INTERNAL MEDICINE

□ CASE REPORT □

Severe Legionnaires' Disease Successfully Treated Using a Combination of Fluoroquinolone, Erythromycin, Corticosteroid, and Sivelestat

Hiroshi Kakeya[1,2], Naomi Ehara[1], Kiyoyasu Fukushima[1], Masafumi Seki[2], Koichi Izumikawa[2], Yoshihiro Yamamoto[2], Katsunori Yanagihara[2], Atsushi Saito[1] and Shigeru Kohno[2]

Abstract

The patient was a 67-year-old man with diabetes mellitus who had been to a hot spring spa a few days before his admission. The diagnosis of *Legionella* pneumonia was made using a urinary antigen assay. Intravenous pazufloxacin and oral clarithromycin were started. However, despite these treatments, he developed acute respiratory distress syndrome (ARDS). He was administered the combination of intravenous pazufloxacin and erythromycin, corticosteroid, and sivelestat for two weeks. Then he was successfully recovered. The outcome suggests that treatment with corticosteroid and sivelestat, in addition to a combination of appropriate anti-*Legionella* antibiotics, should be considered for patients with severe *Legionella* pneumonia with ARDS.

Key words: severe *Legionella* pneumonia, fluoroquinolone, erythromycin, corticosteroid, sivelestat

(Inter Med 47: 773-777, 2008)
(DOI: 10.2169/internalmedicine.47.0677)

Introduction

Legionella is a cause of both community and nosocomial pneumonia. A recent study found that it accounted for 3.9% of community-acquired pneumonia in Japan (1), and that the number of reported legionellosis cases is increasing. A delay of starting of appropriate therapy for *Legionella* pneumonia significantly increases mortality (2). Therefore, the early administration of appropriate antibiotics is most important for successful treatment. Unless anti-*Legionella* antibiotics are selected, the mortality of legionellosis has been reported to be 60-70%; the use of appropriate antibiotics decreases mortality to 10-20%.

In general, *Legionella* pneumonia is a potentially fatal pneumonia that develops rapidly. We report a case of severe *Legionella* pneumonia that was successfully treated with antibiotics, corticosteroid, and the neutrophil elastase inhibitor, sivelestat. The management of *Legionella* pneumonia is also reviewed.

Case Report

In November 2005, a 67-year-old man with diabetes mellitus was admitted to our hospital with high fever, dyspnea, and productive cough. He had visited a hot spring spa four days before admission. Physical examination on admission included: height, 160 cm; weight, 56.5 kg; temperature, 38.6℃; blood pressure, 120/54 mmHg; pulse rate, 96 beats per minute, regular; and respiratory rate, 33 breaths per minute. The patient's palpebral conjunctivae did not appear anemic, and his bulbar conjunctivae were not icteric. The heart sounds were normal, but inspiratory coarse crackles were heard in the left lung.

Laboratory findings on admission included (Table 1): white blood cell (WBC) count, 12,090/μl (neutrophils 87.3%, lymphocytes 7.9%, basophils 0.1%, eosinophils 0.1%, monocytes 4.6%); total bilirubin, 0.5 mg/dl; aspartate

[1]Division of Respiratory Diseases, Japanese Red Cross Nagasaki Genbaku Isahaya Hospital, Isahaya and [2]Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki
Received for publication October 16, 2007; Accepted for publication January 14, 2008
Correspondence to Dr. Hiroshi Kakeya, kakeya@nagasaki-u.ac.jp

Table 1. The Patient's Admission Laboratory Data

Hemogram		Serological test	
WBC	12090/μl	CRP	29.48 mg/dl
seg	87.3 %		
eo	0.1%	Arteial blood gas (room air)	
boso	0.1%	pH	7.499
lymp	7.9%	PaO_2	52.3Torr
mono	4.6%	PCO_2	35.0 Torr
RBC	454×10⁴/μl	HCO_3	27.0 mEq/l
Hgb	13.1 g/dl	BE	- 4.3 mEq/l
Ht	39.3%		
Plt	16.3×10⁴/μl		
ESR	60/92 mm/ h	Bacterial test	
		sputum	
Blood chemistry		bacterial : smear - , culture -	
TP	5.8 g/dl	mycobacteria : smear-, cultu re –	
Alb	3.1g/dl		
T.bil	0.4mg/dl	Urine antigen test	
AST	18IU/l	*Legionella pneumophila*	positive
ALT	13IU /l	*Streptococcus pneumoniae*	negative
LDH	186 IU /l		
ALP	168IU /l		
γ - GTP	62 IU/l		
BUN	13.8mg/dl		
Cre	1.1mg/dl		
Na	133.2mEq/l		
K	4.3mEq/l		
Cl	94.2mEq/l		
GLU	335mg/dl		
HbA1c	6.9mg/dl		

