INTERNAL MEDICINE

□ CASE REPORT □

A Case of Refractory Chronic Respiratory Tract Infection due to *Pseudomonas aeruginosa* Successfully Controlled by Combination of Clarithromycin and Azithromycin

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Abstract

The prognosis of patients with chronic respiratory tract infections, especially diffuse panbronchiolitis, is remarkably improved by long-term administration of low-dose macrolides. However, in some cases, patients are refractory to macrolide treatment and show a low or no response; therefore, new treatment strategies are required. Here we present a patient refractory to either single low-dose clarithromycin or azithromycin but responded remarkably to the combination usage of both macrolides.

Key words: chronic respiratory tract infection, *Pseudomonas aeruginosa*, clarithromycin, azithromycin

(Intern Med 51: 1383-1386, 2012)
(DOI: 10.2169/internalmedicine.51.6985)

Introduction

The prognosis of patients with refractory chronic respiratory tract infections such as diffuse panbronchiolitis, has been dramatically improved owing to the long-term administration of low-dose macrolides. There are some cases, however, that are refractory to such treatment, and newer or improved strategy of treatment is urgently required in clinical settings. We here report a case of refractory chronic respiratory infection caused by *Pseudomonas aeruginosa* that was not well controlled by administration of either single low-dose clarithromycin (CAM) or azithromycin (AZM) but good control was achieved by combined therapy with both macrolides.

Case Report

A 60-year-old woman, previously diagnosed with systemic lupus erythematosus, interstitial pneumonia due to collagen diseases, Sjögren syndrome, and antiphospholipid syndrome, in 1992, 1994, 2003, and 2008, respectively, was followed up clinically at the Department of Dermatology and Respiratory Medicine of Nagasaki University Hospital (NUH), Nagasaki, Japan. She had been taking oral prednisolone (5 mg/day) continuously for 16 years. Interstitial pneumonia gradually progressed, and the lungs showed a honeycomb appearance. The severity of clinical symptoms such as cough and sputum production had gradually increased since 2008. Moreover, the frequency of recurrences of chronic respiratory tract infection due to *P. aeruginosa* had increased since May 2008. Administration of oral CAM (200 mg/day) was initiated in August 2008. The patient was admitted to NUH on January 28, 2009, because the cough and sputum production worsened and she had a persistent high fever.

On admission, she was alert and vital signs were as follows: body temperature, 39.2℃; heart rate, 136 beats/min with a regular rhythm; SpO_2, 89% (on room air); respiratory rate, 24 breaths/min with regular rhythm; and blood pressure, 106/71 mmHg. Physical examination revealed emaciation (height =156.0 cm and body weight =42.5 kg) and diminished respiratory sounds with moist rales in both the

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Received for publication November 21, 2011; Accepted for publication January 16, 2012
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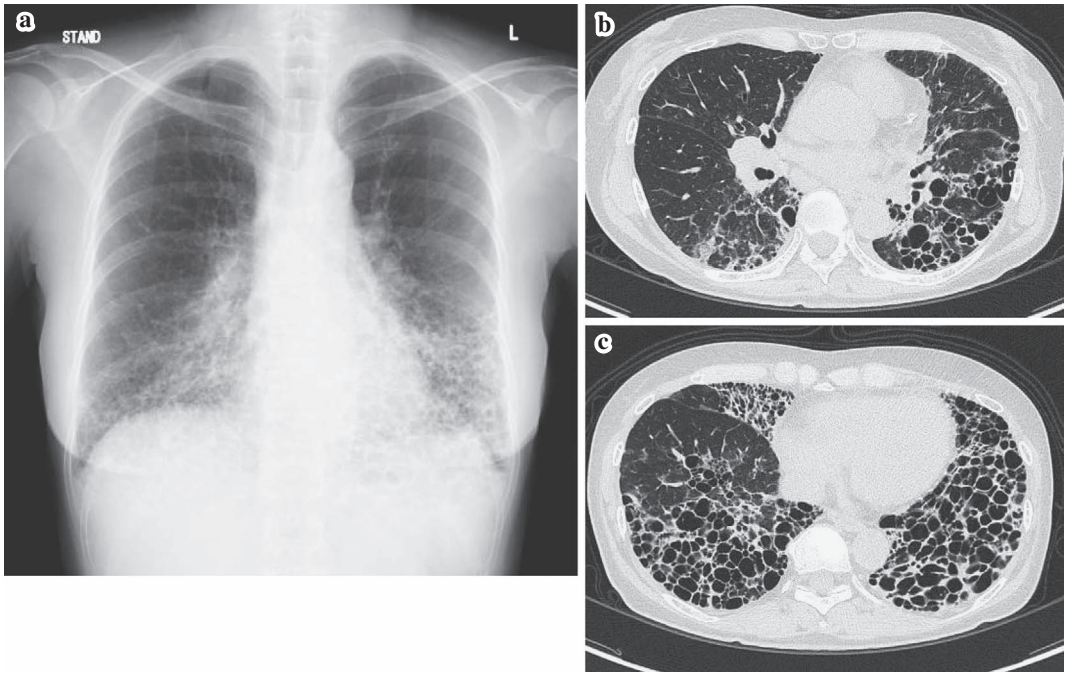

