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Isolated immune-mediated enteritis in patients treated with immune checkpoint inhibitor therapy

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Abstract

Background Immune checkpoint inhibitors (ICIs) commonly cause colitis, but isolated immune-mediated enteritis (IMEN) is poorly characterized. This study describes the clinical features, diagnostic findings, and outcomes of IMEN.

Method We retrospectively identified adults with cancer who developed IMEN within one year of ICI initiation, confirmed as duodenitis, ileitis, or both.

Results Among 20,991 ICI-treated patients, 30 (0.143%) developed isolated IMEN. Median age was 69.5 years; 73.3% were male, and 80% white. The most common malignancies were gastrointestinal/hepatobiliary (26.7%) and melanoma (23.3%). Presenting symptoms included nausea (66.7%), diarrhea (53.3%), and vomiting (46.7%); 62.5% of patients with diarrhea had grade ≥2 severity. Disease involved duodenitis plus ileitis in 50%, isolated duodenitis in 30%, and isolated ileitis in 20%. Median fecal calprotectin levels were highest in duodenitis plus ileitis (1335.5 μg/g), followed by ileitis (319 μg/g) and duodenitis (78 μg/g). Endoscopy showed nonulcerative inflammation in 60% and ulceration in 20%. Hospitalization was longest in duodenitis plus ileitis (median 13.5 days). Corticosteroids were required in 66.7% of ileitis cases; additional immunosuppression was needed in 33.3% of ileitis and 66.7% of duodenitis plus ileitis. Isolated duodenitis improved with supportive therapy alone. Remission occurred in 63.3% overall. ICI therapy was resumed in 12.5%, exclusively in patients with isolated duodenitis. Complications included fistula formation (10%); all-cause mortality was 36.7%.

Conclusions IMEN is a rare but clinically significant ICI-related toxicity. Fecal calprotectin correlates with ileitis severity and not duodenitis, and small-bowel endoscopy facilitates diagnosis and management.

Keywords Immune checkpoint inhibitor, diarrhea, enteritis, duodenitis, ileitis

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Conflict of Interest: None

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Introduction

In recent years, immune checkpoint inhibitors (ICIs), which harness the immune system to target tumors, have revolutionized cancer therapy [1,2]. However, despite their efficacy in providing durable responses to cancer treatment, ICIs are associated with immune-related adverse events (irAEs) stemming from immune activation in non-target tissues [1,3]. Among these, gastrointestinal (GI) toxicities, particularly diarrhea and colitis, are the most commonly observed serious irAEs in patients undergoing ICI therapy (reported incidences: 37% for diarrhea, 8% for colitis) [4]. Severe, life-threatening or fatal effects occur in

7% of patients, and intestinal perforation is reported in 1% of patients [4].

The hallmark symptom of ICI-induced enterocolitis is diarrhea, often accompanied by abdominal pain, nausea and vomiting. Less frequently, patients present with hematochezia and fever [5,6]. In addition, although the presence of colitis has been well-documented in patients undergoing ICI therapy, cases of isolated enteritis without colonic damage are sparsely reported [5,6]. This distinction is clinically significant, as the absence of colonic involvement may delay diagnosis and treatment. Current grading criteria, such as the Common Terminology Criteria for Adverse Events (CTCAE), do not specifically address isolated enteritis; instead, they categorize it under the broader term "enterocolitis." This lack of specific criteria presents a diagnostic challenge.

Case reports of isolated enteritis most frequently describe duodenal involvement, with findings (e.g., villous atrophy, friable mucosa, mucosal shedding, lymphocytic and plasma-cell infiltration, increased intraepithelial lymphocytes, apoptosis) that may mimic celiac disease [5,7]. Distinguishing ICI-induced enteropathy from celiac disease requires serologic testing and clinical context to prevent misdiagnoses, since both conditions can develop after ICI initiation [7]. Endoscopic features (e.g., erythema, erosion, ulcers and duodenal strictures) and histologic markers (e.g., active inflammation and increased intraepithelial lymphocytes) have been proposed as diagnostic criteria; however, these characteristics are inconsistently present, necessitating further research [7].

