CASE SERIES

COVID-19-associated Pulmonary Aspergillosis: A Case Series

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Abstract

Background: With the development of coronavirus disease-2019 (COVID-19) pandemic, there is also increased risk of multiple secondary infections either disease- or drug-related. It includes many bacterial as well as invasive fungal infections.

Patients and methods: There was suspicion of invasive pulmonary aspergillosis (IPA) infection in COVID-19 patients who were critically ill and had acute respiratory distress syndrome (ARDS). We did radiological evaluation and galactomannan assay in these patients.

Result: We have diagnosed COVID-19-associated pulmonary aspergillosis (CAPA) in these patients and started antifungal treatment with voriconazole in all of these COVID-19 patients.

Conclusion: It is very important to report such cases, so that healthcare professionals and authorities related to healthcare will be aware of and may also prepare for the increasing burden of this complication. We describe a case series of CAPA infection.

Keywords: Acute respiratory distress syndrome, Coronavirus disease-2019, Coronavirus disease-2019-associated pulmonary aspergillosis, Galactomannan, Voriconazole.

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Introduction

The world has witnessed the outbreak of COVID-19 which is caused by severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2. This virus was first reported in China in 2019 and spread all over the world within no time as pandemic.[1] Many patients of COVID-19 developed secondary as well as opportunistic infections. As IPA is found mainly in immunocompromised patients, but with the improvement in diagnosis, it has been seen that IPA can also occur in patients who are nonneutropenic.[2,3] In non-neutropenic patients, severe influenza infection is a risk factor for developing IPA and this syndrome is termed influenza-associated aspergillosis (IAA).[4–6] These respiratory viruses cause damage to the respiratory epithelium and the main pathophysiological factors are dysfunction of mucociliary clearance and paralysis of the local immune system.[4] Damage to the alveolus leads to invasive fungal infection and this frequently causes the association of IPA with ARDS in the ICU.[7] So, the existence of CAPA is a possibility in critically ill COVID-19 patients with ARDS. During this second wave of COVID-19, we have seen that many COVID-19 patients are developing other opportunistic infections including IPA in our hospital. Keeping in mind the occurrence of influenza-associated pulmonary aspergillosis, evaluation of the COVID-19 patients for IPA was done. There can be many explanations for this increased IPA like weakened immune system caused by viral infection and compromised innate host defense due to hypoxia. Excessive use of antibiotics, steroids, and immunomodulators can also be a risk factor for opportunistic infection. The main aim of this case series is to make the healthcare workers aware of this serious complication.

Patients and Methods

Our study was a retrospective chart review of the patients with COVID-19 that came to our hospital. RT-PCR was done to detect SARS-CoV-2 RNA in nasopharyngeal and throat swabs of the patients. All the patients were found positive for COVID-19.[8] Initially, symptomatic and supportive home treatment for COVID-19 was given.

When the symptoms worsened, the patients were admitted to the hospital for further treatment and HRCT thorax had also been advised. All of these patients had HRCT findings of cavitary lesions (Figs 1 and 2). The accurate diagnosis of CAPA cannot be made with radiology alone because many atypical radiological signs of COVID-19 and IPA mimic each other. It is essential as well as difficult to discriminate between invasive aspergillosis and tracheal colonization, so, serum galactomannan testing has been done to enhance the diagnosis. In all of these cases, serum galactomannan assay was found to be positive (Table 1).[9] The criteria to diagnose proven invasive fungal infection were not fulfilled because bronchoscopic sampling for cytopathological confirmation was not done. For invasive fungal disease, the specificity of fungal

