Pulmonary Opportunistic Infections in A Lung Cancer Patient Treated with Inhaled Corticosteroid

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Abstract

Opportunistic pulmonary infections, including Pneumocystis jiroveci pneumonia (PcP) and cytomegalovirus (CMV) pneumonitis are uncommon in human immunodeficiency virus (HIV)-seronegative persons who are immunocompromised on account of hematological malignancy, immunosuppressive therapy, or a primary immunodeficiency. PcP remains an infrequent event among patients with solid tumor malignancies. Here we report a 63 year-old stage IIB lung cancer patient who developed fatal PcP and CMV pneumonitis after treated with inhaled steroid, radiotherapy and gefitinib. She had not been treated with chemotherapy; and the radiotherapy she received had not caused obvious leucopenia. In the absence of obvious immunosuppressive effects resulting from chemotherapy or radiotherapy, we suggest that the use of inhaled corticosteroid might increase the susceptibility of pulmonary opportunistic infections in potentially immunocompromised hosts, i.e., COLD or lung cancer patients, even in the absence of marked leucopenia. Susceptible patients who are treated with inhaled corticosteroid developing rapid evolution of dyspnea, substernal chest tightness, nonproductive cough and fever should be considered as suffering from PcP and should be treated accordingly until proven otherwise. Coinfection with other opportunistic pathogens should be identified and treated concurrently. Following up lymphocyte or CD4 count and prophylaxis measures are advocated in selected patients. (J Intern Med Taiwan 2009; 20: 92-96)

Key Words： *Pneumocystis* pneumonia, Cytomegalovirus, Acute respiratory distress syndrome, Lung cancer, Inhaled steroid

Introduction

Opportunistic pulmonary infections, including Pneumocystis jiroveci pneumonia (PcP) and cytomegalovirus (CMV) pneumonitis are uncommon in human immunodeficiency virus (HIV)-seronegative persons who are immuno-compromised on account of hematological malignancy, immunosuppressive therapy, or a primary immunodeficiency. PcP remains an infrequent event among patients with solid tumor malignancies[1]. The incidence of PcP among non-HIV positive solid cancer patients while receiving chemotherapeutic regimens was 1.3% at a cancer hospital[2]; still less the incidence of PcP would be expected to be lower in patients not treated with chemotherapeutic regimens. A long term high-dose systemic steroid therapy and leucopenia are also well-known risk factors and might warrant the use of prophylaxis measures in selected patients[3].

Nevertheless, the significance of inhaled corticosteroid in the development of PcP and CMV pneumonitis in lung cancer and chronic lung disease patients has not been described before. Here we report a 63 year-old stage IIB lung cancer patient who developed fatal PcP and CMV pneumonitis after treated with inhaled steroid, radiotherapy and gefitinib. She had not been treated with chemotherapy; and the radiotherapy she received had not caused obvious leucopenia. In the absence of obvious immunosuppressive effects resulting from chemotherapy or radiotherapy, we suggest that the use of inhaled corticosteroid might increase the susceptibility of pulmonary opportunistic infections in potentially immunocompromised hosts, i.e., chronic obstructive lung disease (COLD) or lung cancer patients, even in the absence of marked leucopenia.

Case report

A 63 year-old lady presented to the emergency department with a one-week course of worsening of dyspnea and low-grade fever. She has a 10-pack-year history of smoking and a diagnosis of mildly COLD with asthmatic feature was made 6 years ago. She also had type 2 diabetes and hypertensive cardiovascular disease. A diagnosis of adenocarcinoma of lung, stage IIB (T2N1M0) was made 18 months prior to this admission. Her disease status was stabilized after treated by radiotherapy and gefitinib. She had never been treated with any chemotherapeutic regimens due to patient's own willing. Her medications included aminophyllin 100 mg t.i.d, amilodipine 10 mg qd and repaglinide 1 mg t.i.d. Inhaled budesonide 400 μ g b.i.d that had been added 2 months prior to admission. Systemic steroid therapy had not been used before. On arrival, she appeared acute ill looking with respiratory rate of 26, blood pressure of 140/90 mmHg, pulse rate of 96 beat per minute and body temperature of 38.2 ℃. Physical examinations
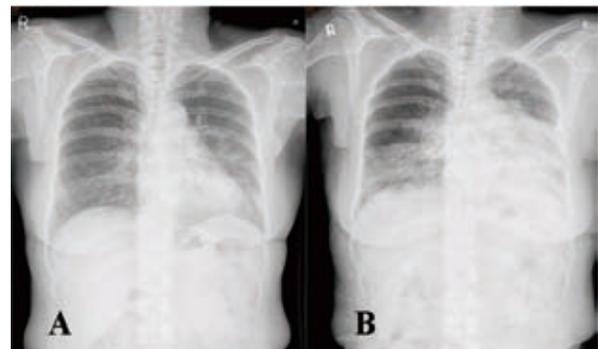

