Influenza in Three Patients with Human Immunodeficiency Virus Infection

Shigeki Nabeshima, Iwao Ariyama, Yong Chong, Kohei Hirotsu, Kyoji Kakuda, Jun Hayashi and Seizaburo Kashiwagi

Abstract

Three Japanese outpatients with human immunodeficiency virus (HIV) infection on anti-retroviral therapy showed evidence of influenza in January 1999. CD4+ T cell counts of these patients prior to the diagnosis of influenza were 72, 248, and 152/mm³, and HIV RNA levels were 19,953, 1,259, and 1,585 copies/ml, respectively. Fever continued 4 to 5 days with no severe complications. One patient showed post-influenzal bronchitis which was effectively treated by antibiotics. None of these patients showed increased serum HIV RNA levels during and after influenza, however, in one patient, a transient reduction of CD4+ and CD8+ cells was seen during the active phase of influenza. Although symptoms of influenza in HIV carriers are generally mild and similar to those in healthy adults, careful follow-up is needed as symptoms of influenza in some HIV-infected patients can be prolonged and serious.

Key words: CD4, CD8, HARRT

Introduction

Influenza remains a prominent cause of morbidity and mortality especially in older persons and patients with cardiovascular diseases or pulmonary diseases (1–3). Annual administration of influenza vaccine is recommended for these high risk groups (4). Immunocompromised hosts, such as patients with human immunodeficiency virus (HIV)-infection, cancer, or leukemia also have an increased risk for infection, severe symptoms, and death (5). An increase in pneumonia-related deaths among young adults, in relation to the HIV epidemic, has occurred in persons in the United States (6). Although it has been reported that symptoms of influenza in HIV-infected subjects are generally mild and similar to those in controls, it has also been reported that, in some HIV-infected patients, symptoms can be prolonged and the complications are remarkable (7–10). Acute interstitial pneumonia caused by influenza virus in HIV-infected patients is sometimes difficult to diagnose because of the similarity to Pneumocystis carinii pneumonia (8, 9). It is unknown whether infection with influenza virus in HIV-infected patients can affect the number of CD4+ lymphocytes or HIV RNA levels in vivo, although the several reports have stated that the vaccination of influenza antigen could increase the replication of HIV (reviewed in 11). At present, the mechanism through which HIV-infected patients can recover from influenza, despite low CD4+ T cell counts, is unknown.

We report here three Japanese patients with influenza A and HIV-infection, all of whom were on anti-retroviral therapy. Exacerbation of the symptoms of influenza and an increase in HIV RNA in blood samples during the clinical course did not occur.

Case Report

Three HIV-infected outpatients receiving anti-retroviral therapy at Kyushu University Hospital showed symptoms of influenza in January 1999. Characteristics of these patients are summarized in Table 1, and the clinical courses are shown in Fig. 1. None had previously been given influenza vaccine.

Case 1

A 23-year-old man with hemophilia A and chronic hepatitis C was on anti-retroviral therapy in our HIV clinic from 1995. The HIV and hepatitis C virus were thought to be transmitted by clotting factors. CD4+ cell counts were stable at 60–90/mm³, and HIV RNA levels were >15,000 copies/ml from 1995 to 1998. Anti-retroviral therapy was insufficient in this case, since protease inhibitors were not able to be administered because of severe intramuscular hemorrhage. Sulfamethoxazole-trimethoprim and clarithromycin were administered from 1997 for prophylaxis of Pneumocystis carinii pneumonia and Mycobacterium avium complex infection, respectively. He had no
opportunistic infections due to the progression of HIV infection, except oral candidiasis. Anti-retroviral therapy of zidovudine and lamivudine was changed to didanosine and stavudine in November 1998 due to a gradual increase of viral load.

