Peer Review File

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Comment 1: Interesting case report. My specific question is -- How do you know the etiology was immunotherapy mediated and from the bevacizumab, since perforation, severe focal colitis, etc is a well established complication of the latter. Without biopsy or histopathology I don't see how you can make the diagnosis.

Reply 1: It is mainly a retrospective diagnosis, and the efficacy of immunosuppressive therapy is the main basis for diagnosing of ICIs-induced colitis.

Changes in the text: 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 are usually normal white blood cell count, increased C-reactive protein, 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.

Comment 2: the study lacks novelty, there has been extensive case reports and cohort studies regarding immune checkpoint inhibitor induced colitis.

Reply 2: On the one hand, the case can tell us when symptoms on ileus occur, conservative treatment such as somatostatin not blind surgery can also benefit the patient. On the other hand, if there is high risk, gastrointestinal endoscopy is not required to diagnose and treat this patient.

Changes in the text: 1. 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 gastrointestinal blood supply, inhibit toxin absorption and inflammation. 2. Gastrointestinal 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 IMC complicated with inflammatory intestinal obstruction, while surgery was not approved.

Comment 3: There is presumed inflammatory intestinal obstruction, however the provided work up has not shown clear evidence of obstruction i.e air fluid fluid level or transition point Which argues against intestinal obstruction. Rather, the dilation is just a manifestation of the severe colitis along with the patient significant diarrhea.

Reply 3: The patient suffering typical symptoms of intestinal obstruction such as aggravating abdominal distension, hypoactive bowel sounds and decreasing anal exhaust and defecation. Besides, 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.

Changes in the text: 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.

Comment 4: ICI-colitis is a diagnosis of exclusion, the authors did not provide the work up of diarrhea, nor the pathology showed classical features of ICI colitis (apoptosis)
Reply 4: It is mainly a retrospective diagnosis, and the efficacy of immunosuppressive therapy is the main basis for diagnosing of ICIs-induced colitis. At the same time, his negative stool cultures and ineffective antibiotics therapy were helpful for excluding infection.
Changes in the text: 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 are usually normal white blood cell count, increased C-reactive protein, 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 ICIsinduced colitis.

Comment 5: The discussion does not include a representative literature review on the topic to reflect the title
Reply 5: Our case reminded us that if patients considered colitis develop increasing abdominal distension, inflammatory intestinal obstruction cannot be excluded and corticosteroids and somatostatin may be required for remission. So, we modify the article to be more match the case.
Changes in the text: Although the mechanism of intestinal injury caused by 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 damage 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 gastrointestinal 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 are usually normal white blood cell count, increased C-reactive protein, 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 ICIsinduced 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 gastrointestinal 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 ICIsinduced 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 immune checkpoint inhibitors in cancer treatment, the incidence of immune-related adverse events 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, cnservative 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.

Comment 6: The English language needs major revisions, The case report Lacks both appropriate context flow and the appropriate clinical discussion format
Reply 6: The article was modified and if there are any inappropriate statements, thank you for pointing out them.
Changes in the text: The discuss of article.

Comment 7: there is limited literature re Xindirizumab and its use for hepatocellular carcinoma.
Reply 7: The ORIENT-32 study demonstrated that the combination of sintilimab and bevacizumab significantly prolonged OS and PFS in the Chinese population receiving first-line treatment for advanced liver cancer.
Changes in the text: The breakthrough of the IMbrave150 and ORIENT-32 trial offers the patients with hepatocellular carcinoma good progress.