Complications During Clinical Courses of *Pneumocystis Carinii* Pneumonia in Patients with Acquired Immunodeficiency Syndrome

Katsuji Teruya, Akira Yasuoka, Masazumi Yamaguchi, Chie Yasuoka, Yoshihiko Yamamoto, Ikumi Genka, Natsuo Tachikawa, Yoshimi Kikuchi and Shinichi Oka

Abstract

**Objective** To describe the incidence of complications before and during therapy of *Pneumocystis carinii* pneumonia (PCP) in patients with acquired immunodeficiency syndrome (AIDS).

**Methods** A retrospective review of the patient’s medical records.

**Patients** A total of 29 patients with AIDS and PCP who were admitted to the AIDS Clinical Center, International Medical Center of Japan from July 1996 to November 1999.

**Results** Adverse effects were found in 24 (88.9%) of 27 patients treated with trimethoprim/sulfamethoxazole (T/S), 6 (46.1%) of 13 treated with parenteral pentamidine, and 2 (20%) of 10 treated with inhaled pentamidine. Infectious and/or non-infectious complications were found in 25 (86.2%) of 29 study patients. Regarding infectious complications, 16 (55.2%) were found on admission and 10 cases (34.5%) with infectious complications were identified during admission; including oral candidiasis (37.9% and 17.2%, respectively) and genital herpes (3.4% and 6.9%, respectively). Cytomegalovirus antigenemia was detected in 4 cases (13.8%) on admission and 12 cases (41.4%) during admission. Non-infectious complications affected 11 cases (37.9%) on admission, and 6 cases (20.7%) during admission, the latter included heart failure (10.3%) and pneumothorax (6.9%). PCP was successfully treated in all but one patient who suffered from repeated pneumothorax.

**Conclusion** Treatment of PCP can be problematic and it is important to be aware of the high incidence of various complications that can occur during the treatment of PCP. (Internal Medicine 40: 221–226, 2001)

**Key words:** trimethoprim/sulfamethoxazole, pentamidine, pneumothorax, heart failure, cytomegalovirus, oral candidiasis

Introduction

*Pneumocystis carinii* pneumonia (PCP) is one of the most common opportunistic infections seen in patients with acquired immunodeficiency syndrome (AIDS) and has been associated with a considerably high rate of mortality (10–20%) (1). The treatment of PCP is now well established and the prognosis has improved (2). However, the management of PCP remains problematic due to adverse effects of trimethoprim/sulfamethoxazole (T/S) or pentamidine and from other infections and/or non-infectious complications during therapy. Furthermore, adjunctive use of corticosteroids in the treatment of PCP can induce other opportunistic infections.

As the number of HIV-1 infected patients is gradually increasing in Japan, the potential for patients with PCP to present to physicians will increase. Therefore, highlighting the complications seen at diagnosis or during therapy of PCP is clinically important and this information is particularly useful for physicians with limited experience in the management of HIV-1 infection.

Patients and Methods

**Patients** A total of 29 patients with AIDS and first episode PCP who were admitted to the AIDS Clinical Center, International Medical Center of Japan from July 1996 to November 1999, were included in this study. The definitive diagnosis of PCP was made by detection of *Pneumocystis carinii* (Pc) in bronchoalveolar lavage from 28 patients. In one patient, PCP was clinically suspected and the diagnosis was confirmed by detection of Pc DNA in serum by the polymerase chain reaction.

**Methods** A retrospective review of the patient’s medical records was undertaken. All adverse events, including adverse effects from...
the prescribed drugs, other infectious and/or non-infectious complications were included, up to and including day 30 post PCP diagnosis.

**Complications during the course of PCP**

Values of sodium (Na) less than 130 mEq and potassium (K) of more than 5.5 mEq were defined as electrolyte disorder. Transaminase values of more than 60 IU/l were considered as liver dysfunction. Blood glucose level of less than 60 mg/dl, white blood cell counts less than $2 \times 10^3/\mu l$, and a serum creatinine level of more than 1.3 mg/dl were also considered abnormal. Other infections were diagnosed based on clinical manifestation and detection of causative organisms. Cytomegalovirus (CMV) pneumonia was suspected clinically in two cases but these were not included in this study because a definitive diagnosis was not made. When CMV antigenemia was positive, cases were listed as infectious complications, however they were not included in the laboratory analysis of infectious complications because they were not considered as onset of active clinical infections.

