Gastrointestinal Tract Adverse Events

12

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Abstract

Immune checkpoint inhibitors (ICIs) have shown significant benefit in cancer patients. Their success, however, is associated with immune-related adverse events (irAEs), which commonly affect the gastrointestinal tract, resulting in diarrhea and colitis. IrAEs range from mild self-limiting to severe life-threatening diseases and potentially limit the use of these medications. Diagnosis of ICI-induced enterocolitis is based on clinical symptoms, physical examination, stool tests, endoscopic and histologic evaluation, and/or imaging. Current management strategy is mainly anti-diarrheal agents for mild symptoms and immunosuppressants (e.g., corticosteroids, and infliximab or vedolizumab) for more severe diseases.

Keywords

Immune checkpoint inhibitors · Immunotherapy · Colitis · Diarrhea · Enterocolitis · Gastrointestinal adverse events

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Enterocolitis

Incidence

ICI-induced enterocolitis is reported in 15–25% of patients receiving cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitors [1–3]. Blockade of programmed death protein-1 and its ligand (PD-[L]1) is associated with lower rate of enterocolitis, up to 10% [4]. However, when combined, the risk of enterocolitis becomes as high as 30% [5]. Alternatively, diarrhea can occur in up to 54% of patients receiving ICI therapy, especially the combinatorial approach [4]. Moreover, diarrhea grade 3 and 4 is the most common serious adverse event leading to ICI discontinuation, occurring in 10% of patients receiving ICIs [3, 6]. Colonic perforation has been reported in ~2% of patients treated with ICI therapy [2, 7]. The occurrence of ICI-induced enterocolitis has been proposed to correlate with favorable response of cancer to ICI therapy, reflected by improved survival rates in these patients compared with those who did not develop ICI-induced enterocolitis [8, 9]. Nonsteroidal anti-inflammatory drugs and fecal microbiome are speculated to play a role in the development of ICI-induced enterocolitis [1, 10–12].

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Clinical Presentation

ICI-induced gastrointestinal toxicities most commonly present as watery diarrhea, followed by abdominal pain, blood or mucous with stool, abdominal distension, nausea and vomiting, and fever [1, 2, 13]. Weight loss might occur in patients with protracted severe ICI-induced enterocolitis [1]. Many patients often have only nonbloody self-limiting diarrhea without the other associated enterocolitis symptoms [14, 15], whereas severe enterocolitis may result in colonic perforation and death [16–18]. The severity of diarrhea and colitis is graded based on the Common Terminology Criteria for Adverse Events *version 5.0* [19]. Enterocolitis generally occurs around 5–10 weeks following initiation of ICI treatment [17, 20]. However, the onset can range from immediately after the first dose to more than 6 months after the last infusion of ICI [13, 21, 22]. Enterocolitis onset can be acute or gradual. A mild self-limiting transient diarrhea might occur after the first few doses of ICI therapy; this diarrhea should not be confused with immune-mediated enterocolitis.

Diagnosis

Patients on ICI treatment who develop gastrointestinal symptoms should be evaluated for other etiologies first [18]. Infectious stool workup should include bacterial (e.g., *Clostridium difficile*), viral (e.g., CMV), parasitic, or fungal infections [23, 24]. Of note, in some cases, ICI-induced enterocolitis and gastrointestinal infections can coexist, which makes it difficult to distinguish between both [25]. Blood tests, such as complete blood count and comprehensive metabolic panel, can assess in the exclusion of other etiologies and the severity of the disease. Additionally, workup for celiac disease, fecal elastase for pancreatic insufficiency, and TSH for thyroid dysfunction should be performed to rule out these etiologies of diarrhea.

Currently, there are no available specific serologic or fecal markers for ICI-induced enterocolitis [26]. Nonetheless, fecal calprotectin and lactoferrin are stool inflammatory markers that have been widely used in the clinical practice for patients with inflammatory bowel disease. Given the similarities between both entities, these markers have also been studied and shown to be of value in the evaluation of ICI-induced enterocolitis [2, 7]. Fecal lactoferrin might be used to determine who should undergo endoscopic evaluation, and fecal calprotectin might be used to monitor for response of enterocolitis to treatment [27, 28].

Cross-sectional abdominal imaging (i.e., computerized tomography (CT) or magnetic resonance imaging (MRI)) can assist in the evaluation of colonic inflammation. Moreover, abdominal imaging might be helpful to assess for colonic perforation, obstruction, and toxic megacolon, which might complicate ICI-induced enterocolitis. Features of ICI-induced enterocolitis on imaging include diffuse wall thickening, mesenteric vessel engorgement, peri-colic fat stranding, and mucosal enhancement [2, 29]. Free intraperitoneal air indicates the presence of bowel perforation [30]. Nevertheless, the sensitivity of imaging to detect enterocolitis is approximately 50%, and therefore, endoscopy is considered the gold standard for the evaluation of enterocolitis [28, 31].

