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ADVANCES IN PEDIATRIC RESEARCH

Rapidly progressive fatal respiratory failure by human metapneumovirus infection in a 2-year-old girl and review of the literature

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Abstract

Human metapneumovirus (hMPV) was discovered in 2001 and it is one of the common viruses that cause respiratory infection in infants, which is usually self-limiting in nature. We report a 2-year-old girl with hMPV infection, who was dead of respiratory failure in a rapidly progressive clinical course. We discuss about the clinical and biological features of hMPV infection with a review of the literature.

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Introduction

The human metapneumovirus was discovered as a single-stranded RNA virus which quite resembles RSV (respiratory syncytial virus) in 2001 [1]. It is a common virus which infects as early as six months old infants, 50% of 2 years old, 75% of 5 years old and almost all of 10 years old children [2, 3]. It is estimated to account for 10% of respiratory infection in children [4]. It has been isolated year-round, but it prevails between February and April in temperate regions and during the spring and summer in subtropical climates [5]. It is prevalent from March through June in Japan, which is interestingly reciprocal of RSV infection prevalence [2,4]. It is highly contagious and thought to be an important causative virus of respiratory infection for not only children but also the adults, especially elderly people [6]. Clinical manifestations are extremely similar to those of RSV infection [1-3]. It presents mostly with upper respiratory infection and self-limiting, while eventually progresses to lower respiratory tract infection in infants and elderly people [7] and it might be serious in immunocompromised patients such as leukemia or transplant recipients [8-11].

We experienced a 2-year-old girl with hMPV infection who showed rapidly progressive respiratory failure to fatal course.

Case report

She was born as a small-for-date baby with a weight of 1800g for a gestational age of 37 weeks by Cesarean section. Development was normal until 9 months old, when she suffered from idiopathic pulmonary edema after HHV-6 (human herpesvirus 6) infection and received artificial respiration management for 10 days. She started to stand by herself at 14 months old and walk at 23 months old. At 21 months old, she contracted influenza type A virus infection with normal clinical course.

She had fever two days before admission and visited our hospital for her first febrile seizure. On the next day, she was checked for influenza virus to be negative at home doctor. In the afternoon, she presented truncal ataxia and was hospitalized for the investigation of truncal ataxia on the third day in our pediatric ward. On admission, she looked less active and presented with a weight of 10 kg, body temperature of 38 ^{O} C, heart rate of 128/min, respiratory rate of 40/min and SpO2 of 95% in a room air. Pharyngitis and otitis media were not found. Respiratory sound was clear and there were no other abnormal physical and neurological findings such as dysphagia and paralysis except for mild truncal ataxia. RSV antigen was negative, but hMPV antigen was positive in the nasopharyngeal swab by immunochromatography test. Blood examinations were as follows; white blood cells of 16400/μL with 72% of neutrophis, Hb of 12.2g/dL, Platelet of 19.0 x 10^4/μL, LDH of 836IU/L, AST of 121IU/L, ALT of 32IU/L, CK of 519IU/L, NH3 of 33μg/dL, ferritin of 1457ng/mL, CRP of 2.94mg/dL, fibrinogen of 337mg/dL and d-dimer of 1.5ng/mL. Serum uric acid and creatinine were increased to 12.5mg/dL and 0.35mg/dL respectively, indicating moderate dehydration. Chest X-ray showed moderate peribronchial cuffing on both sides (Figure 1-A). Brain MRI and lumbar puncture revealed no abnormal findings. She received intravenous continuous infusion for dehydration. In the evening, her respiratory rate was gradually increased and she required oxygen administration of 4L/min by mask to keep SpO2 above 95%. Three hours later, she became restless and respiratory rate was increased to 70/min. Chest-X ray showed increased pulmonary opacity indicating worsening of pulmonary infiltration (Figure 1-B) and she was placed on artificial ventilation and transferred to the intensive care unit immediately. A high dose of methypredonisolone (10mg/kg) was administered for the suspected SIRS (systemic inflammatory syndrome) or RDS (respiratory distress syndrome). Blood examinations revealed normalized uric acid and creatinine values but still elevated LDH of 858IU/L, AST of 113IU/L, and CK of 502IU/L. In spite of intensive care, she was getting worse and dead of acute respiratory failure 6 hours later. Permission of autopsy was not allowed from the parents.

