

Mycophenolate Mofetil-Related Colitis – A Case Report –

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Mycophenolate mofetil (MMF)-related colitis is one of the common causes of afebrile diarrhea in transplant patients. Pathologic diagnosis of MMF-related colitis is difficult because microscopic findings of MMF effects resemble those of graft-versus-host disease, inflammatory bowel disease and ischemic colitis. However, if diagnosed, MMF-induced colitis can be markedly improved by discontinuing the drug. A 70-year-old man having a history of transplantation presented with a one month history of afebrile diarrhea. Colonoscopy revealed patchy erosions. The colonoscopic biopsy specimen showed not only crypt disarray with degenerated crypts and scattered epithelial cell apoptosis, but also stromal inflammatory cell infiltration. A review of his medical records showed that he had been taking immunosuppressive drugs including MMF since his heart transplantation 6 years prior. The histologic findings of colonic mucosa were consistent with MMF-related colitis. After discontinuing MMF, the diarrhea quickly resolved and has not recurred for 10 months.

Key Words : Mycophenolate mofetil; Transplants; Diarrhea; Colitis

Mycophenolate mofetil (MMF) is an important and commonly used drug in the maintenance of immunosuppression for recipients of all types of organ transplantation. It is known that MMF can lead to toxic injuries including ulcerative esophagitis, reactive gastropathy, and graft-versus-host disease (GVHD)-like features in intestinal biopsies throughout the entire gastrointestinal tract. In addition, MMF-related colitis is one of the common causes of afebrile diarrhea in transplant patients who receive MMF.

It has been reported that the colonoscopic biopsy specimen frequently shows histologic features similar to those of GVHD or Crohn's disease in MMF-treated transplant patients with persistent afebrile diarrhea.¹⁻⁷ The morphologic changes in MMF-related colitis have been well described in the literature and a couple of cases have been published from the Korea in the clinical literature.^{8,9} However, it is important to be aware of the detailed pathologic findings for the Korean Pathology Society. Here, we present a case of MMF-related colitis in a patient who was a heart transplant recipient.

CASE REPORT

A 70-year-old Caucasian male presented at The Methodist Hospital (Houston, TX, USA) with a one month history of watery diarrhea occurring 4-5 times per day. At admission, he showed symptoms of dehydration with metabolic acidosis. He was also diagnosed as having acute aggravation of chronic renal failure. He did not report weight loss, loss of appetite, fever, chill or other gastrointestinal symptoms including nausea, vomiting, cramping pain, hematochezia and melena. The patient had an orthotopic heart transplant for non-ischemic cardiomyopathy 6 years prior. Other past medical history findings included hypertension, hypothyroidism, gout, and obstructive sleep apnea. A stool guaiac test was positive, but the stool was negative for *Clostridium difficile* toxin, fecal leukocytes, ova, and parasites. A colonoscopy was performed and showed patchy mucosal granularity throughout the entire colon, diagnosed as "non-specific erosive colitis" (Fig. 1).

