



## The Elusive Colonic Ulcer in Mycophenolate Mofetil Colitis – Is It Inflammatory or Neoplastic?

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### Authors' contributions

*This work was carried out in collaboration among all authors. Author KHC wrote the first draft of the manuscript and performed literature review. Author AR provided the histopathological input and photos. Author RS designed and conceptualize the study. All authors read and approved the final manuscript.*

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Case Study

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### ABSTRACT

**Introduction and Aims:** Gastrointestinal toxicity resulting in diarrhea is a common side effect in patients taking Mycophenolate mofetil (MMF). The challenge is in making the decision to pursue further workup being mindful of malignancy and opportunistic infection in these group of immunosuppressed individuals, or to stop the offending agent and observe. Colonoscopy with biopsies remains the gold-standard diagnostic tool to establish the underlying etiology, but lesions found are often non-specific especially when there is ongoing active inflammation. We report a case of an inflammatory colonic ulcer that turned out to be neoplastic which healed with time making it difficult to locate on subsequent colonoscopies.

**Case Presentation:** A 77-year-old man with a background history of heart transplant was referred for endoscopic resection to a solitary high-grade dysplastic tubular adenomatous lesion in the hepatic flexure. This was detected incidentally while he was being investigated for persistent diarrhea. A solitary ulcer on a background of colitis was visualized on index colonoscopy. The colitis was attributed to MMF. The MMF was stopped and his symptoms improved. A repeated colonoscopy performed 6 weeks later revealed no obvious abnormalities. Upon discussion with the

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patient, he was referred on to an expert endoscopy center for reassessment. In this instance, a 9 mm subtle, flat and mildly erythematous lesion was detected. We were able to define and characterize the lesion better using Narrow Band Imaging. An Endoscopic Submucosal Dissection was then carried out and the lesion resected in an en-bloc fashion. Histopathological evaluation revealed this to be an intramucosal adenocarcinoma.

**Conclusion:** In immunosuppressed patients, given the atypical and often subtle presentation of colon cancers, it is important to be extra vigilant and biopsy all suspicious lesions, particularly solitary ulcers. It is worthwhile to tattoo an area distally to aid in identification if the area needs to be reevaluated or resected at a later date.

*Keywords: Colorectal cancer; endoscopic resection; mycophenolate mofetil; narrow-band imaging.*

## 1. INTRODUCTION

Gastrointestinal toxicity resulting in diarrhea is common in patients taking Mycophenolate mofetil (MMF). The general approach to this adverse event is to taper the dose or switch to its enteric-coated counterpart, negating the need for further investigation when a good response is achieved [1]. However, in the subset of patients suspected of having MMF-induced colitis, clinicians have to contend with a myriad of endoscopic and histologic findings that often overlap with other colonic disorders such as graft-versus-host-disease, inflammatory bowel disease and ischemic colitis [2,3].

## 2. CASE PRESENTATION

A 77-year-old heart transplant patient with chronic renal failure was referred for endoscopic resection of a dysplastic lesion at the hepatic flexure. He had been diagnosed with MMF-induced colitis and at initial colonoscopy, a solitary ulcer at the hepatic flexure was detected amidst a field of active, ongoing inflammation. Biopsies of the ulcer revealed a tubular adenoma with high-grade dysplastic lesion.

The patient was subsequently switched from MMF to Myfortic and became asymptomatic. A repeated colonoscopy was performed six weeks after the switch in medication but by now the ulcer had healed and was not readily visualized. Random biopsies obtained from the hepatic flexure were normal. The reason for the delay in repeated colonoscopy was due to personal reasons. Multiple pathologic reviews of the initial biopsies with our expert gastrointestinal pathologist confirmed the presence of high-grade dysplasia. In view of the inherent risk associated with performing a right hemicolectomy for an 'endoscopically invisible' dysplastic lesion in an individual with cardiac and renal disorder, the patient opted for a referral to an expert center for

a detailed colonoscopy and endoscopic resection.

In this instance, an extremely subtle, flat and mildly erythematous lesion measuring 9 mm was detected at the hepatic flexure (blue arrow in Fig. A). Further interrogation with Narrow Band Imaging (NBI) and high magnification aided our definition of the lesion in question (yellow arrow in Figure B). An Endoscopic Submucosal Dissection (ESD) was performed with the final histology revealing an intramucosal carcinoma (Fig. C and D).

