APTT: 28.5; D-dimer: 1,374 ng/ml; C-reactive protein: 2.4 ng/ml; procalcitonin: 0.09 ng/ml; serum galactomannan antigen: positive; HbA_1c: 8.4; lactate dehydrogenase: 790 U/L; interleukin-6: 55.5 pg/ml; HIV, HBs antigen, HCV: negative; serum ferritin: 508 ng/ml. Based on clinical, radiological, and microbiological features, a diagnosis of covid-associated pulmonary aspergillosis with new onset diabetes mellitus with pulmonary tuberculosis was made and the patient was started on tablet Voriconazole 200 mg BD, oral hypoglycaemic drugs, and antitubercular treatment under DOTS category 1. Patient was discharged on the same treatment; and when reviewed on follow-up after 10 days showed radiological resolution.

Case 3

A 68-year-old male who was apparently well 3 months back when he started having episodes of fever for which he took medication elsewhere for 20 - 25 days. RTPCR for Covid-19 was done at that time which was negative. However, his son and daughter-in-law tested positive for Covid-19 around the same time. After around 1.5 months, patient started having cough with copious amount of expectoration, yellow in colour, mucoid in consistency and sometimes blood tinged. He started having episodes of shortness of breath on climbing upstairs, and generalised weakness. For these complaints he was hospitalised, and his routine blood investigation were done along with CT Thorax. CT scan showed a regular area of consolidation with central breakdown/cavity formation in the anterior basal segment of the left lower lobe. A similar smaller area of peribronchovascular sub pleural consolidation with a central area of breakdown are noted in bilateral upper lobes. Associated parenchymal bands changes were also seen. Few defined small nodular opacities were seen in bilateral upper lobes. Multiple variable sized discrete mediastinal and hilar lymph nodes were also seen.

Following CT scan, fiber-optic bronchoscopy was done and broncho-alveolar lavage fluid was sent for investigation and results showed fungal KOH stain: negative; fungal culture: *Aspergillus*; gene expert for *Mycobacterium tuberculosis*: negative; AFB stain: negative; pyogenic culture showed no growth. Patient was given injection amoxycillin/clavulanate

