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Immune-mediated diarrhea and colitis with normal biochemical, endoscopic and histologic findings: a retrospective study

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Abstract

Background Immune-mediated diarrhea and colitis (IMDC) due to checkpoint inhibition infrequently presents with normal stool biomarkers and no endoscopic or histologic evidence of inflammation. Little is known about the treatment needs and outcomes of this subset of patients. We aimed to describe this entity and clarify the role of immunosuppressive treatments in its management.

Methods This was a single-center, retrospective study of patients treated with immune checkpoint inhibitors who developed clinical symptoms of IMDC, with no evidence of inflammation based on fecal calprotectin or endoscopic/histologic evaluation, between January 2010 and February 2024.

Results Of 1151 patients with IMDC, 131 (11.4%) had no evidence of inflammation. These patients more frequently had PD-1/L1 agent exposure (P=0.019) and presented with less severe diarrhea than patients with evidence of inflammation (P<0.001). This group had a lower rate of hospitalization (P=0.003). Around 40% of patients with no evidence of inflammation required immunosuppressive treatment. There was no difference in clinical symptoms or severity between patients requiring immunosuppression and those who did not.

Conclusions Our study is the first to explore IMDC with no elevations in calprotectin and normal endoscopic/histologic findings. We found that PD-1/PD-L1 inhibition may predispose patients to developing this form of IMDC, which is associated with a lower severity of diarrhea, fewer hospitalizations and lower recurrence rates. Many patients still require immunosuppressive treatment, and a small subset later develop colonic inflammation. Future studies are needed to further elucidate the treatment needs and outcomes of this patient population.

Keywords Immune-mediated diarrhea and colitis, immunotherapy, infliximab, vedolizumab

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Introduction

Immune checkpoint inhibitors (ICIs) have become the standard-of-care treatment for multiple types of malignancy in recent years [1]. ICIs exert their immunostimulatory effects by inhibiting the programmed death-1/ligand-1 (PD-1/L1), cytotoxic T-lymphocyte antigen-4 (CTLA-4), or leukocyte activation gene-3 (LAG-3) immune checkpoints, allowing for more potent antitumor immune responses. Although effective at treating cancer, these immunomodulators come with the risk of generating autoimmune responses—more commonly referred to as immune-related adverse events—that can affect

virtually any organ system in the body [2,3]. Toxicity in the gastrointestinal tract is among the more common and severe immune-related adverse events, with immune-mediated diarrhea and colitis (IMDC) the primary manifestation [2,3].

Almost one third of patients treated with ICIs develop IMDC, which frequently necessitates ICI therapy discontinuation [4,5]. Given the various etiologies for diarrhea and colitis in this patient population, a thorough investigation is essential. After the exclusion of infectious causes, fecal lactoferrin and calprotectin assessments can be useful tools to help identify patients at high risk for active colonic inflammation, with sensitivities of 70% for endoscopic inflammation and 90% for histologic inflammation [6]. Endoscopic evaluation is critical in these patients because certain high-risk features have been associated with worse outcomes and the need for more aggressive treatment [6]. Endoscopically, IMDC presents with a mix of gross and histologic features from multiple colitides, sharing elements from Crohn's disease, ulcerative colitis, and microscopic colitis [7,8].

A small subset of patients receiving ICIs may present with the clinical symptoms of IMDC but, upon further investigation, have no evidence of inflammation in the colon. Previous studies have reported that anywhere from 18-37% of patients may have no obvious signs of mucosal injury upon gross examination of the colon during endoscopy [6,8-11]. These studies typically recommend a biopsy of the normal mucosa to evaluate for underlying histologic inflammation. Interestingly, a reported 8-15% of patients have negative findings for inflammation on both endoscopic and histologic assessments [6,8,10]. Despite these normal findings, these patients continue to have clinical symptoms of diarrhea that are not explained by any other entity. Aside from the 3 studies cited above, the literature on what appears to be a subtype of IMDC with normal endoscopic findings is sparse. In clinical practice, these symptomatic patients may also have normal stool inflammatory markers, with no other identifiable factors that could explain the diarrhea. Very little is known about this disease entity, and whether it represents the early phases of true IMDC or reflects an entirely new entity, such as a possible immune-mediated irritable bowel syndrome (IBS).

The aim of the current study was to explore the clinical characteristics, management and outcomes of patients who had this suspected IMDC subtype, with negative stool inflammatory workup and endoscopic/histologic findings, and to compare this subgroup with a cohort of patients who showed a more classic IMDC presentation.

Patients and methods

Ethics committee approval

This study was approved by the Institutional Review Board (PA18-0472) with a waiver of informed consent.