For patients with ≥ grade 2 diarrhea or colitis symptoms or with persistent grade 1 but positive lactoferrin, colonoscopy with biopsy is highly recommended to evaluate the severity and extent of ICI-induced enterocolitis, as it was reported that severe endoscopic presentation correlates with response of enterocolitis to treatment [7, 32]. Furthermore, endoscopy should be performed as soon as possible following enterocolitis onset to guide treatment options; this approach has been proven to be effective in preventing unfavorable outcomes [7]. Endoscopic manifestations often reveal erythema, edema, exudates, granularity, loss of vascular pattern, erosions, ulcerations, and bleeding (Fig. 12.1) [31–33]. Most commonly, enterocolitis will be extensive, involving the entire colon and ileum, followed by isolated left colon inflammation [31]. Isolated right colon and ileal inflammation has been reported in 10–15% of patients [7]. Therefore, initial endos-

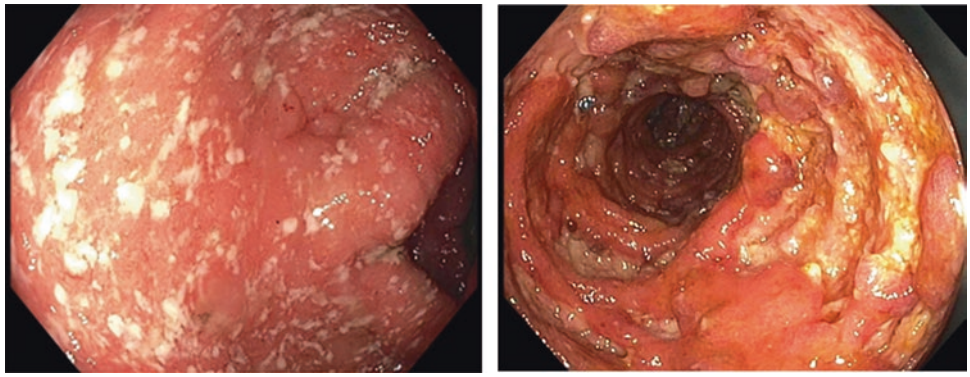

Fig. 12.1 Endoscopy images of immune checkpoint inhibitors–related colitis showing diffuse erythema, edema, inflammatory exudate, loss of vascular pattern, and deep large ulcerations

Table 12.1 Mayo Score for endoscopic presentation

Score	Disease status	Endoscopic features
0	Normal	Normal colon
1	Mild	Erythema, altered vascularity, mild friability
2	Moderate	Diffuse erythema, absent vascular pattern, marked friability, erosions
3	Severe	Spontaneous bleeding and mucosal ulcerations

copy evaluation with full extent colonoscopy is preferred over flexible sigmoidoscopy to detect colonic inflammation proximal to the left colon [34]. Follow-up endoscopy can be sigmoidoscopy if isolated left colon involvement is confirmed initially. Endoscopic inflammation pattern of ICI-induced enterocolitis can be focal, segmental, patchy, or diffuse circumferential [34]. Routine biopsy is recommended even with normal endoscopic evaluation to investigate for a subtype of enterocolitis that mimics microscopic colitis [13, 35]. Mayo Score for endoscopic presentation used in patients with ulcerative colitis can be also used to assess for the severity of ICI-induced enterocolitis (Table 12.1) [36].

Microscopic findings of ICI-induced enterocolitis are categorized into acute, chronic, and microscopic inflammation. Acute inflammation features are the most common and include neutrophil and/or eosinophil infiltration, epithelium apoptosis, cryptitis and crypt microabcesses; chronic inflammation features include crypt architectural distortion, basal lymphoplasmocytosis, granuloma, and Paneth cell metaplasia; and microscopic features are rare and can be either lymphocytic infiltration in the epithelium or subepithelial collagen band deposition [31, 32, 37]. Chronic histologic features are similar to those of Crohn's disease and ulcerative colitis. Active histologic features can be used as a surrogate marker for severe diseases with worse outcomes [7]. Thus, the identification of active features should indicate early initiation of aggressive immunosuppressive therapy. In addition, the status of cytomegalovirus infection on the histopathological examination of the colon tissue should be evaluated [2].

