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Early cure of *Mycobacterium* abscessus tunnel infection while maintaining peritoneal dialysis through a combination of antibiotic treatment and catheter replacement

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Abstract

Mycobacterium abscessus is a rare but important bacterium involved in tunnel infection in patients on peritoneal dialysis. Tunnel infection by *Mycobacterium abscessus* is refractory and easily recurs, becoming a factor for cessation of peritoneal dialysis. We report a case in which tunnel infection by *Mycobacterium abscessus*, which recurred after outpatient antibiotic therapy, was successfully cured by combination antibiotic therapy and replacement of the peritoneal dialysis catheter. A 50-year-old man had undergone peritoneal dialysis since the age of 48 years. *Mycobacterium abscessus* was detected in pus at the peritoneal dialysis outlet, and he was diagnosed with tunnel infection. We administered clarithromycin monotherapy twice in the outpatient setting based on susceptibility; however, owing to relapse, the patient was hospitalized. Thereafter, amikacin was administered in addition to clarithromycin. Subsequently, linezolid and imipenem/cilastatin were also used in combination while monitoring blood concentration and side effects. The peritoneal dialysis catheter was removed on day 16 after hospitalization, and reinserted on day 23. During period of 7 days, the patient's urination and creatinine level was stable. The tunnel infection was cured 40 days from hospitalization, and there was no deterioration in kidney function during treatment. Thereafter, there was no relapse for 400 days, and reduced residual renal function and coagulase negative staphylococcus peritonitis caused shift to hemodialysis. This case demonstrates that both short-term combination antibiotic therapy at the beginning of antimicrobial drug administration and catheter replacement are important for short-term treatment while continuing peritoneal dialysis.

Keywords

peritoneal dialysis; mycobacterium abscessus; tunnel infection; amikacin; antibiotics; pharmacokinetic; drug-resistance

Introduction

Mycobacterium abscessus is a type of non-tuberculous mycobacterium thatis a rare but important causative organism of exit-site infection in patients on peritoneal dialysis or those with tunnel infection or peritonitis [1,2]. In particular, peritonitis due to *Mycobacterium abscessus* has been reported to have a

higher 3-month mortality rate than other types of non-tuberculous mycobacterial peritonitis [3]. It is also known as a refractory disease and recurs easily [4]. It has also been reported that it is difficult to continue with peritoneal dialysis when peritoneal dialysis-associated catheter infection is caused by rapid-growing mycobacteria, including *Mycobacterium abscessus* [4].

Mycobacterium abscessus is a drug resistant bacterium, and must be treated with limited antibacterial drugs [5]. However, in the guidelines of the International Peritoneal Dialysis Society, there are no recommendations for specific antimicrobial treatment for this organism [6]. Previous case reports have described various antimicrobial treatments administered in cases of *Mycobacterium abscessus* exit-site infection, tunnel infection and peritonitis, and the type and duration of antibiotics were not consistent [3,4,7-10]. In addition, despite the use of antibiotics such as amikacin, which require kidney function monitoring, there are case reports that do not mention the dosage, and the pharmacokinetics in patients on peritoneal dialysis is unclear [4]. The following case describes a patient cured of *Mycobacterium abscessus* tunnel infection through a short-term combination antibiotic therapy—including clarithromycin and amikacin—and subsequent underwent catheter replacement, without cessation of peritoneal dialysis.

Case Presentation

The case describes a 50-year-old man (height173cm, weight 74 kg) who was diagnosed with type II diabetes in his 20s. Peritoneal dialysis was started when he was 48 years old because of diabetic nephropathy. The day of hospitalization for *Mycobacterium abscessus* infection is referred to below as "day 1".

After approximately 150 days before hospitalization, incremental peritoneal dialysis with 1.0L Dianeal (a standard lactate-buffered peritoneal dialysis fluid; Baxter Healthcare Corporation, Deerfield, IL, USA) was started, and exchanged twice daily for 4 hours [11]. On 77 days before hospitalization, culture was performed on samples of pus from the exit site, and treatment with cephalexin was started. On 70 days before hospitalization, *Mycobacterium abscessus* was detected from the culture test, and it was considered to be the causative organism. Table 1 shows the susceptibility profile of *Mycobacterium abscessus* in this case (Table 1). Upon consideration of the susceptibility profile, treatment with clarithromycin 200 mg (2 times per day) was started. On 61 days before hospitalization, the patient's condition had improved, and there were no signs of infection. So, clarithromycin was stopped. On 46 days before hospitalization, pus was visible from exit site again, and clarithromycin therapy was re-started, and cultures of pus were examined. Clarithromycin was discontinued after the pus had reduced at the site, and the infection was subsequently considered to be cleared. On 4 days before hospitalization, suppuration was found at the peritoneal dialysis outlet, culture tests were conducted, and treatment with clarithromycin was started again. *Mycobacterium abscessus* was detected from all pus cultures, and in-patient treatment was administered (day 0; Figure 1). Due to the sensitivity profile of the *Mycobacterium abscessus* from this sample, combination therapy of amikacin was started. Amikacin was intravenously administered at 300 mg every 48 hours, and clarithromycin at 200 mg twice a day. Concurrent therapeutic drug monitoring was performed with amikacin therapy. Figure 2 shows the actual blood concentration of amikacin, and the subsequent changes in blood concentration over time (Figure 2). On day 6, we initiated treatment with 600 mg linezolid twice a day. On day 9, the concentration of amikacin in

