CASE REPORTS OF LEPTOSPIROSIS IN SOUTHERN TAIWAN

Kun-Jung Chung, Cheng-Ting Hsiao, Jien-Wei Liu, and Chih-Hsiung Lee

Leptospirosis is a zoonotic disease with worldwide distribution. Animals excrete urine-borne Leptospira spp. into soil or water, which may cause human infection through skin abrasions, mucous membrane contact, conjunctiva exposure, or by swallowing contaminated water. Leptospirosis has protean clinical manifestations ranging from a flu-like illness to a severe or fatal Weil’s syndrome characterized by fever, hemorrhage, jaundice, and acute renal failure. Current diagnostic methodologies for leptospirosis include microscopic agglutination test (MAT), polymerase chain reaction (PCR), and microorganism culture [1]. Because the clinical manifestations of severe leptospirosis often overlap with sepsis of other etiologies, and the serologic diagnostic tools are not always readily available at most hospitals, leptospirosis is probably unrecognized or underdiagnosed by clinicians in most countries. Clinicians at Chang Gung Memorial Hospital-Kaohsiung became alert to the potential for leptospirosis after it was diagnosed in a patient with a full-blown clinical picture of Weil’s syndrome at the hospital’s emergency department in early September 2000. Four additional cases of leptospirosis were subsequently diagnosed within a 2-month period. All of the patients were hospitalized, and presented with high fever, severe myalgia, jaundice, and acute renal failure. Two of these patients who rapidly received doxycycline therapy survived, while the remaining three patients who received delayed penicillin therapy died. These cases suggest that the incidence of leptospirosis may have been underestimated in Taiwan, and underscore the urgent need for increased clinician awareness of this infectious disease.

Abstract: Leptospirosis, a zoonotic disease with worldwide distribution, is often overlooked in Taiwan. Clinicians at our medical center in southern Taiwan became alert to the potential for leptospirosis after the first documented case of severe leptospirosis—Weil’s syndrome was diagnosed at our emergency department in early September 2000. Four additional cases of leptospirosis were subsequently diagnosed within a 2-month period. All of the patients were hospitalized, and presented with high fever, severe myalgia, jaundice, and acute renal failure. Two of these patients who rapidly received doxycycline therapy survived, while the remaining three patients who received delayed penicillin therapy died. These cases suggest that the incidence of leptospirosis may have been underestimated in Taiwan, and underscore the urgent need for increased clinician awareness of this infectious disease.

Key words: leptospirosis Weil’s syndrome Taiwan

CASE REPORTS

Case Reports

Case 1

A previously healthy 27-year-old woman who had suffered from sore throat, headache, conjunctival suffusion, nausea, vomiting, and low abdominal pain for 10 days visited a local clinic where common cold was diagnosed and she was treated accordingly. Her symptoms were temporarily relieved at that time. However, fever and subsequent severe myalgia over limbs, yellowish skin discoloration, and oliguria developed. She was admitted to a local hospital where she was found to have...
infection, dengue fever, and molecular biologic studies were negative for hantavirus. The patient’s condition became apparent 3 days later. Urine and blood serologic studies with Weil’s disease. Improvement in the patient’s condition was noted shortly after sonographic study due to suspicion of leptospirosis. An echocardiogram showed bilateral pleural effusion and slight splenomegaly. Doxycycline was added to the antibiotic regimen due to suspicion of leptospirosis with multiorgan failure, ceftriaxone and inotropic agents were used initially. Sonogram showed a prolonged prothrombin time (PT) of 24.6 seconds (control, 11.5 sec) and activated partial thromboplastin time (APTT) of 62.3 seconds (control, 28.4 sec). Blood chemistry showed elevated blood urea nitrogen (BUN) of 72 mg/dL (normal, 6.0–21.0 mg/dL), creatinine (Cr) of 6.8 mg/dL (normal, 0.4–1.4 mg/dL), aspartate aminotransferase (AST) of 1,172 IU/L (normal, < 37.0 IU/L), alanine aminotransferase (ALT) of 80 IU/L (normal, < 40.0 IU/L), total bilirubin of 7.60 mg/dL (normal, < 1.4 mg/dL) with a direct bilirubin component of 6.93 mg/dL, myoglobin of 408 mg/dL (normal, < 90 mg/dL), and alkaline phosphatase within normal limits. Urinalysis showed proteinuria and microscopic hematuria. Disseminated intravascular coagulation (DIC) profile showed a prolonged thrombin time (TT) of 50 seconds (control, 18.4 sec), decreased fibrinogen concentration of 48.6 mg/dL (normal, 200–400 mg/dL), and elevated fibrin degradation product (FDP) concentration of more than 100 mg/mL (normal, < 10 mg/mL).

