

Original Article

Atypical Pathogens in Adult Patients Admitted with Community-Acquired Pneumonia in Korea

Seung-Joon Lee*, Myung-Goo Lee¹, Man-Jo Jeon¹, Ki-Suck Jung¹,
Hye-Kyeong Lee² and Toshio Kishimoto³

*Department of Internal Medicine, College of Medicine, Kangwon National University,
192-1 Hyoja 2-Dong, Chuncheon 200-701,*

¹*Department of Internal Medicine, College of Medicine, Hallym University,
153 Kyo-Dong, Chuncheon, Kangwon-Do 200-704,*

²*Division of Rickettsial and Zoonotic Diseases, Department of Microbiology,
National Institute of Health,*

5 Nokbeon-Dong, Eunpyeong -Gu, Seoul 122-701, Korea and

³*Department of Virology I, National Institute of Infectious Diseases,
Toyama 1-23-1, Shinjuku-ku, Tokyo 162-8640, Japan*

(Received July 22, 2002. Accepted October 21, 2002)

SUMMARY: This study examined the prevalence of atypical pathogens causing community-acquired pneumonia (CAP) in Korea. We collected sera and clinical data for a period of 1 year for the adult patients consecutively admitted to Chuncheon Sacred Heart Hospital with CAP. The diagnosis was made using serologic methods to detect antibodies for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* spp., *Chlamydia psittaci*, and *Coxiella burnetii*. Among 81 recruited patients, *C. pneumoniae* ($n = 10$, 12.3%) was the leading cause of illness, followed by *M. pneumoniae* ($n = 7$, 8.6%). One case of *C. burnetii* pneumonia was detected, but there were no cases of *Legionella* spp. or *C. psittaci*. Three cases of *C. pneumoniae* pneumonia were co-infected with either *M. pneumoniae* or *C. burnetii*. There was no significant difference between atypical pneumonia and non-diagnosed pneumonia in terms of clinical manifestations. In conclusion, of the atypical pathogens causing CAP, *C. pneumoniae* and *M. pneumoniae* appear to be the important etiologic pathogens in Korea.

INTRODUCTION

The term 'atypical pathogen' refers to a variety of organisms, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* spp., *Chlamydia psittaci*, and *Coxiella burnetii*, that can cause community-acquired pneumonia (CAP)(1). Recent studies showed that atypical pathogens cause CAP more frequently than was previously thought (2,3). In a large-scale study performed in Ohio, USA, these agents were found to cause up to 60% of etiology-proven CAP cases (2). In addition, Liberman et al. (3) reported these organisms to be part of a mixed infection, usually with bacterial pathogens, in about 40% of CAP.

Few studies have described the etiologic role of atypical pathogens causing CAP in Korea (4-6). Therefore, we carried out a prospective study to examine the etiologic role of atypical agents in adult patients admitted to our regional hospital over a 1-year period.

MATERIALS AND METHODS

Patients: Between September 1, 1999, and August 31, 2000, all cases of CAP in adults aged 16 years and older requiring admission to Chuncheon Sacred Heart Hospital, Korea, which holds 500 beds, were recruited for inclusion in the study. CAP

was defined as the presence of at least two symptoms of lower respiratory tract infection, accompanied by acute radiologic infiltration or auscultatory findings suggestive of infection (7). The following criteria were used to exclude patients: (i) discharged from hospital within the 10 days preceding presentation; (ii) immunosuppressed state, such as neutropenia ($<3.0 \times 10^9/L$), post-splenectomy state, use of systemic steroid (prednisone=10 mg/day or equivalent for more than 30 days), use of myelosuppressive drugs within 90 days of presentation, solid organ transplantation, or positive blood test for HIV (8).

Serum samples: A serum sample was obtained within 24 h of admission for serological testing. A second (convalescent) serum sample was obtained at the follow-up appointment. The mean interval between the two samples was 25.5 days (range 14 - 45 days). After admission, serum was separated from blood samples immediately and stored at -70°C until tested.

Laboratory investigations and diagnostic criteria used to determine etiology: Serological tests were done for five pathogens: *M. pneumoniae*, *C. pneumoniae*, *Legionella* spp., *C. psittaci*, and *C. burnetii*.