Risk factors for ICI-induced enterocolitis include the ICI type and dosage, with combination therapies and anti-cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) agents posing higher risks. Other risk factors include the use of nonsteroidal anti-inflammatory drugs, preexisting inflammatory bowel disease, microbiota composition and tumor histology [2,5,6,8,9]. However, the mechanisms and risk factors specific to immune-mediated enteritis (IMEN) remain poorly understood. Even though recognition of ICI-induced enteritis is growing, studies often group enteritis and colitis under the umbrella of enterocolitis, overlooking the unique clinical and pathological features of isolated enteritis [2,5,8,9]. Accordingly, this study aimed to define the clinical, endoscopic, histologic and colonoscopy features, diagnostic approaches, risk factors and outcomes specific to ICI-treated patients with isolated enteritis but without colitis.

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Patients and methods

Patient selection and data collection

For this retrospective cohort study, we performed a database search to identify cancer patients treated with ICIs at a tertiary care center from March 1, 2016, to June 30, 2024. Patient records were reviewed to determine study eligibility according to the following inclusion/exclusion criteria. Adults (≥18 years of age) were eligible if they developed GI symptoms (e.g., diarrhea, abdominal pain, bleeding, nausea/vomiting) within 1 year of the last ICI dose and underwent stool testing for infectious or inflammatory markers. Inclusion required histologic confirmation of small-bowel inflammation (e.g., villous atrophy, increased intraepithelial lymphocytes, apoptosis, or active inflammation) without colonic involvement. Exclusion criteria were pre-existing GI conditions (e.g., inflammatory bowel disease, celiac disease), confirmed infectious diarrhea, concurrent colitis, immune-mediated esophagitis and/or gastritis, radiologic colonic inflammation, and use of non-ICI, GI-toxic medications.

Data collected included demographic data (age, sex, race, ethnicity), cancer characteristics (type, stage), ICI regimens and durations, GI-symptom details (type, timing, and CTCAE grading of diarrhea and enterocolitis), stool biomarker results (calprotectin and lactoferrin), endoscopic and histologic findings, imaging results, treatment modalities (supportive care, steroids, biologics, fecal microbiota transplantation), hospitalizations, treatment responses, recurrence, complications, ICI resumption, and vital status.

Ethics

This study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. Given its retrospective design, the requirement for informed consent was waived.

Statistical analysis

Descriptive statistics were used to summarize patient demographics, clinical features, diagnostic findings, treatments and outcomes of IMEN. Continuous variables, such as age, duration of ICI therapy, calprotectin level, duration of steroid use and time to clinical remission, were reported as medians with interquartile ranges (IQRs). Categorical variables, including cancer type, ICI class, symptom presentation, endoscopic findings and treatment modalities, were summarized using frequencies and percentages. Comparative analyses were conducted to evaluate the differences in subtypes of small-bowel inflammation (e.g., duodenitis, ileitis, multi-site involvement), between patients with isolated IMEN and those with IMEN progressing to immune-mediated colitis, and between patients receiving escalated immunosuppression (e.g., biologics) vs. steroids alone. All analyses were conducted using SPSS software (version 24.0; IBM Corp).

