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The human metapneumovirus: a case series and review of the literature

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Abstract

Human metapneumovirus (hMPV) is an emerging human pulmonary pathogen that is genetically related to respiratory syncytial virus. It has been increasingly associated with respiratory illnesses over the last few decades. Immunocompromised patients are particularly susceptible with resultant morbidity and mortality. We describe our experience with 9 immunocompromised patients diagnosed with pneumonia secondary to hMPV, 2 of whom were successfully treated with aerosolized and oral ribavirin along with intravenous immunoglobulin (IVIG). We suggest that hMPV should be considered in the differential diagnosis of immunocompromised patients with acute respiratory illness. Ribavirin (oral and aerosolized) with IVIG is potentially an effective treatment option for those with severe disease.

Keywords

human metapneumovirus; immunosuppression; hematopoietic stem cell transplant; lung transplant; ribavirin; cellular rejection

Background

Human metapneumovirus (hMPV) is an RNA virus that was first reported in 2001 (1). It was subsequently described as a seasonal virus affecting all age groups. The clinical manifestations range from asymptomatic carriage to accelerated lung transplant rejection and acute respiratory distress syndrome (ARDS) in susceptible individuals. There is no established treatment for hMPV infection; however, successful treatment with intravenous (IV) ribavirin and IV immunoglobulin (IVIG) has been reported (2).

Patients and methods

A retrospective review of the electronic medical records for 9 documented cases of hMPV infection was carried out. This study was approved by the institutional review board. Immunocompromised patients who presented to the Indiana University-Clarian Health Partners campus and who were diagnosed with hMPV infection between the years 2008 and 2009 were evaluated in this series. Patients presented with a broad spectrum of symptoms including cough, signs of upper respiratory infections, occasionally fever, and in a few of them, symptoms severe enough to cause respiratory failure. Taking into account the degree of immunosuppression and the severity of the symptoms, patients were either admitted and managed in the hospital or observed on an outpatient basis.

Results

Nine patients were included in this review (Tables 1 and 2). Six of them had hMPV as a single pathogen. Four nasal swab specimens, 1 nasopharyngeal swab, and 6 bronchoalveolar lavage (BAL) samples were evaluated. Two of the nasal swab samples initially tested negative for hMPV rapid antigen test and then, after more evaluation, BAL returned positive for the hMPV antigen. Seven specimens were tested with the rapid viral antigen test with DFA metapneumovirus identification kit (Diagnostic Hybrids Inc., Athens, Ohio, USA), which uses immunofluorescence assay with a blend of 3 monoclonal antibodies to detect the hMPV antigen. Two other patients tested positive by reverse transcriptase-polymerase chain reaction (RT-PCR) (XTAG® Respiratory Viral panel, Luminex Corp., Austin, Texas, USA). This method is a qualitative nucleic acid multiplex RT-PCR/array bead hybridization procedure. It is intended for simultaneous detection and identification of 12 viral targets (of which MPV is one) in specimens collected from individuals with suspected respiratory tract infections.

Two of these 9 patients, both with hematopoietic stem cell transplant (HSCT), were admitted to the bone marrow transplant unit and treated with inhaled and oral ribavirin along with IVIG. Two other patients, both with lung transplant, were admitted to the hospital and managed with aggressive supportive care. Unfortunately, they both died with ARDS and acute graft rejection (Figs. 1 and 2).

Discussion

Since hMPV was isolated in 2001 (1), many reports have highlighted this virus in an attempt to actually determine its pathologic role. MPV is mainly a seasonal virus with incidence throughout the year. It may affect all age groups with more severe disease in children, elderly, and immunocompromised patients. Radiographic findings are nonspecific, and the diagnosis relies on detection of the antigen or nucleic material in fresh respiratory secretions. PCR is a more sensitive test and might detect hMPV infection in cases of negative viral culture results (3), which might improve the disease management and have a better outcome in the high-risk population.

