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Original Article

Demographic and clinical features of leptospirosis: three-year experience in central Taiwan

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Background and Purpose: Leptospirosis is a major cause of fever in subtropical and tropical areas. The clinical manifestations are protean, ranging from very mild and nonspecific symptoms to severe septic shock and death. This retrospective study investigated the demographic and clinical features of leptospirosis in central Taiwan over 3 years, with emphasis on pulmonary manifestations.

Methods: We analyzed the clinical characteristics of serologically-confirmed leptospirosis cases at a tertiary teaching hospital from October 2002 to October 2005.

Results: Twenty three confirmed cases were included and *Leptospira santarosai* serovar Shermani was the most commonly identified serovar (77.3%). The male-to-female ratio was 2.67:1 and the average age was 42.4 years. Nineteen cases (82.6%) were hospitalized, 3 were diagnosed in the outpatient setting and 1 died before admission. The majority of cases (63.6%) occurred in rainy months (from June to October). Fever (incidence, 100%), anorexia (74%), headache (61%), gastrointestinal upset (53%), myalgia (48%), and cough (48%) were the common clinical manifestations. Fifteen cases (63%) had respiratory symptoms and twelve (52%) had chest roentgenography abnormalities. Multiple nodular densities pattern (42%) was the most common abnormal finding on chest plain film. Three patients met the criteria of Weil's syndrome. The overall mortality rate was 4.3%.

Conclusions: Respiratory symptoms or abnormal findings on chest X-ray were not uncommon in patients with leptospirosis. In addition to hepatic or renal dysfunction, leptospirosis should be seriously considered in patients with pulmonary symptoms and fever, especially in subtropical and tropical areas.

Key words: Leptospirosis; Leukocytosis; Lung; Taiwan; Thrombocytopenia

Introduction

Leptospirosis is a re-emerging disease worldwide [1], and an endemic disease in most tropical and subtropical regions [2]. Leptospirosis is characterized by the development of vasculitis, endothelial damage and inflammatory infiltrates, and clinical manifestations vary from subclinical infection to severe infection and even death [3]. Detailed knowledge of pathogenic mechanisms has proven elusive, and a diverse range of disease appears to be associated with the acute and chronic infection process [4]. Every organ system can be affected by leptospirosis, with renal and hepatic dysfunction most commonly implicated. In Taiwan, leptospirosis is an important but often underestimated cause of acute renal failure [5]. Pulmonary involvement detected clinically or via abnormal chest X-ray was previous reported in approximately 17-70% of patients suffering from leptospirosis [6-8]. In Taiwan, there have been a few case reports of pulmonary abnormality in patients with leptospirosis [9-11]. We conducted this retrospective study of leptospirosis cases over a 3-year period to investigate the epidemiology and incidence of pulmonary abnormalities in patients with leptospirosis in central Taiwan.

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Methods

From October 2002 to October 2005, all patients potentially acquiring leptospirosis with either hepatic or renal dysfunction or acute febrile illness were enrolled. Blood specimens were collected and sent to the Center for Disease Control, Taiwan. Definite diagnosis of leptospirosis was made by microscopic agglutination test (MAT). Symptomatic patients who met one of following criteria were eligible for inclusion: (1) seroconversion from negative to positive; (2) a four-fold or greater increase of MAT titer in paired sera sampled 2 weeks apart; or (3) single serum sample MAT titer >1:400.

All patients' charts were reviewed and demographic data, clinical manifestations, laboratory findings, therapeutic methods, and outcome were recorded. New pulmonary infiltration was regarded as significant chest radiographic abnormality. The abnormalities in chest plain film were recorded and categorized as follows: multiple nodular density, alveolar pattern, interstitial infiltration and pleural effusion. Renal insufficiency was defined as serum creatinine levels increasing from the baseline to at least 0.5 mg/dL, or above 1.4 mg/dL. Hyperbilirubinemia was defined as serum total bilirubin level above 1.3 mg/dL. Defervescence was defined as a body temperature <37.5°C for more than 24 h after the appropriate antimicrobial therapy.

