Immune checkpoint inhibitor-induced diarrhea/colitis: Endoscopic and pathologic findings

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Abstract
The indications of immune checkpoint inhibitors (ICPIs) for cancer treatment have rapidly expanded, and their use is increasing in clinical settings worldwide. Despite the considerable clinical benefits of ICPIs, frequent immune-related adverse events (irAEs) have become nonnegligible concerns. Among irAEs, ICPI-induced colitis/diarrhea is frequent and recognized not only by oncologists but also by gastroenterologists or endoscopists. The endoscopic findings show similarity to those of inflammatory bowel disease to a certain extent, particularly ulcerative colitis, but do not seem to be identical. The pathological findings of ICPI-induced colitis may vary among drug classes. The findings show acute or chronic inflammation, but it may depend on the time of colitis suggested by colonoscopy, including biopsy or treatment intervention. In the case of chronic inflammation determined by biopsy, the endoscopy findings may overlap with those of inflammatory bowel disease. Here, we provide a comprehensive review of ICPI-induced colitis based on clinical, endoscopic and pathologic findings.

Key words: Immune checkpoint inhibitor; Colitis; Diarrhea; Endoscopic; Pathologic
but may depend on the diagnostic timing or treatment intervention. Colonoscopy with biopsy is necessary to confirm ICPI-induced colitis, and early evaluation may avoid exacerbating or prolonging colitis due to treatment resistance.

**INTRODUCTION**

In 1992, Ishida et al.\(^1\) identified a protein on activated T lymphocytes called programmed cell death protein 1 (PD-1), a key player in tumor immunology. In 1996, Leach et al.\(^2\) identified a protein called cytotoxic T-lymphocyte antigen-4 (CTLA-4), another major blocking pathway for the human immune system that was similar to PD-1. Since then, their discoveries have led to the development of immune checkpoint inhibitors (ICPIs) as anticancer drugs and have brought about a major revolution in cancer treatment strategy. Both CTLA-4 and PD-1 deliver negative signals to T-cell-mediated excessive immune activation, known as checkpoints, and ICPIs disrupt the signals mediated by CTLA-4 and PD-1 to prevent T cells from blocking pathways. By inhibiting immune checkpoints, activation of T cells is maintained, thereby helping cancer cells to induce cytotoxic T cell-mediated death. In 2018, Professor Honjo and Professor Allison won the Nobel prize in Physiology or Medicine for their work.

Presently, there are six ICPIs available and approved by the United States Food and Drug Administration for different cancers. Despite the significant clinical benefits of ICPIs, frequent immune-related adverse events (irAEs) in the skin, endocrine organs, gastrointestinal (GI) tract, liver, and lungs and in the musculoskeletal, renal, nervous, hematologic, cardiovascular, and ocular systems have become nonnegligible concerns. Most irAEs have a delayed onset and prolonged duration compared with those from chemotherapy\(^3\). The incidence of irAEs appears to be similar across tumor types\(^4\).

Among irAEs, ICPI-induced colitis/diarrhea is frequent and recognized not only by oncologists but also by gastroenterologists or endoscopists. In this review, we provide a comprehensive review of ICPI-induced colitis based on clinical, endoscopic and pathologic findings.

**ONSET TIMING OF ICPI-INDUCED DIARRHEA/COLITIS**

ICPI-induced diarrhea occurs after an average of three infusions\(^5\), although it can occur immediately after the first infusion. Recent reports suggest that the onset timing of ICPI-induced diarrhea/colitis may differ by ICPI type. ICPI-induced diarrhea/colitis induced by ipilimumab (anti-CTLA-4) usually occurs 6 to 7 wk after the initiation of ipilimumab\(^6\). The median time from last the ipilimumab treatment to diarrhea onset is 11-14 d (range 0-59 d)\(^7,8\). On the other hand, Wang et al.\(^9\) reported that 3.2% of patients (30/973) receiving anti-PD-1 developed ICPI-induced colitis at a median of 25.4 wk (range 0.6-120 wk). ICPI-induced diarrhea/colitis induced by anti-PD-1 seems to occur later than that induced by anti-CTLA-4. After the combined use of ipilimumab and nivolumab or pembrolizumab, 24.4% of patients (79/324) developed ICPI-induced diarrhea/colitis significantly earlier, at a median of 7.2 wk (range 0.7-51 wk)\(^9\). Because the ranges of its onset timing are widely distributed, it is difficult to predict the development of ICPI-induced diarrhea/colitis. In addition, it may be influenced by other drugs, including NSAIDs, antibiotics, or previous anticancer drugs. Moreover, it seems difficult to predict the development of colitis before patients have symptoms\(^9\). We should keep in mind that ICPI-related colitis can occur at any point, even after discontinuation of ICPIs.