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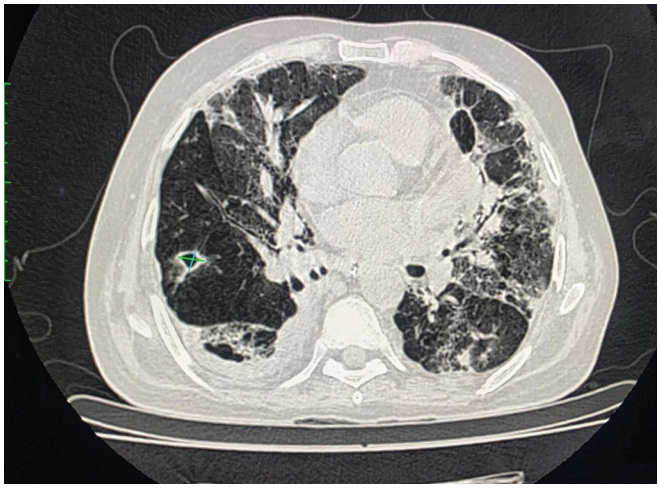

Fig. 1: HRCT thorax showing cavitary lesion in enlarged view with green cross

culture of samples from the upper respiratory tract and tracheal aspirates is low and it can be just colonization. Due to the risk of virus transmission and aerosolization, bronchoscopy was avoided and it could also increase the chances of pulmonary derecruitment. We had taken a decision to start an antifungal agent based on clinical grounds of worsening symptoms and respiratory function in spite of appropriate treatment. So, we had started voriconazole (loading dose 6 mg/kg IV every 12 hours for the first 2 days , followed by maintenance dose of 4 mg/kg every 12 hours).[10] We could not identify any predisposing factor or immunosuppressive cause that could lead to this infection other than severe COVID-19 infection. There was no source of infection in the environment and invasive aspergillosis was not seen in non-COVID patients of the ICU.

Discussion

There is high risk of invasive aspergillosis in influenza patients with ARDS even with no prior immunodeficiency. Invasive pulmonary aspergillosis should be suspected on worsening clinical condition

