Fatal Pneumonia Associated with Temozolomide Therapy in Patients with Malignant Glioma

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This report presents the cases of three patients with fatal pneumonia that was highly suspected to be Pneumocystis pneumonia (PCP) based on serological diagnosis. Their chest radiographs showed bilateral pneumonia and each had presented with severe respiratory failure requiring mechanical ventilation when they arrived at the hospital. Although bronchoscopic sampling could not be performed, their chest computed tomography imaging and a marked elevation of serum KL-6 and β-D-glucan levels were characteristic of Pneumocystis pneumonia. All three were found to have been treated with temozolomide after surgery for malignant glioma. Temozolomide can cause Pneumocystis pneumonia. The three patients did not receive prophylactic medication against Pneumocystis pneumonia during treatment with temozolomide, and their histories suggested that all had delayed seeking treatment. It may be difficult to diagnose Pneumocystis pneumonia because the symptoms are not specific for Pneumocystis pneumonia and they tend to be similar to those of common respiratory infectious diseases. Therefore, patients who receive temozolomide therapy have the potential to develop fatal pneumonia and should be carefully observed. The patients should also be adequately informed about Pneumocystis pneumonia, and prophylaxis against Pneumocystis pneumonia should be considered proactively before treatment with temozolomide is initiated.

Key words: temozolomide – malignant glioma – fatal pneumonia – Pneumocystis pneumonia

INTRODUCTION

Immunocompromised patients are susceptible to infections by various organisms. Pneumocystis pneumonia (PCP) is an opportunistic disease among patients infected with human immunodeficiency virus (HIV). In addition, patients treated with corticosteroid, immunosuppressive drugs, and anti-cancer drugs also have the potential to develop PCP. There is an increased incidence of PCP in patients without HIV (1). The severity and prognosis of PCP differs between HIV and non-HIV patient (2–5). The clinical course tends to be subacute, and the mortality is relatively low in patients with HIV. On the other hand, non-HIV patients with PCP have more aggressive disease with higher mortality rates. Careful observation and/or prophylaxis is needed for patients at risk of developing PCP due to an immunocompromised state other than HIV infection.

Temozolomide, an anti-cancer drug for malignant glioma, is associated with PCP (6–8), and the package insert warns physicians about the risk for PCP. Accurate data on the incidence and mortality of fatal pneumonia or PCP associated with temozolomide are unclear and post-marketing surveillance has been ongoing in Japan. This report presents three cases of fatal pneumonia in patients treated with temozolomide for malignant glioma in the course of just 3 years. These cases were strongly suspected to be PCP based on serological diagnosis. This report considers the background of the fatal outcome for all patients and presents the issues
CASE REPORT

CASE 1

A 67-year-old female presented with severe pneumonia. The patient had received radiation and chemotherapy with temozolomide followed by surgery for glioblastoma 3 months earlier, and after that, the patient had been received maintenance therapy with temozolomide. The patient sought treatment at a private clinic after two cycles of maintenance therapy, because she had a cough and fever. The patient was initially diagnosed to have a common cold. The patient returned 3 days later because the symptoms did not improve. The patient was diagnosed to have pneumonia and therefore was examined by an attending doctor of this hospital. Chest X-rays showed bilateral pneumonia (Fig. 1A) and an arterial blood gas analysis revealed hypoxemia (\( \text{PaO}_2: 63.0 \text{ torr}, \ \text{PaCO}_2: 24.0 \text{ torr} \)), and thus, the patient received oxygen inhalation and empirical treatment with piperacillin–tazobactam (13.5 g/day) and trimethoprim–sulfamethoxazole (trimethoprim 320 mg/day). However, the pneumonia rapidly progressed on the following day (Fig. 1B) and required mechanical ventilation. The patient was transferred to this department on the 7th hospital day because her condition did not improve. Computed tomography (CT) findings of bilateral ground-glass opacities with a mosaic pattern (Fig. 1C), elevation of serum KL-6 and \( \beta-d \)-glucan (KL-6: 4412 U/ml, \( \beta-d \)-glucan: 6840 pg/ml; the normal range of KL-6 and \( \beta-d \)-glucan is <500 U/ml and <20.0 pg/ml, respectively), a negative test for cytomegalovirus antigenemia and no detection of organisms from blood and sputum culture strongly suggested PCP. Steroid pulse therapy was initiated and the dosage of trimethoprim–sulfamethoxazole was increased (trimethoprim 960 mg/day). The lung infiltrative shadow and blood oxygenation started to improve after 2 days (Fig. 1D). However, the patient’s condition was complicated by liver dysfunction, disseminated intravascular coagulation (DIC) and shock. Unfortunately, the patient eventually died from multiple organ failure.

