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SHORT COMMUNICATION

Human metapneumovirus infection in haematopoietic stem cell transplant recipients: a case series

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Abstract Human metapneumovirus (hMPV) is an enveloped virus that causes serious respiratory tract infection among immunocompromised populations especially haematopoietic stem cell transplant (HSCT) recipients. Here, we describe 3 cases of hMPV infection which led to mortality among post HSCT adults. 66 post HSCT adults enrolled between January 2017 and March 2019 at Dr. B. R. Ambedkar Institute Rotary Cancer Hospital, AIIMS, New Delhi, were followed up for a period varying from 16 days to 18 months for any episode of respiratory illness until March 2019. Real time reverse transcriptase polymerase chain reaction (rRT-PCR) was used to detect the virus from appropriate specimens when symptoms of acute respiratory infection appeared. Samples from 88 out of a total of 172 episodes of suspected acute respiratory infection could be tested by rRT-PCR. Of these, 9 episodes were positive for hMPV. Three patients with hMPV associated lower respiratory tract infection (LRTI) expired within 30 days of HSCT. The possible risk factors associated with mortality included LRTI, infection during early post-transplant period (first week following HSCT), absolute lymphocyte count less than 200/µl, absolute neutrophil count less than 500/µl, use of steroid within 30 days prior to infection and need for mechanical ventilation.

Keywords Hematopoietic stem cell transplant (HSCT) · Human metapneumovirus (hMPV) · Respiratory viral infection · Multiple myeloma · Early post-transplant

Introduction

Respiratory viral infections are a significant cause of morbidity and mortality in patients with hematopoietic stem cell transplants. Of the respiratory viral infections reported to affect HSCT recipients, hMPV infection is being increasingly detected [2, 6, 8]. In a systematic review by Shah et al., 2016, the incidence of hMPV infection among HSCT recipients was 7% with a 30-day all-cause mortality of 3% [6]. The first week after HSCT is crucial for such patients and may carry higher morbidity and mortality [2]. The clinical presentation of hMPV infection is similar to that of other respiratory viral infections, ranging from mild upper respiratory tract infection (URTI) to LRTI, respiratory failure and death. The common presenting symptoms of hMPV infection are fever, nasal congestion, rhinorrhea, headache, sore throat, cough and breathlessness. The symptoms may be severe in elderly populations or immunocompromised patients. The incubation period is 4–9 days and viral shedding occurs for 7–14 days [5].

The present study reports the clinical course of hMPV infection in patients who have undergone HSCT and were followed up for any respiratory illness post-transplant.