Patient selection

This was a retrospective, single-center study of patients who received ICI therapy and developed clinical symptoms of IMDC between January 2010 and February 2024. Patients included in the study met the following criteria: 1) older than 18 years; 2) had a cancer diagnosis and received anti-CTLA-4, anti-PD-1/PD-L1, or combination ICI therapy; 3) developed symptoms of IMDC; and 4) were diagnosed with IMDC based either on chart review of clinical characteristics, stool test results, or endoscopic and/or histologic findings. Two groups were created: the negative objective inflammation group, consisting of IMDC patients who underwent lower endoscopy with biopsy or fecal calprotectin testing that was negative for active inflammation (main group used for analysis purposes); and the positive objective inflammation group (those with endoscopic evidence of inflammation or elevated fecal calprotectin levels were included solely for subgroup analysis). Patients with abnormal lactoferrin levels were included only if all other mentioned workup showed normal results. The diagnosis of IMDC was established by chart review of clinical characteristics, stool test results, endoscopic findings, and/or histologic results. Patients whose diarrhea was attributed to other causes or had evidence of endoscopic inflammation, apart from mild edema and histologic inflammation, were excluded. The STROBE checklist was used as a template for data reporting.

Data collection

We extracted demographic data (including age, sex and race), oncologic data (including cancer type, cancer stage and cancer treatment—anti-PD-1/PD-L1, anti-CTLA-4, or combination of both), and IMDC-related clinical variables (clinical symptoms, peak Common Terminology Criteria

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for Adverse Events grade, symptom duration, stool test results, and treatment agents and doses) from electronic health records. Cancer staging was determined according to the American Joint Committee on Cancer's Cancer Staging Manual, 8th edition.

Identification of IMDC

IMDC-related data reviewed included stool infectious workup results (*Clostridioides difficile* testing, gastrointestinal multiplex pathogen panel, stool cultures), results of assessments of inflammatory markers (fecal lactoferrin and/or calprotectin), and lower endoscopy data for all patients treated with ICIs during the period studied. Each set of patient data was then independently screened to identify confirmed or strongly suspected IMDC. Normal workup results were defined as negative fecal calprotectin results and/or normal endoscopic findings, at least at baseline, as well as normal stool infectious workup results. Patients were excluded if other etiologies for their gastrointestinal symptoms, such as ischemic, infectious, tumor-related, drug-induced, endocrine or autoimmune causes were identified, or if they did not have either a baseline stool calprotectin or endoscopic evaluation on record. For patients receiving chemotherapy in tandem with immunotherapy, attempts were made to distinguish between ICI-induced diarrhea and diarrhea caused by other agents based on clinical history. If we were unable to make this distinction, the patient was excluded from our analysis.

Outcomes and definitions

The primary outcome of this study was to describe the clinical characteristics, management and outcomes of patients who had this suspected IMDC subtype, and to compare these variables with a cohort of patients who showed a more classic IMDC presentation.

Statistical analysis

Statistical analyses were performed using SPSS version 24.0 (SPSS Inc, Chicago, IL). The distribution of continuous variables was summarized using medians and interquartile ranges. The distribution of categorical variables was summarized using frequencies and percentages. Continuous variables were compared between groups using the Wilcoxon rank-sum test. The Fisher exact test or chi-square test was used to evaluate associations between categorical variables in group comparisons. Univariate logistic regression was used to identify factors linked to an aggressive disease course needing immunosuppressive therapy in patients whose initial testing was negative for inflammation, and multivariate regression was performed for variables with $P<0.2$ on univariate regression, or those deemed clinically relevant by the authors. All statistical tests were 2-sided, and P-values less than or equal to 0.05 were considered statistically significant.

Results

Demographic information

Out of a total of 1151 patients with IMDC, 131 (11.4%) met the inclusion criteria for the study, representing 0.6% of all patients who received immunotherapy (131/22,061) (Fig. 1). Demographic characteristics are shown in Table 1. Our cohort was predominantly white (86.3%) and male (57.2%) and had a median age of 65.7 years (interquartile range [IQR] 56.2-72.6). Most patients received treatment with PD-1/PD-L1 agents (61.1%); CTLA-4 (13.7%) and combination therapy (25.2%) were less frequently used. Most patients had stage III (22.1%) or IV (67.9%) cancer, with melanoma (29.8%) and genitourinary cancer (27.5%) being the most common, followed by lung (10.7%) and gastrointestinal (9.2%) cancer.

