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Invasive Pulmonary Aspergillosis Following Influenza: Report of Two Cases

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Abstract

Background: Complication of *Aspergillus* pneumonia following severe influenza has been reported in several countries of the world, but was rarely reported in Taiwan. We here reported two cases.

Case Summary: (Case 1) A 45-year-old man of chronic obstructive pulmonary disease (COPD) had dyspnea. He was admitted to the intensive care unit (ICU) with ventilator support due to worsening pneumonia and severe hypoxemia. Influenza A (H1N1) DNA in the nasopharynx sample remained positive after 5 days of oseltamivir therapy. Peramivir was therefore used for additional 5 days. Voriconazole had been used for 2 weeks for *Aspergillus* infection due to high index (4.96) of *Aspergillus* galactomannan (GM) antigen in the blood sample. Imipenem and colistin were used for *Klebsiella pneumoniae* bacteremia and that sputum cultures yielded *Pseudomonas aeruginosa* and *Acinetobacter* baumannii. We used high frequency oscillatory ventilation for severe refractory hypoxemia. The response was poor and he died one month after admission. (Case 2) A 76-year-old man was admitted due to influenza B with dyspnea. He was treated with zanamivir and cefuroxime. As respiratory failure with interstitial infiltration over right lung, he was transferred to the ICU. Piperacillin and levofloxacin were used. Zanamivir (5days) followed by oseltamivir (10days) were used for persistent recovery of influenza-B DNA in the throat samples. Sputum culture yielded *Aspergillus* species and blood *Aspergillus* GM antigen index was 2.25 (positive, $\geq$ 0.5). He received intravenous voriconazole (14 days) followed by oral form (21 days). Then *Aspergillus* GM antigen became 0.38. He was discharged after 6 weeks of hospital stay. As lung fibrosis with dyspnea affecting his daily activity, he needed oxygen therapy at home.

Conclusion: Invasive pulmonary aspergillosis (IPA) is an emerging serious infection in influenza of previously healthy individuals or those with COPD on steroid therapy. It is important to formulate a strategy for diagnosing IPA following influenza A or influenza B pneumonia as in our cases, because *Aspergillus* infection complicating severe influenza has substantially high mortality.

Keywords

aspergillus pneumonia; aspergillosis; influenza A; influenza B

Introduction

Since the 2009 influenza pandemic, invasive pulmonary aspergillosis (IPA) has been increasingly reported as a coinfection in patients with a severe influenza virus infection. This combined *Aspergillus* and influenza infection often has a fatal outcome. A sputum culture with growth of *Aspergillus* may be

regarded as colonization in non- immunocompromised patients. However, an *Aspergillus* isolate from sputum culture should be taken seriously in patients with severe influenza pneumonia, and treatment should be considered early in the disease course. In addition, *Aspergillus* galactomannan (GM) antigen test is helpful in the diagnosis of IPA [1-3].

The most accepted guidelines regarding the diagnosis of IPA come from the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG)[4], which defines cases as proven, probable, or possible. These criteria were derived for immunocompromised cohorts. Nonetheless, other populations have been recognized as at-risk hosts for IPA, such as patients with chronic obstructive pulmonary disease (COPD), chronic liver disease and critical illness [5-8]. Meanwhile, influenza has also been listed as a minor risk factor for IPA [8]. Therefore, influenza might further predispose a COPD patient to the development of IPA.

Case Presentation

CASE 1: A 45-year-old man with COPD, coronary artery disease (CAD) and hypertensive cardiovascular disease (HCVD) suffered from cough and dyspnea for 3 days. He was brought to emergency department on June 24, 2014. He was intubated for ventilator support due to rapidly progressive lung consolidation, extending to bilateral lung fields. Then he was admitted to the ICU. A high Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 23 was noted. Fluid resuscitation and infusion of vasopressors were given. Laboratory data revealed a white blood cells (WBC) of 5200/μL with neutrophils 92.7% and lymphocytes 4.6%; platelet count, 155,000/μL; c-reactive protein, 154 mg/L; procalcitonin, 1.79 ng/ml; lactate, 1.4 mmole/L; creatinine, 2.19 mg/dL and K, 4.19 mmol/L. An arterial blood gas analysis showed pH, 7.404; PCO2, 27.3 mmHg; PO2, 80.5 mmHg; HCO3, 17.2 mmol/L; and base excess, -5.5 mmol/L, under the use of 100% fraction of inspired oxygen (FiO2) with a PaO2/FiO2 (P/F) ratio of 80.5 mmHg. Chest X-ray (CXR) showed bilateral infiltrates, compatible to acute respiratory distress syndrome picture with predominant consolidation on the left lung field (Figure 1A). As polymerase chain reaction (PCR) for influenza-A (H1N1) remained positive after 5 days of oseltamivir therapy, additional peramivir was used for 5days. Then, the PCR for influenza-A (H1N1) became negative.

