Chlamydia pneumoniae pneumonia: An evolving clinical spectrum

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In 1986 Grayston and co-workers isolated a new Chlamydia species (1) which was subsequently named C pneumoniae (2). The initial clinical description of respiratory disease due to C pneumoniae was that of pneumonia of mild to moderate severity affecting young adults with either sporadic or epidemic infection in closed populations (3). It was also noted that C pneumoniae could undergo reactivation in older adults and in such instances it was often a copathogen (4). It accounts for 6 to 10% of cases of community acquired pneumonia requiring admission to hospital (3,4). Since 1986 our knowledge of the spectrum of illness attributed to C pneumoniae infection has increased. We present two cases that illustrate the spectrum of C pneumoniae infection and briefly review the clinical aspects of C pneumoniae infection.

Severe Pneumonia Due to C pneumoniae

Case presentations – Case 1: A 40-year-old female was admitted to the Calgary General Hospital on September 15, 1994 with rapidly progressive pneumonia. She had been well until one week before admission when she noted myalgias, malaise and a rash on the abdomen. These symptoms resolved within 24 h but the next day the patient developed a severe left-sided headache that persisted despite analgesia with acetaminophen and codeine. A nonproductive cough began within 24 h but the next day the patient developed a severe left-sided headache that persisted despite analgesia with acetaminophen and codeine. A nonproductive cough began two days before admission and 24 h later was followed by progressively worsening dyspnea. The patient’s family had also noted that she was mildly confused.

Past history included one uncomplicated vaginal delivery and occasional mild exertional asthma. She had no known al-
lergies and was an Alberta-born Caucasian. She had returned to Calgary two weeks before admission from a driving trip to Idaho, Utah, Nevada and California. She stayed in hotels, not in campgrounds. While in Los Angeles, she briefly visited an exotic pet shop but had no significant contact with any animals or birds. She was a former 15 pack-year smoker and consumed alcohol only on occasion. There was no known prior exposure to tuberculosis and no apparent risk of human immunodeficiency virus infection. She had not had any contact with persons suffering from respiratory illness nor any recognized mouse exposure.

At presentation, she appeared ill and in respiratory distress. She was tachypneic at 26 breaths/min, even with supplemental oxygen. Blood pressure was 120/75 mmHg and pulse was 110/min. Temperature was 39°C. Chest examination revealed coarse crackles that were worse on the left. The remainder of the physical examination was unremarkable apart from a grade I/VI systolic ejection murmur. Initial investigations included hemoglobin 109 g/L, total white blood cell count of 9.9x10⁹/L and a platelet count of 213x10⁹/L. The differential white blood cell count revealed toxic granulation and a marked left shift. Electrolytes, creatinine and liver enzymes were normal. Serum lactate dehydrogenase was elevated at 468 IU/L. There was no evidence of a coagulopathy and urinalysis was normal.

Initial arterial blood gases demonstrated hypoxemia with \( PO_2 \) of 31 mmHg and an oxygen saturation of 58%. A chest x-ray revealed a significant left lower lobe infiltrate (Figure 1). Despite antibiotic and oxygen therapy and supportive management the patient continued to deteriorate and only 4 h after admission had to be transferred to the intensive care unit where she was intubated and ventilated. A repeat chest radiograph at that time demonstrated extension of her left-sided pneumonia and the appearance of a new right upper lobe infiltrate (Figure 2). While ventilated with 100% oxygen her saturation was only 85%.

After arrival in intensive care she was considered too unstable to undergo bronchoscopy or lung biopsy. She was treated empirically with intravenous cefuroxime and erythromycin as well as rifampin via a nasogastric tube. Over the subsequent three days she stabilized but still required ventilation with 60% oxygen. Her fever resolved. Initial blood and urine cultures were negative as were cold agglutinins. Sputum collected via the endotracheal tube revealed a few white blood cells on stain but only normal oral flora on culture. Legionella serological studies and cultures were negative. Viral, mycoplasma and chlamydial studies of respiratory secretions were not obtained. Acute serum was sent for chlamydia serology.

