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CASE SERIES

Development of *Pseudomonas aeruginosa* Drug Resistant Due to Prolonged Use of Broad-Spectrum Antibiotics in Severe Viral Infection/Candidemia Cases

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Abstract: Pre-multidrug-resistant *Pseudomonas aeruginosa* (Pre-MDRP) defined as resistance to any two of the three antibiotics, such as usually carbapenems, fluoroquinolones and aminoglycosides, is usually induced by inappropriate use of these broad spectrum antibiotics. We experienced two such cases: Case 1 is a 13-years old female patient with recurrent respiratory syncytial virus (RSV) infection. The laboratory data and chest X-ray findings mimicked the bacterial pneumonia, and tazobactam/piperacillin (TAZ/PIPC), levofloxacin (LVFX), and meropenem (MEPM). However, her condition did not improve, and pre-MDRP was isolated and treated by ciprofloxacin (CPFX). Case 2 is 66 years old male with the history with *P. aeruginosa* was previously isolated and LVFX was used because bacterial pneumonia was suspected. However, *Candida albicans* from blood followed by pre-MDRP was isolated from sputum, and he was treated by micafungin and CPFX. The cases suggested that prolonged and/or repeated exposure to anti-pseudomonas agents without appropriate microbial diagnosis and de-escalation of antibiotics might be induce the resistant pathogens and the relevance of pre-MDRP might be an early warning stage in antimicrobial resistance.

Keywords: antimicrobial stewardship, *Candida albican*s, *Pseudomonas aeruginosa*, respiratory syncytial virus

Introduction

Pseudomonas aeruginosa is a representative pathogen that often causes severe pneumonia in hospitalized patients and is susceptible to a limited number of antibiotics.[1,2] Therefore, infections caused by this organism are difficult to treat and often require combination therapy. Although the definition of multidrug-resistant *P. aeruginosa* (MDRP) has not been internationally standardized, it is defined as *P. aeruginosa* resistant to ceftazidime (CAZ), ciprofloxacin (CPFX), tazobactam/piperacillin (TAZ/PIPC), imipenem, and amikacin.[3,4] In Japan, it is usually defined as *P. aeruginosa* resistant to carbapenems including meropenem (MEPM), fluoroquinolones including CPFX and levofloxacin (LVFX), and amikacin by the Japan Nosocomial Infections Surveillance, a program of the Ministry of Health, Labour and Welfare, and pre-MDRP has been defined as resistance to any two of the above three antibiotics, such as usually carbapenems, fluoroquinolones and aminoglycosides.[5] The increasing resistance of *P. aeruginosa* is a growing threat to the clinical management of such infections, and pre-MDRP is often seen when antibiotics are used inappropriately.[6]

Therefore, isolation of pre-MDRP means an intermediate resistance state and its recognition will be relevant for early intervention and antimicrobial stewardship (AS) strategies before real MDRP isolation. The management of pre-MDRP may be more important than those of MRRP, which is a serious concern in all over the world. For example, nosocomial pneumonia due to *P. aeruginosa* has a high incidence of MDRP, with an international multi-center retrospective study showing that 30.5% of nosocomial pneumonia secondary to *P. aeruginosa* were MDRP, and this was associated with

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increased in hospital mortality although data from the United States show that 9% of P. *aeruginosa* isolates were MDRP in 2018, down from 15.7% in 2011.[7,8]

In this report, we present two cases of pre-MDRP pneumonia. There are no formal statistical analysis; however, the patients in both cases received excessive antibiotic treatment although one of whom was diagnosed with respiratory syncytial virus (RSV) and the other with Candida infection.

Case Series

Case 1

A 13-year-old female patient with a history of surgery for congenital cardiac defects, including ventricular septal defects and patent ductus arteriosus, was admitted for treatment of severe RSV pneumonia diagnosed based on a positive rapid RSV antigen test (Quicknavi-RSV2, Ohtsuka Co. Ltd., Tokushima, Japan).

She was admitted twice during the same year for pneumonia and had received antibiotic treatment with TAZ/PIPC 4.5 g three times per day via drip infusion and oral LVFX 0.5 g per day for two weeks.

