Received: 30 October 2015 | Accepted: 27 June 2016

DOI: 10.1002/jgf2.16

CASE REPORT

Journal of General and Family Medicine Open Access WILEY

Can we truly rely on the urinary antigen test for the diagnosis? Legionella case report

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Abstract

It is critical to diagnose and treat Legionella pneumonia (LP) immediately after infection because of the associated high mortality. The urine antigen test (UAT) is often used for the diagnosis of LP; however, it cannot detect the serogroups of all Legionella species. A detained medical history and several clinical findings such as liver enzyme elevation and hyponatremia are useful in diagnosis. Some specific types of *Legionella* are found in compost. Herein, we report a case of LP in which the patient's medical history and several clinical findings were useful for diagnosis.

KEYWORDS

compost, gardening, *Legionella longbeachae*, Legionella pneumonia, loop-mediated isothermal amplification, urine antigen test

1 | INTRODUCTION

The urine antigen test (UAT) is often used in the primary care setting for the diagnosis of Legionella pneumonia (LP); however, the test is not adequately sensitive and the results are frequently uncertain. For the present case, the patient's medical history and several clinical findings proved essential for LP diagnosis. The UAT results could not aid the diagnosis owing to its limited sensitivity.

2 | CASE PRESENTATION

A 69-year-old Japanese man presented to the emergency department for a 3 day history of a fever and chills. He did not have a cough, rhinorrhea, pharyngalgia, dyspnea, nausea, diarrhea, or loss of appetite. He had diabetes mellitus (HbA1c 7.0% 11 days before admission) and atrial fibrillation, and he was receiving glimepiride, sitagliptin, and warfarin medication. In terms of risk factors for LP, he was an ex-smoker and a gardener, but had not traveled abroad or taken a public bath.

On physical examination, his body temperature was 36.3°C, his heart rate was 91 beats per minute, his blood pressure was 99/68 mm Hg, his respiratory rate was 16 breaths per minute, and his SpO_2 was 98% in room air. Coarse crackles were heard in his right lower lung field. The rest of the physical examination was normal.

His laboratory test results are shown in Table 1. The blood test showed anemia, thrombocytopenia, liver enzyme elevation, hyponatremia, and elevated creatinine phosphokinase. Proteinuria and microhematuria were revealed via urine analysis. The result of a Legionella UAT was negative. We assessed his sputum Gram stain and classified it as Geckler group 6; no bacteria were detected in the smear. The sputum culture test showed the presence of only alpha-hemolytic *Streptococcus* and *Candida*. It was negative for Legionella though we did not use the buffered charcoal yeast extract agar base to detect Legionella species. A chest radiograph and a computerized axial tomography scan showed consolidation in the right lower lobe (Figures 1 and 2).

Despite the negative UAT result, we initiated ceftriaxone, azithromycin, and minocycline treatment for LP because of a high clinical suspicion based on the clinical history and physical and laboratory findings. We confirmed the diagnosis using a sputum loop-mediated isothermal amplification (LAMP) test (Eiken Chemical Co. Ltd, Japan). We administered levofloxacin because his body temperature was elevated (without relative bradycardia) and his bloody sputum persisted.

TABLE 1 Laboratory data on admission

Complete blood count		Blood Chemistry Serology		Arterial blood gas (Room air)	
White blood cell	7700/μL	T-protein	6.3 g/dL[a]	pH	7.433 mm Hg
Red blood cell	356×10^4/μL[a]	T-bil	0.7 mg/dL	$PaCO_2$	36.0 mm Hg
Hemoglobin	11.2 g/dL[a]	AST	265 U/L[a]	PaO_2	72.5 mm Hg[a]
Hematocrit	31.5%[a]	ALT	61 U/L[a]	HCO_3	23.7 mmol/L
Platelet count	11.9×10^4/μL[a]	LDH	572 U/L[a]	BE	0.2 mmol/L
		ALP	196 U/L	O_2Sat	97.3%
Blood coagulation system		CPK	15510 U/L[a]	AG	12.6 mmol/L
PT	17.7 s[a]	Amy	47 U/L	Lac	9 mg/dL
%PT	42.0%[a]	BUN	28 mg/dL[a]		
PT-INR	1.54[a]	Cr	1.65 mg/dL[a]		
APTT	53.9 s[a]	Na	126 mEq/L[a]		
		K	3.5 mEq/L		
		Cl	92 mEq/L[a]		
		Blood sugar	382 mg/dL[a]		
		CRP	19.79 mg/dL[a]		
Urinalysis				Urinary antigen test	
Specific gravity	1.020	Ketone body	-	Pneumococcus	-
pH	6.0	Blood	3+[a]	Legionella	-
Protein	2+[a]	Leukocyte	-		
Glucose	2+[a]				

[a]Results out of the reference range.

