Case Report

Immune checkpoint inhibitor-induced colitis complicated with inflammatory intestinal obstruction: a case report and literature review

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Background: The combination therapy using anti-angiogenic drugs and immune checkpoint inhibitors (ICIs) has an excellent safety profile and manageable toxicity. However, ICI therapy may lead to a variety of autoimmune events, known as immune-related adverse events (irAEs), which some secondary complications may occur, such as immune-mediated colitis (IMC) and secondary inflammatory intestinal obstruction. It could impact clinical assessments and treatment decisions. Although there are few reports about secondary inflammatory intestinal obstruction related IMC.

Case Description: We report an adult patient who suffered from primary liver cancer, who accepted ICIs (sintilimab) combined with vascular endothelial growth factor (VEGF) inhibitor (bevacizumab). He suffered worsening diarrhea about 5 days following immunotherapy. Computed tomography (CT) revealed the thickening intestinal wall of colon and rectum and massive cerebral gas in the proximal colon cavity. He was hospitalized with a diagnosis of IMC and inflammatory intestinal obstruction. Finally, he underwent the therapeutic option using combined glucocorticoid and somatostatin. His symptoms eased within 3 weeks and he was discharged from the hospital.

Conclusions: IMC with diarrhea as the main manifestation requires early diagnosis and timely treatment. If the condition progresses, inflammatory intestinal obstruction may occur and this is a life-threatening situation. It is effective to accept early glucocorticoid and somatostatin while casual surgery may aggravate intestinal inflammation and injury, even death.

Keywords: Case report; immune checkpoint inhibitors (ICIs); sintilimab; immune-mediated colitis (IMC); inflammatory intestinal obstruction

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Introduction

Immune checkpoint inhibitors (ICIs) enhance the response of the systemic anti-tumor immune response system through the interaction between immune checkpoints and cancer cells. The breakthrough of the IMbrave150 and ORIENT-32 trial offers the patients with hepatocellular carcinoma good progress (1,2). However, the activation of these suppressed T cells may cause autoimmune-system damage to various organs and systems, resulting in a series of inflammatory side effects, immune-related adverse effects (irAEs). ICIs-induced gastrointestinal (GI) toxicities are the most common reason for immunotherapy

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Table 1 The results of blood and fecal tests of the patient

Laboratory tests	10/20/2020	10/26/2020	11/03/2020
Routine blood investigations			
CRP (mg/L)	79.13	53.28	5.44
Hb (g/L)	93	85	87
PCT (ng/L)	0.627	2.300	0.821
NEUT%	78.3	NA	NA
WBC (10^9)	NA	NA	NA
Albumin (g/L)	23.1	30.9	35.1
K^+ (mmol/L)	3.18	3.37	3.32
Fecal examination			
Pus cell	4+/HP	2–5/HP	1–2/HP
RBC	3+/HP	1+/HP	1+/HP
WBC	4+/HP	4+/HP	4+/HP
Bacterial culture	NA	NA	–
The number of stools (/day)	10–20 (watery diarrhea)	10–20 (watery diarrhea)	6 (sparse stool)

CRP, C-reactive protein; Hb, hemoglobin; PCT, procalcitonin; RBC, red blood cells count; WBC, white blood cells count; NEUT%, neutrophil percentage; K^+, potassium ions; NA, normal range; –, not examined.

treatment discontinuation (3). Inflammatory ileus is mainly characterized with GI motility disorders that is common after abdominal surgery, which is due to postoperative a massive release of inflammatory cytokines contributing to the GI motor dysfunction and intestinal edema in patients with GI disorders. The absence of timely treatment may also result in worsened colitis. ICIs-induced colitis is also accompanied by the release of inflammatory cytokines and go on to develop a more serious inflammatory ileus (4,5). We present the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2501/rc).

Case presentation

On October 19, 2020, a 57-year-old man was admitted to the institution with severe diarrhea. His chief complaint is pain in right upper abdominal for 2 months and diarrhea for 20 days. The patient stated that he was diagnosed with liver cancer. He underwent sintilimab (100 mg, ivgtt) combined with bevacizumab (300 mg, ivgtt) at an outside hospital 20 days earlier and noted that diarrhea began to occur about 5 days after therapy (4–5 times per day), stool being thin and yellow. He had mild abdominal distension and abdominal pain, aggravated after meals. During this period, he was slightly relieved after treatment with antidiarrheal drugs, such as montmorillonite powder, and recurred immediately after withdrawal. One week prior to his admission, he suffered severe watery diarrhea and the number of stools was >10/day, but the amount of stool is very small at a time, with a history of dizziness and nausea as well.

