Spontaneous hemoptysis in a COVID-19 patient

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A 65-year-old African American man presented with shortness of breath, gradually worsening for the previous 2 weeks associated with dry cough, sore throat, and diarrhea. He denied fever, chills, chest pain, abdominal pain, nausea or vomiting.

Past medical history: Hypertension, diabetes mellitus, chronic kidney disease, morbid obesity and paroxysmal atrial fibrillation.
Medications: Amiodarone, Carvedilol, Furosemide, Pregabalin and Insulin
Epidemiological history: He did not have any sick contacts or travel history outside the United States and no exposure to animals. He never smoked tobacco.

Physical examination: The patient appeared to be in mild respiratory distress but alert and oriented, Temperature was 37.3^{o}C, saturating at 93% on 3L of oxygen, heart rate 105 beats/minute, blood pressure145/99mm Hg, Respiratory rate 18 breaths/minute. On auscultation, there were crackles on bilateral lung bases and chronic bilateral leg swelling with hyper pigmented changes.

Studies: White blood cell count: 6.0K/Cumm (reference range: 3.5-10.6), absolute lymphocyte count 0.7K/Cumm (1.0-3.8), serum creatinine 2.81mg/dl (0.7 – 1.3), Ferritin 692ng/mL (23.9-336.2), C-reactive protein 159 mg/L (<5), Lactate dehydrogenase 565Units/Liter (140-271), D-dimer >35mg/L (<0.5), and Creatinine phosphokinase 2492Units/Liter (30-223)
Chest X-ray: bilateral pulmonary opacities suggestive of pulmonary edema and/or multifocal pneumonia.

Figure 1

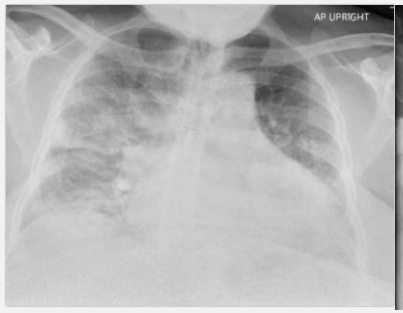
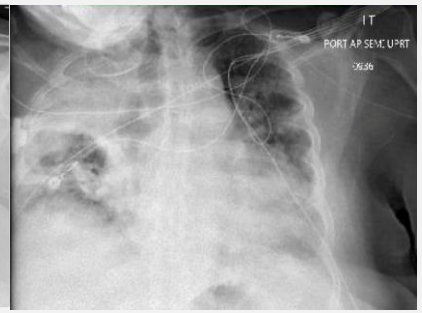
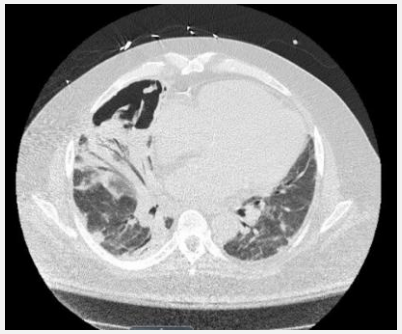


Figure 2



Clinical course Prior to Diagnosis: Therapy was started on Ceftriaxone, Doxycycline, Hydroxychloroquine, methylprednisolone 1mg/kg IV for 3 days and therapeutic dose of subcutaneous enoxaparin. By 3rd day of hospitalization, he required endotracheal intubation, vasopressor support and continuous renal replacement. Antibiotic therapy was then switched to intravenous Vancomycin and Cefepime.
Nasopharyngeal swab for COVID-19 was positive. Blood cultures were negative, respiratory cultures revealed only normal oral flora, so antibiotic therapy was discontinued.
On Day 10, white blood cell count increased to 28K/Cumm, Chest X-ray showed persistent bilateral opacities with left lower lobe consolidation. Repeat respiratory cultures grew *Pseudomonas aeruginosa.* Antibiotic therapy with intravenous Meropenem was started. By Day 20, He was off vasopressors and was extubated.
On Day 23, He developed significant hemoptysis and hypoxia. Chest X-ray revealed right upper lobe collapse (Figure 2). He required reintubation and vasopressor support. Repeat respiratory cultures were positive for *Pseudomonas aeruginosa* and antibiotic therapy was switched to intravenous Ceftolozane-tazobactam.

Diagnostic procedure and result:
Serum Aspergillus galactomannan was elevated to 5.65 (reference range 0-0.49) and serum beta-D glucan was 137pg/ml (reference range: 0-59pg/ml). Respiratory culture revealed *Aspergillus niger*. Intravenous Voriconazole was started on day29 [1]. Ceftolozane-tazobactam was continued for 10 days. By Day 34, Patient's respiratory status significantly improved and was extubated.



