Three Cases of Tsutsugamushi Disease successfully treated with Clarithromycin.

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Three cases of tsutsugamushi disease were successfully treated with clarithromycin, a new macrolide antibiotic. This is the first report describing tsutsugamushi disease in Hirado area and the clinical application of clarithromycin to this rickettsial disease.

Introduction

Tsutsugamushi disease had been considered to be an endemic disease occurring in summer along the large riversides of three northern prefectures in Japan; Akita, Yamagata, and Niigata prefectures. But from autumn through winter in 1946 and 1948, a new type of tsutsugamushi disease broke out in the Izu archipelago and in the east hills of Mt. Fuji. This endemic outbreak prompted the formation of the regional rickettsiosis research group in 1954 and they conducted national wide surveys which revealed the presence of several new types of tsutsugamushi disease. Thereafter increasing number of the cases of tsutsugamushi disease have been reported from many regions of Japan (1). But so far there has been no report on tsutsugamushi disease from Hirado, the northern island of Nagasaki prefecture in Japan. We report here three cases of tsutsugamushi disease successfully treated with clarithromycin, a new macrolide antibiotic.

Case 1

A 49-year-old farmer was admitted to our hospital for headache and skin rash on December 24, 1992. In early December he went to nearby hills and from the middle of the month he noticed headache, chill, and fever with eruptions gradually spread all over the body. On admission, the body temperature 38.6°C, and physical examination revealed swelling of the lymph nodes in the cervical and bilateral inguinal region. And the erythematous papular eruptions were observed mainly on the trunk. An eschar was noted on the upper portion of the right internal malleolus and it was presumed to be the location of the bite by tsutsugamushi mite (Fig. 1). Laboratory data on admission are shown on Table 1. White blood cell count was 7700/mm³ with 48% stab forms and 15% segmented forms of the neutrophils. C reactive protein was 9.3 mg/dl and erythrocyte sedimentation rate was elevated to 42 mm/h. GOT (68 IU/L), GPT (70 IU/L), and LDH (791 IU/L) were slightly elevated. The clinical course of the patient
is illustrated in Figure 2. Immediately after admission, he received oral administration of clarithromycin (CAM) 400 mg per day, and the fever rapidly resolved. The headache subsided in 2 days, the eruptions and the proteinuria noted on admission also gradually disappeared in several days. The antibody titer of IgG and IgM against *Rickettsia tsutsugamushi* in paired sera was diagnostic.

**Case 2**

A 18-year-old man visited our hospital complaining of eruption and fever on January 16, 1993. Early January of this year, the patient went to Kawachi-tohge after returning from Fukuoka City. He developed fever from January 14 and on the evening of the next day he also developed headache and eruption spread all over the body. His body temperature was 38.2°C. Physical examination demonstrated tonsilitis and eruption all over the body but location of the bite could not be identified. Laboratory data of this case are shown on Table 2. White blood cell count was 3200/mm³ with 31% stab and 28% segmented neutrophils. C reactive protein was elevated to 1.1 mg/dl. The clinical course of the patient is illustrated in Figure 3. He received 400 mg of clarithromycin (CAM) per day, and the fever subsided. The eruptions disappeared in a few days and the headache disappeared almost in one day. More than fourfold rise in antibody titer of IgG and IgM against *R. tsutsugamushi* between paired sera was considered to be diagnostic.

A 49-year-old housewife visited our hospital, complaining of chills and general fatigue on November 28, 1992. The patient went to nearby hills on November 15. On consulting day, her body temperature was 36.7°C and physical examination demonstrated neither eruptions nor locations of any bite. Laboratory data are shown on Table 3. White blood cell count was 4000/mm³ with 0% stab and 62% segmented neutrophils. C reactive protein was elevated to 1.7 mg/dl. GOT (50 IU/L), GPT (36 IU/L), and LDH (529 IU/L) were slightly elevated. The clinical course of the patient is illustrated in Figure 4. Because of the common cold-like symptoms, the patient received 750 mg/day of amoxicillin (AMPC) and mefenamic acid but the fever persisted. So the antibacterial drugs were changed to cefotiam hexetyl HCL (CTM-HE) on November 29. However, she still developed high fever and generalized eruptions on December 1. Considering the possibility of the
Table 3. Laboratory data