Figure 1. (A) A chest X-ray showed bilateral patchy ground-glass opacities. (B) A chest X-ray on the following day showed deterioration of infiltrative shadows. (C) A chest computed tomography (CT) scan on admission. Ground-glass opacities with a distinct mosaic pattern were seen in both lungs. (D) After the dose escalation of trimethoprim–sulfamethoxazole with steroid pulse therapy, infiltrative shadows of both lungs improved slightly.
CASE 2

The patient was a 49-year-old male who was transferred to this hospital because of severe pneumonia. He had received radiation and chemotherapy with temozolomide followed by surgery for glioblastoma 5 months earlier and had received maintenance therapy with temozolomide. He was admitted to a hospital because of a seizure due to tumor growth. He had felt breathlessness a few weeks before admission, and respiratory failure progressed after admission. Chest CT showed bilateral ground-glass opacities (Fig. 2A and B), and the attending doctor transferred the patient to this hospital in order to receive intensive treatment. *Staphylococcus aureus* was identified by sputum culture; however, it seemed unlikely that *S. aureus* was the main cause of severe pneumonia because most of the shadows observed by CT were ground-glass opacities rather than air-space consolidation, and there was non-segmental infiltration. Though *Pneumocystis jirovecii* was not detected in sputum by microscopy, PCP was suspected because the serum level of KL-6 and β-D-glucan revealed marked elevation (KL-6: 1233 U/ml, β-D-glucan: 21000 pg/ml). He was treated with trimethoprim–sulfamethoxazole (trimethoprim 960 mg/day) and piperacillin–tazobactam (13.5 g/day) concurrent with prednisolone (80 mg/day). The pneumonia did not improve despite intensive treatment, and the patient developed DIC and multiple organ failure. Furthermore, he was complicated with bilateral pneumothorax (Fig. 2C) and died from respiratory failure.

CASE 3

The patient was a 61-year-old male who had undergone surgery for anaplastic oligoastrocytoma 1 year earlier. The tumor relapsed and temozolomide was initiated for treatment. He had experienced cough, fever and anorexia for 11 days prior to admission. Chest CT showed bilateral ground-glass opacities (Fig. 3A and B), and arterial blood gas analysis revealed severe hypoxemia (PaO2: 46.3 torr, PaCO2: 38.6 torr on 10 l/min of oxygen inhalation) on admission. *Haemophilus influenzae* and *Pseudomonas aeruginosa* were positive in the sputum culture, and *Pneumocystis jirovecii* was not detected in sputum by microscopy. However, it seemed unlikely that *H. influenzae* and *P. aeruginosa* were the main cause of the severe pneumonia because CT showed the same findings described in Case 2. The serum level of KL-6 and β-D-glucan showed marked elevation (KL-6:2820 U/ml, β-D-glucan: 10050 pg/ml). These findings strongly suggested PCP. He was treated with trimethoprim–sulfamethoxazole (trimethoprim 720 mg/day) and meropenem (1 g/day) with

Figure 2. (A) Patchy ground-glass opacities were seen in an apical portion of the lungs. (B) Perihilar predominant ground-glass opacities were seen at the level of the carina. (C) Bilateral pneumothorax had occurred on the 13th day from admission to our hospital.
steroid pulse therapy (methylprednisolone 1 g/day). The pneumonia did not improve despite the treatment, and the patient died on the 8th day in hospital.