Respiratory failure developed later on the same day. She was intubated for mechanical ventilatory support and admitted to the intensive care unit (ICU). Under the impression of possible common cold at a local clinic. However, fever persisted, jaundice and respiratory distress developed 3 days later, and he was transferred to our emergency department on November 11, 2000. Peripheral white cell count was 10,600/mL with 70.0% polymorphonuclear cells, and platelet count was 100,000/mL. Blood chemistry showed AST concentration of 157 IU/L, ALT of 57 IU/L, bilirubin of 4.0 mg/dL. BUN of 47 mg/dL, and Cr of 5.7 mg/dL, and elevated creatine phosphokinase (CPK) at 1,019 mg/dL (normal, 8.0–114 mg/dL). Under suspicion of possible Legionnaire’s disease or leptospirosis, antibiotics, including ciprofloxacin, clarithromycin, and doxycycline, were prescribed for sepsis. The patient’s clinical condition and renal function had improved markedly 1 week later. Subsequent serology study revealed a four-fold increase in titer with paired-sera against leptospiral serogroup Shermani. The patient was discharged 2 weeks after hospitalization.

Case 3
A 79-year-old woman with chief complaints of fever, cough, and shortness of breath for 4 days was admitted to our emergency department on September 10, 2000. On arrival, she was acutely ill but conscious, and had high fever, tachycardia and tachypnea, and lowered blood pressure. Physical examination revealed pale conjunctiva with suffusion, icteric sclera, supple neck, tenderness over the abdomen and lower extremities, bilateral leg edema, and petechiae over both the wrists. Hemogram showed a peripheral white cell count of 17,400/mL with 96.8% polymorphonuclear cells, hemoglobin 11.1 g/dL, and a platelet count of 24,000/mL (normal, 150,000–450,000). Coagulation studies showed a prolonged prothrombin time (PT) of 24.6 seconds (control, 11.5 sec) and activated partial thromboplastin time (APTT) of 62.3 seconds (control, 28.4 sec). Blood chemistry showed elevated blood urea nitrogen (BUN) of 72 mg/dL (normal, 6.0–21.0 mg/dL), creatinine (Cr) of 6.8 mg/dL (normal, 0.4–1.4 mg/dL), aspartate aminotransferase (AST) of 1,172 IU/L (normal, < 37.0 IU/L), alanine aminotransferase (ALT) of 80 IU/L (normal, < 40.0 IU/L), total bilirubin of 7.60 mg/dL (normal, < 1.4 mg/dL) with a direct bilirubin component of 6.93 mg/dL, myoglobin of 408 mg/dL (normal, < 90 mg/dL), and alkaline phosphatase within normal limits. Urinalysis showed proteinuria and microscopic hematuria. Disseminated intravascular coagulation (DIC) profile showed a prolonged thrombin time (TT) of 50 seconds (control, 18.4 sec), decreased fibrinogen concentration of 48.6 mg/dL (normal, 200–400 mg/dL), and elevated fibrin degradation product (FDP) concentration of more than 100 mg/mL (normal, < 10 mg/mL).

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Table. Summary of the clinical characteristics of five patients with leptospirosis

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yr)</th>
<th>Risk factor for exposure</th>
<th>Laboratory diagnosis</th>
<th>Antimicrobial treatment*</th>
<th>Creatinine (mg/dL)</th>
<th>AST (IU/L)</th>
<th>Bilirubin (mg/dL)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27/F</td>
<td>Pet dogs</td>
<td>Leptospira inadai isolated from urine</td>
<td>Doxycycline</td>
<td>6.8</td>
<td>1172</td>
<td>7.6</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>66/M</td>
<td>Mountain hiking</td>
<td>4-fold increase in paired sera (serogroup Shermani)</td>
<td>Doxycycline</td>
<td>5.7</td>
<td>157</td>
<td>4.0</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>79/F</td>
<td>None identified Farmer</td>
<td>1:100 dilution in single serum (serogroup Icterohaemorrhagiae)</td>
<td>Penicillin G</td>
<td>3.6</td>
<td>241</td>
<td>3.6</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>43/M</td>
<td>None identified Farmer</td>
<td>1:200 dilution in single serum (serogroup Shermani)</td>
<td>Penicillin G</td>
<td>2.1</td>
<td>97</td>
<td>15.8</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>60/M</td>
<td>Farmer</td>
<td>16-fold increase in paired sera (serogroup Shermani)</td>
<td>Penicillin G</td>
<td>7.5</td>
<td>4814</td>
<td>8.2</td>
<td>Died</td>
</tr>
</tbody>
</table>