He was admitted to the hospital on January 18, 1999 with high fever, sore throat, dry cough, and myalgia. Onset of flu symptoms was two days before admission (day 1). Body temperature was 39.1°C, and heart rate was 114/min. Physical examination revealed injected pharynx and lymphadenopathy in the neck. Peripheral cyanosis was not seen. White blood cell count was 4,650/mm³, and serum C-reactive protein (CRP) was elevated to 2.0 mg/dl. Levels of serum alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) were elevated to 604 and 1,450 U/l, respectively. No evidence of hypoxemia was found in the arterial blood. Chest X-ray and computed tomography showed no abnormality in the lung field. Influenza A was diagnosed by virus isolation and by influenza antigen using Directigen Flu A (Becton Dickinson & Co., Sunnyvale, CA) from the throat swab taken on day 3, as well as the elevated hemagglutination inhibition (HI) titer in paired sera (Table 2). Neither influenza A antigen or influenza virus from the throat swab were detected on day 5. The subtype of influenza virus was A/H3N2. Body temperature became normal on day 6, and serum CRP was 0.1 mg/dl (Fig 1; Case 1) with no administration of anti-influenza drugs. An antibiotic (cefotiam) was given for 5 days as a prophylactic for a secondary bacterial infection. ALT and LDH levels decreased to 122 and 662 U/l, respectively, one month after the onset of influenza. HIV RNA levels before (November 30, 1998), during (day 3; January 18, 1999), and after influenza (day 13; January 28) were 19,953, 3,162, and 5,012 copies/ml, respectively (Table 1). The reduction of HIV RNA levels in January 1999 was thought to be due to the change of anti-retroviral drugs in November 1998. CD4⁺ cell counts before, during, and after influenza were 72, 87, and 77/mm³, respectively, and CD8⁺ cell counts were 551, 431, and 506/mm³, respectively.

Case 2
A 41-year-old homosexual man with chronic hepatitis B was diagnosed as an HIV carrier in 1997. HIV RNA levels and CD4⁺ cell counts were 25,000 copies/ml, and 53/mm³, respectively. He was placed on highly active anti-retroviral therapy (HAART) with zidovudine, lamivudine, and indinavir in our clinic from 1997. After the treatment, HIV RNA levels and CD4⁺ cell counts ranged from 700–1,600 copies/ml and from 180–250/mm³, respectively. Anti-retroviral drugs were changed to didanosine, stavudine and nelfinavir because of a gradual increase of HIV RNA levels from 1998. Sulfamethoxazole-trimethoprim and clarithromycin were administered from 1997 to didanosine, stavudine and nelfinavir because of a gradual increase of viral load.

He was admitted to the hospital on January 18, 1999 with high fever, sore throat, dry cough, and myalgia. Onset of flu symptoms was two days before admission (day 1). Body temperature was 39.1°C, and heart rate was 96/min. On physical examination, pharynx was injected and tonsils were slightly swollen but with no purulent material. Peripheral cyanosis was not seen. The CRP was 0.5 mg/ml, and white blood cell count was 7,000/mm³. There was no abnormal shadow on the chest X-ray. All the symptoms but cough were alleviated by day 6 (Fig 1; Case 2) without administration of an anti-influenza drug nor antibiotics. Influenza A was diagnosed later based on the elevated HI titer in paired sera (Table 2). The subtype of influenza virus was A/H3N2. On day 7, the patient came to our hospital again with fever, productive cough, and wheeze because of a secondary bronchitis. The chest X-ray revealed no evidence of pneumonia. Causative bacteria were not detected in sputum cultures, and the bronchitis was effectively treated with levofloxacin for 7 days. HIV RNA levels before (December 14, 1998), during (day 2; January 7 and day 5; January 11, 1999), and after (day 13; January 18) influenza were 1,259, 1,585, 1,259, and 631 copies/ml, respectively. However, CD4⁺ cell counts decreased from 248/mm³ (December 14, 1998) to 94/mm³ (day 2) and 47/mm³ (day 5), and were restored to 275/mm³ (day 13). CD8⁺ cell counts before (December 14, 1998), during (day 2 and day 5), and after (day 13) influenza were 496, 292, 244, and 593/mm³, respectively. Total lymphocyte counts were 960, 495, 394, and 1,060, respectively.

Case 3
A 34-year-old heterosexual woman was diagnosed as an HIV carrier in 1996. CD4⁺ cell counts and HIV RNA levels were 50/mm³, and 25,000 copies/ml, respectively. She was treated in our clinic from 1996. HAART improved HIV RNA levels to 500–800 copies/ml, and increased CD4⁺ cell counts to 120–180/mm³. She had no opportunistic infections due to the progression of HIV infection. Sulfamethoxazole-trimethoprim and clarithromycin were administered for prophylaxis of P. carinii pneumonia and M. avium complex infection, respectively. She was placed on anti-retroviral therapy with stavudine, didanosine, and nelfinavir from January 1999, because of a gradual increase of HIV RNA levels (1,500–3,000 copies/ml). Before that, zidovudine, lamivudine, and nelfinavir were administered.

