

Fulminant Myocarditis due to *Chlamydia pneumoniae* Complicated with Peripheral Gangrene and Cerebral Infarction : A Case Report

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Abstract

A woman who had recently had a respiratory tract infection and later received influenza immunization developed myocarditis secondary to *Chlamydia pneumoniae*. She presented with acute heart failure, and developed cardiogenic shock and acute respiratory failure. Her course was complicated by gangrene of the extremities and cerebral infarction. *C. pneumoniae* is an unusual cause of myocarditis and was implicated in this case on the basis of acute and convalescent serologic testing. Even the diagnosis of myocarditis is difficult to make, it requires a high index of suspicion and diagnostic testing aimed at excluding other diagnoses, such as myocardial infarction. Recovery may be complete, although our patient was left with residual deficits with gangrene of the extremities and cerebral infarction. (J Intern Med Taiwan 2009; 20: 155-161)

Key Words : *Chlamydia pneumoniae*, Fulminant myocarditis, Paired serum, Peripheral gangrene, Cerebral infarction

Introduction

Acute myocarditis is often severe or even fulminant, similar to acute myocardial infarction in its rapid onset. Fulminant myocarditis is associated with acute heart failure and considerably high mortality. We report a patient with fulminant myocarditis due to *C. pneumoniae* who was treated with appropriate antibiotics and mechanical cardiac support. Due to aggressive treatment, she recovered the cardiac function and survived. Cardiac involvement of *C.*

pneumoniae is rare and reviewed in this report.

Case presentation

A 41-year-old woman was admitted on October 3 complaining of cough and vomiting. She had had a non-productive cough and headache for 2 weeks in early September. On September 29, she was given influenza immunization. Three days later, she vomited several times and had a cough and shortness of breath severe enough that she sought

emergency care. On admission, her temperature was 37.6 °C, respiratory rate 50/min, heart rate 120/min, and blood pressure 70/50 mmHg. On chest auscultation, she had diffuse crackles throughout both lungs. Her heart rhythm was regular and no murmur was heard. However, she became progressively more dyspneic and developed orthopnea. Chest radiography was consistent with acute pulmonary edema (Fig.1). Her initial blood gas analysis revealed a pH of 7.260, PaCO₂ 40.9 mmHg, PaO₂ 57.2 mmHg, HCO₃⁻ 17.9 mmol/L, base deficit 6 mmol/L, and SaO₂ 85.6%. She was therefore intubated and placed on mechanical ventilation. Her peripheral white blood cell count was 26000 cells per μ L with 82.0% neutrophils, platelet count 70000 per μ L, C-reactive protein 6.6 mg/dl (normal <0.8), fibrin degrading product (FDP) > 32 μ g/mL (<8) and D-dimer >2.0 μ g/mL (<0.5). Electrocardiography showed sinus tachycardia with myocardial ischemia. Her creatine phosphokinase was 2006 IU/L (25-175 IU/L), with a myocardial isoenzyme fraction of 60.3 IU/L (2.3-9.5 IU/L), and her troponin I was >100 (<1.0). Swan-Ganz catheterization demonstrated central venous pressure (CVP) 8 mmHg, pulmonary artery wedge pressure (PAWP) 16 mmHg, cardiac index 2.0 L/min/m², and she was suggested to have cardiogenic shock. M-mode and 2dimensional echocardiography showed mild mitral regurgitation, increased thickness of interventricular septum, poor left ventricular contractility with an ejection fraction of 34%, and color Doppler revealed moderate pulmonary hypertension with an estimated pulmonary artery pressure of 46 mmHg. Emergency coronary angiography showed insignificant stenosis of the obtuse marginal and left anterior descending branches of the left coronary artery. On left ventriculography, there was generalized hypokinesis of the left ventricle and mild MR. The angiographic diagnosis was severe LV systolic dysfunction with patent coronary angiography. Because the patient