Results

Patient characteristics

Among 20,991 patients treated with ICIs, only 30 (0.143%) developed IMEN confirmed through endoscopy and histology (Fig. 1). As shown in Table 1, the median age at first ICI dose was 69.5 years (IQR 51-73.7 years), and most patients were male (73.3%) and White (80.0%). The most common cancer types included GI/hepatobiliary cancer (26.7%) and melanoma (23.3%). The majority (60.0%) had stage III-IV disease. Nivolumab (46.7%), ipilimumab (33.3%) and pembrolizumab (30.0%) were the most used ICIs, with smaller numbers of patients receiving atezolizumab, tremelimumab, cemiplimab, or relatlimab plus nivolumab. PD-1/PD-L1 inhibitors were used in 60.0% of patients, CTLA-4 inhibitors were used in 20.0% of patients, and combination therapies were used in 20.0% of patients. The median ICI treatment duration was 5.4 months (IQR 1.8-13.4 months). Baseline Eastern Cooperative Oncology Group scores were 0 in 26.7% of patients, 1 in 50.0% of patients, and 2-4 in 23.3% of patients. The all-cause mortality rate was 36.7% over a median follow up of 0.8 years (IQR 0.3-1.6). Only 1 death was potentially attributable to IMEN, and concerned a patient who had persistent diarrhea requiring prolonged steroid taper and subsequent discontinuation of cancer therapy. All other deaths were primarily due to cancer progression, with additional causes including septic shock, acute hypoxic respiratory failure, and malignant small bowel obstruction due to malignancy.

Characteristics of IMEN

As shown in Table 2, the most common presenting symptom among patients with IMEN was nausea (66.7%), followed by diarrhea (53.3%), vomiting (46.7%) and abdominal pain (20.0%). Less frequent symptoms included hematochezia/melena (10.0%), bloating (3.3%), and fever (3.3%). The median duration from ICI initiation to symptom onset was 135 days (IQR 47-332.5). Among the 16 patients with diarrhea, 62.5% had a CTCAE grade of 2 or higher. Lactoferrin results were positive in 91.7% of patients (11/12), and the median initial calprotectin level was 323 μg/g (IQR 105-2770 μg/g, n=11), suggesting the presence of intestinal inflammation, although the calprotectin levels may not reliably reflect the overall inflammatory burden. Endoscopic evaluation in all patients revealed predominantly non-ulcerative inflammation (60%), followed by ulcerative changes (20%) and normal mucosa (20%) (Fig. 2). Histologic evaluation was positive in all 30 patients, showing features such as increased intraepithelial lymphocytes, villous blunting or atrophy, crypt apoptosis, cryptitis, a mixed inflammatory infiltrate in the lamina propria, occasional crypt abscesses, and mucosal ulceration in severe cases.