She came to our outpatient clinic on January 29, 1999. She complained of high fever, sore throat, dry cough, myalgia, and rhinorrhea for 3 days. Body temperature was 39.1°C on day 1. Injection of pharynx and lymphadenopathy was not seen. The CRP was 1.9 mg/ml, and white blood cell count was decreased to 2,800/mm³. There were no abnormal shadows on the chest X-ray. Although fever normalized on day 5 (Fig 1; Case 3) with no administration of an anti-influenza drug, dry cough continued for about 2 weeks. Influenza A was diagnosed later based on the elevated HI titer in paired sera (Table 2). Subtype of influenza virus was A/H3N2. On day 14, CRP was 0.1 mg/ml, and white blood cell count was 4,500/mm³. HIV RNA levels before (January 25), during (day 4; January 29) and after (day 14; February 8) influenza were 1,585, 1,000 and 631 copies/ml, respectively. CD4⁺ cell count before (January 25) and after (day 14) influenza were 152 and 183/mm³.
Table 1. Characteristics of Patients with HIV Infection and Influenza

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Subtype*</th>
<th>Duration of fever (days)**</th>
<th>Influenza symptoms</th>
<th>Before influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23 yo</td>
<td>Male</td>
<td>A/H3N2</td>
<td>5</td>
<td>Dry cough, Sore throat, Myalgia</td>
<td>HIV RNA: 19,953</td>
</tr>
<tr>
<td>2</td>
<td>41 yo</td>
<td>Male</td>
<td>A/H3N2</td>
<td>4</td>
<td>Dry cough, Sore throat, Myalgia, Rhinorrhea</td>
<td>HIV RNA: 1,259</td>
</tr>
<tr>
<td>3</td>
<td>34 yo</td>
<td>Female</td>
<td>A/H3N2</td>
<td>4</td>
<td>Dry cough, Sore throat, Myalgia, Rhinorrhea</td>
<td>HIV RNA: 1,585</td>
</tr>
</tbody>
</table>

*Subtype was determined by virus isolation (Case 1) or elevation of hemagglutinin inhibition titer in paired sera (Cases 2 and 3).
**Days with >37.5°C body temperature. 'NT: not tested.

Figure 1. Time courses of influenza A in patients (Cases 1, 2, and 3) with HIV infection. Flu symptoms were remarkable on day 1. Anti-influenza drugs were not administered to any patient. Antibiotics were administered in Cases 1 and 2.

Table 2. Hemagglutinin Inhibition (HI) Titer before and after Influenza in HIV-infected Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>HI titer before influenza*</th>
<th>HI titer after influenza**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A/H1N1/Beijing</td>
<td>A/H3N2/Sidney</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>&lt;16</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>&lt;16</td>
<td>32</td>
</tr>
</tbody>
</table>

*HI titer was tested by standard methods used in Japan, with a starting serum dilution of 1:16. Paired sera were stored at −20°C until tested. **Serum samples for HI titer after influenza were collected at 4 to 5 weeks after the onset of influenza.
Influenza in HIV Carrier

We treated three HIV carriers who had influenza and a normal clinical course of the influenza. Fever (>37.5°C) continued for 4 to 5 days, and there were no severe complications. One patient had post-influenzal bronchitis which was effectively treated with antibiotics. No patient showed increased HIV RNA levels during and after the onset of influenza, although one showed a transient reduction of CD4+ and CD8+ cells during the active phase of influenza.

Several factors are included in the host defense against influenza. Shedding of influenza virus in human volunteers peaks about 48 hours after inoculation of the virus and declines slowly thereafter by days 6 to 8, and correlates with the febrile response (12). Host defense against influenza is divided into two phases, nonspecific primary response and influenza virus-specific secondary response (12), both responses are indispensable to clearance of the influenza virus. Interferons (13, 14), natural antibodies (15), and natural killer cells (16, 17) may play important roles in the former response. The mucous membrane of respiratory system has other nonspecific defenses, such as alveolar macrophages and airway ciliated cells. Important responses are influenza virus-specific immunity mediated by both T cells and neutralizing antibodies, which arise from mid to late phase of infection (12, 18). CD8+ cytotoxic T lymphocytes (CTL) have a cytotoxic effect on influenza virus-infected cells expressing major histocompatibility complex (MHC) class I molecules bound to peptides derived from influenza virus (19, 20). B cells can produce neutralizing antibodies to surface molecules of influenza virus, such as hemagglutinin and neuraminidase, with the help of CD4+ T cells (21–23). The immunoglobulin isotype secreted in the bronchial mucosa is IgA. Another minor protective mechanism of CD4+ T cells against influenza virus is the cytotoxic effect restricted to MHC class II (24, 25). Current data suggest that influenza-specific CD8+ CTL is the main mediator of recovery from influenza illness in mice (26–29), while neutralizing antibodies show resistance to influenza infection, if present in sufficient concentrations before or just after infection (21, 22, 30).

