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Original

Respiratory viral infection's frequency and clinical outcome in symptomatic children with cancer: A single center experience from a middle-income country

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In developing countries, acute respiratory tract infections are a significant cause of morbidity and mortality in children, particularly in pediatric cancer patients. A majority of these illnesses are precipitated by viral infections. In our country, studies were conducted on the single respiratory viral infection in a pediatric hematology-oncology unit; however, the analysis of respiratory viral infections in children with cancer is lacking. The present study aimed to provide analysis of multiple respiratory viral infections and clinical outcome in children with cancer who receive chemotherapy and show signs and symptoms of respiratory tract infections. During January, 2014 and January, 2015 children with cancer under treatment who presented with respiratory tract infections were assessed for viruses by using multiplex real-time reverse transcription polymerase chain reaction (rRT-PCR). Specimens were collected by nasal swabbing at in-patient and out-patient clinics. Overall, 72 samples of respiratory tract infection episodes, collected from children with cancer were evaluated with the simultaneous detection of 20 respiratory viruses. A respiratory viral pathogen was obtained in 56.9% samples. Rhinovirus (24.3%) and co-infection with two viruses (19.5%) were the most frequently isolated pathogens. There were four (9.6%) samples of severe pneumonia. Patients with febrile neutropenic episodes and pneumonia were hospitalized and treated with broad-spectrum antibiotics. Other non-neutropenic and mild respiratory tract infections were treated with supportive care as outpatient procedures. There were no deaths. Because there are no effective antiviral agents for certain respiratory viruses, infection control and early diagnosis are crucial in preventing the spread of infection. Clinical findings and serological results of viral respiratory tract infections help us to accurately determine the treatment approach and avoid the unnecessary use of antibiotics.

Key words: cancer, children, respiratory viral infection.

In developing countries, respiratory tract infections are the significant cause of morbidity and mortality in children especially in immunocompromised pediatric cancer patients.[1] The majority of these illnesses are precipitated by viral infections. Although studies had investigated febrile neutropenia and bacterial, fungal infections during the past decades, the role of respiratory viral infections in children with cancer have been directed at the last years. In our country, studies have been conducted on single viral

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infection in a pediatric hematology-oncology unit or frequency of respiratory viral infections in immunocompetent pediatric patients but not frequency of multiple respiratory viral infections in children with cancer. The present study aimed to identify the viral etiology of infections in children with cancer who receive chemotherapy and show signs and symptoms of respiratory tract infections.

Material and Methods

Between January 1, 2014 and January 1, 2015, all children with cancer who were receiving chemotherapy and who showed signs and symptoms of respiratory tract infections with or without fever were assessed for viruses by using algorithms and molecular techniques (real-time reverse transcription polymerase chain reaction, rRT-PCR) recommended by the United States Centers for Disease Control and Prevention (CDC) and World Health Organization in the Influenza Reference Laboratory of Istanbul University. This prospective clinical study was approved by the local ethical committee and written informed consent was obtained from the parents of enrolled children.

Definitions

Upper respiratory tract infections (URTIs) were defined as the presence of at least one of the following symptoms: fever, sore throat, rhinorrhea, nasal congestion, otitis media, and cough with normal findings of chest examination and chest radiography. Lower respiratory tract infections (LRTIs) were defined as the presence or absence of any of the symptoms of URTI with accompanied by signs on lung auscultation or the presence of new pulmonary infiltrate observed on plain chest radiography and/or computed tomography.

Diagnosis of viral infection

Nasal swabs were collected from all children with the signs and symptoms of respiratory tract infection at inpatient and outpatient clinics. Nasal swabbing involves the insertion of a sterile cotton swab into a nostril and obtaining a specimen from a depth of 2–3 cm; subsequently, this specimen was inserted into a vial containing Virocult, a viral transport medium (Medical Wire & Equipment, Corsham, UK) and transported to the virology laboratory, on the same day at room temperature. The EZ1 Virus mini kit V2.0 (catalog number: 955134, Qiagen, Germany) was used for total nucleic acid extraction. The rRT-PCR-based, multiplex FTD® Respiratory Pathogens 21 kit (Fast-track diagnostics Ltd., Malta) was used for the detection of respiratory pathogens on the RotorGene Q platform (Qiagen, Germany). Etiological pathogens of respiratory viral infections were identified in 1 day by using the multiplex rRT-PCR and allowed the simultaneous detection of 20 respiratory viruses: influenza (A, H1N1, and B), rhinovirus (HRV), respiratory syncytial virus (RSV A/B), parainfluenza (PIV1, 2, 3, and 4), coronavirus (229E, NL63, OC43, and HKU1), human metapneumovirus (hMPV A/B), adenovirus (ADV), enterovirus, parechovirus, and bocavirus (HBoV).

Demographic data (e.g., sex, age, and underlying disease), clinical presentation (URTI/LRTI), concurrent febrile neutropenic episodes, need for oxygen therapy and supportive care, and absolute neutrophil count at the time of infection were collected.