aminotransaminase (AST), 18 IU/l; alanine aminotransaminase (ALT), 13 IU/l; lactic dehydrogenase (LDH), 186 IU/l; creatine kinase (CK), 71 IU/l; blood sugar, 335 mg/dl; HgbA1c, 6.9%; and C-reactive protein (CRP), 29.48 mg/dl. Arterial blood gas analysis on room air showed: PaO_2 52.3 mmHg, $PaCO_2$ 35.0 mmHg, HCO^{-3} 27.0 mM, BE 4.3 mM, SaO_2 89.4%, and pH 7.499.

Chest X-ray on admission showed a consolidation shadow with an air bronchogram in the left lung field (Fig. 1). On chest CT, consolidation with air bronchogram was noted in the left lower lobe (lt S9, S10), and minimal left pleural effusion was observed (Fig. 2).

Sputum smear and culture yielded no significant microbes, and testing for urinary antigen to pneumococci (NOW® *Streptococcus* pneumoniae; Binax, Inc., Portland, ME, USA) was negative. The test for urinary antigen to *Legionella pneumophila* serogroup 1 (NOW® *Legionella*; Binax, Inc.) became positive; based on this finding, *Legionella* pneumonia was diagnosed, even though the sputum culture results were negative.

A fluoroquinolone, pazufloxacin (PZFX) 1 g per day, was given intravenously, and clarithromycin (CAM) 400 mg was given orally. However, no effect was noted, and the lung lesion showed rapid progression. The day after admission, the PaO_2/FiO_2 (P/F) ratio decreased from 261.5 to 167.2. On the 3rd hospital day, the WBC count was 15,410/μl, and the CRP was 35.87 mg/dl; on the 5th hospital day, the WBC was 8,850/μl, and the CRP was elevated to 36.46 mg/dl. The patient's hypoxemia increased, and there was marked progression of the bilateral shadows on chest X-ray, suggestive of ARDS. The patient was placed on mechanical ventilation. When mechanical ventilation was started, a specimen was obtained bronchoscopically to determine the causative microorganism; however, culture of the aspirated fluid showed no significant growth of organisms, including *Legionella* spp. The antibiotics were changed to erythromycin (EM) 600 mg per day, PZFX 1 g per day, and biapenem (BIPM) 0.6 g per day intravenously. Corticosteroid pulse therapy, consisting of methylprednisolone 500 mg per day for 3 days, 250 mg per day for 3 days, and then 125 mg per day for 3 days, was given. Sivelestat (an inhibitor of neutrophil elastase) 300 mg per day was added for 2 weeks. On chest X-ray, the worst infiltrates were found on the 5th hospital day. After the 9th hospital day, the radiographic findings gradually improved, and on the 12th hospital day, the patient was taken off the ventilator.

The patient's CRP decreased to 2.54 mg/dl on the 9th hospital day, and after two weeks of PZFX and EM treatment, the patient's chest X-ray improved. When PZFX was stopped, EM monotherapy was continued. However, on the 19th hospital day, the patient's CRP level increased again to 8.07 mg/dl; thus, the EM was stopped, and intravenous ciprofloxacin (CPFX) was given. His general condition, as well as radiographic and laboratory findings, gradually improved, and the CPFX was given for 10 days. The urinary antigen to *Legionella pneumophila* serogroup 1 became negative on the 30th hospital day. The time-course of events that occurred during his hospitalization is presented in Fig. 3.

