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Epidemiology of Influenza A virus infection in patients with acute or chronic leukemia

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Abstract Influenza infection is a significant cause of morbidity and mortality in immunocompromised hosts, but its importance in adult cancer patients is largely undescribed. We therefore conducted a prospective study of the incidence and clinical features of influenza infection in patients with acute or chronic leukemia. The cohort, which consisted of all adult leukemia patients undergoing remission-induction chemotherapy during the 1991–1992 influenza epidemic, was followed prospectively for development of signs and symptoms of acute infection of the upper or lower respiratory tract. Of these 294 patients, 111 received chemotherapy as inpatients and 183 as outpatients. Throat swabs and nasal washes for viral culture were obtained from all symptomatic patients, who were then followed until all signs and symptoms resolved. Symptoms of respiratory tract infection developed in 37 leukemia patients (13%). Among these, influenza (A/Beijing/H3N2) caused 3 (21%) of the 14 infections that developed during hospitalization but only 1 (4%) of the 23 that developed in the community ($P=0.14$). Influenza patients presented with fever, rhinorrhea, nasal congestion, headache, and myalgia; those with other infections presented with signs and symptoms of lower respiratory tract infection (productive cough, rales, or rhonchi). Development of pneumonia was common in influenza patients, 1 of whom died from a secondary fungal and gram-negative pneumonia. Influenza A virus infections accounted for a substantial portion of acute respiratory infections among adult leukemia patients during a community epidemic. Most infections appeared to be nosocomial and the most likely sources were visitors or hospital personnel. Immunization of household contacts and hospital staff may reduce the risk of influenza infection and its pulmonary complications in leukemia patients.

Key words Influenza
Epidemiology · High-risk populations · Cancer patients
Immunocompromised patients

Introduction

For several years, the frequency of pneumonia cases for which a causative pathogen cannot be identified has increased among neutropenic cancer patients at M. D. Anderson Cancer Center, even though the total incidence of infection has remained largely unchanged. Thus, at our institution, pneumonia of undetermined etiology represents an increasingly large proportion of the total infections in this patient population. Closer examination of this increase demonstrated a pronounced seasonal variation in the excess proportion of unknown organism pneumonias (Fig. 1), with significant peaks during the winter. This pattern is typical of

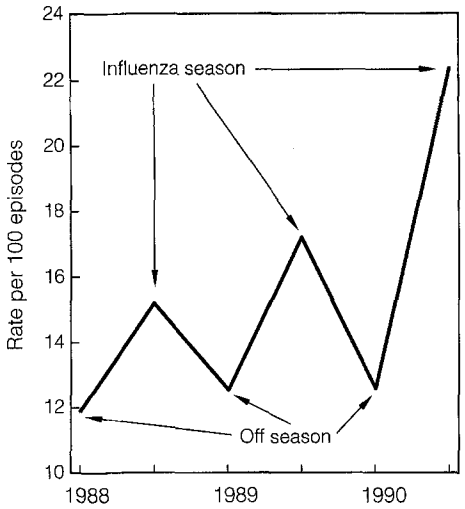

Fig. 1 Incidence of pneumonia of unknown etiology related to season

the increase in hospitalizations for pneumonia and other acute respiratory infections in the general adult population; many of these infections are caused by influenza virus [1, 2, 7–9, 18–20]. Although this has not been previously studied in adult leukemia patients, we hypothesized that some of the winter respiratory infections experienced by cancer patients could be caused by influenza virus and, therefore, conducted a prospective study of the incidence and clinical features of acute influenza infections among patients with acute or chronic leukemia.

Patients and methods

Plans were developed prospectively to conduct surveillance for influenza virus infection among patients with leukemia during the annual community epidemic of influenza. Surveillance for influenza virus infection, conducted by the Influenza Research Center at Baylor College of Medicine, was used to activate the surveillance of leukemia patients and to define the epidemic period.