At admission, his vital signs were as follows: body temperature 36.4 ℃, heart rate 107/min, respiratory rate 20/min and blood pressure 91/61 mmHg. Physical examination upon admission: mild tenderness in the lower abdominal region, a spleen and a palpable liver being felt at 2.0 cm below the inferior edge of the rib and his bowel sounds were decreased. At hospital admission, the major laboratory results of the patient are listed in *Table 1*. Two days after admission, he developed fever (highest temperature 39.0 ℃). Body temperature returned within normal limits by analgesic-antipyretic agent. He was diagnosed as intestinal bacterial infection due to decreasing bowel immunity and given levofloxacin and ornidazole. He presented with increasing abdominal distension on hospital day 3. And physical examination revealed severe distention of the entire abdomen with abdominal mild pain and bowel

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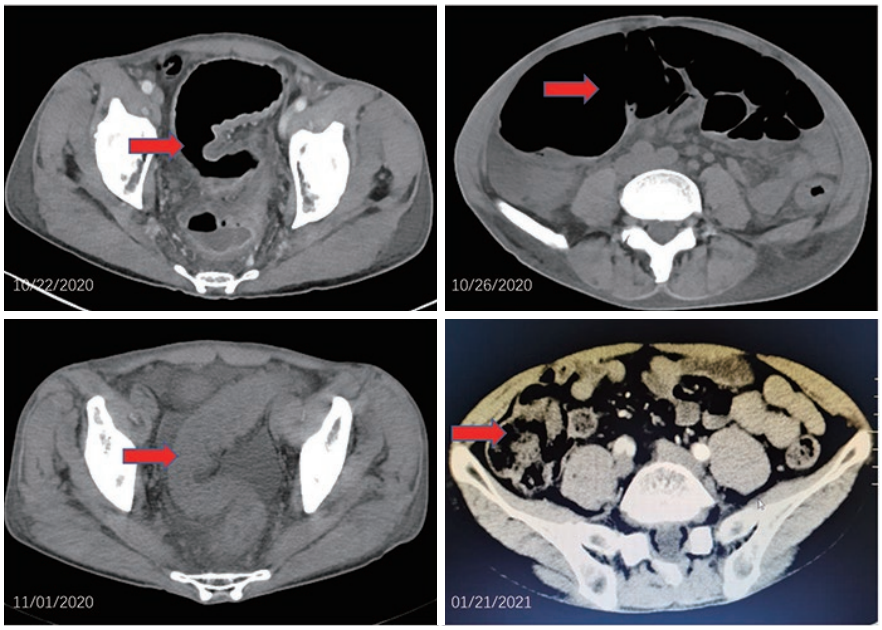


Figure 1 Results of abdominal CT during treatment. 10/22/2020: diffuse bowel wall thickening involving the distal transverse colon, descending colon, sigmoid colon and rectum and a lot of gas in the enteric cavity. 10/26/2020: significant dilatation of the colon and air accumulation. 11/01/2020: relieving bowel wall thickening. 01/21/2021: no intestinal dilatation and thickening of intestinal wall. CT, computed tomography.

sounds were decreased. Computed tomography (CT) showed the thickening intestinal wall and massive cerebral gas in the bowel lumen, suggesting intestinal inflammation (*Figure 1*). Fecal bacterial culture was provided. On hospital day 5, physical examination results were severe expansion with scattered tenderness in the whole abdomen. Shifting dullness appeared and passage of gas of anus decreased. Bowel perforation or obstruction could not be excluded. CT in abdomen as applied immediately. Fortunately, there was no significant accumulation of gas in the abdominal cavity and intestinal perforation is not considered for the time being. However, it was still terrible edema of intestinal wall and gas accumulation in the bowel lumen, a sign of intestinal obstruction. GI endoscopy was not recommended, because the high perforation risk of bowel with edema and hypertension of the bowel lumen. So, a multidisciplinary team (MDT) discussion is required, there was a common agreement that the patient was diagnosed with immune-mediated colitis (IMC) complicated with inflammatory intestinal obstruction, while surgery was not approved. He underwent glucocorticoid and somatostatin with intravenous antibiotics, GI decompression and total parenteral nutrition. After the treatment, the symptom of abdominal distension relieved and his appetite gradually recovered in 5 days. Laboratory markings of him improved and C-reactive protein (CRP) and procalcitonin (PCT) decreased (*Figure 2*). The treatment was well-tolerated without markedly side-effects and other complications. He was discharged in 19 days. Abnormalities were not seen on CT at the first follow-up (2 months later). Re-examination two month later revealed that his symptoms completely disappeared and CT showed that the intestinal wall and the bowel lumen recovered. The patient was cured completely. A timeline of the treatment course is presented in *Figure 3*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Although the mechanism of intestinal injury caused by