Discussion

We successfully treated the patient with severe *Legionella* pneumonia with ARDS using a combination of fluoroquin-

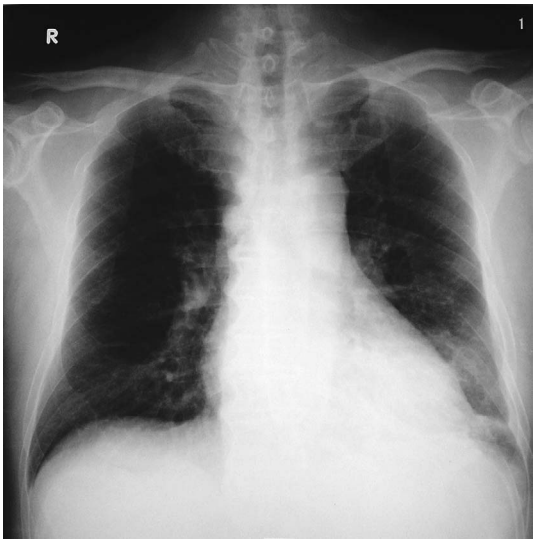

Figure 1. Chest roentgenogram on admission shows consolidation in the left lower field.

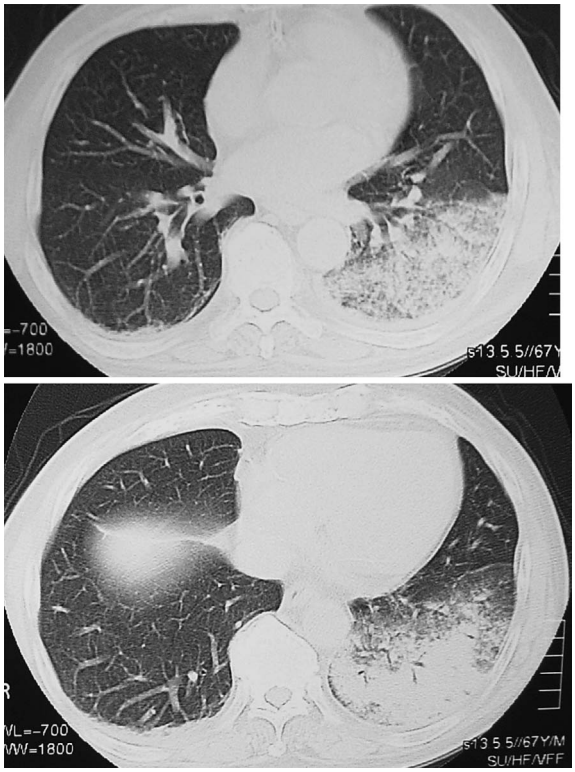

Figure 2. Chest CT on admission shows consolidation, an air bronchogram, and interstitial change in the left lower lobe.

