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CASE REPORT

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Sustained suppression of enterohepatic circulation of mycophenolic acid by antimicrobial-associated diarrhea in a kidney transplant recipient with Crohn's disease: A case report

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Abstract

Mycophenolic acid (MPA) undergoes enterohepatic circulation. A kidney transplant patient on mycophenolate mofetil was treated with tazobactam/piperacillin for pyelonephritis, and developed antimicrobial-associated diarrhea. Consequently, the MPA trough level decreased by approximately 90%. Furthermore, it took approximately a month for the MPA level to normalize even after diarrhea had resolved.

KEYWORDS

antimicrobial-associated diarrhea, broad-spectrum antibiotics, enterohepatic circulation, mycophenolic acid

1 | INTRODUCTION

Mycophenolic acid (MPA) is an immunosuppressant that suppresses T and B cell proliferation by selectively and reversibly inhibiting inosine monophosphate dehydrogenase, a rate-limiting enzyme in the de novo purine biosynthesis pathway.[1] MPA is mainly used to suppress rejection in organ transplantation. MPA is metabolized through phase 2 conjugation by the uridine diphosphate glucuronosyltransferase system to phenyl mycophenolic acid glucuronide (MPAG) and acyl mycophenolic acid glucuronide (AcylMPAG).[2,3] MPAG and AcylMPAG are partially excreted in bile via multidrug resistance-associated protein (MRP) 2.[4,5] MPAG excreted in bile is converted to MPA by β-glucuronidase secreted by enteric bacteria and is reabsorbed. Since MPAG undergoes enterohepatic circulation via bile secretion,[6,7] a secondary peak emerges in the plasma concentration–time profile 4 h or later after administration.

β-glucuronidase produced by intestinal bacteria plays a role in the enterohepatic circulation of MPA. In patients on MPA therapy, concomitant antibiotics such as ciprofloxacin, amoxicillin-clavulanate, enoxacin, norfloxacin, and metronidazole disturb gut microflora and suppress the enterohepatic circulation of MPA.[8–12] Using multivariate analysis, Borrows et al[11] identified oral antibiotics as one of the factors that negatively correlates with MPA trough level. In a previous report,[12] concomitant use of either

oral ciprofloxacin or amoxicillin-clavulanate resulted in a reduction in MPA trough level to approximately 50% of baseline within 3 days of antibiotic commencement, although this level recovered spontaneously to 79% of baseline after 14 days of antibiotic use and normalized within 3 days of antibiotic discontinuation. However, there are no reports on the changes in MPA levels when antimicrobial-associated diarrhea (AAD) occurs.

We report a renal transplant patient treated with MPA, who developed AAD upon taking broad-spectrum antibiotics, resulting in an approximately 90% decrease in MPA trough level. Further, it took roughly a month for the MPA level to normalize even after treatment with antibiotics was completed and diarrhea had resolved. This case report was approved by the ethics committee of Oita University (approval number: 2228) and written informed consent was obtained from the patient.

2 | CASE PRESENTATION

A 28-year-old woman with end-stage renal failure was admitted to Oita University Hospital to undergo living donor kidney transplantation. Her underlying diseases were Crohn's disease and acute tubulointerstitial nephritis due to infliximab. Crohn's disease was followed by gastroenterologists in another hospital. During admission, the patient was taking her habitual medications for Crohn's disease and her condition appeared stable. Table 1 shows the physical and laboratory data, and medications brought to the hospital upon admission. Azathioprine and prednisolone were discontinued after admission, while tacrolimus (6 mg/day), methylprednisolone (20 mg/day), and mycophenolate mofetil (MMF) (2000 mg/day) were started. MMF was taken in two divided doses, and trough MPA level was monitored. MPA levels were quantified using a particle enhanced turbidimetric inhibition immunoassay (PETINIA) performed with the Dimension Xpand Plus system (Siemens Healthcare Diagnostics Inc). Figure 1 illustrates the changes in MPA trough levels and MMF daily doses. Since the MPA trough level measured on day 5 after admission was high at 6.3 μg/ml, one divided dose of MMF was skipped, followed by a dose reduction to 1500 mg/day. On day 6, the patient underwent living donor kidney transplantation. MPA trough levels decreased to 1.4 μg/ml on day 11. On days 21–25, she was treated with ceftazidime (2 g/day) for acute pyelonephritis caused by *Pseudomonas aeruginosa*. The patient was discharged on day 26 as body temperature returned to normal and inflammatory response improved.

