

Review article: mycoplasma pneumoniae-associated acute hepatitis

Abstract

Mycoplasma pneumoniae is a major cause of respiratory infections and a possible etiology of acute hepatitis. Acute hepatitis due to *M. pneumoniae* infection is often combined with presentation of pneumonia, even without lung involvement. The presentations and etiologies of *M. pneumoniae*-associated hepatitis with simultaneous, delayed, or without, lung involvement are different, and should be discussed separately. The most widely available and effective drug of treatment is macrolides, and its clinical outcome is extremely good.

Keywords: hepatitis, *Mycoplasma pneumoniae*

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Introduction

Mycoplasma pneumoniae, one of the smallest organisms that can survive alone in nature, is a common cause of upper respiratory tract infections. The first mycoplasmas were discovered in 1898 by Nocard and Roux in animals with contagious bovine pleuropneumonia. In 1944, Eaton isolated a pathogenic *Mycoplasma* from a patient with atypical pneumonia. It was named *M. pneumoniae* by Chanock in 1962.¹ *M. pneumoniae* is a short rod that is invisible on Gram staining due to lack of a cell wall,² and it can grow under both aerobic and anaerobic conditions. It is a major cause of respiratory infections in school-aged children and young adults.³ Although the incidence of the disease does not vary greatly by season, outbreaks of *M. pneumoniae* infections tend to occur in the summer or early fall.⁴

M. pneumoniae infection is transmitted through aerosols from person to person, and persons with active mycoplasmal infection will carry the organism in the nose, throat, trachea and sputum. Most *M. pneumoniae* infections in adults involve the respiratory tract, and symptoms range from nonproductive cough to severe pneumonia.⁵ The severity of disease appears to be related to the degree to which the host immune response reacts to the infection.⁴

Extrapulmonary manifestations of *M. pneumoniae* infection may be found in the dermatologic, cardiovascular, neurologic, hematologic, musculoskeletal and gastrointestinal systems.⁶ Approximately 25% of patients hospitalized for treatment of *M. pneumoniae* can present extrapulmonary complications at some time during the disease course.⁷ Skin lesions include maculopapular rashes, erythema multiforme minor, and Stevens-Johnson syndrome. Cardiovascular involvement includes myocarditis, pericarditis and rheumatic fever-like syndrome. Neurologic complications include meningoencephalitis, aseptic meningitis, cerebellar ataxia and Guillain-Barre syndrome. Hematologic involvement includes hemolysis with positive Coombs' test and reticulocytosis. Musculoskeletal presentations include nonspecific myalgia, arthralgias and polyarthropathies.

Gastrointestinal manifestations include vomiting, abdominal pain, and albeit rare, pancreatitis and hepatitis.^{7,8} The immune-mediated damage by cross-reactive anti-*M. pneumoniae* antibodies is thought to be responsible for most of the extrapulmonary manifestations.⁹

Simultaneous *M. pneumoniae*-associated pneumonia and acute hepatitis

Elevated liver enzyme assays are frequently observed during *M. pneumoniae* infection. Squadrini et al.,¹⁰ reported that 50% of patients presenting with serologically-confirmed *M. pneumoniae* disease showed evidence of hepatic disorder.¹⁰ The most widely recognized manifestation of *M. pneumoniae*-related hepatitis is elevated alanine aminotransferase (ALT) level. The hepatic dysfunction was found to be transitory and recovery of normal liver function correlated directly with the resolution of the mycoplasma respiratory disease. Although rare, chronic active hepatitis has also been reported.¹¹

The pathogenesis of self-limiting hepatitis may be attributed to several factors, including a direct cytolytic effect mediated by the infecting mycoplasma resulting in perinecrotic edema; immunological, autoimmune disorder resulting from the production of heterophil antibodies; or the mitogenic properties of *M. pneumoniae* acting on lymphocytes, which plays a role in the development of complications involving target organs.⁶ Suzuyama et al.⁸ documented that inflammatory signs such as higher body temperature, greater number of leukocytes, and elevated C-reactive protein (CRP) levels were more likely to appear in patients with abnormal liver function than those with normal liver function.⁸ Doxboeck et al.,¹² noted that patients with *M. pneumoniae*-associated pneumonia and abnormal liver function had higher leukocyte and CRP levels than those with normal liver function.¹² Shin et al.,¹³ found male gender, younger age, and higher CRP were associated with *M. pneumoniae*-related hepatitis.¹³ In summary, patients with simultaneous pneumonia and hepatitis due to *M. pneumoniae* infection have greater disease severity and more acute inflammatory reactions.

