Short Report: Coinfection with Leptospirosis and Scrub Typhus in Taiwanese Patients

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Abstract. We retrospectively analyzed patients with leptospirosis (n = 35), scrub typhus (n = 45), and coinfection (leptospirosis and scrub typhus [n = 7]) to facilitate the detection of coinfection. Our data showed that factors favoring these disease entities included animal contact, an aspartate aminotransferase/alanine aminotransferase ratio > 2 (for leptospirosis); outdoor exposure, lymphadenopathy, splenomegaly, eschar, and elevated alkaline phosphatase levels (for scrub typhus and coinfection); calf tenderness, conjunctival suffusion, jaundice, oliguria, elevated total bilirubin levels and serum creatinine levels (for leptospirosis and coinfection); and maculopapular rash (for scrub typhus). Patients at risk for leptospirosis are often at increased risk for scrub typhus and vice versa. Lack of knowledge of coinfection may jeopardize the health of affected patients. Our study serves as a reminder of potential coinfection and provides clues for its detection.

Leptospirosis, a common spirochetal zoonosis that is distributed worldwide with particular high incidences in tropical and subtropical areas,1-5 was once ignored in Taiwan.6-8 However, because of progressively widespread clinicians’ awareness, a substantially higher number of cases of leptospirosis were recently reported on this island.4-5 Fatality rates in cases of severe leptospirosis may be as high as 22% if affected patients are not timely and appropriately treated.9

Scrub typhus caused by Orientia tsutsugamushi is frequently found in people with outdoor exposure in tropical and subtropical Asian regions, including Taiwan.7-8 Because outdoor activity is a shared risk factor for acquisition of leptospirosis and scrub typhus, coinfection with these two diseases is not uncommon.9,10 The mortality rate in patients with untreated scrub typhus may be as high as 35%.11 Clinical manifestations of these infection entities are protean.1,8 Differential diagnoses of leptospirosis and scrub typhus and awareness of the potential for coinfection is important because penicillin, the drug of choice for treating severe leptospirosis,12 is intrinsically ineffective against rickettsiae.8-10 Unfortunately, definitive diagnoses of leptospirosis and scrub typhus rely mainly on serologic assays, which are not readily available in most clinical laboratories. The objective of the present study was to compare clinical manifestations and daily service–based laboratory data of patients with leptospirosis, those with scrub typhus, and those with coinfections to determine the potential of dual infection and facilitate detection of coinfection.

In this retrospective analysis, we included 86 patients with serologically confirmed leptospirosis and/or scrub typhus who were hospitalized at Chang Gung Memorial Hospital–Kaohsiung between September 2000 and January 2006. Leptospirosis was diagnosed in patients who had at least a fourfold increase in antibody titer against any serotype of leptospirae in paired serum samples or an antibody titer ≥ 1:320 in one serum sample by a microscopic agglutination test (MAT).13 Scrub typhus was diagnosed if patients had a fourfold increase in antibody titer against the Karp, Kato, and Gilliam strains of Orientia tsutsugamushi in paired serum samples or an IgM titer ≥ 1:80 against these strains of O. tsutsugamushi in one serum sample by an indirect immunofluorescence antibody assay (IFA).14 The MATs and IFAs were performed at Center for Disease Control in Taipei, Taiwan. These patients were categorized into leptospirosis (n = 35), scrub typhus (n = 44), and dual infection (n = 7) groups. Comparisons of data of these three groups were performed using the chi-square test or the Kruskal-Wallis H test, where applicable. When significant difference was found in a three-group analysis, further comparisons of data between each group were carried out using Fisher’s exact test. A two-tailed P value < 0.05 was considered statistically significant.

Demographics, histories of animal contact and outdoor exposure, clinical manifestations, and laboratory data of these patients are summarized in Table 1. Animal contact was defined as exposure to either household pets or wild mammals. Outdoor exposure was defined as involvement in either occupational or recreational activities in outdoor settings including forest and transitional terrain between forest and clearings. Individual variables favoring leptospirosis and/or scrub typhus (see comments on interpretation in Table 1) were as follows: 1) animal contact and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio > 2 favored leptospirosis; 2) outdoor exposure, lymphadenopathy, splenomegaly, eschar, and elevated alkaline phosphatase levels favored scrub typhus and coinfection; 3) calf tenderness, conjunctival suffusion, jaundice, oliguria, elevated total serum bilirubin levels and increased serum creatinine levels favored leptospirosis and coinfection; and 4) maculopapular rash favored scrub typhus.

Clinical manifestations specific for leptospirosis (conjunctival suffusion and calf tenderness) usually appear transiently in the early septicemic stage. Jaundice and acute renal dysfunction appear only in patients with the severe form of leptospirosis (Weil’s syndrome).1,2 Clinical features specific for scrub typhus (splenomegaly, maculopapular rash, and eschar) were reported in 50% of patients with primary scrub typhus and less frequently in patients with recurrent scrub typhus.7,8 Maculopapular rash in a patient with scrub typhus often transiently develops on the trunk at the end of the first week of illness and is easily overlooked.15 Abnormal liver function mainly with elevated AST and ALT levels was found in a substantial number of patients with scrub typhus.16 In patients with leptospirosis, jaundice is clinically reflective of hy-
periblirubinemia resulting from intrahepatic cholestasis. The slightly higher level of AST compared with that of ALT in patients with leptospirosis suggested that some of the serum AST is derived from muscles rather than the liver because concurrent myalgia, myositis, hypermyoglobinemia, and elevated levels of creatine phosphokinase are found.