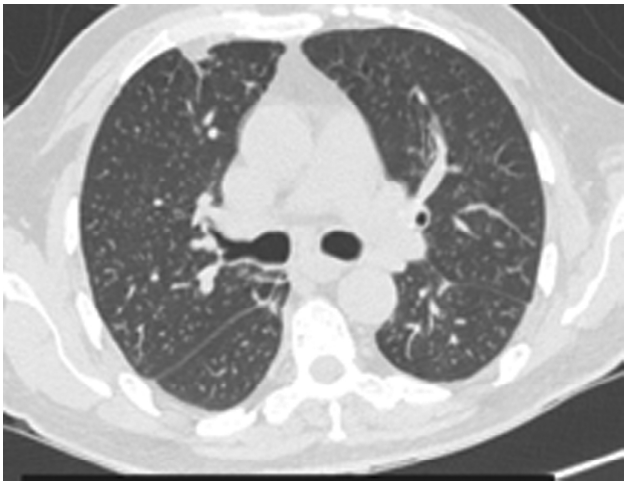

Fig. 5: *CT chest.*

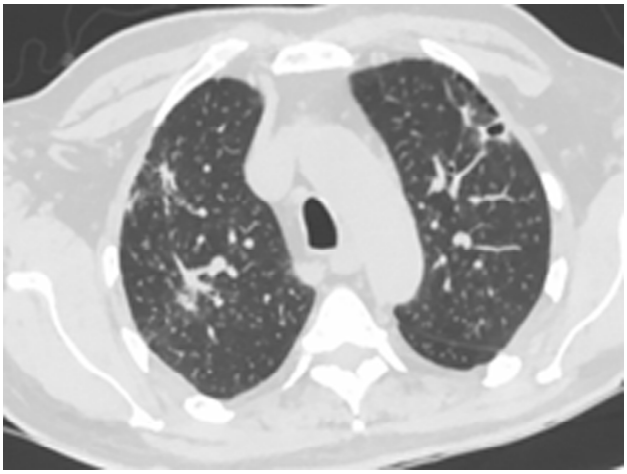

Fig. 6: *CT Chest.*

for 5 days along with other symptomatic treatment. He was a chronic Bidi smoker and used to smoke 24 BD per day for around last 40 years. He was a known case of type 2 diabetes mellitus for last 4 years on and was on oral hypoglycaemic drugs for the same. He was a water supplier by occupation for around 40 years and was vaccinated with covid vaccine single dose in March 2021. Upon admission, his routine blood investigations were done and results were – haemoglobin: 10.20; TLC: 5,500; platelets 1,64,000; blood urea: 34; serum creatinine: 8.70; total bilirubin: 1.35; SGPT: 31; HbA_1c: 8.4; prothrombin time: 17.10 seconds; INR: 1.28; aPTT: 30.90s; procal: 0.05 mg per ml; covid antibodies were positive; total 643; IgG: 16. Repeat CT scan done on 2nd July 2021 showed interstitial pneumonia with CT score of 7/25. A repeat fiber-optic bronchoscopy was done and broncho-alveolar lavage was sent for investigation and results were BAL KOH stain: negative; BAL CBNAAT for *Mycobacterium tuberculosis:* MTB detected in traces; rifampicin resistance: indeterminate; pyogenic culture sensitivity: *Klebsiella pneumonia* which was sensitive to amoxicillin-clavulanate and supportive drugs. Diagnosis of covid-19 pulmonary mucormycosis with type 2 diabetes mellitus with pulmonary tuberculosis was made and patient was started on injection meropenem 500 mg TDS, tablet ciprofloxacin 500 mg BD, injection amphotericin B 5 mg per kg body weight, insulin regular and basal along with other symptomatic treatment. Patient was followed-up in OPD after discharge where he showed improvement.

Case 4

A 31-year-old female started having episodes of fever since 3 months for which she took some medication elsewhere and the fever subsided after 6 days. There was no history of cough, expectoration or shortness of breath associated with fever. After around one week of no fever, she started having complaint of bilateral chest pain more on left then right, non radiating to other sites, relieved for