Varicella-Zoster Virus Reactivation During the Incubation Period for Scrub Typhus: A Case Report

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Patient: Female, 64-year-old
Final Diagnosis: Infection
Symptoms: Fever • hypotension • pain
Medication: —
Clinical Procedure: —
Specialty: Anesthesiology • Infectious Diseases

Objective: Rare coexistence of disease or pathology

Background: Herpes zoster caused by the reactivation of latent varicella-zoster virus is thought to result from the waning of specific cell-mediated immunity. Scrub typhus, an acute infectious disease caused by Orientia tsutsugamushi, affects multiple organs and is characterized by microangiopathies that result in significant vascular leakage and subsequent end-organ injury. Very few cases of reactivation of the varicella-zoster virus following scrub typhus occurrence have been reported. Furthermore, no previous studies have directly investigated whether Orientia tsutsugamushi infection is a potential risk factor for herpes zoster.

Case Report: We present the case of a 64-year-old woman without a previous illness who simultaneously developed herpes zoster of the thoracic dermatome and scrub typhus. Clinical symptoms of scrub typhus appeared during the treatment course for herpes zoster symptoms. Based on positive virus antibody test results, the patient was diagnosed with scrub typhus. This is a unique case of reactivation of the varicella-zoster virus that occurred during a silent incubation period for scrub typhus.

Conclusions: This report indicates the possibility of reactivation of latent varicella-zoster virus following Orientia tsutsugamushi infection, although the relationship between the 2 remains undetermined. Physicians should be aware that scrub typhus might be a potential determinant of varicella-zoster virus reactivation.

Keywords: Coinfection • Herpes Zoster • Scrub Typhus

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Background

Herpes zoster is a disease caused by the varicella-zoster virus (VZV). In individuals who develop chickenpox during childhood, VZV remains dormant in the sensory ganglion of the cranial nerves or the dorsal root ganglion of the spinal cord and can reactivate when cell-mediated immunity declines [1,2]. This reactivation occurs when the immune mechanisms that suppress VZV replication fail to suppress the virus [3]. The potential determinants of a generalized loss of cell-mediated immunity have not been completely elucidated. Scrub typhus has a silent incubation period of 6–21 days after the initial bite of a trombiculid mite larva; after this period, non-specific symptoms and signs appear, such as fever, myalgia, headache, rash, and lymphadenopathy [4,5]. The virus can cause disseminated vasculitis and perivascular inflammatory lesions, resulting in significant vascular leakage and end-organ injury [4]. The exact molecular mechanisms underlying the host’s immune response to O. tsutsugamushi have not been completely elucidated, although the host–pathogen interaction has been revealed [6].

To date, there have been very few cases of VZV reactivation following scrub typhus development [7]. Herein, we present the case of a 64-year-old woman who developed herpes zoster of the thoracic dermatome during the incubation period for scrub typhus. Our unique case highlights the importance of physicians being aware of the possible association between VZV reactivation and scrub typhus.

Case Report

A 64-year-old woman without any underlying diseases visited our pain clinic for severe pain in the right trunk. She was diagnosed with herpes zoster, and showed typical skin lesions at the T6 dermatome 4 days after the onset of prodromal symptoms (which had developed before she visited our clinic). Previously, at a local clinic, she had been prescribed a 7-day course of famciclovir (250 mg thrice a day) and 15-day courses of gabapentin (600 mg thrice a day), tramadol hydrochloride/acetaminophen (37.5/325 mg), and prednisolone (5 mg twice a day). However, uncontrolled pain persisted in the zoster-affected area, and she was admitted to our hospital.

A blood test performed at another hospital 5 days prior to admission to our hospital revealed the following findings:

- White blood cells (WBCs), 6.8×10⁹/L (range, 4.0-10.0×10⁹/L);
- Platelets (PLTs), 216×10⁹/L (range, 140-440×10⁹/L);
- Aspartate aminotransferase (AST), 55 IU/L (range, ~32 IU/L);
- Alanine aminotransferase (ALT), 72 IU/L (range, ~33 IU/L);
- Alkaline phosphatase, 70 IU/L (range, 35-104 IU/L); and
- C-reactive protein (CRP), 0.33 mg/dL (range, ~0.30 mg/dL). When the patient visited our clinic, her skin lesions had improved and scab formation had started (Figure 1). Her vital signs were normal as well. However, the patient reported having a tingling sensation and breakthrough pain that lasted for 10 s and occurred approximately twice an hour; the pain intensity was scored 90/100 on a visual analog scale (VAS). The pain also led to sleep disturbance. Therefore, for pain control, we inserted an epidural catheter at the T6 level. Epidural patient-controlled analgesia (PCA) was administered with a continuous infusion of morphine (0.6 mg; Highmol®, BCworld Pharm) and ropivacaine (2.4 mg; Rocaine®, Reyon Pharm); the loading dose also comprised 0.6 mg of morphine and 2.4 mg of ropivacaine with a lockout interval of 20 min. The patient’s oral medications were changed to pregabalin (150 mg twice a day; Lyrica®, Pfizer Korea), nortriptyline (10 mg twice a day; Sensival®, Ilsung Pharmaceuticals), and tramadol hydrochloride/acetaminophen (37.5/325 mg twice a day; Ultracet®, Janssen Korea). The next day, her pain improved slightly, but she reported drowsiness and nausea. Thus, we changed the background infusion of PCA to 0 mL/h. Electrocardiography and chest radiography findings were unremarkable. However, unlike the blood tests performed 6 days prior, laboratory tests at this point revealed the following abnormalities:

