Influenza in Patients with Human Immunodeficiency Virus Infection*

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Although patients infected with human immunodeficiency virus (HIV) might be expected to have more severe illness due to influenza virus infection than normal persons, the course of influenza in such patients has not been well delineated. We describe six consecutive HIV-infected patients at San Francisco General Hospital in whom influenza virus was isolated from induced sputum or bronchoalveolar lavage specimens between December 1988 and March 1989. Although neither clinical presentation of influenza nor rate of secondary complications appeared to be altered from that in healthy individuals, our power of comparison was limited by small sample size. However, a high prevalence of hypoxemia and a trend toward prolonged duration of illness were identified. Larger, controlled studies are needed to define the course of influenza virus infection in HIV-infected patients as compared with nonimmunosuppressed patients.

(Chest 1990; 98:33-37)

SFGH = San Francisco General Hospital; ELISA = enzyme-linked immunosorbent assay

The incidence of pulmonary complications following influenza infection is known to be increased in patients with certain underlying conditions, particularly cardiac or pulmonary disease.1, 2 In view of the likelihood of increased susceptibility to severe infection, yearly immunization of human immunodeficiency virus (HIV)-infected persons against influenza is recommended by the Immunization Practices Advisory Committee of the Centers for Disease Control,3 Atlanta. However, the effect of HIV infection on the course of influenza illness has not been well studied.

We therefore reviewed the clinical features of virologically confirmed influenza infection in HIV-infected subjects during the 1988-1989 winter season.

METHODS

At San Francisco General Hospital (SFGH), all induced sputum and bronchoalveolar lavage (BAL) specimens from patients suspected of having the diagnosis of Pneumocystis carinii pneumonia are routinely submitted for viral culture. Specimens are inoculated onto three cell lines: human embryonic lung, human foreskin fibroblasts, and primary cynomolgus monkey kidney. Monkey kidney cells are hemadsorbed with washed guinea pig red blood cells five and ten days after inoculation. Hemadsorption-positive cultures are then stained with fluorescent monoclonal antibodies (Boots-Celltech Diagnostics, Plainview, NY) against influenza A and B, as well as against parainfluenza 1-3. Subtyping of influenza A isolates was performed by the Virus Laboratory of the San Francisco Department of Health.

Clinical and laboratory data of patients from whom influenza was isolated were extracted from review of the patient’s medical record.

RESULTS

Between December 1, 1988, and March 30, 1989, induced sputum or bronchoscopy specimens submitted to the Diagnostic Microbiology and Virology Laboratories at SFGH showed P. carinii in 73 patients. Influenza virus was isolated from specimens from eight patients. One patient, an intravenous drug user, was seronegative for antibody to HIV by enzyme-linked immunosorbent assay (ELISA) and has therefore been excluded from this analysis. Another patient, HIV infected, was evaluated entirely as an outpatient; he has been omitted due to insufficient data.

Influenza virus was isolated from induced sputum (six) or BAL (three) specimens in six male patients with HIV infection. Four virus isolates (submitted on Jan 23, 1989, Jan 25, 1989, Jan 31, 1989, and Feb 23, 1989) were influenza B and two (Dec 28, 1988, Jan 31, 1989) were influenza A (H1N1). No concomitant respiratory pathogens were identified in any specimen.

All of the men were homosexual, and one had a history of intravenous drug usage as well. Whereas none had had previous acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections, one had Kaposi’s sarcoma. Stage of HIV infection, as reflected by clinical findings and by CD4 cell count before and after influenza infection, is detailed in Table 1. Review of the medical record indicated that none of the patients had received influenza vaccine in the 1988-1989 season. No patients were receiving zidovudine or other antiviral medications at the time of initial clinical examination.

Symptoms of fever and/or cough began a median of six days (range, 2 to 21 days) before the patients came
to medical attention (Table 2). Cough (productive in four patients), shortness of breath, subjective fever, headache, and nausea were present in the majority of patients (Fig 1). Fever (temperature ≥38.5°C), tachypnea (respirations >20/min), and abnormalities on lung auscultation (rales, rhonchi, or wheezing) were each present in five patients. Median duration of fever was 7.5 days (range, five to 21 days). Two patients had a previous diagnosis of asthma (Table 1); wheezing was detected in the lungs of both individuals at the time of admission to the hospital; however, the clinical course of influenzal illness was not noticeably altered. The peripheral leukocyte count ranged from 5,300 to 10,400/cu mm (median, 6,650/ cu mm), while median arterial oxygen tension on room air was 70.5 mm Hg (Table 2).

