

A Resistant case of mycophenolate mofetil-induced diarrhoea

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Background: Mycophenolate mofetil is one of the standard drugs used in the prevention of rejection in solid organ transplantation. While it is usually well tolerated, it is well known that it can cause an entero-colitis, which usually responds to dose reduction or withdrawal. In a few cases the colitis persists requiring further investigation and treatment.

Case Presentation: We report a case of mycophenolate-induced colitis that persisted on withdrawal of drug and required treatment with high-dose steroids.

Conclusion: There are no established guidelines to aid physicians in the management of these resistant cases, so case reporting will help guide the management of these difficult cases.

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Mycophenolate mofetil (MMF) is one of the cornerstone drugs used in preventing rejection of solid organ transplantation, however, it may rarely be associated with entero-colitis. While often responsive to dose reduction or drug withdrawal, rare cases of persistent colitis require further investigation. We report a case of MMF-induced diarrhoea resistant to initial measures, requiring high-dose steroids for symptom remission. By elucidating the clinical course and eventual outcome in this resistant case, we aim to contribute to the understanding and optimization of care for patients experiencing gastrointestinal complications attributed to MMF therapy and add to limited literature pertaining to this rare adverse drug event.

CASE PRESENTATION

A 57-year-old gentleman underwent a deceased-donor renal transplant. His past medical history was significant for polyarteritis nodosa with renal involvement progressing to end-stage renal disease, requiring continuous ambulatory peritoneal dialysis for 3 years. Post-transplantation, he received a standard immunosuppression regimen with 1000g MMF twice a day, 0.2mg/kg tacrolimus in divided doses and 20mg prednisolone.

Ten days after initiating MMF, he experienced up to fifteen bouts of loose stools daily, accompanied by urgency and abdominal pain without bleeding or mucous per rectum. Physical examination revealed a soft abdomen with minimal, generalised tenderness and a palpable transplanted kidney in the right iliac fossa. Initial laboratory investigations showed a mildly elevated C-reactive protein at 23.4 mg/L (normal range 0-5 mg/L), a normal white cell count ($7.78 \times 10^9/L$) and normal renal function. Stool testing for cytomegalovirus (CMV) using polymerase chain reaction (PCR), bacterial enteric pathogens, parasite and ova were negative.

Despite adjustments to the MMF dosing regimen and subsequent halving of the total daily dose, symptoms persisted, prompting a switch from MMF to everolimus. While there was some improvement, loose stools persisted up to eight times daily, negatively affecting the patient's quality of life. A colonoscopy performed two weeks after cessation of MMF showed pancolitis (**Figure 1**) with histological features suggestive of infective colitis or drug-induced colitis with immunosuppressive drug therapy (**Figure 2** and **Figure 3**). Microscopy showed well-preserved crypt

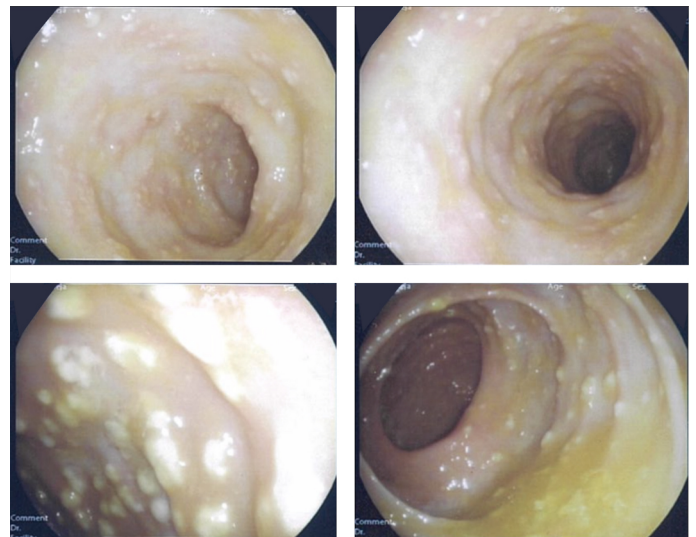


Figure 1 Endoscopy images two weeks after the onset of diarrhoea showing pancolonic oedema, erythema and inflammation with multiple small superficial ulcers with fibrin exudates