Statistical analysis

All results are expressed as mean values ± standard deviation or as percentages. Continuous variables were analyzed by Student's *t* test or Fisher's exact test. Categorical data were compared using chi-squared tests. A value of $p<0.05$ was considered statistically significant and all tests of significance were 2-tailed. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (Version 10.0; SPSS, Chicago, IL, USA) software package.

Results

Demographic data

During the study period, blood samples were collected from 133 patients with suspected leptospirosis and sent to the Center for Disease Control, Taiwan for serologic diagnosis. In total, 23 confirmed cases were identified by MAT. There was a wide range of patient age (18 to 72 years), and more than one-half were older than 40 years. Male patients accounted for more than two-thirds of cases. The mean duration of symptoms prior to hospital admission was 5 days (range, 1-16 days). The monthly distribution of leptospirosis cases is shown in Fig. 1. *Leptospira santarosai* serovar Shermani was the most common serogroup (77.3%).

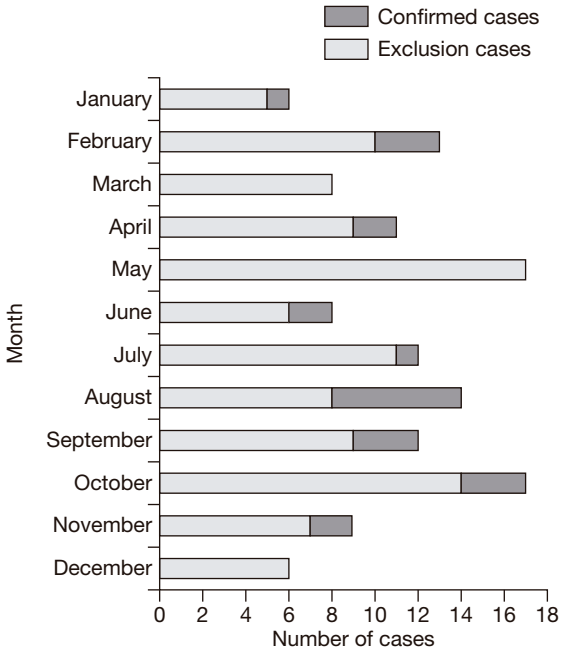

Fig. 1. Monthly distribution of cases of leptospirosis from October 2002 to October 2005.

Risk factors for acquisition of leptospirosis are listed in Table 1. Acquisition was related to occupation in ten patients (43%), 7 of which related to recreational activity, including 3 patients assumed to be infected during canoeing in Southeastern Asia about two weeks before symptom development, and 4 with a history of animal exposure. In 4 patients, no risk factors could be identified.

Clinical presentations

Clinical features are summarized in Table 1 and laboratory findings in Table 2. Fever (100%), anorexia (74%), headache (61%) and gastrointestinal upset (53%) were the common complaints at presentation. Respiratory symptoms included cough (48%), dyspnea (39%), and hemoptysis (13%). Urinalysis data were available in 21 cases. Among these patients, 6 (29%) had microscopic hematuria and 10 (48%) had proteinuria (>100 mg/dL). Thrombocytopenia was found in nine patients, leukocytosis in five, leucopenia in two, and pancytopenia in two. Thirteen (57%) had modestly elevated serum transaminase levels (aspartate aminotransferase, 73.5 ± 82.6 U/L; alanine aminotransferase, 76.6 ± 84.9 U/L), 9 hyponatremia

Table 1. Demographic data, risk factors and clinical features of 23 patients with leptospirosis

Characteristic	No. (%)
Age (years)	
<20	1 (4)
20-40	9 (39)
>40	13 (57)
Mean age (years; ± SD)	42.4 ± 12.5
Male gender	17
Exposure type	
Occupational[a]	10 (43)
Recreational[b]	7 (30)
Unknown	4 (17)
Animal-related[c]	4 (17)
Symptoms	
Fever (>38°C)	23 (100)
Anorexia	17 (74)
Headache	14 (61)
Gastrointestinal upset	12 (53)
Myalgia	11 (48)
Cough	11 (48)
Dyspnea	9 (39)
Signs	
Relative bradycardia[d]	8 (29)
Conjunctival suffusion	5 (22)
Calf soreness/pain	5 (22)
Rash	4 (17)
Meningism	4 (17)
Hemoptysis	3 (13)

Abbreviation: SD = standard deviation

[a]Occupations included farming (5), hunting (1), aquaculture (1), abattoir work (2) and military (1).

