Chapter

Legionella Pneumonia Due to Non-*Legionella pneumophila* Serogroup 1

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Abstract

Legionella pneumophila is one of the important pathogens in community-acquired (CAP) and hospital-acquired pneumonia that can cause severe pneumonia. Early diagnosis and treatment of *Legionella* pneumonia (LP) are essential because inappropriate therapy for *Legionella* pneumonia has been reported to worsen the prognosis. The most frequently identified causative pathogen of *Legionella* pneumonia is *Legionella pneumophila* serogroup 1. *Legionella* pneumonia due to non-*Legionella pneumophila* serogroup 1 is seen in 20% of cases. In diagnosing *Legionella* pneumonia caused by non-*Legionella pneumophila* serogroup 1, the urinary antigen test is usually negative; therefore, we need to suspect *Legionella* pneumonia by clinical information such as symptoms, vital signs, laboratory findings, and radiological findings. Based on our previous report, *Legionella* pneumonia due to non-*Legionella pneumophila* serogroup 1 was a mild to severe pneumonia. In addition, in about half of the patients, we could not suspect *Legionella* pneumonia using a six-point scoring system, which is one of the diagnostic scoring systems. Recently, a new urinary antigen test kit that could theoretically diagnose *Legionella* pneumonia due to non-*Legionella pneumophila* serogroup 1 was released in Japan. This can help in early diagnosis of *Legionella* pneumonia, including the one caused by non-*Legionella pneumophila* serogroup 1.

Keywords: diagnosis, *Legionella* pneumonia, *Legionella pneumophila* serogroup 1, non-*Legionella pneumophila* serogroup 1, urinary antigen

1. Introduction

Legionella pneumonia (LP) is caused by *Legionella* species that are important causative pathogens of community-acquired pneumonia (CAP) and hospital-acquired pneumonia. There are 58 species and three subspecies in the *Legionella* genus [1]. *Legionella* species are small to filamentous, Gram-negative rods [2].

The most frequently identified causative microorganism of *Legionella* pneumonia is *Legionella pneumophila* serogroup 1, accounting for about 80% of cases [3, 4]. In CAP, the rate of LP is reported to be 0.6–8% [5–8], although the rate differs in different areas and countries. However, in severe CAP that satisfies the Infectious Diseases Society of America/American Thoracic Society severe pneumonia criteria [9], LP is one of the most important etiologies, because the rate of LP was reported to be 13.5% in 133 patients [10] and 14.1% in 71 patients

<60 years old [11]. In addition, inappropriate initial therapy for LP was shown to be one of the independent factors predicting a worse prognosis [12]. Therefore, early and appropriate diagnosis of LP is very important to improve the prognosis of LP patients.

The gold standard in the diagnosis of LP is the identification of *Legionella* species in respiratory specimens such as sputum and bronchoalveolar lavage fluid. However, some LP patients have no sputum for culture, a dedicated culture medium, such as Wadowsky-Yee-Okuda-α or Buffered Charcoal Yeast Extract-α medium is needed, therefore identification of *Legionella* species is sometimes difficult, costly and time-consuming.

Currently, a urinary antigen test that detects soluble antigens is widely used for diagnosing LP in daily clinical practice worldwide. This diagnostic method is very useful because the examination procedure is simple and the results are known quickly. In a systematic review and meta-analysis, Shimada et al. reported that the specificity of the *Legionella* urinary antigen test was 99.1% and sensitivity was 74%; therefore, LP cannot be ruled out if this test is negative. Specifically, the sensitivity of the urinary antigen test for diagnosing LP due to non-*L. pneumophila* serogroup 1 is low [13]. Therefore, the *Legionella* urinary antigen test is not useful for diagnosing LP caused by non-*L. pneumophila* serogroup 1.

The diagnostic key for LP due to non-*L. pneumophila* serogroup 1 is to suspect *Legionella* pneumonia based on clinical information such as patients' symptoms, vital signs, laboratory findings, and radiological findings. Therefore, in this chapter, we describe the clinical characteristics of LP due to non-*L. pneumophila* serogroup 1 referred to in previous reports.

2. *Legionella* pneumonia due to non-*Legionella pneumophila* serogroup 1

2.1 Previous reports

In earlier studies, LP due to non-*L. pneumophila* serogroup 1 could be a mild to moderate pneumonia [14, 15], not only a severe pneumonia admitted to intensive care unit [16–20]. Indeed, we reported a case of LP due to *L. pneumophila* serogroup 9 in which initial treatment with single-dose oral azithromycin appeared useful, although oral levofloxacin was administered subsequently [15].

There have been many case reports of LP caused by non-*L. pneumophila* serogroup 1, but there have been few case series. Therefore, we investigated the clinical characteristics of LP due to non-*L. pneumophila* serogroup 1 and compared with LP due to *L. pneumophila* serogroup 1 [21]. There were 11 patients with LP due to non-*L. pneumophila* serogroup 1 between March 2001 and June 2016 in our hospital. Their age range was 58–82 years, and eight patients (72.7%) were male. The most common comorbidities were diabetes mellitus, chronic liver disease, and malignant disease in each of the two patients. The most common symptom was fever (72.7%), followed by cough (54.5%), and sputum (54.5%). The distribution of bacterial strains was *L. pneumophila* serogroup 3 in six patients, *L. pneumophila* serogroup 9 in three patients, *L. pneumophila* serogroup 6 in one patient, and *L. longbeachae* in one patient. As to the severity of pneumonia, about half of the cases (5/11) were mild to moderate according to the pneumonia severity index (PSI) [22], whereas most cases (10/11) were mild to moderate based on CURB-65 [23]. Five patients whose PSI class was less than IV are all improved with oral azithromycin or oral levofloxacin. In contrast, four patients were admitted to the intensive care unit, and all four patients were administered appropriate empiric antimicrobial agents, but three patients died.

