

Community Respiratory Viruses as a Cause of Lower Respiratory Tract Infections Following Suppressive Chemotherapy in Cancer Patients

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ABSTRACT

Background and Purpose: Community respiratory viruses are an important cause of respiratory disease in the immunocompromised patients with cancer. To evaluate the occurrence and clinical significance of respiratory virus infections in hospitalized cancer patients at National Cancer Institute, Cairo University, during anticancer treatment, we studied cases that developed episodes of lower respiratory tract infections (LRTI).

Patients and Methods: Thirty patients with LRTI were studied clinically, radiologically, and microbiologically. Sputum cultures were done and an immunofluorescence search for IgM antibodies of influenza A and B, parainfluenza serotypes 1, 2 and 3, adenovirus, respiratory syncytial virus, Legionella pneumophila, Coxiella burnetii, Chlamydia pneumoniae, and Mycoplasma pneumoniae were performed on serum samples of patients.

Results: The main presenting symptom was cough and expectoration. Hematologic malignancy was the underlying disease in 86.6% of cases. Blood cultures were positive in 11 patients (36.6%) only. Sputum cultures revealed a bacterial pathogen in 13 cases and fungi in 3; whereas viral and atypical bacterial IgM antibodies were detected in 13 and 4 patients; respectively. Influenza virus was the commonest virus detected, being of type B in 4 cases, type A in one case and mixed A and B in another 5 cases; followed by RSV in 5 patients. Taken together, bacteria were identified as a single cause of LRTI in 10 cases, viruses in 6, fungi in 3 and mixed causes in 7. Still, there were 4 undiagnosed cases.

Conclusions: This study showed that respiratory viruses are common in LRTI, either as a single cause or mixed with bacterial pathogens, in hospitalized cancer patients receiving chemotherapy. Diagnostic tests for respiratory viruses should be incorporated in the routine diagnostic study of patients with hematologic malignancies. Also, it must be emphasized that early CT chest is crucial as a base-line prior to initiation of anti-fungal or anti-viral therapy. In cancer patients with a febrile episode and LRTI, tailored therapy is recommended according to the clinical findings of the patient.

Key Words: Respiratory viruses - Lower respiratory tract infections (LRTI) - Infections in cancer patients

INTRODUCTION

Infections have become an expected sequel after the newer chemotherapeutic regimens for cancer patients. Moreover, infection presents a tremendous challenge in cancer care in terms of clinical assessment, diagnosis and treatment in a potentially life-threatening situation [1]. It is important therefore, that centers delivering cancer care should have protocols of investigation and management that are appropriate to that center whilst ensuring a safe outcome for the patient. The emphasis on an individual center approach is important as patterns of infection and antibiotic resistance vary considerably [1].

Immunocompromised patients are susceptible to pulmonary infections, with pathogens including bacteria, viruses and fungi [2]. Community respiratory viruses, such as respiratory syncytial virus (RSV), influenza viruses, parainfluenza viruses, adenoviruses, and picornaviruses, are an important cause of respiratory disease in the immunocompromised adult with cancer. Recent studies have demonstrated that a minimum of 31% of adult bone marrow transplant (BMT) recipients and 18% of adults with leukemia who are hospitalized with an acute respiratory illness have a community respiratory virus infection. The temporal occurrence of these infections in immunocompromised patients tends to mirror their occurrence in the community [1].

Early diagnosis and treatment for pneumonia while receiving cancer chemotherapy and after allogeneic stem cell transplantation are essential to decrease morbidity and mortality accompanying these infections [3]. In hematological patients, pneumonia may be very difficult to diagnose. The main problem is whether to risk invasive procedures to have a reasonable chance of finding the etiological agent weighing the risks of the morbidity and mortality of the procedure [4]. Therefore, we attempted to carry on this study to examine the utility of a serum based indirect immunofluorescence method beside routine sputum cultures in identifying the etiology of pneumonia, in a trial to investigate the contribution of respiratory viruses as a cause of pulmonary infections in a group of cancer patients manifesting with lower respiratory tract infections.

PATIENTS AND METHODS

Thirty patients who developed a febrile episode together with clinical evidence of lower respiratory tract infections (fever, cough, tachypnea, difficulty in breathing, chest retractions, crackles) and/or radiological criteria (local or diffuse infiltrates in chest radiograph) while receiving their chemotherapy at the Medical and Pediatric Oncology departments of National Cancer Institute, Cairo University, over a 12-months period extending from October 2003 to October 2004 were included in the study. All the patients had a complete hemogram with absolute neutrophil count (ANC); arterial blood gas; cultures of sputum, and blood; and chest radiograph. They were started empirically on broad spectrum antibiotics as per the department policy. In patients who were already receiving antibiotics for some other infection, antibiotic therapy was modified according to clinical and radiological picture. After 72-96 hours, if there was improvement, the same antibiotics were continued; in non-responders amphotericin B was started, and were subjected to CT scan according to the clinical status of the patient.