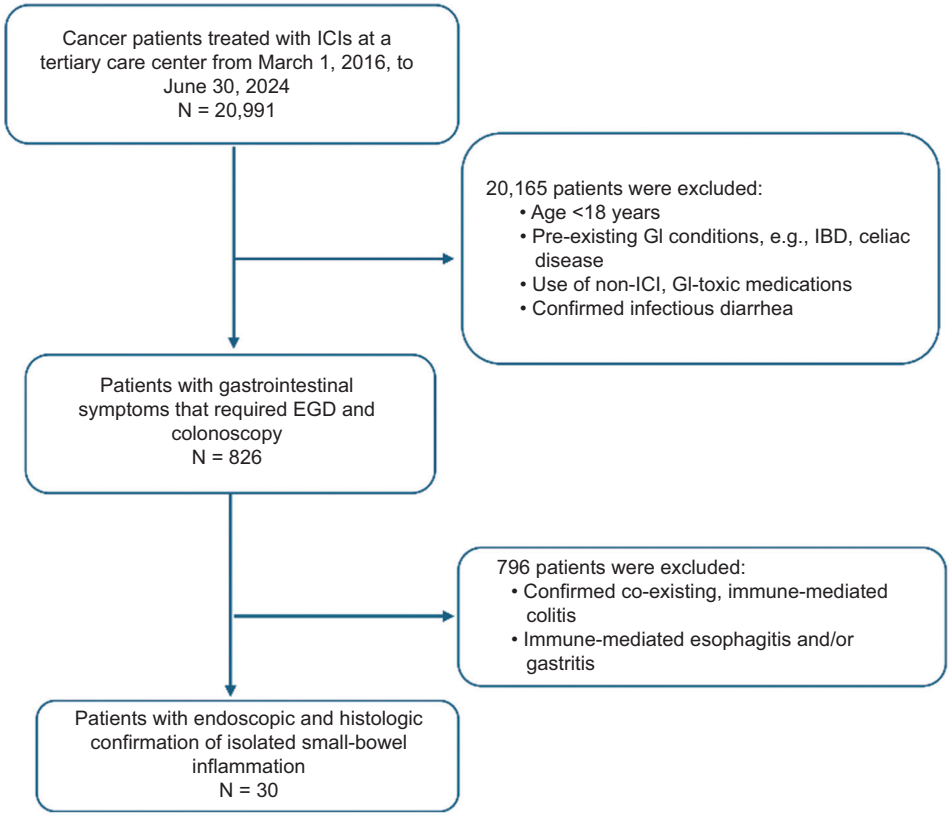

Figure 1 Patient selection flowchart
EGD, esophagogastroduodenoscopy; GI, gastrointestinal; IBD, inflammatory bowel disease; ICI, immune checkpoint inhibitor

Table 1 Patient demographic characteristics, n=30

Characteristics	No. (%)
Age at the time of first dose of ICI, median (IQR), *years*	69.5 (51-73.7)
Sex – Male	22 (73.3)
Race – White	24 (80.0)
Cancer type	
GI/hepatobiliary	8 (26.7)
Melanoma	7 (23.3)
Genitourinary	6 (20.0)
Lung	5 (16.7)
Head and Neck	4 (13.3)
Cancer stage (AJCC)	
I-II	6 (20.0)
III-IV	18 (60.0)
Unspecified	6 (20.0)
ICI therapy received	
Nivolumab	14 (46.7)
Ipilimumab	10 (33.4)
Pembrolizumab	9 (30.0)
Atezolizumab	2 (6.7)
Tremelimumab	1 (3.4)
Cemiplimab	1 (3.4)
Relatlimab + nivolumab	1 (3.4)
Class of ICI therapy received	
PD-1/PD-L1	18 (60.0)
CTLA-4	6 (20.0)
Combination	6 (20.0)
Duration of cancer therapy, median (IQR), *months*	5.4 (1.8-13.4)
ECOG	
0	8 (26.7)
1	15 (50.0)
2-4	7 (23.3)
All-cause mortality	11 (36.7)
Length of follow up, median (IQR), *years*	0.8 (0.3-1.6)

ICI, immune checkpoint inhibitors; IQR, Interquartile range; GI, gastrointestinal; AJCC, American Joint Committee on Cancer; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ECOG, Eastern Cooperative Oncology Group

Table 2 Characteristics of IMEN, n=30

Characteristics	No. (%)
Presenting symptoms	
Nausea	20 (66.7)
Diarrhea	16 (53.3)
Vomiting	14 (46.7)
Abdominal pain	6 (20.0)
Hematochezia/melena	3 (10)
Bloating	1 (3.4)
Fever	1 (3.4)
CTCAE Grade, diarrhea, n=16	
<2	6 (37.5)
≥2	10 (62.5)
CTCAE Grade, enterocolitis, n=16	
<2	13 (81.3)
≥2	3 (18.8)
Lactoferrin positive, n=12[1]	11 (91.7)
First calprotectin levels, median (IQR), n=11[2]	323 (105-2770)
Endoscopy (within 6 months before or after IMEN diagnosis), n= 30[3]	
Ulcerative inflammation	6 (20)
Non-ulcerative inflammation	18 (60)
Normal findings	5 (16.7)
Treatment of IMEN	
Steroids	15 (50.0)
Biologics[4]	7 (23.3)
Median duration from ICI initiation to symptom onset, days (IQR)	135.0 (47.0-332.5)
Number of days of steroids, median (IQR)	63 (37.5-148.3)
Number of steroid tapers, median (IQR)	1 (0.5-2.0)
Hospitalization for IMEN	11 (36.7)
Length of hospitalization, median (IQR), *days*	7 (4-10)
ICI held	16 (53.3)
ICI resumed	3 (10.0)
IMEN clinical remission	19 (63.3)
Time from IMEN to clinical remission, median (IQR), days	28.5 (7-62.5)
Complications at the end of study (fistula formation)	3 (10.0)

