Mycoplasma pneumoniae-associated Hepatitis without Lung Involvement

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Mycoplasma pneumoniae (M. pneumoniae) is a major cause of community acquired respiratory infections. And it also causes a number of extrapulmonary manifestations including cardiovascular, dermatological, musculoskeletal, and hematological systems. But, acute hepatitis without lung involvement is rare in adults. Here, we report a case of 32-year-old man who presented with fever, chilling, myalgia, and headache. Biochemical analysis showed severely impaired liver function and leukopenia. Laboratory tests and liver biopsy demonstrated a hepatocellular pattern of M. pneumoniae-associated acute hepatitis. Clinical symptoms and laboratory parameters are improved rapidly under treatment with macrolide. Therefore, We recommend that physicians should consider a possibility of M. pneumoniae infection in acute hepatitis without lung and extrapulmonary involvement, when other more frequent causes have been excluded. (Korean J Gastroenterol 2017;70:50-53)

Key Words: Mycoplasma pneumoniae; Hepatitis; Adult; Leukopenia

INTRODUCTION

Mycoplasma pneumoniae (M. pneumoniae) is a major cause of community acquired respiratory infections in both children and adults. M. pneumoniae infection also can cause a number of extrapulmonary manifestations including cardiovascular, dermatological, digestive organ, hematological/hematopoietic system, musculoskeletal, sensory organ, and urogenital tract manifestations. Some cases of M. pneumoniae-associated acute hepatitis without lung and extrapulmonary involvement in adults have been reported, but all of them did not present severe clinical manifestations. We report here the case of M. pneumoniae-associated acute hepatitis with severe clinical manifestations in an adult patient.

CASE REPORT

A previously healthy 32-year-old man was admitted to emergency room with fever, chilling, generalized myalgia and headache for 3 days. The patient was not alcoholic, and he did not take any herbs and drugs. There was no recent travel history. Physical examination on admission was normal, except fever (38.5°C). Initial laboratory test demonstrated a white blood cell count (WBC) of 3.0×10^3/μL, hemoglobin of 14.9 g/dL, platelet count of 160×10^3/μL, aspartate aminotransferase (AST) of 174 U/L, alanine aminotransferase (ALT) of 174 U/L, and lactate dehydrogenase (LDH) of 954 U/L. The chest X-ray showed no abnormality. The liver ultrasound showed no abnormality. The liver biopsy was performed. The histological examination of the liver biopsy showed severe injury of hepatocellular damage with infiltration of inflammatory cells. The patient was treated with prednisolone and macrolide, and the patient showed significant improvement.
of 177 U/L, alkaline phosphatase (ALP) of 83 U/L, total bilirubin (T-bil) of 0.6 mg/dL, gamma glutamyltranspeptidase of 110 U/L, and C-reactive protein of 5.5 mg/L (normal range, <5.0 mg/L). Antibody to hepatitis A virus, hepatitis B surface antigen and antibody to hepatitis C virus were negative, but antibody to hepatitis B surface antigen was positive. Chest and abdominal computed tomography did not reveal any abnormal finding except adrenal incidentaloma. Cerebrospinal fluid analysis and urinalysis were also normal. Further, blood and urine culture were negative. The result of peripheral blood smear showed decreased WBC with toxic granules and vacuoles, indicative of acute inflammatory reaction. The patient was discharged from hospital with medication including antipyretics, pain killer and hepatotonics.

Two days later, the patient visited hospital for clinical follow-up. He still suffered from fever (38.1 °C), chilling, and myalgia. Follow-up laboratory tests were deteriorated. They demonstrated a WBC of 2.1×10³/µL with absolute neutrophil count of 1.1×10³/µL, hemoglobin of 14.8 g/dL, platelet count of 124×10³/µL, AST of 1,405 U/L, ALT of 1,466 U/L, ALP of 185 U/L, T-bil of 1.5 mg/dL, and C-reactive protein of 5.4 mg/L. He was admitted to hospital again for further evaluation, and treated with broad spectrum antibiotics (3rd generation cephalosporin) and hepatotonics, but elevation of liver function parameters were progressed as follows; AST of 2,913 U/L, ALT of 3,068 U/L, ALP of 185 U/L, T-bil of 3.3 of mg/dL, and gamma glutamyltranspeptidase of of 329 U/L on the 3rd day of hospitalization. Initial prothrombin time was within normal range, but follow-up prothrombin time was elevated to 17.2 sec (normal range, 11.5-15 sec) on the same day. Antinuclear antibody, anti-neutrophilic cytoplasmic antibody and antimitochondrial antibody were negative. Immunoglobulin M antibodies against herpes simplex virus, cytomegalovirus, epstein-barr virus, hantavirus, leptospira, and orientia tsutsugamushi were also negative. Lastly, immunoglobulin M antibody against *M. pneumoniae* by chemiluminescent immunoassay (index value is 10) was positive twice on repeated test (18, 27 respectively). Antibiotic therapy was changed to azithromycin (500 mg orally once daily) on clinical suspicion of *M. pneumoniae*-associated hepatitis. Liver biopsy was also performed. Symptomatic and laboratory recovery occurred on the 8th day of hospitalization. The patient was discharged from hospital on the 13th day of hospitalization, and eight days later, liver function tests returned to normal range (Fig. 1).

The liver biopsy revealed acute hepatitis with mild lobular activity, moderate porto-periportal activity and no fibrosis so that we could be more certain of *M. pneumoniae*-associated acute hepatitis (Fig. 2), but *M. pneumoniae* DNA was not detected in liver tissue using polymerase chain reaction assay.

