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Legionnaires' Disease in Community-Acquired Pneumonia Requiring Hospitalization in Taiwan

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Background: Legionnaires' disease is a relatively common but underdiagnosed cause of pneumonia. This study was conducted to determine the incidence of Legionnaires' disease in patients with community-acquired pneumonia (CAP). **Methods:** Three hundred and twenty-three consecutive patients with CAP admitted to a teaching hospital in Taiwan were studied. An indirect fluorescent antibody (IFA) for the detection of *Legionella pneumophila* serogroup 1-6 antibodies in serum and an enzyme immunoassay (EIA) for the detection of *L. pneumophila* serogroup 1 antigen in the urine were used for the diagnosis of Legionnaires' disease. **Results:** Twenty-nine patients (9.0%) were diagnosed with Legionnaires' disease. Among them, the male to female ratio was 20:9. Underlying risk factors and diseases included cigarette smoking (21%), chronic obstructive pulmonary disease (21%), disorders of the central nervous system (17%), diabetes mellitus (17%), and heart disease (17%). Fever (97%), cough (69%), hyponatremia (34%), elevated liver enzymes (24%), and gastrointestinal (24%) and neurological (21%) symptoms were common. Forty-eight percent of the patients were complicated by acute respiratory failure, and 3% by acute renal failure. The mortality rate of Legionnaires' disease was 24%. The risk of mortality was higher in patients with hyponatremia, respiratory failure, and those aged over 70 years. **Conclusions:** Legionnaires' disease should be investigated in patients with CAP requiring hospitalization in Taiwan.

Key words: Legionnaires' disease, community-acquired pneumonia

INTRODUCTION

First recognized at the 1976 American Legion Convention in Philadelphia, Legionnaires' disease is the pneumonia caused by bacteria of the genus Legionellaceae[1]. Thereafter, at least 42 species of *Legionella* have been identified, including 15 serogroups of *Legionella pneumophila*[2]. Although *L. pneumophila* serogroup 1 is the dominant cause of Legionnaires' disease in most regions[3,4], other *Legionella* species (such as *L. micdadei* and *L. bozemanii*) and other pneumophila serogroups are being recognized with increasing frequency[5,6]. In addition, there are geographic differences in the distribution of *Legionella* species as human pathogens.

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Deemed as "atypical pneumonia", nonproductive cough and extrapulmonary symptoms such as gastrointestinal difficulties, hyponatremia, and headache are nonspecific clinical manifestations of Legionnaires' disease. However, the mortality rate of Legionnaires' disease is often higher than for "atypical" pneumonia caused by other etiologies. As the clinical and radiographic features do not distinguish Legionnaires' disease from other pneumonias, the diagnosis requires special microbiologic tests: culture, serologic tests, and urinary antigen detection are currently in use for the diagnosis of Legionnaires' disease[6].

Since the first proven case reported in 1985, there have been limited cases and seroepidemiological studies on Legionnaires' disease in Taiwan[7-13]. In order to understand the incidence of Legionnaires' disease in patients with community-acquired pneumonia (CAP) requiring hospitalization, we investigated 323 CAP patients using serology and urinary antigen detection for *L. pneumophila*.

METHODS

Between July 1997 and October 1998, 323 consecutive patients with CAP admitted at Tri-Service General Hospital, a teaching hospital located in northern Taiwan, were

investigated. Blood samples were obtained at the onset of illness (acute phase) and 4-12 weeks later (convalescent phase). Urine samples were collected at the acute stage. Sera were tested for *L. pneumophila* antibody (serogroup 1-6) titer using an indirect fluorescent antibody test (IFA; Zeus, Raitan, NJ, USA), and urine samples were tested for *L. pneumophila* serogroup 1 antigen using an enzyme immunoassay (EIA; Binax, Portland, ME, USA). Both tests were performed according to the manufacturer's instructions. The sensitivity and the specificity of the antibody serology are 40%-60% and 96%-99%, respectively[2]. The sensitivity and specificity of urinary antigen detection for the diagnosis of Legionnaires' disease are 70% and 100%, respectively[2].

