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Clinical Communications

MYCOPLASMA PNEUMONIAE: USUAL SUSPECT AND UNSECURED DIAGNOSIS IN THE ACUTE SETTING

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□ **Abstract**—*Mycoplasma pneumoniae* is one of the most common known bacterial pathogens of the respiratory tract, especially in patients between 5 and 30 years of age. It may be encountered at a relatively high rate in the non-life-threatening fraction of Emergency Department (ED) patients presenting with upper respiratory symptoms or cough. Yet its hallmarks are very non-specific, including a great variety of presentations from mild pharyngitis to potentially life-threatening complications such as the Stevens-Johnson Syndrome. Here, we describe a typical case of pneumonia due to *Mycoplasma pneumoniae* in a young adult with mild pharyngitis as the leading symptom. Disease presentation, complications, diagnostic means, therapeutic options, and suspicious clinical settings are discussed to provide a review on the clinical aspects of the disease that are important in the ED setting. © 2006 Elsevier Inc.

□ **Keywords**—atypical pneumonia; upper airway infection; pharyngitis; *Mycoplasma pneumoniae*

INTRODUCTION

Mycoplasmas are the smallest known free-living organisms. Unlike other bacteria, they lack rigid cell wall structures and are therefore not susceptible to antibiotics that interfere with cell wall synthesis, such as beta-

lactams. Most of the *Mycoplasma* species that can be found in humans act as commensals on mucosal surfaces. However, *Mycoplasma pneumoniae* is a common cause of acute respiratory tract infections, particularly in children and young adults, and related to the syndrome of atypical pneumonia. Other human pathogenic species include *M. genitalium*, *Ureaplasma urealyticum*, and *M. hominis*, which can cause urogenital infections.

M. pneumoniae produces an influenza-like respiratory illness of gradual onset with headache, malaise, fever, and cough that is especially common in young people. Despite its ubiquity in the ambulatory setting, *M. pneumoniae* may be one of the least frequently diagnosed respiratory pathogens in the emergency department (ED), primarily because clinical hallmarks are very non-specific, including a great variety of presentations from mild pharyngitis to potentially life-threatening complications such as the Stevens-Johnson Syndrome.

Despite these difficulties, a correct diagnosis remains crucial for appropriate antibiotic treatment. If *M. pneumoniae* infection cannot be diagnosed with certainty, situations where *M. pneumoniae* infection is likely should be recognized by the physician to allow for empiric treatment. Here, we provide a review on the clinical aspects of *M. pneumoniae* infection together with a case report. Disease presentation, complications, diagnostic

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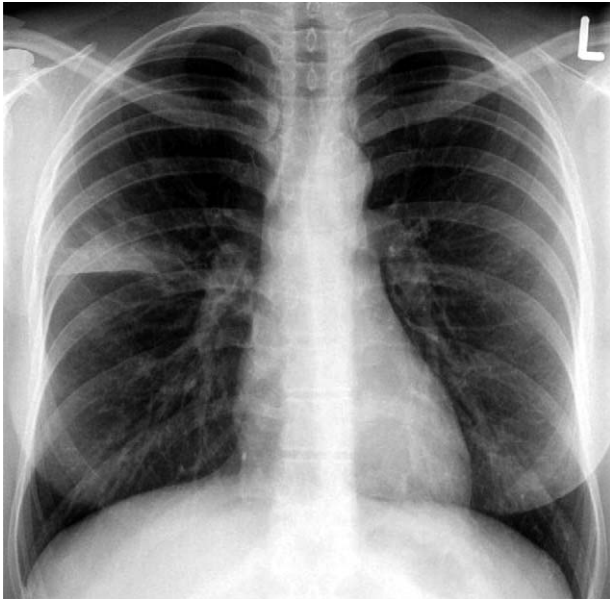


Figure 1. Chest radiograph study performed 2 days after the onset of pharyngeal symptoms revealing a pneumonic infiltrate of the axillary segment (3a) of the right upper lobe.

means, therapeutic options, and suspicious clinical settings are discussed with respect to the needs of emergency physicians.

