

Clinical Characteristics of Legionella Pneumonia Diagnosed with Legionella Urinary Antigen Test

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(Received June 5, 2015; Accepted November 27, 2015)

Objective: The aim of our study was to describe the clinical characteristics of Legionella pneumonia diagnosed with a positive urinary antigen test, and factors associated with severe Legionella pneumonia were investigated.

Methods: We retrospectively investigated the clinical characteristics of patients with Legionella pneumonia diagnosed at Tokai University Hospital between February 2006 and June 2012. The clinical characteristics of ICU cases and non-ICU cases were compared.

Results: Twenty-six patients with Legionella pneumonia were identified (mean age 66.7 ± 19.3). Twenty patients were men (76.9 %). Impaired consciousness was observed in 12 patients (46.2 %), followed by gastrointestinal symptoms (38.5 %). Ten patients had severe pneumonia which required ICU admission. A case-controlled study comparing non-ICU cases and ICU cases demonstrated that cases with diabetes (OR 10.1, 95 % CI 1.1–90.5) and tachycardia (OR 10.1, 95 % CI 1.1–90.5) were significantly associated with ICU admission.

Conclusions: Legionella pneumonia did not always present as severe pneumonia. Extrapulmonary manifestations may be useful clues for diagnosis. Diabetic patients have not only a risk of contracting Legionella pneumonia, but also a risk of progression. Legionella pneumonia should be included in the differential diagnosis even in cases of mild to moderate pneumonia when presenting with extrapulmonary symptoms, especially in diabetic patients.

Key words: Legionella pneumonia, urinary antigen test, community-acquired pneumonia, severe pneumonia, risk factor

INTRODUCTION

Legionella is rare, but one of the important pathogens of severe community-acquired pneumonia. However, the diagnosis of Legionella is difficult because Legionella cannot be detected by gram stain or cultured in routine media. Definitive diagnosis of Legionella requires sputum culture with special media, such as BCYE media, or serological investigation. A high index of suspicion is necessary to diagnose Legionella pneumonia.

Since the outbreak of Legionnaires' disease in 1976, many studies have demonstrated the clinical characteristics of Legionella pneumonia [1]. Presence of extrapulmonary symptoms, such as impaired consciousness, myalgia, arthralgia, nausea, vomiting and diarrhea, were shown to be characteristic to Legionella pneumonia. Abnormal laboratory findings, including hyponatremia, liver dysfunction, renal dysfunction, and elevated creatine kinase, were also suggested to be specific to Legionella pneumonia [2]. These signs and symptoms have been important clues for diagnosis, and provoked physicians to conduct specific microbiological investigation of Legionella pneumonia. Although these findings are important clues for diagnosis, there is a concern that atypical cases without these features are not evaluated for Legionella, which leads to misdiagnosis. It could be speculated that a

substantial number of Legionella pneumonia cases may have been missed with conventional diagnostic methods.

Urinary antigen test for Legionella is a rapid diagnostic test to detect Legionella pneumophila serogroup 1, which has been commercially available in Japan since 2003. Compared to conventional diagnostic methods, the urinary antigen test can confirm the diagnosis of Legionella pneumonia rapidly, within a few minutes [3]. Because of its convenience and ease of use, the threshold to conduct the diagnostic test is low compared to those requiring culturing and serology. These features of the urinary antigen test for Legionella make it possible to diagnose atypical cases of Legionella pneumonia, which would have been missed if only conventional methods were utilized.

According to national surveillance, the number of Legionella pneumonia cases in Japan has been growing since 2010, and reached 1,111 in 2013 [4]. One of the reasons of this increase in cases is thought to be the introduction of the Legionella urinary antigen test for clinical practice. New perspectives on the clinical picture of Legionella pneumonia will be available through the investigation of cases with Legionella pneumonia diagnosed with a positive urinary antigen test.

