We report a case of acute severe hepatitis with *Mycoplasma pneumoniae* infection and transient depression of multiple coagulation factors. A 5-year-old boy, previously healthy, was admitted with pneumonia. *M. pneumoniae* infection was confirmed by serology testing. Liver enzymes were elevated on admission without any past medical history. After treatment with azithromycin for 3 days, pneumonia improved, but the hepatitis was acutely aggravated. Partial thromboplastin time (PTT) was prolonged and depression of multiple coagulation factors developed. Liver biopsy revealed features consistent with acute hepatitis. A week later, liver enzymes were nearly normalized spontaneously. Normalization of prolonged PTT and coagulation factors were also observed several months later. This may be the first case of transient depression of multiple coagulation factors associated with *M. pneumoniae* infection.

**Key Words:** Hepatitis, *Mycoplasma pneumoniae*, depression, coagulation factors

**INTRODUCTION**

*Mycoplasma pneumoniae* (*M. pneumoniae*) is a well known cause of childhood lower respiratory tract infections, reaching up to 40% of community-acquired pneumonia. One recent epidemiologic data showed 6 epidemic peaks at 3-4 years interval over 18 years in Korean children. *M. pneumoniae* infection is also known for its extrapulmonary manifestations. Nausea, vomiting, and abdominal pain are the most common symptoms for extrapulmonary manifestations in Korea. Hepatitis, hematuria, skin rash, gastroenteritis, and myopericarditis were reported in some cases. Gastrointestinal manifestations, such as gastroenteritis, acute and chronic hepatitis, and pancreatitis have been reported. However, severe hepatitis with depressed coagulation factors in children with *M. pneumoniae* infection has rarely been reported. We report a child with acute severe hepatitis with *M. pneumoniae* infection, accompanied with depressed multiple coagulation factors.

**CASE REPORT**

A 5-year-old boy presented with fever and cough for 6 days. He also developed anorexia and lethargy, and then was admitted to Inha University Hospital. Past medical history included atopic dermatitis during infancy. Hepatitis B vaccination was administered as scheduled. Six months prior to admission at a routine health check up, the serum liver enzymes were normal. The patient had no history of a bleeding tendency. There was no family history of hepatitis or liver disease, but the patient had a younger brother with extrinsic asthma.

The patient had fever, cough and nasal obstruction for 6 days. He had abdominal pain, but no vomiting or diarrhea. On admission, he appeared sick. His heart rate was 100/min, respiratory rate 24/min and body temperature 38.7°C. Inspiratory crackles were auscultated at both lung
The liver was slightly enlarged and palpated 2 cm below costal margin. The spleen was not palpable. An erythematous papular rash was noted on both extremities.

Chest X-ray showed diffuse bronchopneumonia in both lungs (Fig. 1). The abdominal sonography showed hepatomegaly with wall thickening of gallbladder. The laboratory tests showed Hb 12.2 g/dL, Hct 35.2%, WBC 4,300/mm$^3$ with 49% neutrophil, 32% lymphocytes, and platelets 237,000/mm$^3$. The serology testing for M. pneumoniae IgM class antibody titer was 4,377 Units/mL (normal range: <770 Units/mL). The bedside cold agglutinin test was positive. The specific antibody test was done by the ELISA method (Immuno Well, GenBio, San Diego, CA, USA). The alanine aminotransferase (ALT) was 100 IU/L and aspartate aminotransferase (AST) 169 IU/L. The total bilirubin was 0.5 mg/dL and the direct bilirubin 0.3 mg/dL. The total protein was 6.2 g/dL, albumin 3.5 g/dL, ammonia 81 μg/dL, and the C-reactive protein was 1.32 mg/dL.

The patient was treated with azithromycin (10 mg/kg/day) for 3 days. On the fourth hospital day, he developed abdominal pain at the upper-right quadrant. Tenderness was noted at the upper-right quadrant. The liver was markedly enlarged and was palpated 8 cm below costal margin, compared to the admission examination.

The liver enzymes increased acutely; AST 2,985 IU/L and ALT 2,725 IU/L. Prothrombin time (PT) was 15.6 seconds (INR: 1.28) and partial thromboplastin time (PTT) was 50.7 seconds (normal range: 30-45 seconds) and increased up to 82.1 seconds a few days later (Fig. 2). The serology testing for HAV, HBV, HCV, cytomegalovirus, and Ebstein-Barr virus were negative. Wilson disease and autoimmune hepatitis were excluded. Factor VIII was 31.0%, factor IX 23.0%, factor XI 43.0%, and factor XII 42.0%. The PTT mixing test failed to correct prolonged PTT. A bleeding tendency was not observed. On the eighth hospital day, a liver biopsy was performed. The hepatic lobules showed features of acute hepatitis such as ballooning degeneration, spotty necrosis and increased Kupffer cell activity, consistent with acute hepatitis, but was unremarkable otherwise (Fig. 3).