peripheral blood was 12.3 μg/mL; it was subsequently discontinued, and imipenem/cilastatinat 500mg/day was started. On day 16, the peritoneal dialysis catheter was removed, and subsequent culture examination thereof was carried out, and no bacteria were detected. On day 19, imipenem/cilastatin was discontinued due to persistent nausea. In addition, linezolid was discontinued due to a decreased platelet count (suspected adverse event). On day 23, the peritoneal dialysis catheter was reinserted, and on day 32, the patient was discharged from the hospital. On day 40, Clarithromycin therapy was discontinued, as the infection appeared to have cured. We judged that the infection cured based on disappearance of pusand local inflammation. During the treatment period, serum creatinine level remained at 11 to 13 (mg/dL) and was almost stable. And, blood urea nitrogen level was also stable in the range of about 70 to 100 (mg/dL). Thereafter, there was no relapse of *Mycobacterium abscessus* infection, and peritoneal dialysis continued until day 400. In this case, peritonitis prevention with vancomycin, clindamycin and ceftazidime was done 18 days before shifting to hemodialysis. However, peritonitis caused by coagulase negative staphylococcus could not be controlled and shifted from peritoneal dialysis to hemodialysis.

Analysis of pharmacokinetic parameters: If amikacin was excreted only in urine or peritoneal dialysate according to the 1-compartment model, the half-life of amikacin in this case was calculated to be 38.5 hours. The urine clearance was 5.8 mL/min (Figure 2).

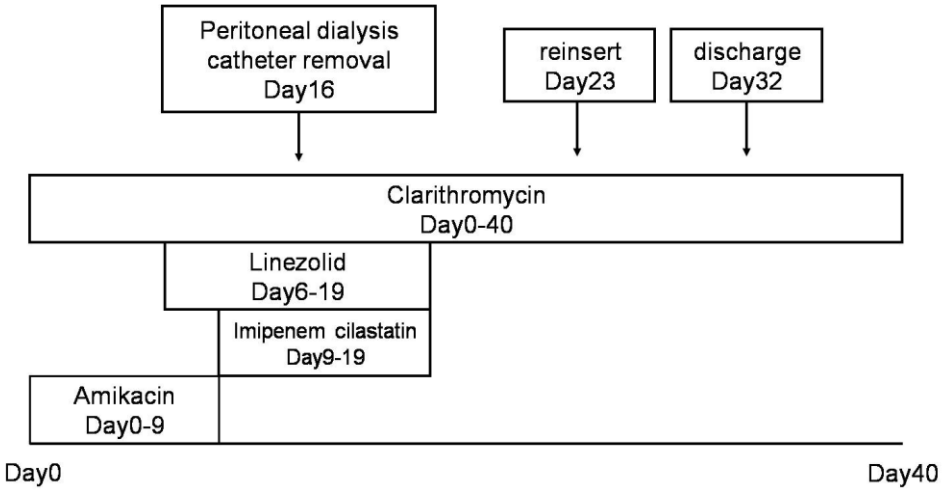

Figure 1: Time schedule of anti-mycobacterial therapy in this case

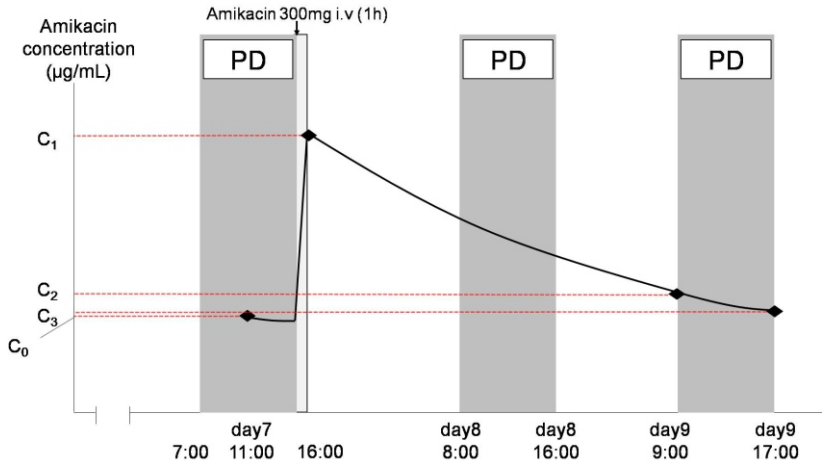

Figure 2: Change of concentration of amikacin
C_1=25.4μg/mL, C_2=12.3μg/mL, C_3=10.8μg/mL, C_0=10.5μg/mL

Table 1: Susceptibility profile of *Mycobacterium abscessus* in this case

Antibiotics	Susceptibility	Minimum Inhibitory Concentration (μg/mL)
Meropenem	I	8
Amikacin	S	16
Clarithromycin	S	≤25
Sulfamethoxazole/trimethoprim	R	>80
Rifampicin	R	>32
Ethambutol	R	>128
Levofloxacin	R	>8
Minocycline	R	>16
Linezolid	S	4
Imipenem cilastatin	S	4

