Mononuclear syndrome with acute hepatitis diagnosed as Mycoplasma pneumoniae infection without lung involvement

Kyoung H. Ko, Min J. Kim, Seung H. Baik, Young K. Yoon

From the Division of Infectious Diseases, Department of Internal Medicine, Korea University College of Medicine, Seoul, South Korea

Correspondence: Young Kyung Yoon, MD, PhD · Division of Infectious Diseases, Department of Internal Medicine, Korea University Anam Hospital, Inchon-ro 73, Seongbuk-gu, Seoul 136-705, South Korea · T: +82-2-920-5096, F: +82-2-920-5616 · young7912@korea.ac.kr

Ann Saudi Med 2016; 36(1): 81-84
DOI: 10.5144/0256-4947.2016.81

Although pneumonia is the hallmark of Mycoplasma pneumoniae infections, it has been associated with protean manifestations such as extrapulmonary involvement. Herein, a rare case of mononuclear syndrome with acute hepatitis and erythema multiforme revealed as M pneumoniae infection without lung involvement is reported. A 30-year-old man, previously healthy, presented with fever and rash with acute hepatitis: AST 603 IU/L, ALT 747 IU/L, prothrombin time 52%. Peripheral blood smears indicated monocytosis with atypical lymphocyte. Bone marrow biopsy revealed increased plasma cell infiltration. M pneumoniae infection was detected by serology testing. After treatment with macrolide, clinical symptoms and signs and serological tests were fully resolved. Diagnosis of this etiologic association is important when patients present with various clinical syndromes without pneumonia, because only specific antimicrobial therapy is effective against M pneumoniae.

Mycoplasma pneumoniae is a member of the Mollicutes class, the smallest and most unusual group of self-replicating prokaryotes that is distinguished from other bacteria by the absence of a cell wall. Although M pneumoniae has been frequently described as one of the most common causes of community-acquired pneumonia (CAP), there has been increasing evidence to implicate this organism as the cause of a wide range of extrapulmonary manifestations in neurologic, cardiovascular, dermatological, gastrointestinal, hematological, musculoskeletal, sensory organ, and urogenital tract systems.1 There are also published reports on extrapulmonary diseases in adults who do not have associated respiratory tract infections.2-4 Here, an unusual case of an adult patient who presented with acute hepatitis with mononuclear syndrome and erythema multiforme caused by M pneumoniae and who was successfully treated with levofloxacin is described.

CASE
A 30-year-old man with a 7-day history of fever and myalgia was hospitalized at the Korea University Hospital, Seoul, South Korea. He had no history of travel or any type of allergic reaction. However, he had been consuming a combination of trimethoprim and sulfamethoxazole since the previous month for a perianal fistula. He had stopped the antibiotic treatment 5 days earlier due to fever. On admission, his body temperature was 38.7°C with a heart rate of 80 beats per minute and a respiratory rate of 18 breaths per minute. Physical examination revealed tenderness on the right upper quadrant area and erythema multiforme on his trunk (Figure 1A). However, he did not complain of itching. The initial complete blood count showed hemoglobin levels of 14.9 g/dL; a platelet count of 170 000/µL; and a white blood cell (WBC) count of 11 090/µL, comprising 40.6% neutrophils, 18.6% monocytes, 31.8% lymphocytes, 6.4% eosinophils, 2.6% basophils, and 5% atypical lymphocytes, a distribution consistent with mononuclear syndrome. Blood chemistry showed an aspartate aminotransferase (AST) concentration of 504 IU/L, alanine aminotransferase (ALT) concentration of 578 IU/L, μ-glutamyl transpeptidase (GGT) concentration of 209 IU/L, alkaline phosphatase (ALP) concentration of 157 IU/L, total bilirubin concentration of 1.18 IU/L, and lactate dehydrogenase concentration of 1148 IU/L. Other laboratory tests showed a prothrom-
bin time of 15.2 second (74%; international normalized ratio [INR], 1.20), erythrocyte sedimentation rate of 13 mm/h, and C-reactive protein level of 81.25 mg/L. Peripheral blood smears indicated normocytic normochromic anemia, monocytosis with atypical lymphocyte, moderate leukocytosis, and neutrophilia with toxic neutrophil changes (Figure 1B). The patient was examined for the major causes of mononuclear syndrome with acute hepatitis: serologic tests for hepatitis A, B, C, and E; anti-Epstein–Barr virus viral-capsid antigen-immunoglobulin (Ig) M; and anti-cytomegalovirus-IgM and human immunodeficiency virus antibody and antigen combination assays were all negative. Autoimmune hepatitis was excluded because of the following results: anti-nuclear antibodies, negative; anti-mitochondrial antibodies, negative; smooth muscle antibody, negative; antibody to liver and kidney microsomes type 1, negative; and IgG level of 956 mg/dL. Furthermore, there was no evidence of hemochromatosis or Wilson disease: ferritin level of 888 ng/mL, serum iron level of 20 µg/dL, transferrin saturation of 10.1%, ceruloplasmin level of 31.7 mg/dL, and serum copper level of 134 µg/dL. Abdominal computed tomography showed reactive gallbladder wall thickening and minor lymphadenopathy around the aorta and portal vein. Chest radiography showed no significant shadows. The patient was treated for 1 week with conservative management without antibiotics.

