

Case Report

Severe Complications from an Unexpectedly High Serum Mycophenolic Acid Concentration in a Patient with Renal Failure Secondary to Lupus Nephritis: A Case Report

Yuji Doi Hirotsugu Kitayama Masayoshi Yamada Yudai Miyama

Shizuoka Children's Hospital, Shizuoka, Japan

Keywords

Mycophenolate mofetil · Lupus nephritis · Acute kidney injury · Mycophenolate acid

Abstract

Mycophenolate mofetil (MMF) is used widely to treat lupus nephritis and is considered safer than other immunosuppressive drugs. Reports on severe complications related to MMF are sparse. We report a case of a patient with lupus nephritis in whom severe complications were possibly caused by MMF. The patient was a 17-year-old girl who received a diagnosis of lupus nephritis at the age of 14 years and had been taking steroid and immunosuppressive agents since then. One week after starting MMF 1 g/day instead of mizoribine owing to symptom relapse and serologic data deterioration, she presented with seizure, accompanied by leukopenia, thrombocytopenia, and renal failure. We discontinued MMF because she had extremely high serum mycophenolate acid concentration (88 µg/mL). A few weeks later, she recovered

without any complications and was discharged. Although rare, clinicians should be aware that serum mycophenolate acid concentration may become extremely high in the setting of acute kidney injury. In such circumstances, they should perform serum concentration monitoring to avoid possible adverse events.

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Introduction

Mycophenolate mofetil (MMF) is an inactive prodrug of mycophenolic acid (MPA) that is now widely used for the treatment of lupus nephritis (LN) owing to its efficacy [1, 2]. MMF is associated with adverse events such as leukopenia, thrombocytopenia, and gastrointestinal symptoms; however, it is considered relatively safe [3] even when an overdose occurs [4–7]. To our knowledge, there are no reports of possible severe adverse events related to MMF. Here, we report a case where unexpectedly high serum MPA level possibly caused severe adverse events in the setting of acute kidney injury (AKI) because of increased disease activity in LN. Despite the occurrence of severe adverse events, the patient was discharged without any complications after discontinuing MMF.

Case Presentation

A 17-year-old girl received a diagnosis of LN at the age of 14 years, and her renal biopsy showed International Society of Nephrologists and Renal Pathology Society (ISN/RPS) class IV-G(A) LN. Her symptoms had been well controlled for more than 1 year with prednisone 2.5 mg every other day, Neoral® 150 mg per day as cyclosporine A (CsA), and mizoribine (MZR) 200 mg per day. Her serum creatinine (SCr), uric acid (UA), urinary protein to creatinine ratio (UP:UC), and urine beta-2 microglobulin (uB2MG) were maintained at around 0.7 mg/dL, 5–7 mg/dL, 0.05, and 50–100 µg/dL, respectively. She began to experience arthralgia and fatigue 2 weeks before she was hospitalized in the present case. Her serum complement component 3 (C3) level decreased (to 20 mg/dL), while her anti-dsDNA antibodies and SCr level increased to 45.3 IU/mL and 1.06 mg/dL, respectively. The UP:UC ratio was 0.12, and uB2MG level was 321 µg/dL. Six days before hospitalization, she began taking MMF (Cellcept®) 1 g per day in two divided doses, instead of MZR, and the dose of prednisone was increased to 30 mg per day. Her height was 159.5 cm, weight was 45.1 kg, and body surface area was 1.43 m² on the day we changed her prescription, implying that she was given 699 mg/m²/day of MMF. Although her symptoms were relieved, she experienced a seizure 6 days later and was hospitalized. She had normal vital signs (heart rate: 112, respiratory rate: 23, SpO₂: 100%, body temperature: 36.6°C, blood pressure: 116/63 mm Hg), and the laboratory results showed AKI stage 3 (SCr: 4.38 mg/dL; urea nitrogen: 48 mg/dL), low glomerular filtration rate (GFR: 12.7 mL/min), and hyperuricemia (UA: 47.2 mg/dL). The fractional excretion of sodium was 45%, and the UP:UC ratio and uB2MG increased to 0.46 and 32,667 µg/dL, respectively. Her serum C3 level was 23 mg/dL, while her anti-dsDNA antibodies decreased to 16.7 IU/mL. The serum trough level of CsA was within the optimal limits (66 ng/mL). We performed a brain magnetic resonance imaging (MRI) scan after she experienced another similar seizure on the same day.

