SEVERE LATE-ONSET NOSOCOMIAL PNEUMONIA CAUSED BY *CHLAMYDOPHILA PNEUMONIAE*

Marko Kutleša[1], Dragan Lepur[1], Oktavija Đaković-Rode[2], Neala Schoenwald[3] and Bruno Barišić[1]

[1]Department of Neuroinfections and Intensive Care Medicine, [2]Department of Serology, [3]Department of Radiology, Dr. Fran Mihaljević University Hospital for Infectious Diseases, Zagreb, Croatia

SUMMARY – We report two cases of severe late-onset nosocomial pneumonia caused by *Chlamydophila pneumoniae*. The clinical course of the disease in these patients suggests that nosocomial pneumonia caused by this agent can lead to profound respiratory insufficiency and acute respiratory distress syndrome, particularly in patients with significant comorbidities and during the postoperative period. Intravenous azithromycin treatment was used to cure pneumonia in both of our patients.

Key words: *Chlamydophila pneumoniae – diagnosis; Chlamydophila pneumoniae – complications; Chlamydophila pneumoniae – therapy; Pneumonia*

Introduction

Chlamydophila (C.) pneumoniae is a common respiratory pathogen known to cause community-acquired pneumonia (CAP), usually mild with benign clinical course[1,2]. Severe CAP due to *C. pneumoniae*, although scarce, has been reported even in immunocompetent patients[3,4]. Acute respiratory distress syndrome (ARDS) is also reported as a complication during CAP caused by *C. pneumoniae*[5,6].

A single case of postoperative *C. pneumoniae* pneumonia after pneumonectomy has been published so far[7]. However, in this case pneumonia occurred on hospital day 4 and the lung infiltration implicated was already present on chest radiography at admission.

In some patients with early-onset ventilator-associated pneumonia, *C. pneumoniae* was detected in bronchoalveolar lavage fluid specimens by use of polymerase chain reaction (PCR)[8]. Nosocomial pneumonia is diagnosed if it occurs within 48 hours of hospitalization; if it develops after more than five days of admission it is referred to as late-onset nosocomial pneumonia with multi-drug resistant microorganisms as usual pathogens[9].

Correspondence to: *Marko Kutleša, MD*, Department of Neuroinfections and Intensive Care Medicine, Dr. Fran Mihaljević University Hospital for Infectious Diseases, Mirogojska 8, HR-10000 Zagreb, Croatia
E-mail: kutlesam@yahoo.com
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We present two cases of serologically confirmed severe late-onset nosocomial pneumonia caused by *C. pneumoniae* during the postoperative period. To the best of our knowledge, *C. pneumoniae* has not yet been described as a pathogen in such a clinical setting.

Case Reports

Case 1

A 76-year-old man was admitted to hospital in March 2007 for severe nosocomial pneumonia. Nine days before admission to our hospital, he underwent coronary artery bypass grafting surgery because of triple vessel coronary disease. The patient's condition aggravated on hospital day 7, manifesting with fever, cough and progressive hypoxemia. Chest radiography showed bilateral infiltrates in the lower lung zones and the diagnosis of nosocomial pneumonia was made. The symptoms progressed with developing respiratory hypoxemic failure in spite of therapy with piperacillin-tazobactam and meropenem.

The patient's medical history revealed a 10-year stable angina pectoris, arterial hypertension, hypercholesterolemia, hypertriglyceridemia and prostatic hypertrophy. Immunosuppression was not detected and epidemiological findings were not etiologically indicative.

At admission, he was febrile (38.1 °C), alert, oriented, restless, cyanotic and respiratory insufficient. His respiratory rate was 51 and pulse 118 beats *per* minute. Chest auscultation revealed crackles bilaterally. No heart murmurs were heard. Postoperative wounds were without signs of infection. Mechanical ventilation was started using open lung strategy.

Laboratory findings: erythrocyte sedimentation rate (ESR) 80 mm/h; C-reactive protein (CRP) 143 mg/L; leukocytosis $14.5x10^9$/L with mature neutrophilia; red blood cell count (RBC) $3.46x10^{12}$/L; hemoglobin (Hb) 107 g/L; hematocrit (Htc) 0.30; platelet count (Plt) $157x10^9$/L; total protein 53 g/L (albumin 25 g/L, globulin 28 g/L); blood glucose (BG) 7.4 mmol/L; aspartate transaminase (AST) 117; and alanine transaminase (ALT) 118. Arterial blood gas analysis at admission revealed respiratory hypoxemic failure; PaO_2 was 65 mm Hg, FiO_2 40%, PaO_2/FiO_2 ratio 162.5 mm Hg, $PaCO_2$ 31.6 mm Hg, pH 7.486 and $SatO_2$ 93.3%.

