Orientia Tsutsugamushi-Induced Leukocytoclastic Vasculitis
-A Case Report
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Scrub typhus (also named Tsutsugamushi disease), a mite-transmitted zoonosis caused by Orientia tsutsugamushi, is an endemic infectious disease in east Asia and Australia. This disease usually presents as an acute febrile illness with non-specific symptoms. We reported a case of the scrub typhus with leukocytoclastic vasculitis who suffered from acute pyrexia of unknown origin and arthralgia. Weil-Felix test and indirect immunofluorescent antibody technique revealed positive findings. The skin revealed multiple palpable painful purpura on bilateral lower limbs. Histopathology revealed leukocytoclastic vasculitis, and immunoperoxidase study disclosed positive staining of the antibody against 56 kD Rickettsial antigen in involved vascular endothelial cells and perivascular stroma. The patient was treated with doxycycline, and the skin lesions subsided in two weeks. To the best of our knowledge, this is the first proven case of leukocytoclastic vasculitis induced by Orientia tsutsugamushi in Taiwan. (Dermatol Sinica 25: 142-146, 2007)

Key words: Scrub typhus, Tsutsugamushi disease, leukocytoclastic vasculitis, Doxycycline

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INTRODUCTION

Scrub typhus (Tsutsugamushi disease) is an acute febrile illness caused by Orientia tsutsugamushi (formerly Rickettsia tsutsugamushi), which was previously included in the genus of rickettsiae. It is transmitted to humans by the bite of tromboculid mites or chiggers in the larval stage.\(^1,2\) Scrub typhus is widespread and is an important cause of acute pyrexia of unknown origin (PUO) in rural Asia, northern Australia, and the Western Pacific islands.\(^3\) Although Scrub typhus involves multiple organs including the skin, lung, heart and central nervous system with potential of causing serious life-threatening complications, such as myocarditis and encephalitis.\(^4-9\) It presents mainly focal lymphocytic vasculitis or perivasculitis, and rarely leukocytoclastic vasculitis (LCV). We hereby describe the first proven case of LCV induced by Orientia tsutsugamushi in Taiwan.

CASE REPORT

A 22-year-old woman, a colleger, had been quite healthy until Sep 20, 2005, when she was admitted to our hospital because of low grade fever and arthralgia for 5 days. Tracing her history, she had traveled to Philippine on July 20, 2005 and came back to Taiwan on September 20, 2005. About 7 days before admission, she noted a reddish papule without itching or tenderness on left big toe, and then, multiple reddish papules, palpable painful purpura and arthralgia over left knee developed in the next two days. On admission, her body temperature was 36.8°C and no lymphadenopathy was noted. Breath sounds were clear and no audible murmur was noted. Examinations of abdomen and central nervous system were normal. On dermatologic examinations, we noted multiple discrete painful palpable purpurae and reddish papules on the lower extremities (Fig. 1). Laboratory tests revealed white blood cell count of 14,050/mm\(^3\) (4000-11,000) with lymphocytes 23.4% and neutrophils 70.1%, hemoglobin 11.5 gm/dl, and platelet count of 360,000/mm\(^3\) (200,000-400,000). Erythrocyte sedimentation

![Image of dermatologic examinations](Fig. 1)

Some discrete reddish papules and palpable purpura on the lower extremities, the lesions shown here do not blanch with a glass slide, indicating hemorrhage.

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* IFA: indirect immunofluorescent antibody technique
rate was 28 mm/hr (<20); C-reactive protein 0.738 mg/dl (<0.8); blood urea nitrogen 12.2 mg/dl (<20), creatinine 0.6 mg/dl (<1.1); Weil-Felix OX-19 test IgM 1:40 positive (Table 1). Chest X-ray film showed diffuse peribronchial cuffing of both lungs. Histopathology revealed edema of the endothelial cells with fibrinoid degeneration within the vessel wall in the dermis. The infiltrate consists mainly of neutrophils and of varying numbers of eosinophils and mononuclear cells with extravasation of erythrocytes and nuclear dusts (Fig. 2). Under the impression of rickettsial infection, antibiotics with doxycycline 500mg q6h were administered. Then the skin lesions and arthralgia were subsided on the second day and she was completely recovered and discharged on the seventh hospital day. The diagnosis of scrub typhus was confirmed later by analysis of sera that revealed IgG antibody titers to *O. tsutsugamushi* of 1:640, respectively (Table 1).

Thereafter, immunoperoxidase technique was performed with antibody against 56 kD outer membrane protein of *Orientia tsutsugamushi* on the formalin-fixed, paraffin-embedded skin biopsy specimens in the department of pathology, Tzu-Chi Medical University Hospital. It demonstrated positive reaction of the antibody against 56 kD Rickettsial antigen in the vascular endothelium and perivascular stroma (Fig. 3).

