Influenza-associated pulmonary aspergillosis in a patient on ECMO

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A B S T R A C T

Invasive pulmonary aspergillosis (IPA) is a well-known disease typically affecting severely immunocompromised patients. Recently, IPA has been described in a new group of patients such as those infected with influenza. In this report, we would like to present a case of pulmonary aspergillosis following influenza infection for the first time in Kuwait, and raise awareness about such unrecognized threatening co-infection.

1. Introduction

Aspergillosis is a leading cause of invasive fungal infections among severely immune-compromised patients, that often results in considerable morbidity and mortality [1]. Patients with hematopoietic stem transplants and hematologic malignancies are the classic risk group highly susceptible to invasive pulmonary aspergillosis (IPA). However, other hosts such as critically ill patients in intensive care units (ICU) are also at risk [1]. More recently, patients infected with severe influenza requiring intensive care, have been increasingly co-infected with pulmonary aspergillosis [2]. Although those cases were associated with high mortality, awareness about such co-infection is lacking and the true burden seems to be underestimated [2]. In this report, we would like to present a previously healthy young man who developed influenza associated aspergillosis (IAA). Despite correct diagnosis was made and treatment with voriconazole was initiated, the patient died eventually.

2. Case

A 42 year old previously healthy Bangladeshi man was admitted to the hospital on May, because of pneumonia (day 0). The infection was soon complicated by adult respiratory distress syndrome (ARDS), for which the patient required high ventilator support. Next day (day 1), the patient was shifted to another hospital to receive veno-venous extracorporeal membrane oxygenation (VV ECMO). His chest X ray revealed pneumonic patches and pleural effusion. A chest CT scan was also done which showed bilateral consolidative patches with air bronchogram consistent with consolidative pneumonia, and mild bilateral pleural effusion. A naso-pharyngeal swab was send for PCR testing, which was positive for H1N1 influenza A virus. The patient received ciprofloxacin 400 mg bid initially (day 0–1), which was then switched to oseltamivir 150 mg twice daily and meropenem 2 g 8 hourly (day 1). In addition, the patient was given methyl prednisolone 40mg initially followed by 70 mg per day. From day 4, the patient started to improve in terms of respiratory parameters, but remained on mechanical ventilation. However, 6 days later (day 10), he became hypoxic and respiratory parameters worsened again. Accordingly, CT scan and bronchoscopy were performed, and BAL specimen was collected. (see Fig. 1). He was started empirically on a loading dose of colistin 9 million international units followed by 3 million units 8 hourly. Vancomycin 1 g bid was added two days later. Despite broad antibacterial coverage and maximal ECMO support, the patient did not respond. The BAL culture grew Acinetobacter. PCR was still positive for influenza A. On day 18, Aspergillus fumigatus was grown from the BAL culture. A preliminary report was sent to the intensivist, who started voriconazole (loading 400 mg bid) then 200mg bid (day 18). Galactomannan test was not done in BAL or serum. A new CXR was taken which showed bilateral pulmonary infiltrate, so chest drains were inserted. Four days later (day 22), he partially improved, and was disconnected from mechanical ventilation. However, the patient became hypoxic two days later (day 24) and was reconnected to the ventilator. CT chest scan taken on day 22 revealed worsening of the consolidation with bilateral pulmonary infiltrate.

Bronchoscopy was done and it showed hyperemia in all respiratory tract mucosa and bloody secretions secondary to severe thrombocytopenia and coagulopathy in both lung sides. In addition, the patient developed cytopenia (white blood cells: 1.6 × 10^9/L, neutrophils:
1.47 × 10^9/L, hemoglobin: 7.3 g/L, and platelets: 26 × 10^9/L). He further deteriorated and became hypotensive and despite inotropic support, died shortly. The fungal isolate was sent to mycology reference laboratory for further workup. Antifungal susceptibility testing by E test (bioMérieux, Marcy l’Étoile, France) showed the following MICs: amphotericin B: 0.125 μg/mL and voriconazole: 0.19 μg/mL.

