Human Metapneumovirus

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Name of Virus: Human metapneumovirus

12.1 Brief Introduction

Human metapneumovirus (hMPV), a frequent cause of acute respiratory illness in young children, was first isolated in 2001. Retrospective serological tests have shown that the virus has been present since at least 1958. Its slow growth and trypsin dependency in culture contributed to its late identification (van den Hoogen et al. 2001). hMPV is most closely related to the avian pneumovirus, a cause of tracheobronchitis in turkeys and other birds and the only other member of the genus metapneumovirus (van den Hoogen et al. 2001).

hMPV is a cause of bronchiolitis and pneumonia, particularly in young children, with a similar clinical picture as respiratory syncytial virus (RSV) infection, its most closely related human pathogen. Infections in adults are most common in the elderly and immunocompromised (van den Hoogen et al. 2004b). By comparison to similar respiratory viruses, transmission is assumed to be through respiratory secretions and fomites (Crowe 2004). The virus has been shown to survive for a prolonged period in nonporous surfaces such as plastic and metal, making such surfaces a potential source for infection (Tollefson et al. 2010). Nosocomial transmission and outbreaks have been reported (Boivin et al. 2007; Cheng et al. 2007; Degail et al. 2012).

12.2 Classification

Family – Paramyxoviridae
Genus – Metapneumovirus

12.3 Epidemiology

First isolated in the Netherlands, hMPV has since been described in many countries and appears to have a worldwide distribution (van den Hoogen et al. 2001; Peret et al. 2002; Stockton et al. 2002; Boivin et al. 2002, 2004; Peiris et al. 2003; Williams et al. 2004; García-García et al. 2006). Infection with hMPV peaks in the late winter and spring in temperate climates (Williams et al. 2004; García-García et al. 2006) and in the late spring and summer in subtropical regions (Peiris et al. 2003). Infection with hMPV is most common in children younger than 2 years of age, and serological evidence of infection is present in most children by the age of 5. Reinfection in older children and adults typically results in milder disease (van den Hoogen et al. 2001; van den Hoogen et al. 2004b).
12.4 Ultrastructure

Negative-contrast electron microscopy of supernatants of infected cells in culture has shown ultrastructural similarities between hMPV and other paramyxoviruses. The viral particles are pleomorphic and may be spherical or filamentous. Spherical particles range from 150 to 600 nm in diameter, with 13–17 nm envelope projections corresponding to surface glycoproteins. The nucleocapsids average 17 nm in diameter (van den Hoogen et al. 2001; Peret et al. 2002). The ultrastructural characteristics of the virus in tissue have not been described.

12.5 Immunology

hMPV is an enveloped, negative-sense, single-stranded RNA virus. Phylogenetic analyses have shown two hMPV lineages, A and B, and at least four sublineages, A1, A2, B1, and B2 (van den Hoogen et al. 2001, 2002; Boivin et al. 2004; Peret et al. 2002). There is conflicting data as to whether the hMPV lineages represent distinct serotypes (van den Hoogen et al. 2004a; Skiadopoulos et al. 2004). Both lineages appear to be globally distributed and circulate randomly during any given season (Boivin et al. 2004). hMPV has three surface glycoproteins: the fusion (F) protein, the attachment (G) protein, and small hydrophobic (SH) proteins of unknown function. hMPV infection begins with attachment of the virus to respiratory epithelial cells. Attachment to the host cell appears to be mediated by nonspecific binding of the G protein to glycosaminoglycans on the cell surface (Thammawat et al. 2008) and by specific binding of the F protein to integrin receptors on the host cell (Cseke et al. 2009). This role of the F protein in cell attachment appears to be unique to hMPV among the paramyxoviruses.

Fusion of the virus to the host cell membrane, mediated by the F protein, results in release of the nucleocapsid into the cell cytoplasm. As with other viruses, transcription of viral proteins and replication ensue, with assembly of virions. Viral surface glycoproteins are incorporated into the host cell membrane and become part of the enveloped virus with the release of viruses from the host cell by budding (Feuillet et al. 2012).

