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CASE REPORT

Critical illness after horizontal nosocomial transmission of human metapneumovirus in the haematology ward

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Abstract - Since its discovery in the Netherlands in 2001, human metapneumovirus (hMPV) is mainly known for its association with severe upper and lower respiratory tract disease in very young, elderly, and immunocompromised individuals. Two critically ill patients are described to illustrate that a) haematologists and intensivists should be aware of the possibility of infection by this recently discovered pathogen and the severe respiratory tract disease manifestations it can cause in patients under their care; b) horizontal transmission between patients is possible on wards despite the presence of high-efficiency particulate aerosol (HEPA) filtration; and c) that although the exact incidence of hMPV infections in immunocompromised (critically ill) patients is as yet unknown, routine testing for hMPV may be considered in this population.

Keywords - **hMPV, human metapneumovirus, critically ill, stem cell transplantation**

Introduction

Acute respiratory tract infections are a major cause of morbidity and mortality worldwide. Several previously unknown respiratory viral human pathogens have recently been identified by newly developed techniques [1]. Since its discovery in the Netherlands in 2001 [2], human metapneumovirus (hMPV) (Figure 1) has been shown to cause disease worldwide across a broad age range, but very young, elderly, and immunocompromised individuals appear to be at greatest risk for severe illness [3]. HMPV is a paramyxovirus with two major genotypes, A and B. Each genotype is represented by two subtypes (A1, A2; B1, B2) [4-6]. HMPV reaches nearly 100% seroprevalence at the age of 5 [2,7,8]. The virus has been circulating in the human population for at least 50 years [2]. Primary infection with hMPV does not induce lifelong immunity. Because of waning immunity and/or the presence of multiple viral genotypes, multiple re-infections are sometimes possible during adult life [4,9]. HMPV shows a strong seasonality and geographical variation, with high incidence during the winter months in moderate climate zones and in the late spring and early summer in the subtropics [9,10]. Initial, mainly self-limiting, symptoms include fever, cough, nasal congestion, hoarseness, and sore throat. These conditions can evolve into those of lower respiratory tract infections like pneumonia and bronchiolitis, and show a strong similarity to, for example, symptoms of respiratory syncytial virus-related disease. More severe illnesses can occur in immunocompromised patients [11]. We describe here two cases of hMPV occurring in two immunocompromised patients, one of whom most likely acquired the pathogen by horizontal, nosocomial transmission.

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Case reports

Case 1

A 51-year-old male with multiple myeloma Durie & Salmon stage IIA was admitted to the ICU (Figure 2). Eleven days prior to admission, an autologous peripheral blood stem cell transplantation (APBSCT) had been performed, which was complicated by bilateral pneumonia during neutropenia, for which piperacillin-tazobactam was started empirically. Because of clinical deterioration, bronchoalveolar lavage (BAL) was performed four days later, and analysed as previously described [12]. Microscopical investigation of the BAL fluid (BALF) yielded no bacteria, yeast, fungi, *Pneumocystis jiroveci*, or acid-fast bacteria. The Aspergillus antigen (galactomannan) tests (Platelia Aspergillus, BIO-RAD, Marnes la Coquette, France) performed on the serum and BALF were negative, as were cultures for respiratory viruses, mycobacteria, legionella, and fungi. The urine antigen test and immunofluorescence examination of the BALF for Legionella pneumophila were also negative. Furthermore, *Mycoplasma pneumoniae*, *Chlamydophyla pneumoniae,* herpes simplex virus, and cytomegalovirus could not be detected in the BALF by means of a polymerase chain reaction (PCR). The patient subsequently developed diarrhoea with worsening of renal function. Stool samples were negative for *Clostridium difficile* toxins A and B, as well as for other bacterial pathogens. Severe respiratory insufficiency and renal insufficiency necessitated ICU admission, intubation, and initiation of mechanical ventilation, and continuous veno-venous haemofiltration. Considering the severity of clinical illness, broad-spectrum antibiotics were empirically started, notwithstanding the absence of a clearly determined etiological agent. Sixteen days after the BAL, the PCR on the BALF was

found positive for hMPV; genotyping revealed type A2. Since the patient's pulmonary condition and ventilator settings (as well as his leukopenia) were already improving at the time the PCR result for hMPV became available, treatment with aerosolized or intravenous ribavirin or intravenous immunoglobulin was renounced. This approach was supported by the finding that current literature does not provide clear evidence for initiating antiviral therapy at this stage of ameliorating infection. The patient was extubated after 42 days, and discharged from the ICU 44 days after admission.

