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Short communication

Epidemiological survey in a day care center following toddler sudden death due to human metapneumovirus infection

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ABSTRACT

We report the sudden death of a 33-month-old child owing to acute respiratory distress syndrome due to human metapneumovirus (hMPV) infection. Of 30 children attending the same day care centre, 26% and 59% had hMPV and multiple infections, respectively; three of six children with pneumonia had a diagnosis of hMPV. hMPV infection is common in childhood viral co-infections but it can cause sudden death.

1. Introduction

Winter virus epidemics are common in childhood, particularly in day care centres. Here, we present a case that highlights the management difficulties associated with a virus-induced sudden death.

2. Observation

2.1. Case description

During the winter season, a 33-month-old girl in a day care centre had an isolated, well-tolerated fever that did not justify further medical evaluation. The fever, which occurred in the afternoon, was resolved by taking paracetamol, and the parents noted nothing amiss in the evening. Unfortunately, she died during the night between midnight and 3:30 am. Her body was sent to the Institute of Forensic Medicine at the University Hospital, and a sudden death investigation was initiated. On admission, various imaging studies were performed, biological samples were collected about 12 h after death, and the autopsy was completed 36 h after death. As an additional measure, children attending the day care centre underwent surveillance for signs of infection.

A hemogram showed normal results, but C-reactive protein levels were elevated (15 mg/L). There was also an isolated spike in the serum creatinine level to 226 μmol/L without an increase in plasma urea levels. Cadaveric phenomena result in high levels of serum potassium and do not allow for a post-mortem interpretation.

Whole-body computed tomography revealed micronodular lesions and ground-glass opacities in the lungs excluding the region under the pleura (Fig. 1). No lesions were detected on skeletal scans. Magnetic resonance imaging showed pulmonary anomalies, as indicated by bilateral pleural effusion, along with cervical and perihilar nodes. Brain magnetic resonance images did not show abnormalities.

Macroscopic examination during autopsy revealed a very heterogeneous and edematous region in the lung parenchyma without suppuration or abscesses. Bilateral pleural effusion and multiple cervicothoracic lymphadenopathies, as well as four black intestinal patches without perforation or peritoneal effusion, were also observed. There was no cardiac malformation, including normal implantation of the large vessels and a closed foramen

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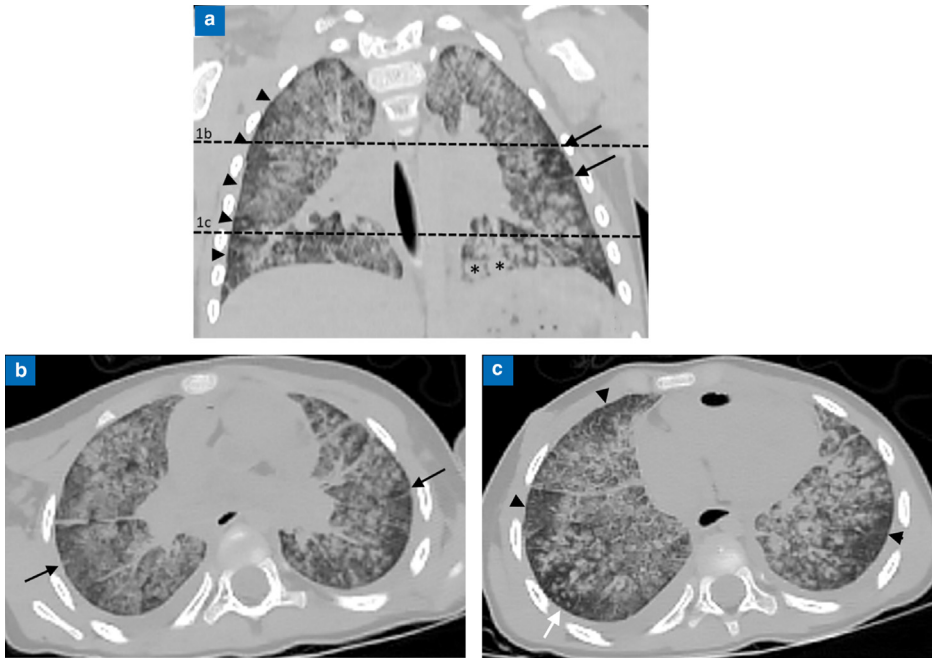