some time by taking some injectable medication from a local practitioner in the village. She also started having shortness of breath which was gradual in onset and progressive in nature. Her oxygen saturation on room air was between 80 to 85% during that period and she was put on home oxygen cylinder therapy of 2 - 3 litre per minute around 15 to 16 hours per day for around 10 days. After 10 days, her saturation improved and she was maintaining saturation of 95% on room air. CT scan of the patient was done at that time which showed multifocal variable-sized ground glass opacities with interlobular septal thickening and fibrosis involving both lungs consistent with atypical viral pneumonia with CORADS score of 6 and CT severity index of 19/25.

However, the RTPCR for covid-19 was negative at the same time. She also started having cough with expectoration aggravated on lying down and while talking. She was diagnosed as a case of type 2 diabetes mellitus 6 month back but was not on any regular medication for the same. She was also a known case of hypothyroidism for the last 6 years for which she was on tablet thyroxine. Patient presented with increased frequency of stools, pain abdomen, weakness and cough on 23rd June 2021 in a private hospital, where her random blood sugar was found to be 36 mg/dl and she was therefore admitted for further management. Routine blood investigation were done along with chest X-ray and CT thorax on 24th June 2021 which showed diffuse fibrointerstitial thickening with patchy ground glass attenuation and sub-pleural atelectatic bands, multiple random ground glass nodules in the right lung field with few of them showing tree-in-bud appearance, two thick-walled cavitatory lesions along anterior aspect of left upper lobe, basal segment of left lower lobe with thick enhancing pleura. Fiber-optic bronchoscopy was done on 25th June 2021 and results were – Gene expert for *Mycobacterium tuberculosis* was negative; ZN staining: negative; GMS stain: positive for fungal hyphae; BAL pyogenic culture: no growth; BAL galactomannan: positive; BAL AFB culture: negative;