In lung transplant recipients, hMPV is a common cause of respiratory illness and is thought to increase the risk of acute and chronic graft rejection (4). Viral infections increase the risk

of developing bronchiolitis obliterans in lung transplant recipients (5) and that impacts their survival significantly.

HSCT recipients and patients with hematologic malignancies (6) are at risk for conducting respiratory viral infections including hMPV. The spectrum of symptoms may vary. Peck et al. (7) showed evidence of asymptomatic parainfluenza virus in HSCT patients when they were followed for 100 days post transplant. MPV-infected patients may have minimal symptoms or remain asymptomatic when they are followed over a period of time (8, 9), and in other cases, they may exhibit signs of respiratory failure and their course gets complicated with fatal pulmonary infections (10, 11).

Although the natural course of this disease can be associated with full recovery, children may have severe disseminated disease with poor outcomes (12), as well as immunocompromised patients (10), who may benefit from early intervention (13). To date, there are no trials examining specific treatments for hMPV. Ribavirin, which disrupts viral purine metabolism and inhibits RNA polymerase, has been shown to be active against hMPV *in vitro* (14). In a mouse model, ribavirin had a significant effect on both hMPV replication rate and the pulmonary inflammation (15). Adding a corticosteroid to the treatment did not change the outcome significantly. Ribavirin in combination with IVIG was reported to be effective in treating hMPV pneumonia in a lung transplant recipient (2), and in another immunocompromised patient (16). Ribavirin has demonstrated *in vitro* inhibition of tumor necrosis factor- α , interferon- γ , and interleukin (IL)-10, suggesting a downregulation in Th1 and Th2 cytokine production and an increase of IL-2 production by peripheral blood mononuclear cells (17). One hypothesis is that ribavirin may augment or terminate T cell immune-mediated damage caused by viral infections.

We treated our immunocompromised patients with oral and inhaled ribavirin owing to the severity of the disease, and lack of other treatment options, as IV ribavirin is not available in the United States. We also thought ribavirin was appropriate, given their disease severity. Clinical improvement was noted, especially in our patient with isolated hMPV infection.

Ribavirin is teratogenic and administration by nebulization must be carried out by a trained respiratory therapist via a SPAG-2 small particle aerosol generator. Additionally, health care providers who are pregnant or attempting to become pregnant should avoid contact with patients receiving treatment with aerosolized ribavirin.

Conclusion

We report the first successful treatment to our knowledge of hMPV infection in 2 immunocompromised patients using oral and aerosolized ribavirin with IVIG. Until more studies determine the optimal treatment for hMPV, this combination is a potential therapeutic option in immunosuppressed patients with severe infection.

References

1. 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(6):719–724. [PubMed: 11385510]

