Life-Threatening Human Metapneumovirus Pneumonia Requiring Extracorporeal Membrane Oxygenation in a Preterm Infant

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ABSTRACT. We present the first report in the literature of a child with human metapneumovirus pneumonia who required extracorporeal membrane oxygenation for survival. This was a 3-month-old premature boy from British Columbia, Canada, who developed severe respiratory failure, experienced failure of high-frequency oscillatory mechanical ventilation, and required extracorporeal membrane oxygenation support for 10 days. This case illustrates the importance of including this newly discovered pathogen among the causes of childhood pneumonia. Pediatrics 2004;114:e517–e519. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0345; human metapneumovirus, viral pneumonia, prematurity, respiratory failure, ECMO, mechanical ventilation.

ABBR EVIAT IONS. hMPV, human metapneumovirus; ECMO, extracorporeal membrane oxygenation; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus; CMV, cytomegalovirus; PCR, polymerase chain reaction.

Human metapneumovirus (hMPV) is a newly discovered cause of acute respiratory tract infection among children and adults that was first reported in the Netherlands. The spectrum of disease ranges from mild upper respiratory symptoms to severe lower respiratory tract disease with respiratory failure necessitating mechanical ventilation. To date, no reports of human patients requiring extracorporeal membrane oxygenation (ECMO) support for severe hMPV bronchiolitis or pneumonia have been published. We describe a premature infant from British Columbia, Canada, with hMPV-associated life-threatening pneumonia who required ECMO support for survival.

CASE REPORT

A 3-month-old boy was admitted to an urban hospital in March 2003, with a 3-day history of rhinorrhea and mild dry cough. In the previous 12 hours, he had developed poor feeding, lethargy, increasing cough, respiratory distress, and cyanosis. No history of fever was documented. The patient’s father and 2 young siblings each had experienced an uncomplicated, brief, nonfebrile, upper respiratory tract infection in the previous 3 weeks.

This infant was born at 27 weeks of gestation (through cesarean section, because of preterm labor), with a birth weight of 1200 g and Apgar scores of 1 and 8 at 1 and 5 minutes, respectively. He developed hyaline membrane disease and had a persistently patent ductus arteriosus, which was treated with indomethacin. Mechanical ventilation was required for 3 weeks. The patient was discharged from the hospital at 2 months of age. Palivizumab was administered at 1 and 2 months of age, and the patient was scheduled to receive a third dose when he became ill. Routine immunizations were given at 2 months, except for pneumococcal conjugate vaccine (Prevenar; Wyeth Pharmaceuticals, Philadelphia, PA).

At the time of arrival at the local community hospital emergency department, the child was sick-looking, with an axillary temperature of 34.9°C, a heart rate of 140 beats per minute, and a respiratory rate of 30 breaths per minute. An intermittent dry cough was present. Bilateral pulmonary rales and decreased breath sounds were noted. Cardiac examination results were normal, but weak femoral pulses and mottled extremities were found. Repeated episodes of apnea led to endotracheal intubation and mechanical ventilation. Blood was taken for cultures, and cefotaxime and vancomycin were administered intravenously. Two boluses of normal saline solution were required to improve circulation. The initial complete blood count revealed a hemoglobin level of 11.4 g/dL, a leucocyte count of 6800 cells per mm$^3$ (40% neutrophils, 56% lymphocytes, 3% monocytes, and 1% eosinophils), and a platelet count of 402 000 platelets per mm$^3$. The C-reactive protein level, serum electrolyte levels, and urinalysis results were normal. An initial chest radiograph showed a diffuse, bilateral, interstitial infiltrate suggesting viral pneumonia, with no focal consolidations or effusions. The patient was transferred to the pediatric intensive care unit (PICU) at British Columbia’s Children’s Hospital.

Twenty-four hours after admission to the PICU, a repeat chest radiograph revealed bilateral patchy infiltrates involving the right upper and middle lobes and the left perihilar region, with areas of atelectasis in the right upper lobe. No pleural pathologic lesions or air leaks were visible. The patient received high-frequency oscillatory mechanical ventilation for 4 days, with no significant clinical or radiologic improvement. Nitric oxide was administered with no clinical effect, and dopamine was required for systemic blood pressure support. Serial chest radiographs revealed worsening bilateral infiltrates with air bronchograms (Fig 1). The results of an echocardiogram were normal except for a small patent ductus arteriosus. Respiratory failure progressed despite maximal conventional critical care support; by day 4, the child exhibited oxygen saturation values ranging from 77% to 88%, with hypercapnia, and the oxygenation index had increased from 13 to 26. An arterial blood gas analysis performed on the morning of day 4 of hospitalization showed a pH of 7.28, an arterial partial pressure of oxygen of 45 mm Hg, an arterial partial pressure of carbon dioxide of 82 mm Hg, and a bicarbonate level of 37 mEq/L. Diffuse, bilateral, pulmonary opacification was observed at that time. After discussion with the family, veno-venous ECMO was initiated.

