Influenza Among Hospitalized Adults with Leukemia

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Influenza is one of the most important respiratory diseases of mankind. Epidemics of influenza occur nearly annually and are associated with considerable morbidity and mortality [1–3]. Although immunocompromised patients are considered to be at high risk for developing serious pulmonary complications, only scant data exist delineating the actual frequency and morbidity and mortality of influenza in adults with cancer [4–8]. To describe the frequency and clinical course of influenza in a subset of severely immunocompromised adults, we prospectively followed all adults with leukemia who were hospitalized at The University of Texas M.D. Anderson Cancer Center (MDACC; Houston) during a 1-year period.

Methods
Study Design

From 1 October 1993 through 30 September 1994, all adults with leukemia who were hospitalized at MDACC were screened daily for signs and symptoms of a respiratory illness. Respiratory secretions were sampled from all patients with an acute respiratory illness. Cultures were performed either at the time of admission or during the hospitalization, depending on when the respiratory illness developed.

Most specimens consisted of combined nasopharyngeal wash and throat swab samples. When available, endotracheal aspirates and bronchoalveolar lavage fluids were cultured as well. The medical records and chest radiographs of patients from whom influenza virus was isolated were reviewed. Only culture-confirmed cases were included in the analysis.

Definitions

An acute respiratory illness was defined as the recent onset (within ≤14 days) of rhinorrhea, nasal and sinus congestion, pharyngitis, coryza, sinusitis, otitis media, cough, and/or a new radiographic pulmonary infiltrate. Fever alone was not an indication for performing a respiratory viral culture. Pneumonia was defined as an acute respiratory illness occurring in association with a new radiographic infiltrate.

A patient was considered to have received therapy for influenza if amantadine, rimantadine, and/or ribavirin was administered for at least 48 hours following the onset of symptoms. All patients also received broad-spectrum antibiotics. As a conservative estimate, an infection was considered to be nosocomial if the illness developed after ≥7 days of hospitalization, since the incubation period ranges from 1 to 5 days [3]. Neutropenia was defined as an absolute neutrophil count of <500/mL. Lymphopenia was defined as an absolute lymphocyte count of <200/mL.

Virological Studies

Specimens for viral culture were collected in normal saline and placed in aveal infusion broth containing 0.5% bovine
albumin, penicillin, gentamicin, and amphotericin B. They were then transported to the laboratory at 4°C and inoculated into four tissue culture lines: Madin Darby canine kidney (MDCK), continuous rhesus monkey kidney (LLC-MK), human embryonic lung fibroblast (WI-38), and human epidermoid carcinoma (HEp-2) cultures. Hemadsorption was performed on the 5th, 10th, and 21st days after inoculation. Influenza infection was confirmed and typed by ELISA and by reverse transcription PCR [9]. When available (in two cases), lung tissue was examined histopathologically for evidence of viral infection.

Statistics

The χ² method was used to determine the statistical significance of linear associations between variables. Student’s t-test was used to compare the means of continuous variables.

Results

Sixteen cases of influenza were identified during the 1-year surveillance period. All isolates were of type A (H3N2). Fifteen cases occurred during an 9-week period from 29 November 1993 to 29 January 1994, in the midst of a community outbreak of influenza. The 16th case occurred in April 1994. During the 9-week outbreak, 45 adults with leukemia were hospitalized at MDACC with an acute respiratory illness, all of whom had respiratory secretions sampled for viral culture. Thus, the frequency of influenza was 33% (15 of 45) among adults with leukemia who were hospitalized with an acute respiratory illness. Two infections (13%) were acquired nosocomially.

The demographic and clinical characteristics of these 15 patients are shown in table 1. None of the patients had received either vaccination or chemoprophylaxis for influenza. Older adults did not have a higher frequency of pulmonary complications or death than did younger adults. The most common presenting symptom was fever, followed in frequency by cough and wheezing.

Eight patients (53%) complained of nasal congestion. Two of five patients evaluated had radiographically documented sinusitis, one of whom had concurrent aspergillus sinusitis. Only five patients (33%) complained of sore throat; however, in some cases this complaint may have been overshadowed by painful chemotherapy-induced mucositis. In 12 (80%) of the 15 patients with influenza, the illness was complicated by pneumonia.

Pneumonia was documented a mean of 8 days (range, 0–24 days) after the onset of symptoms. Chest radiographs revealed unilateral infiltrates in two patients and bilateral infiltrates in 10 patients. Concurrent pulmonary infections were identified in 3 patients (25%) with pneumonia; these were due to Aspergillus species, respiratory syncytial virus (RSV), and combined RSV and Candida species, respectively. All 12 patients were treated with broad-spectrum antibiotics.