By the fourth hospital day it was apparent that her initial improvement was modest at most and had plateaued. She remained seriously ill from a pulmonary perspective. At that point intravenous doxycycline was commenced, the rifampin was stopped and the cefuroxime and erythromycin continued. Thereafter the patient improved steadily and was extubated two weeks after admission. She received 10 days of cefuroxime and erythromycin. The doxycycline was to be discontinued after 10 days of therapy, but after the results of acute and convalescent (drawn on days 1 and 6 of hospitalization) serology were reported, it was continued for another two weeks (Table 1). The patient was discharged 18 days after admis-
sion with resolution of all respiratory symptoms and a marked improvement of the pneumonia opacity on chest radiograph.

Two months later she was seen in follow-up and was entirely well. Her chest radiograph was normal. The results of serological tests are shown Table 2.

**Case 2:** A 40-year old male underwent repair of a right inguinal hernia on November 24, 1994. Postoperatively he developed a mass in his right groin along with fever, chills and sweats. A wound infection was diagnosed and he was treated with ciprofloxacin 250 mg bid orally for 10 days. The swelling decreased but since inflammation was still present a further seven-day course of ciprofloxacin was given. The inflammation resolved but a small fluid collection remained in the right groin.

On December 23, 1994 he developed a cough productive of clear sputum. This cough persisted over the next week and he felt unwell but he did not have fever or chills. His sputum became green in colour and wheezes were heard on auscultation of his chest. Therapy with erythromycin 250 mg qid orally was begun. He continued to cough and the wheezing became more pronounced. Ventolin and beclovent were initiated. On January 8 (day 16) he noted a rash on his hands. This was nonpruritic and looked purpuric. By January 11 (day 17) his rash was worse and he had developed pain and swelling of the left ankle.

He had a past history of asthma triggered by exposure to hay, grass and pollens. He had developed a rash when he was given penicillin in the remote past.

When examined on January 12, 1995 crackles were present on auscultation at the left base and inspiratory wheezes were heard throughout both lung fields. The left ankle joint was tender, slightly erythematous and an effusion was present. A maculopapular rash was present on the trunk and extremities, especially his hands. These lesions were purpuric and some were target lesions. There were no musocall lesions. A chest radiograph showed a reticulonodular infiltrate at the left base (Figure 3). Hemoglobin was 138 g/L, white blood cell count 9.5x10^9/L, platelet count 354x10^9/L. Therapy was begun with doxycycline 100 mg bid orally for 10 days. When seen in follow-up on January 27, 1995 (day 35) he had improved considerably. The rash had disappeared and his cough had decreased markedly in frequency. On auscultation of his chest there were no crackles and only a few wheezes.

Other investigations included positive cryoglobulins, (4+ immunoglobulin [Ig] M and 1+ kappa and lambda). The cryoprecipitable protein was 654 mg/mL. Rheumatoid factor was negative, and the levels of the third and fourth components of complement were normal. Coombs’ test (anti-C3D) was positive. No antibodies to DNA were detected. His C pneumoniae IgG titre by microimmunofluorescence rose from 1:64 on day 20 to 1:256 on day 35 of his illness. Antibodies to Chlamydia psittaci and Chlamydia trachomatis were not detectable at a dilution of 1:16. Mycoplasma pneumoniae antibody titres were less than 1:32 as tested by a complement fixation technique.

**DISCUSSION**

*C pneumoniae* accounts for 6 to 10% of cases of community acquired pneumonia (3). The majority of *C pneumoniae* infections are mild upper respiratory tract infections involving the throat, nose and ears (5-7). However, as illustrated by the presented cases, pneumonia may range from mild to very severe. It is also apparent that *C pneumoniae* pneumonia may be accompanied by extrapulmonary manifestations as in case 2. This patient had a reactive arthritis and erythema multiforme. Braun et al (8) described five patients with acute reactive arthritis after an infection with *C pneumoniae*. Three of these patients had a respiratory tract infection (pharyngitis 1,
bronchitis 2) one to three weeks before onset of arthritis. The remaining two had no respiratory tract symptoms. The duration of the arthritis was two days to two months. All five had knee involvement (one had both knees affected); elbow and wrist were other affected joints and one patient had involvement of the achilles tendon. These five patients also demonstrated *C. pneumoniae*-specific synovial lymphocyte proliferation.

