

# Mycophenolate Mofetil-related Pancolitis in a Kidney Transplant Recipient

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## Abstract

**Gastrointestinal adverse effects are common with mycophenolate mofetil administration, especially diarrhea. We report a case of mycophenolate mofetil-related colitis in a kidney transplant recipient.**

Colonoscopy revealed an ulcerative diffuse colitis. The colonoscopic biopsy specimen showed mild crypt distortion, accompanied by cryptitis and focal graft-versus-host disease like changes. The patient's symptoms improved after we discontinued the mycophenolate mofetil.

A repeat colonoscopy 2 months after we discontinued the mycophenolate mofetil showed reparative changes. Mycophenolate mofetil is an important drug in organ transplant immunosuppression regimens; however, with its widespread use, additional adverse effects continue to be recognized.

**Key words:** *Immunosuppression, Colitis, Diarrhea, Kidney transplant*

## Introduction

Mycophenolate mofetil (MMF) is a potent immunosuppressor that inhibits purine synthesis, which prevents human allograft rejection. The most important adverse effects include hematologic and intestinal disorders. Among them, diarrhea is the most common. The incidence of diarrhea in renal transplant patients maintained on MMF ranges from

12% to 40%.<sup>1-4</sup> Here, we present a case of MMF-related colitis in a kidney transplant recipient. The patient's symptoms dramatically improved after azathioprine was substituted for MMF.

## Case Report

A 36-year-old man who had developed end-stage renal disease of unknown cause underwent living-related kidney transplant. His donor was a 27-year-old woman with 0 HLA mismatches.

The posttransplant course was complicated by transplant renal artery stenosis 4 months after the kidney transplant treated by percutaneous transluminal angioplasty. After that, the serum creatinine concentration remained stable between 180 and 200  $\mu\text{mol/L}$  on an immunosuppressive regimen that consisted of prednisone and MMF.

Fifty months after the transplant, he presented with a 1-month history of watery diarrhea occurring 6 to 8 times per day. On admission, he showed symptoms of dehydration with metabolic acidosis. He reported weight loss of 10 kg, fatigue, and cramping pain. He did not report any loss of appetite, fever, chills, or other gastrointestinal symptoms including nausea, hematochezia, and melena.

Results of stool examinations were negative for *Salmonella*, *Shigella*, *Campylobacter*, *Clostridium difficile* toxin A, *Yersinia*, enterotoxigenic *E. coli*, and parasites. The results of a plasma polymerase chain reaction study for *cytomegalovirus* were negative. The (mycophenolic acid) MPA-area under curve (AUC) was between 30 and 50 mg/h/L. The results of a colonoscopy revealed an ulcerative diffuse colitis from the cecum to the rectum.

The results of the biopsy specimen showed a mild crypt architectural distortion (Figure 1). The lamina propria showed edema and an increased number of

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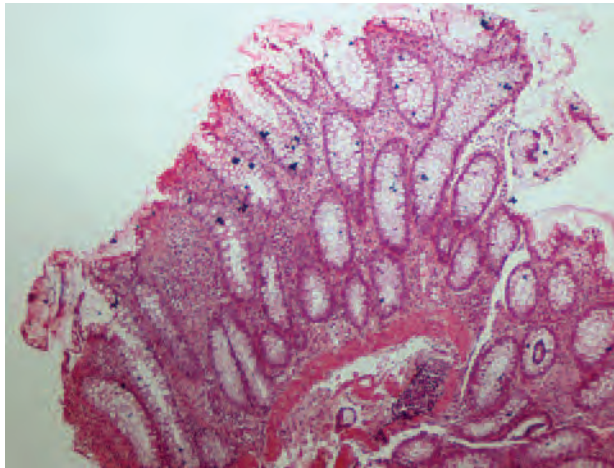
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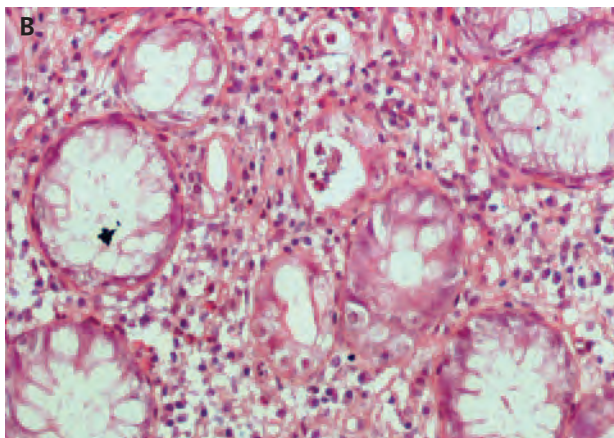
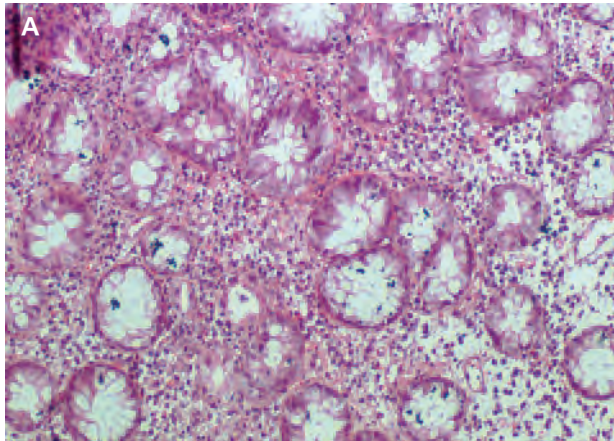
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inflammatory cells containing many neutrophils. Damaged crypts with mucus depletion and cryptitis can be seen in Figures 2A and 2B. Some areas showed surface erosions (Figure 3) and graft-versus-host disease (GVHD)-like changes characterized by an epithelial apoptosis (Figure 4). However, no granuloma or *cytomegalovirus* inclusions were found.