**Results**

The demographic characteristics of patients are listed in Table 1. Twenty-two patients were diagnosed with HIV-1 infection just after the diagnosis of PCP. Among 7 patients who were diagnosed with HIV-1 infection before the onset of PCP, prophylaxis for PCP was not initiated in 4 cases due to the lack of regular visits to the outpatient clinic. One patient failed to start prophylaxis because of his rapid decline in CD4 count. Two patients had received prophylaxis with inhaled pentamidine. No patients were receiving the treatment with antiretroviral drugs at the time of diagnosis of PCP, however two cases had a previous history of antiretroviral therapy.

The measurement of partial pressure of arterial oxygen ($\text{PaO}_2$) in room air on admission was available in 25 cases (86.2%). Nineteen (65.5%) of 29 patients met the criteria of respiratory failure [$\text{PaO}_2$ less than 70 mmHg or (A-a) $\text{DO}_2$ more than 35 mmHg] and were then co-administered corticosteroids.

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of Pts or mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male vs. Female</td>
<td>27 vs. 2</td>
</tr>
<tr>
<td>Age</td>
<td>38±11.7</td>
</tr>
<tr>
<td>CD4 counts (μl) on admission</td>
<td>68.2±57</td>
</tr>
<tr>
<td>Prophylaxis of PCP</td>
<td></td>
</tr>
<tr>
<td>Yes vs. No</td>
<td>2 vs. 27</td>
</tr>
<tr>
<td>$\text{PaO}_2$ (Torr) in room air (n=25)</td>
<td>67.7±15.8</td>
</tr>
<tr>
<td>$\geq 70$ Torr vs. $&lt;70$ Torr</td>
<td>13 vs. 12</td>
</tr>
<tr>
<td>(A-a) $\text{DO}_2$ (Torr)</td>
<td>70.2±76.3</td>
</tr>
</tbody>
</table>

T/S was initially used for the treatment of PCP in all but two cases. When patients were not able to continue T/S because of adverse effects, the therapy was changed to 3 mg/kg of intravenous or 300 mg of inhaled pentamidine until the end of the 21-day treatment course. Intravenous pentamidine was used as an initial therapy in two cases because they were known to have an allergy to T/S. Ten patients finished their initial drugs for the treatment period (nine with T/S and one with pentamidine). T/S was changed to pentamidine in 18 patients. Two patients demonstrated allergic reaction to both drugs. Both were treated successfully, one with clindamycin and primaquine, and the other with atovaquon.

Adverse effects of T/S were found in 24 (88.9%) of 27 patients (Fig. 1). Skin rash and electrolyte disorder were the most common side effects (40.7%). Skin rash and fever were the most common cause of cessation. Only 9 (33.3%) out of 27 patients were able to finish the total course of treatment with T/S. Fever and skin rash occurred between day 8 and day 11 of treatment (data not shown). T/S-induced pneumonitis was suspected clinically in one case. In this case, treatment with T/S was discontinued because of elevation of liver enzyme; the therapy was changed to parenteral pentamidine. After successful treatment of PCP, a single dose of T/S was rechallenged for post-treatment suppression of PCP. He developed fever of 40°C on the day of the rechallenge, and abnormal interstitial shadow on the chest film appeared on the following day. The drug was discontinued after initial administration; the abnormal shadow on chest film was exacerbated for 3 days and subsided gradually, and fever continued for 7 days. We clinically diagnosed this case as drug-induced pneumonitis. We administered diaphenylsulfone, which is a type of sulfonamide, as an alternative, and he again developed pneumonitis on the 14th day of administration, which seems to support the diagnosis.

Administration of pentamidine was also associated with a high frequency of side effects (parenteral: 46.1%, inhaled: 20%) (Fig. 2). Four probable cases of drug-induced pneumonitis occurred (3 with parenteral and 1 with inhaled administration). The diagnoses in these cases were clinically made based on both temporal relationship between administration of the drug and emergence of abnormal interstitial shadow on chest X-ray and spontaneous resolution without any specific treatment after cessation of the drug. In one case, pneumonitis developed with both intravenous and inhaled pentamidine.

Figure 3 shows other infections diagnosed during the course of PCP. Fifteen cases (55.1%) were complicated by other infections at the time the diagnosis of PCP was made. Among them, 11 patients (37.9%) had oral candidiasis and 2 patients (6.9%) had amoebic dysentery. During therapy for PCP, 9 patients (34.5%) were diagnosed with other infections; 5 patients (17.2%) developed oral candidiasis, 2 patients (6.9%) genital herpes, and 2 patients Mycobacterium avium complex infections. All of them were successfully treated. CMV antigenemia was positive on admission (n=4) or became positive during admission (n=12). However, no definitive CMV diseases such as retinitis or pneumonia were documented.

