Fatal Pulmonary Co-infection with Pneumocystis and Cytomegalovirus in a Patient with Acquired Immunodeficiency Syndrome

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Abstract

A 33-year-old homosexual Japanese man who admitted to having sex with men presented with a two-week history of dyspnea and fever. Chest imaging showed diffuse pulmonary frosted-glass-like shadows. A blood test revealed positive HIV antibodies with a CD4 cell count of 66/μL. Bronchoalveolar lavage identified pneumocystis. Although the patient exhibited a transient response to anti-pneumocystis treatment and mega-dose steroid pulse therapy, he eventually died from respiratory failure. An autopsy suggested massive cytomegalovirus and pneumocystis pneumonitis. The pulmonary co-infection with cytomegalovirus may have been worsened by the use of mega-dose steroids, and such therapy should be avoided in patients with a high HIV viral load and low CD4 count.

Key words: Pneumocystis jirovecii, cytomegalovirus, acquired immunodeficiency syndrome, oral candidiasis


Introduction

Pneumocystis pneumonia (PCP) is one of the most common opportunistic respiratory infections in patients with acquired immunodeficiency syndrome (AIDS), and many untreated AIDS patients develop PCP (1). The in-hospital mortality of patients with HIV-related PCP was approximately 60% in the late 1980’s; however, it has recently decreased to approximately 10% owing to the improved diagnosis and treatment of PCP, including the adjunct use of moderate-dose steroid therapy (1). In this report, we present the case of an AIDS patient with PCP that initially responded to treatment with sulfamethoxazole and trimethoprim along with steroid pulse therapy, although the patient later developed fatal respiratory failure. An autopsy revealed findings of massive cytomegalovirus (CMV) pneumonitis as a contributory cause to the patient’s mortality. Since CMV pneumonitis is relatively rare in AIDS patients (2), the pulmonary CMV co-infection may have been worsened by the mega-dose steroid pulse therapy, and the use of such therapy should be avoided in similar cases.

Case Report

A 33-year-old Japanese man presented to his primary care physician with a two-week history of dyspnea, fever, malaise and a poor appetite. A simple chest film and plain chest CT scan showed bilateral frosted-glass-like shadows with mediastinal emphysema. Due to the patient’s hypoxemia (a pulse oximetry oxygen saturation of 85% on ambient air), he was referred to our hospital (Mito Kyodo General Hospi-

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He denied any headaches, nausea, vomiting or diarrhea. There was no history of recent travel or close contact with sick persons with flu-like symptoms. The patient also denied any previous medical or relevant family history. He was a non-drinker and had smoked five cigarettes a day for 10 years, although he had quit one year prior to admission. He had been unemployed for five years and spent most of his time in his own room. He was a man who had sex with men (MSM) and had experienced repeated unprotected sex with unspecified partners. A human immunodeficiency virus (HIV) test performed at 20 years of age had been negative. His height was 183 cm and his weight was 65 kg (body mass index: 19 kg/m²).

On a physical examination, the patient was found to be in acute respiratory distress. His vital signs were as follows: blood pressure = 117/64 mmHg, pulse rate = 122 beats/min and regular, body temperature = 39.5 degree Celsius, respiratory rate = 33 breaths/min and oxygen saturation = 97% while breathing 12 liters of oxygen via a non-rebreather mask. He had lingual thrush (Fig. 1), which revealed numerous budding yeasts on a microscopic examination using 10% KOH staining. Auscultation of the lungs demonstrated fine late-inspiratory crackles bilaterally. The patient’s cardiac sounds were regular, and no gallop sounds or murmurs were detected. His abdomen was soft and flat, without tenderness.

However, there was a perianal lesion of condyloma acuminatum.

The laboratory data were as follows: white blood cells = 12,200/μL (neutrophils, 84%; lymphocytes, 11.8%, eosinophils, 1.3%; basophils, 0.2%; monocytes, 2.9%), hemoglobin = 14.4 g/dL, platelets = 376,000/μL, PT-INR = 1.56 and PTT = 37.6 seconds. Serum chemistry showed a sodium level of 134 mEq/L, potassium level of 3.9 mEq/L, chloride level of 96 mEq/L, BUN level of 19 mg/dL, creatinine level of 0.95 mg/dL, total bilirubin level of 0.4 mg/dL, AST level of 71 IU/L, ALT level of 37 IU/L, lactate dehydrogenase level of 1,370 IU/L, beta-D-glucan level of 71.2 pg/mL (normal range, <= 20.0 pg/mL), sialylated carbohydrate antigen KL-6 level of 3,230 U/mL (normal range, <=500 U/mL) and erythrocyte sedimentation rate of 96 mm/hour. An arterial blood gas analysis performed while breathing 10 liters of oxygen via a non-rebreather mask showed a pH of 7.508, PaO₂ of 123 mmHg, PaCO₂ of 30.9 mEq/L and HCO₃ of 24.0 mEq/L.

Upon further investigations, HIV antibodies were found to be positive, and an RNA quantitation test revealed a titer of 6.7×10⁴ copies/mL with a CD4 cell count of 66/μL. Induced sputum smear tests were negative for bacteria, acid-fast bacilli and pneumocystis. PCR testing of the sputum was negative for *Mycobacterium tuberculosis* and *Mycobacterium avium* complex. CMV IgM antibodies were not detected, although IgG antibodies were positive. Blood cultures revealed no growth of bacteria. A chest X-ray and high-resolution CT showed bilateral diffuse frosted-glass-like shadows and mediastinal emphysema (Fig. 2, 3).

