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BRIEF REPORT

Human metapneumovirus infection after allogeneic hematopoietic stem cell transplantation

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Abstract
Background The clinical characteristics of human metapneumovirus (hMPV)-associated lower respiratory tract infection (LRTI) after allogeneic hematopoietic stem cell transplantation (HSCT) is not well described. We describe the clinical course in eight HSCT recipients suffering from hMPV infection.
Methods We prospectively included all patients with hMPV-associated LRTI after allogeneic HSCT during a period of 1 year. hMPV was diagnosed by multiplex polymerase chain reaction (PCR) from bronchoalveolar lavage (BAL).
Results Eight patients with hMPV-associated LRTI were identified from 93 BAL samples. Three of the eight patients had co-infections with other pathogens. The median age of the patients was 45 years [interquartile range (IQR) 36.8–53.5], the median time posttransplant was 473 days (IQR 251–1,165), 5/8 patients had chronic graft-versus-host disease (cGvHD), and 6/8 patients received immunosuppression. Chest computed tomography (CT) scanning showed a ground-glass pattern in 7/8 patients. Seven of eight patients required hospitalization due to severe symptoms and hypoxemia. All were treated with intravenous immunoglobulin (IVIG), which was combined with oral ribavirin in six patients. The mortality rate was 12.5 % (1/8).
Conclusions hMPV-associated LRTI in allogeneic HSCT recipients are not uncommon and present with unspecific respiratory symptoms, ground-glass pattern in CT scanning, and co-infection.

Keywords Human metapneumovirus · Posttransplant infection · Treatment · Allogeneic hematopoietic stem cell transplantation · Respiratory virus

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Introduction

Respiratory tract infections (RTIs) are common reasons for the consultation of allogeneic hematopoietic stem cell transplantation (HSCT) recipients in outpatient clinics [1]. In recent years, "new" respiratory viruses, such as human metapneumovirus (hMPV) and coronaviruses, were discovered and associated with severe morbidity and mortality in the immunocompromised host [1–3].

hMPV is a single-strand negative RNA virus and belongs to the family of paramyxoviridae, together with respiratory syncytial virus (RSV) and parainfluenza viruses. hMPV can be isolated from respiratory samples from otherwise healthy children with upper/lower (U/L)-RTIs [4]. Seroepidemiological studies indicate a 90 % exposure until adulthood. In HSCT recipients, hMPV-associated LRTIs have been associated with considerable morbidity and mortality [5, 6]. Only a few clinical studies have addressed the clinical presentation, risk factors, and the clinical course.

Methods

Patients

Between June 2009 and June 2010, all patients following allogeneic HSCT with symptoms of LRTI were further examined by computed tomography (CT) scanning and, in case of pulmonary infiltrates, underwent a bronchoalveolar lavage (BAL) with microbiological work-up. LRTI was defined by the presence of coughing, dyspnea, and/or pulmonary infiltrates in CT chest scans [7].

Following an index case of hMPV infection, polymerase chain reaction (PCR) for hMPV was routinely included in the diagnostic work-up.

After diagnosis, clinical and laboratory parameters (including blood count, C-reactive protein, and immunoglobulins) were analyzed and reevaluated prospectively up to 4 weeks. Furthermore, additional clinical and laboratory data were collected from the charts retrospectively. All patients gave written informed consent [approved by the local Institutional Review Board (IRB) EKBB-363/09].

The degree of immunodeficiency was classified according to clinical and laboratory criteria as described previously [8]. Patients with allogeneic HSCT >6 months prior to hMPV diagnosis, acute graft-versus-host disease (aGvHD) grade <2, leukocyte count $>2.0 \times 10^9$/L, lymphocyte count $>0.1 \times 10^9$/L, recipients of maintenance immunosuppressive drugs, or T cell or B cell depletion >3 months prior to hMPV diagnosis were classified as moderately immunodeficient. In case of HSCT <6 months prior to hMPV diagnosis, T cell or B cell depletion <3 months prior to diagnosis, aGvHD-grade >2, leukopenia $<2.0 \times 10^9$/L, lymphopenia $<0.1 \times 10^9$/L, or hypogammaglobulinemia <4.0 g/L, immunodeficiency was classified severe.

