Review

Hell J Surg. 2024 Jul-Sep;94(3):151–156
doi: 10.59869/24039

Acute abdomen in the era of immune checkpoints inhibitors - what the surgeon needs to know: A narrative review

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ABSTRACT

Immune checkpoint inhibitors (ICI) have been approved for the treatment of a variety of malignancies. Immune-related adverse events are rare and might affect a lot of different organs including the intestines. Enterocolitis is a common complication characterised by symptoms such as diarrhoea, abdominal pain, and vomiting. In rare circumstances, bowel perforation, obstruction, or even toxic megacolon might appear. The proper therapeutic management of these conditions is based on case reports or case series. Conservative management is the standard of care in the case of ileus, however, the safety of performing a bowel anastomosis has not been answered yet. This study aims to raise awareness among the medical community, and specifically surgeons, regarding the intestinal complications of ICI, as the uprising administration of these targeted therapies makes this knowledge necessary.

Key Words: *Immune checkpoint inhibitors; acute abdomen; ileus; enterocolitis; immune-mediated colitis; immunotherapy adverse events*

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Submission: 25.10.2024, Acceptance: 15.12.2024

INTRODUCTION

Immunotherapy is a targeted therapy used as first-line treatment for a variety of malignancies including melanoma, non-small cell lung carcinoma (NSCLC), microsatellite-instability (MSI) high and mismatch repair deficiency (dMMR) colorectal cancer [1] and others. Programmed cell death 1 (PD1) and programmed cell death ligand 1 (PDL1) are two well-studied molecular targets, the blockade of

which results in the inactivation of T-cells, preventing immune response. Pembrolizumab and nivolumab are anti-PD-1 immune checkpoint inhibitors (ICIs), while atezolizumab, avelumab, and durvalumab are anti-PD-L1 ICIs. Anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies, such as ipilimumab and tremelimumab, suggest another category of ICIs, which aim at tumor reduction [2]. Immune-related adverse events (irAEs) may affect a variety of organs, such as the liver, colon, endocrine glands, lungs, and skin [2]. Life-threatening immune-related side effects are rare, however, enterocolitis is quite common, usually presenting with diarrhoea, abdominal pain, vomiting, and nausea [3]. In the emergency setting, bowel perforation, obstruction, or even toxic megacolon may appear [2]. This article aims to raise awareness of this relatively new clinical entity, as a high percentage of gastroenterologists and surgeons are not acquainted with it.

METHODOLOGY

A comprehensive literature search was performed from September 1st 2024 to October 31st 2024 across several major databases, including PubMed, Scopus, and Web of Science, to gather relevant information. Keywords such as "immune checkpoint inhibitors", "PD-1 antibodies", "PD-L1 antibodies", "enterocolitis", "intestine", and "intestinal adverse events", were used. The selection criteria were focused on articles published in the English language. Unfortunately, no randomised control studies and no meta-analyses were found, indicating the rare character of this clinical entity.

EPIDEMIOLOGY AND PREDICTIVE MARKERS

Patients treated with anti-CTLA-4 therapy carry a higher risk of developing enterocolitis compared to anti-PD-1 therapy alone (8-20% vs 1.3%, respectively [4]), however, a combination of ICIs has the greatest probability of developing colitis [3]. In particular, in a meta-analysis conducted by Wang et al [5] with 8,863 participants, the incidence of GI irAEs during PD-1/PD-L1 inhibitor monotherapy with 1.3% for all-grade colitis, 0.9% for severe colitis and 1.2% for severe diarrhoea, while combination ipilimumab and nivolumab resulted in the highest incidences of all-grade colitis (13.6%), severe colitis (9.4%) and severe diarrhoea (9.2%) among ICIs. The median period from the initiation of treatment to symptom onset is approximately three months [6]. The GI symptoms present usually after three weeks of treatment but they can appear anytime [7]. High suspicion index and clinical experience lead to earlier diagnosis, which explains the rising incidence of any grade irAEs [8].

Other predisposing factors include previously treated inflammatory bowel diseases (IBD), high doses of ICIs, microbiota rich in firmicutes and poor in Bacteroidetes, previous hepatitis or HIV infection, and other autoimmune diseases [3], which should be taken into consideration before beginning ICI therapy. Predictive biomarkers that could predict the development of toxicities have been described in terms of ipilimumab such as oeosinophils [9] and interleukin-17 [10]. A single-center study by Pavan et al [11] in patients treated with anti-PD-1/PD-L1 therapy for advanced NSCLC revealed an association between low neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and irAEs, with multivariate analysis confirming PLR as an independent predictive biomarker.