Table 1 Demographic characteristics of patients who had IMDC with no objective evidence of inflammation, n=131[1]. Results are given as n (%) unless otherwise indicated

Characteristic	Value
Median (IQR) age at the time of immunotherapy, *years*	65.7 (56.2-72.6)
Male sex	75 (57.2)
White race	113 (86.3)
Type of immune checkpoint inhibitor	
PD-1/PD-L1 agent	80 (61.1)
CTLA-4 agent	18 (13.7)
Combination	33 (25.2)
Median (IQR) duration of immunotherapy, *months*	8.7 (2.8-15.8)
Cancer type	
Melanoma	39 (29.8)
Genitourinary	36 (27.5)
Lung	14 (10.7)
Gastrointestinal	12 (9.2)
Head and neck	5 (3.8)
Other	25 (19.1)
Cancer stage	
I	5 (3.8)
II	8 (6.1)
III	29 (22.1)
IV	89 (67.9)
ECOG performance status	
0	54 (41.2)
1	60 (45.8)
2-4	17 (13.0)
Death, any cause	72 (40.3)
Median (IQR) length of follow up, *years*	1.5 (0.5-3.7)

[1]Initial workup was considered normal if the patient had normal histologic findings on the pathology report, or a calprotectin level lower than 80 μg/g if a baseline lower endoscopy report was not available. A total of 31 patients (23.7%) had both normal calprotectin and endoscopy findings at baseline, 28 (21.4%) had only endoscopy done at baseline, and 72 (55.0%) had only fecal calprotectin ordered at baseline, with all of these studies showing normal results
IMDC, immune-mediated diarrhea and colitis; IQR, interquartile range; PD-1/L1, programmed death-1/ligand-1; CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG, Eastern Clinical Oncology Group

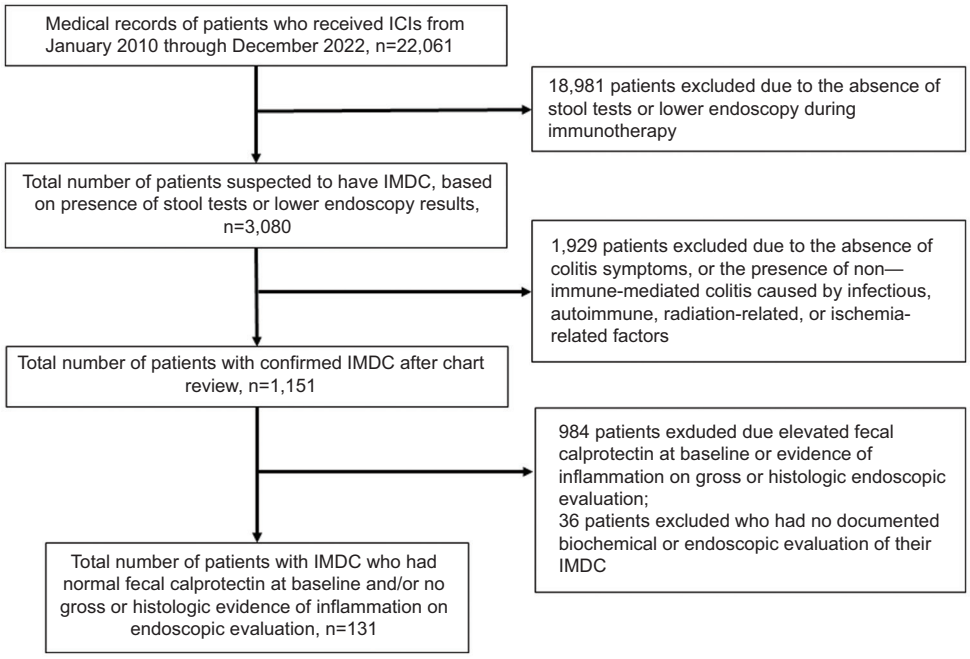

Figure 1 Patient selection flowchart
ICIs, immune checkpoint inhibitors; IMDC, immune-mediated diarrhea and colitis

In addition, 87.0% of patients had an Eastern Cooperative Oncology Group performance status of 0-1. Finally, there was a 40.3% rate of all-cause mortality, with a median follow up of 1.5 years (IQR 0.5-3.7).

Clinical features

Details regarding patient disease characteristics in our cohort can be found in Table 2. IMDC typically occurred about 3.8 months after ICI therapy initiation (IQR 1.6-8.8) and mostly presented as diarrhea of grade 2 or above (65.1% of patients). Diarrhea was the primary symptom, affecting 99.2% of patients, and roughly a quarter of patients (27.5%) had abdominal pain. Less than half of the patients required treatment with steroids (40.5%), and around a quarter needed more aggressive management of IMDC with selective immunosuppressive therapy (SIT; 23.6%). Most patients (58.5%) who required steroids started them within 2 weeks of disease onset, whereas more than half of the patients who needed SIT started the treatment more than 4 weeks after disease onset (58.1%). About half of the patients (49.6%) were hospitalized for their IMDC, for a median of 5 days (IQR 3-8). Of these, 35.4% required rehospitalization at some point in their disease course. Most patients had clinical remission at the time of our analysis (91.6%), with a recurrence rate of 66.7% among patients who restarted ICI therapy after initially stopping it. Of all 131 patients in the cohort, 12 (9.2%) had progression of their IMDC, with either elevated calprotectin or evidence of endoscopic or histologic inflammation at first follow up. Details of these cases can be found in Supplementary Table 1.

