Co-infection with *Nocardia farcinica*, 2009 H1N1 Influenza Virus and *Pneumocystis jirovecii* in an AIDS Patient

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**ABSTRACT**

We report a case of a 36-year-old newly diagnosed HIV-infected man presenting with low-grade fever, productive cough, and weight loss for 5 months. One week before admission, he developed high-grade fever and respiratory distress. His hospital course was complicated by severe pneumonia, right parapneumonic effusion, and respiratory failure, which required ventilatory support, and intercostal drainage. Culture results of endotracheal aspirates (ETA), pleural fluid, and blood revealed *Nocardia farcinica*. Surprisingly, rapid influenza A antigen assay and real-time reverse-transcriptase polymerase chain reaction assay for 2009 H1N1 influenza virus of ETA were also positive. The immunofluorescent assay for the detection of *Pneumocystis jirovecii* demonstrated cysts and trophozoites. He significantly improved after a 10-day therapy with trimethoprim-sulfamethoxazole, imipenem/cilastatin, amikacin, and oseltamivir. This case illustrates the need for a high index of suspicion of co-infection in advanced HIV patients. During the pandemic influenza, clinicians should keep in mind that an influenza virus is one of the leading causes of community-acquired pneumonia. (*J Infect Dis Antimicrob Agents* 2011;28:133-40.)

**Note:** This case had been presented and discussed in the Interhospital Case Conference on Infectious Diseases (ICCID), 7 October 2010, Phetchaburi, Thailand.

**INTRODUCTION**

*Nocardia* species are ubiquitous soil saprophytes, found in organic material, water, and plants worldwide. In immunocompetent hosts, nocardiosis usually presents as cutaneous infections. In immunocompromised hosts, it usually presents as pulmonary or disseminated infections.¹² Approximately one-third of nocardiosis occurs in HIV patients.³ Currently, there have been

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Received for publication: February 7, 2011.
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several reported cases of co-infection in HIV-associated nocardiosis such as mycobacterial, fungal, and *Pneumocystis jirovecii* infections. From our literature review, there is no case report of concomitant disseminated nocardiosis, 2009 H1N1 influenza virus pneumonia, and *Pneumocystis* infection in an advanced HIV-infected patient.

**CASE REPORT**

In August 2010, a 36-year-old Thai man was admitted to a tertiary care university hospital with a 5-month history of low-grade fever, productive cough, and significant weight loss. One week prior to admission, he developed high-grade fever, shortness of breath, and alteration of consciousness. He had no history of rhinorrhea, sore throat, or exposure to patients with influenza-like illness. The patient had no significant past medical illnesses. He denied history of neither illegal intravenous drug use nor unsafe sex.

On physical examination, temperature was 38°C, heart rate was 100/min, blood pressure was 110/50 mmHg, respiratory rate was 30/min, and cutaneous oxygen saturation was 90%. Oral thrush and oral hairy leukoplakia were presented. Pulmonary auscultation revealed decrease in breath sounds and fine crepitations at right lower lung field. Heart sounds were normal. He had no hepatosplenomegaly nor lymphadenopathy. The patient was drowsy, however, there was no sign of meningeal irritation or localizing neurological deficit. Complete blood count revealed a hemoglobin level of 9.7 g/dL, platelet count of 502,000 cells/mm³, and white blood cell count 22,070 cells/mm³ (neutrophil 80%, band form 15%, monocyte 4%, and lymphocyte 1%). Liver function test was remarkable for albumin of 2.1 g/dL and globulin of 4.9 g/dL. The ARCHITECT® HIV Ag/Ab Combo assay (Abbott Diagnostics, Wiesbaden, Germany) for HIV infection was reactive. The CD₄ T-lymphocyte count was 15 cells/μL (4.96%). Chest X-ray showed right middle lobe and right lower lobe consolidation, right pleural effusion, and bilateral reticular infiltration as shown in Figure 1. Computerized tomography scan of brain and cerebrospinal fluid studies were normal.

![Figure 1. An initial chest X-ray demonstrating right middle lobe and lower lobe consolidation, right pleural effusion, and bilateral reticular infiltration.](image)

At the emergency room, the patient was empirically treated with intravenous ceftriaxone and azithromycin to cover community-acquired bacterial pneumonia after taking two sets of aerobic blood culture. Despite the empirical antibiotic treatment, the patient deteriorated rapidly and required ventilatory support within the first 24 hours of admission. The results of Gram stain, acid-fast stain, and modified acid-fast stain of endotracheal aspirates (ETA) revealed branching filamentous organisms as shown in Figures 2 and 3. The immunofluorescent assay (IFA) for the detection of *P. jirovecii* demonstrated *Pneumocystis*
Figure 2. Gram stain of endotracheal aspirates showing a cluster of thin, delicate, gram-positive, beaded branching filaments (original magnifications x 1,000).

