

# Successful treatment of refractory immune checkpoint inhibitor-related colitis after ileostomy creation: case report and literature review

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## Case Report

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# Abstract

## Background

Immune checkpoint inhibitors are widely used for treating malignant tumors, changed the framework of cancer treatment, but on the other hand, Immune-related adverse event occurs due to excessive immune response. Immune checkpoint inhibitor-related colitis shows symptoms similar to ulcerative colitis, and high-dose corticosteroids and anti-TNF-alpha antibodies are recommended, but surgical treatment has not yet been established for cases that are refractory to medical therapy.

## Case presentation

This case involved a 64-year-old male. PD-L1 expression in the recurrent lesion of lung adenocarcinoma was positive, and treatment with pembrolizumab was initiated. Hematochezia and diarrhea were observed 8 weeks after the start of the treatment and was diagnosed as irAE colitis. The patient was treated with corticosteroid, infliximab, mesalazine, and leukocytapheresis for irAE colitis, but was refractory. The patient's performance status was poor, and proctocolectomy and subtotal colectomy according to the treatment of refractory ulcerative colitis were not indicated, so a diverting loop ileostomy was performed to rest the colon. The abdominal symptoms resolved after the surgery, and chemotherapy was resumed 3 months after surgery. Stoma closure could not be performed because the mucosal lesions did not improve on colonoscopy; nevertheless, there were no symptoms of irAE colitis, and nivolumab could be administered from the eighteenth month after surgery. However, it was not effective, and the patient died of the primary disease two years after surgery.

## Discussion and Conclusions

We encountered a case in which a diverting loop ileostomy was performed for irAE colitis refractory to medical treatment, and the symptoms were alleviated. However, surgical treatment of refractory irAE colitis and resumption of ICIs after irAE development need to be fully discussed.

## Background

Immune checkpoint inhibitors (ICIs) are widely used for treating malignant tumors and have changed the framework of cancer treatment. Immune checkpoint inhibitors increase the activation of T-cell and are effective against cancer. On the other hand, T-cells infiltrate various organs and cause an immune response; additionally, an excessive immune response leads to immune-related adverse events (irAEs). (1)

Immune checkpoint inhibitor-related colitis (irAE colitis) exhibits symptoms similar to those of ulcerative colitis, and guidelines recommend high-dose corticosteroids for grade 2 or higher irAE colitis and additional anti-TNF- $\alpha$  antibodies for patients who do not respond (2,3); however, if the medical therapy is ineffective, surgical treatment has not yet been established.

We report a case of irAE colitis that was refractory to medical therapies and was effectively treated with a diverting loop ileostomy.

## Case Presentation

This case involved a 64-year-old male, who underwent chemoradiotherapy for pulmonary adenocarcinoma (cT1bN2M0). One year and six months later, a computed tomography image showed a lesion suspected of recurrence, and a biopsy was performed, the biopsy result of which showed the recurrence of lung adenocarcinoma. The immunohistochemistry of PD-L1 showed Tumor Proportion Score (TPS): 25–49%, and treatment with pembrolizumab was initiated. Hematochezia was observed 8 weeks after the start of the treatment, and diarrhea was observed 9 weeks after the start of the treatment. Although prednisolone was administered with a diagnosis of irAE colitis, the patient's symptoms did not improve, and he was transferred to our hospital for further treatment.

The course of the disease is shown in the Fig. 1. A clinical evaluation was performed using the Rachmilewitz index (Clinical Activity Index: CAI), according to the evaluation of inflammatory bowel disease.