Blood levels of sodium, potassium, urea nitrogen, creatinine, total bilirubin, lactate-dehydrogenase, gamma-glutamyltransferase and alkaline phosphatase were normal. Prothrombin time (PT) and partial thromboplastin time (PTT) were within normal ranges. Urinalysis revealed only mild proteinuria and urine culture was sterile. Sinus tachycardia was recorded on electrocardiogram.

All blood and tracheal aspirate culture samples were sterile and negative, respectively. *Legionella pneumophila* serogroup 1 antigen in urine was negative and so were mycobacterial multiple cultures sampled from tracheal aspirate. First serum sample for serologic testing was obtained on day 6 of the disease. There was no significant antibody titer to *Mycoplasma pneumoniae*, *Legionella pneumophila* serotypes 1-7 and *Chlamydophila psittaci* detected in any serum sample. Antibodies to *C. pneumoniae* were significant for acute infection with 20, 512 and 32 titers of IgM, IgG and IgA, respectively. Second serum sample obtained 14 days later revealed IgG titer of 512 and IgA titer of 64, without detectable IgM.

Upon admission, vancomycin and imipenem were introduced, however, without any effect during the next 48 hours. Consequently, azithromycin was added to the antimicrobial regimen and the patient's condition started to improve in two days. Azithromycin was administered for five days and two other agents were given for 10 days. After initial clinical deterioration due to ARDS, the patient's condition gradually improved over the next week. The treatment proved efficient and the patient recovered within 7 days on mechanical ventilation. Chest radiography performed on day 15 of admission was free from infiltrates and the patient was discharged from the hospital completely recovered.

Case 2

A 68-year-old patient underwent surgery with osteosynthesis because of right radial fracture at another clinical hospital. On hospital day 8, he acquired nosocomial pneumonia with an alveolar infiltrate in the left lower lung zone, seen on chest radiography. Initial antimicrobial treatment consisted of co-amoxiclav and gentamicin intravenously; however, on day 5 piperacillin-tazobactam were introduced because of initial treatment failure. The patient's condition was deteriorating despite this therapy and he was transferred to our hospital.

The patient's past medical history revealed cerebral infarction three years before current illness, with right-sided hemiplegia as a sequel, along with arterial hypertension and diabetes mellitus as his chronic morbidities. Epidemiological findings were not etiologically indicative.

At admission, he was febrile (38.9 °C), normotensive, hemodynamically stable, respiratory sufficient. His respiratory rate was 28, pulse 108 beats *per* minute, and Glasgow Coma Score was 10. Chest auscultation revealed crackles bilaterally and decreased breathing sound on the left side. No heart murmurs were heard. Postoperative wounds were without signs of infection. On day one of admission, pneumonia progressed and the patient required mechanical ventilation.

Laboratory findings: ESR 82 mm/h; CRP 217 mg/L; leukocytosis $19.0x10^9$/L with mature neutrophilia; RBC $3.80x10^{12}$/L; Hb 117 g/L; Htc 0.331; Plt $326x10^9$/L; total protein 77 g/L (albumin 32 g/L, globulin 45 g/L); BG 13.7 mmol/L; AST 50; ALT 70; and urea nitrogen 12.6 mmol/L. Multiple arterial blood gas analyses performed immediately prior to mechanical ventilation revealed PaO_2 of 57 mm Hg; FiO_2 50%; PaO_2/FiO_2 100.6 mm Hg; $PaCO_2$ 42.1 mm Hg; pH 7.431 and $SatO_2$ 87.1%. Blood levels of sodium, potassium, creatinine, total bilirubin, lactate dehydrogenase, gamma-glutamyl transferase and alkaline phosphatase were normal. PT and PTT were normal. Urinalysis revealed proteinuria without leukocyturia and urine culture was sterile.

Electrocardiogram recorded sinus tachycardia. Blood cultures and tracheal aspirates obtained upon admission were sterile. *Legionella pneumophila* serogroup 1 urine antigen was negative. Mycobacterial cultures sampled

from tracheal aspirate were negative. ELISA for antibodies to *Mycoplasma pneumoniae*, *Legionella pneumophila* serotypes 1-7 and *Chlamydophila psittaci* was negative. *C. pneumoniae* antibodies were detected by using microimmunofluorescence (MIF) assay with IgG titer of 512 and IgA titer of 256. Repeat serum sampling obtained 14 days later showed unchanged titers.

