Mycophenolate Induced Colitis: One Year Post Kidney Transplantation

Waleed Al Saadi[1], Issa Al Salmi[1,2], Ehab Mohammed[2], Zakiya AlAjmi[3], Suad Hannawi

[1]Internal Medicine Department, Oman Medical Specialty Board, Muscat, Oman
[2]The Renal Medicine Department, The Royal Hospital, Muscat, Oman
[3]Histopathology Department, The Royal Hospital**,** Muscat, Oman
[4]Department of Medicine, MOHAP, Dubai, UAE

Received: 14 April 2021
Accepted: 18 November 2021

***Corresponding author:** *isa@ausdoctors.net*

DOI 10.5001/omj.2023.14

Abstract

The incidence of End-Stage Kidney Disease (ESKD) has been increasing over the past few years as a direct result of the growing percentages of individuals with metabolic syndrome. From 2001 to 2015 there was 2805 individuals diagnosed with ESKD in Oman with a growing number of patients undergoing renal transplant as the gold standard management of renal replacement therapy. Mycophenolate Mofetil (MMF) is one of the most frequently used medications as a part of the immunosuppressive medications in renal transplant specifically and solid organ transplant generally.

We are reporting a case of (MMF) induced colitis in a young female patient that underwent a living-related kidney transplant. She presented with three months history of watery non-bloody and afebrile diarrhea. Investigations confirmed the diagnosis of mycophenolate-induced colitis by histopathological examination of the colonic biopsies obtained during the colonoscopy procedure, which showed mildly increased crypt apoptosis, mild architectural disarray, and focal crypt attenuation; features consistent with mycophenolate induced colitis. The patient was treated with stopping the causative agent and replacing it with another immunosuppressive medication that led to complete resolution of the symptoms on follow-up appointments. In this case report, we highlighted in brief the underlying mechanism, pathogenesis, and clinical features of mycophenolate-induced colitis.

Keywords: End Stage Kidney Disease (ESKD); Trnsplantation; Mycophenolate Mofetil (MMF); colitis; mycophenolate induced colitis; Colonoscopy; histology; crypt apoptosis; architectural disarray; crypt attenuation.

Introduction

End-stage kidney disease (ESKD) incidence has been increasing over the past few years as a direct result of the growing percentages of individuals with metabolic syndrome (1, 2). From 2001 to 2015, there were 2805 individuals diagnosed with ESKD in Oman. The majority of them caused by diabetic nephropathy (46%), followed by hypertensive nephropathy (19%), and chronic glomerulonephritis (15%) (1, 2). Genetic or inherited disease formed only 4% of the total cases. More strikingly, most of those were aging between 45 to 64 years (1, 2). The preferred method of renal replacement therapy in Oman is hemodialysis, however, a renal transplant program has been established in Oman in 1988 (1-3). The majority of patients in Oman are commercially transplanted abroad in Pakistan and China which is criminalized by the Omani laws (2, 4).

Without the evolvement of immunosuppressive medications, the dream of organ transplant would not have come to be true. Since the first light of hope in the field in 1949 when the Nobel prize winner Phillip Hench discovered the anti-inflammatory effects of steroids and the field of immunosuppressive pharmacology has been growing (5). A decade later in the 1960s, Azathioprine has been proven to be effective in preventing allograft rejection. Cyclophosphamide has been discovered between the 1960s and 1970s, followed by monoclonal antibodies and cyclosporin A (between 1970s and 1980s) (6, 7). In the 90s the eyes of the science endeavors looked toward a much bigger cause of grafts rejections, the T and B lymphocytes. Thus, antimetabolite medications Mycophenolate, and Leflunomide that target the proliferation of these cell lines came to light (6). In the early 2000s, mycophenolate has become a major cornerstone in immunosuppressive regimens, especially in renal transplant patients. The most common mycophenolate side effects have been reported affecting the hematopoietic and the gastrointestinal system (8). We are reporting an interesting case of mycophenolate-induced colitis with an emphasis on the pathogenesis of colitis caused by the mycophenolate and the factors that affect the development of the disease.

