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

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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 Chunchon 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 Chunchon 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 serologic 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-Mycobacterium (Mycoplasma) 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
fourfold or greater increase in the titer for any immunoglobulin class, or a positive IgM titer for any immunoglobulin class between paired sera, or a positive IgM 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 criteria were 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 (±SD) of the patients was 66.3 ± 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-destructed 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 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, 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.

REFERENCES