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CURRENT OPINION

Immune Checkpoint Inhibitor-Induced Colitis: Diagnosis and Management

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Abstract Immune checkpoint inhibitors are monoclonal antibodies indicated for an increasing number of malignant diseases. These agents can cause specific side effects, which need to be anticipated while clear patterns of management need to be established. Immune checkpoint inhibitor-mediated gastrointestinal side effects, including diarrhea and colitis, occur in up to 30% of patients. Severe colitis can lead to severe dehydration or intestinal perforation. Endoscopic lesions and histopathological features of immune checkpoint inhibitor-induced colitis are similar to an inflammatory bowel disease (IBD) flare. Patients with immune checkpoint inhibitor-induced diarrhea and colitis are treated with corticosteroids. Infliximab can be used in cases of corticosteroid failure. Rectosigmoïdoscopy or colonoscopy should be performed when severe immune checkpoint inhibitor-induced colitis is suspected, but endoscopic investigations should not delay treatment. Specific patient education as well as co-operation between oncologists and gastroenterologists is essential.

Key Points

Immune checkpoint inhibitors can cause immune-related side effects, including colitis.

Parallels can be drawn between immune checkpoint inhibitors-induced colitis and an IBD flare in terms of physiopathology and clinical presentation.

The management of checkpoint inhibitors-induced colitis is based on symptomatic treatment, corticosteroids, and infliximab for refractory cases.

Co-operation between gastroenterologists and oncologists is needed.

1 Introduction

We have recently witnessed a paradigm shift in oncology with major advances in immunotherapy for previously almost untreatable malignant diseases. Consequently, patients' overall survival rates and duration of treatments have increased. However, the use of such immunotherapy agents has led to the occurrence of "non-classical" oncology adverse events, such as immune checkpoint inhibitor-induced diarrhea and colitis. Colitis is suspected when diarrhea is accompanied by pain and/or rectal bleeding, presenting like an IBD flare, or is resistant to supportive treatment. In the present manuscript, we discuss these adverse events and propose a management algorithm. A systematic literature search was performed for

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immune checkpoint inhibitors and colitis. Additionally, phase III trials were evaluated for the incidence of gastrointestinal adverse events.

2 Checkpoint Inhibitor Therapy and Immune-Related Side Effects

"Immune checkpoint" proteins are immunosuppressive receptors expressed by activated T lymphocytes, including cytotoxic T-lymphocyte antigen 4 (CTLA-4) [1] and programmed death 1 (PD-1) [2–4]. These checkpoints block the actions of components of the endogenous immune system against tumor cells. Immune checkpoint inhibitors such as monoclonal antibodies directed against CTLA-4 (ipilimumab), PD-1 (pembrolizumab, nivolumab), and programmed death ligand 1 (PD-L1; atezolizumab) have been approved by regulatory authorities and are widely prescribed in advanced malignant melanoma [5–8], lung cancer [9–13], and renal cell carcinoma [14, 15]. Additional indications, including urothelial cancer [16–18], head and neck squamous cell carcinoma [19, 20], gastric cancer [21], mismatch-repair deficient colorectal cancer [22], ovarian cancer [23], Merkel cell carcinoma [24], and Hodgkin lymphoma [25] are under regulatory consideration. This, together with numerous other ongoing clinical studies on these agents, suggests a strong increase in immune checkpoint inhibitor prescriptions in the near future.

Immune-related side effects have been described with all these agents, but are not correlated with tumor response. While most such adverse events remain of a mild intensity, grade III and IV immune toxicities are observed in up to 10% of immunotherapy-treated patients [26].

3 Immune Checkpoint Inhibitor-Induced Diarrhea and Colitis

All-grade immune checkpoint inhibitor-induced diarrhea occurs in up to 30% of patients in clinical trials (Table 1). The incidence of diarrhea is higher in patients receiving CTLA-4-blocking antibodies compared to patients receiving PD-1 receptor inhibitors [29] (Table 1). The disease severity is closely linked to dose exposure for ipilimumab [30], and in a phase II dose-finding study for ipilimumab, the rate of severe diarrhea was higher at the 10 mg/kg dose than at 3 mg/kg (10 versus 1%), reinforcing the dose-related toxicity [8].