The aim of our study was to describe the clinical characteristics of Legionella pneumonia diagnosed by

positive urinary antigen test for Legionella in Japan. In addition, we investigated factors associated with severe Legionella pneumonia by comparing symptoms and laboratory data between patients who were admitted to the intensive care unit (ICU) and patients who were treated at the outpatient clinic or admitted to a non-ICU ward.

Most of the reports demonstrating the clinical characteristics of Legionella pneumonia have been from the United States and European countries, and information on Legionella pneumonia in Asian countries, including Japan, remains scarce. This study will also provide new insights into the clinical picture of Legionella pneumonia in Japan.

PATIENTS AND METHODS

This study was a retrospective observational study of patients who were diagnosed with Legionella pneumonia at the Department of General Internal Medicine in Tokai University Hospital between 1st February, 2006 and 30th June, 2012.

Patients included were older than 16 years, and were not hospitalized at the time of pneumonia diagnosis. The diagnosis of pneumonia was made by the presence of respiratory symptoms and positive findings of chest X ray and/or CT scan. Urinary antigen test for *Legionella pneumophila* serogroup 1 (Binax Now Legionella®) was used for microbiological diagnosis of Legionella.

Data were collected by medical chart review. Information about patient demographics, medical history, signs and symptoms, laboratory data, prescribed antibiotics, and outcome were collected. Medical history included comorbidities, alcohol consumption, smoking habit, and history of exposure to hot springs. Comorbidities were defined as a history of a disease and a newly diagnosed disease. Laboratory data including blood cell count, electrolytes, liver and renal function, creatine kinase, and C-reactive protein (CRP) were collected. To evaluate disease severity, the CURB 65 score was calculated from collected data. The CURB 65 score is a prediction rule for the mortality of community-acquired pneumonia. The score is calculated based on level of consciousness, blood urea nitrogen level, respiratory rate, blood pressure, and age. The score ranges from 0 to 5, with a higher score indicating a higher risk [5].

To investigate factors associated with more severe cases of Legionella pneumonia, we compared the clinical characteristics described above between patients admitted to the intensive care unit (ICU) and patients who were treated at the outpatient clinic or admitted to a non-ICU ward. Indications of admission to ICU included severe respiratory failure requiring endotracheal intubation, and/or circulatory shock requiring hemodynamic monitoring. Univariate analyses were conducted using STATA ver 12.1. The chi square test or Fisher's exact test were used for categorical variables, and Student's t-test or Wilcoxon rank sum test were used for continuous variables. A P-value below 0.05 was considered statistically significant.

RESULTS

Patient characteristics and outcomes of Legionella pneumonia (Table 1)

Patient demographics and medical history

Twenty-six patients were included in the present study. Twenty patients (77%) were male. The mean age was 66.7 years.

The most prevalent co-morbidity was diabetes (38.5%), followed by malignancy, such as colon carcinoma (19.2%). Underlying pulmonary diseases were observed in only 2 patients, which were bronchiectasis and asbestosis. One patient was taking corticosteroids for collagen vascular disease.

Four patients (15.4%) had a smoking habit, and alcoholism was reported in 6 patients (23.1%). Exposure history to hot spring was identified in 5 patients (19.2%).

Clinical signs and symptoms

Mean blood temperature at presentation was 38.0°C. In terms of extrapulmonary symptoms, impaired consciousness was most prevalent and observed in 12 patients (46.2%), followed by gastrointestinal symptoms (nausea, vomiting, and diarrhea) in 10 patients (38.6%). Musculoskeletal symptoms, such as myalgia and arthralgia, were observed in only 3 patients (11.5%).

Laboratory data

Mean white blood cell count was 10638.5 per mm³, and ranged from 3800 to 18500 per mm³. High serum creatinine level was observed in 9 patients (34.6%). Hyponatremia and hyperkalemia were observed in 2 cases (7.7%) and 5 cases (19.2%), respectively. Mean CRP level was 19.8 mg/dl, and ranged from less than 0.09 to 51.9 mg/dl.