All 111 adult patients with acute or chronic leukemia who were hospitalized between 11 November and 31 December 1991 (the epidemic period) at The University of Texas M.D. Anderson Cancer Center were screened for signs and symptoms of acute respiratory infection, including fever (oral temperature $\geq 38°$ C), cough, sore throat, nasal or sinus congestion, coryza, dyspnea, rales, rhonchi, or new infiltrates as noted on chest x-ray. All 183 adult leukemia patients who received chemotherapy as outpatients received standard instructions to return to the clinic for evaluation if their temperature exceeded 38° C or symptoms of infection developed. During the epidemic period, 24 such patients presented to the clinic for evaluation. Twenty-three of these were hospitalized and followed in a manner identical to those whose infections developed during hospitalization; 1, who was found to be afebrile and free of respiratory symptoms at the time of evaluation, was excluded. Patients with fever but no specific signs or symptoms of respiratory tract infection were also excluded. Patients who had undergone bone marrow transplantation are described in a separate report [23]. Eleven patients (8 with mold infections, 2 with *Mycobacterium* spp., and one with *Pneumocystis carinii*) with chronic respiratory infections of more than 2 weeks' duration were also excluded.

Chest x-rays were performed on all patients at the onset of fever and twice weekly thereafter until complete resolution of the symptoms of infection. Cultures of blood, urine, throat and sputum were done in all patients to rule out bacterial and fungal pathogens. A combined nasal wash and throat swab for viral culture was obtained from each eligible patient at the onset of fever. Samples were inoculated onto Madin-Darby canine kidney tissue cultures (MDCK) and observed for cytopathic effects and hemadsorption for 10 days. Identification of influenza viruses was performed by enzyme-linked immunosorbant assay using specific antisera.

Neutropenia was defined as an absolute neutrophil count less than 1000/mm^3 blood. Fever was defined as an oral temperature $\geq 38°$ C that was not temporally related to the administration of blood products or other pyrogenic agents. Because of the short incubation period observed with influenza virus infection (24–72 h), infections in which the initial signs and symptoms developed more than 72 h after the patient's admission to the hospital were considered hospital-associated. Infections in which the initial signs and symptoms developed less than 72 h after admission or prior to admission were considered community-associated.

Differences between categorical variables were tested using Fisher's exact test, and those between continuous variables were tested using the Mann-Whitney test. All statistical tests were computed using BMDP-PC90 (BMDP Statistical Software Inc., 1990).

Results

Of the 111 hospitalized leukemia patients, 14 (13%) developed acute respiratory symptoms. During the same period, 183 leukemia patients received chemotherapy as outpatients; among these, a similar proportion (23 cases, 13%) developed acute respiratory symptoms. All 23 were hospitalized for antibiotic therapy. Influenza A virus was cultured during 3 (21%) of the 14 hospital-associated infections but only 1 (4%) of the 23 community-associated infections ($P=0.14$). These 4 patients were infected with the A/Beijing/H3N2 strain most prevalent in the community during the 1991–1992 epidemic. In approximately half of the other respiratory infections (16), no causative pathogen was identified, despite collection of multiple cultures. The remaining infections were caused by *Streptococci* (6) (predominately from the viridans group), *Xanthomonas maltophilia* (4), fungi (3), and other gram-negative bacilli (2), which were all isolated from both blood and sputum cultures, and respiratory syncytial virus (2), which was isolated from cultures of nasal washes.

Clinical presentation

In most respects, cancer patients with influenza were demographically similar to those with other infections (Table 1). A majority had acute leukemia, approximately half were undergoing initial remission-induction

Table 1 Characteristics of patients

Characteristic	Number of patients	
	Influenza infection ($n=4$)	Other respiratory infection ($n=33$)
Male	2	18
White	2	24
Acute leukemia	2	24
Chronic leukemia	2	9
Initial induction	2	15
Reinduction	1	13
Complete remission	0	3
Relapse	1	2
Antibiotic prophylaxis	4	31
Age (years, mean)	39*	56*
Prior hospital days (mean)	6	3
Prior days neutropenia (mean)	6	8
Days after chemotherapy (mean)	8**	15**

* $P<0.05$
** $P<0.05$

Table 2 Presenting signs and symptoms

Symptom	Number of patients	
	Influenza infection ($n=4$)	Other respiratory infection ($n=33$)
Headache	2*	0*
Myalgia	3	12
Rhinorrhea	3**	7**
Sore throat	2	9
Cough	3	24
Sputum production	1	15
Dyspnea	0	19
Rales or rhonchi	0	10
Positive chest X-ray	0	18
Neutropenia	4	29

* $P<0.05$
** $P<0.05$

therapy, and 81% were neutropenic following a variety of chemotherapeutic regimens, predominantly those that included cytosine arabinoside plus either idarubicin (15 patients, 41%) or fludarabine (14 patients, 38%). Virtually all were receiving prophylactic antimicrobials (generally oral ciprofloxacin plus fluconazole) at the onset of infection.