Figure 3. Modified acid fast stain of endotracheal aspirates showing red-stained filaments of *N. farcinica* against a blue background (original magnifications x 1,000).
cysts and trophozoites. Given the outbreak of 2009 H1N1 influenza virus infection in Thailand, the endotracheal aspirates were tested for influenza virus using the rapid influenza diagnostic test and real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) test for 2009 H1N1 influenza virus. Interestingly, the results were positive for influenza A and 2009 H1N1 influenza virus, respectively.

The patient was diagnosed as co-infection of HIV, nocardiosis, *P. jirovecii*, and 2009 H1N1 influenza virus. Accordingly, imipenem/cilastatin (500 mg IV four times daily), amikacin (400 mg IV twice daily), trimethoprim-sulfamethoxazole (TMP-SMX) (320 mg/1,600 mg IV three times daily), and oseltamivir (150 mg via nasogastric tube twice daily) were administered.

Two days later, a repeat chest X-ray revealed moderate pleural effusion of the right lung. Thoracocentesis was performed and revealed turbid yellowish fluid with nucleated cell count of 8,200 cells/mm³ (neutrophils of 94%, lymphocytes of 4%, mesothelial cells of 1%, and macrophage of 1%). Pleural fluid glucose was 3 mg/dL, whereas serum glucose was 120 mg/dL. The Gram stain and modified acid-fast stain of pleural effusion also showed branching filamentous bacteria. These findings indicated nocardial empyema thoracis which required an intercostal drainage. The culture results of ETA, pleural fluid, and blood were all positive for *Nocardia* spp. which was subsequently identified as *Nocardia farcinica* by using 16S ribosomal DNA and secA1 gene sequencing.7

The patient responded well to the combination therapy and was able to discontinue mechanical ventilation after 10 days of treatment. Fortunately, *N. farcinica* appeared to be susceptible to TMP-SMX (minimum inhibitory concentration was 0.5/9.5 μg/ml) by E-test method. Thus, imipenem/cilastatin and amikacin were discontinued. Three weeks after therapy, a full dosage of TMP-SMX was reduced to 160 mg/800 mg three times daily for the maintenance therapy of nocardiosis. One week later, a follow-up chest X-ray showed significant improvement of right pleural effusion and intercostal drainage was discontinued (Figure 4).

During his recovery period, he developed a hospital-acquired pneumonia from multidrug-resistant *Acinetobacter baumanii*. Despite the intensive respiratory care and colistin therapy, he died 45 days after admission. Permission for autopsy was denied.

**DISCUSSION**

Nocardiosis was first reported as a complication of HIV infection in 1985.8 To our knowledge, there are a few reported cases of AIDS-associated nocardiosis.9-15 In early 1980s, the prevalence of

![Figure 4. A follow-up chest X-ray one month after therapy showing a significant improvement of pulmonary infiltration and right pleural effusion.](image-url)
nocardiosis in patients with AIDS in North America was 0.3%. In previous case series, nocardiosis typically occurred in an advanced AIDS patient with a mean \( \text{CD}_4 \) T-lymphocyte count of 35 cell/\( \mu \)L.

The most common manifestation of nocardiosis in both immunocompetent and immunocompromised patients is pulmonary infection. One-third of pulmonary nocardiosis is associated with pleural effusion. Due to nonspecific clinical and radiologic manifestations, it is not uncommon that pulmonary nocardiosis has been easily misdiagnosed as tuberculosis or bacterial pneumonia. \textit{Nocardiida} spp. frequently spread to any other organs hematogenously, in particular the central nervous system. One-fourth to one half of patients with pulmonary nocardiosis in immunocompromised patients also develop brain abscesses. Interestingly, nocardia bacteremia is rare and mostly found in patients with underlying diseases, including malignancy, transplantation, and endovascular foreign bodies.