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Case reports

Case 1

A 45 year-old male, a non-smoker with no prior known comorbidities was diagnosed with IgG kappa multiple myeloma (ISS II) in early 2018. He received 6 cycles of bortezomib, lenalidomide, dexamethasone and was shifted to bortezomib and dexamethasone 20 mg per week maintenance from August 2018. Stringent complete response was achieved and consolidation treatment with autologous HSCT transplant was performed on March 3, 2019 after high dose melphalan. On the third day of transplant, the patient developed grade 2 mucositis which progressed to grade 3 on seventh day and was managed conservatively. On fourth day, the patient developed febrile neutropenia (absolute neutrophil count = 100/µl, absolute lymphocyte count = 100/µl). Initially he was started on antibiotics piperacillin–tazobactam and meropenem. Since fever persisted, vancomycin and liposomal amphotericin-B were added. Piperacillin–tazobactam was upgraded to colistin on eighth day. He also developed respiratory distress. High resolution computed tomography (HRCT) of chest was suggestive of engraftment syndrome. He was started on prednisolone at a dose of 1 mg/kg/day in view of a likely diagnosis of peri-engraftment respiratory distress syndrome (PERDS). His nasal and throat swab sample, taken on eighth day of transplant for respiratory viral rRT-PCR, was positive only for human metapneumovirus (hMPV). On day nine he became afebrile and his stem cell engrafted on day eleven of transplant. Subsequently, steroid and antibiotics were tapered and stopped on day twelve. On day fifteen, he had recurrence of fever and respiratory difficulty and was worked up for hospital acquired infection. The chest X-ray showed bilateral infiltrates and high resolution computed tomography (HRCT) showed consolidation of the left lower lobe and right middle lobe (Fig. 1). The patient was started on colistin, tigecycline, teicoplanin and azithromycin. Voriconazole and caspofungin were added in view of persistent fever with neutropenia. Bacterial (aerobic) and fungal cultures from sputum, blood and urine were sterile. Anaerobic culture, as well as *Legionella* and *Mycoplasma* PCR from bronchoalveolar lavage fluid were also negative. A cartridge based nucleic acid amplification test for tuberculosis was also negative in the sputum. He developed shock on day eighteen with raised serum procalcitonin levels, requiring maximum vasopressor support with noradrenaline and vasopressin. Multiplex RT PCR for respiratory viruses done on day fifteen and twenty five of HSCT was positive only for hMPV. He developed acute kidney injury (AKI) on day twenty one, secondary to drugs and shock, which was managed conservatively with the dosage modifications of drugs and vasopressor support. In view of persisting tachypnea, hypoxia, respiratory acidosis and vasopressor requirement patient was intubated and was on mechanical ventilation until his demise on the twenty-ninth day of transplantation.

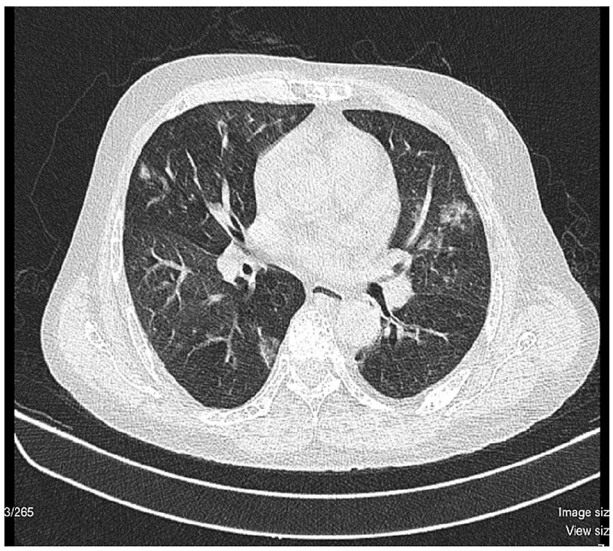

Fig. 1 Computed tomography appearance of case 1 showing bilateral infiltrates

Case 2

A 55 year-old male, a non-smoker was diagnosed with IgG kappa multiple myeloma (ISS III) with scleromyxoedema in March 2018. He achieved complete response after six cycles of bortezomib and dexamethasone, and was put on maintenance with bortezomib and dexamethasone 20 mg per week from October 2018. Consolidation treatment with autologous stem cell transplantation was done after high dose melphalan on 22/2/19 and 23/2/19.

The patient developed grade 2 mucositis on day four of transplant which progressed to grade 3 on day 6 and was managed conservatively. Patient developed febrile neutropenia on day 6 (absolute neutrophil count = 0/µl, absolute lymphocyte count = 30/µl). Initially, he was started on piperacillin–tazobactam and meropenem. Vancomycin and liposomal amphotericin B were added in view of persistent fever with neutropenia. Central line associated bloodstream infection was diagnosed on day 9 of transplant after blood cultures from central and peripheral lines grew extensively drug resistant *Klebsiella pneumoniae*. The central line was removed and antibiotics were modified according to sensitivity. Blood culture was sterile after 8 days. Piperacillin–tazobactam was upgraded to colistin on day 10 since the patient developed tachypnea, and HRCTshowed infiltrates in the right lower zone and left middle zone (Fig. 2). He developed atrial fibrillation on