2. 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(8):862–864. [PubMed: 17692793]
3. Murali S, Langston AA, Nolte FS, Banks G, Martin R, Caliendo AM. Detection of respiratory viruses with a multiplex polymerase chain reaction assay (MultiCode-PLx Respiratory Virus Panel) in patients with hematologic malignancies. *Leuk Lymphoma.* 2009; 50(4):619–624. [PubMed: 19373660]
4. Larcher C, Geltner C, Fischer H, Nachbauer D, Müller LC, Hueer HP. Human metapneumovirus infection in lung transplant recipients: clinical presentation and epidemiology. *J Heart Lung Transplant.* 2005; 24(11):1891–1901. [PubMed: 16297797]
5. Sharples LD, McNeil K, Stewart S, Wallwork J. Risk factors for bronchiolitis obliterans: a systematic review of recent publications. *J Heart Lung Transplant.* 2002; 21(2):271–281. [PubMed: 11834356]
6. Huck B, Egger M, Bertz H, et al. Human metapneumovirus infection in a hematopoietic stem cell transplant recipient with relapsed multiple myeloma and rapidly progressing lung cancer. *J Clin Microbiol.* 2006; 44(6):2300–2303. [PubMed: 16757646]
7. Peck AJ, Englund JA, Kuypers J, et al. Respiratory virus infection among hematopoietic cell transplant recipients: evidence for asymptomatic parainfluenza virus infection. *Blood.* 2007; 110(5):1681–1688. [PubMed: 17502457]
8. Debiaggi M, Canducci F, Sampaolo M, et al. Persistent symptomless human metapneumovirus infection in hematopoietic stem cell transplant recipients. *J Infect Dis.* 2006; 194(4):474–478. [PubMed: 16845630]
9. Debiaggi M, Canducci F, Terulla C, et al. Long-term study on symptomless human metapneumovirus infection in hematopoietic stem cell transplant recipients. *New Microbiol.* 2007; 30(3):255–258. [PubMed: 17802904]
10. Englund JA, Boeckh M, Kuypers J, et al. Brief communication: fatal human metapneumovirus infection in stem-cell transplant recipients. *Ann Intern Med.* 2006; 144(5):344–349. [PubMed: 16520475]
11. Cane PA, van den Hoogen BG, Chakrabarti S, Fegan CD, Osterhaus D. Human metapneumovirus in a haematopoietic stem cell transplant recipient with fatal lower respiratory tract disease. *Bone Marrow Transplant.* 2003; 31(4):309–310. [PubMed: 12621469]
12. Schildgen O, Glatzel T, Geikowski T, et al. Human metapneumovirus RNA in encephalitis patient. *Emerg Infect Dis.* 2005; 11(3):467–470. [PubMed: 15757568]
13. Safdar A. Immune modulatory activity of ribavirin for serious human metapneumovirus disease: early i.v. therapy may improve outcomes in immunosuppressed SCT recipients. *Bone Marrow Transplant.* 2008; 41(8):707–708.
14. Wyde PR, Chetty SN, Jewell AM, Boivin G, Piedra PA. Comparison of the inhibition of human metapneumovirus and respiratory syncytial virus by ribavirin and immune serum globulin *in vitro*. *Antiviral Res.* 2003; 60(1):51–59. [PubMed: 14516921]
15. Hamelin ME, Prince GA, Boivin G. Effect of ribavirin and glucocorticoid treatment in a mouse model of human metapneumovirus infection. *Antimicrob Agents Chemother.* 2006; 50(2):774–777. [PubMed: 16436743]
16. Kamboj M, Gerbin M, Huang CK, et al. Clinical characterization of human metapneumovirus infection among patients with cancer. *J Infect.* 2008; 57(6):464–471. [PubMed: 19027169]
17. Sookoian S, Castaño G, Flichman D, Cello J. Effects of ribavirin on cytokine production of recall antigens and phytohemagglutinin-stimulated peripheral blood mononuclear cells. (Inhibitory effects of ribavirin on cytokine production). *Ann Hepatol.* 2004; 3(3):104–107. [PubMed: 15505595]

Fig. 1.
Bilateral nodular infiltrates and ground glass opacities in hematopoietic stem cell transplant recipient.

Fig. 2.
Patchy airspace disease and ground glass opacities in lung transplant recipient.

Table 1

Demographic and clinical description: lung transplant and other immunosuppressed patients

