Review article
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Mycoplasma pneumoniae pneumonia in children

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Mycoplasma pneumoniae (MP), the smallest self-replicating biological system, is a common cause of upper and lower respiratory tract infections, leading to a wide range of pulmonary and extra-pulmonary manifestations. MP pneumonia has been reported in 10 to 40% of cases of community-acquired pneumonia and shows an even higher proportion during epidemics. MP infection is endemic in larger communities of the world with cyclic epidemics every 3 to 7 years. In Korea, 3 to 4-year cycles have been observed from the mid-1980s to present. Although a variety of serologic assays and polymerase chain reaction (PCR) techniques are available for the diagnosis of MP infections, early diagnosis of MP pneumonia is limited by the lack of immunoglobulin (Ig) M antibodies and variable PCR results in the early stages of the infection. Thus, short-term paired IgM serologic tests may be mandatory for an early and definitive diagnosis. MP infection is usually a mild and self-limiting disease without specific treatment, and if needed, macrolides are generally used as a first-choice drug for children. Recently, macrolide-resistant MP strains have been reported worldwide. However, there are few reports of apparent treatment failure, such as progression of pneumonia to acute respiratory distress syndrome despite macrolide treatment. The immunopathogenesis of MP pneumonia is believed to be a hyperimmune reaction of the host to the insults from MP infection, including cytokine overproduction and immune cell activation (T cells). In this context, immunomodulatory treatment (corticosteroids or/and intravenous Ig), in addition to antibiotic treatment, might be considered for patients with severe infection.

Key words: *Mycoplasma pneumoniae*, Pneumonia, Macrolides, Drug resistance, Child, Corticosteroids

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Introduction

Mycoplasma pneumoniae (MP) is a major cause of community-acquired pneumonia in children and young adults[1,2]. Although more than 200 mycoplasma species have been discovered in animals and humans to date, MP is the most recognized human pathogen among them. MP infection shows a variety of clinical manifestations, ranging from asymptomatic infection to fatal pneumonia or extrapulmonary diseases. MP pneumonia has been reported in 10 to 40% of community-acquired pneumonia cases, and children are the

most susceptible group to MP infection[1,2]. Since summer 2011, a new MP epidemic has been spreading throughout Korea. This epidemic presents some clinical and laboratory characteristics that seem to be different from those of previous epidemics, although the strain subtypes in this epidemic have not been identified yet. In this review, we briefly give an overview of the pathogenesis, epidemiology, clinical manifestations, diagnosis, and treatment of MP infection, including macrolide-resistant MP (MRMP).

Biological characteristics and immunopathogenesis

MP is an exceptionally small prokaryote, which, like viruses, can pass a filter paper. Because of the absence of a cell wall, this organism is insensitive to β-lactam antibiotics and is not stained by Gram staining. Also, MP has an extremely small genome, which makes it a fastidiously growing bacterium requiring the presence of a variety of substances, including nucleotides and sterols, for its replication both within the host and in *in vitro* culture systems[3]. MP is a mucosal extracellular pathogen – not an intracellular pathogen like viruses – and shows no cytopathic effects on other cell culture systems except to the respiratory ciliated epithelium[4]. It has been believed that multiplied MP agents spread to lower respiratory tract cells and induce pneumonia. In this context, the survival of MP initially depends on cytoadherence to the respiratory epithelium of the host. MP has an attachment tip in which a complex of adhesion and interactive adhesion-accessory proteins are localized. After adherence, MP may need to multiply in order to establish an infection, involving colonization and further inflammation of other tissues[5]. *In vitro* studies have shown that mycoplasma species preferentially attach to ciliated respiratory epithelial cells, and induce a cytopathic effect caused by hydrogen peroxide or other toxins (e.g., ADP-ribosylating and vacuolating cytotoxin), and by the gliding motility[6,7]. On the other hand, with the fastidiously growing nature of MP, the evidences of the MP agents in pathologic tissues are limited. MP are neither found beneath nor inside respiratory epithelial cells in animal models, and electronic microscopic examination of samples from patients with severe MP pneumonia, and polymerase chain reaction (PCR) assay of lung aspirate specimens from children with community-acquired pneumonia are also not effective for finding MP agents[8,9].