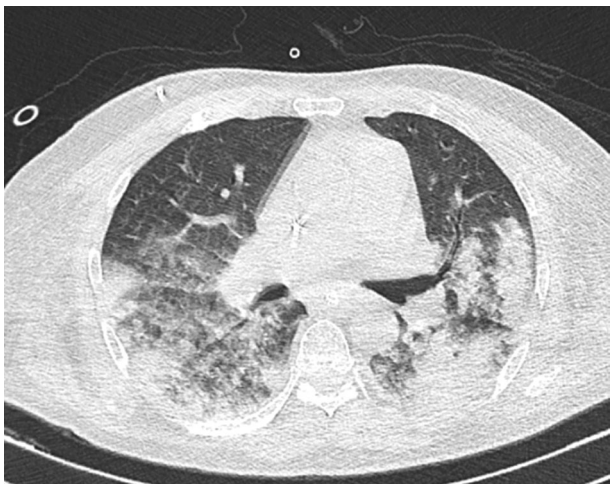

Fig. 2 Computed tomography appearance of case 2 showing bilateral confluent patches of ground glass appearance with consolidation

day ten which was managed conservatively with diltiazem infusion. He also developed AKI due to sepsis and drugs, and appropriate dose modifications were made. The patient was put on non-invasive ventilation on day 12 and invasive ventilation on day 13 in view of the persisting tachypnea, hypoxia and respiratory acidosis. The patient was shifted to the ICU for further management. The rRT PCR respiratory viral panel on endotracheal aspirate on the thirteenth day of transplant was positive only for hMPV. He developed shock on day 13. Bacterial and fungal cultures from endotracheal aspirate and urine did not yield any growth. For persistent neutropenia, the patient received six granulocyte infusions (between day 12 and day 19). In view of high spiking fever, persistent neutropenia and elevated ferritin, haemophagocytic lymphohistiocytosis was suspected and he was given methylprednisolone on day 17 and day 18. The patient succumbed to his illness on day 20.

Case 3

A 54 year-old female, who was a nonsmoker, and was diagnosed with solitary plasmacytoma of D7 vertebra in 2012, underwent laminectomy of D7 vertebra and radiation of D5–D9 vertebrae in June 2012. She relapsed in November 2017 and was diagnosed with IgG lambda type multiple myeloma. She was started on bortezomib, cyclophosphamide, dexamethasone from January 2018. She achieved stringent complete response following 4 cycles of chemotherapy and was started on maintenance with bortezomib and dexamethasone 20 mg per week. Consolidation treatment with autologous stem cell transplant was done on 7/2/19 after high dose melphalan. The patient developed grade 2 mucositis and diarrhoea on day 2 of transplant. On day 6, she developed fever and tachypnoea along with crepitations in the right axillary area. Diarrhea increased to grade 3. Nasal and throat swab samples of the patient taken on fourth day of transplant tested positive only for hMPV by multiplex rRT PCR. In view of febrile neutropenia (absolute neutrophil count = 100/μl, absolute lymphocyte count = 30/μl), with lower respiratory tract infection, she was started on piperacillin–tazobactam, meropenem and vancomycin. On day 8, she developed hypotension requiring inotropic support. Blood gas analysis revealed hypoxia and CO_2 retention. HRCT of the chest showed features suggestive of pneumonia. Piperacillin–tazobactam and meropenem were changed to colistin plus aztreonam and antifungals (caspofungin and voriconazole) were added. The patient was put on invasive mechanical ventilation and shifted to the ICU for close monitoring. She developed AKI due to shock and drugs, and drug doses were appropriately modified. Computed tomography, repeated on day 11, revealed bilateral asymmetric infiltrates (Fig. 3). Differential diagnoses of engraftment syndrome, pulmonary hemorrhage or mixed infection were considered. She was started on prednisolone at a dose of 1 mg/kg/day under adequate antibiotic cover. Tracheostomy was done on day 14 in view of prolonged intubation. Endotracheal aspirate, blood and urine cultures for bacteria and fungi did not yield any isolate. On day 15, the patient deteriorated further as she developed diffuse alveolar hemorrhage. She succumbed to her illness on the sixteenth day of HSCT.