The CAI score at admission was eight. The colonoscopy showed diffuse mucosal erythema and erosions from the rectum to the transverse colon, and mucopurulent adherence to the rectum and sigmoid colon. (Fig. 2) The lesions were similar to those of ulcerative colitis. Additionally, the biopsy also showed cryptitis, crypt abscess, and architectural distortion, similar to ulcerative colitis. Based on the above, the diagnosis of irAE colitis was made and treatment with infliximab and prednisolone (30 mg/day) was started. The symptoms were observed to improve with the treatment, and he was discharged from the hospital on the 10th day (CAI score: 2); however, he suffered from abdominal pain and diarrhea again and was readmitted to the hospital (CAI score: 7). Infliximab, mesalazine (3600 mg/day) and prednisolone (60 mg/day) were initiated for recurrent irAE colitis. No significant symptomatic improvement was observed, and symptomatic improvement was observed with the addition of leukocyte removal therapy (twice weekly). However, the abdominal symptoms reappeared one month later (CAI score: 10), and ciclosporin was added to the treatment with mesalazine and prednisolone. Ganciclovir was initiated because the patient was found to be positive for cytomegalovirus.

Computed tomography images showed no evidence of gastrointestinal perforation, (Fig. 3); however, colonoscopy showed no improvement in the mucosal lesions (Fig. 4) and persistent abdominal symptoms; therefore, the patient was considered to have irAE colitis refractory to medical therapy. We considered the indications for proctocolectomy or subtotal colectomy according to the treatment for refractory ulcerative colitis, but decided that proctocolectomy or subtotal colectomy was not indicated because of the poor performance status of the patient and decided to perform a diverting loop ileostomy for the purpose of resting the colon.

The surgery was performed laparoscopically. A camera port was placed at the umbilicus, the abdominal cavity was searched, and no ascites or abscess was found. The gastrointestinal tract showed edema

throughout; however, no abnormalities were found on the serosal surface. (Fig. 5) A diverting loop ileostomy was performed using the ileum, 30 cm from the terminal ileum.

The perioperative course is shown in the Fig. 6. The abdominal symptoms improved postoperatively, and the patient resumed diet on the third postoperative day. The general condition, abdominal pain, and hematochezia also improved over time (CAI score: 3). Only prednisolone therapy was continued, and the patient was discharged 21 days after the surgery.

Chemotherapy was initiated with pemetrexed three months after the surgery, and prednisolone treatment was completed six months after surgery. Stoma closure could not be performed because the mucosal lesions did not improve on colonoscopy; nevertheless, there were no symptoms of irAE colitis, and the patient was rechallenged with nivolumab 18 months after surgery. The patient developed grade 1 colitis immediately after the administration of nivolumab, which resolved with conservative management and could be continued without further symptoms of irAEs. However, the treatment with nivolumab was not effective, and the patient died of the primary disease two years after surgery.

## Discussion And Conclusion

The first ICIs for metastatic melanoma were first approved by the FDA in 2011, and since then ICIs have become the standard medical treatment for various cancers. However, several irAEs have been reported. (1) These adverse events occur when the suppression of the immune system is impaired by ICIs, presenting symptoms similar to autoimmune diseases, and appearing in all organs, such as the skin, respiratory system, nervous system, endocrine system, and digestive system. Although ICIs-induced diarrhea and colitis occur in approximately 20% of the patients on PD-1 inhibitors, the frequency of severe toxicities is low with only 2–5% of patients. The frequency of irAE colitis differs between CTLA-4 inhibitors and PD-1 / PD-L1 inhibitors. CTLA-4 inhibitors cause more frequent gastrointestinal symptoms than PD-1/PD-L1 inhibitors; ipilimumab causes symptoms in approximately 40% of cases, and severe inflammation occurs in 10–15% of cases. (2–4) PD-1 inhibitors were used in this case, and it is a rare case in terms of the frequency of severe disease. The symptoms of irAE colitis are similar to those of ulcerative colitis; moreover, there is a substantial overlap between irAE colitis and inflammatory bowel disease, both endoscopically and histologically. Therefore, the treatment of irAE colitis should be consistent with the treatment of ulcerative colitis.