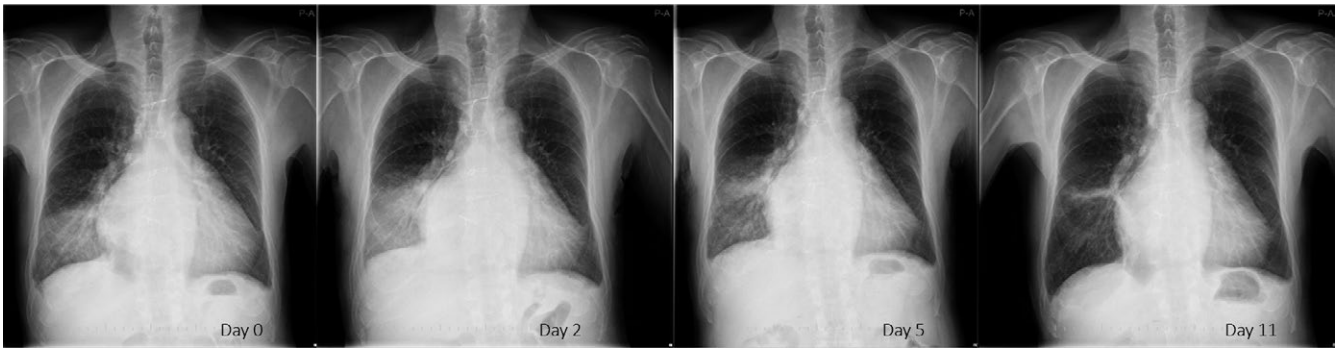


FIGURE 1 Chest radiography findings. The radiograph shows consolidation in the right lower lobe, which gradually disappeared after day 2

Following treatment, he recovered and he was discharged on day 12 (Figure 3).

3 | DISCUSSION

LP comprises 2% to 9% cases of community-acquired pneumonia.[1–5] Generally, legionellosis is caused by infections acquired from a water reservoir or hot spring contamination. The common risk factors of LP are cigarette smoking, chronic lung disease, increasing age, and immunosuppression. This patient had history of smoking and diabetes mellitus, which we considered risk factors of LP.

Generally, in cases of LP, respiratory symptoms such as cough and sputum are not prominent at first. Hyponatremia occurs frequently in legionellosis.[1,6–10] Renal and hepatic dysfunction, elevated creatinine phosphokinase, thrombocytopenia, and leukocytosis are considered the common laboratory abnormalities. Hematuria and proteinuria are also common abnormalities. In this case, the patient only complained of a fever and chills, and he did not have a cough or sputum. However, he eventually presented all the aforementioned laboratory features. A Gram stain of his sputum resulted in its classification as Geckler group 6, which did not aid the diagnosis.

While the mortality rate among patients with community-acquired legionellosis ranges from 16% to 30%, with or without treatment using