T2-weighted fluid-attenuated inversion recovery MRI showed high-density changes in the parietal and occipital lobes (Fig. 1). She recovered quickly from seizure, and her conscious level was clear with a full Glasgow Coma Scale. Cerebrospinal fluid examination was not performed because she was afebrile. Steroid pulse therapy (1 g/day for 3 days) was initiated and MMF was continued, because we thought that the seizure had been caused by neuropsychiatric systemic lupus erythematosus (NP-SLE). We increased the dose of MMF to 1.5 g/day, but it was decreased to 1 g/day after 1 day because of melena that appeared soon after hospitalization. Meanwhile, we discontinued CsA because we could not definitely rule out the possibility of CsA-induced posterior reversible encephalopathy syndrome (PRES). We also performed hemodialysis and plasma exchange for acute renal failure and hyperuricemia. It took several days to obtain the result of total serum MPA trough level analysis from the laboratory. The result showed extremely high MPA level (88 µg/mL), and MMF was discontinued immediately. The serum MPA trough level was measured by enzyme immunoassay method. Severe leukopenia (neutrophil count less than 10 at the nadir), thrombocytopenia (5,000/mm³ at the nadir), and ileus developed soon after, which lasted for approximately 10 days. During that period, we treated her for febrile neutropenia with carbapenem and vancomycin, because she had fever. In addition, we performed red blood cell and platelet transfusions almost daily. All these symptoms recovered gradually after discontinuing MMF. Her serum MPA levels and other laboratory data at each point of her clinical course are shown in Figure 2 and Table 1. During the clinical course, her serum C3 level increased gradually, while anti-dsDNA antibody titers decreased (101 mg/dL and 8.5 IU/mL, respectively). She fully recovered and was discharged with prednisone and MZR prescribed as controlling agents for LN. Her renal function also fully recovered on the day she was discharged. Therefore, we did not perform renal biopsy. The previous changes in MRI disappeared gradually, with no residual lesion on the MRI taken at the outpatient clinic 1 year after discharge (Fig. 1). She did not experience any neurologic sequelae.

Discussion

MMF use is associated with complications that quite often occur with a frequency of more than 1% [5]. The common side effects of MMF include diarrhea, nausea, vomiting, infections, and leukopenia. Other less common complications are esophagitis, gastritis, and gastrointestinal tract hemorrhage [5]. Although most of these symptoms were observed in our case, to our knowledge, there are no reports of these symptoms occurring with graveness.

Here, we report the case of a patient who was hospitalized because of seizures, acute renal failure, and hyperuricemia associated with deteriorating SLE and LN. She developed severe melena, leukopenia, thrombocytopenia, and ileus, which are common adverse events of MMF, soon after hospitalization. Melena, leukopenia, thrombocytopenia, and ileus may be caused by SLE as well. However, as the serologic markers for SLE recovered after admission, we believe that these symptoms were caused by the extremely high serum MPA concentration. With respect to seizures, NP-SLE is a possible cause because she had seizures in the setting of SLE flare. Although her serum CsA level was normal, we could not exclude the possibility of CsA-induced PRES [8]. As PRES can be caused by various medications including MMF [9], there is a possibility that her seizure was caused by MMF. Because MZR was discontinued a week prior

to seizure, we believe that it had no role in seizure. NP-SLE is considered to be the most likely cause for seizure in the context of SLE flare because she was stable with the same dose of CsA for more than 1 year before she was hospitalized.