The antibody titer of *M. pneumoniae* was determined by microparticle agglutination using a commercial Serodia-Myco II kit (Fujirebio, Tokyo). Using this method, *M. pneumoniae* infection was diagnosed if there was a fourfold increase in antibodies between the paired serum samples or an antibody titer of at least 1:160 in at least one serum sample (3).

C. pneumoniae infection was determined by ELISA using a commercial Hitazyme CPN kit (Hitachi, Tokyo). Using this method, serum antibody titers of IgG/A/M were measured. A

*Corresponding author: Mailing address: Department of Internal Medicine, Kangwon National University Hospital, 17-1 Hyoja 3-Dong, Chuncheon-Si, Kangwon-Do 200-947, Korea. Tel: +82-33-258-2377, Fax: +82-33-258-2455, E-mail: medfman@knuh.or.kr

fourfold or greater increase in the titer for any immunoglobulin class between paired serum samples, or a positive IgM (index value 1.6 or greater), was considered *C. pneumoniae* pneumonia (9).

Antibodies to 12 different serogroups of *Legionella* spp. were detected by indirect immunofluorescence antibody assay, which was performed at the National Institute of Health in Korea. Twelve antigens of *Legionella* spp. (*L. pneumophila* serogroups 1 to 6, *L. bozemanii*, *L. dumoffii*, *L. gormanii*, *L. micdadei*, *L. longbeachae*, *L. feelei*) were used. The diagnostic criteria were a fourfold or greater increase of antibody titers or a single titer equal to or greater than 1:128 (3).

Antibody titers of both *C. psittaci* and *C. burnetii* were detected using antigens supplied by the National Institute of Infectious Diseases, Tokyo, in a micro-immunofluorescence test. The diagnostic criterion was a fourfold or greater increase in the titer for any immunoglobulin class between paired sera.

Data analysis: SAS Windows version 6.12 was used. The chi-square or Fisher's exact test was used to determine the significance of differences in proportions between groups. Student's *t* test was used to compare continuous variables. A *P* value of less than 0.05 (two-tailed test) was considered to indicate statistical significance.

RESULTS

Patient characteristics: Eighty-one patients were included in the study. The mean age (\pm SD) of the patients was 66.3 \pm 14.5 years (range: 17 to 92 years). There were 58 patients aged 60 or older (71.6%), and only one patient was under 30. Fifty-two (64.2%) patients were male and 29 (35.8%) were female.

Sixty-five patients (80.0%) had underlying diseases in addition to pneumonia. The major underlying diseases were pulmonary diseases (chronic obstructive pulmonary disease, asthma, or tuberculous-destroyed lung: 48.1%), previous cerebrovascular diseases (17.3%), diabetes mellitus (11.1%), chronic heart diseases (8.6%), and chronic liver diseases (7.4%).

Etiologic pathogens of pneumonia: Paired sera were collected from 25 (30.9%) of the 81 patients. Atypical pathogens were considered to have caused CAP in 15 (18.5%) of the 81 patients (Table 1). Ten cases (12.3%) were caused by *C. pneumoniae*, seven cases (8.6%) by *M. pneumoniae*, and one case by *C. burnetii*. Two cases were co-infected with *M. pneumoniae* and *C. pneumoniae*, and one case with *C. pneumoniae* and *C. burnetii*. There were no pneumonia cases caused by *Legionella* spp. or *C. psittaci*.

Comparison of pneumonia caused by atypical and unknown pathogens: The characteristics of pneumonia,

Table 1. Etiologic diagnosis of atypical pathogens in 81 cases of community-acquired pneumonia

Organism	<i>n</i>	%
<i>Chlamydia pneumoniae</i> ¹⁾	10	12.3
<i>Mycoplasma pneumoniae</i>	7	8.6
<i>Coxiella burnetii</i>	1	1.2
<i>Legionella</i> spp.	0	0
<i>Chlamydia psittaci</i>	0	0
Undiagnosed	66	81.5

¹⁾ Two cases co-infected with *C. pneumoniae* and *M. pneumoniae*, one case co-infected with *C. pneumoniae* and *C. burnetii*.

