Favorable Colitis Outcome After Combination Therapy With Gut Selective Anti-Integrin and Fecal Microbiota Transplantation for Immune Checkpoint Inhibitor Diarrhea and Colitis

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Introduction

- Immune-mediated Colitis (IMC), is the most common of immune-related adverse events (irAEs) often leading to delay/interruption in cancer care with treatment limited to immunosuppressant therapy.
- Vedolizumab, an anti-integrin α4β7 antibody with gut-specific immunosuppressive effects, is effective in management of IMC without interfering with Immune checkpoint inhibitor (ICI) therapy and with no known secondary cancer risk.
- Fecal microbiota transplant (FMT), namely used to treat refractory GI conditions such as Clostridium Difficile Infections, Irritable Bowel Disease and IMC colitis, has been found to be a favorable first-line option for IMC colitis.
- Gut microbiomes play a role in treatment of drug-induced colitis, as well as potentially inducing GI toxicities and/or development of underlying GI infections.
- The composition of gut commensal bacteria is associated with both response to ICI therapy and IMC severity.

We present a case series of two patients with advanced malignancies who developed IMC. They were successfully treated with both anti-integrin therapy and FMT. We contemplate the potential synergistic effect of both therapies.

Case Description

Case 1: A 64-year-old Caucasian woman with metastatic cervical cancer on immune-checkpoint inhibitor immunotherapy (ICI) developed CTCAE grade 3 diarrhea resulting in treatment cessation. Infectious work-up was positive for C. difficile. She reported long-term antibiotic use for chronic urinary tract infections associated with cancer-related uropathy. Colonoscopy demonstrated moderate pancolitis with biopsies showing chronic active colitis.

Case 2: A 77-year-old Caucasian woman with metastatic urothelial cancer on pembrolizumab presented with CTCAE grade 2 diarrhea and dyspepsia. Infectious work-up was negative. Endoscopic evaluation was notable erosive gastropathy and despite normal-appearing colon lymphocytic colitis was noted on histology.

Endoscopic Evaluation

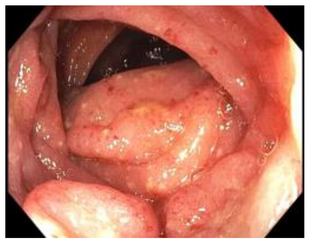


Figure 1. Initial endoscopic evaluation in case 1 following treatment of underlying CDI showing ascending colon inflammation

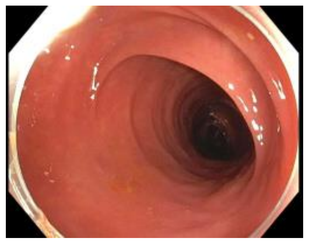
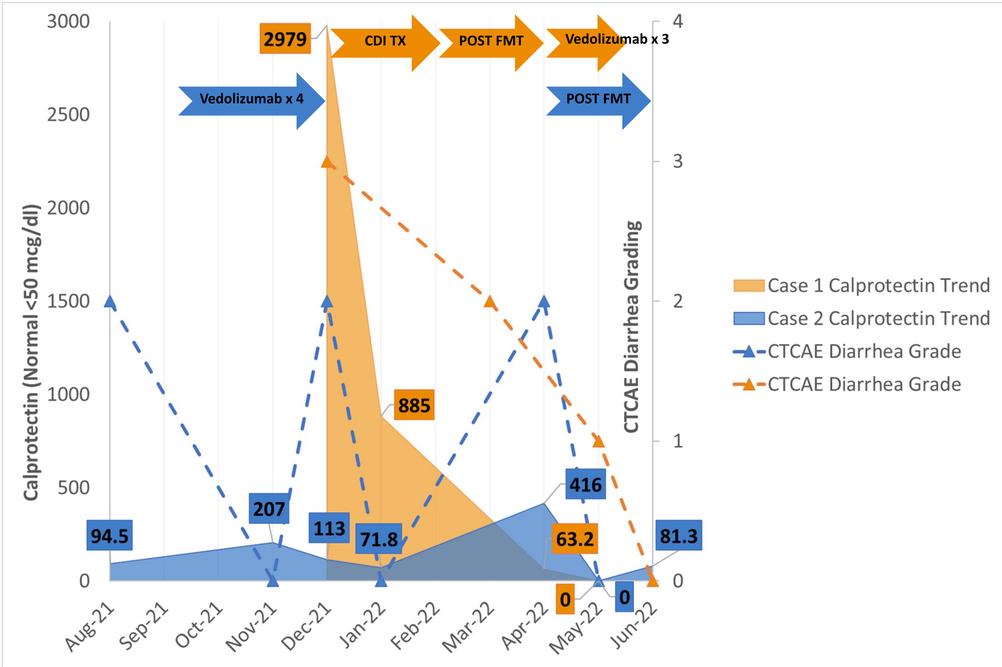