Clinical and/or laboratory manifestations are helpful in making differential diagnosis of leptospirosis and scrub typhus. For example, in an otherwise healthy patient with appropriate exposure history, the combination of jaundice and acute renal dysfunction is strongly suggestive of leptospirosis, but an eschar is suggestive of scrub typhus. Nevertheless, once leptospirosis or scrub typhus is diagnosed, clinicians should be alert to potential coinfection with the other disease because of shared risk factors for acquisition of these diseases.

Previous reports and the present study showed a noteworthy proportions of patients with probable coinfections. A Thai farmer with confirmed leptospirosis who received treatment with high-dose intravenous penicillin and died of acute respiratory distress was reported to be coinfected with *O. tsutsugamushi*. This case underscores the importance of awareness of the potential of scrub typhus in patients with leptospirosis. Tetracycline or its analogs is used to treat patient with either leptospirosis or scrub typhus. For life-threatening leptospirosis, parenterally administered high-dose penicillin remains the treatment of choice. Our study serves as a reminder of potential coinfection and provides clues for diligent search for such a coinfection.

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**REFERENCES**


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**Table 1**

Demographic characteristics, histories of animal contact and outdoor exposure, clinical manifestations, and laboratory findings in patients with leptospirosis, scrub typhus, and dual infection (concurrent leptospirosis and scrub typhus)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Leptospirosis (L)</th>
<th>Scrub typhus (S)</th>
<th>Dual infection (D)</th>
<th><em>P</em> (L vs. S)</th>
<th><em>P</em> (L vs. D)</th>
<th><em>P</em> (S vs. D)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F ratio)</td>
<td>27/8</td>
<td>27/17</td>
<td>5/2</td>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years, median [range]</td>
<td>49 (18–80)</td>
<td>44 (16–75)</td>
<td>53 (39–71)</td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal contact (%)</td>
<td>28 (80)</td>
<td>20 (45)</td>
<td>5 (71)</td>
<td>0.005</td>
<td>0.01</td>
<td>0.62</td>
<td>0.21</td>
</tr>
<tr>
<td>Outdoor exposure (%)</td>
<td>5 (14)</td>
<td>33 (75)</td>
<td>4 (57)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.01</td>
<td>0.33</td>
</tr>
<tr>
<td>Fever, median day (range)</td>
<td>7 (2–21)</td>
<td>7 (2–14)</td>
<td>6 (1–12)</td>
<td>0.74</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache (%)</td>
<td>28 (80)</td>
<td>27 (61)</td>
<td>5 (71)</td>
<td>0.21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia (%)</td>
<td>5 (14)</td>
<td>12 (27)</td>
<td>0</td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain (%)</td>
<td>9 (26)</td>
<td>20 (45)</td>
<td>4 (57)</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calf tenderness (%)</td>
<td>20 (57)</td>
<td>0</td>
<td>2 (29)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.18</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Conjunctival suffusion (%)</td>
<td>12 (34)</td>
<td>0</td>
<td>2 (29)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.78</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Jaundice** (%)</td>
<td>18 (51)</td>
<td>3 (9)</td>
<td>5 (71)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.34</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Oliguria†† (%)</td>
<td>16 (46)</td>
<td>0</td>
<td>3 (43)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.89</td>
<td>&lt; 0.001</td>
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<tr>
<td>Lymphadenopathy (%)</td>
<td>0</td>
<td>33 (75)</td>
<td>4 (57)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Splenomegaly (%)</td>
<td>4 (12)</td>
<td>25 (57)</td>
<td>5 (71)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maculopapular rash (%)</td>
<td>3 (9)</td>
<td>21 (48)</td>
<td>2 (29)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.14</td>
<td>0.34</td>
</tr>
<tr>
<td>Eschar (%)</td>
<td>0</td>
<td>25 (57)</td>
<td>4 (57)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.98</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* ALT = alanine aminotransferase; A = no. of patients; B = no. of patients with data available; AST = aspartate aminotransferase; ALP = alkaline phosphatase.
† For comparisons of data between leptospirosis and scrub typhus using Fisher’s exact test, when *P* is statistically significant.
‡ For comparisons of data between leptospirosis and dual infection using Fisher’s exact test, when *P* is statistically significant.
§ For comparisons of data between scrub typhus and dual infection using Fisher’s exact test, when *P* is statistically significant.
¶ For comparisons of data between leptospirosis and dual infection using Fisher’s exact test, when *P* is statistically significant.
|| For comparisons of data between scrub typhus and dual infection using Fisher’s exact test, when *P* is statistically significant.
# For comparisons of data between leptospirosis and scrub typhus, and dual infection using Fisher’s exact test, when *P* is statistically significant.
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‡‡ For comparisons of data between leptospirosis and scrub typhus, and dual infection using Fisher’s exact test, when *P* is statistically significant.
§§ For comparisons of data between leptospirosis and scrub typhus, and dual infection using Fisher’s exact test, when *P* is statistically significant.
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