Patients with influenza were younger ($P=0.04$) and had been hospitalized longer ($P=0.002$) than those with other infections (Table 1). In fact, 3 (75%) of the 4 influenza infections, compared with only 11 (33%) of the 33 other infections, developed more than 3 days after admission ($P=0.14$). In the 3 hospital-associated influenza infections, transmission of infection from other patients is unlikely because leukemia patients at our institution are confined to private rooms during administration of chemotherapy. Although contact with visitors or hospital staff members with symptoms of infection is discouraged, these groups represent the most likely source of infection for these 3 patients. Information concerning the immunization status of visitors was not available, however, many of the hospital staff were not immunized.

Owing to the decreased inflammatory response accompanying cytotoxic chemotherapy, leukemia patients often do not demonstrate localized signs or symptoms of infection; however, the patients in this series presented with classical signs and symptoms of influenza. Rhinorrhea, nasal or sinus congestion, headache, and myalgia occurred significantly more frequently among the influenza patients than in patients with other respiratory infections (Table 2). In contrast, the latter group of patients presented with symptoms more characteristic of lower respiratory tract infection (productive cough, rales or rhonchi); this clinical picture was confirmed by the frequency of infiltrates noted on chest x-rays (55%). Sore throat, a finding classically associated with influenza infection, did not occur significantly more frequently in the influenza group, perhaps because of the frequency of oropharyngeal mucositis among patients who have received chemotherapy.

Outcome of infection

All 37 patients with respiratory infections received broad-spectrum antibiotics (generally vancomycin plus either imipenem, aztreonam or cefoperazone/sulbactam) from the onset of fever. Twenty-eight patients whose infections did not respond to initial therapy received either amphotericin or fluconazole for presumed or proven fungal infection. None of the patients (including those with influenza infection) received either amantadine or ribavirin.

Of the 4 influenza patients, 3 developed pneumonia 7, 8, and 23 days after the onset of acute respiratory symptoms. In two of these episodes, no organisms other than Influenza A could be identified despite the collection of multiple bacterial and fungal cultures. One of these patients required endotracheal intubation and ventilatory support. The other patient was discharged in an improved but still febrile condition to celebrate the New Year's holiday with her family. She returned 36 h later with a new pulmonary infiltrate and required an additional 10 days of antibiotics and hospitalization to treat her infection.

One patient with influenza (25%) and 9 with other respiratory infections (27%) died of their infections. The patient with influenza, a 20-year-old woman with acute lymphocytic leukemia, developed symptoms of influenza after more than a week of hospitalization. On day 17 of her influenza infection, sinusitis due to *X.*

maltophilia and *Aspergillus* spp., developed and progressed to diffuse bilateral pneumonia on day 23 and to death on day 30. Influenza virus was cultured from respiratory secretions collected on day 4 and was still found in follow-up cultures collected on day 15. At autopsy, *X. maltophilia* and *Aspergillus* spp. were cultured from lung tissue; viral cultures were not collected.

Discussion

Influenza viruses have caused major epidemics and pandemics for at least the last eight centuries and they continue to cause outbreaks of varying severity almost every winter [1, 2, 4, 16, 19]. However, despite the severity and frequency of influenza infections during community epidemics, such infections are rarely reported in studies of infections in leukemia patients. This is puzzling, since the clinical presentation demonstrated by the leukemia patients in this study is typical of that seen in otherwise healthy adults. Although the number of patients in this report is small, this finding is consistent with a previous report of influenza in children with cancer in which there was no difference in signs or symptoms between children with cancer and matched controls without cancer [11]. Similar findings were also noted in a recent report of influenza in immunocompromised patients [13].

In fact, much of the currently available information about influenza infection in cancer patients is contained in two studies reporting that children with cancer are susceptible to influenza virus infections and are at increased risk of serious morbidity or prolonged infection compared with children without malignancies [5, 11]. Our data support the generalization of these findings to adults with leukemia, in whom Influenza A virus caused 38% of all respiratory infections during the 2-month 1991–1992 influenza epidemic in Houston. Furthermore, during the same epidemic period, 29% of all acute respiratory infections among bone marrow transplant recipients hospitalized in our institution were caused by Influenza A [23]. These data suggest that adult cancer patients are at substantial risk of infection during community epidemics and that prevention and surveillance programs should be considered in this population during epidemic periods.