Figure 1. **Radiological findings on admission. a) Chest radiograph showing severe cystic and reticular shadows in both the right and left lower lung fields. b) and c) Chest computed tomography scan images showing the honeycomb appearance of the lungs.**

right and left lower lung fields. No signs of systemic lymphadenopathy, hepatosplenomegaly, or pre-tibial edema were observed. On admission, her white blood cell count was 11.1×10^3/μL with a shift to the left (neutrophils, 83%) and C-reactive protein level was 10.1 mg/dL. The findings of the blood gas analysis were as follows: pH, 7.488; PCO_2, 34.9 torr; PO_2, 91.5 torr; and HCO_3^-, 25.9 mmol/L (O_2 nasal, 1.5 L/min). A microbiological test of the sputum revealed the presence of *P. aeruginosa* at 1×10^5 CFU/mL, and a drug susceptibility test indicated that the minimum inhibitory concentrations (MICs) of gentamycin, ciprofloxacin, and meropenem were 2.0, <0.25, and <0.25 μg/mL, respectively. Chest radiographs showed severe cystic shadows in both the right and left lower lung fields. Computed tomography scans showed a honeycomb appearance of the lungs (Fig. 1). Fig. 2 illustrates the clinical course of this case. Recurrence of chronic respiratory infection was diagnosed on admission, and the administration of tazobactam/piperacillin (4.5g×4/day) was started. Her clinical symptoms and fever were rapidly recovered and tazobactam/piperacillin was continued for 14 days then the patient was discharged. Three days after the discharge, however, the patient was re-admitted to NUH because of high fever. Refractory chronic pulmonary infection due to *P. aeruginosa* was diagnosed again. Although inhaled tobramycin with intravenous ciprofloxacin, followed by tazobactam/piperacillin with intravenous amikacin, and colistin were administered, she did not recover completely. As for long-term macrolide treatment, the previously administered CAM at 200 mg/day was switched to AZM at 250 mg/day every other day; however, this treatment was not effective at all. A single treatment with AZM was not effective; therefore, in August 2009, we initiated combined therapy with CAM at 400 mg/day and AZM at 250 mg/day once daily. This combined treatment reduced the event of high fever but low grade fever continued occasionally after December, 2010. The patient has been receiving both CAM and AZM for 2 years, and only 1 apparent episode of recurrence of chronic respiratory infection which required hospitalization and intravenous antibiotics administration (meropenem and ciprofloxacin for a week in January 2010) has been observed. Combined treatment with CAM and AZM is currently administered at the outpatient clinic. Additionally, an increase in the sensitivity of *P. aeruginosa* to almost all anti-*Pseudomonas* antimicrobial agents was observed after combined administration of anti-pseudomonas antimicrobial agents (Table 1).