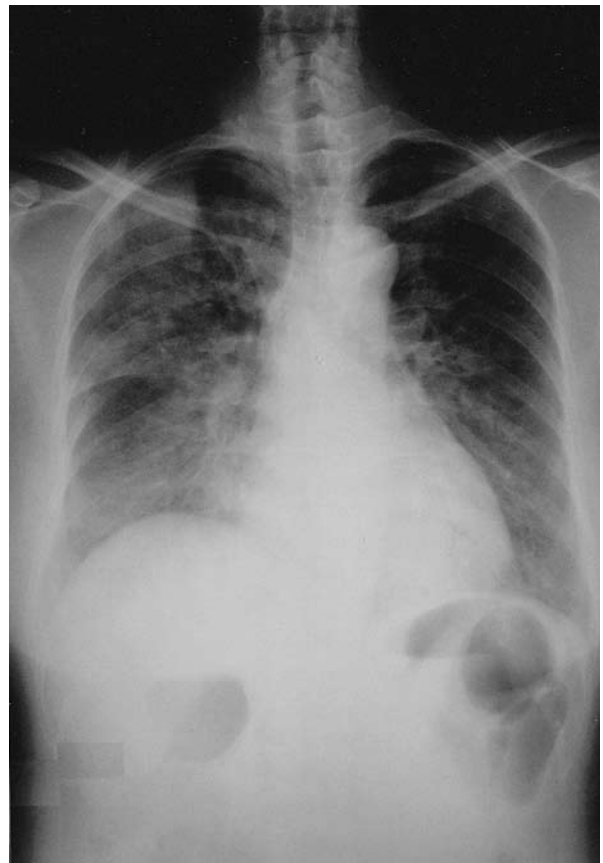


Fig.1.Chest radiography revealing acute pulmonary edema.

was in shock, an intra-aortic balloon pump was placed and inotropic agents with dopamine 7 μ g/kg/min and dobutamine 3 μ g/kg/min were given.

She was treated empirically with cefpirome and levofloxacin. Blood cultures showed no growth. Serologic tests for a number of infectious agents were negative, including tests for influenza A and B and respiratory syncytial virus, and antibodies to hantavirus, adenovirus types 3 and 7, and SARS viruses. Throat swab polymerase chain reaction testing for those viruses was also negative, as were throat cultures for adenovirus, cytomegalovirus, enterovirus, and herpes simplex, respiratory syncytial, coxsackie, and influenza viruses. Tests for *Mycoplasma pneumoniae* IgM and IgG antibody and Legionella antibody were negative. The initial *C. pneumoniae* IgA antibody test was negative, but the IgM antibody titer was <16 and IgG 32.

After two days, the patient's blood pressure stabilized and the intra-aortic pump was removed, and dopamine was also discontinued. However, her fever persisted. On hospital day 5, her extremities were cold and clammy with peripheral cyanosis. Prostaglandin E1 was given, but the cyanosis progressed to gangrene of all fingers on the left hand, the right third and fourth fingers, and the right second and third toes. She was suggested to have disseminated intravascular coagulation (DIC) with microembolization and was anticoagulated with low-molecular weight heparin and given a vasodilator. She was weaned from the ventilator and extubated after 2 weeks of hospitalization. Fever subsided after 2 weeks. Chest radiography at that time revealed resolving pulmonary edema. The antibiotics were continued for 2 weeks. Repeat transthoracic echocardiography after 5 weeks revealed trivial MR, mild PR, TR, mild pulmonary hypertension SPAP 39 mmHg, impaired left diastolic function but improved systolic function with an ejection fraction of 63%.

After 5 weeks of hospitalization, her speech became slurred, and computerized tomography (CT) of the brain (Fig.2) revealed a focal wedge-shaped hypodense lesion at the junction of the left frontal and parietal lobes. Magnetic resonance imaging (MRI) performed after 6 weeks was consistent with focal encephalomalacia involving the left frontal and parietal lobes. MR angiography showed wedged lesion involving left frontal and parietal lobes. No evidence of focal stenosis, aneurysm or vascular anomaly is noted around the circle of Willis. Extra- and transcranial color coded duplex sonography showed no significant limitation of flow in the carotid, subclavian, vertebral, or basilar arteries.

Repeat serology testing for *C. pneumoniae* after a 4-week interval revealed no changes in the IgM titre but a 4-fold rise in the IgG to 128. A 4-week course of doxycycline was therefore given.

