Case Report

Fatal Pneumonia Mixed with Fungus, Cytomegalovirus and Nontuberculous Mycobacterium in a Human Immunodeficiency Virus-Infected Patient

Hsin-Ju Tang, *Wen-Liang Yu

1Department of Nursing, Chi-Mei Medical Center, Tainan City, Taiwan
2Department of Intensive Care Medicine, Chi Mei Medical Center, No. 901 Chunghua Road, Yongkang District, Tainan City 710, Taiwan
3Department of Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei City, Taiwan

Keywords
Cytomegalovirus; HIV; Nontuberculous Mycobacterium; Pneumocystis jiroveci; PCP

Dear Editor

Pneumocystis jiroveci pneumonia (PCP) is one of the most important opportunistic infections in human immunodeficiency virus (HIV)-infected patients [1]. Chest radiography is the preferred initial imaging examination for the evaluation of typical PCP, which commonly shows ground-glass appearance on the chest x-ray (CXR) films [2]. PCP only rarely presents with fulminant respiratory symptoms if diagnosis and treatment are early initiated [3]. However, pneumonia in progression or unresponsiveness to standard anti-PCP therapy in the HIV-infected patients may be due to other etiologies, for example, Cytomegalovirus (CMV), Mycobacterium tuberculosis (MTB) or fungus that may occur along or concurrently with PCP [4, 5].

A 50-year-old man presented to the emergency department complaining of intermittent fever and chills for 3 weeks. He has an 8-year history of HIV infection. He also had dry cough with chest wall pain, general weakness and body weight loss of 5 Kg in recent one month. He denied any hemoptysis, headache or hematuria.

The laboratory data revealed a white blood cell count of 2,200/μL (normal range, 3,200–9,200/μL) with 74% segment, 6% lymphocyte and 11% monocyte; hemoglobin, 9.4 g/dL; and platelet count, 166,000/μL (normal range, 150,000–400,000/μL). The biochemistry data included blood urea nitrogen, 16 mg/dL; creatinine, 1.11 mg/dL; lactic dehydrogenase (LDH), 386 IU/L (normal. 85-227 IU/L), lactic acid, 2.7 mmole/L (normal, 0.4-2.0 mmole/L); procalcitonin, 4.24 ng/mL (normal range, < 0.05 ng/mL), and C-reactive protein, 39.3 mg/L (normal range, < 5 mg/L). The HIV viral load revealed 122,000 copies/mL. The CXR revealed patches and micro nodular interstitial infiltrates of both lung fields (Figure 1). The T-cell markers revealed a low CD4 count (24/μL) and a CD4/CD8 ratio of 14%. The sputum cultures yielded few yeast only. The findings of sputum acid-fast stains were positive, which polymerase chain reaction (PCR) result using Gene Xpert MTB/RIF assay (Xpert) for TB was negative. The results of blood cultures yielded no growth. The data of cryptococcal antigen and Toxoplasma gondii antibodies were negative. The patient received antimicrobial therapy with anti-TB drugs, intravenous sulfamethoxazole/trimethoprim and ceftriaxone. Methylprednisolone by standard dosing regimen for PCP was given as adjunctive initial therapy.

However, dyspnea, hypoxia and change of consciousness developed. He was intubated and was transferred to the intensive care unit with unstable...
hemodynamic status. The CXR showed severely worsening of bilateral consolidation (Figure 2). Thus ceftriaxone was replaced by imipenem. A platelet count of 100,000/μL was noted, which dropped to the lowest level of 22,000/μL. The fibrinogen was 523.8 mg/dL (normal, 200-400 mg/dL); fibrin degradation products, 11.5 ng/mL (normal, <5 ng/mL); and D-dimer, 3037.9 ngFEU/mL (normal, <500 ngFEU/mL). The endotracheal aspirates cultures still yielded few yeast only. The results of serology for *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydia pneumoniae* were all negative. However, his condition was deteriorated and he died on the 8th day of hospitalization. He had positive CMV-PCR results of blood samples and endotracheal aspirates which were obtained on the day before his death. Thereafter, the cytology of endotracheal aspirates with Papanicolaou stains and Grocott methenamine silver stains reported findings of fungal hyphae but no cytological evidence of PCP, which would be characterized by the foamy alveolar casts containing *P. jiroveci*-like organisms. The *Aspergillus* galactomannan (GM) antigen assay was not performed in time before death. The sputum TB culture yielded slowly growing nontuberculous mycobacterium (NTM) after one month of incubation.