Clinical presentation of colitis is diarrhea accompanied by abdominal pain, rectal bleeding, or the presence of mucus in stools. Immune-mediated colitis occurs in 0.3 to 7% of patients (Table 1) and can lead to severe complications such as reflex ileus, colectasia, or intestinal perforation, which requires emergency surgery and can be life-threatening. In a study of the adjuvant use of ipilimumab in stage III melanoma [31], the most important grade III–IV adverse events were gastrointestinal (16%) and 3 of the 475 patients treated with ipilimumab in this trial died of colitis [31].

The treatment of immune checkpoint inhibitor-induced diarrhea should exclude loperamide, because its use could mask higher-grade toxicities and could be dangerous in case of severe colitis. An early treatment with supportive care is necessary to avoid hydroelectrolytic complications or renal failure. Sufficient oral hydroelectrolytic intake and a low fiber diet are general recommendations in acute diarrhea [32].

Diarrhea and colitis occur with a median of 6 weeks into immune checkpoint inhibitor treatment, but can start much later, which is why suspicion for immune-mediated colitis should remain high for the first several months.

Table 1 Rate of gastrointestinal side effects in anti-PD-1, anti-PD-L1, and ant-CTLA4 clinical trials

Author and publication	Treatment	N	Gastrointestinal toxicities: all grade N(%)	Grade III–IV gastrointestinal toxicities N(%)
Hodi et al. [5]	Ipilimumab 3 mg/kg every 3 weeks	131	Diarrhea: 36 (25.7%) Colitis: 10 (7.6%)	Diarrhea: 6 (4.6%) Colitis: 10 (7.6%)
Hodi et al. [5]	Ipilimumab 3 mg/kg + glycoprotein 100 mg every 3 weeks	380	Diarrhea: 115 (30.3%) Colitis: 20 (5.3%)	Diarrhea: 14 (3.7%) Colitis: 12 (3.1%)
Robert et al. [27]	Pembrolizumab 2 mg/kg every 2 weeks	89	0	0
Robert et al. [27]	Pembrolizumab 10 mg/kg every 3 weeks	84	Diarrhea: 1 (1.2%)	Diarrhea 1 (1.2%)
Garon et al. [9]	Pembrolizumab 2 mg/kg or 10 mg/kg every 2 or 3 weeks	495	Diarrhea: 40 (8.1%)	Diarrhea: 3 (0.6%)
Robert et al. [6]	Nivolumab 3 mg/kg every 2 weeks	206	Diarrhea: 39 (16%) Colitis: 2 (1%)	Diarrhea: 2 (1%) Colitis: 1 (0.5%)
Weber et al. [7]	Nivolumab 3 mg/kg every 2 weeks	268	Diarrhea: 30 (11.2%) Colitis: 3 (1.1%)	Diarrhea: 1 (0.3%) Colitis: 2 (0.7%)
Rizvi et al. [10]	Nivolumab 3 mg/kg every 2 weeks	117	Diarrhea: 12 (10.5%)	Diarrhea: 12 (10.5%)
Rittmeyer et al. [28]	Atezolizumab 1200 mg every 3 weeks		Colitis: 2 (<1%)	Colitis: 0

The physiopathology of immune checkpoint inhibitor-mediated colitis is unknown but similarities with IBD are noted. Ulcerative colitis and Crohn's disease are idiopathic chronic relapsing-remitting inflammatory disorders. Their physiopathology is complex and multifactorial. Genetic factors lead to aggressive T cell responses to microbiota and dysbiosis is observed. Recent data suggest that in ipilimumab-treated melanoma patients, a distinct baseline gut microbiota enriched with *Faecalibacterium* and other *Firmicutes* is associated with clinical treatment responses and a higher frequency of ipilimumab-induced colitis [33]. CTLA-4 plays a key role in the accumulation and actions of regulatory T lymphocytes in the intestinal lamina propria [34]. Regulatory T cell functions are directly affected by anti-CTLA-4 treatment [35] and this may lead to modifications in intestinal immune homeostasis [33]. T cell activation during immunotherapy treatment could mime an IBD flare.

