Miliary Tuberculosis Noticed by the Efficacy of Levofloxacin Monotherapy

Kenichiro Yaita, MD,1 Hideki Ohshima, MD,2 Makiko Hayashi, MD,2 Masayuki Nakamura, MD,3 Shin-ichiro Ueda, MD, PhD,4 Yoshiro Sakai, MD, PhD,1 Kenji Masunaga, MD, PhD,1 Koichi Ohshima, MD, PhD,5 and Hiroshi Watanabe, MD, PhD1

1 Department of Infection Control and Prevention, Kurume University School of Medicine
2 Division of Cardiovascular Medicine, Department of Internal Medicine, Kurume University School of Medicine
3 Division of Respiratory, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine
4 Coronary Care Unit, Advanced Emergency Medical Service Center, Kurume University School of Medicine
5 Department of Pathology, Kurume University School of Medicine

Keywords: Mycobacterium tuberculosis, miliary tuberculosis, disseminated tuberculosis, levofloxacin, fluoroquinolones

A 79-year-old male was admitted to our hospital due to suspected community-acquired pneumonia (CAP). He was being treated for type 2 diabetes mellitus, chronic heart failure, and autoimmune hemolytic anemia (taking prednisolone 12.5 mg/day orally). He has past surgical histories that include a left thoracoplasty due to lung tuberculosis (Tb) in 20 s, annuloplasties of the mitral and tricuspid valves due to regurgitation of both that was performed in 60 s, and an atrioventricular node ablation followed by a biventricular pacemaker insertion for paroxysmal atrial fibrillation in 70 s. He experienced dyspnea 20 days before hospitalization, whereupon furosemide was prescribed for suspected heart failure exacerbation, which was effective. Three days before hospitalization, he had fever (38.5 °C), dyspnea (SpO2 96%, ambient room air) and sputum production. A physical examination showed a fine crackle auscultated on the right side of his back. Chest X-ray and computed tomography (CT) examination revealed a shadow of inflammation on the right-lower lobe of his lung (Figure A). Laboratory tests revealed pancytopenia (white blood cell count 2,900/µL (reference range WBC 4000–9000/µL), hemoglobin 9.7 g/dL (reference range 14.0–18.0...
g/dL), platelet count 87,000/µL (reference range 130,000–360,000/µL), and a mild elevation of c-reactive protein (1.73 mg/dL, reference range ≤ 0.20 mg/dL). The sputum was M2 according to Miller and Jones’ classification. Piperacillin/tazobactam 4.5 gm was administered intravenously every 8 hours. He remained febrile on the 3rd hospital day. We performed bone marrow aspiration to check for the cause of an emerging pancytopenia. In addition, an acid-fast bacilli (AFB) smear of the sputum was tested, and the result was negative. Then we changed his antibiotic to levofloxacin (LVFX) 500 mg followed by 250 mg administered orally every day (estimated creatinine clearance: 14 mL/min) for covering *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*. On the day subsequent to the starting of LVFX regimen, he became afebrile. Due to the efficacy of LVFX and no evidence of the atypical pathogens described above (antibody titer to *M. pneumoniae*: <4 (complement fixation method), antibody index to *C. pneumoniae*: IgM 0.33, IgA 1.34 and IgG 1.62 (Enzyme-linked immunosorbant assay method), and urinary antigen of *L. pneumophila*: negative), we expected the possibility of Tb. We re-read the first CT image and detected diffuse small nodular shadows on the patient’s lungs (Figure C). Based on these results, we hurried to re-check the sputum and the gastric juice for a Tb work-up. Although no AFB was detected in either the sputum or the gastric juice, epithelioid cell granulomas (without necrosis, langhans giant cell or AFB) were detected in the bone marrow clot sections (Figure D). We started anti-tuberculosis therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide. Three days following the biopsy report, we detected *Mycobacterium tuberculosis* from the samples (both the sputum and gastric juice) by performing a polymerase chain reaction and he was transferred to a hospital with a tuberculosis ward. After 4 weeks, a sputum culture was positive for *M. tuberculosis*.

LVFX is a clinically useful drug for CAP because this antibiotic covers most of CAP-causing organisms including *Streptococcus pneumoniae*, and atypical pathogens. LVFX is included in the empirical antibiotics in Japanese and American CAP guidelines.1,2
On the other hand, Fluoroquinolones (FQs) involving LVFX are the preferred drugs for drug-resistant Tb and cases that are intolerant to first-line drugs. However, FQs are also known to be a risk factor for delays in the diagnoses of Tb, and monotherapy might be a contributor to rises in the incidence of FQs-resistant strains. Devasia et al. found that more than 10 days of FQs can cause FQs-resistance (Odds ratio 7.0). Dooley et al. reported the incidence of Tb patients who were initially diagnosed as CAP. In Dooley’s report, the median time between presentation to the hospital and the initiation of antituberculosis drugs was longer for the group that had received empirical treatment with FQs, compared with the group that had not (21 days vs 5 days). Our case was also an example of a mimicking of CAP, but ultimately proved to be miliary Tb. Even with serious Tb, the FQs masked the symptoms. And if LVFX had been used for a longer period, a FQs-resistant strain could have developed.

In Japan, the new rate for registered Tb patients per 100,000 population is 16.7, which is about five times the rate in the United States (Ministry of Health, Labour and Welfare, Japan. http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou03/12.html). We are concerned about the fact that LVFX is the top selling antibiotic and is used casually in Japan with an intermediate prevalence of TB.

In conclusion, the unconsidered administration of FQs for “Non-resolving pneumonia” should be cautioned. In cases that show a rapid clinical response to FQs regardless of the ineffectiveness of other antibiotics and the presence of risk factors for Tb (e.g. past Tb history, diabetes mellitus, and glucocorticoid therapy), we should strongly consider the possibility of Tb.

Ethics statement:
This case report was approved by The Ethical Committee of Kurume University (http://www.med.kurume-u.ac.jp/med/joint/rirnri, Research No. 14135).

Conflicts of interest:
There are no conflicts of interest related to this report.

References