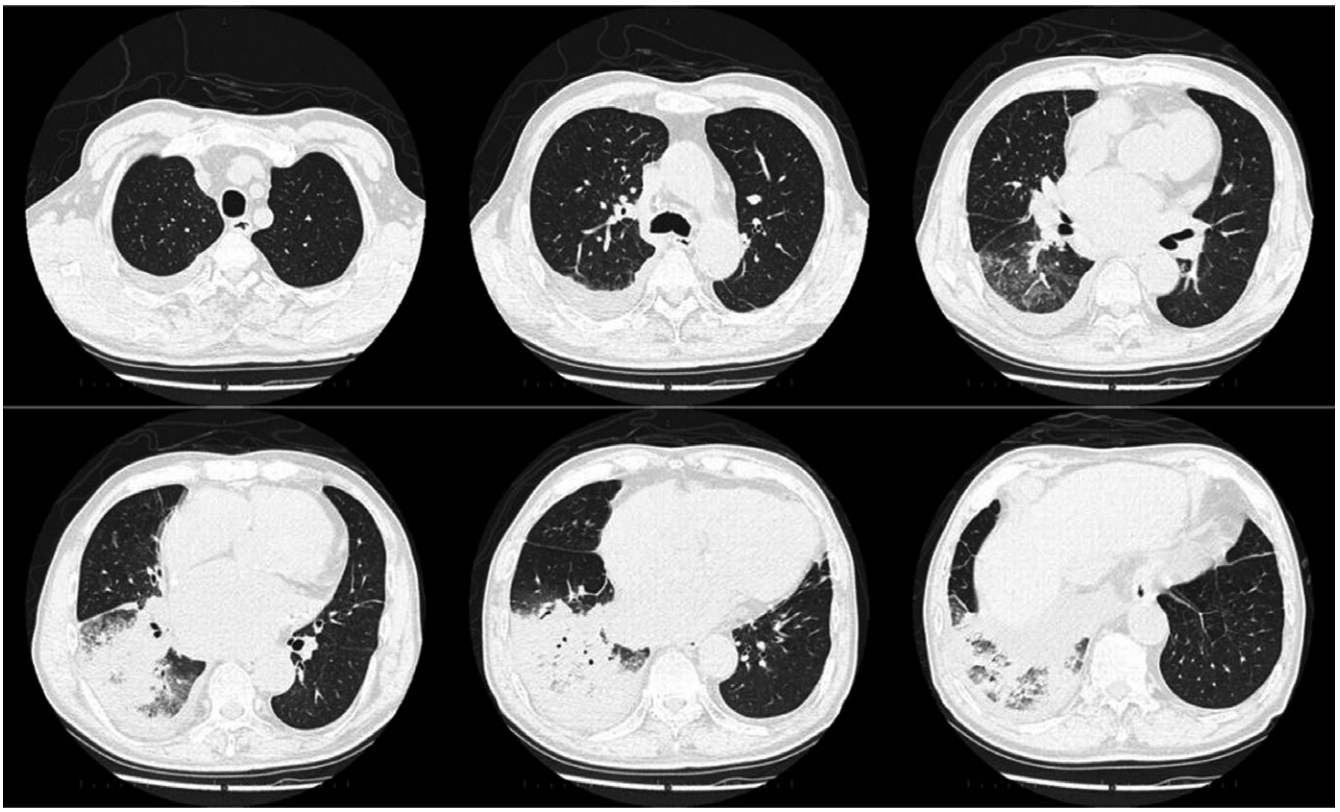
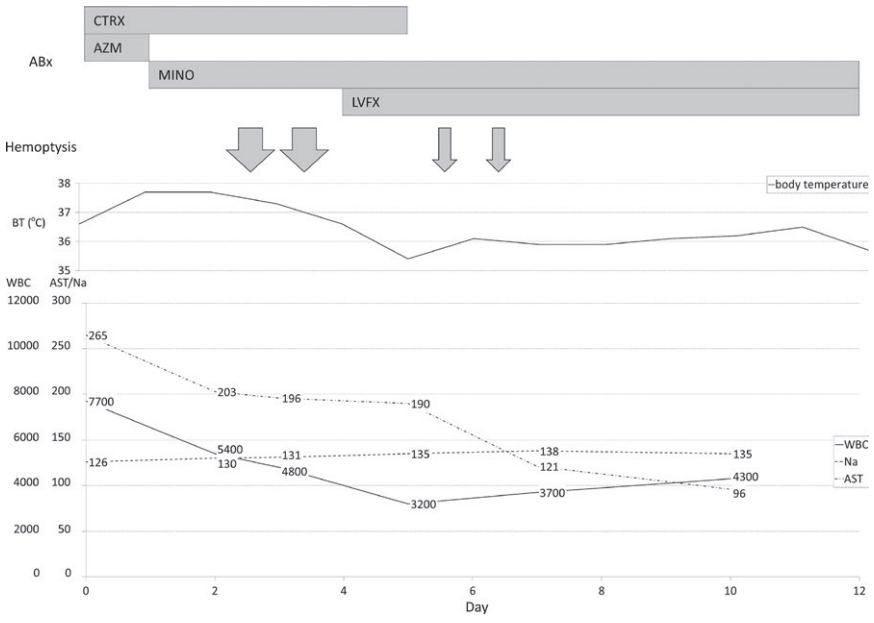