**DISCUSSION**

*M. pneumoniae* infections can involve both upper and the lower respiratory tracts and occur worldwide in children and...
adults. It also causes a wide variety of extrapulmonary disease including almost all organs of the human body. The incidence of *M. pneumoniae*-associated hepatitis was reported ranging from 7-21% and usually occurred with pneumonia. The most noticeable manifestation of *M. pneumoniae*-associated hepatitis is an elevation of ALT level in both adults and children. On the other hand, pulmonary infiltration is more common in children than in adults. Shin et al. and Kim et al. investigated the incidence and clinical characteristics of *M. pneumoniae*-associated hepatitis in adults and children respectively. All of children had pulmonary infiltration, according to findings of Kim et al. Similarly, most of adults, according to findings of Shin et al., showed typical signs and symptoms of *M. pneumoniae* infection such as atypical pneumonia (64%), pleural effusion (32%), and respiratory symptoms including cough, sputum, and chest discomfort (76%). But, there was no description of whether extrapulmonary infections such as urinary tract infection, musculoskeletal infection, etc. were excluded. Further, elevations of aminotransferases were mostly mild. Thus, the conclusion of Shin et al. is that 21% of patients who had both respiratory or other infections and serologically-confirmed *M. pneumoniae* infection occurred with impaired liver function.

A few cases of *M. pneumoniae*-associated acute hepatitis without lung and extrapulmonary involvement in adults are summarized in Table 1. All patients in these cases had a fever and showed impaired liver function test. But, our case showed most severe hepatitis. Liver biopsy was only performed in our case, and it helped us to be certain of *M. pneumoniae*-associated acute hepatitis.

Although the pathogenesis of *M. pneumoniae*-associated hepatitis remains largely unknown, there are two major theories. One is immune modulation, and the other is direct invasion of *M. pneumoniae*. In accordance with these theories, hepatic involvement could be classified into two types based on 7 days between onset of symptoms and peak liver enzyme level. The one is an early-onset hepatitis, in which hematogeneously transferred *M. pneumoniae* causes inflammation at the local site by inducing cytokines, and the other is a late-onset hepatitis caused by the appearance of autoimmune antibodies or localization of an immune complex. Grüllich et al. and Quioc et al. respectively reported two cases of *M. pneumoniae*-associated acute hepatitis with cholestatic pattern of liver enzymes, and explained that rapid improvement under antibiotics suggests a direct infection of hepatobiliary tract. On the other hand, Lee et al. reported *M. pneumoniae*-associated acute hepatitis with hepatocellular pattern of liver enzymes, and explained that the persistent liver enzyme elevation may have been mediated by immunologic mechanism. Therefore, immunomodulatory effects of macrolides to suppress immune response of the host might work.

In this case, the time interval from onset of symptoms to peak liver function test was 9 days, and although the liver biopsy was performed on the day after macrolide initiation, liver tissue mycoplasma polymerase chain reaction was negative. These suggest *M. pneumoniae*-associated acute hepatitis is more likely attributed to immuned-mediated mechanism.

Another interesting feature in this patient was a leukopenia. There are many hematological manifestations due to *M. pneumoniae* infection including autoimmune hemolytic anemia, hemophagocytic syndrome, disseminated intravascular coagulation, thrombocytopenia purpura, and infectious mononucleosis. However leukopenia is rare. This manifests as Table 1. Clinical Features of Patients with Mycoplasma pneumoniae-associated Acute Hepatitis without Lung Involvement in Adults

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Symptoms</th>
<th>Laboratory finding at admission (ALT/ALP/T-bil/WBC)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quioc et al.</td>
<td>18</td>
<td>Female</td>
<td>Fever, epigastric pain, headache</td>
<td>54/575/0.41/4,500</td>
<td>Roxithromycin 150 mg orally twice daily</td>
</tr>
<tr>
<td>Romero-Gómez et al.</td>
<td>22</td>
<td>Male</td>
<td>Fever, back pain</td>
<td>355/150/1.56/ND</td>
<td>Levofloxacin 500 mg IV daily</td>
</tr>
<tr>
<td>Romero-Gómez et al.</td>
<td>22</td>
<td>Female</td>
<td>Fever, asthenia</td>
<td>402/ND/ND/ND</td>
<td>Levofloxacin 500 mg IV daily</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>25</td>
<td>Female</td>
<td>Fever, abdominal pain</td>
<td>777/79/0.5/4,500</td>
<td>Levofloxacin IV Doxycycline orally</td>
</tr>
<tr>
<td>This case</td>
<td>32</td>
<td>Male</td>
<td>Fever, chilling, myalgia, headache</td>
<td>3,068/185/3.3/2,100</td>
<td>Azithromycin 500 mg orally daily</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; ALP, alkaline phosphatase; T-bil, total bilirubin; WBC, white blood cell count; ND, not determined; IV, intravenous.
M. pneumoniae adhesion proteins and glycolipids of the cell membrane with mammalian tissues is a well-known example of molecular mimicry that may trigger autoimmune disorders. Therefore, in addition to antibody against M. pneumoniae, a variety of cross-reactive antibodies may develop through molecular mimicry. And these antibodies might contribute to leukopenia in our case.

In conclusion, this case demonstrates that M. pneumoniae-associated acute severe hepatitis without lung and extrapulmonary involvement can occur in immunocompetent adult. The patient presented fever, chilling, myalgia and headache without any respiratory symptoms. And symptoms and laboratory test are improved rapidly under appropriate antibiotic administration. Therefore, we recommend that physicians should consider a possibility of M. pneumoniae infection in acute hepatitis without lung and extrapulmonary involvement when other more frequent causes have been excluded.

REFERENCES