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Short Communication

A Case of Community-Acquired Pneumonia Due to *Legionella pneumophila* Serogroup 9 Wherein Initial Treatment with Single-Dose Oral Azithromycin Appeared Useful

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SUMMARY: *Legionella* species are important causative pathogens for severe community-acquired pneumonia (CAP). Most cases of *Legionella* pneumonia are due to *Legionella pneumophila* serogroup 1, and CAP due to *L. pneumophila* serogroup 9 is rare. A fourth case of CAP due to *L. pneumophila* serogroup 9 has been reported, and initial treatment using single-dose oral azithromycin appeared useful. Azithromycin or fluoroquinolone injection is usually recommended for the treatment of *Legionella* pneumonia, and no previous reports have shown the effectiveness of single-dose oral azithromycin. This case report is therefore valuable from the perspective of possible treatment for mild to moderate *Legionella* pneumonia using single-dose oral azithromycin.

Legionella pneumonia is caused by *Legionella* species, which are Gram-negative bacilli and is an important cause of severe community-acquired pneumonia (CAP) (1). The most frequently identified causative pathogen for *Legionella* pneumonia is *L. pneumophila* serogroup 1, and approximately 20% of *Legionella* pneumonia cases are not caused by *L. pneumophila* serogroup 1 (2,3); these cases are diagnosed from cultures in Wadowsky-Yee-Okuda (WYO)-α media or buffered charcoal-yeast extract (BCYE)-α media, rather than the urinary antigen test. Only 3 cases of CAP due to *L. pneumophila* serogroup 9 have previously been reported worldwide (4,5); we report the fourth case here. The present patient was initially treated with ceftriaxone injection and a single 2-g dose of oral azithromycin, and that single dose of oral azithromycin was thought to have been useful in treating this patient. Single-dose oral azithromycin may therefore warrant consideration as an initial treatment for mild or moderate *Legionella* pneumonia.

A 65-year-old, previously healthy man developed general malaise and myalgia of the limbs 5 days before admission. The next day, he developed a high fever and visited a local doctor and was administered all-in-one cold and flu capsules. However, the high fever persisted, and he later visited our hospital. His temperature was 37.7°C, his blood pressure was 148/81 mmHg, with oxygen saturation remaining at 94% while breathing ambient air, his respiratory rate was 30 breaths/min, and his level of consciousness remained normal. Chest auscultation revealed inspiratory coarse crackles in the left lower lung, and a chest radiograph showed non-segmental infiltration shadows in the left lower lung field (Fig. 1A). Laboratory tests showed inflammation (C-reactive protein [CRP], 19.51 mg/dL), mildly elevated levels of liver enzymes (aspartate aminotransferase [AST], 49 IU/L; alanine aminotransferase [ALT], 36 IU/L), and hyponatremia (Na, 130 mEq/L) (Table 1). Creatine phosphokinase (CPK) was not measured on admission, but was 167 IU/L on day 2. He was admitted to our hospital for treatment of CAP. The severity of his pneumonia was moderate according to his CURB-65 score (2 points) (6) but was classified as class IV using the Pneumonia Severity Index (105 points) (7).

An expectorated sputum smear (Gram stain) was negative for bacteria, and urinary antigen tests yielded negative results for both *Streptococcus pneumoniae* and *L. pneumophila* (Binax, Portland, ME, USA). The possibility of both bacterial and atypical pneumonia was considered because of the patient's symptoms and laboratory test results. Intravenous ceftriaxone was started at 2 g/day, along with a single 2-g oral dose of azithromycin.

Defervescence to less than 37°C was seen on day 3 after admission (body temperature was 36.1°C) and the infiltration shadow in the left lower lung field was slightly improved (Fig. 1B) on day 4. His CRP concentration decreased to 6.67 mg/dL on day 5. Since

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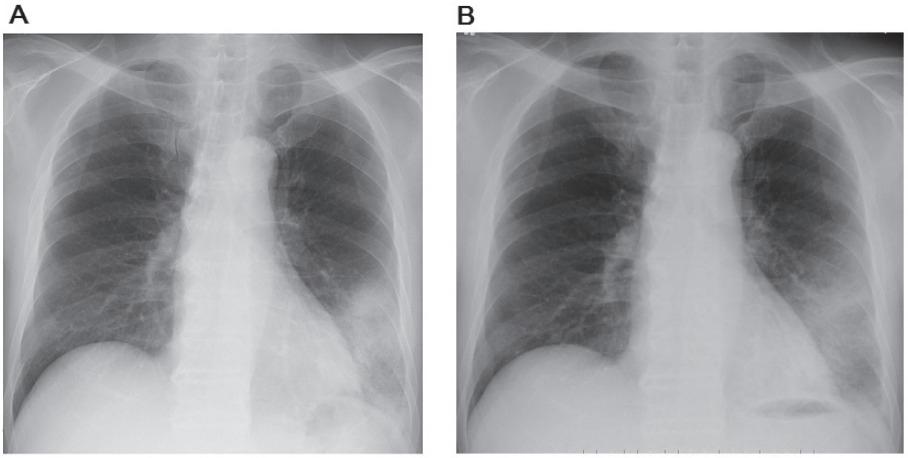

Fig. 1. (A) Chest radiograph on admission shows a non-segmental infiltration shadow in the left lower lung field. (B) Chest radiograph on day 4 after admission shows improvement of the infiltration shadow in the left lower lung field.