A total of 61 patients in the cohort required immunosuppressive treatment with steroids and/or SIT, compared with 70 whose IMDC was managed supportively. A comparison between these groups can be found in Table 3. Patients who required immunosuppressive therapy were more likely to have been hospitalized for their IMDC symptoms ($p<0.001$) and to have required multiple hospitalizations ($P=0.037$). They were also more likely to have had their ICI therapy withheld ($P=0.004$). There was no significant difference in presenting IMDC symptoms or grades between the groups.

Table 4 provides a comparison of IMDC features between patients with normal findings on their workup and those with evidence of inflammation on stool biomarker or endoscopic evaluation. Patients treated with PD-1/PD-L1 agents were more likely to develop IMDC with no objective evidence of inflammation ($P=0.019$). These patients tended to have a lower grade of diarrhea than those with evidence of inflammation on biochemical or endoscopic evaluation ($P<0.001$) but similar grades of colitis ($P=0.154$). Patients with evidence of inflammation were more likely to have been hospitalized ($P=0.003$) and had their ICI therapy withheld ($P=0.003$). However, there was no significant difference in treatments or other outcomes between the 2 groups.

Factors associated with the need for immunosuppressive treatment

A total of 11 factors for immunosuppressive treatment for IMDC were explored in a univariate analysis (Supplementary Table 2). Hospitalization (odds ratio [OR] 3.4, 95% confidence interval [CI] 1.7-7.04; $P=0.001$) and

Table 2 Clinical features of IMDC patients with no objective evidence of inflammation, n=131. Results are given as n (%) unless otherwise indicated

Characteristic	Value
Median (IQR) time from ICI therapy initiation to IMDC, *months*	3.8 (1.6-8.8)
Median (IQR) length of ICI therapy, *months*	8.7 (2.9-15.8)
CTCAE grade diarrhea, N=129	
0-1	45 (34.9)
2 and above	84 (65.1)
CTCAE grade colitis[1], N=128	
0-1	80 (62.5)
2 and above	48 (37.5)
Presenting symptoms	
Diarrhea	130 (99.2)
Abdominal pain	36 (27.5)
Blood or mucus in stool	17 (13.0)
Fever	13 (9.9)
Inflammatory markers	
Abnormal baseline lactoferrin, N=109	47 (43.1)
Median (IQR) calprotectin level at first assessment, μg/g, N=103	50 (17.2.5-54.9)
Median (IQR) calprotectin level at second assessment, μg/g, N=20	50 (34.3-229.0)
Median (IQR) calprotectin level at third assessment, μg/g, N=8	60 (50-317.8)
Lower endoscopy findings	
Histologic inflammation at baseline, N=59	0 (0)
Histologic inflammation at follow up, N=31	9 (29.0)
Median (IQR) time between baseline endoscopy and follow-up endoscopy, days	106.5 (27.3-123.5)
Calprotectin	
Baseline ≤80 μg/g	103 (78.6)
First follow up ≥100 μg/g, N=20	6 (30)
Median (IQR) time between baseline calprotectin assessment and first follow-up calprotectin assessment, days	84 (40.3-122.8)
Treatment	
Supportive[2]	111 (84.7)
Steroids	53 (40.4)
Within 2 weeks of IMDC onset, N=53	31 (58.5)
Within 4 weeks of IMDC onset, N=53	32 (60.4)
>4 weeks after IMDC onset, N=53	12 (22.6)
Median (IQR) number of steroid taper attempts	1 (1-2)
Median (IQR) time from IMDC onset to steroid use, days	2 (0-20.5)
Median (IQR) duration of steroid treatment, days	29 (15.0-54.5)
Intravenous steroids needed	21 (16.0)
SIT[3]	31 (23.7)
Within 2 weeks of IMDC onset, N=31	8 (25.8)
Within 4 weeks of IMDC onset, N=31	15 (48.4)
>4 weeks after IMDC onset, N=31	18 (58.1)
Median (IQR) time from IMDC onset to SIT use, days	30 (15-89)
Multiple SIT agents used, N=31	3 (9.7)
Median (IQR) number of SIT doses	3 (1.5-4)
Fecal microbiota transplant	3 (2.3)
Outcomes	
Clinical remission	120 (91.6)
Median (IQR) duration of IMDC symptoms, days	26 (13.0-66.0)
Hospitalization for IMDC	65 (49.6)
Median (IQR) length of hospitalization, days	5 (3-8)
Multiple hospitalizations, N=65	23 (35.4)
ICI therapy withheld	79 (60.3)
ICI therapy resumed	24 (28.6)
IMDC recurrence after ICI therapy was resumed, N=24	16 (66.7)
All-cause mortality	72 (39.7)
Median (IQR) length of follow up, years	1.5 (0.5-3.7)