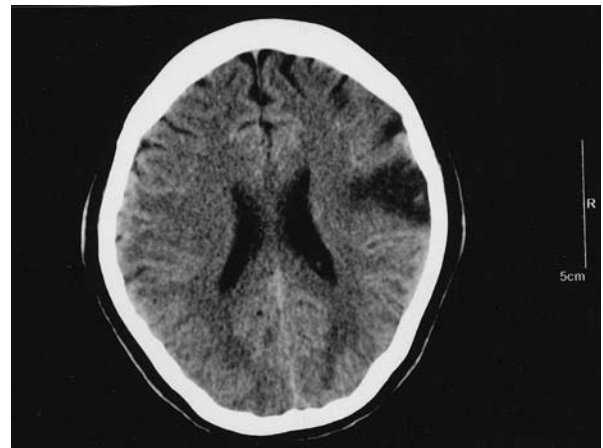


Fig.2. Brain CT showing a focal wedge-shaped hypodense lesion at the junction of the left frontal and parietal lobes.

Despite hyperbaric oxygen therapy, the patient eventually required amputation of her gangrenous digits. Microscopically, the amputated tissue revealed areas of hemorrhage and eosinophilic and amorphous necrotic tissue with absence of nuclei. The patient was eventually discharged with a final diagnosis of fulminant myocarditis due to *C. pneumoniae*, DIC with peripheral gangrene, and cerebral infarction.

Discussion

Chlamydiae are obligate intracellular bacteria with a unique biphasic life cycle and which are difficult to culture. Three chlamydial species pathogenic for humans are *Chlamydia trachomatis*, *Chlamydia psittaci*, and *Chlamydia pneumoniae*. *C. pneumoniae* is the most recently identified, and unlike *C. trachomatis*, it is not sexually transmitted but is spread by aerosolized respiratory secretions and unlike *C. psittaci*, it is not a zoonosis¹. Chlamydiae are common human pathogens, causing a broad spectrum of infectious diseases. Chlamydial infections may involve the heart including endocarditis, myocarditis and pericarditis². Chlamydial infection related to respiratory tract infection associated with inflammatory heart

diseases is *C. pneumoniae*.³ The incubation period for *C. pneumoniae* infection is about 21 days, longer than that of many other respiratory pathogens and it produces biphasic pattern of illness symptoms. The most common clinical syndromes caused by *C. pneumoniae* are pneumonia, bronchitis, sinusitis, and pharyngitis, although some patients are asymptomatic. Other rarer syndromes include otitis media, lumbosacral meningoradiculitis, erythema nodosum, Gullain-Barré syndrome, encephalitis, infective endocarditis, pericarditis, and pleuritis.¹ There has been speculation that *C. pneumoniae* may be related to atherosclerotic cardiovascular disease and adult onset asthma⁴.

A case of fulminant myocarditis related to *C. pneumoniae* was described in this case report. Myocarditis is inflammation of the myocardium caused by a variety of infectious and noninfectious entities. The inflammatory process may affect myocytes, vessels, the conducting system, autonomic nerves, or the interstitium. One or more of at least four mechanisms appear to be involved: (1) direct damage to cells by a pathogen; (2) cytotoxicity caused by a circulating toxin; (3) cytotoxicity caused by infection-induced immune reactions; and (4) nonspecific damage to myocytes resulting from adjacent inflammation. Infectious myocarditis is suspected when unexplained heart failure or arrhythmias occur in the course of a systemic febrile illness or after a respiratory tract infection. Potential infectious agents include viruses, bacteria, rickettsiae, fungi, and parasites, but viruses are the most frequently implicated pathogens. Acute myocarditis and dilated cardiomyopathy are seen most often with enterovirus or adenovirus infection, although cytomegalovirus, parvovirus B19, and influenza A and B, Epstein-Barr, herpes simplex, and respiratory syncytial viruses have all occasionally been identified in some cases of acute myocarditis.³ Bacterial pathogens may cause myocarditis by

establishing metastatic foci in the myocardium in the course of bacteremia. Organisms that have been implicated include *Corynebacterium diphtheriae*, *Neisseria meningitidis*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydia psittaci*, and *Coxiella burnetii*.³

