Annals of Gastroenterology (2025) **38,** 1-5

Office-based flexible sigmoidoscopy allows rapid assessment and management of suspected immune checkpoint inhibitor-related colitis

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Abstract

Background Immune checkpoint inhibitors (ICIs) have transformed cancer treatment but are frequently complicated by immune-related adverse events, including immunotherapy-related colitis (irColitis). Early and accurate diagnosis, including endoscopy, is essential for appropriate management, yet the real-world feasibility and clinical impact of early endoscopic evaluation remain unclear.

Methods We conducted a retrospective analysis of patients who underwent office-based, unsedated flexible sigmoidoscopy between February 2019 and April 2022 as part of the RAPID-GI program at Memorial Sloan Kettering Cancer Center. The program was designed to expedite evaluation of suspected irColitis in ICI-treated patients via rapid GI consultation including sigmoidoscopy. A diagnosis of irColitis was confirmed based on histology review by expert GI pathologists.

Results irColitis was confirmed in 70% (66/94) of patients. Median time from referral to consultation including sigmoidoscopy was 8 days. Visible inflammation was present in 80% of patients with confirmed irColitis vs. 11% without (P<0.001); all irColitis cases showed histologic inflammation. All procedures were completed without sedation using enemas alone for bowel preparation, and no complications occurred. Findings led to management changes in 89% of irColitis cases, including initiation or adjustment of immunosuppressive therapies. Among patients without irColitis, 79% avoided unnecessary immunosuppression and 57% continued or resumed ICI therapy.

Conclusions Office-based flexible sigmoidoscopy is a safe, feasible, and high-yield diagnostic tool for suspected irColitis. A rapid access program enables timely diagnosis, guides therapy, minimizes unnecessary immunosuppression, and facilitates ICI continuation. This model may improve outcomes and should be considered for broader adoption among integrated oncology and gastroenterology care teams.

Keywords Immune-related colitis, immune checkpoint inhibitors, flexible sigmoidoscopy, rapid evaluation, immune-related adverse effects

Ann Gastroenterol 2025; 38 (XX): 1-5

Conflict of Interest: None

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Received 14 February 2025; accepted 14 May 2025; published online 25 June 2025

DOI: https://doi.org/10.20524/aog.2025.0979

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy and have improved survival for patients with various advanced or metastatic cancers [1]. ICIs targeting PD-1, PD-L1 and CTLA-4 inhibit checkpoint protein interactions and therefore enhance anti-tumor immunity. However, off-target inflammation and autoimmunity can cause toxicity in virtually any organ system [1,2]. These adverse events are collectively referred to as immune-related adverse effects (irAEs), while immunotherapy-related colitis (irColitis) is among the most common and the most frequent irAE leading to treatment discontinuation [3].

Workup of suspected irColitis should be rapid, as early identification and prompt treatment can guide the initiation

of appropriate therapy, avoid detrimental colitis outcomes and allow thoughtful reintroduction of ICI when appropriate [2,4]. Together with stool testing for infection and inflammation, early endoscopy and tissue biopsy are essential for correct diagnosis, risk stratification and therapy guidance [2,3]. Current ASCO guidelines for the management of suspected irColitis recommend considering endoscopy or colonoscopy for patients with grade 2 or greater diarrhea, based on common terminology criteria for adverse events, as more severe mucosal inflammation has been linked to steroid refractoriness [5]. As >95% of irColitis cases are thought to involve the left colon, it has been suggested that flexible sigmoidoscopy with biopsies is sufficient for an initial evaluation, and may be more feasible for timely workup [6,7]. Despite multiple guidelines recommending early endoscopic evaluation for suspected irColitis, the real-world feasibility and impact on patient care remain unclear. The aim of this study was to assess the feasibility and impact on patient care of a rapid-access program for office-based sigmoidoscopic evaluations in patients with suspected irColitis.

Patients and methods

Population

This was a retrospective, single-center analysis of patients who underwent office-based, un-sedated flexible sigmoidoscopies at Memorial Sloan Kettering Cancer Center (MSK) between February 2019 and April 2022, as part of RAPID-GI (Rapid Assessment Program for Immunotherapy-related Diarrhea and Gastrointestinal Inflammation), a program launched to facilitate the rapid evaluation and management of suspected irColitis. Referrals to RAPID-GI were made 1) via direct communication from treating oncologists, or 2) by real-time, provider-directed review of electronic requests for gastrointestinal (GI) consultation at our institution that specified an indication of "immunotherapy colitis" or "diarrhea on immunotherapy". Patients were provided expedited clinic appointments, with a goal of ≤7 days, and informed that office-based sigmoidoscopy would be performed at the initial visit. Bowel preparation with 1-2 fleet enemas was administered, either by the patient at home, or by a patient care technician in-office, based on patient preference. No fasting or oral bowel preparation was required. All patients who were referred for concern for irColitis after receipt of ICI therapy and underwent office-based sigmoidoscopy were included in this study. Patients with preexisting inflammatory bowel disease were excluded. This study was approved by the Institutional Review Board at MSK.