In five patients, chest roentgenograms showed increased interstitial markings bilaterally; however, most were without acute change when compared with prior or later roentgenograms. One patient had a chest roentgenogram abnormality believed to represent an acute viral pneumonia (Fig 2); the course of illness in this patient is summarized as follows:

A 42-year-old gay male smoker with a history of mild asthma was admitted to the hospital with complaints of fever, chills, sweats, a cough productive of scant yellow sputum, and increasing shortness of breath of one week's duration. Oral temperature was 38.7°C, heart rate was 130/min, and respiratory rate was 32/min. Examination revealed mild respiratory distress, oral thrush, and diffuse expiratory wheezing. Room air arterial blood gas showed the following: pH, 7.47; PaO₂, 31 mm Hg; and PaCO₂, 56 mm Hg. Chest roentgenogram revealed a diffuse alveolar-interstitial infiltrate bilaterally. Diagnostic bronchoscopy with biopsy was performed on the fifth hospital day because of absence of P. carinii on an induced sputum specimen and lack of response to empiric high-dose intravenous trimethoprim-sulfamethoxazole therapy. Influenza B was later isolated from both the admission sputum and bronchoscopic specimens. The pathologic specimen showed focal chronic inflammation and fibrosis with increased numbers of macrophages. The patient was discharged after nine days of hospitalization with a diagnosis of "bacterial versus viral pneumonia." At the time of follow-up 14 days later, he denied residual respiratory or systemic symptoms other than headache.

The median duration of hospitalization for five patients was five days (range, three to nine days); one patient was treated without hospitalization. Follow-up was available on all six patients at a median of 26 days from the date of onset of symptoms (Table 2). At the time of return visit, respiratory complaints persisted in four patients. One patient complained of nonspecific systemic symptoms in the absence of respiratory complaints, and one patient complained only of headaches. Of the four patients with prolonged respiratory symptoms, one had a previous diagnosis of asthma, and three were cigarette smokers. Three patients were given oral antibiotics for productive cough, and one

### Table 1 — Characteristics of Patients with HIV Infection and Lower Respiratory Tract Influenza Virus Isolation*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>HIV-Associated Illnesses</th>
<th>Other Underlying Illnesses or Factors</th>
<th>T Helper (CD4) Cell/cu mm (Date Tested)</th>
<th>Influenza Type and Date Specimen Submitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Thrush, LAN</td>
<td>Asthma, Smoker</td>
<td>680 (10/24/88)</td>
<td>Influenza A (H1N1) 12/28/88</td>
</tr>
<tr>
<td>2</td>
<td>Kaposi’s sarcoma</td>
<td>Smoker</td>
<td>410 (3/6/89)</td>
<td>Influenza B 1/23/89</td>
</tr>
<tr>
<td>3</td>
<td>Thrush, hairy leukoplakia</td>
<td>Smoker</td>
<td>440 (1/30/89)</td>
<td>Influenza B 1/25/89</td>
</tr>
<tr>
<td>4</td>
<td>LAN, herpes zoster</td>
<td>Smoker</td>
<td>600 (3/16/89)</td>
<td>Influenza A (H1N1) 1/31/89</td>
</tr>
<tr>
<td>5</td>
<td>Thrush</td>
<td>Smoker</td>
<td>320 (1/3/89)</td>
<td>Influenza B 1/31/89</td>
</tr>
</tbody>
</table>

*HIV = human immunodeficiency virus; LAN = generalized lymphadenopathy.

### Table 2 — Clinical Presentation of Lower Respiratory Tract Influenza Infection in HIV-Infected Patients

<table>
<thead>
<tr>
<th>Patient No./Age, yr</th>
<th>Duration of Symptoms Prior to Evaluation, Days</th>
<th>Initial PaO_2/Initial P(A-a)O_2, mm Hg</th>
<th>Length of Follow-up † Days</th>
<th>Symptoms at Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/28</td>
<td>2</td>
<td>68/47</td>
<td>17</td>
<td>Productive cough</td>
</tr>
<tr>
<td>2/41</td>
<td>5</td>
<td>80/51</td>
<td>23</td>
<td>Systemic only†</td>
</tr>
<tr>
<td>3/29</td>
<td>21</td>
<td>108/6</td>
<td>23</td>
<td>Dry cough</td>
</tr>
<tr>
<td>4/29</td>
<td>14</td>
<td>73/27</td>
<td>58</td>
<td>Productive cough</td>
</tr>
<tr>
<td>5/42</td>
<td>4</td>
<td>62/51</td>
<td>40</td>
<td>Productive cough</td>
</tr>
<tr>
<td>6/42</td>
<td>7</td>
<td>56/55</td>
<td>29</td>
<td>Headaches</td>
</tr>
</tbody>
</table>

*P(A-a)O₂ = arterial Po₂ − [(713 × FIo₂) − PaCO₂/0.8].
†Describes length of follow-up dated from the time of onset of symptoms.‡Systemic symptoms were described as fever, nausea, vomiting, headache, and rhinorhea.

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was instructed to use inhaled bronchodilators as needed.

**DISCUSSION**

We describe six patients with HIV infection in whom influenza virus was isolated from induced sputum or BAL specimens at SFGH between December 1988 and March 1989. The patients comprising this report were sufficiently ill to warrant evaluation for *P. carinii* pneumonia. Therefore, we believe that they represent the most severely ill HIV-infected patients seen at our hospital with lower respiratory tract influenza infection during the 1988-1989 influenza season.