[1]Based on CTCAE grading, grade 0-1 colitis refers to asymptomatic cases with clinical or diagnostic observation only
[2]Supportive treatments include hydration and anti-diarrheal medication
[3]SIT agents used to treat colitis included infliximab, vedolizumab, and ustekinumab
IMDC, immune-mediated diarrhea and colitis; IQR, interquartile range; ICI, immune checkpoint inhibitor; CTCAE, common terminology criteria for adverse events; SIT, selective immunosuppressive therapy

continuation of ICI therapy (OR 2.9, 95%CI 1.4-6.2; P=0.004) were associated with the use of immunosuppressive treatment, whereas other factors, such as cancer type and stage, type and duration of immunotherapy, diarrhea and colitis grade, and abnormal baseline lactoferrin were not. Multivariate logistic regression (Table 5) showed that only continuation of ICI therapy was associated with the use of immunosuppressive treatment (OR 3.4, 95%CI 1.3-8.6; P=0.011).

Discussion

Our study is the first to explore what we suspect is a unique subtype of IMDC that presents with normal stool inflammatory biomarkers and no signs of inflammation on endoscopic or histologic evaluation. We found that around 11.4% of patients with IMDC at our institution had completely normal initial workup findings. Patients who received PD-1/PD-L1 monotherapy were more likely to develop this subtype of IMDC. However, despite a higher diarrhea severity among patients with typical IMDC, there were no significant differences observed in outcomes between this "normal" subtype and patients with classic evidence of colonic inflammation—apart from hospitalization rates, which were higher in the inflammation-positive group. Around half of patients with normal workup findings later required immunosuppressive therapy with steroids and/or hospitalization. There was no difference in clinical symptomatology and most outcomes between patients with normal workup findings who did or did not require immunosuppressive therapy. Finally, 9.2% of the patients who initially had normal findings later showed endoscopic, histologic or biochemical features of inflammation.

Table 3 Clinical features of IMDC patients with no objective evidence of inflammation who did or did not receive immunosuppressive therapy, n=131

Characteristic	No. (%)		P-value
	No immunosuppressive therapy, N=70	Immunosuppressive therapy, N=61	
Median (IQR) time from ICI therapy initiation to IMDC, *months*	4.3 (1.7-10.6)	3.2 (1.6-6.5)	0.163
Median (IQR) length of ICI therapy, *months*	9.2 (4.7-19.5)	8.2 (2.2-12.4)	0.061
CTCAE grade diarrhea			0.066
0-1	29/68 (42.6)	16/60 (26.7)	
2 and above	39/68 (57.4)	44/60 (73.3)	
CTCAE grade colitis			0.067
0-1	48/68 (70.6)	32/59 (54.2)	
2 and above	20/68 (29.4)	27/59 (45.8)	
Presenting symptoms			
Diarrhea	70 (100)	61 (100)	
Abdominal pain	17 (24.3)	19 (31.1)	0.435
Fever	8 (11.4)	5 (8.2)	0.574
Blood or mucus in stool	7 (10.0)	10 (16.4)	0.308
Inflammatory markers			
Abnormal baseline lactoferrin, N=108	20/57 (35.1)	27/51 (52.9)	0.081
Median (IQR) calprotectin level at first assessment, μg/g, N=103	50 (16-55)	50 (20.3-50.3)	0.805
Median (IQR) calprotectin level at second assessment, μg/g, N=20	50 (50-55.2)	67.3 (20.1-241.5)	0.667
Median (IQR) calprotectin level at third assessment, μg/g, N=8	50 (50-50)	69.9 (50-341)	0.352
Median (IQR) time between baseline calprotectin assessment and first follow-up calprotectin assessment, days	89 (64-142)	62 (28-95)	0.153
Outcomes			
Clinical remission	61 (87.1)	59 (96.7)	0.061
Median (IQR) duration of IMDC symptoms, days	23 (11-63)	29 (13-68)	0.338
Hospitalization for IMDC	25 (35.7)	40 (65.6)	0.001
Median (IQR) length of hospitalization, days	4 (3-6)	5 (3-8)	0.780
Intravenous steroid administration	0 (0)	21 (34.4)	<0.001
Multiple hospitalizations	5 (17.1)	18 (29.5)	0.037
ICI therapy withheld	34 (48.6)	45 (73.8)	0.004
ICI therapy resumed[1]	13 (38.2)	11 (24.4)	0.331
All-cause mortality	29 (41.4)	27 (44.3)	0.860
Median (IQR) length of follow up, *years*	1.3 (0.4-3.8)	1.7 (0.7-3.5)	0.812

[1]The denominator for these rows is based on the total number of patients who withheld ICI therapy
[2]The denominator for these rows is based on the total number of patients who resumed ICI therapy
IMDC, immune-mediated diarrhea and colitis; IQR, interquartile range; ICI, immune checkpoint inhibitor; CTCAE, common terminology criteria for adverse events