Case presentation

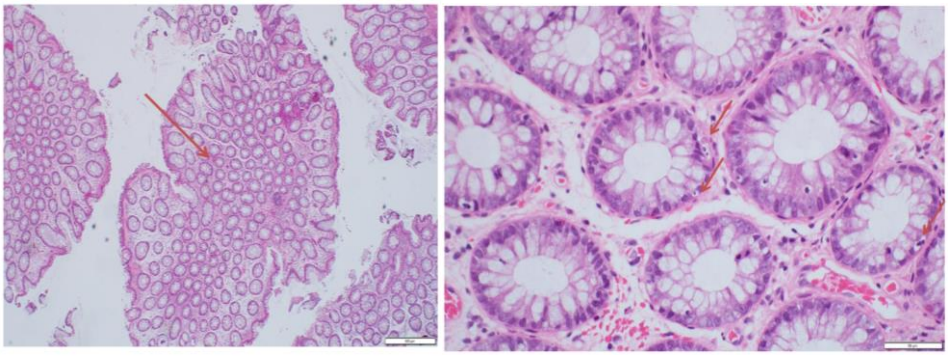
A 42-year-old female, known case of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Diagnosed to have hypertension was during her last pregnancy and started on medications for it. Also, she is known to have end-stage kidney disease (ESKD) secondary to chronic glomerulonephritis (GN) later. Subsequently, she underwent a renal transplant on the 1st of July 2019 (living-related kidney transplant from her brother), Induction immunosuppressive therapy with methylprednisolone (MP), and Basiliximab. In September 2019 She was treated for latent tuberculosis after was confirmed with a positive Quantiferon test with 9 months course of isoniazid and pyridoxine. The patient was discharged home on Tacrolimus 3mg BID, Mycophenolate Mofetil 1000 mg BID, and Prednisolone 15 mg BID as immunosuppressive regimen post-transplant which was started in July 2019.

On the 29th of November 2020, she was referred from a renal unit at her regional secondary hospital for evaluation of derangement in the graft function and proteinuria. During the admission patient reported having longstanding non-bloody watery diarrhea for more than 3 months for which the patient was passing more than 10 motions per day, it was not associated with abdominal pain or fever. She reported no associated nausea or vomiting or other gastrointestinal symptoms. A review of other systems was unremarkable. Her general and systemic examination during the admission were within normal except for mild bilateral pedal edema.

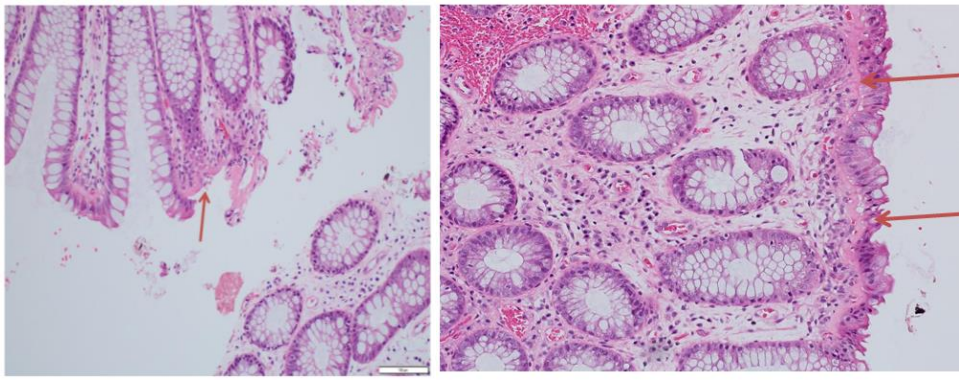
Initial workup showed no raised inflammatory markers, the white blood cells count (WBC) was 5.6x19*9/ L (normal range 2.4 – 9.5), absolute neutrophil count (ANC) of 4.5x10*9/L (normal range 1 – 4.8), lymphocytes 0.7x10*9 (normal range 1.2 – 3.8), eosinophils of 0 and a c-reactive protein of <4.00 mg/L. Erythrocyte sedimentation rate (ESR) came as less than 1. Tumour markers: Cancer Ag 15-3 (CA 15-3) in serum 25 U/ mL (N = 0-33), Cancer Ag 19-9 (CA 19-9) in serum 9 U/m L (N = 0-31), while Cancer Ag 125 (CA-125) in serum 85 U/m L (N = 0-35). Assessment of the renal function showed creatinine of 122 µmol/L, urea of 5 mmol/L, and estimated GFR of 45 mL/min/1.73m2. Urinary proteins were 1.2 g/L. Other biochemical testing showed albumin of 25 g/L (normal range 34 – 50). Fecal microscopy sent during admission showed loose stool consistency, no parasites, ova, or cysts as well as no white or red blood cells. Stool culture showed no bacterial growth. Clostridium difficile testing came negative for Toxin A, B, and GDH. CMV level reported to be lower than 100 copies (below the detection level of the laboratory) and testing for PK virus came negative. Abdomen ultrasound showed no abnormalities except for mild free