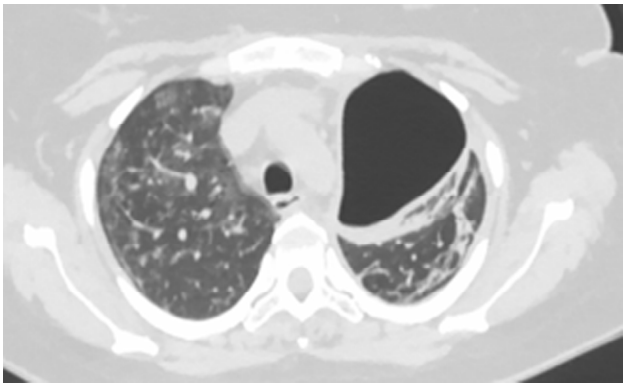

Fig. 7: *CT chest.*

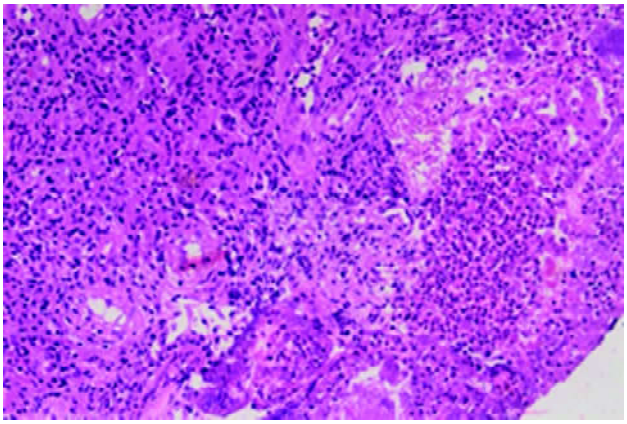

Fig. 8: *Endobronchial biopsy: HPE showing broad septate fungal hyphae in necrotic tissue bits.*

endobronchial biopsy: positive for septate branching hyphae showing acute angle branching with presence of you non-septate broad hyphae, suggestive of pulmonary aspergillosis with mucormycosis. CTPA was done on 26 June 2021 which showed saddle-shaped pulmonary thrombus involving right and left branches of main pulmonary artery, 80 to 90% occlusion of left main pulmonary artery and 20 - 30% occlusion of right main pulmonary artery. Thrombus is seen extending into the right descending lower arteries and segmental branches. Few small filling defects also extending into right descending lower arteries and segmental branches. Few linear filling defects extending into right upper lobe pulmonary artery. On the left side there was eccentric filling defect in the pulmonary artery branches supplying the anterior basal segment of the left lower lobe. MPA: 2.1 cm, RPA: 1.5 cm; LPA 1.3 cm. Colour Doppler of bilateral lower limbs and upper limbs was normal. Echocardiography showed tachycardia, PA prominent, LVEF: 55 to 60%, diastolic relaxation abnormality grade 1; and NT-Pro BNP was raised: 157 pg/ ml. Result of coagulation profile was normal factor 8 functional: 25%; cardiolipin antibody IgG: 8.07 GPL; cardiolipin antibody IgM: 13.2 MPL; homocysteine quantitative: 6.25 micro mol per litre; antithrombin functional: 82.00%; protein C functional: 118%; proteins free antigen: 96%; CRP: 50.4 mg/dl; procalcitonin: 0.77 mg/ ml; TSH: 0.321; sputum for AFB: negative; pyogenic culture: no growth; fungal sputum stain: budding yeast cells with pseudohyphae. Patient was not vaccinated for covid-19. Upon admission routine blood investigations were done and results were – TLC: 23,150; haemoglobin: 10.1; platelet count: 389000; blood urea: 16; serum creatinine: 2.8; total bilirubin: 1.43; SGOT: 20; SGPT: 20; sodium: 136; potassium: 3.9; D-dimer: 1,226 mg/dl; PT: 19.9; INR: 1.49; APTT: 33.0; Covid antibodies were positive: 8.16. Repeat chest X-ray and CT scan were done which showed bilateral interstitial pneumonia with CT severity score of 17/25, but RT PCR for Covid-19 was still negative. Repeat fiberoptic bronchoscopy was done and BAL fluid was sent for investigation. Results of BAL – fungal KOH stain: negative; pyogenic culture showed *Klebsiella pneumoniae*; CBNAAT was negative; Endobronchial biopsy was positive. On the basis of clinical, radiological, and micro biological reports, the diagnosis of Covid-19 associated pulmonary mucormycosis with acute pulmonary embolism with type 2 diabetes mellitus with hypothyroidism was made. Treatment was started with broad-spectrum antibiotics, injection enoxaparin, oral hypoglycaemic drugs, injection amphotericin B along with symptomatic treatment.