A week later, the pneumonia was nearly resolved, and the liver enzymes were decreased; AST was 51 IU/L and the ALT 237 IU/L. The patient was discharged in good condition. A week after discharge, the liver enzymes were normalized; AST 28 IU/L and ALT 43 IU/L. Several months later, the coagulation factors were nearly normalized without specific treatment. Factor VIII was 55.0%, Factor IX 65.0%, Factor XI 84.0%, and Factor XII 41.0%. The PTT mixing test was 38.1 seconds.
The patient is currently being followed up as an outpatient.

**DISCUSSION**

*M. pneumoniae* infection can be associated with dermatologic, cardiologic, neurologic, hematologic, and musculoskeletal manifestations.\(^1\)\(^,\)\(^5\) Gastrointestinal manifestations including hepatitis, acute acalculous cholecystitis,\(^6\) and pancreatitis have been reported.\(^5\) Elevated liver enzymes are frequently observed during *M. pneumoniae* infection in children. Lee et al.\(^7\) and Suzuyama et al.\(^8\) reported that 15.2% and 36.2% of patients presenting with serologically confirmed *M. pneumoniae* infection, respectively, had an evidence of liver involvement. Liver involvement was transitory in these patients, and recovery of liver enzymes to normal range correlated directly with resolution of mycoplasma pneumonia, as demonstrated in our patient.

Most previous case reports showed that liver involvement of *M. pneumoniae* infection is cholestasis rather than hepatic necrosis.\(^9\)\(^,\)\(^10\) Hypoalbuminemia, hyperbilirubinemia, and hepatomegaly are characteristics as signs of hepatobiliary involvement in mycoplasma infections.\(^11\) The rapid progression of hepatomegaly with exacerbation of hepatitis was observed in this case. Moreover, hypoalbuminemia and depressed levels of multiple coagulation factors produced by the liver were also observed, but hyperbilirubinemia was not present in this case. Hyperbilirubinemia usually occurs as the indirect type because of hemolysis in mycoplasma infection. While cholestasis is very rare, some cases of cholestatic hepatitis have been reported in children.\(^9\) Hepatitis has been reported in a case with *M. pneumoniae*-associated multiple organ involvement.\(^12\)

The pathogenesis of *M. pneumoniae*-associated hepatitis is unknown. Nevertheless, possible mechanisms include direct invasion of the organisms and autoimmunity including the production of autoantibodies, such as cold agglutinins.\(^13\)

Liver biopsies have been performed in rare cases of *M. pneumoniae*-associated hepatitis, and showed massive hepatocellular destruction and inflammatory infiltration in one patient,\(^14\) while non-specific, mild lobular hepatitis has also been reported.\(^12\)

Liver biopsies performed on 3 patients showed hepatic dysfunction with histological findings consistent with a non-specific reactive hepatitis in each case.\(^8\) In our case, the liver biopsy showed severe and acute lobular hepatitis.

It is important to consider that liver toxicity has been observed with almost every class of medication. The association of macrolide antibiotics with cholestatic hepatitis is well known.\(^15\)\(^,\)\(^16\) Although erythromycin, clarithromycin, and other macrolides were correlated with cholestatic liver injury, azithromycin was not associated commonly with...
the development of hepatotoxicity. Azithromycin-induced hepatotoxicity has been reported infrequently only in adults. The usual development and time course of the liver injury, from the beginning of azithromycin therapy to the onset of symptoms, has been reported to be 5 to 10 days.\textsuperscript{17,18} In our patient, azithromycin was administered from the 1st to 3rd hospital day and the aggravation of acute hepatitis occurred on the 4th hospital day. Although the possibility remains that azithromycin was the cause of hepatitis in our patient, this is less likely, since the liver enzymes were elevated acutely right after the initiation of azithromycin therapy.

Our patient showed depressed levels of multiple coagulation factors as well as acute hepatitis. In several reports, \textit{M. pneumoniae} infection can be associated with transient acquired factor II, VIII, or X deficiencies with clinical manifestations of bleeding tendency.\textsuperscript{19-21} In our case, coagulation tests revealed prolonged aPTT and decreased coagulation factors activity, including factors VIII, IX, XI, and XII, without any bleeding tendency. The coagulation tests were monitored regularly, and showed progressive normalization without specific treatment. Both the absence of a bleeding tendency in earlier life and the normalization of prolonged PTT and coagulation factor activity suggested that congenital factors deficiency was not the cause of abnormalities.

There was no prior report in the English medical literature on the depression of multiple coagulation factors associated with mycoplasma infection. The pathogenesis of this phenomenon in our patient is unknown. One possible mechanism is a consumptive coagulopathy due to hepatic deterioration. The other mechanism is the presence of circulating inhibitors. It is well established that mycoplasma infection can cause hemolysis due to the development of autoantibodies including cold agglutinins.\textsuperscript{22} The presence of circulating inhibitors specific to coagulation factors is supported by the PTT mixed with normal plasma that failed to correct prolonged PTT.

In conclusion, we report the first case of \textit{M. pneumoniae} infection in a child presenting with acute hepatitis and transient depression of multiple coagulation factors.

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