Disease severity and outcome

CURB 65 scores were 0 in 6 patients, 1 in 2 patients, 2 in 10 patients, 3 in 6 patients and 4 in 2 patients. Length of hospital stay was 27 days (ranged from 16 to 62 days). The 30 day-mortality was 7.7%.

Antibiotic treatment

In all cases, antibiotics effective against Legionella species were used. Azithromycin was administered in 7 cases (26.9%), erythromycin in 6 cases (23.1%), ciprofloxacin in 9 cases (34.6%), levofloxacin in 1 case (3.8%), and pazufloxacin in 3 cases (11.5%). Rifampicin was administered in 2 cases (7.7%) as a combination therapy with other antibiotics.

Comparison between ICU cases and non-ICU cases (Table 2)

Of the 26 patients, twenty-one patients (81%) were admitted to the hospital, and 10 patients (38%) were treated in the intensive care unit.

Patient characteristics and medical history

There were no differences in age and sex between the two groups. Diabetes was more prevalent in the ICU patients (70% for ICU patients and 18.6% for non-ICU patients; $p = 0.015$). Hemoglobin A1c (HbA1c) at the time of diagnosis of Legionella pneumonia

Table 1 Clinical characteristics and outcomes of Legionella pneumonia

	Legionella pneumonia n = 26
Demographics	
Male sex, n (%)	20 (76.9)
Age, mean (SD), years	66.7 (19.3)
Medical history	
Diabetes mellitus, n (%)	10 (38.5)
Malignancy, n (%)	5 (19.2)
Cerebral infarction, n (%)	4 (15.4)
Chronic kidney disease, n (%)	2 (7.7)
Pulmonary disease, n (%)	2 (7.7)
Corticosteroid, n (%)	1 (3.9)
Liver disease, n (%)	1 (3.9)
Smoking habit, n (%)	4 (15.4)
Alcoholism, n (%)	6 (23.1)
History of hot springs, n (%)	5 (19.2)
Signs and symptoms	
Head ache, n (%)	3 (11.5)
Gastrointestinal symptoms, n (%)	10 (38.5)
Myalgia, n (%)	1 (3.9)
Arthralgia, n (%)	2 (7.7)
Impaired consciousness, n (%)	12 (46.2)
Temperature, mean(SD), °C	38.0 (1.3)
Systolic blood pressure, mean(SD), mmHg	127.5 (29.6)
Heart rate, mean(SD), /min	109.3 (26.7)
Heart rate > 120/min, n (%)	10 (38.5)
Respiration rate, mean(SD), /min	24.1 (5.2)
Laboratory data	
White blood cell count, mean(SD), / μ l	10638.5 (4283.4)
Na \leq 130 mEq/L, n (%)	2 (7.7)
K \geq 4.5 mEq/L, n (%)	5 (20)
sCr \geq 1.2 mg/dl, n (%)	9 (34.6)
GPT > 40, n (%)	6 (23.1)
CRP, mean (SD), mg/dl	19.8 (16.5)
Outcome	
Length of hospital stay, median (IQR)	27 (16-62)
30-day mortality, n (%)	2 (7.7)

were available in 6 patients out of 7 ICU patients with diabetes and 2 patients out of 3 non-ICU patients with diabetes. Mean HbA1c was not significantly different between 6 ICU patients with diabetes and 2 non-ICU patients with diabetes (7.7% vs 7.8%; $p = 0.9$).

Clinical signs and symptoms

There were no differences in extrapulmonary symp-

toms (impaired consciousness, myalgia, arthralgia and gastrointestinal symptoms) between the two groups. Heart rate was higher in ICU patients (128.9 bpm for ICU patients and 97.1 bpm for non-ICU patients; $p = 0.002$). Tachycardia (heart rate > 120 bpm) was significantly associated with ICU admission (OR 10.1, 95% CI 1.1-90.5).