12.6 Clinical Features

The clinical features of hMPV in children are similar to those of respiratory syncytial virus. Children may present with an upper respiratory tract infection, evidence of bronchiolitis, including fever, rhinorrhea, cough, and diffuse wheezes and rales, or pneumonia, with dyspnea and localized infiltrates by chest x-ray. Systemic symptoms such as anorexia, vomiting, diarrhea, and myalgias may also be present (Williams et al. 2004, 2006, 2010). Symptoms may be severe, particularly in very young children, and require hospitalization and, in some instances, mechanical ventilation (van den Hoogen et al. 2001; García-García et al. 2006). hMPV is responsible for 4–6% of hospitalizations for acute respiratory infections in young children (García-García et al. 2006; Williams et al. 2010; Boivin et al. 2003).

In otherwise healthy adults, hMPV is an uncommon cause of acute respiratory tract infection and influenza-like illness (Louie et al. 2005; Stockton et al. 2002). More severe diseases, including bronchitis, bronchospasm, and pneumonia, requiring hospitalization and mechanical ventilation are more likely with immunosuppression, underlying disorders, and advanced age (Boivin et al. 2002; Shahda et al. 2011). hMPV has also been identified in sputum and nasal lavages of a small number of patients with acute exacerbation of chronic obstructive pulmonary disease (Rohde et al. 2005).

12.7 Pathologic Changes

The pathological changes of hMPV infection have not been well described, with only a small number of cases reported in the literature. Vargas et al. (2004) described the findings in
bronchoalveolar lavage in children infected with hMPV as consisting of red, round, 3–4 μm inclusions in the cytoplasm of epithelial cells, macrophages, and multinucleated giant cells, as well as nonspecific degenerative changes of the respiratory epithelial cells and abundant neutrophils and macrophages. The presence of cytoplasmic inclusions has not been confirmed in other reports. However, cytoplasmic inclusions are characteristic of other paramyxoviruses, such as parainfluenza, measles, and respiratory syncytial virus. Hence, their presence in hMPV infection would not be surprising.

Degenerative changes of the respiratory epithelium have also been reported in experimental hMPV infections in primates in which mild, multifocal erosive lesions in the conducting airways and increased numbers of macrophages in the bronchioles and alveoli are the salient findings. By immunohistochemistry the virus is localized to the bronchial epithelial cells (Kuiken et al. 2004). Similar findings can occur in humans (Fig. 12.1a). Lung biopsy findings in hMPV infection include acute and organizing diffuse alveolar damage (DAD) and organizing pneumonia, with localization of the virus in bronchial epithelial cells and pneumocytes by immunohistochemistry and in situ hybridization (Sumino et al. 2005; Boivin et al. 2007). Chronic airway inflammation may also be seen (Vargas et al. 2004). A more complete picture of pulmonary hMPV infection awaits further study (Fig. 12.1b–d).

**Fig. 12.1** (a) hMPV infection. Note severe bronchiolitis with ulcerated bronchiolar epithelium. (b) Higher power showing accumulation of intra-alveolar macrophages. (c) Note pulmonary congestion and mild interstitial lymphocytic inflammation. (d) Note prominent formation of hyaline membrane (Courtesy of Dr. S.R. Zaki, Centers for Disease Control and Prevention, Atlanta, GA; from Dail and Hammar’s Pulmonary Pathology, 3rd ed, Ch 11 Viral Infections of the Lung, by Tomashefski, with kind permission of Springer Science + Business Media)
12.8 Diagnosis

Human metapneumovirus grows slowly in a limited number of conventional cell cultures, such as tertiary monkey kidney cells (tMKC), rhesus monkey kidney cells (LLC-MK2), and African green monkey (Vero) cells. Growth in these cell lines is trypsin dependent. Variable cytopathic effects including rounding of cells and cell destruction with or without the formation of syncytia have been reported (van den Hoogen et al. 2001; Peret et al. 2002; Boivin et al. 2002; Deffrasnes et al. 2005; Tollefson et al. 2010). HMPV’s slow and unreliable growth and nonspecific cytopathic effects make routine cultures suboptimal for routine diagnosis of infection.

Reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal aspirates or swabs is the most reliable method to establish the diagnosis of hMPV infection. Up to 2/3 of specimens positive for hMPV by RT-PCR may be negative by culture (Ebihara et al. 2004). Multiplex platforms that allow for the simultaneous detection of several respiratory viruses have the advantage of providing specific results with a rapid turnaround time and are commercially available (Freymuth et al. 2006; Mahony et al. 2007). Other methods for diagnosis include enzyme immunoassays (Fuenzalida et al. 2010) and direct and indirect immunofluorescence (Ebihara et al. 2005; Vinh et al. 2008; Landry et al. 2005, 2008; Jun et al. 2008).

12.9 Differential Diagnosis

The clinical signs and symptoms of hMPV infection are nonspecific and overlap with those of other acute respiratory tract infections. Respiratory syncytial virus is more common than hMPV and is also seen in young children, with a mean age which is slightly younger than hMPV. Infections by other viruses, including adenovirus, coronavirus, and rhinovirus, may present similarly. Influenza must be considered in the differential diagnosis in both children and adults. The cytoplasmic inclusions in epithelial cells, macrophages, and multinucleated giant cells described in one study of bronchoalveolar lavage must be differentiated from those caused by other viruses, such as parainfluenza virus, measles, and RSV (Vargas et al. 2004).

12.10 Prevention

No specific preventive methods are known for hMPV. Respiratory infection control measures to restrict exposure, as well as frequent use of alcohol hand rubs and hand hygiene, have been successful in containing or preventing outbreaks in hospitalized patients (Degail et al. 2012; Cheng et al. 2007).

12.11 Treatment and Outcome

Treatment of hMPV infection is largely supportive. Severe infections may require oxygen therapy or mechanical ventilation in young children and adults with other comorbidities as well as the elderly. Acute respiratory distress syndrome (ARDS) and death have been reported (Boivin et al. 2007; Schlapbach et al. 2011). Rare reports of successful outcomes in immunosuppressed patients with hMPV pneumonia treated with ribavirin and immunoglobulin have been published (Bonney et al. 2009).

12.12 Vaccine

No vaccine is yet available for human metapneumovirus. Animal studies have demonstrated that immunization with inactivated hMPV results in an aberrant immune response with more severe disease upon subsequent hMPV infection (Hamelin et al. 2007), analogous to the experience with children immunized with formalin inactivated RSV (Kim et al. 1969; Kapikian et al. 1969). Therefore, live inactivated hMPV virus vaccines are unlikely candidates for future development.

Other approaches being explored take advantage of the highly conserved and immunogenic F surface protein which has been reported, in some
animal studies, to give rise to neutralizing and protective antibodies against both (A and B) lineages (Skiadopoulos et al. 2004, 2006). These include the use of chimeric, live attenuated vaccines, such as bovine/human chimeric parainfluenza virus type 3 expressing hMPV F protein (Tang et al. 2005) or hMPV/avian MPV C chimera (Pham et al. 2005). Recombinant hMPV vaccines lacking the G and/or SH genes or the M gene (Biacchesi et al. 2004, 2005; Buchholz et al. 2005) or component proteins such as soluble hMPV F protein (Herfst and Fouchier 2008; Cseke et al. 2007) have shown promising results in animal studies. These and other vaccination strategies await further studies and trials in human subjects.

12.13 Clinicopathologic Capsule

hMPV causes acute respiratory infections, ranging from mild upper respiratory infections to severe bronchiolitis and pneumonia. Severe infections are more common in children younger than 2 years of age, the elderly, and the immunosuppressed. Diagnosis depends on identification of the virus in nasopharyngeal swabs or aspirates most commonly by RT-PCR or antigen detection methods. The pulmonary pathological changes of hMPV infection have not been extensively described but include acute and organizing diffuse alveolar damage. Treatment of hMPV is supportive and there are no specific preventive measures.

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