**DISCUSSION**

Scrub typhus (Tsutsugamushi disease) is an acute febrile illness caused by *Orientia tsutsugamushi*, which was previously included in the genus of rickettsiae. It is transmitted to humans by the bite of the larval stage of thombooculid mites or chiggers. Scrub typhus has epidemics in the late fall that affect a wide area of South-East Asia and the Pacific rim including the Korean Peninsula.1, 2 Scrub typhus is widespread and is an important cause of acute pyrexia of unknown origin (PUO). Reports from various countries indicate that scrub typhus, an infectious disease caused by a rickettsia, *Orientia tsutsugamushi*, accounts for 1.8-19.3% of cases of this febrile syndrome.3 Clinically it is an important disease, due to its high incidence and serious complications. Scrub typhus involves multiple organs including the lung, heart and central nervous system, characterized by focal vasculitis or perivasculitis. Myocarditis and encephalitis are the most serious life-threatening complications.4-9 Therefore, the rapid diagnosis of scrub typhus is a major factor in reducing mortality. In review of articles, patients who were infected with scrub typhus in...
Taiwan, were all reported to have fever. Other symptoms were lymphadenopathy (53.2%) \cdot headache (47.7%) \cdot abdominal pain (45.0%) \cdot cough (36.0%) \cdot skin rash (36.0%) \cdot nausea and vomiting (22.5%) \cdot conjunctivitis (12.6%) \cdot neuropathy (7.2%) \cdot diarrhea (6.3%) \cdot bone pain (6.3%) \cdot sore throat (5.4%) \cdot dysuria (1.8%), etc. In dermatological findings, eschar (64.9%) and skin rash (36.0%) had been reported.\(^{10}\) In our case, we noted the symptoms of fever, arthralgia, skin rash and palpable painful purpura but no eschar or other manifestations of scrub typhus. Although the pathologic basis for the cutaneous lesions of rickettsial infections is a lymphocytic vasculitis, but in our case, we noted that the findings of skin histopathology revealed a typical case of LCV. In other rickettsial infections, the maculopapular lesions of Rocky Mountain spotted fever show a focal lymphocytic vasculitis with patchy fibrinoid necrosis of small vessels and extravasation of erythrocytes, and then it progressed to LCV is common, but it is very rare to show cutaneous LCV in scrub typhus.\(^{10-14}\) Traditional concepts in vasculitis center most frequently around the traditional Coombs and Gell classification of immunologic reactions. Of the four types of reactions, Type 3 seems to be still the leading contender in the study of vasculitis. As understanding expands, the possibility of very specific Type 2 reactions directed at the vascular epithelium cannot be ruled out entirely. A Type 3 or immune-complex reaction has always been the most likely possibility in those patients with vasculitis. This can be carried over into the concept of vasculitis associated with infections, wherein the antigens often are the infectious agents.\(^{15}\) The LCV is, independently of its etiology, only initially a predominant neutrophilic process that evolves quite rapidly into a mixed lymphocytic-neutrophilic process.\(^{16}\) In the late phase of the leukocytoclastic form of the disease, the deposition of immune complexes with activation of the complement cascade, release of mediators, lysosomal enzymes, and oxygen free radicals could provoke the expression on the cell membrane of endothelial cells of “not-self” antigens. The dendritic cells (CD1a+ cells) and T cells could initiate a secondary cell-mediated immune response or could contribute to the self-perpetuation the disease. The same endothelial cells might also participate as antigen-presenting cells, releasing inflammatory mediators (anaphylatoxin C and cytokines) that could provoke expression of class I and II major histocompatibility complex antigens (by \(\gamma\)-interferon) on the vascular surface endothelium.\(^{16-19}\) According to the view above, it comes the concept of the dynamic nature of LCV, in which the infiltrate progressively changes from a preponderance of neutrophils over lymphocytes to a predominance of lymphocytes, as a continuum of a single diseases process. The different histologic patterns could be caused mainly by differences in the age of the biopsy specimens. Fortunately, these changes seem apparently not related to the etiology of the vasculitic process.\(^{20}\) Immunoperoxidase technique is critical to demonstrate the presence of a specific 56 kD antigen of Orientia tsutsugamushi, which support the etiological diagnosis LCV in our case. Taiwan is an endemic area for Scrub typhus and it usually presents as an acute febrile illness with non-specific symptoms and should be considered in the differential diagnosis for patients with PUO. Immunoperoxidase technique using paraffin-embedded tissues is generally feasible and readily available to help in establishing the etiological diagnosis.\(^{21}\) To the best of our knowledge, this is the first proven case of Orientia tsutsugamushi-induced LCV in Taiwan.

REFERENCES

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