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Immune Checkpoint Inhibitor–Induced Colitis

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After obtaining patient's consent, this clinical case was discussed in a multidisciplinary panel consisting of oncogastroenterologists (AST, YW, DMF), an abdominal radiologist (YL), two oncologists (MC, JAT), and a gastrointestinal pathologist (DT), with YW as moderator. A summary of the case history and discussion are presented here.

Case History

A 44-year-old White woman with stage 4 renal cell cancer treated with partial nephrectomy followed by pembrolizumab presented shortly after her second cycle with Common Terminology Criteria for Adverse Events (CTCAE) grade 3 diarrhea and grade 2 colitis (bleeding and mucus) with accompanying intermittent lower abdominal cramping and loss of appetite. Her medical history included diffuse B cell lymphoma in remission after therapy and dysfunctional uterine bleeding treated with cervical ablation. Her family history was notable for uterine cancer in her mother and breast cancer in her paternal aunt and maternal grandmother. She is a former smoker with a 6 pack-year history.

On examination she was afebrile. Her body mass index was 49.50 kg/m^2 with normal vital signs. Abdominal examination demonstrated mild subjective lower abdominal tenderness. Laboratory abnormalities included mild anemia with a hemoglobin of 11.4 g/dL and renal insufficiency with a creatinine of 1.25 mg/dL. Stool inflammatory biomarkers, namely, lactoferrin and calprotectin, were positive and elevated at 1000 μg/g, respectively. Infectious work up with a gastrointestinal multiplex panel was negative. Contrast-enhanced computed tomography scan of the abdomen demonstrated bowel wall thickening along the distal transverse colon, descending colon and sigmoid colon with pericolonic stranding (Figure 1). Lower endoscopic evaluation showed pancolonic ulcerative inflammation (Figure 2), characterized by diffuse erythema, deep ulcers occupying >50% of the colon, loss of vascularity, edema, and friability with increased severity in the distal colon. Biopsies from the right and left colon showed marked activity including cryptitis and crypt abscesses (Figure 3).

Given the negative infection workup and lack of other obvious etiologies in the differential diagnosis, the patient was given the diagnosis of immune checkpoint inhibitor (ICI)–induced colitis. Based on the moderate to severe severity of her clinical presentation as well as features on colonoscopy, pembrolizumab therapy was held and she received a tapering dose of prednisone in conjunction with antidiarrheals with plans to initiate biologic therapy. After 2 doses of vedolizumab, despite clinical improvement in symptoms, she developed significant sinus discomfort and arthralgias that led to transition

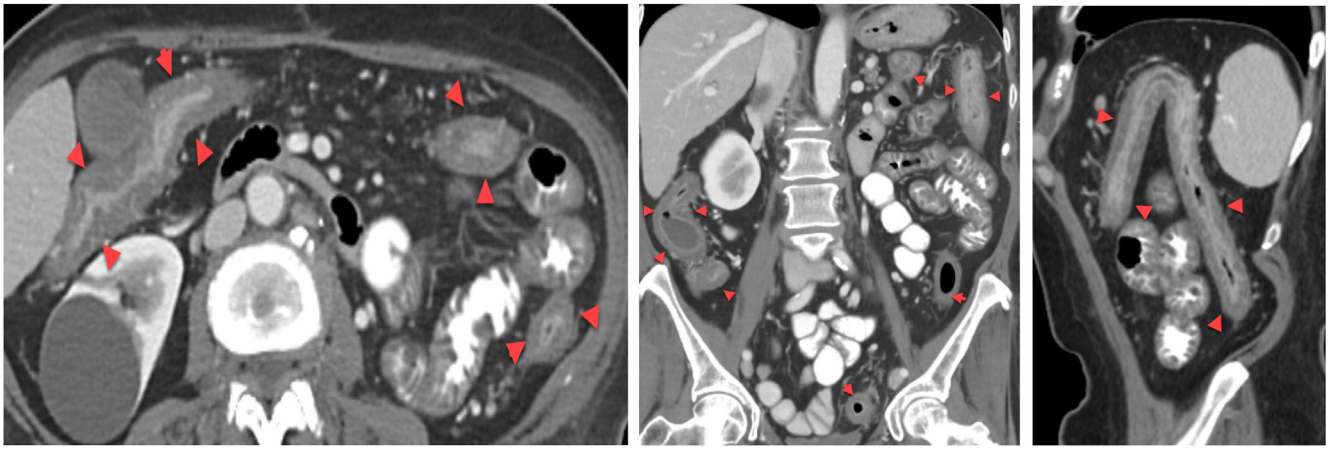

Figure 1. Computed tomography of chest, abdomen and pelvis, axial (*left*), coronal (*middle*), and sagittal (*right*) images showed pancolitis (*arrowheads*): wall thickening with enhancement.