Treatment

Current treatment recommendations of ICI-induced enterocolitis depends on the clinical severity only [38]. For patients with grade 1 toxicity, usually conservative management with adequate oral hydration, diet modification, and close follow-up monitoring is recommended. Antimotility agents can be used after exclusion of infectious etiology but are often not recommended [28]. Mesalamine (i.e., 5-ASA) has been reported to be effective in mild grade diarrhea [39]. Usually ICI therapy can be continued in grade 1 disease. If conservative management fails or symptoms progress to higher grade, more aggressive treatment strategy is required.

For a grade 2 and higher toxicity, ICI therapy should be halted, temporarily for grade 2 and 3 and permanently for grade 4 [27, 28, 40]. The mainstay treatment for grade 2 and higher ICI-induced enterocolitis is immunosuppressive therapy to hamper the inflammation. These include corticosteroids and other more potent immunosuppressants (e.g., infliximab and/or vedolizumab) [3, 41, 42]. The recommended oral corticosteroid for ICI-induced enterocolitis is prednisone or equivalent with a dose of 1–2 mg/kg. Intravenous corticosteroid (e.g., methylprednisolone) is indicated in patients with grade 3–4 enterocolitis. Corticosteroids should be tapered over 4 weeks after symptoms resolution, as steroid treatment for less than 30 days has been shown to be associated with less frequent infectious events [31]. The use of steroid enema and budesonide was reported in case studies but are not standard practice, especially for grade 3–4 enterocolitis [20, 23, 39, 43].

In cases of refractory to corticosteroid treatment, infliximab (anti-TNF) and vedolizumab (anti-integrin) are recommended [3, 41, 44]. Screening for HIV, tuberculosis, and hepatitis B and C should be performed before initiating these agents. Early use of infliximab is reported to be associated with shorter duration of immunosuppressant treatment and improved clinical outcome [41, 42, 45]. Contraindications for infliximab include bowel perforation and active infection, especially sepsis [17]. Response to infliximab therapy is usually within 1–3 days [13], while some patients may need more than one dose [39]. The stated response rate to infliximab is as high as 85% [2]. Vedolizumab is a potential substitute for infliximab with encouraging clinical outcomes, comparable efficacy, and favorable safety profile [46]. Currently, it is recommended as third-line agent after failure of infliximab or if infliximab is contraindicated. Early introduction of potent immunosuppressive therapy (i.e., infliximab or vedolizumab) improves the outcomes of ICI-induced enterocolitis regardless of steroid response, especially in patients with severe disease presentation [47]. Reports have shown that mycophenolate mofetil can be used in the treatment of ICI-induced enterocolitis [42]. Recently, fecal microbiota transplantation has been proposed to be effective in patients with ICI-induced enterocolitis that is refractory to available immunosuppressive therapy [48].

After resolution of enterocolitis to grade 1 or less, ICI therapy might be resumed, especially PD-(L)1 inhibitors [17]. Enterocolitis symptoms can recur after weeks to months from resolution of the initial episode to mimicking inflammatory bowel disease. Recurrence of gastrointestinal symptoms requires comprehensive evaluation for the ICI-enterocolitis with similar approach to the first episode [23]. Repeat immunosuppressant treatment may be needed. Of note, in patients with high suspicion of bowel perforation or toxic megacolon, surgical consultation is warranted [17, 42, 49, 50].

Conclusion

The recognition of ICI-induced enterocolitis is increasing with the wide use of ICI therapy in the past few years. The diagnosis and the severity measures of ICI-induced enterocolitis are based on multiple evaluation modalities, such as laboratory tests, abdominal imaging, and endoscopic assessment. The cornerstone treatment of ICI-induced enterocolitis is corticosteroid therapy, followed by infliximab and vedolizumab. The ultimate goal is to provide appropriate treatment to keep the enterocolitis in remission while continuing ICI treatment. Further prospective studies are still needed to improve the management strategy of ICI-induced enterocolitis.

Gastroenteritis

Although nausea and vomiting are frequent symptoms in cancer patients. In patients treated with ICI therapy, it has been reported that nausea and vomiting, especially if severe enough, might be a consequence of immune-mediated gastritis [27, 51]. The body of evidence regarding this disease is very limited. After ruling out other etiologies, esophagogastroduodenoscopy with biopsy can help to establish the diagnosis of ICI-