**Figure 1.** Biopsy Specimen Showing Colonic Mucosa With Mild Crypt Architectural Distortion



**Figure 2A.** Colonic Mucosa Revealing Lamina Propria Inflammation  
**2B.** Colonic Mucosa Showing Damaged Crypts With Cryptitis

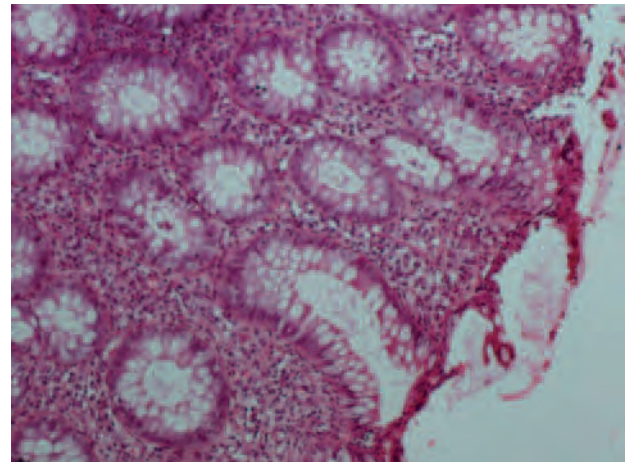


Symptoms regressed within 5 days after switching from MMF to azathioprine. The role of MMF in inducing colitis is discussed. A control colonoscopy showed reparative changes after 2 months. His symptoms improved and he maintained a stable creatinine concentration.

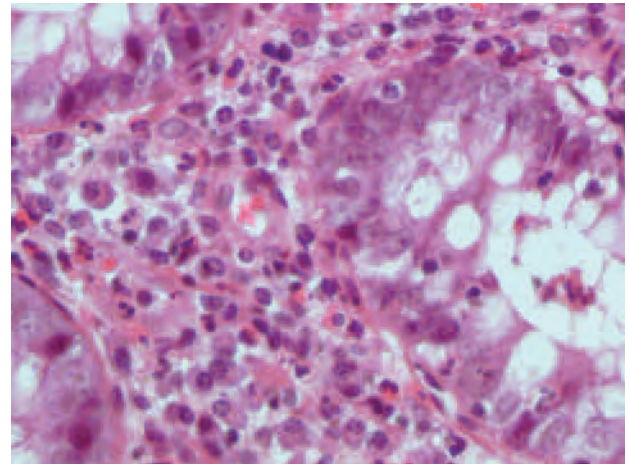
## Discussion

Diarrhea is a common complication after transplant, with an incidence being as high as 12%. Causes for the diarrhea can be identified in 80% of the cases, with infections being the most-common cause (41.5%) followed by immunosuppressive medications (34%).<sup>5</sup> Two-thirds of diarrhea episodes develop in the late posttransplant period (> 6 months after the transplant). Almost all immunosuppressive drugs may cause diarrhea. The incidence of diarrhea is higher with MMF compared with other immunosuppressive drugs.<sup>5, 6</sup> Our patient received only MMF in addition to prednisone.

**Figure 3.** Colonic Mucosa Showing Surface Erosion



**Figure 4.** GVHD-Like Pattern. The Crypts Show Epithelial Cells Apoptosis



Mycophenolate mofetil, a commonly used immunosuppressive drug for solid-organ transplants, has resulted in a dramatic decrease in graft rejection. Mycophenolate mofetil acts by inhibiting inosine monophosphate dehydrogenase, which results in selective inhibition of the de novo pathway for purine synthesis. Purine synthesis can occur via the de novo and/or the salvage pathway in most cells. However, lymphocytes are unique in that they almost exclusively use the de novo pathway. Therefore, administration of MMF results in selective inhibition of lymphocyte proliferation.<sup>1,7</sup>

One of the main adverse effects of MMF is gastrointestinal irritation, especially diarrhea, secondary to damage of enterocytes, which is dose related, occurring in 31% and 36.1% of patients receiving 2 and 3 g of MMF.<sup>8,9</sup>