On admission, chest radiography revealed slight ground-glass opacities in both lung fields (Figure 1A), and arterial oxygen saturation was 95% (while breathing 10 L/min O_2 via a face mask). *P. aeruginosa*, which showed well susceptibility including MEPM, LVFX, and TAZ/PIPC, was isolated from her sputum. The minimum inhibitor concentrations (MICs) of isolated bacteria were determined by a Phenix M-50 system (Becton Dickinson, Franklin Lakes, NJ, USA) and Lysys@S4 (Shimazu Diagnostics, Tokyo, Japan) based on the broth microdilution method. MEPM drip infusion of 1.0 g three times per day and high-flow nasal cannula management were started at this time (day 0). Laboratory data on day 0 were as follows: white blood cell (WBC) count, $9.62 \times 10^3/\mu L$, with 78.2% neutrophils, 13.7% lymphocytes, 4.7% monocytes, 2.9% eosinophils, and 0.5% basophils; platelet count, $49.1 \times 10^4/\mu L$; hemoglobin, 10.2 g/dL; blood urea nitrogen, 13.6 g/L; serum creatinine, 0.88 mg/dL; aspartate aminotransferase (AST), 15 U/L; alanine aminotransferase (ALT), 15 U/L; and C-reactive protein (CRP), 1.07 mg/dL. These conditions suggested the recurrences of viral pneumonia due to RSV rather than bacterial pneumonia due to *P aeruginosa*. The isolated bacteria might not be the true pathogen but just colonized bacteria, however, the primary physicians continued the antibiotic because they were afraid of her pneumonia exacerbation due to secondary bacterial co-infection.

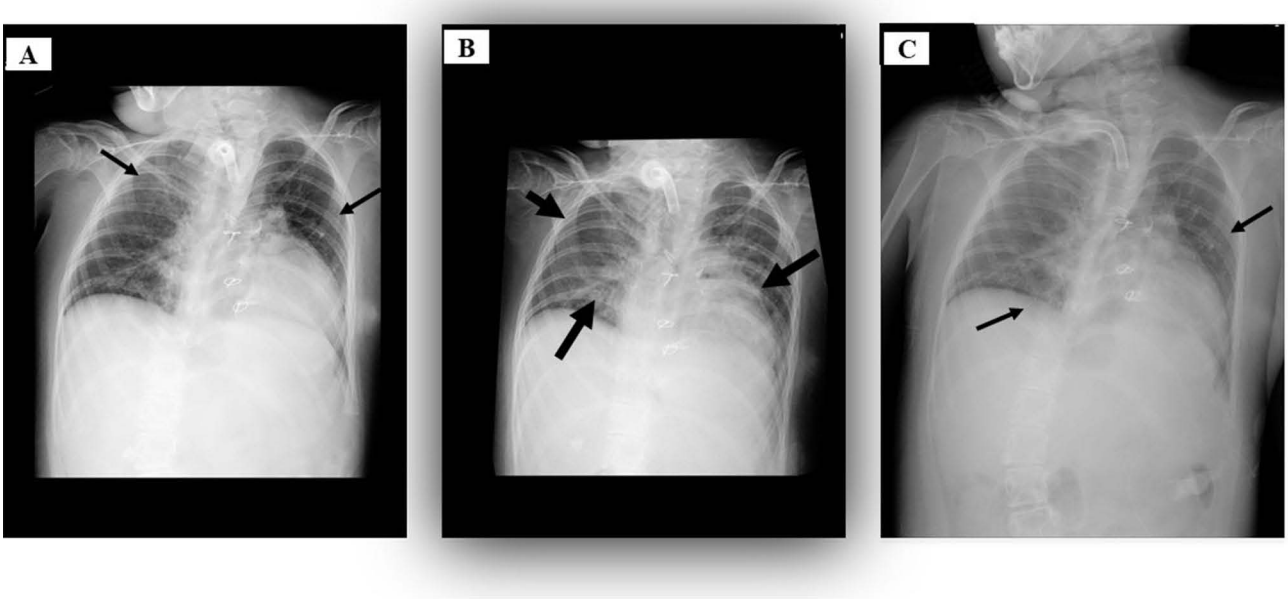

Figure 1 Chest X-ray findings in Case 1 on Day 0 (**A**), Day 10 (**B**), and Day 14 (**C**). Arrows indicate ground glass opacities with infiltration shadows. The pneumonia improved with appropriate treatment.

After 10 days, her condition, including respiratory status and laboratory data, worsened, and drug susceptibility of isolated *P aeruginosa* from her sputum changed as follows: resistance to MEPM and TAZ/PIPC, and intermediate, which meant they exhibited only moderate susceptibility to LVFX. We diagnosed that pre-MDRP was isolated from her sputum and started CPFX 0.3 g once daily because the isolated organisms showed susceptibility to CPFX and her chest radiograph had also worsened (Figure 1B).

