

A case of doxycycline-resistant tsutsugamushi meningoencephalitis

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Abstract

Here we report a case of doxycycline-resistant tsutsugamushi meningoencephalitis. A 63-year-old man with altered mental status was diagnosed with a tsutsugamushi infection by a local clinic and administered standard doxycycline treatment for 5 days without improvement. Azithromycin treatment for 3 days dramatically improved his clinical status.

INTRODUCTION

Scrub typhus, also known as tsutsugamushi disease, is an acute febrile illness caused by infection with *Orientia tsutsugamushis*.¹ In Korea, tsutsugamushi disease mainly occurs in rural regions during the fall.^{2,3} Most patients with tsutsugamushi disease respond to doxycycline medication.¹ If appropriate treatment is not implemented, multiple organ failure can occur.¹ We report a case of tsutsugamushi meningoencephalitis in which doxycycline treatment failed but complete response was achieved with azythromycin.

CASE REPORT

A 63-year-old man was admitted because of fever, headache, generalized malaise and altered mental statuses. Two weeks before admission, the patient was healthy and working on his farm. Five days before admission, he was diagnosed with tsutsugamushi disease because of the diagnosis of an eschar and a positive tsutsugamushi Ig M antibody at other medical facility. Despite prompt doxycycline treatment, his mental status worsened over 5 days.

Upon admission, fever (37.8°C), enlarged bilateral axillary lymph nodes and a maculopapular rash were observed. There was a 1.5 x 1.0 cm dark brown eschar on the left popliteal area (Figure 1).

Upon neurological examination, the patient was stuporous. He showed meningism and withdrawal to painful stimuli. Bilateral light reflexes and doll's eye were present. There were no focal neurologic signs. White blood cell counts were 10.64 (4.0 ~ 10.0 x 10⁹/L, neutrophils 78.1%), the aspartate aminotransferase (AST) was 70 IU/L, and the alanine aminotransferase (ALT) was 82 IU/L. Brain magnetic resonance imaging was

normal and did not show meningeal enhancement. Analysis of the cerebrospinal fluid (CSF) showed a pressure of 110 mmH₂O (100 -180 mmH₂O), yellowish color, a white blood cell count of 44/mm³ (lymphocytes 80%), protein levels of 163 mg/dL (15 – 45 mg/dL), and glucose levels of 71 mg/dl (blood glucose 135 mg/dl). Growth for fungi, mycobacterium tuberculosis, and bacteria were negative both in the blood or CSF. Ig M antibody for tsutsugamushi infection performed in our hospital was negative.

The patient was diagnosed with tsutsugamushi meningoencephalitis based on laboratory findings, an endemic area in the fall, a history of working on a farm, and an eschar. We considered his doxycycline treatment to be ineffective and began treating him with oral azithromycin 500 mg/day



Figure 1. A 1.5x1 cm sized dark brown-colored eschar is shown in the left popliteal area.

for 2 weeks. His consciousness began to improve from the third day after azithromycin medication. The patient was discharged 10 days later without neurological sequelae.

DISCUSSION

One of the most important clinical findings for the diagnosis of tsutsugamushi disease is the presence of an eschar even after negative serologic tests.⁴ In the serological diagnosis, indirect immunofluorescence antibody titers of 1:400 or more has a specificity of 96%.⁵ Antibody to *Rickettsia tsutsugamushi* as demonstrated by the indirect fluorescent antibody test lasts an average of 49 weeks.⁶ Negative finding of tsutsugamushi Ig M antibody performed in our hospital was possibly due to treatment with doxycycline.³

Approximately 2 to 5% of tsutsugamushi disease cases show central nervous system invasion.⁷ Twenty five cases of tsutsugamushi meningoencephalitis confirmed by rickettsial DNA tests from the CSF showed CSF WBC counts from 0 to 110/mm³ (lymphocytes 51.9% ± 23.9%) and protein levels over 50 mg/dl.⁸

Progression of tsutsugamushi meningoencephalitis despite doxycycline therapy is unusual. The first drug of choice for tsutsugamushi disease is doxycycline 200 mg/day; alternately chloramphenicol 2.0 g for 1 to 5 days can be used. Some strains of *Orientia tsutsugamushi* are poorly responsive to standard antirickettsial drugs including tetracyclines or doxycycline.⁹ For example, only one of three Chiangrai strains tested in cell culture was fully susceptible to doxycycline.⁹ Some experts have proposed the use of alternative drugs, such as azithromycin or combination therapy including a rifampicin.^{10,11}

In our case, despite of doxycycline treatment, clinical course of patient worsened steadily. We thought that the patient was poorly response doxycycline. And then, we quickly replaced by azithromycin, resulting in improving patient's illness. Therefore, in the endemic area including Korea and Southeast Asia, tsutsugamushi disease requires more carefully diagnosis, close clinical follow-up and appropriate selection of a therapeutic drug.

DISCLOSURE

Conflict of interest: None

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