□ CASE REPORT □

Recurrent Pneumonia due to Persistent *Chlamydia Pneumoniae* Infection

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Abstract

Two cases of recurrent pneumonia due to *Chlamydia pneumoniae* are described. *C. pneumoniae* was continuously detected from the nasopharynx in both patients by the polymerase chain reaction and/or culture even with appropriate antibiotic therapy during the first episode. After eradication of *C. pneumoniae* with long-term macrolide therapy, the respiratory symptoms of both patients completely disappeared and no relapse was observed. These data indicate that new treatment strategies may be necessary to eradicate the organism in patients prone to persistent infection.
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Key words: macrolide, long-term therapy, eradication, cell culture, polymerase chain reaction

Introduction

Chlamydia pneumoniae is now known to play a major role in a variety of respiratory disorders (1). *C. pneumoniae* has been demonstrated to be a causative agent of pneumonia, bronchitis, pharyngitis and sinusitis. Most studies, including those in Japan, have shown that *C. pneumoniae* is the third or fourth most common cause of community-acquired pneumonia (1, 2). Infection with *C. pneumoniae* usually is mild, although patients with underlying medical conditions can become quite ill. There have been some reports of persistent respiratory infection with *C. pneumoniae*, the symptoms of which were often recurrent or persistent (3–5). Here, we report two cases of recurrent *C. pneumoniae* pneumonia even with appropriate antibiotic therapy.

Case Report

Case 1

A 73-year-old man visited our hospital on May 9, 2000, complaining of a continuous cough, sputum production, wheezing and shortness of breath on exertion for one week. He was admitted on the same day because a chest radiograph revealed an infiltrative shadow in the right lower and left upper lung fields (Figs. 1 and 2). On admission, his temperature was 37.3°C, pulse rate was 82 beats/min and blood pressure was 142/82 mmHg. The laboratory data revealed mild elevation of the white blood cell (WBC) count (10,400/mm^3) and C-reactive protein (5.9 mg/dl, CRP). We suspected atypical pneumonia because he had a continuous and obstinate cough. He had no prulent sputum production and had not undergone a physical examination of the chest. WBC count revealed a mild elevation (6). He was treated with minocycline (200 mg/day) for two weeks and both his symptoms, except for the cough, and chest radiograph improved. This case was diagnosed as a case of *C. pneumoniae* pneumonia because seroconversion of *C. pneumoniae*-specific antibody measured by the microimmunofluorescene (MIF) test was observed among paired serum samples and the gene of *C. pneumoniae* was detected from a nasopharyngeal swab specimen by the polymerase chain reaction (PCR) (Table 1). After the treatment, his PCR was still positive and a mild cough continued for long period.

He returned to our hospital on September 20, 2000, complaining of an increasing cough for one week. A chest radiograh revealed an infiltrative shadow in the right lower lung field at the same site observed during the first episode. He was treated with clarithromycin 400 mg/day for three weeks and both his symptom and chest radiograph improved. However, his PCR for *C. pneumoniae* was still positive (Table 1).

By February 11, 2001, he was exhibiting a loss of appetite and a severe night cough, and he visited our hospital on February 13, 2001. A chest radiograph disclosed an infiltrative shadow in the same lung field observed during both the first and second episodes. He was treated with sparfloxacin (400 mg/day) for ten days followed by azithromycin (500 mg/day) for three