Table 2 Comparison of clinical characteristics and outcomes between non-ICU patients and ICU patients with Legionella pneumonia

	Non-ICU (n = 16)	ICU (n = 10)	P-value
Demographics			
Male sex, n (%)	12 (75.0)	8 (80)	1.00
Age, mean (SD), years	62.2 (22.6)	73.9 (9.5)	0.14
Medical history			
Diabetes mellitus, n (%)	3 (18.6)	7 (70)	0.015
Malignancy, n (%)	5 (31.3)	0 (0)	0.12
Cerebral infarction, n (%)	1 (6.3)	3 (30)	0.26
Chronic kidney disease, n (%)	1 (6.3)	1 (10)	1.00
Pulmonary disease, n (%)	1 (6.3)	1 (10)	1.00
Corticosteroid, n (%)	1 (6.3)	0 (0)	1.00
Liver disease, n (%)	1 (6.3)	0 (0)	1.00
Smoking habit, n (%)	3 (18.8)	1 (10)	1.00
Alcoholism, n (%)	5 (31.3)	1 (10)	0.35
History of hot springs, n (%)	3 (18.8)	2 (20)	1.00
Signs and symptoms			
Head ache, n (%)	2 (12.5)	1 (10)	1.00
Gastrointestinal symptoms, n (%)	6 (37.5)	4 (40)	1.00
Myalgia, n (%)	1 (6.3)	0 (0)	1.00
Arthralgia, n (%)	2 (12.5)	0 (0)	0.51
Impaired consciousness, n (%)	9 (56.3)	3 (30)	0.25
Temperature, mean(SD), °C	38.1 (1.4)	37.6 (1.0)	0.38
Systolic blood pressure, mean (SD), mmHg	127.3 (19.7)	127.8 (42.3)	0.96
Heart rate, mean (SD), /min	97.1 (22.1)	128.9 (21.8)	0.002
Heart rate > 120/min, n (%)	3 (18.8)	7 (70)	0.02
Respiration rate, mean (SD), /min	22.3 (5.0)	26 (5.1)	0.21
Laboratory data			
White blood cell count, mean (SD), /μl	9793.8 (3819.3)	11990 (4832.6)	0.21
Na ≤ 130 mEq/L, n (%)	1 (6.3)	1 (10)	1.00
K ≥ 4.5 mEq/L, n (%)	4 (26.7)	1 (10)	0.62
sCr ≥ 1.2 mg/dl, n (%)	4 (25)	5 (50)	0.23
GPT > 40, n (%)	4 (25.0)	2 (20)	1.00
CRP, mean (SD), mg/dl	16.1 (14.3)	25.6 (6.0)	0.16
Outcome			
Length of hospital stay, median (IQR)	23 (10–32)	53 (24–66)	0.11
30-day mortality, n (%)	0 (0)	2 (20)	0.14

Abbreviations: SD, standard deviation; IQR, interquartile range; sCr, serum creatinine; GPT, glutamic pyruvic transaminase; CRP, C-reactive protein

Laboratory data

No laboratory data were significantly associated with ICU admission. Although the mean CRP level was higher in ICU patients (25.6 mg/dl for ICU patients and 16.1 mg/dl for non-ICU patients; $p = 0.16$), this difference was not statistically significant.

Outcome

Median length of hospital stay was not significantly different between patients who were admitted to the ICU and patients who were admitted to the non-ICU ward (53 days vs 23 days; $p = 0.11$). The 30-day mortality in ICU patients was 20 % (2 patients), and no non-ICU patients died.

DISCUSSION

Our study had three major findings. First, impaired consciousness and gastrointestinal symptoms were frequently observed in patients with Legionella pneumonia. However, other features, such as myalgia and arthralgia, which have been reported to be characteristic to Legionella pneumonia were observed in only a limited number of cases. Second, less than half of the cases with Legionella pneumonia presented as severe pneumonia requiring ICU admission. Third, diabetes was significantly associated with patients who were treated in the ICU.

