Applying the Naranjo Scale in diagnosing an atypical case of chronic mycophenolate mofetil-induced colitis in a heart transplant recipient

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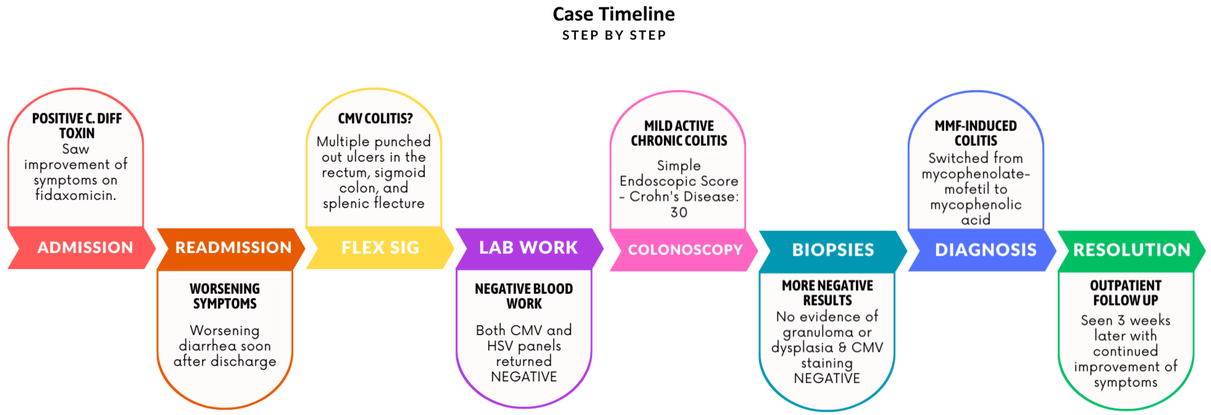
Background

- Mycophenolate mofetil (MMF) is an inhibitor of inosine monophosphate dehydrogenase often used for immunosuppression in transplants or autoimmune diseases.
- MMF is an ester of mycophenolic acid (MPA) designed for immediate release. In comparison, the enteric coated MPA formulation delays exposure in the GI tract.[5]
- Diarrhea is MMF's most common side effect, seen in 13-64% of users.[1]
- Kidney transplants are most significantly associated with MMF colitis, making up 58% of solid organ transplant cases.
- Few cases of MMF colitis have been reported in heart transplant patients.[2]
- Watery, non-bloody afebrile diarrhea associated with weight loss and abdominal pain usually occurs within the first six months of treatment but can be as late as 15 years after starting treatment. [2,3]

Case

- **62-year-old male patient**
- Past Medical Hx: Type 2 diabetes, hypercholesterolemia, hypertension, mild chronic obstructive pulmonary disease, **heart transplant nine years ago on mycophenolate mofetil** and sirolimus, and chronic diarrhea
- **Presenting with worsening chronic diarrhea that developed increased frequency, urgency, bowel incontinence, sporadic melena, and fevers**.

Figures



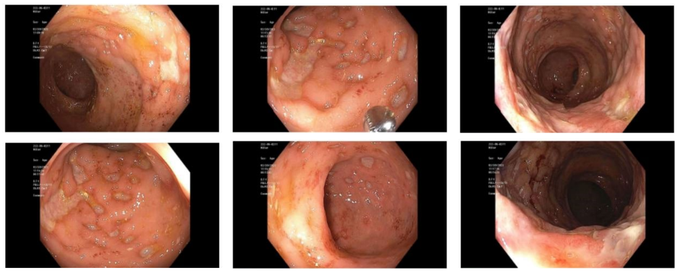


Figure 1. Colonoscopy demonstrating multiple ulcerations in the rectum,which is uncommon in MMF-colitis as it is often found to spare the rectum.

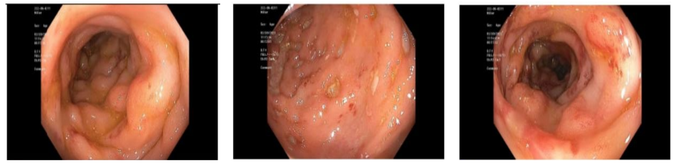


Figure 2. Colonoscopy demonstrating multiple ulcerations in the rectosigmoid junction and sigmoid colon.

Table 1. Adverse Drug Reaction Probability (Naranjo) Scale

Question	Yes	No	Do Not Know	Score
Are there previous conclusive reports of this reaction?	+1	0	0	1
Did the adverse event appear after the drug was given?	+2	-1	0	2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	1
Did the adverse reaction reappear upon re administering the drug?	+2	-1	0	0
Were there other possible causes for the reaction?	-1	+2	0	2
Did the adverse reaction reappear upon administration of placebo?	-1	+1	0	0
Was the drug detected in the blood of other fluids in toxic concentrations?	+1	0	0	0
Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose?	+1	0	0	1
Did the patient have a similar reaction to the drug or a related agent in the past?	+1	0	0	0
Was the adverse event confirmed by any other objective evidence?	+1	0	0	0
			Total Score:	7

Discussion

- Diarrhea in transplant patients increases their risk of morbidity and mortality.
- In solid organ transplant patients, diarrhea prevalence is 20-50%, with the most common causes being medications and infections.[4]
- The patient's atypical presentation and initial positive *Clostridium difficile* toxin with fidaxomicin improvement complicated the diagnosis.
- While the patient's symptoms were uncharacteristically severe for MMF colitis, his negative work up and Naranjo score of 7/16 suggest a diagnosis of MMF-colitis.

Conclusions and Implications

- Clinical and histopathological findings of MMF colitis often mimic that of other diseases such as Crohn's or CMV colitis
- There are currently no guidelines on treatment of MMF colitis, leaving treatment decisions up to individual practitioners.
- Of note, blood levels of MMF have been shown to poorly correlate with MMF toxicity. It is thought that GI complications of MPA therapy may instead be due to local toxicity in the GI tract.[5]
- Several small randomized trials and retrospective analyses demonstrate improved GI symptoms reported by patients after switching from MMF to enteric coated MPA, strengthening this proposed pathophysiologic mechanism.[6,7,8,9]
- Consideration should therefore be given to the physiology-based pharmacokinetics and pharmacodynamics of MMF and its related medications

References

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