Table 1. Characteristics of 15 adults with leukemia who were hospitalized with influenza A virus infection during the winter of 1993–1994.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of patients (n = 15)</th>
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<tbody>
<tr>
<td>Age (y): mean (range)</td>
<td>49 (28–77)</td>
</tr>
<tr>
<td>Sex: male/female</td>
<td>11/4</td>
</tr>
<tr>
<td>Type of leukemia</td>
<td></td>
</tr>
<tr>
<td>Acute myelogenous</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Acute lymphocytic</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Chronic myelogenous</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Hairy cell</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>10 (66)</td>
</tr>
<tr>
<td>Lymphopenia¹</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Symptoms²</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Cough</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Sputum</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (27)</td>
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</tbody>
</table>

* Fewer than 500 neutrophils/mL.
¹ Fewer than 200 lymphocytes/mL.
² During the first week of the illness.

Four (33%) of the 12 patients with pneumonia died of progressive respiratory failure at a mean of 24 days (range, 8–31 days) after the onset of symptoms. Two of these four patients had concurrent pulmonary infections: one had RSV and candidal infection and the other had RSV infection. Autopsies were performed on these two patients and revealed changes consistent with viral pneumonia, including diffuse alveolar damage, intracytoplasmic inclusions, and syncytial cells. One patient also had lobar candidal pneumonia.

Although not statistically significant, there was a tendency toward a higher frequency of pulmonary complications and death among patients who had more recently received chemotherapy and who had more chemotherapy-induced myelosuppression. Thus, patients with pulmonary complications developed symptoms at a mean of 9 days (median, 9 days) after receiving chemotherapy, compared with a mean of 36 days (median, 20 days) for patients without pulmonary complications.

Patients who died developed symptoms at a mean of 5 days (median, 6 days) after receiving chemotherapy, compared with 18 days (median, 10 days) for patients who survived. Similarly, pneumonia developed in 9 (90%) of 10 patients who developed symptoms within 14 days of receiving chemotherapy, vs. 3 (60%) of 5 patients who developed symptoms >14 days after receiving chemotherapy.

Although the majority of patients were neutropenic at the onset of the illness, patients who died tended to have more...
persisting neutropenia. Three (75%) of four patients who died were neutropenic at the onset of the illness, and all three patients remained neutropenic 2 weeks later. In contrast, 7 (64%) of 11 patients who survived were neutropenic at the onset, and only 3 patients (27%) remained neutropenic 2 weeks later.

With regard to lymphopenia, 1 (25%) of 4 patients who died was lymphopenic at the onset of the illness, and 2 of the 4 were lymphopenic 2 weeks later. In contrast, 6 (55%) of 11 patients who survived were lymphopenic at the onset, and 3 (27%) remained lymphopenic 2 weeks later.

Nine patients (including 8 with pneumonia) were treated for influenza for a mean of 12 days (range, 6–29 days) with amantadine (n = 3), rimantadine (n = 4), aerosolized ribavirin (n = 1), and rimantadine and aerosolized ribavirin (n = 1). The length of time between the onset of illness and the initiation of therapy tended to be longer among patients who died (mean, 13 days; median, 11 days) than among patients who survived (mean, 8 days; median, 7 days), although the difference was not statistically significant.

Among the 15 patients, the initial isolate of influenza virus was from combined nasopharyngeal wash and throat swab specimens from 12, endotracheal aspirates from 2, and bronchoalveolar lavage fluid from 1. During the course of the illness, influenza virus was isolated from a bronchoalveolar lavage or endotracheal aspirate from four of the seven patients who had such samples obtained. Virus was shed for a mean of 3.5 days (range, 1–23 days); however, follow-up cultures were not performed systematically.

**Discussion**

Viral pneumonia in the immunocompromised adult has traditionally been attributed primarily to the herpesviruses, particularly cytomegalovirus [10, 11]. Over the past decade, there has been a growing recognition that community respiratory viruses such as RSV, parainfluenza virus, and adenovirus are a frequent cause of serious respiratory disease among immunocompromised adults [12–24]. This study highlights the importance of influenza, a potentially preventable community respiratory infection, in adults with leukemia.

During the wintertime community outbreak, one-third of the adults with leukemia who were hospitalized with an acute respiratory illness were documented by culture to be infected with influenza virus. This is a minimum estimate of the frequency of influenza, since the study did not include clinically or serologically confirmed cases and respiratory viral cultures were not performed for patients who presented with fever alone or nonrespiratory illnesses. Furthermore, the study included all patients with a respiratory illness of ≤14 days’ duration, some of whom may have already ceased shedding virus when their respiratory secretions were sampled. In the Houston community that year, the influenza epidemic was moderately severe (personal communication, P. W. Glezen), as it was in the rest of the United States, and 99% of the isolates were of influenza type A (H3N2) [25].