The guidelines for irAEs have been published by the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO) and others, which recommend treatment strategies based on a certain level of consensus. (2,3) These guidelines recommend that the patients with grade 2 or higher irAE colitis should discontinue treatment with ICIs and receive high-dose systemic corticosteroids, and steroid-resistant patients should be treated with infliximab. Recently, vedolizumab has been reported to be effective in cases that are refractory to steroids and infliximab. Mesalazine has also been reported to be effective for maintenance therapy. (5) Although the surgical treatment of refractory irAE colitis is not specified in the guidelines, it was managed equally with ulcerative colitis. For irAE colitis with perforation,

a subtotal colectomy with ileostomy and sigmoidostomy is recommended because colonic lesions are generally extensive and segmental colonic resection is generally followed by a severe inflammation of the remaining colon in the postoperative phase. However, there have been some reports of deaths within a few days after subtotal colectomy. (6) Moreover, subtotal colectomy is considered invasive and risky for most patients with severe irAE colitis. In addition, there are case reports of ileostomy after colonic perforation in irAE colitis, and the prognosis was poor outcome. (7) In contrast, some studies have reported that ileostomy is effective in the management of refractory irAE. Moreover, in one case, a diverting loop ileostomy was performed to treat Fournier gangrene accompanied by refractory irAE colitis, and the patient reported that the colitis was also found to improved. (8,9)

In this case, prednisolone, infliximab, and mesalazine did not significantly improve the symptoms significantly, and leukocytapheresis was performed. Medical treatment improved the symptoms for a period of time, and the irAE colitis recurred and was extremely refractory to medical treatment; therefore, surgical treatment is considered; however, the performance status was 3. A subtotal colectomy was invasive and risky; therefore, we had to choose a less invasive surgery. Based on these reasons, an ileostomy was performed to rest the colon, and abdominal symptoms were resolved in the early postoperative period, and could the ICI treatment be resumed. However, a postoperative colonoscopy showed no improvement in the mucosal lesions, and stoma closure could not be performed.

The difference between irAE colitis and ulcerative colitis is that irAE colitis is a side effect of cancer treatment by ICIs. There is a conflicting view that the discontinuation of ICIs is preferable for severe irAE colitis; however, the continuation of ICIs is preferable for oncology. In other words, it is necessary to consider ways to avoid the discontinuation of ICIs in the treatment of irAE colitis, including surgical treatment. There is limited evidence on the safety of resuming treatment with ICIs in patients whose treatment was interrupted due to the onset of irAEs. In a report of 24079 irAE cases registered in the World Health Organization VigiBase database, 452 patients rechallenged ICIs and 130 (28.8%) patients showed the recurrence of irAEs, and colitis, pneumonia, and hepatitis were shown to have high recurrence rates. (10) In another report of 167 patients with irAE colitis, one-third of the patients who rechallenged ICIs relapsed with irAE colitis. (11) It has been reported that the risk-reward ratio of anti-PD-1 or the anti-PD-L1 rechallenge is within acceptable limits, and some have reported that the risk-reward ratio of anti-PD-1 or anti-PD-L1 rechallenge is within acceptable limits. (12) These reports suggest that a rechallenge therapy with ICIs is acceptable under close monitoring, although further studies are needed. Currently, the standard surgical procedure for treating ulcerative colitis is proctocolectomy. Appendicostomy, cecostomy, and ileostomy have been performed for ulcerative colitis since the early 1900s to restore the colon. Moreover, ileostomy was commonly performed for toxic colitis in patients with IBD. Subsequently, proctocolectomy was also performed; however, the mortality rate was high due to intraoperative fecal spillage. Turnbull et al. pointed out that fecal spillage occurs during colonic manipulation and proposed diverting ileostomy and decompression colostomy in 1971. (13) The colostomy, also known as Turnbull-Blowhole colostomy, decompresses the colon; however, it was reported to have the unexpected benefit of temporary remission of the disease in most patients. With improvements in the management, the Turnbull-Blowhole colostomy has rarely been performed, but has recently begun to be reevaluated. The

Turnbull-Blowhole colostomy has been reported to be effective for toxic ulcerative colitis in pregnancy. (14,15) Since decompression of the colon was not necessary in this case, a Turnbull-Blowhole colostomy was not necessary; nevertheless, it may be an option for patients with irAE colitis complicated by toxic megacolon, who are in poor general condition.