Figure 2. Initial endoscopic evaluation in case 2 showing normal appearing mucosa at the time of initial work-up for grade 3 ICI-related diarrhea.

Table 1. Clinical Features and Findings

	Case 1	Case 2
Age	64	77
Gender	Female	Female
Cancer Type	Gyn (Stage IV)	GU (Stage IV)
ICI Type	Anti-PD-1	Anti-PD-1
ICI Infusions	6	9
CTCAE grade (Diarrhea)	Grade 3	Grade 2
GI Panel	C. Difficile DNA +, Toxin -	Negative
Stool Inflammatory Biomarkers	Lactoferrin +, Calprotectin *2979	Lactoferrin +, Calprotectin *416
Endoscopy	Mayo Score 2 pancolitis	Normal colonic mucosa
Histology	Chronic active colitis	Lymphocytic Colitis
Management	FMT followed by Vedolizumab	Vedolizumab followed by FMT
Colitis Status	Remission	Remission
Cancer Status	Stable Disease	Remission

Chart 1. Calprotectin trend and CTCAE Diarrhea Grading throughout treatment course for case 1 and 2.



Patient Course

Case #1

- Diagnosed with IMC colitis and suspected underlying CDI.
- Received oral Vancomycin with stable diarrhea but improved Calprotectin.
- Immunosuppressant therapy deferred due to concern for recurring CDI.
- FMT recommended for eradication of CDI and treatment of IMC colitis.
- Post FMT stool frequency persisted (6 stools/day) with improved consistency and calprotectin further decreased (885 → 63.2).
- Second FMT vs. biologic therapy discussed and she opted for the latter.
- After 2nd infusion of Vedolizumab clinical remission achieved.
- Remained off ICI therapy given stable disease on re-imaging in June 2022.

Case #2

- Normal appearing colon with IMC colitis confirmed on histology. EGD notable for erosive gastropathy managed with PPI.
- Complete clinical response following 2 doses of Vedolizumab.
- ICI restarted with recurrent grade 2 diarrhea and further elevated calprotectin.
- Prednisone given by PCP for concurrent URI with improvement in diarrhea.
- ICI placed on hold given stable disease noted on repeat CT imaging.
- Vedolizumab subsequently held as well (4 infusions completed).
- Further diarrhea flares managed with anti-diarrheals. Calprotectin (113 → 71.8).
- Recurrent grade 2 diarrhea with peak in calprotectin (416) treated with FMT.
- Clinical remission achieved x 1 month with negative calprotectin (<50).
- Flare after FMT was controlled successfully with Questran. Calprotectin 81.3.

Discussion

- As is evident in case #1 ICI colitis and infectious colitis can certainly co-exist and further influence the proper course of treatment.
- Normal appearing colon mucosa on endoscopy does not preclude the presence of underlying colitis.
- Timing of ICI resumption is preferred post induction phase of biologic therapy to ensure control of IMC following re-challenge with immunotherapy.
- Patient compliance with anti-diarrheals and stool study collection may have impacted diarrhea control and understanding severity in case #2.
- The use of FMT in succession to (before or after) biologic therapy appears to have a synergistic effect with both patients, case 1 and 2, achieving clinical remission as per CTCAE diarrhea grading +/- normalizing calprotectin level.
- The microbial composition within the GI tract should be at the forefront of considerations in work-up and management of ICI colitis.

Conclusions

- FMT for the treatment of IMC represents a novel approach to manipulate the gut microbiome of IMC patients to confer clinical benefit and has been demonstrated to be a favorable upfront option in managing ICI colitis.

- Studies looking into the synergistic effect of gut selective immunosuppression with therapeutic manipulation of the gut microbiome need to be considered.