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Community respiratory virus infections in patients with hematologic malignancies

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Abstract

Background and Objective. **Pneumonia occurred frequently in patients receiving treatment for hematologic disorders, particularly after hematopoietic stem cell transplant. Some of these pneumonias have a viral etiology, herpesvirus and cytomegalovirus being classically recognized pathogens. The increased awareness of the importance of community respiratory viruses in this setting led us to conduct a survey of the cases of pneumonia occurring in patients with hematologic malignancies over an eight year period.**

Design and Methods. **From January 1991 to November 1998, 224 bronchoalveolar lavages (BAL) were performed in 204 patients with hematologic malignancies and a suspected lower respiratory tract infection (RTI).**

Results. **A community respiratory virus was isolated from the BAL in 21 patients (9% of BAL). The viruses isolated were influenza A (8), non-polio enterovirus (8), adenovirus (3), parainfluenza (2) and 1 rhinovirus. All the non-transplanted patients with RTI were adults while half the stem cell transplant (SCT) recipients with RTI were children (100% vs 50%, $p < 0.04$). Overall, 76% of patients in whom respiratory viruses were found in the BAL developed pneumonia and 10 died from it (48% overall and 63% with pneumonia). There were no differences in the overall incidence of community respiratory virus infection of mortality ratebetween patients receiving autologous and allogeneic transplants. No difference in the occurrence of pneumonia between the SCT and non-SCT groups was observed, although more SCT recipients died from their pneumonia. Neutropenia was not an apparent risk factor for the development of pneumonia or mortality.**

Interpretation and Conclusions. **In conclusion, our single-center experience confirms the importance of conventional respiratory viruses in serious lower respiratory tract infections. These infections are associated with a high mortality rate in SCT recipients.**

Key words: community respiratory viruses, pulmonary infections, immunocompromized hosts

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Pneumonia is a frequent infectious complication during treatment for hematologic malignancies, especially after a hematopoietic stem cell transplant (SCT). Most viral pneumonias in these patients have been traditionally associated with herpesviruses and, especially, cytomegalovirus after SCT.[1,2] In recent years, however, it has been recognized that community respiratory viruses (CRV) are a significant cause of disease in several institutions. Specifically, respiratory syncytial virus, influenza A and B, parainfluenza, adenovirus and the picornaviruses have been recognized as causing pneumonia in immunocompromized hosts, particularly in patients with hematological malignancies treated with intensive chemotherapy or undergoing SCT.[3-8] We report on our experience with lower respiratory tract infections caused by these viruses over an eight year period.

Design and Methods

Between January 1991 and November 1998, 224 bronchoalveolar lavage (BAL) procedures were performed in 204 patients with a hematologic malignancy and signs/symptoms of a lower respiratory tract infection (LRTI). A LRTI was defined as fever plus cough, dyspnea and/or newly-appearing signs of pulmonary disease on physical examination (usually crackles and/or wheezing), while pneumonia was defined by the above plus a new pulmonary infiltrate on chest X-ray. Upper RTI (URTI) was defined as the presence of nasal congestion with rhinorrhea and sneezing.

Neutropenia was defined as an absolute neutrophil count $< 0.5 \times 10^9$/L, and patients were considered to be on immunossuppressive treatment if they were receiving steroids, cyclosporine or antithymocyte globulin at the time of infection. Antiviral therapy directed against the virus isolated was not used in any patient.

For statistical analysis Fisher's exact test was used to compare categorical data between groups.

Virologic techniques

All respiratory specimens were obtained by BAL and submitted for routine aerobic, anaerobic, mycobacterial and fungal culture as well as parasite

examination. For viral diagnosis, specimens were inoculated into each of four cell lines: human fibroblasts (MRC5), human epithelial cells (Hep-2 and A-549) and Madin-Darby canine kidney cells (MDCK). Viral cultures were incubated for two weeks, four weeks for cytomegalovirus, on a roller drum at 35ºC. Viruses were identified on the basis of cytopathic effect in cell cultures and the identification confirmed by staining with fluorescein-conjugated monoclonal antibodies.[8]

Results

A CRV was isolated from BAL fluid from 21 patients (9% of BAL). One patient had an influenza A virus plus a non-polio enterovirus isolated from the same BAL sample, and thus 22 virus isolates are reported herein. The viruses isolated were influenza A (8), non-polio enterovirus (8), adenovirus (3), parainfluenza (2) and rhinovirus (1). The clinical characteristics of these patients are shown in Table 1. There were 15 men and 6 women, with a median age of 29 years (range 5-70). Nearly all patients had leukemia or lymphoma, and 12 developed the infection after a SCT (6 autologous and 6 allogeneic), while 7 had recently received conventional intensive chemotherapy, one had been treated with steroids only and one had not received any treatment for his malignancy.