We encountered a case in which ileostomy was performed for irAE colitis refractory to medical treatment, and the symptoms were alleviated. The indications for the treatment with ICIs are expected to expand and the number of such cases will increase in the near-future. The surgical treatment of irAE colitis also needs to be evaluated and analyzed.

## **Abbreviations**

ICIs: Immune checkpoint inhibitors, irAEs: immune-related adverse events, irAE colitis: Immune checkpoint inhibitor-related colitis, TPS: Tumor Proportion Score, CAI: Clinical Activity Index, FDA: U.S. Food and Drug Administration, ASCO: American Society of Clinical Oncology, ESMO: European Society for Medical Oncology, IBD: Inflammatory Bowel Disease

## **Declarations**

### **Ethics approval and consent to participate**

Ethical approval is not required for publication of a single case report at the Ethics Committee Kindai University Faculty of Medicine. Written informed consent was obtained from the patient.

### **Consent for publication**

Written informed consent was obtained from the patient and patient's family for the publication of this case report and accompanying images.

### **Availability of data and materials**

The datasets used and/or analyzed during this study are included in this paper and shall be available from the corresponding author upon request.

### **Competing interests**

The authors declare that they have no competing interests.

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### **Authors' contributions**

K.D. and J.K. performed the literature review and collected the clinical data. K.D. and J.K. performed the surgery. K.D. prepared the first manuscript. J.K. and K.U. supervised the contribution. All authors (K.D., Y.M., Y.Yane, H.U., T.W., Y.Yoshioka, M.I., T.T., K.U., J.K.) participated in further drafting and revision of the manuscript. All authors read and approved the final manuscript.