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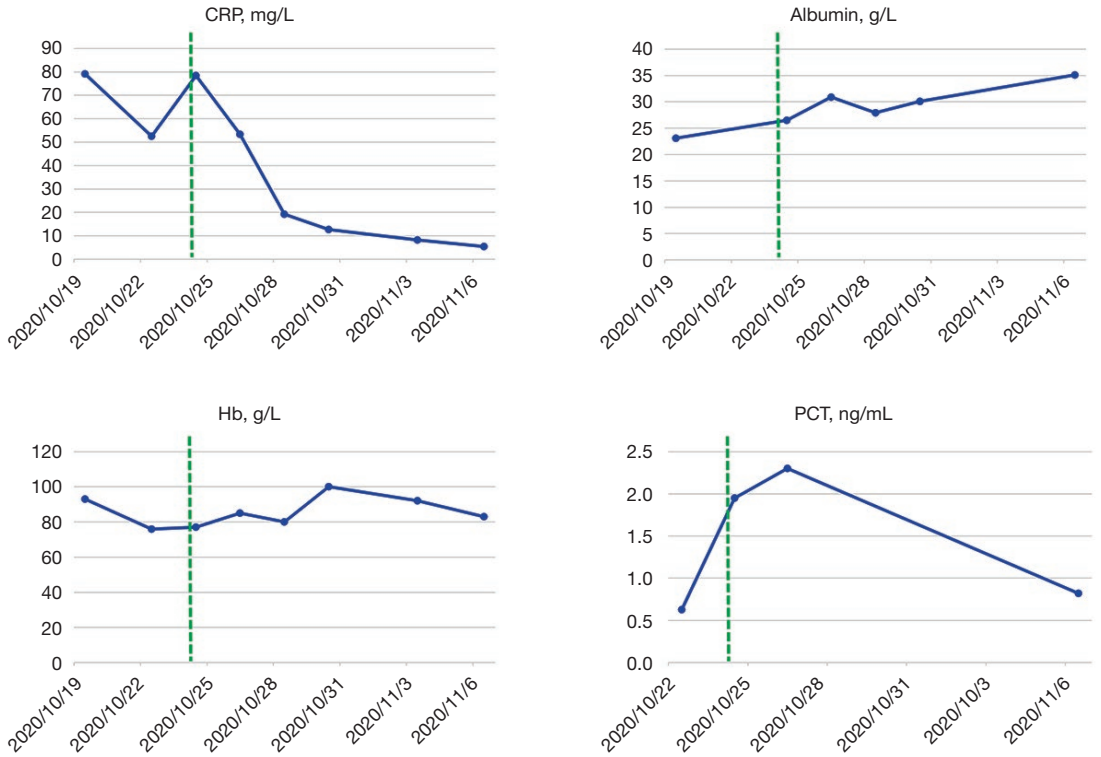


Figure 2 Changes of CRP, albumin and Hb and PCT levels during treatment during treatment. The green dotted line represents the start of glucocorticoids use. CRP, C-reactive protein; Hb, hemoglobin; PCT, procalcitonin.