On the eighth day of hospitalization, the patient’s body temperature increased to 40°C, and he had abdominal distension due to ascites. Liver function tests revealed increased levels of AST (603 IU/L), ALT (747 IU/L), GGT (231 IU/L), ALP (200 IU/L), and total bilirubin (3.86 IU/L), and increased prothrombin time (18.7 seconds, 52%, INR 1.57). To exclude spontaneous bacterial peritonitis and relieve abdominal discomforts, diagnostic and therapeutic paracentesis was performed. In total, approximately 2 L of the ascites was drained from

Figure 1. (A) Erythema multiforme on the trunk, showing target lesions. (B) Peripheral blood morphology demonstrating atypical lymphocytes with irregular margins and abnormal granules (Wright–Giemsa, 100×). (C) Bone marrow biopsy showing increased plasma cell infiltration (hematoxylin and eosin, ×400). (D) Bone marrow biopsy with plasma cells positive for CD138 arranged in a membranous pattern (CD 138 stain, ×400).
his abdomen. Fluid analysis revealed a WBC count of 380 per mm$^3$ (3% neutrophils, 89% lymphocytes, and 8% monocytes), albumin levels of 1.5 g/dL, protein levels of 3.0 g/dL, and a serum-ascites albumin gradient (SAAG) of 1.3, values consistent with portal hypertension. The transthoracic echocardiography was normal, and liver ultrasonography revealed only non-specific findings. Owing to the high bleeding risk due to the prolonged prothrombin time, a liver biopsy was not performed. Bone marrow biopsy revealed increased plasma cell infiltration \( \text{(Figure 1C and 1D)} \). The \( M \) \textit{pneumoniae} IgM antibody titer on enzyme immunoassay (eIA) was 1:80 on admission. However, it increased to 1:640 on the 10th day of hospitalization \( \text{(Table 1)} \). Repeated tests for cold agglutinins were negative. On the 10th day of hospitalization, the patient was administered levofloxacin (500 mg/day for 17 days), 3 days after which the fever resolved. The patient was discharged in good condition, with marked improvement in ascites \( \text{(Table 1)} \). No relapse was noted over a 3-month follow-up period after completion of the antibiotic therapy, and the \( M \) \textit{pneumoniae} IgM antibody titer decreased to 1:80.

**DISCUSSIONS**

Since \( M \) \textit{pneumoniae} was first isolated from the sputum of a patient with atypical pneumonia in 1944, this organism has been the most common pathogen associated with atypical CAP in adults, accounting for 11% to 15% CAP cases worldwide. \( M \) \textit{pneumoniae} infection occurs in epidemics that occur periodically every 3 to 7 years. In South Korea, approximately 3-year cycles of pneumonia caused by \( M \) \textit{pneumoniae} have been observed in children since the mid-1980s. Interestingly, since the 1990s, this epidemic pattern has been interrupted, with a trend toward longer cyclic epidemics and a broader age distribution of susceptible groups and more adult patients. However, data are limited in adults.

Although pneumonia has been a hallmark of \( M \) \textit{pneumoniae} infection, its clinical significance is not confined solely to respiratory tract infections. The case discussed here had hepatic, dermatological, hematological, and cardiovascular manifestations without lung involvement. Direct invasion by locally induced cytokines, neurotoxin production, vascular occlusion by vasculitis or thrombosis, and an immune-mediated process such as autoimmunity have been suggested as possible mechanisms. Particularly, there have been 3 cases of \( M \) \textit{pneumoniae} infection in adults with liver involvement and no signs of pneumonia. However, there has been no prior report on mononuclear syndrome with acute hepatitis associated with mycoplasma infection in children and adults.

The SAAG helps clinicians determine the presence (SAAG>1.1) or absence of portal hypertension (SAAG<1.1). Therefore, a SAAG of 1.3 is suggestive of ascites resulting from portal hypertension. On the basis of a WBC count <500 per mm$^3$, a polymorphonuclear count <250 per mm$^3$, SAAG ≥1.1, and a total protein level ≥2.5 g/dL, clinicians can identify cardiac diseases to be a cause of ascites. However, the transthoracic echocardiograph was normal, and the patient had no underlying cardiac diseases. If the total protein level was <2.5 g/dL, ascites could be a case of uncomplicated cirrhotic ascites. On the contrary, patients with acute hepatitis and ascites may present normal total protein levels in the early stage of the disease, as in the case reported. Although it is difficult to determine the definite cause of ascites, the possibility of it resulting from acute hepatitis cannot be excluded.

| Days after admission | Before antibiotic therapy | After antibiotic therapy | Discharge* |
|---------------------|--------------------------|--------------------------|------------|
| AST, IU/L           | 504                      | 603                      | 158        | 65 | 23 |
| ALT, IU/L           | 578                      | 747                      | 122        | 77 | 46 | 31 |
| TB, mg/dL           | 1.18                     | 3.86                     | 10.3       | 6.59 | 3.94 | 1.13 |
| INR                 | 1.21                     | 1.72                     | 1.49       | 0.99 | - | - |
| aPTT, s             | 32.3                     | 37.2                     | 17.9       | - | - | - |
| Mycoplasma pneumoniae IgM antibody titer | - | - | 1:640 | 1:640 | 1:320 | 1:80 |

* Asterisk indicates a month after discharge from the hospital.