Statistical analysis

All analyses were performed using the SPSS software (ver. 13.0.). A univariate descriptive analysis was performed for qualitative data by the frequency distribution of percentages in several categories. The statistical significance of the differences between the various groups was tested using the Chi-squared test. A $p < 0.05$ was considered statistically significant.

Results

Seventy-two samples of respiratory tract infection episodes, collected from 48 children (22 boys, 26 girls) with cancer, were evaluated. The median age was 8.0 (0.6–18) years. The underlying diagnosis of the patients were brain tumors and sarcomas (30 patients); leukemia/lymphoma (9 patients) and others (9 patients).

A respiratory viral pathogen was detected in 56.9% (41/72) of the analyzed samples; among these, one virus was detected in 80.5% (33/41) of episodes, whereas the co-detection of two viruses was recorded in 19.5% (8/41) of episodes. Distribution according to the months is shown in Figure 1.

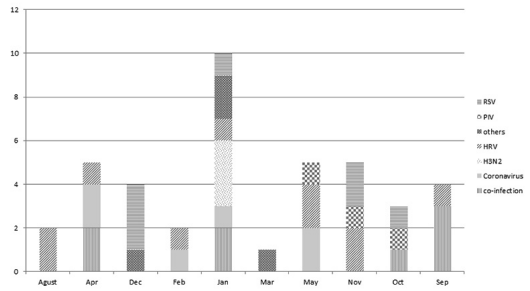

Fig. 1. Distribution of viral pathogens (in numbers) according to months.
HRV: rhinovirus, PIV: parainfluenza, RSV: respiratory syncytial virus

Table II. Respiratory Tract Infection Episodes with Co-infection.

Pathogens	N
HRV+coronavirus	2
HRV+enterovirus	2
Influenza B+RSV	1
ADV+hMPV	1
ADV+PIV	1
HRV+ADV	1

ADV: adenovirus, hMPV: human metapneumovirus, HRV: rhinovirus, PIV: parainfluenza, RSV: respiratory syncytial virus

Rhinovirus was the most commonly isolated pathogen of respiratory viral infection as a single viral agent (N=10; 24.3% samples) or as a co-infecting agent (N=5 samples) with other viruses. RSV (N= 8) and coronavirus (N=8) were the second and third most common pathogens, mostly as a single viral agent (Table I). The most frequently detected co-infections with two viruses were HRV + enterovirus (N=2) and HRV + coronavirus (N=2) (Table II).

URTI and clinical LRTI were detected in 80.6% (N=58) and 19.4% of the patients, all of the episodes. Viral agents were detected in 51.7% (30/58) of the patients with URTI and in 78% (11/14) of those with LRTI (p=0.069) (Table III). A total of 36.3% of the patients with LRTI who were detected to have viral agents required oxygen therapy.

None of the patients were admitted to the intensive care unit for mechanical ventilation, and there were no deaths due to respiratory tract infections. In total, 27.3% of the patients were detected to have a single viral agent and 25% of the co-infected patients had clinical LRTI.

Almost one third (25/72) of all episodes were admitted for neutropenic fever (absolute neutrophil count $<500/mm^3$), of which, a respiratory tract virus was detected in 60% (15/25) and no one had a positive blood or urine culture. In almost half of the non-neutropenic cases (55%, 26/47), a viral respiratory tract pathogen was also detected (p=0.703).

Table I. Distribution of Respiratory Viruses in Episodes with Detected Viruses (N=41; a co-infection was detected in eight episodes)

	Episodes		
Virus	Single agent, N	Co-infection, N	Total, N (%)
HRV	10	5	15 (36.5)
RSV	7	1	8 (19.5)
Coronavirus	6	2	8 (19.5)
PIV	3	1	4 (9.7)
Influenza	3	1	4 (9.7)
hMPV	2	1	3 (7.3)
Adenovirus	1	2	3 (7.3)
hBoV	1	0	1 (2.4)
Enterovirus	0	2	2 (4.8)

hBoV: bocavirus, hMPV: human metapneumovirus, HRV: rhinovirus, PIV: parainfluenza, RSV: respiratory syncytial virus

Table III. Clinical Characteristics in 72 Episodes.

Characteristics	N (%)
RV detected	41 (56.9)
URTI	58 (80.6)
LRTI	14 (19.4)
Febrile neutropenia	25 (34.7)
RV detected febrile neutropenia	15 (36.5)

LRTI: lower respiratory tract infection, RV: respiratory virus, URTI: upper respiratory tract infection,

In four episodes, the clinical course was severe and all patients suffered from LRTI that required hospitalization and oxygen therapy; of these, three had neutropenic fever, and the viral agents detected were HRV, PIV, and HRV + coronavirus co-infection. In the fourth case of non-neutropenic fever, hMPV was detected. Fifty percent of patients with non-neutropenic fever with URTI in whom a viral pathogen was detected did not receive any antibiotics.

Among those who were detected to have or not have respiratory virus, symptoms such as cough, fever, nasal flow, neutropenia, and LRTI were not statistically significant in terms of the clinical findings (p=0.24, 0.39, 0.67, 0.97, and 0.69, respectively).

