

## First Report of an *Orientia tsutsugamushi* Type TA716–Related Scrub Typhus Infection in Thailand

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### Abstract

*Orientia tsutsugamushi* causes scrub typhus and is a rural zoonosis endemic in the Asia Pacific region. This is the first report of *O. tsutsugamushi* TA716–like strain in a human in Thailand. The patient was in the 1st trimester of pregnancy when she developed scrub typhus. The *O. tsutsugamushi* strain TA716 was detected from her admission blood sample, and the pregnancy ended in spontaneous abortion. The effects of scrub typhus in pregnant women and the pregnancy outcome are sparsely documented in the published medical literature. Improved clinical recognition and laboratory diagnosis will be essential to better define the morbidity caused by this zoonosis especially in pregnancy.

**Key Words:** *Orientia tsutsugamushi*—Pregnancy—Scrub typhus—TA716.

### Introduction

**O**RIENTIA TSUTSUGAMUSHI CAUSES scrub typhus, a zoonosis endemic in the rural areas of the Asia Pacific region. It remains of great public health importance as a cause of febrile illness that is difficult to diagnose clinically. Mortality rates as high as 60% were reported before the use of antibiotics. Virulent strains can cause a fulminant illness with pneumonia, myocarditis, disseminated intravascular coagulation, and death. This is the first report of *O. tsutsugamushi* TA716–like strain infection in a human in Thailand. There are less than 25 total pregnancy cases of scrub typhus described in the published literature (Kim et al. 2006).

### Case Study

A 34-year-old Karen refugee from Burma with a gravidity of five and parity of three presented to Shoklo Malaria Research Unit antenatal consultation in Maela Refugee camp on the Thailand–Burma border in October 2004. She reported

9 weeks of amenorrhea. She had intermittent fever for 5 days and had self-medicated with a single dose of quinine 150 mg and paracetamol 1 g, the day before. Seven days before presentation she developed pain in her left inguinal area. For 5 days she had intermittent fever with chills and rigors; headache; muscle, joint, and back pain; and dysuria, dizziness, and vomiting.

On examination, she was febrile with a temperature of 38.5°C, pulse rate 100 beats/min, and respiratory rate 26 breaths/min. The physical examination was marked by a typical eschar found on the upper left thigh with associated lymphadenopathy in the surrounding inguinal area but not elsewhere on the body. Her uterine fundus, liver, and spleen were not palpable, respiratory fields were clear, and the finding from the neurological examination was normal.

Her white blood cell count was  $5.0 \times 10^9/L$  (NR 4.5–10.0), including  $0.8 \times 10^9/L$  lymphocytes and  $3.9 \times 10^9/L$  neutrophils. The platelet count was suppressed at  $83 \times 10^9/L$  (NR 140–450), and hematocrit result was normal at 36%. A gestational sac

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of approximately 7 weeks with no fetus, or no visible fetal heart beat, was detected by pelvic ultrasound. Urine  $\beta$ -HCG was positive. Her urine dipstick had specific gravity of 1.015, protein 1+ and ketones 3+. Her urine sediment, malaria smear, and rapid tests for Leptospirosis (Biomerieux, Marcy l'Etoile, France) and Dengue (PanBio Duo Cassette, Panbio, Brisbane, Australia) were negative. Blood and urine culture were negative. Scrub typhus infection was confirmed by serological evaluation using microimmunofluorescence using a previously described method (Luksameetanasan et al. 2007) that gave total Ig titers of 1:3 200 and  $\geq$ 1:25 600 for admission (day 5 of fever) and convalescent specimens (day 12 of fever), respectively. *O. tsutsugamushi* was isolated *in vitro* in Vero cells (designated isolate FPW1038) (Luksameetanasan et al. 2007) from the admission whole-blood sample. The nucleotide sequence of the entire 56-kDa type-specific antigen gene determined that isolate FPW1038 (GenBank no. EF213087) grouped with type strain TA716 (GenBank no. U19905; 95.9% identity) (Blacksell et al. 2008). Isolate FPW1038 demonstrated much lower identity with Karp (80.6%), Kato (88.0%), Gilliam (79.8%), TA763 (83.3%), TA686 (84.9%), Kawasaki (77.8%), and Boryong (79.5%) type strains.