Microbiological studies: Sputum samples were processed for the identification of aerobic bacteria, fungi and mycobacteria using standard laboratory procedures. The results of blood cultures performed during the febrile episode were recorded.

Indirect immunofluorescence (IF) for the detection of IgM antibodies to influenza A and B, parainfluenza serotypes 1, 2 and 3, adenovirus, respiratory syncytial virus, Legionella pneumophila serotype 1, Coxiella burnetii, Chlamydia pneumoniae, and Mycoplasma pneumoniae were performed on serum samples of patients: The reagents for indirect immuno-fluorescence were supplied by Vircell SL (Pneumoslide Ig M), France. The slides were read by Olympus IX70 fluorescent microscope. Interpretation of results was done according to degree of positivity of fluorescence, which was either ++ positive, + weak positive and ± equivocal. Only positive cases were considered as a cause of LRTI in our group of patients.

Patients were followed up for their response to initial empirical antibiotic therapy, length of hospitalization and any recurrence of the same respiratory symptoms later in the following courses of chemotherapy. The main outcome measures analyzed were the severity of pneumonic symptoms, the duration of infection episode, the recurrence of respiratory symptoms and the mortality related to the pneumonic infection.

RESULTS

Thirty patients (22 children and 8 adults) during or after receiving their chemotherapy, presenting with clinical and/or radiological evidence of lower respiratory tract infection were studied. The age of the pediatric group ranged between 2 to 17yrs with a median age of 8.5yrs. They were 17 males and 13 females. Their diagnosis was acute lymphoblastic leukemia (n=12), acute non-lymphoblastic leukemia (n=11), Non-Hodgkin's lymphoma (n=3), solid tumors [Ewing's sarcoma, Wilms' tumor, Neuroblastoma, and Rhabdomyosarcoma] (n=4). The main presenting symptom was cough and expectoration in all patients, otitis media in 5 patients, tachypnea in 2 patients, and only one adult presented with respiratory distress.

Chest X-ray was done for all patients except two who presented with otitis media; they were normal (n=26) except in four patients who showed evidence of bronchopneumonic patches. CT chest was not done routinely, only if the clinical condition was not improving within 7 to 10-days from initiation of antibiotics (n=17), seven CT scans showed pulmonary infiltrates

suggestive of fungal infection. The duration of hospitalization ranged between one to four weeks. Two AML patients died, while ten patients had recurrence of their respiratory symptoms after complete recovery of their infectious episode.

Viral IgM antibodies: Detected by indirect IF were encountered in 13 cases, either being the sole cause of infection detected (n=6) or in addition to other causes (n=7); in 3 of these cases 2 types of viral antibodies were found giving a total of 16 isolates. Influenza virus was the commonest virus detected, being of type B in 4 cases, type A in one case and mixed A and B in another 5 cases. RSV was encountered primarily in adult patients as it was positive in 4 adults and in only one of the pediatric age group, who was 17 years old. Adenovirus IgM antibodies were detected in one case only. Blood cultures were positive in 11 patients namely 4 adults and 7 of the pediatric group; 6 of them had respiratory virus IgM antibodies.

Bacterial pathogens: Sputum cultures revealed a bacterial pathogen in 13 cases. Taken together, bacterial pathogens either isolated from cultures or as IgM antibodies of atypical causes of pneumonia; being pure or mixed with other causes accounted for 17 cases. They were: *Klebsiella pneumoniae* (n=4), *Pseudomonas aeruginosa* (n=2), *Klebsiella group 47* (n=1), *Enterobacter aerogenes* (n=1) and *Acinetobacter baumannii* (n=2); for the gram positives methicillin resistant *Staphylococcus aureus* (MRSA) (n=2) and *Streptococcus pneumoniae* (n=1). The mixed cases were found concomitant with IgM antibodies of RSV, influenza A, B or mixed A and B. In addition IgM antibodies for *Legionella*, *Chlamydia* and *Mycoplasma* were encountered in 2, 1 and 1 of the cases, respectively. Thus, bacterial causes of atypical pneumonia were recorded in 4 patients.

Fungal cultures showed fungal growth in 3 cases, which were *Aspergillus* species. Fungi were the sole pathogen isolated in the 3 positive cases.

On trying to find out the main cause of infection in the 30 cases, bacteria were the sole respiratory pathogen recovered at the time of infection in 10 cases (33.3%), in 6 cases (20%) respiratory virus IgM antibodies were the only cause encountered, and fungi in n=3 patients.