The common clinical manifestations of myocarditis include fever, arthralgia, and malaise. Laboratory tests may show leukocytosis, an elevated sedimentation rate, eosinophilia, and elevated levels of cardiac enzymes. The electrocardiogram may show ventricular arrhythmias or heart block. The clinical spectrum of disease varies from asymptomatic cases to fulminant heart failure, including left ventricular dysfunction with or without cardiac dilatation. Endomyocardial biopsy is the gold standard for the diagnosis of myocarditis, despite its limited sensitivity and specificity. However, it has been suggested that the diagnosis should not be based on histologic findings alone. Other diagnostic tests including autoimmune serum markers are also important. In fact, the diagnosis requires a high index of suspicion and depends on a constellation of findings rather than on any particular diagnostic test. Because various features of myocarditis may mimic those of myocardial infarction, coronary angiography may be necessary to obtain the correct diagnosis.⁵

Hoefler et al reported a female patient with fulminant *C. pneumoniae* myocarditis in whom an early diagnosis was made by endomyocardial biopsy.⁶ We did not do a biopsy in our patient, but a number of finding in her case are most consistent with *C. pneumoniae* myocarditis. She probably had a mild respiratory tract infection one month prior to hospitalization. The rapid onset of symptoms progressing to shock, and severe left ventricular dysfunction were consistent with a diagnosis of acute fulminant myocarditis. Cultures and serologic tests for a wide range of pathogens were all negative, including the initial results of tests for

anti-*C. pneumoniae* IgM, IgA, and IgG antibody. It was the 4-fold rise in the IgG titer in the convalescent serum that supported the diagnosis.

Dowell et al reviewed the available approaches for the diagnosis of *C. pneumoniae* infection, including serologic testing, culture, DNA amplification, and tissue diagnostics in 2001. The microimmunofluorescence antibody test is the only currently recommended method of serologic testing. Acute infection is defined by a 4-fold rise in IgG or an IgM titer of ≥ 16 ; use of a single elevated IgG titer is discouraged. Past exposure is indicated by an IgG titer of ≥ 16 . Neither an elevated IgA titer nor any other serologic markers are valid indicators of persistent infection. IgM antibody may appear approximately 2 to 3 weeks after the onset of illness but not in reinfection. Therefore, failure to detect IgM antibodies does not exclude *C. pneumoniae* infection. IgG antibody is produced after exposure to the organism and is detectable for months to years. After primary infection, the peak IgG response occurs at about 6 to 8 weeks, whereas it is more rapid after reinfection, usually within 1 to 2 weeks. Therefore, a 4-fold change in IgG antibody titers between acute and convalescent sera obtained 4 to 8 weeks apart provides the most reliable indication of an acute infection.⁷

Confirmation of a positive *C. pneumoniae* culture result requires propagation of the isolate or confirmation by use of PCR. Four of the 18 currently available PCR assays have met proposed criteria for optimal validation. Immunohistochemical staining is helpful when control antibodies and tissue are used consistently. However, staining artifacts may occur, so that there is a substantial learning curve required to achieve adequate performance of this test.⁷

Tong et al reported a patient with *C. pneumoniae* myocarditis in combination with influenza A.⁸ The recent influenza immunization might have had some role in precipitating *C. pneumoniae* myocarditis in

our patient. Erythromycin, tetracycline and doxycycline are active in vitro against *C. pneumoniae*, as are the newer macrolide-like antibiotics, such as azithromycin and clarithromycin. These achieve high intracellular concentrations. Newer fluoroquinolone agents such as gatifloxacin and gemifloxacin also have in vitro activity against *C. pneumoniae*¹. The initial empiric antibiotic regimen we used included levofloxacin, which has also been effective in treating *C. pneumoniae*.

Cases of inflammatory heart diseases due to *C. pneumoniae* are summarized in table 1. These patients have prolonged respiratory tract symptoms before cardiac manifestation. Some respiratory virus infection or vaccination may facilitate such chlamydial infection of the heart. Most of these patients are diagnosed with acute- and convalescence-phase paired serology tests. Survived patients were treated with tetracycline, macrolide and fluoroquinolone. In addition to antibiotics treatment, aggressive cardiac support was necessary for fulminant myocarditis.

In summary, the combination of appropriate antibiotics plus mechanical cardiac support allow recovery of the patient's cardiac function. Her clinical course was unfortunately complicated by peripheral cyanosis which progressed to gangrene. This gangrenous complication suggested due to DIC or invasive cardiac procedures did not respond to anticoagulants, anti-platelet agents, or vasodilators. Then she developed the focal neurologic deficit which may be due to thromboembolization to the brain. Examination of the intra- and extracranial arterial system excluded these vessels as the source of the emboli. The cause of late onset cerebral infarction was unexplained.