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Data collection

Data regarding demographics, GI symptoms, diarrhea workup, including infectious studies and fecal calprotectin, endoscopy and pathology reports, management strategies, including the impact of sigmoidoscopic evaluation, and clinical outcomes, including ICI rechallenge, were collected from the electronic medical record. Endoscopic scoring of colitis severity was based on the Mayo endoscopic scoring system, typically used in ulcerative colitis, given the lack of a validated scoring system for irColitis. A diagnosis of irColitis was confirmed if the histological findings were deemed to be consistent with previously described patterns of active irColitis, upon review by expert GI pathologists [8,9].

Statistical analysis

Continuous variables were summarized as mean and standard deviation if normally distributed, and as median and interquartile range (IQR) if not normally distributed. Categorical variables were summarized as counts and percentages. Student's *t*-tests and Wilcoxon's rank sum tests were used to compare continuous variables, while chi-square tests were used for categorical variables. An alpha of 0.05 was considered significant. Statistical calculations were performed using Stata Statistical Software: Release 17 (StataCorp, College Station, TX).

Results

Patient population

A total of 94 patients underwent office-based sigmoidoscopy for the initial evaluation of suspected irColitis. The baseline characteristics for patients who underwent initial evaluation are summarized in Table 1. Fifty-five (59%) patients were male, and the median age (IQR) was 67 (58-74) years. Melanoma was the most common cancer type (29%), followed by genitourinary (28%), lung (26%), and gastrointestinal (9%) malignancies. Anti-PD-(L)1 monotherapy was the most common therapy (56%), followed by combination CTLA-4/PD-1 therapy (41%). The median (IQR) time from GI referral to evaluation, including flexible sigmoidoscopy, was 8 (range 5-15) days.

Clinical presentation and evaluation

IrColitis was confirmed in 66 (70%) of patients who underwent initial evaluation. Diarrhea was the most common

Table 1 Characteristics of patients undergoing office-based flexible sigmoidoscopy for initial evaluation of suspected irColitis (n=94)

Characteristics	Confirmed irColitis (n=66)	Negative for irColitis (n=28)	P-value
Age at colitis onset (years), median (IQR)	67.5 (58-77)	66.5 (59.5-71)	0.61
Sex, n (%)			
Male	38 (58)	17 (61)	0.78
Female	28 (42)	11 (39)	
Cancer Type, n (%)			
Melanoma	24 (36)	3 (11)	0.023
Genitourinary	12 (18)	14 (50)	
Lung	18 (27)	6 (21)	
Gastrointestinal	5 (8)	3 (11)	
Head and neck/endo	2 (3)	0 (0)	
Other	5 (8)	2 (7)	
Immunotherapy type, n (%)			
Anti-PD-(L) 1	34 (52)	19 (68)	0.43
Combination CTLA-4/PD-1	31 (47)	8 (28.5)	
Experimental ICI	1 (1)	1 (3.5)	
Duration of ICI, median days (IQR)	184.5 (84-385)	472.5 (168-844.5)	0.003
Time from ICI to diarrhea onset, median days (IQR)	108.5 (43-287)	258 (103.5-524.5)	0.011
Time from GI symptom onset to GI clinic referral, median days (IQR)	15 (8-34)	12 (2-21)	0.027
Time from GI symptoms to flex sig, median days (IQR)	23.5 (16-47)	22 (12.5-28.5)	0.16
Time from GI referral to flex sig, median days (IQR)	7 (5-15)	8 (6-15)	0.56
Symptoms, n (%)			
Diarrhea	66 (100)	26 (93)	0.028
Abdominal pain	22 (33)	13 (46)	0.23
Fever	1 (2)	0 (0)	0.51
Rectal bleeding or mucus	15 (23)	4 (14)	0.35
Endoscopic severity*, n (%)			
Normal (Mayo 0)	13 (20)	25 (89)	<0.001
Mild (Mayo 1)	24 (36)	3 (11)	
Moderate (Mayo 2)	19 (29)	0 (0)	
Severe (Mayo 3)	10 (15)	0 (0)	
Steroids prior to evaluation, n (%)	37 (56)	4 (14)	<0.001
Management implications			
Steroids started/increased, n (%)	30 (45)	3 (11)	0.001
Steroids discontinued/decreased, n (%)	11 (17)	0 (0)	0.022
Biologic started/escalated, n (%)	33 (50)	0 (0)	<0.001
Immunosuppression avoided, n (%)	1 (2)	22 (79)	
ICI continued or rechallenged with future courses, n (%)	21 (32)	16 (57)	0.009