How do HIV-infected patients generally clear the influenza virus as can healthy individuals? No severe effect of influenza was seen in the present three patients. As the influenza virus became negative on day 5 after the onset of symptoms in case 1, there was an early elimination of influenza virus. Experimental infection with influenza virus to immunodeficient mice may aid in assessing immune responses in HIV patients with influenza. Athymic nude mice, which lack mature CD4+ and CD8+ T cells, cannot clear influenza virus, and finally die (31). Transfer of neutralizing antisera (32) or helper T cell-rich immune splenocytes (33) into nude mice after infection cannot clear influenza virus, while CTL-rich immune splenocytes can do so (33). CD4+ T cell-deficient mice infected primarily with influenza can clear the virus completely by the virus-specific CD8+ CTL (34, 35). On the contrary, CD8+ T cell-deficient mice show poor virus clearance and high mortality in primary infection with influenza virus (24, 25, 36, 37). Thus, CD8+ CTL to influenza virus is considered to be the main effector cells in virus clearance both in the presence or absence of CD4+ T cells in mice. Furthermore, CD8+ CTL against conserved internal viral proteins, such as nucleoprotein, play an important role in the protection against the infection with heterotypic virus (28, 38).

It is possible that CD8+ CTL against influenza virus can clear the virus even in cases of a reduced CD4+ T cell count, because CD8+ cell counts in the present patients were normal (approximately 500/mm³) before the onset of influenza. They may have a sufficient number of memory CD8+ T cells to become effector CTL after infection with the influenza virus. However, CTL activity to influenza antigens may not solely depend on CD8+ cell number but rather the quality of CD8+ CTL. Shearer et al reported four HIV-infected patients who completely lost antinfluenza CTL activity, but did not lose allogeneic CTL activity (39). This selective loss of CTL activity to the influenza virus means a functional change of CD8+ CTL observed in some but not all HIV-infected patients. It is possible that such patients may show severe influenza symptoms or complications if influenza infection occurs. Another possible mechanism functioning in the present patients is that the patients had sufficient antibodies to neutralize the influenza viruses. Paired sera of the three patients revealed that remaining CD4+ T cells in these three HIV-infected patients may have the capacity to help B cells produce neutralizing antibodies (Table 2).

Influenza virus infection did not increase HIV RNA levels in any of the 3 patients. Lymphocytopenia can occur during the acute phase of influenza infection in humans, but the mechanism is unknown (40, 41). The transient decline in the CD4+ T cell count in case 2 is possibly due to this phenomenon, but not to the progression of AIDS, because CD8+ T cells were also transiently reduced in number in correlation with CD4+ T cell count. Some patients with HIV infection have severe complications after influenza virus infection (7–10), and deaths attributed to influenza and pneumonia in the group most affected by AIDS showed an increase in United States (6). Factors related to an increase in the risk of complication of influenza are

<table>
<thead>
<tr>
<th>During influenza</th>
<th>After influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA (copies/ml)</td>
<td>CD4 (copies/ml)</td>
</tr>
<tr>
<td>3,162</td>
<td>87</td>
</tr>
<tr>
<td>1,585</td>
<td>94</td>
</tr>
<tr>
<td>1,000</td>
<td>NT</td>
</tr>
</tbody>
</table>
unknown. Function and number of CD8+ as well as CD4+ T cells in HIV-infected patients may provide a clue to predict the risk of complications.

It is controversial as to whether inactivated influenza vaccine given to HIV-infected patients can induce an enhancement of HIV replication. This enhancement is most likely to occur in patients with a good response to vaccine and whose CD4+ T cell counts are >200/mm³ (42). Patients whose CD4+ T cell counts are <100/mm³ respond poorly to vaccination, so there is little reason to vaccinate these advanced HIV-infected patients (42, 43). Treatment with HAART was reported to cause a recovery of the antibody response to influenza antigens (44). However, there are patients who recover from influenza despite low CD4+ T cell counts, as noted in the present case 1. Immune responses to influenza vaccine probably differ from those to natural infection of the influenza virus. Induction of CTL response is reported to be poorer in case of inactivated virus vaccine than with live attenuated vaccine (45). Before assessing the risk for use of influenza vaccine, prospective studies in adequate numbers need to be done to identify influenza patients with HIV infection who had severe complications of influenza.

References