**LOCATION**

Geukes Foppen et al.\(^11\) reported total colonoscopy in 62 of 92 patients (67%) suspected of ICPI-induced colitis. Of these patients, 68% showed pancolitis (> 3 affected
 segments), and the ascending colon had more severe colitis than the descending colon. In cases where a total colonoscopy was not performed, patients with colitis in the ascending colon can be underestimated by sigmoidoscopy alone. Abdominal computed tomography (CT) findings may be useful not only to evaluate perforation, obstruction, and toxic megacolon but also to evaluate inflamed lesions due to ICPIs. The common CT findings of 16 patients treated with ipilimumab showed that 75% of patients had diffuse colitis patterns, and 25% had segmental colitis[13]. CT was not sufficient to diagnose colitis when using endoscopic evaluation as the gold standard because it has a high false-negative rate and low sensitivity[13]. In contrast, Garcia-Neuer et al[14] reported that CT was useful for predicting ICPI-induced colitis with a positive predictive value of 96% and a negative likelihood ratio of 0.2 in 34 diarrhea patients who underwent both CT and colonoscopy with biopsy. Early sigmoidoscopy without bowel preparation has merit to assess ICPI-induced colitis because it can be performed more easily and earlier than total colonoscopy. Therefore, the combined use of sigmoidoscopy and CT may be useful to evaluate ICPI-induced colitis at an earlier stage.

ENDOSCOPIC EVALUATION AND FINDINGS

There are several reports about the endoscopic findings of ICPI-induced colitis. Wang et al[15] observed that endoscopic inflammatory findings were found in more than 80% of patients with ICPI-induced diarrhea/colitis. Common endoscopic inflammation findings are reported as exudates, loss of vascular pattern, granular or edematous mucosa, patch or diffuse erythema, aphtha and ulcerations (Figure 1)[13,15]. Most of the inflammatory changes, including pathological changes, are dominantly more diffuse than patchy[15], but patchy distribution was endoscopically observed in half of the patients with diarrhea[15]. These endoscopic findings resemble those of inflammatory bowel disease (IBD) to a certain extent, particularly with ulcerative colitis (UC)[16,18], but sometimes look different from a UC-like pattern (Table 1).

Wang et al[13] reported in 53 patients with diarrhea, clinical symptoms did not always correlate with other endoscopic findings except for the presence of ulceration, which had a strong relationship with higher colitis. Similarly, another retrospective study showed that there was no significant correlation between diarrhea/colitis symptoms and endoscopic findings in 92 patients who developed diarrhea. They also reported that pancolitis and the presence of ulceration are indicators for steroid-refractory colitis[13]. Geukes Foppen et al[19] reported that the Mayo score was associated with the presence of ulceration. Abu-Sbeih et al[19] categorized endoscopic findings as low-risk and high-risk for steroid-responsiveness. High-risk findings included either ulcers deeper than 2 mm and/or larger than 1 cm in surface area or endoscopically extensive colitis from the proximal colon to the splenic flexure. These patients require frequent use of infliximab or vedolizumab and more frequent and longer hospital stays than non-high-risk patients[19]. They also reported that timely early colonoscopy decreased the duration of steroid treatment[19]. If the colonoscopy shows normal mucosal findings, we are not always able to exclude the presence of ICPI-induced colitis, as cases of isolated ileitis[20] or enteritis without colitis[21] can also occur. We can also rule out microscopic colitis or other infectious diseases such as Clostridoides difficile or cytomegalovirus[3]. Therefore, early colonoscopy with mucosal biopsy from colorectal and ileum-end mucosa is necessary not only to evaluate the severity and distribution of colitis[11] but also to ensure shorter and less intense treatment[19].