[1]n= ***, patients who were tested for lactoferrin
[2]n= ***, patients who got tested for calprotectin
[3]n=***, patients who underwent endoscopy
[4]Number of people who received infliximab = 2, Number of people who received vedolizumab = 6, with 1 person requiring both vedolizumab and infliximab for enterocolitis
Of 30 patients who had IMEN, 2 of them later developed IMC
IMEN, immune mediated enteritis; CTCAE, common terminology criteria for adverse events; IQR, interquartile range; ICI, immune check-point inhibitors

Half of the patients received steroids, and 23.3% were treated with biologics (vedolizumab in 6, infliximab in 2, and 1 receiving both). The median steroid duration was 63 days (IQR 37.5-148.3 days), with 1 taper (IQR 0.5-2.0). IMEN resulted in hospitalization for 36.7% of patients (median stay 7 days; IQR 4-10 days). ICI therapy was withheld in 53.3% of patients and resumed in 10%. Clinical remission was achieved in 63.3% of patients with IMEN, with a median time to remission of 28.5 days (IQR 7-62.5 days). At the end of the study, 10% of patients had developed complications (fistula formation), and 2 patients subsequently developed immune-mediated colitis.

Comparison between patients with duodenitis, ileitis or both

Among the 30 patients with isolated enteritis, 80% (n=24) had isolated duodenitis, 10% (n=3) had isolated ileitis, and 10% (n=3) had both (Table 3). Most patients (66.7%) with duodenitis had been treated with PD-1/PD-L1 inhibitors. In contrast, patients with ileitis or multi-site involvement were equally likely to have received PD-1/PD-L1 therapy, CTLA-4 therapy, or combination therapies (33.3% of patients in each category). This suggests a potential predominance of PD-1/PD-L1/PD-L1-related toxicity in patients with upper-small-bowel involvement.

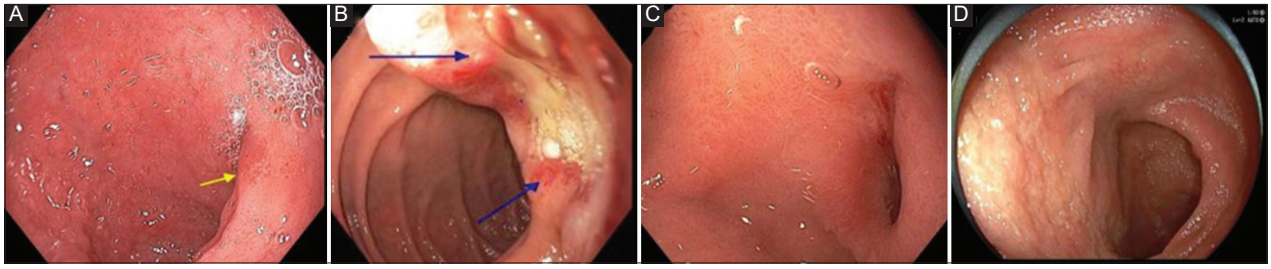

Figure 2 Endoscopic features of ICI enteritis. (A) Non-ulcerative inflammation of the duodenum; (B) ulcerative inflammation of the duodenum; (C) duodenal deformity after immune-mediated enteritis; (D) non-ulcerative inflammation of the ileum
ICI, immune checkpoint inhibitor

In terms of presenting symptoms, nausea was the most frequent symptom in the patients with duodenitis (70.8%), whereas diarrhea was the most common symptom in patients with ileitis (100%). Nausea, vomiting, and diarrhea were equally common in patients with both types of enteritis (66.7%). Abdominal pain was noted only in the patients with duodenitis (20.8%) and in patients with both types of enteritis (33.3%). Among patients with diarrhea, CTCAE grade 2 or higher was observed in 66.7% of patients with duodenitis, 66.7% of patients with both types of enteritis, and 33.3% of patients with ileitis.