Since MP infection, similar to other infections, is controlled by the host's immune system, and the majority of MP-infected patients recover from the disease without pneumonia, it is possible that acute lung injury in affected patients is associated with the patient's immune response. In MP infection, the innate and adaptive immune system of the host work together against insults from the infection. The mediators (proteins) from the innate immune reaction may affect the adaptive immune reaction. Toll-like receptors (TLRs) and possibly intracellular sensors, in infected cells and macrophages, that recognize MP components induce anti-pathogenic proteins and other proteins, including pro-inflammatory cytokines[10,11]. These proteins may affect the cells of the adaptive immune system. Lipoproteins derived from mycoplasmas, such as macrophage-activating lipopeptide 2, have been reported to induce cytokines and chemokines from macrophages through TLRs[12,13]. These cytokines recruit immune cells, including T cells, leading to further production of cytokines, and may be involved in the inflammatory responses toward MP infection.

Many immunological studies have revealed that various cytokines, including interleukin (IL)-2, IL-8, and IL-18; other reactive substances; and immune cells, including antigen-presenting cells and T cells, are involved in the immune reaction to MP[14-16]. Since it is believed that major pro-inflammatory cytokines induced by MP infection are important mediators for lung defense and lung injury, cytokine imbalance may be responsible for lung injury in this infection.

T cells may have a crucial role in the acute lung injury induced by MP infection, as well as by other viral infections such as influenza virus infection. Previous reports on these infections showed that T cell deficiency mice or T cell depressed mice with immune suppressants had less severe pneumonia with prolonged survival time and little pathologic findings compared to control mice[17-19]. Furthermore, some clinical characteristics of MP pneumonia also help postulate the pathogenesis of lung injury due to MP. We previously found that the severity of pneumonia was correlated with lymphocyte counts at presentation, and early immunemodulators (corticosteroids) induced rapid recovery of severe pneumonic consolidations within several days[20,21].

Finally, it is unknown whether the whole MP agent itself or other substances (MP components or mediators from the host) induce immunological inflammation in lung lesions. For this issue, we introduce a new concept for the immunopathogenesis of acute lung injury in MP or influenza virus infections by using a hypothesis involving the 'protein homeostasis system' of the host[2,19]. Briefly, we postulated that the adaptive immune system is one among the protein homeostasis systems *in vivo*. B cells control proteins, except small proteins, through antibodies, and T cells control small proteins (peptides) through cytokine production or through their effect on cell-bound pathogenic proteins or through T cell receptors. During the incubation period of MP infection, substances including pathogenic proteins are produced in a focus (possibly a secondary immune organ near the primary infection sites). The substances spread and reach lung cells as main target cells, and various tissues for

extrapulmonary manifestations via systemic circulation. Immune cells start to control these substances, and clinical symptoms and signs begin to appear. The pathogenic proteins bind to lower respiratory tract cells of which receptors have affinity to them, and this process induces cell injury and/or production of other proteins through signaling pathways to the nucleus of affected cells. Immune cells are recruited to the lesions to control the action of the pathogenic proteins and proteins from injured cells. Initially, nonspecific T cells and nonspecific antibodies are involved in this reaction. During this process, hyper-activated immune cells (mainly T cells) produce inflammatory cytokines and counter-inflammatory cytokines, leading to a cytokine imbalance associated with further lung cell injury. After the emergence of specific T cell clones and specific antibodies that efficiently control the pathogenic proteins, tissue injury ceases and a repair reaction begins with the immune cells.

Epidemiology

MP infection is endemic in the larger communities of the world, but epidemics, lasting several months to years, periodically occur every 3 to 7 years. In Korea, 3 to 4-year cycles of MP pneumonia have been observed from the mid-1980s to present. Pneumonia cases peak mainly in the fall or winter seasons, and epidemics last approximately 12 to 18 months[22,23]. Occasionally, local outbreaks have been reported in close contact settings, such as schools, military barracks, and inpatient institutions.