All patients with concurrent febrile neutropenic episodes and pneumonia were hospitalized, and broad-spectrum antibiotics with anti-pseudomonal activity were administered. Patients with non-neutropenic fever and well status were followed up as outpatients with or without antibiotic treatment. Three patients with H3N2 influenza A were treated with oseltamivir.

Discussion

Many viral agents causing respiratory tract infection may be asymptomatic or cause different clinical symptoms in different patients from mild complications to death. These clinical findings are related to the virus and an individual immune-mediated component. While it is possible to take precautions against nosocomial infections or the redundant use of antibiotics, it is also possible to enable vaccine and drug trials aimed at the most frequent agents.[2] In light of this basic information, many countries have evaluated the observed clinical findings and the most commonly detected viral agents in various groups of patients with respiratory tract infections.

During the last few years, the polymerase chain reaction (PCR) test is used around the world to detect viral agents causing respiratory tract infections. This technique has been shown to have higher sensitivity than viral culture along with an ability to detect multiple respiratory viruses in one single sample simultaneously with a high sensitive diagnosis within a time span of 6–24 hour.[3-7]

In our country, there have been studies in which PCR was used for research on the effect of viral agents in immunocompetent children who were admitted to the hospital with respiratory tract infections or who were treated in the hospital due to LRTI, in addition to the studies in which the clinical features of these viral agents are researched. In these studies, which often included influenza and fall-winter periods, the most common types of agents were influenza A (H3N2) (36.6–39.2%) and RSV (32–55.6%).[8-11] In the group of immunosuppressed patients, there were small case series in which the clinical features of 2009 H1N1 influenza A were evaluated during their pandemic periods.[12,13]

In our study, no cases of H1N1 were observed during a 1-year period. In our country, there have been no studies in which viral agents causing respiratory tract illnesses in the group of children with underlying immunodeficiencies or cancer patients and their clinical features were observed.

Influenza is suggested to be a frequent pathogen of URTI both in immunocompetent and immunocompromised children.[14,15] In our series of children with cancer, HRV was found to be the most frequent (24.3%) viral respiratory tract infection pathogen. However, in most published series on pediatric cancer, HRV has not been included in the viral panel.[14,16] The high incidence of HRV can also be attributed to the inclusion of HRV in the diagnostic testing panels during recent years, which has led to similar cases.[17-21] In the present study, no seasonal differences were observed in the incidence of HRV infection; similarly, certain past studies have also reported the absence of any seasonal differences.[19,21-23]

In total, 5 of the 15 patients with HRV infection

were hospitalized with neutropenic fever, and 2 with additional LRTI requiring oxygen therapy. Almost half of those having non-neutropenic fever (7/15, 46.6%) did not require any antibiotics; these patients were followed up. According to previous studies, HRV can either cause mild URTI or remain asymptomatic in certain patients. However, little evidence is available to prove that HRV can cause severe LRT symptoms in both immunocompetent and immunocompromised individuals.[19,24,25] Therefore, the reason why HRV infections were observed in different clinics as a cause of more severe respiratory tract infections or asymptomatic respiratory tract infections can be understood via the HRV sub-group studies.

In our study, the second most common cause was co-infection with two viruses (19.5%), more frequently with HRV. Viral co-infections were reported as 8–69.9% in various studies[7,26,27] that do not include the group of immunocompromised patients and as 9–24%[17,18,23] in immunocompromised patients. As there have been fewer studies where multiple viral agents were observed in the group of immunocompromised patients and there have not been studies with a concurrent control group, a correct comparison of co-infection's clinical severity with regard to patients' immunity levels is not possible. The most common agents observed in co-infections were also the most frequent single agents both in our study and others. There are challenging results about the clinical findings in the co-infection state in immunocompromised hosts. Few studies have reported that multiple-virus infections are correlated with lesser disease severity[26-30], while others have indicated a higher disease severity in children with mixed respiratory infections.[31,32] Our patients who were infected by the same agents with co-infection (HRV + enterovirus, HRV + coronavirus), whereas neutropenic had moderate to severe clinical infection, whereas non-neutropenic patients were followed up as outpatients with no antibiotic treatment. In our series, no significant differences were observed in terms of the disease severity between co-infected patients and those infected with a single virus.

However, almost as a generalized finding, LRTI is markedly associated with severe neutropenia and lymphopenia. This finding emphasizes the importance of pulmonary cytotoxic T lymphocyte responses for the clearance of respiratory viral infections.[33,34]

In our cases, 50% of non-neutropenic children with detected respiratory virus did not receive antibiotics, while the remaining children received antibiotics either for LRTI or other clinical findings. Pediatric patients with cancer may face more severe complications of influenza compared with healthy children. Centers for Disease Control and Prevention guidelines recommend yearly vaccination in such patients[35]. Although only four patients were infected with influenza in our series, vaccination early in the season should be recommended.

In conclusion, it should be kept in mind that viruses are a major cause of respiratory tract infections in children. Because there are no effective antiviral agents for certain respiratory viruses, infection control and early diagnosis are crucial in preventing the spread of infection in children with cancer. Clinical findings and serological results of viral respiratory tract infections help us to accurately determine the treatment approach and avoid the unnecessary use of antibiotics.

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