

Chapter 7

Immune Checkpoint Inhibitors-Induced Colitis



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Abstract Immune checkpoint inhibitors (ICIs) have shown significant benefit in cancer patients, but are associated with immune-related adverse events (irAEs), that can affect the gastrointestinal tract resulting in diarrhea and colitis. IrAEs range from mild self-limiting to severe life-threatening disease, which potentially limit the use of these medications. Diagnosis of ICI-induced colitis is based on clinical symptoms, physical examination, stool tests, endoscopic 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 cases.

Keywords Immune checkpoint inhibitors · Colitis · Diarrhea · Corticosteroids
Infliximab · Steroids · Immunotherapy

The Incidence of ICI-Induced Colitis

ICI-induced colitis, which shares some similarities with inflammatory bowel diseases (IBDs), is observed in 25–30% of patients receiving anti CTLA-4 agents [1–3]. Anti-PD-1 antibodies are associated with lower rate of gastrointestinal (GI) adverse events, approximately 10% [4]. However, combination therapy with both

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CTLA-4 and PD-1 blockers raised the risk of GI toxicities to about 45% which is much higher than monotherapy [5]. Grade 3 or 4 diarrhea was reported to be among the most commonly reported serious adverse events and occurs in 10% of cases receiving ICIs [3, 6].

Clinical Presentation of ICI-Induced Colitis

Among all the clinical symptoms of ICI-induced GI toxicities, the most common presentation is watery diarrhea followed by abdominal pain, hematochezia, nausea/vomiting, and fever [1, 2, 7]. Weight loss has also been found in patients with ICI-induced colitis [1]. Many patients often have only non-bloody self-limiting diarrhea without other associated symptoms [8, 9], whereas severe colitis may result in colonic perforation and death [10–12]. The severity of diarrhea and colitis is graded based on the Common Terminology Criteria for Adverse Events (version 4.03). Details of CTCAE criteria for diarrhea and colitis are shown in Table 7.1 [13].

Diarrhea adverse event generally occurs around 6–7 weeks following commencement of ICI treatment [11, 14]. However, the onset can range from immediately after the first dose to more than 4 months after the last dose [7, 15, 16].

Diagnostic Tools for the Evaluation of ICI-Induced Colitis

Patients on ICI treatment who develop acute onset of diarrhea should be evaluated for infectious etiology first [12]. Stool tests for bacterial infection, *C. difficile*, viral, parasitic, or fungus should be performed to rule out infectious causes before conferring a diagnosis of ICI-induced diarrhea or colitis [17, 18]. It was noted that in some cases, ICI-induced colitis and GI infection can coexist [19].

Currently, there are no available specific serologic or fecal markers for ICI-induced colitis [20]. Fecal calprotectin is a stool inflammatory marker that has been widely used in the clinical practice for patients with inflammatory bowel disease. It has also been reported as a diagnostic or predictive tool for ICI-induced colitis [2]. However, the association between the increased fecal calprotectin level and ICI-induced colitis is not well established [20].

For patients who have \geq grade 2 diarrhea and colitis symptoms, endoscopy with biopsies is highly recommended to further evaluate the severity of ICI-induced GI toxicity [21, 22]. Endoscopic manifestations often reveal erythema, edema, erosions, ulcers, exudates, granularity, loss of vascular pattern, and bleeding [23]. About 43% colonic inflammation is distributed throughout the ileum and colon, while 34% is limited to left colon alone. The rest is normal colon exam [24]. The inflammation pattern can vary from diffuse circumferential, patchy, segmental, to

Table 7.1 Common terminology criteria for adverse events of diarrhea and colitis

Gastrointestinal disorders					
Adverse events	Grade				
	1	2	3	4	5
Diarrhea	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	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death

isolated and focal type. For patients who had normal appearing colon on the exam, routine biopsy is required to rule out a subtype of colitis, which mimics microscopic colitis [7, 25]. Although colitis presented with significant endoscopic inflammation accounts for 79% and normal endoscopic exam in 21% [24].

Microscopic findings from inflamed colon are presented with three categories: acute, chronic, and microscopic inflammation [22, 25]. Acute inflammation features include neutrophil and/or eosinophil infiltration, epithelium apoptosis, cryptitis, and crypt microabscesses, which account for 23% of colitis; chronic inflammation features include crypt architectural distortion, basal lymphoplasmocytosis, granuloma, and Paneth cell metaplasia, that account for 60% of colitis; and microscopic colitis can present with features of lymphocytic infiltration in the epithelium and/or sub-epithelial collagen band deposition which is 8% [24]. Chronic histologic features share fair similarity with both Crohn's disease and ulcerative colitis. In addition, the absence of cytomegalovirus infection on histopathological examination of the colon tissue should be confirmed [2].