Table 1. Laboratory data upon admission

Peripheral blood			Blood chemistry			Arterial blood gas (room air)		
WBC	8,200	/μL	PG	180	mg/dL	pH	7.498	
Neut	84.2	%	TP	5.9	g/dL	PaO_2	73.1	Torr
Lymph	11.6	%	Alb	2.7	g/dL	$PaCO_2$	27.5	Torr
Mono	4.1	%	T-bil	0.3	mg/dL	HCO_3^-	21.1	mEq/L
Baso	0.1	%	AST	49	IU/L			
RBC	407×10^4	/μL	ALT	36	IU/L	Bacterial examination		
Hb	14.0	g/dL	LDH	256	IU/L	Sputum culture		
Ht	40.2	%	ALP	302	IU/L	*Legionella pneumophila*		(+)
Plt	20.2×10^4	/μL	BUN	13	mg/dL	serogroup 9		
			Cr	0.80	mg/dL	Blood culture		(–)
			Na	130	mEq/L	Urinary antigen tests		
			K	4.1	mEq/L	*Streptococcus pneumoniae*		(–)
			Ca	8.1	mg/dL	*Legionella pneumophila*		(–)
			CPK	167	IU/L	*Mycoplasma pneumoniae*		
			CRP	19.51	mg/dL	PA antibody		< 40
			PCT	0.25	ng/mL	*Chlamydophila pneumoniae*		
						IgM antibody		0.20 C. O. I.

Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Baso, basophil; BUN, blood urea nitrogen; CPK, creatinine phosphokinase; Cr, creatinine; CRP, C-reactive protein; Hb, hemoglobin; Ht, hematocrit; LDH, lactate dehydrogenase; Lymph, lymphocyte; Mono, monocyte; Neut, neutrophil; PCT, procalcitonin; PG, plasma glucose; Plt, platelet; RBC, red blood cell; T-bil, total-bilirubin; TP, total protein; WBC, white blood cell.

body temperature had normalized, and the infiltration shadow in the left lower lung field and inflammatory response had improved, ceftriaxone was changed to oral levofloxacin (500 mg/day) on day 6. As the pneumonia did not relapse, the patient was discharged from the hospital on day 9, and oral levofloxacin was stopped on day 10.

After leaving our hospital, a *Legionella* species was isolated on WYO-α media using the sputum sample taken on admission. *L. pneumophila* serogroup 9 was finally identified from the Oxoid *Legionella* latex test (Thermo Fisher Scientific, Waltham, MA, USA) and *Legionella* Agglutination Latex Reagent (Pro-Lab Diagnostics, Richmond Hill, Canada). The source of infection could not be identified, because the patient had not gone to either a hot spring or a spa, nor had he been exposed to a recirculating bath, used a garden hose or used gardening soil.

In the present report, *L. pneumophila* serogroup 9 was the causative microorganism of CAP. To the best of our knowledge, the present patient is the fourth case worldwide to be reported as a clinical case study; one other case was from Japan (4), and 2 cases were from the United States (5). All patients, except for the present case, were treated with erythromycin (2 patients were treated intravenously and 1 patient orally); one patient who was treated intravenously died, and the two other patients recovered. In the present case, the patient was given ceftriaxone injection and a single 2-g dose of oral azithromycin following oral levofloxacin treatment, and the clinical course was good.

The single 2-g dose of oral azithromycin was administered as microspheres and released slowly, which dramatically improves the adverse event profile of the immediate-release sachet formulation. After a single 2-g dose of oral azithromycin, the mean area under the curve during the initial 24 h ($AUC_{0\text{-}24}$) in serum and alveolar macrophages has been reported as 10.0 mg·h/L

and 7,028 mg·h/L, respectively, in lung cancer patients (8), while the $AUC_{0\text{-}24}$ with intravenous azithromycin was 8.2 μg·h/mL and 14,944 μg·h/mL, respectively, in healthy adults (9). Those results indicated that a single 2-g dose of oral azithromycin leads to higher concentrations in both serum and alveolar macrophages, the same as intravenous azithromycin, although the $AUC_{0\text{-}24}$ in alveolar macrophages from a single 2-g dose of oral azithromycin was approximately half of that with intravenous administration, and the measured concentrations differed between subjects. Single 2-g doses of oral azithromycin are reportedly well tolerated and as effective as a 7-day course of levofloxacin in the treatment of mild to moderate CAP among adult outpatients (10). Although *Legionella* pneumonia was not evaluated in this study, a single 2-g dose of azithromycin could represent a useful treatment option for mild to moderate *Legionella* pneumonia as well as other pneumonias, because of the high concentrations indicated above.

In this case, the patient was treated not only with oral azithromycin, but also subsequently with oral levofloxacin, which is effective for patients with *Legionella* pneumonia. We therefore cannot conclusively state that the single 2-g dose of oral azithromycin was effective for this patient. However, we consider that the single 2-g dose of oral azithromycin was effective, at least as initial therapy, because the patient in our case showed obvious improvements in symptoms such as fever, inflammatory response, and infiltration shadows in the left lower lung.

Regarding treatment of hospitalized patients with *Legionella* pneumonia, parenteral azithromycin or parenteral fluoroquinolones such as levofloxacin and moxifloxacin are recommended (11). We think this represents a valuable case report, because no previous reports have suggested the effectiveness of a single 2-g dose of oral azithromycin. Case reports using a single 2-g dose of oral azithromycin for patients with *Legionella* pneumonia are expected to accumulate and clarify whether patients can be safely treated using this regimen.

Conflict of interest None to declare.

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