Endoscopic presentation of immune checkpoint inhibitor-induced colitis is similar to inflammatory colitis with a loss of vascular pattern, friability, spontaneous bleeding, and ulcerations (Figs. 1a and b). Histologically, immune checkpoint inhibitor-mediated colitis presents similar to ulcerative colitis, with lympho-plasmocytic and polynuclear epithelial infiltration and cryptitis. In some cases, granuloma are found, alike Crohn's disease [36] (Fig. 2).

According to the Naranjo adverse drug reaction probability scale [38], immune checkpoint inhibitor-mediated colitis is defined as an adverse drug reaction. Indeed, its physiopathology is coherent and there is an improvement of colitis following drug discontinuation. An early management of immune checkpoint inhibitor-induced diarrhea may prevent severe complications and decrease rates of hospitalization. Checkpoint inhibitor treatment should be discontinued when grade II diarrhea occurs or in the case of persistence of grade I diarrhea. In ipilimumab- and nivolumab-treated melanoma patients, treatment discontinuation did not affect response rates [6, 39]. It therefore appears safer to discontinue and delay immune checkpoint inhibitor therapy and treat diarrhea or colitis, than it is to continue therapy.

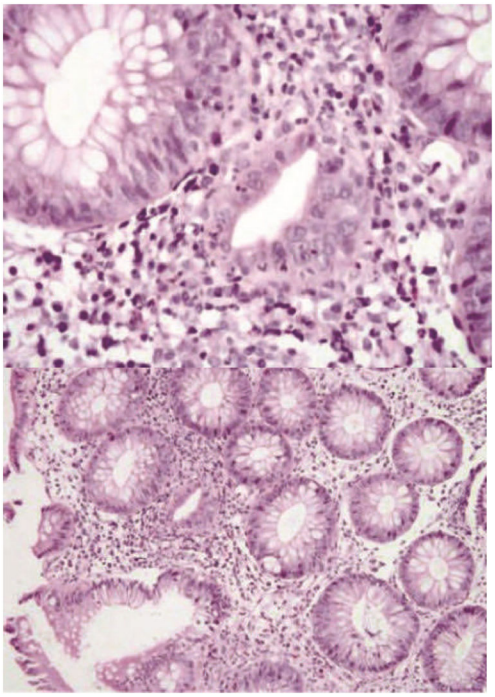

Fig. 2 Histopathology of a biopsy of immune checkpoint inhibitor-induced colitis showing crypt destruction and neutrophilic infiltrates in the crypt epithelium. Reproduced with permission from Maker et al. [37]

4 Endoscopic Assessment

Endoscopic assessment should not delay the empiric treatment with corticosteroids (see below). If diarrhea responds to supportive treatment and oral corticosteroids, endoscopic assessment is not necessary. In the case of a severe flare with only a moderate response or absence of response to corticosteroids, rectosigmoïdoscopy (or colonoscopy if possible) should be performed. Endoscopic assessment is useful to confirm mucosal inflammation and assess its severity. Recent data suggest that the presence of colonic ulcerations may be predictive of a steroid-refractory course in patients with ipilimumab-mediated enterocolitis [40]. Endoscopic assessment could thus be a prognostic tool to identify future steroid-refractory patients.