Diagnostics of viral infection

In all patients, BAL samples were analyzed with an established multiplex PCR assay (RespiFinder®) [9]. RespiFinder® is able to detect 14 RNA viruses, one DNA virus, and four bacteria: adenovirus, *Bordetella pertussis*, *Chlamydophila pneumoniae*, coronavirus 229E/NL63/OC43, hMPV, influenza A/B, influenza A/H5N1, *Legionella pneumophila*, *Mycoplasma pneumoniae*, parainfluenza types 1 to 4, respiratory syncytial virus A/B, and rhinovirus [10]. For infection control reasons, all patients were screened weekly by nasopharyngeal swabs during outpatient follow-up until they became negative with the same assay.

Cytopathological work-up

Standardized cytopathological work-up of BAL samples included absolute cell counts, immunophenotyping of lymphocytes, and immunostaining for RSV, cytomegalovirus (CMV), and influenza virus. Standardized bacteriological cultures to identify bacteria, fungi, and mycobacteria were performed.

Radiological work-up

CT images were analyzed by two independent radiologists being aware of clinical findings, underlying disease, and posttransplant immunodeficient status. Images were compared retrospectively with earlier and later series within a 4-week period of time.

Data analysis

The SPSS 13 software package (http://www.SPSS.com) was used to calculate the medians and interquartile ranges (IQRs). We used non-parametric tests due to the non-normal data distributions.

Results

Patient characteristics

Between June 2009 and June 2010, eight cases of hMPV-associated LRTI were identified among 93 patients undergoing bronchoscopy and BAL for LRTI. The overall incidence of hMPV-associated LRTI was, hence, 8.6 %. The median time posttransplant was 473 days (IQR 251–1,165). Five patients had chronic graft-versus-host

disease (cGvHD) and four of these patients had previously biopsy-proven bronchiolitis obliterans and were immunosuppressed with prednisone, tacrolimus, and mycophenolic acid (Table 1). Six cases occurred during March and April 2010. The infections were not epidemiologically related and we could not identify contact exposures between patients. The clinical characteristics at diagnosis are presented in Table 1. The performance score (Karnofsky scale) was decreased by 20 % compared to previous visits (median before = 90 %, median at diagnosis = 70 %). Dry cough and fever were commonly present (in 8/8 and 7/8 patients, respectively) at diagnosis, whereas only half of the patients presented with a runny nose or dyspnea New York Heart Association (NYHA) score >II.

Laboratory findings

At diagnosis, the median total lymphocyte count was significantly lower compared to 4 weeks earlier (778 vs. 1,378/μL, $p = 0.04$) and the C-reactive protein (CRP) level was significantly higher (41.3 vs. 3.7 mg/L, $p = 0.005$). Hemoglobin, neutrophil, platelet, and immunoglobulin levels remained unchanged. Four weeks after diagnosis, only IgG levels (8.8 vs. 16.9 g/L, $p = 0.032$) and reticulocyte count increased (67 vs. 120/μL $p = 0.0457$) after therapeutic interventions (see below), whereas the hemoglobin, neutrophil, lymphocyte, platelet, IgA, and IgM levels did not change significantly.

Radiologic findings

Prior to BAL, a chest CT scan was performed in each patient. The typical CT findings of two patients are shown in Fig. 1. Although CT findings are unspecific for viral infections, ground-glass pattern opacities were the most frequent findings, detected in 7/8 patients, but nodules with halo (5/8) and alveolar/interstitial infiltrates (4/8) were also common findings. In 6/8 patients, expiratory imaging was performed. In these patients, no air trapping as a sign for active bronchiolitis obliterans was present.

Spirometry findings

At the time of diagnosis, spirometry findings indicated a drop in the FEV1 of 20 % of the median as compared to earlier spirometry. CO diffusion capacity was slightly reduced. Parameters were restored to baseline levels 2 months after infection.

