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The clinical impact of coronavirus infection in patients with hematologic malignancies and hematopoietic stem cell transplant recipients

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ABSTRACT

Background: Compared to other respiratory viruses, relatively little is known about the clinical impact of coronavirus (CoV) infection after hematopoietic stem cell transplant (HSCT) or in patients with hematologic malignancies.
Objectives: To characterize the role of CoV in respiratory tract infections among HSCT and hematologic malignancy patients.
Study design: We conducted a retrospective review of all cases of CoV infection documented by polymerase chain reaction, (PCR)-based testing on nasopharyngeal and bronchoalveolar lavage fluid samples between June 2010 and 2013. Cases of CoV infection occurring in HSCT and hematologic malignancy patients were identified and the clinical characteristics of these cases were compared to other respiratory viruses.
Results: CoV was identified in 2.6% ($n = 43$) of all samples analyzed ($n = 1661$) and in 6.8% of all samples testing positive for a respiratory virus ($n = 631$). 33 of 38 (86.8%) of patients in whom CoV was identified were HSCT and hematologic malignancy patients. Among these patients, CoV was detected in 9.7% of unique infection episodes, with only rhinovirus/enterovirus (RhV/EnV) infection being more common. Group I CoV subtypes accounted for 76.3% of cases, and 57% of infections were diagnosed between December and March. CoV infection was associated with upper respiratory tract symptoms in most patients, similar to other respiratory viruses. Possible and proven lower respiratory tract disease was less common compared to other respiratory viruses except RhV/EnV.
Conclusions: CoV is frequently detected in HSCT and hematologic malignancy patients in whom suspicion for a respiratory viral infection exists, but is less likely to progress to lower respiratory tract disease than most other respiratory viruses.

1. Background

The clinical significance of respiratory viruses such as influenza, respiratory syncytial virus (RSV), parainfluenza viruses (PIVs), human metapneumovirus (hMPV), rhinovirus (RhV), and adenovirus (AdV) in patients with hematologic malignancies or recipients of autologous or allogeneic hematopoietic stem cell transplant (HSCT) is well described [1–8]. Far less data have been published that specifically address the impact of coronavirus (CoV) infection in these patients [9]. Lower respiratory tract disease (LRTD) due to CoV has been described on a case-report level [10–14], but a retrospective analysis of 46 bronchoalveolar lavage (BAL) samples obtained from HSCT recipients with any acute pulmonary process did not identify CoV in any sample [3]. Later, a prospective surveillance study in allogeneic HSCT recipients performed at a single center over the course of one year found a relatively high cumulative incidence of CoV infection (11%) in the first 100 days following allogeneic HSCT, but only one case in which CoV was detected in a lower respiratory tract sample [15]. Other series studying the impact of respiratory viral infections have not specifically or directly assessed the clinical impact of CoV in patients with hematologic malignancies and HSCT recipients [16–22].

2. Objectives

With an apparently high frequency of infection but relative paucity of information pertaining to the impact of CoV in patients

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with hematologic malignancies and HSCT recipients, we conducted a retrospective review of all CoV infections at our institution over a three year period in order to further characterize the role of CoV in respiratory tract infections in these patients.

3. Study design

3.1. Clinical specimen and data collection

All nasopharyngeal (NP) and BAL samples submitted from outpatient clinics and inpatient wards for respiratory virus testing between June 01, 2010 and July 01, 2013 at Oregon Health and Science University (OHSU) were included in this study. Demographic and clinical information pertaining to each patient testing positive for CoV or other respiratory viruses assayed as part of a multiplex PCR panel (described below), were obtained by medical chart review.

A patient was considered to have a hematologic malignancy if they were diagnosed with, and were receiving treatment for, any type of leukemia, lymphoma, multiple myeloma, aplastic anemia, mastocytosis, myelodysplastic syndrome, or amyloidosis. All patients who underwent allogeneic or autologous HSCT, or cord blood transplant (CBT), were included and classified as such regardless of the underlying disease necessitating transplant.

3.2. Respiratory virus testing

Testing was performed using a multiplex respiratory virus PCR panel assay (xTAG RVP; Luminex) [23] per manufacturer's instructions. Since this assay does not distinguish between RhV and enterovirus (EnV), these results are grouped together in this analysis. The CoV PCR reagents that are included in the RVP testing kit were further validated for clinical testing (under College of American Pathologists (CAP)- and Clinical Laboratory Improvement Amendments (CLIA)- regulatory conditions) by the OHSU molecular diagnostics lab.

3.3. Definitions

A unique episode of infection was counted at the initial identification of a respiratory virus in an NP or BAL sample. When the same respiratory virus was identified in multiple consecutive samples from the same patient without interim negative test results, this was considered as representative of prolonged shedding, and was therefore counted as a single unique episode of infection.