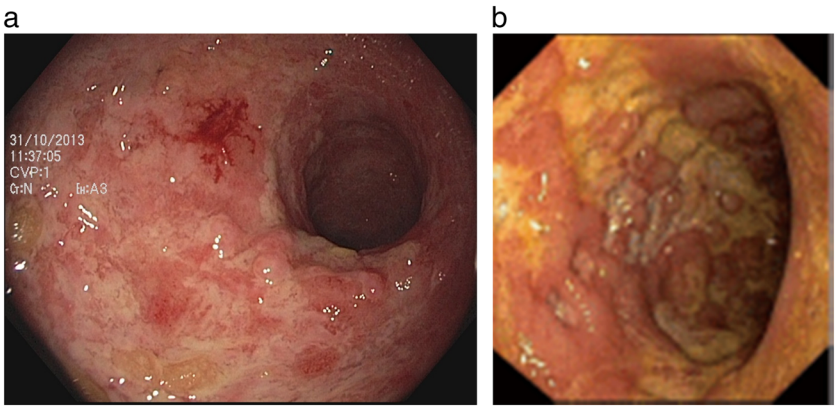

Fig. 1 **a**. Endoscopic view of a rectal flare in ulcerative colitis. Vascular pattern disparition, spontaneous bleeding and ulcerations. **b**: Endoscopic view of deep ulcerations and vascular pattern disparition in a patient treated with ipilimumab [23]

Biopsies of the colon should be performed to rule out other etiologies of colitis such as *Cytomegalovirus* colitis. A *Cytomegalovirus* polymerase chain reaction (PCR) can be performed on the colonic biopsies but the most specific sign is the presence of *Cytomegalovirus* inclusions in epithelial cells [41]. A colonoscopy with biopsies of both healthy and pathological mucosa is therefore necessary in case of persistent NCI CTC v4 grade I–II diarrhea, grade III–IV diarrhea, or rectal bleeding; or for colitis confirmation before infliximab treatment. Elementary lesions described in endoscopy are: vascular pattern disappearance, erythema, bleeding, and ulcerations [36].

While colonoscopy is considered as the gold standard exploratory technique, rectosigmoïdoscopy also appears as a feasible option. Indeed, total colonoscopy requires an efficient bowel preparation and general sedation in the vast majority of cases [42]. A rectosigmoïdoscopy can be performed without sedation with a simple enema preparation, and can lead to a rapid diagnosis.

5 Management of Immune Checkpoint Inhibitor-Induced Colitis

For all patients, it is important to rule out causal infections, with stool sample screening for *Clostridium difficile* toxin, and serum *Cytomegalovirus* PCR. Differential diagnoses such as immune checkpoint inhibitor-induced coeliac disease and immune hyperthyroidism should also be ruled out. Indications for endoscopy should be considered as aforementioned.

Stool frequency, rectal bleeding, abdominal pain intensity, dehydration, and peritonitis should be assessed. Severe immune checkpoint inhibitor-induced colitis is comparable to severe acute colitis in IBD, defined by a Lichtiger score > 10 [43] (Table 2). A severe flare can lead to colectasia and intestinal perforation. Assessing severity in side-effect graduation during immune-mediated colitis is based on the general condition evaluation (ECOG performance status), the number of stools per day, presence of stools during the night, presence of rectal bleeding, abdominal pain, and the use of anti-diarrheal therapy. This simple clinical score can easily be calculated and followed daily and could be useful in immune checkpoint inhibitor-induced colitis.

For fewer than six stools per day over baseline (grade I or II diarrhea based on NCI CTC v4), ambulatory treatment is possible. In case of grade I diarrhea (<4 stools/day over baseline) treatment continuation is possible with close medical supervision. In case of persistence or worsening of symptoms, immune checkpoint inhibitor treatment should be withheld. Treatment may be considered upon resolution to grade 0–I. Biology and bacteriology assessments should be systematically performed even in an outpatient care management. Racecadotril 100 mg three times per day together with oral rehydration and close clinical and biological observation could be initiated as supportive care therapy [44].

Meanwhile, corticosteroids are currently used at a fixed dose of 1 mg/kg/day and can be raised to 2 mg/kg/day in refractory or severe cases [45, 46]. Two to five days following the control of digestive symptoms, a progressive corticosteroid decrease can be initiated for a 1–2-month period associated with a prophylaxis therapy with trimethoprim and sulphamethoxazole [47].

A lack of improvement in symptoms over a 24-h period justifies hospitalization, intravenous corticosteroids, and intravenous rehydration. Despite abdominal pain and diarrhea, loperamide and opioids should be avoided [30].