2.2 Diagnostic scoring system

We cannot rule out LP by a negative result of the urinary antigen test because the sensitivity of this test is not very good. To diagnose LP with a negative urinary antigen test, we need to suspect it based on the symptoms, vital signs, laboratory examinations, and radiological findings.

In 1998, Cunha advocated a diagnostic scoring system for LP called the "Winthrop-University Hospital (WUH) criteria" [24]. The WUH criteria comprised 15 clinical findings and seven laboratory findings, and it was therefore thought to be too complicated to use in the daily clinical practice.

In 2009, Fiumefreddo proposed a six-point scoring system for predicting LP [25], and this scoring system was validated by Haubitz [26]. This scoring system comprised one symptom, one vital sign, and four laboratory findings. The criteria for the six items are listed in **Table 1**. A score ≥5 had very high specificity (99.0%) and a high positive predictive value (17.4%), whereas a score <2 had high sensitivity (94.4%) and a high negative predictive value (99.6%). In our previous reports [21], using a cutoff value of ≥2 points, the sensitivity of this scoring system was 54.5% for non-*L. pneumophila* serogroup 1 patients and 95.7% for *L. pneumophila* serogroup 1 patients. Therefore, we could not rule out LP due to non-*L. pneumophila* serogroup 1 using this six-point scoring system. In **Figure 1**, the patient number

Temperature	>39.4°C
C-reactive protein	>187 mg/L
Lactate dehydrogenase	>225 mmol/L
Platelets	<171 × 10^9/L
Serum sodium	<133 mmol/L
Unproductive cough	

Table 1.
Criteria for each item in the six-point scoring system.

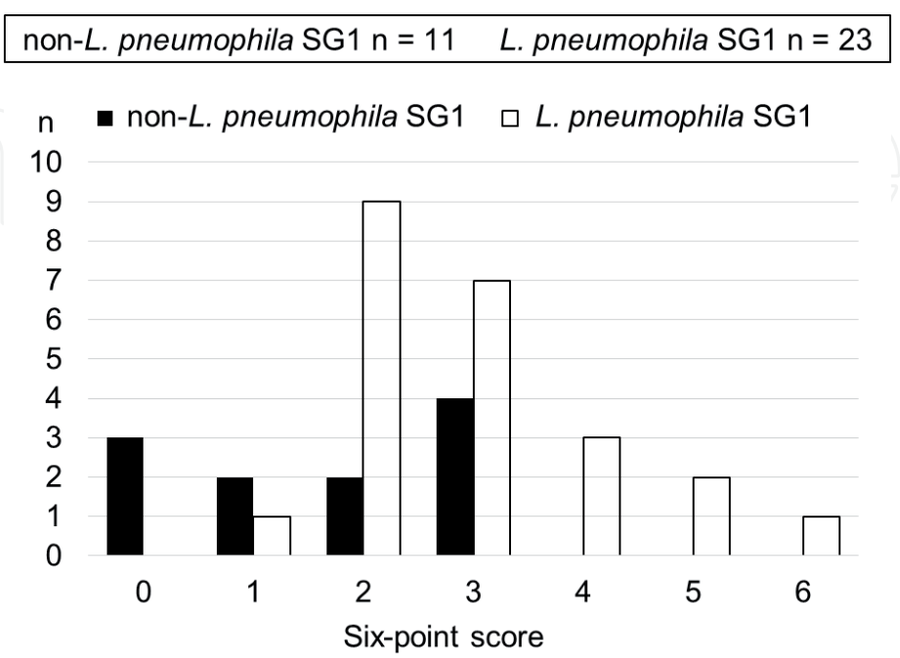

Figure 1.
Total scores of the six-point scoring system in Legionella pneumonia due to non-L. pneumophila serogroup 1 and L. pneumophila serogroup 1.

and total scores of the six-point scoring system in LP due to non-*L. pneumophila* serogroup 1 and *L. pneumophila* serogroup 1 are shown [21].

3. Future perspective

Patients with LP have a worse prognosis if they are not treated with appropriate antibiotic therapy as soon as possible. Some patients with LP due to *L. pneumophila* serogroup 1 have a negative urinary antigen test, and patients with LP due to non-*L. pneumophila* serogroup 1 are usually negative on this test. Therefore, it is important to suspect LP based on the clinical findings. However, as shown in our previous report, there are some LP patients in whom we cannot suspect LP based on the clinical findings specific to LP due to non-*L. pneumophila* serogroup 1. Thus, a simple method and a rapid test kit for diagnosing LP due to non-*L. pneumophila* serogroup 1 are needed.

In February 2019, Asahi Kasei Pharma Corporation released a urinary antigen test kit that could diagnose LP due to non-*L. pneumophila* serogroup 1, not only due to *L. pneumophila* serogroup 1. This kit uses an immunochromatographic method that has a monoclonal antibody recognizing a ribosomal protein L7/L12 unique region of *L. pneumophila* serogroups 1–15.

In the future, we expect that early diagnosis of LP including non-*L. pneumophila* serogroup 1 will be possible using this test kit.

4. Conclusion

LP due to non-*L. pneumophila* serogroup 1 can be a mild to severe pneumonia. To diagnose LP, there are some patients with LP caused by non-*L. pneumophila* serogroup 1 that could not be suspected to have LP based on their clinical findings, although diagnostic scoring systems have been reported to be useful for predicting LP. We need to investigate the usefulness of the new urinary antigen test kit that could theoretically diagnose these patients.

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Conflict of interest

The authors declare no conflict of interest.

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