

Dear Editors,

Enclosed is our revised manuscript entitled “Bilateral pneumothorax and pneumomediastinum during colonoscopy in a patient with intestinal Behcet’s disease: a case report” (Manuscript ID: 71604) by Mu et al. Thank you and the reviewers for their valuable comments and suggestions. We hope this revision will meet your final approval for publication in *World Journal of Clinical Cases*.

According to the comments, we have made several changes in the revised manuscript, which were highlighted in red. Appended to this letter is our itemized responses to the comments. The comments are reproduced and our responses are given directly afterward.

Reviewers' Comments:

Reviewer #1:

1.what is the type of gas used during colonoscopy, is it air or co2.

We appreciate the reviewer’s comments. Air was used during colonoscopy, because the CT scan of abdomen and pelvis before colonoscopy didn’t show signs of intestinal perforation. To be clearer and in accordance with the reviewer concerns, we revised the text in the “*History of present illness*” section as follows: “To determine the severity of intestinal lesions and rule out intestinal tumors, the patient underwent a **routine** diagnostic colonoscopy **using air insufflation** under nontracheal intubation intravenous general anesthesia (propofol)”, and revised the text in the “FINAL DIAGNOSIS” section as follows: “Due to the past history of spontaneous ileocecal perforation and the presence of ileocecal stenosis and deep ulcers, it was speculated that this perforation occurred in the ileocecal area and was caused by a pressure-related injury to the muscle layer of the deep ulcers induced by **air** insufflation during the endoscopy”.

2.you mentioned that the patient was under general anesthesia, and mentioned again that there was a difficulty inserting an endotracheal tube just after colonoscopy.

I'm sorry for my confusing expression. The patient was under non-tracheal intubation intravenous general anesthesia with propofol during colonoscopy. Ondansetron was also used to prevent vomiting. No analgesics and other sedatives were used. We revised the text in the "*History of present illness*" section as follows: "To determine the severity of intestinal lesions and rule out intestinal tumors, the patient underwent a routine diagnostic colonoscopy using air insufflation under **nontracheal intubation intravenous general anesthesia (propofol)**".

3. there is difficulty understanding the endoscopic findings of both colonoscopies, also why you proceed with a second colonoscopy despite the history of spontaneous perforation in the index colonoscopy. Is there other modalities with a less risk of perforation.

I'm sorry for my confusing expression. The first colonoscopy was performed 12 years ago, and showed colonic ulcers which were considered to be a manifestation of intestinal Behcet's disease. Spontaneous ileocecal perforation happened 11 years ago. Then the patient received irregular treatment, and didn't experience unbearable abdominal symptoms. However, before this admission, he suffered intermittent abdominal pain, bloating and reduced defecation for six months. The CT scan of the abdomen and pelvis before colonoscopy revealed bowel wall thickening in the terminal ileum, ileocecal area and appendix, ileocecal stenosis and incomplete bowel obstruction. We couldn't determine whether the intestinal lesions had progressed, because the previous colonoscopy was performed 12 years ago and the CT scan couldn't reveal bowel ulcers. We also needed to rule out intestinal tumors because the patient was 58 years old and the CT scan showed thickening of the bowel wall. After fully communicating with the patient, we decided to perform a colonoscopy. The second colonoscopy confirmed the diagnosis and severity of intestinal Behcet's disease, and provided evidence for follow-up treatment under the guidance of a rheumatologist. Unfortunately, bowel perforation occurred during the second colonoscopy.

We revised the text in the "*History of past illness*" section as follows: "**The patient underwent a colonoscopy 12 years prior, and colonic ulcers were observed. Because the**

patient had oral and perianal ulcers and the colonic ulcers were considered to be a manifestation of intestinal BD, the patient was diagnosed with intestinal BD by a rheumatologist. He had suffered severe pain in the right lower abdomen 11 years prior. Acute appendicitis was initially suspected, but spontaneous ileocecal perforation was confirmed during an emergency exploratory laparotomy, and surgical repair of the ileocecal perforation was performed. He still suffered from the recurrence of oral and perianal ulcers but did not experience unbearable abdominal symptoms after taking prednisone and leflunomide irregularly”.

We revised the text in the “*History of present illness*” section as follows: “**To determine the severity of intestinal lesions and rule out intestinal tumors**, the patient underwent a routine diagnostic colonoscopy using air insufflation under nontracheal intubation intravenous general anesthesia (propofol)”.

Reviewer #2:

1.First, to clarify whether the perforation happened after colonoscopy or before. It will be good to present CXR and abdominal x-ray before colonoscopy if authors had this detail.

We are grateful for the comments. Spontaneous ileocecal perforation happened 11 years ago. During this admission, the patient didn't have symptoms and signs of bowel perforation before colonoscopy, and the CT scan of abdomen and pelvis before colonoscopy didn't show signs of bowel perforation. Upon withdrawal of the colonoscope, the patient suddenly experienced shortness of breath and confusion and gradually developed cyanosis. Then pneumothorax and pneumoperitoneum were confirmed. Therefore, we speculated that the perforation happened during colonoscopy. We didn't see obvious perforation on endoscopy. However, it's possible that tiny bowel perforation occurred before colonoscopy, but caused severe symptoms and signs due to air insufflation during endoscopy. It's regretful that we didn't have CXR and abdominal x-ray before colonoscopy. We will pay attention to this important issue when meeting similar condition next time.

We revised the text in the “*Imaging examinations*” section as follows: “The computed tomography (CT) scan of the abdomen and pelvis **before colonoscopy** revealed bowel wall thickening in the terminal ileum, ileocecal area and appendix, ileocecal stenosis and incomplete bowel obstruction”.

2.Second, did the authors use CO2 or air insufflation in colonoscopy. Please add this information as well.