By day 14, her respiratory condition, including chest X-ray findings, had improved (Figure 1C).

Case 2

A 66-year-old male patient who had previously undergone surgery for esophageal cancer developed *P. aeruginosa* pneumonia, for which MEPM was administered at 1 g three times per day although he had a history of pneumonia approximately two weeks ago and had received oral LVFX 0.5 g per day for 10 days.

Before surgery, the isolated organisms showed good susceptibility to most antibiotics, including MEPM, LVFX, and TAZ/PIPC. The minimum inhibitor concentrations (MICs) of isolated bacteria were determined by a Phenix M-50 system (Becton Dickinson, Franklin Lakes, NJ, USA) and Lysys@S4 (Shimazu Diagnostics, Tokyo, Japan) based on the broth microdilution method.

Laboratory data on the day of his presentation (day 0) were as follows: WBC count, $6.56 \times 10^3/\mu L$, with 53.5% neutrophils, 37.2% lymphocytes, 8.1% monocytes, 0.8% eosinophils, and 0.4% basophils; platelet count, $56.8 \times 10^4/\mu L$; hemoglobin, 7.8 g/dL; blood urea nitrogen, 10.9 g/L; serum creatinine, 0.49 mg/dL; AST, 35 U/L; ALT, 45 U/L; and CRP, 6.96 mg/dL.

Chest radiography and computed tomography (CT) showed slight infiltration shadows in both lower lung fields (Figure 2A and B). These conditions suggested the recurrences of bacterial pneumonia due to *P. aeruginosa*. Therefore, the primary physicians continued the antibiotic because they were afraid of his pneumonia exacerbation.

Seven days later, his condition did not improve, and *Candida albicans* was isolated from his blood. Therefore, 75 mg of caspofungin was administered on day 1, followed by intravenous administration of 50 mg/day for 14 days. However, drug susceptibility of isolated *P aeruginosa* from his sputum changed as follows: resistance to MEPM and TAZ/PIPC, and intermediate susceptibility to LVFX. We diagnosed that pre-MDRP was isolated from her sputum on day 14, when pneumonia did not improve. Therefore started CPFX 0.3 g once daily because the isolated pre-MDRP showed susceptibility to CPFX.

The patient's pneumonia and respiratory status had improved by day 21.

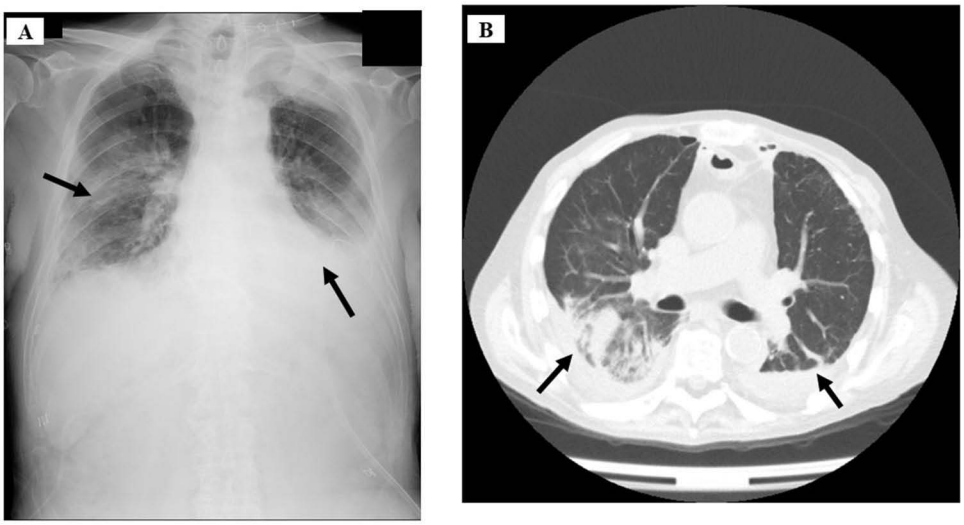

Figure 2 Chest X-ray (**A**) and computed tomography (**B**) findings in Case 2 on Day 0. Arrows indicate infiltrative shadows and pleural effusion.