MMF is the 2-morpholinoethyl ester of MPA and is rapidly absorbed and de-esterified to MPA after oral administration. MPA concentration increases rapidly after intake and drops quickly [10]. The majority of MPA is metabolized into MPA glucuronide (MPAG) in the liver by UDP-glucuronosyltransferase (UGT), which is pharmacologically inactive [4]. A second peak, which contributes to approximately 30% of total exposure, appears due to enterohepatic recirculation of MPAG [10]. More than 90% of glucuronide metabolites are renally excreted [4]. Among the reports of MMF overdose that we could find, our patient had the highest serum MPA concentration although she took only 1 g daily. She had good compliance with her prescriptions over the past years, and we checked the remaining medications when she was hospitalized. We strongly believe that she did not take an overdose. In addition, she did not take any over-the-counter drugs or herbal medications. She was gradually losing her appetite prior to admission and did not eat an unbalanced diet with too much purine. Serum MPA concentration was high even after plasma exchange (Table 1). It is known that hemodialysis does not reduce serum MPA concentration [11], and our report suggests that plasma exchange has little or no effect in reducing serum MPA concentration. Figure 2 shows a very slow clearance rate of serum MPA, which probably was affected by AKI, because most of the metabolites of MPA are renally secreted [10]. At the time of admission, our patient was on CsA and steroids other than MMF. CsA impairs enterohepatic cycling of MPAG, and corticosteroids induce UGT and enhance glucuronidation [10]. Our case showed extremely high serum MPA level, although CsA and prednisone could have lowered serum MPA levels. Hence, we think that AKI due to increased disease activity in LN led to severe delay in MPA clearance, resulting in or contributing to such severe symptoms. We could not find any reports on the influence of MZR and therefore did not measure serum MZR level. However, we believe that MZR did not have serious effects on her clinical course because it was discontinued 6 days prior to her admission. Another possibility for the high concentration of MPA is its low metabolism rate. The bioavailability of MPA metabolism has been reported to be associated with genetic polymorphism of UGT1A7 and UGT1A9 [12]; however, we did not clarify the metabolism of MPA.

Our patient had extremely high serum UA levels. She had no family history suggestive of Lesch-Nyhan syndrome or any metabolic disorder. She did not drink or take any medicine other than the ones we prescribed. The immunosuppressive mechanism of MMF is similar to that of MZR. They both inhibit the de novo pathway of purine synthesis by blocking inosine monophosphate dehydrogenase, which plays a role in UA metabolism [13]. Unlike patients who are on MZR, it is rare for patients on MMF to have high serum UA levels. This is probably because MMF also enhances the activity of hypoxanthine-guanine phosphoribosyl transferase, which is important to maintain normal serum UA [13]. As MMF has an effect on purine metabolism, we think that MMF can cause serum UA elevation.

Pharmacokinetic monitoring of MPA may not be performed in everyday practice for assessing the safety of MMF. However, MMF dose and MPA exposure have a poor relationship owing to significant inter- and inpatient variability, and overexposure may occur especially in a setting with low GFR [12]. Some studies have suggested serum concentration monitoring for effectiveness. The recommended levels for the trough are between 1 and 3.5 mg/L and for area under the curve (AUC) from 0 to 12 h are 30–60 mg h/L [14]. Recent reports recommend

the use of AUC from 0 to 12 h for better outcomes [15]. Based on our findings, we suggest that serum concentration monitoring is useful for detecting any abnormal increase in serum MPA concentration in low GFR setting, and it is clinically important to avoid MPA overexposure for safety concerns. Although quite rare, clinicians should be aware of the possibility that serum MPA concentrations can become extremely high even in regular dosing with low GFR, resulting in very severe complications. In the case of renal failure, clinicians should consider therapeutic drug monitoring (by measuring not only trough levels, but also AUC) and reduce the dose of MMF if needed.

Statement of Ethics

Informed consent was obtained from the patient and her caretakers. This article does not contain any studies with human participants performed by any of the authors.

Disclosure Statement

The authors declare that there is no conflict of interest to disclose regarding the publication of this article. The authors declare no competing financial interests.

Author Contributions

Yuji Doi took care of the patient and was the major contributor in writing the manuscript. Hirotsugu Kitayama, Masayoshi Yamada, and Yudai Miyama took care of the patient, and read and approved the manuscript.