CASE REPORT

A previously healthy 26-year-old woman presented to our ED with a sore throat. She complained of a mild cough producing whitish mucus, hoarseness, headache, and musculoskeletal pain for the previous 2 days. Vital signs were normal (blood pressure 125/80 mm Hg, heart rate 80 beats/min, respiratory rate 18 breaths/min, oral temperature 36.4°C). On examination, there was an exudate of the posterior pharyngeal wall. Auscultation of the lungs was normal. Laboratory findings were as follows: WBC 11,000/ μ L, ESR normal, C-reactive protein moderately elevated (6.6 mg/dL, reference range < 0.5 mg/dL), capillary blood gas analysis while breathing ambient air: pO₂ 82.9 mm Hg, pCO₂ 32 mm Hg, pH 7.457, O₂-Sat. 97%. Surprisingly, the environmental history revealed that her spouse had a *Mycoplasma pneumoniae*-induced pneumonia complicated by a Stevens-Johnson Syndrome 2 weeks prior. Our patient's symptoms were mild and compatible with, but not specific for *M. pneumoniae* infection (1). Yet, we considered the diagnosis for the following reasons: clear history of exposure, cough producing sputum, and musculoskeletal pain. A chest X-ray study was performed, which showed an infiltrate of the right upper lobe (Figure 1). The

diagnosis of pneumonia, most likely secondary to *M. pneumoniae*, was established. Empiric antibiotic treatment against *Mycoplasma* was initiated according to current recommendations using a macrolide, in this case erythromycin 250 mg p.o. q.i.d. for 14 days (2,3). A throat swab or sputum culture was not performed. The patient was discharged from the ED. On ambulatory follow-up after 1 week, the patient was symptom-free and infection with *Mycoplasma* could be confirmed by a 10-fold increase in anti-*Mycoplasma* IgG-titer (20.4 U/mL at presentation, 200.0 U/mL after 7 days), whereas IgM was normal at both times. A control pulmonary chest X-ray study (not shown) 28 days after presentation was normal.

DISCUSSION

In the present case, pharyngitis and cough were the leading symptoms of *M. pneumoniae*-associated pneumonia. Generally, pharyngitis may be caused by an extensive variety of agents of both viral and bacterial origin (Table 1). Infection with *M. pneumoniae* runs low in this list (< 1% of all pharyngitides) and is self-limiting, requiring no treatment. However, pharyngitis and cough are the most common respiratory tract symptoms [12% to 73% and 93% to 100%, respectively (1)] of *Mycoplasma* upper-airway-infection, which in turn may progress to pneumonia or tracheobronchitis in 5% to 10% of cases (3). Other symptoms occurring with both types of *M. pneumoniae* infection include fever (93% to 100%), malaise, headache, myalgias, rhinorrhea, ear discomfort and chest discomfort (1).

Table 1. Causative agents found in upper respiratory infection (pharyngitis)

Viral	
Rhinovirus	20%
Coronavirus	≥ 5%
Adenovirus	5%
Herpes simplex	4%
Parainfluenza and Influenza	4%
Coxsackie-A, EBV, CMV, HIV-1	< 1% each
Bacterial	
Streptococcus pyogenes Group A	15–30%
Streptococcus pyogenes Group C	5–10%
Corynebacterium diphtheriae	≥ 1%
Mycoplasma pneumoniae	< 1%
Chlamydia pneumoniae and Mycoplasma hominis	Unknown
Corynebacteria other than C. diphtheriae, Neisseria gonorrhoeae, Yersinia enterocolitica, Treponema pallidum, and agents causing mixed anaerobic infections (i.e., Plaut Vincent's angina; peritonsillar abscess)	<1% each

Data adapted from (4).

Table 2. Causative agents found in community-acquired pneumonia

Causative agents found in community-acquired pneumonia	In all patients U.S.A. (5)*	In patients presenting to EDs and primary care physicians with mild to moderate pneumonia (Fine Risk Class I-III) Canada (6)†	In patients requiring hospital admission U.S.A. (7)§
Viral	2–15%		12.7%
Bacterial			
Unidentified		51.6%	
Streptococcus pneumoniae	20–60%	5.9%	12.6%
Mycoplasma pneumoniae	1–6%	15%	32.5%
Chlamydia pneumoniae	4–6%	12%	8.9%
Haemophilus influenzae	3–10%	4.9%	6.6%
Staphylococcus aureus	3–5%	1.1%	3.4%
Moraxella catharralis	1–2%	1.1%	0.76%
Legionella spp.	2–8%		3.0%
Aspiration	6–10%		
Enterobacteriaceae			2.8%
Pseudomonas spp.			1.7%
Pneumocystis spp.			1.4%
Mycobacterium tuberculosis			1.4%
Coxiella burnetii			
Anaerobes			
Mixed infection			2%

* Based on integration of data from 15 studies on community-acquired pneumonia from North America.

† Prospective randomized series enrolling 507 patients for the comparison of moxifloxacin and clarythromycin treatment.

§ Population-based active surveillance study of 2776 patients from Ohio.