During annual outbreaks of influenza, the attack rate in the community may be as high as 10%–40%, and rates approaching 80% may be observed among high-risk and institutionalized persons. School and industrial absenteeism often triples and emergency-room visits for respiratory complaints double [7–10]. Thus, the fact that influenza infection represented 21% of all hospital-associated respiratory infections during the epidemic period is not surprising. Nosocomial acquisition of influenza infection has been previously documented among children, the elderly, and patients with chronic underlying diseases [3, 10]. However, the attack rates observed in both hospitalized (3%) and community-based (1%) leukemia patients were surprisingly low. There are several possible explanations for this phenomenon. First, because cultures were obtained only in the hospital, community patients may have been cultured later in their illness than hospitalized patients, thus reducing the probability of documenting the presence of the influenza virus. Analysis of paired sera (which was not included in this study) could also have documented additional cases of infection. Another possibility is that the leukemia patients successfully practiced reverse isolation, a precaution routinely encouraged in neutropenic cancer patients.

Primary influenza pneumonia and secondary bacterial pneumonia are the most frequent, serious complications of influenza virus infection and these conditions represent the major cause of influenza-associated mortality [1, 2, 6, 16, 18–20]. During the peak of the 1991–1992 influenza epidemic, pneumonia and influenza represented 7.9% of all deaths in The United States [16]. Previous reports suggest that pulmonary complications occur in approximately 9.5% of all cases of influenza. Higher rates are observed in patients over the age of 50, and among patients over 70 years of age they often exceed 70% [1, 2, 6, 18–20]. Among our patients with leukemia, 3 of the 4 influenza infections were complicated by pneumonia (1 of which was fatal), exceeding rates previously reported among children with cancer during the 1971–1975 epidemics in Memphis, Tennessee [5], and the 1984–1986 epidemics in Rochester, New York [11], as well as those reported among patients with hematological malignancies during the 1988–1990 epidemics in Stockholm, Sweden [13]. However, the same proportion of bone marrow transplant recipients (6 of 8) developed pneumonia during this epidemic in our institution [23]. Our findings suggest that, during some epidemics, the risk of serious morbidity is substantial among immunocompromised cancer patients and may approach that observed in elderly patients. However, influenza epidemics are characterized by cyclic variations in susceptibility of populations at risk of serious morbidity. Thus, the frequency of serious complications can be expected to demonstrate similar variation and, in epidemics in which the susceptible population is at low risk of complications, may reflect the lower rates reported in previous epidemics.

Although annual immunization against influenza virus infection is recommended for immunocompromised hosts [15], it has not generally been practiced in cancer patients, partly because of the lack of information about the clinical significance of influenza virus infections and the efficacy of the vaccine in this population. Although a study completed recently at our institution

demonstrated a very promising 71% response rate to a two-dose vaccine regimen [14], previous studies of immunization of cancer patients suggest that serological responses are suboptimal [15]. Furthermore, protection may not be conferred even by a serological response generally considered protective in healthy adults because of the damage done by chemotherapy to the mucosa of the respiratory tract. For these reasons, immunization of leukemia patients with influenza virus vaccine may not reliably prevent influenza virus infection. However, immunization of household contacts (especially school-aged children) and hospital staff should be effective and is recommended by the Centers for Disease Control [15]. In the absence of contraindications, annual immunization of individuals in these groups should be encouraged to reduce the risk of transmitting influenza infection to neutropenic leukemia patients. In the past, this has proved to be a daunting task in some cases, because of the resistance of some medical professionals to influenza immunization [12, 21, 22]. However, aggressive educational programs emphasizing the seriousness of influenza infection in this population should be effective in persuading personnel to accept immunization for the benefit of their patients.

The most important features of influenza infection are its epidemic nature and the morbidity and mortality associated with its pulmonary complications. We have shown that adult patients with leukemia are at risk of infection with influenza viruses during community epidemics and that, during some epidemics, they experience significant morbidity due to pulmonary complications of influenza infection. Unlike most infections threatening this population, influenza virus infection is largely preventable, and thus immunization of patients, their contacts and hospital personnel affords a unique opportunity to reduce the risk of infection among patients with leukemia.

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