The type of ICI therapy administered is known to impact the risk for IMDC and the way it manifests. Anti-PD-1/PD-L1 agents have been found to pose a lower risk for the development of IMDC, with an overall incidence of 1.2-10% compared with a 13.6-37% incidence among patients receiving CTLA-4 and/or combination therapies [4,12]. Patients who develop IMDC while receiving treatment with PD-1/PD-L1 agents tend to have a milder disease course, with a longer time to disease onset, fewer symptoms with lower grades of colitis, and a lower rate of ulceration on endoscopic evaluation [13]. Our study adds to this growing body of knowledge by showing that anti-PD-1/PD-L1 therapy may be associated with a unique subtype of IMDC that presents with no evidence of biochemical, endoscopic or histologic inflammation, manifesting only as the clinical symptoms of diarrhea and/or abdominal pain.

The reason for this discrepancy in the severity of toxicity of these different treatment types lies in their mechanisms. Although both the CTLA-4 and PD-1/PD-L1 proteins belong to the CD28/B7 family, they differ substantially in the signaling pathways they activate, the timing of their expression and the cells they target. Specifically, PD-1 is expressed later in the immune response by "exhausted" T cells in peripheral tissue that have undergone long-term stimulation in chronic disease [14]. In contrast, CTLA-4 is primarily expressed by immune cells in the lymphoid tissue, and inhibits T-cell activation early in the immune response [14]. CTLA-4 is thought to play a role in the negative selection process, and is a crucial element in preventing autoimmune disease—more so than PD-1/PD-L1 [14,15]. For this reason, blockade of CTLA-4 induces a more potent autoimmune response than blockade of other agents, which is consistent with our findings.

A key clinical question that the current study aimed to address was whether there is a need for immunosuppressive therapies among patients who have IMDC with no objective

Table 4 Comparing clinical features among IMDC patients with negative objective evidence of inflammation versus positive evidence of inflammation. Results are given as n (%) unless otherwise indicated

Features	No. (%)		P-value
	Negative objective findings, N=131 (11.7)	Positive objective findings, N=984 (88.3)	
Median (IQR) time from ICI therapy initiation to IMDC, *months*	3.7 (1.7-8.2)	3.2 (1.3-8.6)	0.525
Median (IQR) length of ICI therapy, *months*	6.5 (2.7-14.1)	5.4 (1.5-15.2)	0.171
CTCAE grade diarrhea			<0.001
0-1	45 (35.2)	163 (17.5)	
2 and above	83 (64.8)	771 (82.5)	
CTCAE grade colitis			0.154
0-1	79 (62.2)	515 (55.4)	
2 and above	48 (37.8)	415 (44.6)	
ICI type			0.019
PD-1/L1	79 (60.3)	466 (47.4)	
CTLA-4	19 (14.5)	174 (17.7)	
Combination	33 (25.2)	344 (35.0)	
Presenting symptoms			
Diarrhea	131 (100)	928 (98)	0.153
Abdominal pain	34 (26.6)	377 (39.8)	0.004
Fever	13 (10.2)	109 (11.5)	0.767
Blood or mucus in stool	17 (12.5)	129 (13.6)	0.890
Inflammatory markers			
Abnormal baseline lactoferrin, N=108	47 (42.3)	741 (84.2)	<0.001
Median (IQR) calprotectin level at first assessment, μg/g, N=103	50 (17.2-55)	317 (116.5-844.5)	<0.001
Median (IQR) calprotectin level at second assessment, μg/g, N=20	58 (50-70)	131 (50-381)	0.290
Median (IQR) calprotectin level at third assessment, μg/g, N=8	80 (80-80)	78.6 (50-302)	0.973
Median (IQR) time between baseline calprotectin assessment and first follow-up calprotectin assessment, days	101.5 (64-142)	64 (28-105)	0.018
Outcomes			
Clinical remission	120 (89.8)	901 (93.4)	0.140
Median (IQR) duration of IMDC symptoms, days	21 (10-57)	30 (11-65)	0.237
Hospitalization for IMDC	65 (49.2)	612 (63.1)	0.003
Median (IQR) length of hospitalization, days	5 (3-9)	6 (4-10)	0.095
Intravenous steroid administration	21 (26.7)	311 (31.8)	0.270
Multiple hospitalizations	22 (36.1)	246 (40.9)	0.497
ICI therapy withheld[1]	.85 (66.9)	747 (79.0)	0.003
ICI therapy resumed[2]	24 (42.4)	261 (35.0)	0.190
All-cause mortality	29 (41.4)	27 (44.3)	0.860
Median (IQR) length of follow up, *years*	1.4 (0.5-3.0)	1.5 (0.5-3.2)	0.560

