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Orthotopic Heart Transplant Recipient with Enteric-coated Mycophenolate Sodium (Myfortic) Induced Colitis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 66-year-old
Final Diagnosis: Drug-induced colitis
Symptoms: Abdominal discomfort • anorexia • diarrhea • weight loss
Medication: Enteric-coated mycophenolate sodium (Myfortic)
Clinical Procedure: Colonoscopy • colon biopsy
Specialty: Cardiology • Infectious Disease

Objective: Rare disease

Background: Mycophenolic acid is an immunosuppressive drug commonly used in solid organ transplantation to prevent acute and chronic allograft rejection. There are 2 common preparations of mycophenolic acid including mycophenolate mofetil (Cellcept), and enteric-coated mycophenolate sodium (Myfortic) which was developed to reduce the high rate of gastrointestinal side effects seen with Cellcept. Cases of mycophenolate mofetil induced colitis have been described in solid organ transplant patients and rarely in heart transplant patients, but enteric-coated mycophenolate sodium induced colitis is very rare and has not been reported in heart transplant patients.

Case Report: A 66-year old male with an orthotopic heart transplant was admitted with diarrhea. The patient was on an immunosuppression regimen including mycophenolate mofetil for 10 weeks post-transplantation until complaining of soft stools and bloating. At this time, he was switched to enteric-coated mycophenolate sodium. At week 11 post-transplantation, the patient was admitted to the hospital with worsening diarrhea. Extensive workup was unrevealing. Colonoscopy with biopsy showed features of mycophenolic acid induced colitis. Enteric coated mycophenolate sodium was discontinued, and the patient's diarrhea markedly improved over the next 48 hours. The patient had no signs of colitis or solid organ rejection at 7-month follow up appointment.

Conclusions: Although a diagnosis of exclusion, enteric-coated mycophenolate sodium induced colitis should be considered in the differential of an orthotopic heart transplant patient with diarrhea as discontinuing the medication can improve symptoms and avoid costly workups, however, patients should be monitored closely for signs of rebound rejection.

MeSH Keywords: Colitis • Heart Transplantation • Mycophenolic Acid

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Background

Mycophenolic acid is an immunosuppressive drug commonly used in solid organ transplantations to prevent acute and chronic allograft rejection. It inhibits inosine monophosphate dehydrogenase, a key enzyme in the *de novo* purine biosynthesis pathway, thus inhibiting DNA synthesis and cell division [1]. There are 2 common preparations of mycophenolic acid including mycophenolate mofetil (Cellcept), which is directly absorbed in the stomach with a high bioavailability, and mycophenolate sodium (Myfortic), an enteric coated formulation absorbed in the intestine which was developed to reduce the high rate of gastrointestinal side effects seen with Cellcept [2]. The efficacy of preventing rejection has been shown to be similar between the 2 formulations in kidney and liver transplant patients [3–5]. Cases of mycophenolate mofetil induced colitis have been described in solid organ transplant patients, and rarely in heart transplant patients [6–7]. However, to the authors knowledge after a review of English literature, there has not been a case reported of enteric-coated mycophenolate sodium induced colitis in an orthotopic heart transplant patient.

Case Report

A 66-year-old male with a history of ischemic heart disease refractory to intervention and reduced ejection fraction underwent an orthotopic heart transplantation with immunosuppression induction including pre-operative tacrolimus and mycophenolate mofetil, intra-operative basiliximab and methylprednisolone, and post-operative basiliximab and methylprednisolone with an oral prednisone taper.

Immunosuppression was maintained with a regimen including mycophenolate mofetil 1500 mg 2 times daily, tacrolimus 0.5 mg 2 times daily with dose adjusted for target serum level of 10–15 ng/mL, and prednisone 10 mg every morning and 5 mg every night. Additionally, the patient was on an antimicrobial prophylaxis regimen including fluconazole, valganciclovir, and sulfamethoxazole-trimethoprim.

The patient did well until post-transplantation week 10 when he was seen in clinic with 5.3 kg weight loss (8% body mass) over the preceding month accompanied by bloating, anorexia, and 3 loose non-bloody bowel movements per day. At this time, he was taking magnesium oxide, senna glycoside (Senokot), mycophenolate mofetil, and pantoprazole, which can all cause diarrhea. Physical examination was non-contributory with soft, non-tender, nondistended abdomen. With mycophenolate mofetil as a potential cause of diarrhea the patient was switched to enteric-coated mycophenolate sodium 1080 mg 2 times daily. Additionally, senna glycoside was discontinued, and magnesium oxide was switched to magnesium chloride.