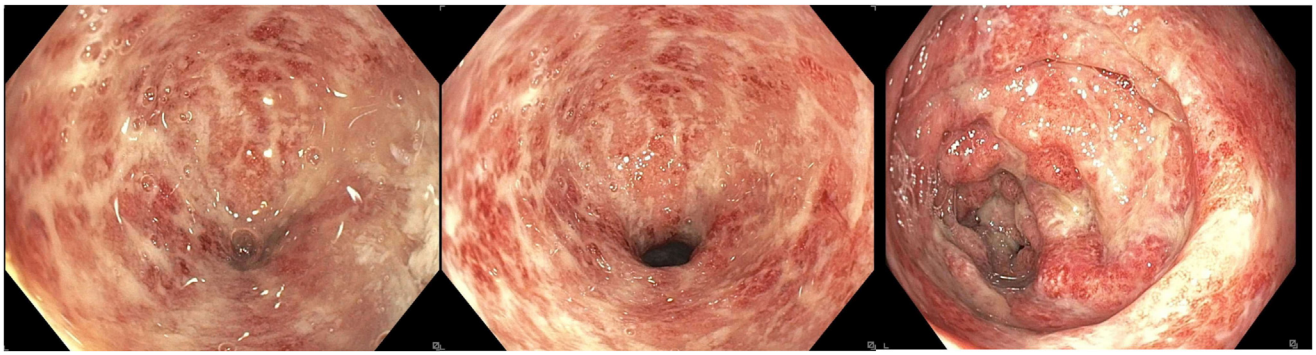

Figure 2. Endoscopic presentation. Severe panulcerative colitis characterized by diffuse erythema, loss of vascularity, edema, and friability being more severe in the distal colon.

to ustekinumab, given the patient's preference. She reported similar side effects after 2 doses of ustekinumab and given plans to restart ICI therapy, she underwent fecal microbiota transplantation (FMT), which is investigational treatment, as her favored next treatment instead of further immunosuppression given the potential risk of complications for long-term use and our center's expertise. This procedure resulted in clinical and endoscopic remission for 10 months despite ICI resumption. However, she had a recurrence of colitis thereafter, characterized by abdominal pain and bloody diarrhea for which she received a second FMT, which kept her in remission for 3 more months with the use of antidiarrheals as needed. This is speculated to be due to increased accumulated dose of ICI over time. A repeat colonoscopy performed for a recurrence 6 weeks after her last dose of ICI showed worsened pancolitis with features of moderate active chronic colitis characterized by crypt architectural distortion, basal plasmacytosis, Paneth cell metaplasia, and crypt abscess formation with crypt destruction seen on histology.

Immunotherapy is presently on hold, and she has been managed with tofacitinib for refractory colitis and is currently pending follow up. Her cancer remains in remission at this time and she is under active surveillance.

Question: What do you need to know about ICI rechallenge in patients with ICI colitis?

A. Since steroid is required for the index colitis event, ICI rechallenge should not be considered.

B. The recurrence rate of colitis is low, and ICI rechallenge can always be considered if clinically indicated at any time.

C. Since cytotoxic T-lymphocyte associated protein 4 (CTLA-4) agent is associated with more severe gastrointestinal toxicity, rechallenge should be limited to programmed cell death ligand 1 (PD-L1) monotherapy.

D. Despite recurrence rate of 35%, ICI can be restarted once colitis received adequate treatment, with lower risk from PD-L1 monotherapy.