* Doxycycline was started early in Cases 1 and 2, while Penicillin G was started late in the remaining cases. AST = aspartate aminotransferase; F = female; M = male.
emergency department on September 23, 2000. Laboratory tests were normal except for thrombocytopenia with a platelet count of 75,000/mL and AST of 241 IU/L. Three days later, she developed hemoptysis, jaundice, oliguria, and bilateral calf tenderness. Repeated laboratory data showed acute hepatic and renal failure. Leptospirosis was suspected and penicillin was administered on Day 7 of hospitalization. The patient’s clinical condition deteriorated despite the intensive treatment and she died on Day 11 of hospitalization. Serology study subsequently disclosed leptospiral serogroup Icterohaemorrhagiae in a single serum specimen with 1:100 dilution, indicating seropositivity for leptospirosis [1].

**Case 4**

A 43-year-old farmer was admitted to our ICU via the emergency department on December 4, 2000, with the chief complaints of fever, bilateral calf pain, headache, and abdominal pain for 4 days and subsequent progressive jaundice and respiratory distress. Hemogram showed a peripheral white cell count of 20,560/mL with 10% band form granulocytes, and a platelet count of 34,000/mL. Blood chemistry showed potassium at 2.1 meq/L (normal, 3.5–4.5 meq/L), and AST concentration of 97 IU/L, ALT of 30 IU/L, Cr of 2.1 mg/dL, bilirubin (direct/total) of 7.0/15.8 mg/dL, and CPK of 471 mg/dL. Coagulation studies showed DIC-like coagulopathy with prolonged APTT, PT, TT, and elevated FDP. He was treated for bacterial sepsis with multiorgan failure. Hemoptysis, subconjunctival hemorrhage, petechiae over the lower limbs, and shock developed abruptly on Day 4 of hospitalization. Penicillin was added on Day 6 of hospitalization because of suspected leptospirosis. The patient died of overwhelming sepsis on Day 15 of hospitalization. Serology study subsequently disclosed leptospiral serogroup Shermani in a single serum specimen with 1:200 dilution, indicating probable leptospirosis [1].

**Case 5**

A previously healthy 60-year-old farmer, suffering from diarrhea and vomiting for 3 days, accompanied by abdominal pain, fever and chills, jaundice, and decreased urine output, visited our emergency department on December 26, 2000. Hemogram revealed a normal peripheral white cell count of 6,600/mL and decreased platelet count of 14,000/mL. Blood chemistry showed elevated AST at 4,814 IU/L, ALT of 1,526 IU/L, bilirubin of 8.2 mg/dL, and Cr of 7.5 mg/dL. Severe calf myalgia and shortness of breath developed 2 days later and penicillin was administered under the impression of leptospirosis. The patient died on Day 6 of hospitalization due to progressive multiorgan failure. Subsequent serology study revealed a 16-fold increase in titer with paired sera against leptospiral serogroup Shermani.

**Discussion**

While leptospirosis has a worldwide distribution, it is also underdiagnosed globally [2–4]. There are several possible causes of underdiagnosis: most cases of leptospirosis are subclinical, or they have mild clinical manifestations and are self-limited; lack of clinician awareness of leptospirosis renders the disease unrecognizable; and adequate diagnostic tools are not always readily available at most hospitals, making confirmation of clinical suspicion difficult, if not impossible. A previous report from the
Leptospirosis was first reported in Taiwan in 1976 [13]. Twenty years elapsed until further cases of leptospirosis were reported in Taiwan in 1996 [14]. Probably as a result of greater clinician alertness, leptospirosis has been sporadically reported in Taiwan thereafter. This sporadic reporting suggests that leptospirosis in Taiwan is more likely to be an ignored infectious disease rather than a newly emerging one. Leptospirae are found worldwide, and are particularly distributed in tropical and subtropical areas [15]. Taiwan geographically lies in a subtropical area where leptospirae prevail. The large agricultural population in southern USA found that active, as opposed to passive, surveillance for leptospirosis disclosed a five-fold increase in its actual incidence [2]. As a result, the need for a high index of suspicion and awareness of the clinical manifestations of leptospirosis cannot be overemphasized.