Mortality was attributed to respiratory virus infection if death was due to respiratory failure without identification of a cause other than a respiratory virus [19].

Respiratory virus inpatient-acquired infection was defined as onset of new symptoms, 4 days or more after admission to an inpatient ward.

Criteria for possible and proven LRTD were identification of a respiratory virus in an NP sample (possible LRTD) or BAL sample (proven LRTD), along with new pulmonary infiltrates on thoracic imaging [24].

3.4. Statistical analysis

Comparison of categorical variables between viral groups was performed using two-tailed Fisher's exact test.

Table 1
CoV detection in patient samples and unique episodes of infection.

Virus	Specimens positive			Unique episodes of infection	
	Total (%[a])	NP	BAL	All patients (%[b])	HM[c] + HSCT (%[d])
RhV/EnV	342 (54.2)	305	37	225 (48.8)	148 (43.6)
PIV 3	58 (9.2)	52	6	34 (7.4)	29 (8.6)
CoV	43 (6.8)	40	3	38 (8.2)	33 (9.7)
hMPV	42 (6.6)	38	4	38 (8.2)	25 (7.4)
RSV A	35 (5.5)	33	2	29 (6.3)	27 (8.0)
Influenza A	35 (5.5)	32	3	30 (6.5)	26 (7.7)
RSV B	26 (4.1)	23	3	22 (4.8)	18 (5.3)
Influenza B	14 (2.2)	12	2	12 (2.6)	12 (3.5)
PIV 4	11 (1.7)	11	0	11 (2.4)	9 (2.6)
AdV	11 (1.7)	9	2	8 (1.7)	2 (0.6)
PIV 2	10 (1.6)	8	2	10 (2.2)	8 (2.4)
PIV 1	4 (0.6)	4	0	4 (0.9)	2 (0.6)

[a] Percentage of 631 positive specimens.
[b] Percentage of 461 unique episodes of infection in all patients who had RVPs submitted.
[c] Hematologic malignancy.
[d] Percentage of 339 unique episodes of infection in HM and HSCT patients.

4. Results

4.1. CoV identification in patients with hematologic malignancies and HSCT recipients

A total of 1661 NP and BAL samples obtained from the general hospital inpatient and outpatient populations - inclusive of, but not limited, to HSCT recipients and hematologic malignancy patients - were analyzed. Of these, 631 samples (38%) submitted during 461 unique episodes of infection tested positive for a respiratory virus (Table 1). CoV was the third most-common virus identified after RhV/EnV and PIV3, accounting for 43 (6.8%) positive samples. Three BAL specimens were positive for CoV (see below), representing 7% of all CoV-positive samples.

Of the 461 unique episodes of infection, 339 (73.5%) were in the hematologic malignancy and HSCT patient populations (Table 1). CoV was identified in 38 (8.2%) episodes among all patients, and 33 (9.7%) of episodes among hematologic malignancy and HSCT patients. 19 (57.5%) of the 33 episodes of CoV infection in the HSCT and hematologic malignancy population were diagnosed during the winter months of December–March (Fig. 1).

38 samples from the 33 hematologic malignancy and HSCT patients tested positive for CoV, with the majority (76.3%) being Group I subtypes (NL63 ($n = 15$) and 229E ($n = 14$)), as compared

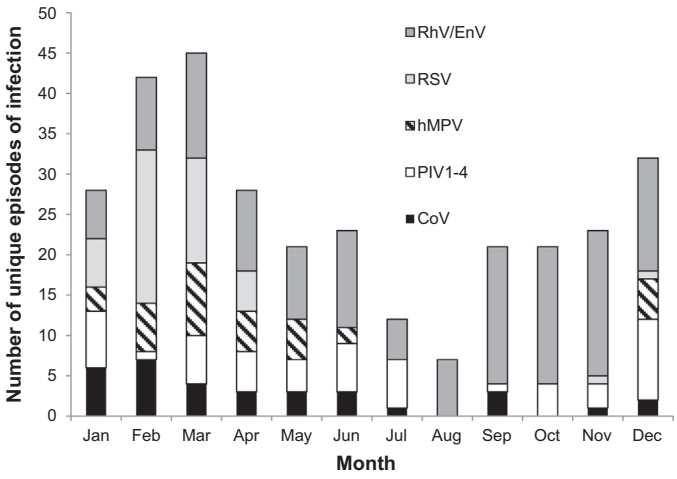

Fig. 1. Detection of CoV and other respiratory viruses in HSCT recipients and hematologic malignancy patients by month during the study period.