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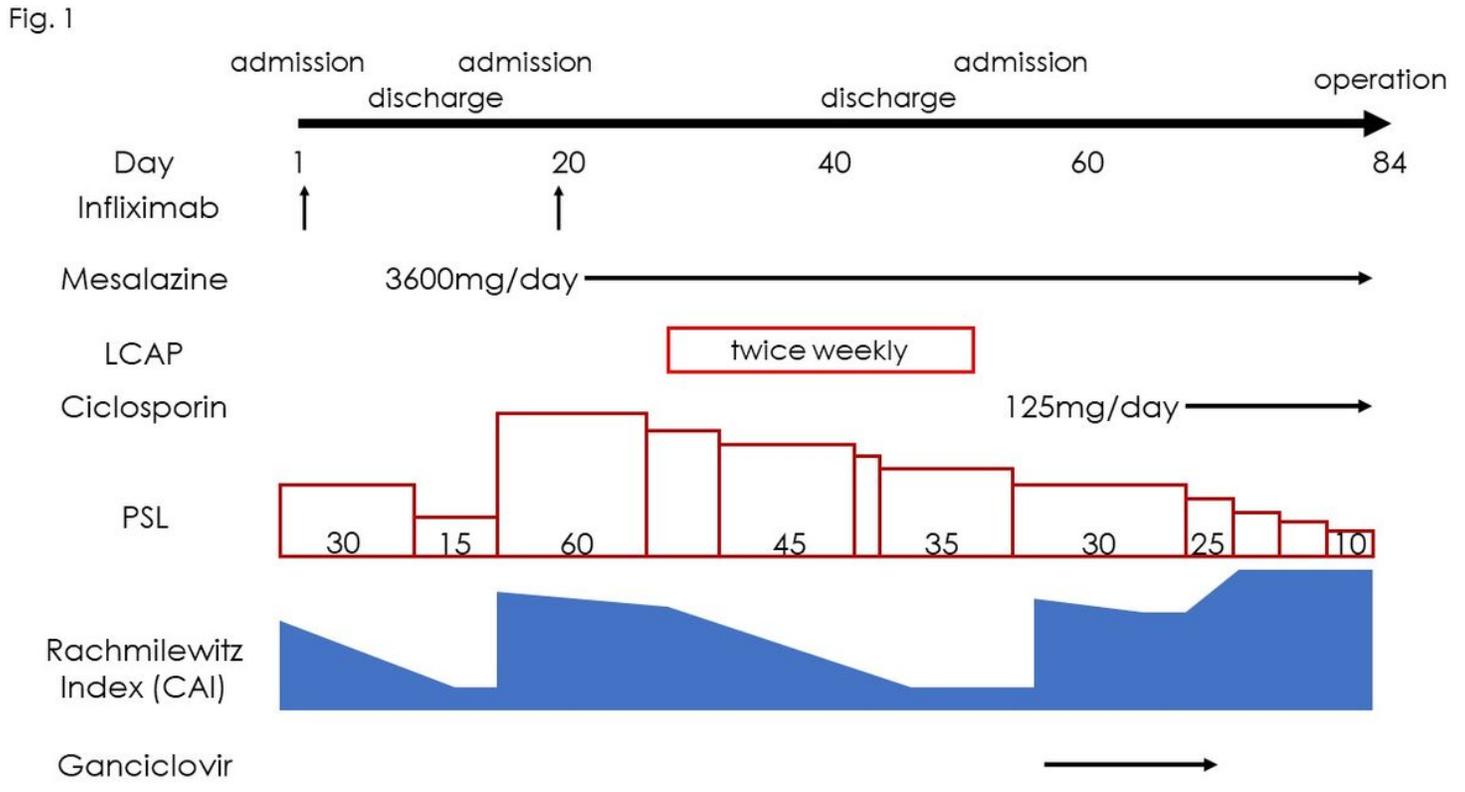
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## Figures

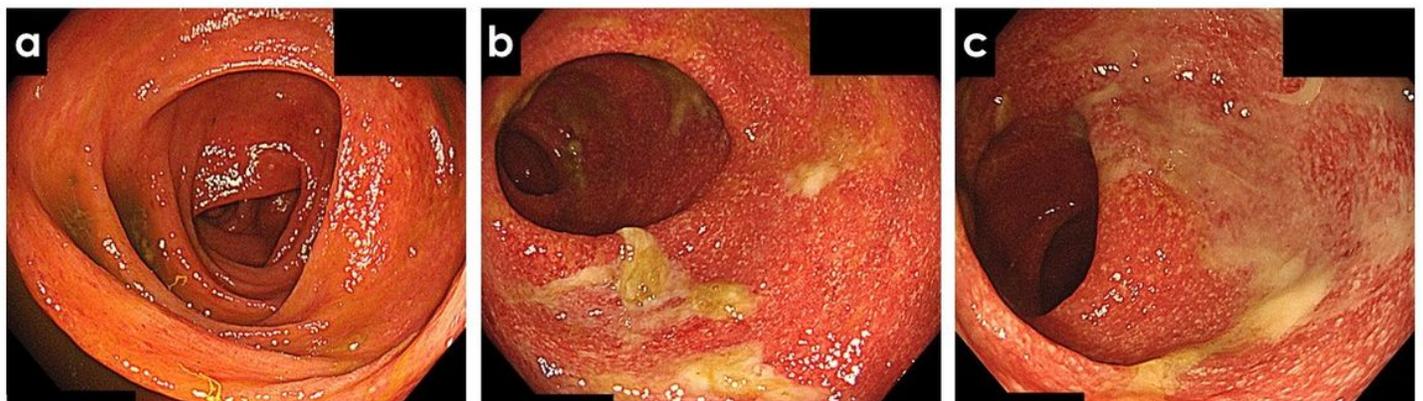


**Figure 1**

Course of the disease from admission to operation.