A CT scan of the chest demonstrated patchy airspace opacities throughout both lungs, cavitating lesions in the bilateral upper lobes and right lung base. Cavitary lesion in the right lung base measured up to 6.5 x 5.3 cm and demonstrated an air-crescent suggestive of invasive aspergillosis. Spontaneous hemoptysis, elevated serum levels of galactomannan and beta-D glucan, respiratory fungal culture showing *Aspergillus niger*, radiological evidence of cavitary lesion with air-crescent sign in a lymphopenic patient with impaired lung integrity from COVID-19 viral infection and improvement with Voriconazole therapy strongly support the diagnosis of invasive pulmonary aspergillosis. This meets the criteria for invasive pulmonary aspergillosis according to modified AspICU algorithm for influenza patients who were lacking host factors per European organization for Research and Treatment of Cancer Mycoses Study Group (EORTC-MSG) consensus criteria used to define aspergillosis in immunocompromised patients [2].

Treatment and follow up: Therapy with Voriconazole was continued intravenously for first few days. Serum Voriconazole trough level was 2.8µg/ml (therapeutic range is 1-5µg/ml). On Day 40, IV Voriconazole was switched to oral tablet 300mg BID for total duration of six weeks. Twice weekly, liver function tests were monitored. Follow up serum galactomannan level was measured every 10 days, improved to 1.27 and 0.17. The patient was discharged to rehabilitation facility on Day 58.

Final Diagnosis: Superinfection with invasive pulmonary aspergillosis due to *Aspergillus niger* in an immunocompetent patient with COVID-19 pneumonia.

Discussion:
Invasive pulmonary aspergillosis (IPA) is a fatal disease and typically occurs in the immunocompromised population. IPA may develop in ICU patients without classic host risk factors. Diagnosing IPA is challenging. Published algorithms are available to diagnose IPA in patients with severe influenza needing ICU admission [2, 3].
Bronchoscopy with BAL cultures and galactomannan are helpful for diagnosis of IPA but may not be feasible in patients with COVID-19 pneumonia because bronchoscopy is considered as an aerosolizing procedure and adds to risk of infection to health care personnel. Serum aspergillus galactomannan has been extensively studied in immunocompromised population with sensitivity of approximately 70% [1]. However, in patients who are non-neutropenic, serum galactomannan sensitivity of around 25% has been reported [4].
Finding elevated serum galactomannan level was the turning point in our management to promptly initiate antifungal treatment and perform further investigation. Further research is required to investigate efficacy of serological assays in non-neutropenic and COVID-19 patients.
There are few case series reported from China and Europe describing invasive pulmonary aspergillosis as an emerging complication in critically ill COVID-19 patients [4-11]. There are eight publications identified by PubMed search with total of 38 cases. Detailed clinical data were not available in a report which included 8 patients.
Of 30 patients with COVID-19 and IPA, 15 were more than 70 years old (50%), 11 patients were between 50-69 years old (36.7%), only 4 patients between 30-49 years old (13.3%). 23 patients were men (76.7%), 7 were women (23.3%).
Bronchial alveolar fluid/tracheal aspirate culture was positive for Aspergillus in 24 patients, negative in 6 patients. Out of 6 culture negative, fungal PCR was positive in one patient for Aspergillus fumigatus. Out of 24 culture positive patients, 22 are Aspergillus fumigatus (88%), one is Aspergillus flavus and species was not identified in one patient. Aspergillus niger causing IPA in this population has not been previously reported. Elevated serum galactomannan >0.5 was found only in 4 patients (18%), negative in 22 patients (82%), data were unavailable for 4 patients. Regarding antifungal treatment, 21 received treatment, 9 did not. Sixteen received azole treatment, 2 received liposomal Amphotericin B and 8 patients received Echinocandin. 5 patients had combination treatment (Voriconazole and Anidulafungin) and 2 patients had change of treatment during the course. One patient had Azole resistant Aspergillus fumigatus, and treatment was switched to liposomal Amphotericin B. Out of 30 patients, 18 (60%) died and 12(40%) were alive at the time of reporting.
Pathogenetic mechanism of developing invasive fungal infection in patients with COVID-19 is not completely understood; profound lymphopenia, dysregulation of immunity, cytokine storm and disruption respiratory mucosal integrity are possible contributory reasons.
Our case illustrates the importance of considering invasive mold, particularly Aspergillus superinfection in critically ill COVID-19 patients with continued respiratory compromise. Appropriate serological markers and respiratory fungal culture in combination with chest CT scanning are recommended for early diagnosis.

References:

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