Fig. 1. Postmortem computed tomography (CT). Thin-section coronal (a) and axial (b, c) reconstructed (5 mm section thickness) chest CT images show multiple ill-defined micronodules (white arrows) or ground-glass opacities excluding the region under the pleura (arrowheads) and some macronodules at the bases (asterisk) with interlobular septal thickening (black arrows).

ovale. Macroscopic findings were not suggestive of pericarditis, dilated cardiomyopathy, or ischemic lesions.

Pulmonary histological analysis showed signs of diffuse and bilateral interstitial pneumopathy including alveoli destruction, polymorphonuclear neutrophil infiltration, and septal disruption. Inflammation of the cervical and mediastinal lymph nodes was noted.

Digestive mucous membranes were replaced by fibrin, had ischemic aspects, and were associated with a major mesenteric ganglionic conglomerate. No anomalies were found at microscopic study of the heart. Both imaging and histological results were consistent with bilateral infectious pneumonia, probably complicated by acute respiratory distress syndrome (ARDS).

Extensive microbiological investigations (direct examinations, culture preparations) failed to detect any bacterial pathogens in body fluids (blood, cerebrospinal fluid, respiratory secretions, urine, pericardial) or organs (lungs, liver, brain, heart, lymph nodes, digestive tract). Molecular polymerase chain reaction (PCR) assays of respiratory secretion samples targeting pertussis toxin, legionella, mycoplasma, and chlamydia were also negative. However, a multiplexed PCR analysis with Anyplex II RV16 of respiratory secretion samples that detects a panel of 16 viruses (influenza virus, respiratory syncytial virus [RSV], parainfluenza virus, rhinovirus, adenovirus, enterovirus, coronavirus, metapneumovirus, and bocavirus) yielded positive results, namely, the presence of both human metapneumovirus (hMPV) and bocavirus (HBoV). hMPV had a high early cycle threshold value (24.1), which indicated a high viral load, whereas HBoV had a value close to its lower limit of detection. As confirming evidence, hMPV was also detected in lung biopsy samples, as well as biopsy samples of other organs. Cytomegalovirus (CMV) was identified in a lung biopsy sample, but the copy number was low (< 500 UI/mL). The overall results of post-mortem virologic samples are summarized in Table 1. Therefore, the final diagnosis was determined to be ARDS triggered by hMPV-induced pneumonia.

2.2. Day care center surveillance

Owing to the seriousness of the girl's sudden death, health authorities implemented a plan for surveilling the children who attended the same day care centre. The plan was enacted 24 h after the death and parents and practitioners were advised to contact the pediatrics emergency units at the University Hospital if a child appeared ill. During the ensuing 2 weeks, 30 children (17 girls and 13 boys) from the day care centre were admitted to the hospital. The median age was 25 months (range 4–35 months). All children were symptomatic, with upper respiratory tract infections (45%), lower respiratory tract infections (25%), or flu-like syndrome (13%).

Table 1
Postmortem virology samples.

	PCR multiplex AII RV16	CMV	PVB 19	Adenovirus	Enterovirus	HSV/VZV
Respiratory secretion	hMPV, HBoV			Negative	Negative	
Lung	hMPV	< 540/mL	Negative			
Blood		Negative	Negative	Negative	Negative	
Myocardium	Negative	Negative	Negative		Negative	
Pericardial fluid	Negative	Negative				
Liver	Negative	Negative	Negative			
CSF					Negative	Negative

hMPV: human metapneumovirus; HBoV: bocavirus; CMV: cytomegalovirus; PVB 19: parvovirus B19; HSV: herpes simplex virus; VZV: varicella-zoster virus; CSF: cerebral spinal fluid; PCR: polymerase chain reaction.