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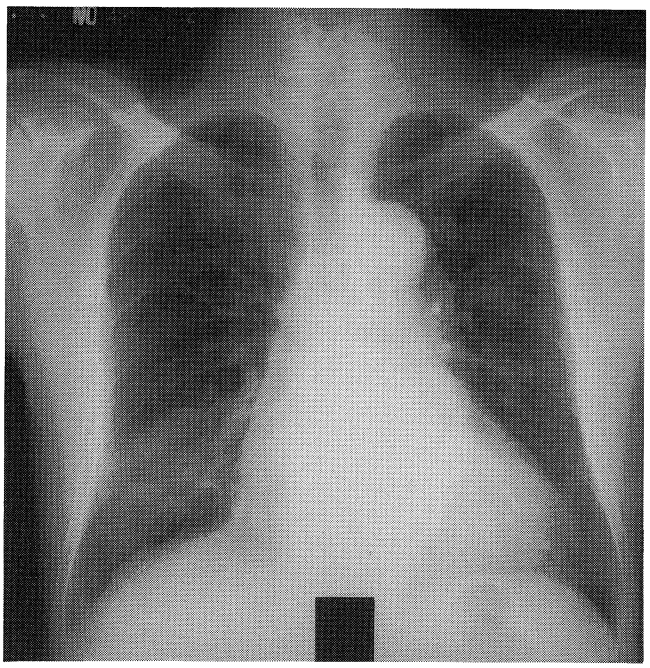
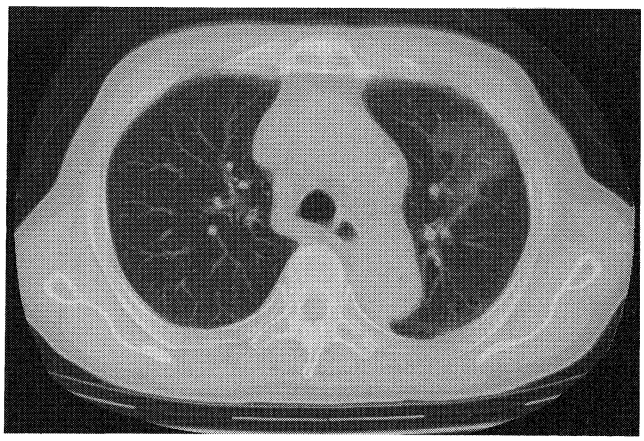


Figure 1. Chest radiograph on admission (case 1) shows an infiltrative shadow in the right lower lung and left upper lung fields.



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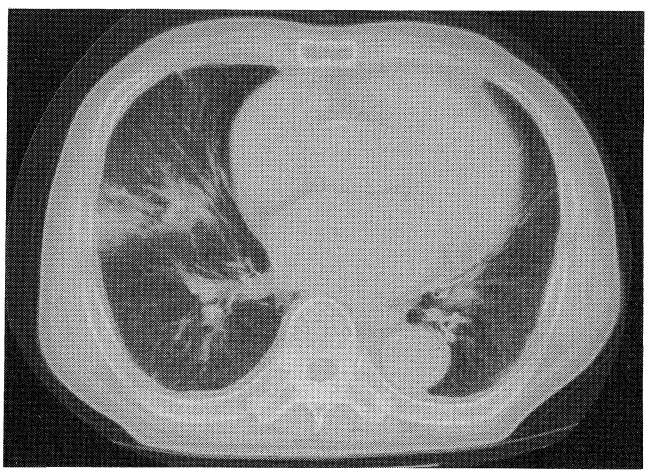

B

Figure 2. Chest computed tomographic scan on admission (case 1) demonstrates an infiltrative shadow in the left upper lung field (A) and right lower lung field (B).

days, followed by 1,000 mg once per week for six weeks. Finally, his symptoms completely disappeared and his PCR for *C. pneumoniae* became negative.

Case 2

A 32-year-old woman visited our hospital on July 15, 2000, complaining of a continuous cough and general fatigue for one week. Her chest radiograph revealed an infiltrative shadow in the left middle lung field (Figs. 3 and 4). Her temperature was 36.8°C, pulse rate was 68 beats/min and blood pressure was 110/62 mmHg. The laboratory data revealed mild elevation of the WBC count (10,000/mm^3) and CRP (1.9 mg/dl). We suspected atypical pneumonia because she had a continuous and obstinate cough. She had no sputum production and had not undergone a physical examination of the chest. WBC count was almost normal (6). She was treated with clarithromycin (400 mg/day) for two weeks and both her symptoms and chest radiograph improved. This case was diagnosed as a case of *C. pneumoniae* pneumonia because seroconversion of *C. pneumoniae*-specific antibody measured by the MIF test was observed among paired serum samples and *C. pneumoniae* was detected from a nasopharyngeal swab specimen by both cell culture and the PCR (Table 1).