In Thailand, \textit{N. farcinica} is the most commonly isolated species from patients identified by 16S rDNA sequencing. Common clinical manifestations are pulmonary infections (43%), brain abscess (30%) and wound infections (15%). \textit{N. farcinica} isolates are generally sensitive to amikacin, linezolid, and imipenem, but frequently resistant to third-generation cephalosporins, clarithromycin, ciprofloxacin, gentamicin, and tobramycin. The resistance of \textit{N. farcinica} to TMP-SMZ may vary geographically. In the US, TMP-SMZ resistance increased from 67% in the 1990s to 91% in the 2000s. In patients with severe nocardiosis, most infectious disease specialists recommend empiric antibiotic coverage with two or three intravenous agents, such as amikacin, imipenem/cilastatin, or TMP-SMX, while waiting for the results of susceptibility testing. Initial treatment (induction therapy) should be administered intravenously for at least three to six weeks and/or until clear evidence of clinical improvement. In immunocompromised hosts, the total duration of therapy (intravenous followed by oral) in disseminated nocardiosis is generally recommended for at least one year.

According to the Clinical and Laboratory Standards Institute (CLSI) guidelines, broth microdilution (BMD) is the standard method for antimicrobial susceptibility testing of \textit{Nocardiida} species. The BMD method is resource-intensive and is impractical for many laboratories. Thus, the Epsilometer test (Etest) method has been proposed as an alternative to the BMD method. The Etest method is simpler, cheaper and more available in Thailand. However, there have been only a few comparative studies between BMD and Etest. Therefore, diagnostic accuracy of Etest is still controversial. In this case, BMD was not tested, but Etest revealed susceptibility to TMP-SMX and the patient responded well to TMP-SMX.

The 2009 H1N1 influenza virus was recently detected in Mexico and California in April 2009 and became the first pandemic influenza virus of the 21st century. In Thailand, the first case was reported on May 12, 2009. The spectrum of disease severity ranges from asymptomatic infection to fatal pneumonia. Currently, there are a few case reports of the 2009 H1N1 influenza virus infection in HIV patients worldwide. HIV patients with low \( \text{CD}_4 \) T-lymphocyte count have been reported to suffer from severe complications of this influenza. As a result, early influenza antiviral therapy is generally recommended for AIDS patients with clinical suspicion of influenza infection. At the present time, most of the 2009 H1N1 influenza virus and H3N2 influenza virus are susceptible to neuraminidase inhibitors, including oseltamivir and zanamivir, but are resistant to amantadine and rimantadine. Current seasonal H1N1 influenza virus is generally resistant to
oseltamivir, but is sensitive to zanamivir, amantadine, and rimantadine. Thus, influenza A virus subtype identification is vital for choosing appropriate antiviral therapy of severe influenza infection.

Pneumocystis jirovecii pneumonia (PCP) is the most prevalent opportunistic infection among HIV-infected patients with low \( \text{CD}_4 \) T-lymphocyte count (< 200 cells/\( \mu \text{L} \)).\(^{36} \) Common clinical presentations are subacute fever, nonproductive cough, and progressive dyspnea. Typical chest X-ray findings are bilateral perihilar interstitial infiltrations which progressively evolve into diffuse ground-glass opacification. Interestingly, pleural effusion is rare in PCP.\(^{37} \) It is essential to identify this organism by using microscopic examination or polymerase chain reaction of respiratory tract specimen, since \textit{Pneumocystis} cannot be cultured.\(^{38} \) \textit{Pneumocystis} has two life cycle forms, a trophic form and a cyst form. Trophic forms can be detected with Giemsa stain, whereas cysts can be demonstrated with Gomori methenamine silver stain. IFA for \textit{P. jirovecii} has higher sensitivity than conventional stains because this test can detect both trophic and cyst forms.\(^{38,39} \) \textit{Pneumocystis} colonization is more prevalent among HIV-infected patients, and has been reported approximately 46% in one study.\(^{40} \) Therefore, it is very difficult to differentiate between clinical infection and subclinical infection in this patient. Nevertheless, high dose TMP-SMX, a drug of choice for PCP therapy, is also effective against most \textit{Nocardia} species.

There have been many reported cases of co-infection in HIV patients with pulmonary nocardiosis, such as \textit{Pseudomonas aeruginosa}, aspergillosis, cryptococcosis, histoplasmosis, \textit{M. tuberculosis}, and PCP.\(^{46} \) To our best knowledge, this case is the first case report of AIDS patient with multiple co-infection including disseminated \textit{N. farcinica} (bacteremia, multilobar pneumonia, and empyema thoracis), 2009 H1N1 influenza virus, and \textit{P. jirovecii}.

In conclusion, HIV-infected patients with low \( \text{CD}_4 \) T-lymphocyte count are predisposed to develop multiple concurrent infections. During the pandemic influenza, clinicians should keep in mind that an influenza virus is one of the leading causes of community-acquired pneumonia. Rapid and accurate identification of \textit{Nocardia} isolates to the species level and influenza A virus subtypes is vital for the definite diagnosis and effective treatment.

References