LCAP: leukocytapheresis, PSL: prednisolone

Fig. 2



**Figure 2**

Colonoscopy showing diffuse mucosal erythema and sporadic erosions from (a) transverse colon to (b) sigmoid colon and (c) rectum. The mucopurulent adherence was found in the sigmoid colon and rectum.

Fig. 3

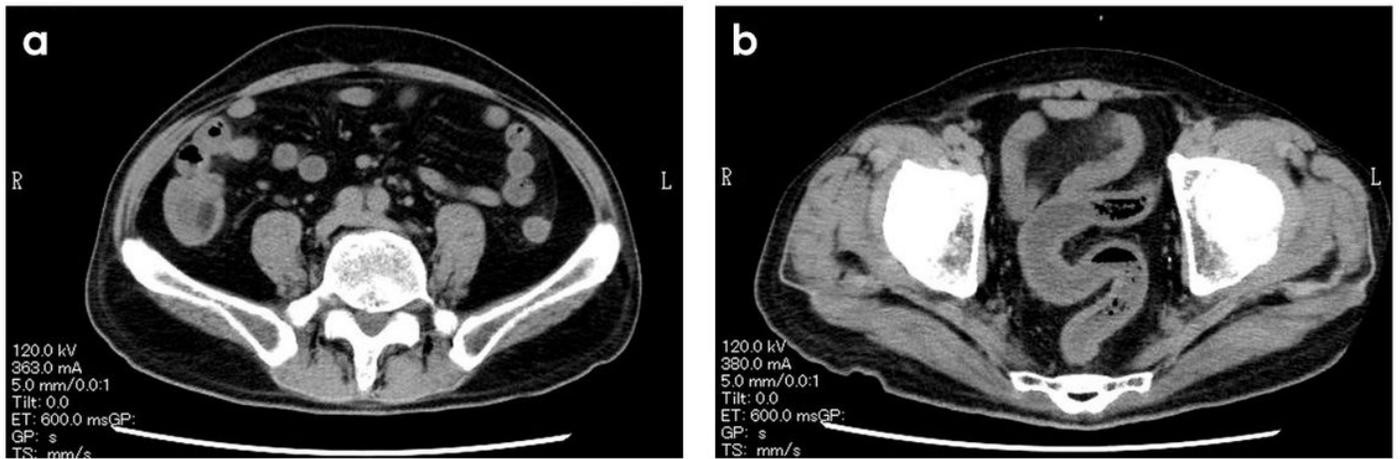


Figure 3

Computed tomography demonstrating no evidence of gastrointestinal perforation, (a) and showing edema from the small intestine (a) to colorectum (b).