- WBC, 7.42×10⁹/L;
- Platelets, 89×10⁹/L;
- AST, 426 IU/L;
- ALT, 380 IU/L;
- CRP, 16.37 mg/dL. We consulted an infectious disease physician and a hepatologist regarding the elevated liver enzymes and CRP; they suspected drug-induced, autoimmune, or viral hepatitis and recommended additional laboratory tests and periodic follow-up. Because she did not report symptoms other than those of herpes zoster, we observed her without any additional treatment and performed tests periodically. On hospitalization day 3, her VAS score had decreased to 40/100; however, she presented with a fever (38.3°C) that showed a pattern of improvement and exacerbation. Her other vital signs were normal.

Figure 1. Skin lesions of a 64-year-old woman with herpes zoster showing erythematos maculopapular and vesiculobullous eruptions along the right anterior chest.
On hospitalization day 4, her blood pressure (BP) began to drop gradually with the fever and was 70/40 mmHg early in the morning. The heart rate had increased to 120 beats/min, while the oxygen saturation had decreased to 92%. She was confused and had abdominal distension and generalized swelling. For supportive treatment, 3 L/min of oxygen was administered through a nasal cannula, and an intravenous (IV) norepinephrine (Norpin®, Dalim Biotech) infusion at 0.15 mg/h started simultaneously. Along with additional blood tests, blood and urine culture tests were performed to determine the cause of fever. The epidural catheter was removed, and the catheter tip was sampled for a culture analysis to rule out any infection. The findings of the additional tests were as follows: WBC, 5.1×10^9/L; PLT, 53×10^9/L; AST, 374 IU/L; ALT, 269 IU/L; CRP, 22.95 mg/dL; procalcitonin, 1.25 ng/mL (range, ~0.5 ng/ml); and lactic acid, 3.3 mmol/L (range, 0.5-2.0 mmol/L). No specific bacteria were found in the culture tests. Plain radiography revealed pulmonary congestion as well as ileus in the mid-abdomen. Several tests confirmed that the patient’s condition was deteriorating, but the cause of the symptoms could not be identified. Therefore, the following empirical antibiotics were administered intravenously for the treatment of unspecified fever: 4 g of piperacillin sodium and 0.5 g of tazobactam (thrice a day; Tabactam®, Dong Kwang Pharm) and ciprofloxacin (400 mg twice a day; Citopcin®, HK inno.N). Simultaneously, for the diagnosis of the fever, a thorough history taking was conducted again. We found that the patient once hiked in the mountains and had visited an acquaintance’s farm 3 weeks prior to symptom onset, but had not gone outdoors since VZV reactivation. Through physical examination, an eschar was observed on the patient’s right thigh (Figure 2). Therefore, we suspected that scrub typhus was the cause of the fever and abnormal laboratory test results. The virus antibody test was positive for O. tsutsugamushi, and the patient was diagnosed with scrub typhus. The empirical antibiotics were discontinued, and oral doxycycline (100 mg twice daily for 7 days; Doxycycline Tab®, Youngpoong Pharmaceuticals) was prescribed. In addition, a Foley catheter was inserted, and IV furosemide (20 mg twice daily; Lasix®, Handok Pharmaceuticals) was administered for 2 days to improve oliguria and systemic edema. The patient’s dyspnea gradually improved, and oxygen saturation was maintained at 95%. The systolic BP increased to 120-150 mmHg from the day after diagnosis. After 3 days of doxycycline administration, her body temperature stabilized below 37°C, and her heart rate was maintained at 90-100 beats/min. The IV norepinephrine administration was discontinued. After 8 days, the liver enzyme and CRP levels had normalized, most of the symptoms had improved, and antibiotic administration was discontinued. The intensity of herpes zoster-related trunk pain was scored 20-30/100 on the VAS scale. After confirming that the patient was in a stable state, she was discharged on hospitalization day 16.

