Chlamydophila (Chlamydia) pneumoniae as a Cause of Community-Acquired Pneumonia in Thailand†

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Abstract

Chlamydophila (Chlamydia) pneumoniae infection is increasingly reported worldwide nowadays. We studied twelve Thai adults presenting with the clinical symptoms and signs of community-acquired pneumonia (CAP) due to *C. pneumoniae* (TWAR) at Pramongkutklao Hospital in Bangkok, Thailand. Their mean age was 38 (range 21-73) years. Six patients lived in Bangkok. Seven patients had comorbid diseases (four cases with allergic asthma, one each with diabetes mellitus, chronic obstructive pulmonary disease and coronary artery disease). *C. pneumoniae* pneumonia presented as subacute pneumonia in 6 patients. The clinical manifestations were mild (IDSA risk class I-III) except in 4 patients who had preexisting allergic asthma, COPD and coronary heart disease. The diagnosis of *C. pneumoniae* pneumonia was based on microimmunofluorescence (MIF) antibody technique (IgM titer $\geq$ 1:16, IgG $\geq$ 1:512, IgA $\geq$ 1:256 with or without fourfold rises). The clinical conditions were consistent with the primary infection (IgM titer of 1:16 or higher) in 6 patients and reinfection (IgG titer of 1:512, IgA titer of 1:256 or higher without rises of IgM titer) in the other 6 patients. Minimal bilateral pleural effusion was detected in only one patient. Coinfection was demonstrated in 2 patients (one each with *S. pneumoniae* and *K. pneumoniae*). All patients markedly improved after a 2-week course of macrolide, doxycycline or newest fluoroquinolone therapy. All patients had done well at one year of follow-up. *C. pneumoniae* infection has been recently recognized and a high seroprevalence (37%) in Thai school children and 100 per cent in young male Thai military conscripts has been reported. This report suggests that this infection, *C. pneumoniae,* may be a common pathogen of CAP in Thailand.

Key word : *Chlamydophila Pneumoniae*, *Chlamydia Pneumoniae*, Chlamydophila, Chlamydia, TWAR, Community-Acquired Pneumonia, CAP, Atypical Pneumonia, Atypical Pathogen, Respiratory Tract Infection, Sinusitis, Microimmunofluorescence, MIF, Fluoroquinolone, Thailand.

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Chlamydophila (Chlamydia) pneumoniae (TWAR)[1] is an obligatory intracellular pathogen. Unlike *C. psittaci*, it usually causes human infections by inhalation not association with an avian contact[2,3]. At present, it is believed to be the most common cause of human *chlamydial* infections and can cause a variety of clinical manifestations[4-6]: rhinosinusitis, pharyngolaryngitis, tracheobronchitis, and mild or life-threatening pneumonia[7]. Recently, there have also been increasing reports, suggesting a special association of this infection with bronchial asthma[8-10], ischemic stroke[11] and coronary heart disease (CHD)[12-15]. Worldwide seroepidemiological studies revealed that approximately 50 percent of adults had antibodies to this pathogen and had a seroconversion of 6-9 percent annually[3,5]. It contributes approximately 10 percent of community-acquired pneumonia (CAP) in adult patients all over the world[4]. Nunthapisud et al, in 1992, found a seroprevalence of 37 percent in Thai school children[16] and 100 percent in Thai military recruits (Nunthapisud et al, unpublished) in 1999. To our knowledge, this is the first report of *C. pneumoniae* pneumonia in Thailand.

REPORT CASES

Case 1.

A 21-year-old woman presented with a fever, nonproductive cough, left-sided pleuritic chest pain and shortness of breath for one week. Two weeks previously, she had an URTI and her symptoms worsened. On examination, she had a temperature of 39°C, a respiratory rate of 20/min, a pulse rate of 98 beats/min, and a BP of 120/80 mmHg. ENT examination showed a mild pharyngitis without postnasal drip. Chest auscultation showed fine crackles at the left lower lung areas. Laboratory studies revealed a hemoglobin of 13 g/dL, a WBC count of 9.2×10^9/L (78% neutrophils). Chest radiographs showed a patchy infiltrate in the left lower lung (retrocardiac) region and X-ray of paranasal sinuses revealed a haziness in both maxillary sinuses. Sputum culture yielded normal flora. MIF antibody tests for *C. pneumoniae* revealed an IgM titer of 1:64 and an IgG titer of more than 1:512. The patient's condition markedly improved after a 2-week course of erythromycin therapy without any complications.

Case 3.

A 27-year-old healthy man presented with a fever, non productive cough, shortness of breath and malaise for 10 days. A few days later, his clinical condition worsened. He developed a progressive dyspnea. On the day of admission, his temperature was 39°C, respiratory rate 24/min, pulse rate 108/min, and BP 140/90. ENT and skin examination were normal. Chest auscultation revealed bronchial breath sounds and bilateral lower lung crackles. Laboratory studies showed a WBC count of 13.6×10^9 /L (76% neutrophils). A chest radiograph revealed bilateral airspace pneumonia without pleural effusions. Arterial blood gas analysis revealed a pH of 7.32, a $PaCO_2$ of 30 mmHg and a PaO_2 of 72 mmHg. Empirical therapy with cefuroxime and doxycycline were started. His condition markedly improved after a 2-week course of doxycycline. Sputum and nasopharyngeal swab culture were negative. Serologic tests for *Rickettsia, M. pneumoniae, Legionella* species and respiratory viruses were all negative but those for *C. pneumoniae* were positive.

Case 10.

A 52-year-old woman, with a history of diabetes mellitus, hypertension and left-sided hemiparesis for 5 years, had an URTI two weeks previously. One week later, she developed a fever, dry cough and shortness of breath. On examination, she had a temperature of 38.4°C, a respiratory rate of 22/min, a pulse rate of 110 beats/min and a BP of 170/100 mmHg. ENT examination showed only a mild pharyngitis. Chest auscultation revealed generalized rhonchi. Laboratory studies revealed a hemoglobin of 14 g/dL, a WBC count of 9.7×10^9/L (63% neutrophils). A chest radiograph showed bilateral interstitial infiltrates with lower lobe predominance. The paranasal sinus films were normal. The sputum examination and culture were negative. MIF antibody tests for *C. pneumoniae* showed a fourfold rise of IgG alone. Her clinical condition markedly improved after a 2-week course of clarithromycin.

Case 11.

A 60-year-old man, with underlying COPD, presented with a fever, productive cough with abundant brownish sputum, and shortness of breath for 3 days. A few hours prior to admission, his clinical condition worsened. He developed

progressive dyspnea with impending respiratory failure. On the day of admission, his temperature was 38.6°C, respiratory rate 28/min, pulse rate 118/min, and BP 150/90. He was in respiratory distress with use of accessory respiratory muscles. ENT and skin examination were normal. Chest auscultation revealed generalized wheezing and rhonchi on bilateral lungs. Laboratory studies showed a WBC count of 16.8×10^9/L (91% neutrophils). A chest radiograph revealed bilateral airspace pneumonia without pleural effusion. Arterial blood gas analysis revealed a pH of 7.26, a $PaCO_2$ of 44 mmHg and a PaO_2 of 56 mmHg. Conventional therapy and ventilatory support, as there was acute exacerbation of COPD, were given. Empirical therapy with ceftriaxone and clarithromycin were started. His blood cultures yielded no growth and sputum culture grew *K. pneumoniae*. Serologic tests for *Rickettsia, M. pneumoniae, Legionella* species and respiratory viruses were all negative but those for *C. pneumoniae* were positive. His condition markedly improved and the ventilator was subsequently withdrawn after a 3-week course of supportive treatment for acute exacerbation of COPD.

Case 12.

A 73-year-old woman with preexisting coronary heart disease presented with a fever, nonproductive cough, progressive dyspnea on exertion and paroxysmal nocturnal dyspnea (PND). Two weeks previously, she was admitted to a general hospital near her home for investigation and treatment. Her condition worsened. On examination, she had a temperature of 37°C, a respiratory rate of 22/min, a pulse rate of 106/min and a BP of 140/90. The jugular venous pressure (JVP) was elevated. Chest auscultation revealed generalized fine crackles, rhonchi and wheezes in all lobes. Laboratory studies showed a hemoglobin of 12.8 g/dL, a WBC count of 10.8×10^9/L (82% neutrophils). Chest radiographs demonstrated bilateral interstitial infiltrates (lower lung predominance), cardiomegaly and minimal pleural effusions. The first impression was CHF, aggravated by CAP. Serologic tests for *C. pneumoniae* were positive with an IgG level of 1:16 with a fourfold rising. The patient rapidly improved after doxycycline and conventional treatment for CHF. The co-morbid diseases of all patients are summarized in Table 1, clinical features in Table 2, and laboratory data in Table 3.