Figure 4 shows non-infectious complications that occurred...
Complications of PCP in AIDS

Figure 1. Adverse effects of trimethoprim/sulfamethoxazole (T/S) in 27 HIV-1-infected patients with Pneumocystis carinii pneumonia. Shaded bars indicate an adverse effect by which T/S was ceased. Some cases experienced plural adverse effects.

Figure 2. Adverse effects of pentamidine isetionate in HIV-1-infected patients with Pneumocystis carinii pneumonia. White bars indicate total patients with that adverse effect. Some cases experienced plural adverse effects.

during the course of admission for PCP. Non-infectious complications affected 11 patients (37.9%) on admission, and 6 patients (20.7%) during treatment. Two patients had already been intubated before the diagnosis of PCP.

Adrenal insufficiencies were identified in 3 cases (10.3%) on admission. Among them, hyponatremia, hyperkalemia, and/or skin pigmentation were documented. The diagnosis was confirmed by elevation of adrenocorticotropic hormone (ACTH) in the serum. Heart failure (3 cases), pneumomedastinum (3 cases), and pneumothorax (2 cases) were severe complications during therapy.

Discussion

Drug therapy for the treatment of PCP with either T/S or parenteral pentamidine is effective. However, the incidence of toxic adverse effects associated with the therapy has been significant (3, 4). In their study, only half of the patients completed the 21-day treatment course without changing drugs. In our study, a markedly high incidence (88.9%) of adverse effects related to T/S were observed and only 33.3% of the patients completed a 21-day course of treatment without chang-
Figure 3. Infectious complications in 29 HIV-1-infected patients with Pneumocystis carinii pneumonia (PCP). White bars indicate complications seen at the diagnosis of PCP, and shaded bars are those seen during the therapy. *MAC: Mycobacterium avium complex, **CMV: Cytomegalovirus.

Figure 4. Non-infectious complications in 29 HIV-1-infected patients with Pneumocystis carinii pneumonia (PCP). White bars indicate complications seen at the diagnosis of PCP, and shaded bars are those seen during the therapy. *SIADH: syndrome of inappropriate secretion of ADH, **CVD: cerebrovascular disease.
Complications of PCP in AIDS

The present study showed that patients with AIDS and Pneumocystis carinii pneumonia (PCP) have a high incidence of complications, including pneumothorax, which is believed to occur by rupture of sub-pleural cysts (25). Chow et al (25) reported that, in a series of 100 patients with PCP, 35% of patients with cystic PCP developed pneumothorax versus 7% of patients with non-cystic PCP, a statistically significant difference. In our patients, cystic lesions were documented by the chest computed tomographic scan before the onset of pneumothorax in all cases, and 2 of 4 cases with pneumothorax were antecedent by pneumomediastinum. It has been reported that inhaled pentamidine for prophylaxis is associated with an increased risk of pneumothorax (26). However, in the present 4 cases of pneumothorax, none had a history of inhaled pentamidine and two developed pneumatoceles during therapy. The precise mechanism of formation of cystic lesion in the lungs needs further study.

In conclusion, a very high incidence of complications was noted during the course of PCP with adverse effects from the administered drugs; T/S and pentamidine showed a markedly high incidence. It remains to be elucidated whether or not such a high incidence of adverse events of anti-PCP drugs is peculiar to patients with HIV infection. Here, the incidence of other infections was also high, but they could be treated successfully. Pneumothorax and pneumomediastinum were not rare complications and pneumothorax was the cause of death in one case. Treatment of PCP can be problematic and it is important to be aware of the high incidence of various complications that can occur during this treatment.

Acknowledgements: The authors thank Helen Fraser for the careful reading and editing of the manuscript.

This work was supported by the Ministry of Health and Welfare of Japan, and the Organization of Pharmaceutical Safety and Research.

References

6) Yoshizawa S, Yasuoka A, Kikuchi Y, et al. A 5-day course of oral desensitization to trimethoprim-sulfamethoxazole (T/S) is successful in patients with human immunodeficiency virus type-1 infection who were previously intolerant to T/S but had no sulfamethoxazole-specific IgE. Ann Allergy Asthma Immunol 85: 241-244, 2000.