FIGURE 2 Computed tomography findings. The image shows the consolidation spanning the entire right lower lobe region



ABx = antibiotics CTRX = ceftriaxone AZM = azithromycin
BT = body temperature MINO = minocycline LVFX = levofloxacin

FIGURE 3 Clinical course of the patient

inactive antibiotics such as beta-lactam agents, it reduces to less than 10% in patients with community-acquired LP treated with potent therapies.[11–15] In many countries, such as Japan, USA, and UK, cases of legionellosis should be reported immediately to the public health department. This is because earlier detection and appropriate diagnosis and treatment are very important for reducing the associated high mortality risks.

The commercial UAT (Alere BinaxNOW® Legionella Urinary Antigen Card) is an immunochromatographic membrane assay that is used to detect the *Legionella pneumophila* serogroup 1 soluble antigen

TABLE 2 Correlation between UAT, LAMP, and culture tests[19]

		UAT			LAMP		
		+	−	Total	+	−	Total
Culture	+	13	9	22	21	1	22
	−	0	113	113	0	113	113
		13	122	135	21	114	135

in human urine.[16] A vast majority of community-acquired LP cases are caused by this species and serogroup.[4,17,18] Although it is very useful to define a diagnosis of LP, it is of limited use to detect non-serogroup 1 *L. pneumophila* and other species. The sensitivity and specificity of UAT for detecting other serogroups and species are currently unknown.

LAMP (Loopamp Legionella Detection Kit *E*) is a nucleic acid amplification method[19] to specifically amplify the target gene using four primers specific to six distinct regions. The whole amplification reaction continuously takes place under isothermal conditions. We used this method to support our legionellosis diagnosis. The sensitivity and specificity of this method are 91.3% (21/23) and 100% (112/112), respectively.[20] The correlation between UAT, LAMP, and culture tests is shown in Table 2; almost all patients (21/22) with positive cultures tested positive for LP via LAMP, while only 59.1% of patients (13/22) with positive cultures tested positive for LP via a UAT.[19] We hypothesized that the cause of this case of LP was non-serogroup 1 *L. pneumophila* infection or an infection from another species, because the positive results were obtained using the LAMP method, and negative results were observed using the UAT.

Inhalation or ingestion of potting soil is associated with LP. We identified several cases of legionellosis with causes related to gardening (see Table 3). While a few patients were infected by *L. pneumophila*, most patients were infected by *L. longbeachae*. This species was first isolated in 1980 from a patient with pneumonia in Long Beach, California.[21] Interestingly, the UAT was negative for all patients infected with *L. Longbeachae*. We also assembled data regarding the distribution of *Legionella* species in Japanese potting soils (see Table 4). Similar reports have been published for distribution in other areas such as America, Australia, and Europe.[22,23] These reports consistently indicate that that *L. pneumophila* is not commonly found in the soil. Therefore, we should consider other Legionella species as the causative pathogen particularly when the soil is the possible pathway of infection, as in this case. Although we were not able to identify which *Legionella* species was the pathogen in this case, we speculated it was *L. longbeachae* or other related species and not *L. pneumophila*, because this patient was a gardener. This speculation explains both the negative result with the UAT and the positive result of the LAMP test.