[b]Four from swimming in a river, 3 from canoeing.

[c]Dog (3 cases, including 2 farmers), cat, rodent.

[d]Relative bradycardia: pulse rate increase less than 10 beats/min/°C from baseline.

(serum sodium, 135.2 ± 4.4 mmol/L) and 11 hypokalemia (serum potassium, 3.5 ± 0.5 mmol/L). Nine cases had renal insufficiency (serum creatine, 1.66 ± 1.48 mg/dL). Leukocytosis (11.1 ± 6.3 × 10^3 vs 7.3 ± 3.1 × 10^3 cells/mm^3, p=0.038), dyspnea (56% vs 29%, p=0.383), and longer hospital stay (7.3 vs 6.6 days, p=0.918) were observed in patients with renal insufficiency. Eight cases had hyperbilirubinemia and two of these had jaundice. Only three patients had both renal insufficiency and hyperbilirubinemia. Compared with those without bilirubinemia, patients with hyperbilirubinemia were more likely to have leukocytosis (11.2 ± 7.2 × 10^3 vs 7.3 ± 3.1 × 10^3 cells/mm^3, p=0.022), thrombocytopenia (63% vs 27%, p =0.221), dyspnea (63% vs 27%, p=0.179) and longer hospital stay (7.6 vs 4.9 days, p=0.727), but less headache (38% vs 73%, p=0.179).

All 23 patients had available chest roentgenograms. More than one-half (52%) of chest films were abnormal, and these findings could be grouped into four patterns (Fig. 2). Radiographically, 5 cases had small nodular density pattern, 3 alveolar infiltration pattern, 2 interstitial linear pattern and 2 pleural effusion pattern. One case with initial alveolar infiltration progressed to acute respiratory distress syndrome and death. Fifteen patients (65%) had respiratory symptoms initially (such as cough, dyspnea or hemoptysis). Compared with those with normal chest films, patients with abnormal chest radiography had a higher incidence of leukocytosis (33% vs 9%, p=0.317) and dyspnea (75% vs 27%, p=0.400), longer hospital stay (7.2 vs 6.5 days, p=0.400) and less headache (58% vs 64%, p=1). Three cases had splenomegaly based on imaging studies, including abdominal ultrasonography or computed tomography.

Nineteen cases (82.6%) were hospitalized, 3 were treated and followed up in the outpatient setting and 1 (4.3%) died before admission. Three patients met the criteria of Weil's disease, and one of these died. All patients received effective antibiotic treatment [12]. A

Table 2. Laboratory findings of 23 patients with leptospirosis

Condition	Case no. (%)	Range
Leukocytosis, WBC >12,000/mm^3	5 (22)	2400-26,300
Leukopenia, WBC <4000/mm^3	2 (9)	2400-26,300
Anemia (hemoglobin <13 g/dL)	9 (39)	7-16.4
Thrombocytopenia (platelet count <140,000/mm^3)	9 (39)	13,000-432,000
Pancytopenia	2 (9)	
Azotemia, blood urea nitrogen >20 mg/dL	7 (30)	5-88
Renal insufficiency, serum creatine >1.4 mg/dL	9 (39)	0.8-7.6
Elevated transaminase (alanine aminotransferase >40 U/L)	13 (57)	10-401
Hyponatremia (serum sodium <135 mmol/L)	9 (39)	128-141
Hypokalemia (serum potassium <3.5 mmol/L)	11 (48)	2.8-4.9