PATHOLOGY

The histologic features of ICPI-associated colitis may vary among drug classes, i.e., CTLA-4 inhibitors and PD-1/PDL1 inhibitors. Although they are nonspecific, some findings can be helpful clues to diagnose and speculate about the class of inhibitors. On the other hand, there is significant overlap between ICPI-associated colitis and other types of colitis, making the differential diagnosis difficult.

The histologic findings of CTLA-4-associated colitis are relatively consistent across most studies. The previously reported histologic features of CTLA-4 associated colitis are similar to those of autoimmune colitis[24]. They include lamina propria expansion due to dense lymphoplasmacytic infiltrate, increased intraepithelial lymphocytosis, and apoptosis in the crypts. Neutrophilic cryptitis and crypt abscess are also found. At times, there is prominent eosinophilia in the lamina propria. Although dense lymphoplasmacytic lamina propria expansion is reminiscent of other mimics, the lack
Table 1  Summary of endoscopic and pathological findings of immune-related diarrhea and colitis

| Endoscopic findings | Pathological findings |
|---------------------|-----------------------|
| **Endoscopic features** | Like autoimmune colitis: (1) lamina propria expansion due to dense lymphoplasmacytic infiltrate; (2) increased intraepithelial lymphocytosis; (3) apoptosis in the crypts; (4) neutrophilic cryptitis and crypt abscess; (5) occasional prominent eosinophilia in the lamina propria; (6) the lack of findings of basal plasmacytosis, crypt distortion, or granulomas. |
| (1) Exudates; (2) loss of vascular pattern; (3) granular or edematous mucosa; (4) patch or diffuse erythema; (5) aphtha; (6) ulceration | |
| **Inflammatory distribution** | Anti-CTLA-4 associated colitis |
| (1) Diffuse; (2) patchy (dominantly more diffuse than patchy) | (1) Expansion of lamina propria by lymphoplasmacytic infiltrate; (2) the increase in intraepithelial neutrophils and neutrophilic crypt abscess; (3) crypt distortion; (4) increased crypt cell apoptosis |
| **Risk factors for steroid-refractory colitis** | Anti-PD1/anti-PDL1-associated colitis |
| (1) Extensively inflamed area (e.g., pancolitis); (2) deeper ulceration | (1) Expansion of lamina propria by lymphoplasmacytic infiltrate; (2) the increase in intraepithelial neutrophils and neutrophilic crypt abscess; (3) crypt distortion; (4) increased crypt cell apoptosis |

CTLA-4: Cytotoxic T-lymphocyte antigen-4; PD1: Programmed cell death protein 1; PDL1: Programmed cell death receptor ligand 1.

of findings of basal plasmacytosis, crypt distortion, or granulomas can help the differentiation.

The most common findings of anti-PD1/anti-PDL1-associated colitis are the expansion of the lamina propria by lymphoplasmacytic infiltrate and features of active colitis[23,27]. The latter are characterized by an increase in intraepithelial neutrophils and neutrophilic crypt abscess (Figure 2A). Other findings include crypt distortion, increased crypt cell apoptosis, features of ischemic colitis, and collagenous colitis (Figure 2B). Although, in the study by Gonzalez et al[26], there were no cases with increased intraepithelial lymphocytosis commonly observed in CTLA-4-associated colitis, Chen et al[23] and Bavi et al[27] described features of lymphocytic colitis in a minority of their cases with anti-PD1/anti-PDL1. In the latter studies, a PD-1 inhibitor and CLTA-4 inhibitor were prescribed for their patient population either in combination or sequentially. Therefore, it is unlikely that this finding is related to PD-1 inhibition alone.

As mentioned, the histologic features of ICPI-associated colitis are nonspecific and can mimic other type of colitis, including infectious colitis, IBD, graft versus host disease (GVHD), and other drug-induced colitis. Although infectious colitis typically shows features of active colitis, increased apoptosis and crypt atrophy/dropout are not typical features[25]. ICPI-associated colitis lacks the features of chronicity that characterize IBD[29]. The lamina propria expansion by lymphoplasmacytic infiltrate can discriminate from GVHD although increased crypt apoptosis is the sine qua non of the diagnosis of GVHD[30]. Despite the histopathological differential diagnostic points, clinical correlation and medical history are indispensable for discrimination between ICPI-associated colitis and mimics (Table 1).