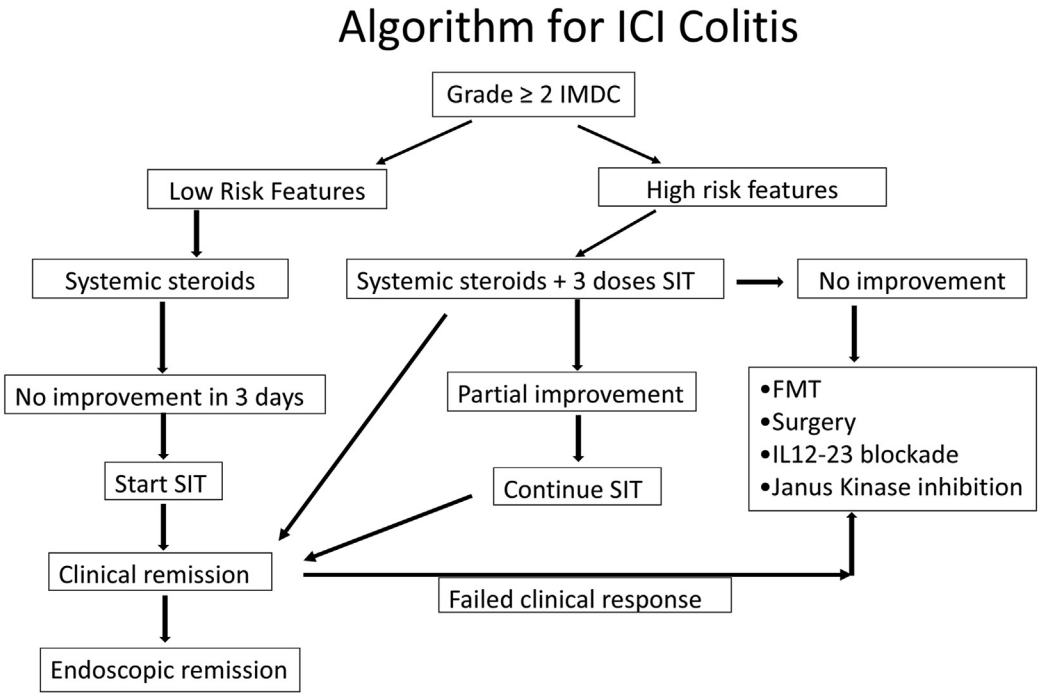

Figure 3. Algorithm to manage immune mediated colitis. ICI, immune checkpoint inhibitor; FMT, fecal microbiota transplantation; IL, interleukin; IMDC, immune-mediated diarrhea and colitis; SIT, selective immunosuppressive therapy.

Look on page 24 for the answer and see the *Gastroenterology* website (www.gastrojournal.org) for more information on submitting to *Gastro* Grand Rounds.

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Conflicts of interest
These authors disclose the following: Dr Faleck received consulting fees from Ferring, Gilead, Janssen, and Teva. Dr Wang received consulting fees from Janssen, IOTA, Ilyapharma, Sorriso, BioTech, Kanvas Bio, and Mallinckrodt. The remaining authors disclose no conflicts.

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Answer (Page 21): Despite Recurrence Rate of 35%, ICI Can Be Restarted Once Colitis Received Adequate Treatment, With Lower Risk From PD-L1 Monotherapy

The correct answer is D. Multicenter study has shown the risk of colitis recurrence after ICI rechallenge is about 35%. However, the recurrent episode is usually less severe than the index event. PD-L monotherapy at rechallenge is associated with lower risk of recurrence and more delayed onset while CTLA-4 is associated with higher risk of recurrence and more rapid onset. Steroid requirement for colitis is not a contraindication to ICI rechallenge. As long as colitis is adequately treated with mucosal healing, the risk of recurrence will be dramatically reduced. Concurrent biologic treatment can be a potential strategy on ICI rechallenge to decrease the recurrence from 35% to 17%.

Multidisciplinary Case Discussion

YW: Based on the clinical presentation and evaluation of this toxicity, how does one assess severity of the adverse event to tailor therapy appropriately from an oncology perspective?