Case 2

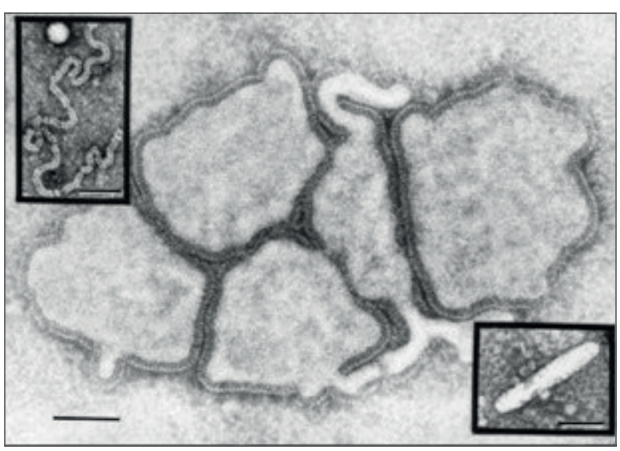
Four days after the first patient was admitted, his 64-year-old male hospital roommate with diagnosed stage IV mantle cell lymphoma was also admitted to the ICU because of respiratory insufficiency and hypotension (Figure 2). An APBSCT was performed 11 days before admission to the ICU, and was complicated by bilateral pulmonary infiltrates during the subsequent neutropenic phase, for which piperacillin-tazobactam was empirically started. Because of clinical deterioration, BAL was performed five days later. Again, all bacteriological, mycological, and virological investigations of the BAL mentioned previously were found to be negative. The patient also developed unexplained renal insufficiency and diarrhoea with negative cultures and Clostridium toxins. The renal insufficiency was probably due to acute kidney injury; no signs of glomerulonephritis were found on either renal echography or urine microscopy. He was admitted to the ICU with respiratory insufficiency, hypotension, tachycardia, and fever. The hyperdynamic circulation was most likely due to a distributive (septic) shock. The patient was treated with non-invasive ventilation, fluid resuscitation, and norepinephrine. Progressive respiratory insufficiency necessitated intubation. Twenty-four hours after intubation, the patient died due to persisting respiratory failure, despite the use of several rescue ventilation strategies (high-frequency ventilation, addition of nitric oxide, and prone-position ventilation). Post-mortem-performed PCR of the ante-mortem-obtained BALF revealed hMPV genotype A2. Post-mortem pathological examination was declined.

Discussion

Tens of thousands of patients undergo haematopoietic stem cell transplantation (HSCT) annually, 10% to 25% of whom are admitted to the ICU [13-15]. Figures vary to some extent around the world. Patients are admitted to the ICU less frequently after autologous HSCT than after allogeneic HSCT (38%-47% versus 53%-62%) [13,14]. ICU admission after HSCT is a significant risk factor for mortality, and carries a grim prognosis. In the Netherlands, ICU mortality after autologous HSCT is 36% and even 50% to 100% after allogeneic HSCT [16]. ICU mortality of more than 56% and even much higher are cited for patients requiring invasive mechanical ventilation [13-18]. Therefore, pulmonary complications are among the most life-threatening complications in haematopoietic stem cell (HSC) recipients. About 25% of all HSC recipients develop pulmonary complications [19]. Autologous HSC recipients have fewer pulmonary complications compared to allogeneic HSC recipients [17]. Because of the broad differential diagnosis of infectious and non-infectious causes, and since diagnostic work-up and making a final diagnosis can be very troublesome, the occurrence of pulmonary infiltrates in this category of patients provides a diagnostic challenge for clinicians.

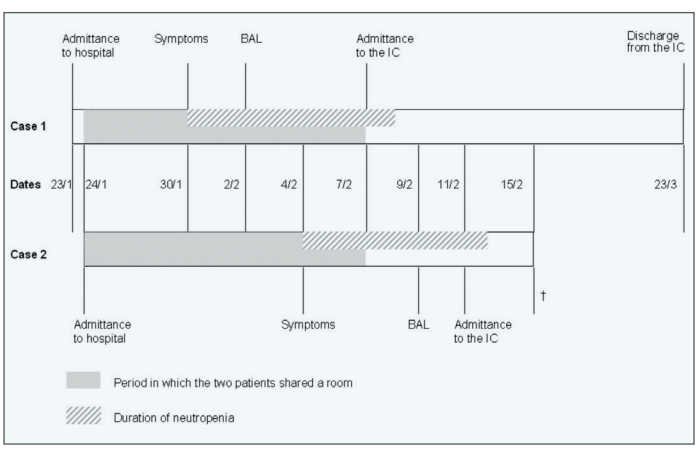
Infectious and non-infectious aetiologies are found in 55% and 40% of these patients respectively (in 5% of the patients, the aetiology of the pulmonary complications was unknown) [19]. Because of better prophylactic, diagnostic, and therapeutic strategies (including pre-emptive strategies) for infections, today non-infectious or inflammatory conditions (e.g. pulmonary toxicity of administered chemotherapeutic agents) are the major pulmonary causes of morbidity and mortality after HSCT [20]. Considering