Age (years)/gender	Underlying disease	Significant medications	Time of diagnosis	Presenting symptoms	Radiographic findings	Method of diagnosis	Microbiologic studies	Treatment	Outcome
52/M	COPD, lung transplant 10/07, acute cellular rejection	Prednisone, tacrolimus	March 2009	Productive cough, dyspnea	Chest CT: small nodular and tree-in-bud opacities	Flexible bronchoscopy, BAL	BAL positive for hMPV Ag	Supportive	Died of respiratory failure
66/F	COPD, lung transplant 1/05, acute cellular rejection	MMF, prednisone, tacrolimus	March 2009	Productive cough, dyspnea	Chest CT: no pathologic findings	Flexible bronchoscopy, BAL	BAL positive for hMPV Ag, <i>Pseudomonas aeruginosa</i> and <i>Escherichia coli</i>	Supportive+antimicrobial treatment	Partial recovery; worsened lung function
53/F	COPD, lung transplant 1/04, acute cellular rejection	MMF, prednisone, sirolimus, thymoglobulin	February 2008	Fever, dyspnea, cough	Chest CT: ¹ patchy airspace disease and ground glass opacities	Nasopharyngeal swab	BAL positive for hMPV Ag	Supportive	Died of respiratory failure
68/M	COPD, lung transplant 7/06, acute cellular rejection	MMF, prednisone, sirolimus	May 2009	Productive cough, dyspnea	CXR: patchy airspace interstitial disease	Flexible bronchoscopy, BAL	BAL was positive for hMPV PCR and <i>P. aeruginosa</i>	Supportive+antimicrobial treatment	Partial recovery; worsened lung function
27/F	Fibrosing mediastinitis	Previous treatment with steroids and cyclophosphamide	February 2009	Fever, dyspnea, productive cough	Chest CT: scattered airspace opacities	Nasal swab	Positive for hMPV Ag	Supportive	Alive
66/F	Breast cancer	No recent treatment	April 2009	Dry cough, dyspnea	CXR: airspace opacities	Nasal swab	Positive for hMPV Ag	Supportive	Alive

M, male; COPD, chronic obstructive pulmonary disease; CT; computed tomography; BAL, bronchoalveolar lavage; hMPV, human metapneumovirus; Ag, antigen; F, female; MMF, mycophenolate mofetil; CXR, chest x-ray; PCR, polymerase chain reaction.

¹ See Figure 2.

Table 2

Demographic and clinical description: hematologic malignancies and hematopoietic stem cell transplant (HSCT) recipients

Age (years)/gender	Underlying disease	Time of diagnosis	Presenting symptoms	Radiographic findings	Method of diagnosis	Microbiologic studies	Treatment	Outcome	BMT conditioning	Steroid during treatment	Treatment of GVHD	GVHD prophylaxis
73/M	CLL, GVHD, Matched unrelated HSCT 8/06	March 2009	Productive cough, fever, dyspnea	Chest CT ¹ : bibasilar tree-in-bud nodularity and ground glass opacities	Flexible bronchoscopy, BAL	BAL positive for hMPV Ag	Aerosolized and oral ribavirin+IVIG	Recovered	TBI, fludarabine, and alemtuzumab, DLI 4/07	Yes, prednisone 60 mg orally daily	Prednisone and tacrolimus, then prednisone and MMF	Unknown
43/F	AML, M2, GVHD, Matched unrelated HSCT 8/07	March 2009	Productive cough, dyspnea, rhinorrhea	Chest CT: Scattered foci of alveolar opacities and ground glass opacities	Flexible bronchoscopy, BAL	BAL positive for hMPV Ag, <i>Pseudomonas aeruginosa</i> and <i>Aspergillus</i> species	Aerosolized and oral ribavirin+IVIG +antifungal and antimicrobial treatment	Recovered	Busulfan, clofarabine	Yes, methylprednisolone 50 mg IV daily	Methylprednisolone 50 mg, sirolimus, and tacrolimus	MTX, cyclosporine
65/F	MM, IgA, autologous HSCT 12/05	April 2009	Productive cough, dyspnea, chest pain	Chest CT: Scattered small nodules in the right upper lobe	Flexible bronchoscopy, BAL	BAL positive for hMPV Ag	Supportive	Recovered	Melphalan	No	NA	NA

BMT, bone marrow transplant; GVHD, graft-versus-host disease; M, male; CLL, chronic lymphocytic leukemia; CT, computed tomography; BAL, bronchoalveolar lavage; IVIG, intravenous immunoglobulin; TBI, total body irradiation; DLI, donor lymphocyte infusion; MMF, mycophenolate mofetil; AML, acute myelogenous leukemia; M2, a subtype of AML; hMPV, human metapneumovirus; Ag, antigen; IV, intravenous; MTX, methotrexate; MM, multiple myeloma; IgA, immunoglobulin A; NA, not applicable.

¹ See Figure 1.