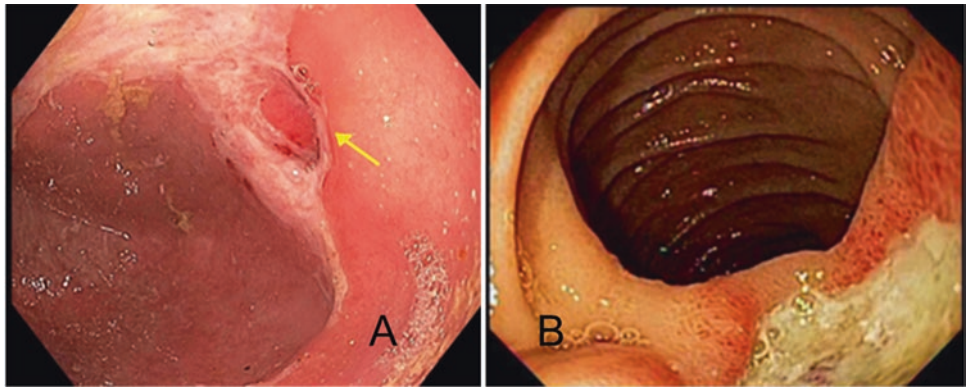

Fig. 12.2 Endoscopy findings of gastritis related to immune checkpoint inhibitors. Endoscopy images demonstrating deep, large, mucosal ulceration in the stomach (**a**) and bleeding mucosal ulceration the duodenum (**b**) [54]

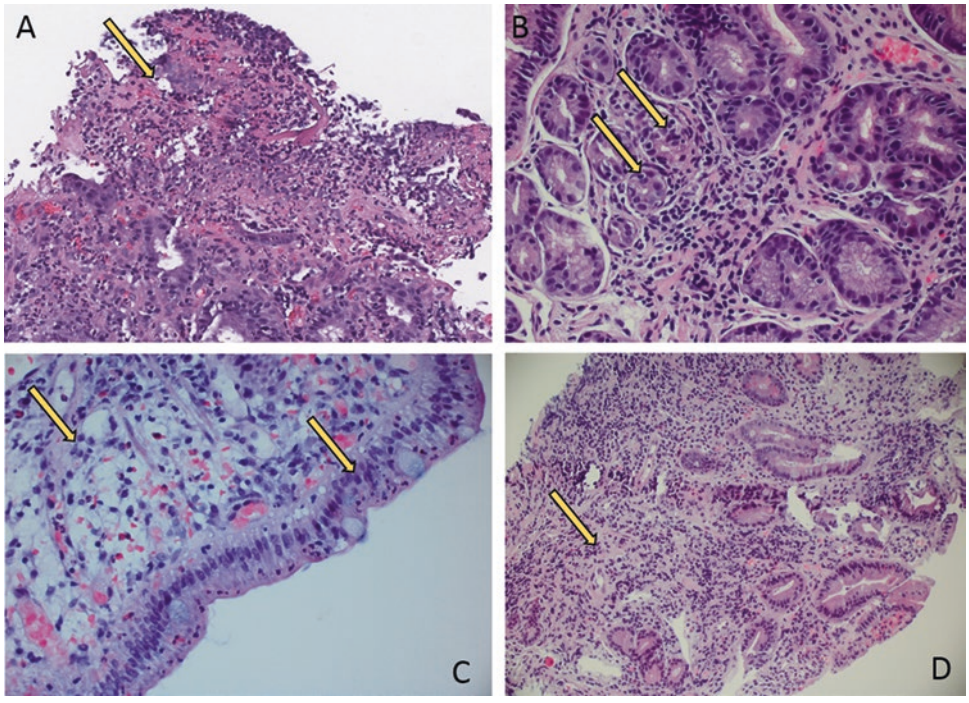

Fig. 12.3 Histologic features of immune checkpoint inhibitor–related upper gastrointestinal injury: (**a**) denudation of epithelium with fibro-inflammatory exudates, (**b**) active gastritis with neutrophils in epithelium; chronic gastritis with lymphocytes in lamina propria, (**c**) increased intraepithelial neutrophils, lamina propria edema and increased neutrophils in lamina propria, villous blunting, and (**d**) duodenum: shows altered architecture and gland drop out [54]

related gastroenteritis. Endoscopically, erythema, edema, friability, erosions, and ulcerations might be observed (Fig. 12.2). Histologically, commonly described features in the gastric mucosa are lamina propria expansion and intraepithelial neutrophilic infiltration. In duodenal biopsies, villous blunting, lymphoplasmacytic lamina propria expansion, as well as plasma cells and eosinophils infiltrates, neutrophilic cryptitis, and/or villitis have been reported (Fig. 12.3) [52, 53]. The appropriate treatment for such toxicity still is unclear. The reported

medical treatments include proton pump inhibitors, H_2 blockers, corticosteroids, and vedolizumab [54]. The role for these treatment modalities still needs further investigation.

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