Considering the similarity with IBD, an evaluation of the severity of immune-mediated colitis could be assessed with the Lichtiger score (Table 2) [43]. Severe colitis, with grade III–IV diarrhea and abdominal pain, corresponding to a Lichtiger score > 10 is identified in up to 10% of cases in our experience. In this case, hospitalization in a colitis-experienced unit is mandatory. Immune checkpoint inhibitors must be discontinued. In case of abdominal symptoms suggesting peritonitis, abdominal computed tomography seeking colonic perforation must be performed. If there is no argument for gastrointestinal perforation, endoscopic assessment should be performed within a short period of time to rule out any other differential diagnosis. Corticosteroid infusion with a dose of 1 mg/kg/day is recommended. Corticosteroids tapering should be considered within 1 to 2 months.

In case of deterioration despite corticosteroids, infliximab (anti-TNF-alpha) should be discussed with a single dose of 5 mg/kg [30, 46, 48]. TNF-alpha is a proinflammatory cytokine that plays a fundamental role in inflammatory colitis. Anti-TNF alpha antibodies have been developed for the treatment of IBD since the year 2000, and are indicated in corticosteroid-resistant (absence of response with 1 mg/kg/day of methylprednisone) severe acute colitis or as a maintenance therapy in corticosteroid-dependent (relapse after steroids tapering under 20 mg/day) or severe IBD. Exposure to infliximab does not seem to worsen overall survival in cancer [49].

Following the suspension of immunotherapy and the settlement of the symptoms, the resumption of immunotherapy appears to be an option if (i) the side effect has returned to baseline, (ii) the steroid dose is reduced to ≤10 mg/day prednisone without the need for the addition of other immunosuppressive drugs, and (iii) the

Table 2 Acute severe colitis evaluation (Lichtiger score of colitis severity in inflammatory bowel diseases) [43]

Number of stools per day (more than usual)	0–2	0
	3–4	1
	5–6	2
	7–9	3
	10 and more	4
Stool during the night	No	0
	Yes	1
Rectal bleeding (percentage)	Absent	0
	<50%	1
	> or =50%	2
	100%	3
Fecal incontinence	No	0
	Yes	1
Abdominal pain	None	0
	Light	1
	Mild	2
	Intense	3
General condition	Perfect	0
	Very good	1
	Good	2
	Mild	3
	Bad	4
	Very bad	5
Provoked abdominal pain	None	0
	Light	1
	Mild and diffuse	2
	Important	3
Anti-diarrheal necessity	No	0
	Yes	1
TOTAL:		
Definition: **acute severe colitis defined by a score ≥ 10**		

benefit of immunotherapy reintroduction is important and counterbalances the potential risk.

A definitive discontinuation of immunotherapy is indicated in case of grade IV adverse immune dysfunction, recurrent grade III, or grade II adverse events without resolution within 3 months under appropriate treatment [50].

No preventive treatment has shown sufficient efficacy. In a double blind phase II study by Weber et al. [51] comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma, budesonide did not affect the rate of grade ≥ 2 diarrhea compared to placebo [51].

Antibiotics are known to be helpful for severe colitis in IBD. There is no data available for immune checkpoint inhibitor-induced colitis, but as a parallel with IBD, a probabilistic antibiotherapy could be proposed in severe cases [52]. *Clostridium difficile* colitis associated with immune-mediated colitis can exist; therefore, potential *C. difficile* infection should be assessed by *C. difficile* toxin in the stool, and treated (oral metronidazole or vancomycin). Concomitant treatment with both antibiotics and steroids for patients on checkpoint inhibitors is not uncommon.

No data is available regarding systematic preventive anticoagulation, local therapy, or cyclosporine in immune-mediated colitis contrary to IBD severe flare management.

Despite these restrictions, an algorithm for immune-mediated colitis could be proposed based on the similarities with IBD (Fig. 3) [29, 30, 50, 53, 54].

Considering the 10 to 30% incidence of gastrointestinal side effects, patients should be informed of the treatment's potential gastrointestinal toxicity and its management.