In conclusion, the medical history and clinical findings are key to diagnosing LP, because the UAT is not always helpful owing to its limited sensitivity. In particular, when gardening is the route of infection, because the occurrence of *L. pneumophila* in the soil is rare, other species such as *L. longbeachae* should be considered as the potential causative pathogen for LP. In addition, in such cases, the clinicians should

TABLE 4 *Legionella* species occurring in Japanese compost

	References:[32]	References:[24]
L. bozemanii	9	13
L. longbeachae	8	9
L. micdadei	5	7
L. pneumophila	2	1
L. cincinnatiensis	1	2
L. birminghamensis	1	1
L. gormanii	1	1
L. oakridgensis	0	2
L. spp.(cannot identify)	4	8
Legionella positive	16	22
Sample size	17	30

L. pneumophila is not the main species found in compost.

TABLE 3 Legionella cases caused by gardening

Time	Nation	Character	Outcome	UAT	Species	References
1996/7	Japan	52, m	Death		*L. longbeachae*	24
1999/7	Japan	83, m	Survive	-	*L. longbeachae*	25
2000/5	USA	77, f			*L. longbeachae*	22
2000/5	USA	45, m	Death		*L. longbeachae*	
2000/6	USA	46, f			*L. longbeachae*	
2000/8	Netherlands	81, m	Death		*L. longbeachae*	26
2000/8	Netherlands	69, m	Death		*L. longbeachae*	
2004/12	Netherlands	67, m	Death		*L. longbeachae*	
2001/5	Australia	40s, m	Survive	+	*L. pneumophila*	27
2004/8	Japan	72, m	Survive	-	*L. longbeachae*	28
2009/10	Japan	74, m	Survive	-	*L. longbeachae*	29
Not noted	New Zealand	79, f	Death		*L. longbeachae*	30
Not noted	Switzerland	60, m		+	*L. pneumophila*	31

be careful in interpreting the result of the UAT, because the results can be negative even when these species are present. The LAMP test is useful with higher sensitivity and specificity than UAT when the clinical suspicion of legionellosis is high although UAT is negative.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