DISCUSSION

Chlamydophila (Chlamydia) pneumoniae is believed to be transmitted by respiratory tract secretions and causes human infections of many different patterns. The clinical manifestations range from asymptomatic or mild upper respiratory tract infection (URTI) to life-threatening pneumonia. There is no pathognomonic clinical and radiographic patterns that could help in differentiation of *C. pneumoniae* pneumonia from other causes. Some patients may develop characteristic biphasic illnesses, starting with the initial symptoms of URTI (pharyngitis, rhinosinusitis and hoarseness) and followed by symptoms of lower respiratory tract infection (LRTI) in 1-4 weeks[4]. Recently, there have been several reports, demonstrating the association of this persistent infection with bronchial asthma[8-10], ischemic stroke[11] and atherosclerotic heart diseases[12-15]. Currently, many more investigations are being conducted to elucidate the role of *C. pneumoniae* among these entities.

Several seroepidemiological studies have shown that *C. pneumoniae* antibodies have been found consistently more often in men than in women[3]. There has not been an association of this infection with smoking. In our report, the mean age of the patients was 38 (range 21-73) years and eight patients were younger than 40. There was also no sex preponderance. Eight patients had co-morbid diseases: allergic rhinitis and asthma (4 patients), diabetes mellitus (1), COPD (1), and CHD (1) (Table 1).

There were no specific clinical features associated with *C. pneumoniae* pneumonia. Six patients had subacute onset of mild pneumonia with previous or simultaneous URTI (one each for

Table 1. Co-morbid diseases in 7 out of 12 patients with *C. pneumoniae* pneumonia.

Co-morbid diseases	No. of patients	%
Allergic asthma	4	33
Chronic obstructive pulmonary disease	1	8
Diabetes mellitus	1	8
Coronary heart disease	1	8

pharyngitis and rhinitis and four for sinusitis). The average interval from the onset of URTI symptoms to the presentation was 7 (range 4-14) days. The most common symptoms and signs of our patients were cough, shortness of breath, fever, sore throat, chest pain, malaise, headache, and diarrhea respectively (Table 2). It tended to be mild (IDSA risk class I-III) in young patients and more severe (IDSA risk class IV-V) in older ones, including two patients with preexisting COPD and heart disease who needed hospitalization.

Table 2. The clinical features of 12 patients with *C. pneumoniae* pneumonia.

Symptoms	No. of patients	%
Cough	12	100
productive	4	33
non productive	8	67
Shortness of breath	10	83
Fever	8	67
Sore throat	6	50
Chest pain	5	42
Malaise	5	42
Headache	4	33
Hoarseness	2	17
Diarrhea	1	8
Signs		
Fever (temperature of $\geq$ 38 °C)	7	58
Respiratory rate $\geq$ 30/min	3	25
Pulse $\geq$ 125/min	3	25
Wheeze	5	42
Pulmonary crackles	5	42
Pulmonary rhonchi	5	42
Laboratory studies		
Normal WBC (WBC = 4.0-11.0x10^9/L)	7	58

Chest auscultation revealed rhonchi and crackles in all but two patients. Like previous reports of primary infection pneumonia in young adults and reinfection pneumonia in elderly patients, we found 5 young patients, consistent with primary infection and 5 older ones with reinfection. This infection was thought to precipitate CHF and exacerbate acute respiratory symptoms in elderly patients with ischemic heart disease and COPD respectively. Fortunately, both patients had a good recovery after an appropriate antibiotic and conventional treatment for CHF and COPD.