Fig.1. Chest radiography obtained in admission and on the 4th hospital day. Noting increased opacity of the lower lung fields.
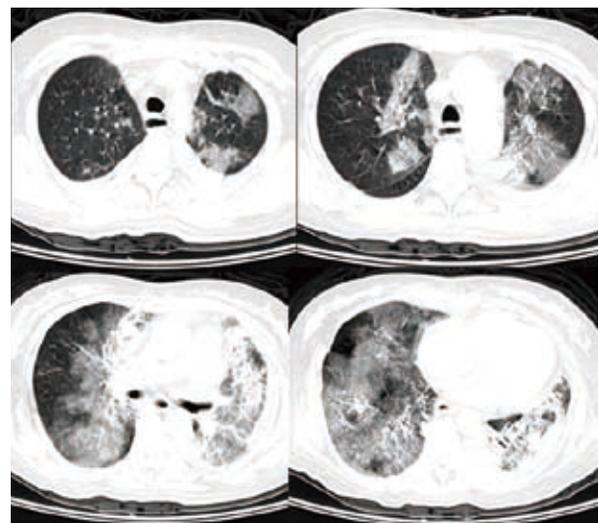

Fig.2. CT without contrast enhancement showed patchy consolidation (especially in the central region of both lungs and left lower lobe) and ground-glass opacity in all lobes.

disclosed diffused wheezing sound and grade I pitting edema of legs. The results of laboratory examinations included a white blood cell count of 14100/μL, with neutrophil 85.2 %, and lymphocyte 12.3%(total lymphocyte count of 1734/μL), a hemoglobin of 10.9 gm/dL, and a platelet count of 272,000 / μL. The results of arterial blood gas analysis showed pO_2 72 mmHg, pCO_2 48 mmHg and HCO_3^- 28 mmole when she was using O_2 cannula 5 liters per minute. Chest radiographies obtained on admission showed ground glass opacity over bilateral hilar regions (Figure 1A). Oral levofloxacin was prescribed. She had progressive dyspnea and required the use of Bi-level Positive

Airway Pressure® ventilator support. Broad-spectrum antibiotic therapy with meropenum plus clarithromycin was instituted on the 4th hospital day. On the sixth hospital day, she required tracheal intubation; mechanical ventilation and was admitted to the intensive care unit. Chest radiographies obtained on the 4th hospital day showed diffused ground glass opacity over the lower lung fields, indicating a progression of infectious process (Figure 1B). An unenhanced computed tomography (CT) of the chest showed ground-glass opacity involving nearly all lobes (Figure 2). The patient deferred bronchoscopic examination and open lung biopsy. Extensive microbiological follow-up after admission, including cultures of the blood and nebulised saline-induced sputum were negative for bacteria, mycobacteria and fungi. The results of anti-mycoplasma antibody and urine Lengionella antigen tests were negative. The result of sputum cytology was negative for malignant cells. Though the result of Giemsa staining was negative for P. jiroveci, polymerase chain reaction (PCR) of the sputum obtained from the endotracheal tube aspiration on the 8th hospital day was positive for P. jiroveci. Trimethoprim-sulfamethoxazole (TMP-SMX) given intravenous (IV) was begun. High titer of CMV viral load was also found in both sputum and serum specimen, indicating pulmonary CMV infection with viremia, rather than an asymptomatic carrier state. Ganciclovir 60 mg per day was started then. Despite of best supportive care, she developed profound hypoxic respiratory failure and eventually died of multiple organ dysfunction syndrome on the 22th hospital day.

Discussion

Other than acute exacerbation of chronic bronchitis, her primary lung cancer and preceding radiotherapy raised the concern of disease progression and radiation pneumonitis. The time from the completion of lung radiation therapy to the onset of pneumonitis was not helpful for determining the etiology of the pneumonitis[4]. Gefitinib had been reported to cause acute interstitial pneumonia but had not been reported to cause immunodeficiency[5]. Though our patient did not present with marked leucopenia, she should still be regarded as a relative immunocompromised host due to underlying lung cancer, treated with radiotherapy and probably an effect of inhale corticosteroid therapy. Radiation to the thorax can increase the risk of developing PcP by producing significant lung parenchymal lesions or by causing a decreased blood lymphocytes[6]. Paradoxically, the "photographic negative of post-radiation pneumonia" describes PcP may spare lung that is included in a radiation port either during the course of therapy or months after its completion is a distinct finding in PcP[7]. In a study involving patients with solid or hematological malignancies who acquired PcP, all solid cancers patients were treated with steroid. The authors concluded that PCP can be presented as subacute, febrile, hypoxemic, and diffuse pulmonary involvement in cancer patients treated with long-term high dose steroids. Prophylaxis measures might be underused in these cancer patients[8]. Nevertheless, on reviewing medical literature, the association between inhaled corticosteroid and the development of PcP had been reported in only one asthmatic children[9]. We had found no report regarding to the inhaled corticosteroid and the development of PcP in patients with COLD or lung cancer. Systemic adverse effects such as adrenal suppression, cataract formation, decreased growth in children, interfered bone metabolism and purpura had been described in patients who were treated with larger doses of inhaled corticosteroid with increased systemic absorption. In addition to oropharyngeal candidiasis, it is also possible that a state of local immunosuppression in the lung could be caused by prolonged use of inhaled corticosteroid. We suggest

that the use of inhaled corticosteroid might increase the susceptibility of pulmonary opportunistic infections in potentially immunocompromised hosts, i.e., COLD or lung cancer patients, even in the absence of marked leucopenia.