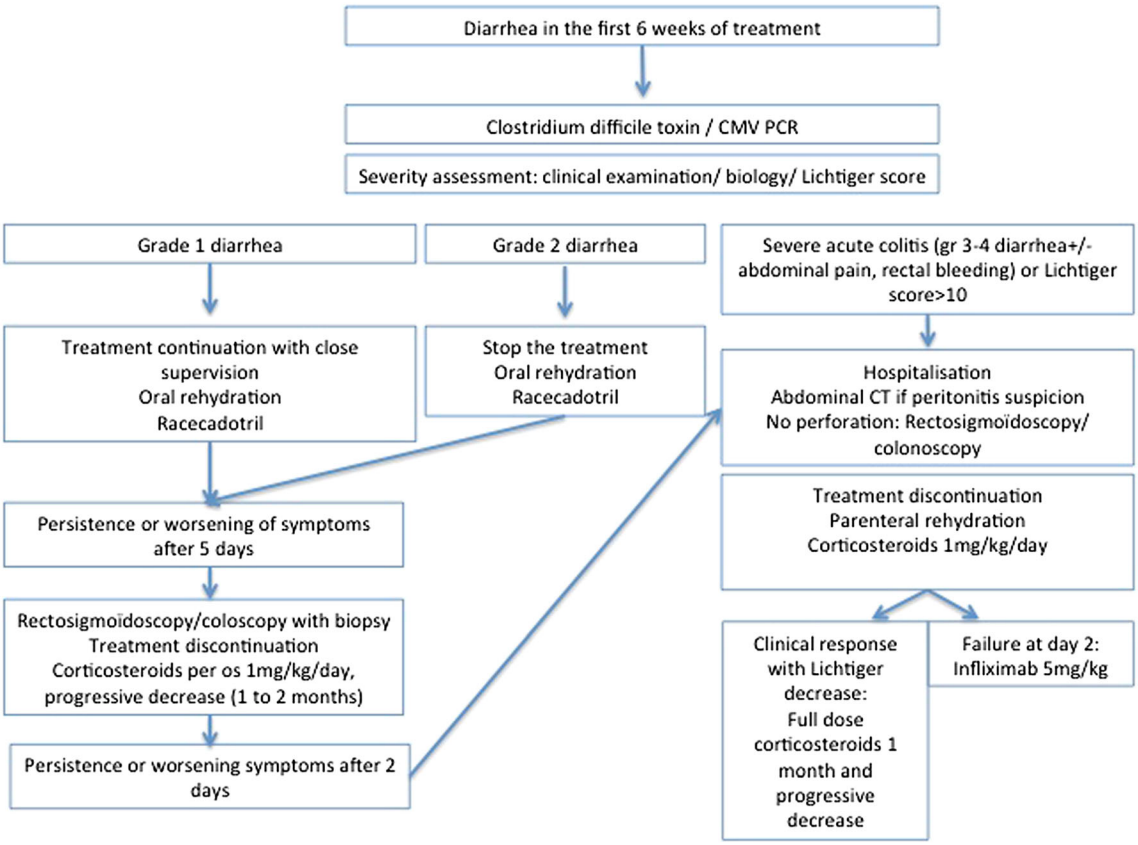

Fig. 3 Proposed management of immune checkpoint inhibitor-induced colitis

Education is important in the early management of immune checkpoint inhibitor-mediated colitis and decreases diagnostic delay [50]. Collaboration between oncologists and gastroenterologists is necessary for the management of immune-mediated colitis.

6 Conclusions

Immune checkpoint inhibitor-mediated colitis is underestimated and justifies a specific management to optimize immunotherapy drug exposure. We believe that the clinical presentation of immune checkpoint inhibitor-mediated colitis is similar to that of an IBD flare. However, oncologic patients' specificities must be taken into account. As in colonic IBD, the Lichtiger score can help in assessing severity, as it is a simple clinical score. Endoscopy with biopsies should be performed to confirm the diagnosis in severe or persistent colitis and rule out alternative diagnoses. The early treatment with corticosteroids and supportive care is primordial. Oncologists should be aware of this frequent and potentially severe side effect which justifies a multidisciplinary management.

Compliance with Ethical Standards

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Conflict of Interest Vered Abitbol has acted as a consultant for Hospira and Abbvie, given lectures for Hospira, and received travel support from Takeda, Janssen, and Pfizer. All other authors declare no conflicts of interest.

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