Case 5

A 60-year-old female, a known case of diabetes for the last 3 years, presented to us on 28/06/21 for swelling of face (Rt > Lt), right eye ptosis, and deviation of mouth (left) were present. She was evaluated for mucomycosis and nasal endoscopy and biopsy was done on 30/06/21. KOH: Broad aseptate hyphae and septate hyphae seen; fungal culture: *Aspergillus fumigatus* isolated in culture. Impresssion: k/c/o mucormycosis. 30/06/21 (CECT chest) Impression: F/S/O Nectrotising consolidation with cavitation and centrilobar nodules surrounding it and mediastinal lyphadenopathy as described – likely infective aetiology – ? Tubercular. The CEMRI study reveals mucosal thickening, heterogenous enhancement of B/L maxillary, B/L ethmoid, Rt frontal and B/L sphenoid sinuses with extra and intracranial involvement of right optic nerve infarct and intracranial involvement (dorsal enhancement, cavernous sinus involvement, left ICA partial thrombosis and an acute lacunar right frontal infarct) as described. 20/07/21 – HBsAg: NR; Anti-HCV Ab: NR; HIV I and II: NR.

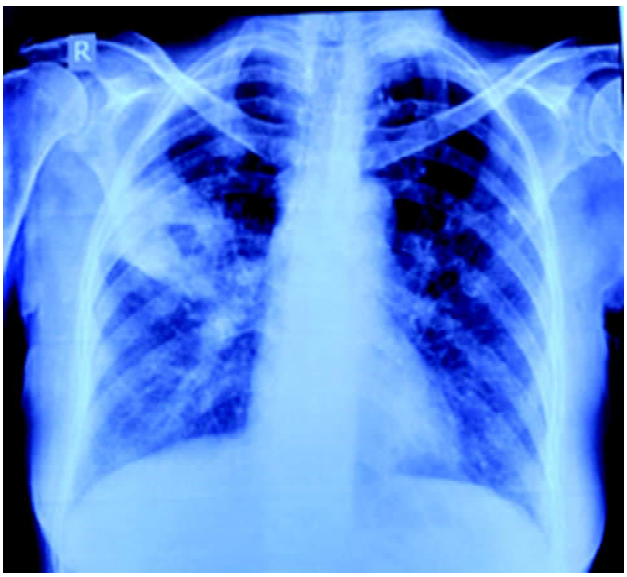

Fig. 9: *Chest X-ray.*

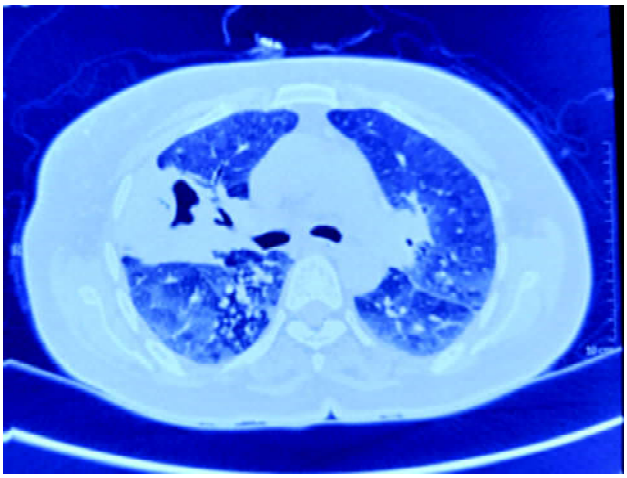

Fig. 10: *CT chest.*

CBNAAT (25/07/2021) – Mtb detected (low); no Rif resistance detected. 28/07/2021 – Fungal Culture (KOH): No fungal elements seen. 02/08/2021 – Blood urea: 21.0 mg/dl; S. creatinine: 0.50 mg/dl; Magnesium: 1.2 mg/dl; Na: 137 mg/dl; K: 2.7 mg/dl; Hb: 9.7 gm/dl; TLC: 3,200/UL; 28/07/21- D-Dimer: 1,384 mg/ml; 28/07/21 – Bronchoscopy Impression: Infective?? On the basis of clinical, radiological and micro-biological reports, the diagnosis of Covid-19 associated Rhino-orbital mucormycosis with pulmonary aspergillosis with diabetes type 2 was made.

Inj. Amphotericin B was started and total Amphotericin B given: 4,800 mg. Patient was discharged and followed up in OPD.

Discussion

Clinicians are alert to the possibility of bacterial co-infection as a complication of lower respiratory tract viral infection; for example, a recent review found that 72% of patients with COVID-19 received antimicrobial therapy. However, the risk of fungal co-infection, in particular COVID-19 associated pulmonary aspergillosis (CAPA), remains underappreciated. For secondary invasive pulmonary aspergillosis in influenza patients, the median time to diagnosis is between 5 and 10 days after ICU admission[23].

Fungal co-infections associated with global COVID-19 might be missed or misdiagnosed. Further, as a life-threatening infectious disease, COVID-19 patients showed overexpression of inflammatory cytokines, and impaired cell-mediated immune response with decreased CD4 and CD8 T-cell counts, indicating its susceptibility to fungal co-infection. The main fungal pathogens for fungal co-infections in severe COVID-19 patients are *Aspergillus* and *Candida*. Other infrequent opportunistic pathogenic fungi caused lung infections also need to be considered, such as *Mucor* and *Cryptococcus*[22].

The radiological differentiation between IPA and COVID-19 is often complex. For instance, ground-glass opacities and dense consolidation are often found in COVID-19 and IPA. CT may help distinguish between "typical" COVID pneumonia (bilateral peripheral ground glass opacity which may be rounded or associated with intralobular septal thickening giving a crazy paving pattern) and "typical" invasive pulmonary aspergillosis (nodular consolidation with a ground glass halo)[21].