Patients were categorized as having definite and probable Legionnaires' disease according to the following definitions. Definite diagnosis was defined as (1) a fourfold rise in IFA titer between the acute phase and the convalescent phase and a final titer≧1:256, or (2) a positive urinary antigen (ratio to negative [RTN]≧3.0). Probable diagnosis was defined as (1) a single titer of IFA≧1:256, (2) elevation of IFA titer to≧1:256, but not a fourfold increase, or (3) an RTN value of urinary antigen≧2.5 but < 3.0.

Demographic data, clinical characteristics, and clinical outcomes were collected, recorded in worksheets, and analyzed.

RESULTS

Three hundred and twenty-three patients were enrolled in the study. Their acute stage sera were collected for IFA testing; 14% (45/320) also received IFA testing of convalescent phase sera. Four patients showed a fourfold rise of antibody titer with a final titer up to≧1:256, including one patient with a urinary RTN≧3.0. Three hundred and seventeen patients received a urinary antigen test, and a positive result (RTN ≧ 3.0) was noted in 10 patients. Thirteen patients fulfilled the criteria for definite Legionnaires' disease.

Of the 17 patients with an IFA titer≧1:256 for the acute stage sera, one had a urinary antigen RTN ≧ 3.0 and two showed a fourfold increase in antibody titer in the convalescent phase. A twofold increase in IFA titer to 1:256 was found in one patient. Urinary antigen was weakly positive (RTN≧2.5 but < 3.0) in one patient with an IFA titer less than 1:64 in the acute phase serum. Accordingly, 16 patients fulfilled the criteria for probable Legionnaires' disease.

In total, 29 cases (9.0%) were diagnosed as having Legionnaires' disease. Among the 314 patients who received both tests, 26 patients were diagnosed by either or both methods, including 20 patients (77%) with positive IFA, and eight (31%) with positive urinary antigen. Only one patient had a high acute phase antibody titer (1:512) associated with a positive urinary antigen test (Table 1).

Table 1 Results of serologic antibody and urinary antigen for the diagnosis of Legionnaires' disease

Acute phase antibody titer		Convalescent phase antibody titer			Urinary antigen assay (ratio to negative, RTN)			
No. of cases	Titer	No. of cases tested	2-fold increase	4-fold increase	No. of cases tested	≧ 3.0	< 3.0 , ≧ 2.5	<2.5
2	≧ 1:1024	0	0	0	1	0	0	1
3	1:512	0	0	0	2	1	0	1
12	1:256	7	2	2	9	0	0	9
6	1:128	2	1	0	6	0	0	6
297	≦ 1:64	36	0	2*	296	6	1	289
3	Not done	0	0	0	3	3	0	0
323	Total	45	3	4	317	10	1	306

* One with urinary antigen RTN ≧ 3.0 and final titer=1:256; another with urinary antigen RTN<2.5, and final titer=1:256.

Among the 29 cases of Legionnaires' disease, the male to female ratio was 20:9. The elderly were the major group of patients, and the mean age was 55.7 years with a range of 19-95 years. Most patients (79%) had chronic underlying diseases or status including cigarette smoking (21%), chronic obstructive pulmonary disease (21%), central nervous system (CNS) disease (17%), diabetes mellitus (17%), heart disease (17%), pulmonary tuberculosis (14%), aspiration (10%), malignancy (10%), alcoholism (7%), chronic liver disease (7%), nasogastric intubation (7%), and steroid use (7%). Six patients (21%) had no underlying disease or predisposing factor.

Fever and cough (especially nonproductive cough) were the most frequently seen clinical presentations. Extrapulmonary manifestations such as hyponatremia, elevated liver enzymes, and gastrointestinal and neurological symptoms were often seen. All of the patients with Legionnaires' disease presented with pulmonary infiltrates (usually bilateral) on chest radiographs. Twenty-four percent of patients had pleural effusion, and 14% of the patients had consolidation on admission (Table 2).

Forty-eight percent (14/29) of the patients were complicated by respiratory failure and required mechanical ventilation. One patient developed acute renal failure. The mortality rate was 24% (7/29). The mortality rate was higher in patients with hyponatremia (50%, 5/10), respiratory failure (50%, 7/14), and in those older than 70 years (40%, 4/10).