Fig. 4

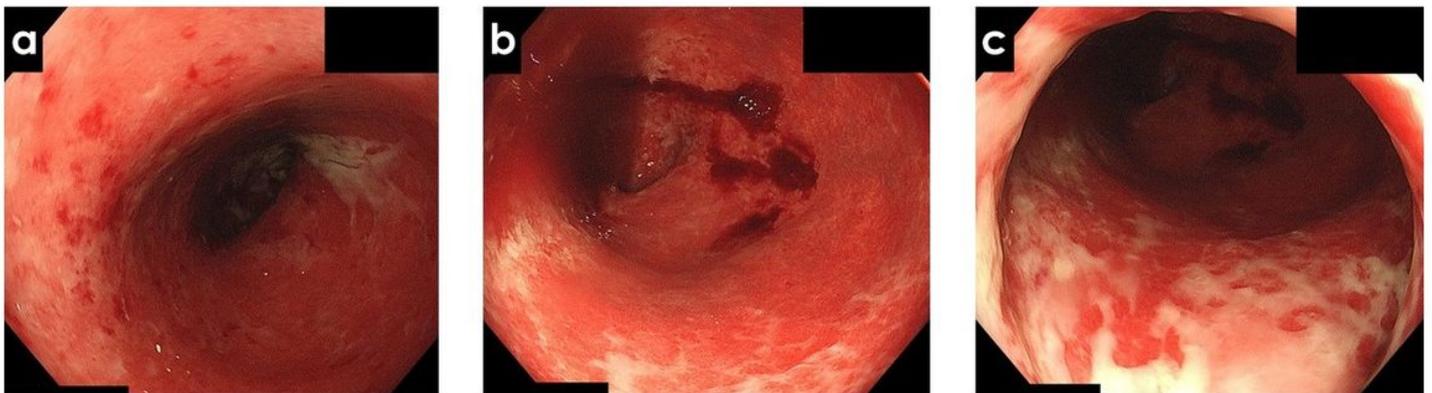
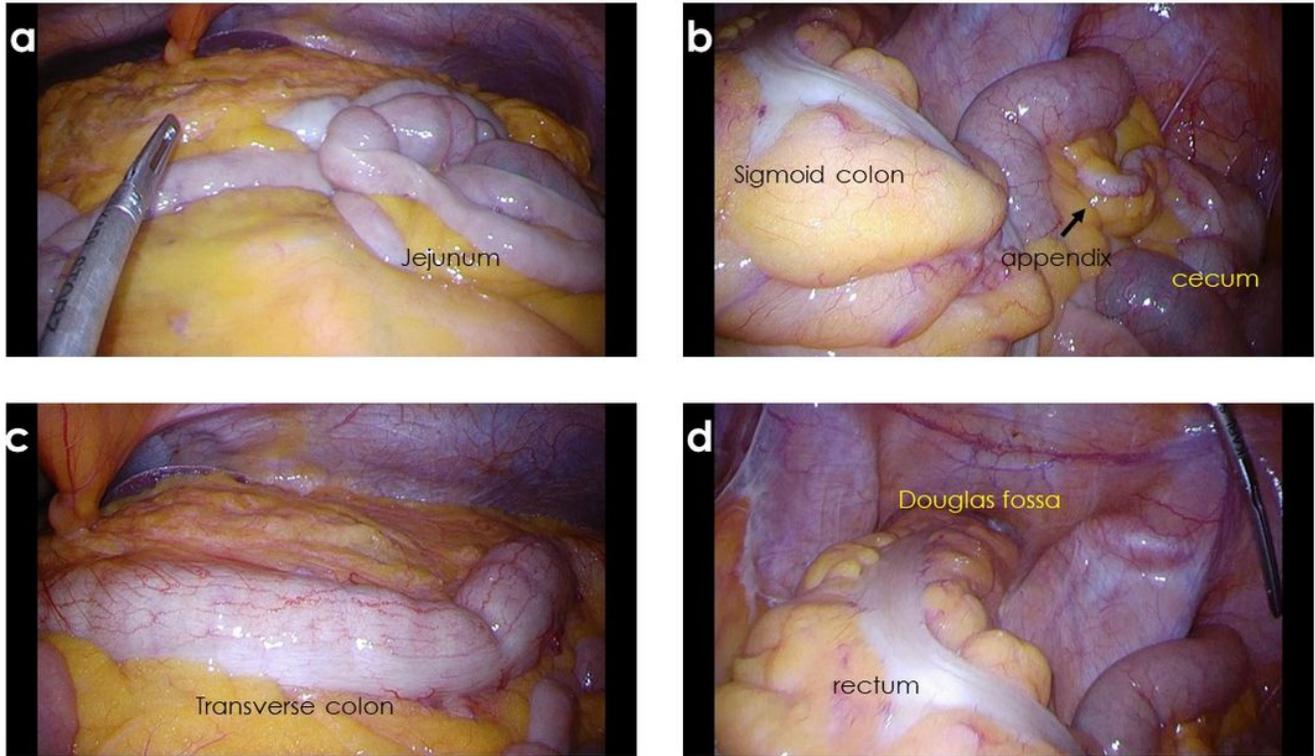