Liver enzyme levels were normal, and initial blood cultures were negative. Nasopharyngeal aspirates, repeated 4 days apart, were negative for Bordetella pertussis in polymerase chain reaction.
(PCR) assays and were negative for viruses in direct immunofluorescence tests and cultures; tested viruses included adenovirus, respiratory syncytial virus (RSV), influenza A and B, and parainfluenza types 1, 2, and 3. A bronchoalveolar lavage specimen contained epithelial cells and occasional neutrophils, histiocytes, and Gram-positive cocci, but no organisms were isolated. No Pneumocystis jiroveci (previously Pneumocystis carinii) or fungus was recovered. Tracheal viral cultures and PCR assays for cytomegalovirus (CMV) and herpes simplex virus types 1 and 2 were negative, as was a CMV early antigen test. Cultures from tracheal aspirates were negative for Ureaplasma urealyticum, Chlamydia trachomatis, Mycoplasma hominis, and Mycoplasma pneumoniae. Serum was negative for immunoglobulin M antibodies to M pneumoniae, CMV, and herpes simplex virus. Urine and stool cultures were negative for bacteria. No adeno-, rotavirus, or enterovirus was detected in the stools with enzyme-linked immunosorbent assays or cultures. After 5 days of treatment with cefotaxime and vancomycin, and negative bacterial culture findings, antibiotics were discontinued. A reverse transcriptase-PCR assay of tracheal secretions, which was performed at the National Microbiology Laboratory (Winnipeg, Manitoba, Canada), was positive for hMPV. The primers used for amplification and sequencing were based on the hMPV F gene sequence, ie, MPVF1 (5′-CTTTGGACCTTAATGACAGTG-3′) and MPVF1r (5′-GACAAGCTGGGTAGAGAC-3′), which were used to amplify a 450-base pair fragment of the F gene.2 Appropriate positive and negative control assays were performed, and the amplified PCR product was confirmed with sequence analysis. Phylogenetic analysis of the F gene sequence from the infant’s isolate revealed that the causative virus was similar to previous Canadian isolates of hMPV (Fig 2).

The child was successfully decannulated from ECMO after 10 days and required an additional 5 days of conventional mechanical ventilation. After 20 days in the PICU and 1 month of hospitalization, the patient was discharged from the hospital with bronchodilators for 1 month and no supplemental oxygen. He has been monitored in the respiratory and neonatal follow-up clinics, currently receives no medications, and has no respiratory or definite neurologic sequelae to date.

**DISCUSSION**

The complete clinical spectrum of hMPV disease is not fully defined. Most infections occur in the winter months, as happened for this infant. Clinical manifestations produced by this new member of the Paramyxoviridae family resemble those of RSV disease and include fever, cough, rhinorrhea, sore throat, wheezing, and bronchiolitis.1,2,4 Other manifestations are tachypnea, retractions, flaring, hoarseness, and stridor. Less commonly, pneumonia develops and leads to respiratory failure necessitating mechanical ventilation.1,5 However, no reports of patients requiring ECMO because of hMPV respiratory infections have been published.

Lower respiratory tract infections that progress to respiratory failure and necessitate ECMO support are associated with increased morbidity and mortality rates. ECMO support has been used in the treatment of life-threatening infections caused by viruses, bacteria, fungi, mycobacteria, and atypical organisms.6–12 The success of this respiratory support mode has been variable, ranging from no effect to
complete recovery. A key consideration is whether lung injury is reversible during the limited period in which ECMO support can be maintained. In this case, hMPV-induced lung injury resolved substantially during 10 days of lung rest with ECMO support.

Repeated tests for common causes of pneumonia were performed and yielded negative results. These tests for other common pathogens, including direct immunofluorescence tests for RSV, are sensitive and the results support hMPV as the etiologic agent in this case. The possible source of infection for this infant might have been 1 of his 3 sick household contacts, none of whom was screened for respiratory viruses. The patient did not meet the diagnostic criteria for severe acute respiratory syndrome and was not screened for it. To date, no pediatric cases of severe acute respiratory syndrome have been documented in British Columbia.

Reverse transcriptase-PCR has been used as the laboratory tool for diagnosis in the majority of hMPV studies. The detection of hMPV in this case may indicate only respiratory tract coinfection, rather than the real cause of pneumonia, but this seems unlikely, considering the epidemiologic, clinical, and laboratory evidence. Coinfection with other viral pathogens, including RSV, adenovirus, influenza A and B, and CMV, has been documented, but no evidence of such agents was obtained in this case, despite appropriate investigations. As recently noted, asymptomatic or subclinical hMPV infections seem to be rare, and the evidence to date suggests that hMPV is a causative agent of respiratory tract infections, especially among children <5 years of age. In reports to date, hMPV was recovered most commonly from nasopharyngeal aspirates and rarely from tracheal aspirates, but the optimal specimen for patients with hMPV pneumonia is unclear.

There is inadequate evidence to allow comments on prematurity as a risk factor for the development of severe hMPV pneumonia. Most adults have antibodies to hMPV. Infants lacking antibodies as a result of premature delivery may have greater difficulty coping with hMPV infection, like RSV infection.

CONCLUSIONS

The severity of disease in this case illustrates why pediatricians and other practitioners should include the emerging hMPV in the list of infectious causes of childhood pneumonia. The clinical suspicion should be higher for patients lacking evidence of other common respiratory pathogens. ECMO support may be necessary for survival for some of these patients and should be considered, because pulmonary injury may be reversible.

ACKNOWLEDGMENTS

We thank Dr David Scheifele, British Columbia’s Children’s Hospital, for critical review of the manuscript.

REFERENCES

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*Pediatrics* 2004;114:e517
DOI: 10.1542/peds.2004-0345

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