Table 2 Clinical presentation, radiographic finding and complication of legionnaires' disease

Finding	No. of patients	(%)
Clinical presentation		
Cough	20	(69%)
Productive	7	
Non-productive	13	
Hyponatremia*	10	(34%)
Elevation of liver enzymes	7	(24%)
Gastrointestinal symptoms	7	(24%)
Neurological symptoms	6	(21%)
Severe headache	2	
Complication		
Respiratory failur	14	(48%)
Acute respiratory distress syndrome	4	
Acute renal failure	1	(3%)
Radiological finding		
Infiltrate	29	(100%)
Bilateral	21	
Unilateral	8	
Pleural effusion	7	(24%)
Consolidation	4	(14%)

†Including mechanical ventilation, rheumatoid arthritis and retroperitoneal abscess
* Hyponatremia was defined as a serum sodium concentration less than or equal to 130 mEq/L.

DISCUSSION

Legionella species are the causative agents in 1%-5% of adult CAP cases, and in up to 16% of CAP cases requiring hospitalization[4]. In Taiwan, 8.6% (42/487) of patients with pneumonia in unspecified populations showed positive serology for *L. pneumophila* in 1996[8]. Another study was conducted on 223 hospitalized patients with pneumonia at a teaching hospital, and 9.4% of patients with poor responsiveness to conventional antimicrobial therapy were diagnosed as having Legionnaires' disease[9]. In this study, *L. pneumophila* was considered as the causative agent in 9% of patients with CAP requiring hospitalization based on urinary antigen and limited paired serologic testing.

Several studies have indicated that Legionnaires' disease most often develops in elderly men[14]. This predilection is probably related to cigarette smoking. Epidemiologic studies had shown that elderly male patients who smoke have an elevated risk of acquiring Legionnaires' disease[3]. Some studies suggest that the primary mode of transmission of Legionnaires' disease may be by aspiration rather than aerosolization[15]. In this study, aspiration and aspiration-prone conditions such as CNS disorders and nasogastric intubation were seen in some patients. Similar to other studies, fever and cough (especially nonproductive cough) were the most frequent manifestations[4,9,14]. In addition, gastrointestinal symptoms, neurological abnormalities, hyponatremia, and elevated liver enzymes were common at presentation.

Because of the high frequency of respiratory failure, patients with community-acquired Legionnaires' disease are significantly more likely to be admitted to an intensive care unit[5]. The mortality rate of 24% seen in our study is similar to the rates of 15%-25% reported in the literature[5,16,17]. The high mortality rate and high complication rate make Legionnaires' disease an important cause of severe pneumonia[5]. The mortality can be lowered if the disease can be diagnosed rapidly and appropriate antimicrobial therapy instituted early. Culturing has been recognized as the "gold standard" method for the diagnosis of Legionnaires' disease. Unfortunately, as in our survey, 65% (13/20) of patients did not expectorate sputum. In comparison with other tests, IFA testing has a relatively low sensitivity of 40%-60%[5]. A single titer≧1:256 in a patient with pneumonia constitutes presumptive evidence for Legionnaires' disease, and a fourfold rise in titer is diagnostic. Four to 12 weeks are often required for the detection of an antibody response, but patient compliance in obtaining the convalescent sample is poor, and was only 14% in this study. With the above limitations, serology is of use primarily in epidemiologic studies.

As early as 1979, it was shown by Berdal[18] that a specific antigen was present in the urine of patients with Legionnaires' disease. The Legionella urinary antigen test detects only *L. pneumophila* serogroup 1, which is considered to cause about 80% of Legionella infections[19]. Because of the easy collection and transport of specimens, and the test being rapid to perform, its use in every clinical laboratory is recommended[20,21]. However, the usefulness of urinary antigen testing needs to be further studied by simultaneously using cultures on selective media as a gold standard, as it only reliably detects *L. pneumophila* serogroup 1 infections.

In conclusion, at least 9% of CAP cases might be caused by Legionnaires' disease in Taiwan. We recommend that investigators studying the incidence of Legionella infection in their community or country use urinary antigen testing in concert with acute and convalescent serology. The urinary antigen test is rapid and more sensitive than serology, and both of these tests are more readily available than culture. Moreover, since there are geographic differences in the distribution of *Legionella* species as human pathogens, further studies using simultaneous culture methods and rapid tests are warranted to determine the prevalence of Legionnaires' disease in CAP as well as the distribution of the species and serogroups of *Legionella* in Taiwan.