*Endoscopic Mayo Score: 0=normal endoscopic appearance; 1=erythema, decreased vascular pattern, mild friability; 2=marked erythema, absent vascular pattern, friability, erosions; 3=spontaneous bleeding, ulceration

irColitis, immune-related colitis; ICI, immune checkpoint inhibitor; GI, gastrointestinal, IQR, interquartile range

symptom, seen in 66 (100%) patients with confirmed irColitis compared to 26 patients (93%, P=0.028) who were negative for irColitis (Table 1). Rates of abdominal pain (33% vs. 46%, P=0.23) and rectal bleeding (23% vs. 14%, P=0.35) were similar across both cohorts.

Flexible sigmoidoscopy revealed a normal endoscopic appearance (Mayo 0) in 89% of patients who were negative for irColitis, compared with 20% in patients with confirmed irColitis (P<0.001). In patients with confirmed irColitis, 36% had mild inflammation, erythema and decreased vascular pattern (Mayo 1); 29% had findings of moderate inflammation with marked erythema, friability and erosions (Mayo 2); and 15% had severe inflammation with spontaneous bleeding and ulceration (Mayo 3). Among the patients without irColitis, 11% had mild mucosal abnormalities (Mayo 1), but the pathology did not support a diagnosis of irColitis. All patients tolerated the sigmoidoscopy examination, no cases were aborted due to patient discomfort, and no adverse events, such as clinically significant bleeding, infection or bowel perforation, were noted.

Management implications

Patients who were found to have irColitis were more likely to have been started on empiric steroids prior to flexible sigmoidoscopy, compared to those negative for irColitis (56% vs. 14%, P<0.001). Following their flexible sigmoidoscopy, 59 (89%) patients with confirmed irColitis had changes to their medication regimen, including 39% of patients who initiated colitis medications and 50% who had a change in their colitis regimen. Management changes included 15 (23%) patients who started infliximab, 23 (35%) who started vedolizumab, and 30 (45%) who either initiated or had an increase in their steroid dose.

In patients with a negative workup for irColitis, 79% of patients avoided immunosuppressive medications altogether. More patients with a workup negative for irColitis were able to continue or resume their ICI (57% without irColitis vs. 32% with irColitis, P=0.009). No patients with a negative index flexible sigmoidoscopy were subsequently diagnosed with an immune-related enterocolitis that might have been missed on their index evaluation.

Alternative diagnoses

Alternative causes of GI symptoms diagnosed among patients with a negative workup for irColitis (n=28) can be found in Table 2. Common among these were concomitant cancer medications (29%), intestinal infections/diverticular disease (18%), cancer infiltration in the GI tract (14%) or newly diagnosed exocrine pancreatic insufficiency attributed to ICI (14%).

Discussion

Our study highlights the importance of early referral and rapid endoscopic evaluation of suspected irColitis to confirm the diagnosis and guide appropriate management. We report a median time of 8 days from GI referral to evaluation, including flexible sigmoidoscopy, suggesting that rapid evaluation is feasible via a dedicated program. Furthermore, we observed sigmoidoscopy to have excellent accuracy in determining the cause of lower GI symptoms for patients on ICI, with a clear impact on patient management.

Table 2 Etiologies of GI symptoms among patients with initial exam negative for irColitis (n=28)

• Diarrhea attributed to concomitant oral tyrosine kinase inhibitor (Axitinib n=4, Lenvatinib n=4)
• Overflow diarrhea due to obstructing rectal tumor (n=3), anastomotic narrowing (n=1), or constipation (n=1)
• Abdominal cramping due to diverticulitis that resolved with antibiotic (n=2) or MiraLax (n=1)
• Loose stool due to immune-related exocrine pancreatic insufficiency (n=4)
• Diarrhea due to enteropathogenic and enteroaggregative *Escherichia coli* resolved with antibiotics (n=1)
• *Clostridioides difficile* recurrence with pseudomembranous colitis requiring FMT (n=1) • Loose stool due to IBS (n=1)
• Mild non-specific inflammation, not consistent with irColitis (n=3)
• Unclear cause, resolved without intervention (n=3)