peritoneal fluids, otherwise normal study. The patient underwent colonoscopy which showed normal-appearing mucosa and no abnormalities detected, however, multiple biopsies were taken throughout the colon. In addition, the patient underwent an allograft renal biopsy as a part of the evaluation for the derangement in the renal function.

She was discharged on the 3rd of December 2020 to a close follow-up appointment to trace the histopathology reports of both renal and colonic biopsies, during which she continued the same immunosuppressive regime. The allograft kidney biopsy was reported as no evidence of active rejection, no glomerular pathology by light microscopy, only IgM deposits of unknown significance are noted on immunofluorescence. Immunohistochemistry testing was negative for C4d and CMV. The colonic biopsies taken from the sigmoid colon showed mildly increased crypt apoptosis, mild architectural disarray, and focal crypt attenuation. This was accompanied by a mild increase in the subepithelial collagen band with focal surface epithelial sloughing (figure 1). Mycophenolate Mofetil was stopped and replaced with Everolimus with close follow-up appointments to check for the progression of the graft derangement and trend of diarrhea. On subsequent visits, the patient reported complete resolution of diarrhea and further testing showed relatively stable graft function.



A **B**



C **D**

Figure 1 Shows the colonic biopsies taken from the sigmoid colon. It showed mild increased crypt apoptosis, mild architectural disarray, and focal crypt attenuation. This was accompanied by mild increase in the subepithelial collagen band with focal surface epithelial sloughing. ***A.*** 2X Preserved architecture, ***B.*** 40X Basal apoptosis, ***C.*** 20X Thickened subepithelial collagen, ***D.*** 20x Thickened collagen with epithelial separation.

Table 1. Laboratory test results during the admission

Test		**Admission 29/11/2020**	**30/11/2020**	**Discharge 3/12/2020**
Complete blood count	Hemoglobin	10.3 g/dL	9.6 g/dL	9.4 g/dL
	Platelets	200x10*9/L	193x10*9/L	155x10*9/L
	Total WBC	5.6x10*9/L	5.1x10*9/L	5.8x10*9/L
	Neutrophils	4.5x10*9/L	4.5x10*9/L	4.3x10*9/L
	Eosinophils	0x10*9/L	0x10*9/L	0x10*9/L
C-reactive proteins		<4 mg/L	NA	NA
Renal function test	Creatinine	122 umol/L	122 umol/L	104 umol/L
	Urea	5.0 nmol/L	7.4 nmol/L	12.3 nmol/L
	eGFR	45 mL/min/1.73 m2	45 mL/min/1.73 m2	54 mL/min/1.73 m2
Urine protein creatinine ratio	Total proteins	1.20 g/L	NA	NA
	Ratio	406.1 mg/umol	NA	NANA
Tacrolimus level		NA	7.4 ug/L	8.0 ug/L

Discussion

Mycophenolate is a prodrug that was first isolated from the organism Penicillium Brevicompactum that is metabolized by the liver to its active drug formulation; mycophenolic acid (MPA). First described having antibacterial and anti-neoplastic activities (8, 9). Mycophenolic acid causes prevention of the de novo synthesis of cells by reversible inhibition of inosine monophosphate dehydrogenase causing derangement in the intracellular pool of the nucleotides leading to an arrest in the proliferation of the T and B lymphocytes, hence causing immunosuppression (8-10).