ALT: Alanine aminotransferase, aPTT: activated partial thromboplastin time, AST: aspartate aminotransferase, IgM: immunoglobulin M, INR: international normalized ratio, TB: total bilirubin.
Several diagnostic serologic methods are available for epidemiological studies or clinical diagnosis of M pneumoniae infection; however, they are not standardized. This case showed a fourfold IgM and IgG titer increase on EIA during the acute phase compared to the convalescent phase. Measurement of specific M pneumoniae IgM antibodies for diagnosis during the early phase of M pneumoniae infection has been possible with EIA because it is commercially available, with sensitivities and specificities of 35% to 77% and 49% to 100%, respectively. However, because these assays have low diagnostic yields within a week after onset of initial infection, misdiagnosis or late diagnosis is a possibility during this period, as in this case. Delays in diagnosis can directly affect the clinical outcome. Thus, paired-sample serologic tests are needed for definitive and rapid diagnosis.

Trimethoprim–sulfamethoxazole has been known to cause hepatitis, although serious toxicity is a rare event.\(^8,9\) It is challenging to indicate a causal association between a drug and hepatic injury, especially when there are more than 1 factor. In this case, an objective causality assessment based on the Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) scale, which reflects hepatic injury to be due to a specific medication, suggests that trimethoprim–sulfamethoxazole did not cause fulminant hepatitis in the patient. The score of 4 points, indicates that a specific drug was not the cause of hepatitis.\(^10\)

Standard treatment of extrapulmonary infection caused by M pneumoniae has not yet been established. Treatments range from symptomatic treatment alone, antibiotics alone, a combination of antibiotics and corticosteroids, to corticosteroids alone. Furthermore, optimal antibiotic dosages and duration are not clear. Antibiotics for M pneumoniae infection include fluoroquinolones, tetracyclines, and macrolides. However, macrolide-resistant M pneumoniae has emerged and has been widespread in East Asia since 2000.\(^6\) This case was initially treated with symptomatic management for a week, followed by levofloxacin as an empirical therapy without administering corticosteroids. However, it is difficult to determine the optimal antimicrobial treatment regimen for acute hepatitis caused by M pneumoniae because fluoroquinolones and macrolides have frequently been associated with adverse events, including hepatotoxicity. More experience is required to improve treatment regimens for extrapulmonary infections caused by M pneumoniae.

In conclusion, this case suggests that M pneumoniae should be added to the list for the differential diagnosis of acute hepatitis and mononuclear syndrome in adults even without pneumonia, because specific antibiotics are required to prevent potentially severe infection.

REFERENCES

1. Narita M. Pathogenesis of extrapulmonary manifestations of Mycoplasma pneumoniae infection with special reference to pneumonia. J Infect Chemother. 2010; 16:162–9.
2. Quicío JJ, Trabul JB, Drouhin F, Malbrunot C, Vallet-Pichard A, Pol S, et al. Acute cholestatic hepatitis revealing Mycoplasma pneumoniae infection without lung involvement in an adult patient. Eur J Gastroenterol Hepatol. 2009; 21:220–1.
3. Romero-Gómez M, Otero MA, Sánchez-Muñoz D, Ramírez-Arcos M, Larraona JL, Suárez García E, et al. Acute hepatitis due to Mycoplasma pneumoniae infection without lung involvement in adult patients. J Hepatol. 2006; 44:827–8.
4. Lee SW, Yang SS, Chang CS, Yeh HJ, Chow WK. Mycoplasma pneumoniae-associated acute hepatitis in an adult patient without lung infection. J Chin Med Assoc. 2009; 72:204–6.
5. Lee KY. Pediatric respiratory infections by Mycoplasma pneumoniae. Expert Rev Ant Infect Ther. 2008; 6:509–21.
6. Saraya T, Kuriyama D, Nakagaki K, Sasaki Y, Niwa S, Takagoshi H, et al. Novel aspects on the pathogenesis of Mycoplasma pneumoniae pneumonia and therapeutic implications. Front Microbiol. 2014; 5:410.
7. Chang JH, Kwon YS, Kim BK, Son BK, Lee JE, Lim DH, et al. A case of acute hepatitis with Mycoplasma pneumoniae infection and transient depression of multiple coagulation factors. Yonsei Med J. 2008; 49:1055–9.
8. Thies PW, Dull WL. Trimethoprim-sulfamethoxazole-induced cholestatic hepatitis. Inadvertent rechallenge. Arch Intern Med. 1984; 144:1691-2.
9. Muñoz SJ, Martínez-Hernández A, Madrey WC. Intrahepatic cholestasis and phospholipidosis associated with the use of trimethoprim-sulfamethoxazole. Hepatology, 1990; 12:342–7.
10. Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol. 1993; 46:1323–30.