The colonoscopic biopsy specimen showed diffuse crypt distor-

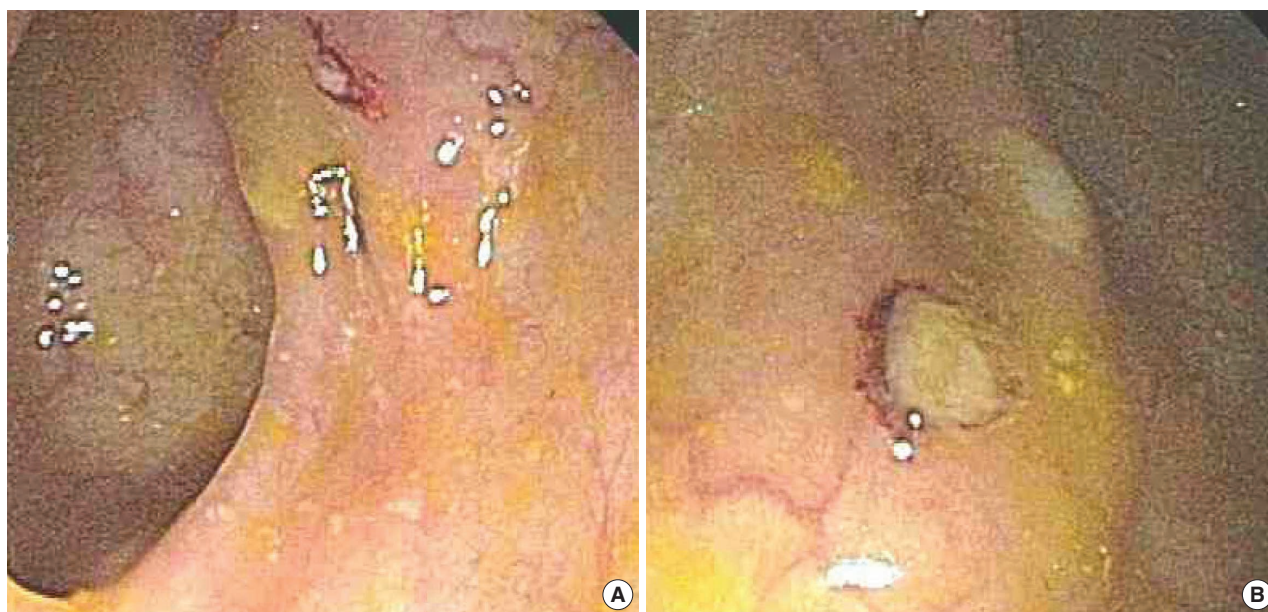


Fig. 1. Colonoscopic findings reveal multiple small erosive patches through the entire colon.

tion and crypt loss on low magnification, suggesting inflammatory bowel disease (IBD) (Fig. 2). However, definitive histologic evidence of typical IBD such as granuloma, active cryptitis or crypt abscess was lacking. The stroma revealed diffuse edema and moderate lymphoplasmacytic infiltration. Occasional neutrophilic and eosinophilic infiltration was also identified. Interestingly, a few scattered small crypts with more eosinophilic cytoplasm, larger nuclei and more prominent nucleoli were identified. They showed less frequent mitoses than adjacent unaffected crypts. One of them was accompanied by a few neutrophilic infiltrations, suggesting mild cryptitis. There were some large cells with prominent nucleoli simulating cytomegalovirus (CMV) infection. However, no unequivocal viral inclusions were identified and CMV immunohistochemical staining was negative. In addition, a few apoptotic crypt epithelial cells were noted with an incidence of up to 3/100 crypt cells on high magnification. The possibility of GVHD was considered, but was considered non-diagnostic. Overall microscopic findings were not definitive for any specific condition such as IBD, CMV infection or GVHD.

On review of the medical records, we learned that the patient had received immunosuppressive therapy since his heart transplantation 6 years prior and that the regimen included MMF (1,500 mg twice daily), prednisone (5 mg once daily) and sirolimus (1 mg once daily). He had made no changes to that regimen recently. The microscopic findings in conjunction with the clinical history of MMF therapy were consistent with a diag-

nosis of MMF-related colitis. MMF was discontinued and replaced by azathioprine, after which the diarrhea quickly resolved. The patient did well without recurrent diarrhea or rejection for 10 months.

To verify the biological behavior of epithelial changes seen in our biopsy, additional immunohistochemical staining for E-cadherin, beta-catenin and Ki-67 were done using an autostainer (Ventana Medical Systems, Inc., Tucson, AZ, USA). The primary antibodies used in this study were E-cadherin (1 : 500, Zymed, San Francisco, CA, USA), beta-catenin (1 : 200, Zymed) and Ki-67 (1 : 100, Invitrogen, Carlsbad, CA, USA). The atrophic crypts showed weak and incomplete membranous staining for E-cadherin and beta-catenin (Fig. 3) that was lower than adjacent unaffected crypts. The Ki-67 labeling index was lower in the affected crypts than that of the unaffected crypts.