Randomized controlled trials showed that mycophenolate if used with cyclosporin and steroids causes better prevention of allograft rejection compared to a regimen based on azathioprine with other immunosuppressive medications (11). Thus, since the early 2000s, mycophenolate has been widely used in solid organ transplanted patients (12, 13). Two widely available formulations of the drugs used world-widely; mycophenolate mofetil (MMF) (6, 8, 9, 13), which was used in our patient, and the enteric-coated mycophenolate sodium (4). The oral bioavailability of the mycophenolate mofetil is about 80-94% (14, 15). After its absorption, mycophenolate is metabolized by the liver to produce the active drug form; the mycophenolic acid (MPA) which will be 97-99% bound to blood albumin. Only the free blood MPA exerts the pharmacological effects of immunosuppression (16). Mycophenolic acid is eliminated predominantly by the renal system, however, a small portion is removed through the gut (17).

The side effects of mycophenolate are directly proportionate to the blood concentration of the mycophenolic acid level (18). In addition, lower concentrations have been responsible for more rejection probability (18). In a sense, mycophenolate is a double-edged sword. In this patient, we used 1000 mg twice daily oral dose. The concentration of the MPA in the blood has been reported to be affected by many factors including protein binding factors, enterohepatic circulation interruptions, and a decrease in the haptic glucuronyl transferase activity that is used in the metabolism of the prodrug, which can be caused using glucocorticoids. The level of serum binding to albumin is affected by the level of serum albumin and the use of aspirin (19, 20). In our case patient’s serum albumin in the presentation was 25 g/L because of proteinuria and the patient was not on aspirin. Other drugs that can increase the level of blood mycophenolic acid are antivirals like acyclovir and probenecid that is used for hyperuricemia which were both not used by our patient (12, 16, 18, 21, 22).

Mycophenolate is targeting rapidly growing tissues that depend on purine synthesis. The two major organs dependent on this pathway for regeneration are lymphocytes and gut cells (6, 23, 24). Lymphocytes (B and T cells) are more dependent on this pathway (90%), hence the immunosuppression (23, 25). Thus, patients on MMF are vulnerable to T and B lymphocytes dependent organismal infections such as cytomegalovirus (CMV), candida, herpes viruses, bacterial pneumonia, and to larger extent septicemia (9). However, enterocytes are caught in the fire as they are partially dependent on the pathway (26, 27). To elaborate, enterocytes are 50% dependent on the pathways targeted by mycophenolate (26, 27), and it is estimated that 45% of patients develop gastrointestinal side effects (8, 13, 26-29), such as simple diarrhea, esophagitis, GERD, enteritis, and colitis like our patient (30). Gastrointestinal symptoms of MMF include nausea, vomiting, diarrhea, and abdominal pain mostly happening in the first six months from the initiation of the therapy (26-28). However, it has been reported that patients on MMF can develop mycophenolate-induced colitis between six months and 15 years after the first use of MMF with an average of 3 years (31). In our patient, the symptoms started after one and a half year from the initiation of the treatment after the transplant.

Although MMF-induced colitis is a recognized disease entity still many of the disease features remains shady and unclear. Thus, no official guidelines were formulated for the management of patients complicated by colitis. The most recognized mechanism of pathogenesis of MMF induced colitis is the production of acyl glucuronide a metabolite of the mycophenolic acid that directly promotes the release of cytokines like IL-6, TNF- alpha, and mRNA as well as it binds to the plasma proteins, nucleic acids, and the lipids to form a neoantigen that subsequently triggers the immune system to cause inflammation in form of colitis by hypersensitivity and autoimmunity pathways (26). Another well-recognized theory is that since MMF has antibacterial properties it poses damage to the normal gut flora leading to anaerobic organism growth that causes by its turn tissue damage and inflammation (24). Furthermore, studies suggested further changes like superimposed infections by CMV, campylobacter, and other bacteria which our workup for the patient has excluded. Moreover, Impaired mucosal regeneration and increase in the goblet cells with reducing the number of the absorptive cells leads to impaired absorption and diarrhea which was absent in the histopathological examination of our patient colonic biopsies (26).