Impaired consciousness and gastrointestinal symptoms were frequently observed in patients with Legionella pneumonia in the present study. Previous studies showed that extrapulmonary symptoms were characteristic to Legionella pneumonia [6, 7]. Kierby *et al.* showed that gastrointestinal symptoms were observed in 54.2% of patients with Legionella pneumonia [6]. In the present study, a similar trend was observed. Impaired consciousness was observed in 46.2% of patients and gastrointestinal symptoms were observed in 38.6% of patients. On the other hand, arthralgia was observed in 7.7% of patients, and myalgia in only 3.9% of patients in the present study. These numbers were low compared to the results of a previous study, which reported that myalgia was observed in 43% of patients [8]. Several laboratory findings have been reported to be characteristic to Legionella pneumonia. Hyponatremia, liver dysfunction, renal dysfunction, and elevated creatine kinase were reported to be characteristic features of Legionella pneumonia [2]. Sopena *et al.* reported that hyponatremia was observed in 28.9%, elevated AST in 60%, and elevated CK level in 32.3% of patients [9]. However, in the present study, these features were observed in only a limited number of patients.

In the present study, less than half of the cases with Legionella pneumonia presented as severe pneumonia requiring ICU admission. Legionella pneumonia has been known to be a cause of severe pneumonia [10]. In the guideline on the management of community-acquired pneumonia by the Infectious Disease Society of America, urinary antigen tests for *Legionella pneumophila* were recommended for patients with severe community-acquired pneumonia, but not for patients with mild to moderate illness [11]. In the present study, the 30-day mortality of Legionella pneumonia was high (7.7%), but more than half of the patients could be successfully managed in non-ICU settings. Mild to moderate cases of Legionella pneumonia will be missed if indication of urinary antigen tests were limited to patients with severe pneumonia. Legionella pneumonia should be included in the differential diagnosis of mild to moderate pneumonia, as well as severe pneumonia.

Our current study demonstrated that diabetes was significantly associated with patients who were treated in the ICU. Previous studies have investigated the prognostic factors of Legionella pneumonia, and El-Ebiary *et al.* demonstrated that hyponatremia ($\text{Na} \leq 136 \text{ mEq/L}$) was one of the independent risk factors of mortality in cases of severe Legionella pneumonia [12].

In the present study, although an association was not identified with hyponatremia, diabetes and tachycardia were significantly associated with cases requiring ICU care. Diabetes has been identified as a risk factor of several infections, possibly due to its immunosuppressive effect [13, 14]. In diabetic patients, Legionella pneumonia may progress to severe disease; therefore, early diagnosis and appropriate treatment with careful follow-up are necessary for such patients.

There are some limitations in our study. Due to the retrospective nature of the study design, medical history, symptoms, and signs may not have been collected by medical staff at the time of consultation, which may lead to underestimation of the presence of these factors. This bias is most problematic when information can only be collected through active questioning by medical staff. In our institute, medical records are formulated to collect co-morbidities, basic demographics, and vital signs, which may have avoided the loss of data on these factors.

Second, the number of included cases in our study was small. Statistical analysis may have failed to detect factors associated with ICU cases in a case-control study. Only univariate analysis was conducted due to the number of ICU cases not being large enough to include more than one factor in the multivariable model. Studies with a larger number of cases are required to evaluate risk factors with multivariable analysis.

In conclusion, to the contrary of previous belief, Legionella pneumonia did not always present as severe pneumonia. Impaired consciousness and gastrointestinal symptoms were associated with many cases of Legionella pneumonia and may be useful clues for diagnosis. Diabetic patients have not only a risk of contracting Legionella pneumonia but also a risk of progressing to a severe case requiring ICU admission. Legionella pneumonia should be considered for differential diagnosis even in cases of mild to moderate pneumonia when presenting with extrapulmonary symptoms such as impaired consciousness and gastrointestinal symptoms, especially in diabetic patients.

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