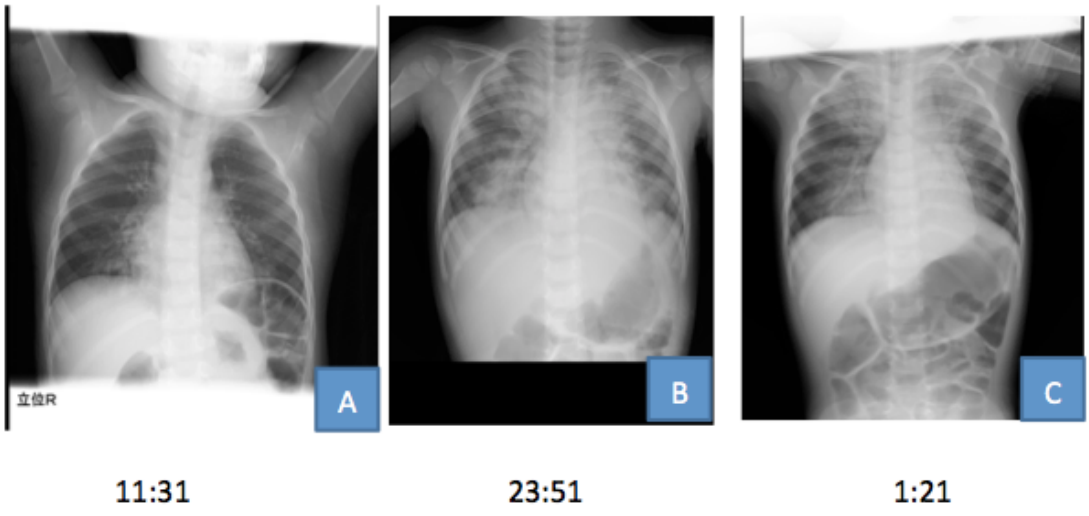

Figure 1. Sequential chest X-ray of the patient

Chest X-ray on admission, the lungs were mildly hyperinflated and moderate peribronchial cuffing was noticed (A). Before intubation, increased perihilar and lower lung opacities on both sides without silhouetting the heart border were found (B). One hour after intubation, perihilar, upper and lower lung interstitial prominence was still noticed (C). The number below indicates the time of each examination performed.

Discussion

Human metapneumovirus consists of 8 genes and it has F-glycoprotein, G-glycoprotein and SH glycoprotein on the surface, in which F-glycoprotein is important for the adhesion and fusion to the target cells [12]. G-glycoprotein is also associated with virus adhesion, but G-glycoprotein is found to be dispensable for infection. In the core of a virus, N-protein, P-protein, and L-protein exist complexed with viral RNA [12]. P-protein and L-protein have transcriptional activity. It is speculated that anti-F-glycoprotein antibody works as a neutralizing antibody. Genetically, two subgroups are identified and each subgroup is further divided into two subtypes [13].

hMPV is transmitted in the droplet and contact infection manner and its incubation period is 4 to 6 days [4]. While RSV infects most of the infants under 6 months old, hMPV usually infects the infants of one year old and older [2,4]. Thus, it is speculated that transmitted antibody from the mother may function as protection or there are differences in the immune responses against RSV and hMPV, although the clinical manifestations of both viruses are quite similar and indistinguishable. It is considered that IgG antibody for hMPV is negative up to 8 days after the onset of disease and re-infection is frequently observed, indicating that IgG antibody does not persist for a long period [4, 14].

As an isolation of hMPV has been difficult technically, viral detection has been performed by RT-PCR method. Recently, clinical test to detect hMPV antigen by immunochromatography is established and is widely used in the bed-side diagnosis of hMPV infection. Although its sensitivity is inferior to that of RT-PCR method, this is practically useful enough from the clinical point of view [15].

There are few reports of the hMPV pneumonia case with rapidly progression of respiratory failure such as this case. Co-infection with bacteria or fungi is considered to be a risk factor of fatal cases with hMPV pneumonia in immunocompromised hosts [16, 17]. It is reported that an introduction of extracorporeal membrane oxygenation (ECMO) saved a premature baby of three months old with severe hMPV pneumonia [9]. Gupta et al. also have reported a 32-months-old infant who survived the respiratory failure of severe hMPV pneumonia through ECMO as an oldest case [18]. It is said that innate immune system through TLR-4 (Toll-like receptor 4) is important to pathophysiology of hMPV pneumonia [19].

It has been reported that glycoprotein G of hMPV is involved in viral toxicity by inhibiting TLR-4 and mitochondrial signal transduction system [20, 21]. Interestingly, it has been reported that alveolar macrophage contributes as a deteriorating factor in hMPV pneumonia, while it works as a protecting factor in RSV pneumonia in mice model [22]. In this case, markedly elevated ferritin was observed at admission, indicating the increased activation of macrophages. This might be related with rapidly progressive hMPV pneumonia in this patient. Although there are no proven treatments for hMPV pneumonia so far and supportive therapy is recommended as a standard treatment [3], a few anecdotal reports of satisfactory results with ribavirin and intravenous immunogloblin therapy have been reported [23-25].

From the fact of her previous episode of pulmonary edema of unknown etiology, she might have some genetic background for deterioration of respiratory failure. Although, hMPV infection is considered to be self-limiting in most of the cases, we have to be careful for the management of hMPV infection in infants, because it may progress to fatal course. Further clinical and basic investigation is required to disclose the perspective of hMPV infection and establish a novel preventive and therapeutic strategy.

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