**DISCUSSION**

The three cases of fatal pneumonia presented herein were strongly suspected to have PCP based on serological diagnosis. The definitive diagnosis of PCP is made by the detection of organisms in respiratory samples such as sputum, bronchoalveolar lavage (BAL) fluid or lung tissue. No organisms could be detected by microscopy in sputum specimens from Cases 2 and 3. The detection sensitivity of organisms thought to be higher in BAL fluid than sputum. However, it is difficult to obtain respiratory samples in cases with severe respiratory failure. Bronchoscopy could not be performed at the initial visit because all three cases presented with severe respiratory failure. Therefore, PCP was diagnosed and the treatment was started based only on their backgrounds and clinical findings. First, those patients were thought to be immunocompromised hosts because they were under treatment with corticosteroid and temozolomide, which are associated with a risk for opportunistic infections, including PCP. Secondly, chest CT showed bilateral diffuse ground-glass opacities with sparing of the lung periphery. The pneumonia did not improve despite the treatment, and the patient died on the 8th day in hospital.

Figure 3. (A) A CT scan at the level of the upper lobes. Severe emphysematous change was seen in both lungs and diffuse ground-glass opacities were seen in the residual lungs. (B) A CT scan at the level of the lower lobes. The right lower lobe showed bullous emphysema. Ground-glass opacities sparing the lung periphery were seen on the left lower lobe.

Our cases showed severe respiratory failure and died despite aggressive treatment for PCP. In general, PCP in non-HIV patients has a tendency to show a poorer prognosis than that in HIV patients (3–5,18). There is a difference in the number of neutrophils in BAL fluid in HIV and non-HIV patients, and it is estimated that the higher number of neutrophils contributes to the severity of PCP and poor prognosis in non-HIV patients (19).
mechanical ventilation is a prognostic factor for PCP (20,21). These cases suggest that the starting treatment for PCP before the patients’ condition becomes severe could improve prognosis. The current cases all showed the patient’s delay in the starting treatment for PCP. Case 1 was misdiagnosed as a common cold and the patient had been observed for 3 days without appropriate treatment. Case 2 did not seek treatment, even though he had experienced a cough and fever for 11 days. If they had received appropriate treatment earlier, then their condition would not have become so severe and they could have most likely survived. It is therefore important for patients and doctors to recognize the possibility of developing PCP during treatment with temozolomide. In conclusion, physicians should be aware of the risk of fatal pneumonia or PCP in patients under treatment with temozolomide and, prophylaxis should thus be considered proactively in those patients. Sufficient training to ensure appropriate monitoring and risk management related to PCP is needed for all physicians who use temozolomide. In addition, all patients treated with temozolomide should be advised to go to their doctor immediately when they experience symptoms of PCP.

Conflict of interest statement

None declared.

Table 1. Patients’ characteristics and laboratory data on admission

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tbody>
<tr>
<td>Age</td>
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<td>49</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>M</td>
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<tr>
<td>Concomitant use of corticosteroid</td>
<td>Betamethasone, 4 mg/day</td>
<td>Betamethasone, 6 mg/day</td>
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<td>Duration of temozolomide therapy</td>
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<td>3.5 months</td>
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<td>Radiation therapy</td>
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<td>+</td>
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</tr>
<tr>
<td>Lymphocyte (μl⁻¹)</td>
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<tr>
<td>CD4 T-Cell (μl⁻¹)</td>
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<td>CRP (mg/dl)</td>
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<td>KL-6 (U/ml)</td>
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</tr>
<tr>
<td>β-1,3-Glucan (pg/ml)</td>
<td>6840</td>
<td>21 000</td>
</tr>
</tbody>
</table>

*Duration of temozolomide therapy is defined as the time from the first administration of temozolomide to the onset of symptoms.

†Pre-treatment delay time is defined as the time from the onset of symptoms and the induction of appropriate treatment for PCP.

References