The patient continued to have watery diarrhea, weight loss, and dehydration requiring hospital admission on post-transplantation week 11. At this time, the differential included infectious colitis (e.g., cytomegalovirus, bacterial pathogens, and adenovirus), medication induced colitis (e.g., mycophenolic acid, proton pump inhibitors), and less likely, ischemic colitis. In the hospital, extensive infectious disease workup was positive only for parainfluenza virus from nasopharyngeal swab and negative for all else including blood culture, blood serology, *Helicobacter Pylori* antigen, gastrointestinal polymerase chain reaction (PCR) panel, stool culture, viral PCR, toxoplasma IgG antibody, *Clostridium difficile* antigen/toxin, and cytomegalovirus PCR. The patient had an endomyocardial biopsy on post-transplantation week 11 which was negative for acute cellular rejection (ISHLT 2004 grade 0) and negative for pathologic and chronic antibody-mediated rejection (ISHLT 2013 grade pAMR0). His serum trough mycophenolic acid level was 2.4 mcg/mL. A computed tomography (CT) scan of the abdomen and pelvis was unrevealing.

The patient was sent for colonoscopy which showed mildly congested mucosa through the entire colon in a patchy distribution predominantly at the colonic folds (Figure 1) and an area of significantly congested mucosa at the appendiceal orifice and cecum (Figure 2). Colonic biopsies revealed features (Figure 3) that have been associated with mycophenolate mofetil related colitis, including crypt abscess formation involving dilated crypts with flattened and attenuated epithelium and apoptotic bodies [6,8,9]. Additionally, PCR for cytomegalovirus in the colon biopsy was negative.

Enteric-coated mycophenolate sodium was discontinued, and the patient's gastrointestinal symptoms resolved over the next 48 hours. His immunosuppressant regimen after the colitis episode included tacrolimus 0.5 mg 2 times daily with dose adjusted for target serum level of 10–15 ng/mL, and prednisone 10 mg every morning and 5 mg every night. With endomyocardial biopsies showing no signs of rejection, the patient was tapered off prednisone and placed on a calcineurin-inhibitor sparing regimen of tacrolimus plus sirolimus, both at 0.5 mg twice daily. Up to post-transplantation week 40, the patient had no further symptoms of colitis and no signs of rejection based on endomyocardial biopsy despite the modified immunosuppression regimen. Because the lack of colitis symptoms he did not undergo an additional colonoscopy.

Discussion

Lymphocytes rely almost exclusively on *de novo* synthesis of purine and therefore mycophenolic acid adequately suppresses T and B lymphocytes responsible for cytotoxic and antibody mediated graft rejection [10]. Notably, enterocytes

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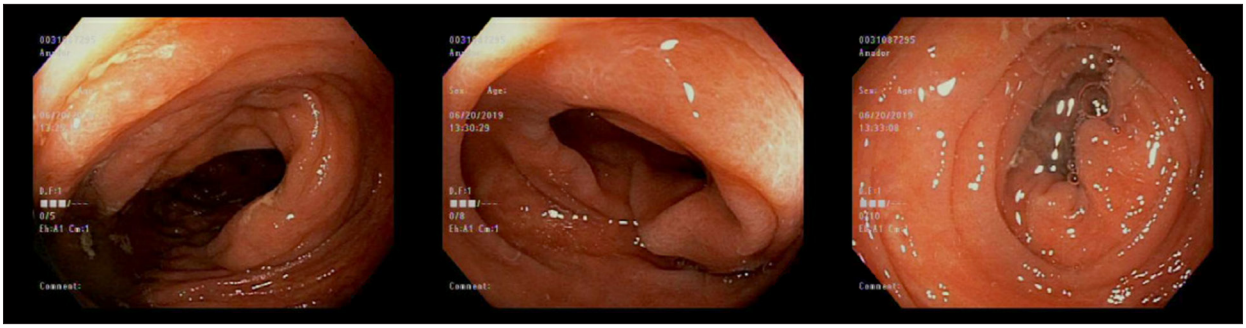

Figure 1. Colonoscopy showing ascending colon, transverse colon, and descending colon (from left to right) with mildly congested mucosa through the entire colon in a patchy distribution predominantly at the colonic folds.