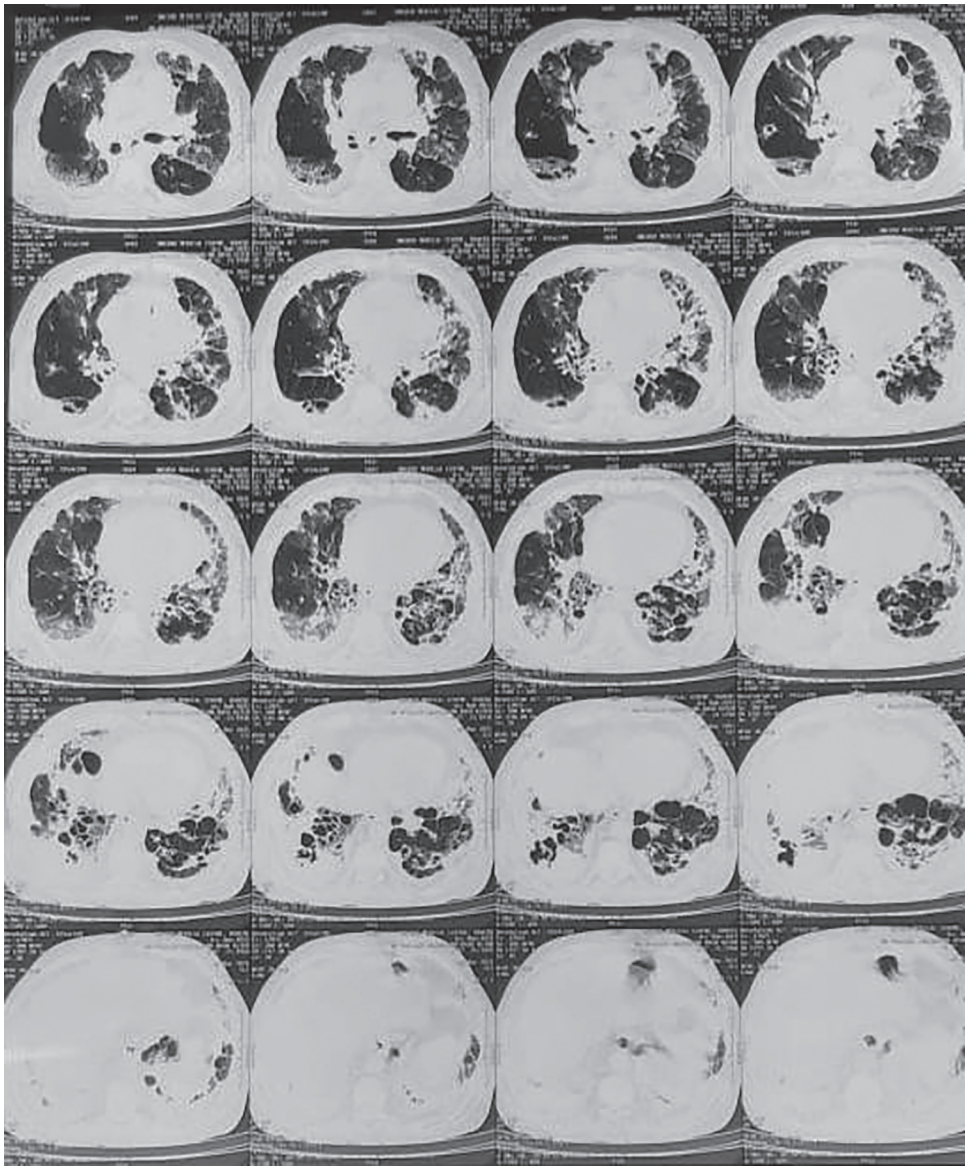

Fig. 2: HRCT thorax showing multiple cavitary lesions

Table 1: Patients' characteristics, clinical course, and outcome

S. no.	*Sex*	*Age in years*	*Medical history*	*CT score*	*Days after symptoms to the onset of CAPA*	*Galactomannan assay*	*Antifungal treatment*	*Outcome*
1	M	57	DM-II Asthma Old Koch's chest	18/25	26 days	3.296	Voriconazole	Died
2	M	34	No	19/25	34 days	1.42	Voriconazole	Survived
3	M	81	DM-II	16/25	38 days	2.66	Voriconazole	Died
4	M	39	No	12/25	28 days	2.81	Voriconazole	Survived
5	M	55	DM-II	18/25	30 days	2.55	Voriconazole	Died
6	M	33	No	14/25	27 days	2.69	Voriconazole	Died
7	M	50	No	22/25	30 days	1.15	Voriconazole	Died
8	F	23	No	19/25	24 days	1.75	Voriconazole	Survived
9	F	65	DM-II Ca. cervix	24/25	28 days	1.249	Voriconazole	Died

that is unresponsive to conventional treatment of COVID-19. Ground-glass opacities and some other atypical radiological findings can be found in both COVID-19 and IPA so difficult to differentiate.[11] Antigen-based laboratory test galactomannan assay is done to support the diagnosis of IPA but cannot confirm the diagnosis. Thus, microbiological evaluation should be done to confirm the diagnosis. However, a more complicated issue is to differentiate between fungal colonization and invasive disease, which need confirmation by bronchoscopic sampling and fungal culture. To handle these issues, a thorough approach is needed to define and diagnose IPA in COVID-19 patients. Our case series suggests that there is an increased risk of developing IPA in critically ill COVID-19 patients. Delayed diagnosis can increase mortality as well as burden to healthcare. Therefore, serum galactomannan testing for the presence of Aspergillus in COVID-19 patients who do not respond to treatment should be considered.[12] The specimen of choice for diagnosis of IPA is bronchoalveolar lavage fluid and lung biopsy. The gold standard investigation to prove diagnosis is tissue culture and tissue microscopy of primarily sterile specimens showing invasive growth of septate fungal hyphae. As biopsies in COVID-19 patients are of very high risk, therefore, are avoided by many physicians. It is needed to confirm the possibility of IPA in COVID-19 patients in further clinical trials. With this case series, we would like to draw attention to look for CAPA in critically ill patients who are not responding to the treatment.

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