The consensus case definition of IAPA/CAPA from Verweij and colleagues were adapted for clinical decision making before the 2020 ECMM/ISHAM consensus criteria[14]. In patients with no underlying immunosuppression, severe SARS-CoV-2-related pneumonia seems at low risk of invasive fungal secondary infection, especially aspergillosis[15]. Among our patients, 4 out of 5 were diabetic. One of them was a new onset diabetic. Prolonged use of corticosteroids is known to be a risk factor for invasive fungal disease[16]. 2 out of 5 were on steroids during covid treatment, while 3 patients had not produced any documents in support of steroid therapy. However, the numbers are too small to determine whether it could be attributed to STEROID SARS-CoV-2 therapy. In diagnosing CAPA, little was known on the performance of serum GM and the 'panfungal' marker BDG. Serum GM testing in neutropenic non-CAPA patients with proven invasive aspergillosis has been shown to have a sensitivity of around 70%, and 25% in the non-neutropenic host[17]. 4 patients out of 5 were s. galactomannan positive. 3 patients out of 5 were BAL galactomannan positive, 1 was negative. CAPA patients are generally non-neutropenic and sensitivity of serum GM reported in these patients are similarly low (15.6% - 21%)[18,19]. Whilst BDG testing is nonspecific, its sensitivity in the ICU population for invasive fungal disease has been shown to be high (88%)[20]. 2 patients out of 5 were s. beta d glucan positive. BAL CBNAAT was positive for 3 patients and negative for 2 patients. BAL for KOH mount was negative for all the patients while fungal culture

Table I: Comparision of Investigation reports of all cases.

Lab investigations	Case 1	Case 2	Case 3	Case 4	Case 5
Presentation after covid test positive	54	30	*	*	*
S. Galactomanan	+	+	+	+	*
BAL Galactomanan	-	+	+	+	*
S. Beta D glucan	+	+	*	*	*
BAL CBNAAT	-	+	+	-	+
BAL Fungal culture	*Candida tropicalis*	-	*	*	*Aspergillus fumigatus*
BAL KOH mount	-	-	-	-	-
Endobronchial biopsy	*	*	*	+	*
Pyogenic culture	*Klebsiella pneumonia*	*	*Klebsiella pneumonia*	*Klebsiella pneumonia*	
Diabetes mellitus	-	New onset	Type 2 DM	Type 2 DM	Type 2 DM

was positive for 2 patients, one for candida and other for aspergillus. Endobronchial biopsy was positive for only 1 patient.

IPA can complicate severe COVID-19 pneumonia. The diagnosis of CAPA is often challenging and requires a high index ofsuspicion. A constellation of clinical and biochemical tests are required to establish the diagnosis. Timely diagnosis and management are required for better outcomes. If left untreated, the complications of fungal pneumonia can be fungal sepsis, dissemination to brain, skin, liver, spleen, kidneys, etc., blood vessel invasion leading to haemoptysis, myocardial infarction, septic emboli. The mortality of untreated infection can be up to 80% in mucormycosis, while in treated cases it comes up to 25%[24].