Figure 4

Colonoscopy findings after treatment. Mucosal redness, erosion, and mucopurulent adherence are observed, and there is no improvement compared to the time of admission. (a) Sigmoid colon (b) Rectosigmoid colon (c) Lower rectum

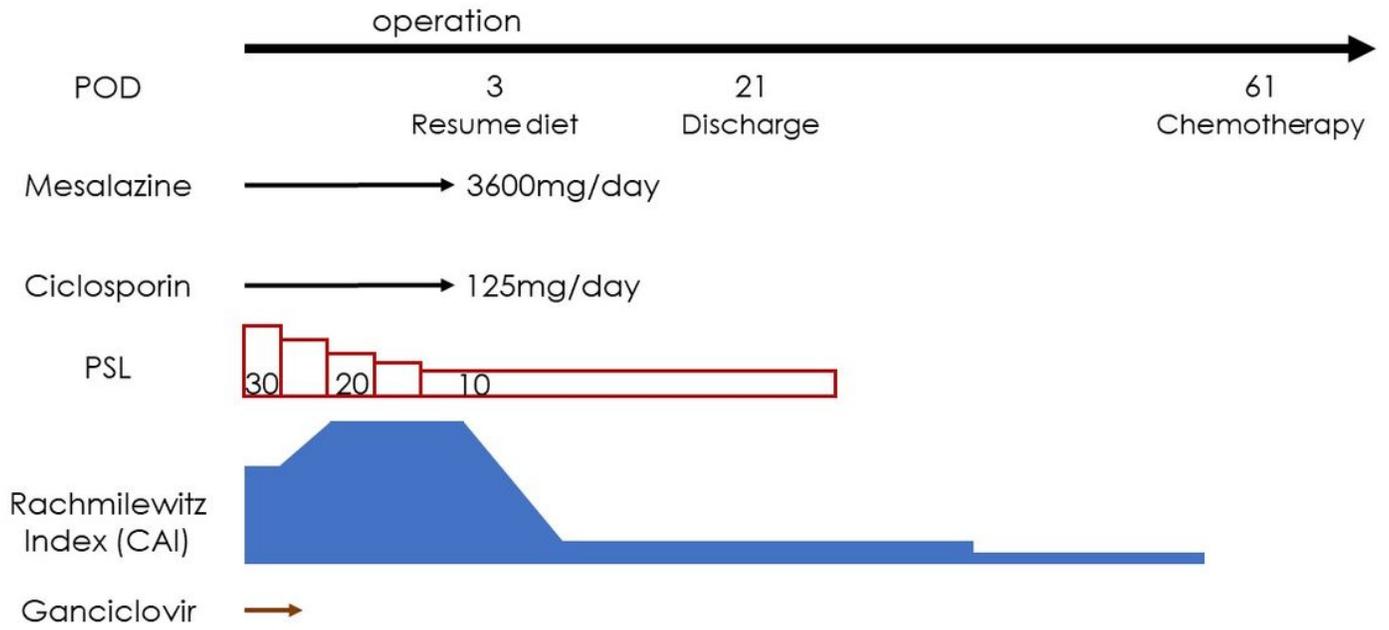
Fig. 5



**Figure 5**

There is no ascites or abscess, but gastrointestinal tract is slightly edematous. The serosal surface of the tract is intact. (a) Jejunum is slightly edematous. (b) Sigmoid colon, cecum and appendix is shown. (c) Transverse colon is almost normal. (d) Edema is observed in the mesorectum. Ascites is not shown in the Douglas fossa.

Fig. 6



**Figure 6**

Course of the disease in the perioperative period.

POD: Postoperative day, PSL: prednisolone