The inflammatory biomarkers were notably higher in the patients with both types of enteritis. The median calprotectin level was 1335.5 μg/g for those with both types of enteritis, compared with 78 μg/g for those with duodenitis and 319 μg/g for those with ileitis. The lactoferrin positivity rate was 100% for patients with both types of enteritis, compared with 58.3% for those with duodenitis and 66.7% for those with ileitis. The histologic evaluation highlighted a greater inflammatory burden in the patients with ileitis and in those with both types of enteritis (100% in each vs. 0% in the patients with duodenitis), whereas the endoscopic evaluation revealed a greater inflammatory burden in the patients with both types of enteritis (100%) and in those with duodenitis (91.6%) than in those with ileitis (0%). Computed tomography scans of the abdomen were positive for inflammation in 66.7% of patients with both types of enteritis. In terms of treatment, intravenous steroids were used in 33.3% of patients with both types of enteritis, vs. 16.7% of patients with duodenitis and 0% of patients with ileitis. The use of biologics was higher in patients with both types of enteritis (66.7%), compared to those with duodenitis (16.7%) or ileitis (33.3%). Isolated duodenitis demonstrated a favorable response to supportive therapy alone, including proton pump inhibitors, H2 receptor antagonists, or ondansetron. The hospitalization rates were highest in the patients with both types of enteritis (66.7%), and their median hospital stay was longer (13.5 days), compared with 6.5 days for the patients with duodenitis and 0 days for the patients with ileitis. Clinical remission was achieved in 100% of patients with both types of enteritis, compared with 66.7% of those with ileitis and 58.3% of those with duodenitis. ICI therapy was more often withheld in patients with ileitis (66.7%) than in those with duodenitis (54.2%) or both types of enteritis (33.3%), and ICI treatment was resumed in 12.5% of patients with duodenitis, compared with none of the patients in the other 2 groups.

Discussion

Although GI toxicities from ICIs are well documented, most of the literature centers on colonic involvement. In contrast, isolated or predominant small-bowel injury remains underrecognized and underreported, creating a gap in understanding its clinical behavior, diagnostic features, and therapeutic approaches. This study presents a comprehensive characterization of isolated IMEN, a rare but clinically significant condition in patients treated with ICI therapy. Our findings highlight several important clinical, endoscopic and histologic features that distinguish isolated enteritis from the more commonly recognized ICI-induced colitis. In our study, IMEN often presented with nonspecific symptoms, such as non-bloody diarrhea, nausea and vomiting, with a delayed onset of up to 1 year following ICI therapy. Endoscopic evaluation was unrevealing in some cases. Histologically, IMEN is characterized by villous blunting, intraepithelial lymphocytosis and crypt apoptosis; these findings contrast with the neutrophil-predominant inflammation seen in colitis. Additionally, biomarkers like fecal calprotectin may be variably elevated in patients with IMEN and do not consistently correlate with disease severity. These distinct features underscore the need for heightened clinical awareness and tailored diagnostic strategies for IMEN.

In our cohort, only 0.143% of ICI-treated patients developed histologically confirmed enteritis, underscoring its rarity. ICI-induced duodenitis and ileitis pose a diagnostic challenge for patients and clinicians for several reasons [10]. First, patients may present with nonspecific GI symptoms that could mimic other GI disease entities, including dyspepsia, gastritis, celiac disease and enteropathy induced by nonsteroidal anti-inflammatory drugs [10]. The lack of specific symptoms highlights the importance of having an appropriate level of suspicion regarding ICI-induced enteritis, and of obtaining a comprehensive evaluation, including upper endoscopic imaging, in possibly affected patients, to avoid delaying a diagnosis and therapy.