Abbreviation: WBC = white blood cells

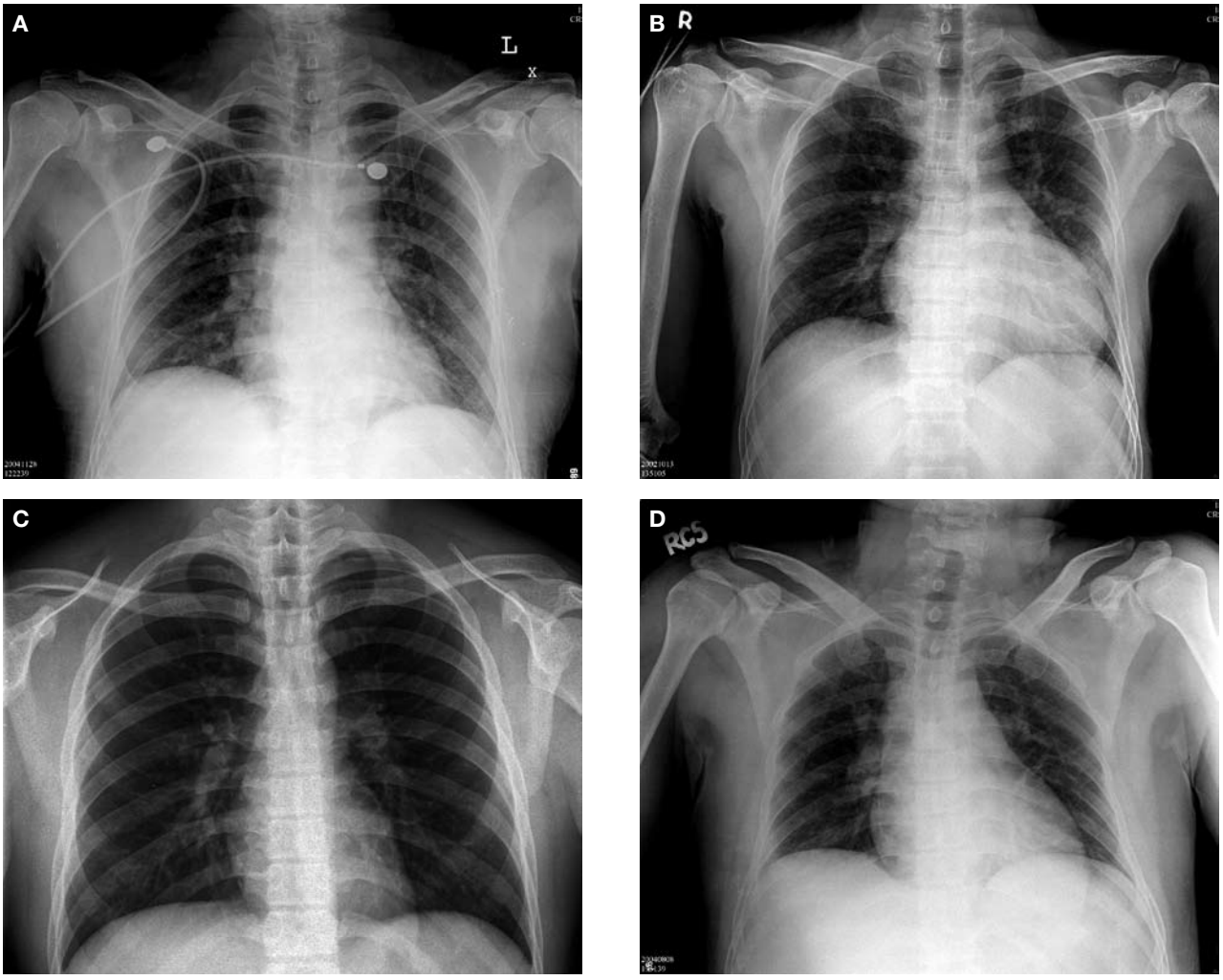

Fig. 2. Four kinds of abnormal chest radiography. Small nodular density pattern (A); interstitial linear pattern (B); alveolar infiltration pattern (C); pleural effusion pattern (D).

single agent was used in 8 of 23 patients (35%), and combination therapy was used in 15 patients (65%). The most commonly prescribed drug was minocycline. The mean time to defervescence of hospitalized patients was 2.3 days (range, 1-5 days).