Like other atypical pneumonia, WBC counts remained in the normal range (4.0-11.0x 10^9 /L) in 7 patients and was slightly elevated in the remaining including two patients with coinfection (one each with *S. pneumoniae* and *K. pneumoniae*). Most patients produced only scanty mucoid sputa and made it quite difficult to obtain specimens for identification of responsible organisms

Chest radiographs in *C. pneumoniae* pneumonia ranged from unilateral subsegmental infiltrates to severe diffuse bilateral airspace disease[17]. We found a focal segmental infiltrate in six patients, multiple segmental infiltrates in two patients, combination of airspace and interstitial patterns in two patients, and one each for interstitial infiltrates and lung consolidation. It tended to involve the lower lobe of both lungs. Bilateral minimal pleural fluid was found in only one patient with preexisting coronary heart disease. However, this could represent concomitant CHF in this patient.

All patients had a positive serological response by the MIF test. Six patients had positive IgM antibodies with a titer of 1:16 or higher together with IgG titer of 1:512 or more in the acute phase sera. In six patients who lacked IgM response, the diagnosis of reinfection was made by the clinical pictures and demonstration of a fourfold increase of the IgG titer (Table 3). Our positive serological tests had to have reproducible results before the final conclusion was made.

Generally, the organism responded well to erythromycin, clarithromycin, azithromycin, tetracycline, doxycycline and the newest fluoroquinolones (levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, gatifloxacin, moxifloxacin)[18-20]. It has had a tendency to recur and cause persistent infection[21]. Nowadays, the optimum dose and duration of therapy are uncertain. However, the recommended treatment for acute *C. pneumoniae* pneumonia to prevent persistent infections includes a prolonged course (at least 2 or preferably 3 weeks) of doxycycline, erythromycin (2 g/d), newest fluoroquinolones[5] or azithromycin (1.5 g over 5 days). All our patients improved rapidly after a 2-week course of macrolide, doxycycline, or the newest fluoroquinolones with no evidence of recurrence after one year follow-up.

In summary, we studied twelve patients with *C. pneumoniae* pneumonia. Physicians should consider and search for this infection in patients

Table 3. Characteristics and laboratory data of twelve patients with *C. pneumoniae* pneumonia.

Patient No.	Age/Sex	Co-morbid diseases	Presence of URTI	*C.pneumoniae* titer (Acute/Convalescent)* IgM	IgG	IgA	Sputum Culture (Bacteria)	Chest Radiographic pattern	IDSA** risk class
1	21/F	-	+	64/NA	1024/NA	NA	Negative	focal segmental	II
2	23/F	-	+	8/8	8/512	NA	Negative	bilateral segmental	II
3	27/M	-	+	neg/NA	2048/NA	NA	Negative	bilateral airspace	IV
4	24/M	PAR, asthma	+	neg/64	1024/1024	32/256	Negative	focal segmental	II
5	29/F	PAR, asthma	-	64/neg	512/2048	32/256	Negative	focal segmental	II
6	30/M	PAR, asthma	+	64/32	512/1024	256/256	*S. pneumoniae*	focal segmental	II
7	34/F	PAR, asthma	-	512/128	1024/2048	128/128	Negative	consolidation	III
8	36/M	-	+	neg/NA	256/NA	256/NA	Negative	focal segmental	II
9	44/M	-	+	8/8	8/256	NA	Normal flora	focal segmental	II
10	52/F	DM	+	neg/8	8/512	NA	Negative	diffuse interstitial	IV
11	60/M	COPD	-	8/8	16/1024	NA	*K. pneumoniae*	diffuse airspace	V
12	73/F	CHD	+	neg/8	8/512	NA	Negative	diffuse interstitial, bilateral pleural effusion	V

* microimmunofluorescence (MIF); URTI = upper respiratory tract infection; neg = negative; NA = not applicable; PAR = perennial allergic rhinitis; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CHD = coronary heart disease

** The Infectious Disease Society of America (IDSA) Scoring System[19].

with atypical pneumonia and no definite etiologic organisms, particularly in elderly patients with comorbid diseases.