Differentiating ICI-related small-bowel injuries from other entities (e.g., preexisting celiac disease, ICI-induced celiac-like

Table 3 Comparison of clinical variables between duodenitis and ileitis

Variables	Isolated enteritis, n=30(%)		
	Isolated duodenitis, n=24 (80)	Isolated ileitis, n=3 (10)	Both, n=3 (10)
ICI class type			
PD-1/PD-L1	16 (66.7)	1 (33.4)	1 (33.4)
CTLA-4	4 (16.7)	1 (33.4)	1 (33.4)
Combination	4 (16.7)	1 (33.4)	1 (33.4)
Presenting symptoms			
Nausea	17 (70.8)	1 (33.4)	2 (66.7)
Vomiting	11 (45.8)	1 (33.4)	2 (66.7)
Diarrhea	12 (50)[1]	3 (100)	2 (66.7)
Abdominal pain	5 (20.8)	0 (0)	1 (33.4)
CTCAE diarrhea grade ≥2, n=16[2]	8[1] (66.7)	1 (33.4)	2 (66.7)
CTCAE enterocolitis grade ≥2, n=16[3]	2 (16.7)	0 (0)	1 (33.4)
Calprotectin, median (IQR), n=11[4]	78 (201-2805)	319 (315-323)	1335.5 (1167.8-1503.3)
Lactoferrin positivity, n=12[5]	7 (58.3)	2 (16.7)	3 (100)
CT abdomen positive inflammation	8 (33.4)	0 (0)	2 (66.7)
Colonoscopy			
Positive	0	2 (66.7)	3 (100)
Negative	8 (33.4)	0 (0)	0 (0)
Positive histology	0	3 (100)	3 (100)
Endoscopy (EGD)			
Positive	22 (91.6)	0 (0)	3 (100)
Negative	2 (8.4)	0 (0)	0 (0)
Positive histology	24 (100)	0 (0)	3 (100)
Histology characteristics			
Intraepithelial lymphocytes	4 (16.7)	N/A	1 (33.3)
Lamina propria mixed inflammation (lymphocytes,plasma cells, neutrophils, eosinophils)	17 (70.8)	N/A	2 (66.7)
Villous blunting	7 (29.1)	N/A	1 (33.3)
Cryptic injury (neutrophils in crypt epithelium, crypt abscesses, increased apoptosis)	4 (16.7)	N/A	1 (33.3)
Ulceration/erosions (epithelial erosion)	5 (20.8)	N/A	0 (0)
Median days of hospitalization, median (IQR)	6.5 (3-8)	0 (0)	13.5 (9.8-17.3)
Clinical remission achieved	14 (58.4)	2 (66.7)	3 (100)
ICI held	13 (54.2)	2 (66.7)	1 (33.4)
ICI resumed	3 (12.5)	0 (0)	0 (0)

[1]50 Half of the isolated duodenitis cases presented with diarrhea. Of these, 50% had CTCAE grade ≥2, and 12.5% had grade ≥2 enterocolitis, suggesting possible undetected jejunal inflammation due to lack of biopsies

[2, 3]n= ***, patients with diarrhea

[4]n= ***, patients who were tested for lactoferrin

[5] n= ***, patients who were tested for calprotectin

ICI, immune check- point inhibitors; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; CTCAE, common terminology criteria for adverse events; CT, computed tomography; EGD, esophagogastroduodenoscopy; IQR, interquartile range

enteropathy, and seronegative duodenitis) remains a diagnostic challenge. The histopathologic features of these conditions often overlap, making it difficult to rely on histology alone for definitive classification [11]. In our study, patients with a prior diagnosis of celiac disease were excluded to avoid confounding and allow a more focused evaluation of ICI-associated enteropathies. Celiac serology may also be considered as part of the standard evaluation in this population, to identify ICI-induced, *de novo* seropositive celiac enteropathy.

A high proportion of patients showed significant inflammation on endoscopy, cross-sectional imaging or both, and these individuals were more likely to have involvement of both the duodenum and ileum. Although endoscopic findings were central to diagnosis, 20% of patients had histologic disease despite a normal endoscopic appearance, underscoring the importance of biopsy in symptomatic patients. In these cases, tissue was obtained through a standardized random biopsy protocol: multiple random biopsies were taken from normal-

appearing duodenal mucosa, and similarly, random terminal ileal biopsies were obtained when the ileum appeared normal. These systematic sampling practices explain the detection of histologic abnormalities despite unremarkable visual findings.