Discussion

Leptospirosis has become an increasingly recognized zoonosis worldwide as well as in Taiwan [9-11,13]. Three laboratory-confirmed patients were treated in the outpatient setting in this report, suggesting the presence of mild illness and the potential for underdiagnosis. Similar to earlier reports [5,9], *Leptospira santarosai* serovar Shermani (77.3%), was the most common causative agent in the present study (77.3%). The majority of cases of leptospirosis have occurred in the wet seasons [9,14], and the same phenomenon was observed in our patients (61%). Similar to previous series [3,9], males (74%) were affected more often than females. In general, farmers, veterinarians and butchers have a higher risk of acquiring leptospirosis [1]. In contrast to reports from developed countries [2,15], 43% of patients in our study acquired leptospirosis from environmental exposure and 39% from recreational activities. The reason for this difference is unclear and may only become evident with further large population-based study in this setting.

As in other series [7,15], the clinical manifestations of leptospirosis in this study were not specific. Fever, anorexia, headache and gastrointestinal upset (such as nausea, vomiting) were the most common complaints. Conjunctival suffusion, regarded as pathognomonic for leptospirosis [4,15], was seen in only 22% of patients. Twenty to seventy percent of patients have been found to have pulmonary involvement [6,8],

and 65% of our patients had pulmonary symptoms. Although cough was the most common respiratory complaint, dyspnea (39%) and hemoptysis (13%) also occurred. Pulmonary manifestations, without associated jaundice or renal dysfunction, can be the prominent presentations in severe leptospirosis [10,16-18]. In our study, all three patients with hemoptysis had abnormal chest radiography and hepatic dysfunction. Abnormal chest radiographs were documented in 11% to 67% of leptospirosis cases in previous studies [8,19]. In this study, 53% of patients presented abnormal pulmonary radiographic findings. Of the four radiographic patterns identified, small nodular lesion was the most common.

In a study from Hawaii, thrombocytopenia was found in 58% and leukocytosis in 39% of leptospirosis patients [15]. Patients with leptospirosis may present with afebrile neutropenia without classical signs [20]. Thrombocytopenia can be found in up to 50% of leptospirosis patients with renal failure, and is a poor prognostic factor [21]. Other poor prognostic factors in leptospirosis include dyspnea, oligouria, leukocytosis, and abnormalities of chest radiographs and electrocardiograms [22]. As Dupont et al [22] and Pertuiset et al [23] indicated, leukocytosis is more likely to be observed in severe leptospirosis.

Renal failure is frequently reported in patients with leptospirosis (16-69%) [2,3,7]. A previous case-control study in Taiwan found a higher acute renal failure rate (86.4%) [9]. In our study, 39% of patients had renal insufficiency, but none required renal replacement therapy. The variation in the percentage of renal failure might be due to hospital-based selection bias and to different definitions in various studies.

Mortality in leptospirosis has ranged from 1% to 25% [7,18]. Weil's disease, characterized by impaired hepatic and renal function, is the severe form of leptospirosis, with an increased risk of mortality [1]. The clinical manifestations of leptospirosis are protean and nonspecific, and early serologic testing can be negative [24]. MAT serology is usually insensitive in the early stage of leptospirosis [3]. This false-negative result makes the clinical diagnosis of leptospirosis more difficult. Among our patients, the most common tentative diagnosis was leptospirosis (43%), followed by fever of unknown origin (17%), urinary tract infection, pneumonia and viral infections. Pulmonary tuberculosis was the intitial impression in one of our patients.

In conclusion, leptospirosis mainly occurred in the rainy months in central Taiwan. Pulmonary symptoms and abnormal chest radiographs were not uncommon. In addition to hepatic or renal dysfunction, leptospirosis should be seriously considered in patients with pulmonary manifestations, abnormal chest X-ray, fever and risk of exposure.

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