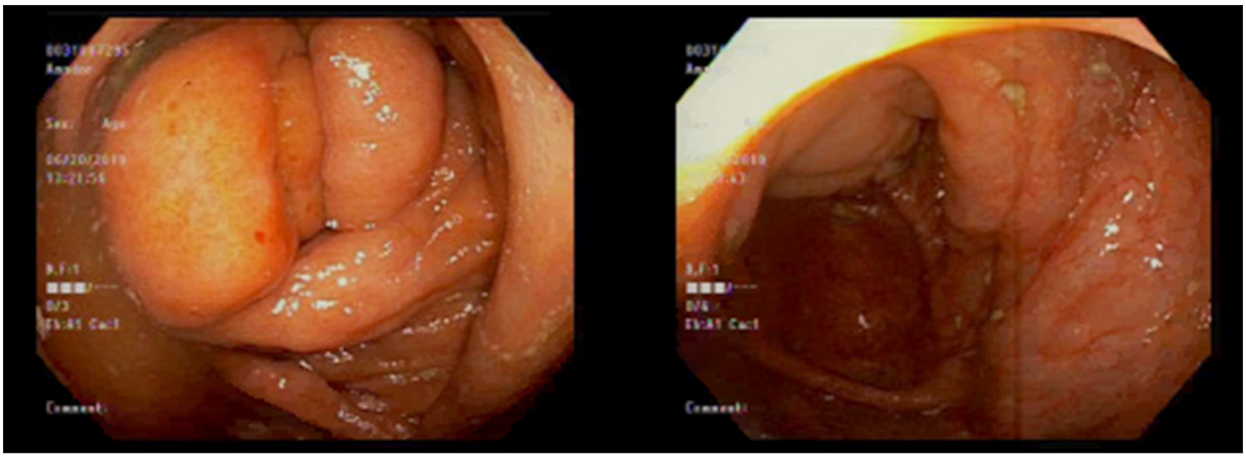

Figure 2. Colonoscopy showing appendiceal orifice with significantly congested mucosa (**left**) and cecum with edematous mucosa (**right**).

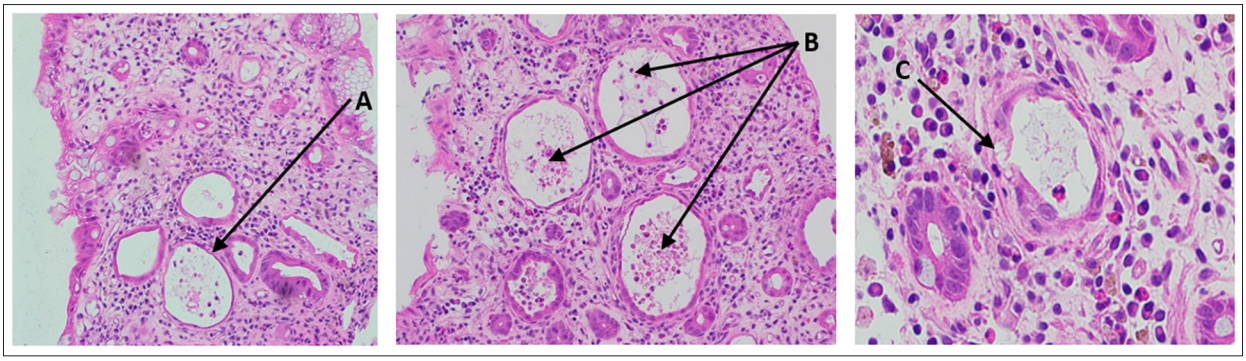

Figure 3. Colonic biopsies with cryptitis and crypt abscess formation B) involving dilated crypts with flattened and attenuated epithelium A) and apoptotic bodies C).

are only approximately 50% dependent on the *de novo* pathway and can utilize the purine salvage pathway as well [11]. However, under certain conditions, such as anorexia where dietary intake of purines is reduced, enterocytes become more reliant on the *de novo* synthesis pathway and the presence of mycophenolic acid can halt cell divisions of enterocytes resulting in epithelial injury and gastrointestinal symptoms including diarrhea [12].

Colitis induced by mycophenolate mofetil and enteric-coated mycophenolate sodium are very rare and remain a diagnosis of exclusion [1,3,10]. Two case reports of mycophenolate mofetil induced colitis after heart transplantation have been reported in the English literature. One report discusses a case arising 13 years after the initiation of mycophenolate mofetil therapy suggesting that the diagnosis should be considered in the evaluation of late onset post-transplantation diarrhea [7]. Another case discusses the importance of considering mycophenolate

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mofetil induced colitis in heart transplant patients and the difficulty of the diagnosis given that the disease can mimic other more common causes of the symptoms such as infectious colitis, irritable bowel disease (IBD), ischemic colitis and rarely graft versus host disease (GVHD) [13].

Cases of rebound rejection after discontinuation of mycophenolic mofetil have been reported [10] and thus for mild and moderate cases of diarrhea, continuation of mycophenolic mofetil with a dose reduction or switching to enteric-coated mycophenolate sodium can be considered. At onset of gastrointestinal symptoms, our patient was switched from mycophenolate mofetil to enteric-coated mycophenolate sodium with hope of symptom resolution, however, his diarrhea persisted for 18 more days. The colonic biopsy showed features typical of mycophenolate induced colitis including cryptitis, crypt abscess formation involving dilated crypts with flattened and attenuated epithelium, and apoptotic bodies [3,8,10]. With the infectious workup negative and no signs of ischemic colitis, the most likely diagnosis was drug induced colitis. Enteric-coated mycophenolate sodium was discontinued, and the diarrhea symptoms resolved over the next few days. At 40 weeks post-transplantation, our patient has not had another episode of colitis and has showed no signs of rejection on follow-up endomyocardial biopsies.

Conclusions

Though a diagnosis of exclusion, enteric-coated mycophenolate sodium induced colitis should be considered in the differential of an orthotopic heart transplant patient with diarrhea as discontinuing the medication can improve symptoms and avoid costly workups, however, patients should be monitored closely for signs of rebound rejection.

Conflicts of interest

None.

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