It is suggested that many of the myocarditis due to *C. pneumoniae* are undiagnosed, increased recognition of this bacterium may yield more reports of *C. pneumoniae* myocarditis. Inflammatory heart diseases like endocarditis, myocar-

Table 1. Summary of cases of inflammatory heart diseases due to *Chlamydia pneumoniae*

Reference	Age(y)/gender	Clinical manifestation	Cardiac involvement	Complication	Serum MIF for <i>C. pneumoniae</i>	PCR for <i>C. pneumoniae</i>	Treatment	outcome
9	59/M	skin rash for 2 months, cough for 1 month	endocarditis	multiple spleen infarctions	IgM 128, IgG 256 after 60days		tetracycline,surgery	survived
10	26/M	cough, pneumonia for 2 months	myocarditis		IgM 64, IgG 512	heart,lung	doxycycline penicillin	died
11	37/M	cough, fever, arthritis, erythema nodosum for 1 week	myocarditis	reactive arthritis	IgM<8, IgG >2048 after 18 days		penicillin and netilmicin	survived
12	50/F	diarrhea, vomiting,and fever for 4 days, pneumonia	endocarditis	DIC, MOF	IgM negative, IgG 64 to 1024 over the 5-day		erythromycin and ceftriaxone, tetracycline	died
8	18/M	vomiting,myalgia, fever,pneumonia	myocarditis	Acute renal failure generalized convulsion, acute respiratory failure	IgM positive, IgG 256 day 5, IgG 512 on day 19, influenza A antibody positive		erythromycin and cefotaxime, doxycycline	survived
13	13/F	shortness of breath, nausea for 1day, pneumonia	pericarditis	hemorrhagic pericardial effusion	positive IgG and IgA using sandwich enzyme-linked immunosorbent assays (sELISAs)	pericardial effusion	Azithromycin, cefuroxime and pericardial drainage	survived
6	24/F	tracheobronchitis for 2 months, collapse, chest pain, pneumonia	fulminant myocarditis (EF 10%)	respiratory failure, pleural effusion, hepatomegaly, ascities		endomyocardium; alsoPCR positive for parvovirus B19	ceftriaxone and erythromycin (ECMO and BVAD)	survived
present case	41/F	cough 1month,vomiting, pneumonia	fulminant myocarditis (EF 34%)	respiratory failure, DIC, peripheral gangrene,cerebral infarction	IgM<16 and IgG 32 initially, IgG 128 after 4 weeks		levofloxacin, cefpirome (IABP)	survived
14	24/F	unproductive cough, fatigue more than 2 months,abdominal pain	fulminant myocarditis (EF 10%)	respiratory failure, bilateral pleural effusion, peritoneal effusion	IgG 64 on day 5 and IgG 16 on day 21, influenza B	myocardium; also PCR positive for <i>C. psittaci</i> and parvovirus B19 in myocardium	ceftriaxone and erythromycin (ECMO and BVAD)	survived

Note: Y=years, M= male, F= female, MIF= microimmunofluorescens, PCR=polymerase chain reaction, DIC= disseminated intravascular coagulation, MOF=multiorgan failure, EF= ejection fraction, IABP= intra-aortic ballon pumping, ECMO= extracorporeal membrane oxygenation, BVAD=biventricular assist device

ditis, and pericarditis related to respiratory tract infection without definite diagnosis should be highly suspicious for *C. pneumoniae* infection.

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Chlamydia pneumoniae 引起的猛暴性心肌炎，併發末梢肢體發紺、腦部血管阻塞：一病例報告

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摘 要

一位患有上呼吸道感染曾接受過流感疫苗注射的女性病患，病發猛暴性心肌炎，導致心臟衰竭、心因性休克及呼吸衰竭，且併發末梢肢體發紺、腦部血管阻塞。*Chlamydia pneumoniae* 引起的心肌炎是少見的，須藉由急性期及恢復期血清來診斷。猛暴性心肌炎在臨床上不易被診斷出來，但仍需高度懷疑及且排除其他可能原因(例如心肌梗塞)，作為鑑別診斷的依據。猛暴性心肌炎可經由適當抗生素及心臟支持療法，使病患獲得治癒，但此個案已產生合併症，且末梢肢體接受截肢手術。