**Figure 2.** Eschar on the patient’s right thigh.

**Discussion**

Scrub typhus is a serious public health problem in the Asia-Pacific region; it threatens one billion people globally and causes illness in one million people each year [8]. Scrub typhus is an acute febrile illness that generally causes non-specific signs and symptoms [9]. It is clinically characterized by fever with chills, headache, and body ache; multiorgan dysfunction is observed during the second week of illness [10]. If it is undiagnosed, diagnosed late, or untreated, fatal complications (such as encephalitis, cardiomyopathy, and pneumonia) can develop [9]. A necrotic eschar, surrounded by a red areola, at the site of the mite bite is a typical scrub typhus marker and has been observed in 60-100% of patients with scrub typhus [5,9]. Patients with scrub typhus can be differentiated from those affected by other diseases through history taking, identification of specific symptoms (such as eschar), and laboratory tests (such as serological tests [indirect fluorescent antibody and enzyme-linked immunosorbent assays], polymerase chain reaction, and biopsy of an eschar [showing lympho-histocytic vasculitis]) [9,11].

Our patient had no specific symptoms other than those typical of herpes zoster at admission. Inpatient examination confirmed increased levels of liver enzymes and CRP and a decreased PLT count; hepatitis of an unspecified cause was first suspected because symptoms of infection, such as fever, were not observed. Since there was an asymptomatic incubation
period, other specific symptoms of typhus were not identified, and it was difficult to initially diagnose typhus. After the patient presented with a fever and an eschar was formed (ie, after the typical symptoms of typhus appeared), an antibody test was performed and typhus was diagnosed. Coincidentally, the clinical symptoms of scrub typhus developed in the presence of herpes zoster symptoms. We assumed that the patient might have had a VZV reactivation. *O. tsutsugamushi* is transmitted by the bite of trombiculid mite larvae based on history and clinical manifestation (Figure 3).

Some cases of scrub typhus with co-infections have been reported previously [12-14]. As noted in these reports, diagnosing a patient with such dual infections is challenging and the patient’s symptoms are often severe. In particular, only 1 case report on VZV reactivation following scrub typhus development has been reported [7]; the authors of that report described the first case of herpes zoster in a patient with scrub typhus. However, unlike our patient, their patient presented with VZV reactivation during the treatment period. In our case, it was more difficult to diagnose scrub typhus initially because the patient had symptoms of herpes zoster during an entirely asymptomatic incubation period for scrub typhus.

VZV reactivation usually occurs when cell-mediated immunity declines [15,16]. The incidence rate of herpes zoster is 3-5/1,000 person-years and has increased continuously across all age groups [17]. The risk factors that could explain variations in immunity include age, sex, genetic susceptibility, immunosuppressive therapy, psychological stress, mechanical trauma, and underlying cell-mediated immune disorders [16]. However, individuals without underlying immunosuppression also develop herpes zoster, and little is known about the causes of the disease in them. Therefore, if herpes zoster occurs despite the absence of risk factors, considering whether there are other causes of declining cell-mediated immunity is necessary.

The level of VZV-specific cell-mediated immunity determines the risk and severity of VZV reactivation [18]. In particular, interactions of T-lymphocyte subsets are assumed to be balanced to ensure a normal immune function. In case of aberrant changes in the lymphocyte counts, the immune system becomes disordered and a series of pathological changes occur; these ultimately increase the potential for infection in the body [19].

In 1 study, the absolute numbers of CD3+, CD4+, and CD8+ T cells were significantly lower in patients with herpes zoster than in the controls [3]. Hur [7] suggested that scrub typhus induced sufficient stress to reactivate the VZV; this factor can cause generalized cell-mediated immunosuppression, which can result in premature aging of the immune system [16]. Several clinical and experimental studies have revealed post-infection immunosuppression; immunosuppression acquired during severe infection can lead to a more complex immunosuppressed state and increased susceptibility to secondary infectious agents [20]. An immunological study revealed that multiple cytokines and chemokines released by the host defense mechanism play a significant role in activating various immune-related signaling pathways during an *O. tsutsugamushi* infection, including those for the stress response, autophagy, apoptosis, and innate immunity [6]. However, how scrub typhus affects changes in the cell-mediated immunity has not yet been completely elucidated, and no previous studies have directly investigated whether scrub typhus is a potential determinant of the VZV reactivation risk. Moreover, our patient was healthy without any underlying disease, but was over 60 years of age; an advanced age could be considered a risk factor for herpes zoster. Further evidence on the effect of scrub typhus on absolute lymphocyte counts, T cells, and cytokine functions related to VZV-specific cell-mediated immunity is required to establish their interactions in a similar population.

**Conclusions**

This is the first report of VZV reactivation occurring during a silent incubation period for scrub typhus. This provides evidence that scrub typhus might be a potential cause of VZV reactivation, and physicians must be aware of this. The effect of scrub typhus on VZV-specific cell-mediated immunity, however, remains undetermined and could be a subject of future studies.

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References: