

Peer Review File

Article information: <http://dx.doi.org/10.21037/apm-21-58>

Reviewer A

Comment 1: This is a single case report describing a patient who developed severe enteritis after combined CTLA-4 and PD-1 regimen for melanoma. Very challenging case with hemorrhagic shock from the severe enteritis. Review the history, wonder if early infliximab could help to alleviate the dramatic disease course.

Reply 1: We agree with this comment. Infliximab could have been introduced earlier.
Changes in the text: Page 7, Lines 2-3

Comment 2: Recommend to add endoscopic pictures of the enteritis with ulcers to the figure, so readers can learn more from direct visualization of these serious lesions.

Reply 2: We added an endoscopic picture of the per-operative endoscopy showing deep ulcers.
Changes in the text: figure 2

Reviewer B

Comment 1: I have read the manuscript by Trystram et al on ulcerative enteritis and have the following remarks: The title is sound.

Abstract Line 1, corticosteroid-resistant, Line 6, patients with, Line 7, but has never been described in enteritis independent of colitis; Line 8 with acute, delete “inflammatory”. Line 8, ileitis, Line 9, then had a GI bleed; Line 11 surgical exploration with enteroscopy was performed. This revealed; Line 12 jejunoileitis, with active bleeding, Meckel’s Line 13, Two infliximab infusions were given due to bleeding., Line 14, These resulted in; Line 15, locations.

Intro: Line 1 immune-mediated; Line 9 diarrhea, 35.4% colitis 8.8%; Line 11 deaths, Line 13 compared to, Line 16, cases of enteritis independent of colitis; Line 18, delete It is ...; Line 22, who had been treated by surgery in October 2017 had.

Page 4: Line 1, of an anti-; Line 5, Both complete; Line 6, were negative The contrast-injected; Line 7 bowel and; Line 8 A diagnosis; Line 9 was given ; Line 10, for three days,; Line 12, On day 2... (at a dose of) Line 13, GI bleed with acute reduction in globulin required; Line 17, deglobulisation is a word not understood by the reviewer. Reword. Line 18, pattern, Line 19, with frank blood. Line 20, A stool specimen was cultured; Line 23, or human herpes; Line 25, shock that required.

Page 5: Line 2, were examined. There were multiple; Line 3, centimeters, Line 4, was found 60 cm... This was invaginated, Line 5, lumen which... visible bleeding, Line 6, delete this line, Line 7, delete “extensive resection”, Line 8, patient continued to have

hematochezia, Line 10, was no evidence of an anastomotic leakage. Line 14, He showed, Line 15, injection, Line 16, transfusions, Line 18, enteroscopy revealed, Line 19, abnormalities, and a CT scan revealed stable disease and Line 20, complete remission of enteritis, Line 21, after steroid tapering, Line 22, patient's history.

Page 6: Line 1, effect, Line 8, heterogeneous, Line 10, few studies have documented lesions of the ileum seen, Line 11, histologic abnormalities were described mainly for colon: acute ... Line 13, cells, Line 16, diseases, with, Line 17, and the, Line 18, replace pejorative, wrong choice of wording (worsening) Line 20, does not reveal, Line 22, and the introduction steroids (in the absence of acute surgical abdomen) Line 23, is correlated, Line 24, cases, Line 25, bleeding varies from 10 to 64%.

Page 7: Line 3, enteritis, Line 4, ulcerations, as well as other small bowel lesions were active bleeding sites. Line 5, delete "was not initially described". Line 8, recommended, this derives from, Line 12, severity based on, Line 13, regimen improves the prognosis in, Line 14, delete "Nevertheless", Line 15, indication of Infliximab in severe, Line 16, patients, Line 17, Infliximab, Line 19, indications for _____ are, Line 23, not been reported.

Page 8: Line 6, delete "Nevertheless", Line 10, complications delete "and if possible perform" Line 15, histologic remission in immune-mediated enteritis.
This reviewer has suggested word changes throughout the paper.

Reply 1: We agree with these comments which improve the quality of the paper. Changes have been made accordingly.

Changes in the text: all through the paper as indicated.

Comment 2: However, this manuscript should not be published without several photographs of the histologic appearance of this ulcerative enteritis. If the authors are saying this enteritis is new, then show us. I'm not sure that Fig 1 has importance.

Reply 2: Figure 1 has been removed. We added pictures of pathological findings.

Changes in the text: Figures 3A and 3B with adequate figure legends page 11

Comment 3: And in Figure 2 the wall thickening is well shown, but the "diffuse enhancement after injection of contrast material" is not clear. Do the authors mean that "the vascular pattern to the affected part shows _____"? "Enhancement" means nothing here. Description must be better.

Reply 3: We agree with this comment. CT scan pictures were changed.

Changes in the text: Figure 1A and 1B with adequate figure legends

Reviewer C

Comment 1: The authors should show the colonoscopic findings, resected specimens, and pathological findings in figure. There is not enough evidence from the CT figure alone to attribute that the cause of hemorrhagic shock was a diffuse ulcerative

enteritis after Ipilimumab and Nivolumab.

Reply 1: We agree. Pictures of both per-operative endoscopy and histological lesions were added.

Changes in the text: Figure 2 (endoscopic picture), Figure 3A and 3B (pathological findings) with adequate figure legends

Comment 2: The authors described that the patient “presented a metastatic relapse” in P3L23. What is the recurrence site? Is there a possibility of bleeding from small bowel metastasis? The authors should show the proof that there are no metastases in the ileum.

Reply 2: the patient presented an isolated metastatic lymph node relapse. The per-operative endoscopy allowed us to analyse the small bowel almost until the ligament of Treitz and only ulcerated lesions were visualized. The patient is still in remission in March 2021 with a morphological follow-up including an FDG-PET.

Changes in the text: page 3, line 19

Comment 3: The authors wrote “A complete infectious and neurological workup was negative. However, the authors also described “The diagnosis of immune-mediated enteritis and encephalitis was retained” Why did the authors diagnose as encephalitis? I cannot understand the reason, because the reason for suspecting encephalitis is not written.

Reply 3: We agree with this comment. The diagnosis of encephalitis is doubtful and has not been fully documented. We delete this point from the text.

Changes in the text: page 4, line 4

Comment 4: The authors described that Infliximab was an effective treatment for this patient. However, the use of Infliximab should be more cautious for the patients with malignant disease. The authors should discuss more carefully in this point.

Reply 4: A recent paper has raised this specific point. The negative impact of infliximab on survival remains uncertain. The discussion has been modified accordingly.

Changes in the text: page 7, lines 13-19

Comment 5: Figure 1A shows small bowel obstruction. However, there is no extravasation in Meckel diverticulum in this figure. Please show us more helpful figure. I think the resected specimen is more helpful for diagnosis.

Reply 5: we agree with this comment. This figure is not relevant and has been withdrawn. Pictures of endoscopic lesions and pathological findings were added. CT scan pictures were modified

Changes in the text: figure 1A and 1B (CT scan pictures); figure 2 (endoscopic picture); Figure 3A and 3B (histological figures) with adequate figure legends.

Comment 6: Figure 2 shows the detailed date. It seems to be unfavorable from the viewpoint of personal information protection. Please make appropriate corrections.

Reply 6: Thanks for this comment, we deleted the date

Changes in the text: figure 4

Comment 7: The authors wrote “To our knowledge, this is the first case of massive digestive bleeding attributed to iatrogenic diffuse enteritis in P7L1-3. This expression is inappropriate, because several authors reported massive intestinal bleeding after colectomy for ulcerative colitis especially from Japan. Please change the expression.

Reply 7: Thanks for this comment, we changed the expression.

Changes in the text: page 6, line 21