Vancomycin and imipenem introduced upon admission were futile. On hospital day 5, azithromycin was added, vancomycin was discontinued and imipenem therapy continued for five more days. Azithromycin was administered for seven days intravenously with significant clinical and laboratory improvement. After seven days of azithromycin therapy, chest radiography revealed complete regression of the previously noted infiltration. The patient was mechanically ventilated for 20 days and was discharged from the hospital with good recovery in May 2007. His impairment caused by chronic diseases was the same as noted prior to hospitalization.

Discussion

We present two cases of late-onset nosocomial pneumonia caused by *C. pneumoniae* that occurred after coronary artery bypass grafting surgery and after surgery for right radial fracture. Endotracheal anesthesia was applied during the surgical procedures. In both cases, the disease was severe and complicated by respiratory insufficiency that required mechanical ventilation; in one case ARDS developed as well. Our patients were burdened with multiple chronic diseases and were in postoperative period when nosocomial pneumonia occurred.

On serologic antibody testing by MIF assay used for the diagnosis of *C. pneumoniae*, both of our patients met the criteria for an acute infection. MIF assay is presently the method of choice and the most commonly used specific and sensitive assay that allows identification of *C. pneumoniae* as an etiologic agent[10,11]. We used it according to the manufacturer's recommendation (Savyon Diagnostics, Israel).

When late-onset nosocomial pneumonia occurs, the presumed etiologic agents are usually multi-drug resistant gram-positive or gram-negative bacteria, especially in previously intubated patients. As antimicrobial treatment guidelines were developed accordingly, they do not contain agents active against atypical pathogens.

The most important risk factor for nosocomial pneumonia caused by multi-drug resistant microorganisms is its late onset, i.e. after 5 days of hospitalization[12]. In our patients *C. pneumoniae* nosocomial pneumonia developed on days 7 and 8 of hospital stay, thus this agent should be considered in the etiology of severe nosocomial pneumonia, even in late-onset cases, and appropriate adjustment of antimicrobial treatment is mandatory. Our patients were administered azithromycin primarily for the possible *Legionella* infection; since *C. pneumoniae* is susceptible to this agent, it cured their pneumonia.

C. pneumoniae is a rare cause of nosocomial pneumonia; however, it should probably be searched for and suspected more frequently, especially during epidemic years like the one when the patients reported were diagnosed. To determine the true incidence of *C. pneumoniae* as an agent of nosocomial respiratory infection, paired serology samples should be obtained in every patient with nosocomial pneumonia. A major obstacle in serology testing is retrograde diagnosis, which makes clinicians unjustifiably reluctant to collect samples when indicated.

The clinical course of the disease in our patients suggested that nosocomial pneumonia due to this agent could be late in onset and lead to profound respiratory insufficiency and ARDS, thus clinical suspicion is of crucial importance and any delay in appropriate antimicrobial treatment may result in an adverse outcome. Our second patient took significantly more time to recover; one of the reasons certainly was a delay in appropriate antimicrobial treatment. In our experience, intravenous azithromycin therapy proved efficacious and we can recommend it for the management of any atypical nosocomial pneumonia, with treatment time ranging from 5 to 7 days.

Early antimicrobial treatment that covers atypical agents can prove efficacious in both early- and late-onset cases of severe nosocomial pneumonia. Certainly, this approach should be used in elderly patients with significant comorbidities, during postoperative period and in years characterized by an increased incidence of atypical pneumonia.

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Sažetak

KASNI NASTUP TEŠKE NOZOKOMIJALNE PNEUMONIJE UZROKOVANE BAKTERIJOM *CHLAMYDOPHILA PNEUMONIAE*

M. Kutleša, D. Lepur, O. Đaković-Rode, N. Schoenwald i *B. Baršić*

Prikazuju se dva slučaja kasnog nastupa teške bolnički stečene pneumonije uzrokovane bakterijom *Chlamydophila pneumoniae*. Klinički tijek bolesti u ovih bolesnika ukazuje na to da bolnički stečena pneumonija izazvana ovim uzročnikom može dovesti do teške respiracijske insuficijencije i sindroma akutnog respiracijskog distresa, poglavito u bolesnika sa značajnim istodobno prisutnim bolestima i tijekom poslijeoperacijskog razdoblja. U oba bolesnika se za liječenje pneumonije primijenio intravenski azitromicin.

Ključne riječi: *Chlamydophila pneumoniae – dijagnostika; Chlamydophila pneumoniae – komplikacije; Chlamydophila pneumoniae – terapija; Pneumonija*