Results of bronchial lavage and co-infections

At the initial diagnosis of hMPV infection, co-infections were observed in three patients: one with rhinovirus in the nasopharyngeal swab, one with *Moraxella catarrhalis* in BAL, and one with coronavirus OC43 in BAL, respectively. Notably, during outpatient follow-up, nasopharyngeal swab screening could only repeatedly detect hMPV in patients with initial co-infection indicated in previous BAL samplings. No fungal or mycobacterial co-infections were detected. No CMV reactivation was present. The findings of BAL fluids are summarized in Table 2. At the time of diagnosis of hMPV infection, cytology in BAL showed predominant macrophages (67 %) and lymphocytes (10 %). It is important to note that patient 1 was in marrow aplasia at the time of BAL, which explains why only a few lymphocytes (6×10^6/L) were observed (Table 2). For patient 6, BAL was performed for virological diagnosis but, unfortunately, no quantitative differential cell count was done.

Treatment and outcome of hMPV-associated LRTI

Treatment

All patients were treated with weekly intravenous immunoglobulin (IVIG) 0.5 g/kg bodyweight. The median treatment duration was 3 weeks. Furthermore—based on expert opinion and Bonney et al. [11]—six patients received oral ribavirin, starting with a loading dose of 600 mg on the first day, 200 mg TID for the next 2 days, with a further increase of the dosage every 2 days until a maximum dose of 600 mg TID was reached. The median duration of ribavirin treatment was 17 days, with four patients receiving the maximum dose for a median time of 1 week. Treatment with ribavirin was based on the decision by the treating physician, depending on the clinical manifestations.

Treatment-related complications

Overall, treatment was well tolerated, with no significant adverse events, except for the requirement of red blood cell (RBC) transfusion support, which was needed in 4/6 ribavirin-treated patients, due to the well-known adverse effect of ribavirin on RBCs and erythropoiesis [12]. Hemoglobin levels started to decrease in ribavirin-treated patients after 7 days of treatment. Due to low hemoglobin levels and associated symptoms of anemia, 4/6 patients treated with ribavirin required a total of 24 erythrocyte transfusions.

Outcome

Seven of eight patients (87.5 %) required hospitalization due to poor clinical condition, indicated by a reduced Karnofsky scale score and a dyspnea NYHA score of III.

Table 1 Patient baseline characteristics

Patient	Age (years)	Gender	Underlying disease[a]	Remission[b]	Time postTx (days)[c]	Fever	Cough	Running nose	Dyspnea (NYHA)[d]	Co-infection[e]	cGvHD[f]	BO[g]	IS[h]	SID[i]	Treatment	Outcome
1	51	F	B-ALL	Unknown	9	38.5	+	−	I	No	0	No	CsA, Pred	3	IVIG[j] Ribavirin[k]	Died
2	37	F	B-ALL	CR	60	38.5	+	+	I	Rhinovirus	Moderate	No	CsA, Pred	3	IVIG[j] Ribavirin[k]	Survived
3	36	F	AML	CR	1,460	37	+	−	III	*M. catarrhalis*	0	No	None	0	IVIG[j] Ribavirin[k]	Survived
4	27	M	CML	CR	550	38.2	+	−	III	No	Moderate	Yes	Tac, Pred, MMF	2	IVIG[j] Ribavirin[k]	Survived
5	57	F	MM	CR	315	39	+	+	III	Coronavirus OC53	Moderate	Yes	Tac, Pred, MMF	1	IVIG[j] Ribavirin[k]	Survived
6	38	F	AML	PD	395	39	+	+	II	No	0	No	None	0	IVIG[j] Ribavirin[k]	Survived
7	54	M	MM	CR	2,310	38.5	+	−	III	No	Moderate	Yes	Tac, Pred, MMF	1	IVIG[j]	Survived
8	53	M	NHL	CR	870	38.7	+	+	II	No	Moderate	Yes	CsA, Pred, MMF	1	IVIG[j]	Survived
Median	45				473	38.5							3 Tac, 3 CsA 4 MMF, 6 Pred			