On day 34, the patient presented to the emergency outpatient department because of a high fever of 39.1°C and discomfort during urination. Computed tomography detected swelling in the transplanted kidney and increased

TABLE 1 Physical and laboratory data (upper table), and drugs that the patient brought to the hospital on admission (lower table)

Physical and laboratory data		Laboratory data	
Height (cm)	156.5	Blood urea nitrogen (mg/dl)	71.6
Weight (kg)	66.6	Serum creatinine (mg/dl)	5.49
Body temperature (℃)	35.6	Serum sodium (mmol/L)	139
C-reactive protein (mg/dl)	0.07	Serum potassium (mmol/L)	4.42
Total protein (g/dl)	7.39	Serum chloride (mmol/L)	108.4
Serum albumin (g/dl)	3.77	Serum calcium (mg/dl)	8.66
Total bilirubin (mg/dl)	0.3	Serum inorganic phosphorus (mg/dl)	5.04
Aspartate transaminase (U/L)	6.4	Serum cystatin C (mg/dl)	5.06
Alanine transaminase (U/L)	4.6	White blood cell count ($\times 10^3$/μl)	19.83
Alkaline phosphatase (U/L)	109	Red blood cell count ($\times 10^6$/μl)	3.13
γ-Glutamyl transpeptidase (U/L)	12.5	Hemoglobin (g/dl)	10.4
Creatine kinase (U/L)	21	Hematocrit (%)	30.2
Lactate dehydrogenase (U/L)	86	Platelet ($\times 10^3$/μl)	172.0

Medications brought to hospital	Dose/day	Medications brought to hospital	Dose/day
Calcitriol	0.25 μg	Losartan	25 mg
Rabeprazole	10 mg	Azathioprine	50 mg
Epinastine	20 mg	Prednisolone	2.5 mg
Ketotifen	2 mg		

adipose tissue surrounding it. Pyuria was found, and urine culture yielded *P. aeruginosa* and *Enterococcus faecalis*. The patient was readmitted and intravenous tazobactam/piperacillin (TAZ/PIPC) was started. Figure 2 illustrates the course of antimicrobial treatment and the condition of diarrhea. After initiation of TAZ/PIPC, body temperature and CRP level decreased. Watery stool developed on day 37, but *Clostridium difficile* (CD) toxin and antigen tests were negative. A gastroenterologist of our hospital was consulted, who reported no relapse of Crohn's disease in the medical record. Since a susceptibility test revealed a high minimum inhibitory concentration of TAZ/PIPC against *P. aeruginosa*, the antibiotic therapy was changed from TAZ/PIPC to meropenem (MEPM) on day 39, despite the clinical efficacy of TAZ/PIPC. MPA trough level decreased markedly to 0.2 μg/ml on days 39 and

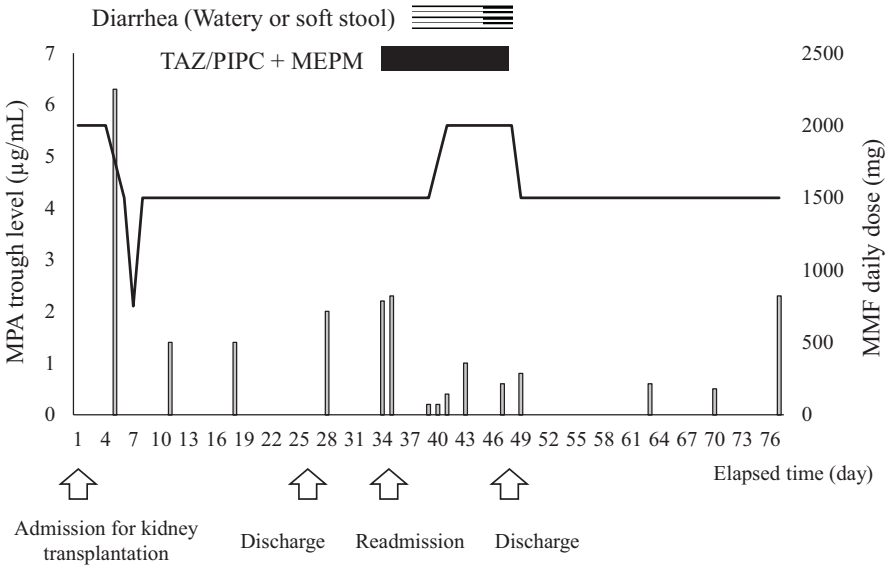

FIGURE 1 Changes in MPA trough level and MMF daily dose. The black solid line represents MMF daily dose (right vertical axis) and gray column represents MPA trough level (right vertical axis). MPA, mycophenolic acid; MMF, mycophenolate mofetil; TAZ/PIPC, tazobactam/piperacillin; MEPM, meropenem