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REFERENCES

1. Fraser DW, Tsai TR, Orenstein W, Parkin WE, Beecham HJ, Sharrar RG, Harris J, Mallison GF, Martin SM, McDade JE, Shepard CC, Brachman PS. Legionnaires' disease: description of an epidemic of pneumonia. N Engl J Med 1977;297:1189-97.
2. Chang FY, Yu VL. Legionella infection. In: Kasper DL, Braunwald E, Fauci AS, Martin JB, Hauser SL, Longo DL, Jameson JL, eds. Harrison's Principles of Internal Medicine, 16th ed. New York: McGraw-Hill, 2005:870-874.
3. Marston BJ, Lipman HB, Breiman RF. Surveillance for Legionnaires' disease. Risk factors for morbidity and mortality. Arch Intern Med 1994;154:2417-22.
4. Lieberman D, Porath A, Schlaeffer F, Lieberman D, Boldur I. *Legionella* species community-acquired pneumonia: a review of 56 hospitalized adult patients. Chest 1996;109:1243-9.
5. Vergis EN, Akbas E, Yu VL. *Legionella* as a cause of severe pneumonia. Semin Respir Critic Care Med 2000;21:295-304.
6. Waterer GW, Baselski VS, Wunderink RG. *Legionella* and community-acquired pneumonia: a review of current diagnostic tests from a clinician's viewpoint. Am J Med, 2001;110:41-8.
7. Liu YC, Cheng DL, Shi FW, Huang WK, Wang JH. Legionnaires' disease- a case report. J Formos Med Assoc 1985;84:1180-5.
8. Pan TM, Yea HL, Huang HC, Lee CL, Horng CB. *Legionella pneumophila* infection in Taiwan: a preliminary report. J Formos Med Assoc 1996;95:536-9.
9. Lin SF, Chang SC, Yea CL, Pan TM, Hsieh WC. Clinical features of legionellosis: experience of 21 cases at a teaching hospital in Taiwan. J Infect Dis Soc ROC 1996;7:29-35.
10. Tang RB, Shen HD, Chou NS, Chang LY, Wang SC, Liu LC, Hwang B, Cheng DL. Serological evidence of *Legionella pneumophila* infection in children. Chin Med J 1988;42:29-34.
11. Lin SL, Chen HS, Yu CJ, Yen TS. Legionnaires' disease with acute renal failure: report of two cases. J Formos Med Assoc 1995;94:123-6.
12. Wang RS, Liu CY, Liu YC, Cheng KK. Legionnaires' disease following cardiac transplantation. Chin Med J 1989;44:336-40.
13. Chen MSG, Yang YR, Shen HD. *Legionella pneumophila* antibodies as detected by IFA. Proc Natl Sci Counc ROC(A) 1983;7:249-54.
14. Sopena N, Sabria-Leal M, Pedro-Botet ML, Padilla E, Dominguez J, Morera J, Tudela P. Comparative study of the clinical presentation of *Legionella* pneumonia and other community-acquired pneumonias. Chest 1998;113:1195-200.
15. Yu VL. Could aspiration be the major mode of transmission for *Legionella*? Am J Med 1993;95:13-5.
16. Edelstein PH, Meyer RD. Legionnaires' disease–a review. Chest 1984;85:114-20.
17. Fang GD, Fine M, Orloff J, Arisumi D, Yu VL, Kapoor W, Grayston JT, Wang SP, Kohler R, Muder RR, Yee YC, Rihs JD, Vickers RM. New and emerging etiologies for community-acquired pneumonia with implication for therapy. A prospective multicenter study of 359 cases. Medicine 1990;69:307-16.
18. Berdal BP, Farshy CE, Feeley JC. Detection of *Legionella pneumophila* antigen in urine by enzyme-linked immunospecific assay. J Clin Microbiol 1979; 9:575-8.
19. Reingold AL, Thomason BM, Brake BJ, Thacker L, Wilkinson HW, Kuritsky JN. *Legionella* pneumonia in the United States: the distribution of serogroups and species causing human illness. J Infect Dis 1984;149: 819.
20. Kohler RB, Winn Jr. WC, Wheat LJ. Onset and duration of urinary antigen excretion in Legionnaires' disease. J Clin Microbiol 1984;20:605-7.
21. Stout JE, Yu VL. Legionellosis. NEJM 1997;337:682-7.