## 3. DISCUSSION

MMF is a prodrug of mycophenolic acid (MPA) which was first approved by the United States Food and Drug Administration (USFDA) in 1995 for renal transplant recipients to prevent organ rejection. MPA acts by selectively and reversibly inhibiting Inosine Monophosphate Dehydrogenase (IMPDH), an enzyme that is essential for de novo Guanosine-5-monophosphate (GMP) synthesis. This then negates the proliferation of B-cell and T-cell lymphocytes that relies exclusively on GMP, thus resulting in an effective immunosuppressive state [4]. Aside from its use in renal, heart and liver transplant, MMF plays an important role in lupus nephritis and was also studied for its antitumorogenic potential [5].

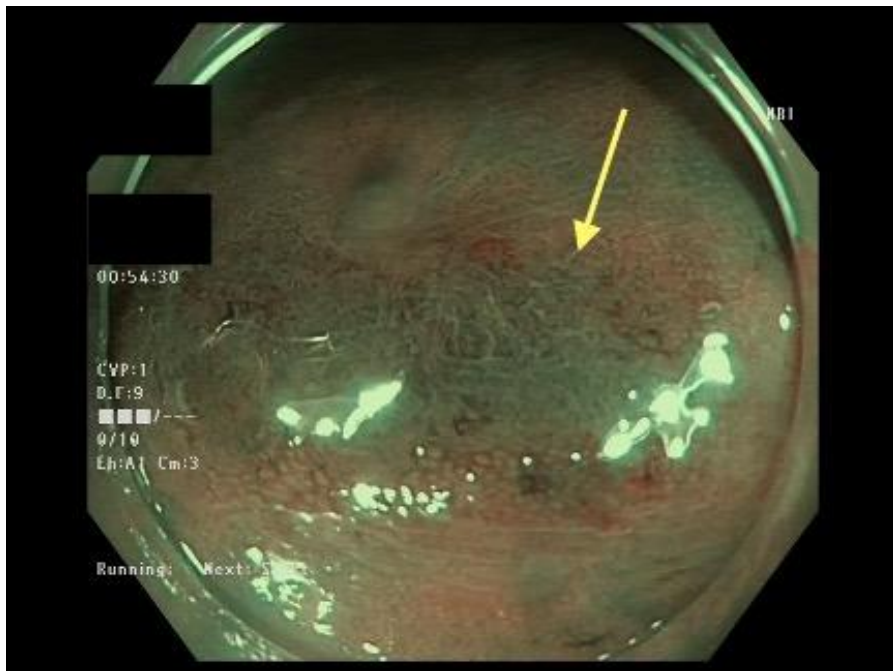
The diagnosis of MMF-related colitis relies first on the knowledge that the patient is taking the drug. Izower et al. [2] suggests possible under-reporting of MMF-related colitis as a number of pathology request forms were devoid of drug history. The rarity of such disorder and its resemblance to other colonic pathologies further compounds the issue and directs the pathologist to other more common diseases first. The endoscopic features in itself are at best descriptive in terms of ulcers and erythema and

are in no way characteristic [2,3]. Even though histological findings are better defined in terms of increased epithelial apoptosis with apoptotic cell death playing a central pathogenic role in

mucosal injury, it is prudent to remember that a majority of other abnormal histology do occur and are not necessarily confined within this definition [2,6,7,8].