Radiology especially CT scan is important to evaluate bowel perforation, obstruction, and toxic megacolon that are complications of severe ICI-induced colitis. Features of colonic inflammation on imaging include diffuse wall thickening, mesenteric vessel engorgement, peri-colic fat stranding, and mucosal enhancement in patients with ICI-induced colitis [2, 26]. Free intraperitoneal air indicates the presence of bowel perforation [27]. However, the sensitivity of detecting evidence of colitis on imaging is only 50% if endoscopy is used as the gold standard for

inflammation [24]. For selected patients with high suspicion for toxic megacolon or perforation, abdominal imaging should be obtained to provide early guidance for further management.

Management and Clinical Outcomes of ICI-Induced Colitis

Current management of ICI-induced diarrhea and colitis depends on the severity of the symptoms [28]. For patients with grade 1 diarrhea, usually conservative managements with over the counter anti-diarrheal agents, adequate oral hydration, diet modification, and close follow-up monitoring are recommended. It has also been reported that 5-ASA may be effective in those with milder grade diarrhea [29]. Usually, ICI can be continued for grade 1 symptoms. If patients fail conservative management, or symptoms progress to higher grade level, more aggressive management strategy is required.

For grade 2 and above diarrhea and colitis, holding immunotherapy is highly recommended [30, 31]. The main treatment options for higher grade of ICI-induced diarrhea/colitis are immunosuppressants to reverse the effect of ICI, and hamper the inflammation. These include corticosteroids and other nonsteroidal immunosuppressants, e.g., infliximab and/or vedolizumab [3, 32, 33]. The forms of corticosteroid reported to be used for ICI-colitis include hydrocortisone enema, oral budesonide, and systematic use of corticosteroids (intravenous form of steroid and oral prednisone). Intravenous corticosteroid is indicated in patients who have severe symptoms that require hospitalization especially for grade 3 and above toxicities. Long steroid taper duration over 4–6 weeks is recommended to minimize the rebound symptoms. The standard dose of initial steroid treatment is 1 mg/kg/day, but can be increased to 2 mg/kg if symptoms are refractory within 2–3 days. The use of steroid enema and budesonide was reported in case studies only [14, 17, 29, 34]. For cases refractory to corticosteroid treatment, anti-TNF agents such as infliximab and adhesion molecule blocker, e.g., vedolizumab had been reported to be successful in case studies [3, 32, 35]. Indeed, early use of infliximab is associated with shorter duration of immunosuppressant treatment and improved clinical outcome [32, 33, 36]. The contraindications for biological agents include bowel perforation and infection, especially sepsis [11]. The response to infliximab therapy is usually within 1–3 days [7], while some patients may need more than one dose [29]. The reported response rate to infliximab was as high as 83–100% [2].

When symptoms resolve or improve to grade 1 or less after steroid treatment, resuming checkpoint inhibitor may be considered especially non-CTLA-4 agents [11]. Recurrent GI symptoms after the initial episode can occur months after successful treatment and may require complete evaluation for the same etiology [17].

Other immunosuppressive agents such as tacrolimus or mycophenolate mofetil have also been reported in case studies for the treatment of ICI-induced colitis [33]. It should be noted that, for patients with high suspicion of bowel perforation or toxic megacolon, steroids should be withheld and a surgical consultation should be

obtained [11]. Surgery with colectomy is usually reserved for patients with serious GI complications, e.g., colonic perforation [33, 37, 38]. Avoidance of nonsteroidal anti-inflammatory drugs (NSAID) is usually recommended to prevent exacerbation of gastrointestinal symptoms based on case reports [1, 39].

Conclusion

The recognition of ICI-induced colitis is increasing with the wide use of ICIs in the past few years. It shares some characteristics with IBD; however, presents with much broader range of manifestations than IBD. The diagnosis and the severity measures of ICI-induced colitis are based on multiple evaluation modalities. Early use of immunosuppressants, e.g., corticosteroids, infliximab and/or vedolizumab can lead to quick symptom improvement in severe cases. The ultimate goal is to provide maintenance treatment to keep the colitis in remission while keeping patients on ICI treatment to maximize its benefit if they are deemed to be good responders. Further studies are still required to further improve the management strategy.

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