DISCUSSION

The main function of MMF is inhibition of B and T lymphocytes. MMF is converted into its active form, mycophenolic acid (MPA), within the liver.¹⁰ MPA is a potent inhibitor of inosine monophosphate dehydrogenase, a key enzyme in the *de novo* pathway of purine synthesis.¹⁰ Because lymphocytes are 90% dependent on this pathway of purine synthesis, lymphocyte proliferation is selectively inhibited by MPA, which makes MMF an effective immunosuppressant.¹⁰ However, enterocytes are also 50%

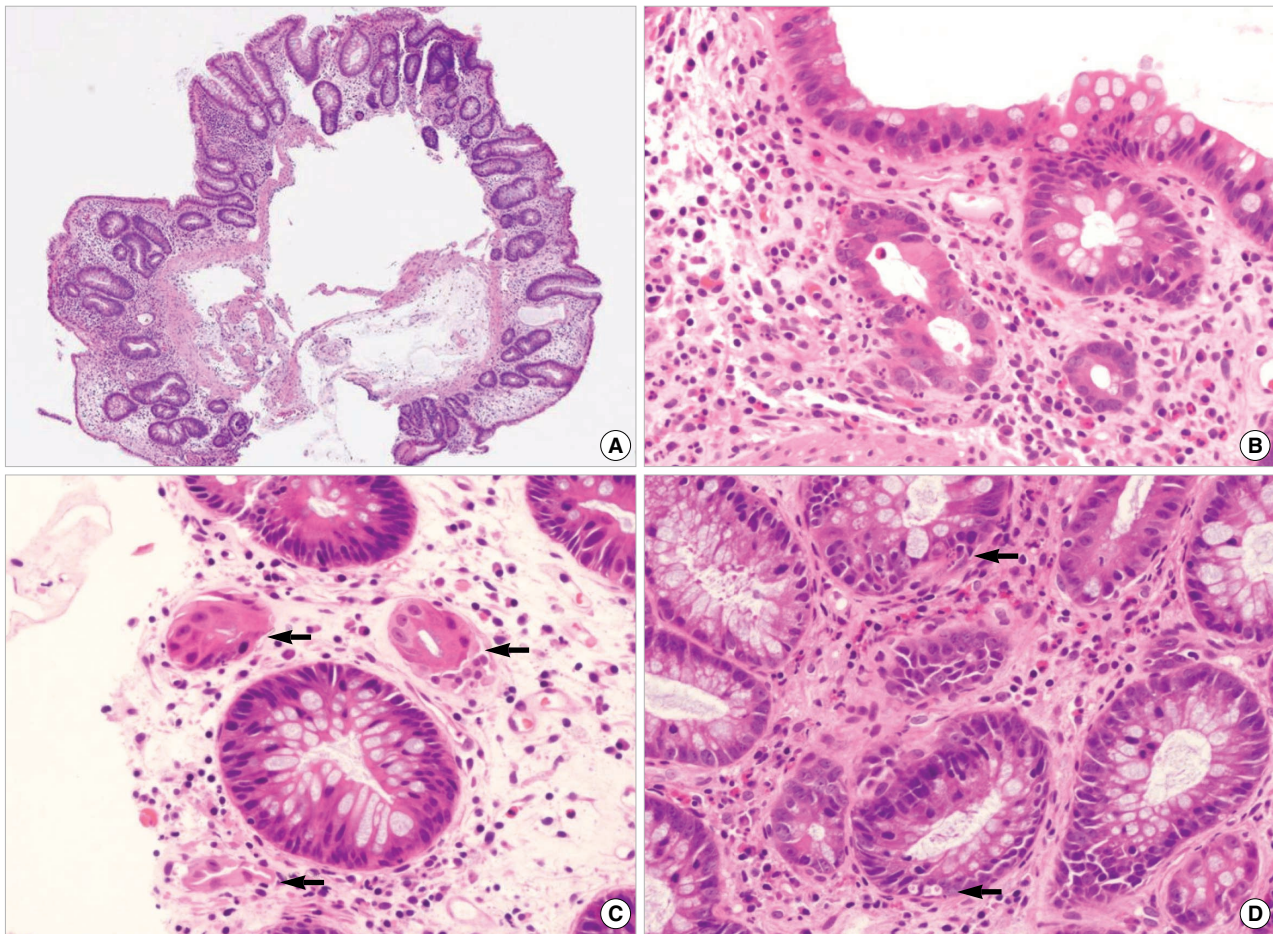


Fig. 2. Histologic findings of a colonoscopic biopsy specimen show crypt disarray and inflammatory cell inflammation in lamina propria (A). Many lymphocytes, plasma cells eosinophils and neutrophils infiltrate the lamina propria. A crypt lined by cuboidal cells with large round nuclei and prominent nucleoli is present with a few neutrophils, simulating a cytomegalovirus infection (B). Several damaged crypts (arrows) are admixed with less involved ones. One of them reveals epithelial flattening, but dilatation and intraluminal debris are not present (C). A single epithelial cell in apoptosis (arrows) is observed (D).