Table 2 summarizes the clinical characteristics of the infections and the observed differences between SCT recipients and non-transplanted patients. All non-transplanted patients with a CRV infection were adults, while only half of the SCT recipients with LRTI were children (100% vs 50%, $p < 0.04$). There were no obvious differences in other demographic characteristics between the groups. Overall, 16 (76%) of the 21 BAL+ve patients developed pneumonia, which proved to be fatal in ten cases. Thus the mortality rate due to pneumonia in patients with a BAL documented viral infection was 48% and the mortality rate in patients with pneumonia was 63%. Among SCT recipients, the overall incidence of a CRV infection did not differ between those who received an autologous or allogeneic transplant. Specifically, 6/165 (3.6%) allogeneic and 6/349 (1.7%) autologous transplant recipients developed a CRV infection (p= 0.1).

There were no apparent differences in the incidence of pneumonia between the SCT and non-SCT groups (83% vs 67%), but more patients in the former group died of pneumonia (75% vs 11%, respectively, $p < 0.03$). This difference was due to the higher mortality in patients with pneumonia among SCT recipients than among non-transplanted patients (90% vs 17%, respectively, p= 0.01). Mortality did not differ between autologous (5/6) and allogeneic (4/6) SCT recipients.

The presence of neutropenia was not an apparent risk factor for the development of pneumonia or death, since 11/13 (85%) neutropenic patients vs 5/8 (63%) non-neutropenic patients developed pneumonia (p= 0.2) and 6/13 (46%) vs 4/8 (50%), respectively, died (data not shown).

Other pathogens that may have contributed to the onset of respiratory signs/symptoms were isolated from 4 patients, from blood (n= 2) or BAL (n= 2),

Table 1. Characteristics of patients with a respiratory virus isolated from BAL.

Num. of patients	21
Sex: male	15
Num. children (<16 yr)	6
Age (median, range)	29 (5-70)
Underlying disease	
acute myelogenous leukemia	4
acute lymphoblastic leukemia	7
non-Hodgkin's lymphoma	6
Hodgkin's disease	2
chronic lymphocytic leukemia	1
neuroblastoma	1
Treatment prior to infection	
autologous SCT	6 (4 BMT, 2 PBSCT)
allogeneic SCT	6 (3 BMT, 3 PBSCT)
conventional chemotherapy	7
steroids only	1
no treatment	1

BAL, bronchoalveolar lavage; SCT, hematopoietic stem cell transplantation; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation.

Table 2. Respiratory viruses isolated from BAL, clinical characteristics and outcome.

	Total (%)	*SCT (%)*	*Non-SCT (%)*	*p*
All patients	21	12	9	
Virus isolated				
adenovirus	3	2	1	
enterovirus	8	5	3	0.6
influenza A	8	4	4	
parainfluenza	2	1	1	
rhinovirus	1	1	0	
Num. of adults	15 (71)	6 (50)	9 (100)	0.04
Neutropenia ($0.5x10^9$/L)	13 (62)	7 (58)	6 (67)	0.4
Immunosuppressed and/or neutropenic	15 (71)	10 (83)	5 (56)	0.2
Time from last CHT or SCT				
<60 days	14 (67)	9 (75)	5 (56)	
>60 days	7 (33)	3 (25)	4 (44)	0.2
Other pathogens isolated	4 (19)	3 (25)	1 (11)	0.4
Pneumonia	16 (76)	10 (83)	6 (67)	0.3
Death from pneumonia	10 (48)	9 (75)	1 (11)	< 0.03
Mortality among patients with pneumonia	10/16 (63)	9/10 (90)	1/6 (17)	0.01

BAL, bronchoalveolar lavage; SCT, stem cell transplantation; CHT, chemotherapy.

Table 3. Characteristics of infections by different viruses.

	A-vir	*Infl.*	*E-vir*	*P-infl.*	*R-vir*
No. of cases	3	8	8	2	1
Children*/adults	_	2/6	4/4	0/2	0/1
CHT/SCT	_	4/4	3/5	1/1	0/1
October-March	1	8	7	1	1
Fever at diagnosis	3	8	8	2	1
URTI	2	5	5	2	1
Other pathogens isolated	0	1*	3*@#	1°	0
Pneumonia	3	7	6	1	0
Died from pneumonia	2	4	5	0	0