By September 23, 2000, she was experiencing a cough and general fatigue again, and she visited our hospital on September 28, 2000. A chest radiograph revealed an infiltrative shadow in the same lung field during the first episode. She was treated with clarithromycin (400 mg/day) for six weeks. Finally, her symptoms completely disappeared and the results of the PCR and culture for *C. pneumoniae* became negative (Table 1).

Culture and PCR

Nasopharyngeal swab specimens were obtained from both patients for isolation in cell cultures and the PCR. The swab specimens were placed in a sucrose-phosphate-glutamate transport medium. Culturing for *C. pneumoniae* was performed in cycloheximide-treated HEp-2 cells grown in a 24-well cell culture plate as reported previously (7). The *C. pneumoniae*-specific primers used for PCR were from the DNA base sequence within the 53-kDa protein gene established in our laboratory (8). This assay was performed as previously described (9), and it was carried out without prior knowledge of the culture results.

Table 1. Results of the PCR, Culture and Antibody Titer and Treatment Regimens for Two Cases of *Chlamydia pneumoniae* Pneumonia

	Date	PCR	Culture	Antibody titer		Treatment (duraiton)
				IgM	IgG	
Case 1	May 9, 2000	+	–	<16	32	Minocycline (2 weeks)
	May 23, 2000	+	–	<16	128	
	September 20, 2000	+	–	<16	512	Clarithromycin (3 weeks)
	October 19, 2000	+	–	<16	512	
	February 13, 2001	+	–	<16	256	Sparfloxacin (10 days)
	February 23, 2001	+	–	<16	256	Azithromycin (6 weeks)
	April 5, 2001	–	–	<16	256	
	June 1, 2001	–	–	<16	256	
Case 2	July 15, 2000	+	+	16	16	Clarithromycin (2 weeks)
	July 29, 2000	+	+	128	32	
	September 28, 2000	+	+	16	32	Clarithromycin (6 weeks)
	October 12, 2000	+	+	<16	32	
	November 28, 2000	–	–	<16	32	
	February 16, 2001	–	–	<16	32	
	March 24, 2001	–	–	<16	16	

+: positive for *C. pneumoniae*, –: negative for *C. pneumoniae*.

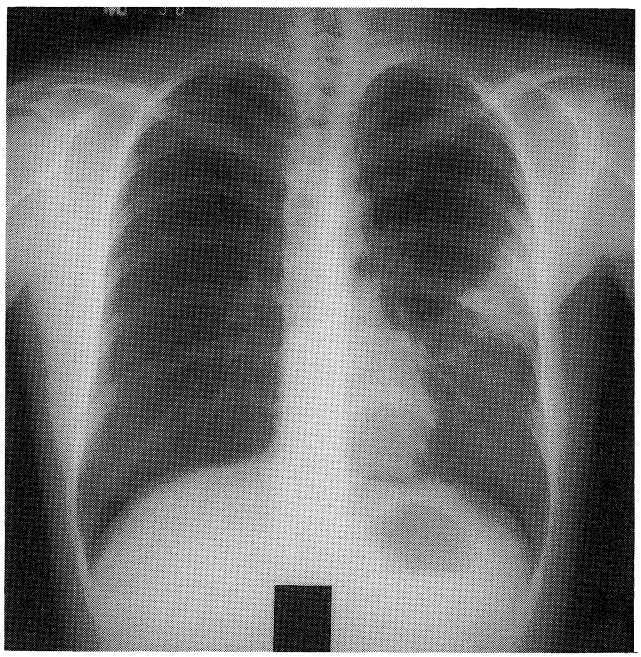

Figure 3. Chest radiograph of case 2 shows an infiltrative shadow in the left middle lung field.