dependent on the *de novo* pathway of purine synthesis, which accounts for their selective vulnerability to MMF's antimetabolic effects within the gastrointestinal tract.¹⁰

One of the main side 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, respectively.^{1,11} The upper gastrointestinal (GI) tract may also be effected by MMF, with a clinical feature similar to that of nonsteroidal anti-inflammatory drugs, presenting with ulcerative esophagitis, reactive gastropathy type changes, and duodenal ulcers.³

Parfitt *et al.*³ reported histologic characteristics of MMF-related colitis, which included crypt architectural disarray, lamina propria edema, increased lamina propria inflammation, dilated damaged crypts, increased crypt epithelial apoptosis and GVHD-like changes.³ Our case showed most of the features that were men-

tioned by Parfitt *et al.*³ except for "dilated damaged crypt". Instead of dilated damaged crypt, scattered small crypts with abundant eosinophilic cytoplasm were prominent in our case, which we considered to be part of a spectrum of damaged and atrophic crypts along with "dilated damaged crypt". The expression of E-cadherin and beta-catenin, both of which are important factors in maintaining normal epithelial architecture in inflammatory conditions, seemed to be weaker and more incomplete in the atrophic crypts in our case (Fig. 3), and the Ki-67 labeling index was lower than adjacent uninvolved crypts.¹ These immunohistochemical findings suggested that morphologic changes in crypts were associated with MMF's antimetabolic effect. However, the biological importance of these immunohistochemical findings remains unclear.

MMF-related colitis has been known to show Crohn's disease-like or GVHD-like histologic changes.¹⁻⁷ The crypts show archi-