Initial sputum culture from endotracheal aspirate yielded *Aspergillus* species only. The sputum Gram stains and cytology did not find the hyphae appearance. Blood *Aspergillus* GM antigen index was high (4.96) using the double sandwich enzyme immunoassay with a cutoff OD of ≥ 0.5 by Platelia *Aspergillus* Ag assay (Bio-Rad Laboratories, Marnes-La-Coquette, France). Intravenous hydrocortisone (200mg daily) therapy has been used for 6 days before *Aspergillus* GM testing. After 14 days of voriconazole therapy, followed-up *Aspergillus* GM antigen test became normal (0.27). Follow-up CXR showed near resolution of left lung infiltration. However, nosocomial pneumonia over right lung developed on the 21th day of hospitalization. The Antibiotic therapy with imipenem and colistin was initiated as subsequent *Klebsiella pneumoniae* bacteremia and follow-up sputum culture yielding *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. However, hypoxemia could not be corrected. Abdominal echo did not show the presence of intra-abdominal infection. We used high frequency oscillatory ventilation (HFOV) with paralysis and intermittent positive-pressure breathing mode for the patient due to severe hypoxemia and worsening pneumonia (Figure 1B) with a peak inspiratory pressure of >30cmH2O. The response was poor and the patient died after 36 days of admission. Prone positioning

and extracorporeal membrane oxygenation (ECMO) were not utilized as hospice palliative care was provided after failure of HFOV therapy.

Case 2: A 76-year-old man with COPD, CAD and HCVD suffered from dyspnea and was admitted to the ward on February 23, 2015 under the diagnosis of influenza virus type B. He was treated with zanamivir and cefuroxime. As respiratory failure, he was transferred to the ICU with an APACHE II score of 15 on February 26, 2015. Laboratory data revealed a WBC of 12,400/μL with neutrophils 85.1%% and lymphocytes 6.9%; platelet count, 143,000/μL; c-reactive protein, 44.2 mg/L; procalcitonin, 1.11 ng/ml; lactate, 1.1 mmole/L; creatinine, 1.0 mg/dL and K, 4.95 mmol/L. Arterial blood gas showed pH, 7.307; PCO2, 43.5 mmHg; PO2, 67.6 mmHg; HCO3, 22 mmol/L; base excess, -3.8 mmol/L; FiO2, 100 %; and P/F ratio, 67.6 mmHg. Mixed alveolar process and interstitial infiltration over right-sided middle and lower lung fields were noted in the CXR film (Figure 1C). Antibiotics were shifted to piperacillin and levofloxacin. Zanamivir (5days) followed by oseltamivir (10days) was used for persistence of influenza-B DNA by PCR analysis. Initial sputum culture from endotracheal aspirate yielded *Aspergillus* species only and *Aspergillus* GM antigen index was 2.25 (positive, $\geq$ 0.5) in the blood sample obtained before initiation of piperacillin therapy. The sputum Gram stains and cytology did not find the hyphae appearance. Intravenous hydrocortisone (200mg daily) therapy has been used for 7 days before *Aspergillus* GM testing. Intravenous voriconazole (14days) followed by oral form (21days) were used. Follow-up *Aspergillus* GM antigen test after voriconazole therapy showed a normal result (0.38). He was successfully extubated on March 17 and was transferred to the ward on March 19, 2015. Later, CXR disclosed lung fibrosis (Figure 1D). After 2 weeks of respiratory rehabilitation, the condition has greatly improved. Thus he was discharged on April 7, 2015. As affecting the daily activity due to dyspnea, he needed use of oxygen at home.

Outcome & follow up

Case 1: The response was poor and the patient was critically discharged after 36 days of admission.

Case 2: He was discharged after 40 days of admission. As affecting the daily activity due to dyspnea, he needed use of oxygen at home. He maintained regular follow up at the cardiology and chest medicine outpatient departments for one year and a half.

