CASE REPORT

Successful treatment of septic shock and respiratory failure due to leptospirosis and scrub typhus coinfection with penicillin, levofloxacin, and activated protein C

Yu-Feng Wei a, Chien-Tung Chiua, Yung-Fa Lai a, Chung-Hsu Lai b,c,* Hsi-Hsun Lin b,d

a Division of Pulmonary Medicine, Department of Internal Medicine, E-Da Hospital/I-Shou University, Kaohsiung County, Taiwan
b Division of Infectious Diseases, Department of Internal Medicine, E-Da Hospital/I-Shou University, Kaohsiung County, Taiwan
c Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung City, Taiwan
d Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan

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Leptospirosis and scrub typhus are common zoonoses and coinfection with both diseases has been reported sporadically, particularly in tropical and subtropical areas. A 53-year-old male presented with acute hypoxemic respiratory failure and septic shock due to leptospirosis and scrub typhus coinfection confirmed by serological assessments. Antibiotics, including intravenous penicillin and levofloxacin, were administered and human recombinant activated protein C was added because of a high risk of death due to septic shock with multiple organ failure. The patient’s hemodynamics and hypoxemia substantially improved 4 days later and he had a complete recovery from the disease after 10 days of hospitalization. Coinfection of leptospirosis and scrub typhus may easily go unrecognized by physicians in febrile travelers or patients in the region where both diseases are endemic. In severe and critical cases of leptospirosis, scrub typhus, or coinfection with both, the use of APC in addition to appropriate antibiotic treatment and standard critical care might provide a greater chance for survival and a favorable outcome.

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* Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, E-Da Hospital 1, Yi-Da Road, Jiau-shu Tsuen, Yan-chau Shiang, Kaohsiung County, Taiwan.
E-mail address: laich6363@yahoo.com.tw (C.-H. Lai).
Introduction

Leptospirosis and scrub typhus are common zoonoses worldwide, with particularly high incidences in tropical and subtropical areas, including Taiwan.\(^1,2\) Cases of coinfection have been reported in the literature.\(^3-7\) The definite diagnosis of leptospirosis and scrub typhus relies mainly on serologic assays, which are not available in most clinical laboratories; potential coinfection with other diseases is easy to miss if only one disease is tested for.

Human recombinant activated protein C (APC), an antithrombotic, profibrolytic and anti-inflammatory agent, confers a relative 22% reduction in mortality in patients with severe sepsis and \(\geq 2\) organ dysfunctions.\(^8\) There have been few case reports of tropical infections and refractory multiple-organ failure treated with APC.\(^9\) Herein we report the first case, to the best of our knowledge, of septic shock secondary to leptospirosis and scrub typhus coinfection, with a good response to APC in addition to standard critical care and antibiotic treatment. The relevant literature is also reviewed.

Case report

A 53-year-old previously healthy fruit salesman presented to our emergency department with a 1-week history of high-grade fever, cough with scanty sputum, myalgia and headache. The symptoms persisted and progressive shortness of breath developed after initial treatment at the local clinic. No travel or animal contact history was reported.

On arrival he was in acute distress, with a body temperature of 40°C, pulse rate of 103 beats/min, blood pressure of 100/62 mmHg, respiration rate of 24 breaths/min and pulse oxygen saturation of 90% on room air. Physical examination revealed a clear consciousness without conjunctival suffusion or icteric sclera. The neck was supple without palpable lymphadenopathy. Auscultation of the chest disclosed bilateral fine crackles without cardiac murmurs. The abdomen was ovoid without local tenderness or marked hepatosplenomegaly. There was no skin rash, petechia or eschar. The remaining examinations were unremarkable.

The blood examination revealed a leukocyte count of 6510 cells/mm\(^3\) (87.1% neutrophils, 5.4% lymphocytes and 6.0% monocytes); a hemoglobin level of 13.6 g/dL; and a platelet count of 62,000 platelets/\(\mu\)L. Biochemical examinations revealed impaired renal function with a serum creatinine level of 3.4 mg/dL and blood urea nitrogen of 44 mg/dL. Abnormal liver function was shown by aspartate transaminase (AST) 66 U/L, alanine transaminase (ALT) 45 U/L and total bilirubin 2.46 mg/dL. The prothrombin time and partial thromboplastin time were within normal limits. Urinalysis revealed microscopic hematuria (25–50 red blood cells/high power field (HPF) by sediment examination) and proteinuria (1+ by urine dipstick) without pyuria. Electrocardiography showed sinus tachycardia. Chest radiography showed cardiomegaly with a prominent bilateral pulmonary trunk and minimal consolidation in the left upper lung field (Fig. 1A). The patient was admitted to the intensive care unit (ICU) with a diagnosis of severe sepsis with impending respiratory failure.

Progressive respiratory distress and shock developed after arrival at the ICU. Endotracheal intubation with mechanical ventilation was performed and vasopressor therapy was applied for hemodynamic maintenance. Follow-up chest radiograph showed a progressing bilateral consolidation (Fig. 1B). The infectious diseases specialist was consulted and leptospirosis or rickettsioses, including acute Q fever, scrub typhus, and murine typhus, were suspected because of impaired renal and liver function, which are commonly seen in leptospirosis and rickettsioses, respectively. Both diseases are endemic in southern Taiwan.

Empiric antibiotics with intravenous penicillin G (for the treatment of leptospirosis) and levofloxacin were initiated (for the treatment of rickettsioses and possible severe Gram-negative bacterial infection). In addition to antibiotic treatment, early goal direct therapy (EGDT) was instituted with a central venous catheter placement.