PATHOPHYSIOLOGY

Antibody PD-1 blockages result in the inactivation of T cells [2]. Blocking the PD-(L)1 axis leads to an increased number of CD8+ cells, especially near the tumour site, with high expression of the cytotoxic granzyme B pathway [12]. The inhibition of the PD-L1 by the innate immune system and the inhibition of colitis through a regulatory population of CD4+CD25-PD-1 T cells have been associated with the pathophysiology of ICI-induced colitis although more data are needed [5]. PD-1-induced colitis induces a high concentration of mucosal and intraepithelial CD8+ T-cells population [3,2]. The Th17/ IL-17 axis is also responsible for the production of chemokines CXCL8 and GM-CSFF by intestinal epithelial cells, which attract neutrophils, forming a mucosal barrier [12]. Neutrophil infiltration is a common characteristic of ICI-mediated colitis (IMC) biopsies after both anti-CTLA-4 and anti-PD1 therapy [12].

Anti-CTLA4 antibodies prevent the interaction between CTLA-4 receptor, which is found on regulatory T-cells, and its ligand, B7 [2]. This intervention results in increased CD28 activity, and promotes a direct response of the cytotoxic T-cells against tumour cells [2]. Toxicity from anti-CTLA-4 antibodies is dose-dependent, whereas toxicity from anti-PD-1/PD-L1 is independent of doses [8]. For example, severe-grade toxicities due to Pembrolizumab were similar at doses of 10 mg/kg and its FDA-approved dosage of 2 mg/kg [13].

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Diarrhea is the most frequent symptom, usually without blood in stool, associated with urgency [2]. Rectum and sigmoid colon are affected in the majority of patients, however, the small intestine might also be involved [3], which can result in bowel obstruction [2]. Enteritis may exist without the presence of concomitant colitis [14]. Endoscopy reveals focal areas of inflammation with pen-

etrating oeosinophils and neutrophils, as well as ulcerations in almost 80% of the cases, which can lead to perforation [3]. At first, two types of enterocolitis were identified; active colitis with neutrophilic crypt microabscesses, atrophy and cell apoptosis, and lymphocytic colitis with increased intraepithelial lymphocytes [15]. The level of diarrhoea is not correlated with endoscopic findings [14]. Histological findings include lamina propria expansion, villous bleeding, intraepithelial neutrophils/ lymphocytes, and increased crypt/gland apoptosis [7]. These pathologic features are non-specific and commonly seen in IBD as well [14]. On the other hand, crypt rupture with adjacent histiocytes, either isolated or forming granulomas, suggests a rather unusual finding, which was identified in almost half of the biopsies of ICI-mediated colitis [15]. Collins et al [4] classified gastrointestinal (GI) irAEs into four clinicopathologic categories: acute colitis, microscopic colitis, acute gastritis, and coprostasis, reporting one case of necrotising enterocolitis and generally good response to corticosteroids.

Differential diagnosis includes cytomegalovirus (CMV) colitis, hepatitis, Clostridium difficile, celiac disease, and IBD [3]. Fecal lactoferrin, fecal calprotectin, stool culture, Clostridium difficile antigen, and serology studies including CMV, are essential laboratory tests in order to rule out infection and IBD [2,14,7]. The use of immunochemistry to rule out CMV colitis is also suggested [15]. Young age and the presence of Paneth cells favor the diagnosis of IBD [15]. A thorough medical history, laboratory and serology tests, endoscopy and histopathology, are required to set the diagnosis of ICI-mediated colitis and differentiate it from other types of colitis.

GI AEs are classified into four categories based on the seriousness of the clinical manifestation, in order to guide the therapeutic management [2]. Grade 3 and Grade 4 ICI-induced colitis are defined as severe irAEs with more than 7 diarrhoeic stools per day [2]. Intense abdominal pain, fever, sepsis and rectal bleeding are warning signs which indicate that a Computed Tomography (CT) should be upfront performed to exclude complications such as perforation, abscess formation, and toxic megacolon [2].

THERAPEUTIC MANAGEMENT

Intravenous or oral rehydration, based on the severity of the symptoms, is essential for fluid restoration and resuscitation, as well as electrolyte replacement. Loperamide may also be useful to reduce the frequency of diarrhoea [8]. The first-line treatment for ICI-induced colitis is corticosteroid therapy, budesonide, prednisone or methylprednisolone, dependent on the grade of diarrhoea, after an infectious cause is ruled out [2]. The majority of patients, 60-80% respond positively [3]. Corticoid resistant colitis may require infliximab, mycophenolate mofetil, or vedolizumab alternatively [2]. However, TNF-a inhibitors should be avoided in case of possible colonic perforation [3]. In severe cases, withdrawal and permanent discontinuation of ICIs is required [2,16]. Readministration of anti-CTLA-4 in patients with previous ICI-induced enterocolitis is associated with increased possibility of relapse [6]. In addition, it should be taken into consideration that the administration of cortisone may conceal fever and other clinical manifestations of a possible bowel perforation [7]. The key-points of ICI-induced GI irAEs, including symptoms, differential diagnosis, diagnostic and therapeutic management are provided in Table 1.

TABLE 1. Key-points regarding ICI-related GI irAEs.