Air insufflation was used during colonoscopy, because the CT scan of abdomen and pelvis before colonoscopy didn't show signs of intestinal perforation. We revised the text in the “*History of present illness*” section as follows: “To determine the severity of intestinal lesions and rule out intestinal tumors, the patient underwent a **routine** diagnostic colonoscopy **using air insufflation** under nontracheal intubation intravenous general anesthesia (propofol)”, and revised the text in the “FINAL DIAGNOSIS” section as follows: “Due to the past history of spontaneous ileocecal perforation and the presence of ileocecal stenosis and deep ulcers, it was speculated that this perforation occurred in the ileocecal area and was caused by a pressure-related injury to the muscle layer of the deep ulcers induced by **air** insufflation during the endoscopy”.

3.Last, it will be good to add more critical discussion about the possibility of bowel perforation from colonoscopy in BD patients and how to differentiate spontaneous bowel perforation from iatrogenic perforation from the colonoscopic procedure (for example, table that contains incidence/abdominal signs and symptoms/film x-ray/colonoscopic finding etc.)

Thank you for your comments! We modified the text in the “DISCUSSION” section as follows: “Intestinal oval-shaped **deep** ulcers are characteristic lesions in patients with intestinal BD **that can involve the intestinal muscle layer. Therefore, bowel perforation, especially ileocecal perforation, may occur as a complication of intestinal BD. In this case, spontaneous ileocecal perforation had occurred 11 years prior. Unfortunately, life-threatening iatrogenic bowel perforation associated with colonoscopy occurred during this admission.**

Adult patients with spontaneous bowel perforation usually have specific causes, such as Crohn's disease, scleroderma, intestinal non-Hodgkin's lymphoma and intestinal BD. The incidence of spontaneous bowel perforation in patients with Crohn's disease was reported to be 1.5%^[3], but the incidence is unclear in patients with BD. Spontaneous bowel perforation in patients with intestinal BD could be single or multiple and is not limited to the ileocecal region^[4, 5]. Patients can experience severe abdominal pain, abdominal distention, nausea, vomiting, obstipation and fever^[2, 4-6] and often require surgical intervention^[2, 4, 5, 7], such as colonic repair and enterectomy. BD with spontaneous intestinal perforation could be confused with other common acute abdominal diseases, for example, acute suppurative appendicitis, due to the similarities of the abdominal symptoms and signs. An abdominal X-ray or a CT scan before colonoscopy or surgery can facilitate the detection of the occurrence of spontaneous bowel perforation.

It is estimated that the incidence of iatrogenic intestinal perforation is 0.016–0.8% for diagnostic colonoscopies and 0.02–8% for therapeutic colonoscopies^[8]. Iatrogenic colonoscopic perforation could be detected while performing colonoscopy or after colonoscopy based on early symptoms, such as persistent abdominal pain and distention, or later symptoms and signs, such as fever, leukocytosis and abdominal rebound tenderness as a result of peritonitis^[9]. In general, the sigmoid colon is the most common site of perforation (53–65%)^[8]. Due to the existence of ileocecal deep ulcers, patients with intestinal BD are at higher risk of perforation, and the ileocecal area may be the most common site of perforation. Insufflation and biopsy may lead to pressure-related and mechanical injuries of the colonic wall. Therefore, for patients with suspected intestinal BD, careful operation is required for endoscopy. It is necessary to reduce the amount of air insufflation or use carbon dioxide (CO₂) insufflation. Biopsies should be taken from the mucosa at the edges of the ulcers. Endoscopists should pay attention to the patient's abdominal signs, especially when performing colonoscopy under general anesthesia”.

We described the manifestation of spontaneous bowel perforation and iatrogenic colonoscopic perforation in the main text. But due to the lack of data on incidence of

spontaneous bowel perforation and the similarity of clinical symptoms and signs of spontaneous bowel perforation and iatrogenic bowel perforation, it's regrettable that it's difficult for us to list a satisfactory table.

Editorial Office's comments:

The authors report a case of bowel perforation during colonoscopy with pneumomediastinum, pneumoretroperitoneum and bilateral pneumothorax. This is a very uncommon complication and its report is of scientific interest. However, the chronology of the events that took place needs to be exposed with greater clarity. For example, I have understood that the patient suffered a first episode of spontaneous bowel perforation and then a second episode of perforation associated with the colonoscopy, but in the reviewer's comments it is evident that they had a different understanding after reading the manuscript. It would be interesting to know what type of surgical repair was performed in the first episode of perforation and what was the exact site of the gut that was perforated. When using abbreviations such as ANA for the first time, it is important to write their full meaning. The findings of the colonoscopy should be more thoroughly described in the manuscript, including technical details such as the type of gas used, whether biopsies were taken and if the patient was sedated or under general anesthesia. The management of the complication could also be further described, with the number of days the patient received parenteral nutrition and the inclusion of blood test results.

We appreciate your comments!

In order to clarify the chronology of the events more clearly, we modified previous confusing expression and added more details in the "CASE PRESENTATION" section. Surgical repair of ileocecal perforation was performed in the first episode of perforation. But we don't know the details of the surgery because the medical records have been lost for many years.

Thank you for reminding the abbreviations. We have written the full meaning of ANA and CT.

We have described the findings of the colonoscopy more thoroughly in the “*Imaging examinations*” section and added technical details. The biopsies were taken from the mucosa at the edge of the ulcers without damage to the muscle layer, and no perforation after the biopsies was seen on endoscopy. Therefore, we considered the iatrogenic intestinal perforation was a pressure-related injury to the muscle layer of the deep ulcers induced by air insufflation during endoscopy.

More details about the management of the complication were added in the “OUTCOME AND FOLLOW-UP” section.

Yours sincerely,

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