Coupled with this high infection rate was a high rate of pulmonary complications. Eighty percent of these infections were complicated by pneumonia, and the associated mortality of 33% was also high. The risk of developing pneumonia and the mortality tended to be higher among patients who had more recently received chemotherapy and who were therefore more myelosuppressed; however, less-myelosuppressed patients were also at risk.

A more clear-cut increased risk of pneumonia and death for patients with chemotherapy-induced myelosuppression has been demonstrated with regard to another community respiratory virus, RSV [15–18, 24]. The role of the various components of the host defense system, such as neutrophils and humoral and cell-mediated immunity, in the pathogenesis of lower respiratory tract disease due to the community respiratory viruses is poorly understood and needs to be studied.

Surprisingly scant data exist regarding the frequency and morbidity and mortality of influenza virus infections in severely immunocompromised adults with cancer. Two previous studies involving 28 adult bone marrow transplant (BMT) recipients and 37 adults with leukemia who were hospitalized at MDACC with an acute respiratory illness during the 1991–1992 community epidemic of influenza also documented a high frequency of influenza: 29% and 11%, respectively [7, 8]. The frequency of pulmonary complications was also high: 6 (75%) of the 8 BMT recipients and 3 (75%) of the 4 leukemia patients with influenza developed pneumonia, with an associated mortality of 17% and 33%, respectively.

The high frequency and morbidity and mortality observed in these studies and in the current study of severely immunocompromised patients are in contrast with the generally mild, self-limited disease observed in a study of 25 “immunocompromised” patients in Stockholm [6]. In that study, only three patients (12%) developed pneumonia, and only one patient died (a BMT recipient with aplastic marrow). This wide spectrum of observations probably reflects the wide spectrum of immunocompromised patients being evaluated. The majority of the patients in the Stockholm study were considerably less “immunocompromised” than BMT recipients and patients with leukemia. In less immunocompromised patients, the clinical course of influenza may be more comparable to that in immunocompetent persons.

Pneumonia complicating influenza is frequently of bacterial or mixed viral/bacterial origin [3]. Since all surviving patients in our study were treated with broad-spectrum antibiotics, and since these patients did not have lung tissue sampled for histopathology, it was not always clear whether these patients had primary influenza virus pneumonia and/or secondary pneumonia due to other microorganisms.

In the two fatal cases in which lung tissue was available for review, histopathology revealed changes consistent with viral pneumonia, suggesting that influenza played a significant role
in these pneumonias; however, RSV was also isolated from both patients before death and may have contributed to the pathology.

The Centers for Disease Control and Prevention recommend that immunocompromised patients undergo annual influenza vaccination, as well as chemoprophylaxis with amantadine/rimantadine during community outbreaks of influenza type A [26]. Our study suggests that the risks of influenza are especially high among severely myelosuppressed patients. Unfortunately, these patients are less likely to mount an adequate antibody response to active immunization [27–29].

Although the effectiveness of amantadine/rimantadine in preventing influenza in severely immunocompromised patients has not been established, it has been well demonstrated in other populations of patients. On the basis of our own experience of the significant morbidity and mortality associated with influenza in severely immunocompromised patients, we have initiated a more aggressive prophylactic strategy including rigorous hospital infection control measures, influenza vaccination of immunocompromised patients and their contacts, and rimantadine/amantadine prophylaxis for patients during community outbreaks of influenza.

An effective therapy for established influenza virus type A infections in immunocompromised patients has not been demonstrated. Whether therapy with amantadine/rimantadine alone can prevent the progression of uncomplicated influenza to pneumonia is not known. Studies of uncomplicated influenza infections in immunocompetent adults and anecdotal reports of lower respiratory tract disease in immunocompetent and immunocompromised adults suggest that amantadine/rimantadine and/or ribavirin (aerosolized or intravenous) may be of benefit [30–36].

Treatment of immunocompromised patients with amantadine/rimantadine alone, however, is limited by the rapid emergence of resistant strains of influenza A [37–40]. Therapy with aerosolized ribavirin is limited by the cumbersome process of administering an aerosol for many hours a day, the risk of environmental contamination, and the high cost. Whether the addition of passive immunotherapy with immunoglobulin may be of benefit needs to be studied, although this therapeutic modality is inherently limited by the frequent antigenic variation of the influenza virus.

With influenza virus type B, the options for chemoprophylaxis and therapy are even more limited than with type A virus since amantadine/rimantadine is not active against type B virus. During community outbreaks, influenza should be considered in the evaluation of an immunocompromised adult with an acute respiratory illness. It is particularly important to recognize influenza in hospitalized patients so that appropriate infection control measures can be implemented promptly.

Because of the high morbidity and mortality associated with influenza in immunocompromised patients, effective prophylactic and therapeutic regimens need to be defined. Defining effective therapeutic regimens for these patients will be globally beneficial since influenza is such an important cause of serious respiratory disease in the general community.

References