The epidemiological and clinical characteristics of MP infection, such as the appearance of a cyclic epidemic and lymphopenia, are similar to that of other systemic viral infections, including measles and influenza[2]. The susceptible population to MP, especially the young age group, would increase in number during the 3 to 4 years of the inter-epidemic period, and this age group may serve as the reservoir of the epidemics. The susceptible group would move to younger generation and most of adult generation would acquire immunity to MP over time. Seroepidemiological studies on MP infection have proven this finding: the seropositivity of immunoglobulin (Ig) G antibodies against MP is progressively greater with increasing age[24], and persons >40 years old may have a seropositivity rate of near 100%. Although MP pneumonia is known to be predominant in school-aged children, in Korea, the 4 to 6 years age group was the most prevalent group, and the age of children among whom MP infection was prevalent appeared to become younger, with low frequencies of infection in the adult group in recent MP epidemics[22,23].

The exact infection rate in a population during an MP epidemic is unknown. However, serologic studies suggest that during an epidemic, a significant proportion of the susceptible population (>50%) may be infected, manifesting asymptomatic or mild phenotypes, although the proportion of MP pneumonia patients may be very low.

The subtypes of MP are believed to be different in each epidemic, like in seasonal (inter-pandemic) influenza, although few studies exist for genes other than P1 gene. In a previous report, one P1 subtype of MP was found to be predominant in an epidemic; however, another P1 subtype might be predominant in other epidemics[25]. Recently, MRMP strains have been identified in epidemics in Far East Asian countries, including Japan, China, Korea and other countries[26-29]. The strains were mutated mainly in nucleic sequences of 23S rRNA or ribosomal proteins. In Korea, an investigation group found that in the 2011 epidemic, more than 50% of the isolated MP strains were MRMP strains[30]. Although patients infected with MRMP were reported to have the prolonged fever duration, compared to the patients infected with macrolide-sensitive strains, few cases showed treatment failure with macrolide treatment[31,32]. Given that MP pneumonia is a host immune-mediated and self-limited disease, the clinical implications of alternative antibiotic treatments for patients with MRMP strains require further evaluation. In addition, Narita recently proposed an interesting postulation that MRMP strains may exhibit less efficient protein synthesis because of ribosomal mutations, and that the drug resistance of MP itself does not directly lead to clinical severity[33]. We found that in the 2011 epidemic, the positive rate of PCR was far less than, and the initial negative rate of IgM antibody at presentation was higher than that of the 2006 to 2007 epidemic (unpublished observation).

Clinical manifestations

The most common clinical manifestation of MP infection is pneumonia. Other respiratory symptoms such as pharyngitis, otitis media, bronchitis, sinusitis, croup and bronchiolitis are also observed. The incubation period of MP pneumonia is 1 to 3 weeks. MP pneumonia patients present with acute onset of fever, sore throat, malaise, and headache; however, coryza is not usual, like that in influenza. After 3 to 7 days onset of constitutional symptoms, cough and radiographic evidence of pneumonia appear. Fever ranging from 38℃ to 39.5℃ is commonly seen. The clinical symptoms and physical findings of suspected pneumonia are often poorly correlated with the radiographic finding of pneumonia (walking pneumonia). The clinical course in untreated patients is variable, but most symptoms are resolved within 2 to 4 weeks, even in antibiotic-nonresponsive, progressive pneumonia[20].

The radiographic findings of MP pneumonia are pleomorphic. Interstitial and bronchopneumonic patterns are common, and

segmental and/or lobar pneumonic patterns with pleural effusions are not rare. We previously found that older children (>6 years), who have a more mature immune system, had longer duration of fever, higher C-reactive protein, and more severe pulmonary lesions and lower leukocyte counts with lymphocyte differentials than the younger group (<5 years)[21].

MP infection has shown an association with asthma. The infection may precede the onset of asthma, exacerbate the asthma, or play a part in asthma chronicity in some children and adults[1,34]. Extrapulmonary involvement in MP infection has been identified in neurologic, dermatologic, hematologic and other immunologic disorders. Skin rash is the most frequently seen manifestation, and central nervous system complications, such as meningoencephalitis and Guillain-Barre syndrome, are rarely seen. MP is a major cause of childhood encephalitis. Immunopathogenetic mechanisms are known to be involved in the extra-pulmonary manifestations of MP[35].