Figure 1. Human metapneumovirus (hMPV) image



Credits to Charles D Humphrey, Centers for Disease Control and Prevention (CDC), Atlanta, GA 30333, USA

Figure 2



the infectious complications during the early engraftment phase (0 to 30 days after transplant), the most prevalent pathogens causing infection are bacteria, and to a lesser extent Candida species. Clinical deterioration despite the administration of broad-spectrum antibiotic therapy necessitated BAL in our patients. Although some interference of the prior antibiotic therapy with bacterial growth cannot be completely ruled out, cultures yielded no resistant microorganisms. If neutropenia persists, infection with Aspergillus species should also be considered. On the other hand, diffuse alveolar haemorrhage (DAH) and peri-engraftment acute respiratory distress syndrome (ARDS) have been reported to occur in both allogeneic and autologous HSC recipients, usually during the first 30 days. Bronchiolitis obliterans organizing pneumonia (BOOP) occurs exclusively in allogeneic HSC recipients with acute and chronic graft-versus-host disease. However, ARDS and BOOP are both descriptive terms, which can be sub-classified according to the underlying cause. Idiopathic pneumonia syndrome occurs at any time following transplant [21], and this terminology indicates that no clear infectious cause could be detected.

Viruses, however, should also be considered in the differential diagnosis of critical respiratory illnesses, especially in immunocompromised patients. Radiographic findings in viral pneumonia in adults – which consist mainly of patchy or diffuse ground-glass opacity with or without consolidation and reticular areas of increased opacity – are variable and overlapping, though, and therefore provide only non-specific findings. This is also true for computed tomographic findings, which consist of poorly defined centrilobular nodules, ground-glass attenuation with a lobular distribution, segmental consolidation, or diffuse ground-glass attenuation with thickened interlobular septa [22]. These non-specific findings necessitate the use of other diagnostic strategies like BAL. Before the findings reported here, BALF samples from patients in our hospital's ICU were "only" routinely checked for herpes simplex types I and II, cytomegalovirus, respiratory syncytial virus, influenza A and B, and parainfluenza viruses. This was not routinely performed for hMPV because of the difficulty of culturing hMPV. The development of a PCR for hMPV subsequently made routine evaluation possible, and this has now been implemented as part of the routine first-line diagnostic work-up. In a recent series of patients initially diagnosed with idiopathic pneumonia syndrome after HSCT with symptoms of lower respiratory tract disease, 3.0% tested positive for hMPV when PCR was performed on stored BALF samples [11]. Therefore, it is not unlikely that hMPV is a more common cause of respiratory disease in immunocompromised patients with underlying haematological disease than previously recognized. Especially in this subset of patients it can give rise to serious morbidity [3] and mortality [23-25], often necessitating ICU admission, as was the case for our patients.

The transmission of hMPV between our two patients most likely resulted from aerosolized cough occurring inside a room with double occupancy, whereas the primary source of the virus remains obscure. Genotyping the hMPV viruses also linked both patients, confirming an identical genotype, namely hMPV type A2, and is compatible with the hypothesized horizontal transmission. No factors that could potentially increase the risk of horizontal transmission on the ward were identified: the bronchoscopies were performed in the bronchoscopy suite, non-invasive ventilation was not attempted, and no nebulization of medication was performed. To our knowledge, this is the first report on horizontal, nosocomial transmission of hMPV. Apparently, horizontal transmission between patients is possible on wards despite the presence of HEPA filtration. A HEPA-grade device is defined as any filter capable of trapping at least 99.97% of particles with a diameter of 0.3 mm [26]. It is likely that the use of a HEPA filter will succeed in preventing mobilization of bacteria, fungi, moulds, and endotoxin suspensions across its filter element for large bacteria like *Pseudomonas aeruginosa* and *Acinetobacter* species (7 mm), but it is far less likely that this filter will succeed in removing viruses (a diameter of around 0.02 micron) [26]. Therefore, neither *direct* nosocomial transmission (resulting from aerosolized cough between patients in the same room) nor *indirect* nosocomial transmission (resulting from viruses entering with air from outside the room while being filtered by a HEPA device) can be prevented by use of these HEPA devices. An approach with implementation of strict single-room isolation of *all* immunocompromised patients with idiopathic pneumonia until PCR results of viral pathogens in the BALF are found to be negative could perhaps be useful to prevent transmission of viruses. Other potentially useful options are the use of devices that utilize ultraviolet germicidal irradiation to sterilize air and inactivate microorganisms by disrupting DNA strands [27]. However, neither guidelines for infection surveillance nor preventive isolation are currently available for hMPV. As described, hMPV most often causes diseases of and symptoms in the upper and lower respiratory tracts. Until now, the combination of an hMPV infection with renal failure and diarrhoea in our patients has never been described. Whether this could be an indication of the seriousness of the disease and thus provides a diagnostic clue is unclear, since PCR on urine and stool was not performed in our patients.