The diagnosis of *P. jiroveci* requires special stains of specimen obtained from lower respiratory tract either bronchoavelolar larvage (BAL) or hypertonic saline induced sputum production, which is less sensitive. Compared with conventional staining, molecular techniques based on PCR have superior sensitivity for the diagnosis of *P. jiroveci* in both sputum and BAL specimens. Detection of *P. jiroveci* in oropharyngeal secretion by molecular technique has made invasive diagnostic procedure such as BAL or open lung biopsy potentially avoidable for the purpose of establishing the diagnosis of PcP. *P*atients with chronic lung disease have higher rate of subclinical *P. jiroveci* infection[10]. The prevalence of *P. jiroveci* DNA is low or absent in oropharyngeal secretions in the absence of PcP[11]. The question of whether these patients with underlying pulmonary diseases and detectable but low amounts of *P. jiroveci* DNA represent truly colonized carriers and a possible reservoir for this pathogen requires further evaluation[12]. Although not as sensitive as in HIV-seropositive patients, performing CD4 count is advocated in the presence of steroid dosage > 15 mg prednisolone or equivalent per day; had > 3 month period of steroid therapy and total lymphocyte < 600 cell/mm^3. CD4+ cell count could serve as a biological marker to determine timing with regard to commencement and discontinuation of prophylaxis. HIV-seronegative patients with PcP were older than AIDS patients with a more acute course, more like to be febrile, lower median room air arterial oxygen tension and worst prognosis[13].

The symptoms and signs of CMV pneumonitis were non-specific, and included the following: chest pain, cough, haemoptysis, shortness of breath, fever, sweats, and cervical lymphadenopathy. The diagnosis can be established with the use of serological tests, PCR in blood, PCR or immuno-histochemistry in lung tissue (obtained through either transbronchial or open lung biopsy), as well as with analysis of BAL fluid[14]. The introduction of molecular-based diagnostic tests, such as the pp65 antigen test and PCR, has allowed clinicians to intervene earlier in the course of infection, resulting in better outcome. CMV antigenemia is useful for predicting the surveillance bronchoscopy result, and also predicts the development of CMV disease in the majority of patients missed by the surveillance bronchoscopy[15]. It is also worth noting that tuberculosis, cryptococcous and CMV pneumonitis could be developed simultaneously in patients with PcP[16]. Previous or concomitant CMV infection was a risk factor for PcP itself[17,18], This case also highlights the need for extensive investigations of other opportunistic infections even after establishing the diagnosis of PcP in a relative immunocompromised host.

In conclusion, we suggest that the use of inhaled corticosteroid might increase the susceptibility of pulmonary opportunistic infections in potentially immunocompromised hosts, i.e., COLD or lung cancer patients, even in the absence of marked leucopenia. Susceptible patients who are treated with inhaled corticosteroid developing rapid evolution of dyspnea, substernal chest tightness, nonproductive cough and fever should be considered as suffering from PcP and should be treated accordingly until proven otherwise. Coinfection with other opportunistic pathogens should be identified and treated concurrently. Following up lymphocyte or CD4 count and prophylaxis measures are advocated in selected patients.

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肺部機緣性感染於一接受吸入性類固醇治療之肺腺癌病患：病例報告

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摘　要

肺部機緣性感染包括巨細胞病毒肺炎(cytomegalovirus, CMV pneumonitis)及肺孢子蟲感染 (Pneumocystis jiroveci pneumonia, PcP)在非人類免疫不全病毒感染之免疫不全病患，包括血癌及接受免疫抑制劑治療者等仍不屬常見。回顧醫學文獻並沒有發現吸入性的類固醇治療會在慢性肺病或是肺癌的病患導致機緣性感染；在此我們報告一位六十三歲肺腺癌病患於接受吸入性類固醇治療、放射治療及標靶治療(geftinib)後發生致死性的PcP及CMV肺炎。在沒有因為使用化學治療且沒有證據顯示放射治療引發明顯的白血球缺乏的情況下，我們強調使用吸入性類固醇於易感受性之宿主，例如慢性肺病及肺癌等之病患時若發生快速進展的氣喘、胸悶及發燒等症狀應及早懷疑肺部機緣性感染的可能，亦應注意合併其他機緣性感染的可能。臨床醫師可藉由分子生物學的方法及早診斷，並應視情況追蹤CD4淋巴球的數量及投與預防性或治療性的抗生素。