MORBIDITY ASSOCIATED WITH ICPI-INDUCED DIARRHEA/COLITIS AND TREATMENT

IrAEs involving the GI tract range from mild to severe events[8] and are well reported for anti-CTLA4 but less well reported for anti-PD-1 and anti-PD-L1 and for combined anti-CTLA4 plus anti-PD-1. Most clinical trials distinguish diarrhea from colitis even though they overlap in most practical cases. Diarrhea is evaluated based on an increase in stool per day or ostomy output. Colitis is evaluated based on clinical symptoms (abdominal pain, mucus or blood in stool) or diagnostic observations based on radiographic and/or colonoscopy findings. The severity is usually classified based on the Common Terminology Criteria for Adverse Events (Table 2).

Morbidity associated with ICPI-induced diarrhea/colitis and treatment
colitis[36]. Anti-CTLA4-related colitis is reportedly associated with mouth ulcers, anal lesions and extraintestinal irAEs[17]. A recent meta-analysis of 34 studies that included 8863 patients in clinical trials revealed that, for anti-CTLA4 alone (ipilimumab), all grades of colitis occurred in 9.1% (95% confidence interval (CI), 6.6%-12.5%) of participants, grade 3/4 colitis occurred in 6.8% (95%CI: 5.3%-8.6%) of participants, and grade 3/4 diarrhea occurred in 7.9% (95%CI: 5.5%-11.4%) of participants. Similarly, for anti-PD-1 alone (nivolumab or pembrolizumab), the rates were 1.4% (95%CI: 1.1%-1.8%), 0.9% (95%CI: 0.7%-1.3%), and 1.3% (95%CI: 1.0%-1.7%), respectively. For anti-PD-L1 alone (atezolizumab), the rates were 1.0% (95%CI: 0.4%-2.2%), 0.6% (95%CI: 0.2%-1.6%), and 0.3% (95%CI: 0.1%-1.1%), respectively[36]. For anti-CTLA4 (ipilimumab) plus anti-PD-1 (nivolumab), the rates were 13.6% (95%CI: 7.7%-22.9%), 9.4% (95%CI: 4.8%-117.4%), and 9.2% (95%CI: 6.8%-12.3%), respectively. ICPI-induced diarrhea/colitis induced by anti-CTLA-4 can develop more often and more severely than ICPI-induced diarrhea/colitis induced by anti-PD-1. Combined anti-CTLA4 plus anti-PD-1 treatment is also more strongly associated with diarrhea/colitis than single-drug treatment[36]. Ipilimumab is commonly used at either 10 mg/kg or 3 mg/kg. There were similar rates of severe colitis at these doses, but severe diarrhea was more frequent at a dose of 10 mg/kg than at 3 mg/kg[36]. Recently, Marthey et al[17] showed that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with an increased risk of ICPI-induced colitis induced by CTLA-4 (2/38, 5% vs 11/35, 31%, P = 0.003). Therefore, the use of NSAIDs may affect the incidence of ICPI-induced diarrhea/colitis. Table 3 shows a summary of the incidence of immune-related diarrhea or colitis based on representative clinical trials.

In the case of grade 1 diarrhea/colitis, antidiarrheal drugs and/or oral hydration with electrolyte substitution can be initiated. In cases of persistent or grade 2 or higher diarrhea or rectal bleeding, it is necessary to confirm colitis or to rule out GI infection by testing for stool leukocytes, stool cultures, IBD, or tumor-related GI symptoms. In particular, Clostridioides difficile toxin and/or antigen test, cytomegalovirus DNA polymerase chain reaction, and tests for stool ova and parasites should be carried out in every patient with diarrhea treated with ICPIs. Sigmoidoscopy or colonoscopy combined with mucosal biopsy needs to be performed to confirm the presence of colitis and to rule out GI metastasis because it is not uncommon in lung cancer or melanoma. If ICPI-induced colitis is diagnosed, an oral steroid is recommended. In the case of grade 3/4 diarrhea/colitis or persistent symptoms after oral steroids for several days, changing the treatment to intravenous steroids should be considered, and an infusion solution with electrolytes should be given. If patients respond to intravenous steroids within several days, they should be switched to oral steroids and tapered. However, if they fail to respond to steroid infusion, treatment with anti-TNF-α should be considered[37]. Recently, a case series reported that vedolizumab was a safer and more theoretic alternative than anti-TNF in patients with steroid-dependent or partially refractory ICPI-induced enterocolitis[38]. In the near future, vedolizumab may be effective and safe because it inhibits the migration of mucosal-associated T lymphocytes without inducing immune suppression and does not show an increased risk of serious infections in patients with UC or Crohn’s disease[39,40].
CONCLUSION