The differential diagnosis of respiratory insufficiency in this AIDS patient included pulmonary infections, such as bacterial pneumonia (*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Chlamydia pneumoniae* or others) or infection with mycoplasma, fungi (*Pneumocystis jirovecii*, Cryptococcus, Aspergillus) or viruses (CMV), as well as a non-infectious pathology, such as eosinophilic pneumonia, or idiopathic interstitial pneumonitis, including diffuse alveolar damage. Among these differential diagnoses, a diagnosis of PCP was suspected based on epidemiology (the most common AIDS-
defining infection) and the patient’s clinical course (subacute progression of dyspnea and fever) and imaging findings (bilateral diffuse frosted glass-like shadows).

Following tracheal intubation, fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) was performed, and the BAL fluid smear stained with Grocott’s stain demonstrated *Pneumocystis jirovecii* cysts (Fig. 4). Other BAL fluid smear and cytologic tests were negative for bacteria, acid-fast bacilli and multinucleated inclusion-body giant cells. Polymerase chain reaction testing of the BAL fluid was negative for *Mycobacterium tuberculosis* and *Mycobacterium avium* complex. Therefore, at that point, a diagnosis of AIDS-related PCP was considered.

Oral trimethoprim/sulfamethoxazole (ST) (960 mg per day) and intravenous fluconazole (200 mg every 24 h) were administered. The patient also received methylprednisolone at a dose of 1,000 mg per day for three days under a possible diagnosis of acute interstitial pneumonitis, subsequently followed by oral prednisolone at a dose of 80 mg for two days and 40 mg for five days. The mega-dose of steroids was used as an empiric option for the treatment of possible interstitial pneumonitis. Antiretroviral therapy was not administered. On day 4 after admission, the patient’s respiratory condition improved, and the trachea was extubated. He did not experience diarrhea, vomiting or constipation during the entire course of admission. However, on day 9, he developed again shortness of breath and fever. Treatment with intravenous vancomycin at a dose of 0.5 g every 12 hours and tazobactam/piperacillin at a dose of 4.5 g every six hours were administered due to the possibility of bacterial co-infection. In addition, the patient again received methylprednisolone at a dose of 500 mg for three days followed by oral prednisolone at a dose of 80 mg for two days, 40 mg for five days and 20 mg for two days (Fig. 5). The antibiotics were also switched to dorcipenem at a dose of 0.5 g every 12 hours and minocycline at a dose of 100 mg every 12 hours on day 14, while SMX/TMP was switched to intravenous pentamidine at a dose of 0.3 g every 24 hours.

The patient’s clinical status worsened after the second episode of respiratory failure and he eventually died on day 22 after admission. An autopsy was conducted, which revealed the following findings. The lungs were remarkably consolidated (Fig. 6). The alveoli were filled with foamy eosinophilic exudate, and the alveolar septa were markedly thickened due to heavy fibroblastic proliferation and hemorrhage. Foci of *P. jirovecii* were identified diffusely with eosinophil infiltration (Fig. 7). Furthermore, findings suggestive of massive CMV pneumonitis, i.e., numerous inclusion body giant cells along with inflammatory cell infiltrates, were present throughout the lungs (Fig. 8). Disseminated CMV infection was also identified in the adrenal glands,
heart, liver, right kidney, pancreas, spleen, thyroid and vermiform appendix. The pathology suggested that massive CMV pneumonitis in addition to PCP may have contributed to the patient’s respiratory failure and death. In addition, condyloma acuminatum was found in the anus. Neither the brain nor eyes were available for a post-mortem examination.

Discussion

In HIV-infected patients with progressive respiratory deterioration and strongly suspected PCP, the diagnosis of PCP should be confirmed and other concurrent pathological processes should also be ruled out, including other co-infections, such as CMV or tuberculosis, congestive heart failure and pulmonary embolism (3). In order to facilitate this diagnostic process, timely bronchoscopy is usually considered, with a rapid analysis of BAL fluid. However, the absence of inclusion body giant cells in the BAL fluid or increased IgM antibodies against CMV cannot be used to rule out active CMV pneumonitis (4, 5), as observed in the present case. Eye examinations for possible CMV retinitis may also provide clues for the early diagnosis of CMV infection.

It is important to consider the possibility of pulmonary co-infection with pneumocystis and CMV in AIDS patients with especially low CD4 counts and high HIV viral loads, despite the finding of negative BAL results or IgM antibodies against CMV, as demonstrated in this case (4). More importantly, mega-dose corticosteroid use may have induced the worsening of concurrent CMV pulmonary co-infection, and thus such dosing of these drugs should be safely avoided in AIDS patients with PCP (6, 7). The recommended dose of adjunct steroids for PCP in AIDS patients is usually moderate: approximately 2 mg/kg of methylprednisolone.

When administering such a high doses of steroids, clinicians must have a high index of suspicion due to the increased risk of infection with CMV, other fungi or mycobacteria (1). Since the incidence of CMV pneumonitis in AIDS patients is relatively rare, the use of mega-dose steroid therapy may have been associated with the worsening of disseminated CMV infection in our patient (8, 9). Another possible complication associated with the use of corticosteroids includes the increased risk of pneumothorax (1).

In conclusion, there is a risk of pulmonary co-infection with pneumocystis and CMV in AIDS patients with very low CD4 counts and high HIV viral loads. Negative tests for serum IgM antibodies against CMV and the absence of inclusion body giant cells are not reliable findings for ruling out active CMV infection. Since it is difficult to diagnose and timely treat pulmonary CMV infection, preventing CMV co-infection is important by avoiding the administration of mega doses of steroids.

Author’s disclosure of potential Conflicts of Interest (COI).
Makoto Aoki: Employment, Sakura Seiki Corp.

References

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