MC: The type of immune-related adverse event is important to determine management and safety in rechallenge. Certain toxicities have such a high mortality that rechallenge is almost never warranted including myocarditis, myasthenia gravis, pneumonitis, Guillain–Barre syndrome, and encephalitis as examples. On the other end of the spectrum are endocrinopathies that, once stabilized from their initial event, may be a scenario for immunotherapy rechallenge. The decision to rechallenge with immunotherapy once a patient experiences an immunotherapy adverse event is nuanced. Patients who are experiencing a remission from a toxicity can often continue remission off of therapy.[1]

JAT: Colitis is a recognized toxicity from anti–programmed cell death protein 1 (PD-1) therapy and the timing of onset of colitis after starting pembrolizumab implicates pembrolizumab as the etiology for the colitis in this case. Typically, such severe colitis is associated with dual immunotherapy, including ipilimumab and anti–PD-1, but in this case pembrolizumab monotherapy triggered the toxicity.[2] The severity and duration of ICI-induced colitis is greater if it involves previously irradiated gastrointestinal (GI) tract, which is to be considered given the history of lymphoma.

Here, this patient seems to have a grade III–IV colitis based on the history, endoscopic findings, and biopsy results. The adverse impact is accentuated by the pattern of recurrent colitis despite stopping pembrolizumab and expert GI management which may increase the risk of life-threatening complications such as GI perforation.

YW: What would affect your decision making on the optimal time and candidacy to resume ICI after colitis?

MC: The severity of the initial episode, success in management of colitis through intervention, and the status of the patient's cancer will all influence this decision. Resuming ICI therapy could be considered for select patients who have achieved clinical remission from their colitis and are ideally off of immunosuppression.[3]

JAT: In this case, the cancer seems to be in remission. Hence, considering the refractory colitis, she may benefit from active surveillance off immunotherapy. Should there be a future progression of cancer in the future confirmed via biopsy, non-ICI options available include surgery, focused radiation therapy, and other systemic agents including tyrosine kinase Inhibitors and chemotherapy.[4]

YW: What are the usual radiographic features of immune mediated colitis (IMC) to suggest diagnosis and severity?

YL: The frequent findings of immunotherapy-induced colitis on contrast-enhanced computed tomography scans are wall thickening, enhancement, adjacent fat stranding, and regional lymphadenopathy. The severity of the colitis usually related with the extent of wall thickening and enhancement. Some cases have bowel loop dilatation, or transition sign of obstruction. Severe cases can have bowel perforation associated with extraluminal air accumulation and significant mesentery fat infiltration and stranding.[5]

YW: How is endoscopic evaluation useful in the management of IMC?

DMF: Endoscopy is a critical component in the initial evaluation of suspected IMC. The role of endoscopy is 2-fold: first, to confirm the diagnosis because $\leq$25% of patients with suspected IMC will have alternative diagnoses found after a thorough investigation.[6] Second, the endoscopic and histological severity are currently the best predictors of IMC disease course and can help to risk stratify patients for appropriate medical therapy better than symptoms alone can.[7] Patients with moderate to severe inflammation may benefit from the early initiation of biologic therapies versus patients with milder or microscopic inflammation in whom less immunosuppressive therapies such as budesonide may be effective first line therapies.[8]

Furthermore, endoscopy is a useful tool for monitoring response to colitis therapies. Repeat endoscopic evaluation with biopsies may be considered to evaluate patients with nonresponse and to exclude superimposed opportunistic infections, such as cytomegalovirus. Finally, rechallenge with ICI after resolution of IMC is an increasingly common consideration and demonstration of endoscopic healing may provide some reassurance regarding decreased rates of recurrent colitis, though prospective studies are needed to explore this further.[9]

YW: Clinical symptom severity does not corelate well with endoscopic severity in patients with colitis. Endoscopic evaluation provides a reliable assessment of the toxicity to guide therapy. Furthermore, with a goal for mucosal healing to reduce the risk of recurrence, endoscopy may serve as an additional useful tool to assess treatment response. As endoscopic

remission (mucosal healing) has been shown to be a better treatment target to reduce colitis recurrence, not clinical remission.[10]

YW: What is the spectrum of histological patterns, severity and /or chronicity on histology in IMC?

DT: IMC encompasses a wide array of histological patterns, reflecting the diverse mechanisms through which ICIs can trigger colonic inflammation.