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การศึกษาลักษณะทางคลินิกในผู้ป่วยปอดอักเสบจากเชื้อ *Chlamydophila (Chlamydia) pneumoniae* (TWAR)†

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คณะผู้รายงานได้ทำการศึกษาลักษณะทางคลินิกของผู้ป่วยปอดอักเสบที่เกิดจากการติดเชื้อ *Chlamydophila (Chlamydia) pneumoniae* (TWAR) ในผู้ป่วยผู้ใหญ่ที่เข้ามารับการตรวจรักษาที่โรงพยาบาลพระมงกุฎเกล้าจำนวน 12 ราย อายุเฉลี่ย 38 ปี (ช่วงอายุ 21–73 ปี) ผู้ป่วย 6 รายมีภูมิลำเนาอยู่ในกรุงเทพมหานคร ผู้ป่วย 7 รายมีโรคเรื้อรังได้แก่ โรคหอบหืด และภูมิแพ้ (4 ราย), โรคเบาหวาน (1 ราย), โรคหลอดลมอักเสบอุดกั้นเรื้อรัง (1 ราย), และโรคหลอดเลือดหัวใจตีบ (1 ราย) ภาวะปอดอักเสบเป็นชนิดกึ่งเฉียบพลัน 6 ราย ส่วนใหญ่มีอาการทางคลินิกไม่รุนแรง (IDSA risk class I–III) มีเพียง 4 รายที่มีอาการรุนแรง (IDSA risk class IV–V) เนื่องจากมีโรคเรื้อรังร่วมด้วย การวินิจฉัยภาวะนี้ใช้การตรวจเลือดด้วยวิธีมาตรฐาน microimmunofluorescence (MIF) โดยใช้เกณฑ์การวินิจฉัยเมื่อระดับแอนติบอดีย์ต่อเชื้อ *C. pneumoniae* ชนิด IgM ≥ 1: 16 และหรือ IgG ≥ 1 : 512, IgA ≥ 1 : 256 หรือผลการตรวจเลือดซ้ำระยะเวลา 2–3 เดือนต่อมาพบระดับแอนติบอดีย์เพิ่มขึ้น 4 เท่าและมากกว่า ผู้ป่วย 6 รายมีลักษณะทางคลินิกเข้าได้กับการติดเชื้อปฐมภูมิ (IgM ≥ 1 : 16) และผู้ป่วย 6 รายมีลักษณะเข้าได้กับการติดเชื้อซ้ำ (IgG ≥ 1 : 512 หรือ IgA ≥ 1 : 256 หรือผลการตรวจเลือดซ้ำพบระดับแอนติบอดีย์เพิ่มขึ้นเกิน 4 เท่าโดยไม่พบระดับแอนติบอดีย์ชนิด IgM) พบน้ำในช่องเยื่อหุ้มปอดเล็กน้อยในผู้ป่วย 1 ราย และพบการติดเชื้อชนิดอื่นร่วมด้วย 2 ราย ได้แก่เชื้อ *S. pneumoniae* และ *K. pneumoniae* ผู้ป่วยทุกรายหายเป็นปกติหลังได้รับการรักษาด้วยยาปฏิชีวนะ macrolide, doxycycline หรือ fluoroquinolones รุ่นใหม่ เป็นระยะเวลาอย่างน้อย 2 สัปดาห์ ไม่พบโรคแทรกซ้อนหรือเกิดการกลับเป็นซ้ำในระยะเวลา 1 ปีต่อมา ได้เคยมีรายงานการศึกษาทางด้านระบาดวิทยาพบความชุกของการติดเชื้อชนิดนี้ในเด็กไทย 37% ในปี 2535 และ 100% ในกลุ่มผู้ป่วยทหารเกณฑ์ในปี 2542 รายงานนี้เป็นรายงานลักษณะทางคลินิกของผู้ป่วยผู้ใหญ่ที่ป่วยด้วยอาการปอดอักเสบที่เกิดจากการติดเชื้อ *C. pneumoniae* รายงานแรกของประเทศไทย

คำสำคัญ : แคลมมิโดฟิลล่า นิวโมนิอิ, แคลมมิเดีย นิวโมนิอิ, ทวาร์, ปอดอักเสบ, ภาวะติดเชื้อของระบบทางเดินหายใจส่วนล่าง, ภาวะติดเชื้อของระบบทางเดินหายใจส่วนบน, โพรงจมูกอักเสบ, ไมโครอิมมิวโนฟลูออเรสเซนท์, ฟลูออโรควินโนโรน, ประเทศไทย

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