[1]The denominator for these rows is based on the total number of patients who withheld ICI therapy
[2]The denominator for these rows is based on the total number of patients who resumed ICI therapy
IMDC, immune-mediated diarrhea and colitis; IQR, interquartile range; ICI, immune checkpoint inhibitor; CTCAE, common terminology criteria for adverse events

evidence of inflammation. Steroids and biologic agents, such as infliximab, vedolizumab and ustekinumab, are a mainstay of IMDC treatment [16,17], but come with the risk of side-effects and concerns about decreased ICI efficacy [18-20]. Clinicians, therefore, try to limit patient exposure to these agents if possible. Surprisingly, we found that IMDC patients with no objective evidence of inflammation still frequently required immunosuppression at an equal rate to those with fecal calprotectin elevations or endoscopic evidence of inflammation. Possible reasons for initiating immunosuppressive treatment in this population include symptoms refractory to supportive treatment, a high suspicion of ICI exposure as a causative factor, hospitalization for diarrhea symptoms, and a need to achieve symptom control for continuation of ICI therapy. Although counterintuitive, this result highlights the importance of both having a high clinical suspicion for IMDC in ICI-treated patients presenting with lower gastrointestinal symptoms, and not shying away from immunosuppressive treatments—even in the absence of any specific evidence of inflammation. We were unable to find any predictive factors to identify those patients who had IMDC with no evidence of inflammation

Table 5 Multivariate analysis of factors associated with immunosuppressive treatment with steroids for IMDC among patients with no initial evidence of inflammation, n=131

Covariate	OR (95%CI)	P-value
Diarrhea CTCAE – grade 2 and above vs. others	2.5 (0.9-6.5)	0.072
Colitis CTCAE – grade 2 and above vs. others	1.3 (0.5-3.2)	0.621
CTLA-4 regimen – yes vs. no	0.5 (0.1-2.1)	0.329
Abnormal baseline lactoferrin – yes vs. no	1.8 (0.8-4.2)	0.206
Hospitalization – yes vs. no	2.4 (1.0-5.8)	0.053
ICI therapy continued vs. discontinued	3.4 (1.3-8.6)	0.011*

*Significant at P<0.05

IMDC, immune-mediated diarrhea and colitis; OR, odds ratio; CI, confidence interval; CTCAE, common terminology criteria for adverse events; CTLA-4, cytotoxic T-lymphocyte antigen 4; ICI, immune checkpoint inhibitor

who were at risk for needing immunosuppressive treatment, aside from hospitalization. This poses a unique challenge in this subset of patients, because management of IMDC will have to be guided purely by clinical symptoms. This is in contrast to the more classic manifestation of IMDC, where endoscopic features can be used to predict the need for immunosuppressive therapy, and SIT in particular [6,8], and monitoring of stool biomarkers such as fecal calprotectin and repeat endoscopic evaluation can evaluate patients' responsiveness to treatment [16,21].

Whether there is a true absence of inflammation in this IMDC subtype is also unclear, and will need to be investigated further. The colonic inflammation typically associated with IMDC has been linked to the development of colon adenoma [22]. Endoscopic surveillance is therefore recommended for patients presenting with typical IMDC. This relationship has not been explored, however, in patients with normal endoscopic findings, and is typically not recommended for patients with IBS [23]. There are very few studies detailing the prevalence of functional diarrhea or IBS in a cancer patient population. One study reporting the prevalence of IBS in the general population suggested that diarrhea-predominant IBS had a prevalence of 5.5% [24]. Another study examining causes of diarrhea in cancer patients estimated a prevalence of 10-40% for the symptom in general, but did not include functional or IBS-related diarrhea [25]. The current study showed that around 0.6% of patients receiving immunotherapy develop diarrhea after treatment initiation, with no clear cause for their symptoms aside from ICI therapy. Because this is far below the reported prevalence for typical causes of diarrhea, we believe that this may represent a novel, possible immune-related adverse event affecting the gastrointestinal tract. Interestingly, gastropathy and enteropathy have been described as part of an overarching autonomic dysfunction related to checkpoint inhibition, although it remains unclear how this may factor into these diarrheal symptoms [26,27]. Future studies will be needed to explore the role of endoscopic surveillance in this patient population and further clarify the risks for IMDC progression and recurrence among patients with no objective evidence of inflammation on initial evaluation.