In our case report, we found no initial biochemical evidence of inflammation (e.g., no raised C-reactive proteins or raised white blood cell counts) which did not agree with the previously

published report by Moroncini and colleagues (32), however, a review report by Farooqi et.al showed that patients with MMF induced colitis could have negative initial workup (30). The most common imaging findings of the disease are thick-walled edematous bowel with occasional fat stranding that can be evident by ultrasonic evaluation, or computerized tomography (CT), or even magnetic resonance enterography (MRE) (15). In contrast, our patient ultrasonic evaluation showed none of the mentioned findings.

Specific histopathological features of MMF-related colitis include crypt architectural disarray, increased lamina propria inflammation, dilated damaged crypts, increased crypt epithelial apoptosis, and GVHD- like changes (33). In our patient, the colonoscopy showed a deceiving normal mucosa in comparison to what has been shown in the tissue examination. A previous study showed that up to 47% of patients could have normal appearance mucosa in patients with histopathological evidence of MMF induced colitis (26), which also was suggested by Papadimitriou et. al that there is a poor correlation between the severity of the colitis by colonoscopy and histological disease activity (34). In contrast, the other portion of patients with MMF colitis reported having erythema with multiple petechiae, erosions, and ulcerations with exudative base and flat margins (35).

In a study published in 2015 where they analyzed patients post solid organ transplant presented between the year 2000 to 2010 with MMF-associated colitis, they analyzed 36 patients' cases and found that only 9% of patients had colitis diagnosed by colonoscopy (26). The most common presentation was diarrhea in 83% of patients. Half of the patients had a histological feature of acute colitis-like changes, 36% of patients had inflammatory bowel disease-like features, 5.6% had ischemic-like changes, and 8.3% of patients had changes similar to graft versus host disease changes (26). However, the classically described changes of the MMF-associated colitis are crypt architecture disarray, dilated damaged crypts, and increased epithelial apoptosis, which was identical to our patient histopathological findings (30). In further analysis of the previously mentioned study, they found an increased risk of MMF-associated colitis in renal transplant patients compared to other solid organ transplant cases, and the least rate being in patients with liver transplants (26). This can be explained by the fact that the active metabolite of the drug (i.e., mycophenolic acid) is eliminated by the urinary system which is affected in a patient with renal transplant (23). Our patient was admitted with deterioration of the graft function and developed symptoms during this period which could have increased the level of the mycophenolic acid in the

blood leading to the complication. Other suggested reason is the fact that the renal transplanted patients require more immunosuppressive medications compared to other transplanted solid organ (26). As the drug is metabolized to the active form in the liver, this could explain the lower rates of colitis in this subgroup.

At last, there is no current guideline that draws the roadmap to treat patients with MMF-associated colitis. Different reports used different expert opinion-based practices including the most commonly used approach by solely stopping or lowering MMF doses (30, 32), which is similar to our approach. In our patient, the MMF has been stopped after confirming the diagnosis by histopathology and the medication was replaced by Everolimus. Other reports used other approaches like adding steroids as part of the treatment (11). However, no study has compared the efficacy of different treatment options. In our patient, the symptoms stopped subsequently after stopping the mycophenolate and she did not have further episodes during her follow-up appointments. Other reports used other approaches like adding prednisone and/or infliximab as part of the treatment, Bouhbouth et al. used a single infusion of 5 mg/Kg of infliximab after failure of response to MMF discontinuation, and 50 mg of prednisolone IV daily for 2 weeks (36). However, no study has compared the efficacy of different treatment options. In our case, still the cause of the renal derangement was under investigations and no specific reason found.

Conclusion

MMF-induced enterocolitis is uncommon, and it may be associated with debilitating complications. This case shows a unique presentation of MMF-induced colitis with normal biochemical and imaging findings initially. There is not many available data regarding why some patients have refractory colitis, why some getting it shortly after using the medications while others get it late, besides the limited data regarding the management approach with the benefits of oral or IV steroids, or biologic therapy with infliximab, also the need for endoscopic reassessment for mucosal recovery and healing. We suggest that there is a need for further evaluation of MMF-associated colitis to formulate an evidence-based method to approach patients with MMF-associated colitis, including the criteria for the colonoscopy, possibly mandating biopsy as a large portion of patients can have normal mucosa by the endoscopy and evaluating treatment options efficacy.