The CD4 count is predictive of the risk for developing PCP in patients with HIV infection. Our patient had a low CD4 count (24/μL), so empirical therapy against PCP was promptly started. Besides, CMV and NTM diseases could develop in such a low CD4 count status [5]. According to a report of 521 HIV-positive patients in USA, PCP (24%), NTM (11%) and TB (9%) were responsible for hospitalized respiratory diseases and mortality was 10%
for NTM disseminated cases [6]. The Xpert of PCR test can identify TB with high sensitivity (82-94%) and specificity (92-98%), which facilitates timely diagnosis and earlier appropriate management of MTB cases [7, 8]. In sputum positive for acid-fast bacilli smear, a negative Xpert result may usually imply NTM, which would rapidly grow after one week of incubation. We kept anti-TB therapy during the first week of course for the patient while pending on TB culture results. Besides, false-negative Xpert result could very occasionally occur [7, 8]. Some multiplex PCR assays able to discriminate between the MTB and clinically important NTM species are encouraging, which might need further clinical validation [9, 10].

The serum LDH has been reported to be elevated in most patients with PCP and CMV pneumonia [11]. The diagnosis of PCP relies on cytological characteristics of encysted sporozoites (by Papanicolaou stain) or cystic walls (by Grocott methenamine silver stain) on stained respiratory specimens [12]. CMV is the most frequent viral pneumonia seen in persons with HIV infection. Most cases of pneumonia occur in persons with a CD4 cell count less than 50 cells/μL. The presence of CMV in the respiratory specimens usually represents viral shedding, rather than actual pneumonitis. However, CMV pneumonia is often indicative of disseminated disease and is associated with significant mortality in an HIV-infected patient [11]. CMV pneumonia can manifest with second hit of fatal pneumonia subsequent to successful anti-PCP therapy, or initially as a primary pneumonia mimicking PCP [13, 14]. With regard to fungal hyphae noted in cytology, no further information could identify the true etiology in our patient. *Penicillium marneffei* and *Aspergillus* species, especially *A. fumigatus*, frequently cause invasive pneumonia in an HIV-infected patient [11]. The *Aspergillus* GM antigen assay has been demonstrated to facilitate rapid detection of invasive aspergillosis, but cross-reactivity was observed with *Penicillium marneffei* infection [15, 16]. The use of the GM antigen assay may facilitate earlier diagnosis of aspergillosis and penicilliosis for HIV-infected patients.

Rapid and accurate diagnosis of etiologies for pulmonary infections remains a great challenge for physicians who manage HIV-infected patients. For future improvement of outcome, the tests for *Aspergillus* GM antigen, fungal cultures, PCR for *P. jiroveci* and CMV from serum, induced sputum and/or bronchoalveolar lavage, could be initiated as earlier as appropriate, albeit they are not all included in the current system of routine diagnostic approach.

In conclusion, CMV, fungus, NTM and/or TB should be prudently considered in HIV patients with a CD4 count less than 50/μL, especially when pneumonia has no therapeutic response to anti-PCP therapy. However, we could not exclude the possibility of the development of resistance of *P. jiroveci* to sulfamethoxazole/trimethoprim of the preferred drug regimen.

**Conflicts of Interest**

All authors declare no potential conflicts of interest or financial support.

**References**


