

A Case of Co-Infection with *Orientia Tsutsugamushi*, Acute Hepatitis B, and *Mycoplasma Pneumoniae* in a Child with Fever and Systemic Rash

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Abstract

Background: Systemic rash combined with prolonged fever requires a differential diagnosis of possible diseases including infectious diseases. Although scrub typhus can cause co-infection with leptospirosis, co-infection with *Orientia tsutsugamushi* and *Mycoplasma pneumoniae* is thought to be rare, with only one case reported in a young adult. However, to date, there have been no reports of simultaneous co-infection with three pathogens, including *Orientia tsutsugamushi*, hepatitis B, and *Mycoplasma pneumoniae*.

Case: We report a child simultaneously co-infected with *Orientia tsutsugamushi*, acute hepatitis B, and *Mycoplasma pneumoniae*, which made her prolonged fever and systemic rash with mild itching. On day 2 of hospitalization, an eschar on the left inguinal area became prominent and antibodies against *Orientia tsutsugamushi* showed levels $\geq 1:1520$. Owing to an elevation in the levels of liver enzymes at admission, IgM for hepatitis B surface antigen was positive and IgG for hepatitis B surface antigen was negative. Following two days of tetracycline administration, the fever subsided and the systemic area skin rashes gradually improved.

Conclusion: Proper evaluation based on the presenting symptoms during the illness is important to ensure that the differential diagnosis is not overlooked.

Keywords: *Orientia tsutsugamushi*; *Mycoplasma pneumoniae*; Hepatitis

Introduction

Systemic rash combined with prolonged fever requires a differential diagnosis of possible diseases including infectious diseases. When combined with multiple cervical lymphadenopathies, evaluation of the causes of generalized infection is inevitable [1]. To prevent overlooking a combined diagnosis, the possibility of co-infection should be examined when suspicious symptoms develop, even during the illness.

Although scrub typhus can cause co-infection with leptospirosis in approximately 6% [2], co-infection with *Orientia tsutsugamushi* and *Mycoplasma pneumoniae* is thought to be rare, with only one case reported in a young adult [3]. However, to date, there have been no reports of simultaneous co-infection with three pathogens, including *Orientia tsutsugamushi*, hepatitis B, and *Mycoplasma pneumoniae*.

Here, we report a child simultaneously co-infected with *Orientia tsutsugamushi*, acute hepatitis B, and *Mycoplasma pneumoniae*, which made her prolonged fever and systemic rash with mild itching. To the best of our knowledge, this is the first report of co-infection with three pathogens, including *Orientia tsutsugamushi*, acute hepatitis B, and *Mycoplasma pneumoniae*, in a child manifesting prolonged fever and systemic rash.

Case Report

A 12-year-old, previously healthy girl presented with a 7-day fever. The child complained of mild nausea, but did not experience vomiting. In addition, she did not exhibit any respiratory symptoms such as a cough and sputum during the illness. Upon physical examination, she showed an acutely ill-looking appearance. There were erythematous nodular rashes with mild itching all over the child's body, including the face and trunk. Multiple cervical lymph nodes sized approximately 1.0 cm to 1.5 cm was palpable on both the neck and supraclavicular areas. However, there was no hepatomegaly or splenomegaly. She was vaccinated as scheduled. She lived with her parents and one elder brother. Her family belonged to the middle class. The child had no

history of travel or animal contact. She did not take any medicines except antipyretics before admission (Figure 1).

At admission, the child's body temperature was 40.0°C, blood pressure was 100/60 mmHg, and respiratory rate was 20/min. To differentiate the possible diseases, such as viral infection, bacterial infection or immune-related diseases, we performed chest CT including neck and abdominal CT. There were no abnormal findings on her chest computed tomography (CT). The neck CT revealed multiple ovoid-shaped lymph nodes in both the cervical and supraclavicular areas (Figure 1). On

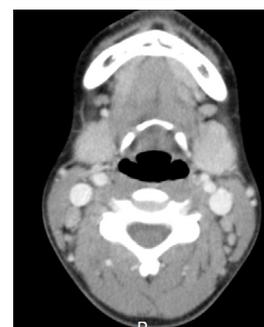


Figure 1: On neck computed tomography, multiple lymph nodes less than 2 cm-size in both cervical chain and supraclavicular area were observed.

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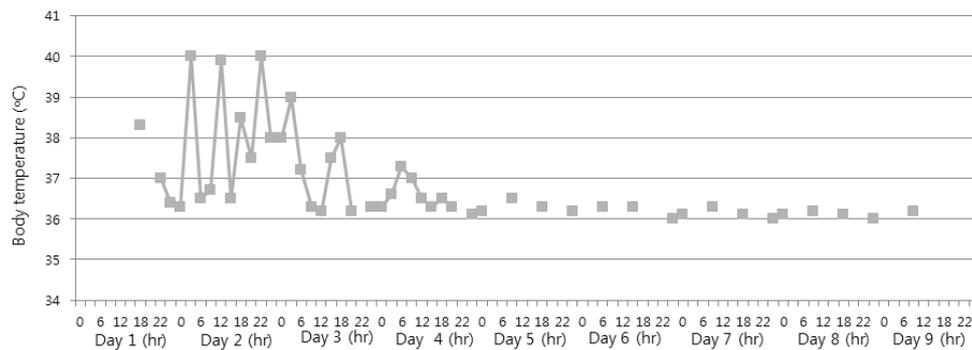


Figure 2: Fever patterns during the hospitalization.