The combination of endoscopic and pathological findings may help diagnose ICPI-induced colitis as well as exclude infectious colitis, including *Clostridioides difficile* or cytomegalovirus, ischemic colitis, other drug-induced colitis, or segmental diverticular colitis. However, there are no specific findings because the endoscopic and pathological findings can depend on the time of colitis proven by biopsy or treatment intervention. In cases of persistent or grade 2 or higher diarrhea or rectal bleeding, colonoscopy evaluation is necessary to confirm ICPI-induced colitis and to rule out other diseases. Early evaluation and intervention may avoid exacerbating or prolonging colitis.
Table 2  Definition of diarrhea and colitis based on Common Terminology Criteria for Adverse Events v5.0

| CTCAE Term | Definition | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | CTCAE v5.0 Change |
|------------|------------|---------|---------|---------|---------|---------|------------------|
| Diarrhea   | A disorder characterized by an increase in frequency and/or loose or watery bowel movements | Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline | Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL | Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL | Life-threatening consequences; urgent intervention indicated | Death |
| Colitis    | A disorder characterized by inflammation of the colon | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Abdominal pain; mucus or blood in stool | Severe abdominal pain; peritoneal signs | Life-threatening consequences; urgent intervention indicated | Death |

ADL: Activities of daily living; CTCAE: Common Terminology Criteria for Adverse Events.

Table 3  Summary of incidence of immune-related diarrhea and colitis

| ICPI | Target | Author | Year | Plus other drugs | n | Cancer type | Any grade diarrhea/colitis, n (%) | Grade 3 diarrhea/colitis, n (%) |
|------|--------|--------|------|------------------|---|-------------|----------------------------------|---------------------------------|
| Nivolumab PD-1 | Topalian et al | 2012 | None | 296 | Solid cancer | 33 (11)/ND | 3 (1)/ND |
| | Weber et al | 2013 | None | 34 | Melanoma | 13 (38.2)/0 (0) | Not observed |
| Pembrolizumab PD-1 | Weber et al | 2015 | None | 268 | Melanoma | 30 (11.2)/ND | 1 (0.4)/ND |
| | Larkin et al | 2015 | None | 315 | Melanoma | 60 (19.2)/4 (1.3) | 7 (2.2)/2 (0.6) |
| | Ferris et al | 2016 | None | 236 | SCCHN | 16 (6.8)/0 (0) | 0 (0)/0 (0) |
| | Kang et al | 2017 | None | 330 | GC/GEJC | 23 (7)/2 (1) | 2 (1)/1 (< 1) |
| | Hamid et al | 2013 | None | 135 | Melanoma | 27 (20) | 1 (1) |
| | Garon et al | 2015 | None | 495 | NSCLC | 40 (8.1)/ND | 3 (0.6)/ND |
| | Ribas et al | 2015 | None | 361 | Melanoma | 32 (8.9)/5 (1.4) | 2 (0.6)/2 (0.6) |
| | Herbst et al | 2016 | None | 690 | NSCLC | 46 (6.7)/6 (0.9) | 2 (0.3)/4 (0.6) |
| | Ribas et al | 2016 | None | 655 | Melanoma | 115 (18)/112 (1) | 6 (1)/7 (1.1) |
| | Mok et al | 2019 | None | 636 | NSCLC | 34 (5)/7 (1) | 5 (< 1)/4 (< 1) |
| | Weber et al | 2008 | None | 88 | Melanoma | 5 (5.6)/4 (4.5) | 5 (5.6)/4 (4.5) |
| | Weber et al | 2009 | None | 57 | Melanoma | 20 (35)/ND | 10 (18)/ND |
| | Weber et al | 2009 | Budesonide | 58 | Melanoma | 19 (33)/ND | 8 (14)/ND |
| | Wolchok et al | 2010 | None | 214 | Melanoma | 58 (27)/ND | 11 (5.1)/ND |
| | Hodi et al | 2010 | None | 131 | Melanoma | 43 (32.8)/10 (7.6) | 7 (5.3)/7 (5.3) |
| | | gp100 | 380 | | | 146 (38.4)/20 (5.3) | 17 (4.5)/12 (3.2) |
| | | Dacarbazine | 247 | | | 81 (32.8)/11 (4.5) | 10 (4.0)/5 (2.0) |
| | | Margolin et al | 2012 | None | 72 | Melanoma | 30 (42)/ND | 6 (8.5)/ND |
| | | Kwon et al | 2014 | None | 399 | Prostate cancer | 199 (51)/27 (7) | 64 (16)/18 (5) |
| | | Larkin et al | 2015 | None | 311 | Melanoma | 103 (33.1)/36 (11.6) | 19 (6.1)/27 (8.7) |
| | | Eggemann et al | 2016 | None | 471 | Melanoma | 194 (41.2)/73 (15.5) | 46 (9.8)/39 (8.2) |