There are several limitations to our study design and findings. It was a retrospective study, and data were limited to whatever information could be found in patients' electronic health records, which may be lacking. Additionally, the decision was made to include patients with abnormal fecal lactoferrin values as long as other biomarkers, such as fecal calprotectin or endoscopic evaluation results, were negative. This was done to increase our sample size and improve our study's statistical power. Whether this can truly be considered as "no objective evidence" of inflammation is debatable. Another limitation is the fact that many patients did not have a complete workup at initial evaluation. Patients who had normal endoscopy findings with no calprotectin assessment results on record may have had underlying fecal calprotectin elevations, and patients with normal calprotectin levels may have had underlying endoscopic inflammation that was never identified, which would increase the risk of misclassification. Moreover, we were unable to guarantee evaluation of the small bowel in all cases, so cases of isolated small bowel disease may have been missed—although this condition is very rare. We were also unable to detail the reasons why immunosuppressive therapy was administered in patients with no laboratory or endoscopic evidence of inflammation. The judgement was at the discretion of treating physicians based on clinical assessment, evaluation result and symptom response to supportive treatment. Finally, given that follow-up evaluation with repeat fecal calprotectin and endoscopic evaluation is not routinely performed among this cohort, our study may have underestimated the number of patients who later develop colonic inflammation.

Our study is the first to explore a unique and puzzling subtype of IMDC, presenting with no elevations in fecal calprotectin and normal endoscopic findings. We found that PD-1/PD-L1 inhibition may predispose patients to developing this specific form of IMDC, which presents with a lower severity of diarrhea, but has similar management needs and outcomes to those of IMDC with evidence of inflammation. Many patients with this IMDC subtype still require immunosuppressive treatment, despite otherwise normal workup findings, and a small subset of patients later develop colonic inflammation. Future studies are needed to elucidate the treatment needs and outcomes of this interesting patient population.

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Summary Box

What is already known:

- Immune-mediated diarrhea and colitis (IMDC) is a very common side-effect of immune checkpoint inhibition
- Fecal calprotectin and endoscopic findings are key biomarkers that help diagnose and risk-stratify patients
- Steroids and biologic agents are the cornerstones of treating IMDC
- There is a subset of patients treated with checkpoint inhibitors who present with typical manifestations of IMDC, without any objective evidence of inflammation

What the new findings are:

- Around 11.4% of patients who develop IMDC will not have any objective evidence of inflammation, including normal calprotectin levels and no macroscopic or histologic inflammation on endoscopy
- Almost half of these patients will require immunosuppression with steroids (40.4%) or selective immunosuppressive therapy (23.7%) for resolution of their symptoms
- Patients with IMDC who have normal inflammatory biomarkers at baseline tended to have less severe disease symptomatology and decreased hospitalization

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Supplementary material

Supplementary Table 1 Patients with progression of endoscopic, histologic, and biochemical features of immune-mediated diarrhea and colitis at first follow up[1], n=12

Feature	No. (%)
Median (IQR) time from baseline to first follow up, *days*	63 (32.8-93.8)
Site of inflammation	
Ascending colon	2 (16.7)
Transverse colon	3 (25.0)
Descending colon	3 (25.0)
Rectum	2 (16.7)
Endoscopic features	
Normal	4 (33.3)
Non-ulcerative inflammation[2]	2 (16.7)
Ulcerative inflammation	3 (25.0)
Histologic features	
Normal	3 (25.0)
Acute active inflammation	6 (50.0)
Chronic inflammation	4 (33.3)
Inflammatory markers	
Abnormal baseline lactoferrin	9 (75.0)
Median (IQR) calprotectin, *μg/g*	219 (17.2-288.3)
Median (IQR) change in calprotectin[3], *μg/g*	34.4 (0-193.7)

[1]All patients who underwent a baseline lower endoscopy were included in the baseline cohort. Those within this subgroup who had a second lower endoscopy were categorized as first follow up
[2]Non-ulcerative inflammatory findings observed in the baseline lower endoscopy included erythema and loss of vascularity
[3]Change in calprotectin indicates the change in calprotectin levels from baseline to follow up that would indicate progression in patients with normal features
IQR, interquartile range

Supplementary Table 2 Univariate analysis of factors associated with immunosuppressive treatment with steroids for IMDC among patients with no initial evidence of inflammation, n=131

Covariate	OR (95%CI)	P-value
Cancer type – melanoma vs others	0.7 (0.4-1.6)	0.481
Stage III-IV vs I-II	0.7 (0.2-2.3)	0.559
Time between initiation of ICI therapy and IMDC onset	0.9 (0.9-1.0)	0.079
Length of immunotherapy	1.0 (0.9-1.0)	0.967
Diarrhea CTCAE – grade 2 and above vs others	2.0 (0.97-4.3)	0.061
Colitis CTCAE – grade 2 and above vs others	2.0 (0.97-4.2)	0.059
CTLA-4 regimen – yes vs no	0.5 (0.16-1.9)	0.341
Abnormal baseline lactoferrin – yes vs no	0.4 (0.22- 1.04)	0.063
Hospitalization – yes vs no	3.4 (1.7-7.04)	0.001*
ICI therapy continued vs discontinued	2.9 (1.4-6.2)	0.004*
ICI therapy resumed – yes vs no	0.6 (0.2-1.5)	0.240

*Significant at P<0.05
IMDC, immune-mediated diarrhea and colitis; ICI, immune checkpoint inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte antigen 4