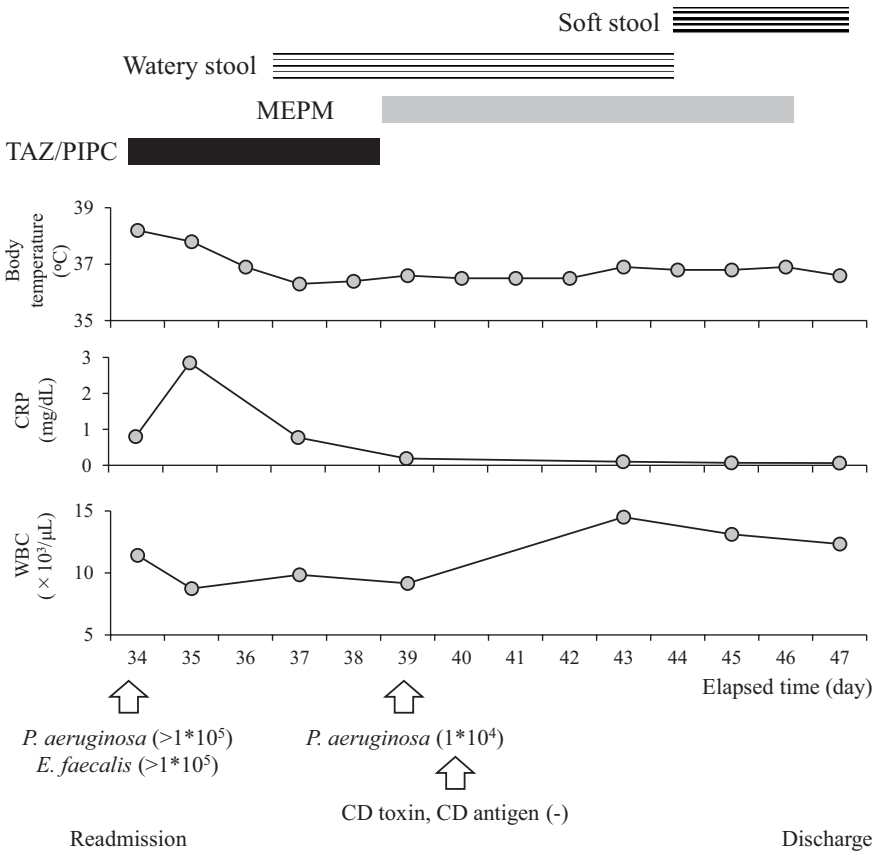

FIGURE 2 Course of antibiotic treatment and diarrhea condition. TAZ/PIPC, tazobactam/piperacillin; MEPM, meropenem; CRP, C-reactive protein; WBC, white blood cell; *P.*, *Pseudomonas*; *E.*, *Enterococcus*; CD, *Clostridium difficile*

40. Therefore, the MMF dose was increased to 2000 mg/day on day 40. MPA trough level increased to 1 μg/ml on day 43. Watery stool continued until day 44, improved to soft stool on day 45, and diarrhea was resolved on day 47, 1 day after discharge. Although the MPA trough level on day 49 remained low at 0.8 μg/ml, the dose of MMF was decreased to 1500 mg/day due to the concern of a steep increase in MPA level following improvement of diarrhea. At subsequent hospital visits, MPA trough levels on days 63, 70, and 77 were 0.6, 0.5, and 2.3 μg/ml, respectively. It took 30 days for the MPA trough level to recover to the pre-AAD level (2.2–2.3 μg/ml).