Discussion/Conclusion

Combination treatment of antimicrobial drugs is often performed in case reports of peritoneal dialysis-associated catheter infection with *Mycobacterium abscessus*. Referring to the review of exit-site infection by *Mycobacterium abscessus* by Hibi et al., 6 of 10 cases reported have included multi-drug combination therapy with amikacin and clarithromycin. However, there were no cases in which blood concentration monitoring was performed, and even cases with no description of usage and dosage exist . Pharmacokinetics of antibiotics in patients on peritoneal dialysis are often different from the general healthy population. This is because there are many antimicrobial drugs that are excreted through urine, and patients on peritoneal dialysis are considered to have decreased clearance thereof. Therefore, it is necessary to find an antibacterial drug treatment strategy that optimizes pharmacokinetic or pharmacodynamic parameters against *Mycobacterium abscessus* infection by accumulation of detailed case reports.

Amikacin is one of the key drugs in non-tuberculosis mycobacterium infection. In this case, considering that the daily urine volume exceeds 1,000 mL throughout the treatment period and that the minimum inhibitory concentration of amikacin of the causative bacterium is as high as 16 μg/mL, 300 mg (about 4 mg/kg) was administered every 48 hours (The Sanford guide to antimicrobial therapy and Japanese Antibacterial Agents TDM guideline) [12]. However, the half-life of amikacin in this case was very long, and long-term continuation was discontinued for 9 days because of the possibility of deteriorating renal function. Smeltzer et al have reported the pharmacokinetic parameters of the 5 cases where in the amikacin administered intravenously to patients without peritonitis sustained peritoneal dialysis [13]. In their case series, the half-life of amikacin in such patients was thought to be 26.0–64.7 hours, consistent with the present case. However, in this case series study, the daily urine volume is not described. In our case it was thought that there was almost no clearance due to peritoneal dialysis (Figure

2), but Smeltzer et al. reported that the average peritoneal dialysis clearance was 2.0mL/min/1.73m2. In this case, the amikacin concentration in the peritoneal dialysate was not measured, and there is a difference in the calculation process of the dialysis conditions and parameters, so it is not possible to compare it directly. The Sanford guideline recommends 4 mg/kg for patients with creatinine clearance less than 10mL/min. On the other hand, Japanese guidelines describe a method of administering 4 mg/kg every 48 hours to patient with end stage renal disease. We concerned about elevated concentrations of amikacin in the blood and started 300 mg every 48 hours. After that, we thought to control blood concentration by TDM. Nevertheless, in this case the blood concentration was very high. In other words, the recommendation of the Sanford Guidelines may be excessive.

Given the long half-life of amikacin and the sustained elevated blood concentration thereof in this case, it is suggested that amikacin may exert a strong bactericidal effect on *Mycobacterium abscessus* in this case. There is only limited information on the synergistic effect of amikacin against *Mycobacterium abscessus*, but it has been reported that in combination with linezolid and amikacin, a synergistic effect was observed in *in-vitro* studies [14]. In this case, linezolid was also administered with continued elevated amikacin blood concentration, and antimicrobial activity may have increased by synergistic action. The duration of treatment for peritoneal dialysis-related infection with *Mycobacterium abscessus* has been reported to be range from 5–48 weeks . Considering that this case had been cured in about 6 weeks, it may be possible to treat with appropriate antimicrobial treatment for a shorter period.

This case had recurred despite 4 weeks of clarithromycin monotherapy treatment before in-patient treatment. Therefore, as this was a refractory infection, the patient was treated under hospitalization. The difference between treatment under hospitalization and outpatient treatment was that combination antibiotic therapy was performed, and the peritoneal dialysis catheter was replaced in this case. Hibi et al. reported that catheter removal was performed in seven of ten patients with *Mycobacterium abscessus* exit-site infection and tunnel infection . Two of these patients were able to continue peritoneal dialysis after reconstituting the peritoneal dialysis catheter, after transferring to hemodialysis, but treatment was completely switched to hemodialysis in three patients, and one patient underwent palliative care. Recommendations on peritoneal dialysis-associated catheter infection by the International Peritoneal Dialysis Society recommends removal of catheters against intractable catheter infections [6]. Even in this case, it was suggested that the removal of the catheter contributed to the healing, although it was not considered to be an early catheter removal in terms of the onset of infection.

There are two important points in this case report. The first point is that *Mycobacterium abscessus* tunnel infection, which was difficult to cure with clarithromycin monotherapy, is curable in a short duration without cessation of peritoneal dialysis with acombination of antimicrobial medication and catheter withdrawal. The second point is to report the pharmacokinetics of intravenous amikacin in patients on peritoneal dialysis with tunnel infection by *Mycobacterium abscessus*. Although there are reports of several cases of tunnel infections in recent years, the pharmacokinetics of amikacin has not been stated outstandingly.

Based on this case report, we believe that this report is important for accumulating future cases.

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