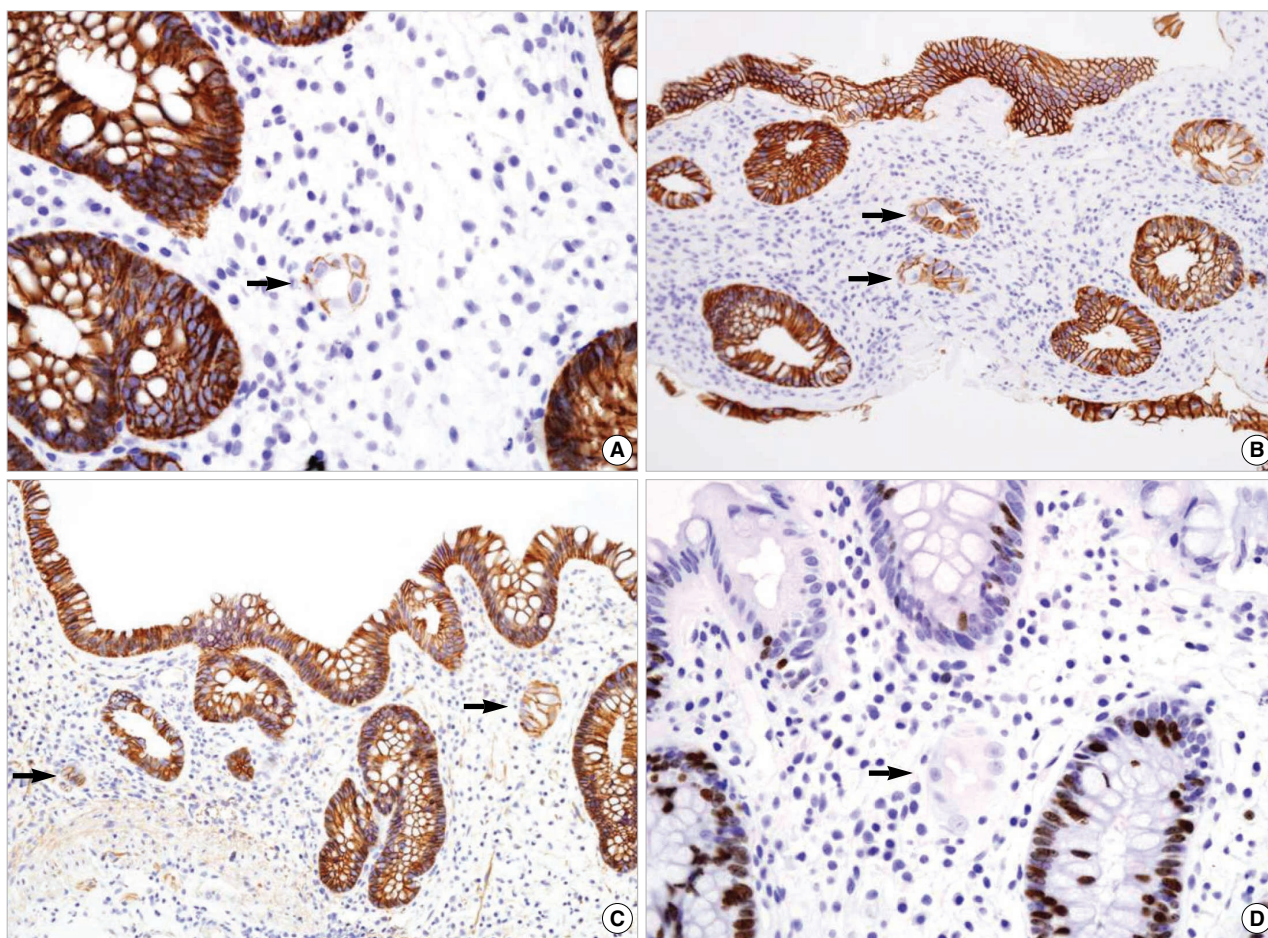


Fig. 3. Immunohistochemical staining for E-cadherin (A, B), beta-catenin (C) and Ki-67 (D) of a colonoscopic biopsy specimen. The atrophic crypts show weaker and more incomplete membranous staining of E-cadherin and beta-catenin (A-C) and a lower Ki-67 labeling index (D) than adjacent uninvolved crypts.

tectural disarray including crypt distortion, crypt angularity, bifid crypts and variation in crypt diameter, and the lamina propria is edematous with inflammatory cell infiltration.^{1-3,7} However, the crypt architectural disarray due to MMF has been reported to be milder than in typical cases of IBD.³ Patchy foci of neutrophils in the lamina propria may also be seen in some MMF cases.³ Aside from the above features, the increase in crypt epithelial cell apoptosis is also found in MMF-related colitis, which may better explain the GVHD-like features than the IBD.³ Our case showed crypt disarray with a few foci of damaged atrophic crypts and crypt epithelial cell apoptosis, and edema and inflammatory cell infiltration in the lamina propria. Although those findings were typical for neither IBD nor GVHD, it was difficult to suggest MMF-related colitis at initial evaluation without a history of MMF taking.

MMF-related colitis also should be differentiated from other causes of persistent afebrile diarrhea in transplant patients includ-

ing *Campylobacter*, CMV and bacterial overgrowth. In this biopsy, a few large nuclei with prominent nucleoli were seen in the involved crypts, causing us to suspect CMV infection, but immunohistochemical staining for CMV was negative.

Our patient had made no changes in his drug regimen, nor any other lifestyle change that provoked the onset of diarrhea. We proposed the idea that the patient's progressive renal failure may have increased the concentration of MMF to a level that produced colonic toxicity.

In conclusion, MMF-related colitis can be misdiagnosed as IBD or GVHD, if MMF treatment is not provided by the clinician to the pathologists. However, if the biopsy is correctly diagnosed at the time of evaluation, diarrhea can be easily cured by reduction or cessation of MMF treatment. Therefore, clinicians should inform the pathologist of the clinical history of MMF therapy. Likewise, the pathologist should be familiar with the effects of MMF on the GI tract, and should inquire about any

history of MMF therapy if the microscopic findings are suggestive of that diagnosis.

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