Journal of Microbiology, Immunology and Infection (2016) xx, 1–7

Available online at www.sciencedirect.com

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journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

High-level ambient particulate matter before influenza attack with increased incidence of *Aspergillus* antigenemia in Southern Taiwan, 2016

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Received 4 May 2016; received in revised form 11 September 2016; accepted 28 September 2016
Available online ■ ■ ■

KEYWORDS
aspergillosis;
epidemic;
galactomannan;
influenza;
particulate matter

Abstract We found significant correlation between the incidence of severe influenza and *Aspergillus* antigenemia among medical intensive care unit patients for 7-month observation (coefficient $\gamma = 0.976$, $p < 0.001$). High-level ambient pollution was noticed for 2 months before the epidemic, highlighting that influenza patients might coinfect with aspergillosis in the community.

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http://dx.doi.org/10.1016/j.jmii.2016.09.001

Introduction

Invasive pulmonary aspergillosis (IPA) was identified in 23–29% of critically ill patients with severe influenza A (H1N1)-related pneumonia.[1,2] However, Martin-Loeches and Valles[3] raised the query of possible overdiagnosis based on *Aspergillus* galactomannan (GM) antigen in the serum of patients with severe influenza. Martin-Loeches et al[4] isolated *Aspergillus* spp. as a pathogen of hospital-acquired pneumonia in 8.7% of 46 critically ill influenza A (H1N1) patients, which indicates the study that assessed the effect of early corticosteroid therapy but was not intended to diagnose IPA for influenza patients.[4] The above studies mentioned prior corticosteroid use as a risk factor for IPA in severe influenza patients.

On the contrary, Garcia-Vidal et al[5] found that high numbers of fungal spores and subsequent circulating respiratory viruses, such as influenza A, in the ambient air increase the development of IPA 2–6 weeks later, suggesting that patients might acquire IPA outside the hospital. Nevertheless, they could not explain the reasons of increased environmental spores and did not mention the coexistence of IPA in the influenza patients.[5] In fact, influenza A viral infection might predispose the previously healthy patients to *Aspergillus* superinfection by suppression of cellular immunity.[6] Patients with unusually severe influenza might hint depressed T-cell function, thus becoming vulnerable to IPA.[7] Therefore, we postulate a transmission mode of previous exposure to environmental spores promoting IPA in severe influenza patients.

In Taiwan, an influenza epidemic peaked in February 2016, which caused chaotic situations to the health care facilities and record-breaking death toll in Taiwan (http://www.chinapost.com.tw/taiwan/national/national-news/2016/03/09/460225/CDC-under.htm). To understand the incidence of IPA in severe influenza patients, we retrospectively reviewed the cases of severe influenza and positive *Aspergillus* GM antigen from the adult patients hospitalized in the medical intensive care units (ICUs) of two hospitals (A and B) in Tainan city, southern Taiwan, from August 1, 2015 through February 29, 2016. Hospital A is a tertiary referral medical center with 96 adult ICU beds. Hospital B is a regional cancer center with 63 adult ICU beds.

GM is a cell wall component released by *Aspergillus* spps. during active hyphal growth in tissues, thus detection of GM in blood reflecting a true *Aspergillus* infection rather than contamination from airway isolation.[8,9] The Food and Drug Association of the United States has approved the use of Platelia *Aspergillus* enzyme immunoassay to detect GM in blood, which allows doctors to diagnose life-threatening aspergillosis sooner. The revised definitions for invasive fungal disease of the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) has accepted GM test as one of the microbiological criteria for diagnosing probable IPA.[10]

Before the influenza epidemic, high-level atmospheric fine particulate matter (PM) with a diameter of 2.5 μm (designed $PM_{2.5}$) was frequently alarmed by Taiwan Air Quality Monitoring Network. High-level $PM_{2.5}$ would cause discomfort such as sore eyes, sore throat, or cough and people should consider reducing outdoor activity. Therefore, we reviewed levels of atmospheric PM as an index of ambient air pollution in Tainan city, which might contribute to increased environmental *Aspergillus* spores.[11]

Methods

A confirmed influenza case was defined as at least one positive assay for testing influenza, such as rapid influenza diagnostic tests, real time polymerase chain reaction (PCR), and viral isolation for specimens of nasopharyngeal swab and/or lower respiratory tract aspirates. Severe influenza was regarded as those influenza patients admitted to ICUs.

Aspergillus GM was detected using Platelia *Aspergillus* Ag assay (Bio-Rad Laboratories, Marnes-La-Coquette, France) in serum with a positive cut-off value of optical density index ≥ 0.5.

Data of $PM_{2.5}$ were obtained from Taiwan Air Quality Monitoring Network (http://taqm.epa.gov.tw/taqm/en/). Above high-level $PM_{2.5}$ concentrations were defined by an index of ≥ 54 $\mu g/m^3$. The cumulative hours of above high-level $PM_{2.5}$ per month was regarded as the exposure time of people to ambient air pollution.

Proportions were compared using the $\chi 2$ test or Fisher's exact test. Pearson's correlation coefficient was used to determine the relationship between the incidences of severe influenza and *Aspergillus* antigenemia among the medical ICU patients. A p value < 0.05 indicated statistical significance (2-tailed test).

Results

Incidence of severe influenza and *Aspergillus* antigenemia

A total of 2712 hospitalized medical ICU patients (1640 in hospital A and 1072 in hospital B) were identified during the observed 7-month period. In February 2016, a total of 54 patients (32 in hospital A, 22 in hospital B) were diagnosed with severe influenza and 33 patients (24 in hospital A, 9 in hospital B) were positive for *Aspergillus* GM test (Table 1). The incidence trends of adult patients with severe influenza and/or positive *Aspergillus* antigenemia in medical ICU patients were significantly increased in February 2016 compared with those in previous 6 months in both the hospitals (Table 1 and Figure 1A). Furthermore, monthly incidences of *Aspergillus* antigenemia and severe influenza were highly positively correlated (Pearson's correlation coefficient $\gamma = 0.976$, $p < 0.001$; Figure 1B). The number of noninfluenza patients with *Aspergillus* antigenemia significantly increased in hospital A and overall patients but did not increase significantly in hospital B during the influenza epidemic (Table 1).

Types of influenza and patients with *Aspergillus* antigenemia

Among the total 54 severe influenza patients in February 2016, influenza A was identified in 45 patients, including 35 patients with influenza A(H1N1)pdm09 virus and 10 patients with influenza A virus different to (H1N1)pdm09 and H3N2.

Please cite this article in press as: Yu W-L, et al., High-level ambient particulate matter before influenza attack with increased incidence of *Aspergillus* antigenemia in Southern Taiwan, 2016, Journal of Microbiology, Immunology and Infection (2016), http://dx.doi.org/10.1016/j.jmii.2016.09.001