In community-acquired pneumonia, *M. pneumoniae* is identified as the etiologic agent in roughly 3% to 20% of cases, depending on the population studied (Table 2) and subject to cyclical variation with peaks every 4–7 years (8). Generally, it is believed to account for 15% to 20% of all pneumonias (9). Importantly, in at least five studies of pneumonia in ambulatory patients *M. pneumoniae* was the leading pathogen (15% to 34% of all cases), highlighting the importance of this pathogen for emergency physicians (6). The highest incidence of *M. pneumoniae* infection and of pulmonary involvement is found in the age group between 5 and 20 years (8). The incubation period is 2–3 weeks (1). If multiple members of a family are affected, they often present serially with 2–3 week intervals (10). On initial physical examination, pulmonary auscultation is often normal. Hence, abnormal findings on lung examination have a limited sensitivity for detecting pneumonitis that is seen on radiograph (11). Later in the disease, up to 80% of patients with radiologic pneumonitis develop scattered rales or wheezes (1). Chest X-ray study shows either a bronchopneumonia-like pattern, disc-like atelectasis, nodular infiltrations, or hilar adenopathy (1).

Complications

As many as 25% of patients with *M. pneumoniae* infection may experience extrapulmonary complications such as nervous system involvement (up to 7% of infected

patients: encephalitis, cerebellar ataxia, transverse myelitis, Guillain-Barré Syndrome, peripheral neuropathies), cardiac involvement (1% to 8.5% of patients: myocarditis, pericarditis), respiratory distress syndrome, lung abscess, hemolytic anemia, coagulopathies, musculoskeletal symptoms (up to 14%), isolated mucositis, disseminated infection (in the immunocompromised host), and skin rashes of different severity (in up to 25%) (8,10,12). For most complications, secondary autoimmunity has been suggested to be responsible (10). The most severe form of skin complication is the Stevens-Johnson Syndrome (SJS) occurring in up to 7% of cases of *Mycoplasma pneumoniae* (3,13), preferentially affecting young males and characterized by a generalized exanthema, high fever, mucositis and catarrhal symptoms (14). In pediatric patients, SJS is almost exclusively caused by *M. pneumoniae* infection, whereas a similar skin rash, Erythema multiforme, which is less severe, has a different body-distribution and histology is mainly due to *Herpes simplex* infection (14). In the adult population, SJS is mostly drug-induced (15). Drugs that have been implicated in this mechanism include antimicrobial sulfonamides, aminopenicillins, cephalosporins, quinolones, NSAID oxicams, allopurinol, steroids, carbamazepine, phenobarbital, phenytoin, and the muscle-relaxant chlormezanone, which has now been withdrawn from many markets (15,16). Immediate discontinuation of offending drugs has been shown to reduce fatal outcomes (17). Hence, if SJS occurs under treatment for *M. pneu-*

Table 3. Procedure for bedside cold agglutination test

1. Draw patient's blood into a tube containing anticoagulant (e.g., citrate; standard tubes for determination of prothrombin activity can be used)
2. Cool in ice water for 30 s to 5 min
3. Tilt tube on the side and examine for coarse agglutination of red cells on the tube wall
4. The test is positive if agglutination occurs
5. Rewarming should redissolve the agglutination, recooling should reproduce it
6. The strength of the agglutination correlates with the severity of the *M. pneumoniae* pneumonia

Adapted from (3,10).

moniae, the antimicrobial class should be switched immediately (13).

Diagnosis

The diagnosis of *M. pneumoniae* pneumonia cannot be secured by clinical means alone but requires laboratory confirmation. Available methods are: detection of cold agglutinin; IgA, IgM, or IgG; direct antigen detection (e.g., by antigen-capture enzyme-linked-immunoassay/EIA); antigen-amplification (by polymerase-chain-reaction/PCR); or culture (10). Unfortunately, no method generally allows for reliable rapid diagnosis upon presentation of the patient. Therefore, treatment usually must be initiated on an empiric basis (2).

However, in the ED, bedside testing for cold agglutinin (CA) is of potential interest (see Table 3 for instructions). The formation of CA is a non-specific early IgM reaction against the red cell "T" antigen that develops in about 50% of all patients 1–2 weeks after infection (3,18). According to one series of patients with positive *Mycoplasma* serology, the incidence of CA is highest in the pediatric population (95% of patients aged 0–19 years) and decreases with age (82% between age 20 and 39 years; 51% at age 40) (19). Mild forms of hemagglutination may also occur with other conditions (e.g., viral infection, vasculitis, lymphoma), leading to a loss in specificity (3,18). Of those, *Influenza* is the most important confounder (causing CA in 20% of seropositive cases), whereas the other conditions usually preclude suspicion of a *M. pneumoniae* infection on clinical grounds alone (19). In the appropriate clinical setting (i.e., when a lower respiratory tract infection is suspected, or e.g., in the presence of a skin rash), positive CA testing is usually very suggestive and helpful for diagnosing *M. pneumoniae* infection (3,10). This is also illustrated by a series of patients with lower respiratory infection (22% prevalence of *M. pneumoniae*), where the sensitivity and specificity of the cold agglutinin test were