GI, gastrointestinal; irColitis, immune-related colitis; FMT, fecal microbiota transplantation; IBS, irritable bowel syndrome

The use of flexible sigmoidoscopy is beneficial, as it can be performed rapidly, without the need for sedation or a full bowel prep, and it is sufficient to diagnose and assess severity in the vast majority of irColitis cases. A prior systematic review found that 98% of patients with irColitis who underwent endoscopic evaluation had disease detected in the left colon [6]. Indeed, no cases initially diagnosed as "not irColitis" in our series were subsequently found to have a more proximal inflammatory toxicity that was missed on the sigmoidoscopic exam. Our study also confirms the importance of endoscopic evaluation for a correct diagnosis, as 30% of patients did not have irColitis detected on sigmoidoscopy: most of these avoided steroids and many were able to resume ICI.

Finally, prior studies have suggested that early endoscopic evaluation is essential for appropriate disease management. One study found that patients who underwent endoscopic evaluation after 30 days, compared to within 30 days from symptom onset, required a longer duration of steroids, had more recurrent symptoms and received later biologic add-on therapy, which has been associated with poorer outcomes [3,10,11]. Similarly, in our series 89% of patients with confirmed irColitis underwent changes to their colitis treatment regimen following endoscopic evaluation: 39% of the patients initiated medications for colitis treatment and 50% had changes in their treatment regimen, including 23% who started infliximab, 35% who started vedolizumab, and 45% who either initiated or had an adjustment in steroid dosage.

The strengths of our study include the large cohort of patients undergoing evaluation for irColitis, with uniform evaluation and management by a single provider. To our knowledge, this is the first study to evaluate the use of office-based flexible sigmoidoscopy, which offers significant advantages in terms of accessibility as well as safety, for example among patients with multiple comorbidities who may be at high risk or have contraindications for anesthesia. We also show the feasibility of a rapid evaluation program, which requires close communication between oncologists and GI specialists to optimize care delivery. Finally, we provide additional evidence to support the use of sigmoidoscopy as the preferred initial evaluation for patients with suspected irColitis, given its safety, tolerability and high diagnostic yield.

The primary limitation of our study is the focus on a specialized practice at a tertiary care cancer center, which may limit the generalizability to other practice settings. All sigmoidoscopies were performed in an outpatient setting; therefore, patients who were evaluated as inpatients and may have had more severe disease, were excluded from this population. Additionally, as the focus of this study was patients undergoing endoscopic evaluation as part of RAPID-GI, we do not have a comparator group of patients who underwent

GI evaluation without endoscopy to isolate the impact of GI specialty evaluation from the results of the endoscopy on patient care. Similarly, we also lack a comparison group of patients who underwent endoscopic evaluation under anesthesia, rather than office-based evaluation. Future directions include evaluating the feasibility of implementing this model in other hospital systems and community-based practices, as well as comparing the time to evaluation between this model and standard endoscopy pathways. Further studies should also assess the adequacy of flexible sigmoidoscopy compared with full colonoscopy in similar patient populations, and evaluate its cost-effectiveness.

Summary Box

What is already known:

- Immune checkpoint inhibitors (ICIs) enhance anti-tumor immunity but can cause off-target inflammation leading to immune-related adverse events, including immunotherapy-related colitis (irColitis)
- The diagnosis of irColitis typically involves stool tests for infection and inflammation, along with endoscopy and biopsies for accurate diagnosis and risk assessment
- Early diagnosis and intervention is critical in managing irColitis, to avoid severe complications and optimize outcomes

What the new findings are:

- Office-based flexible sigmoidoscopy, performed without sedation or full bowel preparation, is an effective and rapid diagnostic tool for suspected irColitis
- No cases initially diagnosed as "not irColitis" were subsequently found to have a more proximal inflammatory toxicity that was missed on the sigmoidoscopy
- Flexible sigmoidoscopy with biopsy has an immediate impact on patient care and management plans, as 89% of patients with confirmed irColitis had changes in their management
- Endoscopic evaluation is essential for proper diagnosis, as 30% of patients did not have irColitis detected on sigmoidoscopy: most of them avoided steroids and many were able to resume ICI

In summary, office-based flexible sigmoidoscopy is a safe and effective tool for the rapid diagnosis of irColitis and exclusion of alternative etiologies of symptoms, with an immediate impact on patient care and management plans. Given its high diagnostic yield and rapid availability, without the need for sedation and full bowel preparation, flexible sigmoidoscopy should be considered as a first-line approach for diagnosis in patients with suspected irColitis. Dedicated programs to facilitate the rapid evaluation of patients with suspected irColitis are feasible and can enhance patient outcomes.

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