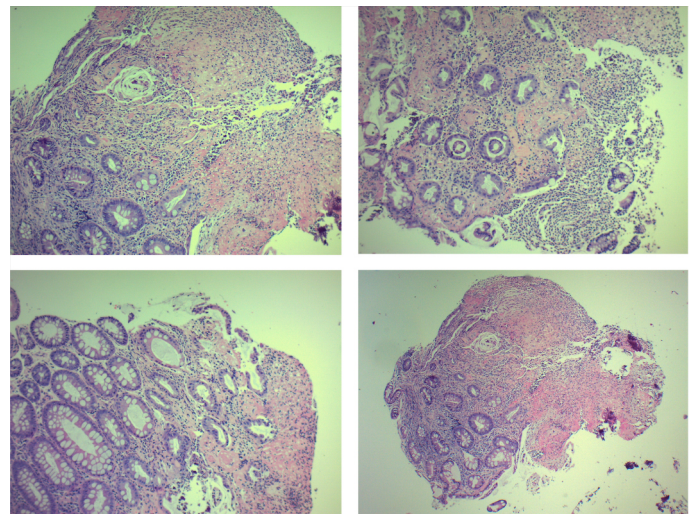


Figure 2 Right colonic biopsies showing acute ulceration, ischaemic changes and fibrin deposition within the stroma

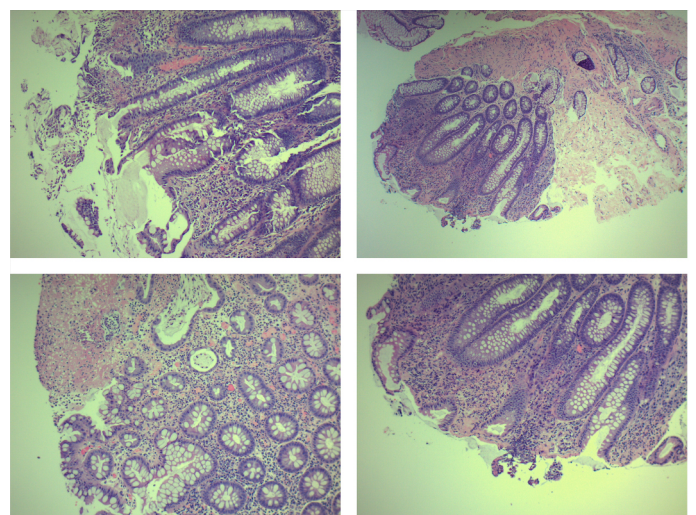


Figure 3 Left colonic biopsies showing similar features to those seen on the right

architecture with foci of acute surface ulceration and an inflammatory infiltrate in the underlying stroma. Faecal calprotectin levels were also markedly elevated at over 2000µg/g (normal range <200µg/g). Prednisolone was thus increased to 40mg daily.

Despite treatment with high-dose steroids, symptoms persisted, leading to consideration of infliximab. A repeat endoscopy performed after two weeks of high-dose steroids, showed similar histological features of severe inflammation as the previous endoscopy. It also confirmed the absence of CMV infection by a lack of viral inclusion bodies and a negative immunostain. The exclusion of infective causes and primary inflammatory gastrointestinal disorders strengthened the working diagnosis of drug-induced colitis. Symptoms improved gradually during treatment with high-dose steroids, with complete resolution at six weeks post-cessation of MMF. Clinical improvement was also reflected by biochemical normalization of inflammatory markers and faecal calprotectin levels. Steroids were gradually decreased to maintenance levels and the patient remained symptom-free on maintenance immunosuppression as per local protocols for post-transplantation patients. Infliximab infusions were withheld in view of maintained clinical response to steroid-only therapy.