1. **Active colitis with apoptosis:** This is a common pattern, characterized by neutrophilic crypt abscesses, prominent crypt epithelial cell apoptosis, and crypt atrophy and dropout. It resembles other colitis with prominent apoptosis, like acute GVHD.
2. **Lymphocytic colitis-like pattern:** This pattern involves increased intraepithelial lymphocytes and surface epithelial injury, often with increased apoptosis, but without crypt atrophy. It can mimic lymphocytic colitis.
3. **Collagenous colitis-like pattern:** This pattern features subepithelial collagen deposition, similar to collagenous colitis. It can be difficult to diagnose without considering the clinical context.
4. **Ulcerative colitis (UC)-like pattern:** This pattern shares features with UC, including crypt abscesses, ulcerations, and a mixed inflammatory infiltrate. It can be difficult to distinguish from idiopathic UC.
5. **GVHD-like pattern:** This pattern resembles GVHD, with crypt apoptosis, crypt dropout, and a mixed inflammatory infiltrate. It can be challenging to differentiate from GVHD in patients with a history of transplantation.
6. **Mixed colitis pattern:** This pattern combines features of different IMC patterns, such as active colitis with lymphocytic infiltration and apoptosis. It underscores the heterogeneity of IMC.

In our practice, patterns 1, 2, and 6 are common. In addition to these established patterns, emerging research is uncovering other potential patterns, such as Crohn's-like colitis, eosinophilic colitis, and mixed patterns with features of both microscopic colitis and UC. As our understanding of IMC evolves, the spectrum of histological patterns is likely to expand further.

It is important to note that the histological patterns of IMC can overlap with other forms of colitis, making accurate diagnosis challenging. Therefore, a comprehensive approach incorporating clinical history, endoscopic findings, and histological evaluation is crucial for accurate diagnosis and management of IMC.[11]

YW: Regarding colitis therapy, how does one choose among different options and the optimal duration?

DMF: Approach to selection of an initial agent for treatment for IMC hinges on several considerations: (1) IMC severity, (2) concomitant immune-related adverse events, (3) type of cancer, (4) likelihood of rechallenge with ICI, and (5) patient comorbidities (eg, congestive heart failure, multiple sclerosis).

YW: Both infliximab and vedolizumab are effective in achieving remission in colitis, allowing for immunotherapy rechallenge. The complication rate from biologics is dramatically lower than prolonged steroid treatment and is favored.[12]

DMF: In a case of nonresponse to a first therapy, one may consider switching classes, for example, from vedolizumab to infliximab, or infliximab to anti–interleukin (IL)-12/23 or IL-23 inhibitor, with occasional use of JAK inhibitors.[12]

With regard to the duration of therapy, limited retrospective data suggest that completing induction therapy (compared with more limited dosing) may decrease the chance of a colitis relapse.

YW: The duration of biologic agent is usually determined based on the corticosteroid free clinical and endoscopic remission and/or normalization of calprotectin level.[13]

Although fecal transplant is presently an investigational option, preliminary data show remarkable success with 80%–85% efficacy in refractory cases, as well as in treatment-naïve patients with a favorable safety profile. It could become a potential future standard-of-care option given its minimal complication rate, rapid effect, and high efficacy.[14]

Discussion

IMC is one of the most frequently encountered side effects from ICIs with an overall incidence of 10%–30%.[15] Cytotoxic T-lymphocyte-associated protein 4 blockade, as well as combination therapy with PD-1/PD-L1 blockade confers increased risk of this toxicity as does an underlying history of inflammatory bowel disorders.[16,17]

Clinically, patients often present with diarrhea (increased stool frequency and consistency) and/or colitis (abdominal pain, rectal bleeding, or the presence of mucus in stools) approximately 2 months to $\leq$2 years after ICI exposure.[13] Rarely, complications such as ileus, colonic distension, and toxic megacolon, intestinal perforation may increase the risk of mortality. The CTCAE version 5.0,[18] which relies heavily on clinical signs and symptoms alone is used routinely to grade the severity of clinical presentation of IMC; however, it correlates poorly with the degree of endoscopic colonic inflammation.[19]

Stool evaluation with a gastrointestinal multiplex panel is important to promptly rule out an infectious etiology, frequently encountered in an immunocompromised cancer patient population. Stool inflammatory biomarkers, namely, calprotectin, can serve as an important indicator of severity of inflammation and may also be used to assess for treatment response.[20]