Discussion

This case series describes the clinical course of infection with hMPV as the etiological agent for lower respiratory tract infection identified among 3 patients who underwent

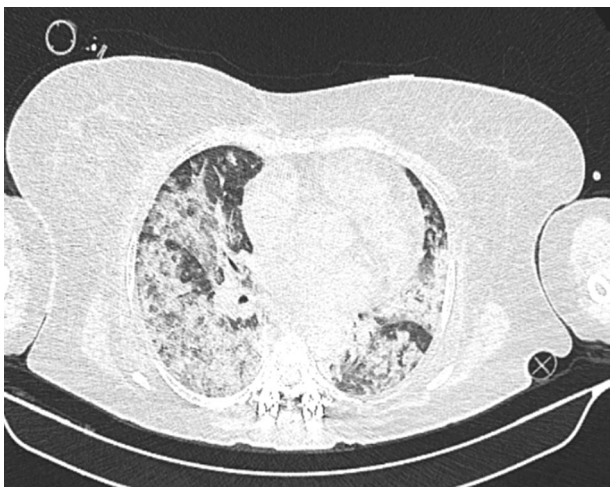

Fig. 3 Computed tomography of chest of case 3 showing bilateral consolidation

Table 1 Details of Haematopoietic stem cell recipients infected with human metapneumovirus and possible risk factors associated with poor outcomes

Sl. no	Age (year)	HSCT date	hMPV diagnosed date	Interval (days) HSCT & infection	Date of death	Interval (days) between hMPV infection & death	Cause of death	Co-pathogen	Possible risk factors associated with poor outcomes						
									Underlying haematologic disease	Type of graft	ANC (< 500/ µl) at the time of diagnosis	ALC (< 200/ µl) at the time of diagnosis	Use of steroid within 30 days prior to infection	Mechanical ventilation	Early post HSCT period (day 1 to day 7)
1	43	11-April-2017	7-May-2018	391	NA	NA	NA	Nil	IgG Kappa multiple myeloma	Autologous	No	No	No	No	No
2	19	10-October-2017	31-January-2018	113	NA	NA	NA	Nil	Mixed phenotype acute leukemia, relapsed Ph positive ALL	Allogenic	No	No	Yes	No	No
3	49	18-October-2017	11-September-2018	328	NA	NA	NA	Nil	IgG Kappa multiple myeloma	Autologous	No	No	No	No	No
4	63	21-January-2018	29-January-2018	8	NA	NA	NA	Nil	IgG Kappa multiple myeloma	Autologous	No	No	Yes	No	Yes
5	42	25-January-2019	29-January-2019	4	NA	NA	NA	Nil	Hodgkin's lymphoma nodular sclerosis IVB	Autologous	Yes	Yes	Yes	No	Yes
6 (Case 3)	54	7-February-2019	11-February-2019	4	23-February-2019	12	Acute respiratory failure, refractory shock, LRTI	Nil	IgG Lambda multiple myeloma	Autologous	Yes	Yes	Yes	Yes	Yes
7	28	11-February-2019	19-February-2019	8	NA	NA	NA	Nil	Hodgkin's lymphoma nodular sclerosis IVB	Autologous	Yes	Yes	Yes	No	Yes
8 (Case 2)	55	22-February-2019	7-March-2019	13	14-March-2019	7	Refractory shock, Acute kidney injury, ARDS, febrile neutropenia	Klebsiella pneumoniae in blood	IgG Kappa multiple myeloma	Autologous	Yes	Yes	Yes	Yes	No
9 (Case 1)	45	3-March-2019	11-March-2019	8	1-April-19	21	Refractory shock, LRTI, AKI	Nil	IgG Kappa multiple myeloma	Autologous	Yes	Yes	Yes	Yes	Yes