3. Discussion

We have demonstrated, in this report, that aspergillosis can complicate influenza pneumonia and lead to a poor outcome. Of note, this is the first reported case in Kuwait, suggesting that the disease is probably overlooked.

It is well known that patients with influenza can be secondarily infected by bacterial pathogens such as Streptococcus pneumonia and Staphylococcus aureus [3]. Recently, Aspergillus, has been recognized as a potential secondary pathogen among influenza infected patients. In a recent review article on influenza-associated aspergillosis (IAA) by Vanderbeke et al., the epidemiology of IAA was thoroughly studied. Up to June 2018, 128 cases were found. Majority of cases were reported from Europe followed by North America. Surprisingly, no cases were reported from India, South America or the Middle East [4]. This suggests that the disease is either underreported or restricted to certain geographic regions.

In fact, many clinicians are not aware of such co-infection (IAA) especially in the absence of classic risk factors for invasive aspergillosis, therefore, diagnosis might be missed [2]. Even if Aspergillus was grown in a respiratory culture from an ICU patient, such fungal growth may be considered as colonization rather than infection [2].

A good clinical algorithm has been proposed by Blot et al to diagnose invasive pulmonary aspergillosis in ICU setting. The algorithm helps to discriminate between Aspergillus respiratory colonization from putative invasive pulmonary Aspergillus infection [5]. When this algorithm was applied to our case, all the criteria were met to classify it as putative invasive pulmonary aspergillosis. The fulfilled criteria in our patient included the following: a positive BAL culture growing Aspergillus fumigatus, compatible signs and symptoms, abnormal medical imaging, and glucocorticoid treatment.

In addition, our patient had additional risk factor for invasive fungal infection, which is ECMO. This advanced modality, which has been introduced in Kuwait in 2012, is a life-saving procedure which provides respiratory support for ill patients with acute severe respiratory failure. Patients on ECMO are usually the most critically ill among other ICU patients and are even more susceptible to infection because ECMO, itself, appears to weaken their immune defense [6]. In a retrospective cohort study using data from the Extracorporeal Life Support Organization registry, there was a strong association between ECMO support and influenza associated aspergillosis. It was shown, through multivariate analysis, that male sex, influenza, and use of ECMO for respiratory support were significantly associated with increased risk of Aspergillus involvement [6]. Further, survival was statistically lower in Aspergillus infected patients compared with overall survival rates among all ECMO patients [6].

Besides ECMO, the patient had received steroid treatment shortly after admission, and this further predisposed him to invasive Aspergillus infection. In a prospective multicenter study on invasive fungal infections among ICU patients, Aspergillus infection occurred in a median rate of 6.31 per 1000 admissions, and steroid treatment was the major host factor [7].

Regarding our case, the etiologic agent, i.e. Aspergillus fumigatus, was isolated, and it was susceptible to voriconazole and amphotericin B. Additionally, the patient had received the drug of choice i.e. voriconazole throughout the course of disease [8]. Despite all of this, he died eventually.

The poor outcome could be explained by two facts: firstly, the high mortality rate observed in patients with IAA (~57%) [4]. Secondly, therapeutic drug monitoring to voriconazole was not performed as it was not available. It is well known that serum level of voriconazole is unpredictable and is affected by drug interactions and hepatic function. Therefore, therapeutic drug monitoring should be a standard of care [9].

4. Conclusion

Influenza associated aspergillosis may lead to a poor outcome even in immune competent individuals. Therefore, increased awareness of such threatening co-infection should be considered. In patients infected with influenza and who are deteriorating, efficient and timely diagnostic workup should be expanded to include aspergillosis.

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Consent

Written informed consent was obtained from the patient or legal guardian(s) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

A written consent was not obtained as the patient passed away.

Declaration of competing interest

There are none.

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