REFERENCES

1. Fang GD, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy. A prospective multicenter study of 359 cases. Medicine (Baltimore). 1990;69:307.
2. Bartlett JG, Mundy LM. Community-acquired pneumonia. N Engl J Med. 1995;333:1618.
3. Marston BJ, Plouffe JF, File TM Jr, et al. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance Study in Ohio. The Community-Based Pneumonia Incidence Study Group. Arch Intern Med. 1997;157:1709.
4. von Baum H, Ewig S, Marre R, et al. Community-acquired Legionella pneumonia: new insights from the German competence network for community acquired pneumonia. Clin Infect Dis. 2008;46:1356.
5. Cunha BA, Burillo A, Bouza E. Legionnaires' disease. Lancet. 2015;387:376–85.
6. Kirby BD, Snyder KM, Meyer RD, Finegold SM. Legionnaires' disease: report of sixty-five nosocomially acquired cases of review of the literature. Medicine (Baltimore). 1980;59:188.
7. Mulazimoglu L, Yu VL. Can Legionnaires disease be diagnosed by clinical criteria? A critical review Chest 2001;120:1049.
8. Yu VL, Kroboth FJ, Shonnard J, et al. Legionnaires' disease: new clinical perspective from a prospective pneumonia study. Am J Med. 1982;73:357.
9. Cunha BA, Pherez FM, Nouri Y. Legionella community-acquired pneumonia (CAP) presenting with spontaneous bilateral pneumothoraces. Heart Lung. 2008;37:238–41.
10. Garcia MC, Ebeo CT, Byrd RP Jr, Roy TM. Rhabdomyolysis associated with pneumococcal pneumonia: an early clinical indicator of increased morbidity? Tenn Med. 2002;95:67–9.
11. Fraser DW, Tsai TR, Orenstein W, et al. Legionnaires' disease: description of an epidemic of pneumonia. N Engl J Med. 1977;297:1189.
12. Benin AL, Benson RF, Besser RE. Trends in legionnaires disease, 1980-1998: declining mortality and new patterns of diagnosis. Clin Infect Dis. 2002;35:1039.
13. Fernández JA, López P, Orozco D, Merino J. Clinical study of an outbreak of Legionnaire's disease in Alcoy, Southeastern Spain. Eur J Clin Microbiol Infect Dis. 2002;21:729.
14. Blázquez Garrido RM, Espinosa Parra FJ, Alemany Francés L, et al. Antimicrobial chemotherapy for Legionnaires disease: levofloxacin versus macrolides. Clin Infect Dis. 2005;40:800.
15. Mykietiuk A, Carratalà J, Fernández-Sabé N, et al. Clinical outcomes for hospitalized patients with Legionella pneumonia in the antigenuria era: the influence of levofloxacin therapy. Clin Infect Dis. 2005;40:794.
16. Alere Scarborough, Inc. Package insert of Alere BinaxNOW® Legionella Urinary Antigen Card Rev. 6 (January 2013).
17. Yu VL, Plouffe JF, Pastoris MC, et al. Distribution of *Legionella* species and serogroups isolated by culture in patients with sporadic community-acquired legionellosis: an international collaborative survey. J Infect Dis. 2002;186:127.
18. Helbig JH, Uldum SA, Bernander S, et al. Clinical utility of urinary antigen detection for diagnosis of community-acquired, travel-associated, and nosocomial legionnaires' disease. J Clin Microbiol. 2003;41:838.
19. Eiken Chemical Co. Ltd, Japan. Product information of Loopamp Legionella Detection Kit E. Rev. March 2013.
20. Yamaguchi K, Tateda K, Nakamori Y, et al. LAMP hou wo mochiita Mycoplasma pneumoniae to Legionella spp. ni yoru kokyuki kansenshou no jinsoku shindan shiyaku no hyouka. [The LAMP method assessment of the rapid diagnostic test reagent for Mycoplasma pneumoniae and Legionella app.]. Jpn J Med Pharm Sci. 58, No 4, 565–71. Article in Japanese.
21. McKinney RM, Porschen RK, Edelstein PH, et al. *Legionella longbeachae* species nova, another etiologic agent of human pneumonia. Ann Intern Med. 1981;94:739–43.
22. Centers for Disease Control and Prevention (CDC). Legionnaires' Disease associated with potting soil–California, Oregon, and Washington, May-June 2000. MMWR Morb Mortal Wkly Rep. 2000;49:777–8.
23. Casati S, Conza L, Bruin J, Gaia V. Compost facilities as a reservoir of *Legionella pneumophila* and other *Legionella* species. Clin Microbiol Infect. 2010;16:945–7.
24. Koide M, Arakaki N, Saito A. Distribution of *Legionella longbeachae* and other *legionellae* in Japanese potting soils. J Infect Chemother. 2001;7:224–7.
25. Suzuki K, Tachibana A, Hatakeyama S, Yamaguchi K, Tateda K. Clinical characteristics in 8 sporadic cases of community-acquired Legionella pneumonia. Nihon Kokyuki Gakkai Zasshi. 2002;40:282–6.
26. den Boer JW, Yzerman EP, Jansen R, et al. Legionnaires' disease and gardening. Clin Microbiol Infect. 2007;13:88–91.
27. Wallis L, Robinson P. Soil as a source of *Legionella pneumophila* serogroup 1 (Lp1). Aust N Z J Public Health. 2005;29:518–20.
28. Kubota M, Tomii K, Tachikawa R, et al. *Legionella longbeachae* pneumonia infection from home garden soil. Nihon Kokyuki Gakkai Zasshi. 2007;45:698–703.
29. Shinohara Y, Takabe K. Nougyou juujisha ni okeru Legionella haien (toku ni Legionella longbeachae) no kikensei ni tsuite. [Risk of Legionella pneumoniae infection (especially due to Legionella longbeachae) among agricultural workers.]. Kyosai Examiner's Report. 2011;29:29–40. Article in Japanese.
30. Kingston M, Padwell A. Fatal legionellosis from gardening. N Z Med J. 1994;107:111.
31. Piso RJ, Caruso A, Nebiker M. Hose as a source of Legionella pneumonia. A new risk factor for gardeners? J Hosp Infect 2007;67:396–7. Epub 2007 Nov 19.
32. Koide M, Saito A, Okazaki M, Umeda B, Benson RF. Isolation of *Legionella longbeachae* serogroup 1 from potting soils in Japan. Clin Infect Dis. 1999;29:943–4.

How to cite this article: Miyata J, Huh JY, Ito Y, Kobuchi T, Kusukawa K, Hayashi H. Can we truly rely on the urinary antigen test for the diagnosis? Legionella case report. *J Gen Fam Med*. 2017;18:139–143. https://doi.org/10.1002/jgf2.16