<table>
<thead>
<tr>
<th>Peripheral blood</th>
<th>Biochemistry</th>
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<tbody>
<tr>
<td>RBC 465X10⁹/mm³</td>
<td>Bil 0.42 mg/dl</td>
</tr>
<tr>
<td>Hb 11.6g/dl</td>
<td>T.P. 7.6 g/dl</td>
</tr>
<tr>
<td>Ht 34.2%</td>
<td>ALP 142 IU/L</td>
</tr>
<tr>
<td>WBC 4000/mm³</td>
<td>GOT 50 IU/L</td>
</tr>
<tr>
<td>St 0%</td>
<td>GPT 36 IU/L</td>
</tr>
<tr>
<td>Seg 62%</td>
<td>LDH 529 IU/L</td>
</tr>
<tr>
<td>Eo 0%</td>
<td>BUM 12.9 mg/dl</td>
</tr>
<tr>
<td>Plts 18.7X10⁹/mm³</td>
<td>Cr 0.9 mg/dl</td>
</tr>
<tr>
<td>ESR N.D.</td>
<td>Na 139 mEq/L</td>
</tr>
<tr>
<td>protein (-)</td>
<td>K 4.2 mEq/L</td>
</tr>
<tr>
<td>sugar (-)</td>
<td>Cl 102 mEq/L</td>
</tr>
<tr>
<td>RBC 25/30/F</td>
<td>CRP 1.7 mg/dl</td>
</tr>
<tr>
<td>WBC 1/F</td>
<td></td>
</tr>
</tbody>
</table>

Urinalysis

protein (-) sugar (-) CRP 1.7 mg/dl

Discussion

Tsutsugamushi disease is an infectious disease caused by
Rickettsia tsutsugamushi transmitted by the bite of larval
tsutsugamushi mite. The transmission of R. tsutsuga-

mushi to tsutsugamushi mite from generation to genera-

tion is by ovarian transmission. This is the reason why the

outbreak of tsutsugamushi disease may become endemic

but not truly epidemic (2). Reports of regional occurrence

are therefore important in regional medical treatment. All

three patients in this report went to nearby hills 1-2 weeks

before onset. Although the high value of IgG titer in case

2, immediately after the onset, suggested an inapparent

infection of tsutsugamushi disease (3). The patient's

symptoms developed soon after he went to Kawachi-tohge,

a resort area in Hirado. Therefore, other possibility of

infection was hardly conceivable. Although an eschar is

valuable for the diagnosis of tsutsugamushi disease, it was

not identified in our case 2 and 3. Nakagawa et al also

reported a case of tsutsugamushi disease without eruption

or eschar, and emphasized that one should be aware of

tsutsugamushi disease without eschar (4). Traditionally

tetracycline and its analogs or chloramphenicol have been

considered to be the mainstay in treating tsutsugamushi
disease (1). However, the adverse reactions often make it
difficult to administrate these drugs particularly to

pregnant women, children, and patients allergic to them.

Macrolide antibiotics, on the other hand, are considered to

be safe drugs due to more than 40 years clinical use, and

erthromycin was already proved to have strong growth-
inhibiting action against R. tsutsugamushi in vivo (5).

But its clinical efficacy had been considered to be weak.

Clarithromycin is one of the newly developed macrolide
derivatives which is stable in gastric acid compared to

conventional macrolide antibiotics and shows outstanding
tissue transfer (6). Single oral administration of 200 mg
clarithromycin reportedly yielded a maximum blood
concentration of 1.16 μg/ml (7). In vitro drug susceptibil-

ity test, the MIC of clarithromycin against Rickettsia

rickettsii, R. conorii, and R. israelii was at 1-2 μg/ml,

several times higher than that of erythromycin (8), but

there are no report on the clinical application of this
antibiotic to tsutsugamushi disease as far as we know. In

these three reported cases here, the effect of clarithromy-

cin was almost comparable to that of minomycin whose
effect is already shown in clinical trials (9). This is the
first report, to our knowledge, on the effectiveness of
clarithromycin in the cases with tsutsugamushi disease.
We believe that the clinical application of this new
macrolide antibiotic in this disease should be further
studied.
References