Reference

1. Al Alawi I, Al Salmi I, Al Mawali A, Al Maimani Y, Sayer JA. End-Stage Kidney Failure in Oman: An Analysis of Registry Data with an Emphasis on Congenital and Inherited Renal Diseases. Int J Nephrol. 2017;2017:6403985.
2. Al Ismaili F, Al Salmi I, Al Maimani Y, Metry AM, Al Marhoobi H, Hola A, et al. Epidemiological Transition of End-Stage Kidney Disease in Oman. Kidney Int Rep. 2017;2(1):27-35.
3. Al Alawi IH, Al Salmi I, Al Mawali A, Sayer JA. Kidney Disease in Oman: a View of the Current and Future Landscapes. Iran J Kidney Dis. 2017;11(4):263-70.
4. Al Rahbi F, Al Salmi I. Commercial Kidney Transplantation: Attitude, Knowledge, Perception, and Experience of Recipients. Kidney Int Rep. 2017;2(4):626-33.
5. Hench PS, Kendall EC, Slocumb CH, Polley HF. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocortical hormone in arthritis: preliminary report. Ann Rheum Dis. 1949;8(2):97-104.
6. Wiseman AC. Immunosuppressive Medications. Clinical journal of the American Society of Nephrology : CJASN. 2016;11(2):332-43.
7. Starzl TE. History of clinical transplantation. World J Surg. 2000;24(7):759-82.
8. Hood KA, Zarembski DG. Mycophenolate mofetil: a unique immunosuppressive agent. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 1997;54(3):285-94.
9. Ritter ML, Pirofski L. Mycophenolate mofetil: effects on cellular immune subsets, infectious complications, and antimicrobial activity. Transpl Infect Dis. 2009;11(4):290-7.
10. Ransom JT. Mechanism of action of mycophenolate mofetil. Therapeutic drug monitoring. 1995;17(6):681-4.
11. Srinivas TR, Meier-Kriesche H-U. Minimizing immunosuppression, an alternative approach to reducing side effects: objectives and interim result. Clinical journal of the American Society of Nephrology : CJASN. 2008;3 Suppl 2(Suppl 2):S101-S16.
12. Staatz CE, Tett SE. Pharmacology and toxicology of mycophenolate in organ transplant recipients: an update. Archives of Toxicology. 2014;88(7):1351-89.
13. Mele TS, Halloran PF. The use of mycophenolate mofetil in transplant recipients. Immunopharmacology. 2000;47(2-3):215-45.
14. Allison AC, Eugui EM. The design and development of an immunosuppressive drug, mycophenolate mofetil. Springer Seminars in Immunopathology. 1993;14(4):353-80.
15. Bullingham R, Monroe S, Nicholls A, Hale M. Pharmacokinetics and bioavailability of mycophenolate mofetil in healthy subjects after single-dose oral and intravenous administration. Journal of clinical pharmacology. 1996;36(4):315-24.
16. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. Clinical pharmacokinetics. 2007;46(1):13-58.
17. Metz DK, Holford N, Kausman JY, Walker A, Cranswick N, Staatz CE, et al. Optimizing Mycophenolic Acid Exposure in Kidney Transplant Recipients: Time for Target Concentration Intervention. Transplantation. 2019;103(10):2012-30.
18. Md Dom ZI, Coller JK, Carroll RP, Tuke J, McWhinney BC, Somogyi AA, et al. Mycophenolic acid concentrations in peripheral blood mononuclear cells are associated with the incidence of rejection in renal transplant recipients. Br J Clin Pharmacol. 2018;84(10):2433-42.