The patient was commenced on Zithromax<sup>®</sup> (Pfizer, Sydney, Australia) 500 mg stat followed by 250 mg once per day for a total treatment of 5 days. After 3 days' treatment, her pelvic ultrasound was repeated, and the gestational sac had become smaller and pregnancy demise was suspected. After 38 days she experienced vaginal bleeding and had a manual vacuum aspiration for retained products.

## Discussion

*O. tsutsugamushi*-type strain TA716 was originally isolated from Berdmores' Ground Squirrel (*Menetes berdmorei*) in Thailand in 1963 (Elisberg et al. 1968), and before this case has never been reported in humans in Thailand. To our knowledge, the only other report of human infection with *O. tsutsugamushi* strain TA716 was in Malaysia during 1975–1976 (Shirai et al. 1979). Recent studies have determined that the *O. tsutsugamushi* Karp strain is the dominant strain causing human infections in Thailand with lower proportions of Gilliam (Luksameetanasan et al. 2007, Blacksell et al. 2008), which has implications for the composition of diagnostic assays. Further studies are required to determine the extent of *O. tsutsugamushi* TA716-related strains causing human disease to determine clinical and diagnostic implications. *O. tsutsugamushi* isolate FPW1038 is the first human strain related to type TA716 where the entire 56-kDa type-specific antigen gene has been sequenced and compared to other *O. tsutsugamushi* reference-type strains (Blacksell et al. 2008). Further genetic characterization of isolate FPW1038 for diagnostic and vaccine development purposes is underway including 47 kDa and *groEL* genes. Advances in the recognition of scrub typhus and improved laboratory understanding for diagnostics (Blacksell et al. 2008) should help clarify the importance of this disease in the Asia Pacific area, particularly in pregnancy (Kim et al. 2006).

*O. tsutsugamushi* causes scrub typhus and is a rural zoonosis endemic in the Asia Pacific region. This is the first report of *O. tsutsugamushi* TA716-related strain (FPW1038) causing acute disease in a human in Thailand. The patient was in the 1st trimester of pregnancy when she developed scrub typhus.

The *O. tsutsugamushi* TA716-related strain FPW1038 was isolated from her admission blood samples, and the pregnancy ended in spontaneous abortion. Improved clinical recognition and laboratory diagnosis will be essential to better define the morbidity caused by this zoonosis especially in pregnancy.

In this case the scrub typhus infection was associated with early pregnancy loss. The evolution of both the diagnosis of pregnancy and *O. tsutsugamushi* prevented confirmation of the cause of the miscarriage. The effects of scrub typhus in pregnancy are poorly described in the literature, partly due to the difficulty in confirming the diagnosis and the lack of prospective follow-up of pregnancies from women residing in endemic areas. Nevertheless, miscarriage has been reported to have occurred as a result of poorly controlled illness from inappropriate treatment regimens (Mathai et al. 2003). The problem of efficacious treatment is not unique to pregnancy, but is complicated by the limited range of drugs that can be safely administered in the 1st trimester. Recent advances in the recognition of scrub typhus and improved laboratory understanding for diagnostics should help clarify the importance of this disease in the Asia Pacific area, particularly in pregnancy.

*O. tsutsugamushi* TA716-related strain FPW1038 was isolated for the first time in a human in Thailand in October 2004. The typical features of her scrub typhus illness responded rapidly to azithromycin, but the woman had a spontaneous abortion. The epidemiology of scrub typhus in pregnancy remains poorly described.

## Ethical Clearance

The patient in this trial was part of a larger trial on the epidemiology of fever in pregnancy on the Thailand–Burma border that was approved by the Oxford Tropical Research Ethics Committee, UK (#013-03).

## Acknowledgments

We wish to thank the patient for participation in this trial, and the SMRU and MORU staff for their diligent work. This study was funded by the Wellcome Trust of Great Britain as part of the Wellcome Trust–Mahidol University–Oxford Tropical Medicine Research Programme.

## Disclosure Statement

The authors have no competing financial interests exist.

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