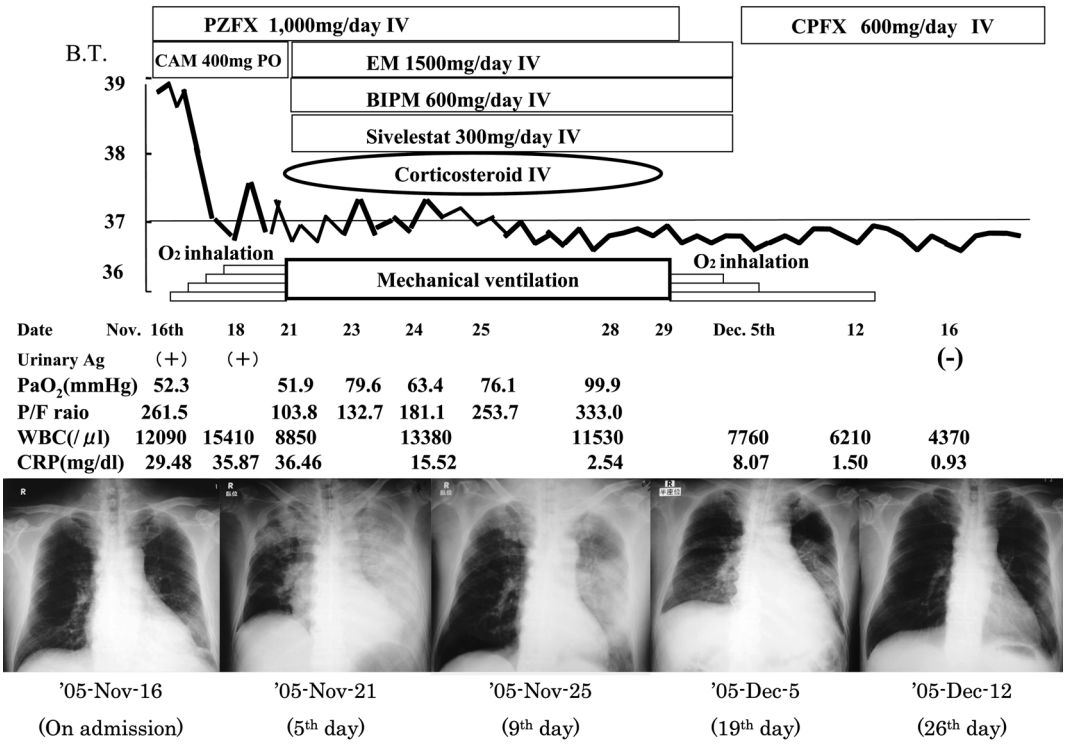

Figure 3. The patient's clinical course.

olone, erythromycin, corticosteroid, and sivelestat.

Legionella spp. are intracellular pathogens; thus, antibiotics with adequate intracellular penetration are more likely to be efficacious. The minimal extracellular concentration inhibiting intracellular growth of bacteria (MIEC) is important for evaluating intracellular antimicrobial activity. MICs of β-lactams for *L. pneumophila* are low, but the MIECs are high. For example, the MIC of carbapenems is 0.125 μg/ml,

while the MIEC is >64 μg/ml (3). This suggests that β-lactams, which do not efficiently penetrate into host cells, are not clinically effective. In contrast, both the MICs and MIECs of macrolides and fluoroquinolones are low. However, the effect of a representative macrolide, erythromycin, is only bacteriostatic (4). On the other hand, fluoroquinolones have greater bactericidal activity and better intracellular penetration than macrolides (3).

In patients with *Legionella* pneumonia treated with either CPFX (n=9) or EM (n=18), there were significant differences in the duration of pyrexia. However, normalization of leukocytosis and a 50% decrease in the C-reactive protein (CRP) level occurred in a relatively shorter time frame in the group treated with CPFX than in the group treated with EM. Furthermore, the duration of antibiotic treatment was significantly shorter in those treated with CPFX than in those treated with EM (5). Both the guidelines of the American Society for Microbiology (6) and the American Thoracic Society recommend new injectable macrolides, including AZM and intravenous fluoroquinolone, as the first choice treatment for *Legionella* pneumonia (7). In Japan, only EM of the macrolides and CPFX and PZFX of the fluoroquinolones are now available as injectable anti-*Legionella* antibiotics.

The MICs of CPFX and PZFX are 0.032 μg/ml; these are better than the MICs of macrolides (EM, CAM, AZM). The MIECs of PZFX and CPFX are reported to be 0.063 μg/ml and 0.032 μg/ml, respectively (3). The intracellular penetration rate of CPFX into neutrophils is approximately twice as that of PZFX (8). Both CPFX and PZFX (9) are reported to be clinically effective. However, there are no clinical randomized studies that have compared the efficacy and safety of CPFX and PZFX. In the western countries, levofloxacin (LVFX) given by injection is recommended as the drug of first choice for the treatment of severe pneumonia including legionellosis. The MIEC of LVFX is better than that of CPFX and PZFX. Furthermore, LVFX has been shown to have a better postantibiotic effect (PAE) against *L. pneumophila* strains compared to other antimicrobials, including CPFX, AZM, and EM (10). Injectable LVFX will be available within a few years in Japan.

In mild to moderate *Legionella* pneumonia cases, anti-*Legionella* antibiotic monotherapy may be adequate; however, in severe cases, the combination of antibiotics and other immunomodulators should be considered. The *in vitro* activities of combination antimicrobial therapy against *Legionella* spp. Have been studied (11). Synergy occurred to a significantly greater extent for the CAM-LVFX and AZM-LVFX combinations compared to the EM-LVFX combination. The AZM-LVFX combination had a significantly greater synergy than did either the EM-CPFX combination or the CAM-CPFX combination. Combination therapy involving the new macrolide and fluoroquinolone appears to be an ideal regimen. The present patient was started on CAM-PZFX and then switched to EM-PZFX, which resulted in substantial improvement. However, to date, there are no clinical or experimental data dealing with the effectiveness of the combination of PZFX and macrolides. In this case, BIPM was added to the EM-CPFX combination therapy on the 5th hospital day, since mixed bacterial infection was not excluded when considering his initial clinical course. However, no microbial organism was detected by bronchoendscopy examination, but *Legionella* urinary antigen was positive.