Both patients became respiratory insufficient after a period of neutropenia of about one week. Since this period of neutropenia remained limited to a period of no longer than ten days in both patients, it is likely that the prognosis of the acquired viral infection after APBSCT was determined less by the limited time span of the neutropenia (a host factor) than by the hMPV infection itself (the virulence of the infectious agent). This hypothesis is supported by the finding that, apart from the category of patients after stem cell transplantation, non-immunocompromised patients can also suffer from serious morbidity due to hMPV infection. In this category of immunocompetent adults, the regularly applied diagnostic tools can likewise fail. For example, the cause of community-acquired pneumonia remains unknown in 17% to 48% of cases [28]. Carrat et al. studied the prevalence of respiratory virus infections in patients with chronic cardiac or pulmonary disorders admitted to the ICU for acute cardiorespiratory failure. He took nasal swabs of 122 patients admitted to the ICU during two consecutive winters. The positivity rates for the respective viruses were as follows: influenza virus: 6.6%, RSV: 4.9%, rhinovirus: 3.3%, hMPV: 1.6%, and coronavirus: 0.8% [29]. Unfortunately, no other viruses were studied.

In the literature there is an ongoing discussion on whether hMPV infection should be treated. It can be envisaged that a wait-and-

see policy can be advocated if the disease course is relatively mild or the disease is already improving. In more severely ill patients, starting treatment with aerosolized or intravenous ribavirin [30] and/or intravenous immunoglobulins [31] can be considered. There is perhaps an even greater indication for starting antiviral therapy in the presence of prolonged neutropenia or persisting immunosuppression, in order to attempt to prevent progressive morbidity and subsequent mortality.

Conclusions

Although hMPV is mainly known for its association with severe illness in very young, elderly, and immunocompromised individuals, it can also give rise to serious morbidity and potential mortality in non-immunocompromised patients. Haematologists and intensivists should therefore be aware of the possibility of infection by this recently discovered pathogen, and the severe disease manifestations it can cause in patients under their care. For adults presenting with respiratory symptoms and a background of pre-existing respiratory disease or for those who are immunocompromised, the use of hMPV real time PCR or other nucleic acid-base techniques must be part of a routinely used respiratory virus diagnostic package. In these high-risk patients, isolation and a rapidly confirmed diagnosis of hMPV infection would end the diagnostic search and allow the clinician to focus on providing supportive care and counselling the patient and family about the natural history of the infection. However, management of these patients with regard to infection surveillance, preventing the spread of this highly contagious viral disease, and recommendations for therapy still have to be defined.