Case 2 had mild oligoarthritis involving ankle and elbow. He also had erythema multifforme. This condition has not been previously associated with *C. pneumoniae* infection. *Erythema multifforme* has been associated with a wide variety of infectious agents including *C. psittaci* and lymphogranuloma venereum infection (9). Erythema multifforme can also be due to a variety of drugs, so we can’t be sure that it was due to *C. pneumoniae* in our patient. Case 2 also had evidence of circulating immune complexes in the form of positive cryoglobulins. It is possible that these complexes contributed to the arthritis.

As is the case for *M. pneumoniae*, the spread of *C. pneumoniae* may occur within a family unit (10-13).

Other extrapulmonary manifestations of *C. pneumoniae* infection include erythema nodosum, thyroiditis, encephalitis and Guillain-Barré syndrome (14-17). One patient had meningitis, hepatitis, iritis and atypical erythema nodosum attributed to *C. pneumoniae* infection (18).

Of much more importance clinically is the association between *C. pneumoniae* lower respiratory tract infection and reactive airways disease (19). Hahn et al (19) noted that three of 19 patients with acute *C. pneumoniae* infection wheezed at enrolment into their study and five more developed wheezing during the course of their illness.

The symptoms and signs of lower respiratory tract infection due to *C. pneumoniae* are not distinctively and clinically cannot be distinguished from those due to a variety of other respiratory tract pathogens (4,20). Likewise the radiographic manifestations of this infection are nonspecific. McConnell et al (21) noted that in primary infections unilateral alveolar opacities were most common while those with reactivation of infection were more likely to have interstitial opacities. This group was also more likely to have bilateral opacities. Pleural effusions were common and rarely the radiographic appearance was that of noncardiogenic pulmonary edema.

The laboratory diagnosis of *C. pneumoniae* is detailed by Peelings (22). These two cases presented illustrate some of the current difficulties in obtaining an early laboratory diagnosis that may be useful for management of *C. pneumoniae* infections. In case 1, the patient had a fourfold rise in IgG antibody titre by complement fixation to a genus-specific chlamydial antigen by day 6 of hospitalization, but a significant *C. pneumoniae*-specific antibody response could not be demonstrated until day 23 by microimmunofluorescence. The antibodies detected in the complement fixation test are antibodies to chlamydial lipopolysaccharide, which are usually seen early in infection (21). In this particular case, the complement fixation titre was useful in the decision to continue tetracycline therapy. But case 2 is more typical of the serology seen in the majority of infections in adults. The complement fixation test remains negative even when a four-fold rise in *C. pneumoniae* IgG antibody titre can be demonstrated by microimmunofluorescence. For adult infections, serodiagnosis using IgM antibodies is insensitive because primary infections occur in early teenage years and IgM antibodies are rarely produced in reinfection. Molecular methods such as polymerase chain reaction or direct fluorescent antibody assays may provide a more rapid laboratory diagnosis, but these techniques are, at present, costly and not widely available. Carefully done laboratory studies show that about 41% of patients with primary *C. pneumoniae* infection have a second respiratory pathogen present and 18% of patients with recurrent infection have another pathogen as well (21,23).

Hammerschlag (24), in a review of the antimicrobial susceptibility and therapy of infections caused by *C. pneumoniae*, concluded that two to three weeks of doxycycline or erythromycin (2 g/day) or azithromycin 1.5 g over five days is appropriate therapy of this infection in adults while erythromycin or clarithromycin was appropriate in children.

It is evident from the cases presented and the literature cited that the spectrum of illness associated with *C. pneumoniae* infection is just becoming apparent and it is likely that, with the widespread availability of diagnostic services for this infection, we have not yet finished defining its clinical spectrum.

REFERENCES
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