Corticosteroids are an important natural inhibitor of inflammation and are sometimes used to suppress life-threatening systemic inflammation. High-dose corticosteroid pulse therapy is reported to be effective for treating severe *Legionella* pneumonia (12). Recently, a randomized, controlled study found that chronic, low-dose corticosteroid therapy was effective in patients with severe community-acquired pneumonia (13). Thus, in these patients, low-dose corticosteroid therapy appears to be ideal. In the present case, methylprednisolone was given for 9 days. On the other hand, the long-term use of corticosteroids is immunosuppressive. At present, the optimal dose and duration of corticosteroid treatment have not been determined.

Patients with *Legionella* pneumonia frequently develop acute respiratory distress syndrome (ARDS). The present patient developed ARDS on the 5th hospital day. It was reported that KL-6 levels were elevated in plasma from patients with ARDS (14). In this case, KL-6 level was within normal limited as 427 U/ml (normal range: <500 U/ml) on admission. On the other hand, serum soluble IL-2 receptor (sIL-2R), a marker of lymphocyte activation, as IL-6 and IL-8, was reported to be significantly higher in patients with subsequent acute lung injury (ALI) (15). In this case, sIL-2R was elevated at 905 U/ml on admission, although IL-6 and IL-8 were not examined. Since little is known about the mechanism of ARDS in *Legionella* pneumonia, the analysis and evaluation of serum cytokines including KL-6 and interleukins are required in clinical studies.

Neutrophil elastase is thought to be an important mediator of acute lung injury. This suggests that inhibiting the activity of the enzyme could prevent the development and progression of ARDS. Sivelestat is a specific inhibitor of neutrophil elastase that was developed by Ono Pharmaceutical Co. Ltd in Japan. It is reported that the inhibitor of neutrophil elastase, sivelestat, plays a protective role in the lung with ischemia-reperfusion injury (16), lipopolysaccharide-induced injury (17), and bleomycin-induced fibrosis (18). Its effect on acute lung injury in clinical trials remains controversial (19). On the other hand, there are some case reports of severe *Legionella* pneumonia cases that were treated successfully with antibiotics, corticosteroid, and sivelestat (20, 21). No clinical trials of sivelestat involving patients with severe *Legionella* pneumonia have been undertaken. Taking into account the mechanism of sivelestat, sivelestat could be a valuable immunomodulator. Further investigations are warranted to evaluate the role that corticosteroids and sivelestat could play in the treatment of patients with severe *Legionella* pneumonia.

The severity of *Legionella* pneumonia tends to be underestimated during the early stage. In the present case, the severity was estimated as moderate on the time of admission; however, ARDS developed a few days later despite the early administration of appropriate therapy. Tan et al reported that, despite appropriate therapy and initial clinical improvement, more than half of patients showed worsening of the infiltrate and pleural effusion within the first week (22). Thus, patients with *Legionella* pneumonia should be observed in hospital. In mild cases, monotherapy with oral fluoroquinolones, AZM, or telithromycin (23) may be adequate. However, even such patients should be hospitalized, since *Legionella* pneumonia can rapidly deteriorate. In moderate cases, intravenous fluoroquinolone monotherapy or combination therapy with intravenous fluoroquinolone and a new macrolide should be given. In more severe cases, the addition of corticosteroid and sivelestat should be considered.

References

1. Saito A, Kohno S, Matsushima T, et al. Prospective multicenter study of the causative organisms of community-acquired pneumonia in adults in Japan. J Infect Chemother **12**: 63-69, 2006.

2. Heath GH, Grove DI, Looke DFM. Delay in appropriate therapy of *Legionella* pneumonia associated with increased mortality. Eur J Clin Microb Infect Dis **15**: 286-290, 1996.

3. Higa F, Akamine M, Haranaga S, et al. In vitro activity of pazufloxacin, tosufloxacin and other quinolones against *Legionella* species. J Antimicrob Chemother **56**: 1053-1057, 2005.

4. Sabria M, Pedro-Botet ML, Gomez J, et al. Fluoroquinolones vs macrolides in the treatment of Legionnaires disease. Chest **128**: 1401-4105, 2005.