autologous HSCT for multiple myeloma and expired within 30 days of transplantation when the patients had severe neutropenia, lymphopenia and a severely compromised immune system. HMPV was the sole virus detected in the three patients who expired. No other virus was detected in the rRT-PCR respiratory viral panel, which also included influenza virus, rhinovirus, adenovirus, respiratory syncytial virus and parainfluenza virus. However, the blood culture sample from case 2 also grew Klebsiella pneumonia, which could also have contributed to the adverse outcome.

Out of nine patients (Table 1) who were infected with hMPV, all had LRTI and three expired giving a mortality rate of 33% for hMPV-LRTI. Mortality rates among HSCT recipients due to infection by hMPV have been reported to vary from 11 to 43% [1, 4, 8]. All these studies highlight hMPV as the prime agent leading to mortality.

Seven out of 9 hMPV infection episodes in our patients occurred in the winter season, in the months of January to March, with the usual symptoms of rhinitis, fever, cough and breathlessness. Upper respiratory tract infection with hMPV may lead to lower respiratory tract infection and respiratory failure. No association of hMPV mortality has been established with different types of underlying hematological malignancies, however 6 out of nine patients infected with hMPV post-HSCT in our study had multiple myeloma as the underlying disorder.

Infection within the first week of transplant was associated with a poor outcome. Of 9 hMPV infected patients, the 3 patients described above had onset of symptoms after a mean duration of 5 days after HSCT and died within a mean period of 16 days after the onset. The mean duration of survival for these patients was 22 days after the transplantation.

The incubation period is 4–9 days and viral shedding has been reported to vary from 7 to 14 days [5], however prolonged viral shedding upto 90 days has been reported in immunocompromised hosts [4]. In case number 1, in this series, viral shedding was seen upto 17 days and hMPV was the only organism isolated from the patient after extensive evaluation.

It is important to rule out associated secondary bacterial infections that could contribute to the severe outcome, though neutropenic patients are given antibiotic treatment at the onset of fever and yield of cultures is expected to be low. One of our cases had *Klebsiella* infection. However a blood culture repeated after 8 days of tailored antibiotic therapy was sterile.

Earlier studies have also reported intensive immunosuppression, preexisting pulmonary disease, low ANC, low ALC and steroid use as risk factors associated with poor outcomes [4, 6, 7].

Anecdotal reports of ribavirin based therapy being effective at preventing deaths from hMPV in immunocompromised patients have been challenged due to lack of a control group. In a systematic review by Shah and coworkers, bivariate regression analysis using data from 19 case reports of hMPV infection showed that ribavirin therapy did not have a significant protective effect against hMPV-mortality [0.58 (0.18–1.85); $p = 0.337$]. Another study comparing mortality rates in 23 HSCT recipients with hMPV-LRTI who received aerosolized ribavirin and intravenous immunoglobulin with those who did not receive the treatment demonstrated similar mortality rates in both groups [7]. In our hospital, ribavirin is not being used for hMPV infection, based on lack of adequate evidence. To prevent in-unit transmission of hMPV, testing of patients with URTI and immediate isolation of cases, as well as implementation of rigorous hygiene measures, need to be ensured.

The research for many anti-hMPV vaccines [3] and studies in animal models showing efficacy for specific monoclonal anti-hMPV antibody [7] are under development and may herald better management of this infection in the future. Clinical trials to study the efficacy of existing antiviral drugs active against hMPV infections are urgently needed. Treating physicians should keep a high index of suspicion and actively search for this infection in patients with higher risk for poorer outcomes.

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Compliance with ethical standards

Conflict of interest All authors report no conflicts of interest.

Ethical standards The data was ethically approved by the institution; (Ref. No.: IECPG/713/19-01-2017,OT-03/2017).

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