Table 2. Comparison of the clinical characteristics of atypical pneumonia and unspecified pneumonia

	Atypical pneumonia ¹⁾ (<i>n</i> = 15)	Unspecified pneumonia ²⁾ (<i>n</i> = 66)	<i>P</i> value
Age, year (mean \pm SD)	62.8 \pm 18.9	67.1 \pm 13.4	0.31 ³⁾
Days from onset to admission (median, range)	7 (1-30)	5 (1-30)	0.27 ³⁾
Fine's score ⁶⁾	92.5 \pm 41.7	103.8 \pm 41.3	0.36 ³⁾
Admitted to intensive care unit	9 (60.0%)	43 (65.2%)	0.94 ⁴⁾
Mortality	1 (6.7%)	7 (10.6%)	1.00 ⁵⁾

¹⁾ Pneumonia caused by *M. pneumoniae*, *C. pneumoniae*, *Legionella* spp., *C. psittaci*, or *C. burnetii*.

²⁾ Pneumonia of unspecified etiology in this study.

³⁾ Student's *t* test.

⁴⁾ Chi-square test.

⁵⁾ Fisher's exact test.

⁶⁾ Score for describing the severity of pneumonia in the PORT study (ref. 10).

including time of onset, severity, and mortality, were compared between pneumonia caused by atypical pathogens and pneumonia of unspecified etiology (Table 2). We could not find any statistical differences between the two groups.

DISCUSSION

This study detected atypical pathogens in 18.5% of patients requiring admission to hospital for CAP in Korea. There have been few reports on the epidemiology of atypical pathogens in Korea (4-6). A recent report (total number of patients, *n* = 157) showed that *C. pneumoniae* caused CAP in 14.0% of patients and *M. pneumoniae* in 12.1% (11). However, it was impossible to eliminate selection bias in that study, since it involved patients seen at nine hospitals over a period of 3 years. In contrast, the patients in our study were seen at one hospital, and all cases of CAP requiring admission to the hospital were recruited by experienced doctors.

In previous studies, 10 to 60% of CAP cases were reported to be caused by atypical pathogens. Of these pathogens, *C. pneumoniae* was the leading cause of atypical pneumonia in most studies. Woodhead (12) reviewed 26 prospective studies from 10 European countries (total number of patients, *n* = 5,961), and found that *C. pneumoniae* was the most frequent (in approximately 17% of all cases) causative pathogen of CAP, second only to *Streptococcus pneumoniae*. Steinhoff et al. (13) reported that 11.4% of CAP cases were caused by *C. pneumoniae*. One Korean study that focused only on *C. pneumoniae* found that it was the causative pathogen in 18% of CAP cases (14). Our result (12.0%) is similar to the results of these studies.

In our study, *Legionella* spp. (0 cases), *C. psittaci* (0 cases), and *C. burnetii* (1 case) played a very small role in CAP. There have been no reports of *C. psittaci* or *C. burnetii* pneumonia in the Korean literature. Therefore, we postulate that these two pathogens rarely cause CAP in Korea. In 2001, Song et al. (6), using a urine *Legionella* antigen test in 54 cases recruited in Korea, reported no *Legionella* cases among these CAP patients. In another Korean study (4), using sputum PCR and serum indirect fluorescence antibody assay, 2.3% of CAP cases were found to be caused by *Legionella* spp. Therefore, *Legionella* spp. seem to be rare pathogens in Korea. It is well known that the etiologic pathogens of CAP differ considerably according to geographic location (15).

Many reports have shown that pneumonia caused by

atypical pathogens cannot be differentiated from usual bacterial pneumonia, such as pneumococcal pneumonia, in terms of clinical characteristics (16,17), and we found no clinical differences between pneumonia caused by atypical pathogens and pneumonia of unspecified etiology, possibly typical bacterial pneumonia, in this study.

This study has some limitations. First, serum pairing was performed in 31% of the patients. Therefore, it is possible that atypical pathogens were underestimated. However, even in a large-scale study such as that performed in Ohio, USA ($n = 2,774$), paired serum sampling was performed in only 44% of the cases (2). Second, because our hospital is located in a rural area in a developing country, more than 70% of our patients were over 60 years old. Most of the residents in rural Korea are farmers, and most are fairly old. Future studies should obtain more complete serum pairing and include younger patients.

In conclusion, atypical pathogens play some role in CAP in Korea, as in other countries. Among these pathogens, *C. pneumoniae* and *M. pneumoniae* are the most common.

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