References

1. Pabbaraju K, Wong S, McMillan T, et al: Diagnosis and epidemiological studies of human metapneumovirus using real-time PCR. J Clin Virol 2007; 40:186-92.
2. van den Hoogen BG, de Jong JC, Groen J, et al: A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001; 7:719-24.
3. Sumino KC, Agapov E, Pierce RA, et al: Detection of severe human metapneumovirus infection by real-time polymerase chain reaction and histopathological assessment. J Infect Dis 2005; 192:1052-60.
4. Boivin G, Mackay I, Sloots TP, et al: Global genetic diversity of human metapneumovirus fusion gene. Emerg Infect Dis 2004; 10:1154-7.
5. Peret TC, Abed Y, Anderson LJ, et al: Sequence polymorphism of the predicted human metapneumovirus G glycoprotein. J Gen Virol 2004; 85:679-86.
6. Sloots TP, Mackay IM, Bialasiewicz S, et al: Human metapneumovirus, Australia, 2001-2004. Emerg Infect Dis 2006; 12:1263-6.
7. Ebihara T, Endo R, Kikuta H, et al: Seroprevalence of human metapneumovirus in Japan. J Med Virol 2003; 70:281-3.
8. Wolf DG, Zakay-Rones Z, Fadeela A, et al: High seroprevalence of human metapneumovirus among young children in Israel. J Infect Dis 2003; 188:1865-7.
9. Hamelin ME, Prince GA, Gomez AM, et al: Human metapneumovirus infection induces long-term pulmonary inflammation associated with airway obstruction and hyperresponsiveness in mice. J Infect Dis 2006; 193:1634-42.
10. van den Hoogen BG, Osterhaus DM, Fouchier RA. Clinical impact and diagnosis of human metapneumovirus infection. Pediatr Infect Dis J 2004; 23:S25-32.
11. Englund JA, Boeckh M, Kuypers J, et al: Brief communication: fatal human metapneumovirus infection in stem-cell transplant recipients. Ann Intern Med 2006; 144:344-9.
12. Jacobs JA, De Brauwer E. BAL fluid cytology in the assessment of infectious lung disease. Hosp Med 1999; 60:550-5.
13. Soubani AO, Kseibi E, Bander JJ et al: Outcome and prognostic factors of hematopoietic stem cell transplantation recipients admitted to a medical ICU. Chest 2004; 126: 1604-11.
14. Huynh TN, Weigt SS, Belperio JA. Outcome and prognostic indicators of patients with hematopoietic stem cell transplants admitted to the intensive care unit. J Transplant 2009; 917297.
15. Hayani O, Beihany AAl,Zarychanski R et al: Impact of critical care outreach on hematopoietic stem cell transplant recipients: a cohort study. Bone Marrow transpl 2010; 25:1-7.
16. Geerse DA, Span LFR, Pinto-Sietsma SJ et al: Prognosis of haematological malignancies admitted to the intensive care unit: Sequential Organ Failure Assessment (SOFA) trend is a powerful predictor of mortality. Eur J Int Med 2011; 22:57-61
17. Price KJ, Thall PF, Kish SK et al: Prognostic indicators for blood and marrow transplant patients admitted to an intensive care unit. Am J of Respir Crit Care Med 1998; 876-84.
18. Huaringa AJ, Leyva FJ, Giralt SA et al: Outcome of bone marrow transplantation patients requiring mechanical ventilation. Crit Care Med 2000; 28:1014-17.
19. Lim do H, Lee J, Lee HG, et al: Pulmonary complications after haematopoietic stem cell transplantation. J Korean Med Sci 2006; 21:406-11.
20. Watkins TR, Chien JW, Crawford SW. Graft versus host-associated pulmonary disease and other idiopathic pulmonary complications after haematopoietic stem cell transplant. Semin Respir Crit Care Med 2005; 26:482-9.
21. Afessa B, Peters SG. Major complications following haematopoietic stem cell transplantation. Semin Respir Crit Care Med 2006; 27:297-309.
22. Kim EA, Lee KS, Primack SL, et al: Viral pneumonias in adults: radiologic and pathologic findings. Radiographics 2002; 22:S137-49.
23. Cane PA, van den Hoogen BG, Chakrabarti S, et al: Human metapneumovirus in a haematopoietic stem cell transplant recipient with fatal lower respiratory tract disease. Bone Marrow Transplant 2003; 31:309-10.
24. Huck B, Egger M, Bertz H, et al: Human metapneumovirus infection in a haematopoietic stem cell transplant recipient with relapsed multiple myeloma and rapidly progressing lung cancer. J Clin Microbiol 2006; 44:2300-3.
25. O'Gorman C, McHenry E, Coyle PV. Human metapneumovirus in adults: a short case series. Eur J Clin Microbiol Infect Dis 2006; 25:190-2.
26. Demers RR. Bacterial/viral filtration: let the breather beware! Chest 2001; 120:1377-89.
27. Menzies D, Popa J, Hanley JA, et al: Effect of ultraviolet germicidal lights installed in office ventilation systems on workers' health and wellbeing: double-blind multiple crossover trial. Lancet 2003; 362:1785-91.
28. File TM. Community-acquired pneumonia. Lancet 2003; 362:1991-2001.
29. Carrat F, Leruez-Ville M, Tonnellier M, et al: A virologic survey of patients admitted to a critical care unit for acute cardiorespiratory failure. Intensive Care Med 2006; 32:156-9.
30. Raza K, Ismailjee SB, Crespo M, et al: Successful outcome of human metapneumovirus (hMPV) pneumonia in a lung transplant recipient treated with intravenous ribavirin. J Heart Lung Transplant 2007; 26:862-4.
31. Wyde PR, Chetty SN, Jewell AM, et al.: Comparison of the inhibition of human metapneumovirus and respiratory syncytial virus by ribavirin and immune serum globulin in vitro. Antiviral Res 2003; 60:51-9.