

Patient Report

Fatal hemorrhagic pneumonia caused by human metapneumovirus in an immunocompetent childAlejandro F. Donoso,¹ José A. León,¹ Jorge F. Camacho,¹ Pablo I. Cruces¹ and Marcela Ferrés²¹Pediatric Intensive Care Unit, Padre Hurtado Hospital, San Ramón and ²Catholic University Clinical Hospital, Santiago, Chile**Key words** acute distress respiratory syndrome, human metapneumovirus, immunocompetent, pneumonia, post-mortem necropsy.

Human metapneumovirus (hMPV) was recently discovered in 2001 in Holland. This agent causes acute respiratory tract infections in children and adults.¹ The range of clinical manifestations varies from asymptomatic infection to severe pneumonia and acute respiratory failure.^{1–3} When this agent coexists with the respiratory syncytial virus (RSV) in bronchiolitis, symptoms are more severe.⁴ Williams *et al.* found, in more than 25 years of investigation, that 12% of lower respiratory tract infections in children was caused by hMPV.²

Fatal cases of hMPV in both healthy and immunocompromised children have been rarely described in the literature so far.^{5,6}

The aim of the present study was to report the case of a pediatric, immunocompetent patient who presented with severe acute respiratory distress syndrome (ARDS), for whom there was a fatal outcome, and in whom hMPV was the only etiologic agent found even on post-mortem necropsy. The Institutional Review Board approved the presentation of this report.

Case report

A previously healthy, 2-year-old girl suffered an episode of diarrhea, vomiting and fever 1 month before admission. She was treated with antipyretics and oral fluids. One week later she developed mild respiratory distress and coughing. Bronchopneumonia was diagnosed and amoxicillin and inhaled salbutamol were administered. She developed transient improvement but coughing and vomiting continued, and the subject was febrile. No other family member had respiratory symptoms. She did not travel abroad.

At the Emergency Room her vital signs were temperature 37.5°C, pulse saturation 97% in room air, respiratory rate 52 breaths/min and heart rate 170 beats/min. Prior to hospital admission chest radiograph showed a right-sided bronchopneumonia (Fig. 1). Thus, the patient received 2 L/min of oxygen through a nasal cannula (saturating 96%), parenteral fluids, i.v. ampicillin and inhaled salbutamol. Laboratory tests indicated hematocrit 31%, hemoglobin 9.7 g/dL, white blood cell (WBC)

count 14.800 cells/mm³, platelet count 121 000/mm³, and C-reactive protein 8 mg/L (normal value <10 mg/L).

Three hours after hospital admission the patient suffered sudden respiratory and cardiovascular collapse. The clinical parameters at that point were temperature 38°C, tachycardia 176 beats/min, tachypnea 90 breaths/min, and pulse saturation 79% in fraction of inspired oxygen (FIO₂) of 0.5. The patient was transferred to the pediatric intensive care unit (PICU) where she was pale, tachypneic, had capillary refill >2 s, and pediatric Glasgow coma scale of 10/15. The patient was intubated immediately while invasive monitoring was initiated. She received fluid boluses of normal saline and 10% albumin solution (60 mL/kg in total), blood products (20 mL/kg of packed red blood cells and 10 mL/kg of fresh frozen plasma), vasoactive drugs (dopamine at 20 µg/kg/min and epinephrine 1 µg/kg/min) and empiric antibiotherapy (cefotaxime).

Laboratory tests indicated metabolic acidosis (pH 7.31, bicarbonate 11.4 mmol/L, base excess -11), hyperglycemia (283 mg/dL) and hypoalbuminemia (1.3 g/dL). Full blood count indicated hematocrit 21.7%, hemoglobin 6.7 g/dL, WBC count 23 500 cells/mm³ with 11% lymphocytes, and platelet count 90 000/mm³.

Severe pulmonary edema and hemorrhage from the endotracheal tube were observed in PICU (Fig. 2). She was switched to high-frequency oscillatory ventilation (mean airway pressure 30 cmH₂O, amplitude 60 cmH₂O, frequency 10 Hz) but the patient never responded adequately to any therapy. Within the next 60 min she rapidly developed systemic hypotension, anuric renal failure, progressive metabolic acidosis (pH 6.91) and finally cardiac arrest. Although cardiopulmonary resuscitation was performed for 50 min, the patient died 3 h and 30 min after PICU admission.