Table 2
Results of microbiological and radiological investigations of contact cases at day care center.

Sex/Age (months)	Multiplexed PCR (Virus)	Pneumococcal urinary Ag	Legionella urinary Ag	PCR Chlamydia/Mycoplasma	Radiography
M/33[a]	hMPV, RSV, Rhinovirus[a]	Negative[a]	Negative[a]		Pneumonia[a]
F/29[a]	hMPV, HBoV[a]	Negative[a]	Negative[a]		Pneumonia[a]
M/22	hMPV, HCoV-OC43		Negative	Negatives	Normal
F/20	hMPV, HCoV-NL63, Adenovirus, Rhinovirus		Negative	Negatives	Normal
M/25	hMPV	Negative	Negative	Negatives	Pneumonia
F/17	hMPV		Negative	Negatives	Normal
F/28	hMPV, HBoV, HCoV-OC43		Negative	Negatives	Normal
M/23	hMPV, HCoV-NL63, Rhinovirus		Negative		Normal
M/25[a]	HCoV-NL63[a]			Negatives[a]	Pneumonia[a]
M/34[a]					Pneumonia[a]
F/34[a]					Pneumonia[a]
F/20	Rhinovirus	Negative	Negative		
M/11		Negative	Negative		
M/16	Influenza B, HBoV				Normal
F/11					Normal
F/32					Normal
F/23	Influenza B, Adenovirus	Negative	Negative	Negatives	Normal
M/4	Adenovirus	Positive	Negative	Negatives	Normal
M/20	HCoV-OC43, Enterovirus			Negatives	Normal
F/32	Influenza B, HCoV-NL63		Negative	Negatives	Normal
F/34	Influenza A			Negatives	Normal
F/31					
M/10					
F/30	RSV		Negative	Negatives	Normal
F/21	HBoV, Rhinovirus		Negative	Negatives	Normal
F/33	Rhinovirus		Negative	Negatives	Normal
F/25					
M/15	Negative		Negative	Negatives	Normal
M/35	Adenovirus		Negative	Negatives	Normal
F/35	Adenovirus, HCoV-NL63		Negative	Negatives	Normal

F: female: M: male; hMPV: human metapneumovirus; RSV: respiratory syncytial virus; HBoV: bocavirus; HCoV: coronavirus; PCR: polymerase chain reaction.
[a] Hospitalized children.

Five required hospitalisation (median hospital stay was 3 days) for lower respiratory tract infections (Table 1) and received probabilistic antibiotics. Although severity was not assessed, one of the five children received oxygen for 24 h. Some children underwent imaging and microbiological investigation.

Multiplexed PCR (Anyplex II RV16) was performed for 22 children and a respiratory virus was identified in 21 of these cases. Children were predominantly infected with hMPV (8/22), coronavirus (8/22), followed by rhinovirus (6/22), and adenovirus (5/22); 12 had co-infections. Abnormal radiographic results were observed in 24% of the children, some of which were associated with a respiratory virus. The overall results are summarized in Table 2. Analysis of environmental samples obtained from within the nursery showed low-level bacterial contamination without *Legionella* or other pathogenic bacteria.

