Case Report
Life-threatening Scrub Typhus with Hemophagocytosis and Acute Respiratory Distress Syndrome in an Infant

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Summary
Scrub typhus is a rickettsial disease, caused by Orientia tsutsugamushi, which is transmitted via the bite of a chigger. This disease is one of the most important infectious diseases in the Asia-Pacific area; however, a severe infant case has not yet been reported. Here, we present the case of an 8-month-old boy with scrub typhus accompanied by hemophagocytic lymphohistiocytosis (HLH). His rapid course was complicated by acute respiratory distress syndrome (ARDS), status epilepticus and disseminated intravascular coagulation (DIC). He recovered after clarithromycin therapy and intensive supportive care. Although being extremely rare, scrub typhus can be life-threatening in an infant; therefore, physicians in endemic countries should be aware of the necessity for early recognition and prompt treatment of suspected cases.

Key words: scrub typhus, Orientia tsutsugamushi, hemophagocytic syndrome, infant.

Introduction
Scrub typhus, also known as tsutsugamushi disease, is an acute febrile illness caused by Orientia tsutsugamushi, which is transmitted by the bite of a mite [1]. The clinical manifestations are non-specific, including fever, skin rash, myalgia, gastrointestinal disturbances and lymphadenopathy [1]. Severe complications of scrub typhus can involve multiple organs, which often pathologically associated with vasculitis [2] and rarely cause hemophagocytic lymphohistiocytosis (HLH) [3, 4]. Exposure occurs primarily in adults and children who participate in outdoor activities, and scrub typhus in infants is extremely rare. To our knowledge, we are the first to report a severe case of scrub typhus in an infant that led to HLH and acute respiratory distress syndrome (ARDS).

Case Report
An 8-month-old male infant was referred to our clinic for a 10-day history of fever. He was previously treated for a presumed upper respiratory tract infection at a local hospital. Because the laboratory findings from one day before admission suggested HLH, he was transferred for further care. The patient was born by normal vaginal delivery and had no previous history of illness. He lived in Jeollanam-do, which is a rural area in Korea in which scrub typhus is endemic. His parents were healthy and employed in an office environment.

On physical examination, the patient appeared acutely ill and pallor. He had a temperature of 38.9°C, a heart rate of 120 beats per min, a respiratory rate of 28 beats per min, a blood pressure of 110/42 mmHg, and weighed 9.3 kg. Hepatosplenomegaly was observed, but there was no significant lymphadenopathy or skin rash. A 1-cm-sized necrotic eschar was found in the right inguinal area (Fig. 1). A generalized tonic–clonic seizure occurred suddenly within 2 h of admission and ceased an hour later. However, he then developed rapidly respiratory failure with pulmonary hemorrhage and was admitted to the intensive care unit for ventilator support. A chest radiograph (Fig. 2) showed bilateral ground-glass opacities. Complete blood counts revealed 13,910/mℓ white blood cell, 7.1 g/dl hemoglobin and 78 × 10⁹/μl platelets. The prothrombin time and partial thromboplastin time were prolonged. Blood biochemical tests showed the following abnormal results: aspartate aminotransferase, 598 U/L; alanine aminotransferase, 340 U/L; total protein,
4.2 g/dl; albumin, 2.1 g/dl; lactic dehydrogenase, 10 600 U/L; fibrinogen, 53 mg/dl; D-dimer, 7.6 mcg/ml; FDP, 36.1 mcg/ml; ferritin, 7970 mcg/L. Other biochemical parameters were within normal limits. Serologic test for *O. tsutsugamushi* (indirect hemagglutination) antibody (IgM) was positive at 1:80. Culture, serology and polymerase chain reaction for other infectious etiologies were negative. HLH was diagnosed by established clinical criteria; five of the eight criteria were met. The possibility of primary HLH due to a defect of the perforin (PRF1), MUNC13-4 or syntaxin 11 genes was excluded through gene study.

On the basis of a diagnosis of scrub typhus, therapy with intravenous clarithromycin (15 mg/kg/day divided every 12 h for 14 days) was initiated. Because the patient’s condition rapidly deteriorated with ARDS and the development of disseminated intravascular coagulation (DIC) in the setting of HLH, a dexamethasone and etoposide-based chemotherapeutic regimen was also administered. No new bleeding was noted from day 3, and fever subsided on day 4 with recovery of respiratory condition. He was extubated on day 10 and was discharged from our ward on day 35.

**Discussion**

The key to diagnose scrub typhus is finding a typical eschar, which is the result of the insect bite that transmits the pathogen. Unless there is a high level of suspicion, diagnosis can be missed as the clinical features are non-specific. Although our patient presented with a typical eschar, the lesion was initially overlooked as it was hidden under his diaper. Compared with previous reports, the clinical course of our patient was progressive. This suggests that additional factors along with the delay in recognition and treatment may trigger an activation of the immune system. Previous reports emphasized the importance of early diagnosis and prompt therapy to shorten the disease course and reduce mortality [5].

The basic pathology of scrub typhus is vasculitis, and such microangiopathies may involve any part of organs [6]. However, recent reports have suggested that the cytokine storm associated with the immune response to *O. tsutsugamushi* infection might be involved in the pathogenesis of complicated scrub typhus [4, 7]. Once the cytokine cascade has been triggered, this condition can become a potentially life-threatening illness in which the immune system loses its regulatory function. Primary HLH appears to have a genetic etiology, whereas secondary HLH may occur together with a variety of underlying diseases [8]. In the literature, there are only a few cases of HLH associated with scrub typhus in adults, whereas similar reports for children are extremely rare [3, 4, 9]. In our case, five out of the eight diagnostic criteria for HLH were fulfilled. Other causes for HLH were excluded, and the patient was diagnosed with scrub typhus-associated HLH. Our patient also had ARDS with pulmonary hemorrhage, which may be explained by the combination of pulmonary involvement in the context of scrub typhus, as well as thrombocytopenia and coagulopathy due to HLH [10, 11].

There are a few case reports of infants with scrub typhus in the literature.
infection in children and adults is believed to be direct exposure to a chigger during outdoor activities, scrub typhus in infants who live mostly indoors is uncommon. We suspected that our patient was exposed at or near his residence, which is in a rural area of Korea. Our case and two previously reported cases [12] of infants who developed scrub typhus suggest that a secondary route to exposure may exist such as chiggers hidden in clothing brought in from outdoors.

In summary, we described a rare case of scrub typhus that resulted in severe complications in an infant. *O. tsutsugamushi* infection may involve to multiple organs via endothelial cells and macrophages. Because scrub typhus is extremely rare in infants, diagnosis and treatment of this age group are challenging for pediatricians. As the disease can progress rapidly, early diagnosis and timely initiation of appropriate therapy are critical.

References