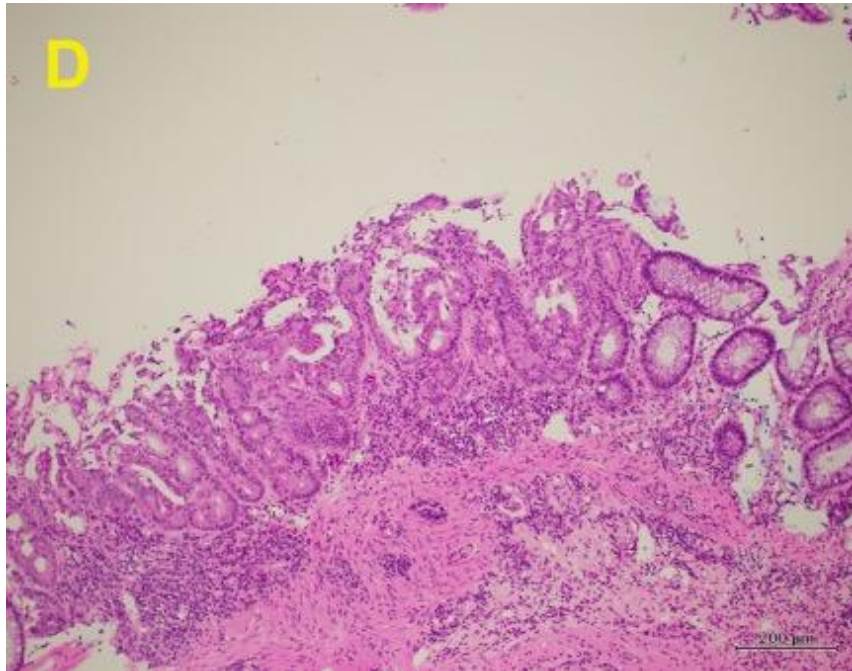
**Fig. A. Lesion on white light endoscopy**



**Fig. B. Lesion on narrow-band imaging**



**Fig. C. Endoscopic submucosal dissection in progress**



**Fig. D. Final histology revealing intramucosal adenocarcinoma on low magnification power (Hematoxylin-eosin stain)**

Due to the lack of understanding in the mechanism of diarrhea in MMF-induced colitis, the first option is to withhold the drug and substitute it with Myfortic; both of which were done for our patient. [9] Following routine bloodwork and stool tests which ruled out more common diarrheal-related causes, he was subjected to a colonoscopy to look for more

sinister pathologies, namely colorectal malignancy. In view of the latter, a full response from drug cessation was not awaited. It has been reported that gross macroscopic and microscopic abnormalities in MMF-induced colitis can be expected in up to 59% of the time and this includes the aforementioned ulcers and erythema in addition to other non-specific findings [2].

In cases where endoscopic findings were positive, a high index of suspicion for more advance pathology such as malignancy is required. Targeted biopsies would help, and this is especially true when solitary ulcers are encountered. It is however challenging that in light of chronic immunosuppression and active inflammation, the presentation and appearance of colon cancers can be atypical and difficult to discern.

Furthermore, ulcers that are caused by MMF-induced colitis may heal with drug withdrawal leaving behind an almost vanishing lesion that could be easily missed if not for earlier biopsies flagging the warning of high-grade dysplasia. Literature is lacking when it comes to defining endoscopic features of malignant lesions in the background of MMF-induced colitis. Thus, a low threshold in performing biopsies and referral to an expert center is recommended. Neglecting the healed solitary ulcer deemed at present to be amenable for endoscopic resection would have otherwise been disastrous.

#### 4. CONCLUSION

This case highlights several important learning points for future clinical practice in this group of patients. Firstly, background knowledge that these immunosuppressed patients may harbor a more sinister pathology is vital. Colonic ulcers when encountered should be cautiously evaluated and not overlooking it as inflammatory given the underlying circumstances of colitis. Clinical judgment for more investigations in terms of endoscopies can be arranged earlier if suspicions are high and need not adhere strictly to the consensus of awaiting response following drug cessation.

Secondly, targeted biopsies with detailed reporting of the suspicious sites are vital for future reassessments. Our case illustrates a painstaking effort in attempts to relocate the ulcer by the time it has healed. Solitary ulcers in particular should be tattooed several folds distally

if possible, to make it easier for identification later on.

Lastly, careful colonoscopic inspection with decent withdrawal time is mandated and if available, dye-based or optical chromoendoscopy may be utilized to assist in characterizing the area of interest. To the best of our knowledge, this case report is unique in describing a vanishing colonic malignancy and has yet to be described before due to its rarity. Although the small colonic cancer is not a cause of the diarrhea, our patient's age and immunosuppressed state from MMF made further workup possible. The early diagnosis saved our patient from being subjected to a high-risk surgery.

#### CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

#### ETHICAL APPROVAL

It is not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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