Discussion

Long-term administration of low-dose erythromycin treatment, established by Kudoh et al., has remarkably improved the prognosis of patients with diffuse panbronchiolitis (1, 2). Apart from their anti-microbial activity, macrolides were found to have immunomodulatory effects, and these effects were extensively studied in Japan. These macrolides have been found to be highly effective in (a) reducing the amount of sputum produced via suppression of mucin secretion by blocking chloride channels of bronchial epithelial cells (3, 4); (b) blocking and inhibiting the accumulation of neutrophils and lymphocytes, neutrophil elastase activity, cytokine production, and adherence to cells (5-7); (c) decreasing and disrupting biofilm formation by *P. aeruginosa* (8); and (d) suppressing *P. aeruginosa* quorum-sensing systems as cell-to-cell communication (9). In fact, these effects work

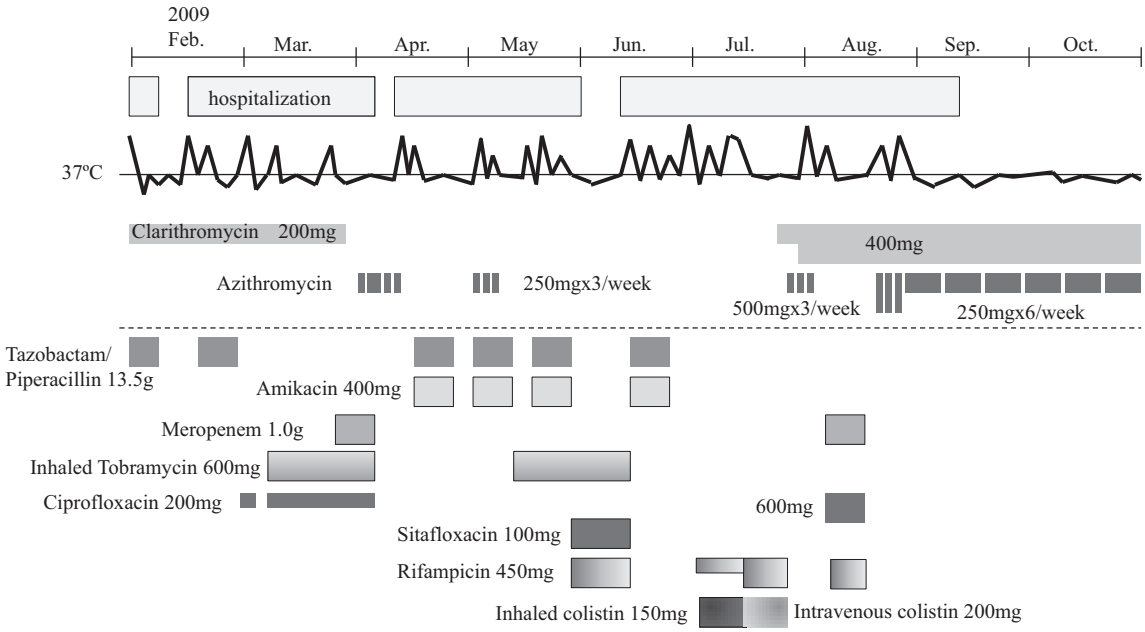

Figure 2. **The clinical course of the patient. Fever was not reduced by either single low-dose clarithromycin or azithromycin, but the patient did markedly respond to the combination of both macrolides.**

Table 1. **Minimum Inhibitory Concentration (MIC) of Antimicrobials against *Pseudomonas aeruginosa***

	2008 Dec.	2009 Jan.	Feb.	May	2010 Jan.	Aug.	2011 Jan.	Apr.	Sep.	Dec.
P. aeruginosa (CFU/mL)	2×10^6	1×10^5	1×10^7	6×10^7	1×10^7	1×10^6	2×10^7	5×10^7	2×10^7	5×10^6
PIPC	≤0.5	1.0	≥32	≥32	≥32	≥32	≥32	16.0	≥32	≥32
CAZ	1.0	1.0	≥32	≥32	≥32	16.0	8.0	4.0	≥32	16.0
CFPM	≤0.5	8.0	≥32	≥32	≥32	16.0	8.0	4.0	16.0	8.0
AZT	≤0.5	≤0.5	≥32	≥32	≥32	16.0	≤0.5	4.0	16.0	8.0
MEPM	≤0.5	≤0.5	1.0	8.0	4.0	2.0	2.0	2.0	2.0	1.0
GM	2.0	2.0	4.0	4.0	2.0	2.0	2.0	1.0	1.0	2.0
CPFX	≤ 0.5	≤ 0.5	≤ 0.5	1.0	2.0	2.0	2.0	2.0	2.0	2.0

PIPC: piperacillin, CAZ: ceftazidime, CFPM: cefepime, AZT: aztreonam, MEPM: meropenem, GM: gentamicin, CPFX:ciprofloxacin, MIC: μg/mL

integrally and lead to a better outcome in patients with chronic bacterial pulmonary infection.