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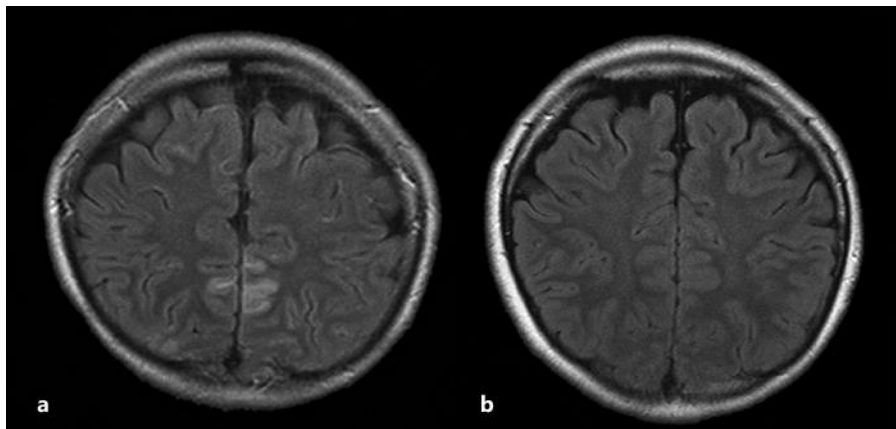


Fig. 1. T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI. **a** MRI image at the time of admission showed high-density changes in the parietal and occipital lobes. **b** MRI image taken 1 year later showed disappearance of previous changes.

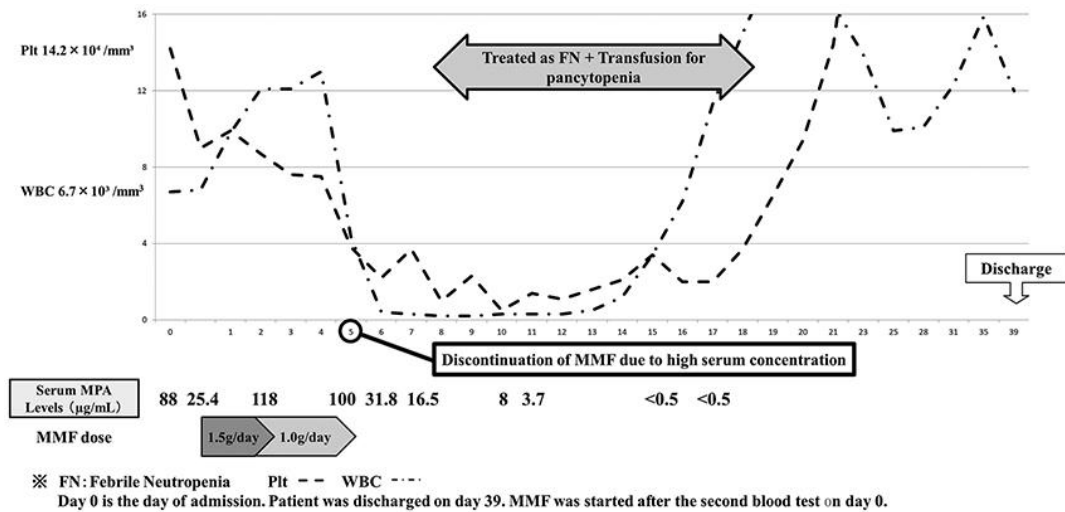


Fig. 2. Serum MPA levels, and WBC and platelet counts during the clinical course.

Table 1. Serum MPA levels and laboratory data associated with renal function during the clinical course

	Days since admission										
	0	1*	2†	5	6	7	10	11	15	21	35
MMF, $\mu\text{g/mL}$	88/25.4		118	100	31.8	16.5	8	3.7	<0.5		
UA, mg/dL	47.2/13.3	25.4	35.4	30.3	36.8	12.6	7.3	9.1	8.7	3.3	5.1
Cr, mg/dL	4.68/1.98	1.98	3.68	4.02	1.62	2.65	2.28	3.43	2.49	0.54	0.48
uB2MG, $\mu\text{g/dL}$	32,667		11,666						934	39,369	326
UP/Cr	0.46		0.39	0.81					1.06	0.54	0.13
FeNa, %	3.7		15	1.8	1.5				0.3	0.54	

The second data on day 0 were recorded after hemodialysis (HD) and before starting MMF. * The data on day 1 were recorded after plasma exchange (PEX) and HD. † The data on day 2 were recorded after PEX. All other serum MMF levels are trough level. MMF was discontinued on day 5. The patient received PEX and HD on day 6, and no further PEX or HD was performed during the admission period. UA, uric acid; uB2MG, urinary beta-2 microglobulin; UP/Cr, urinary protein to urinary creatinine ratio; FeNa, fractional excretion of sodium.