An increased susceptibility, increased severity, and/or prolongation of influenza illness in HIV-infected individuals might be expected. Defects in T-cell and humoral responses in these patients have been well documented, as has impaired production of interferon. Antibody response to influenza vaccination is poor, particularly as stage of HIV illness advances, and there is a selective loss of an influenza-specific, HLA-restricted cytotoxic T-lymphocyte response in persons with HIV infection.

Data from this series of patients suggest that the course of influenza in HIV-infected patients is not markedly worsened. Given that SFGH serves approximately 700 to 800 HIV-infected patients (Martinez S, unpublished data), the small number of patients with influenza illness severe enough to warrant evaluation for *P. carinii* pneumonia is to some extent reassuring. Although the prevalence of influenza in the 1988-1989 season, the virulence of predominant virus strains during this interval, and the lack of advanced immunosuppression in our cohort are variables that have not been controlled for, our findings agree with those findings of the scant published literature to date. No increased incidence or alteration in clinical presentation of influenza was noted in patients at risk for HIV infection in a New York City emergency room in 1988, and none of seven HIV-seropositive residents in a drug-treatment center developed symptoms during an influenza A (H1N1) outbreak compared with 14 (37 percent) of 38 seronegative individuals.

The clinical features of influenza were not unique...
Influenza

in this group of patients. However, the relatively poor oxygenation at the time of presentation (median P(A-a)O₂ = 49 mm Hg) is of concern. While we were not able to distinguish clinical differences in patients with influenza A (H1N1) infection from those with influenza B infection, most authorities agree that influenza B, the predominant strain in our series, tends to cause a relatively mild illness. influenza A (H1N1) also has typically caused a benign illness since its reappearance in 1977, although an outbreak in elderly patients in 1978 was reported to be unusually serious in 1987. Despite the fact that the predominant influenza virus strains in the United States in the 1988-1989 season were influenza B and influenza A (H1N1), the proportion of deaths associated with pneumonia and influenza exceeded the epidemic threshold. Therefore, generalized statements about the expected severity of illness caused by these particular virus subtypes are not possible, and prospective comparison with a non-HIV-infected group of patients with influenza in a given year will be necessary to further assess severity of illness in patients with HIV infection.

Prolonged respiratory illness was present in four of six HIV-infected patients in this series, despite the rarity of advanced HIV infection in the sample. No serial virologic assessment of respiratory tract shedding was performed, yet previous studies have demonstrated a close correlation of the duration of fever with length of viral shedding. In this series, persistence of fever for a median of 7.5 days seems prolonged when compared with those findings of previous reports. In addition, a recent report of shedding of parainfluenza 3 virus for greater than two months from the respiratory tract of two children with AIDS lends further support to the possibility of prolonged viral shedding in HIV-infected patients.

Although the pathogenesis of influenza virus infection is incompletely understood, humoral, T-cell, and interferon responses are each important in determining the course of illness. The presence of serum antibody against the influenza hemagglutinin protects against acquisition of influenza A infection in mice and in humans and may prevent severe pulmonary parenchymal disease if infection does occur. Studies in chickens suggest that clearance of influenza A virus may be facilitated by antibody to the neuraminidase. Old BALB/c mice have delayed development of cytotoxic T-cell lymphocyte activity and prolonged viral shedding when compared with young mice, and regeneration of respiratory tract epithelium following influenza is delayed in nude as opposed to immunocompetent mice. Rising titers of interferon correlate closely with decreasing virus titer in mice and with resolution of clinical symptoms in influenza-infected men.

Only one patient in this series had evidence of a primary viral pneumonia (prevalence 16.7 percent; 95 percent confidence intervals, 0 to 46.5 percent). Studies in athymic mice suggest that the T-cell response may actually enhance parenchymal inflammation, so that deficient cellular immunity in HIV-infected hosts may in fact protect against early pulmonary abnormalities. A review of the English literature revealed only two reports of pneumonitis in HIV-infected patients with influenza, one a primary viral process and the other a secondary bacterial infection. In view of impaired neutrophil bactericidal activity and increased susceptibility to bacterial pneumonias in HIV-infected patients, it seems striking that no patient exhibited evidence of a secondary bacterial infection in this series. However, accurate comparison of the rate of pneumonitis in HIV-infected patients with that of previous estimates of 4.9 to 9.1 percent in patients with influenza is not possible with our current data.

In summary, we found that HIV-infected patients with influenza virus infection have a typical clinical presentation and a rate of secondary complications similar to those of normal subjects. Although possible trends toward more serious respiratory compromise and a prolonged duration of illness were identified in this series, our small sample size allows only tentative conclusions. Prospective, controlled trials of larger numbers of patients using standardized clinical, virologic, and serologic measurements are needed to more accurately assess the response of HIV-infected patients to influenza infection.

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