WJGP  | https://www.wjgnet.com  | September 10, 2019  | Volume 10  | Issue 2  | 23
| Immunotherapeutics | CTLA4 and PD1 | Wolchok et al. | 2013 | None | 53 | Melanoma | 18 (34.0)/5 (9) | 3 (6)/2 (4) |
|--------------------|-------------|----------------|------|-------|-----|-----------|----------------|-------------|
|                    | Larkin et al. | 2015 | None | 315 | Melanoma | 138 (44.1)/37 (11.8) | 29 (9.3)/24 (7.7) |
|                    | Schadendorf et al. | 2017 | None | 407 | Melanoma | 30 (7.4)/40 (9.8) | 25 (6.1)/32 (7.9) |
|                    | Wolchok et al. | 2017 | None | 313 | Melanoma | 142 (45)/40 (13) | 29 (9.6)/28 (6) |
|                    | Hellmann et al. | 2017 | None | 77 | NSCLC | 16 (21)/4 (5.2) | 1 (1.3)/3 (3.9) |
|                    | Motzer et al. | 2018 | None | 547 | Renal cell carcinoma | 145 (27)/ND | 21 (4)/ND |
| Durvalumab PD-L1 | Antonia et al. | 2017 | None | 473 | NSCLC | 87 (18.3)/ND | 3 (0.6)/ND |
|                    | Motzer et al. | 2018 | None | 475 | NSCLC | 88 (18.5)/ND | 3 (0.6)/ND |
|                    | Loibl et al. | 2019 | None | 92 | Breast cancer | 26 (28.3)/ND | 3 (3.3)/ND |
| Atezolizumab PD-L1 | Herbst et al. | 2014 | None | 277 | Solid tumors or hematological malignancies | 29 (10.5)/ND | 0 (0)/ND |
|                    | Rosenberg et al. | 2016 | None | 311 | Urothelial carcinoma | 24 (8)/3 (1) | 1 (0.3)/2 (1) |
|                    | Fehrenbacher et al. | 2016 | None | 142 | NSCLC | ND | ND/2 (1) |
| Avelumab PD-L1 | Socinski et al. | 2018 | None | 393 | ABCP | 70 (17.8) | 11 (2.8) |
|                    | Chung et al. | 2019 | None | 150 | GC/GECJ | ND/2 (1.3) | ND/1 (0.7) |
|                    | Barlesi et al. | 2019 | None | 396 | NSCLC | 24 (6)/ND | 0 (0)/ND |

1 Dose-limiting colitis was not observed in this trial;
2 progressed after ipilimumab;
3 Immune-related event;
4 No atezolizumab-related grade 4 but adverse events were reported, but only one patient showed Grade 5 cardiac failure.

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