References

1. Marr KA, Platt A, Tornheim JA *et al*. Aspergillosis Complicating Severe Coronavirus Disease. *Emerg Infect Dis* 2021; 27: 18.
2. Walsh TJ, Gamaletsou MN, McGinnis MR *et al*. Early Clinical and Laboratory Diagnosis of Invasive Pulmonary, Extrapulmonary, and Disseminated Mucormycosis (Zygomycosis). *Clin Infect Dis* 2012; 54 (Suppl. S1): S55-S60.
3. Dupont D, Menotti J, Turc J *et al*. Pulmonary aspergillosis in critically ill patients with Coronavirus Disease 2019 (COVID-19). *Med Mycol* 2021; 59: 110-14.
3. Bartoletti M, Pascale R, Cricca M *et al*. Epidemiology of Invasive Pulmonary Aspergillosis Among Intubated Patients With COVID-19: A Prospective Study. *Clin Infect Dis* 2020.
4. Verweij PE, Rijnders BJA, Brüggemann RJM *et al*. Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: An expert opinion. *Intensive Care Med* 2020; 46: 1524-35.
5. Lamoth F, Glampedakis E, Boillat-Blanco N *et al*. Incidence of invasive pulmonary aspergillosis among critically ill COVID-19 patients [manuscript published online ahead of print 10 July 2020]. *Clin Microbiol Infect* 2020. doi:10.1016/j.cmi.2020.07.010.
6. Rutsaert L, Steinfort N, Van Hunsel T *et al*. COVID-19-associated invasive pulmonary aspergillosis. *Ann Intensive Care* 2020; 10: 71.
7. Koehler P, Cornely OA, Böttiger BW *et al*. COVID-19 associated pulmonary aspergillosis. *Mycoses* 2020; 63: 528-34.
8. Verweij PE, Gangneux JP, Bassetti M *et al*. European Confederation of Medical Mycology; International Society for Human and Animal Mycology; European Society for Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; ESCMID Study Group for Infections in Critically Ill Patients. Diagnosing COVID-19-associated pulmonary aspergillosis. *Lancet Microbe* 2020; 1: e53-5.
9. Jenks JD, Mehta SR, Taplitz R *et al*. Point-of-care diagnosis of invasive aspergillosis in non-neutropenic patients: Aspergillus galactomannan lateral flow assay versus Aspergillus-specific lateral flow device test in bronchoalveolar lavage. *Mycoses* 2019; 62: 230-6.
10. Flikweert AW, Grootenboers MJJH, Yick DCY *et al*. Late histopathologic characteristics of critically ill COVID-19 patients: different phenotypes without evidence of invasive aspergillosis, a case series. *J Crit Care* 2020; 59: 149-55.
11. Wahidi MM, Lamb C, Murgu S *et al*. American Association for Bronchology and Interventional Pulmonology (AABIP) statement on the use of bronchoscopy and respiratory specimen collection in patients with suspected or confirmed COVID-19 infection [manuscript published online ahead of print 18 March 2020]. *J Bronchology Interv Pulmonol* 2020. doi:10.1097/LBR.0000000000000681.
12. Rodrigues ML, Nosanchuk JD. Fungal diseases as neglected pathogens: a wake-up call to public health officials. *PLoS Negl Trop Dis* 2020; 14: e0007964.
13. Rodrigues ML, Albuquerque PC. Searching for a change: the need for increased support for public health and research on fungal diseases. *PLoS Negl Trop Dis* 2018; 12: e0006479.
14. Koehler P, Bassetti M, Chakrabarti A *et al*. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis* 2020.
15. Fekkar, Lampros, Mayaux *et al*. Invasive Fungal Infections during COVID-19. *Amer J Respirato Critical Care Med* 2021; 203: 3.
16. Donnelly JP, Chen SC, Kauffman CA *et al*. Revision and update of the consensus definitions of invasive fungal disease from the European Organisation for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis* 2020; 71(6): 1367-76.
17. Meersseman W, Lagrou K, Maertens J *et al*. Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. *Am J Respir Crit Care Med* 2008; 177 (1): 27-34.
18. Arastehfar A, Carvalho A, van de Veerdonk FL *et al*. COVID-19 associated pulmonary aspergillosis (CAPA): From immunology to treatment. *J Fungi (Basel)* 2020; 6 (2): 91.
19. Salmanton-Garcia J, Sprute R, Stemler J *et al*. COVID-19 associated pulmonary aspergillosis: an analysis of epidemiological and clinical characteristics of 186 international cases from FungiScope® Registry and the literature. *Emerg Infect Dis* 2021; 27(4).
20. LahmerT, Neuenhahn M, Held J *et al*. Comparison of 1,3-â-D-glucan with galactomannan in serum and bronchoalveolar fluid for the detection of *Aspergillus* species in immunosuppressed mechanical ventilated critically ill patients. *J Crit Care* 2016; 36: 259-64.
21. https://doi.org/10.1016/j.mmcr.2020.06.002
22. Ge Song, Guanzhao Liang, Weida Liu. Fungal Co-infections Associated with Global COVID-19 Pandemic: A Clinical and Diagnostic Perspectivefrom China.
23. Woon H, Chong 1, Biplab K *et al*. State of the art review of secondary pulmonary infections in patients with COVID-19 pneumonialnfection 2021; 49: 591-605.
24. Smith JA, Kauffman CA. Pulmonary fungal infections. *Respirology* 2012; 17 (6): 913-26.