F female, *M* male, *B-ALL* acute lymphatic leukemia, *AML* acute myeloic leukemia, *CML* chronic myeloic leukemia, *MM* multiple myeloma, *NHL* non-Hodgkin lymphoma, *CR* complete remission, *PD* progressive disease

[a] Hematologic disease prior to hematopoietic stem cell transplantation (HSCT)

[b] State of remission after HSCT

[c] Time of positive human metapneumovirus (hMPV) polymerase chain reaction (PCR)

[d] Clinical stage according the New York Heart Association (NYHA) score I–IV

[e] Other pathogens found in bronchoalveolar lavage (BAL)

[f] Chronic graft-versus-host disease grading according to [25]

[g] Bronchiolitis obliterans was biopsy-proven cases only prior to the diagnosis of hMPV infection

[h] Immunosuppression

[i] Amount of criteria for severe immunosuppression as suggested by [8]

[j] Standard dose 0.5 g/kg bodyweight

[k] Standard dose 600 mg TID

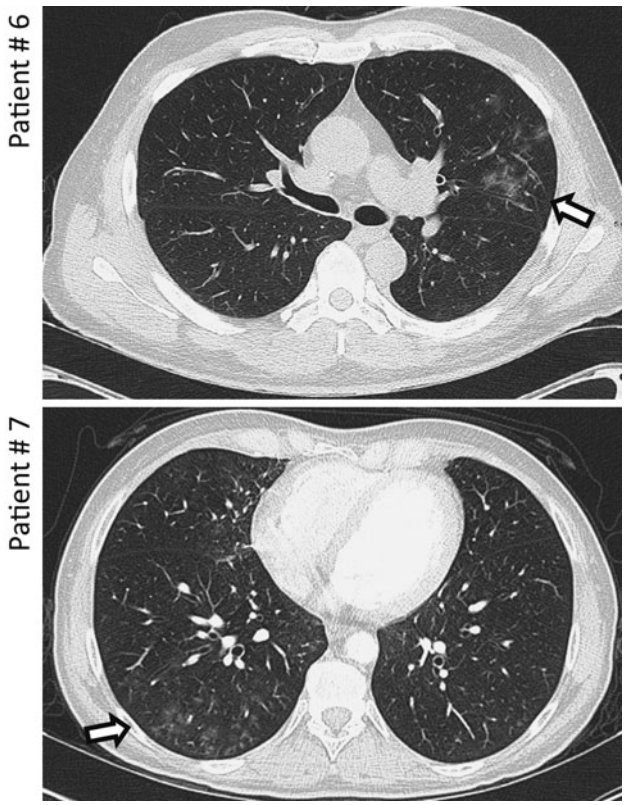

Fig. 1 Chest computed tomography (CT) findings at diagnosis. Patients are marked according to the code used in the tables. The *arrows* indicate ground-glass pattern

No further specified score was used to decide on the requirements of hospitalization.

One patient (number 1) required intensive care and assisted ventilation. Despite immediate treatment with IVIG and oral ribavirin, rapid respiratory failure and exhaustion developed and the patient died 39 days after the diagnosis of hMPV pneumonia from multi-organ failure. This patient has been infected within 30 days of transplantation. Surviving patients became asymptomatic (i.e., no coughing or sneezing, dyspnea NYHA score <II) after a median of 21 days. Seven of eight patients were discharged with clinically improved conditions after a median of 13 days. Treatment was stopped when clinical and laboratory improvement was observed or hMPV was no longer detectable in nasopharyngeal swab screening. hMPV in nasopharyngeal swabs could no longer be detected after a median of 2 weeks. Overall, clinical recovery was excellent 2 months after infection, indicated by a 90 % Karnofsky score. Respiratory recovery as assessed by the lung function test was reached in the same time period.