***M. pneumoniae*-associated acute hepatitis without pneumonia**

Viral hepatitis accounts for most cases of acute hepatitis. Some bacterial infections are often associated with acute hepatitis, such as *Salmonella*, *Rickettsia*, *Brucella* or *M. pneumoniae*.¹⁴ Hepatitis due to *M. pneumoniae* was first described in 1975.¹⁵ Selected cases of *M. pneumoniae*-associated acute hepatitis were retrieved from MEDLINE and are summarized in Table 1.^{9,14,16,17}

In general, acute hepatitis due to *M. pneumoniae* without lung infection has been largely documented in children with a cholestatic pattern.^{9,10} Hyperbilirubinemia usually occurs as the indirect

type, mostly because of hemolysis in mycoplasma infections. In contrast, adults with *M. pneumoniae* infection have demonstrated a hepatocellular pattern of liver enzymes without jaundice.¹⁴⁻¹⁷ According to these reports, the fever of individuals with *M. pneumoniae* subsided rapidly, on average in 1 to 2 weeks after treatment, but ALT did not normalize till about one month later. The persistent ALT elevation may be mediated by immunological mechanisms, such as cross-reactive antibodies induced by *M. pneumoniae* interacting with sialyloligosaccharides on hepatic cells.¹⁹ The outcomes of these cases were extremely good, and no mortality was reported. In children, *M. pneumoniae* has been reported to be implicated in infectious mononucleosis or Kawasaki disease with hepatic manifestations.^{16,20}

Table 1 Outcomes of *M. pneumoniae*-associated acute hepatitis

Reference	Gender	Age(year)	Symptoms	Liver Function at Admission		Treatment	Outcomes		
				AST/ ALT	ALP/ BIL		Fever regress (day)	Liver function normalize (week)	Anti-IgM disappear (month)
Narita et al., ¹⁶	M	5	Fever, lymphadenopathy, polymorphous exanthema	2375/1488	ND/ND	IV clarithromycin	5	4	ND
Narita et al., ¹⁶	M	10	Fever, lymphadenopathy	129/240	ND/ND	Oral minocycline	ND	3	ND
Arav-Boger et al., ⁹	M	10	Fever, maculopapular rash	674/524	310/2.8	Oral erythromycin	14	4	3
Quioc et al., ¹⁸	F	18	Fever, epigastria, headache	72/46	212/7	Oral roxithromycin	ND	2	6
Romero-Gomez et al., ¹⁴	M	22	Fever, backpain	217/355	150/1.56	IV levofloxacin	7	4	2
Romero-Gomez et al., ¹⁴	F	22	Fever, asthenia	236/402	ND/ND	IV levofloxacin	14	4	2
Lee et al., ¹⁷	F	25	Fever, abdominal pain	584/777	70/0.5	IV levofloxacin, oral doxycycline	7	4	ND

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BIL, total bilirubin; F, female; M, male; ND, non-determined; IV, intravenous; anti-IgM, anti-*M. pneumoniae* antibodies

Delayed acute hepatitis after acute *M. pneumoniae* infection

On the basis of previous reports, the delayed onset of liver injury after *M. pneumoniae* infection was largely due to the use of treatment drugs.²¹ The time course of liver injury has been reported to be 5 to 10 days. The association of macrolide antibiotics with cholestatic hepatitis is well-known,²² and azithromycin-induced hepatotoxicity has also been reported in adults.²³

Diagnosis

Because *M. pneumoniae* is an intracellular pathogen, cultures are not always available and those that are usually exhibit slow growth with low sensitivity, making them unreliable for routine diagnosis. There is little evidence to indicate direct invasion of *M. pneumoniae*.¹⁴ Few previous liver pathology reports demonstrated non-specific findings, either hepatocellular destruction with inflammatory infiltration or lobular hepatitis.^{24,25} Since liver biopsy in patients

with *M. pneumoniae* infection is usually nonspecific, it might not be necessary to confirm diagnosis.

The characteristic findings of patients with *M. pneumoniae*-associated acute hepatitis with or without pneumonia are fever, elevated liver function test, positive IgM serology against *M. pneumoniae* followed by IgG seroconversion, with resolution by antibiotics and exclusion of other possible etiologies. It is advisable to test simultaneously for both IgM and IgG in paired specimens collected 2 to 3 weeks apart, and a fourfold or greater rise in antibody titers indicates a current or recent infection.²⁶ In some adults with previous *M. pneumoniae* infection, long-term high seroprevalence of IgG antibodies and lack of an IgM response were observed, and that imposes serious limitations on the use of serology as the sole means for diagnosis of *M. pneumoniae* infection.^{1,27} Thus, a feasible approach would be to incorporate polymerase chain reaction (PCR) and the serological studies for IgG and IgM for optimum diagnosis of *M. pneumoniae* infections.

Treatment and outcome

M. pneumoniae has no cell wall and therefore is naturally resistant to penicillin, cephalosporins, all beta-lactams and vancomycin, sulfonamides, trimethoprim, and rifampin. *M. pneumoniae* is susceptible to macrolides, cyclines, and quinolones. Interestingly, macrolides were more frequently used in patients with *M. pneumoniae*-associated hepatitis than quinolones. The reason might be that macrolides metabolize in the liver and are excreted primarily in the bile in contrast to quinolones which metabolize via renal excretion.²⁸ Up to now, no consensus on the duration of therapy with macrolides has been reached, and treatment schemes spanning from one to three weeks have been described. Clinical outcomes have been favorable in published cases, and no associated fatalities have been reported to date. However, eradication of *M. pneumoniae* from immunocompromised individuals can be extremely difficult, and requires prolonged therapy.

Conclusion

M. pneumoniae is a major cause of respiratory infections and a possible etiology of acute hepatitis. Acute hepatitis due to *M. pneumoniae* infection is often combined with presentation of pneumonia, even without lung involvement. The most widely available and effective drug of treatment is macrolides, and its clinical outcome is extremely good.

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None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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