78.3% and 92%, respectively, using a cutoff titer of $\geq 1:64$ (19). The bedside version of the test normally turns positive at the same titer (2,3). Until recently, hemagglutination has been the most widely used routine laboratory test for *M. pneumoniae* infection (3,10). Since the advent of highly specific serology (see below), the usefulness of CA testing has been questioned by many authors (18). However, recent data demonstrate a reasonable test validity in the appropriate clinical setting, suggesting that the CA test may have been underestimated (19).

Specific serology is nowadays the most important routine laboratory test, but a result normally takes 2 days or even 15 days when paired serum samples have to be analyzed. Serology becomes positive 1–2 weeks after the onset of symptoms. IgM leads the serologic response and is practically always present in children, whereas it is often absent from young adult age onwards due to the experience of reinfection—the majority of adults over 40 years of age has an isolated IgG response, as seen in our patient (20); IgA then may serve as a substitute early response marker (18). In the past, Ig has been assayed by complement fixation (CF) testing [sensitivity and specificity of 90% and 94%, respectively (18)]. Nowadays the superior EIA techniques are in use, yielding a sensitivity and specificity of 97.8% and 99.7%, respectively, when both IgM and IgG are measured (20). Ig testing is considered positive either with a titer 1:32 or a fourfold increase in titer of paired serum samples taken 2–3 weeks apart, as was the case in our patient (10). Elevated IgM and IgG levels persist for several months and years, respectively (8). Importantly and of note to emergency physicians, commercial rapid bedside tests for IgM or IgG and requiring < 10 min have recently been developed, representing a potentially useful but costly (> \$10 per test) alternative to bedside agglutinins for immediate results (21). For unpaired samples, sensitivity is roughly similar to cold agglutinin testing (2,19,21). Direct unamplified antigen tests of the sputum such as the indirect immune assay, antigen-capture EIA, and the direct nucleotide detection are scarcely used today because they are both insensitive (requirement for high antigen densities in the sample) and unspecific (due to cross-reactivities with other *Mycoplasma* species of the respiratory tract) (10). The PCR nucleic acid amplification methods can provide results with 100% specificity within 1 day. Yet sensitivity is currently around 60% and testing is available as routine in only few centers. However, these methods may become much more important in the future as their validation progresses (10). *Mycoplasma* culture of throat swabs, sputum, or organ tissue (sensitivity around 60%) requires meticulous handling of the specimen, elaborate microbiological testing, and takes up to 4 weeks to grow (10). Hence, it is mainly used in

clinical studies and in the management of extrapulmonary complications, but not for routine (3,10).

Treatment

Treatment in the acute setting has to be empiric. According to current guidelines, first-line options against bacterial agents of atypical pneumonias including *M. pneumoniae* consist of a macrolide or a tetracycline (2,3). If needed (e.g., in case of a suspected adverse reaction to a first-line antibiotic), newer Quinolones would be an alternative, e.g., Levofloxacin or Moxifloxacin (22). Although *M. pneumoniae* infection can be self-limited, antibiotic treatment is believed to alleviate the severity of the symptoms, and shorten the course of the disease when compared to no treatment (2,22). The fact that treatment leads to negative PCR for *Mycoplasma* within 24 h further suggests that it may also reduce infectivity and spread among family members (10). Indeed, antibiotic prophylaxis has proven effective in preventing spread of the infection in close communities, such as among military recruits (3). At present it is unknown if extrapulmonary complications such as the SJS can be avoided by very early anti-mycoplasmal treatment (2).

To summarize, pneumonia due to *M. pneumoniae* (or other atypical agents) is always a possible diagnosis in a patient presenting to the ED with signs of upper airway infection and should not be overlooked. The following signs may suggest the entity, in this order: history of exposure (keep in mind that family members may develop symptoms in 2–3-week intervals), associated skin symptoms, age 5–20 years (the elderly are usually unaffected), productive cough and fever, headache and musculoskeletal pain (1,3,13). Then additional tests such as a chest radiograph study and bedside cold agglutinins can be obtained. For subsequent decisions whether a patient should be hospitalized, two pneumonia severity scores are available (23,24).

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