Gastrointestinal adverse effects are due to specific and nonspecific effects of MMF on the gastrointestinal tract. One nonspecific effect is increased immunosuppression leading to increased susceptibility of the gastrointestinal mucosa to infection by microorganisms and viruses. Increased immunosuppression does not increase susceptibility to any single organism but results, more likely, in infection, with less pathogenic organisms, as well as increased symptoms in cases where infections may have remained subclinical.<sup>1</sup>

Mycophenolate mofetil also has specific effects on enterocytes. These cells are approximately 50% dependent on the de novo pathway for purine synthesis. Because enterocytes have a high turnover, inhibition of proliferation by MMF can have a dramatic effect on mucosal integrity. Interestingly, after administration, the highest concentrations of MMF have been found in the gastrointestinal tract, which may exacerbate the effect of MMF on these cells.<sup>1,7</sup>

The main function of MMF is inhibition of B and T lymphocytes. Mycophenolate mofetil is converted into its active form, MPA, within the liver. There is evidence that in lymphocytes, with increased exposure to MMF, there is induction of inosine monophosphate dehydrogenase expression, which may counteract the effects of MMF.<sup>1,7</sup>

The mechanism of epithelial damage in MMF-related diarrhea has not been determined. However, immune dysregulation caused by MMF could be involved through any of the mechanisms postulated for colonic damage in GVHD.<sup>10-12</sup> Although direct

MMF cytotoxicity cannot be ruled out, it is possible that the observed enterocyte injury may be indirectly mediated by the immunosuppressive effects of MMF. Also, MMF has been shown to lead to the death of activated T lymphocytes.<sup>11, 12</sup> This effect may be especially important in the gastrointestinal tract where continuous lymphocyte activation takes place owing to contact with various luminal antigens.<sup>13, 14</sup> In addition, reduced intestinal mucosal protection against invasive bacteria or toxic agents has been suggested as a mechanism of injury among animals treated with MMF.<sup>13, 14</sup> Finally, some histologic changes may be explained by microvascular injury.<sup>12</sup>

Graft-versus-host disease is most commonly associated with allogeneic hematopoietic stem cell transplant; it occurs less frequently in blood-transfusion and solid-organ transplant recipients, with incidences varying by organ. Graft-versus-host disease is reported more often in intestinal or liver transplant recipients.<sup>15</sup> Few cases of GVHD after a kidney transplant have been reported, and these were due to blood transfusions.<sup>16, 17</sup> Our patient had not received a transfusion.

The gastrointestinal adverse effects of MMF are common. Inadequate exposure to MPA owing to dose reductions, omissions, or noncompliance limit its clinical benefits, leading to an increased risk of rejection and graft loss.<sup>18-20</sup> The results of clinical trials significantly demonstrate a reduced risk of acute rejection episodes among patients receiving MMF, compared with those receiving placebo or azathioprine.<sup>18</sup> Among adult kidney transplant recipients, enteric-coated mycophenolate sodium (EC-MPS) has been shown to be therapeutically equivalent to MMF with a similar pharmacokinetics profile. Conversion from MMF to EC-MPS can be undertaken safely without compromising its effectiveness in de novo and maintenance renal transplant recipients.<sup>19</sup> Also, there is an increase in MPA serum levels. This might be explained because of better gastrointestinal absorption with EC-MPS. This therapy permits the use of lower doses of calcineurin inhibitors. Smaller calcineurin inhibitor dosages and better tolerability of EC-MPS could be the underlying causes of improvement in renal function.<sup>18, 20</sup> Our patient was converted from MMF to azathioprine because of the unavailability of EC-MPS in Tunisia.

Because of its complex pharmacokinetics, many factors can influence MPA exposure, including

kidney and liver functions, levels of serum albumin, alterations in absorption, and combination with other immunosuppressive agents; MPA monitoring is not yet accepted widely owing to the complexities of MPA pharmacokinetics, a lack of accurate measurement tools, and MPA AUC calculations.<sup>21, 22</sup>

The recent APOMYGRE<sup>23</sup> and FDCC<sup>24</sup> trials failed to produce unequivocal results of the benefit of therapeutic drug monitoring of MPA, although many previous studies have suggested its use in demonstrating that 12-hour area under the plasma concentration-time curve (AUC<sub>0-12</sub>), but not the trough level (C<sub>0</sub>), correlates with clinical outcomes and adverse effects.<sup>22, 25</sup> A correlation between acyl-MPA glucuronide and gastrointestinal adverse effects also has been reported.<sup>26</sup> Data from dose-finding trials for MMF and from a study in which patients were randomized to a low, intermediate, or high target MPA-AUC suggest that the risk of diarrhea is related to the MMF dosage.<sup>27-29</sup> In our patient, the target AUC range was intermediate in the therapeutic range.

## Conclusions

Mycophenolate mofetil colitis is defined by the clinical and pathological absence of any cause for the gastrointestinal symptoms, by resolution of diarrhea with no intervention other than substituting another agent for MMF, and by the presence of typical histopathologic changes. The observation that discontinuation of MMF resulted in improvement of our patients symptoms changes strongly the suggestion that MMF or one of its metabolites may be implicated in the development of colitis seen in our patient.

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