Discussion

During a period of 1 year, we could identify eight cases of hMPV-associated LRTI in patients following allogeneic HSCT, as found in the BAL of patients undergoing bronchoscopy because of respiratory symptoms and infiltrates in CT scan. The literature on hMPV infections following allogeneic or autologous HSCT is still scarce [13–19] and often incomplete. Conditioning regimens, remission status, immunosuppression, and laboratory data, clinical signs and symptoms, and duration of illness, as well as diagnostic microbiological methods, are often not reported.

Our prospective data show that hMPV is not uncommon. Even later than 1 year after transplantation, hospitalization was required in the majority of patients due to a reduction in performance scores and drop in lung function. Initial clinical signs of hMPV infection are unspecific [1, 20] and similar to other viral infections. Chest CT scans predominantly showed a ground-glass pattern, which is also an unspecific and common finding in patients with other viral infections [18]. We, therefore, recommend bronchoscopy for patients suffering from LRTI and showing a ground-glass pattern in the CT scan. This does not only allow for the searching of viral infection using a multiplex PCR, but also for concomitant bacterial infection.

Short interval from transplant to infection, intensive immunosuppression, as well as preexisting pulmonary

Table 2 Bronchoalveolar lavage findings

Patient	Age (years)/ gender	Macrophages % (cells × 10^6/L)	Lymphocytes % (cells × 10^6/L)	Neutrophils % (cells × 10^6/L)	Eosinophils % (cells × 10^6/L)	Mast cells/ HPF
1	51/F	84 (97.4)	5 (6)	10 (12)	1.1 (1)	0
2	37/F	–	–	–	–	–
3	36/F	84 (99.54)	12 (14)	2 (2)	2 (2)	0
4	27/M	80 (203)	15 (38)	5 (13)	0 (0)	0
5	57/F	38	7	55	0	0
6	38/F	–	–	–	–	–
7	54/M	54 (188)	8 (28)	38 (132)	0 (0)	0
8	53/M	38 (83.6)	32 (70)	30 (66)	0 (10)	10
	Median	67 %	10 %	20 %	0 %	0/HPF

Patient 2 was diagnosed only by nasopharyngeal swab. No BAL was performed. For patient 6, BAL was available, but no quantitative differential count of leukocytes was performed

F female, *M* male, *HPF* high power field at standard microscopy

alterations like bronchiolitis obliterans may affect the clinical course of hMPV, as well as other viral infections [8, 21]. Hence, the importance of single or combinations of risk factors needs to be examined in larger studies.

The outcome of our patients was favorable, except for one patient who suffered from hMPV infection shortly after transplantation (overall survival 87.5 %). A significantly lower mortality rate was observed in our patients compared to the literature, where mortality rates of up to 50 % are reported. However, most of these patients with a poor outcome suffered from hMPV infection which occurred within the first month posttransplant (Table 3). The lack of reports of infections in the later posttransplant period clearly indicates a potential underreporting or

Table 3 Review of the literature

Patient no.	Age	Gender	Basic disease	Type of graft	Time postTx	Co-infection	Treatment	Outcome	Reference
1	63	Male	MM	Auto	1,885	None	None	Died	Huck et al. [19]
2	46	Male	MM	Allo	8	None	Corticosteroids	Died, idiopathic pneumonia	Englund et al. [17]
3	54	Female	MDS	Allo	22	None	Aerosolized ribavirin	Died, idiopathic pneumonia and sepsis	
4	24	Female	ALL	Auto	18	HSV	None	Survived, but died on relapse of disease	
5	30	Male	AML	Allo	0	Parainfluenza virus	Corticosteroids	Died, aGvHD, parainfluenza pneumonia, shock	
6	46	Male	AML	Allo	13	None	Corticosteroids	Died, idiopathic pneumonia	
7	33	Female	ALL	Allo	7	–	None	Died	Cane et al. [16]
8	na	Female	CML	Allo	19	Pneumonia, RSV	na	Survived	Oliveira et al. [15]
9	na	Male	NHL	Auto	2	Pneumonia	na	Survived	
10	na	Male	ALL	Allo	10	Sepsis, influenza B	na	Died	
11	na	Female	MM	Auto	277	RSV	na	Survived	
12	na	Male	PNH	Allo	0	None	na	Survived	
13	na	Male	CML	Allo	17	Pneumonia	na	Survived	
14	na	Male	CML	Allo	0	None	na	Survived	
15	na	Female	CML	Allo	0	None	na	Survived	
16	na	Female	CML	Allo	46	None	na	Survived	
17	na	Male	CML	Allo	28	None	na	Survived	
18	na	Female	SAA	Allo	97	None	na	Survived	
19	40	Female	Hodgkin	Allo	101	Influenza A, coronavirus	Oseltamivir	Died on day 112	Campbell et al. [13]
20	58	Female	na	na	na	None	na	unknown	Franquet et al. [18]
21	27	Male	na	na	na	None	na	unknown	
22	58	Male	na	na	na	None	na	unknown	
23	23	Male	na	na	na	None	na	unknown	
24	44	Male	na	na	na	None	na	unknown	
Median	44 (30–54)	14 male 10 female		15 allo 4 auto 5 not available	17 (4.5–37)			8 died, 11 survived, 5 unknown	