Risk factors for exposure to leptospirae include occupational exposure (farmers and ranchers, abattoir workers, trappers, veterinarians, loggers, sewer workers, rice-field workers, and military personnel), recreational activities (freshwater swimming, canoeing and kayaking, trail biking, and hunting), and household environmental factors (domestic dogs and livestock, rainwater catchment systems, and rodent infestation) [5]. All of the cases in this report except for Case 3 had distinct histories of either animal or environmental exposure risk factors for contracting leptospirosis. The diagnosis of leptospirosis is indicated by at least a four-fold increase in paired sera against leptospiral antigens. The rapid fatality resulting from overwhelming sepsis in Cases 3 and 4 made comparison of the serum titers at convalescence and septic phases impossible.

The incubation period of leptospirosis ranges between 7 and 14 days. A clinically milder form of this disease can be found in approximately 90% of infections. The acute septicemic phase begins abruptly with high fever and headache (>95%); chills, rigors, and myalgia (>80%); conjunctival suffusion (30%–40%); abdominal pain (30%); anorexia, nausea, and vomiting (30%–60%); and a pretibial maculopapular cutaneous eruption (<10%) lasting from 3 to 7 days [6]. During this period of time, spirochetes may be recovered from blood or cerebrospinal fluid culture. Conjunctival suffusion and muscle tenderness, most notable in the calf and lumbar area, are the most distinguishing physical findings. Two of the five patients in this report presented with conjunctival suffusion. All of the patients showed clinical and laboratory evidence of myositis, and they all complained of myalgia and abdominal pain and had higher serum concentrations of AST than ALT. A large portion of their AST was presumably from a muscular source instead of the liver. In addition, Case 1 had elevated serum myoglobin, and both Cases 2 and 3 had elevated serum CPK.

In more severe forms of leptospirosis, the course of the illness may be biphasic. In the subsequent immune phase (4 to 30 d), spirochetes are no longer found in the blood but may be excreted in the urine. The separation between these two phases is often unclear. In the most severe icteric form of leptospirosis — Weil’s syndrome, the aforementioned symptoms and signs for anicteric patients are more severe and prolonged, and profound jaundice rapidly develops about 3 to 7 days after the beginning of illness. The mortality rate varies from 5% to 40% [7].

Hemorrhagic complications are common in severe leptospirosis. Thrombocytopenia, commonly seen in leptospirosis, was found in all our patients and was in the range of 14,000 to 100,000/µL. Coagulation studies were performed in three patients, and disclosed prolonged PT, APTT, and TT and increased FDP, suggestive of DIC.

Pulmonary involvement occurs in 20% to 70% of patients with leptospirosis, and is presumably due to vascular injury [8]. Cough and hemoptysis are the most prominent signs reflective of pulmonary damage. Severe respiratory distress and pulmonary hemorrhage are not characteristics of leptospirosis in the western hemisphere, but in Oriental populations a comparatively higher frequency of these characteristics and more severe clinical conditions have been found [9].

Renal impairment is frequently seen, and is more severe in Weil’s syndrome than in anicteric leptospirosis. Azotemia, oliguria, and anuria commonly occur during the second week of the illness but may appear as early as 3 to 4 days after the onset [4, 5]. Remarkably, renal histopathology for Case 1 showed thrombotic microangiopathy which was compatible with thrombotic thrombocytopenic purpura (TTP). It seems likely that TTP is a complication of leptospirosis. Leptospirosis-associated TTP is rarely seen [10], and its mechanism and clinical implications deserve further study.

It is well known that penicillin is the drug of choice for acute and severe leptospirosis. Doxycycline is reserved for prophylaxis and mild infection. Double-blind and placebo-controlled studies have demonstrated that oral doxycycline 100 mg twice daily for 1 week is beneficial in shortening the course of early leptospirosis [11], and that intravenous penicillin 1.5 million units four times daily for 7 days decreases the duration of fever and renal impairment in severe, late illness [12]. Penicillin should be given even if the diagnosis is ascertained late in the course of disease. In our patients, doxycycline was prescribed early in both Cases 1 and 2, and both patients survived. The remaining patients who received delayed therapy with penicillin died. Further study is required to determine whether or not a timely and effective antimicrobial therapy is an independent prognostic factor for survival.

Leptospirosis in Taiwan
Taiwan and the increasing island-wide number of urban residents raising pets may contribute to the high incidence of leptospirosis on this island [16]. Additionally, in Taiwan, there have been an increasing number of foreign laborers from South-East Asian countries, and an increasing number of brides from either these tropical countries or from the southern provinces of China, where leptospirae prevail. These people may suffer from incubation-stage leptospirosis at the time of their arrival. The septic and immune phases of leptospirosis might subsequently develop [17]. Awareness of the clinical manifestations of leptospirosis and its inclusion in the list of differential diagnosis is of particular importance in Taiwan.

References