*A-vir: adenovirus; Infl.: influenza A; E-vir: enterovirus; P-infl.: parainfluenza; R-vir: rhinovirus; SCT, stem cell transplantation; CHT, chemotherapy; URTI, upper respiratory tract infection. *One patient who died had an influenza A virus and a non-polio enterovirus isolated from the same BAL sample, and a previous BAL performed three weeks early showed* Pneumocystic carinii *cysts. Post-mortem examination showed signs of adult respiratory distress syndrome. °One patient had a parainfluenza virus and an* Haemophilus influenzae *isolated from the same BAL sample and survived the infection. @One patient had a prior bacteremia by Acinetobacterium baumanii. The patient died and an autopsy was not done. #One patient who died had a prior bacteremia by* Pseudomonas aeruginosa *and viridans streptococci. Post-mortem examination showed signs of adult respiratory distress syndrome.*

around the time that the BAL procedure was performed. There were two cases of bacteremia caused by *Acinetobacter baumanii* and *Pseudomonas aeruginosa* plus *Streptococcus viridans*, and *Haemophilus influenzae* was isolated from the same BAL sample as a parainfluenza virus. One patient had *Pneumocystis carinii* cysts in a BAL performed three weeks earlier, which was not found in the later BAL from which an influenza A virus and a non-polio enterovirus were isolated.

Table 3 summarizes the clinical characteristics associated with the different viruses isolated. Most patients (15/21) had concurrent or preceding symptoms of an URTI. Mortality among patients with both LRTI and URTI was 54% (6/11), while it was 40% (2/5) among those with LRTI only. Most infections (18/21) occurred between October and March. There are, however, too few cases in each category to identify any clinically relevant differences between infections caused by the viruses isolated.

Discussion

Over an eight year period nine percent of BAL samples from patients with a hematologic malignancy and signs/symptoms of a LRTI had a CRV isolated at our institution. This incidence is lower than the 15-30% rates reported in other studies,[3-5] but in other studies both BAL and nasopharyngeal samples from patients with URTI and/or LRTI were examined, while we studied only BAL samples from patients with a LRTI. The CRV isolated in our center, however, differ markedly from those reported in previous studies. Respiratory syncytial virus (RSV) is usually the most frequently isolated CRV, followed by influenza, parainfluenza, adenovirus and the picornaviruses, mainly rhinovirus. Surprisingly, we found no case of RSV infection. This is certainly not due to the lack of community RSV infections in our area or to the lack of experience in our laboratory in diagnosing them, since confirmed RSV infections are frequently diagnosed at our institution in young children during winter months.[9] Non-polio enteroviruses were the most frequently isolated viruses in our patients. Although enteroviruses are well-known respiratory pathogens, to our knowledge this predominance among CRV isolated in patients with hematologic malignancies has not been previously reported.

Although the incidence of pneumonia did not apparently differ between SCT recipients and non-transplanted cases, more patients in the former group died from pneumonia. This difference has been previously observed in CRV infections.[6,10,11] These findings are not surprising since pulmonary complications, especially respiratory infections, have a higher mortality following transplantation than in other patient groups.[1,12] Diagnosis was based on viral cultures in this series of patients. There are, however, rapid detection methods based on immunofluorescence techniques for these CRV that are currently being studied in our center and elsewhere. These techniques should allow an earlier diagnosis and, it is to be hoped, improve the prognosis of patients with those infections by being able to intervene swiftly with an effective therapy.

We were unable to study the effect of antiviral therapy on outcome since none of our patients was treated for their viral infection. At present there are no treatment options for some viruses, such as the enteroviruses and rhinoviruses, although research in this field may yield active agents in the near future.[13] For the other CRV there are active antiviral agents, although their impact on patient outcome remains an unresolved issue. Ribavirin is active against respiratory syncytial virus, adenovirus and parainfluenza viruses,[4-7,10,11] amantadine/rimantadine are active against influenza A,[5,6,11] and cidofovir is active against adenovirus and all herpes viruses, including acyclovir and ganciclovir resistant strains.[14]

Since therapy is currently of limited proven value, the only real impact that hematologists and transplant physicians may have on these infections is their prevention. The mainstain of such prophylaxis in patients with symptoms of an URTI or LRTI, avoid interpatient transmission of infections during hospitalization by the staff and avoid outpatient contact with children and adults with respiratory symptoms.[15] To prevent nosocomial spread of influenza virus, special emphasis should be placed on vaccination of hospital staff caring for immunocompromized patients and the use of antiviral prophylaxis with amantadine in patients exposed to the virus in whom vaccination has been shown to be ineffective.

In summary, our single-center experience confirms the importance of CRV in serious LRTI, there being a high mortality rate in SCT recipients with pneumonia. The frequent isolation of enteroviruses has not been previously reported and may indicate that the relative contribution of different CRV may differ between geographic areas and from one institution to another.

Contributions and Acknowledgments

YG designed the study, was responsible for data management and prepared the manuscript. RM supervised all the study, performed the data analysis and participated in writing the paper. NR participated in the preparation of the paper and in collaboration with RL carried out the microbiological studies. IB collaborated in patient care and data management. JS is the head of the Division and participated in writing the paper.

Disclosures

Conflict of interest: none.

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Manuscript processing

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