It is also well established that 14- and 15-membered macrolides possess these immunomodulatory effects but not 16-membered macrolides (10). We investigated the differences in these effects between CAM, a 14-membered macrolide, and AZM, a 15-membered macrolide. We discovered that AZM and CAM exerted different immunomodulatory effects in murine dendritic cells (11). AZM increased interleukin (IL)-1 production and inhibited the excess immune response, whereas CAM inhibited IL-2 and IL-6 production; thus, these macrolides possess anti-inflammatory activities. Fukuda et al. reported that pneumolysin activity was inhibited by CAM rather than by AZM, although both the macrolides inhibited hemolytic activity (12). Moreover, Morinaga et al. reported the presence of a correlation between macrolides and MUC5AC production in bronchial epithelial cells *in vitro* (13). CAM, AZM, and telithromycin (TEL) inhibited the production of MUC5AC *in vitro*; however, CAM and TEL, but not AZM, significantly inhibited the activity of nuclear factor-κB (NF-κB). On the other hand, Araki et al. showed that AZM exerted stronger effects on the inhibition of MUC5AC expression induced by *Haemophilus influenzae* than did CAM (14).

Since two major macrolides, CAM and AZM indicated various and excellent immunomodulating effects, treatment with both AZM and CAM may be considered in cases of refractory chronic pulmonary airway infections. A review of the clinical course of the present patient indicated the apparent inhibition of exacerbation by the combined treatment with AZM and CAM, although a single administration of CAM and AZM did not reduce exacerbation. The dose of CAM was decreased from 400 mg/day to 200 mg/day 1 year after the initiation of the combination therapy with

AZM and CAM, because the condition of the patient improved. However, fever, cough, and sputum production were observed again, and the dose of CAM was again increased to 400 mg/day. The reason we increased the amount of CAM was that immunomodulating effects of macrolides have been proven to be increased depending on their amount *in vivo* experiment (12, 13). The clinical symptoms gradually improved. Thus, administration of low-dose CAM was not effective in the present case. Additionally, the administration of AZM was also considered given as 500 mg/day for every other day at first, however, we switched to 250 mg/day six days a week due to the hepatotoxicity and fever that occurred during administration of 500 mg/day every other day. Many of the studies cited above indicated that the immunomodulatory effects of macrolides are dose dependent, and this may have been reflected in the present case as well.

Through *in vivo* study, we have proved the efficacy of the combination use of AZM and CAM in choric pulmonary *P. aeruginosa* infection mice model previously established by Yanagihara et al. (15). We compared the bacterial burden in lung tissues between 5 treatment groups: (a) low-dose CAM (20 $mg \cdot kg^{-1} \cdot day^{-1}$), (b) high-dose CAM (200 $mg \cdot kg^{-1} \cdot day^{-1}$), (c) low-dose AZM (20 $mg \cdot kg^{-1} \cdot day^{-1}$), (d) high-dose AZM (200 $mg \cdot kg^{-1} \cdot day^{-1}$), and (e) low-dose of CAM and AZM (20 $mg \cdot kg^{-1} \cdot day^{-1}$). The bacterial burden in the lung tissues was apparently lower in the 2 groups that received high-dose macrolides and in the group that received a combination of AZM and CAM compared to the groups that received low-dose macrolides (data not shown). Further *in vivo* or *in vitro* experiments are warranted.

Drug susceptibility of *P. aeruginosa* in the present case became more resistant during the repeated usage of antimicrobial agents for repeated exacerbation events. *P. aeruginosa* tended to be more sensitive to antimicrobial agents after the initiation of combined therapy with CAM and AZM. This finding might be explained by the significant reduction in exacerbation with a decrease in the use of antimicrobial agents, and it highlights another benefit of the novel combination of macrolides.

Conclusion

We encountered a severe refractory chronic pulmonary infection case that was successfully controlled by the combination use of CAM and AZM. Our findings indicate that combined therapy with macrolides can be considered as a treatment option for refractory chronic pulmonary infection.

Author's disclosure of potential Conflicts of Interest (COI).

Kohno S: Honoraria, Taisho Toyama Pharmaceutical Co., Ltd. and Pfizer Japan Inc. Research Funding, Taisho Toyama Pharmaceutical Co., Ltd. and Pfizer Japan Inc.

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