DISCUSSION

Mycophenolate is an immunosuppressive medication that has been used to prevent acute allograft rejection since the 1990s. Mycophenolic acid (MPA) is available as two formulations, mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS). MMF is a prodrug that enhances MPA's bioavailability, while EC-MPS aims to reduce gastrointestinal adverse effects, primarily diarrhoea, by delaying MPA release into the small intestine instead of the stomach.^{1,2} Consequently, switching from MMF to EC-MPS is typically the first-line approach when GI tolerability becomes an issue with MMF. Unfortunately, at the time of this case, EC-MPS was not available locally, and obtaining it would have taken months, making this strategy unfeasible for our patient.

Mode of action of MMF

MPA is a potent inhibitor of lymphocyte proliferation. It inhibits inosine monophosphate dehydrogenase (IMPDH) which is the rate-limiting enzyme in de novo synthesis of guanosine nucleotides in lymphocytes.³ Other fast-replicating cells in the body, like the gastrointestinal (GI) epithelial cells, partially rely on IMPDH to proliferate. While the exact pathogenic means by which MPA causes diarrhoea is unclear, it is hypothesized that MPA affects GI epithelial cells in a similar way to lymphocytes, inhibiting their proliferation, disrupting fluid absorption, leading to diarrhoea.

MMF-related colitis

In a cohort of post-transplant patients treated with a tacrolimus and MPA-based immunosuppression, diarrhoea was reported in up to 45% of patients.⁴ Post-transplant diarrhoea is a challenging symptom to treat. Possible causes include viral infections such as CMV, iatrogenic injury secondary to MMF, post-transplant inflammatory bowel disease (IBD) or ischaemic colitis. Due to the clinical overlap between the above syndromes, it is suggested that a biopsy is obtained to differentiate between the aetiologies.⁵

A wide spectrum of histological changes may be seen in MMF-associated colitis, however, important microscopic clues that point towards MMF-related colitis, include a mixed pattern of injury (typically a combination of crypt apoptosis, isolated crypt damage and architectural distortion) and possible proximal accentuation of pathologic changes. The need for clinical correlation and follow-up is emphasized by the occurrence of dual pathology in patients treated with MMF.⁶ The diagnostic hallmark of MMF-related colitis is an IBD-like histological pattern in association with increased epithelial apoptosis, while apoptotic cell death seems to be a potential pathogenetic factor of mucosal injury.⁷

There are no well-established protocols currently available on how to treat MMF-induced colitis, likely due to the overlapping and highly variable nature of the clinical syndrome. Therefore, case reports are the main body of knowledge to guide clinicians.

Case reports of previous MMF-induced colitis show that symptoms improve after decreasing the dose of

MMF or discontinuation. In a recent literature review, 12 out of 13 cases responded to such measures.⁸ The remaining case was a highly resistant colitis where an infusion of infliximab was necessary to reduce the stool frequency. A systematic review found that 98% of the cases of mycophenolate-induced colitis resolve within 20 days of discontinuation of the MMF.⁹ This contrasts to the reported case where symptoms resolved after 48 days of discontinuing MMF.

CONCLUSION

While MMF-induced colitis typically responds to simple measures like dose reduction or drug withdrawal, resistant cases can occur with an increase in the duration and severity of symptoms. In refractory cases, alternative therapeutic interventions are considered such as immunomodulatory or biologic agents. While MMF-induced colitis is the most likely cause of gastrointestinal symptoms in renal transplant patients receiving MMF, dual pathology may also occur, therefore alternative diagnoses must be thoroughly investigated. As there are no established guidelines in the management of these resistant cases, there is a need to highlight these difficult cases to aid in management and investigation, and to treat in a timely manner as symptoms can become debilitating.

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