abdominal CT, diffuse periportal thickening with gallbladder wall thickening was observed. The white blood cell count was 5420 cells/mm³ with 58.1% neutrophils, 33.4% lymphocytes, and 1.5% basophils; a hemoglobin level of 12.4 g/dL; and a platelet count of 149,000 platelets/ μ L. C-reactive protein was 2.85 mg/dL and erythrocyte sedimentation rate was 9 mm. The serum aspartate aminotransferase (AST), alanine transaminase (ALT), and gamma-glutamyl transpeptidase were 263, 225 U/L and 60 U/L, respectively. Prothrombin time was 15.8 sec (reference, 10.0 sec to 13.0 sec), partial thromboplastin time 34.6 sec (reference, 30 sec to 47 sec), and D-dimer values were 1.94 μ g/mL (reference, <0.55 μ g/ml). Immunoglobulin M (IgM) for Epstein-Barr virus (EBV) viral capsid antigen (VCA), Immunoglobulin G (IgG) for EBV nuclear antigen, EBV VCA, and early antigen were all negative. Polymerase chain reaction (PCR) for cytomegalovirus was negative in serum. Specific IgM for *Mycoplasma pneumoniae* was negative at admission. No growth was identified on the blood culture.

Owing to an elevation in the levels of liver enzymes, including AST and ALT at admission, we performed a hepatitis work-up, including viral markers of hepatitis A, hepatitis B, and hepatitis C, on the third day of hospitalization. IgM for hepatitis B surface antigen was positive and IgG for hepatitis B surface antigen was negative. Hepatitis B e antigen and Hepatitis B e antibody were negative, as were IgM and IgG for hepatitis B core antibody. Serum hepatitis B virus DNA levels measured by real-time PCR were 22400 IU/mL. In addition, we found positive conversion of specific IgM against *Mycoplasma pneumoniae* with an index \geq 27.0 and increased levels of AST and ALT on day 4 of hospitalization. Since the child had no respiratory symptoms, we could not perform PCR using sputum.

An eschar on the left inguinal area became prominent on day 2 of hospitalization. We investigated the possibility of *Orientia tsutsugamushi* infection by serological tests. Antibodies against *Orientia tsutsugamushi* showed levels \geq 1:1520. The child was administered tetracycline from day 2 of hospitalization, the day after the eschar was discovered. Following two days of tetracycline administration, the fever subsided and the systemic area skin rashes gradually improved (Figure 2).

In terms of the acute hepatitis B and *Mycoplasma pneumoniae* infection, supportive care was provided without antiviral agents. The child was discharged on day 9 of hospitalization with some improvement in the levels of liver enzymes: AST, 43 U/L and ALT, 186 U/L.

Discussion

In the present study, we report a child acutely co-infected with hepatitis B, *Mycoplasma pneumoniae*, and *Orientia tsutsugamushi*. The infectious agents were identified by serological tests on the basis of clinical manifestations. Although there might be no direct connection

between the three pathogens, we have identified a case of simultaneous co-infection with these pathogens. Based on the treatment guidelines for each infection, active treatment with tetracycline was implemented only for *Orientia tsutsugamushi* and the patient recovered without further complications.

When patients present with a fever and rash, the differential diagnosis is very broad. Thorough history-taking and physical examination are important for accurate diagnosis and to prevent overlooking other diseases. Although the patient in the present study had no history of travel, the eschar constituted a clue for *Orientia tsutsugamushi*. In addition, although she denied any respiratory symptoms, the persistent fever and systemic area skin rash prompted the need to evaluate the possibility of *Mycoplasma pneumoniae* infection. *Orientia tsutsugamushi* infection is characterized by acute febrile illness with lymphadenopathy, skin rash, and malaise; however, in the present study, the eschar, one of the most important clues for the diagnosis of *Orientia tsutsugamushi*, developed later than the aforementioned symptoms.

Although *Mycoplasma pneumoniae* can be detected in asymptomatic children [4], the patient in the present study showed positive conversion of specific IgM against *Mycoplasma pneumoniae* during the early phase of hospitalization and was not exposed to any respiratory infection during the illness. Although *Mycoplasma pneumoniae* has a high affinity for respiratory epithelium, production of a variety of cytokines and reactive substances, as a result of direct invasion or autoimmune response, can cause extra-pulmonary manifestations, including hepatitis [5]. The host immune system affects the severity of *Mycoplasma pneumoniae* infection and some cases of *Mycoplasma pneumoniae* infection are self-limiting [6]. In the present case, it is inconclusive whether *Mycoplasma pneumoniae* infection contributed to hepatitis, prolonged fever, and skin rash as extra-pulmonary manifestations; however, the acute elevation of specific IgM levels against *Mycoplasma pneumoniae* cannot be ignored. Some cases of *Mycoplasma pneumoniae* infections are self-limited and thus, recovery and improvement of extra-pulmonary manifestations area possibly solely with supportive care without the administration of antibiotics.

Although the child received the hepatitis B vaccine according to the recommended schedule, IgG for hepatitis B surface antigen was negative. On the basis of other hepatitis B virus markers, she was diagnosed as having an acute hepatitis B infection and supportive care was provided with a gradual improvement in liver enzymes levels. Follow-up for identification of the seroconversion of IgG for hepatitis B surface antigen is needed.

Conclusion

In summary, we reported a child presenting with persistent fever

and systemic area skin rash as having a co-infection with hepatitis B, *Mycoplasma pneumoniae*, and *Orientia tsutsugamushi*. Physicians should be aware of the possibility of coinfection in patients presenting nonspecific symptoms, such as fever and rash. Proper evaluation based on the presenting symptoms during the illness is important to ensure that the differential diagnosis is not overlooked.

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