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Discussion

P. aeruginosa is an opportunistic pathogen that causes ventilator-acquired pneumonia (VAP). VAP caused by *P. aeruginosa* is usually multidrug-resistant and is associated with severe infection and increased mortality as well as higher rates of treatment failure, relapse, and death.[9]

In this report, we present two patients who received excessive and/or prolonged antibiotic administration, one of whom was finally diagnosed with RSV infection and the other with Candida infection. Delayed and/or misdiagnosis of non-bacterial infections usually leads to overuse of antibiotics, which increases the incidence of drug-resistant bacteria and related pneumonia.

Among these bacteria, *P. aeruginosa* most frequently develops multidrug resistance. In our case, the first patient was diagnosed with RSV infection, for which she received TAZ/PIPC, since co-infection with bacteria is common in RSV infection,[10] with pre-MDRP subsequently isolated following overuse/long-term use of broad-spectrum antibiotics. The second patient was diagnosed with *P. aeruginosa* pneumonia, with a delayed diagnosis of Candida co-infection, in which long-term use of broad-spectrum antibiotics induced a pre-MDRP infection. In both cases, the overuse/long-term use of broad-spectrum antibiotics likely induced pre-MDRP infection, although pathogens other than bacteria were also present.

Antimicrobial stewardship has gained momentum in Japan, prompting the adoption of various strategies, including early initiation of antimicrobial therapy followed by de-escalation, to optimize antimicrobial use.[11,12] The duration of therapy should be guided by disease pathophysiology rather than isolated inflammatory markers, including CRP, with adherence to established guidelines and clinical recommendations. In Japan, compared with other countries, including the United States, the national health insurance system usually covers all residents in Japan, with most people having easy access to clinics/hospitals, making antibiotics relatively inexpensive.[13] In addition, isolated biomarkers, such as CRP, are used to evaluate the patients' inflammation status, and is considered a more important guide for the need to receive antibiotics than procalcitonin, the patients' clinical status, and guideline recommendations.[14] Therefore, use of antibiotics in Japan likely differs from that in other countries and may be difficult to fully understand over the long term. "Pre-MDRP" is region-specific in Japan and may limit generalization, however, its recognition was relevant for early intervention and AS strategies in our cases because we could avoid real MDRP isolation, which might be more serious concern at the bedsides. The concept of pre-MDRP may be more important than those of MRRP.

Furthermore, the duration of antimicrobial therapy depends on disease state. For example, for pneumonia, the standard treatment period is 5 days, with the treatment discontinued after fever resolution for 48–72 hours.[11,15] In our cases, broad-spectrum antibiotics had been used inappropriately for a long duration due to misdiagnosis of the main pathogens and pathophysiology. The usual recommended treatment duration for *P. aeruginosa* pneumonia is 7–10 days.[16] Although it was previously recommended that antibiotics should be continued for a minimum of 14–21 days to reduce the risk of relapse, recent guidelines have recommended a 7-day course of therapy for VAP, regardless of the causative pathogen. Our experience emphasizes the need to understand patients' conditions, major clinical etiologies, and pathogens by appropriate investigations and laboratory examinations, including conventional bacterial cultures and measurement of procalcitonin, as recommended by established guidelines, in patients who do not respond as expected to antibiotic therapy.[12,17]

In limitations, it appears that antibiotic overuse leads to pre-MDRP, however this causal link is not strongly demonstrated. Alternative explanations, such as prior colonization or hospital acquisition, are not also sufficiently explored. There are only two patients in this case series; therefore, it is difficult to draw firm conclusions from these two cases. We need long-term follow-up data assessing recurrence, persistence, or outcomes following discharge to be clearer the microbiological mechanisms of resistance investigated.

Conclusions

In conclusion, we present two cases of pneumonia, one due to recurrent RSV infection and the other due to candidemia, both of which developed pre-MDRP infection following excessive antibiotic administration. Our experience suggests that it is important to identify the main pathogens and pathogenesis other than bacteria, and not to unnecessarily administer antibiotics for an extended period, as this might induce resistance in bacterial strains due to inappropriate antibiotic usage. Sample size is small, however, this report suggested that RSV infection and candidemia sometimes mimic the bacterial infection. Rapid diagnosis and de-escalation of antibiotics are key points to appropriate management of the patients infected with microbiological pathogens. More huge size and longer period study will be needed.

Ethics

The reporting of these cases and related studies was approved by the Institutional Review Board of Saitama Medical University International Medical Center (approval no. #2022-072) on September 07, 2022. The study was registered as UMIN000047992. Written informed consent for publication of case details and accompanying images was obtained from the adult patient and from the minor patient's parent in accordance with the Declaration of Helsinki.

Disclosure

The author reports no conflicts of interest in this work.

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