In the remaining cases, respiratory viral IgM antibodies were detected concomitant to other causes (n=7). In 4 cases, no cause for respiratory infection could be demonstrated by the methods used. Table 1 illustrates the most probable cause of infection in the 30 cases studied.

For the mixed cases, i.e. cases with bacterial pathogens in addition to viral IgM antibodies detected (n=7), they were 2 adults and 5 children. In the adults, the bacteria were *Klebsiella pneumoniae* and MRSA and in the 2 cases the virus was RSV. In the pediatric group, the mixed cases were MRSA+ influenza A, *Chlamydia* + influenza A and B, *Acinetobacter baumannii* + influenza A and B, *Streptococcus pneumoniae* + influenza A and B and *Mycoplasma* + influenza B.

Table (1): The most probable cause of infection in 30 cancer cases with lower respiratory tract infection while receiving their chemotherapy at national cancer institute.

	Adults		Pediatric		Total	
	N	%	N	%	N	%
Bacterial pathogens	2	25	8	36.3	10	33.3
Viral-IgM antibodies	2	25	4	18.2	6	20
Fungal pathogens	1	12.5	2	9.1	3	10
Mixed	2	25	5	22.7	7	23.3
Undiagnosed	1	12.5	3	13.6	4	13.3
Total	8	100	22	100	30	100

DISCUSSION

The lung is a common site of infection in patients with cancer. The spectrum of pulmonary infection depends on the underlying immunologic deficit or deficits. In neutropenic patients, gram-negative bacterial infections predominate early, whereas fungal infections (*Aspergillus*, *Zygomycetes*, *Fusarium* species) are common if neutropenia persists. In patients with impaired cellular immunity, viral infections predominate and may coexist with bacterial (*Legionella*, *Nocardia*), mycobacterial, and fungal (*Aspergillus*, *Histoplasma*, etc.) infections. *Pneumocystis carinii* pneumonia is also common in this setting. Infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* are the primary bacterial infections encountered in patients with impaired humoral immunity [3,5].

Infections by respiratory viruses (influenza, RSV, parainfluenza virus, and adenovirus) are a leading cause of morbidity in healthy hosts but are

generally self-limited to the upper respiratory tract. Each year respiratory virus outbreaks are an important cause of hospitalization, in particular during influenza epidemics [6]. Immunocompromised subjects living in the community are exposed to these seasonal outbreaks of respiratory viruses and they are at high risk of severe lower respiratory complications [7]. It has been shown that pneumonia has a major impact on the prognosis of neutropenic cancer patients during aplasia after chemotherapy, especially in terms of survival [8].

In the present study, respiratory viruses were detected by indirect immunofluorescence for viral IgM antibodies as a sole cause in 20% and concomitant with other causes in another 23% of cancer patients with clinical and radiological evidence of LRTI during chemotherapy induced aplasia. Several reports have estimated that respiratory viruses account for 20-27% of viral infections in immunocompromised patients with acute lung diseases who undergo a BAL procedure [7,9]. Influenza virus was the commonest respiratory virus type detected in this study especially in children. Similarly, it was reported that influenza is the most important cause of acute respiratory illness leading to hospitalization among children during community epidemics; it can cause extensive nosocomial outbreaks with serious morbidity and mortality among specific groups of children [10].

Influenza was followed by RSV as the second common virus detected in the present study. In a similar study where a respiratory virus was identified in 48% of upper or lower RTI episodes, influenza virus was the commonest isolated virus followed by RSV in adults with hematologic malignancies [11]. Although RSV is known to be the most important cause of LRTI in young children [12], still only one positive case of RSV in pediatric age group was encountered in our cases. It is to be mentioned that RSV was primarily positive in our adult cases. This could be explained by that maybe we did not study pediatric patients at the peak time of RSV as seasonal variation of RSV chest infection is known to occur [12].

As regards clinical manifestations in our patients, their main presentation was fever together with cough and expectoration. Similarly, the main frequent clinical manifestations in bone marrow transplant recipients with respira-

tory tract viral infections were cough and fever, while pneumonia occurred in 31% of cases [13]. In our study, the cases with an identified viral infection as a single agent, had self-limited respiratory illnesses with no mortality recorded. Similarly, in a group of pediatric patients undergoing hematopoietic stem cell transplant who were analyzed for the presence of respiratory viruses, the morbidity of respiratory infections was generally mild and no mortality was observed [14].