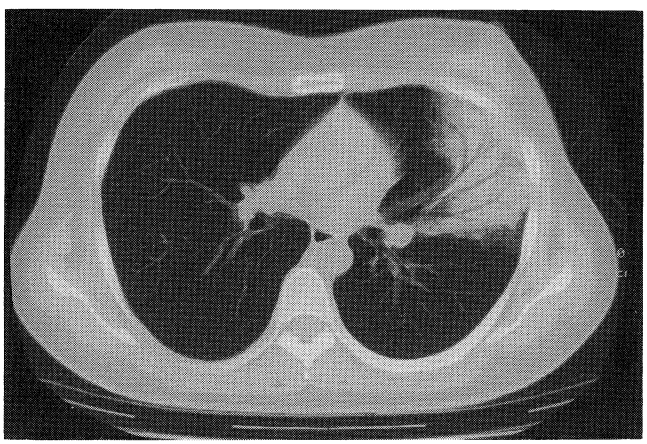

Figure 4. Chest computed tomographic scan of case 2 demonstrates an infiltrative shadow in the left middle lung field.

Serology

Serum samples were obtained from all subjects and stored at –70°C until testing. The MIF test was used for titration of IgG and IgM antibodies against *C. pneumoniae* (1), using formalinized elementary bodies of the *C. pneumoniae* KK-pn15 strain (10) as antigens. Rheumatoid factors were absorbed with Gullsorb (Gull Laboratories, Salt Lake City, Utah, USA) before IgM titrations.

Discussion

Recurrent respiratory tract infections due to *C. pneumoniae* have been described (3–5, 11). Kleemola et al (11) reported three cases of recurrent *C. pneumoniae* pneumonia diagnosed

by serology during epidemics of pneumonia among military trainees. The intervals between the first and second episodes of pneumonia were three weeks to three months. Interestingly, all three recorded cases received treatment with ampicillin or penicillin during the first episode rather than with antibiotics known to be effective agents. In addition, infiltration shadows on chest radiographs appeared in different lung fields during the first and second episodes. In both of the present cases, in contrast, pneumonia recurred despite the administration of antibiotics with appropriate anti-chlamydial therapy. Furthermore, the infiltrative shadows on chest radiographs appeared at the same site during the first and second and/or third episodes in both cases. These findings indicate that the pneumonias of these patients might have occurred by reactivation with the same strain rather than by reinfection with different strains. Our findings were contradictory to those reported by Kleemola et al (11). The difference may be due to the persistent infection in our cases.

Macrolides, tetracyclines and quinolones are effective for *C. pneumoniae* infection. On the basis of the currently available data, a two to three week course of treatment is recommended for *C. pneumoniae* infection (12). However, in the present cases, we could not eradicate the *C. pneumoniae* from the nasopharynx with a two to three week course of treatment with macrolide or tetracycline and symptoms recurred. Similar observations have also been made in previous reports (3–5). Recently, long- term macrolide therapy trials have been undertaken for eradication of *C. pneumoniae* from deep tissues, secondary prevention of cardiovascular diseases or improvement or prevention of asthma symptoms (13–17). In our cases, we tried long-term macrolide therapy, a six-week course of clarithromycin or azithromycin. Finally, we were able to eradicate the *C. pneumoniae* from the nasopharynx. These data indicate that new treatment strategies may be necessary to eradicate the organism in patients prone to persistent infection.

Most epidemiological studies have been performed using serology because the organism is difficult to grow in cell cultures. With the development of PCR techniques for the clinical laboratory, it is now possible to detect *C. pneumoniae*-specific DNA in clinical specimens. Recurrent respiratory symptoms have been reported to occur in some patients with a continuous PCR or who have been culture positive for *C. pneumoniae* (3–5). These observations were also noted in our cases. After the PCR or culture for *C. pneumoniae* became negative, the respiratory symptoms of both patients completely disappeared and no relapse was observed. Therefore, the PCR test may be a useful method for determining whether to continue or stop treatment. However, we could not confirm the eradication of *C. pneumoniae* from the deep tissues.

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