Figure 1. Findings of serial chest radiographies: (A) initial image revealed minimal consolidation in the left upper lung field; and (B) chest radiography showed a rapidly progressing bilateral lung consolidation on the next day.
Despite intensive care and adequate antimicrobial therapy, however, oliguric renal failure and metabolic acidosis developed 12 hours later. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 29, and we decided to start infusion of human recombinant activated protein C (APC) 18 hours after admission to the ICU.

The patient’s general condition improved and urine output increased gradually. The vasopressor was tapered off on day 3 of hospitalization. Follow-up chest radiography revealed resolution of the consolidation and the patient’s endotracheal tube was removed on day 4 of hospitalization. His blood and urine cultures were all negative for bacterial growth and sputum culture revealed the growth of normal flora. The patient was discharged after 10 days in hospital and was asymptomatic at 1-month follow up.

Leptospirosis and scrub typhus coinfection was confirmed by serologic tests. The results of the initial serologic tests (7 days after disease onset) were negative for leptospirosis and rickettsioses (Q fever, scrub typhus and murine typhus) using the microscopic agglutination test and immunofluorescence antibody assay, respectively. The serum tested on day 22 after disease onset was positive for leptospirosis (1:1600 for *Leptospira shermani*) and scrub typhus (IgG 1:320 and IgM 1:160 for *Orientia tsutsugamushi*), but negative for Q fever and murine typhus.

**Discussion**

Leptospirosis is an increasingly recognized disease in Taiwan and is caused by spirochetes of the *Leptospira* species.10 Humans acquire infection by contact with the urine of an infected animal or exposure to contaminated water or soil. The spectrum of symptoms in human infections is extremely broad, ranging from subclinical disease to a severe form of jaundice and acute renal dysfunction, known as Weil’s disease.1 Scrub typhus, caused by *O.tsutsugamushi* infection, frequently occurs in the South Pacific, Northern Australia and Asia, including Taiwan.2,11,12 Human infections often present as an acute febrile illness characterized by a typical primary lesion (eschar), lymphadenopathy, skin rash and other non-specific symptoms, such as headache, chills, cough and malaise. Other important clinical features include abnormal liver function and moderate thrombocytopenia.2,11,12 Serious complications, such as acute respiratory distress syndrome, acute pancreatitis, renal failure and septic shock, have also been described.13

Coinfection with leptospirosis and scrub typhus has been sporadically reported, especially in regions where both diseases are endemic, such as Thailand and Taiwan.3–7 The clinical characteristics of reported cases are summarized in **Table 1.**3–7 It is difficult for clinicians to become aware of coinfection with leptospirosis and scrub typhus due to the nonspecific clinical manifestations, which can mimic various febrile illnesses. Lee et al reported that animal contact and an AST/ALT ratio >2 favored leptospirosis and a maculopapular rash favored scrub typhus.4 These characteristics seemed to be of little help, however, since our patient did not have either manifestations. Eschar, the

**Table 1**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Case number</th>
<th>Animal contact</th>
<th>Laboratory examinations</th>
<th>Treatment regimen</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watt7</td>
<td>2003</td>
<td>Thailand</td>
<td>9</td>
<td>Agricultural workers</td>
<td>Elevated bilirubin and creatinine (5/9)</td>
<td>N/A</td>
<td>Alive</td>
</tr>
<tr>
<td>Wang6</td>
<td>2003</td>
<td>Taiwan</td>
<td>1</td>
<td>Yes</td>
<td>Elevated bilirubin and creatinine (5/7), elevated carbon dioxide (5/7), decreased hematocrit (5/7)</td>
<td>Ceftriaxone and doxycycline</td>
<td>Alive</td>
</tr>
<tr>
<td>Lu5</td>
<td>2005</td>
<td>Taiwan</td>
<td>7</td>
<td>Yes</td>
<td>Elevated bilirubin (5/7)</td>
<td>Penicillin and minocyclin</td>
<td>Died</td>
</tr>
<tr>
<td>Lee4</td>
<td>2007</td>
<td>Taiwan</td>
<td>1</td>
<td>No</td>
<td>Elevated bilirubin (5/7)</td>
<td>Penicillin, levofloxacin and activated protein C</td>
<td>Alive</td>
</tr>
<tr>
<td>Chen3</td>
<td>2007</td>
<td>Taiwan</td>
<td>1</td>
<td>No</td>
<td>Elevated bilirubin and creatinine</td>
<td>Moxifloxacin, imipenem, plasma exchange, activated protein C</td>
<td>Alive</td>
</tr>
<tr>
<td>Present report</td>
<td>2009</td>
<td>Taiwan</td>
<td>1</td>
<td>None</td>
<td>Elevated bilirubin and creatinine</td>
<td>None</td>
<td>Alive</td>
</tr>
</tbody>
</table>

N/A = not available.
distinctive characteristic of scrub typhus caused by the chigger bite, is found in only about 23–67% of cases of scrub typhus in Taiwan.\textsuperscript{12} Without the characteristic eschar skin lesion and conjunctival suffusion for scrub typhus and leptospirosis, respectively, and a history of animal contact or exposure to a rural or field environment, it would be unlikely for clinicians to suspect scrub typhus or leptospirosis in this patient. In Taiwan, scrub typhus and leptospirosis should be one of the differential diagnoses in febrile travelers with septic shock. In severe and critical cases of leptospirosis, scrub typhus, or patients in the region where both diseases are endemic, but may pass unrecognized by physicians in febrile travelers or patients in the region where both diseases are endemic. In severe and critical cases of leptospirosis, scrub typhus, or coinfection with both, the use of APC in addition to appropriate antibiotic treatment and standard critical care might provide a greater chance for survival and a favorable outcome.

Conflict of interest statement

None of the contributing authors have any conflicts of interest to disclose.

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References