19. Jung H-Y, Lee S, Jeon Y, Choi J-Y, Cho J-H, Park S-H, et al. Mycophenolic Acid Trough Concentration and Dose Are Associated with Hematologic Abnormalities but Not Rejection in Kidney Transplant Recipients. jkms. 2020;35(24):e185-0.
20. Mourad M, Malaise J, Chaib Eddour D, De Meyer M, König J, Schepers R, et al. Correlation of mycophenolic acid pharmacokinetic parameters with side effects in kidney transplant patients treated with mycophenolate mofetil. Clinical chemistry. 2001;47(1):88-94.
21. Chakrabarti K, Frame D, Al Abbas M, McCune WJ. The use of mycophenolate mofetil area under the curve. Curr Opin Rheumatol. 2021;33(3):221-32.
22. Jaklic A, Collins CJ, Mrhar A, Sorror ML, Sandmaier BM, Bemer MJ, et al. High prevalence of potential drug interactions affecting mycophenolic acid pharmacokinetics in nonmyeloablative hematopoietic stem cell transplant recipients. Int J Clin Pharmacol Ther. 2013;51(9):711-7.
23. Lamba V, Sangkuhl K, Sanghavi K, Fish A, Altman RB, Klein TE. PharmGKB summary: mycophenolic acid pathway. Pharmacogenet Genomics. 2014;24(1):73-9.
24. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology. 2000;47(2-3):85-118.
25. Karnell JL, Karnell FG, 3rd, Stephens GL, Rajan B, Morehouse C, Li Y, et al. Mycophenolic acid differentially impacts B cell function depending on the stage of differentiation. J Immunol. 2011;187(7):3603-12.
26. Calmet FH, Yarur AJ, Pukazhendhi G, Ahmad J, Bhamidimarri KR. Endoscopic and histological features of mycophenolate mofetil colitis in patients after solid organ transplantation. Ann Gastroenterol. 2015;28(3):366-73.
27. Maes BD, Dalle I, Geboes K, Oellerich M, Armstrong VW, Evenepoel P, et al. Erosive enterocolitis in mycophenolate mofetil-treated renal-transplant recipients with persistent afebrile diarrhea. Transplantation. 2003;75(5):665-72.
28. Davies NM, Grinyo J, Heading R, Maes B, Meier-Kriesche HU, Oellerich M. Gastrointestinal side effects of mycophenolic acid in renal transplant patients: a reappraisal. Nephrol Dial Transplant. 2007;22(9):2440-8.
29. Meier-Kriesche HU, Davies NM, Grinyo J, Heading R, Mamelok R, Wijngaard P, et al. Mycophenolate sodium does not reduce the incidence of GI adverse events compared with mycophenolate mofetil. Am J Transplant. 2005;5(5):1164; author reply 5-6.
30. Farooqi R, Kamal A, Burke C. Mycophenolate-induced Colitis: A Case Report with Focused Review of Literature. Cureus. 2020;12(1):e6774-e.
31. Goyal A, Salahuddin M, Govil Y. A Unique Case of Mycophenolate Induced Colitis after 10 Years of Use. Case Reports in Gastrointestinal Medicine. 2016;2016:3058407.
32. Moroncini G, Benfaremo D, Mandolesi A, Gabrielli A. Mycophenolate mofetil-induced colitis in a patient with systemic sclerosis. BMJ Case Reports. 2018;2018:bcr-2018-224829.
33. Parfitt JR, Jayakumar S, Driman DK. Mycophenolate mofetil-related gastrointestinal mucosal injury: variable injury patterns, including graft-versus-host disease-like changes. The American journal of surgical pathology. 2008;32(9):1367-72.
34. Papadimitriou JC, Cangro CB, Lustberg A, Khaled A, Nogueira J, Wiland A, et al. Histologic features of mycophenolate mofetil-related colitis: a graft-versus-host disease-like pattern. Int J Surg Pathol. 2003;11(4):295-302.
35. Lee S, de Boer WB, Subramaniam K, Kumarasinghe MP. Pointers and pitfalls of mycophenolate-associated colitis. Journal of clinical pathology. 2013;66(1):8-11.

36. Bouhbouh S, Rookmaaker MB. Rapid resolution of persistent mycophenolate mofetil-induced diarrhoea with a single dose of infliximab. Nephrol Dial Transplant. 2010;25(10):3437-8.