Diagnosis

Although a variety of serologic assays and PCR techniques have been used for the diagnosis of MP infection, methods for the early diagnosis of MP pneumonia are limited because of the lack of IgM antibodies and the variable detection rate of PCR products in the early stages of the infection[1,2].

Serologic assays, including complement fixation assay, microparticle agglutination assay, enzyme-linked immunosorbent assay, and enzyme-linked immunoassay, need paired serum samples for a definitive diagnosis, showing seroconversion or a 4-fold increase in titer. The sensitivities of serologic assays for the detection of MP antibodies are known to vary[36,37]. We previously reported that more than 45% of patients with MP pneumonia were seroconverters whose IgM antibodies were negative in the early stage of MP infection[20,21]. Therefore, short-term paired IgM serologic tests may be mandatory for early and definitive diagnosis in patients with severe pneumonia[2,21].

Recently, PCR assay has been applied for the early detection of MP infection. PCR is an attractive alternative test to MP culture. Several gene targets have been used, including the P1 gene and the 16S rRNA gene[37]. The results from PCR studies have shown variable sensitivities and specificities between children and adult groups, when compared with serologic results[38,39]. PCR results can be affected by the materials obtained from different sites of the respiratory tract, by the stage of disease, and by diverse technical errors. In our studies, the detection rate of PCR tests in the 2006 to 2007 epidemic was 12 to 30%[21,40], but it was less than 5% in the 2011 epidemic. It is unknown whether MRMP strains are poorly colonized on the upper respiratory tract compared to other strains. In addition, MP can remain in the respiratory tract for a long time without symptoms, especially in younger children after primary infection[41]. Thus, PCR study alone is not sufficient for a definitive diagnosis of MP infection. Use of a combination of serologic assays and PCR may be an ideal method for the diagnosis of MP infection.

Treatment

MP infection is usually mild and self-limited, without a need for a specific treatment. Because MP has no cell wall, antibiotics such as macrolides, tetracyclines, and quinolones have been used for treating MP pneumonia. For children, only macrolides (erythromycin, clarithromycin, roxithromycin, and azithromycin) are used because of the potential side effects of alternative drugs (tetracycline and fluoroquinolones). Although earlier studies reported that antibiotic therapy for young adult patients induced more rapid resolution of fever and cough[42,43], this therapy could not prevent the progression to severe pneumonia in some patients, as well as the associated extrapulmonary diseases. Patients infected with MRMP strains have prolonged fever duration; however, in general, disease progression was not observed with macrolide treatment[31,32]. These findings suggest that in MP infection, the substances that induce the fever and the substances that induce the pneumonia may differ *in vivo*. Moreover, the effects of antibiotic treatment for MP pneumonia in children are still controversial[44].

Some investigators have reported that a change of antibiotics showed good outcome in MRMP-infected patients[45,46]. However, others have reported that patients properly treated with antibiotics showed progressive pneumonia[47,48]. In children and adults who were nonresponsive to antibiotics and showed progressive disease, including those with MRMP, many investigators have reported that additional corticosteroids are effective, especially in those with severe MP pneumonia[20,47-51]. In addition, experimental studies have also reported the beneficial effect of corticosteroids on MP infections[52,53]. We previously reported that the use of immune-modulators (prednisolone) for antibiotic-nonresponsive MP pneumonia patients was effective in improving clinical and radiographic findings[20,21]. In this 2011 epidemic, we used prednisolone (1 mg/kg) early, with a macrolide (chlarithromycin) or/and a non-macrolide antibiotic (amoxicillin/clavulanate or cefuroxime) for MP pneumonia patients who had persist fever for >48 hours after admission. The majority of the patients defervesced without disease progression within 24 to 48 hours, even in those who received only a non-macrolide antibiotic. The small group of patients who did not response to this

therapy received intravenous methylprednisone (10 mg/kg for 2 to 3 days, tapering within a week) or intravenous Ig (1 g/kg/day, 1 to 2 doses), and all patients improved clinically and radiographically within several days without side effects (unpublished observation). These findings may again verify the notion that the pathogenesis of pneumonia in MP infection is immune-mediated[2]. Nevertheless, further controlled clinical studies for corticosteroids and candidate antibiotics (quinolones and tetracyclines) for children with MRMP infection are needed.

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