A subtype analysis revealed key differences between patient groups. Duodenitis was the most common form of isolated enteritis and appeared strongly associated with the use of PD-1/PD-L1 inhibitors, whereas ileitis and duodenitis plus ileitis were evenly distributed across ICI classes. Diarrhea was more frequent and severe in ileitis (100%) and combined site (66.7%) cases, which were also associated with higher calprotectin levels, greater histologic inflammation, and more intensive treatment (e.g., higher biologic use and hospitalization rates). These findings suggest that ileal or multifocal small bowel involvement may represent a more aggressive phenotype of IMEN, warranting earlier escalation of therapy.

Jejunal involvement has rarely been reported in patients with ICI-related enteritis. To date, only 1 case has described isolated jejunitis, in which jejunal ulcers were observed. Computed tomography angiography revealed active extravasation at multiple sites in the proximal jejunum, necessitating surgical resection of approximately 40 cm of ulcerated bowel [12]. Although jejunal biopsies are not routinely performed, this case highlights that isolated jejunitis—though rare—should be considered in the differential diagnosis and may warrant targeted evaluation in patients with suspected IMEN.

Although clinical remission was achieved in most patients (63.3%), only 12.5% were able to resume immune checkpoint inhibitor (ICI) therapy, highlighting the substantial difficulty of safely rechallenging ICIs after IMEN and its negative impact on continuity of cancer treatment. Among the 16 patients in whom ICI therapy was held, 13 did not resume ICIs within 3 months of the index event: 10 patients (76.9%) due to persistent or recurrent enteritis symptoms, 2 patients (15.4%) due to other immune-related adverse events (arthritis in one patient and pneumonitis in another), and 1 patient (7.7%) due to patient preference. Notably, we found that patients with ileitis or combined duodenitis/ileitis had higher remission rates (100% and 66.7%, respectively) than did patients with duodenitis alone (58.4%), which may reflect differences in both disease biology and treatment intensity.

This retrospective study was subject to several limitations, including referral bias, variability in diagnostic evaluation and limited generalizability due to its single-center design. Small subgroup sizes, particularly for ileitis and combined duodenitis–ileitis, reduced the statistical power. Given that jejunal evaluation is not routinely performed in our current clinical practice, jejunitis could have been under-reported, though we noted that none of the patients who underwent jejunal biopsy in a small sub-cohort of our patients showed histologic inflammation. Although techniques such as enteroscopy and double balloon enteroscopy were used when clinically indicated, the limited number of biopsies raises the possibility of underdiagnosis and represents an additional limitation.

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Summary Box

What is already known:

- Diarrhea (37%) and colitis (8%) are the most common serious immune-related adverse events from immune checkpoint inhibitor (ICI) therapy
- Isolated enteritis cases often involve the duodenum, with findings that can mimic celiac disease (e.g., villous atrophy, friable mucosa, lymphocytic infiltration)
- Risk factors for ICI-induced enterocolitis include ICI type/dose, combination therapy, anti–cytotoxic T-lymphocyte–associated protein 4 agents, use of nonsteroidal anti-inflammatory drugs, pre-existing inflammatory bowel disease, microbiota and tumor histology; mechanisms for isolated enteritis remain unclear
- Recognition of ICI-induced enteritis is increasing, but most studies group it with colitis, and few retrospective cohort studies exist

What the new findings are:

- Among 20,991 ICI-treated patients, only 30 (0.143%) developed histologically confirmed immune-mediated enteritis (IMEN), highlighting its rarity
- Most patients showed significant inflammation on endoscopy, cross-sectional imaging, or both, with many having both duodenitis and ileitis; 20% had histologic disease despite normal endoscopy, emphasizing the importance of biopsy in symptomatic patients
- While clinical remission was observed in 63.3% of patients, only 12.5% restarted ICI therapy, reflecting persistent barriers to treatment resumption after IMEN
- Patients with ileitis or combined duodenitis/ileitis had higher remission rates (100% and 66.7%) than those with duodenitis alone (58.4%), suggesting differences in disease biology and treatment response

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