3 | DISCUSSION

In this case, AAD occurred after initiation of intravenous TAZ/PIPC therapy, causing a marked reduction in MPA trough level. As mentioned in Section 1, MPA undergoes enterohepatic circulation via enzyme secreted by intestinal bacteria,[6,7] resulting in a second peak 4 h or later after administration. Furthermore, the time of appearance of the second peak fluctuates widely between individuals and within individuals.[13] The trough concentration is highly affected by this second peak and therefore has a low correlation with the area under the curve (AUC_{0-12}).[14] Hence, AUC_{0-12} calculated by multiple blood sampling or limited sampling strategy is recommended as an index that reflects MPA exposure in the body.[15–19] Trough level, meanwhile, is used as an alternative indicator when multiple blood sampling is not possible. A previous report indicated that concomitant use of oral antibiotics with MMF reduced MPA trough level by approximately 50%, while AUC_{0-12} of MPA decreased by only 10%–30%.[12] This is because inhibition of enterohepatic circulation mainly affects AUC_{0-12} of the second peak and has little effect on AUC_{0-12} of the first peak. Moreover, in that study, MPA trough levels recovered spontaneously to approximately 80% of pre-treatment level on the 14th day of oral antibiotic treatment and normalized on the 3rd day after discontinuation, suggesting a transient reduction of MPA level. Therefore, when the MPA trough level decreases due to antibiotic use, an increase in MMF dose is considered unnecessary or even undesirable due to the risk of toxicity. However, in our case, the MPA trough level decreased by approximately 90%, which was considerably greater than the previous report. Since we predicted also a greater decrease in AUC_{0-12} compared to the previous report, MMF daily dose was increased from 1500 to 2000 mg. Consequently, the trough level increased to 45% of that before the initiation of TAZ/PIPC.

With the concern that the MPA trough level would increase after recovery from diarrhea, the daily dose of MMF was returned to 1500 mg shortly after discharge. Nevertheless, it took roughly a month before the MPA level recovered to the level before diarrhea development. The patient's adherence to MMF medication was unclear, but there was no report of low adherence in the doctor's consultation notes. Additionally, the time of medication and the time of blood collection during hospitalization did not vary. MPA trough levels fluctuated in the range of 1.5–3.0 μg/ml for over a year since day 77. The CD toxin and antigen tests were negative, and no symptoms other than diarrhea, such as abdominal pain and hematochezia, were found. No endoscopy was performed because of the low possibility of CD infection. In the case of CD infection, recovery of the intestinal flora usually takes 2–3 months, even when diarrhea is resolved. Although the time for the intestinal flora to recover is unknown in the case of AAD, it presumably took roughly 1 month in the present case. TAZ/PIPC and MEPM have broad-spectrum antibacterial activities, and the administration period of 13 days was relatively long. Both Gram-positive and Gram-negative bacteria such as *Peptostreptococcus*, *Corynebacterium*, *Bacteroides*, *Clostridium*, *Streptococcus*, *Lactobacillus*, and *Escherichia coli* generate β-glucuronidases associated with enterohepatic circulation.[20,21] TAZ/PIPC and MEPM exert antimicrobial activities against almost all these bacteria. We speculate that excessive killing of β-glucuronidase-producing bacteria may have resulted in the prolonged time for the intestinal flora to recover.

The target MPA trough level measured by the PETINIA method has been reported to range from 1.3 to 4.5 μg/ml.[14] However, the usefulness of this target range has not been fully validated. Therefore, the use of AUC_{0-12} has been recommended for TDM of MPA, except during the maintenance period when the pharmacokinetics is stable.[14] The magnitude of AUC_{0-12} decrease due to AAD remains unclear because only trough plasma MPA levels were measured in this patient. This is a limitation of this case report. Further, severe diarrhea generally accelerates gastrointestinal transit time. The possibility that accelerated gastrointestinal transit time may affect MPA absorption cannot be ruled out. This is also a limitation of this case report. On the other hand, MMF itself can also cause adverse events such as infection and diarrhea.[22,23] However, diarrhea and infection in this patient developed when the trough levels were within and below, respectively, the target range, although AUC was not measured. Therefore, MMF is unlikely to be the cause of these conditions.

This is the first case report on the changes in the MPA trough level after the development of AAD. The novelties

of this report are that the MPA trough level decreased by approximately 90% due to severe diarrhea caused by broad-spectrum anti-microbial agents, and it took roughly a month to recover to the pre-diarrhea level. If diarrhea develops when broad-spectrum antibiotics are used, the MPA trough level decreases markedly and possibly takes some time to recover to the level before diarrhea. Hence, careful monitoring of MPA level is necessary, and determining AUC_{0-12} by multiple blood sampling or limited sampling strategy may have to be considered.

AUTHOR CONTRIBUTION

RT: measured the samples, analyzed and interpreted the data, and drafted the article. AM: treated the patients and revised the article. RT: analyzed and interpreted the data and revised the article. TA, TS, and HM: diagnosed the disease and treated the patients and revised the article. HI: provided intellectual content of critical importance and revised the article. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

This case report was approved by the ethics committee of Oita University (approval number: 2228) and written informed consent was obtained from the patient.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy. The patient provided consent for the publication of this report.

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