An autopsy was conducted indicating vascular congestion of the alveolar septa, macrophage desquamation and recent hemorrhage in the alveoli, and alveolar collapse on the whole right lung and two-thirds of the left lung. These findings were compatible with bilateral hemorrhagic bronchopneumonia. No other abnormalities were found in the other organs.

On post-mortem the laboratory tests were as follows: blood and sputum cultures for bacteria and fungi on chocolate agar with media supplements, trypticase soy blood agar, and MacConkey's agar were negative; blood polymerase chain reaction (PCR) for *Mycoplasma pneumoniae* was negative.

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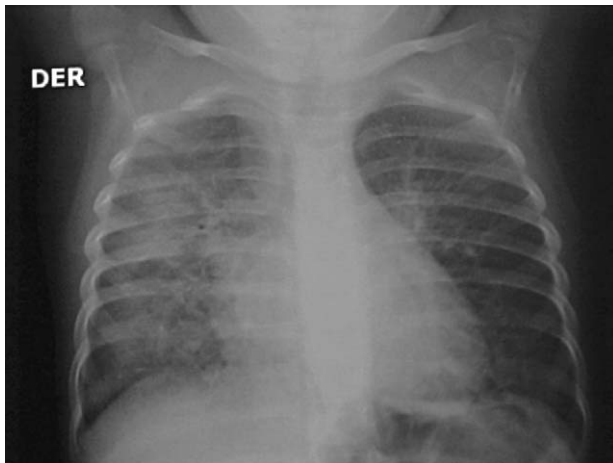


Fig. 1 Chest radiograph at admission, indicating bilateral infiltrates, predominantly on the right side.

Post-mortem lung tissue was inoculated onto shell vial culture of MDCK and H292 cells (ATCC CCL-34 and CRL-1848, respectively), followed by immunofluorescence (IF) with monoclonal antibodies against RSV, parainfluenza virus types 1, 2 and 3, influenza virus types A and B, and adenovirus (VRK, Viral Respiratory Kit, cat. B1029-86, Bartels, Issaquah, USA). None of them were detected. In addition, the same lung tissue taken from the autopsy was also inoculated onto conventional cell monolayer culture, including fibroblasts foreskin (FS), human epithelioma (HEp-2), human rhabdomyosarcoma, and African green monkey kidney (BSC-1) cells. Although a non-typical cytopathic effect was observed in FS cells, the cells were negative for Varicella zoster virus (VZV) antigens and the supernatant was negative for VZV, enterovirus and hMPV on PCR (or reverse transcriptase-PCR [RT-PCR]). Furthermore, passage to LL-MK2 cells yielded nothing.

In order to detect hMPV, RNA was extracted from the post-mortem lung tissue, using a High Pure Nucleic Acid isolation kit (Roche Diagnostics, Mannheim, Germany) according to the

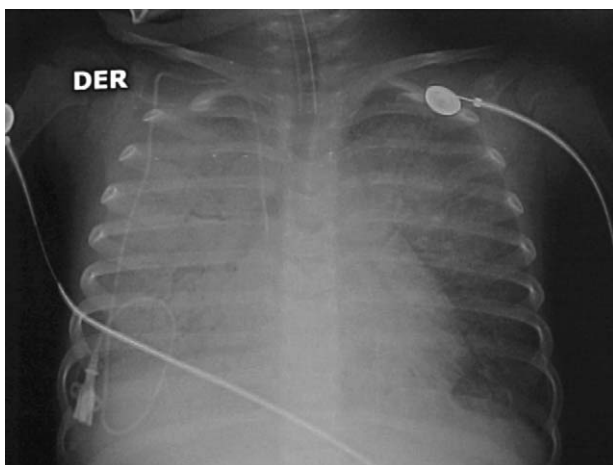


Fig. 2 Chest radiograph after intubation, indicating bilateral extensive lung consolidations, predominantly on the right side.

instructions, and one-step RT-PCR for two regions from the hMPV genome was performed. The positive control of hMPV was kindly donated by Dr Guy Boivin (Centre Recherches Infectologie, Quebec, Canada). PCR products were analyzed on electrophoresis in a 2% agarose gel with ethidium bromide, and confirmed to be 347 bp *fusion protein* (F) gene fragment and the 213 bp *nucleoprotein* (N) gene fragment of hMPV.⁷ This qualitative in-house RT-PCR was positive.