Conclusion

Viral influenza is a seasonal infection associated with significant morbidity and mortality. In the United States more than 35,000 deaths and 200,000 hospitalizations due to influenza occur annually, and the number is increasing [9]. Multiple reports describe secondary pneumonia caused by less common microorganisms. These include *Aspergillus* sp, *Chlamydia pneumoniae*, β-hemolytic streptococci, and *Legionella pneumophila*. IPA may complicate influenza pneumonia in previously healthy adults, or those with COPD on corticosteroid therapy [10]. Both of our reported patients have received corticosteroid therapy before testing *Aspergillus* GM assay, supporting the pathogenetic link between steroid use and development of IPA [11, 12]. Both our patients had a period of lymphopenia (< 1,000/μL) before diagnosing IPA, suggesting pathogenetic link between lymphocyte dysfunction and development of IPA. The major protective host response against invasive aspergillosis is T-helper type 1 lymphocyte mediated cytokine production that the phagocytes are activated to kill the fungus [13]. Other conditions

to IPA include disruption of mucosa and loss of ciliary clearance in the tracheobronchial tree during severe influenza illness [1].

Recently, cases of IPA after influenza in the immunocompetent patients or in the ICU patients have been reported in several other countries, like Korea [2,14], The Netherlands [3], Belgium [12], Switzerland [15], Japan [16], Taiwan [17] and France [18]. It is important to formulate a strategy based on *Aspergillus* GM antigen detection for IPA following influenza [18, 19], including influenza A and influenza B pneumonia as in our cases. Our current report reinforces that IPA should be considered in influenza patients, particularly with COPD, who are unresponsive to initial antiviral and antibiotic treatments. Early diagnosis and treatment of *Aspergillus* infection complicating influenza is mandatory as high mortality, especially with a high APACHE II score.

The voriconazole therapy was effective for IPA in both of our patients, which was compatible with resolution of pneumonia and "normalization" of follow-up *Aspergillus* GM levels. We believed that the cause of death for case 1 was severe and difficult-to-treat nosocomial bacteremia and pneumonia by organisms with multi-drug resistance. The use of serial *Aspergillus* GM level for therapeutic monitoring is recommended for some patient subpopulations such as hematologic malignancy, according to the updated guidelines by the Infectious Diseases Society of America in 2016 [21]. Our report further supports this recommendation, which could be extended to severe influenza patients with IPA.

The limitation of our report included lack of semi-quantitative assessment for *Aspergillus* culture of bronchoalveolar lavage fluid in the diagnostic algorithms [20]. Decision of prone positioning for ventilation and ECMO might be made earlier in the course of case 1.

Figures

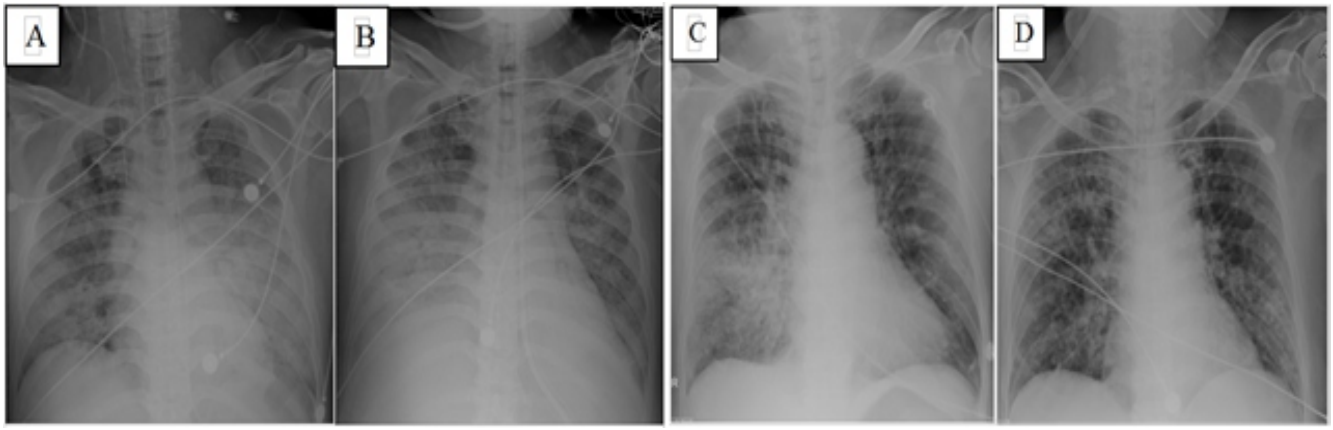

Figure 1: CXR showing acute respiratory distress syndrome predominantly on left lung field (A); worsening pneumonia over right lung field in the case 1(B); persistent mixed alveolar process and interstitial infiltration over right-sided middle and lower lung fields (C) and lung fibrosis (D) in the case 2.

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