3. Discussion

The radiological data presented herein are suggestive of bilateral infectious pneumonia, especially viral pneumonia. Pneumonia due to hMPV is characterized by multiple ill-defined nodules or ground-glass opacities along the bronchovascular bundles in both of the lungs [1]. ARDS [2] was diagnosed despite the absence of hyaline membranes (from the second day) based on radiological and histological demonstration of diffuse interstitial and alveolar edema, inflammatory cell infiltrate (polynuclear neutrophil influx), and alveolar hemorrhage. ARDS in this case was probably complicated by systemic failure, hemodynamic shock, renal failure, and intestinal necrosis.

hMPV-induced pneumonia was indicated by a high viral load detected in respiratory secretions and lung biopsies. As further support, no other well-described human pathogens besides HBoV and CMV were detected. HBoV was present at low levels in one nasopharyngeal sample and may have simply been a bystander as it was not found in lung parenchyma samples and its pathogenic potential is debated [3]. CMV was present at a low level in one lung biopsy sample in the absence of CMV viremia. Specific anti-CMV IgM immunoglobulins are likely unrelated to the sudden death observed in this case, and asymptomatic CMV reactivation frequently occurs during infections caused by other agents. Immune system evaluation (weight dosage of immunoglobulins) was performed on post-mortem samples, but a diagnosis of immunodeficiency was impossible without precise functional and quantitative analysis of lymphocytes, polymorphonuclear leukocytes, and monocytes. However, we did not try to quantify T-cell-receptor excision circles (TRECs) from the neonatal screening sample.

Pediatric cases of severe ARDS due to hMPV are rare, with only five cases are recorded in the literature, three of which resulted in death [4,5]. One patient died of uncontrolled ARDS [6], whereas another died after acute pulmonary hemorrhage soon after admission [7]; neither patient had any significant medical history. Another patient presented with a secondary immunodeficiency owing to immunosuppression for hepatic transplantation [5]. Immunodeficiency has been linked to severe viral respiratory infections. Additional associations include TLR4 mutations with severe RSV bronchiolitis [8], IFIH1 loss-of-function mutations (which prevent sensing of viral RNA) with severe RNA virus (RSV and human rhinovirus) infections [9], and IRF7 [10] and IRF 9 [11] with severe influenza pneumonitis. All these genes are involved in innate immunity and interferon pathways and have been implicated in a theory proposing that monogenic inborn errors of immunity underlie susceptibility to specific infections [12]. In the diseases noted above, the patient might not have any

additional infections, and hence standard immunological tests would have yielded normal results. This premise is compatible with our case, as there was no remarkable medical history.

To our knowledge, this is the first report of an hMPV infection presenting in toddler sudden death. Our case highlights the importance of systematic forensic investigation in such situations: Only via a systematic analysis of the autopsy, radiological, histological, and biological findings were we able to pinpoint the cause of this sudden death. These findings also demonstrate the usefulness of systematic viral screening in sudden death cases and of molecular tools for detecting causative viruses, most notably hMPV. These post-mortem investigations were realized according to French National Authority for Health (HAS) recommendations for cases of sudden death in a child that were published in 2007 [13].

Among the 22 nursery children tested, eight were infected with hMPV, with a co-infection rate of 75%. In winter, numerous viruses colonize the upper respiratory tract of children in communal settings [14]. The observation of multiple co-infections, with up to three different viruses in some children, indicates that proximity among young children promotes transmission and exchange of pathogens (Table 2). Owing to its high sensitivity, PCR may detect several pathogens, which introduces confusion since it cannot distinguish between causative pathogens and other potentially infectious agents or residual pathogenic signatures of prior infections. However, healthy portage of hMPV is exceptional [15]. PCR analysis needs to be integrated into a global approach to determine the implications of specific infectious agents in a given disease.

Our report shows that hMPV and other respiratory viruses have diverse effects with poor specificity, from modest respiratory symptoms, to full-blown infections, to death. It also underscores the difficulty of identifying etiological agents in young, closely interacting children with respiratory tract infections, owing to the high prevalence of many viruses in these groups.

4. Conclusion

Our results show that hMPV causes a wide spectrum of symptoms in young children, ranging from minimal respiratory damage to fatal lung damage. Because of its high prevalence, particularly in community settings, it can play a role in the sudden death of a child. Thus, virologic investigation via multiplexed PCR that is systematically extended to the pulmonary parenchyma could be a useful etiological tool, particularly during winter epidemics.

Disclosure of interest

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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