5. Haranaga S, Tateyama M, Higa F, et al. Intravenous ciprofloxacin versus erythromycin in the treatment of *Legionella* pneumonia. Intern Med **46**: 353-357, 2007.

6. Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Disease Society of America. Clin Infect Dis **31**: 347-382, 2000.

7. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis **44**: S27-72, 2007.

8. Mikami H, Tsuneda R, Hori T, et al. Penetration of pazufloxacin into human polymorphonuclear leukocyte and human tissue culture cells and its intracellular bacterial activity. Jap J Chemother **43**: S-2, 120-125, 1995 (in Japanese).

9. Higa F, Shinzato T, Toyama M, et al. Efficacy of pazufloxacin mesilate in Legionnaires' disease: a case report and in vitro study of the isolate. J Infect Chemother **11**: 164-168, 2005.

10. Smith RP, Baltch AL, Michelsen PB, Ritz WJ, Alteri R. Use of the microbial growth curve in postantibiotic effect studies of *Legionella pneumophila*. Antimicrob Agents Chemoter **47**: 1081-1087, 2003.

11. Martin SJ, Pendland SL, Chen C, Schreckenberger P, Danziger LH. In vitro synergy testing of macrolide-quinolone combinations against 41 clinical isolates of *Legionella*. Antimicrob Agents Chemother **40**: 1419-1421, 1996.

12. Yonemaru R, Homma S, Yamasawa F, et al. A case of Legionnaires' disease cured with a combination of erythromycin and steroid therapy. Nihon Kyobu Shikkan Gakkai Zasshi **29**: 1499-1504, 1991 (in Japanese).

13. Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia. Am J Crit Care Med **171**: 242-248, 2005.

14. Sato H, Callister ME, Mumby S, et al. KL-6 levels were elevated in plasma from patients with acute respiratory distress symdorome. Eur Respir J **23**: 142-145, 2004.

15. Takala A, Jousela I, Takkunen O, et al. A prospective study of inflammation markers in patients at risk of indirect acute lung injury. Shock **17**: 252-257, 2007.

16. Takayama M, Ishibashi M, Ishii H, et al. Effects of neutrophil-elastase inhibitor (ONO-5046) on lung injury after intestinal ischemia-reperfusion. J Appl Physiol **91**: 1800-1807, 2001.

17. Inoue Y, Seiyama A, Tanaka H, et al. Protective effects of a selective neutrophil elastase inhibitor (sivelestat) on lipopolysaccharide-induced acute dysfunction of the pulmonary microcirculation. Crit Care Med **33**: 1814-1822, 2005.

18. Taooka Y, Maeda A, Hiyama K, Ishioka S, Yamakido M. Effect of neutrophil elastase inhibitor on bleomycin-induced pulmonary fibrosis in mice. Am J Resp Crit Care Med **156**: 260-265, 1997.

19. Zeiher BG, Artigas A, Vincent JL, et al. Neutrophil elastase inhibition in acute lung injury: Results of the STRIVE study. Crit Care Med **32**: 1695-1702, 2004.

20. Narita Y, Naoki K, Horiuchi N, et al. A case of *Legionella* pneumonia associated with acute respiratory distress syndrome (ARDS) and acute renal failure treated with methylprednisolone and sivelestat. Nihon Kokyuki Gakkai Zasshi **45**: 413-418, 2007 (in Japanese).

21. Oguma A, Kojima T, Himeji D, Arinobu Y, Kikuchi I, Ueda A. A case of *Legionella* pneumonia complicated with acute respiratory distress syndrome treated with methylprednisolone and sivelestat sodium in combination with intravenous erythromycin and ciprofloxacin. Nihon Kokyuki Gakkai Zassi **42**: 956-960, 2004 (in Japanese).

22. Tan MJ, Tan JS, Hamor RH, File TM Jr, Breiman RF. The Radiologic Manifestations of Legionnaire's Disease. Chest **117**: 398-403, 2000.

23. Carbon C, Moola S, Velancsics I, Leroy B, Rangaraju M, Decosta P. Telithromycin 800 mg once daily for seven to ten days is an effective and well-tolerated treatment for community-acquired pneumonia. Clin Microbiol Infect **9**: 691-703, 2003.