Symptoms	Clinical condition	Differential diagnosis	Laboratory exams	Imaging	Therapeutic management
Diarrhoea, fecal incontinence, rectal bleeding, mucus in stool, anemia, weight loss	Enteritis, colitis, Enterocolitis	IBD	Fecal calpronectin , fecal lactoferrin	Endoscopy with biopsies (pathology including immunochemistry)	ICI withdrawal Fluid and electrolyte administration Loperamide
Abdominal pain, psepsis	Bowel perforation, abscess formation, peritonitis	Infection (CMV, hepatitis, Clostridium difficile)	Stool culture, Cl. Difficile antigen, serology for CMV	CT abdomen	Corticosteroids
Vomiting Nausea	Bowel obstruction	Celiac disease			Infliximab, Mycofenolate Mofetil vedolizumab
Fever	Toxic megacolon				Surgery, bowel resection with or without anastomosis

Yasuda et al [17] published the first case of nivolumab-related small bowel perforation where an end ileostomy was performed. Kim et al [18] reported a case of proximal jejunum perforation in a patient with NSCLC treated with Pembrolizumab, who underwent resection and primary anastomosis without postoperative complications. Another case with small bowel perforation and concomitant inflammatory changes of the ileum was reported in a 65-year-old woman treated with Pembrolizumab [3]. No signs of colon or rectal involvement were detected, resection of the small bowel with primary anastomosis was performed, pathology revealed non-caseating granulomatous inflammation and the patient reinitiated pembrolizumab after a few weeks. Primary small bowel anastomosis with a linear staple is reported in several cases without postoperative complications [19]. Kiraci et al [20] published a case report of Pembrolizumab-related appendiceal perforation in a patient treated for advanced melanoma. Conservative management of contained perforation of the appendix in frames of IMC (ICI-mediated colitis) has also been reported [21]. The perforation can be associated with the presence of stricture distal to the dilated loop [22], or it can be a result of rapid tumor regression [23]. In patients treated with immunotherapy, who develop acute abdominal pain, with or without diarrhoea, urgent imaging should be performed to exclude life-threatening surgical complications, such as perforation [20].

Calini et al [24] published a retrospective cohort of 31 patients treated with ICIs who underwent elective or urgent colorectal procedures. Colonic perforation was the main indication for urgent surgery, in which a stoma was performed, while it was associated with a significant risk of postoperative mortality. Even elective cases with curative intention were associated with high morbidity, while only one patient (5,9%) developed an anastomotic leak. Multivisceral resection that was performed in almost half of the elective cases might have contributed to the high morbidity rates. In the same study, mortality was up to 22.2% in the emergency group and 4.5% in the elective one. In the NICHE study [25], where a combination of ipilimumab and nivolumab was administered in 40 patients as neoadjuvant therapy, the anastomotic leakage was 10%. Laparoscopic primary closure of the defect was performed in a case of cecum perforation, which developed in a patient with oesophageal cancer treated with nivolumab by Cho et al [7]. On the contrary, fulminant pancolitis with multifocal areas of ulcerations resistant to conservative treatment leading to GI bleeding and perforation has also been described [26]. However, the safety of an anastomosis or primary closure in the acute setting is not established yet.

Intestinal pseudo-obstruction causing ileus is another very rare manifestation of ICI-related GI irAEs. Prolonged abdominal distention, bloating, vomiting, and constipation are the main symptoms [27], while the median onset is 36 days [16]. A colonoscopy typically reveals mucosal oedema. Imaging should be performed to exclude malignancy progression and possible perforation. Therapeutic management is based on case reports and consists of cessation of immunotherapy [16] in combination with corticosteroid treatment [27]. Administration of infliximab has also been reported for cortisone-resistant cases [28]. Ileus was most frequently reported in PD-1 treatment, while no statistical difference exists between monotherapy and combination therapy [16], in contrast with colitis. Early diagnosis, prompt treatment, and close monitoring of the patients are important to prevent life-threatening complications such as perforation and peritonitis [27]. No surgical intervention is reported for ICI-related bowel obstruction. However, even in this case, close monitoring of the patient is required.

CONCLUSIONS

The increasing use of ICI in oncology will lead to a concomitant rise in ICI-related GI irAEs. A high index of clinical suspicion and experience leads to earlier diagnosis and better outcomes. ICI enterocolitis is a contemporary disease that most surgeons are not acquainted with and it can cause acute abdomen. A multidisciplinary approach and good cooperation among oncologists, gastroenterologists, pathologists, and surgeons are required to achieve the ultimate clinical outcomes. The possibility of bowel perforation in the emergency setting must be excluded soon to avoid mortality. The safety of primary bowel anastomosis or primary closure in patients treated with anti-PD1 and anti-PDL1 is a question not answered yet. Last but not least, ICI-related bowel obstruction requires drug withdrawal and nonoperative management. More structured clinical studies are necessary to guide surgical decision making.

Ethical standards declaration: *Ethical approval was not obtained from the medical research ethics committee, due to the nature of this study.*

Conflict of interest: *There are no conflicts of interest to declare.*

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