Early endoscopic evaluation promptly identifies high-risk features of colitis, which thereby facilitates rapid and efficacious management decreasing steroid dependency and improving overall outcomes (prolonged hospitalization, and recurrence rates).[21] High-risk endoscopic features such as extensive inflammation and ulcers >2 mm deep or >1 cm are associated with more frequent need for selective immunosuppressive therapy (SIT).[7,8,19] Furthermore, our group devised a scoring system for various endoscopic features of IMC that had a high specificity for predicting SIT use among patients with scores of ≥4. We also found that the time to endoscopy was correlated positively with time to SIT initiation.[22]

CTCAE grade 1 IMC, which is mild and self-limiting with a lower colonic inflammatory burden confirmed by calprotectin, is managed with supportive care, such as hydration, bland diet, antidiarrheals (once infection has been ruled out) or 5-ASA based therapies with cholestyramine and ICI is usually resumed.[23]

The management of CTCAE grade ≥2 IMC requires withholding ICI and expeditious immunosuppression. Lower risk endoscopic features are treated with weight-based systemic corticosteroids (prednisone or equivalent with a dose of 1–2 mg/kg) with a taper over a duration of 4 weeks after symptom resolution. If no improvement is noted clinically after 3 days, SIT with either infliximab or vedolizumab is administered to attain clinical remission. Pre-biologic labs (i.e., HIV, tuberculosis, and hepatitis panel) are highly recommended to screen for latent infection and prevent reactivation upon immunosuppression. Early introduction of SIT for moderate to severe IMC with high-risk endoscopic features is associated with favorable clinical outcomes regardless of steroid response. Please refer to our algorithm for the current guidelines on the evaluation and management of checkpoint inhibitor colitis (Figure 3).[24]

Our group demonstrated that in comparison to vedolizumab, although infliximab has a significantly favorable shorter median duration from first dose to symptom improvement (13 days vs 18 days; $P = .012$), vedolizumab has better outcomes in regard to hospitalization (10 days vs 14 days; $P = .043$), histological remission ($P = .011$), and recurrence of IMC ($P = .009$).[25]

Ustekinumab has been shown to induce mucosal healing in IMC in refractory cases indicating that IL-12/23 blockade may serve as a therapeutic target and alternative to long-term steroid dependency.[12]

Anecdotal reports demonstrate utility of tofacitinib in the therapy of IMC.[26,27] Although its oral route of administration and fast onset of action make this drug an attractive therapy in refractory IMC, the risk of thromboembolic phenomenon in a cancer population as well as the loss-of-function mutations in JAK1 associated with resistance to PD-1 blockade in melanoma owing to loss of interferon-driven tumor cell growth hindrance needs through evaluation and clinical validation.[28]

Biologics are often administered via intravenous infusions or subcutaneous injections and can lead to injection site related side effects such as redness, itching, bruising, pain, or swelling. Rarely, headaches, fevers, rashes, hives, or severe allergic reactions may occur. Rarer, serious side effects of biologics are secondary to immunosuppression and include reactivation of tuberculosis or hepatitis B and infection or sepsis. With regard to the risk posed by biologics in patients with active cancer, robust evidence is lacking and mainly available from registries and observational studies and hence therapy is based on expert consensus. As patients with previous or active cancer were excluded from clinical trials and short-term follow-up may have posed an underestimation of the cancer or cancer recurrence risk of these immunosuppressants.[29]

Gut dysbiosis is implicated in cancer initiation, progression, and sensitivity to chemotherapeutic agents in the tumor microenvironment.[30–32] In particular, unique bacterial signatures have been established among ICI responders, non-responders, and those with a lower threshold for IMC.[33,34]

Gut microbiome modulation in gnotobiotic mice via FMT from cancer patients alters antitumor immunity and response to ICI therapy.[35] FMT, although investigational, has been demonstrated to be effective and safe in patients with ICI-induced enterocolitis refractory to immunosuppression from our center expertise.[14,35–38]

The case presented highlights the complexity of management of inflammatory colitides with immunosuppression in an already immunocompromised patient. While immune checkpoint blockade has revolutionized cancer care, gastrointestinal toxicities are common, severe and often greatly impact quality of life. Early endoscopic evaluation and prompt immunosuppression one infectious etiologies have been ruled out in moderate to severe cases can positively impact outcomes. FMT, though currently investigational shows excellent promise and benefit as a therapeutic option.

Keywords: Immune Checkpoint Inhibitors; Colitis; Gastrointestinal Toxicity; Fecal Transplant.

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