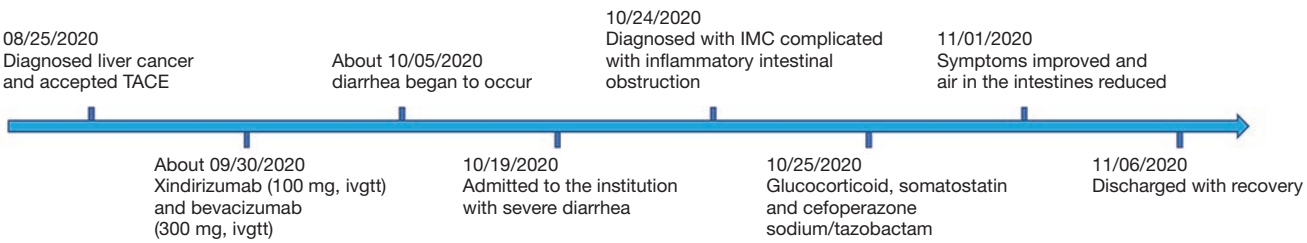


Figure 3 Timeline of the clinical course. TACE, transcatheter arterial chemoembolization; ivgtt, intravenous drip; IMC, immune-mediated colitis.

immune checkpoint blockage remains unclear, it is thought to be related to the role of immune checkpoints resulting in the over-activation of T cell and production of inflammatory cytokines (6). These damaging factors may lead to cause the damage of intestinal wall smooth muscle cells and contractile dysfunction of gut (4,5). Simultaneously, the sympathetic excitation and parasympathetic suppression of gut with these inflammatory factors can generate various GI dysfunctions including motility problems. Combination decreasing gut motility with edema and effusion of the bowel wall are with much stasis of bowel contents, resulting in the adynamic or paralytic ileus.

Colitis complicated with ileus is a relatively uncommon but potentially fatal and serious irAE. They can occur at any time, including after discontinuation of ICIs. Earlier diagnosis and treatment can have a good response to steroids, preventing effectively the occurrence of inflammatory intestinal obstruction (7-9). In the setting of sintilimab therapy and other drugs, it is not easy to distinguish immune-associated colitis from colitis. The main symptoms of colitis are diarrhea. Colitis is typically a diagnosis of exclusion. Other causes of diarrhea are needed to be ruled out. There

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are usually normal white blood cell count, increased CRP, low serum albumin levels and anemia (10). Simultaneously, negative stool cultures and ineffective antibiotics were helpful for preliminarily excluding bacterial infections. In addition, abdomen/pelvis CT may be a sensitive examination mode. A retrospective analysis indicates that the correct diagnosis of immune colitis has a positive predictive value (PPV) of 96% (11). Then, empiric trial of corticosteroids can start after ruling out infection. Resolution of diarrhea with corticosteroids is also good evidence on ICIs-induced colitis.

Sure, if it is not prompt diagnosis and treatment, inflammatory ileus may occur. Typical finding is aggravating abdominal distension, hypoactive bowel sounds and decreasing anal exhaust and defecation. CT may be a sensitive examination identifying ileus. However, it may be without typical air-fluid levels and show just edema of intestinal wall and gas accumulation in the bowel lumen in early incomplete ileus. So, if patients develop relative symptoms, inflammatory ileus cannot be excluded without typical CT image. Besides, although surgery is the main measure for the traditional treatment of intestinal obstruction, the operation is not only difficult to determine the location of the obstruction, but also easy to cause intestinal injury due to the serious intestinal adhesion and inflammation in the acute stage, resulting easily in postoperative bleeding, infection, intestinal fistula, short bowel syndrome and other serious complications, and even postoperative inflammatory intestinal obstruction again. Somatostatin can reduce the secretion of digestive juices such as pancreatic juice, improve GI blood supply, inhibit toxin absorption and inflammation (12). So, when the people diagnosed colitis suffers severe abdominal distension and decreasing anal exhaust, corticosteroids and somatostatin may be required for remission.

In the case reported here, we present a patient with advanced primary liver cancer undergoing sintilimab combined with bevacizumab. He then experienced symptoms from colitis to inflammatory ileus. Though the bevacizumab-induced colitis cannot be excluded, we cling to ICIs-induced colitis. He was then given corticosteroids and somatostatin. A good clinical effect was obtained that diarrhea and abdominal distension relieved.

In summary, with the increasingly common application of ICIs in cancer treatment, the incidence of irAEs also increases. Immune-associated colitis, as a common irAEs, may lead to serious complications such as intestinal obstruction and intestinal perforation. Early glucocorticoid may be effective and minimize the risk of intestinal toxicity by our case. When symptoms on ileus occur, conservative treatment such as somatostatin not blind surgery can also benefit the patient. Nevertheless, the conclusions may insufficient because of the lack of data from larger studies and further accumulation of clinical trials and real-world data is still required.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2501/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2501/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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