Additionally, a real-time quantitative RT-PCR assay for Andes hantavirus using Light Cycler TM instrument (Roche Molecular Biochemicals) in peripheral blood mononuclear cells was negative. PCR primers amplified a segment of S segment equivalent to 234 bp (Gen Bank NC 003466). In addition, IgM and IgG for hantavirus were also negative.

Discussion

Human metapneumovirus has been recently classified as a new member of the Paramyxoviridae family, increasing the list of the well-known viral pathogens of the respiratory tract.¹ Since its initial report studies about its epidemiologic behavior and clinical manifestations have risen dramatically. In infants and young children the lower respiratory tract infections caused by hMPV are very similar to the ones caused by RSV, influenza and parainfluenza viruses. Although the spectrum of clinical manifestations of hMPV infection is not completely defined as yet, the most frequent manifestations include cough, coryza and pharyngitis. Fever, wheezing, stridor and respiratory failure are observed in more severe cases.^{2,8,9} Non-respiratory symptoms such as conjunctivitis, otitis media, vomiting, diarrhea, or rash are occasionally reported.

Human metapneumovirus could be more severe in patients with underlying medical conditions such as chronic lung disease caused by prematurity, cardiac disease, and immunodeficiency. There is currently controversy about its role in increasing the symptoms in asthmatic patients compared with RSV, adenovirus, influenza and parainfluenza virus, but the biologic significance of this association is unclear.²

Co-infection with hMPV and other virus, such as RSV or severe acute respiratory syndrome-coronavirus, has been reported and may contribute to more severe clinical manifestations.⁴⁻¹⁰ Because shell vial cultures with IF, one of the most reliable laboratory tests for common respiratory viruses, could not detect any other respiratory virus; and RT-PCR, which is considered to be the best laboratory test for diagnosis of hMPV infection, clearly detected hMPV-RNA in the present patient, it is reasonable to assume that hMPV was the only agent involved in the fatal pneumonia. The accumulation of cases, however, and comprehensive microbiological analysis including (RT-) PCR for other respiratory viruses are needed to confirm that infection with hMPV alone can result in such severe lung disease.

Few studies on fatal cases have been reported in children. Pelletier *et al.* published a report on an infant who died due to severe and refractory ARDS. That patient had an underlying immunodeficiency and the exact cause of death could not be established because the autopsy was not performed.⁶ Ulloa-Gutiérrez *et al.* reported another severely ill, 3-month-old preterm boy with

hMPV pneumonia who underwent extracorporeal membrane oxygenation for 10 days.³ An immunocompetent, 1-year-old girl was reported recently. That patient, who presented with fever, cough and diarrhea developed rapidly an extensive pneumonia and then pulmonary edema and hemorrhage, and finally refractory shock. That patient died a few hours after admission.⁵ That case resembles that of the present patient very well in terms of immunocompetency, severity, rapid onset of symptoms, and outcome.

Based on genetic analysis of F gene, hMPV can be divided into two major genotypes that are further classified into 22 subgroups. Although correlation between genotypes and phenotypes (pathogenicity) is not precisely known, it will be important to determine genotype in such severe cases.^{2,6} Unfortunately we could not perform genotype analysis of hMPV detected in the present patient.

It is very important to understand the real impact of hMPV infections in different populations, the complete spectrum of manifestations, and the risk factors that can predict a poor outcome including age, underlying medical conditions, co-infection with other respiratory virus, and certain genotypes.

We believe that the present case should warn us about the occasional role of hMPV as an agent of severe lung infection in children without a predisposing condition. We recommend including this agent within the causes of severe and potentially fatal pneumonia in children.

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