As regards cases with more than one pathogen encountered, namely a bacterial cause besides respiratory viruses IgM antibodies, these could be true mixed cases or bacterial infections occurring as a complication to a previous viral infection. In our opinion, it's more convincing to consider that viral infections preceded the occurrence of bacterial causes of infections, as IgM antibodies take 2 to 4 weeks to appear which most probably happened before hand. In agreement with our postulation, it has been stated that secondary bacterial pneumonia occurs more frequently following primary viral infections in the immunocompromised hosts [15]. Viral-bacterial co-infections in humans are well-documented. Viral infections often lead to bacterial super-infections. In vitro and animal models for influenza, as well as molecular microbiology study of viruses and bacteria, provide an understanding of the mechanisms that explain how respiratory viruses and bacteria combine to cause disease [15]. Moreover, it was concluded that when respiratory viruses are recovered in BAL samples of hospitalized patients, severe lower respiratory tract complications were frequent and were observed in highly immunosuppressed patients [7]. Recent data supports that prevention of bacterial super-infection is likely to depend on effective antiviral measures [15].

Pulmonary disease in the immunocompromised host remains a major cause of morbidity and has a high mortality. Blood cultures are positive only in 25% of cases and even if positive they cannot be interpreted as indicating the pathogen from the diseased lung itself [16]. In the present study, Blood cultures were positive in 11 patients, 6 of them had respiratory virus IgM antibodies. Collection of sputum is difficult in children and often contaminated with commensal organisms is upper respiratory tract. Throat and nasopharyngeal swab cultures have

a reliable correlation only in 6% [17]. Oropharyngeal mucosa may be overgrown by bacteria or fungus without distinction between colonization and superinfection. Thus, a definite diagnosis is seldom established by these non-invasive means. Therefore, the choice of serum as a sample in the present study for the detection of several respiratory pathogens besides culture was convenient especially in children who are at risk to develop complications from invasive procedures.

Radiological criteria, namely local or diffuse infiltrates in chest radiographs and chest computerized tomography (CCT) scan are essential procedures for diagnosis, but it must be emphasized that radiographic appearances are often deceptive in immunocompromised hosts and usually not helpful in making a specific etiologic diagnosis. In the current study, chest X-ray was of no help to reach a diagnosis and CCT scan aided in the diagnosis in the majority of cases.

Rapid diagnostic techniques with high degree of sensitivity and specificity should be used to reach the proper diagnosis without delay as the management differs in different causes of infection. In a recent study that compared routine viral cultures to direct fluorescent antibody stains, in the detection of community acquired respiratory viruses, it was found that both tests had comparable sensitivity and specificity, but in 86% of cases viral cultures became positive after patient had been discharged from the hospital [18]. Therefore, IF was considered a rapid and sensitive method for the diagnosis of LRTI caused by respiratory viruses [19]. Polymerase chain reaction has the potential to increase both sensitivity and specificity of diagnostic procedures and to decrease the time to results availability. However, its use for the detection of respiratory viruses raises several unresolved issues including sample processing and the need for assays capable to detect at least 9 pathogens [7].

In the present study, 3 cases were proven to be fungal by a positive culture and imaging. Although constituting only 10% of LTRI, yet fungal infections have to be clinically expected and vigorously investigated in cancer patients receiving chemotherapy as these infections were accompanied by remarkable morbidity and mortality. In the recent years, invasive aspergillosis has become a major cause of infection-related

morbidity and mortality in neutropenic cancer patients and recipients of stem cell transplants [20]. In addition to invasive aspergillosis, Legionella was also associated with prolonged episodes and thus the diagnostic work out should include a search for Legionella. It was reported that patients who had Legionnaires' disease were more likely to be immunosuppressed, especially those who have diabetes, cancer, AIDS, or end stage renal disease [21].

Thus, it is evident from the results of the present study that LRTI in cancer patients are caused by a variety of pathogens. Reliable diagnostic methods are recommended for the identification of the exact cause of infection, so that antimicrobial therapy is directed to the specific pathogen. It is hoped that this approach lowers the days of hospitalization, directs specific therapy and so reduces the selective pressure for resistance. Optimal therapies need to be defined in controlled trials; however, it appears that a favorable response will hinge on the initiation of therapy at an early stage of the respiratory illness.

In conclusion, in hospitalized patients who develop LRTI while receiving chemotherapy, the possibility of viral respiratory disease should actively be considered, to ensure that effective preventive and antiviral treatment may be initiated. Although respiratory viruses were associated with self-limited illnesses in our group of patients, still they were frequently accompanied by bacterial super-infections. Frequent screening for respiratory viruses should be incorporated in the routine diagnostic study of cancer patients receiving their chemotherapy especially those with hematologic malignancies as they are more vulnerable to LRTI.

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