na information not available, *MM* multiple myeloma, *MDS* myelodysplastic syndrome, *ALL* acute lymphatic leukemia, *AML* acute myeloic leukemia, *CML* chronic myeloic leukemia, *NHL* non-Hodgkin lymphoma, *PNH* paroxysmal night hemoglobinuria, *SAA* severe anaplastic anemia, *HSV* herpes simplex virus, *RSV* respiratory syncytial virus

underdiagnosis, as only a few centers perform BAL in patients with lower respiratory symptoms. The remarkable better survival in our patients might be due to early diagnosis and the improved "net state of immunity". Most of our patients had persistent immunosuppressive treatment because of cGvHD or—like in patient 6—immunosuppressive treatment has been stopped only a few weeks before infection and had to be restarted later due to the clinical relapse of cGvHD. We, therefore, speculate that cGvHD and immunosuppressive treatment is a risk factor for clinically relevant hMPV infection.

We cannot clarify if the treatment with IVIG and ribavirin was responsible for the therapeutic effect and the good outcome due to the lack of a control group. However, case reports and small case series have described favorable outcomes upon treatment with ribavirin and IVIG [11, 22]. IVIG treatment was given in all our cases, but the amount of hMPV-neutralizing antibodies in IVIG formulations remains unclear. Randomized studies on the hMPV treatment are still missing and will be difficult to perform due to the relatively small case number in single centers. Recommended treatment with ribavirin is based on expert opinion [3, 23], which is supported by data from in vitro cell cultures and mouse models [24]. In our center, we use oral ribavirin in severely immunocompromised patients with hMPV infection. This was well tolerated, except for hemolysis with the need for repetitive RBC transfusions. This needs to be considered as a severe side effect. Hence, a careful analysis of the potential risks and benefits is recommended before making the decision to start ribavirin treatment in selected patients with severe infection. Several other treatment strategies were described in the literature. Patients treated with corticosteroids, aerosolized ribavirin, or oseltamivir did not survive [13, 15–19].

Limitations of our study are the relatively small number of patients with hMPV LRTI, the single-center approach, and the lack of a proper control group for our treatment approach. However, due to the availability of clinical and laboratory data, including lung function tests and CT scans, we are able to properly describe the clinical course of hMPV LRTI in recipients of allogeneic HSCT.

In summary, hMPV infection is not uncommon in allogeneic HSCT recipients, even later than 1 year after transplantation. In our case series, most patients suffered from persistent immunosuppression and/or cGvHD. If patients suffer from respiratory symptoms and a ground-glass pattern in the CT scan, we recommend BAL with specific viral testing. If patients are treated with IVIG and ribavirin, the clinical outcome of hMPV infection is good. Due to ribavirin-associated hemolysis, the drug needs to be given with caution. The effectiveness and safety of a combined treatment with IVIG and ribavirin needs to be assessed in prospective therapeutic trials.

Conflict of interest All authors do not have a conflict of interest.

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